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Contributors

Numbers in parentheses indicate the pages on which the author's contribution begins.

Yiannis Fiamegos (27) Department of Chemistry, University of Ioannina, GR-451 10 Ioannina, Greece

Gunther Fischer (143) Geibelstraße 15, D-04129 Leipzig, Germany

Valerii V. Mezheritskii (1) Research Institute of Physical and Organic Chemistry, Rostov-on-Don State University, 344090 Rostov-on-Don, Russia

George Pilidis (27) Department of Chemistry, University of Ioannina, GR-451 10 Ioannina, Greece

Alexander P. Sadimenko (219) Department of Chemistry, University of Fort Hare, Alice 5701, Republic of South Africa

George Varvounis (27) Department of Chemistry, University of Ioannina, GR-451 10 Ioannina, Greece

Preface

Volume 95 of *Advances in Heterocycle Chemistry* commences with Part I of an update of *Peri-Annulated Heterocyclic Systems* by Valerii V. Mezheritskii (Rostov-on-Don State University, Russia). This chapter comprises an update of a review published in Volume 51 of our series (1990) by the same author together with V. V. Tkachenko. The present chapter is concerned with naphthalene derivatives with a four-membered peri-annulated heterocyclic ring.

Varvounis, Fiamegos, and Pilidis (University of Ioannina, Greece) have contributed the third part of their overview of pyrazol-3-ones, which deals with the reactions of substituents.

Recent progress in the chemistry of 1,2,4-triazolo[1,5-a]pyrimidines, which is of increasing importance in drug research, is the subject of a review by G. Fischer (University of Leipzig, Germany).

The final chapter is a further installment in the ongoing series on the organic chemistry of heterocyclic ligands in metallic complexes. The present contribution covers organoiron, organoruthenium, and organoosmium poly-pyridine complexes and is again authored by Alexander Sadimenko (Fort Hare University, Republic of South Africa).

Alan R. Katritzky
Gainesville, Florida

Peri-Annulated Heterocyclic Systems. Part I

VALERII V. MEZHERITSKII

Research Institute of Physical and Organic Chemistry, Rostov-on-Don State University,
344090 Rostov-on-Don, Russia

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I. Introduction

The present-day chemistry of heterocyclic compounds with a closed aromatic ($4n + 2$ electrons) and nonaromatic ($4n$ electrons) π -system is based on heteromonocycles (e.g., I–III) and their *ortho*-fused derivatives (e.g., IV–VI) (Figure 1).

The distinguishing feature of *ortho*-annulation is the possibility of formally extracting the parent heteromonocycle from the fused structure (IV–VI) (*cf.* formulas I–III and IV–VI). Moreover, the chemical characteristics of the *ortho*-fused compounds to a large extent reproduce the properties of their heteromonocyclic precursors. In particular, the fundamental qualities are retained that govern their properties, including π -excess and π -deficiency, which originate from the nature and hybridization character of the heteroatom (or atoms). With certain qualifications the so-called bridged heterocyclic systems where the heteroatom belongs simultaneously to two or three rings may also be assigned to this type.

The specific feature of *peri*-annulation consists in the fact that the extraction of a heteromonocycle is impossible. Therefore, the minimum structural unit in this case is the tricyclic framework, for instance, (VII–IX). It is therefore obvious that *peri*-annulated heterocyclic systems possess qualitatively new structural features sufficient to separate these substances into an independent domain distinct from the array of the heteromonocyclic and *ortho*-fused heterocycles.

Nonetheless no treatise or monograph on the chemistry of heterocycles contains a mention, let alone an entire chapter, on *peri*-fused heterocyclic compounds as independent objects worthy of special consideration, equal to those of heteromonocyclic and *ortho*-fused substances. The previously published chapter (90AHC(51)1) and present review attempts to remedy this situation.

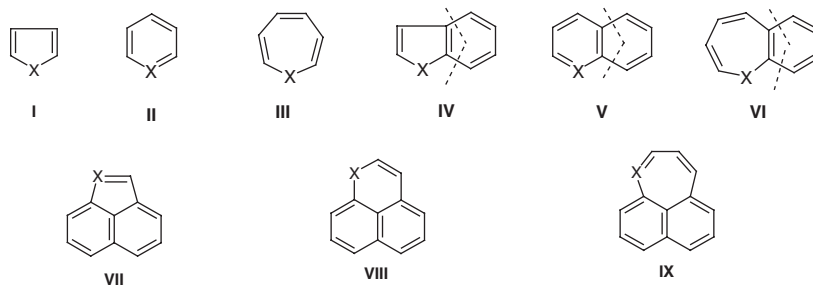


Figure 1. Types of heterocyclic systems

The introduction to the first publication (90AHC(51)1) dedicated to syntheses of *peri*-annulated heterocyclic naphthalene derivatives outlined the problems of this new field. Nomenclature was considered, some basic concepts were introduced, a classification of all presumable structural types containing a heterocycle from four-membered to seven-membered rings, and the principles of their building were discussed. We have not limited the present review to synthetic procedures but tried to consider all the aspects of the chemistry of *peri*-fused heterocyclic systems taking into account the new findings that have appeared since the first review (90AHC(51)1). The presentation follows the previously developed sequence, describing successively compounds with larger heterocycles, with increasing number of heteroatoms in the heteroatom order N, O, S, and occasionally other heteroatoms.

The immense amount of information available induced us to divide it into separate chapters. This first chapter draws the attention to *peri*-fused heterocyclic naphthalene derivatives with a four-membered heterocyclic ring.

Those *peri*-annulated heterocycles with a closed π -system that possess a double bond or another π - or p -electron “bridge” situated in the *peri*-position of the naphthalene ring opposite to the heterocycle should be set apart. Examples include the 16π -electron *peri*-fused heterocyclic acenaphthylene derivatives XII and XV, whose 14 p - and π -electrons are situated on the perimeter of the heteroaromatic skeleton forming an aromatic contour (according to Hückel), while two π -electrons occupy an internal orbital.

Electronic structures of XII and XV should be compared with *peri*-annulated heterocyclic pair X and XI and pair XIII and XIV, respectively, each lacking a vinyl chain in the *peri*-position opposite to the heterocycle (Figure 2). The heterocyclic triad X, XI, and XII and triad XIII, XIV, and XV should be compared with their isoelectronic hydrocarbons XVI, XVII, and XVIII. In the hydrocarbon triad XVI, XVII, and XVIII the first two compounds, plydiene and aceplydiene, belong to the so-called unsaturated aromatic hydrocarbons possessing two 4π -electron nonbonding orbitals and a pronounced divinyl character of the seven-membered ring, which is prone to addition and not to substitution reactions (81MI1281, 73MI1240). They do not fit the Hückel $(4n+2)\pi$ rule in spite of the presence of 14π -electrons.

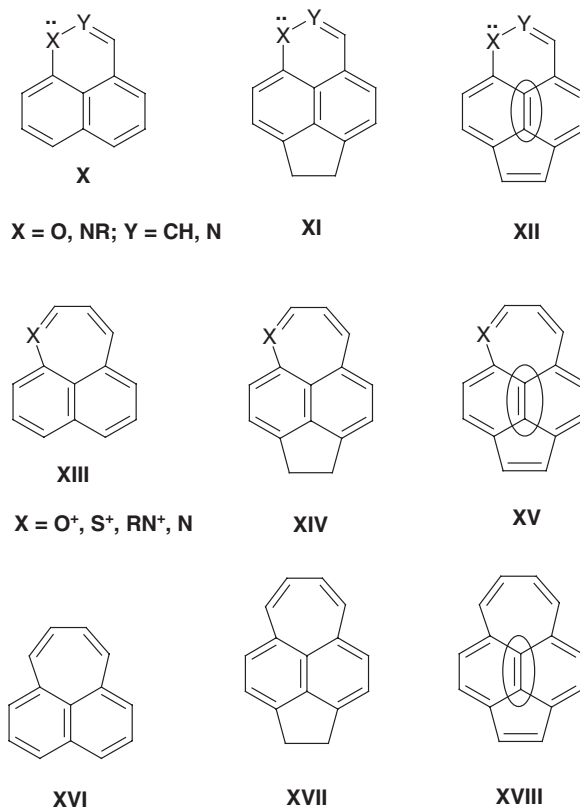


Figure 2. Examples of aromatic and nonaromatic *peri*-annulated carbocyclic and heterocyclic systems

In contrast, aceplyedilen (XVIII, Figure 2) is aromatic since it contains a closed 14π -electron (Hückel) external contour with alternating double bonds. The peripheral electrons are believed to play the dominant part in the formation of a stable 14π -electron ensemble (57JOC36), (64HCA1172). The internal double bond in XVIII may be regarded as having a proper importance but as part of the overall electronic system.

The above principle is apparently also true for heterocyclic systems X, XI, and XII and also XIII, XIV, and XV. The comparison of the degree of aromaticity of heterocycles XII and XV with that of aceplyedilen (XVIII) is as appropriate as the likening of the aromaticity of 6π -electron five- and six-membered heterocycles to that of benzene or more generally of the aromaticity of aromatic hydrocarbons to heteroaromatic compounds (85MI280).

Each of the above real and hypothetical heteroaromatic systems should possess a specific set of characteristics and its own chemistry whose study may be a subject of extensive fundamental research.

Not only is the investigation of the chemical reactions of novel heteroaromatic compounds of interest, but also the comparison of their physical properties (magnetic susceptibility, dipole moments, etc.), spectral characteristics (UV, IR, and NMR spectra), and the calculation criteria on going from nonaromatic structures XI and XIV to aromatic ones XII and XV, Figure 2.

II. *Peri*-Annulated Heterocyclic Naphthalene Derivatives with a Four-Membered Hetero Ring

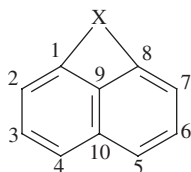
This section treats the hypothetical and real compounds with formula XIX whose positions 1 and 8 of the naphthalene framework are bonded to a single X heteroatom (Figure 3).

In addition to article (90AHC(51)1) where the methods of preparation of these compounds were systematized, J. Nakayama published in 1981 (81MI2682) a review in Japanese, perhaps not available, dedicated to the chemistry of the *peri*-fused naphthalene derivatives with four-membered carbon and hetero rings.

These strained structures are of interest for theoretical and experimental studies. The recent semiempirical (95MI1696) and *ab initio* (01JST287) calculations of the structural parameters of such molecules have provided information on their stability and made it possible to suggest the conditions for their existence and isolation.

Roohi et al. (01JST287) suggested as stability criteria for the *peri*-fused naphthalenes XIX the quantities r (the value of the ratio of bond angles C4–C10–C5/C1–C9–C8) and p (the value of the torsion angle C1–C9–C10–C5). Based on these calculations a structure should have an r value not exceeding 1.4 in order to exist. Thus, structures with the following X could be relatively stable: CH₂ (1.40); C=O (1.37); S (1.30); SO (1.26); SO₂ (1.24); PH (1.25); PHO (1.23). In contrast the structures with X=NH or O having r 1.51 and 1.54, respectively, should be extremely unstable (*cf.* the values of naphthalene, r = 1, and acenaphthene, r = 1.14).

The p value is related to the extent of coplanarity of the naphthalene skeleton. In the stable molecules (X = C, S, P) the p value falls into the range 0–2.8° meaning that the naphthalene framework is a virtually planar highly conjugated aromatic π -system. When nitrogen or oxygen is involved as heteroatom (X = N, O) the p values



XIX

(X = N, PR, O, S, SO, SO₂, BR, SiR₂, GeR₂)

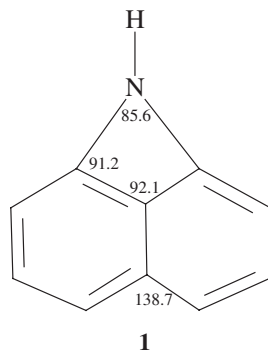
Figure 3. General formula of *peri*-fused heterocycles with a four-membered hetero ring

are 18.7° and 22.6° , respectively. To put it differently, in the latter case the naphthalene skeleton resembles a gable roof and suffer from significantly distorted conjugation of the aromatic π -system. Just these strong distortions in the aromatic skeleton and not the strain in the nitrogen or oxygen four-membered ring are apparently the main obstacle to the generation and existence of these molecules. Actually, a large number of stable representatives of four-membered heterocycles with a nitrogen or oxygen ring heteroatom are described, among them also their benzoannulated derivatives (84MI2237, 84MI1363).

A. NAPHTH[1,8-BC]AZETE

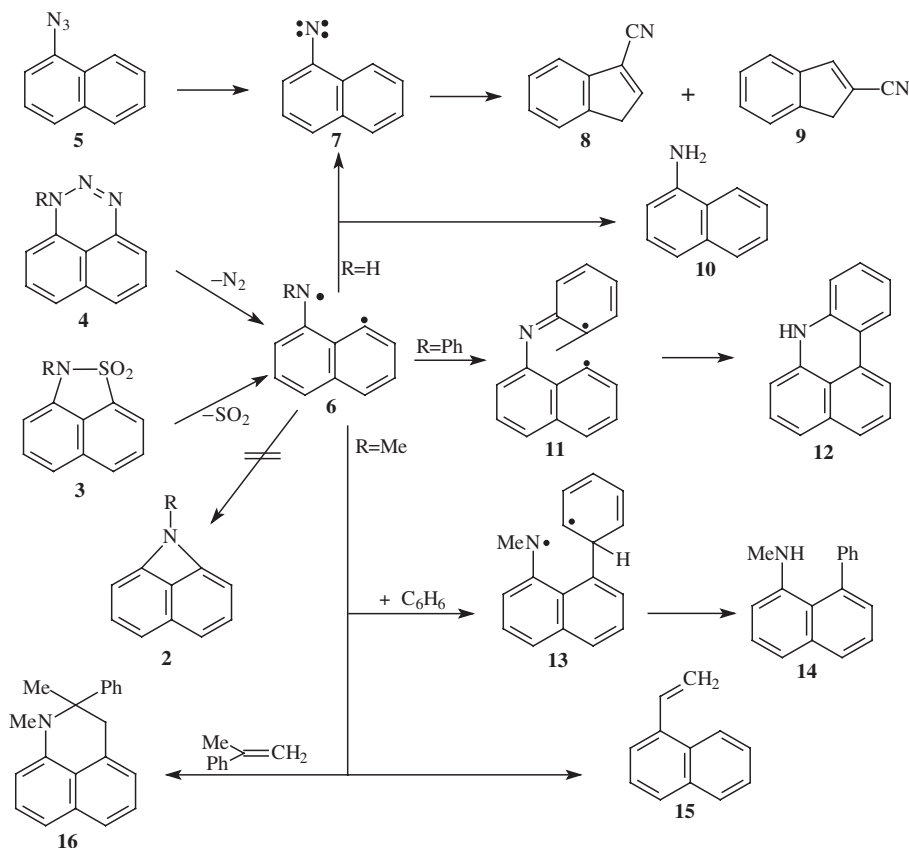
Despite all attempts to synthesize naphth[1,8-*bc*]azete or its derivatives **2** not a single example has been prepared and no traces of such compounds as intermediates in chemical reactions have been found in keeping with the theoretical analysis (Figure 4).

The plan for the preparation of naphth[1,8-*bc*]azete (**2**) was based on sulfur dioxide elimination from naphtho[1,8-*de*]thiazole *S,S*-dioxide (**3**, Scheme 1) or on nitrogen liberation from naphtho[1,8-*bc*]triazine (**4**) under pyrolysis ($500\text{--}800^\circ\text{C}$) or photolysis (68CC1026, 69JA1035, 70JCS(C)298, 72JOC2152). In all investigated instances biradical **6** formed as a key intermediate. Inasmuch as this biradical cannot close into a four-membered azetidine heterocycle as stated above, it suffers further transformations into a whole set of isolated and identified compounds **8**, **9**, **12**, and **14–16**, Scheme 1. For instance, biradical **6**(R = H) undergoes fragmentation in two ways generating a pair of isomeric cyanoindenes **8** and **9** and naphthylamine **10**. Presumably nitrene **7** as a reactive intermediate is a precursor to the formation of indenes **8** and **9**. Three research groups (75TL3845, 77TL943, 80CC499) unsuccessfully later tried to obtain naphtho[1,8-*bc*]azetidene **2** via nitrene **7** generated by a photolysis of azide **5**.



$$r = 1.51; p = 18.7^\circ \text{ (calculated values)}$$

Figure 4. General formula, bond angles in the hetero ring, and other calculated parameters of naphth[1,8-*bc*]azete



Scheme 1

Biradical **6**, R = Ph, converts into benzo derivative of naphtho[1,8-*bc*]pyridine (**12**), and **6**, R = Me transforms depending on the reaction conditions and the presence of other reagents into 1-methylamine-8-phenylnaphthalene (**14**), 1-methylideneamino-naphthalene (**15**), or *peri*-fused azine (**16**).

B. NAPHTHO[1,8-*bc*]PHOSPHETE

In conformity with the calculations the *peri*-fused heterocycles with a phosphorus atom proved to be quite stable. For instance, treating 1,8-dilithionaphthalene (**18**) with (*N,N*-diisopropylamino)dichlorophosphine afforded in a 75% yield a *P*-substituted naphtho[1,8-*bc*]phosphete (**19**) that took up tungsten pentacarbonyl to form a complex compound **20** (02AG(E)3897). The latter on further reaction with platinum tetratriphenylphosphinate and carbon monoxide suffers a recyclization of the four-membered ring into a five-membered one (**20**→**21**). The reaction of 1,8-dilithionaphthalene with a phenyl dichlorophosphine gave instead of an expected

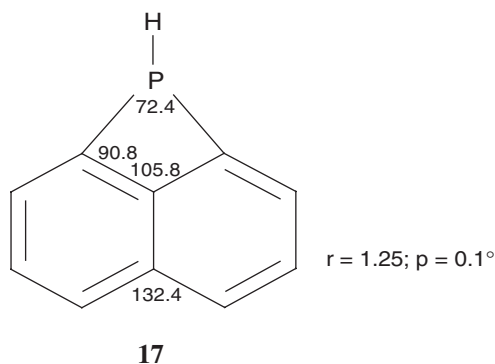
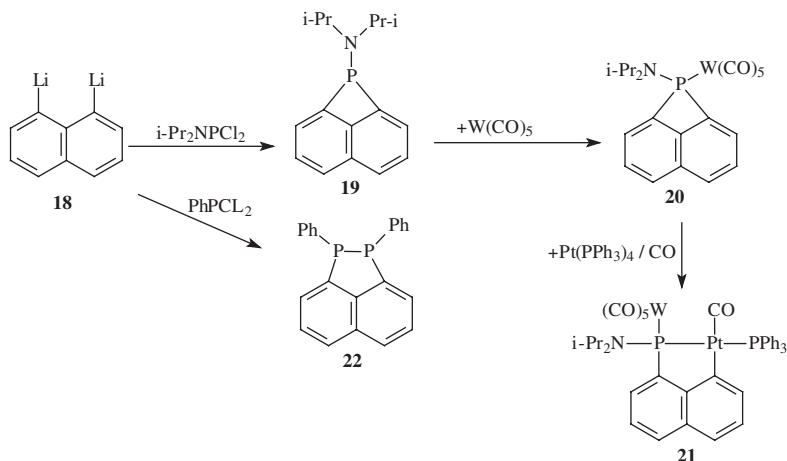


Figure 5. General formula, bond angles in the hetero ring, and the other calculated parameters of naphtho[1,8-*bc*]phosphete

(*P*-phenyl)naphtho[1,8-*bc*]phosphete a product resulting from closure to a five-membered heterocycle forming *peri*-annulated diphosphetol (**22**) (Scheme 2). The structures of compounds **19** and **22** were proved by X-ray diffraction analysis. The X-ray data for **19** provide bond lengths, bond angles, and the coplanar position of the hetero ring and the naphthalene skeleton, these and the other parameters have values close to those calculated for the simplest naphtho[1,8-*bc*]phosphetol (**17**) (Figure 5). Compound **19** is a white powder, very soluble in organic solvents (the melting point is not mentioned). The ^1H and ^{13}C NMR spectra show the symmetry of the molecule and confirm the structure of the compound with *peri*-phosphete **19** interesting opportunities arise for the preparation of unusual substances, e.g., **20** and **21**, by uncommon reactions.

C. NAPHTH[1,8-*bc*]OXETE

A 1933 patent claimed the preparation of naphth[1,8-*bc*]oxete (**23**) along two routes: α -naphthol oxidation by iron(III) chloride, and 1,8-dihydroxynaphthalene dehydration (33BRP394,511) at 300 °C under a carbon dioxide atmosphere.

Structure **23** (Figure 6) was assigned based on the elemental analysis, the cryoscopic measurement of the molecular weight, and its behavior in the chemical reactions. The compound formed in a good yield, was quite stable, and high melting (about 300 °C). These characteristics and its chemical behavior according to some chemists (66CRV593, 70JOC4261) hardly fit the assigned structure. A. Gordon (70JOC4261) in 1970 checked the results of the patent (33BRP394,511) carefully executing the oxidation of α -naphthol with iron(III) chloride precisely under the conditions described and thoroughly separating the products and succeeded in isolating and identifying only the initial α -naphthol (**24**) and the previously described (28CB362, 31JCS1265) product of its oxidative dimerization **25**. In another experiment, the dark glassy residue obtained after a 15 min heating of 1,8-dihydroxynaphthalene (**26**) under a CO₂ atmosphere was subjected to a number of procedures for reaction mixture separation (extraction, sublimation, chromatography, etc.). Some of initial dihydroxynaphthalene (**26**) was isolated, and the residue was an intractable tar. It was concluded (70JOC4261) based on these test experiments that the information in the patent (33BRP394,511) on the synthesis of naphth[1,8-*bc*]oxete (**23**) was erroneous (Scheme 3).

Interesting results were obtained by pyrolysis of naphtho[1,8-*bc*]-1,2-oxathiol *S,S*-dioxide (**26**) with sulfur dioxide elimination. Depending on the addition to the pyrolyzed mixture of either methanol or carbon monoxide, two pairs of isomeric compounds, **28** and **29** or **30** and **31**, respectively, were formed in high yield and in an ~1:1 ratio (71TL4093) (Scheme 4).

At first glance it would seem that the formation of isomer pairs provides conclusive evidence of naphth[1,8-*bc*]oxete intermediate (**27**) involvement. However, taking into consideration the drastic pyrolysis conditions (680 °C) and the predicted instability of the naphth[1,8-*bc*]oxete (**23**) structure, it is more likely that not a four-membered oxetane heterocycle, but a pair of interconverting biradical intermediates **A** and **B** takes part in the reaction where the formation of the new C¹-O covalent bond occurs simultaneously with the rupture of the existing C⁸-O bond (**A** \rightleftharpoons **B**).

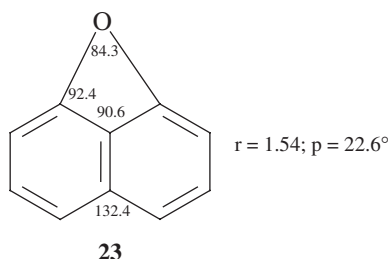
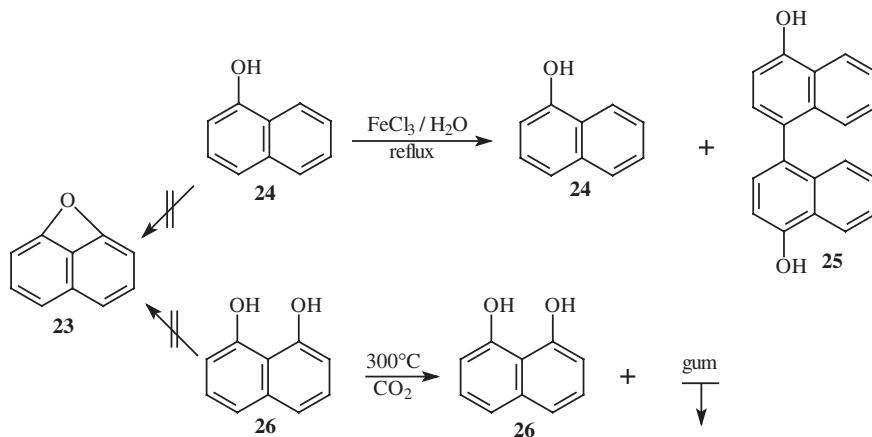
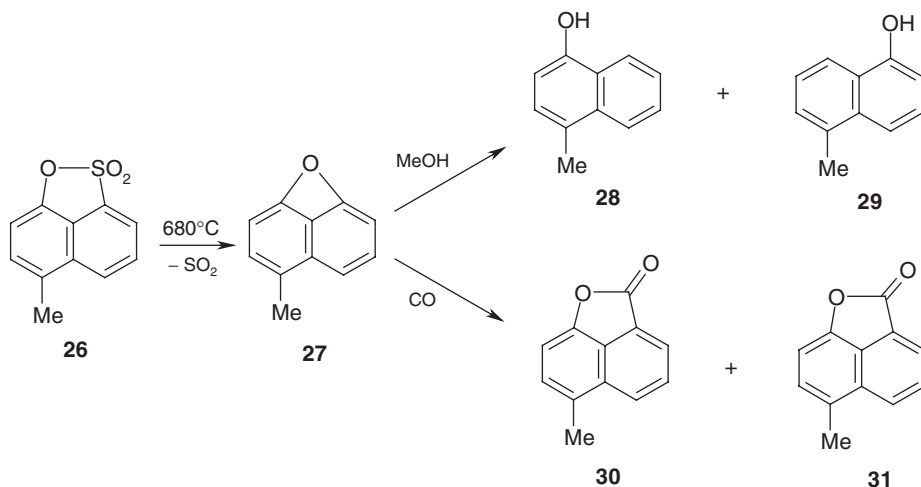


Figure 6. General formula, bond angles in the hetero ring, and other calculated parameters of naphth[1,8-*bc*]oxete



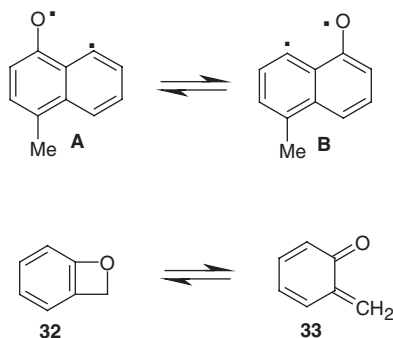
Scheme 3



Scheme 4

The stabilization of *ortho*-fused benzoxete (**32**) occurred by valence isomerization into a quinoid isomer (**33**) (84MI1363). Such benzoid–quinoid processes are impossible for naphth[1,8-*bc*]oxete because of structural reasons. Therefore, the biradicals isomerization (**A** \rightleftharpoons **B**) seems likely (Scheme 5).

Apart from the above attempts, the failed efforts to prepare naphth[1,8-*bc*]azete and naphth[1,8-*bc*]oxete were mentioned in (74JA6532) but the experiments were not published.



Scheme 5

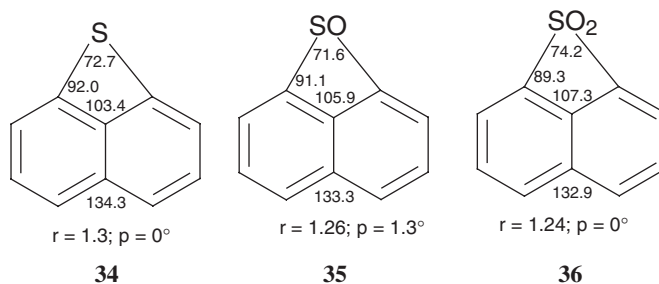
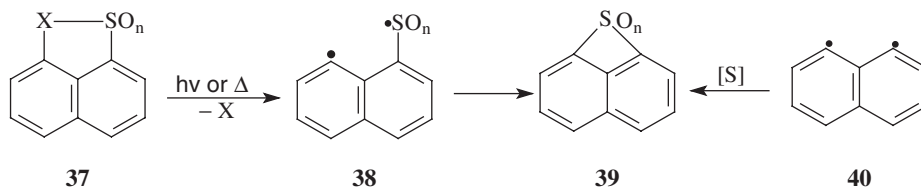
D. NAPHTHO[1,8-*bc*]THIETE AND ITS *S*-OXIDES

Figure 7. General formulas, bond angles in the hetero ring, and other calculated parameters of naphtho[1,8-*bc*]thiete and its *S*-oxides

The calculated r and p values (01JST287) predict that all three representatives of this heterocyclic system shown in Figure 7 [parent naphtho[1,8-*bc*]thiete (**34**) and its two *S*-oxides (**35** and **36**)] should be sufficiently stable to exist in a free state. Experimental data are consistent with theory. All the three compounds have been prepared by several teams.

The first to be obtained was *S,S*-dioxide **36** (65AG(E)786, 67LA96). The parent naphtho[1,8-*bc*]thiete (**34**) and its sulfoxide **35** were prepared 10 years later (74JA6532, 76JA6643, 79JA7684, 81JCS(P1)413, 83TL821).

The design strategy for this system is based either on the decomposition of other *peri*-annulated heterocycles with a five- or six-membered hetero ring capable of eliminating an atom or a group of X atoms under photolysis or thermolysis (**37** → **38** → **39**), or on generating a 1,8-dehydronaphthalene intermediate **40** followed by its reaction with certain sulfur-containing reagents (**40** → **39**) (Scheme 6).



Scheme 6

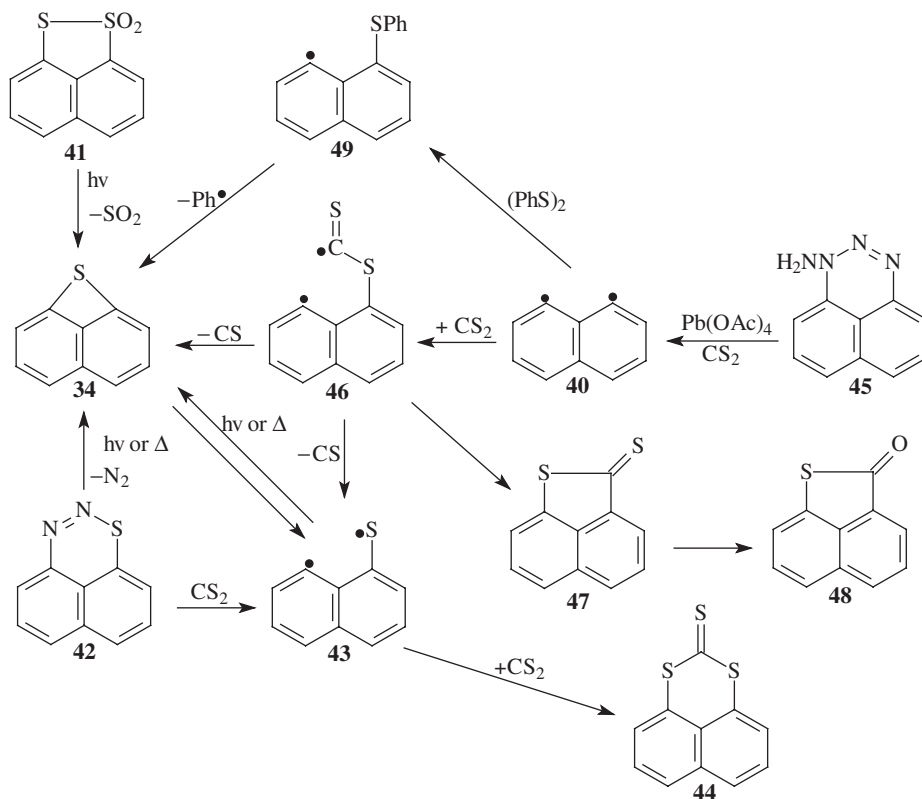
Naphtho[1,8-*bc*]thiete (**34**) or (**39** $n=0$) can be prepared by the photolysis of naphtho[1,8-*bc*]-1,2-dithiol 1,1-dioxide (**41**), (74JA6532, 76JA6643), and also by the photolysis or thermolysis of naphtho [1,8-*de*]-1,2,3-thiadiazine (**42**) (79JA7684).

The irradiation of dithiol 1,1-dioxide **41** for 9.5 h in dilute, dry, and oxygen-free benzene under a nitrogen atmosphere furnished naphtho[1,8-*bc*]thiete (**34**) after evaporation and chromatography on silica gel in a 97% yield. A more feasible preparative synthesis of this compound avoiding some of the special conditions of the above procedure is the photolysis of naphthothiadiazine **42** that is carried out by irradiating 1 mmol of **42** in 120 ml of a solvent (acetone, acetonitrile, benzene, or methanol) with a 120 W high-pressure mercury lamp in a Pyrex glass reactor at room temperature. This photolysis proceeds strikingly easily. After just 5 min irradiation the initial red solution turns light yellow with vigorous nitrogen liberation. After 15–20 min the irradiation is complete, and **34** is quantitatively isolated as in the previously described procedure.

The formation of naphthothiete (**34**) from dithiol **41** and naphthothiadiazine (**42**) is preceded by biradical intermediate **43** as proven by the photolysis of naphthothiadiazine (**42**) in carbon disulfide. After 15 min irradiation alongside naphthothiete (**34**) obtained in a 52% yield there also formed in a 22% yield naphtho[1,8-*de*]-2,4-dihydro-1,3-dithiin-2-thione (**44**) resulting from the reaction of biradical **43** with carbon disulfide (Scheme 7).

The behavior of naphthothiadiazine (**42**) on thermolysis was investigated. The compound when dissolved in 2-ethoxyethyl ether at 155 °C under a nitrogen atmosphere led to the formation of the expected naphthothiete (**34**) in 30% yield and three minor products whose structures were not rigorously determined; 12% of the initial unreacted compound was also recovered.

A reactive specie of an outstanding interest, 1,8-dehydronaphthalene (**40**), can be generated by oxidation of 1-aminonaphtho[1,8-*de*]-1,2,3-triazine (**45**) (69JCS(C)756, 69JCS(C)760, 69JCS(C)765). The behavior of 1,8-dehydronaphthalene is essentially different from that of dehydrobenzene (benzyne), presumably because of the singlet diradical structure of the former, although it is also prone to cycloaddition to olefins and to radical reactions (69JCS(C)756, 69JCS(C)760, 69JCS(C)765, 71JA3802, 75JA681, 75BCJ932). The transformations of 1,8-dehydronaphthalene (**40**) in carbon disulfide studied by J. Nakayama et al. provided a complex mixture of products. From the mixture naphthothiete (**34**) was isolated in a 6–8% yield, and also in still lower yields (3–5%) the other *peri*-fused heterocycles (**44**, **47**, and **48**) were separated. The routes of formation are shown in Scheme 7. Usually the reactions of



Scheme 7

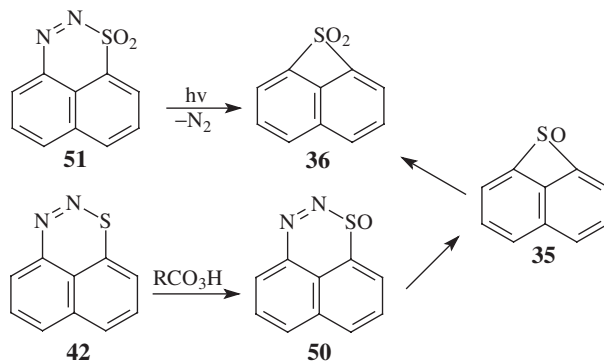
1,8-dehydronaphthalene with organic compounds give a large number of intractable tars.

In a still lower yield (1%) naphthothiete (**34**) was present in the mixture with the other products when 1,8-dehydronaphthalene (**40**) reacted with diphenyl disulfide (83TL821).

Thus, the best laboratory procedure for preparation of naphtho[1,8-*bc*]thiethene (**34**) is the photolysis of naphtho[1,8-*bc*]thiadiazine (**42**).

Inasmuch as naphtho[1,8-*bc*]thiethene (**34**) was successively prepared by photolysis and thermolysis of naphtho[1,8-*bc*]thiadiazine (**42**), Nakayama et al. (79JA7684) hoped to obtain in the same fashion naphtho[1,8-*bc*]thiethene *S*-oxide (**35**) from naphtho[1,8-*de*]-1,2,3-thiadiazine *S*-oxide (**50**, Scheme 8). They attempted to synthesize sulfoxide **50** by oxidation of thiadiazine (**42**) with *m*-chloroperbenzoic acid (*m*-CPBA). However, this reaction carried out at room temperature with an equivalent amount of *m*-CPBA occurred with nitrogen liberation and with the formation of naphtho[1,8-*bc*]thiethene *S*-oxide (**35**) in 71% yield instead of the expected sulfoxide (**50**).

Therefore, the preparation of naphtho[1,8-*bc*]thiethene *S*-oxide (**35**) proved to be easier than expected due to the instability of sulfoxide **50** with *S*-oxide **35**



Scheme 8

naphtho[1,8-*bc*] thiethene sulfone (**36**) was isolated in a 4% yield. However, 3 equiv of (*m*-CPBA) afforded naphtho[1,8-*bc*]thiethene *S,S*-dioxide (**36**) in a 93% yield. Nakayama et al. (79JA7684) believed that under the mild conditions used sulfone **36** was the product of sulfoxide **35** oxidation and does not originate from thiadiazine (**42**) oxidation into sulfone **51** with its subsequent transformation into naphtho[1,8-*bc*]thiethene *S,S*-dioxide (**36**). Actually, naphthothiadiazine sulfone (**51**) is well known to be stable on heating and decomposes with nitrogen liberation only at harsh irradiation. Just the irradiation of naphthothiadiazine *S,S*-dioxide (**51**) furnished sulfone **36** as the first representative of *peri*-annulated heterocyclic naphthalene derivatives with a four-membered hetero ring (65AG(E)786, 67LA96).

1. Physical Properties and Spectral Characteristics of Naphtho[1,8-*bc*]thiethene and Its *S*-Oxides (**34–36**)

(65AG(E)786), (67LA966), (74JA6532), (76JA6643), (79JA7684), (81JCS(P1)413), (83TL821), (84MI3403). The main published sources containing the majority of information on their physical properties are printed in bold type.

The parent naphtho[1,8-*bc*]thiethene crystallized from hexane as a colorless substance, mp. 40–42 °C. Its two *S*-oxides **35** and **36** are also colorless crystalline compounds, mp. 105–106 °C (from hexane) and 183–184 °C (from methanol), respectively. All compounds are stable on melting and sublimation under reduced pressure. Being colorless, all compounds have no absorption band in their electronic spectra higher than 320 nm. In the IR spectrum of naphtho[1,8-*bc*]thiethene (**34**) taken in CCl₄ appeared an unexpected series of high-frequency bands at 3050, 1922, 1780, 1657, and 1615 cm⁻¹ that totally disagreed with the structure of **34** and was not discussed in (76JA6643). These bands are apparently due to the presence of phosgene that readily formed from carbon tetrachloride on irradiation. At least in the IR spectrum of sulfoxide **35** recorded as a KBr pellet the band with the highest wave number was observed at 1467 cm⁻¹. In each ¹H NMR spectrum of compounds **34–36** appear two two-proton doublets and one two-proton triplet showing the presence of six aromatic protons and the symmetry of the structure. In the proton-decoupled ¹³C NMR

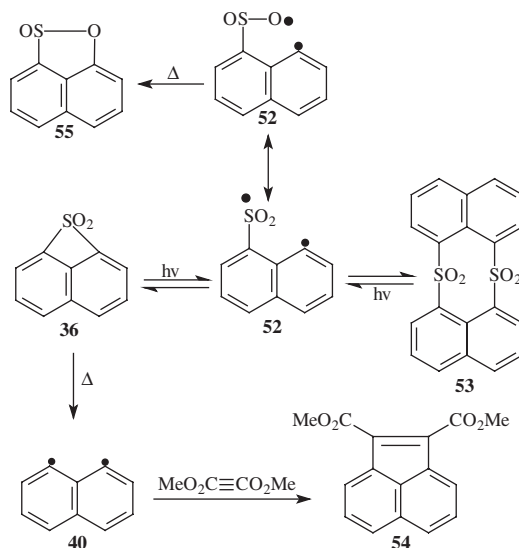
spectra six signals of carbon atoms are observed excluding the possibility of dimer formation.

The X-ray diffraction analysis of naphtho[1,8-*bc*]thiete *S,S*-dioxide (**36**) (76JA6643) revealed the coplanar position of the four-membered hetero ring and the naphthalene skeleton, and the r value [the ratio of bond angles C4–C10–C5/C1–C9–C8 ($132.5/106^\circ$)] equaled 1.25 in good agreement with the calculated data as were also many other parameters.

2. Reactions of Naphtho[1,8-*bc*]thiete (**34**) and Its *S*-Oxides (**35**, **36**)

The known transformations of naphtho[1,8-*bc*]thiete (**34**) and its *S*-oxides **35**, **36** in the majority of instances consist of hetero ring opening due to irradiation, heating or to the action of chemical reagents. However, two types of reactions are known that are directed to the sulfur atom and do not cause ring opening: oxidation to *S*-oxides, and *S*-alkylation giving sulfonium salts.

a. Photolysis and Thermolysis (67LA96, 79JA7684, 81MI2682). The photolysis or thermolysis of naphtho[1,8-*bc*]thiete (**34**) and its *S*-oxides **35** and **36** induces a homolytic cleavage of one or both sulfur bonds with the naphthalene core generating the corresponding biradical species **43**, Scheme 7 and **52**, Scheme 9. Further reactions of these biradicals depend on the presence or absence of other reagents. For instance, on heating or irradiating naphtho[1,8-*bc*]thiete (**34**) in a carbon disulfide environment the latter reacts with biradical **43** leading to naphtho[1,8-*de*]-2,4-dihydro-1,3-dithiin-2-thione (**44**, Scheme 7), whereas on irradiating sulfone **36** in the absence of other reagents biradical **52** combines to a dimer (**53**, Scheme 9). Interestingly, if in place of



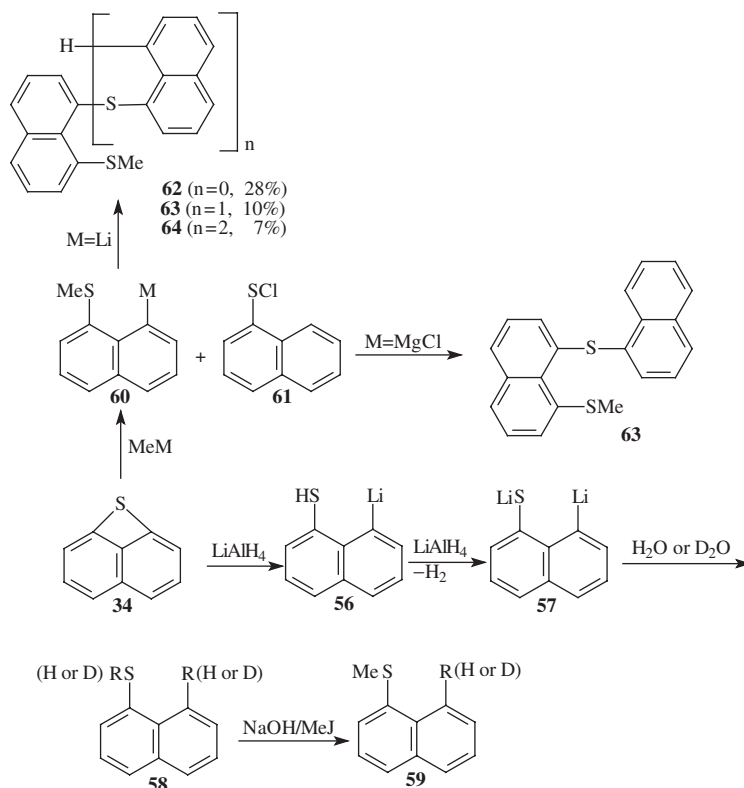
Scheme 9

irradiation sulfone **36** is transferred into a gas phase on thermolysis biradical **52** instead of dimerizing is transformed into a five-membered hetero ring (**52** → **55**). Inasmuch as homolytic cleavage of the hetero ring is reversible, the final products **44** and **53** are present in the mixture with the initial compounds **34** and **36**.

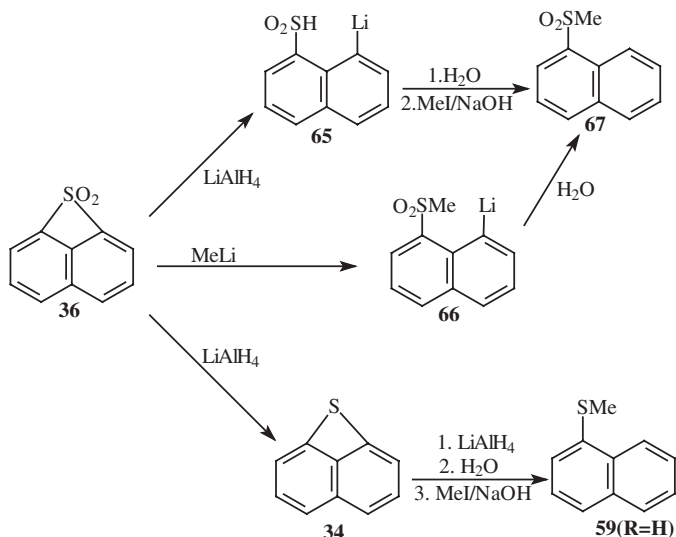
Under severe thermolysis conditions both sulfur bonds to the naphthalene skeleton in sulfone **36** can suffer homolytic cleavage with SO_2 liberation and formation of 1,8-dehydronaphthalene (**40**) capable of electrocyclic capture with dimethyl acetylenedicarboxylate (**40** → **54**).

b. Reactions with Nucleophilic Reagents. The calculation of electron density distribution in **34** that we performed by the PM3 method for publication in this review showed that the largest negative charge is localized on the 1,8-atoms of the naphthalene skeleton (-0.156), and the largest positive charge (0.197), on the sulfur atom. These results should permit prediction of the direction of attack by the positive and negative fragments of chemical reagents.

Reactions were studied between naphtho[1,8-*bc*]thiete (**34**, Scheme 10) and nucleophiles including metal hydrides and organometallic compounds (76JA6643).



Scheme 10



Scheme 11

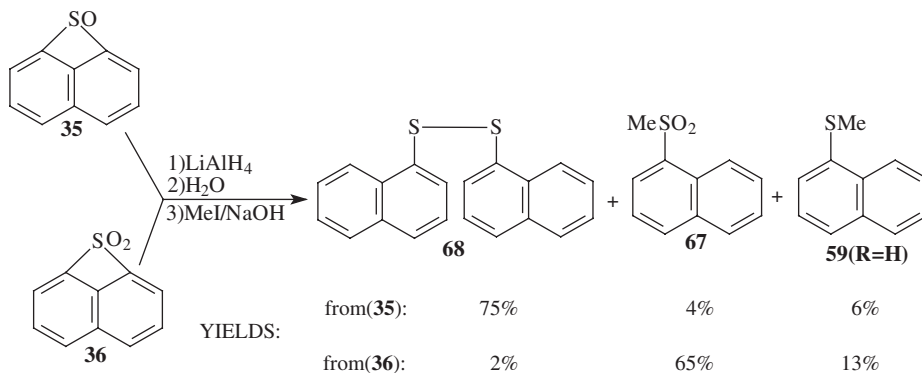
The nucleophilic reagent attacks the sulfur atom and the $\text{S}-\text{C}^1$ bond is ruptured. The exact mechanism is unknown.

The reaction of naphthothiete (34) with the lithium aluminum hydride first gives 1,8-lithionaphthalenethiol (56) and then dilithium derivative (57), which on treating with water or deuterium oxide transformed into thiol or its deuterio analog (58), respectively. The latter when alkylated with methyl iodide afforded a stable methyl naphthyl sulfide 59 whose structure was unambiguously proved. Thus, J. Meinwald et al. confirmed the assumed sequence of transformations.

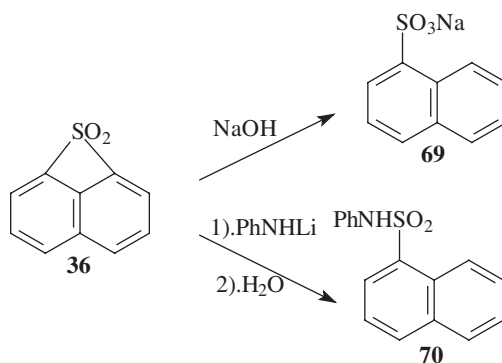
Naphthothiete (34) with methyllithium ($\text{MeM}=\text{MeLi}$, Scheme 10) formed 8-lithio-1-naphthyl methyl sulfide (60, $\text{M}=\text{Li}$) that on taking up 1 or 2 equiv of additional 34 was converted into dimer 63 or trimer 64. Sulfide 60 at treating with water formed methyl 1-naphthyl sulfide (62). Dimer 63 was also prepared by an independent synthesis between 60 ($\text{M}=\text{MgCl}$) and 1-naphthyl thiochloride (61).

The reaction of naphthosulfone (36, Scheme 11) with the lithium aluminum hydride takes two directions. The first route consists in reduction to naphthothiete (34) with subsequent transformations represented in Scheme 10: ($34 \rightarrow 56 \rightarrow 57 \rightarrow 58 \rightarrow 59$) on quenching dilithium intermediate 57 with water ($\text{R}=\text{H}$). The second path involves opening the hetero ring with the nucleophile without reduction ($36 \rightarrow 65 \rightarrow 67$) also analogous to ($34 \rightarrow \rightarrow \rightarrow 59$) for naphtho[1,8-*bc*]thiete proper (cf. Schemes 10 and 11). Methyl naphthyl sulfone (67) thus obtained was also prepared by an independent synthesis by treating naphtho[1,8-*bc*]sulfone (36) with methyllithium followed by quenching with water ($36 \rightarrow 66 \rightarrow 67$).

The reaction of naphtho[1,8-*bc*]thiete *S*-oxide (35) with lithium aluminum hydride is more complex, and its main product is dinaphthyl disulfide (68, Scheme 12) arising as a result of a series of successive transformations where disproportionation of one



Scheme 12

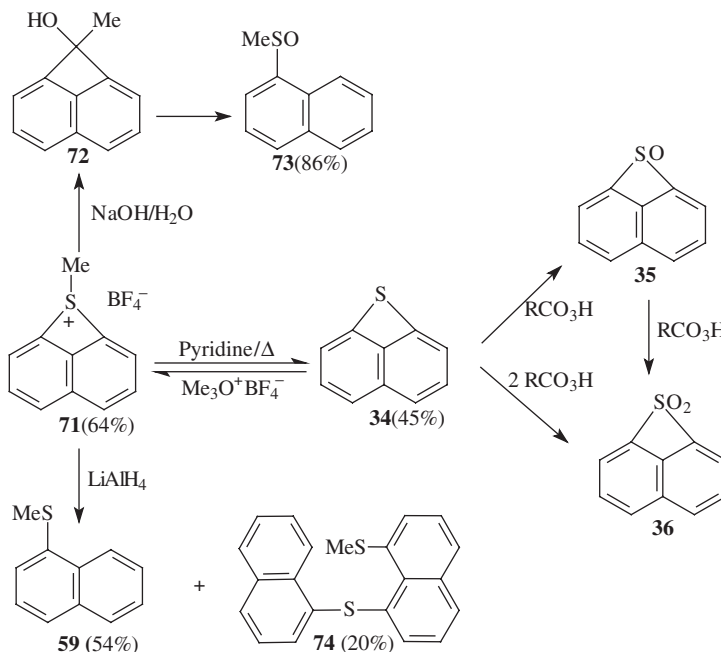


Scheme 13

of the intermediates plays a key role. The disproportionation and other reactions of the sulfur derivatives are treated in more detail in (73M12). Thus, the reactions of naphtho[1,8-*bc*]thiete *S*-oxide (35) and *S,S*-dioxide (36) with the lithium aluminum hydride followed by methylation catalyzed by bases results in the formation of the same compounds but in different proportions (Scheme 12).

Meinwald et al. (76JA6643) described reactions with sodium hydroxide and lithium phenylamide leading to the formation of sodium 1-naphthalenesulfonate (69) and 1-naphthalenesulfonamide (70), respectively. Again, the negatively charged fragment of the reagent attacks the sulfur atom, followed by protonation of the C¹ atom of the naphthalene core (Scheme 13).

c. Reactions at the Sulfur Atom Without Hetero Ring Opening. The known reactions of this type are rare; they include oxidation and alkylation (Scheme 14). Oxidation, already mentioned, is affected by peracids. Reaction of naphtho[1,8-*bc*]thiete (34) with one equiv of a peracid affords sulfoxide 35, and with two equiv



Scheme 14

sulfone **36**. The latter also can be obtained by oxidation of sulfoxide **35** with a peracid.

Naphtho[1,8-*bc*]thiethene with trimethyloxonium tetrafluoroborate in dichloromethane led to the formation of sulfonium salt **71**, as white needle crystals with mp 146–147 °C, stable on recrystallization from 2-propanol. The methyl group gives a sharp singlet at 3.82 ppm.

Sulfonium salt **71** in boiling pyridine suffers demethylation to give naphtho[1,8-*bc*]thiethene (**34**), and alkali converts it into methyl naphthyl sulfoxide (**73**). Reductive opening of the hetero ring occurs in reaction with **71** and LiAlH₄ leading to methyl naphthyl sulfide (**59**, R=H) and a dimeric sulfide **74**. Dimer **74** presumably forms from dilithium derivative (**57**, Scheme 10) (originating from naphtho[1,8-*bc*]thiethene (**34**) and LiAlH₄) and methylsulfonium cation of **71**.

E. NAPHTHO[1,8-*bc*]BORETE

The simplest naphtho[1,8-*bc*]borete (**75**) is unknown. However, the results of semiempirical calculations that we have performed by the AM1 method (Figure 8) and are first published in the present review suggest the compound to be stable.

The first specimen in this series, *N,N*-di-*iso*-propylamino-naphtho[1,8-*bc*]borete (**76**), was obtained in 1994 (94AG(E)1247) by a reaction of 1,8-dilithionaphthalene (**18**) with di-*iso*-propylaminoboron dichloride (Scheme 15).

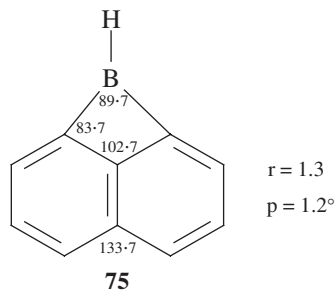
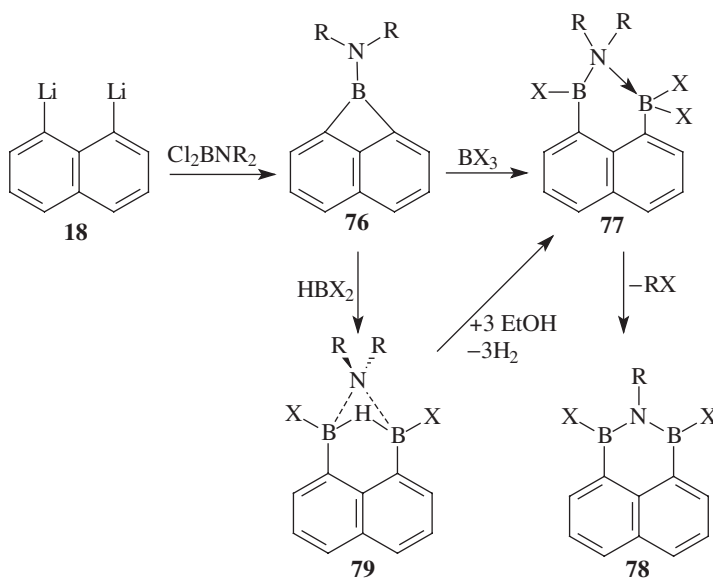


Figure 8. General formula, bond angles and the other parameters of the simplest naphtho[1,8-*bc*]borete calculated by the AM1 method

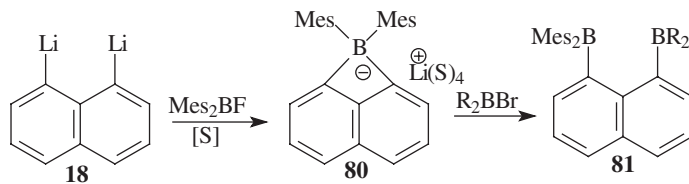


R = *i*-Pr; 78, X = Cl (a), Br (b), OEt (c); 79, X = H (a), Et (b)

Scheme 15

The reaction was carried out under mild conditions (hexane, -20°C), and the product was purified by sublimation under reduced pressure. The yield of **76** was 89%, mp. 84°C . The structure was confirmed by ^1H , ^{13}C , and ^{11}B NMR spectra, by its mass spectrum and X-ray diffraction. The X-ray data show that the values of the bond and torsion angles indicating the molecule's viability are close to the calculated values (Figure 8) neglecting the difference between the substituents at the boron atom (H or *i*-Pr₂N). The hetero ring and the naphthalene framework are virtually coplanar, and the *r* is also about 1.3.

Compound (**76**, Scheme 15) reacted under mild conditions (hexane, -20°C) with boron trichloride or tribromide to form naphtho[1,8-*cd*][1,2,6]azadiborinine (**78**).



Mes = 2,4,6-Me₃C₆H₂; S = THF or Py; 81, R = Me (a), Ph (b)

Scheme 16

This ring-expansion of the four-membered hetero ring into a six-membered one is preceded by rupture of the B–C bond and formation of nonisolable intermediate **77** followed by elimination of the *iso*-propyl chloride or bromide.

Naphthoborete (**76**) with diborane and diethylborane (HBX₂, X = H, Et) yielded μ -di-*iso*-propylaminodiboranes (**79a** and **79b**). In this case a B–H–B bridge forms preceding further processes. Compound (**79a**) was regarded by A. Hergel et al. as a stabilized isomer (**77**, X = H). They believed that this assumption was proved by the replacement of three hydrogen atoms attached to boron in compound (**79a**) by ethoxy groups at treatment with ethanol (**79a** → **77**, X = OEt). Intermediate (**77**, X = OEt) eliminates a molecule of ethyl isopropyl ether transforming into *peri*-annulated borodiazine (**78c**).

The treatment of 1,8-dilithionaphthalene (**18**) with dimesitylboron fluoride gave heterocyclic anion **80** with counterion [Li(THF)₄]⁺ or [Li(Py)₄]⁺ (02MI1982). The counterion character depends on the solvent used for recrystallization of the primary product. Salts **80** were characterized by their NMR spectra proving the presence of a symmetrically substituted naphthalene core. While **80** with the [Li(THF)₄]⁺ counterion is unstable and quickly loses THF at room temperature, crystals with the [Li(Py)₄]⁺ counterion are sufficiently stable to be subjected to the X-ray diffraction analysis (Scheme 16).

The treatment of **80** with dimethyl- or diphenylboron bromide induced hetero ring opening yielding 1,8-diboron-substituted naphthalenes (**81**). J. D. Hoefelmeyer et al. recently (04JCS(D1254)) studied more complex transformations of salts **80**.

F. NAPHTHO[1,8-*bc*]SILETE

The simplest naphtho[1,8-*bc*]silete (**82**) is unknown (Figure 9). Yet the results ($r = 1.19$, $p = 0.1$) of the semiempirical calculations that we have performed by the AM1 method for publication in the present review suggest the compound to be planar and capable of existence under common conditions.

The first two specimens of these structures were *Si*,*Si*-dimethyl- and *Si*,*Si*-diethylnaphtho[1,8-*bc*]silettes (**84a** and **84b**) (76CC775), (83CC866), and later (00MI15582), were more complex *Si*,*Si*-dialkyl derivatives **84c**–**84e**.

1,8-Dilithionaphthalene (**18**) and dichlorodialkylsilanes reacted cleanly at 0 °C and at room temperature without needing oxygen removal and exclusion of atmospheric moisture. Yang and Shechter (76CC775) believed that the reaction proceeded

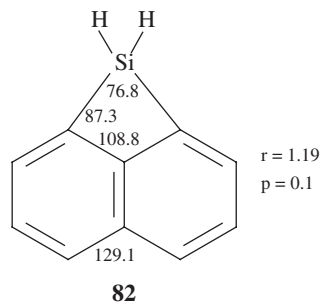
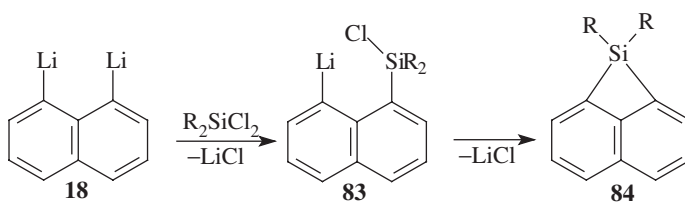


Figure 9. General formula and some calculated parameters of naphtho[1,8-*bc*]silete



Scheme 17

stepwise as shown in [Scheme 17](#). The products were purified by high vacuum distillation and more thoroughly by preparative gas chromatography. The yields were in the range 25–70%. All the compounds exception (**84e**) were colorless oils. The structures of the compounds were unambiguously proved by ¹H, ¹³C NMR, and mass spectra, and by elemental analyses.

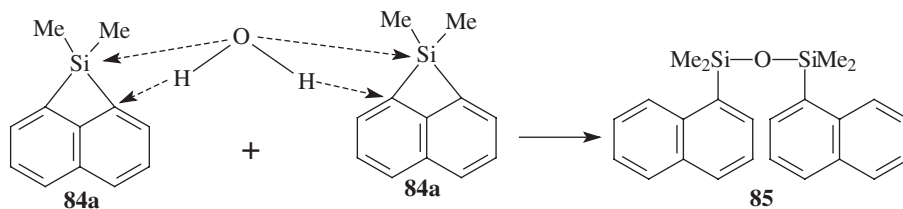
1. Chemical Properties

According to semiempirical calculations by the AM1 method the 1,8-atoms of the naphthalene skeleton linked to silicon are the most electron-rich. An electrophilic attack should take this direction and is well demonstrated by the reaction of silete (**84a**) in air that suffers a fast deliquescence due to reaction with water vapor resulting in dimer **85** ([Scheme 18](#)).

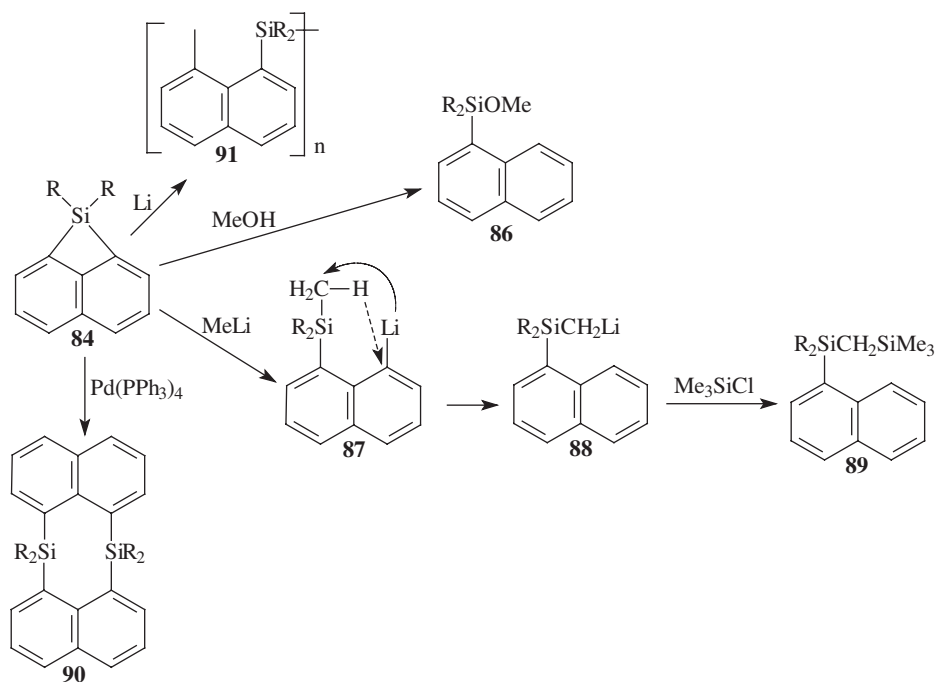
Dimethyl derivative **84a** is the most hygroscopic whereas naphthosilenes (**84**) with ethyl and larger alkyl substituents are stable in air.

The reactions of *Si,Si*-dialkylnaphthosilenes (**84**) with various nucleophiles are shown on [Scheme 19](#).

A *peri*-bridged naphthalene compound was described ([94JOM137](#)) where the 1,8-positions of the naphthalene skeleton were connected to a germanium atom (**94**). This compound was obtained from dialkylgermanium dichloride and



Scheme 18

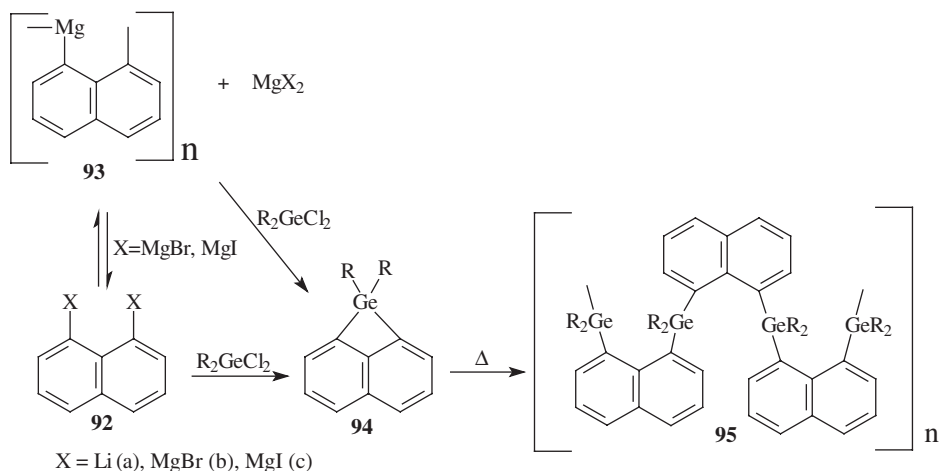


Scheme 19

1,8-dilithionaphthalene (**92**, X = Li) or 1,8-naphthalenediylmagnesium (**93**). Organo-magnesium compound **93** formed on treating with THF a 1,8-dimagnesium naphthalene derivative (**92**, X = MgBr₂, MgI₂) and **93** with dimethylgermanium dichloride furnished *Ge,Ge*-dimethyl(1,8-naphthalenediyl)germete as an only product. By contrast, with 1,8-dilithionaphthalene the product always contained as impurity dimers such as compound **90**, (Scheme 19) with Ge atoms instead of Si.

The freshly prepared *Ge,Ge*-dimethyl(1,8-naphthalenediyl)germete (**94**) is an oily fluid that on standing in a deuterobenzene solution forms a solid precipitate of polymer (**95**) with various units of number *n* (Scheme 20).

A considerable number of naphtho[1,8-*bc*]cyclobutanes was synthesized where the bridging atom between the 1,8-positions of the naphthalene structure was carbon



Scheme 20

(Figure 3, X = CR₂). Inasmuch as these compounds are hydrocarbons and not heterocycles they are outside the scope of this review. The interested reader should consult the following publications: (74JA8116), (77JA2371), (80CC190), (82TL2715), (83JA6096), (83JA6104), (83CC866) (83JA7786), (85JA7597), (91JOC1663).

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Pyrazol-3-ones. Part III: Reactivity of the Ring Substituents

GEORGE VARVOUNIS, YIANNIS FIAMEGOS, and GEORGE PILIDIS

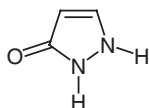
University of Ioannina, Department of Chemistry, GR-451 10 Ioannina, Greece

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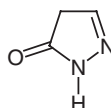
I. Introduction

The present article is Part III of a three part series. In Part I (01AHC(80)73) the synthesis and applications of pyrazol-3-ones **I** and **II** are described. In Part II (04AHC(87)141) the reactions of the ring atoms of pyrazol-3-ones **I** and **II** are given. Both of these articles cover the literature since January 1964. As in Part I and II, the present work is a follow up of the major work on pyrazolones published by Wiley and Wiley in the "Chemistry of Heterocyclic Compounds" series of monographs (64MI1). The literature of this chapter has been searched up to August 2005.



(I)

1,2-dihydro-3H-pyrazol-3-one



(II)

2,4-dihydro-3H-pyrazol-3-one

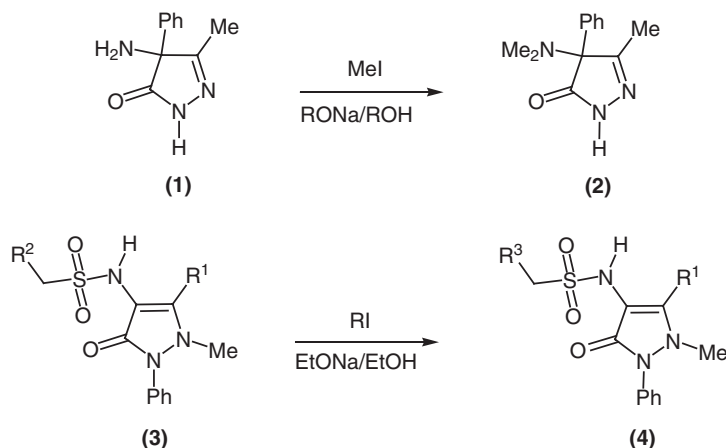
Following the trend of Parts I and II, throughout Part III all pyrazolones have been named according to the IUPAC recommendations as pyrazol-3-ones and not as pyrazol-5-ones. The IUPAC nomenclature numbers the ring clockwise whereas most organic chemists are used to an anti-clockwise numbering.

II. Alkylation

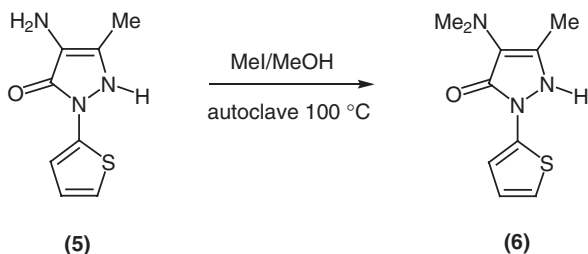
Alkylation of pyrazol-3-ones usually occurs not only on side-chain substituents such as primary amino groups but also on the nitrogen atom of the unsubstituted lactam group. Alkylation can also occur on a stabilized carbanion generated from a methyl group by a strong base.

A. BY REACTION WITH ALKYL HALIDES

4-Amino-2,4-dihydropyrazol-3-one **1** was smoothly methylated at N-2 and dimethylated at the 4-amino group in a sodium alkoxide solution containing methyl iodide to give pyrazol-3-one **2** (72JHC1219) (Scheme 1). In a Japanese patent Naito (70JAP(K)6534), claims that N1-(3-oxopyrazol-4-yl)sulfonamides **3a,b** could be mono- or dialkylated by treatment with methyl- or ethyl iodide in the presence of ethanolic sodium ethoxide to give alkylated pyrazol-3-one derivatives **4c-f**. On the other hand, methanolic 4-amino-1,3-dihydropyrazol-3-one **5** containing methyl iodide required heating in an autoclave at 100 °C in order to give 4-dimethyl derivative **6** in only 44% yield (79AP853).



(a) $R^1 = \text{H}$, $R^2 = \text{NH}_2$, (b) $R^1 = \text{Me}$, $R^2 = \text{CH}_2\text{NH}_2$, (c) $R^1 = \text{H}$, $R^3 = \text{Me}_2\text{N}$, (d) $R^1 = \text{Me}$, $R^3 = \text{CH}_2\text{NHMe}$, (e) $R^1 = \text{Me}$, $R^3 = \text{CH}_2\text{NMe}_2$, (f) $R^1 = \text{Me}$, $R^3 = \text{CH}_2\text{NEt}_2$

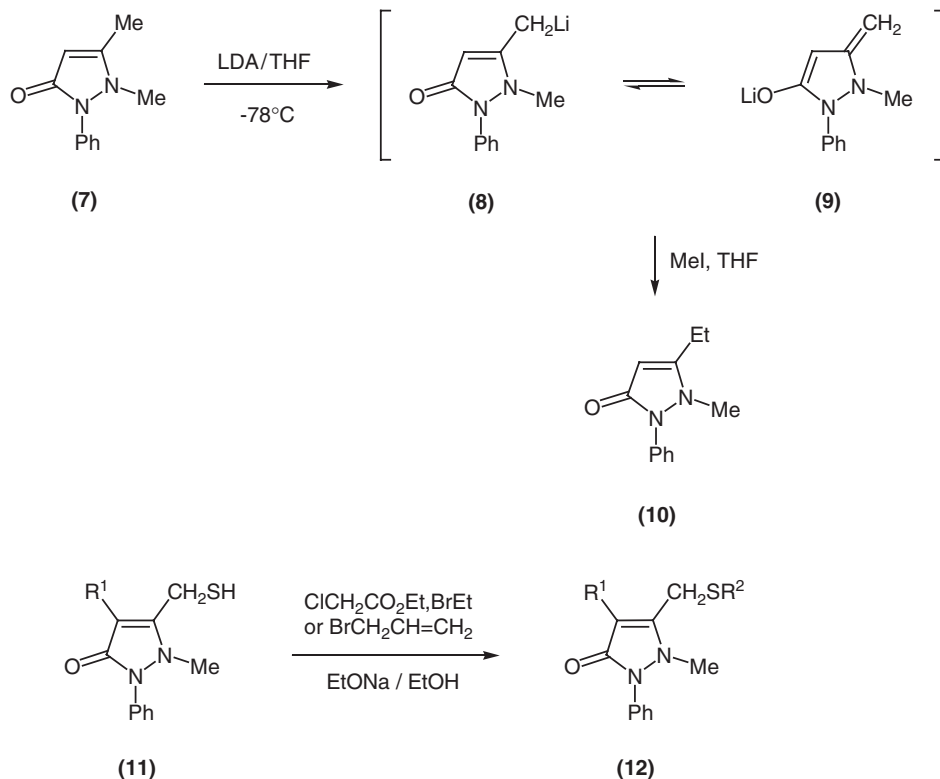


Scheme 1

Methylation of the 5-methyl group of pyrazol-3-one **7** was achieved by treating **7** with lithium diisopropylamine at $-78\text{ }^\circ\text{C}$ followed by the addition of methyl iodide to the stabilized lithium salt **8/9**. 5-Ethylpyrazol-3-one **10** was obtained in 82% yield (95T10941) (Scheme 2). Ito and Ueda (69CPB1309) alkylated 5-mercaptomethylpyrazol-3-one **11a,b** with ethyl chloroacetate, ethyl bromide or allyl bromide in ethanolic sodium ethoxide and obtained the corresponding *S*-alkylated pyrazol-3-ones **12c,d**, in very good yields.

In a search for new anti-cancer agents Abdel-Rahman (92FA319) (Scheme 3) obtained dipyrazol-3-one derivative **15** by heating two equivalents of 5-aminopyrazol-3-one **13** with 2-chloro-1-(piperazin-1-yl)ethanone derivative **14** in DMF.

The amino group of 2-aminopyrazol-3-one **16** was even more difficult to alkylate with methyl iodide (81JHC957) (Scheme 4). The reaction proceeded slowly under a variety of conditions and it was necessary to operate at higher temperatures, which lead to deamination of starting material. Thus, reaction of 5-aminopyrazol-3-one **16** with methyl iodide in ethanol at $100\text{ }^\circ\text{C}$ in a sealed tube gave a mixture containing pyrazol-3-ones **17a,b**, **18a,b** and **19a,b**.

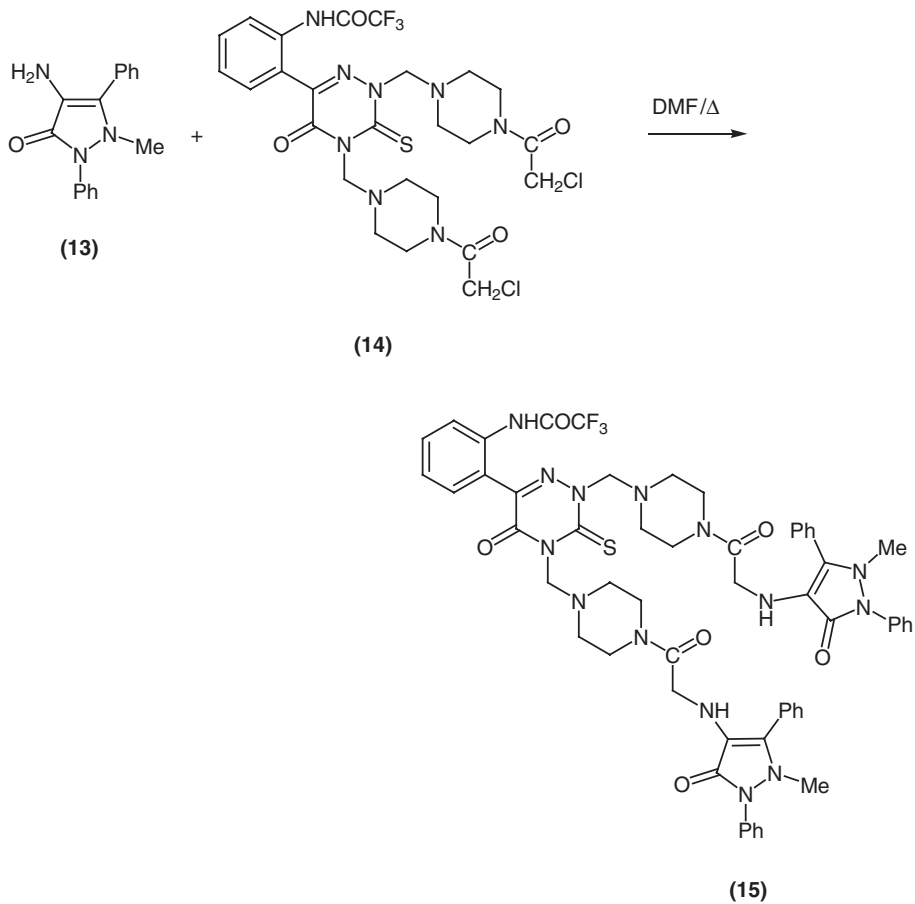


(a) $R^1 = \text{Me}$, (b) $R^1 = \text{Br}$, (c) $R^1 = \text{Me}$, $R^1 = \text{CH}_2\text{CO}_2\text{Et}$, Et or $\text{CH}_2\text{CH}=\text{CH}_2$
 (d) $R^1 = \text{Br}$, $R^2 = \text{CH}_2\text{CO}_2\text{Et}$, Et or $\text{CH}_2\text{CH}=\text{CH}_2$

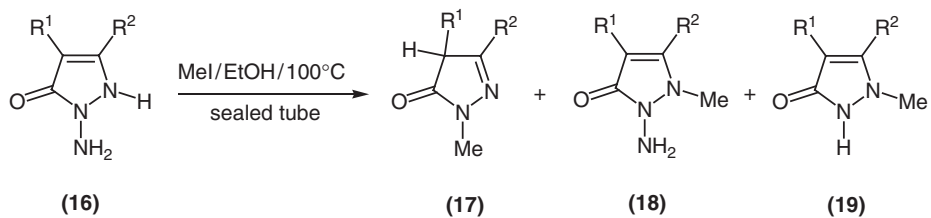
Scheme 2

B. WITH ESTERS OF SULFONIC AND CARBONIC ACIDS

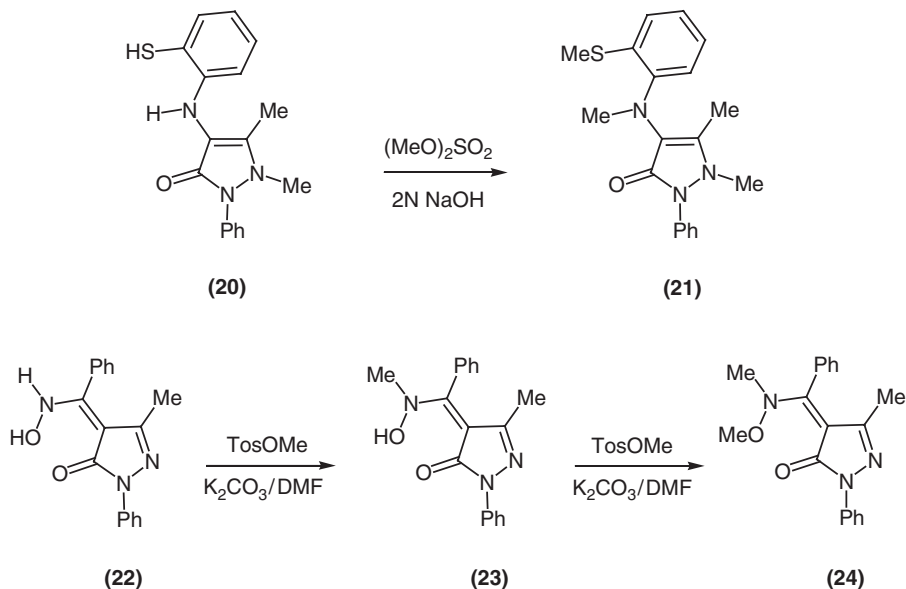
Although dimethyl sulfate was used as a methylating agent for the ring nitrogen and carbonyl oxygen atoms of pyrazol-3-ones, its use for methylating substituents on the pyrazol-3-one ring is limited. Thus in one case, the secondary amino and mercapto groups of 4-[(2-mercapto-phenyl)amino]pyrazol-3-one **20** were methylated at room temperature with an alkaline solution containing excess dimethyl sulfate to give pyrazol-3-one **21** (76CJC993) (Scheme 5). The secondary amino group of 4-(hydroxyaminophenylmethylene)pyrazol-3-one **22** was selectively methylated with one equivalent of methyl 4-toluenesulfonate (TosOMe) to give the *N*-hydroxy-*N*-methylenaminone **23**. The methylation of **23** with a further equivalent of methyl 4-toluenesulfonate led to the formation of 4-[(methoxymethylamino)phenylmethylene]pyrazol-3-one **24** (03EJOC1209).



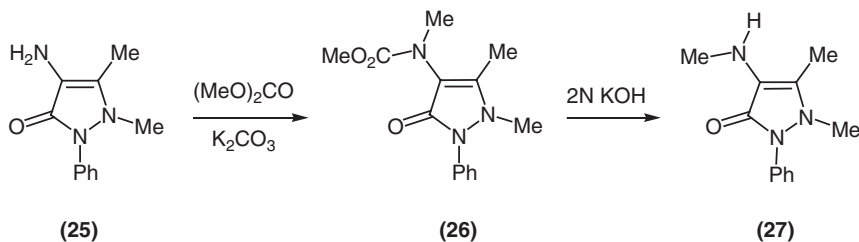
Scheme 3

(a) $R^1 = \text{Ph}$, $R^2 = \text{Me}$, (b) $R^1 = \text{Me}$, $R^2 = \text{Ph}$

Scheme 4



Scheme 5

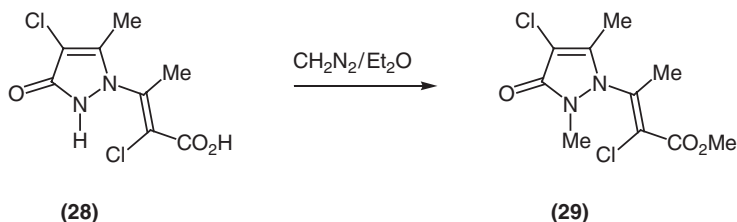


Scheme 6

Monomethylation of the 4-amino group of pyrazol-3-one **25** was achieved with methyl carbonate (89JCR(S)312) (Scheme 6) in two steps by treatment of **25** first with dimethyl carbonate and potassium carbonate to obtain the ester **26** which was then hydrolyzed to 4-methylaminopyrazol-3-one **27**.

C. WITH DIAZOMETHANE

The carboxylic acid group of the α,β -unsaturated side chain and amide nitrogen atom of pyrazol-3-one **28** were methylated with an ethereal solution of diazomethane to give the pyrazol-3-one ester **29** (80JA4983) (Scheme 7).



Scheme 7

III. Acylation

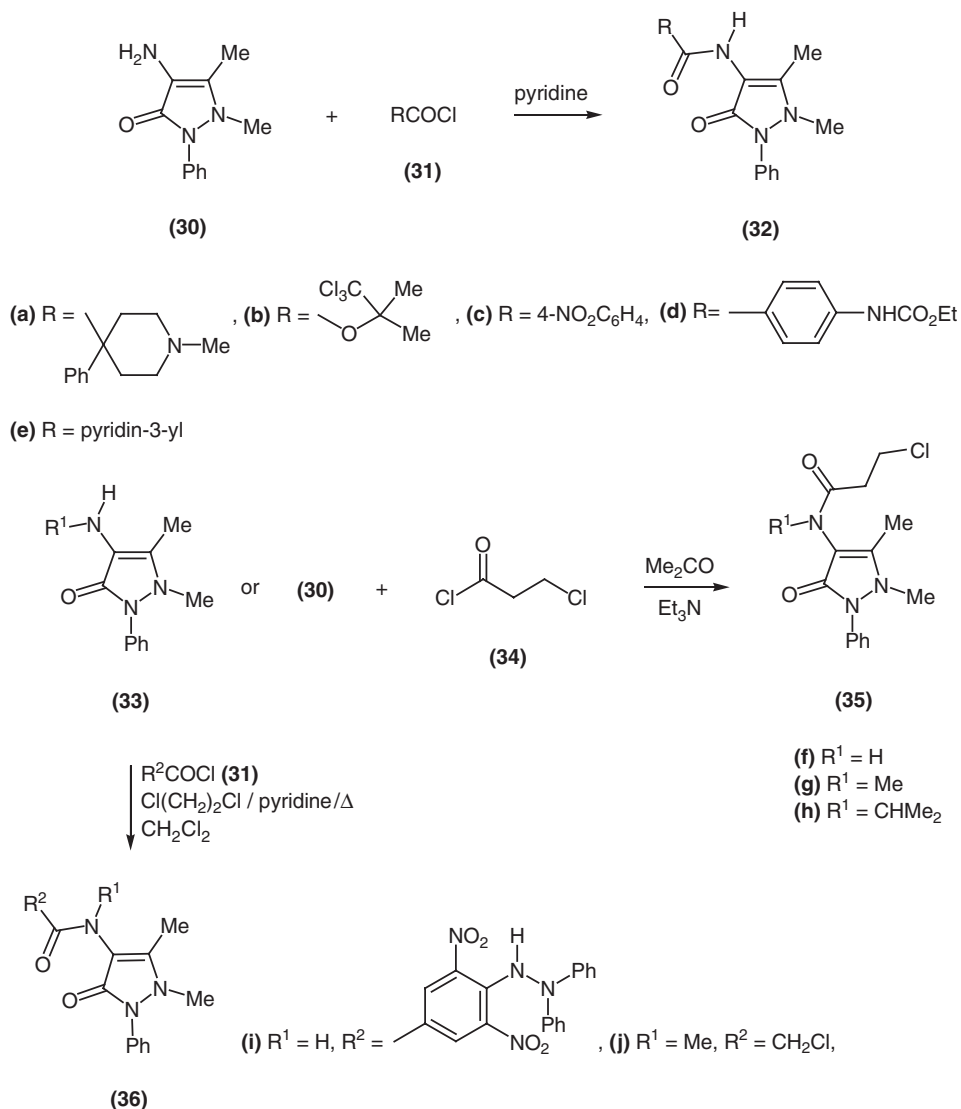
Most of these reactions were carried out with 4-amino-1,2-dihydro-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one (4-aminoantipyrene). The acid chlorides were prepared separately or generated *in situ* from the corresponding carboxylic acid in the presence of the aminopyrazol-3-ones.

A. WITH ACID CHLORIDES OR ANHYDRIDES

Acylation of 4-aminoantipyrene **30** with chloro(1-methyl-4-phenylpiperidin-4-yl)methanone **31a** *tert*-butoxycarbonyl chloride **31b**, 4-nitrobenzoyl chloride **31c**, ethyl 4-(chlorocarbonyl)phenylcarbamate **31d** or chloro(pyridine-3-yl)methanone **31e** in pyridine afforded the corresponding *N*-(3-oxopyrazol-4-yl)-4-amides **32a–e** in moderate to excellent yields (71PHA439, 72JDR89, 91S309) (Scheme 8). Treatment of 4-aminoantipyrene **30** or 4-substituted aminopyrazol-3-ones **33g,h** with β -chloropropionyl chloride **34** in acetone containing triethylamine afforded the *N*-(3-oxopyrazol-4-yl)propanamides **35f–h** (68AF850). Acyl substitution of 4-(*N,N*-diphenylhydrazino)-3,5-dinitrobenzoyl chloride **31i** by 4-aminopyrazol-3-one **33i** in boiling 1,2-dichloroethane containing pyridine, and chloroacetyl chloride **31j** by 4-methylaminopyrazol-3-one **33j** in dichloromethane, gave the corresponding pyrazol-3-ones **36i,j** (01RRC363, 02PHA829).

In a German patent (70GEP1930337) (Scheme 9) 4-aminopyrazol-3-ones **37a–c** were acylated with acid chlorides **38a–c** in pyridine to give the corresponding amides **39a–c**. The amide **39d** was prepared by reacting 5-aminopyrazol-3-one **37d** with acetic anhydride.

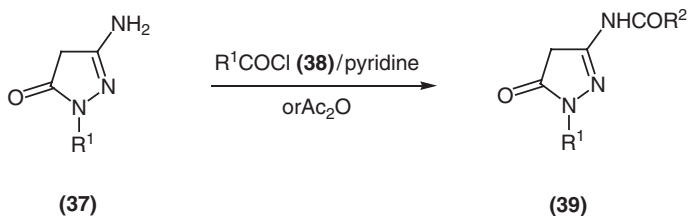
Earlier in this section it was mentioned that 1,2-dihydro- and 2,4-dihydropyrazol-3-ones are not acylated on the pyrazol-3-one ring atoms when mild acylating conditions prevail. It is noteworthy that 1,2-dihydropyrazol-3-one ring atoms are not acylated with acetic anhydride in acetic acid even after heating to reflux. However, Coutts et al. (75CJC3637) (Scheme 10) demonstrated that this was not always the case with 2,4-dihydropyrazol-3-ones. When 4-(2-amino or nitrobenzyl)pyrazol-3-ones **40a,b** or **40c,d** were heated to reflux in acetic anhydride for 1–3 h, the corresponding triacetyl- and monoacetylpyrazoles **41a,b** or **42c,d** were obtained. At ambient temperature 4-(2-aminobenzyl)pyrazol-3-one **40a** reacted with benzoyl chloride in dilute sodium hydroxide to give dibenzoylpyrazol-3-one **43**. Surprisingly, heating



Scheme 8

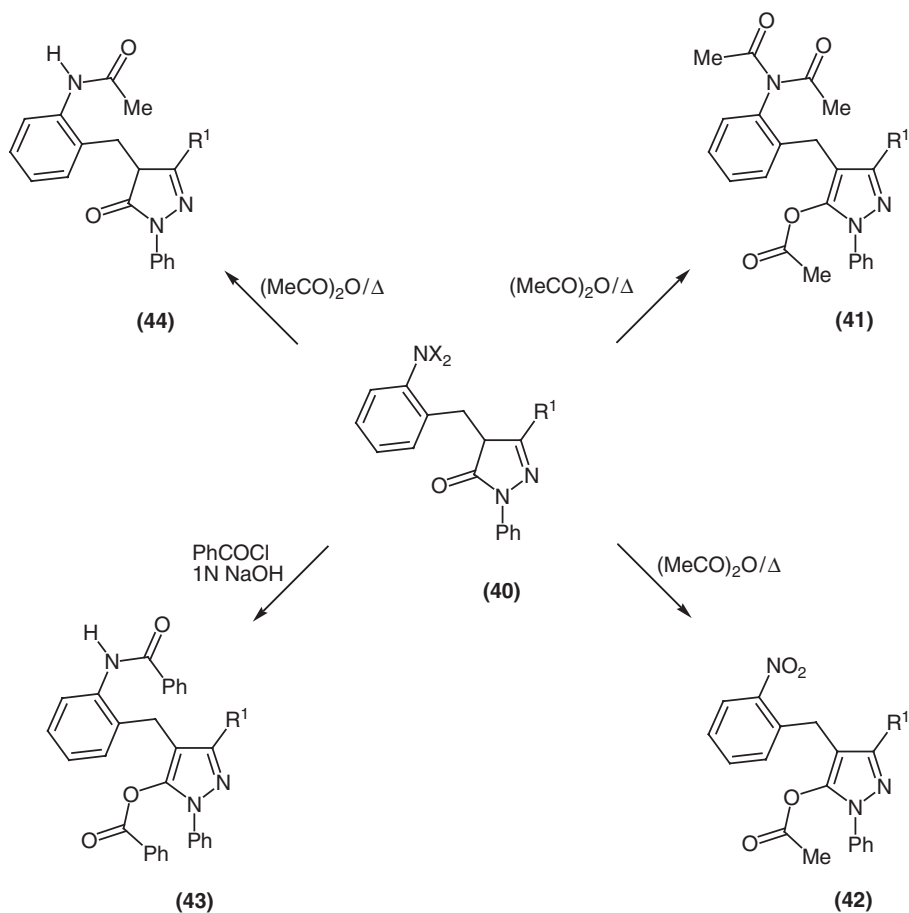
4-(2-aminobenzyl)pyrazol-3-ones **40a,b** in acetic anhydride for 1 h under reflux afforded pyrazol-4-yl(methyl)(phenyl)acetamides **44a,b**.

The acylation of 4-aminoantipyrine **30** took place with acid chlorides **45d,f** and the respective acid chlorides prepared *in situ* from the carboxylic acids **45a–c,e**. Thus, 2-cyanoarylacrylic acids **45a–c,e**, triethylamine and 4-aminopyrazol-3-one **30** at 0°C were treated with phosphorus oxychloride while acid chlorides **45d,f** were treated with triethylamine and pyrazol-3-one **30** at 0°C to afford the corresponding *N*-(3-oxopyrazol-4-yl)acrylamides **46a–f** in moderate yields (91JIC612) (Scheme 11).



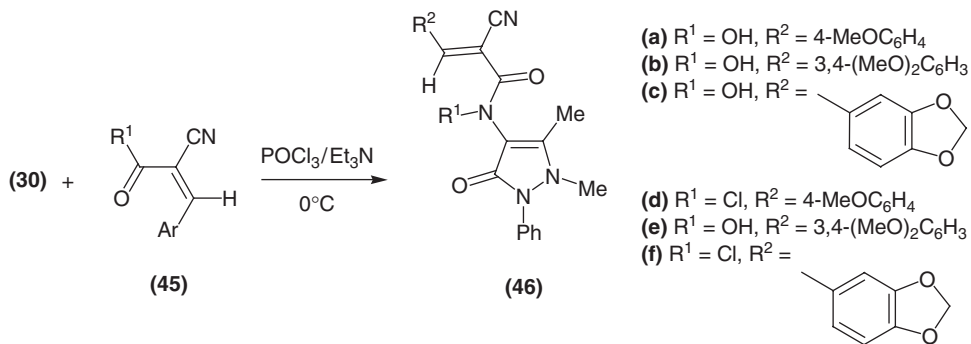
(a) $\text{R}^1 = 2-(n\text{-C}_{18}\text{H}_{37}\text{S})\text{C}_6\text{H}_4$, $\text{R}^2 = \text{Ph}$, (b) $\text{R}^1 = 2-(\text{CHFClF}_2\text{O})\text{C}_6\text{H}_4$, $\text{R}^2 = 4-(n\text{-C}_{16}\text{H}_{33}\text{O})\text{C}_6\text{H}_4$,
 (c) $\text{R}^1 = 2-(\text{CHFClF}_2\text{O})\text{C}_6\text{H}_4$, $\text{R}^2 = 4-n\text{-C}_{19}\text{H}_{38}$, (d) $\text{R}^1 = 4-(n\text{-C}_{16}\text{H}_{33}\text{SO}_2)\text{C}_6\text{H}_4$, $\text{R}^2 = \text{Me}$

Scheme 9

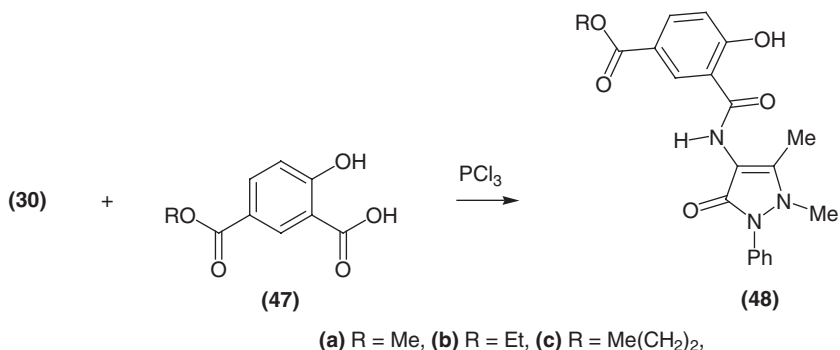


(a) $\text{R}^1 = \text{Me}$, $\text{X} = \text{H}$, (b) $\text{R}^1 = \text{Ph}$, $\text{X} = \text{H}$, (c) $\text{R}^1 = \text{Me}$, $\text{X} = \text{O}$, (d) $\text{R}^1 = \text{Ph}$, $\text{X} = \text{O}$

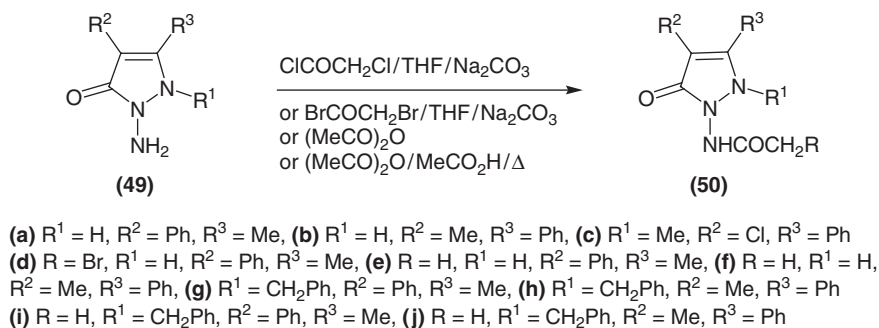
Scheme 10



Scheme 11



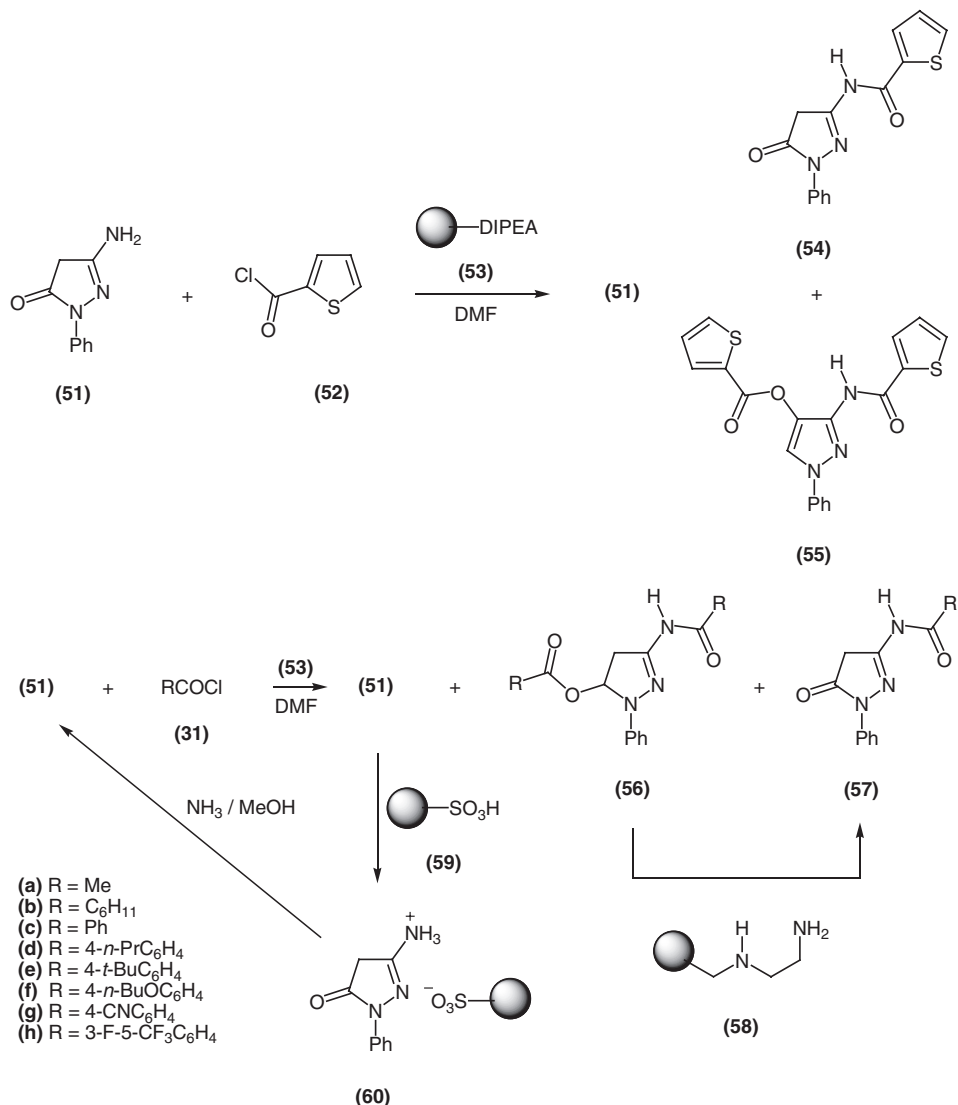
Scheme 12



Scheme 13

The second example of an acylation during which the acid chloride is generated *in situ* (67BCF88) (Scheme 12) involves the reaction of 4-aminopyrazol-3-one **30** with 2-hydroxy-5-(methoxycarbonyl)benzoic acids **47a-c** where phosphorus trichloride is used and gives methyl 3-[(3-oxopyrazol-4-yl)amino]carboxylates **48a-c**.

The strongly nucleophilic primary amino group of pyrazol-3-ones **49a,b** (Scheme 13) reacted under mild conditions with chloroacetyl chloride or bromide,



Scheme 14

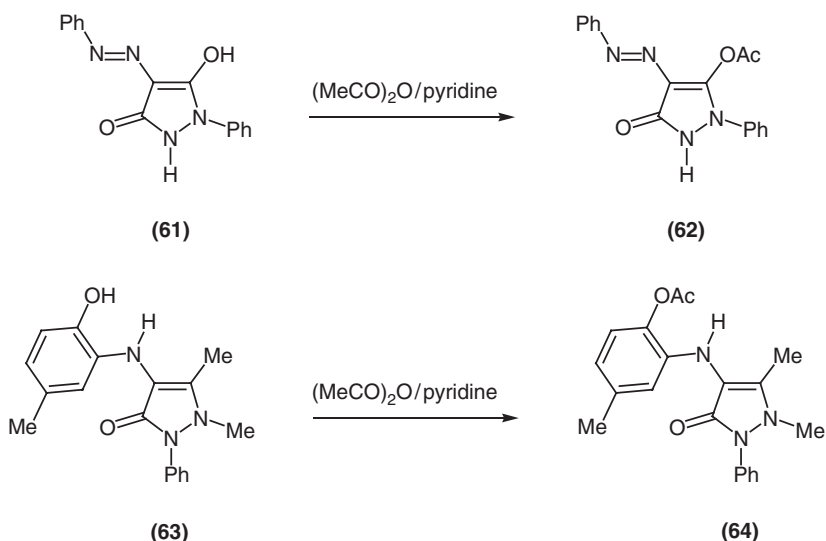
or with acetic anhydride to give 2-(3-oxopyrazol-2-yl) amides **50c–f**. However, 2-amino-1,4,5-trisubstituted pyrazol-3-ones **49j,h** were acetylated by heating at 100 °C with a mixture of acetic anhydride and acetic acid to give 2-(3-oxopyrazol-2-yl) acetamides **50i,j** (81JHC957).

Fu and Shuttleworth (03TL3843) (Scheme 14) set out to develop conditions for *N*-acylating 5-aminopyrazol-3-ones used in previous years as building blocks in the construction of 6,5-fused heterocycles. The simple reaction of 5-aminopyrazol-3-one **51** with 2-thiophenecarbonyl chloride **52** in DMF in the presence of polymer-supported Hunig's base **53**, however, turn out to be extremely capricious. Under

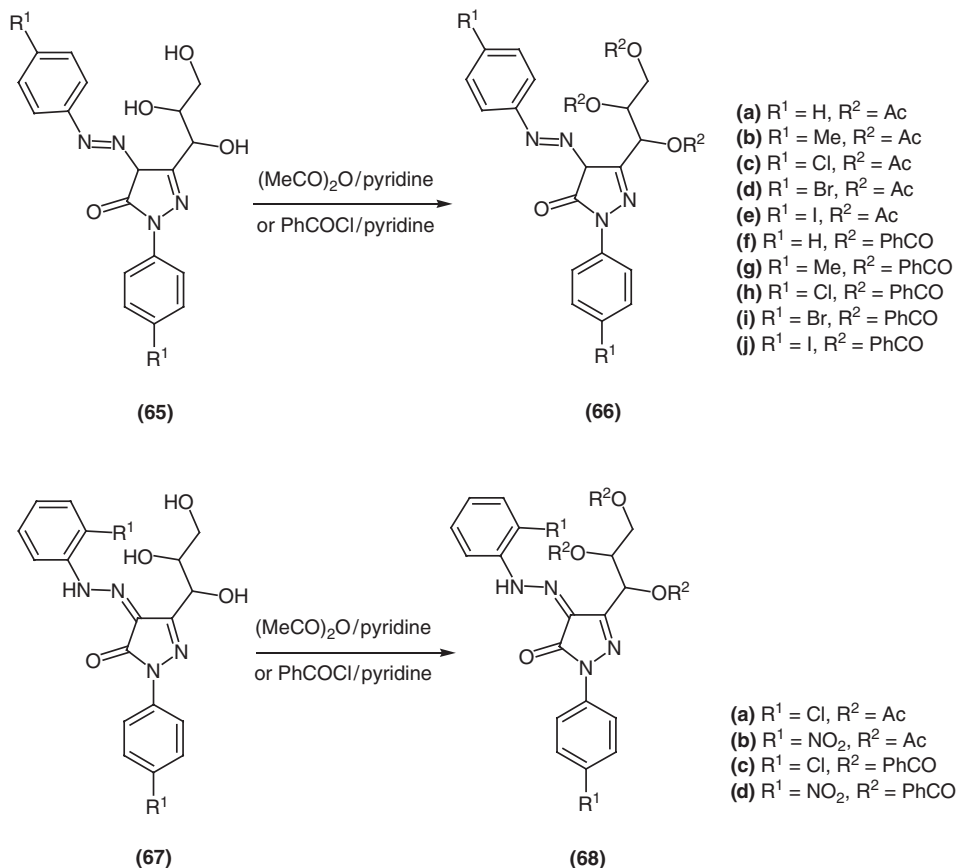
varying conditions of temperature, solvents, substrate/reactant ratios, organic bases and use of carboxylic acid esters instead of acid chlorides, LC-MS analysis of the reaction mixture indicated the presence of starting amine **51**, and acid chloride **52**, the desired 4-*N*-acylpyrazol-3-one **54**, and *bis*-acylated product **55**. This problem was circumvented by utilizing a sequence of functionalized polymers serving both as stoichiometric reagents and purification media. The method developed involved initially treating pyrazol-3-one **51** with acid chloride **31** in tetrahydrofuran in the presence of polymer-supported Hunig's base. After removal of the resin the filtrate that contained a mixture of amine **51**, acid chloride **31**, *bis*-acylated derivative **56** and the desired product **57**, was treated with polymer-supported sulfonic acid resin **59**. The amine **51** was found to be bound to the resin to give resin-bound amine **60**, that was removed from the mixture and the filtrate treated with *N*-(2-aminoethyl) aminomethylpolystyrene **58**, which efficiently reacted with the *bis*-acylated derivative **56** to furnish the desired product **57** in high levels of purity. The remaining supported-amine **58** also served to sequester any remaining acid chloride in the reaction mixture. The method was applied to acid chlorides **31a-i**, however the yields of products **57** varied from excellent (81%) for **57a** and moderate (25–44%) for **57b-i**.

Acetylation of 5-hydroxypyrazol-3-one **61** with acetic anhydride in pyridine at room temperature afforded 5-acetyloxy pyrazol-3-one **62a** (68JCS(C)2251) (Scheme 15). The hydroxy group of 4-[(2-hydroxyphenyl)amino]pyrazol-3-one **63** was acetylated in the same way to give the acetate derivative **64** (74CJC2932).

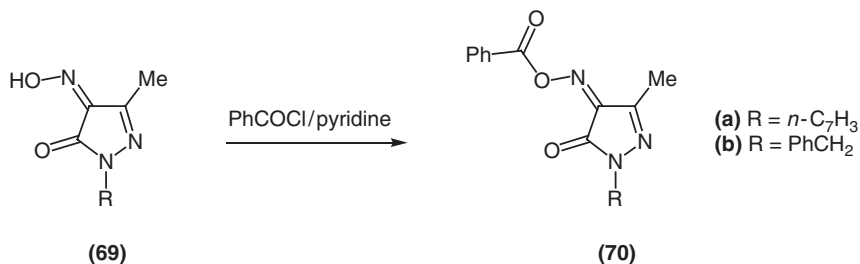
Similar reaction conditions were used for both acetylation and benzylation of 5-(1,2,3-trihydroxy)pyrazol-3-ones **65a-e** and 3-(1,2,3-trihydroxy)pyrazole-4,5-dione-4-(phenylhydrazone) **67a,c** that gave the corresponding triacetyl derivatives **66a-j** and **68a-d** (68JCS(C)2248, 88PHA77) (Scheme 16).



Scheme 15



Scheme 16

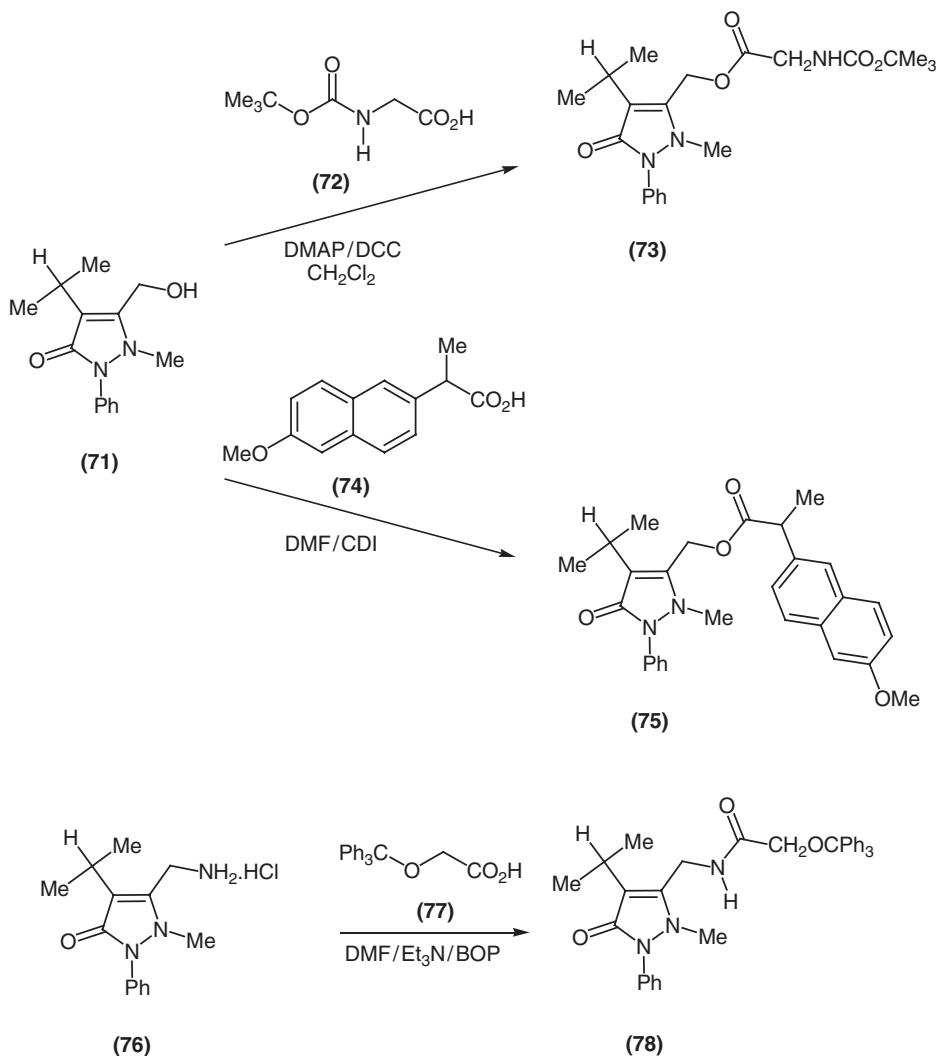


Scheme 17

Lanovaya et al. (87JOU1773) (Scheme 17) presented the only example of a benzoylation of an oxime group of a pyrazol-3-one. Thus, pyrazol-4,5-dione 4-oximes **69a,b** were treated with benzoyl chloride in pyridine to give the benzoyloxy derivatives **70a,b** in good yields.

B. WITH ACTIVATED CARBOXYLIC ACIDS

Smooth esterification of 5-hydroxymethylpyrazol-3-one **71** was possible with *N*-*tert*-butoxycarbonyl glycine **72** in 1,2-dichloromethane in the presence of DMAP and DCC to yield pyrazol-3-one ester **73** (02EJP121) (Scheme 18). Compound **71** was also esterified with 2-(6-methoxy-2-naphthyl)propionic acid **74** in DMF and in the presence of CDI to give pyrazol-3-one ester **75**. Coupling of 5-aminomethylpyrazol-3-one hydrochloride **76** with trityloxyacetic acid **77** in DMF containing triethylamine and (benzotriazol-1-yloxy)*tris*(dimethylamino) phosphonium hexafluorophosphate (BOP) afforded pyrazol-3-one amide **78**.

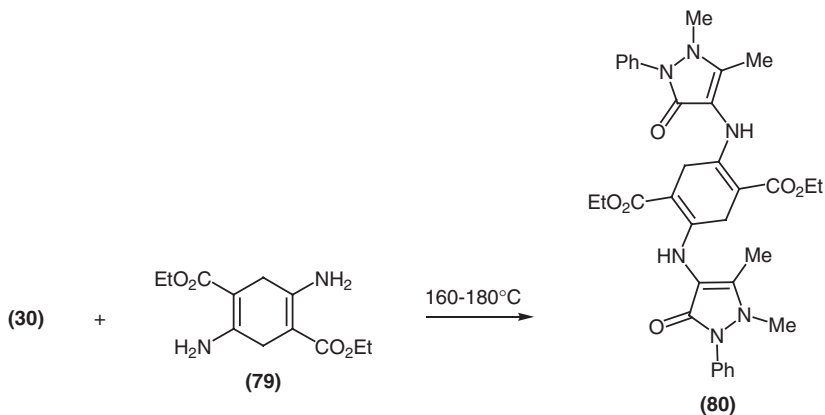


Scheme 18

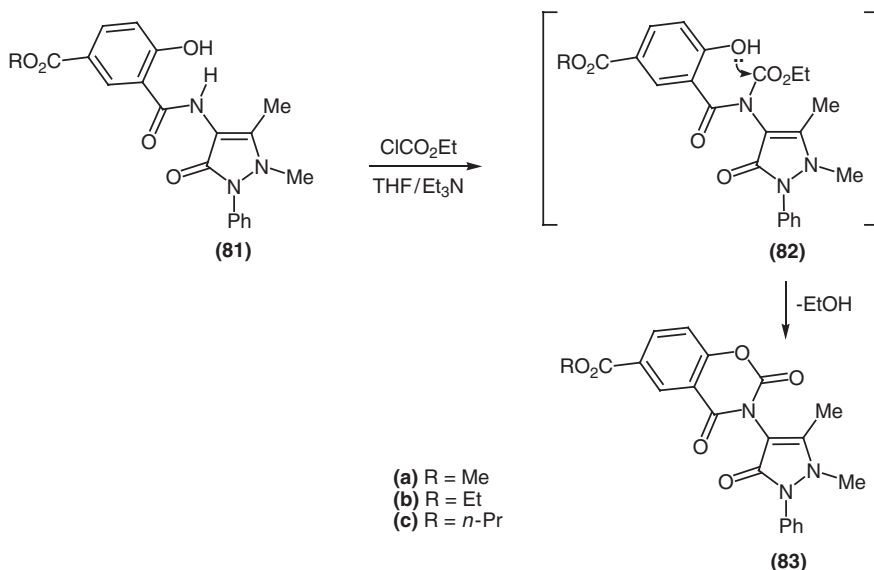
C. WITH ESTERS OR HALOFORMATES

A reaction that leads to an interesting cyclohexadiene-bridged *bis*pyrazol-3-one **80** was reported by Metwally and Afsah (84PHA95) (Scheme 19). Diethyl-2,5-diaminocyclohexa-1,4-diene-1,4-dicarboxylate **79** was heated with pyrazol-3-one **30** at 160–180 °C to give, after ipso substitution of the amino groups of **79**, diethyl-2,5-*bis*(3-oxopyrazol-4-yl)amino derivative **80**.

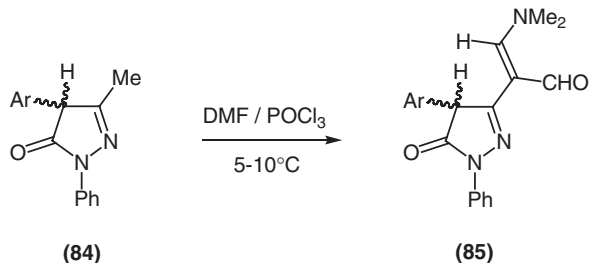
In the presence of triethylamine the amide group of pyrazol-3-ones **81a–c** was first acylated with ethyl chloroacetate and the resulting intermediate carbamate **82** cyclized by nucleophilic acyl substitution initiated by the phenolic hydroxyl group. The 4-benzoxazinepyrazol-3-ones **83a–c** were obtained in 60–75% yield (67BCF88) (Scheme 20).



Scheme 19

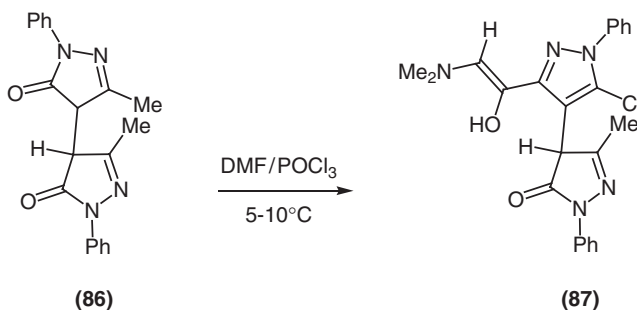


Scheme 20



(a) Ar = Ph, (b) Ar = 4-ClC₆H₄

Scheme 21



Scheme 22

D. BY THE VILSMEIER FORMYLATION

The application of the Vilsmeier reaction to (*E/Z*)-arylmethylenepyrazol-3-ones **84a,b** by Awad and Hassan (89CCC706) (Scheme 21) caused diformylation of the methyl group to give (*E/Z*)-aminoacrolein derivatives **85a,b** in good yields.

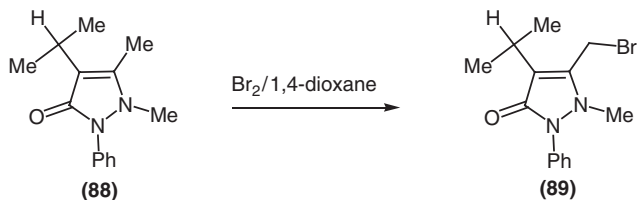
Under low temperature Vilsmeier conditions 4,4'-bipyrazol-3,3'-dione **86** was diformylated at the methyl group of one of the pyrazol-3-one rings that was converted into 3-chloropyrazole. The product **87** remained with one pyrazol-3-one ring intact. When the temperature was increased to 75 °C a furo[2,3-*c*:5,4-*c'*]dipyrazole derivative was obtained (92BCJ1652) (Scheme 22).

IV. Halogenation

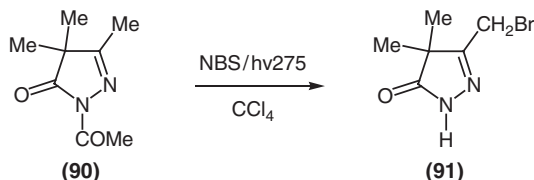
The only halogenation reactions of the ring substituents of pyrazol-3-ones known are those with bromine, *N*-bromosuccinimide and hydrogen bromide.

A. WITH BROMINE

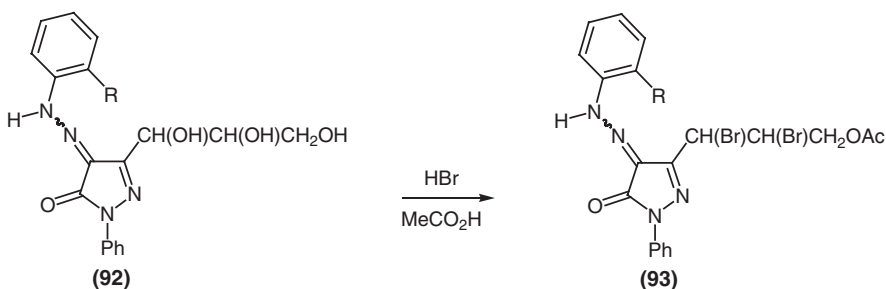
5-Bromomethylpyrazol-3-one **89** was prepared by treating 5-methylpyrazol-3-one **88** with bromine in 1,4-dioxane (02EJP121) (Scheme 23).



Scheme 23



Scheme 24

(a) R = Cl, (b) R = NO_2

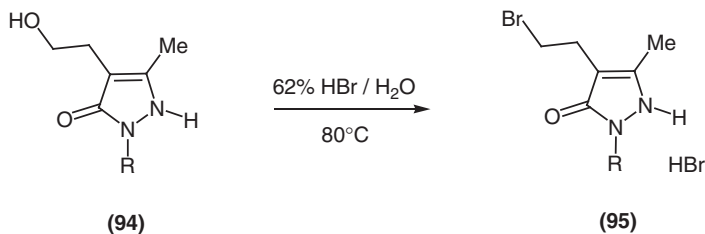
Scheme 25

B. WITH *N*-BROMOSUCCINIMIDE

Selective bromination of the methyl group at position 5 of 4,4,5-trimethylpyrazol-3-one **90** (69JOC1717) (Scheme 24) took place when a solution of the compound and *N*-bromosuccinimide in carbon tetrachloride was irradiated with a 275 W sun lamp. The deacetylated 5-bromomethylpyrazol-3-one **91** was obtained in 53% yield.

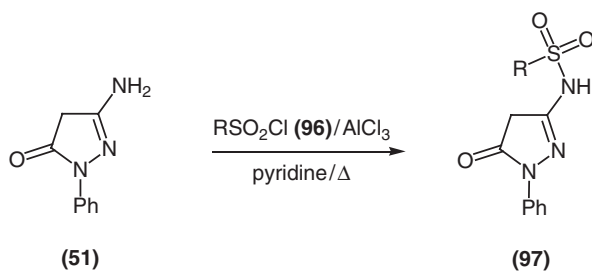
C. WITH HYDROGEN BROMIDE

The 1,2,3-trihydroxypropyl side chain of pyrazol-3-ones **92a,b** was efficiently brominated at positions 2 and 3 by reaction with hydrogen bromide acetic acid. The products, 2,3-dibromopropyl acetates **93a,b** were obtained in 71% and 70% yield, respectively (88PHA77) (Scheme 25).



(a) R = H, (b) R = Me

Scheme 26

(a) R = Me, (b) R = Ph, (c) R = 3-NO₂C₆H₄, (d) R = 4-AcNHC₆H₄

Scheme 27

4-(2-Hydroxyethyl)pyrazol-3-ones **94a,b** were converted into the corresponding 4-(2-bromoethyl)pyrazol-3-one **95a,b** by heating at 80 °C with 62% aqueous hydrobromic acid (99EJMC967) (Scheme 26).

V. Sulfonation

A. OF 5-AMINOPYRAZOL-3-ONES

In a German patent (70GEP1930337) (Scheme 27) 2,4-dihydro-5-sulfonylamino-pyrazol-3-ones such as compounds **97a-d**, were characterized as useful color formers for purple dyes in silver halide color photography. They were prepared by heating 5-aminopyrazol-3-one **51** with sulfonyl chlorides **96a-d** in pyridine containing aluminum trichloride catalyst.

In a second German patent (70GEP1935272) (Scheme 28) the preparation of 5-methylsulfonyl-aminopyrazol-3-one **99** took place simply by reacting 5-amino-1,2-dihydropyrazol-3-one **98** with methylsulfonyl chloride at room temperature.



Scheme 28

VI. Diazonium Salt Coupling

4-Diazopyrazol-3-one salts have been prepared *in situ* and kept for a short period at low temperature by either diazotization of 4-aminopyrazol-3-ones or by diazo group transfer onto 4-unsubstituted 2,4-dihydropyrazol-3-ones from 4-toluenesulfonylazide or aziridinium salts. Coupling these diazonium salts with carbon nucleophiles is the most common reaction (04AHC(87)141).

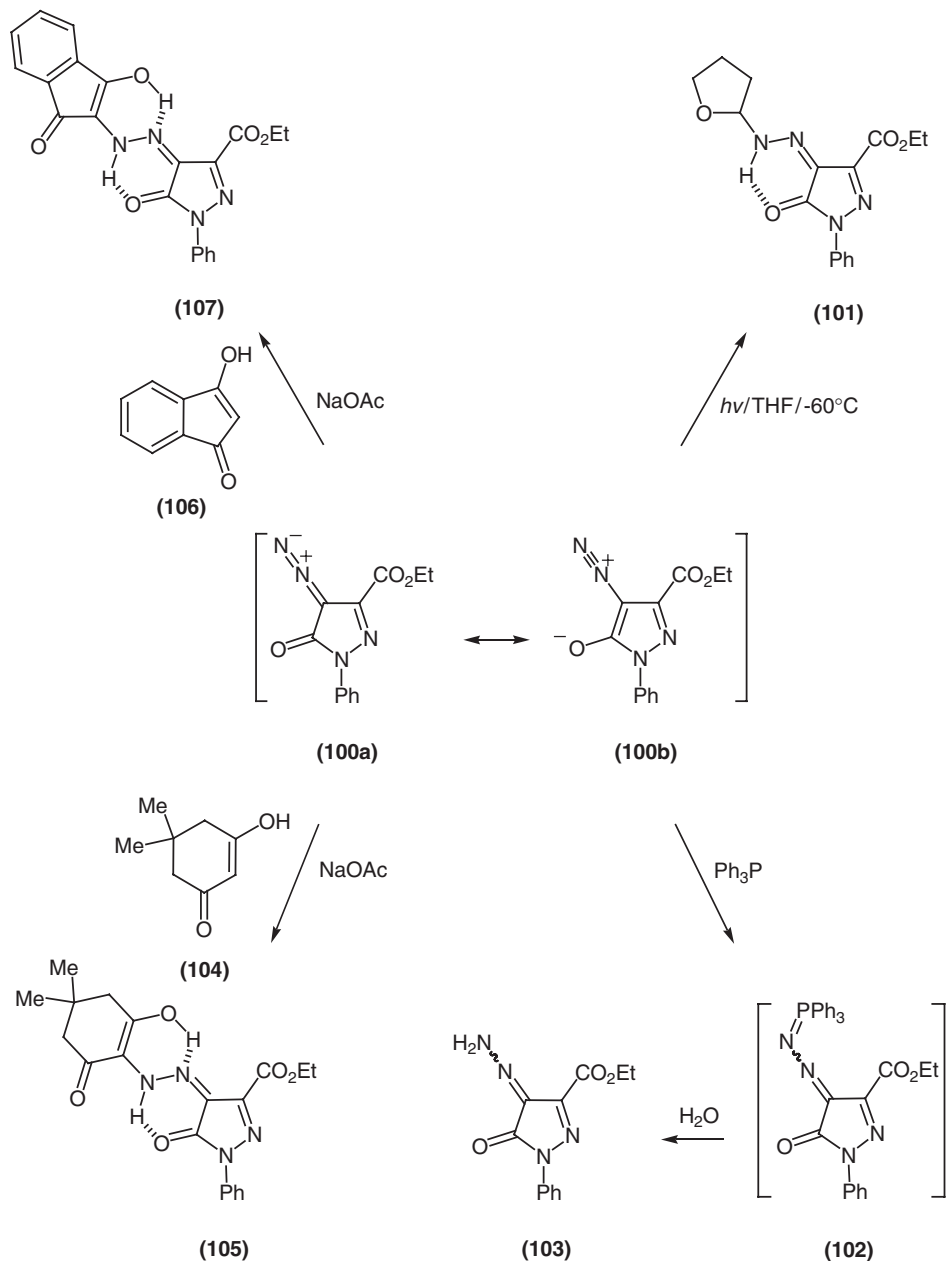
A. DIAZOPYRAZOL-3-ONE COUPLING

The mesomeric diazo compound **100a/100b**, derived from diazo group transfer to the appropriate pyrazol-3-one, was irradiated for 10 h in tetrahydrofuran to give the hydrazone chelated adduct **101** as the only product (78H199) (Scheme 29). Mesomeric **100a/100b** reacts also with triphenylphosphine to give intermediate (*E/Z*)-phosphazine **102** which is extremely sensitive to water and hydrolyzes to (*E/Z*)-hydrazone **103**. 3-Hydroxy-5,5-dimethyl-cyclohex-2-enone **104** and 3-hydroxy-inden-1-one **106** readily couple with **100a/100b** in the presence of sodium acetate to give hydrazone derivatives **105** and **107**, respectively.

Ravindran (04IJC(A)1245) (Scheme 30) reported that diazotization of 4-aminopyrazol-3-one **30** followed by coupling with pentane-2,4-dione gave, via diazonium salt **108**, 3-[(3-oxopyrazol-4-yl)hydrazono]pentane-2,4-dione **109**.

VII. Condensation

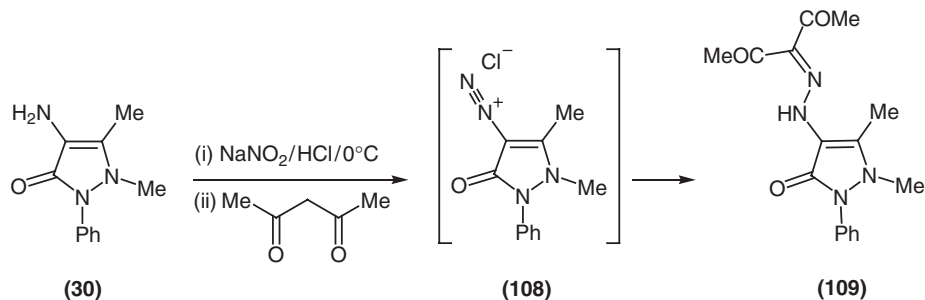
Condensation reactions can be grouped into two categories. The first category involves pyrazol-3-ones with formyl, acyl, nitroso, α,β -unsaturated oxo, 3-oxo-2-azobutyric acid ethyl ester or acetonitrile substituents at position 4 or formyl substituents at position 5 and their reaction with carbanions, heterocyclic methylcarbenium salts, primary and secondary amines, diamines, heterocyclic perchlorates, hydroxylamine, hydrazines, urea or thiosemicarbazide. The second category involves pyrazol-3-ones with amino, hydrazino, heteroaromatic amino, acetyl or acetonitrilo groups at position 4 and their reaction with aryl or heteroaromatic aldehydes or cyclic ketones.



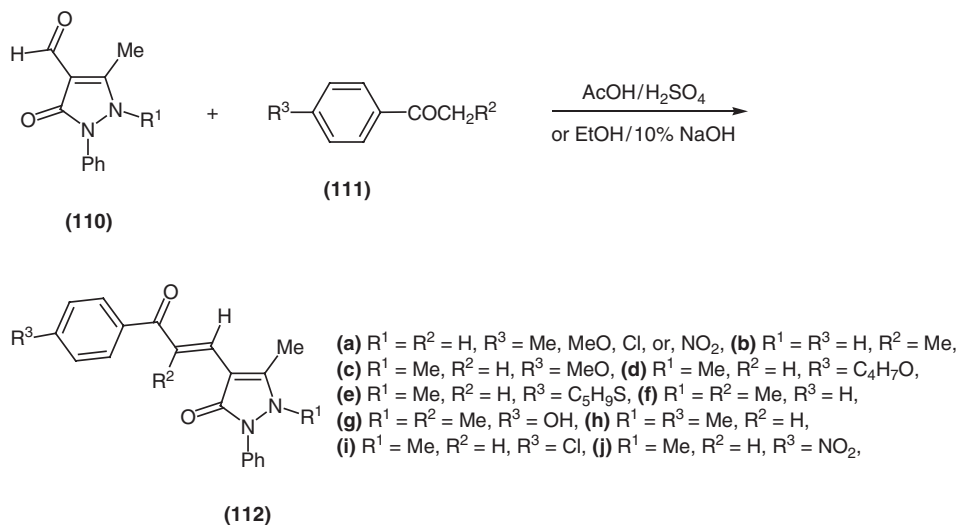
Scheme 29

A. OF 4- OR 5-FORMYLPYRAZOL-3-ONES

Condensations of 1,2-dihydro-4-formylpyrazol-3-ones have been reported with carbanions derived from acetophenone derivatives, heterocyclic methylcarbenium



Scheme 30

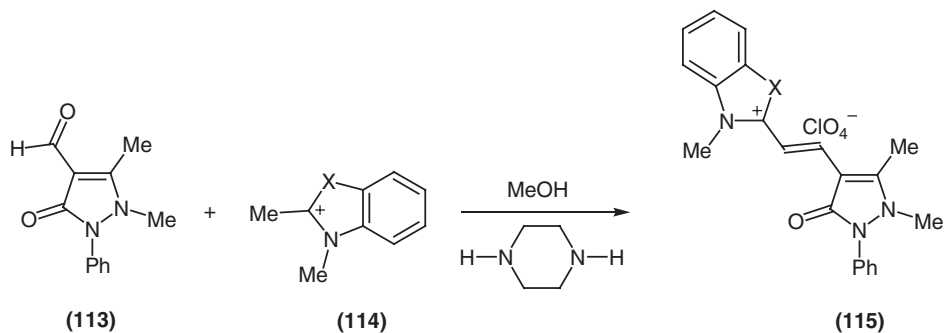


Scheme 31

salts, aniline and thiosemicarbazides. On the other hand, 2,4-dihydro-4-(or 5-)formylpyrazol-3-ones have been condensed only with primary amines.

Massarani et al. (69AF2020) (Scheme 31) studied the reactions of 1,2-dihydro-4-formylpyrazol-3-ones **110a–j** with acetophenones **111a–j**. The reactions worked best in acetic acid containing a catalytic amount of concentrated sulfuric acid and afforded 4-[3-oxo-3-phenyl(or 4-methylphenyl)prop-1-enyl]pyrazol-3-ones **112a–j**, in very good yields. The reactions could also take place under basic conditions for 4-formylpyrazol-3-ones **110c,h–j**. Thus, reaction of the latter with acetophenones **111c,h–j** in ethanol containing 10% aqueous sodium hydroxide, afforded the corresponding pyrazol-3-ones **112c,h–j**, where with the exception of compound **112c**, the yields on average were higher than those obtained in an acidic medium.

Kokkinos and Markopoulos (80JPR543) (Scheme 32) condensed 1,2-dihydro-4-formylpyrazol-3-one (antipyrene aldehyde) **113** with benz(imida, oxa, thia or selenaz)olium perchlorates **114a–d** in methanol containing piperazine and obtained 4-[(*E*)-2-[benz(imida, oxa, thia or selenaz)zol-2-yl]ethenyl]pyrazol-3-one perchlorates



(a) X = NMe, (b) X = O, (c) X = S, (d) X = Se

Scheme 32

115a–d. The color change of these compounds as potential dyes was investigated as a function of the heteroatoms. Similar perchlorates were synthesized with the following heterocyclic rings: pyridinium, pyrylium, acridinium, xanthylium, thioxanthylium and chinolinium.

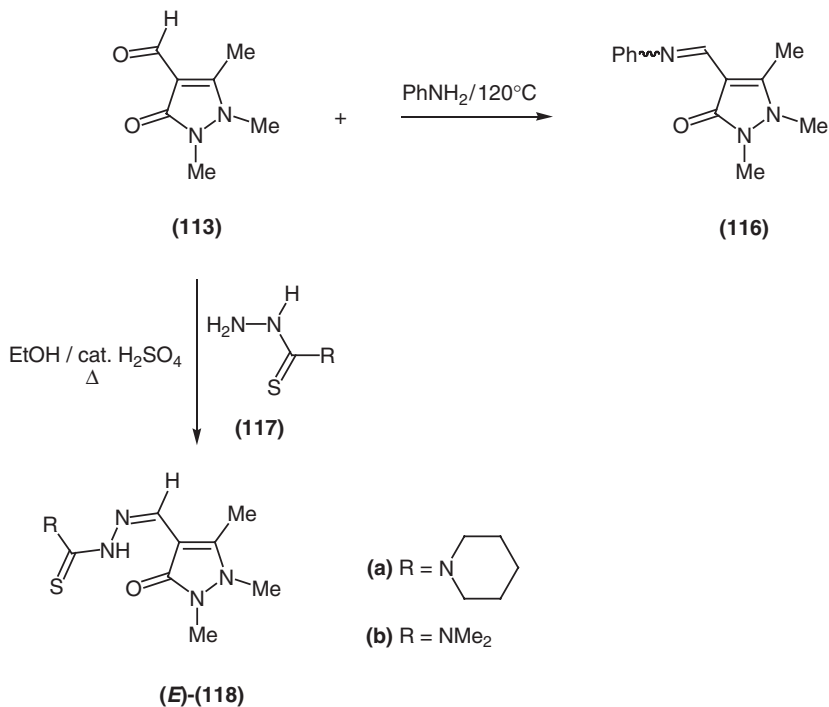
Although condensation of 3-oxopyrazole-4-carbaldehyde **113** with aniline to give 4-phenyliminomethylpyrazol-3-one **116** in 75% yield required heating at 120 °C, condensation between **113** and piperidine-1-carbothioic acid hydrazide **117a** or 4,4-dimethylthiosemicarbazide **117b** took place in boiling ethanol with a catalytic amount of concentrated sulfuric acid to yield (3-oxopyrazol-4-ylmethylene)hydrazide (*E*)-**118a,b** in good yield (81AJC1117, 03JCC105) (Scheme 33).

Masarani and co-workers (69AF1721) (Scheme 34) studied the condensation of 2,4-dihydro-4-formyl-5-methyl(or phenyl)pyrazol-3-one **119** with a large number of aliphatic and aromatic primary amines **120a,b** and aliphatic secondary amines **123c,d** using refluxing ethanol. The primary amines **120a,b** afforded the corresponding 4-aminomethylenepyrazol-3-ones **122a,b** derived after tautomeric rearrangement of the initial condensation product, intermediate **121**. The first step of the reaction between **119** and secondary amines **123c,d** is addition to give intermediate **124**. Loss of water from the latter provided cyclic aminomethylenepyrazol-3-ones **125c,d**. The yields of both reactions are on average very good.

El Khadem and El Ashry (68JCS(C)2248) (Scheme 35) prepared for further study a large variety of imines of 4-azophenyl-2,4-dihydro-5-formylpyrazol-3-one **126**. The nucleophiles were hydroxylamine hydrochloride, urea, phenylhydrazine and a large number of arylamines **120**. Heating in ethanol gave the corresponding (*E/Z*)-5-iminopyrazol-3-ones **127** in good yields.

B. OF 4-ACYLPYRAZOL-3-ONES

There are several reports on condensation reactions of 4-acylpyrazol-3-ones with primary amines (70LA75, 81AJC1117, 90M1023, 98JMC4001, 00JCR(M)622, 02IJC(A)554, 03JHC963), two of which describe reactions with thiourea and

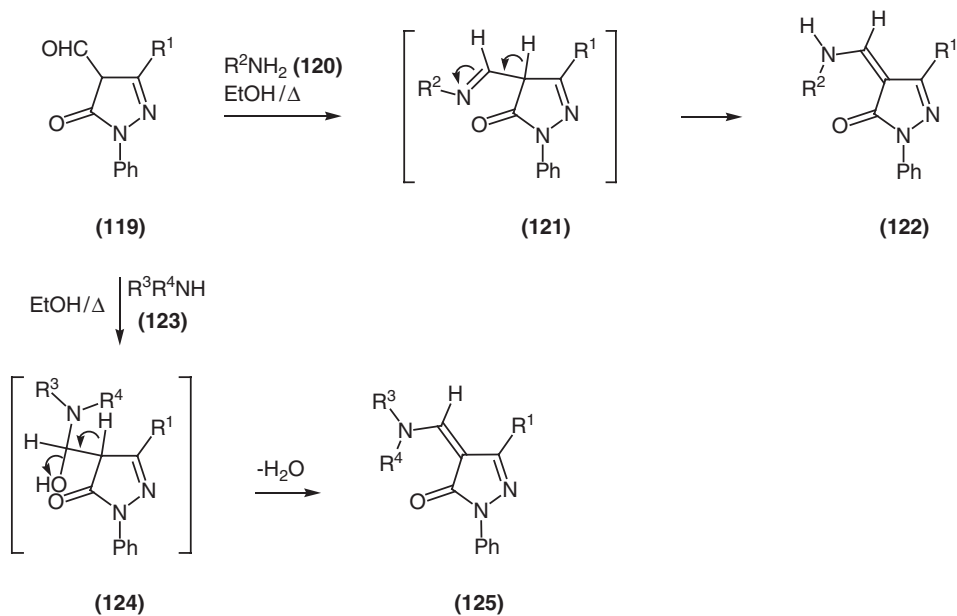


Scheme 33

2-cyanothioacetamide (00JCR(M)622, 03JHC963) (Scheme 36). Thus, condensation of **128** with benzylamine **120a** and arylamines **120b–e** in hot ethanol afforded the (*E/Z*)-4-iminopyrazol-3-ones **133a–e**. Condensation of the carbanion derived from the acetyl group of **128** with arylaldehydes **129f–j** in a basic ethanolic medium afforded 4-(3-arylacryloyl)pyrazol-3-ones **130f–j**. The latter were heated in ethanol with arylamines **131k,l** to afford (*E/Z*)-4-[1-(4-arylphenylimino)-3-aryllallyl]pyrazol-3-ones **132m–p**.

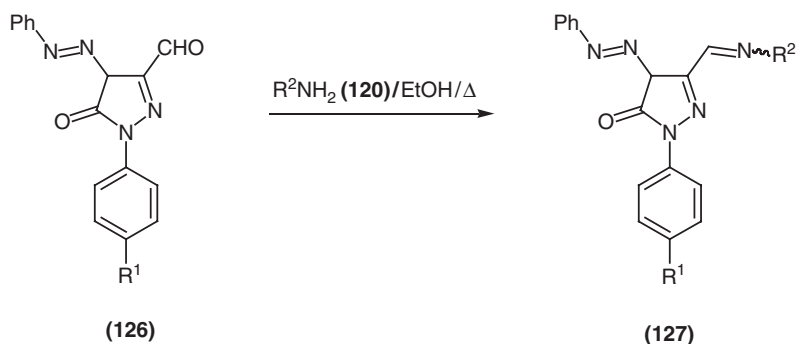
Condensation of 4-aminobenzenesulfonamide **135a** and 4-amino-*N*-(heteroaryl)benzenesulfonamides **135b–f** with 4-benzoylpyrazol-3-one **134** was reported by Maurya et al. (04IJC(A)763) (Scheme 37) to take place in boiling ethanol under various conditions. With **135a** acetone was a co-solvent; with **135e** glacial acetic acid and sodium acetate were added, and with **135f** a catalytic amount of 1 N hydrochloric acid was used. The corresponding (*E/Z*)-imines **136** were obtained in good yields.

The condensation between 4-acylpyrazol-3-ones **137a,b** and *n*-propylamine to give 4-(phenylpropylaminomethylene or 3-phenyl-1-propylaminopropylidene)-pyrazol-3-ones **139a,b** may go via the addition products **138a,b** which lose water by conjugative elimination of hydroxyl anion and deprotonation from position 1 of the ring (98JMC4001) (Scheme 38). More interesting is the reaction between 4-chloroacetylpyrazol-3-one **140** with thiourea **140a** or 2-cyanothioacetamide **140b** in boiling ethanol with or without triethylamine or in aqueous sodium carbonate at 70 °C, to



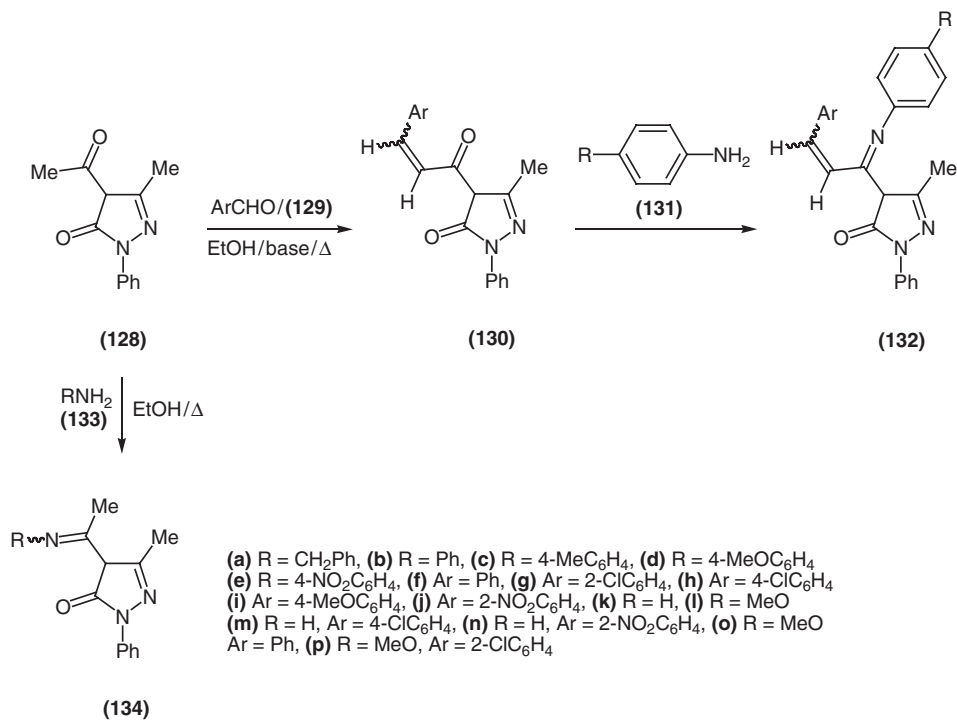
- (a) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$, 4- HOC_6H_4 , 4- MeOC_6H_4 , 4- EtOC_6H_4 , 4- $\text{EtO}_2\text{CC}_6\text{H}_4$ or 4- AcNHC_6H_4 ,
 (b) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Ph}$, 4- HOC_6H_4 , 4- MeOC_6H_4 , 4- EtOC_6H_4 , 4- $\text{EtO}_2\text{CC}_6\text{H}_4$ or 4- AcNHC_6H_4 ,
 (c) $\text{R}^1 = \text{Me}$, $\text{R}^3 = \text{R}^4 = (\text{CH}_2)_4$, $(\text{CH}_2)_5$, $(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ or $(\text{CH}_2)_2\text{NMe}(\text{CH}_2)_2$,
 (d) $\text{R}^1 = \text{Ph}$, $\text{R}^3 = \text{R}^4 = (\text{CH}_2)_4$, $(\text{CH}_2)_5$ or $(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$

Scheme 34

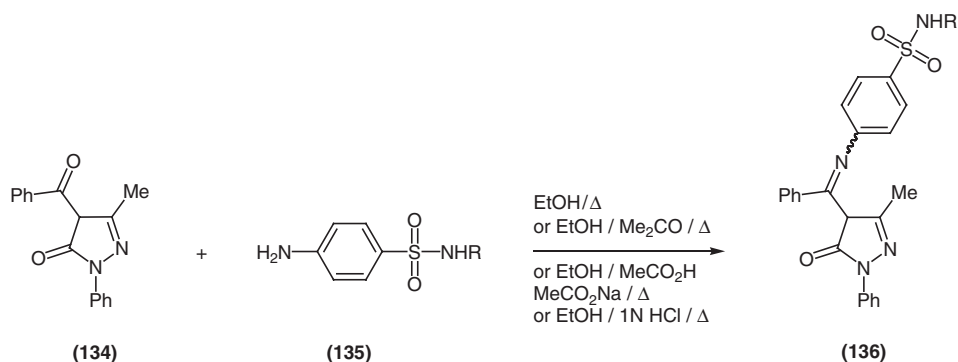


- $\text{R}^1 = \text{H}$ or Br , $\text{R}^2 = \text{OH}$, CONH_2 , PhNH , Ph , 2- MeC_6H_4 , 3- MeC_6H_4 , 4- MeC_6H_4 , 4- MeOC_6H_4 ,
 2- ClC_6H_4 , 3- ClC_6H_4 , 4- ClC_6H_4 , 4- BrC_6H_4 , 2- IC_6H_4 , 3- Cl , 4- BrC_6H_4 , 4- $\text{NH}_2\text{AcC}_6\text{H}_4$ or
 4- $\text{NH}_2\text{SO}_2\text{C}_6\text{H}_4$

Scheme 35



Scheme 36

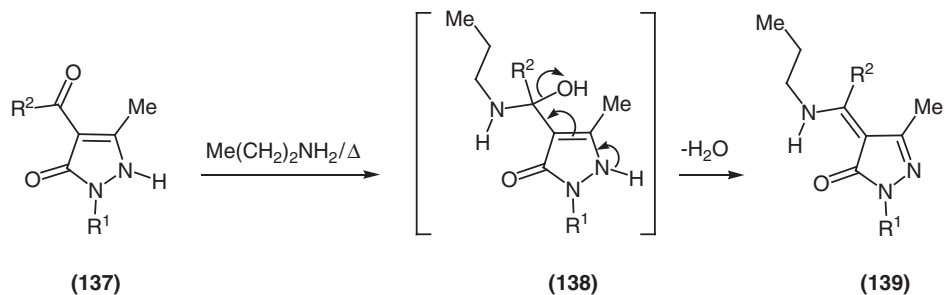


(a) R = H, (b) R = 5-methylisoxazol-3-yl, (c) R = pyrimidin-2-yl, (d) R = 4-methylpyrimidin-2-yl, (e) 4,6-dimethylpyrimidin-2-yl, (f) 2,4-dimethoxypyrimidin-6-yl

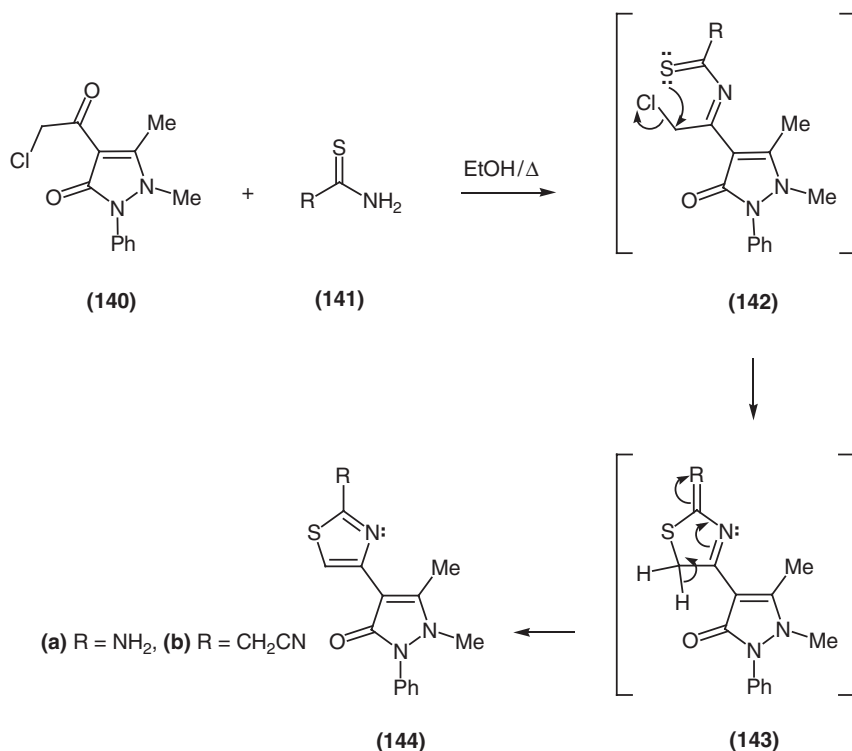
Scheme 37

give 4-(2-amino-thiazol-4-yl)pyrazol-3-one **144a** or [4-(3-oxopyrazol-4-yl)-thiazol-2-yl]acetonitrile **144b** (00JCR(M)622).

The condensation of 4-acyl-1,2-dihydropyrazol-3-ones **145a–c** with ethylenediamine **146d** or 1,3-diaminopropane **146e** in refluxing ethanol gave the corresponding bipyrazol-3-ones **147f,i,l** and **147g,j,m**. Similar treatment of pyrazol-3-ones **145a,b**



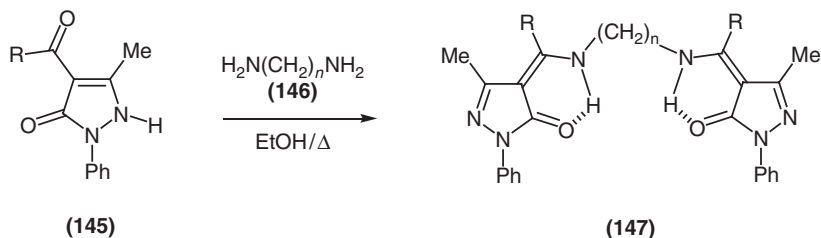
(a) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$, (b) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{CH}_2\text{Bn}$



Scheme 38

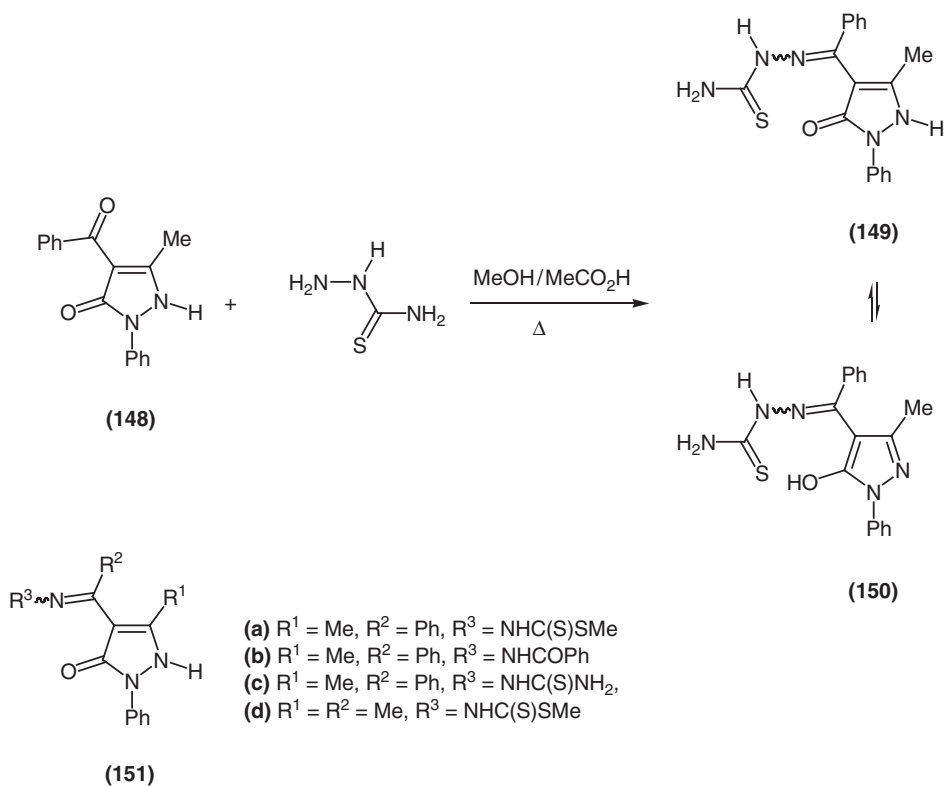
with 1,4-diaminobutane **146n** afforded the bipyrazol-3-ones **147h** and **147k**, respectively (99POL3041) (Scheme 39).

Tang et al. (00JPH23) (Scheme 40) heated pyrazol-3-one **148** and thiosemicarbazide in methanol with glacial acetic acid catalyst and isolated the tautomeric mixture (*E/Z*)-**149/150** in 79% yield. From an X-ray crystal structural analysis of compound **149/150** it was shown that its photochromic phenomenon was due to



(a) R = Ph, (b) R = CH₂C(Me)₃, (c) CH(Ph)₂, (d) n = 2, (e) n = 3, (f) R = Ph, n = 2,
 (g) R = Ph, n = 3, (h) R = Ph, n = 4, (i) R = CH₂C(Me)₃, n = 2, (j) R = CH₂C(Me)₃, n = 3,
 (k) R = CH₂C(Me)₃, n = 4, (l) R = CH(Ph)₂, n = 2, (m) R = CH(Ph)₂, n = 3, (n) n = 4

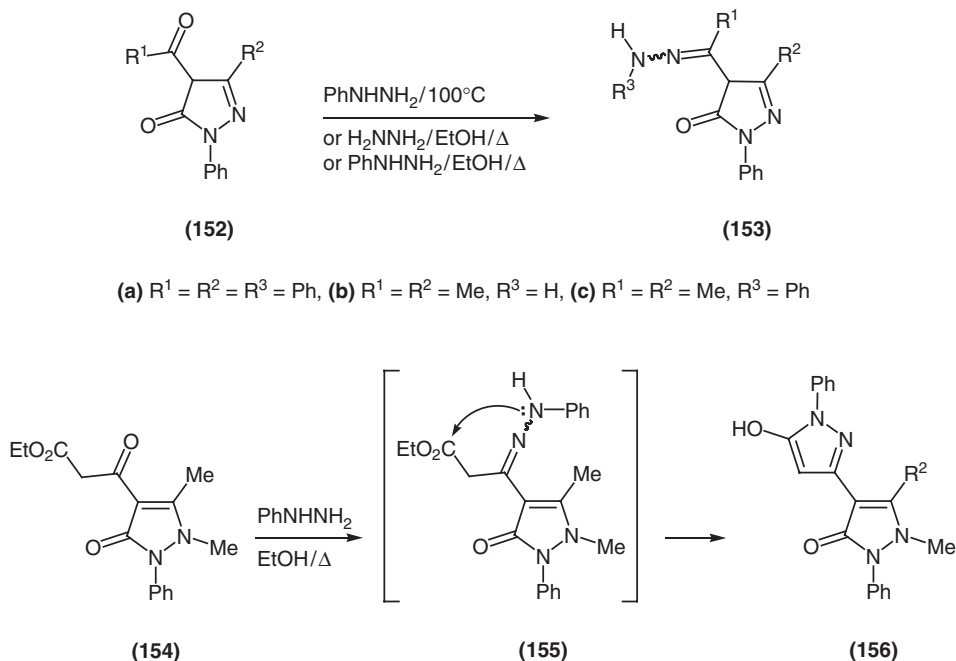
Scheme 39



Scheme 40

photoisomerization from the enol to the keto form. From infrared spectra analysis an intramolecular proton transfer mechanism was proposed as shown in Scheme 40. Analogous derivatives **151a-d** were synthesized by a similar manner.

Fahmy and co-workers (73IJC1) (Scheme 41) used phenylhydrazine both as a reactant and solvent in the condensation with 4-benzoylpyrazol-3-one **152a**, at 100 °C

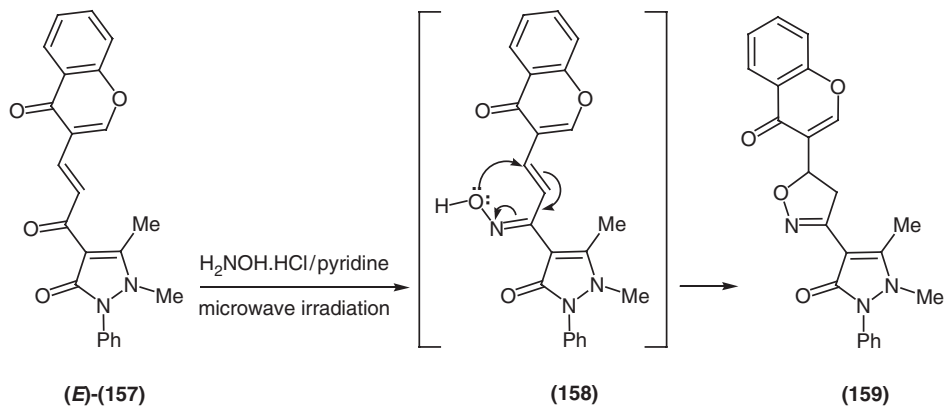


Scheme 41

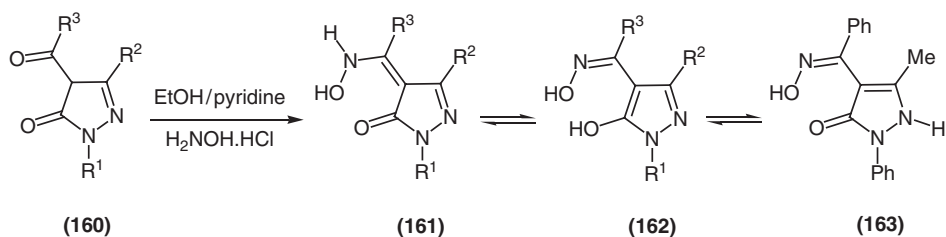
and the product (*E/Z*)-4-(hydrazonomethyl)pyrazol-3-one **153a** was obtained in 90% yield. On the other hand, Awad (90M1023) and Stachel and Papenberg (81AP65) reported that 4-acetylpyrazol-3-one **152b** condensed with hydrazine and ethyl (pyrazol-4-yl)-3-oxopropanoate **154** condensed with phenylhydrazine by heating to reflux in ethanol to afford (*E/Z*)-4-(hydrazonomethyl)pyrazol-3-one **153b** and (pyrazol-5-yl)pyrazol-3-one **156**, in excellent yields, respectively. The initial condensation leads to imine **155**, which undergoes intramolecular acyl substitution followed by tautomerization.

Reddy and co-workers (05HC235) (Scheme 42) treated 4-[3-(4-oxo-4*H*-chromen-3-yl)acryloyl]pyrazol-3-one **157** with hydroxylamine hydrochloride in pyridine under microwave irradiation, to obtain, after condensation via intermediate **158** followed by intramolecular conjugate addition, the 4-[5-(4-oxo-4*H*-chromen-3-yl)isoxazol-3-yl]pyrazol-3-one **159**, in 63% yield.

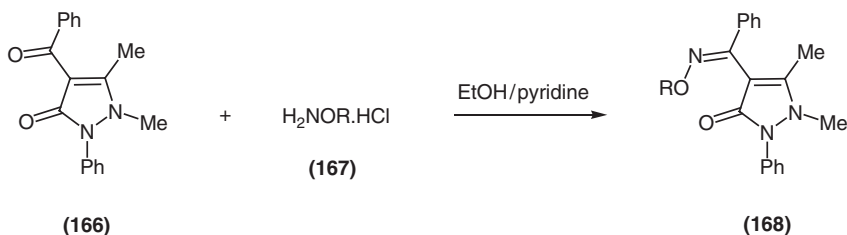
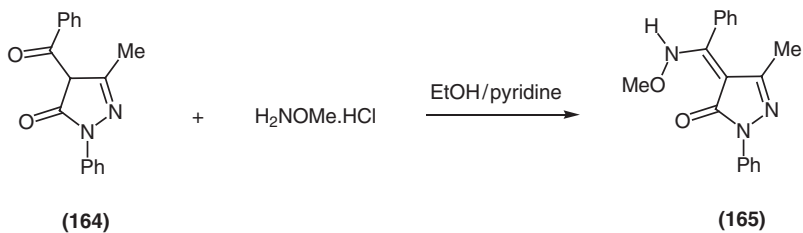
Holzer et al. established (03EJOC1209, 03JOC7943) (Scheme 43) that for 4-acylpyrazol-3-ones and their condensed derivatives the medium used for recrystallization plays a crucial role in determining which tautomeric structure these compounds will adopt in the solid state. Single-crystal X-ray analyses have shown that either hydroxypyrazole or pyrazol-3-one structures can exist. On the other hand, by NMR spectroscopy in DMSO- d_6 solution, mixtures of the 5-hydroxypyrazole and pyrazol-3-one tautomers are present, whereas in CDCl_3 or C_6D_6 solutions the 5-hydroxypyrazole tautomeric form predominates. The 4-acylpyrazol-3-ones **160a-i**, easily accessible from the corresponding 2,5-disubstituted-2,4-dihydropyrazol-3-ones



Scheme 42

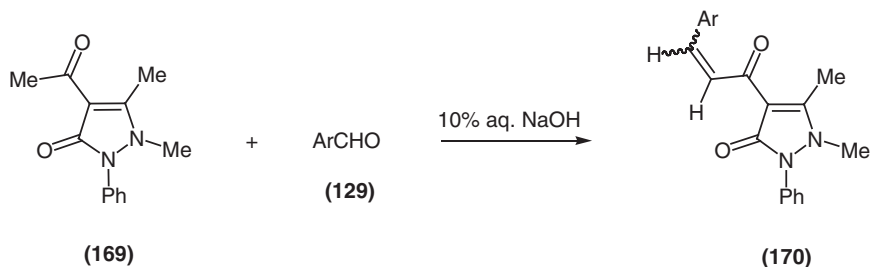


- (a) $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Ph}$, (b) $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{thien-2-yl}$, (c) $\text{R}^1 = \text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{H}$,
 (d) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$, (e) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{R}^3 = \text{Me}$, (f) $\text{R}^1 = \text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Me}$,
 (g) $\text{R}^1 = \text{Bn}$, $\text{R}^2 = \text{R}^3 = \text{Me}$, (h) $\text{R}^1 = \text{Bn}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Ph}$, (i) $\text{R}^1 = \text{R}^3 = \text{Ph}$, $\text{R}^2 = \text{Me}$



- (a) $\text{R} = \text{H}$, (b) $\text{R} = \text{Me}$

Scheme 43



(a) Ar = Ph, (b) Ar = 4-MeOC₆H₄, (c) Ar = 4-ClC₆H₄, (d) Ar = 4-MeC₆H₄

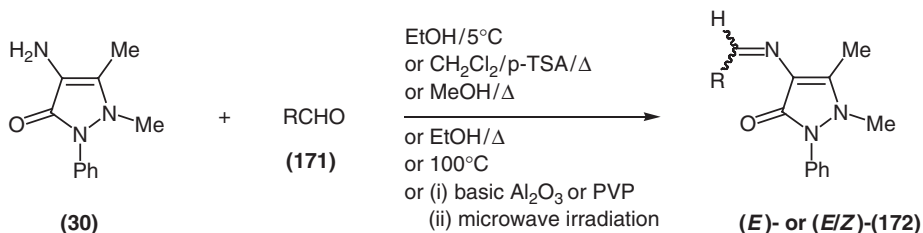
Scheme 44

by heating with acetyl chloride, phenylacetyl chloride or benzoyl chloride with calcium hydroxide in 1,4-dioxan, were transformed into the corresponding oximes **161/162/163a-i** by treatment with hydroxylamine hydrochloride in ethanol containing pyridine. For oximes **161/162/163f,i** single-crystal X-ray analysis and detailed NMR spectroscopic investigations showed that these compounds are present as (*Z*)-configured enaminopyrazol-3-ones **161** in the solid state and in DMSO-*d*₆ solution. From the similarities of the chemical shifts, particularly in the ¹³C NMR spectra, and the results of NOE-difference experiments, pyrazol-3-ones **161/162/163a-e,g,h** also exist mainly in this isomeric form. However, in some of these derivatives a second set of minor signals is seen in their NMR spectra. Since there are no signals due to a C (*sp*³)-H fragment and (*E/Z*)-oxime mixtures are excluded on the grounds of ¹³C chemical shifts, a quick exchange between tautomeric forms in solution cannot be excluded. The authors also describe the synthesis of 4-(methoxyaminophenylmethylene)pyrazol-3-one **165** and 4-[hydroxyl(or methoxy)iminophenylmethyl]-pyrazol-3-ones **168a,b** by respectively treating 2,4-dihydro-4-benzoyl-3*H*-pyrazol-3-one **164** with hydroxylamine hydrochloride and 1,2-dihydro-4-benzoyl-3*H*-pyrazol-3-one **166** with hydroxylamine hydrochloride or *O*-methylhydroxylamine hydrochloride **167a,b**, in ethanol containing pyridine.

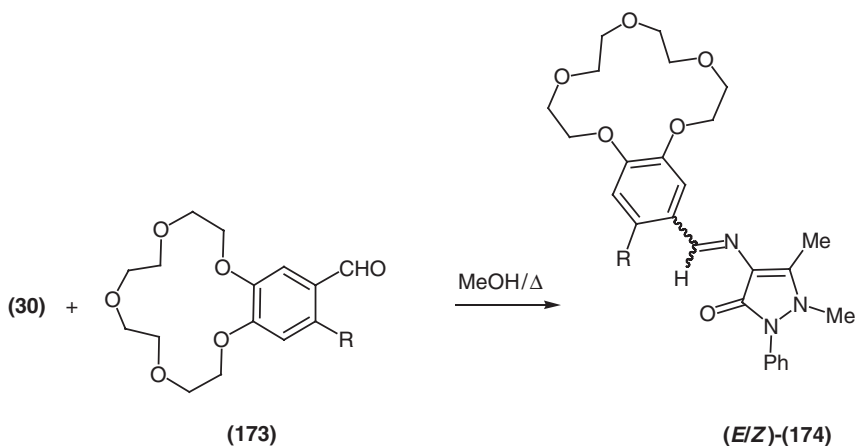
In Scheme 44 (83AP76), the enolate anion derived from the 4-acetyl group of pyrazol-3-one **169** in ethanolic 10% aqueous sodium hydroxide was condensed with aromatic aldehydes **129a-d** to give the corresponding (*E/Z*)-4-cinnamoylpyrazol-3-ones **170a-d**, in 67–86% yield.

C. OF 4- OR 5-AMINOPYRAZOL-3-ONES

Condensation of 4-amino-1,2-dihydropyrazol-3-ones with aryl or heteroaryl aldehydes or cyclic ketones are by far the most frequently described reactions of aminopyrazol-3-ones. The reactions take place in cold ethanol, refluxing ethanol or methanol, refluxing dichloromethane with a catalytic amount of *p*-toluenesulfonic acid, by heating in neat aldehyde at 100 °C or by microwave heating on a solid support. Several reports (79AP853, 92IJC(B)366, 92PJC899, 01JIC47) (Scheme 45) describe the condensation of 4-aminopyrazol-3-one (4-aminoantipyrine) **30** with



(a) R = thien-2-yl, (b) R = Ph, (c) 4-MeC₆H₄, (d) R = 2-HOC₆H₄, (e) R = 3-HOC₆H₄, (f) R = 4-HOC₆H₄, (g) R = 4-NO₂C₆H₄, (h) R = 2-ClC₆H₄, (i) R = 5-Br,2-HOC₆H₃, (j) R = 3,5-(Br)₂,2-HOC₆H₂, (k) R = 3-MeOC₆H₄, (l) R = 4-MeOC₆H₄, (m) R = furan-2-yl, (n) R = pyridin-3-yl, (o) R = pyridin-2-yl, (p) R = pyridin-4-yl, (q) R = pyrrol-2-yl, (r) R = indol-3-yl, (s) 2-chloro-7-methoxyquinolin-3-yl



(a) R = H, (b) R = OH

Scheme 45

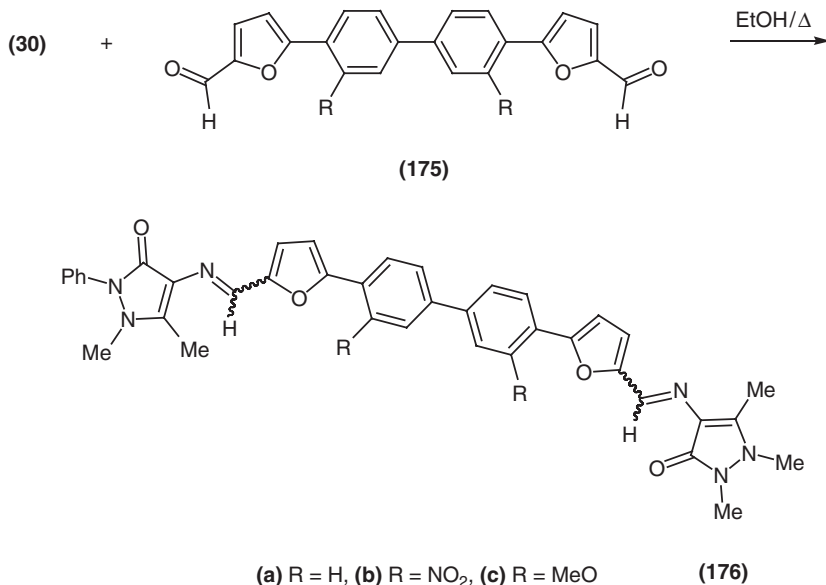
a variety of aldehydes such as thiophene-2-carbaldehyde **171a** and arylaldehydes **171b–k,s** in refluxing ethanol, whereas Abou-Ouf et al. (72JDR89) (Scheme 45) used neat 2-hydroxybenzaldehyde **171d** and 4-methoxybenzaldehyde **171l** at 100 °C. The products, (*E/Z*)-4-[(2-thienyl or arylmethylidene)amino]pyrazol-3-ones **172a–l,s** were obtained in yields between 50% and 85%. Agarwal (95JICS263) reported that after heating to reflux pyrazol-3-one **30** and furan-2-carbaldehyde **171m** for 3 h in ethanol, (*E*)-4-[(furan-2-ylmethylene)amino]pyrazol-3-one **172m** was isolated. Interestingly, Radhakrishnan and Indrasenan (89IJC(A)234) heated in methanol pyrazol-3-one **30** and pyridine-3-carbaldehyde **171n** and obtained (*E*)-4-[(pyridin-3-ylmethylene)amino]pyrazol-3-one **172n**, in 95% yield. However, when the same authors (90IJC(A)243) reacted pyrazol-3-one **30** with pyridine-2-carbaldehyde **171o** in ethanol at 5 °C the condensation product was a diastereomeric mixture of (*E/Z*)-4-[(pyridin-2-ylmethylene)amino]pyrazol-3-one **172o**. Again, single isomers of (*E*)-4-[substituted methylene)-amino]pyrazol-3-ones **172b,m–p** were obtained in good yields

when pyrazol-3-one **30** was heated to boiling with the corresponding aldehydes **171b,m-p** in the presence of a catalytic amount of *p*-toluenesulfonic acid (03JMS375). Vanden Eynde and Fromont (97BSB393) found that condensation of 4-aminopyrazol-3-one **87** with heteroaromatic aldehydes **171a,m-r** worked well under solvent free conditions, using either basic aluminum oxide or poly-4-vinylpyridine (PVP) solid supports and microwave irradiation. The two solid supports gave comparable results. Average yields for (*E/Z*)-iminopyrazol-3-ones **172a,m-r** ranged from 70% to 95% and reaction times varied from 10 to 20 min, well below the times reported when conventional methods were used. Hayvali and co-workers (01JMS223) (Scheme 29B) condensed pyrazol-3-one **30** with benzaldehyde derivatives **173a,b** in boiling methanol and isolated (*E/Z*)-4-[(substituted methylene)amino]pyrazol-3-ones **174a,b**.

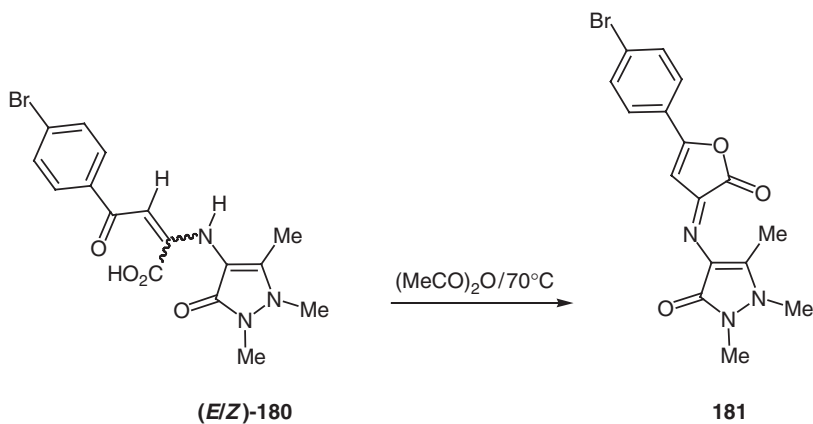
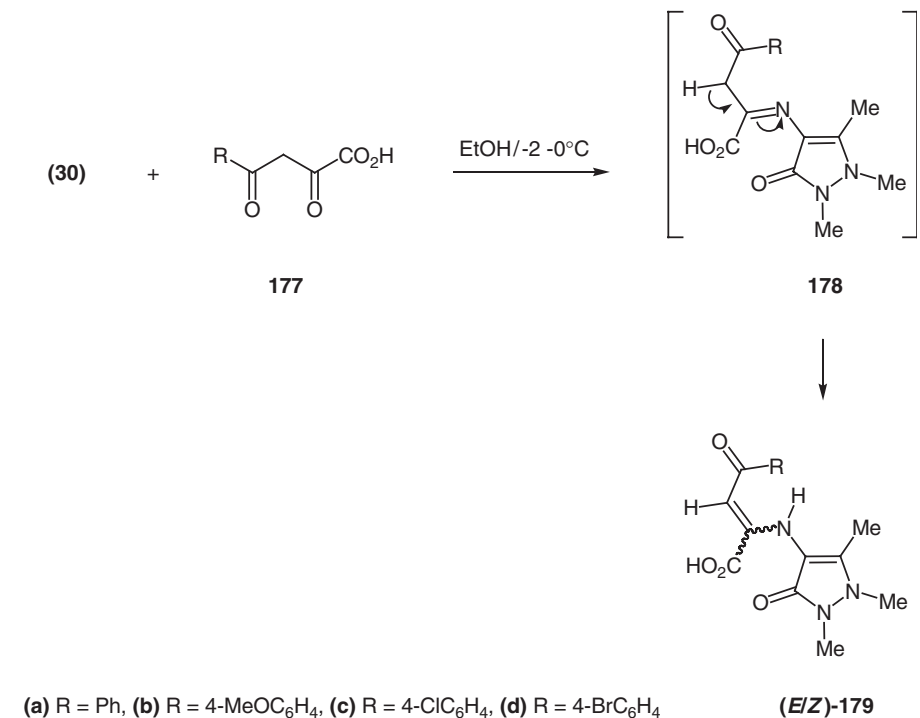
Similar conditions were used to condense pyrazol-3-one **30** with 5-[4-(5-formylfuran-2-yl)biphenyl-4-yl]furan-2-carbaldehydes **175a-c** to give (*E/Z*)-4-[[5-(4'-substituted biphenyl-4-yl)furan-2-ylmethylene]-amino]pyrazol-3-ones **176a-c** in 45%, 52% and 20% yields, respectively (92JOU431) (Scheme 46).

Condensation of pyrazol-3-one **30** with 4-aryl-2,4-dioxobutyric acids **177a-d** in ethanol at -2 to 0°C gave a mixture of (*E/Z*)-4-oxo-4-aryl-2-(3-oxopyrazol-4-ylamino)but-2-enoic acids (*E/Z*)-**179a-d** (Scheme 47) (03RJOC869). Perhaps **30** initially condenses with butyric acids **177a-d** to give intermediate imines **178a-d** which then tautomerize to the products (*E/Z*)-**179a-d**. Heating (*E/Z*)-**180** in acetic anhydride at 70°C caused intramolecular conjugate acyl substitution and gave 4-[5-(4-bromophenyl)-2-oxo-furan-3-ylideneamino]pyrazol-3-one **181**.

4-Aminopyrazol-3-ones react efficiently with cyclic ketones in refluxing ethanol. Petrova et al. (69PHA391) (Scheme 48) obtained 4-(5-oxopyrazolidin-4-ylideneamino)pyrazol-3-one **183** by heating pyrazol-3-one **30** with pyrazol-3,4-dione **182**,

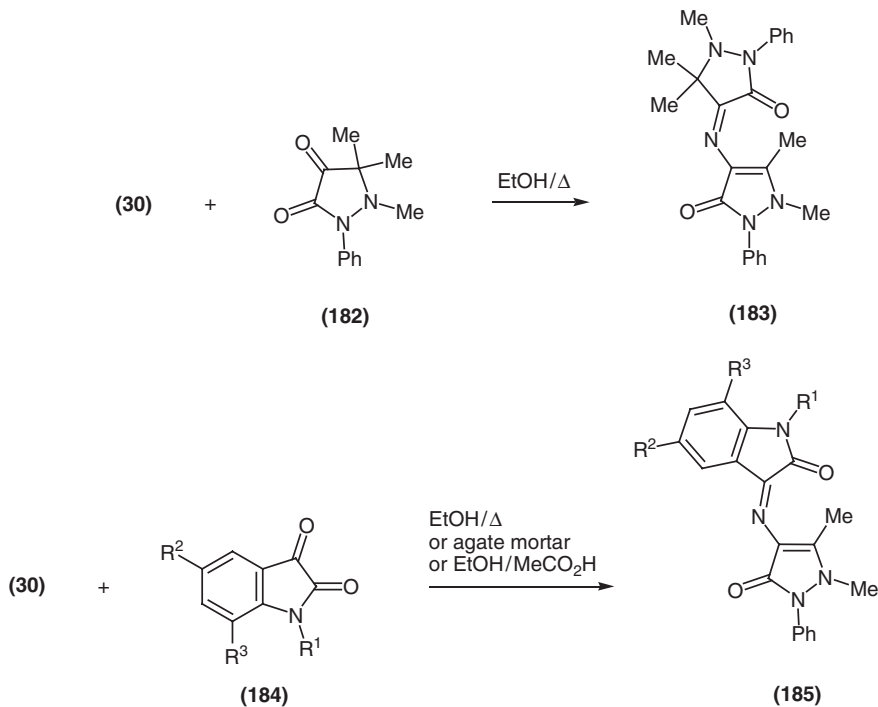


Scheme 46



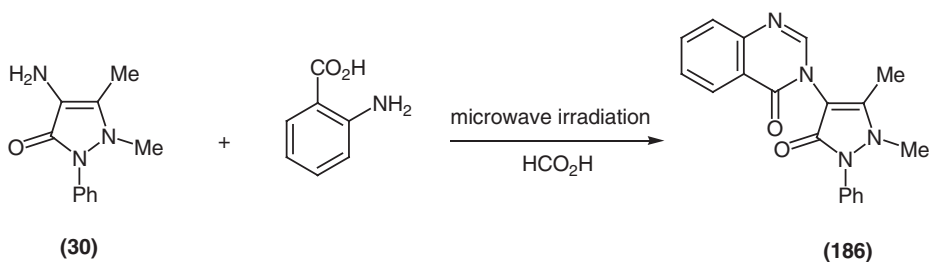
Scheme 47

whereas Sengupta and Gupta (82IJC(B)72), Dandia and co-workers (03OPP401) and Jain and co-workers (03SC563) (Scheme 31B), obtained 3-(3-oxopyrazol-4-ylimino)indol-2-ones **185a,b** through condensation of pyrazol-3-one **30** with indan-1,2-diones **184a-h** by heating in ethanol, grinding in an agate mortar or reacting at room temperature in ethanol containing glacial acetic acid. The yields were generally over 90%.



(a) $R^1 = R^2 = R^3 = \text{H}$, (b) $R^1 = R^3 = \text{H}$, $R^2 = \text{Me}$, (c) $R^1 = R^3 = \text{H}$, $R^2 = \text{Et}$, (d) $R^1 = \text{H}$, $R^2 = R^3 = \text{Me}$, (e) $R^1 = R^2 = \text{H}$, $R^3 = \text{F}$, (f) $R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = \text{F}$, (g) $R^1 = \text{H}$, $R^2 = \text{Et}$, $R^3 = \text{F}$, (h) $R^1 = R^3 = \text{H}$, $R^2 = \text{Cl}$

Scheme 48

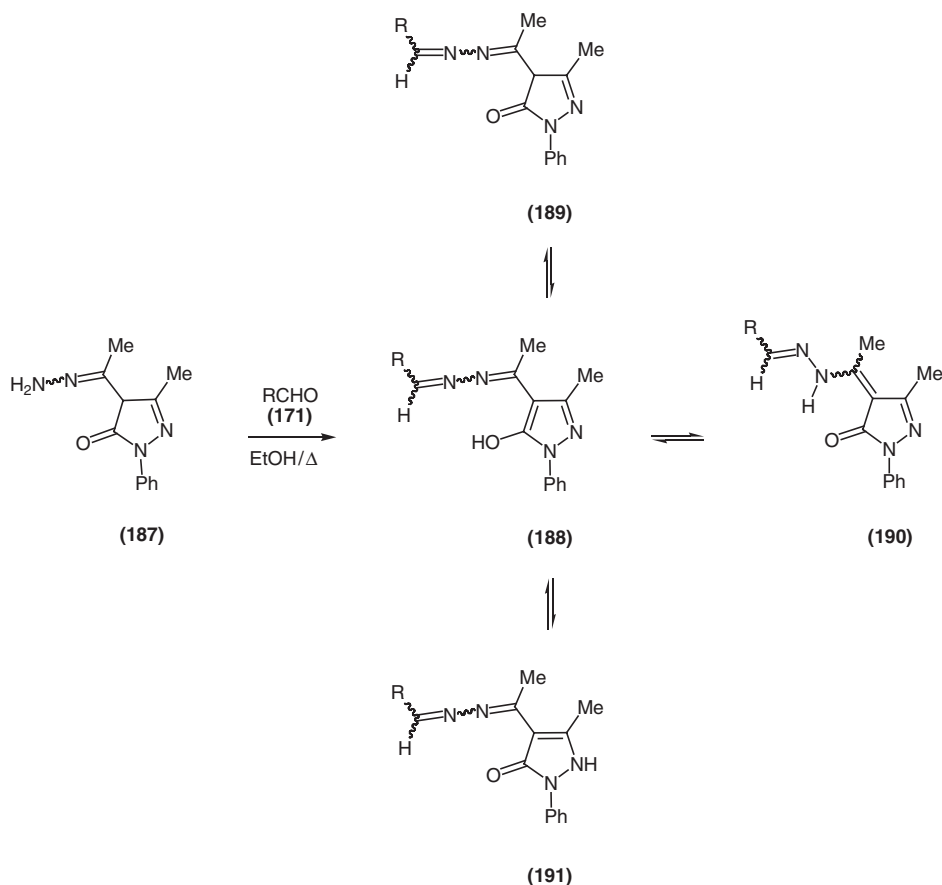


Scheme 49

In a multi-component reaction of pyrazol-3-one **30**, 2-aminobenzoic acid and formic acid at 190 °C for 1 h under microwave irradiation, the Niementowski reaction gave 3-(3-oxopyrazol-4-yl)-3*H*-quinazolin-4-one **186**, in 88% yield (O3CCA365) (Scheme 49).

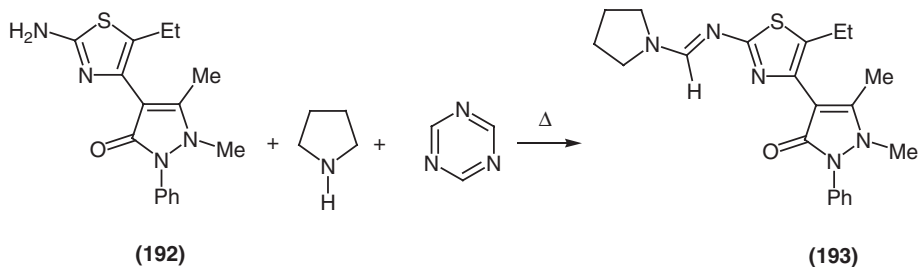
D. OF 4-HYDRAZONOETHYLPYRAZOL-3-ONES

Timtcheva et al. (95DP131) (Scheme 50) studied the IR, NMR and the absorption and fluorescence spectra of 16 unsymmetrical azines **188** derived from the condensation of (*E/Z*)-4-(1-hydrazonoethyl)pyrazol-3-one **187** with various aldehydes **171**. Comparisons with the electronic spectra of these compounds and the results of NMR and IR spectroscopy and also PPP-SCF-CI quantum chemical calculations suggest that the predominant tautomeric form in solution is enol **188**. The other tautomeric forms of **188** are keto forms **189–191**.

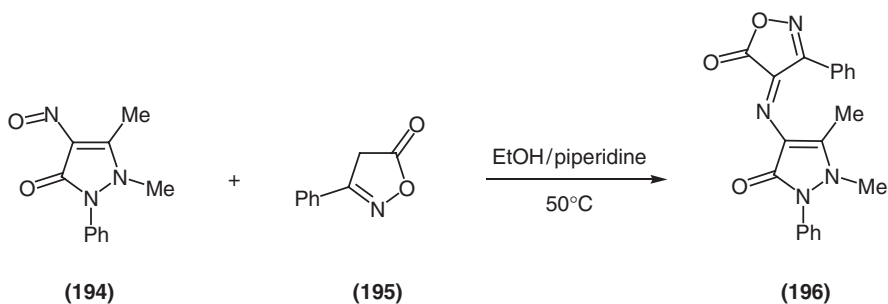


R = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄, 4-FC₆H₄, 4-CHOC₆H₄, 4-NO₂C₆H₄, 4-Me₂NC₆H₄, 4-Et₂NC₆H₄, 4-(1-piperidyl)C₆H₄, 4-(4-morpholinyl)C₆H₄, 4-(1-pyrrolidinyl)C₆H₄, 2-naphthyl, 9-anthracenyl, 9-ethyl-3-carbazoyl or 4-(Me₂N)styryl.

Scheme 50



Scheme 51



Scheme 52

E. OF 4-(2-AMINO-1,3-THIAZOL-4-YL)PYRAZOL-3-ONE

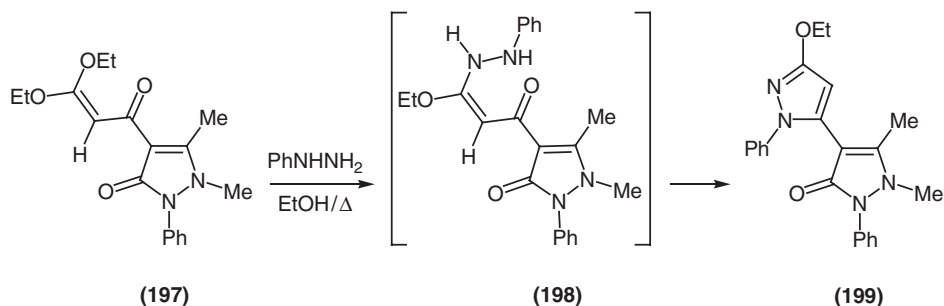
The three-component reaction of pyrazol-3-one **192** with *s*-triazine and pyrrolidine gave the methylideneamino derivative **193** in 76% yield without affecting the pyrazol-3-one ring (82JHC753) (Scheme 51).

F. OF 4-NITROSPYRAZOL-3-ONES

Wentrup et al. (78AG731) (Scheme 52) condensed 4-nitrosopyrazol-3-one **194** with 3-phenylisoxazol-5(4*H*)-one **195** in ethanol at 50 °C with piperidine as catalyst and obtained 4-(3-oxopyrazol-4-ylimino)isoxazol-5-one **196** in about 60% yield.

G. OF 4-(SUBSTITUTED ACRYLOYL)PYRAZOL-3-ONES

The reaction of 4-(3,3-diethoxyacryloyl)pyrazol-3-one **197** with phenylhydrazine in refluxing ethanol afforded 4-(pyrazol-5-yl)pyrazol-3-one **199** in about 70% yield. In the first step addition of phenylhydrazine to the β -carbon of the α,β -unsaturated side chain occurs followed by elimination of ethanol to give intermediate **107** which then condenses intramolecularly (81AP65) (Scheme 53).



Scheme 53

H. OF 2-(3-OXOPYRAZOL-4-YLAZO)KETONES OR ESTERS

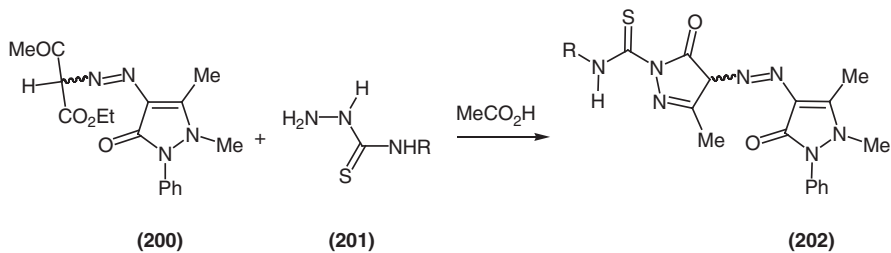
Farghaly et al. (81PHA93) (Scheme 54) adopted an efficient method of synthesizing 4-substituted azopyrazol-3-one derivatives where the azo group is connected directly to a pyrazolone ring. 2-(3-Oxopyrazol-4-ylazo)-3-oxobutanoic acid ethyl ester **200** reacted with 4-substituted thiosemicarbazides **201a–f** in glacial acetic acid to give 4-(3-oxopyrazol-4-ylazo)-5-oxopyrazole-1-carbothioic acid amides **202a–f** in 63–75% yield. Ester **200** reacted also with hydrazine hydrate **203a** or substituted hydrazines **203b–k** in refluxing glacial acetic acid to afford 4-(5-oxopyrazol-4-ylazo)pyrazol-3-ones **204a–k** in 75–80% yield. Using similar reaction conditions 3-(3-oxopyrazol-4-ylazo)pentane-2,4-dione **205** was condensed with hydrazine hydrate **203a** or substituted hydrazines **203b–j,l** to give the corresponding 4-(pyrazol-4-ylazo)pyrazol-3-ones **206a–j,l**, in 50–60% yield.

Nine years later Farghaly et al. (90AP833) (Scheme 55) described a similar reaction between **205** with 2-hydrazino-3-aryl-3*H*-quinazolin-4-ones **207a–d** but also used a catalytic amount of concentrated sulfuric acid and isolated 2-[4-(3-oxopyrazol-4-ylazo)pyrazol-1-yl]quinazolin-4-ones **208a–d**, in good yield.

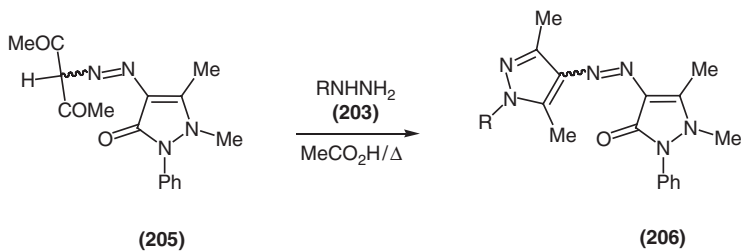
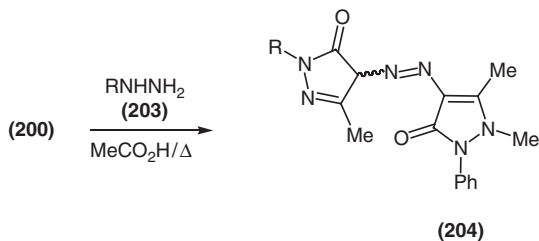
Further work by Farghaly et al. (90AP833) (Scheme 56) included the condensation of ester **200** with 2-hydrazino-3-aryl-3*H*-quinazolin-4-ones **207a–d** in refluxing ethanol that afforded 4-hydrazonepyrazol-3-ones **209a–d** in 72–83% yield. Intramolecular acyl substitution between the hydrazone NH and the ester groups of compounds **209a–d** in refluxing glacial acetic acid afforded pyrazol-3-ones **210a–d** in high yield. The latter compounds could be prepared in one step from ester **200** and hydrazines **207a–d** by heating under reflux in glacial acetic acid. It is worth noting that contrary to the previous reactions (Scheme 54) the products described here do not contain an azo function but instead a hydrazone function.

I. OF 2-[(3-OXOPYRAZOL-4-YL)HYDRAZONO]MALONIC ACID ESTERS OR SUBSTITUTED ACETONITRILES

Elnagdi et al. (82JCS(P1)989) (Scheme 57) condensed hydrazone derivatives **211a–c** with hydrazine hydrate by heating in ethanol and obtained (*E/Z*)-4-[2-(pyrazol-4-ylidene)hydrazino]pyrazol-3-ones **212a–c**. In a similar fashion Farghaly et al. (90AP833)

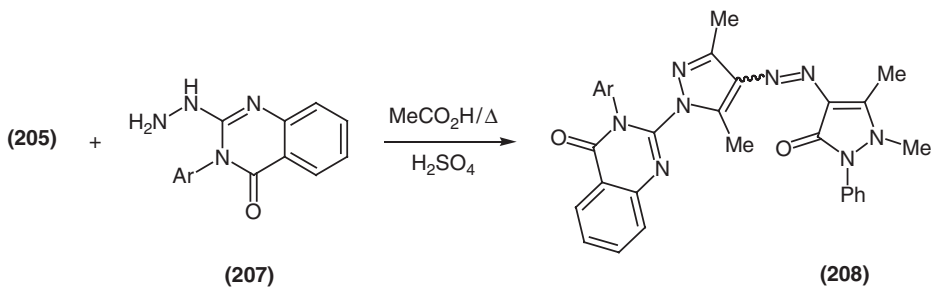


(a) R = *n*-C₄H₉, (b) R = Ph, (c) R = 3-MeC₆H₄, (d) R = 4-MeC₆H₄, (e) R = 2-MeOC₆H₄, (f) R = 4-ClC₆H₄



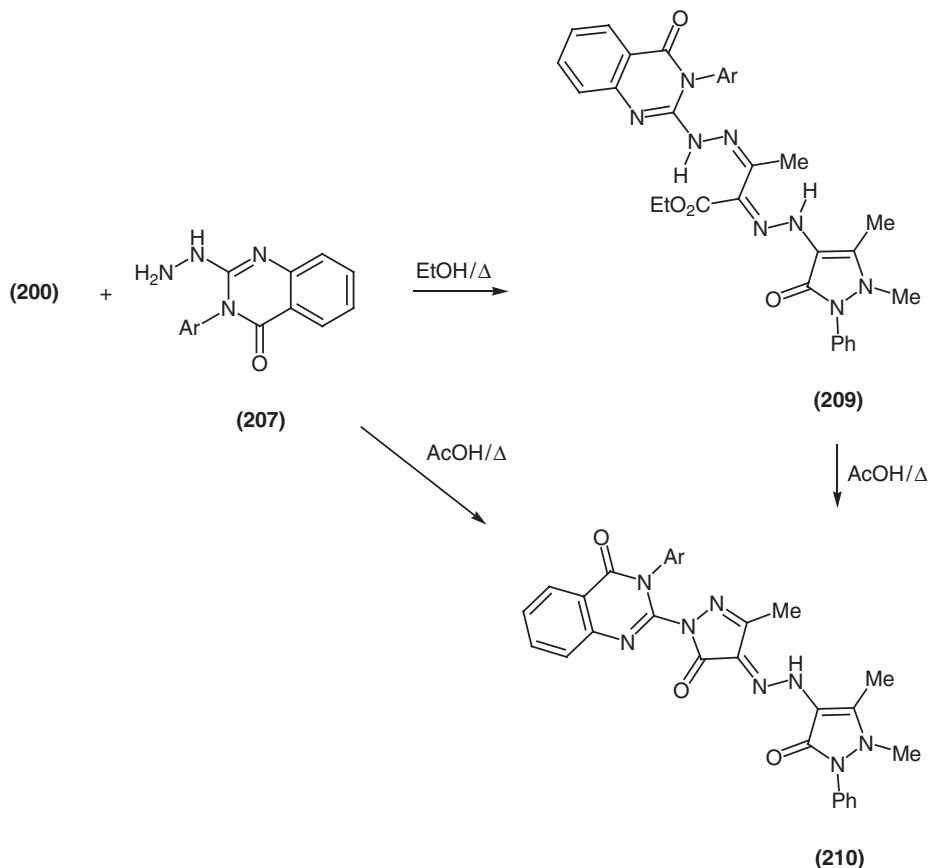
(a) R = H, (b) R = Ph, (c) R = 2-MeC₆H₄, (d) R = 4-MeC₆H₄, (e) R = 4-ClC₆H₄, (f) R = 4-BrC₆H₄, (g) R = 2,4-(NO₂)₂C₆H₃, (h) R = 4-H₂NSO₂C₆H₄, (i) R = 4-MeCONHSO₂C₆H₄, (j) R = 4-(2-pyridyl)-NHSO₂C₆H₄, (k) R = 4-[2-(4,6-dimethylpyridyl)]NHSO₂C₆H₄, (l) R = 4-(2-pyrimidyl)-NHSO₂C₆H₄

Scheme 54



(a) Ar = Ph, (b) Ar = 4-MeC₆H₄, (c) Ar = 4-ClC₆H₄, (d) Ar = 4-BrC₆H₄

Scheme 55



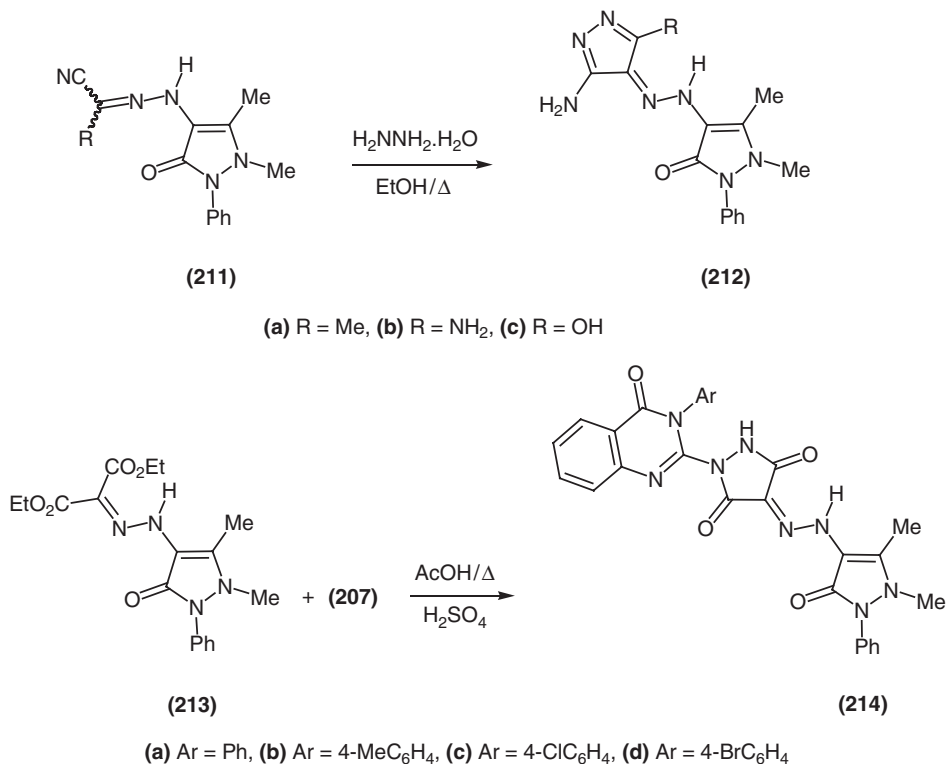
(a) Ar = Ph, (b) Ar = 4-MeC₆H₄, (c) Ar = 4-ClC₆H₄, (d) Ar = 4-BrC₆H₄

Scheme 56

prepared [(3-oxopyrazol-4-yl)hydrazono]-1-(4-oxoquinazolin-2-yl)pyrazolidine-3,5-diones **214a-d** directly from 2-[(3-oxopyrazol-4-yl)hydrazono]malonic acid diethyl ester **213** and hydrazines **207** by heating in glacial acetic acid containing a catalytic amount of sulfuric acid.

J. OF 3-(3-OXOPYRAZOL-4YL)-3-OXOPROPIONITRILES

Elnagdi and co-workers (84AP289) (Scheme 58) described both nucleophilic and electrophilic reactions of 3-(3-oxopyrazol-4-yl)-3-oxopropionitrile **215**. Therefore, **215** was condensed with benzaldehyde or salicylaldehyde in refluxing ethanol containing triethylamine and with hydroxylamine, hydrazine hydrochloride or phenylhydrazine to give the corresponding pyrazol-3-one derivatives **216**, **217**, **218** and **219a,b** in, 60%, 25%, 72% and 95% yield, respectively.



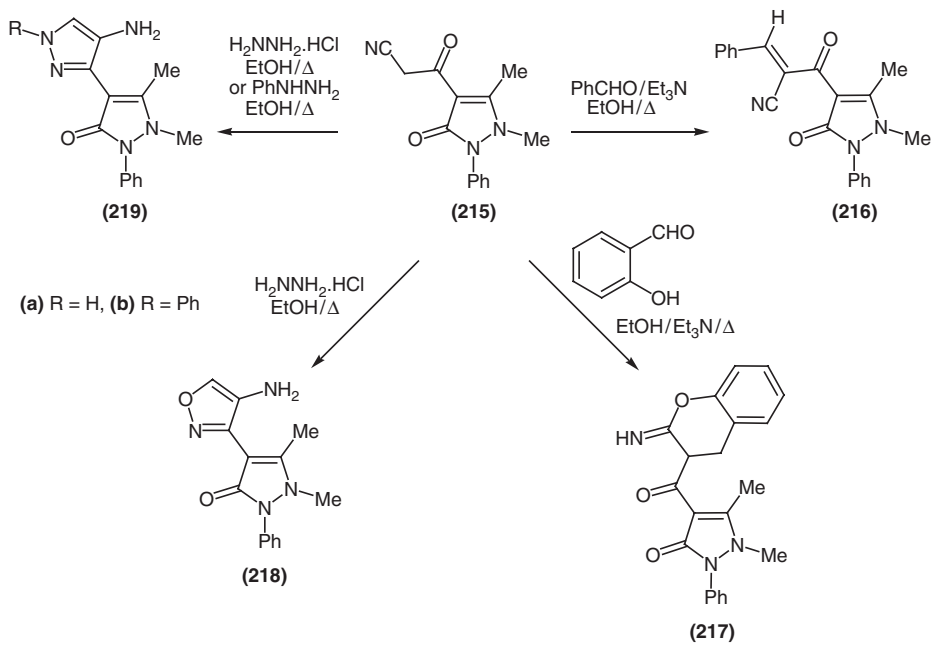
Scheme 57

Elmaati and co-workers (03JHC481) (Scheme 59) heated 3-(3-oxopyrazol-4-yl)-3-oxopropionitrile **220** with readily available 2-dimethylaminomethylene-3-(phenylhydrazono)-indan-1-one **221** in ethanol containing a catalytic amount of piperidine and isolated pyrazol-3-one derivative **224**. The reaction is postulated to occur via initial Michael addition to give intermediate **222**, elimination of dimethylamine to **223** followed by cyclization between the enolic OH and nitrile groups.

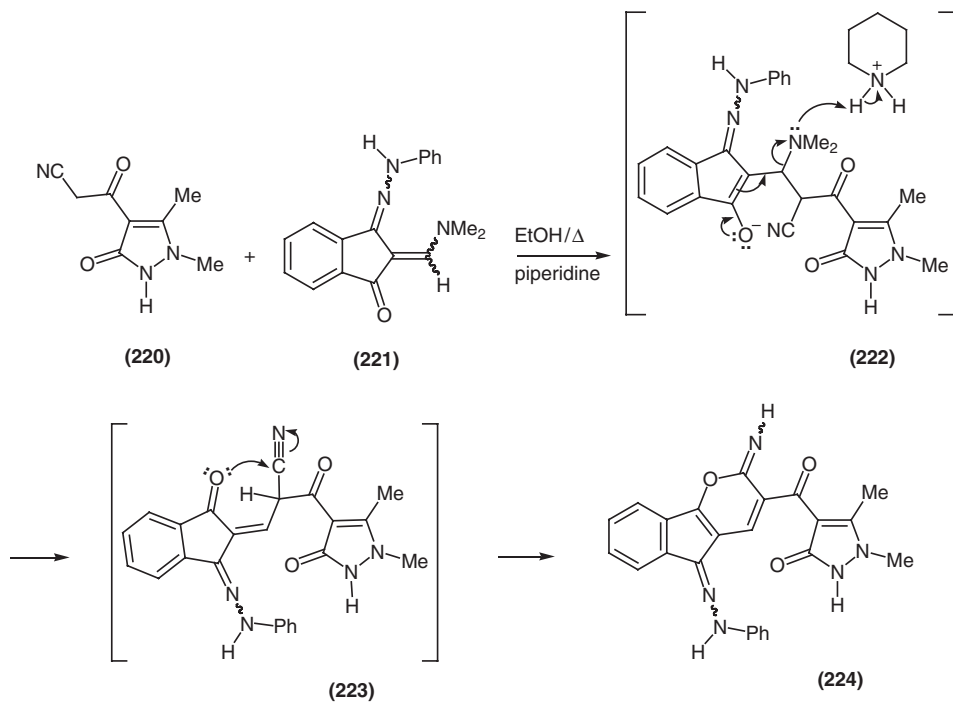
K. OF MISCELLANEOUS SIDE CHAINS

Appropriate side chains at position 4 of pyrazol-3-ones can either intramolecularly cyclize or react with nucleophiles to form otherwise inaccessibly substituted rings.

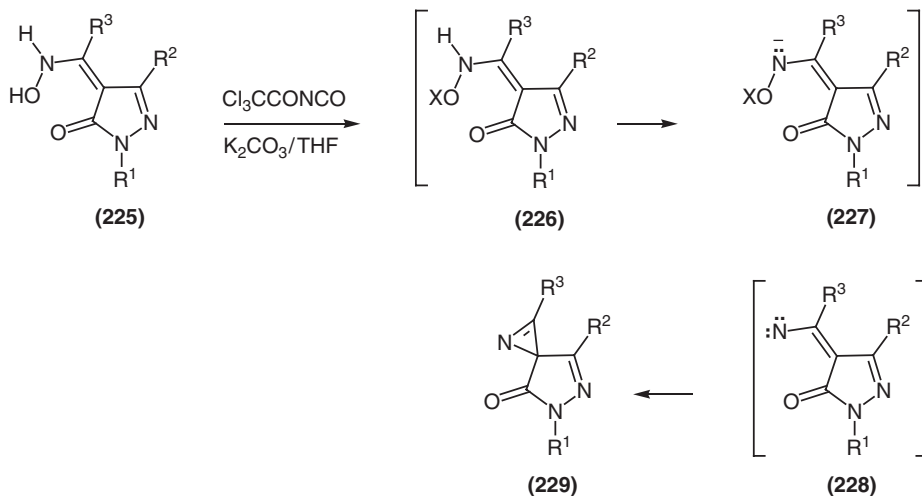
Holzer et al. (03JOC7943) (Scheme 60) reacted pyrazol-3-ones **225a-h** with trichloroacetyl isocyanate, a mild cyclodehydrating reagent, and potassium carbonate in tetrahydrofuran and obtained the corresponding azirinespiropyrazol-3-ones **229a-h** 38–64% yield. No trace of the expected 6*H*-pyrazolo[4,3-*d*]isoxazoles, resulting from cyclodehydration, were detected. The structure of compounds **229a-h** was based on single-crystal X-ray analyses of derivatives **229f,h**. A possible reaction mechanism envisages a Lossen-type reaction where compounds **226** as vinylogous



Scheme 58



Scheme 59



X = CONHCOCl₃

(a) R¹ = R² = Me, R³ = Ph, (b) R¹ = R² = Me, R³ = thien-2-yl, (c) R¹ = R² = Ph, R³ = H,

(d) R¹ = Ph, R² = Me, R³ = H, (e) R¹ = Ph, R² = R³ = Me, (f) R¹ = R² = Ph, R³ = Me,

(g) R¹ = Bn, R² = R³ = Me, (h) R¹ = Bn, R² = Me, R³ = Ph

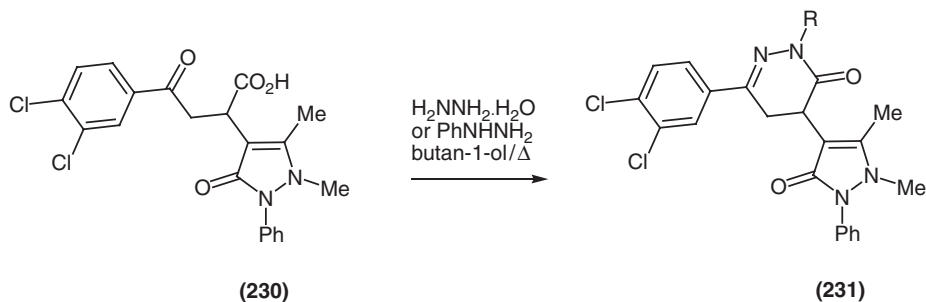
Scheme 60

hydroxamic acids are attacked by trichloroacetyl isocyanate at the OH function. After base-induced abstraction of the NH proton from **226**, elimination of OX⁻ from **227** then leads to nitrene **228** which, in contrast to the Lossen reaction, can be stabilized not by rearrangement but by azirine ring closure to afford spiro compounds **229**.

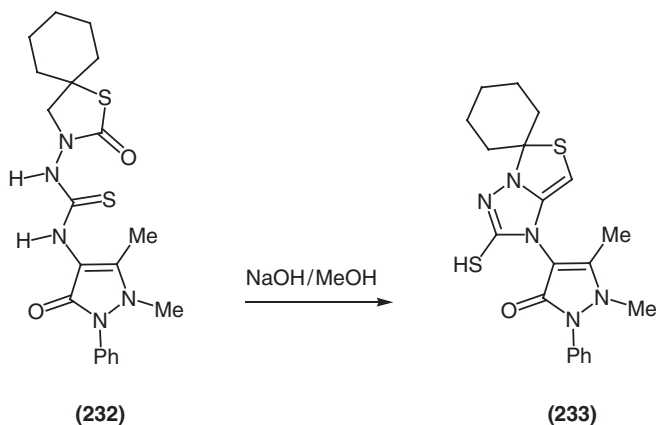
Sayed and co-workers (03MOL322) (Scheme 61) heated pyrazol-3-one **230** with hydrazine hydrate or phenylhydrazine in butan-1-ol and obtained the (3-oxopyrazol-4-yl)pyridazin-3-ones **231a,b** in good yields. The reaction most probably occurs by initial condensation between the keto group of the side chain and the hydrazines followed by intramolecular acyl substitution of the intermediate hydrazone. Shaker (03PS1175) found that pyrazolylcyclohexane-spirothiazolidinone **232** underwent cyclodehydration on heating in methanolic sodium hydroxide to give pyrazolylcyclohexane-spirothiazolotriazole **233**, in 64% yield.

VIII. Nucleophilic Addition

This category of reactions may involve nucleophilic addition either by or to the pyrazol-3-one side-group. The side-group can be a variety of functionalities such as amino, methyl, hydroxyethyl, hydrazonyl, aminoethylidene, carbothioic acid hydrazide, dialkylaminomethylidene or an α,β -unsaturated unit.



(a) R = H, (b) R = Ph



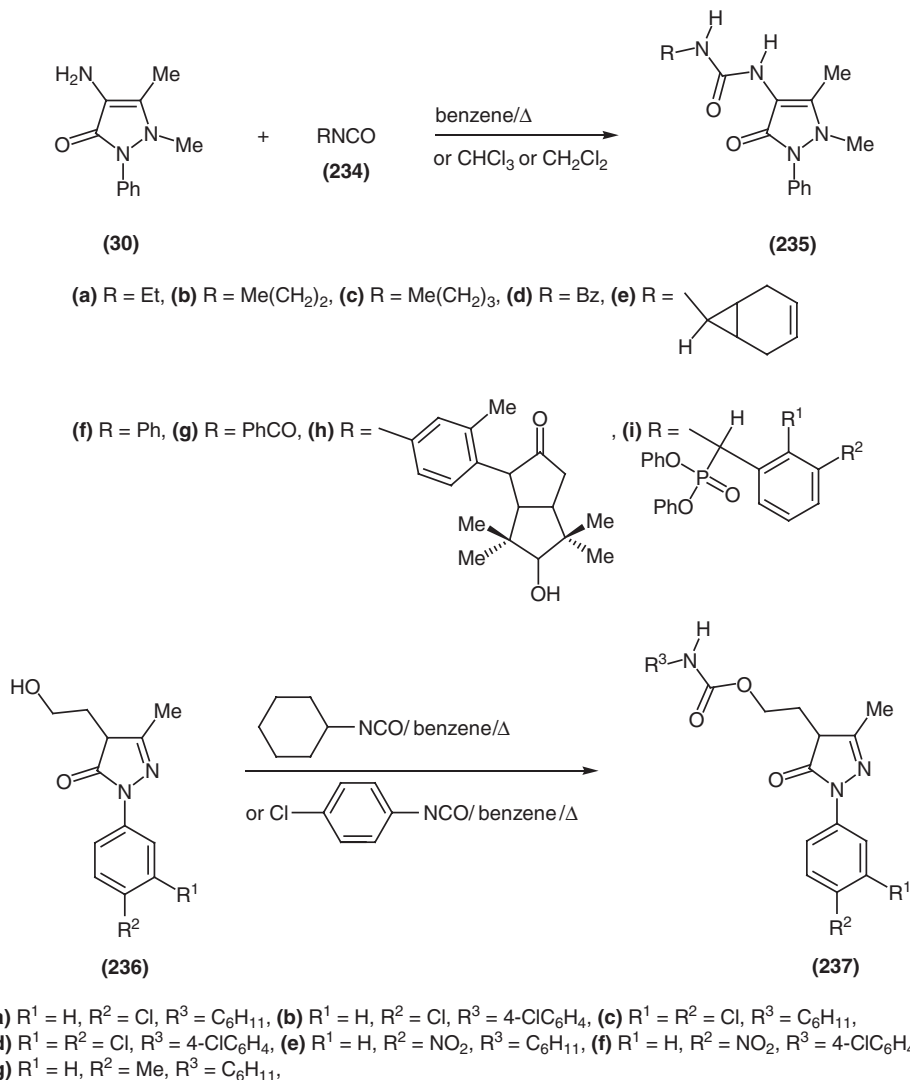
Scheme 61

A. TO ISOCYANATES, ISOTHIOCYANATES, OR CARBON DISULFIDE

The most frequently reported reaction of this kind utilizes 4-aminopyrazol-3-one **30** as the nucleophile. Both aliphatic and aromatic isocyanates **234a–i** have been used and the conditions include heating in benzene or stirring at room temperature in chloroform or dichloromethane. The products, pyrazol-3-one ureas **235**, were obtained in yields 70–91% (81PHA91, 92S1223, 96RCB403, 01JCR(S)470) (Scheme 62). 4-Hydroxyethylpyrazol-3-ones **236a–g** have also been reported to add to cyclohexylisocyanate or 4-chlorophenylisocyanate in refluxing benzene to afford the ethylcyclohexyl(or aryl)carbamates **237a–g** (84CZ285).

The amino group of 2-aminopyrazol-3-ones **238a,b** was forced to add to phenylisocyanate on heating with benzene in a sealed tube at 100 °C for several hours. The 2-(3-oxopyrazol-1-yl)-3-phenylureas **239a,b** were obtained in 70% and 80% yields, respectively (81JHC957) (Scheme 63).

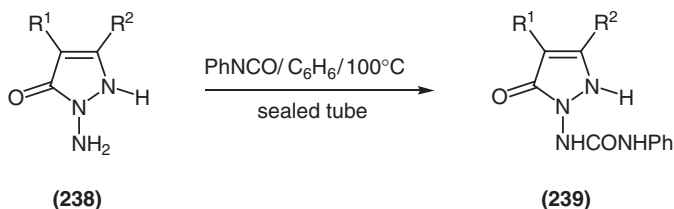
For the reactions of 4-aminopyrazol-3-one **30** with alkyl or aryl isothiocyanates **240a–l**, the preferred conditions were boiling in methanol containing pyridine, boiling in ethanol (80PHA596, 91SUL151, 03CHE1002, 03JJC(B)2006, 03JCC105)



Scheme 62

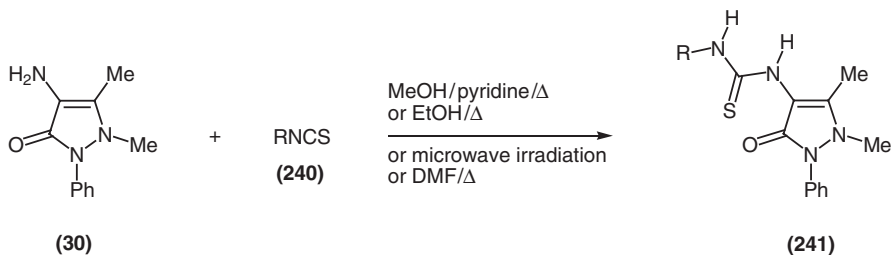
(Scheme 64), microwave irradiation at 50 °C (01JCC73) and, in the case of benzoyl isothiocyanates **240o,p** heating in DMF (02PCJ77). The (3-oxopyrazol-4-yl)thioureas **241a-l** and the 1-aryyl-3-(3-oxopyrazol-4-yl)thioureas were obtained in yields ranging from 56% to 90%.

Addition of the sulfur atom of 3-oxopyrazole-4-carbothioic acid hydrazide **242** to carbon disulfide followed by an intramolecular acyl-type substitution of unstable intermediate **243** gave 4-(5-thioxo[1,3,4]thiadiazol-2-yl)-pyrazol-3-one **244** in 41% yield (01BPA279) (Scheme 65) when heated in ethanolic potassium hydroxide.



(a) $R^1 = \text{Ph}$, $R^2 = \text{Me}$, (b) $R^1 = \text{Me}$, $R^2 = \text{Ph}$

Scheme 63

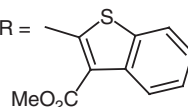


(a) $R = \text{Et}$, (b) $R = n\text{-C}_6\text{H}_4$, (c) $R = \text{C}_6\text{H}_{11}$, (d) $R = \text{Bz}$, (e) $R = \text{Ph}$, (f) $R = 2\text{-MeC}_6\text{H}_4$, (g) $R = 3\text{-MeC}_6\text{H}_4$,

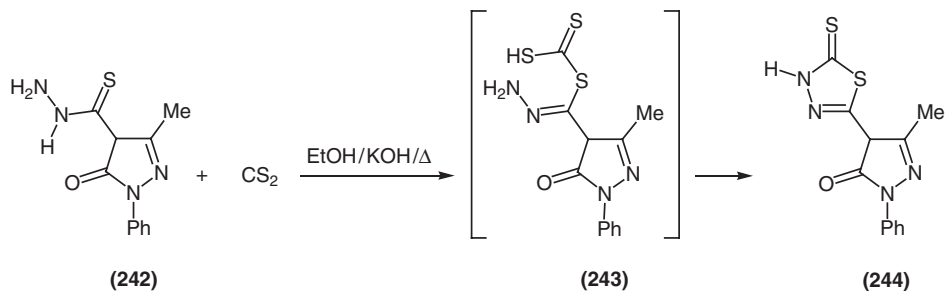
(h) $R = 4\text{-MeC}_6\text{H}_4$, (i) $R = 4\text{-MeOC}_6\text{H}_4$, (j) $R = 2\text{-ClC}_6\text{H}_4$, (k) $R = 2\text{-BrC}_6\text{H}_4$, (l) $R =$

(m) $R = 4\text{-BrC}_6\text{H}_4$, (n) $R = 2\text{-ClC}_6\text{H}_4$, (o) $R = 4\text{-ClC}_6\text{H}_4\text{CO}$

(p) $R = 4\text{-NO}_2\text{C}_6\text{H}_4\text{CO}$



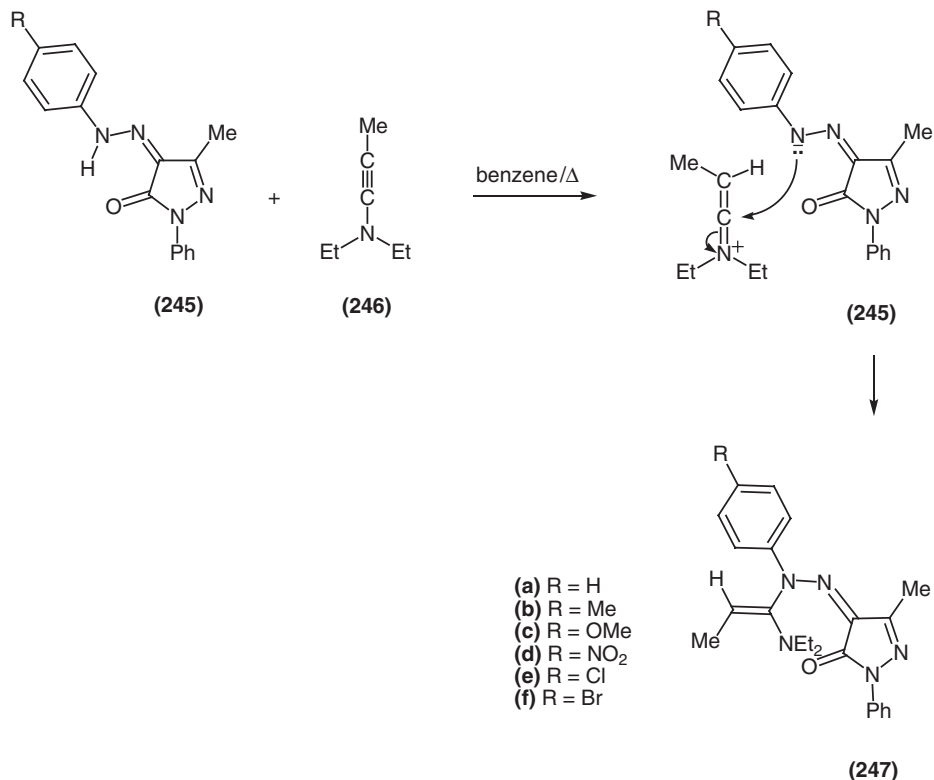
Scheme 64



Scheme 65

B. TO METHYL-*N,N*-DIETHYLAMINOACETYLENES

Pyrazol-3-ones **245a-f** with methyl-*N,N*-diethylaminoacetylene **246** in benzene at 0°C gave the addition products **247a,b,d-f** in 80–90% yield but addition product **247c** in only 27% yield. The authors (79JPR43) propose that hydrogen abstraction of



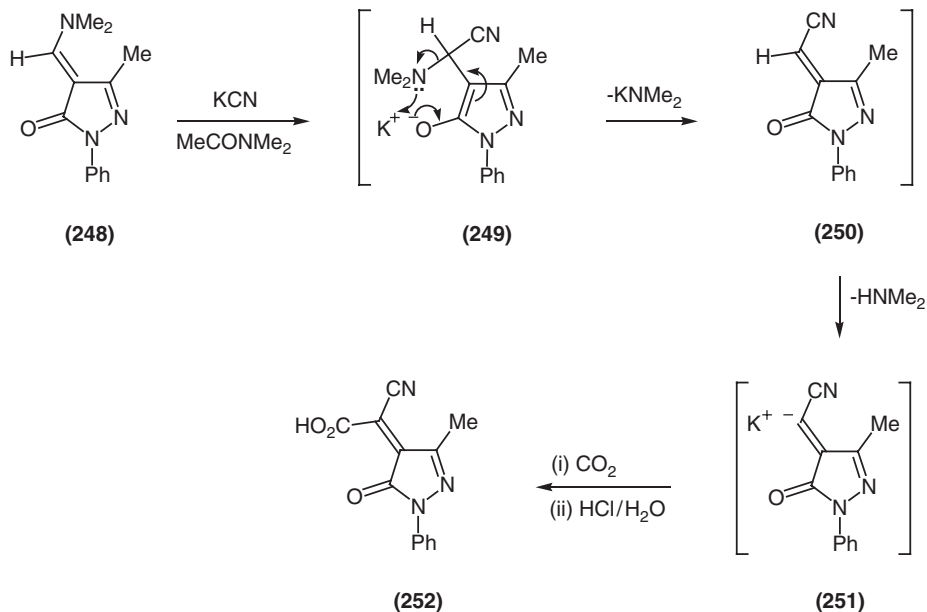
Scheme 66

the hydrazone NH by the aminoacetylene occurs to give the intermediate salt followed by addition (Scheme 66).

C. BY ADDITION-ELIMINATION TO α,β -UNSATURATED COMPOUNDS

El'tsov and co-workers (85JOU596) (Scheme 67) have proposed a mechanism for the reaction of 4-[(dimethylamino)methylidene]-pyrazol-3-one **248** with cyanide ion in the presence of dimethylacetamide followed by the addition of carbon dioxide and then acidification that gives cyano(3-oxopyrazol-4-ylidene)acetic acid **252**. Addition of cyanide ion to the α,β -unsaturated functionality of **248** affords **249** which eliminates dimethylamine to give **250**. Proton abstraction from **250** gives the pyrazol-3-one salt **251**, which is converted into the acid **252** by bubbling in carbon dioxide and then acidifying. The progress of the reaction up to intermediate **251** was monitored by UV and IR spectroscopy.

Reaction of 2-(4-arylidene-5-oxopyrazol-3-yl)-3-dimethylaminopropenals occurs with secondary amines. The reactivities of the α,β -unsaturated carbonyl and dimethylaminoacrolein functionalities of pyrazol-3-ones **253a,b** were compared by reaction with piperazine, morpholine or piperidine in boiling ethanol or in hot 2 N



Scheme 67

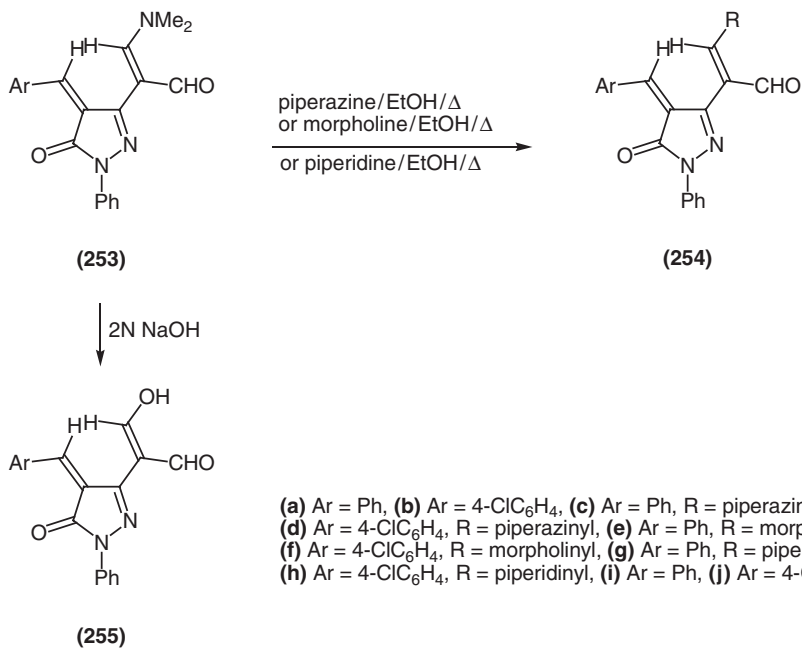
NaOH. The products were the corresponding aminoacroleins **254c–h** and acroleins **255i,j**. The reactions show that addition–elimination occurs faster at the acrolein moiety whereas potential addition to the α,β -unsaturated carbonyl moiety is much slower (89CCCC706) (Scheme 68).

Ila and co-workers (02JOC4916) (Scheme 69) demonstrated that 5-[4-(2-substituted cyclopropyl)-2-methylsulfanyl-4-oxo-but-2-enyl]pyrazol-3-one **258** can be obtained by conjugate addition–elimination of 5-lithiomethylpyrazol-3-one **256**, obtained *in situ* by the action of *n*-butyllithium on pyrazol-3-one **7**, with 1-(2-substituted cyclopropyl)-3,3-bismethylsulfanylpropenone **257**. Compound **258** was not characterized but reacted further with ethereal trifluoroborane in refluxing benzene to afford cyclopenta[*e*]indazol-3-one **259** in 73% yield.

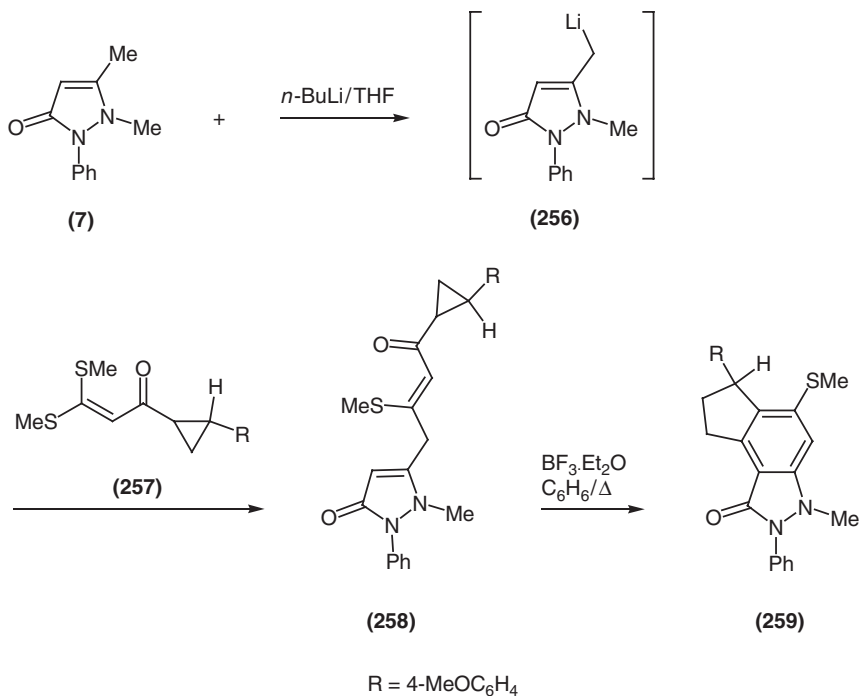
The addition–elimination reaction between 2-cyano-3,3-isomethylsulfanylthioacrylamide **260a**, [bis(methylthio)methylidene]malonitrile **260b**, bis(methylthio)methylene-cyanoacetamide **260c** or ethoxy-methylenemalonitrile **260d** by 5-aminopyrazol-3-one **30** in refluxing ethanol with piperidine, caused in the first three reactions loss of methyl sulfide ion and in the last reaction loss of ethoxide anion and yielded the corresponding pyrazol-3-one derivatives **261a–d** in 75–85% yield (02SC3509) (Scheme 70).

D. BY MICHAEL ADDITION

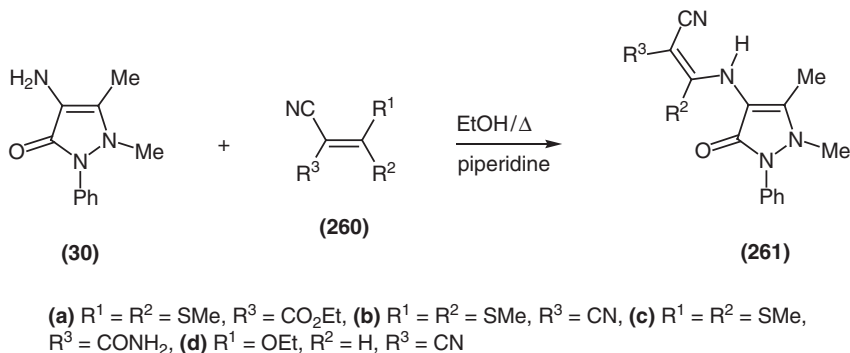
Heating 4-(1-aminoethylidene)pyrazol-3-one **262** and benzylidenemalonitrile in ethanol containing piperidine as catalyst afforded 6-(3-oxopyrazol-4-yl)



Scheme 68



Scheme 69



Scheme 70

nicotinonitrile **268** in 40% yield (02JHC309) (Scheme 71). The reaction may proceed initially by Michael addition of enamine **264** to **263**, intramolecular addition of amino to cyano in **265**, tautomerization of **266** to **267** and air oxidation of the latter.

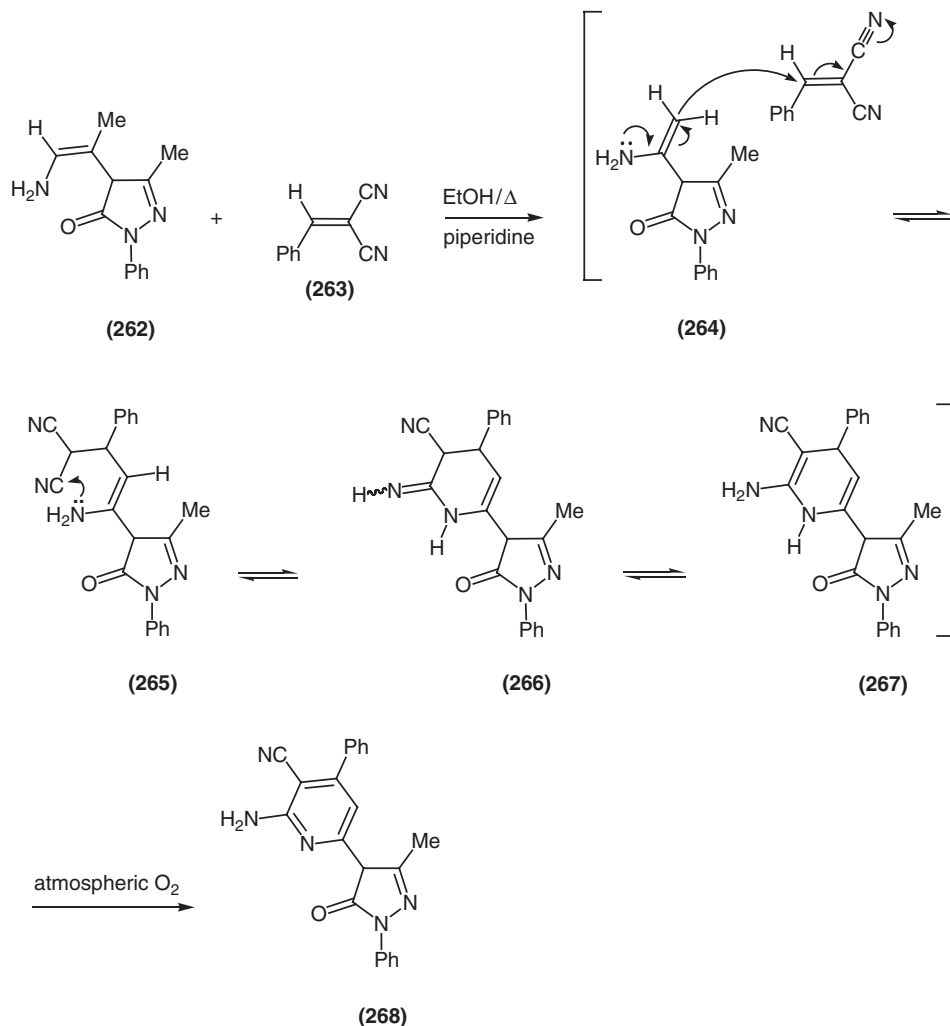
IX. Nucleophilic Substitution

A large variety of substitution reactions are known. The leaving group can be attached directly to the pyrazol-3-one ring or be at the end or inside an aliphatic side chain and less seldom on an aromatic ring. Leaving groups include chloride, bromide, hydroxide and methylthio anions as well as secondary or tertiary amines. The pyrazol-3-one ring may bear nucleophilic groups such as amino, alkyl amino, hydroxy or methyl. Nucleophilic substitution of derivatives of carboxylic acids both directly attached to the pyrazol-3-one ring or at the end of aliphatic side chains is quite common. Ring formation via intramolecular acyl substitution of appropriate side chains has also been reported.

A. OF 4-BROMO(OR 4-HYDROXY)PYRAZOL-3-ONES

Krohn and Stenns (89AP351) (Scheme 72) used a 4% aqueous solution of benzyltrimethylammonium hydroxide containing sodium hydroxide to convert 1,2-dihydro-4-bromopyrazol-3-ones **269a,b** into the 4-hydroxypyrazol-3-ones **270a,b** while Dorn and Ozegowski (98JPR437) demonstrated the ease of displacement of the bromine atom of 3,4-dihydropyrazol-3-one carboxylic acids **271a-c** by thiocyanate and azide anions and by hydroxylamine to afford 4-substituted derivatives **272a-c**.

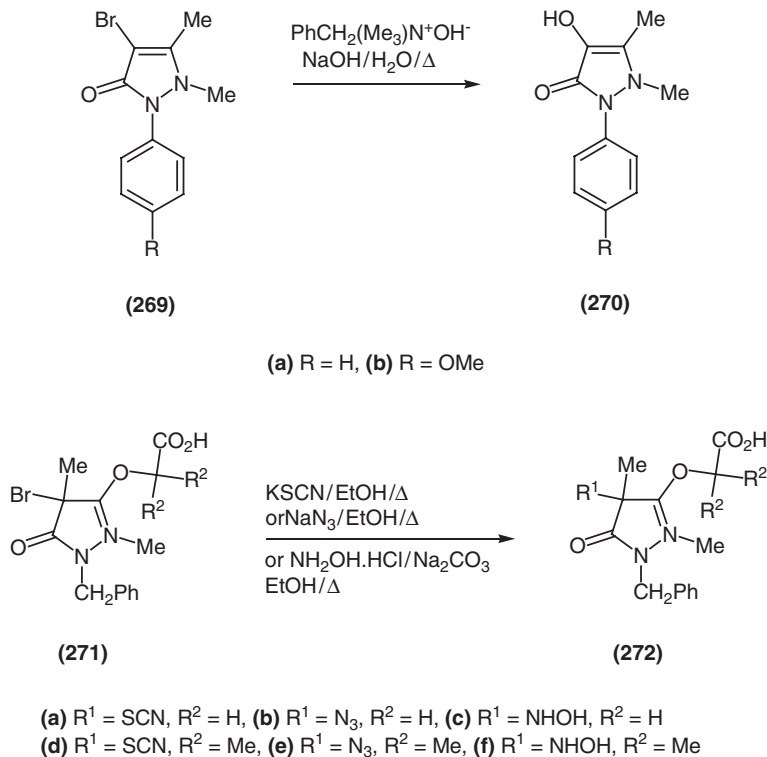
The hydroxyl group of 4-hydroxypyrazol-3-one **273** becomes a leaving group when protonated by dimethylamine hydrochloride in refluxing ethanol. It is plausible that the reaction occurs via displacement of water aided by the mesomeric effect from N-2. Intermediate **274** is then attacked by dimethylamine to give 4-dimethylamino-pyrazol-3-one **275** (72JHC1219) (Scheme 73).



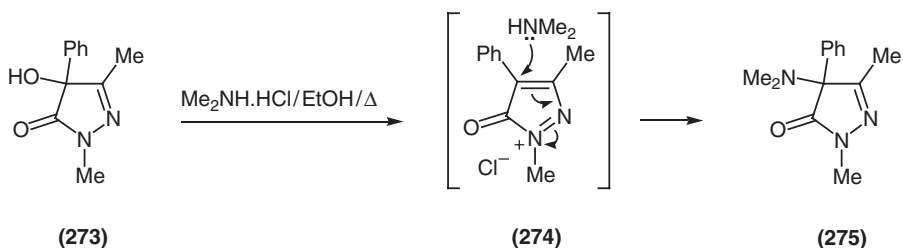
Scheme 71

B. OF 4- OR 5-SUBSTITUTED METHYLPYRAZOL-3-ONES

Bromomethyl-*N,N,N*-trimethylmethanaminium iodide and piperidinomethyl substituents on positions 4 or 5 of pyrazol-3-ones are prone to lose bromide, trimethylamine and piperidine, respectively, by appropriate nucleophiles. Thus, 5-[(2-aminoethylamino)methyl]pyrazol-3-ones **278a–e** and pyrazol-3-ones **280a,b** were obtained in excellent yield by heating 5-bromomethylpyrazol-3-ones **276a–e** with 1,2-diaminoethanes **277a–e** or pyrazol-3-one **276b** with 2-aminobenzene **2789a** or 2-mercaptobenzoic acid **279b** in benzene containing potassium carbonate and copper powder (69CPB490, 70CPB1994, 70CPB2058) (Scheme 74).

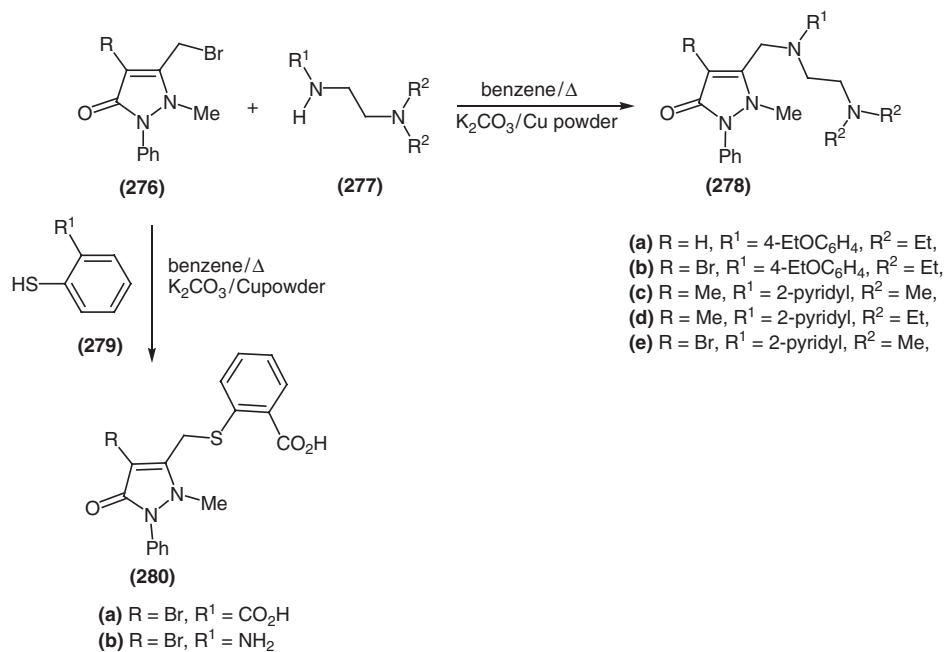


Scheme 72

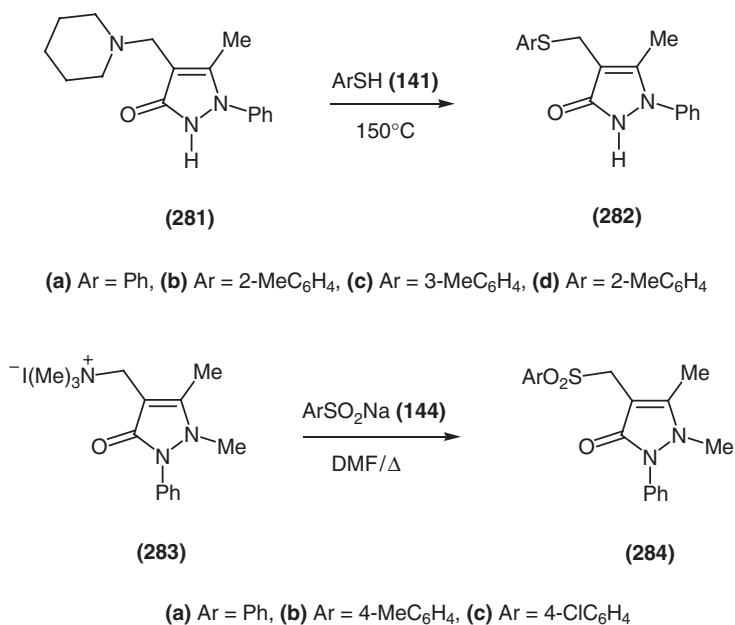


Scheme 73

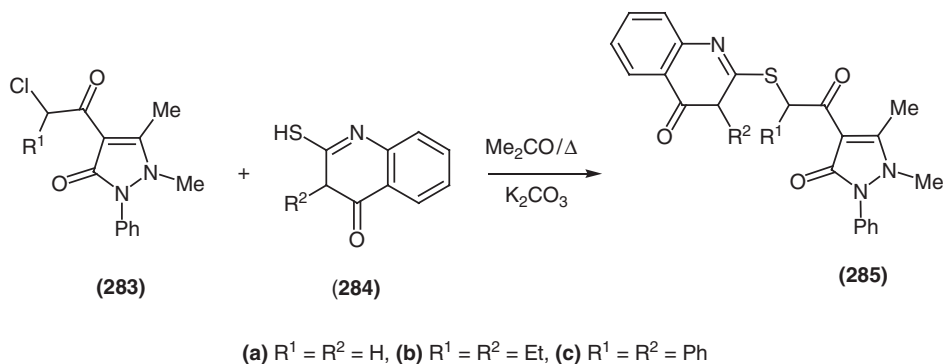
Mustafa et al. (64T531) (Scheme 75) reported that 4-piperidinomethylpyrazol-3-one **281** could be converted into 4-arylthiomethylpyrazol-3-ones **282a–d** by heating at 150 °C with thiols **141a–d**. The yield of pyrazol-3-ones **282a–d** was 70–77%. On the other hand, Messinger (73AP603) (Scheme 75) described the synthesis of 4-(arylsulfonyl)methylpyrazol-3-ones **284a–c** by nucleophilic substitution of Mannich base salts of pyrazol-3-ones **283** with sodium sulfinates **144a–c** in hot DMF. Pyrazol-3-ones **284a–c** were obtained in 82%, 67% and 74% yield, respectively.



Scheme 74



Scheme 75



Scheme 76

C. OF 4-(2-CHLOROACETYL)PYRAZOL-3-ONES OR 3-CHLORO-*N*-(3-OXOPYRAZOL-4-YL)PROPANAMIDES

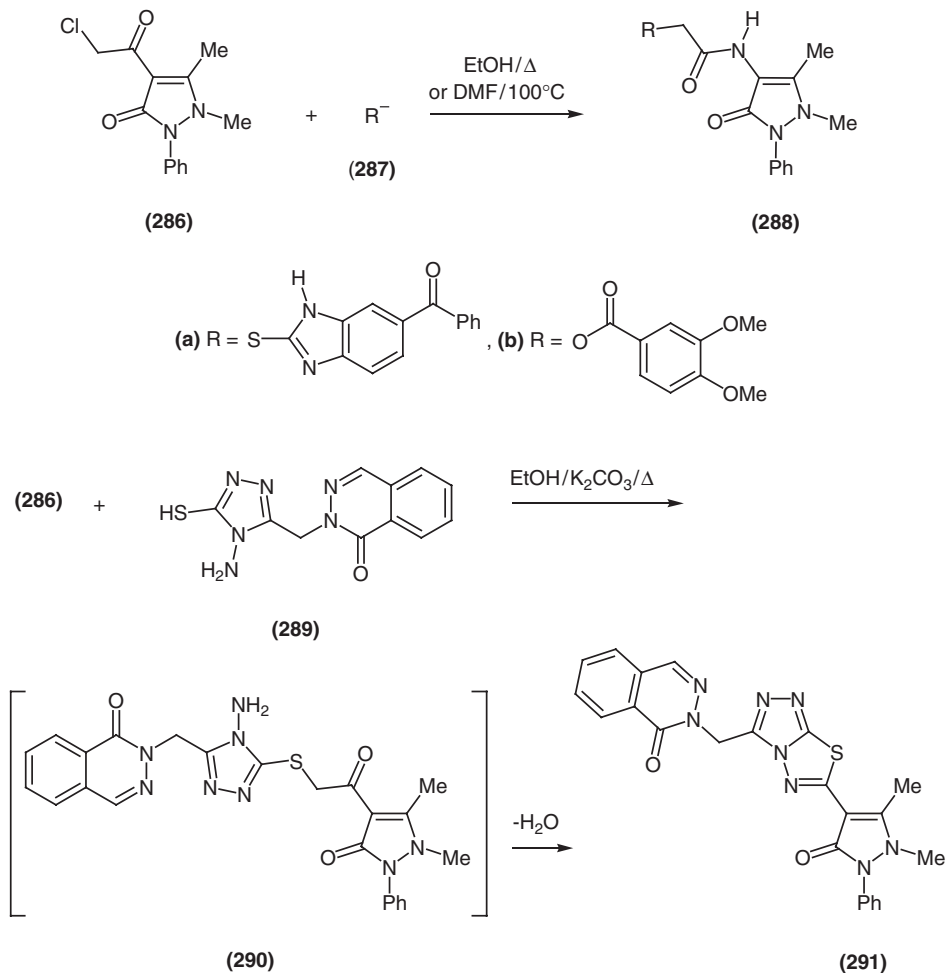
The chlorine atom of 4-(2-chloroacetyl)pyrazol-3-ones **285a–c** was displaced relatively easily by 2-mercapto-3*H*-quinolin-4-ones **286a–c** in boiling acetone containing potassium carbonate to afford the 4-substituted pyrazol-3-ones **287a–c** in good yields (90AP623) (Scheme 76).

There was more interest in this type of functionalization by Hassanein (99PS101), Guersoy et al. (00EJMC359) and Hassanein again in a more recent paper (03PS1987) who used 4-(2-chloroacetyl)pyrazol-3-one **286** as a substrate for substitution with various nucleophiles (Scheme 77). Thus, **286** was reacted with (2-mercapto-3*H*-benzimidazol-5-yl)phenylmethanone **287a** in boiling ethanol, with sodium 3,4-dimethoxybenzoate **287b** in DMF at 100 °C or with 2-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-ylmethyl)-2*H*-phthalazin-1-one **289** in boiling ethanol containing potassium carbonate to yield the corresponding pyrazol-3-ones **288a–b** and **291**, in 63–96% yield. The latter reaction is postulated to occur via intermediate **290** which cyclocondenses.

El-Taweel (04PS1267) (Scheme 78) reported two interesting reactions involving 4-chloro-acetylpyrazol-3-one **286**. The first reaction is similar to the previous one but takes place in aqueous DMF. It involves displacement of chloride ion from **286** by thioacetamides **292a–d** to give sulfide derivatives **293a–d** in good yields. In the second reaction thioacetamides **294a,b** displace chloride ion from **286** to produce intermediates **295** that cyclocondense to the corresponding pyrazol-3-ones **296a,b**.

When 4-(2-chloroacetyl)pyrazol-3-one **297** was heated with 4-substituted-5-furan-2-yl[1,2,4]-triazole-3-thiones **298a–e** in acetone containing potassium carbonate, substitution occurred to give the corresponding pyrazol-3-ones **299a–e** in 63–96% yield (03M465) (Scheme 79).

The chlorine atom of 3-chloropropanamides **300a–w** was displaced relatively easily by amines **301a–w** in boiling ethanol to afford the 4-substituted pyrazol-3-ones **302a–w** in good yields (68AF850) (Scheme 80).



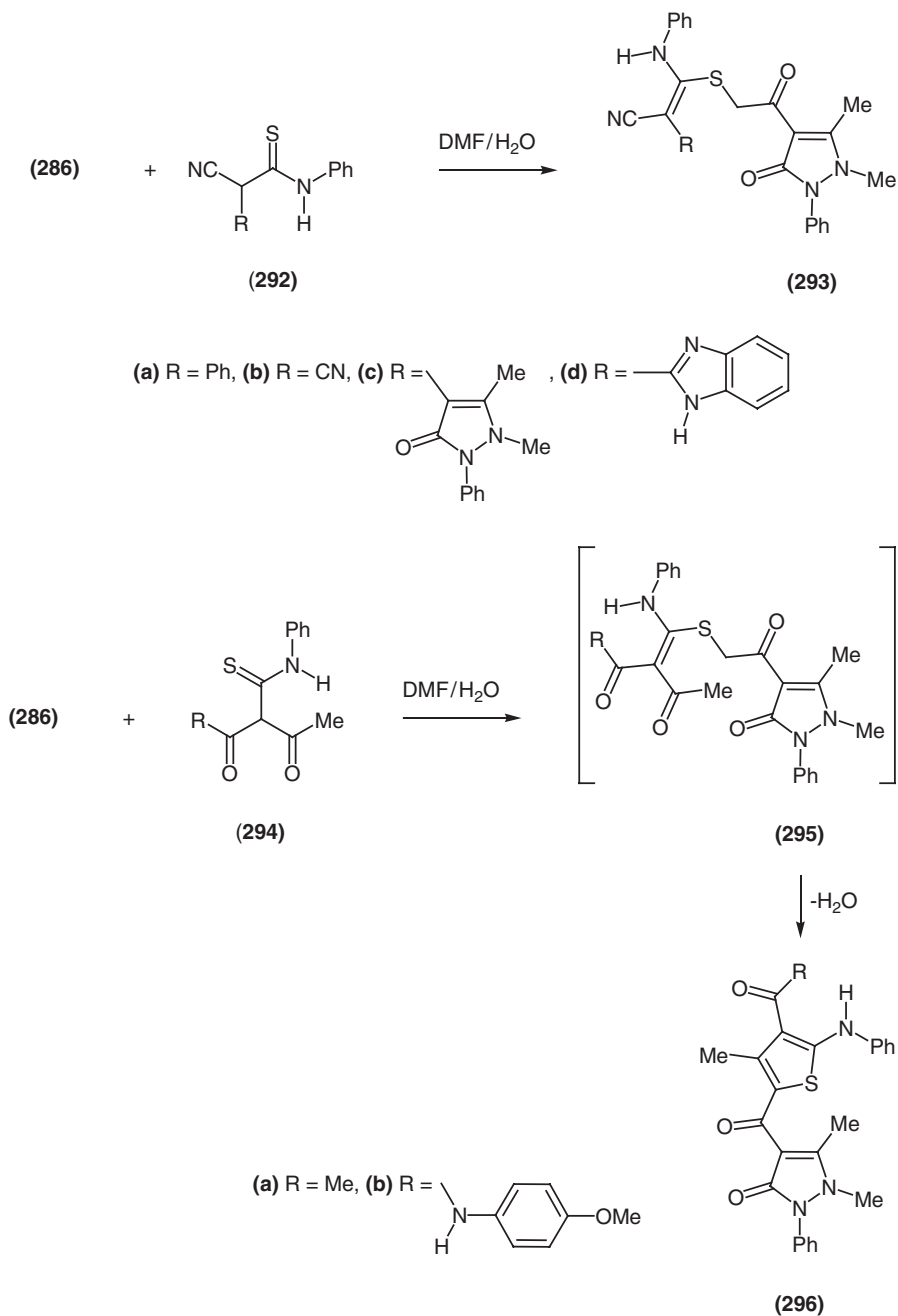
Scheme 77

D. OF 2-(ARYLHALO)PYRAZOL-3-ONES

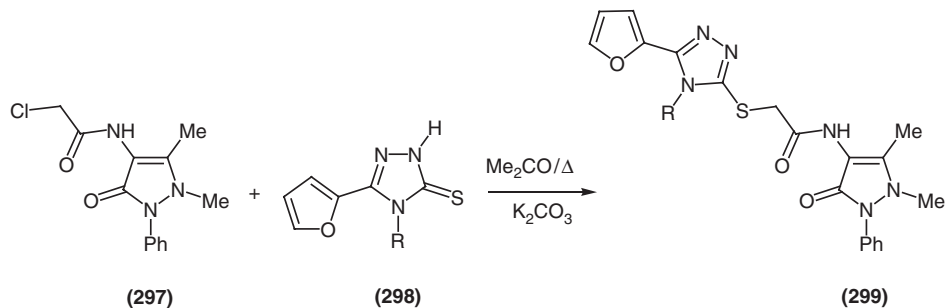
The chloro group of 2-(2-chloro-5-nitrophenyl)pyrazol-3-one **303** was displaced by morpholine which was used both as solvent and nucleophile. The reaction was reported by Ainsworth and Suschitzky (67JCS(C)1003) (Scheme 81) and gave 2-(2-morpholin-4-yl-5-nitrophenyl)pyrazol-3-one **304**.

E. WITH 4- OR 5-AMINO- OR 4-(3-AMINOPROPYL)PYRAZOL-3-ONES

An amino group at position 4 or 5 of the pyrazol-3-one ring is a good nucleophile that can displace halogens from aromatic rings, β -amino groups from α,β -unsaturated esters, *N*-methylaniline from benzaminium iodides and the hydroxyl

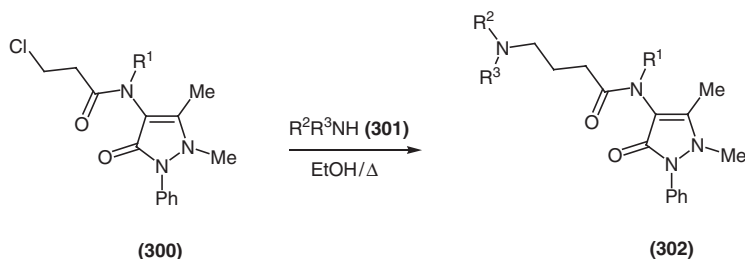


Scheme 78



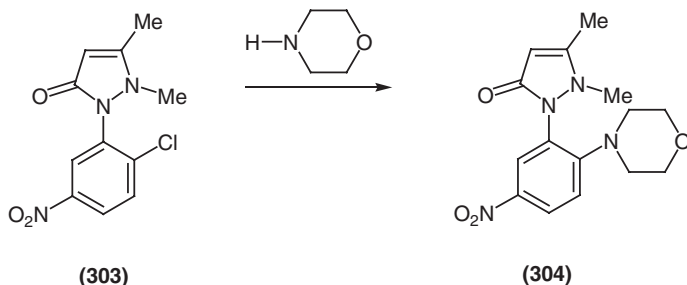
(a) R = Me, (b) R = *n*-Bu, (c) R = Ph, (d) R = 4-ClC₆H₄ or (e) R = 4-BrC₆H₄

Scheme 79

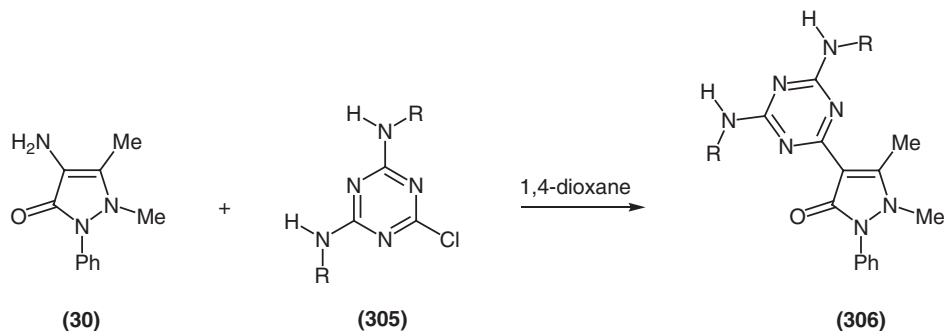


(a) R² = R³ = Et, (b) R¹ = H, R² = R³ = CH₂CH=CH₂, (c) R¹ = H, R² = H, R³ = 4-EtOC₆H₄, (d) R¹ = R² = H, R³ = Et, (e) R¹ = H, R² = R³ = (CH₂)₅, (f) R¹ = H, R² = R³ = CHMe(CH₂)₄, (g) R¹ = H, R² = R³ = CH₂CH(Me)(CH₂)₃, (h) R¹ = H, R² = R³ = (CH₂)₂CH(Me), (i) R¹ = H, R² = R³ = (CH₂)₂CH(Et)(CH₂)₂, (j) R¹ = H, R² = R³ = (CH₂)₂CH(Et)(CH₂)₂, (k) R¹ = H, R² = R³ = (CH₂)₂CH(CHMe)(CH₂)₂, (l) R¹ = H, R² = R³ = (CH₂)₂CH(C₆H₁₁)(CH₂)₂, (m) R¹ = H, R² = R³ = (CH₂)₂CH(Ph)(CH₂)₂, (n) R¹ = H, R² = R³ = CH₂CHC(Ph)(CH₂)₂, (o) R¹ = H, R² = R³ = (CH₂)₂O(CH₂)₂, (p) R¹ = H, R² = R³ = (CH₂)₂N(Me)(CH₂)₂, (q) R¹ = H, R² = R³ = (CH₂)₂N(Ph)(CH₂)₂, (r) R¹ = Me, R² = R³ = (CH₂)₅, (s) R¹ = Me, R² = R³ = (CH₂)₂CH(Ph)(CH₂)₂, (t) R¹ = Me, R² = R³ = (CH₂)₂O(CH₂)₂, (u) R¹ = CH(Me)₂, R² = R³ = (CH₂)₅, (v) R¹ = CH(Me)₂, R² = R³ = CH₂CH(Me)(CH₂)₂, (w) R¹ = CH(Me)₂, R² = R³ = (CH₂)₆

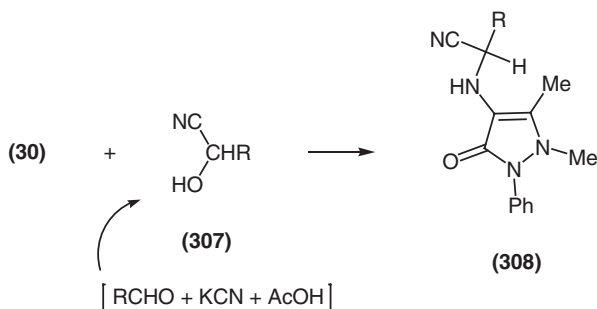
Scheme 80



Scheme 81



(a) R = Ph, (b) R = 2-MeC₆H₄, (c) R = 3-MeC₆H₄, (d) R = 4-MeC₆H₄, (e) R = 2-MeOC₆H₄,
 (f) R = 3-MeOC₆H₄, (g) R = 4-MeOC₆H₄, (h) R = 4-EtO₂CC₆H₄, (i) R = 4-AcC₆H₄, (j) R = 2-ClC₆H₄,
 (k) R = 3-ClC₆H₄, (l) R = 4-ClC₆H₄, (m) R = 4-BrC₆H₄, (n) R = 2-NO₂C₆H₄, (o) R = 3-NO₂C₆H₄,
 (p) R = 4-NO₂C₆H₄.

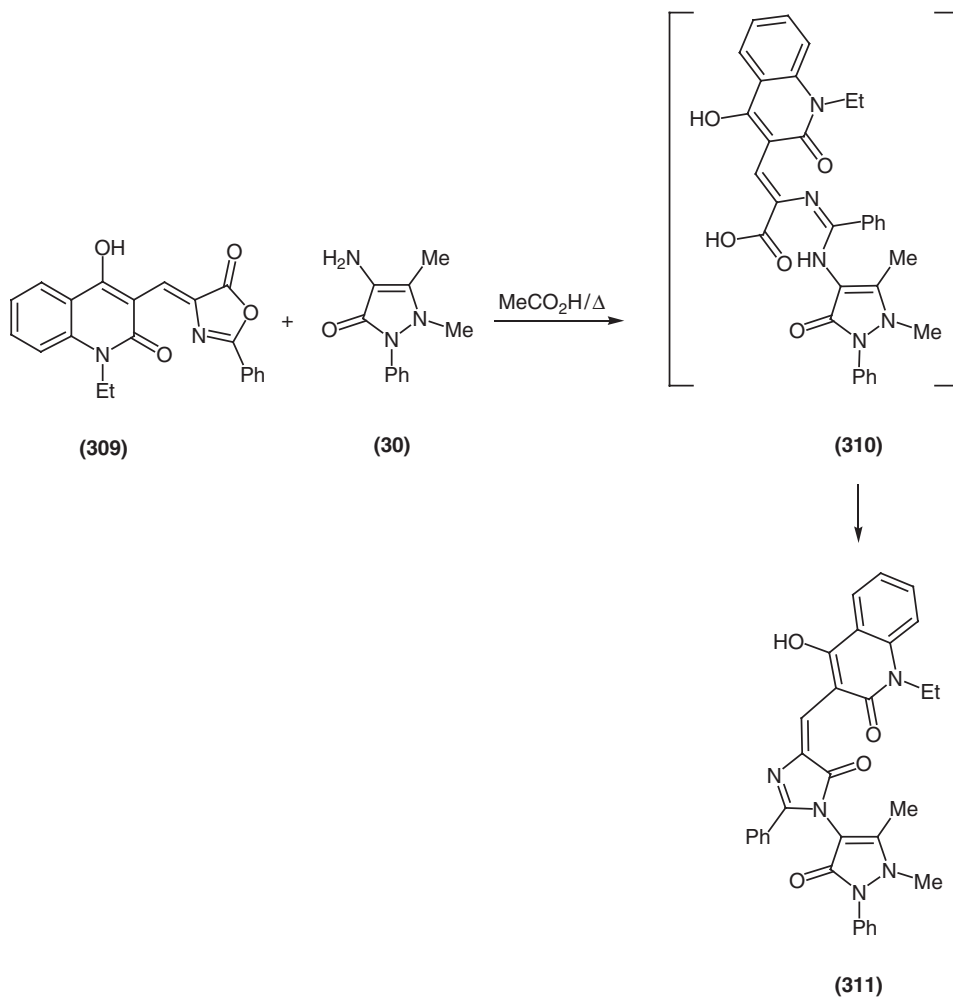


(a) R = Me₂CHCH₂, (b) R = PhCH=CHCH₂, (c) R = Ph, (d) R = 2-HOC₆H₄,
 (e) R = 3-HOC₆H₄, (f) R = 4-HOC₆H₄, (g) R = 4-MeOC₆H₄, (h) R = 4-OH,
 3-MeOC₆H₃, (i) R = 3-BrC₆H₄, (j) R = 3,5-(Br)₂C₆H₄, (k) R = 2-ClC₆H₄, (l)
 R = 4-ClC₆H₄, (m) R = 4-Me₂NC₆H₄, (n) R = 3-NO₂C₆H₄, (o) R = 4-NO₂C₆H₄,
 (p) R = 2-furfuryl

Scheme 82

group from NCCH(R)OH. Mehta and Parekh (86JIC414) (Scheme 82) synthesized a large number of 4-[(4,6-diarylamino-1,3,5-triazin-2-yl)amino]pyrazol-3-ones **306a–q** by heating pyrazol-3-one **30** and 2-chloro-4,6-diarylamino-1,3,5-triazine **305a–q** in 1,4-dioxane. The products **306a–q** were obtained in yields ranging from 70% to 91%. In route to the synthesis of (3-oxopyrazol-4-yl)sydnonimine hydrochlorides Kamdar et al. (87JIC420) prepared 4-(α -cyanobenzyl-amino)pyrazol-3-ones **308a–p** using RC(CN)(OH)H, prepared by adding the appropriate aldehyde to aqueous potassium cyanide and acetic acid, with pyrazol-3-one **30**. The yield of **308a–p** ranges from 58% to 82%.

By heating together 3-(5-oxooxazol-4-ylidenemethyl)-1*H*-quinolin-2-one **309** and 4-aminopyrazol-3-one **30** in glacial acetic acid, El-Taweel and co-workers (01BCF287) (Scheme 83) obtained the pyrazol-3-one **311**. This is the product of

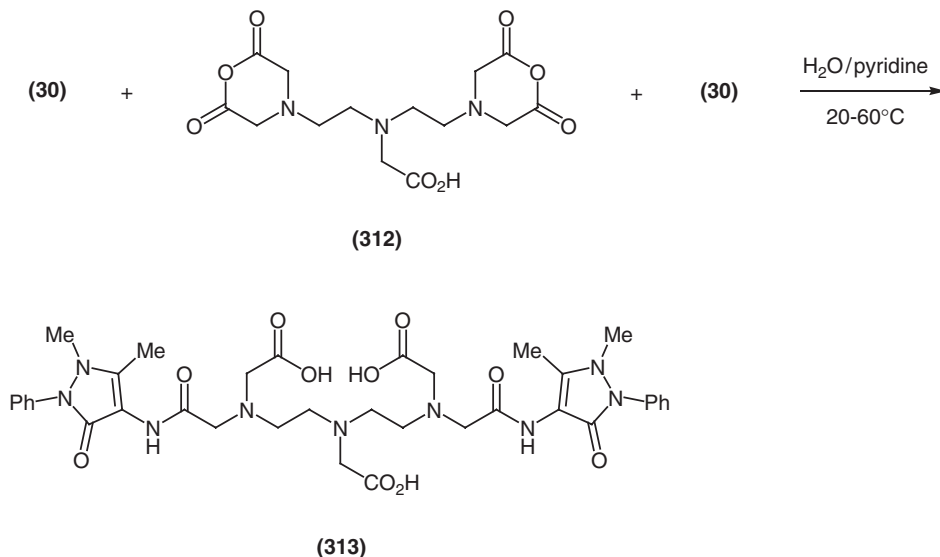


Scheme 83

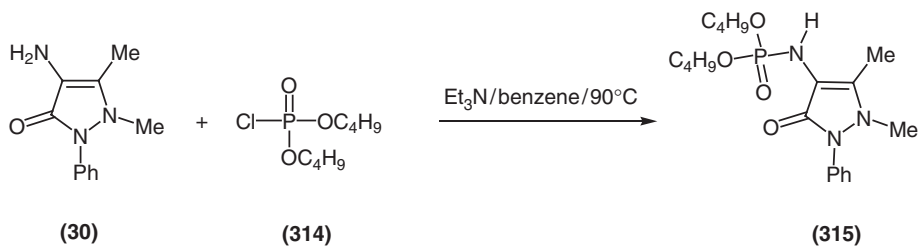
initial attack by the amino group of **30** at position 2 of the oxazolin-5-one, ring opening to give intermediate **310** and then ring closure by acyl substitution.

Ring opening of the anhydride group in the two rings of *bis*[2-(2,6-dioxomorpholin-4-yl)-ethyl]-amino}acetic acid **312** by two equivalents of 4-aminopyrazol-3-one **30** required only heating up to 60 °C in aqueous pyridine to give the *bis*pyrazol-3-one-4-amide derivative **313** (03SC2811) (Scheme 84).

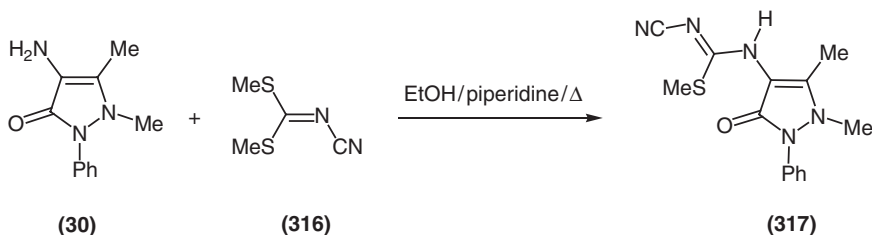
In four reports (86ZC301, 03BMC2285, 04S1655, 04SC805) 4- or 5-amino- or 4-(3-aminopropyl)- pyrazol-3-ones were used in nucleophilic acyl-type substitutions with dibutyl phosphorochloridate, *N*-cyanodithiocarbonimidic acid dimethyl ester, a (thioxomethanesulfinyl)methanethione derivative and (*E/Z*)-3,5-dimethylpyrazole-1-*N*-nitrocarboxamide. Thus, substitution of chloride ion from dibutyl



Scheme 84



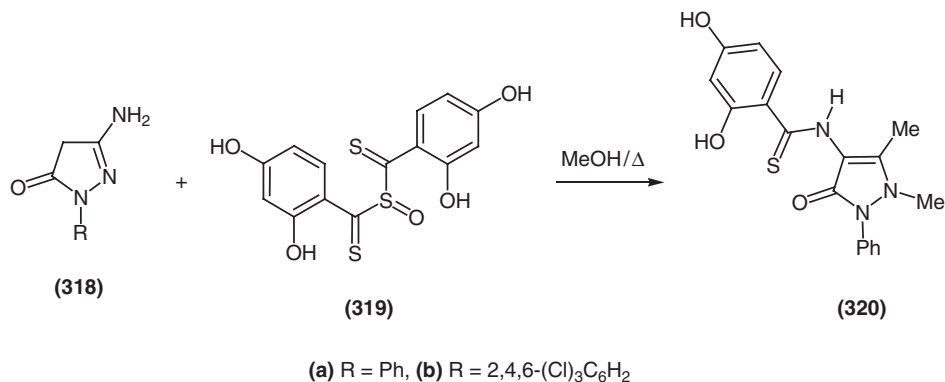
Scheme 85



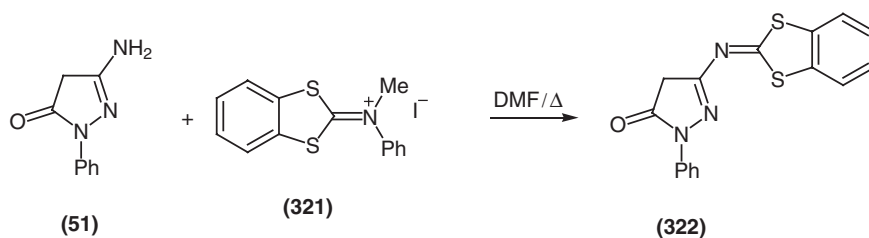
Scheme 86

phosphorochloridate **314** by the amino group of 4-aminopyrazol-3-one **30** in benzene containing triethylamine at 90°C , afforded pyrazol-3-one **315** in 90% yield (86ZC301) (Scheme 85).

Alqaradawi and Elgemeie (04SC805) (Scheme 86) showed that the methylthiolate ion from *N*-cyanodithiocarbonimidic acid dimethyl ester **316** can be displaced by the



Scheme 87



Scheme 88

amino group of 4-aminopyrazol-3-one **30** by heating in ethanol containing piperidine, to give pyrazol-3-one **317**.

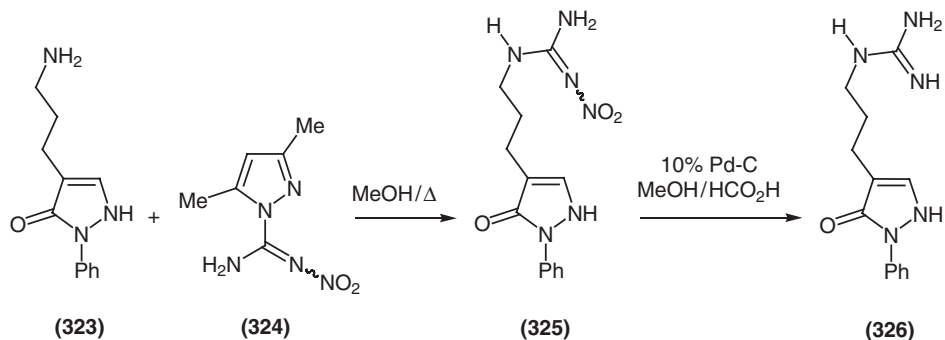
An uncommon substitution was described by Matysiak and Niewiadomy (03BMC2285) (Scheme 87) who obtained *N*-(3-oxopyrazol-4-yl)thiobenzamide **320** by heating in methanol 5-aminopyrazol-3-ones **318** with (2,4-dihydroxyphenyl)-[(2,4-dihydroxyphenyl)thioxomethanesulfinyl]methanethione **319**.

An example of nucleophilic substitution involving a quaternary ammonium salt such as [*N*-(1,3-benzodithiol-2-ylidene)]-*N*-methylbenzaminium iodide **321** and 5-aminopyrazol-3-one **51** was described by Sprague and Heikes (79S297) (Scheme 88). The reaction required heating in dry DMF at 120 °C with anhydrous sodium carbonate but iminobenzothiadiazolepyrazol-3-one **322** was obtained in only 34% yield.

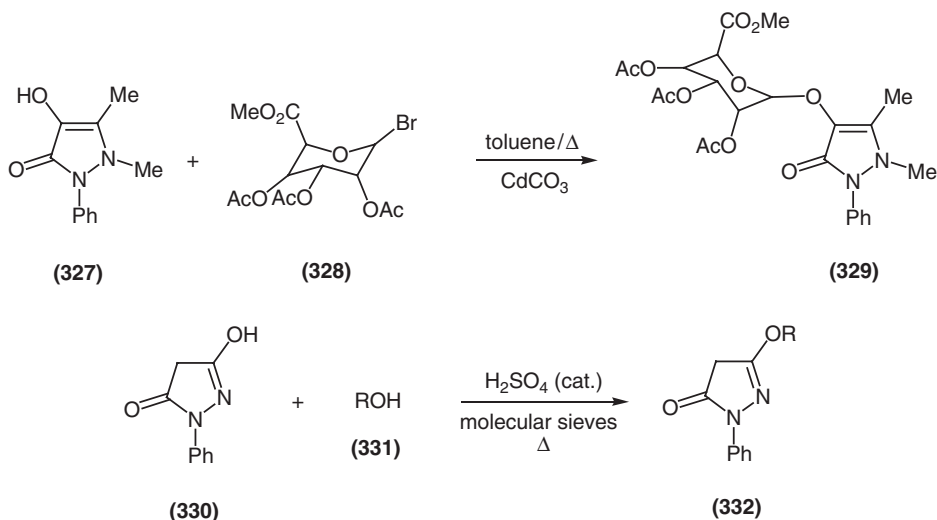
The aliphatic amino group of 4-(3-aminopropyl)pyrazol-3-one **323** was nucleophilic enough to displace 3,5-dimethyl-1*H*-pyrazole from (*E/Z*)-3,5-dimethylpyrazole-1-*N*-nitrocarboxamide **324** by heating in methanol. The product **325** was then catalytically hydrogenated in methanol and formic acid to give *N*-[3-(3-oxopyrazol-4-yl)propyl]guanidine **326** after cleavage of the nitro group (04S1655) (Scheme 89).

F. WITH 4- OR 5-HYDROXYPYRAZOL-3-ONES

The hydroxy group in positions 4 and 5 of 1,2-dihydro- and 2,4-dihydropyrazol-3-ones, respectively, has been used successfully by Krohn and Stens (89AP351) and



Scheme 89

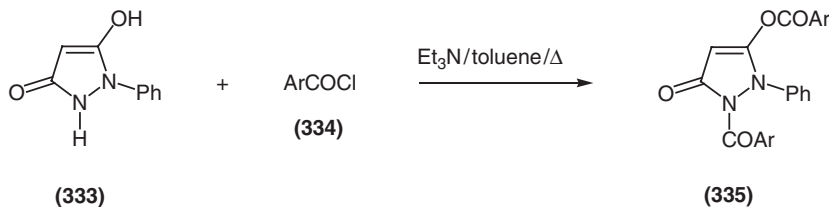


(a) R = Me, (b) R = Et, (c) R = *n*-Pr, (d) R = *i*-Pr, (e) R = *n*-Bu, (f) R = *sec*-Bu, (g) R = allyl

Scheme 90

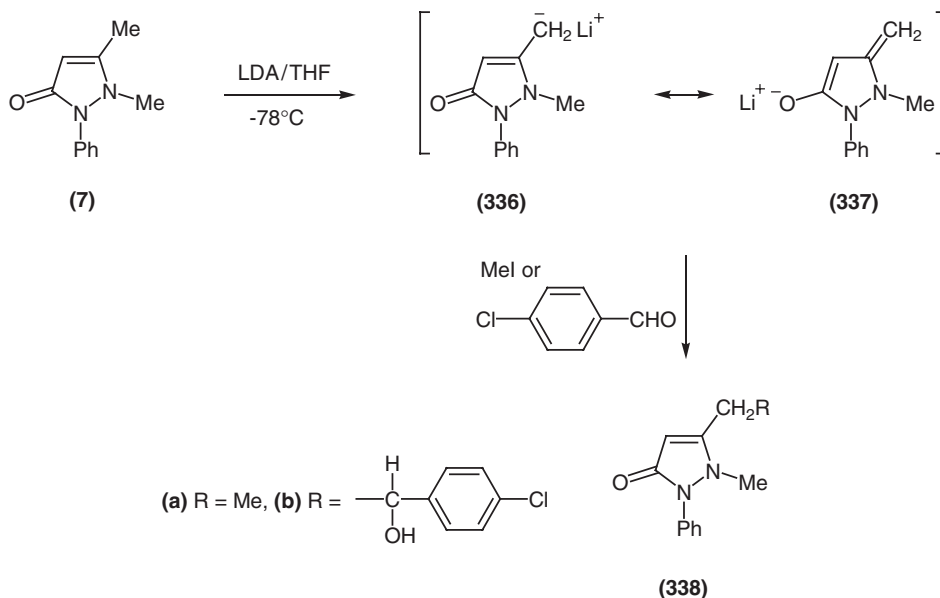
Molinari and Oliva (96JHC479) in nucleophilic substitutions (Scheme 90). The glycosidation of 4-hydroxypyrazol-3-one **327** by bromosugar **328** required heating in toluene in the presence of cadmium carbonate as catalyst. Pyrazol-3-one sugar **329** was obtained in 69% yield. On the other hand, 5-hydroxypyrazol-3-one **330** displaced water from primary, secondary and allylic alcohols **331a–g** by heating to reflux under catalytic acidic conditions and in the presence of 3 Å molecular sieves. 5-Alkoxy-pyrazol-3-ones **332a–g** were obtained in 24–90% yield.

5-Hydroxypyrazol-3-one **333** formed the O- and N-acylated pyrazol-3-ones **335a–e** with a slight excess of two equivalents of aroyl chlorides **334a–e** and triethylamine in boiling dry toluene (98M871) (Scheme 91).



(a) Ar = Ph, (b) Ar = 2-ClC₆H₄, (c) Ar = 4-ClC₆H₄, (d) Ar = 4-MeC₆H₄, (e) Ar = 2,4-(Cl)₂C₆H₃

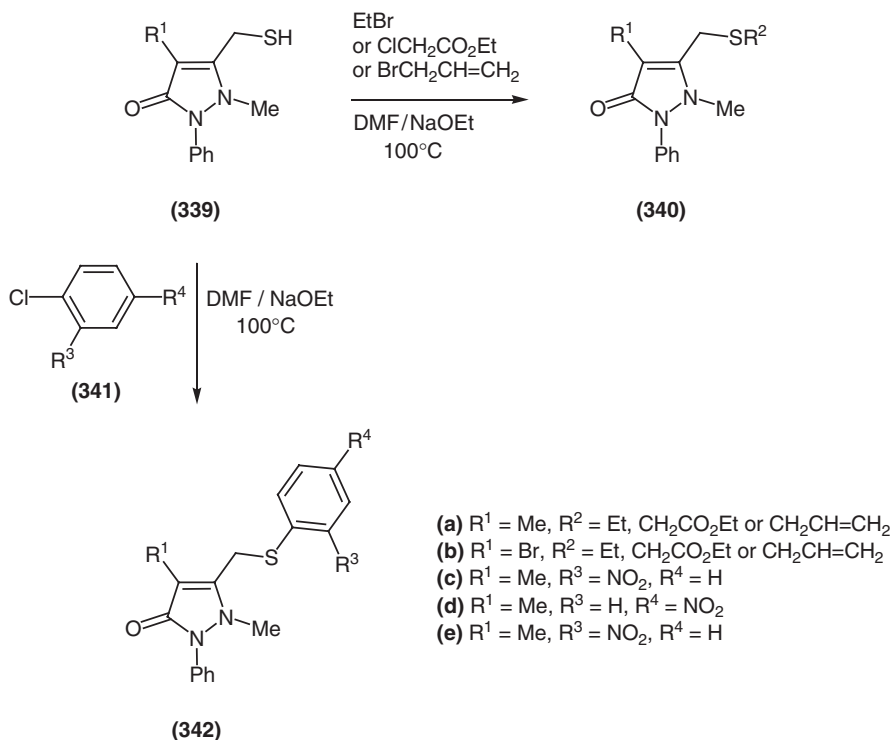
Scheme 91



Scheme 92

Under strongly basic conditions such as lithium diisopropylamide (LDA) in anhydrous tetrahydrofuran at -78°C , pyrazol-3-one **7** is lithiated at the methyl group of position 5 to form ionic species **336**, which is stabilized by conjugation with the carbonyl group to anionic species **337**. The carbanion intermediate **336** is more stable and reacts with methyl iodide or 4-chlorobenzaldehyde to give the corresponding substitution and addition products **338a,b** in 82% and 86% yield, respectively (95T10941) (Scheme 92).

Ito et al. (69CB1309, 70CPB2058) (Scheme 93) published in two consecutive papers substitution reactions by 5-mercaptomethylpyrazol-3-ones **339a,b** with ethyl bromide, ethyl chloroacetate, allyl bromide or aryl halides **341c–e**. The preferred conditions involved heating in DMF at 100°C in the presence of sodium ethoxide. The products, 5-alkylsulfanylmethylpyrazol-3-ones **340a,b** and 5-arylsulfanylmethylpyrazol-3-one **342c–e**, were obtained in 80–90% yield.



Scheme 93

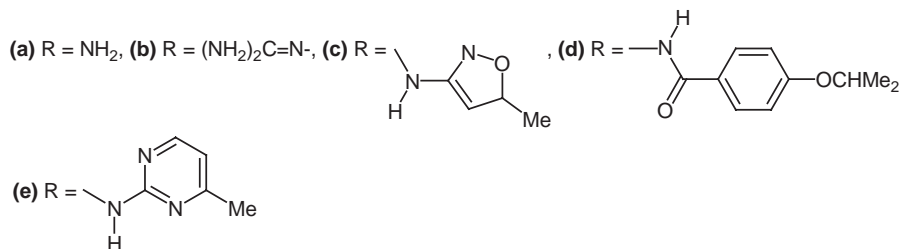
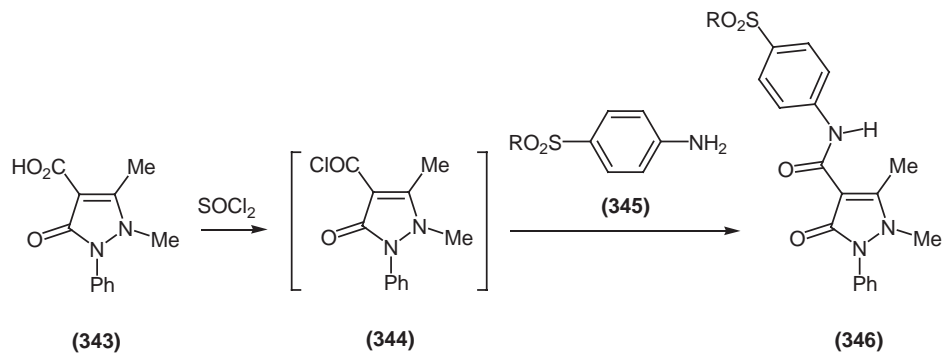
G. OF ACYL OR IMINE SUBSTITUTED PYRAZOL-3-ONES

3-Oxopyrazole-4-carboxylic acid **343** was treated with thionyl chloride to give the acid chloride **344** which was not isolated but treated with sulfonamides **345a–e** to afford the pyrazol-3-ones **346a–e** in good yield (76PHA149) (Scheme 94).

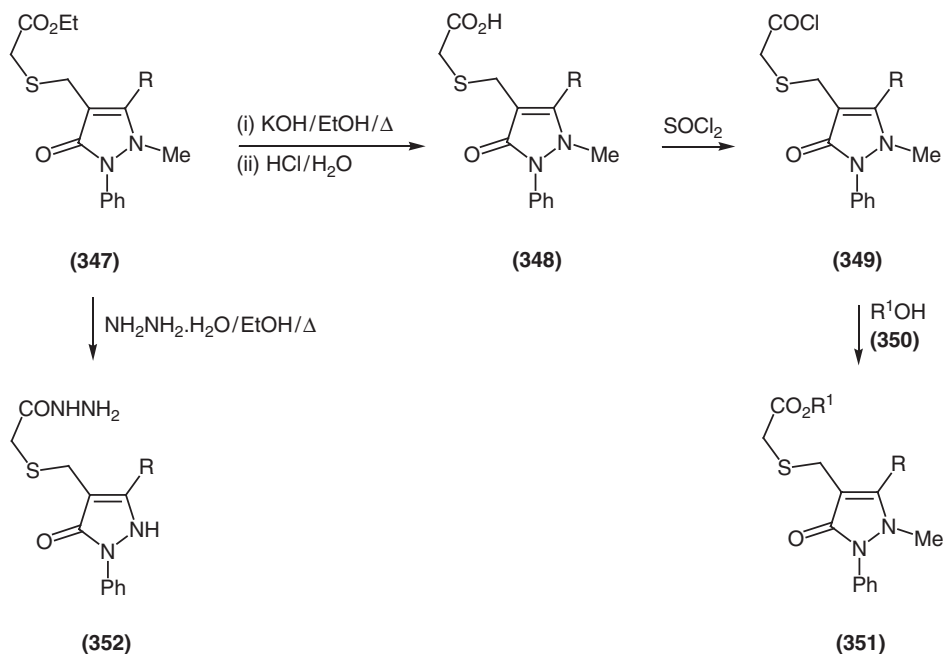
The 5-ethoxycarbonylmethylthiomethylpyrazol-3-ones **347a,b** have undergone several useful transformations (69CB1309) (Scheme 95). The ester group of **347a,b** were hydrolyzed to the corresponding acids **348a,b** by heating in ethanolic potassium hydroxide. The acids **348a,b** were converted into the acid chlorides **349a,b** by hot thionyl chloride. The latter were then transformed into the esters **351c** by heating with the appropriate alcohols **350c**. On the other hand, esters **347a,b** with hydrazine hydrate, afforded the corresponding hydrazides **352a,b** in 80% and 75% yield, respectively.

Pyrazol-3-one ethyl esters **353a,b** were transesterified to the corresponding methyl esters **354a,b** by heating first in 15% aqueous hydrochloric acid to obtain the corresponding acids and then heating the acids in saturated methanolic hydrogen chloride (82JOC214) (Scheme 96).

Replacement of the dimethylamino group of three molecules of dimethyl(3-oxopyrazol-4-ylmethylene)ammonium perchlorate **355** by the three amino groups of one molecule of *tris*(2-aminomethyl)amine **356** in boiling methanolic sodium methoxide, gave the *tris*pyrazol-3-one amine **357**, in 73% yield (03IJC(A)318) (Scheme 97).

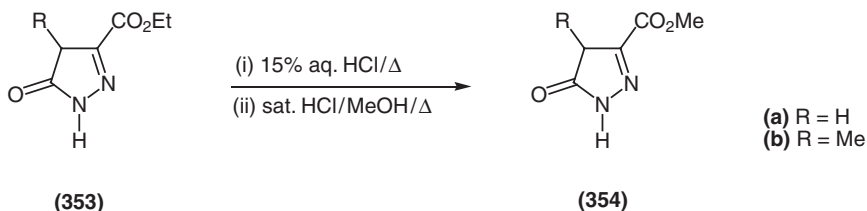


Scheme 94

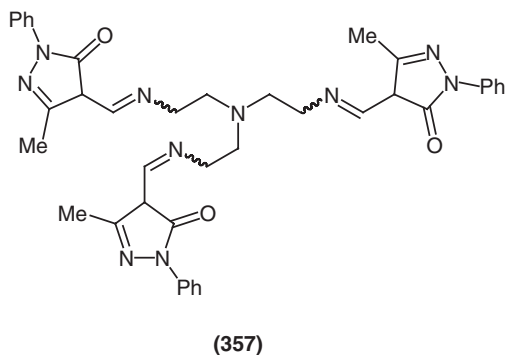
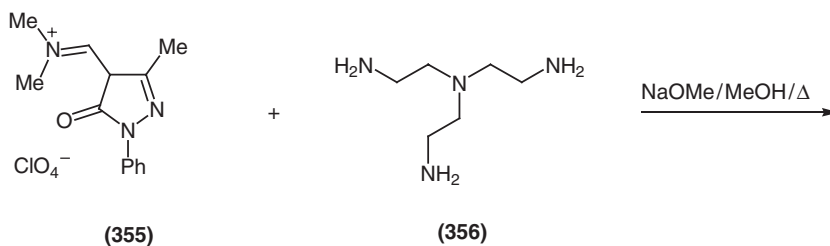


(a) $\text{R} = \text{Me}$, **(b)** $\text{R} = \text{Br}$, **(c)** $\text{R} = \text{Me}$ or Br , $\text{R}^1 = \text{Me}$, $\text{CH}(\text{Me})_2$, $\text{CH}_2\text{CH}(\text{Me})_2$, or $(\text{CH}_2)_2\text{Me}_2$

Scheme 95



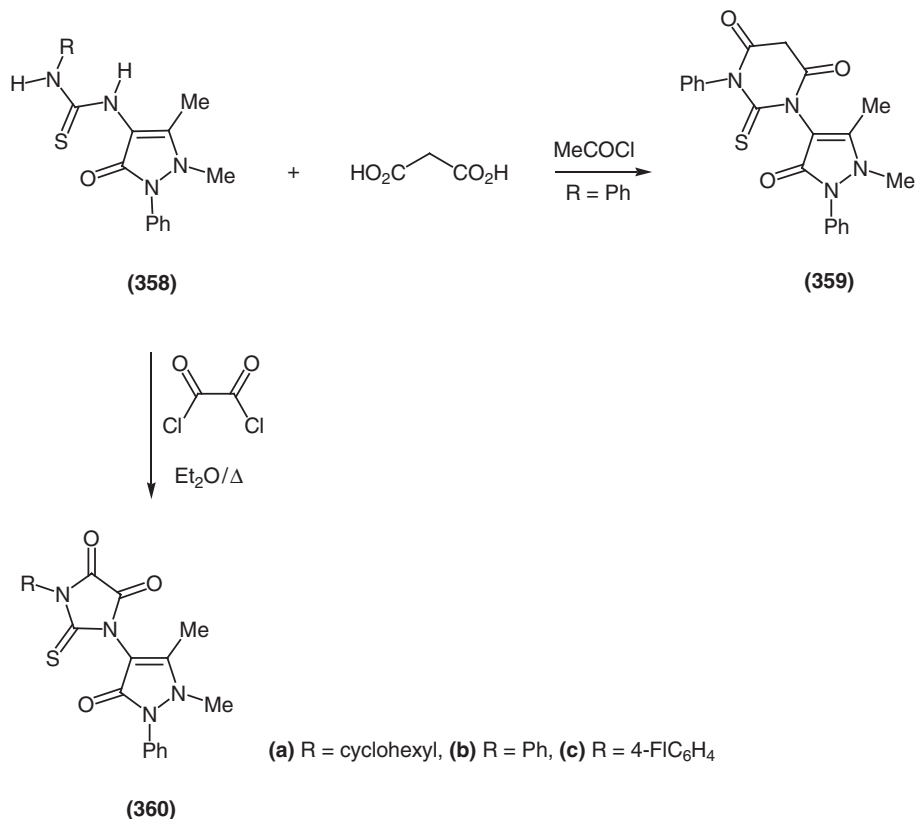
Scheme 96



Scheme 97

H. WITH 1-(3-OXOPYRAZOL-4-YL)-3-SUBSTITUTED THIOUREAS

1-(3-Oxopyrazol-4-yl)-3-phenylthiourea **358** with malonic acid in acetyl chloride afforded, after consecutive inter and intra acyl substitutions on *in situ* generated malonic acid dichloride, 1-(3-oxopyrazol-4-yl)-2-thioxopyrimidine-4,6-dione **359** (03IJC(B)2006) (Scheme 98). On the other hand, treatment of 1-(3-oxopyrazol-4-yl)-3-substituted thioureas **358a–c** with oxalyl dichloride in refluxing diethyl ether resulted in a similar type of cyclization and produced 1-(3-oxopyrazol-4-yl)-3-substituted-2-thioxoimidazolidine-4,5-diones **360a–c** (03IJC(B)2853).



Scheme 98

X. Solvolysis

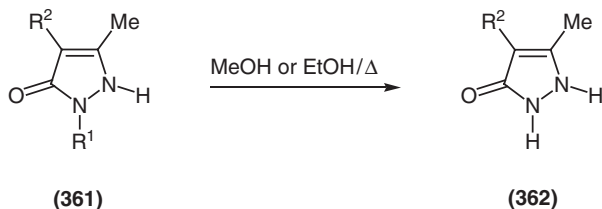
A. OF CARBONYL AND ARYLSULFONYLPYRAZOL-3-ONES

Mild solvolytic cleavage of 2-acetyl, 2-aminocarbonyl, alkoxycarbonyl or 2-arylsulfonylpyrazol-3-ones **361a–c** by boiling in methanol or ethanol for several hours affords the corresponding pyrazol-3-ones **362a–c** (96T1579, 97T5617, 97TL2329, 01T2031) (Scheme 99).

Removal of the acetyl group from *N*-(3-oxopyrazol-2-yl)acetamides **363a,b** with anhydrous hydrazine yielded the 2-aminopyrazol-3-ones **364a,b** (81JHC957) (Scheme 100).

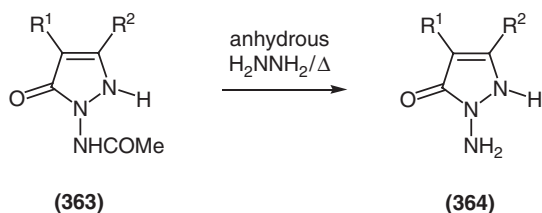
Treatment of pyrazol-3-one **365** with aqueous sodium hydroxide followed by acidification resulted in the acid **366** in 73% yield (88JHC139) (Scheme 101).

Boc-deprotection and hydrolysis of the ester group of pyrazol-3-one **334** in boiling trifluoroacetic acid gave the pyrazol-3-one amino acid **335** in only 27% yield (99EJMC967) (Scheme 102).



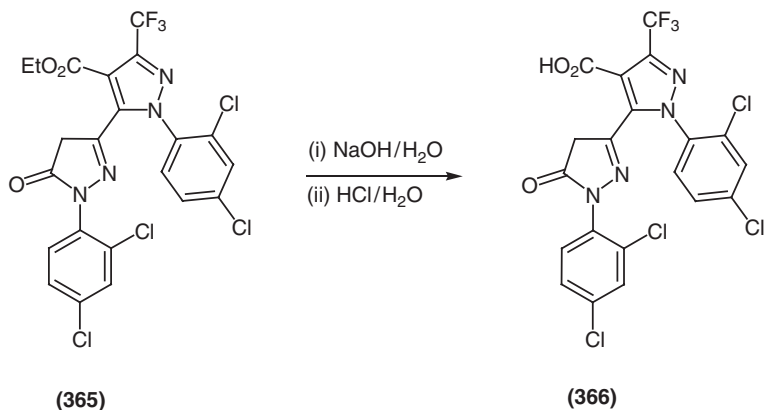
(a) $R^1 = \text{CONHPh}$, $R^2 = \text{SCOPh}$, (b) $R^1 = \text{CO}_2\text{Me}$, $\text{CO}_2\text{Bu-}t$, CONH_2 or CONHPh , $R^2 = \text{MeO}$, EtO , PhO , $4\text{-NO}_2\text{C}_6\text{H}_4$ or $\text{EtCO}_2\text{CH}_2\text{S}$, (c) $R^1 = \text{CONH}_2$, $R^2 = \text{N}(\text{Me})\text{CH}_2\text{CO}_2\text{Et}$

Scheme 99



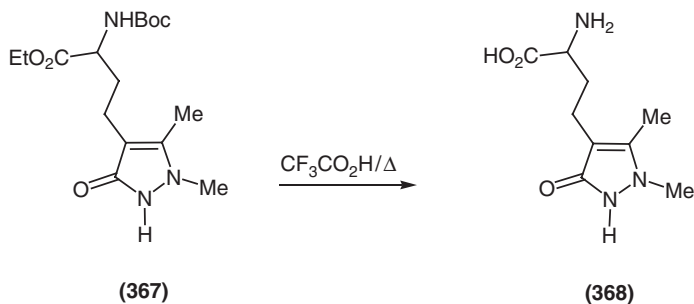
(a) $R^1 = \text{Ph}$, $R^2 = \text{Me}$, (b) $R^1 = \text{Me}$, $R^2 = \text{Ph}$

Scheme 100

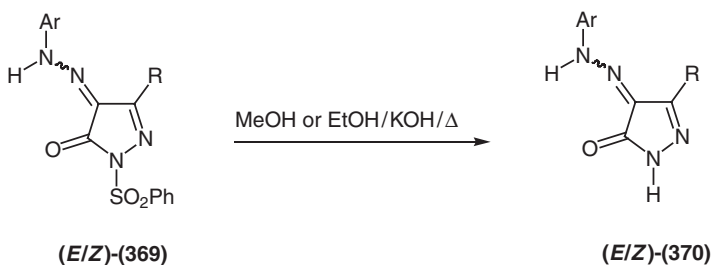


Scheme 101

Desulfonation of (*E/Z*)-2-phenylsulfonylpyrazol-3-ones **369a,b** does not occur using the mild conditions described earlier but requires the addition of potassium hydroxide to the methanolic or ethanolic solution. The hydrazone remained unaffected and the products (*E/Z*)-5-phenyl(or phenylamino)-4-(arylhydrazono)pyrazol-3-ones **370a,b** were obtained in 60–85% yield (85JIC54) (Scheme 103).



Scheme 102



(a) R = Ph, Ar = Ph, (b) R = NPh, Ar = Ph, 2-MeC₆H₄, 4-MeC₆H₄ or 4-MeOC₆H₄

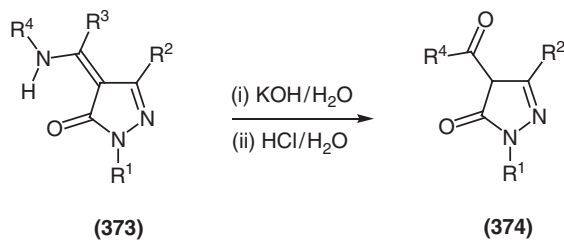
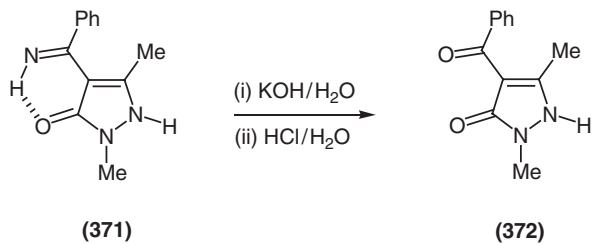
Scheme 103

B. OF 4-(IMINOPHENYLMETHYL OR PHENYLAMINOMETHYLENE)PYRAZOL-3-ONES

The iminophenylmethyl or phenylaminomethylene groups in pyrazol-3-ones **371a** or **373b** were hydrolyzed by heating in 10–20% aqueous potassium hydroxide to afford after acidification, the corresponding 4-hydroxy(phenyl)methylidene-, 4-acetyl- or 4-formylpyrazol-3-ones **372a** or **374b,c** in near quantitative yield (73CB332, 74CPB207, 89JPS239) (Scheme 104).

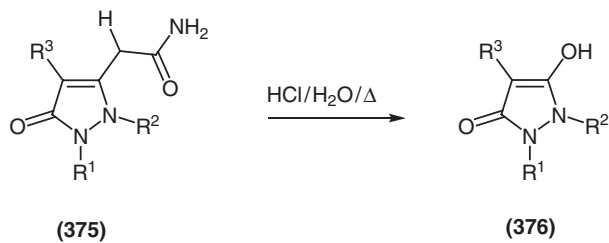
C. OF (5-OXOPYRAZOL-3-YL)ACETAMIDE OR 4,4-(DIMORPHOLIN-4-YL)PYRAZOL-3-ONE

The hydrolytic removal of the acetamide group from pyrazol-3-ones **375a–c** and the morpholino groups from pyrazol-3-one **377** was achieved by heating in aqueous hydrochloric acid and gave 5-hydroxypyrazol-3-ones **376a–c** and pyrazol-3,4-dione **378**, respectively (65LA134, 68M2157) (Scheme 105).

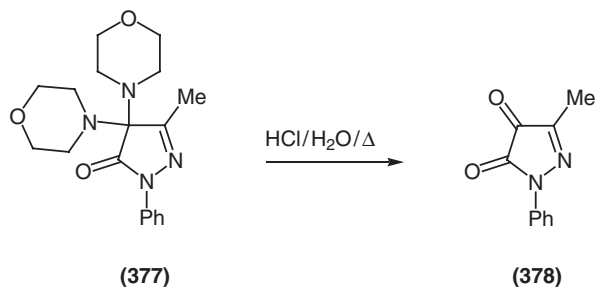


(a) $R^1 = R^4 = \text{H}$, $R^2 = R^3 = \text{Me}$, (b) $R^1 = \text{Ph}$, 3-MeC₆H₄, 4-CIC₆H₄, or 4-MeOC₆H₄, $R^2 = 2\text{-HOC}_6\text{H}_4$, $R^3 = \text{H}$, $R^4 = \text{Ph}$

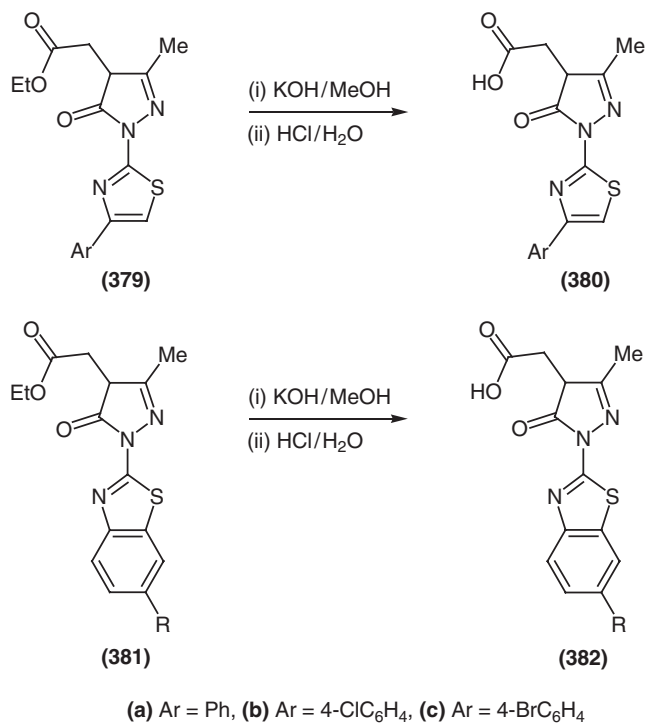
Scheme 104



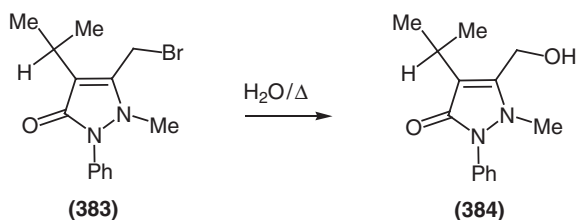
(a) $R^2 = R^3 = \text{H}$, $R^1 = \text{Me}$, (b) $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, (c) $R^1 = R^2 = R^3 = \text{Me}$



Scheme 105



Scheme 106



Scheme 107

D. OF 4-(ETHOXYCARBONYLMETHYL)PYRAZOL-3-ONES

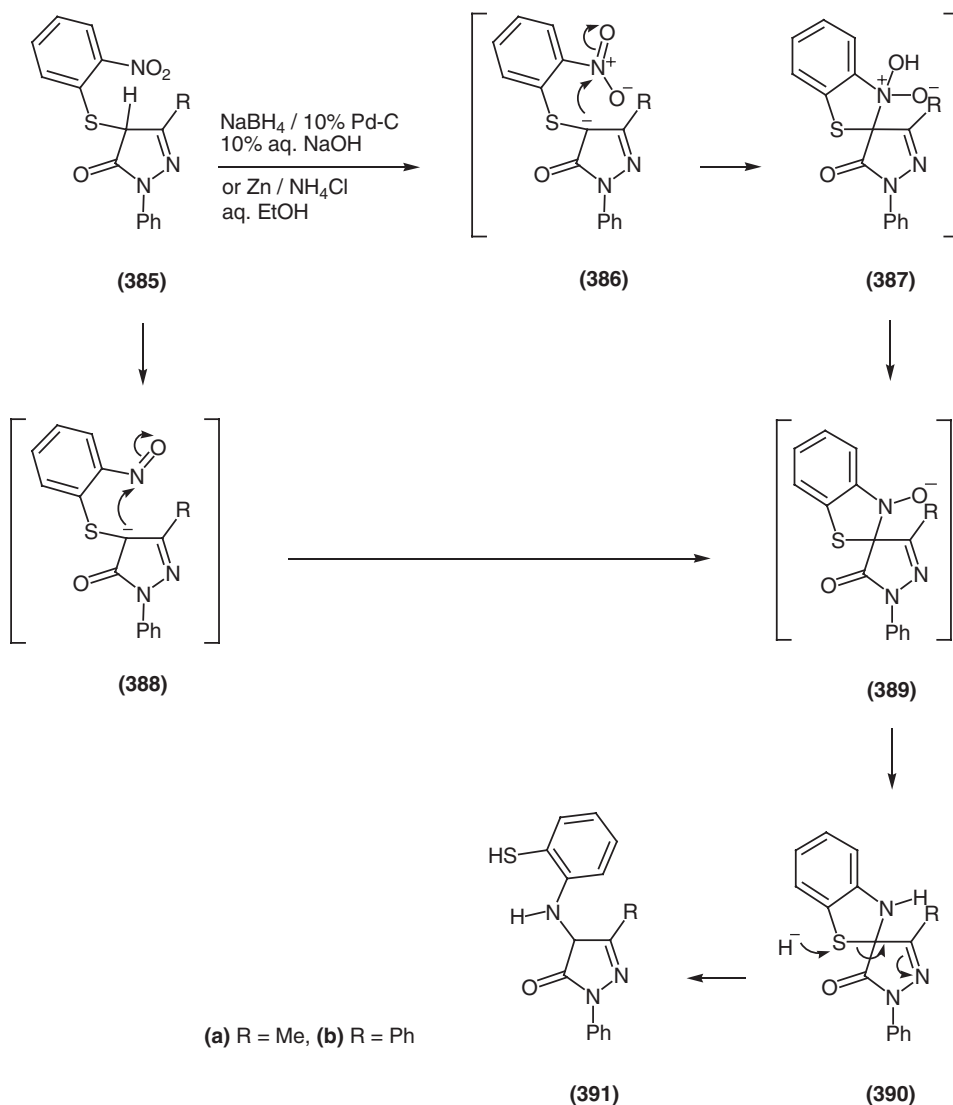
Singh and co-workers (82IJC(B)869) (Scheme 106) hydrolyzed 2-(thiazol-2-yl)pyrazol-3-one esters **379a–c** and 2-(1,3-benzothiazol-2-yl)pyrazol-3-ones **381a–c** by heating in methanolic sodium hydroxide and obtained after acidification the respective pyrazol-3-one carboxylic acids **380a–c** and **382a–c** in near quantitative yield. Some of the compounds exhibited good anti-inflammatory activity.

5-Bromomethylpyrazol-3-one **383** was hydrolyzed to 5-hydroxymethylpyrazol-3-one **384** by heating in water (02EJP121) (Scheme 107).

XI. Rearrangement

A. 4-[(2-NITROPHENYL)THIO]PYRAZOL-3-ONES

In an attempt to prepare cyclic hydroxylamines Coutts et al. (76CJC993) (Scheme 108) reduced an aqueous alkaline solution of 4-[(2-nitrophenyl)thio]pyrazol-3-ones **385a,b** with sodium borohydride in the presence of 10% palladium-on-charcoal. The products were a mixture of spiro[1,3-benzothiazole-2,4'-pyrazol]-3'-ones **390a,b** and

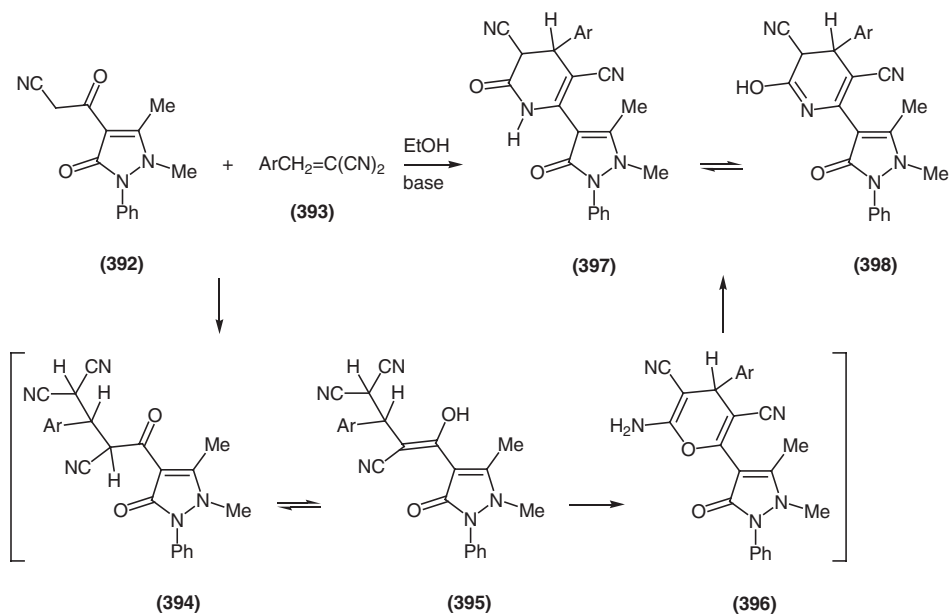


Scheme 108

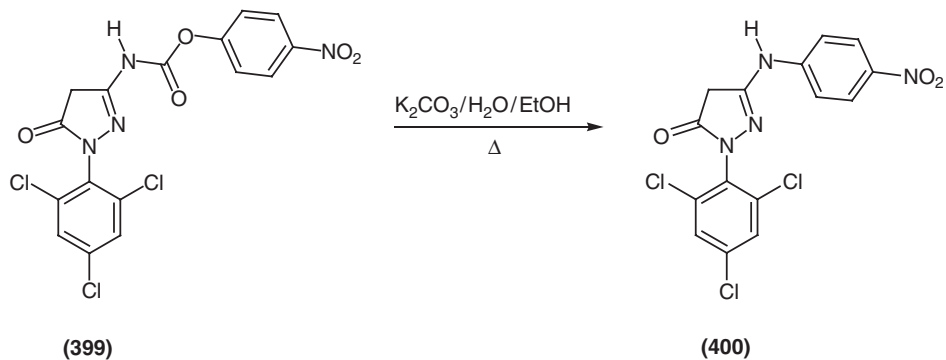
4-[(2-mercaptophenyl)amino]pyrazol-3-ones **391a,b**. On the other hand, the reduction of pyrazol-3-ones **385a,b** in aqueous ethanol with zinc and ammonium chloride resulted in good yields of spiro compounds **390a,b**. In order to verify the assumption that the spiro compounds **390a,b** are obtained first and then further reduced to pyrazol-3-ones **391a,b** compound **390a** was treated with sodium borohydride in a mixture of 1,4-dioxane and aqueous sodium hydroxide to afford, as expected compound **391a**. Thus, the proposed mechanism involves either intramolecular cyclization of carbanion **386** to give addition compound **387** which is further reduced to nitroxide intermediate **389** and then to spiro compound **390**, or reduction of the nitro group in **385** to give nitroso intermediate **388** which then follows similar reductive steps to final product **391**.

B. 3-(1,5-DIMETHYL-3-OXO-2-PHENYLPYRAZOL-4-YL)-3-OXOPROPIONITRILE

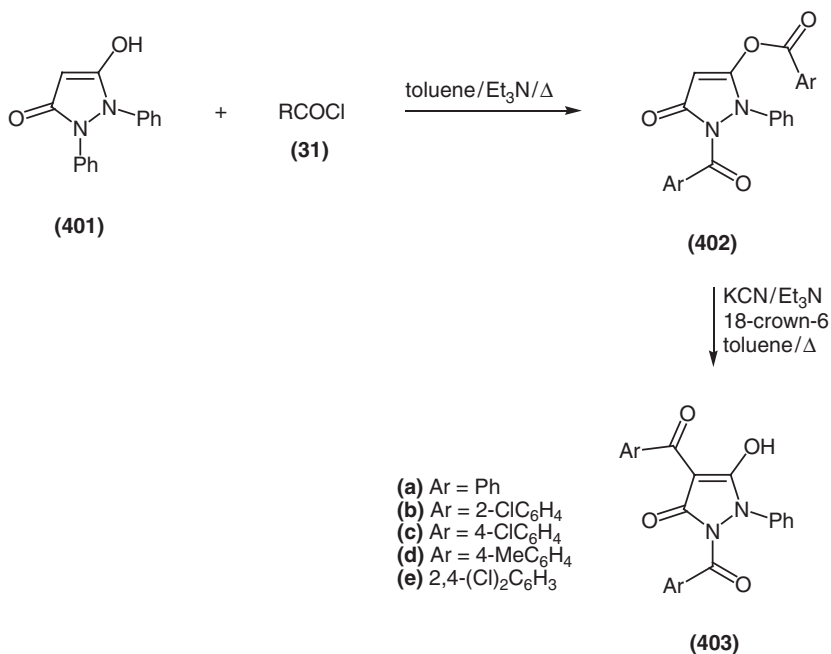
Pyrazol-3-one **392** reacts with arylidene malononitriles **393a-c** in basic ethanolic medium to yield the 6-(3-oxopyrazol-4-yl)-2-oxo-1,2,3,4-tetrahydropyridine/2-hydroxy-6-(3-oxopyrazol-4-yl)-3,4-dihydropyridine adducts **397/398a-c** in a 1:1 ratio (87AP140) (Scheme 109). The mechanism is assumed to proceed via intermediate **396** formed from Michael adduct **394** or possible isomer **395**. The pyran derivative **396** rearranges to the pyrid-2(1*H*)-one/2-hydroxypyridine tautomeric mixture **397/398**.



Scheme 109



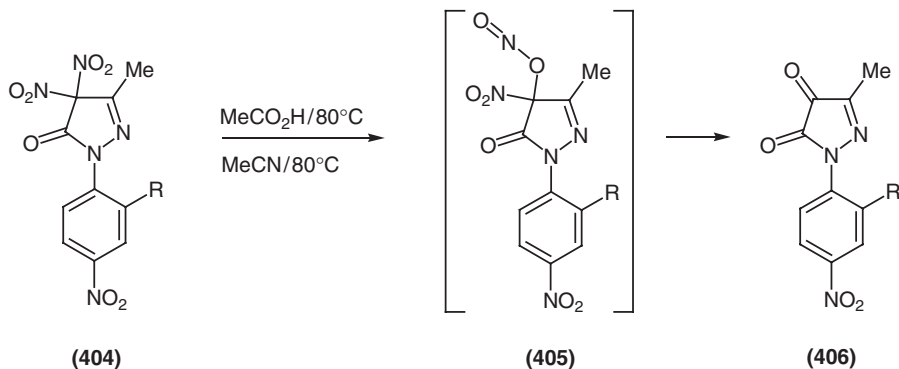
Scheme 110



Scheme 111

C. [5-Oxo-1-ARYLPYRAZOL-3-YL]CARBAMIC ACID 4-NITROPHENYL ESTER

The carbamic acid aryl ester group of pyrazol-3-one **399** underwent a Smiles rearrangement when heated under reflux in ethanol containing aqueous potassium carbonate and gave 5-(4-nitrophenylamino)pyrazol-3-one **400** in 75% yield (84JOC5247) (Scheme 110).

(a) R = H, (b) R = NO₂

Scheme 112

D. 5-HYDROXY-1,2-DIPHENYLPYRAZOL-3-ONE

5-Hydroxypyrazol-3-ones **401** formed the *O*- and *N*-acylatedpyrazol-3-ones **402a–e** with a slight excess of two equivalents of aroyl chlorides **31a–e** and triethylamine in boiling dry toluene (98M871) (Scheme 111). The anionic Fries rearrangement of esters **402b,d** was performed by using two equivalents of potassium cyanide, one equivalent of triethylamine and a catalytic amount of 18-crown-6 in refluxing toluene. The rearranged pyrazol-3-ones **403b,d** were obtained in 55% and 89% yield, respectively.

E. 5-METHYL-4,4-DINITRO-2-(4-NITROPHENYL)PYRAZOL-3-ONE

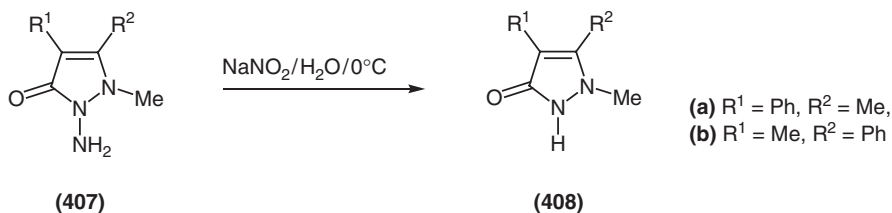
Thermal decomposition of 4,4-dinitro-2-(4-nitrophenyl)pyrazol-3-ones **404a,b** in hot acetic acid or acetonitrile yielded pyrazol-4,5-diones **406a,b** (99T10447) (Scheme 112). The reaction is envisaged to occur via a nitro–nitrito rearrangement where intermediate **405** gives off nitrogen oxides.

XII. Elimination

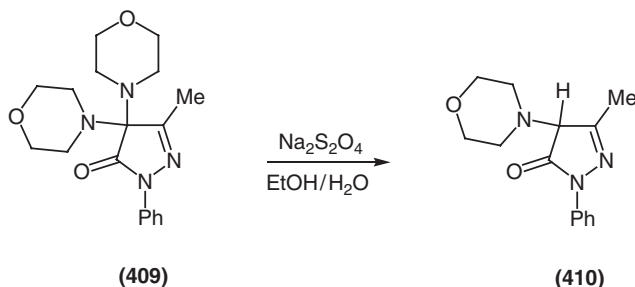
A. DEAMINATION VIA DIAZOTIZATION

2-Aminopyrazol-3-ones **407a,b** were converted into the 2-unsubstituted derivatives **408a,b** by diazotization with nitrous acid (72JHC1219) (Scheme 113).

Selective reductive deamination of one of the morpholino groups of 4,4-dimorpholin-4-ylpyrazol-3-one **409** was achieved by treatment with sodium dithionite in aqueous ethanol. 4-Morpholin-4-ylpyrazol-3-one **410** was obtained in 80% yield (68M2157) (Scheme 114).



Scheme 113



Scheme 114

B. DEFORMYLATION

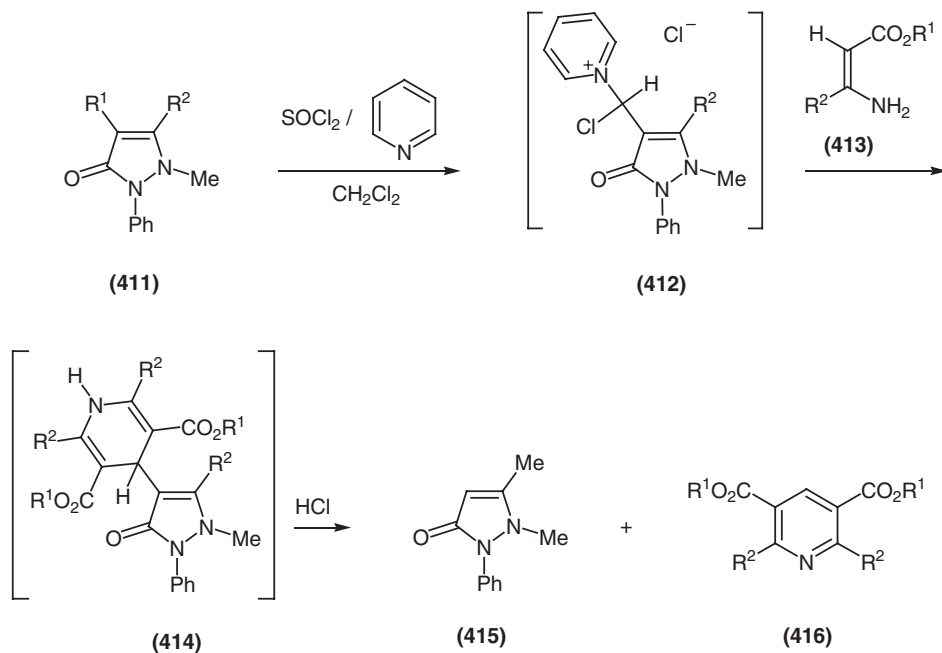
Under acidic conditions, Hantzsch-type intermediates **414a–d** prepared by the reaction of pyrazol-3-one **411** with thionyl chloride and pyridine, followed by addition of ethyl-3-amino-2-butenates **413a–d**, undergo an elimination of the 4-substituent to yield pyrazol-3-one **415** and pyridine **416a–d**. The salt **412**, which was not isolated, was expected to react with butenoates **413** to yield dihydropyridines **414**. Cleavage of the C-4 dihydropyridine/C-4' pyrazol-3-one bond could probably occur at C-4' due to the particular electronic delocalization in the enaminone-like moiety (94H815) (Scheme 115).

C. DEPROTECTION AND DECARBOXYLATION

Pyrazolones **417a–d** were debenzylated by catalytic hydrogenation to yield the 4-(2-hydroxyphenyl)derivatives **418a–d** (89JPS239) (Scheme 116). The tautomeric mixture **419/420** was decarboxylated over one week by heating the solid sample at 50 °C. The product also existed as a tautomeric mixture of **421/422** and was obtained in 90% yield. The coupling constant of the α,β -unsaturated moiety was 9.8 Hz, typical of a (*Z*)-isomer (91JHC1961).

Debenzylation of *N*-(3-oxopyrazol-2-yl)-acetamides **423a,b** by catalytic hydrogenation in methanol with a catalytic amount of acetic acid afforded the 1-unsubstituted derivative **424a,b** (81JHC957) (Scheme 117).

Boc-deprotection of pyrazol-3-one **425** required heating in trifluoroacetic acid and gave the pyrazol-3-one amino acid **426** in 63% yield (99EJMC967) (Scheme 118).



(a) $\text{R}^1 = \text{R}^2 = \text{Me}$, (b) $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Me}$, (c) $\text{R}^1 = t\text{-Bu}$, $\text{R}^2 = \text{Me}$, (d) $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Ph}$

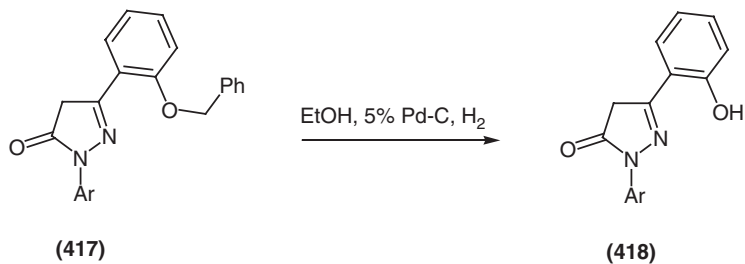
Scheme 115

The ester group of pyrazol-3-one **427** was hydrolyzed in boiling aqueous 10% sodium hydroxide and the resulting carboxylic acid, without isolation, was decarboxylated by heating in 3 N hydrochloric acid to give pyrazol-3-one **428**, in 87% yield (01JMC3730) (Scheme 119).

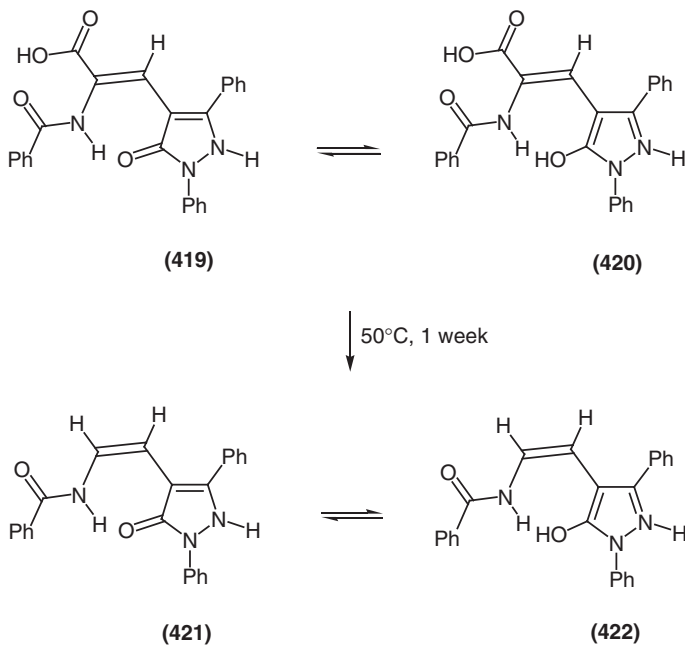
Hydrolysis of the ester group of pyrazol-3-one **429** in alkaline solution followed by decarboxylation of the intermediate carboxylic acid **430** under acidic conditions gave the tautomeric pyrazol-3-one/pyrazol-3-ol mixture **431/432** (04H2537) (Scheme 120). In CDCl_3 **431** existed with its tautomer 1-(4-methoxybenzyl)pyrazol-5-ol **432** in a 1.7:1 ratio. In benzene however 1-(4-methoxybenzyl)pyrazol-3-ol **431** predominated by 90% over the pyrazol-5-ol tautomer. The 4-methoxybenzyl protecting group of 4-acylpyrazol-3-ones **433a-e** and (*E*)-4-dimethylaminomethylidenepyrazol-3-one **436** could be conveniently removed from the pyrazolone nucleus by treatment with trifluoroacetic acid to give 2-unsubstituted adducts **434a-e/435a-e** as keto-enol tautomeric mixtures and 1-unsubstituted pyrazol-3-one **437**, respectively.

D. BY RING FORMATION

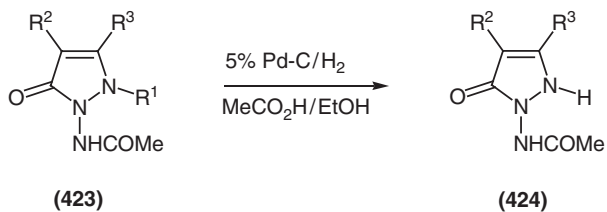
The exocyclic α,β -unsaturated moiety of 4-arylmethylidenepyrazol-3-ones **438a,b** underwent condensation followed by intramolecular substitution with hydrazines or hydroxylamine leading to 5-membered ring formation. Thus, pyrazol-3-ones **438a,b**



(a) Ar = H, (b) Ar = 3-MeC₆H₄, (c) Ar = 4-ClC₆H₄, (d) Ar = 4-MeOC₆H₄

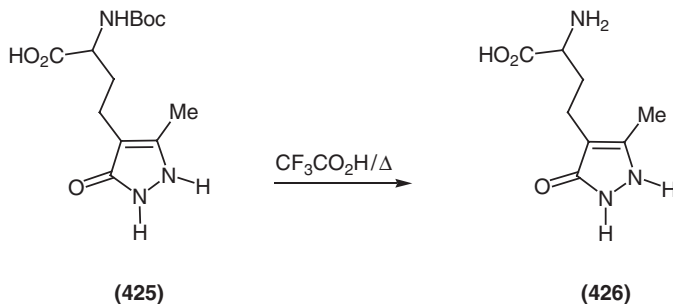


Scheme 116

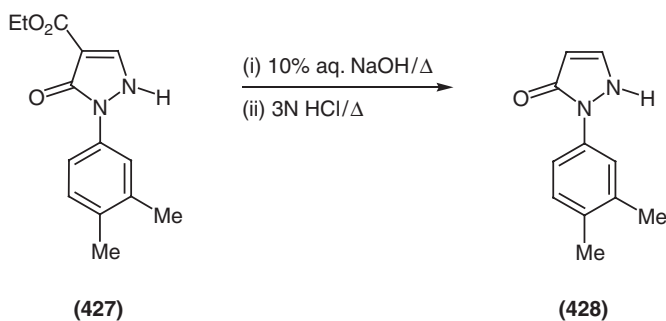


(a) R¹ = PhCH₂, R² = Ph, R³ = Me
 (b) R¹ = PhCH₂, R² = Me, R³ = Ph

Scheme 117



Scheme 118



Scheme 119

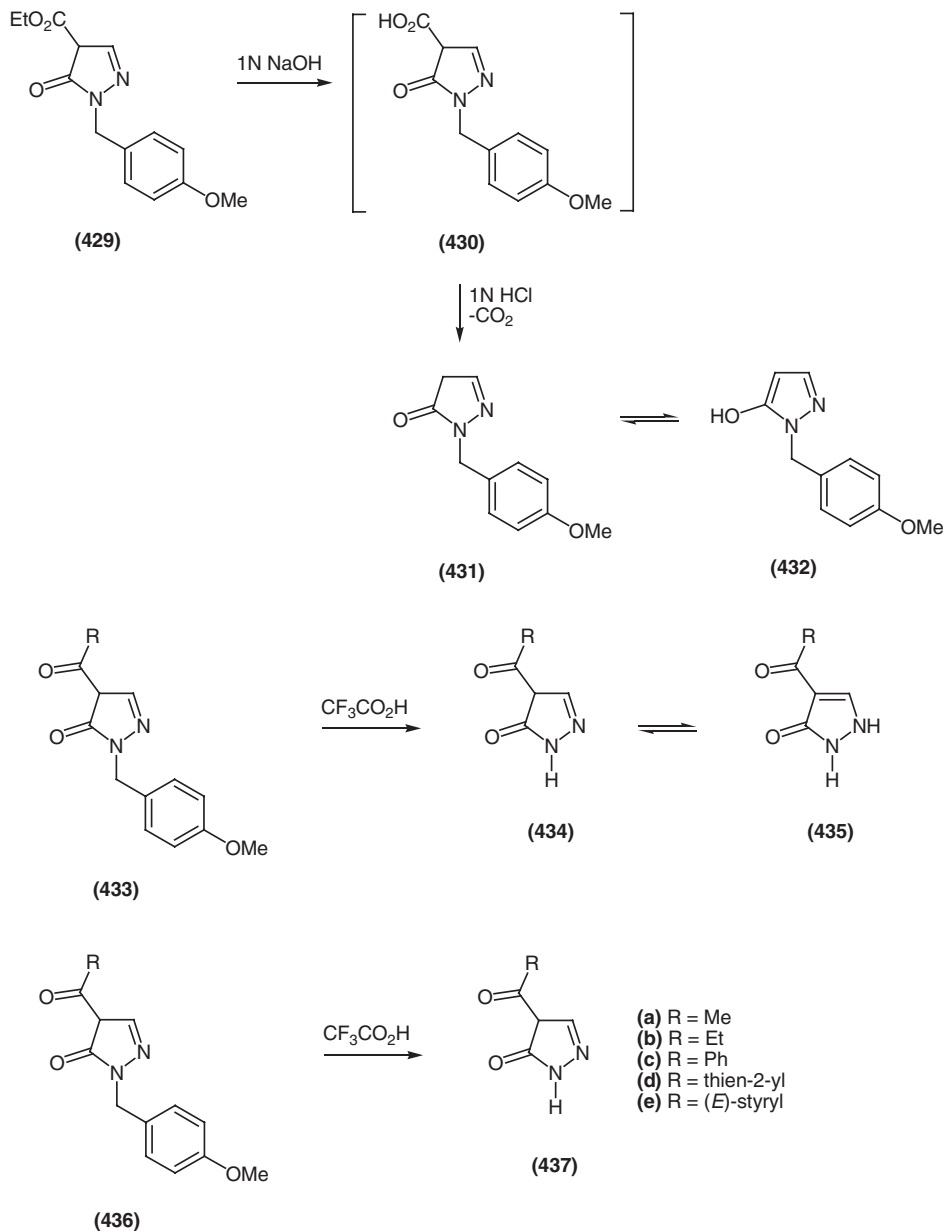
reacted in ethanol with hydrazine hydrate, phenylhydrazine or hydroxylamine hydrochloride, to afford the pyrazolpyrazol-3-ones **439a,b** and **440a,b** and the isoxazolypyrazol-3-ones **441a,b**, respectively (89CCC706) (Scheme 121).

Trivedi and Desai (92IJC(B)366) (Scheme 122) reacted 4-arylideneaminopyrazol-3-ones **442** with mercaptoacetic acid or 2-mercaptopropionic acid and obtained the 3-(pyrazol-4-yl)-2-arylthiazolidin-4-ones **444** in 50–82% yields. The reaction occurs via the adduct **443** which cyclocondenses to the product.

Pyrazol-3-one **445** was shown to be a versatile precursor by Hamama (01SC1335) (Scheme 123) for the synthesis of binary heterocycles containing a pyrazol-3-one ring. Thus, reaction of pyrazol-3-one **445** with hydrazine hydrate, 1,2-diamino benzene, thiourea or hydroxylamine hydrochloride in refluxing ethanol afforded 4-[(3-oxopyrazol-4-yl)(phenyl)methyl]pyrazol-3-one **446**, 3-[(3-oxopyrazol-4-yl)phenylmethyl]-benzo[b][1,4]diazepin-2-one **447**, 5-[(3-oxopyrazol-4-yl)phenylmethyl]-2-thioxopyrimidin-4-one **448** and 4-[(3-oxopyrazol-4-yl)(phenyl)methyl]isoxazol-5-one **449**, respectively, in moderate to good yields.

XIII. Michael-Type Additions

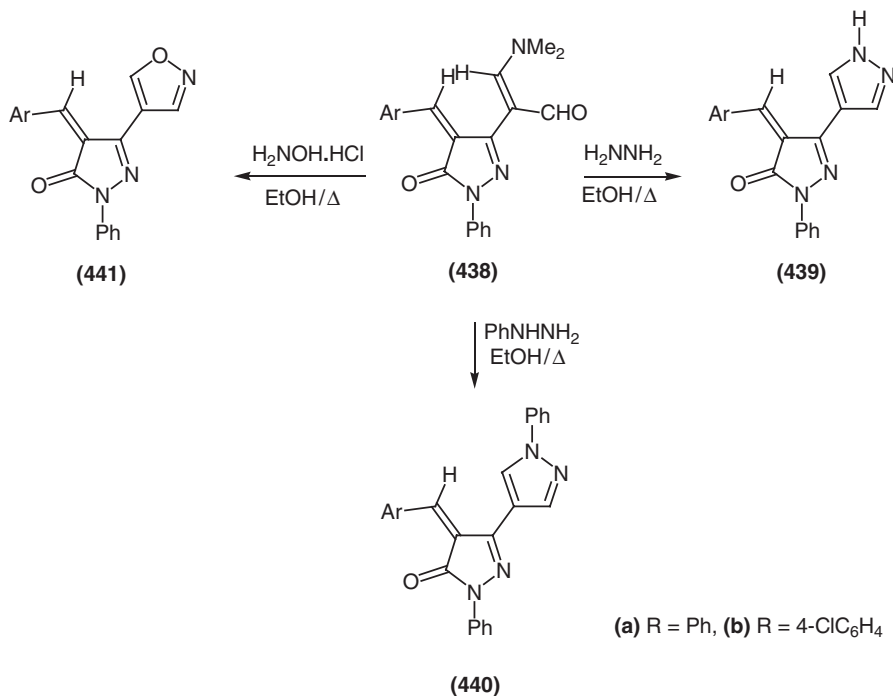
Conjugate addition readily occurs onto 4-substituted methylenepyrazol-3-ones since the exocyclic double bond and the carbonyl group of these compounds act as a typical α,β -unsaturated group.



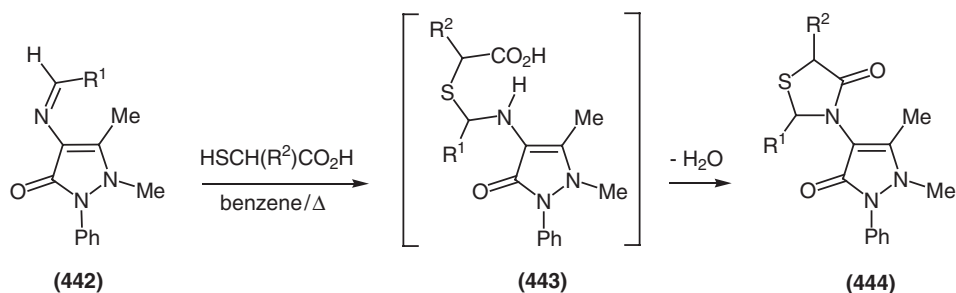
Scheme 120

A. BY ACTIVATED CARBON COMPOUNDS

The reaction of (*E/Z*)-4-arylidene-pyrazol-3-ones **450a-c** with reactive methylene compounds such as diethyl or dimethylmalonate, ethylcyanoacetate or



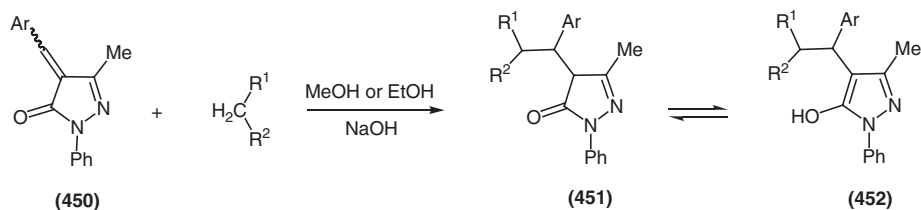
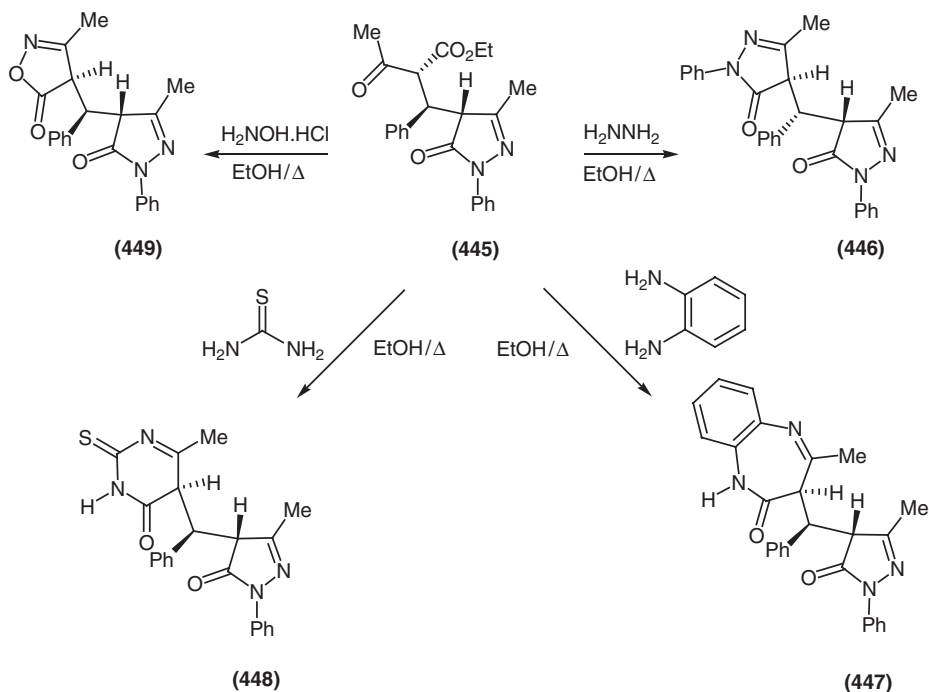
Scheme 121



Scheme 122

cyanoacetamide in alcoholic solution containing sodium hydroxide afforded the corresponding addition products **451/452c-j**. These adducts were almost exclusively enol tautomers **452** (79AP478) (Scheme 124).

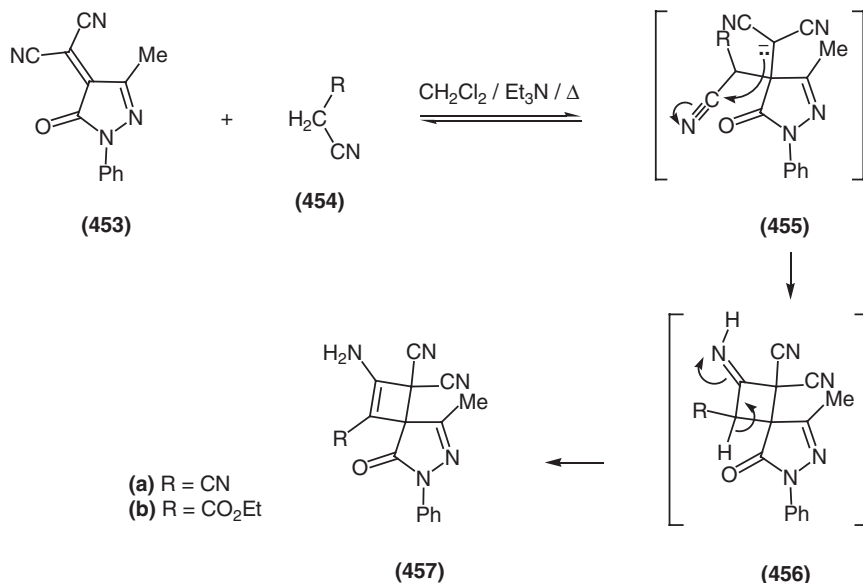
Metwally et al. (91LA961) (Scheme 125) reacted 4-(dicyanomethylene)pyrazol-3-one **453** with malononitrile **454a** or ethyl cyanoacetate **454b** in dichloromethane containing triethylamine and obtained stable spiro-pyrazol-3-ones **457a,b**. The formation of these adducts was explained by a 1,2-addition pathway where initial



(a) Ar = 4-MeC₆H₄, R¹ = R² = CN, (b) Ar = 4-MeOC₆H₄, R¹ = R² = CN, (c) Ar = 4-MeC₆H₄, R¹ = R² = CO₂Me, (d) Ar = 4-MeOC₆H₄, R¹ = R² = CO₂Me, (e) Ar = 4-MeC₆H₄, R¹ = R² = CO₂Et, (f) Ar = Ph, R¹ = CN, R² = CONH₂, (g) Ar = 4-MeC₆H₄, R¹ = CN, R² = CONH₂, (h) Ar = 4-MeOC₆H₄, R¹ = CN, R² = CONH₂, (i) Ar = Ph, R¹ = CN, R² = CO₂Et, (j) Ar = 4-MeC₆H₄, R¹ = CN, R² = COEt

addition of the carbanion derived from **454** to the exocyclic double bond gives intermediate **455** which intramolecularly cyclizes to **456** and then tautomerizes to the product.

Matsugo and Takamizawa (86JHC1159) (Scheme 126) treated 4-(1-methylethylidene)pyrazol-3-ones **458a,b** with acetone in refluxing triethylamine and obtained the addition products **462a,b** in 80% and 77% yield, respectively. However when



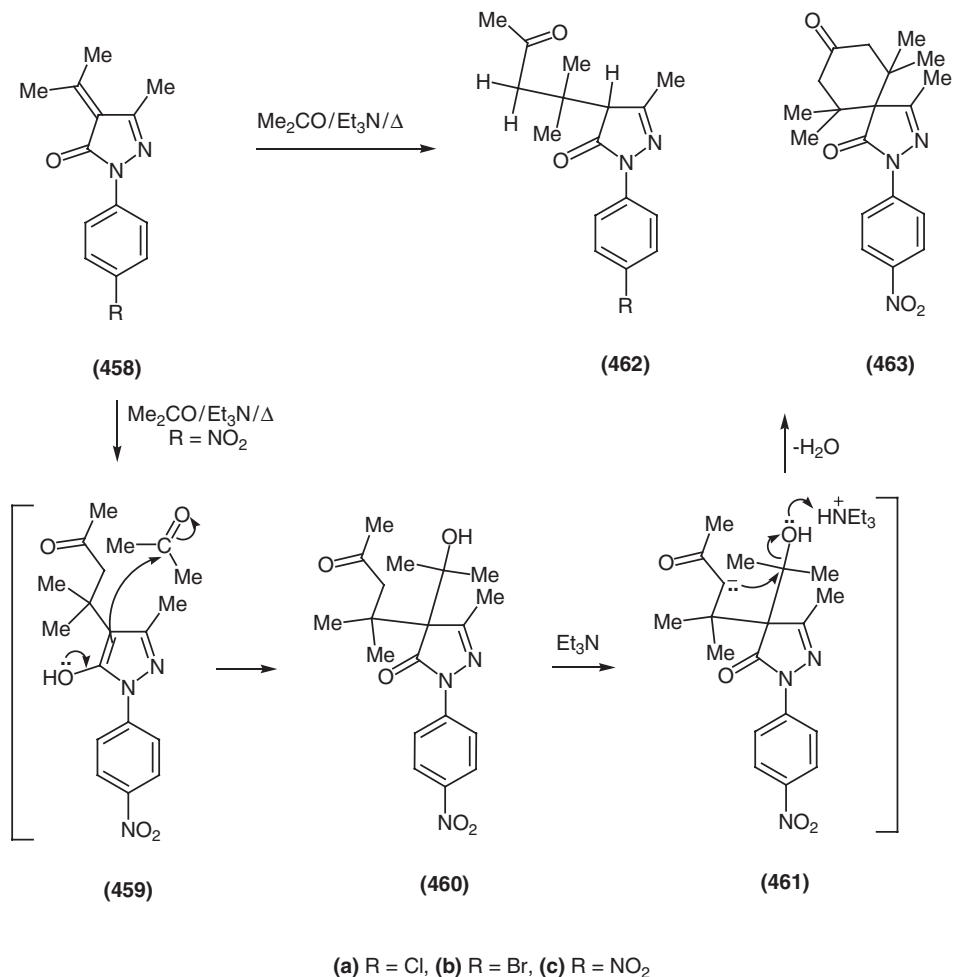
Scheme 125

pyrazol-3-one **458c**, with a 4-nitrophenyl substituent at position 4, was reacted under the same conditions, the spiropyrazol-3-one derivative **463** was obtained in 63% yield. The formation of **463** can be explained by initial addition of acetone enolate to the exocyclic double bond to give intermediate **459**, enolization to 3-hydroxypyrazol **460**, nucleophilic addition of C-4 of the latter to a second molecule of acetone, intramolecular nucleophilic substitution in **461** to give product **463** and elimination of water.

The reaction of 4,4'-bipyrazolylidene-3,3'-dione **464** with diazomethane was investigated by Hennig et al. (89JPR584) (Scheme 127). The mechanism proposed involves initial attack by diazomethane onto position 4 or 4' of compound **464** to give intermediate inner salt **465**. Intramolecular cyclization of the latter gave dispirooundeca-3,9-diene-1,7-dione **466** in 47% yield. This compound was found to be unstable upon standing at room temperature. When heated in ethanol it quickly converted to 4-(pyrazol-4-ylmethylene)pyrazol-3-one **467**, whose isomeric structure was unambiguously assigned by X-ray crystallography.

The isolation of pyrazolylpyrazol-3-one/*bis*(pyrazolyl)methane perchlorates **469/470b-d** was made possible by reaction of the stable benzylidenepyrazol-3-one perchlorate **468b-d** with pyrazol-3-one **7**. Compound **468a** was obtained by the reaction of **7** with 4-dimethylaminobenzaldehyde **171a** in methanol containing perchloric acid. When this reaction was performed with benzaldehyde **171b** or with arylaldehydes with less cation stabilizing groups such as 4-nitrobenzaldehyde **171c** or 4-hydroxy-3-methoxybenzaldehyde **171d**, the result was direct isolation of methane perchlorates **469/470b-d**, respectively (83M219) (Scheme 128).

The addition of pyrroles **472i-m** and indoles **475c-h** to 4-(dicyanomethylene)pyrazol-3-ones **471a,b** gives (pyrazol-4-yl)(pyrrol-3-yl or indol-3-yl)malononitriles

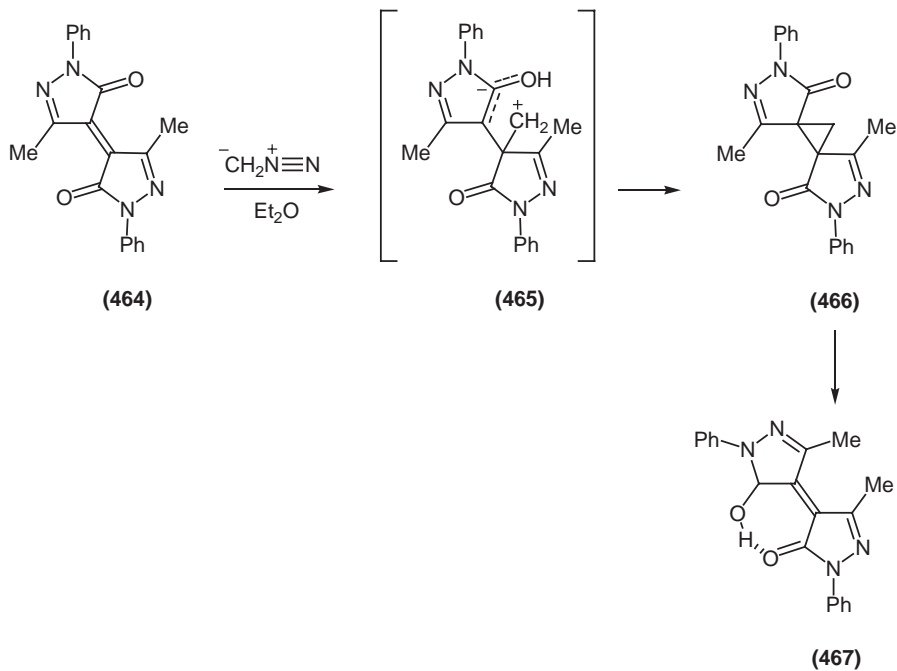


Scheme 126

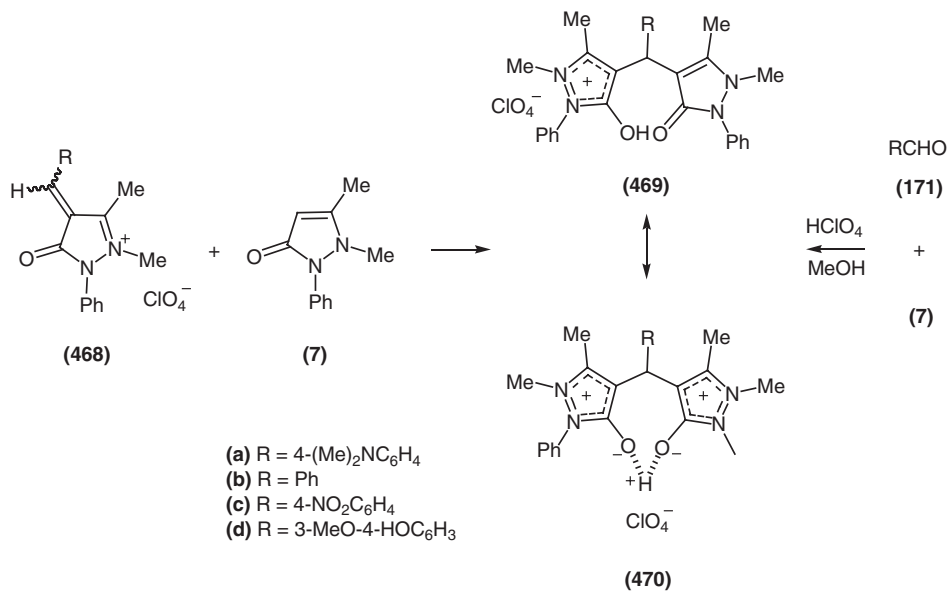
473i-m and **476c-h**, respectively (92LA7) (Scheme 129). Malononitriles **473i-m** and **476c-h** were subjected to either photolysis in ethanol or acetone, or thermolysis in DMF at 100 °C to yield, after elimination of hydrocyanic acid, (*E/Z*)-4-methylenepyrazol-3-ones **474i-m** and **477c-h**, respectively. An NMR study of compounds **474i-m** and **477c-h** showed they exist as 70/30 *E/Z* isomeric mixtures. UV-VIS data of several compounds are discussed by means of AM1 and INDO/S-CI calculations. An X-ray crystallographic analysis of compounds **477a** is presented.

Junek et al. (92M581) (Scheme 130) demonstrated that the reaction of *N,N'*-diphenyldiaza-18-crown-6 **478** with pyrazol-3-one **479** in acetic acid at 40 °C afforded addition product **480** which could be converted into the (*E/Z*)-diphenyldiaza-18-crown-6-*bis*pyrazolideneacetonitrile **481** by heating in methanol containing mercury.

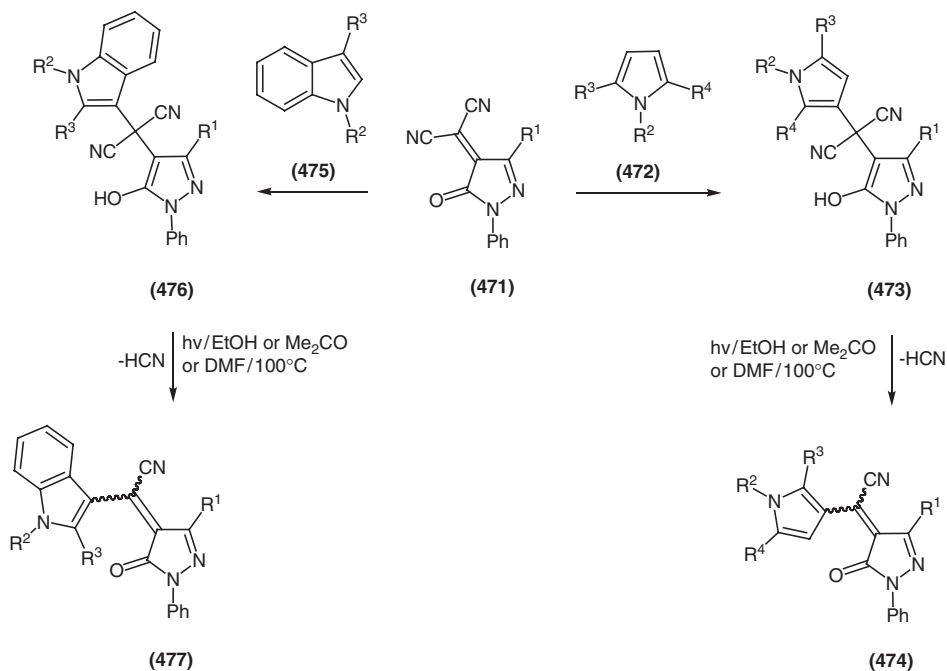
Abdel-Rahman and Abdel-Ghany published two papers (89SC1987, 91SC1281) (Scheme 131) concerning the reaction of (*E/Z*)-arylmethylenepyrazol-3-ones with



Scheme 127



Scheme 128



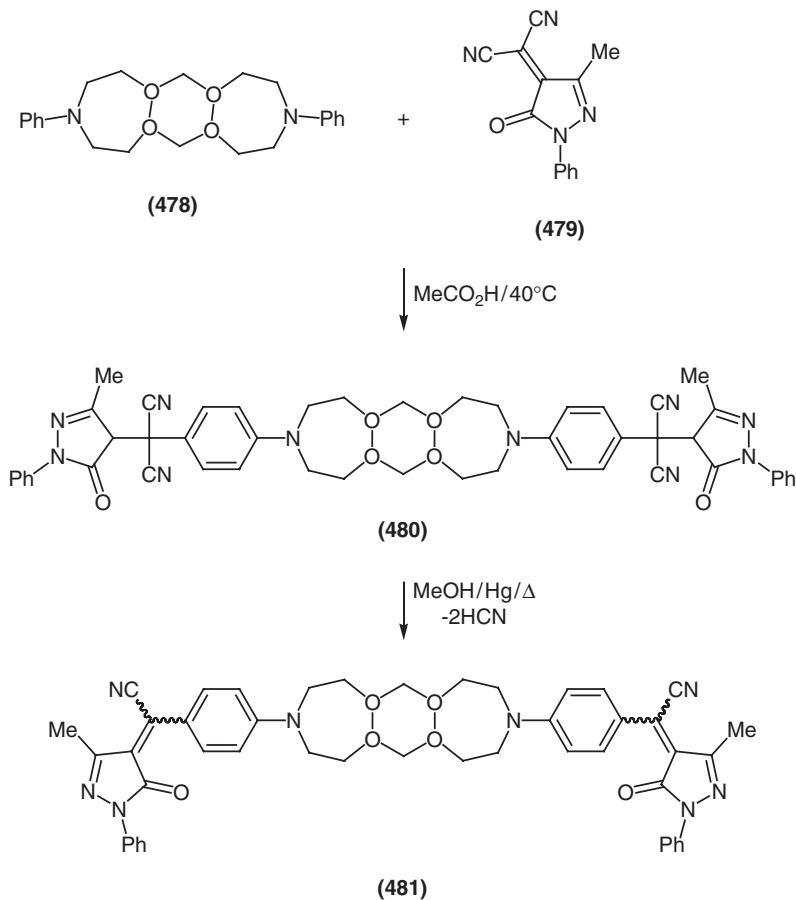
(a) $\text{R}^1 = \text{Me}$, (b) $\text{R}^1 = \text{Ph}$, (c) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{H}$, (d) $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$, (e) $\text{R}^1 = \text{R}^3 = \text{Me}$, $\text{R}^2 = \text{H}$, (f) $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$, (g) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{R}^3 = \text{Me}$, (h) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$, (i) $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{R}^4 = \text{H}$, (j) $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{R}^4 = \text{Me}$, (k) $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{Me}$, (l) $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{R}^4 = \text{H}$

Scheme 129

enamines. In the first paper pyrazol-3-ones **482a–d** with 1-piperidinocyclohexane **483** or 1-morpholinocyclohexene **485** in refluxing acetonitrile gave pyrazol-3-ones **484a–d** and **486a–d**, respectively. In the second paper pyrazol-3-ones **482a–d** with enamines **483** or **485** in acetonitrile at room temperature afforded the Diels–Alder type dihydropyran adducts **488a–d** ($\text{X} = \text{CH}_2$ or O). Upon heating in acetonitrile, **488a–d** ($\text{X} = \text{CH}_2$ or O) gave the corresponding Michael-type adducts **484a–d** and **486a–d**. It was therefore proposed that the reaction of **482** with either **483** or **485** in refluxing acetonitrile proceeds via zwitterionic intermediates **487** that cyclize to products. Further evidence of an intermediate **487** was obtained by the reaction of adducts **488a–d** with tetracyanoethylene in refluxing acetonitrile (Scheme 132). It was proposed that products **490a–d** are derived from ring opening of **488** to **487**, nucleophilic addition of the carbanionic form of **487** to tetracyanoethylene and intramolecular cyclization of intermediate **489** to give the final products.

B. BY GRIGNARD REAGENTS

The addition of aliphatic and aromatic Grignard reagents **492a** to (*E/Z*)-4-arylidenpyrazol-3-ones **491b** was reported by Zimaity et al. (78IJC876) (Scheme 133)

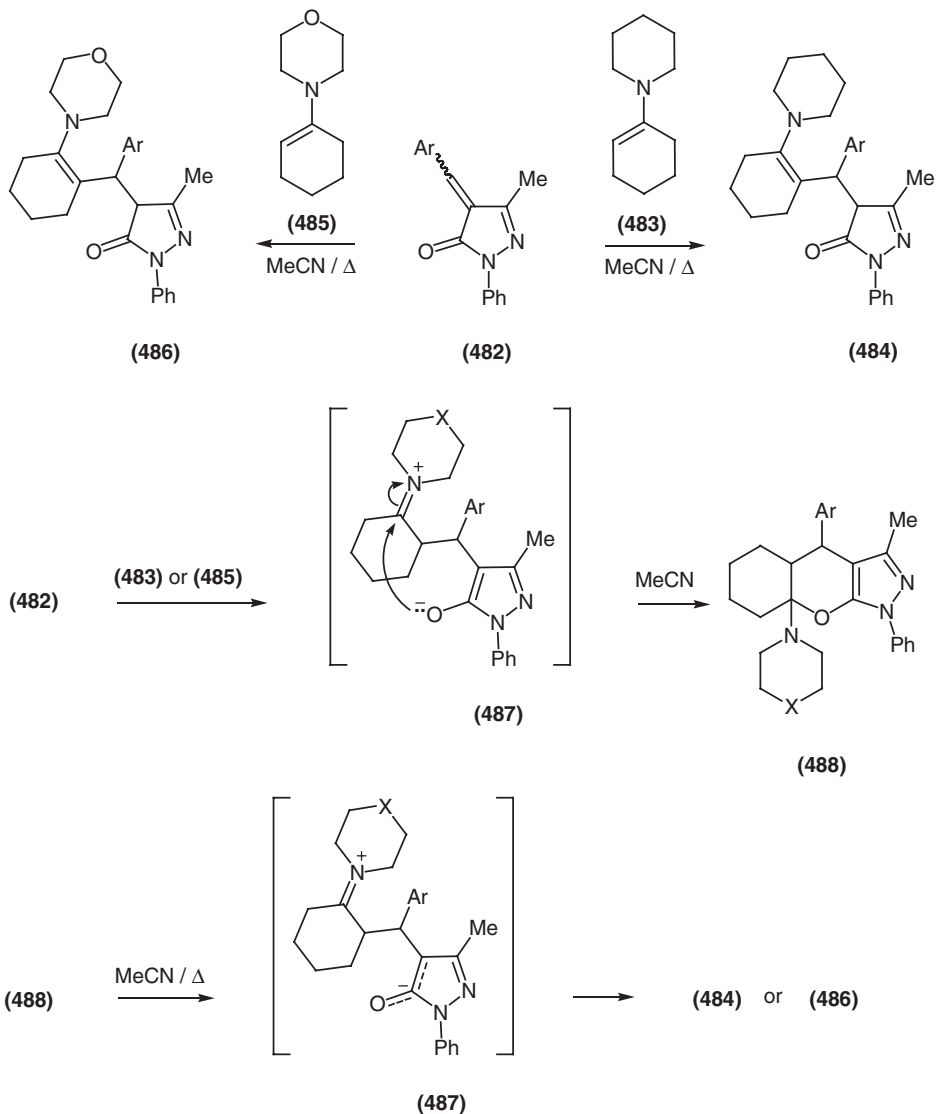


Scheme 130

to afford 4-diaryl(or arylalkyl)methylpyrazol-3-ones **493c-k** in yields ranging from 64% to 73%.

C. BY SECONDARY AMINES AND PHENOLS

The additive behavior of the exocyclic double bond in position 4 of (*E/Z*)-4-arylidene-pyrazol-3-ones **494a-c** was investigated with secondary amines and thiophenols. Thus, piperidine, morpholine, thiophenol or 4-methylthiophenol gave the corresponding addition products **495d-f**, in good yields (72JPR612, 78IJC876) (Scheme 134).

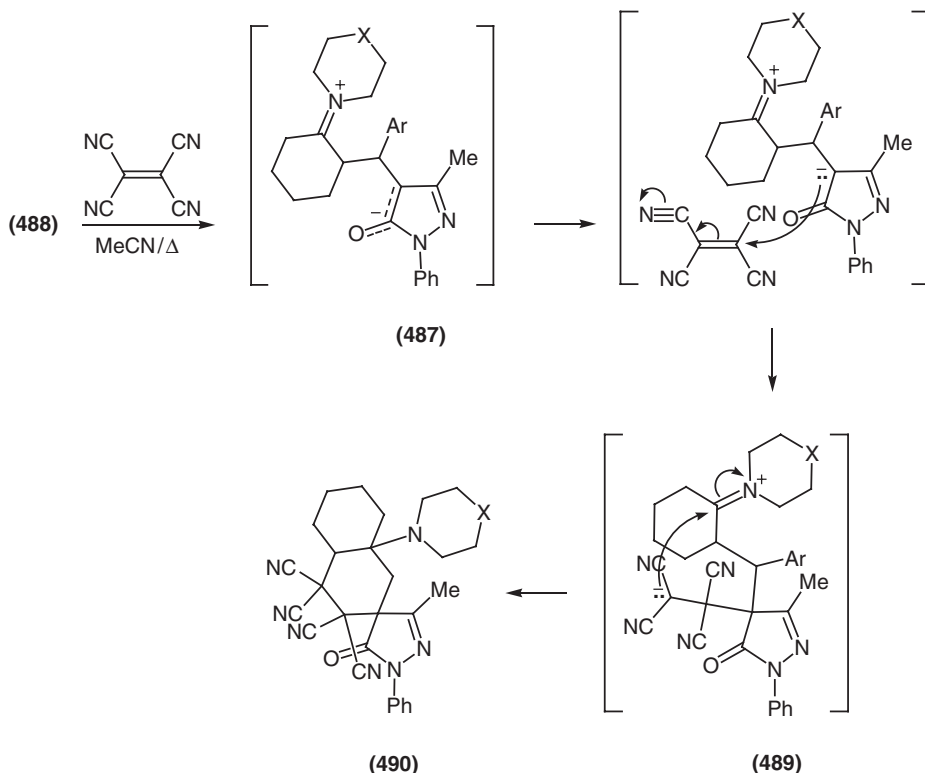


(a) Ar = Ph, (b) Ar = 4-ClC₆H₄, (c) Ar = 4-NO₂C₆H₄, (d) Ar = 4-MeOC₆H₄

Scheme 131

XIV. Oxidation

Pyrazol-3-ones have been oxidized by a variety of oxidizing agents such as molecular oxygen, bromine, iodine-potassium iodide, ozone in oxygen, hydrogen peroxide, 3-chloroperbenzoic acid, electrooxidation, potassium hexacyanoferrate(III), potassium ferricyanide, aqueous periodic acid, aqueous methanolic sodium

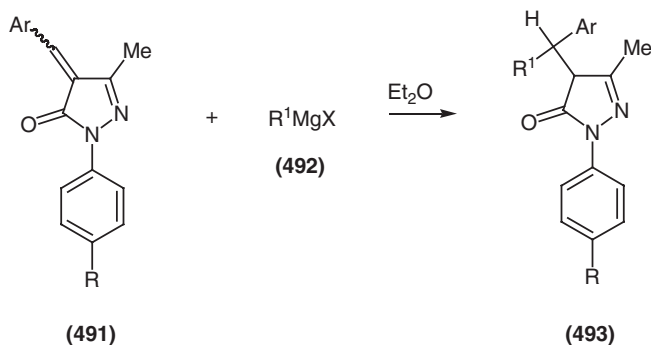


Scheme 132

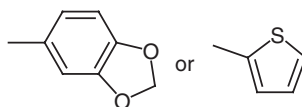
metaperiodate and lead tetraacetate with boron trifluoride etherate, pyridinium chromate and potassium permanganate. Apart from various useful modifications on pyrazol-3-one ring side chains, new rings may be formed, cleavage of side chains have occurred and selective coupling reactions have taken place.

A. WITH MOLECULAR OXYGEN

The oxidation of [(3-oxopyrazolyl)(methyl)amino]methanesulfonate **496** by molecular oxygen, catalyzed by copper sulfate, at pH 5 and 30 °C, conditions that are important for pharmaceutical stability, was studied by Yoshioka et al. (79AP81) (Scheme 135). Three products were isolated, Scheme 135. 4-Formylaminopyrazol-3-one **498**, 4-aminopyrazol-3-one **30** and *N*-(3-oxopyrazol-4-yl)formamide **499**. Compounds **30** and **499** emerge from a common intermediate **497**. 4-Hydroperoxy-pyrazol-3-one **498** is the product of further oxidation of the amino group of compound **30** and *N*-(3-oxopyrazol-4-yl)formamide **499** is the product of further oxidation of the methyl group of the 4-methylamino substituent of intermediate **497**.



- (a) $\text{R}^1 = \text{Me, Ph or cyclopentyl,}$
 (b) $\text{R} = \text{Cl, Ar} = 4\text{-MeOC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-Me}_2\text{NC}_6\text{H}_4,$
 (c) $\text{R} = \text{Cl, R}^1 = \text{Me, Ar} = 4\text{-MeOC}_6\text{H}_4,$
 (d) $\text{R} = \text{Cl, R}^1 = \text{Me, Ar} = 4\text{-NO}_2\text{C}_6\text{H}_4,$
 (e) $\text{R} = \text{Cl, R}^1 = \text{Me, Ar} = 4\text{-Me}_2\text{NC}_6\text{H}_4,$



- (f) $\text{R} = \text{Cl, R}^1 = \text{Me, Ar} =$
 (g) $\text{R} = \text{Cl, R}^1 = \text{Ph, Ar} = 4\text{-MeOC}_6\text{H}_4,$
 (h) $\text{R} = \text{Cl, R}^1 = \text{Ph, Ar} = 4\text{-NO}_2\text{C}_6\text{H}_4,$
 (i) $\text{R} = \text{Cl, R}^1 = \text{Ph, Ar} =$
 (j) $\text{R} = \text{Cl, R}^1 = \text{Ph, Ar} = 4\text{-Me}_2\text{NC}_6\text{H}_4,$
 (k) $\text{R} = \text{Cl, R}^1 = \text{cyclopentyl, Ar} = 4\text{-MeOC}_6\text{H}_4,$

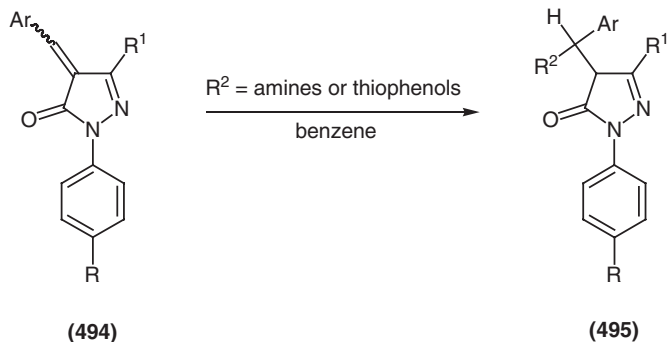
Scheme 133

B. WITH BROMINE OR IODINE-POTASSIUM IODIDE

The 4-[(5-oxopyrazol-4-yl)arylmethyl]pyrazol-3-ones **500a–s** were dissolved in 20% aqueous sodium hydroxide and treated with saturated iodine-potassium iodide to afford the cyclopropane derivatives **501a–s** (84JIC640) (Scheme 136).

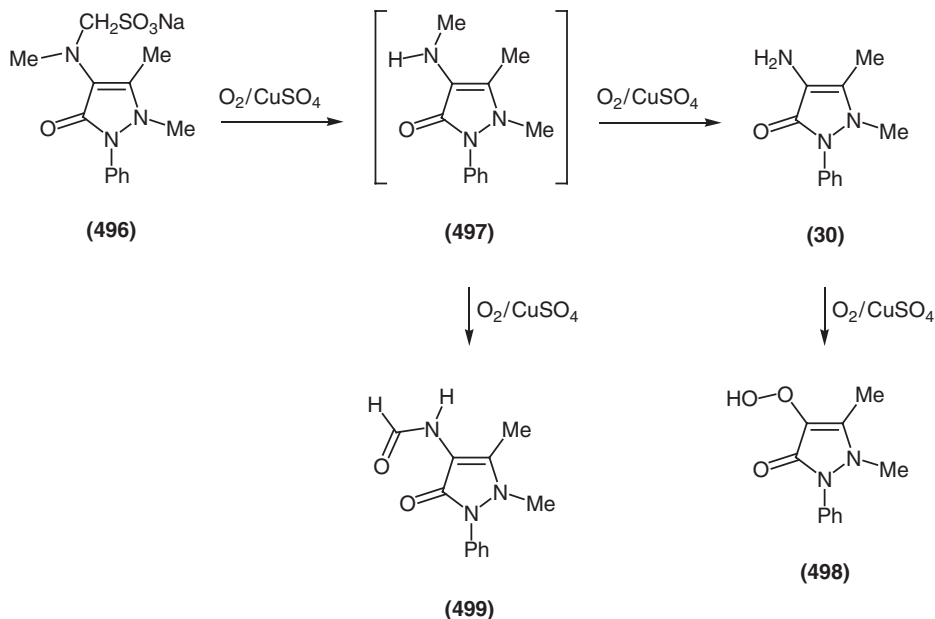
C. WITH OZONE

Harnish et al. (69JOC1687) (Scheme 137) introduced a dilute stream of ozone in oxygen into a methylene chloride solution of pyrazol-3-one azomethine **502** and obtained major reaction products **503a–d**, and minor products **503g**, and **504e,f**. Based on the relative rates of disappearance of compounds **502**, **503b** and **503d** (**502** > **503b** > **503d**) the authors propose (Scheme 138) that ozone adds to the azomethine nitrogen by electrophilic attack, followed by ring closure to form an oxaziridine ring with concomitant loss of an oxygen molecule. An alternative mechanism involves electrophilic π complex formation of the type proposed for



- (a) $\text{R}^1 = \text{Me}$, $\text{R} = \text{Cl}$, $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$, (b) $\text{R}^1 = \text{Me}$, $\text{R} = \text{Cl}$, $\text{Ar} = 4\text{-NO}_2\text{C}_6\text{H}_4$,
 (c) $\text{R}^1 = \text{pyrid-3-yl}$, $\text{R} = \text{H}$, $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$, (d) $\text{R}^1 = \text{Me}$, $\text{R} = \text{Cl}$, $\text{R}^2 = \text{piperidino}$,
 (e) $\text{R}^1 = \text{Me}$, $\text{R} = \text{NO}_2$, $\text{R}^2 = \text{morpholino}$, $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$,
 (f) $\text{R}^1 = \text{pyrid-3-yl}$, $\text{R} = \text{H}$, $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$, $\text{R}^2 = \text{piperidino}$, morpholino , thiophenolino
 or $4\text{-methylthiophenolino}$

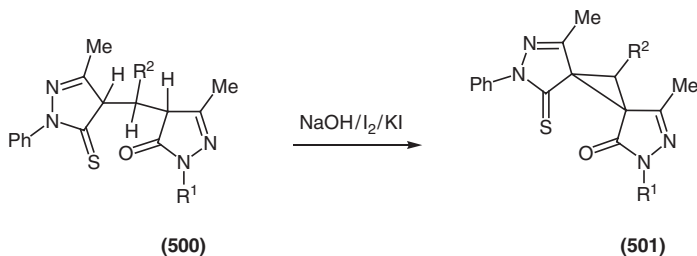
Scheme 134



Scheme 135

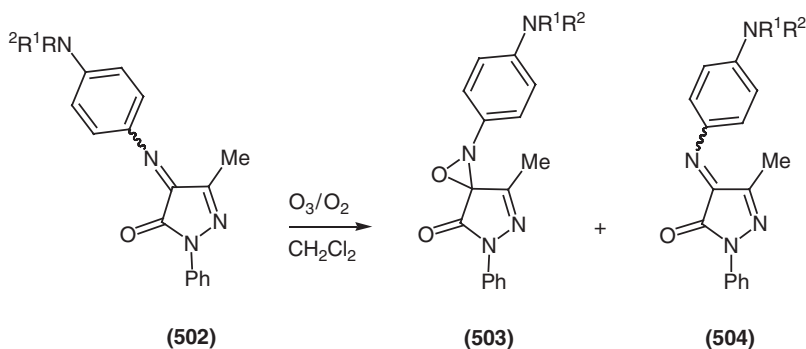
ozonation of carbon-carbon double bonds (67JA4473), cationic oxaziridine ring formation and loss of an oxygen molecule to give an oxaziridine derivative.

Demethylation and oxidation of the dimethylamino moiety with ozone was explained by a number of free radical ionic reactions leading to an intermediate hydroxymethylamino derivative. One such sequence was proposed to involve



(a) $R^1 = R^2 = \text{Ph}$, (b) $R^1 = \text{Ph}$, $R^2 = 2\text{-HOC}_6\text{H}_4$, (c) $R^1 = \text{Ph}$, $R^2 = 3\text{-HOC}_6\text{H}_4$, (d) $R^1 = \text{Ph}$, $R^2 = 4\text{-HOC}_6\text{H}_4$
 (e) $R^1 = \text{Ph}$, $R^2 = 2\text{-NO}_2\text{C}_6\text{H}_4$, (f) $R^1 = \text{Ph}$, $R^2 = 3\text{-NO}_2\text{C}_6\text{H}_4$, (g) $R^1 = \text{Ph}$, $R^2 = 4\text{-NO}_2\text{C}_6\text{H}_4$, (h) $R^1 = \text{Ph}$, $R^2 = \text{OCH}_2\text{Ph}$,
 (i) $R^1 = \text{Ph}$, $R^2 = \text{OCH}_2\text{C}_6\text{H}_3\text{OH-3}$, (j) $R^1 = \text{Ph}$, $R^2 = \text{C}_6\text{H}_5\text{O}$, (k) $R^1 = \text{H}$, $R^2 = \text{Ph}$, (l) $R^1 = \text{H}$, $R^2 = 2\text{-HOC}_6\text{H}_4$,
 (m) $R^1 = \text{H}$, $R^2 = 3\text{-HOC}_6\text{H}_4$, (n) $R^1 = \text{H}$, $R^2 = 4\text{-HOC}_6\text{H}_4$, (o) $R^1 = \text{H}$, $R^2 = 2\text{-NO}_2\text{C}_6\text{H}_4$, (p) $R^1 = \text{H}$,
 $R^2 = 3\text{-NO}_2\text{C}_6\text{H}_4$, (q) $R^1 = \text{H}$, $R^2 = 4\text{-NO}_2\text{C}_6\text{H}_4$, (r) $R^1 = \text{H}$, $R^2 = \text{OCH}_2\text{Ph}$, (s) $R^1 = \text{H}$, $R^2 = \text{OCH}_2\text{C}_6\text{H}_3\text{OH-3}$

Scheme 136



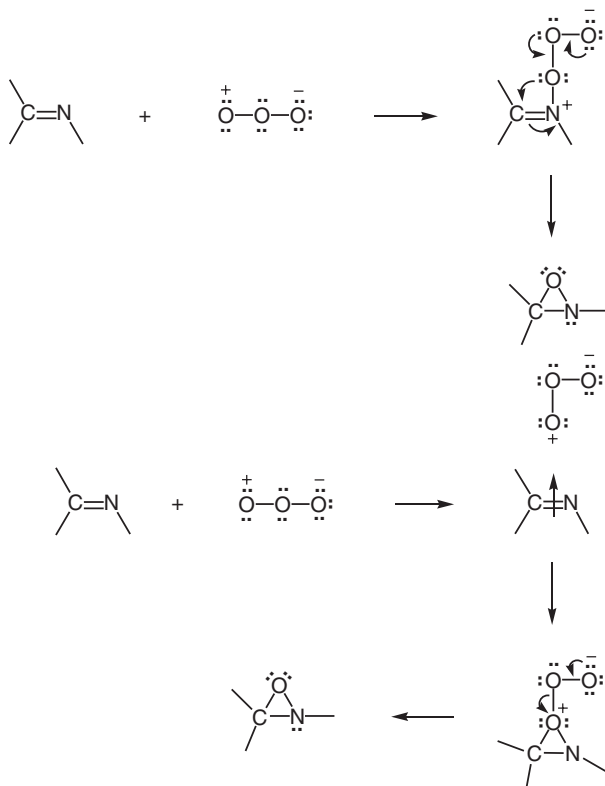
(a) $R^1 = R^2 = \text{Me}$, (b) $R^1 = \text{H}$, $R^2 = \text{Me}$, (c) $R^1 = \text{H}$, $R^2 = \text{CHO}$, (d) $R^1 = \text{Me}$, $R^2 = \text{CHO}$,
 (e) $R^1 = \text{H}$, $R^2 = \text{Me}$, (f) $R^1 = \text{Me}$, $R^2 = \text{CHO}$, (g) $R^1 = \text{NO}_2$, $R^2 = \text{NH}_2$

Scheme 137

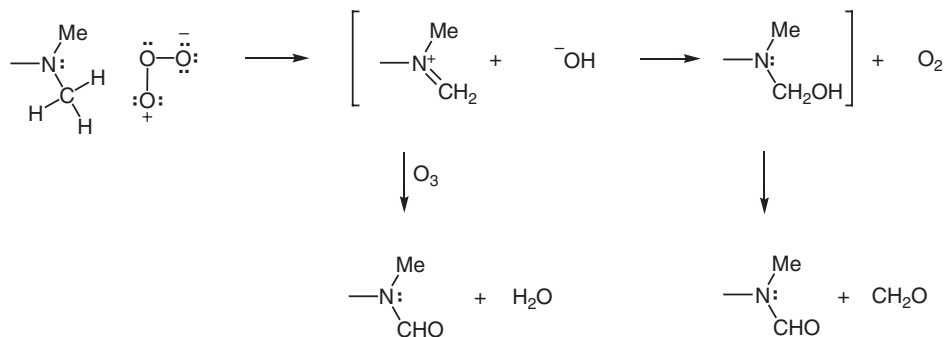
electrophilic attack at the hydrogens α to nitrogen as shown in Scheme 139. The intermediate hydroxylamino derivative may eliminate formaldehyde, leading to demethylated derivatives, or be oxidized by ozone to the formyl derivative and other oxidation products.

D. WITH HYDROGEN PEROXIDE OR 3-CHLOROPERBENZOIC ACID

Oxidation of 4-(substituted methylene)pyrazol-3-ones **505a–k** with 30% hydrogen peroxide in methanolic sodium hydroxide afforded 1-oxa-5,6-diazaspiro[2.4]-hept-6-ene-4-ones **506a–k** in good yields (83JCS(P1)325) (Scheme 140).

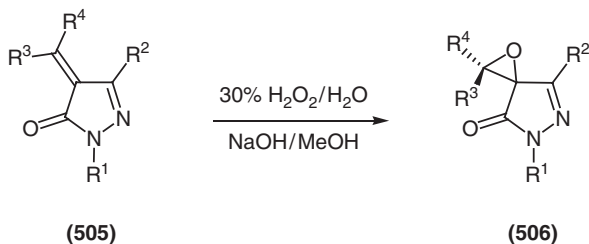


Scheme 138



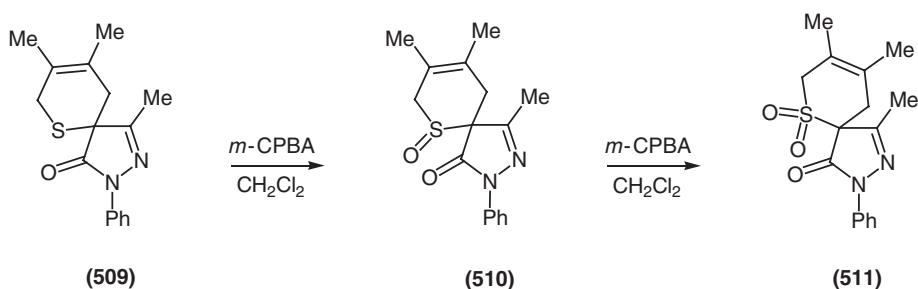
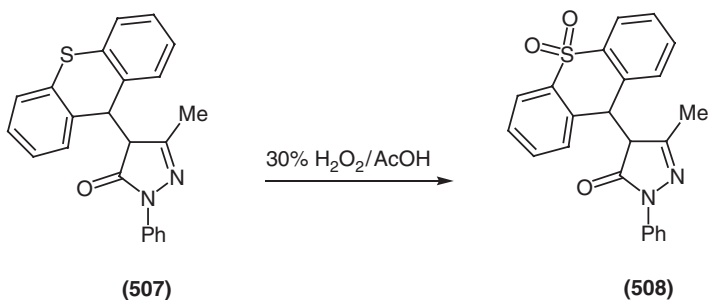
Scheme 139

The sulfur atoms of 4-(thioxanthen-9-yl)pyrazol-3-one **507** and spiropyrazol-3-one **509** can be oxidized, respectively, with 30% hydrogen peroxide in acetic acid or one equivalent of 4-chloroperbenzoic acid in dichloromethane to give the corresponding pyrazol-3-one-10,10-dioxide **508** and sulfoxide **510**. Treatment of the latter with a



(a) $R^1 = \text{Ph}$, $R^2 = R^3 = R^4 = \text{Me}$, (b) $R^1 = R^2 = \text{Ph}$, $R^3 = R^4 = \text{Me}$
 (c) $R^1 = 4\text{-MeOC}_6\text{H}_4$, $R^2 = R^3 = R^4 = \text{Me}$, (d) $R^1 = R^4 = \text{Ph}$, $R^2 = \text{Me}$,
 $R^3 = \text{H}$, (e) $R^1 = R^2 = R^4 = \text{Ph}$, $R^3 = \text{H}$, (f) $R^1 = 4\text{-MeOC}_6\text{H}_4$, $R^2 = \text{Me}$,
 $R^3 = \text{H}$, $R^4 = \text{Ph}$, (g) $R^1 = 4\text{-NO}_2\text{C}_6\text{H}_4$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = \text{Ph}$, (h)
 $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = 4\text{-(Cl)}_2\text{C}_6\text{H}_3$, (i) $R^1 = \text{Ph}$, $R^2 = \text{Me}$,
 $R^3 = \text{H}$, $R^4 = 4\text{-NO}_2\text{C}_6\text{H}_4$, (j) $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = 2\text{-naphth-2-yl}$,
 (k) $R^1 = R^2 = \text{Ph}$, $R^3 = \text{H}$, $R^4 = \text{naphth-2-yl}$

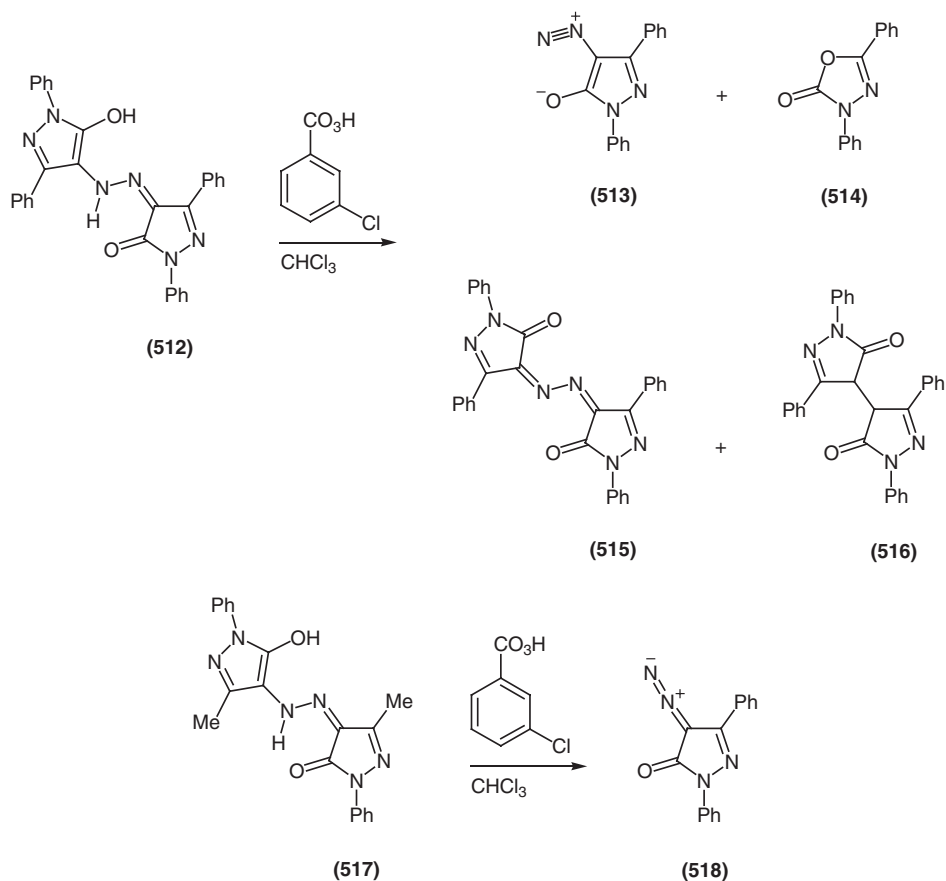
Scheme 140



Scheme 141

further equivalent of 4-chloroperbenzoic acid afforded sulfone **511** (82JHC437, 00CHE152) (Scheme 141).

Oxidative cleavage of pyrazol-4,5-dione-4-[*N*-(pyrazol-4-yl)]hydrazone **512** occurred with 3-chloro-perbenzoic acid (73G179) (Scheme 142) to give a mixture containing pyrazole diazonium salt **513**, oxadiazol-5-one **514**, hydrazone derivative

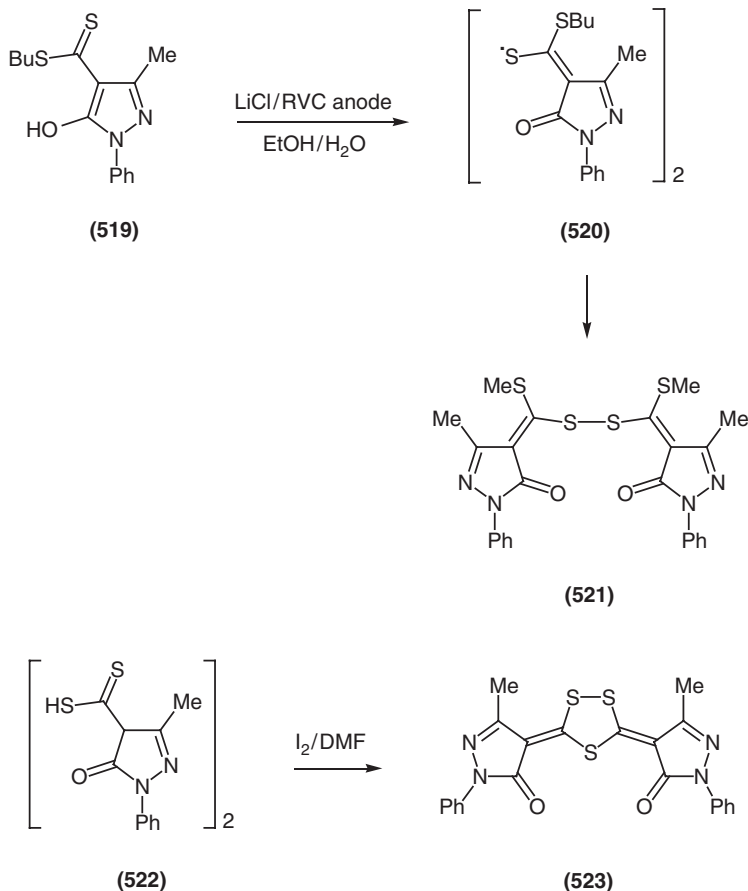


Scheme 142

515 and the *bis*pyrazole **516** in 72%, 0.5%, 10% and 17% yield, respectively. Oxidation of hydrazone **517** under similar conditions gave pyrazol-3-one diazonium salt **518** in 63% yield. The other components were not identified.

E. BY ELECTROOXIDATION

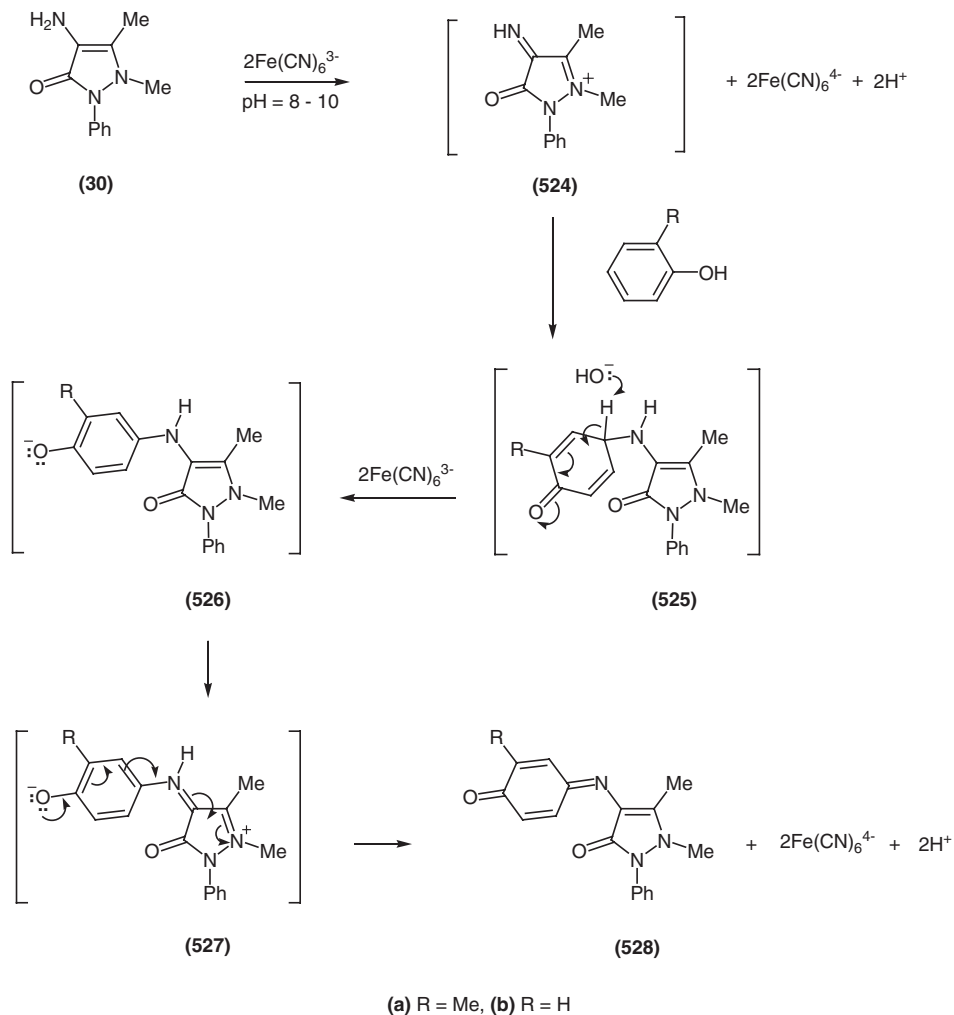
Electrooxidation of 5-hydroxypyrazol-3-dithiocarboxylate **519** in aqueous ethanol containing lithium chloride took place on a glassy carbon electrode surface at 0.8 V to afford *bis*methylenedithioacetalpyrazol-3-one **521** in 92% yield (76JCS(P1)1706, 00SC4353) (Scheme 143) via the pyrazol-3-one radical **520**. Pyrazol-3-one-4-dithiocarboxylic acid **522** was oxidized with iodine in DMF to give the 4-[5-(3-oxo-pyrazol-4-ylidene-3-one)-1,2,4-trithioxolan-3-ylidene]pyrazol-3-one **523**. The exact mechanism is not known but may involve thio radicals and the elimination of HS^- .



Scheme 143

F. WITH POTASSIUM AND COPPER COMPLEXES

Barton et al. (87CJC2082) (Scheme 144) described a standard procedure for the estimation of phenols at low (ng/mL) concentration in potable water supplies. The method consists in measuring the intensity of the red color formed when the phenol is oxidized with potassium hexacyanoferrate(III) at pH 8–10 in the presence of excess 4-aminoantipyrene **30**. The product of this oxidation using 2-methylphenol was *p*-quinonepyrazol-3-one **528a**, unequivocally identified by X-ray crystallography. A mechanism was first proposed by Faust and Mikulewicz (67WR509) for phenol itself and more recently modified by Stalikas and co-workers (00ACA315). In the first step the amino group of pyrazol-3-one **30** is oxidized by hexacyanoferrate(III) anion to cation **524** which couples with the *para* position of phenol. The resulting adduct **525** is converted into the anionic phenoxide intermediate **526** which is oxidized to intermediate **527** and then converted into the stable *p*-quinonepyrazol-3-one **528**.

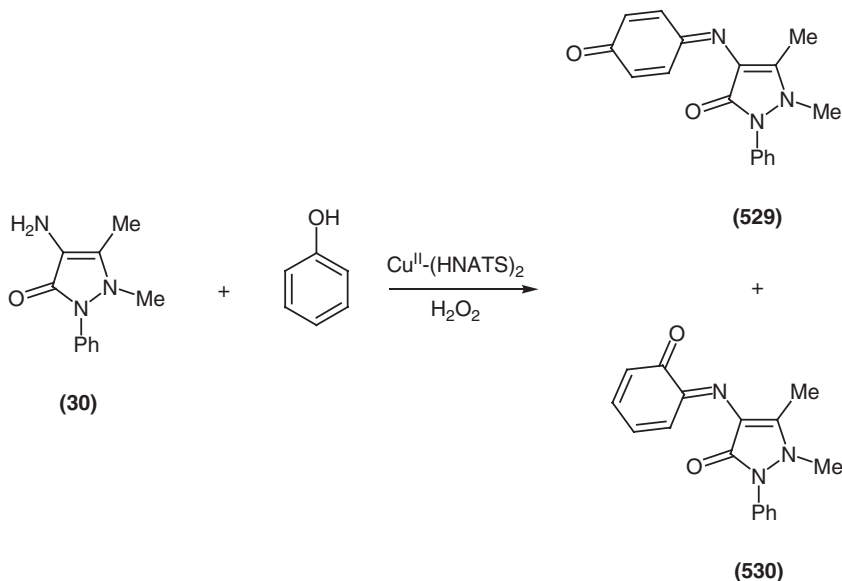


Scheme 144

Two other oxidants, potassium peroxomonosulfate and peroxodisulfate, were also tested but proved less efficient than potassium hexacyanoferrate(III).

More recently Tang et al. (02PJC1527) (Scheme 145) coupled 4-aminopyrazol-3-one **30** with phenol using hydrogen peroxide catalyzed by the copper complex of 2-hydroxy-1-naphthaldehyde-2-aminothiazole [Cu^{II}-(HNATS)₂] in water at pH 6.4, to yield 4-(4-oxocyclohexa-2,5-dienylideneamino)-pyrazol-3-one **529** and 4-(6-oxocyclohexa-2,4-dienylideneamino)pyrazol-3-one **530**.

Trihydroxypropyl groups attached to position 5 of pyrazol-3-ones are prone to cleavage during oxidation with aqueous periodic acid and give the aldehyde. This method was used to obtain 5-formylpyrazol-3-ones **532a** and **534a,b** from the corresponding 5-trihydroxypropylpyrazol-3-ones **531a** and **533a,b** (68JCS(C)2248, 88PHA77) (Scheme 146).



Scheme 145

G. WITH SODIUM METAPERIODATE

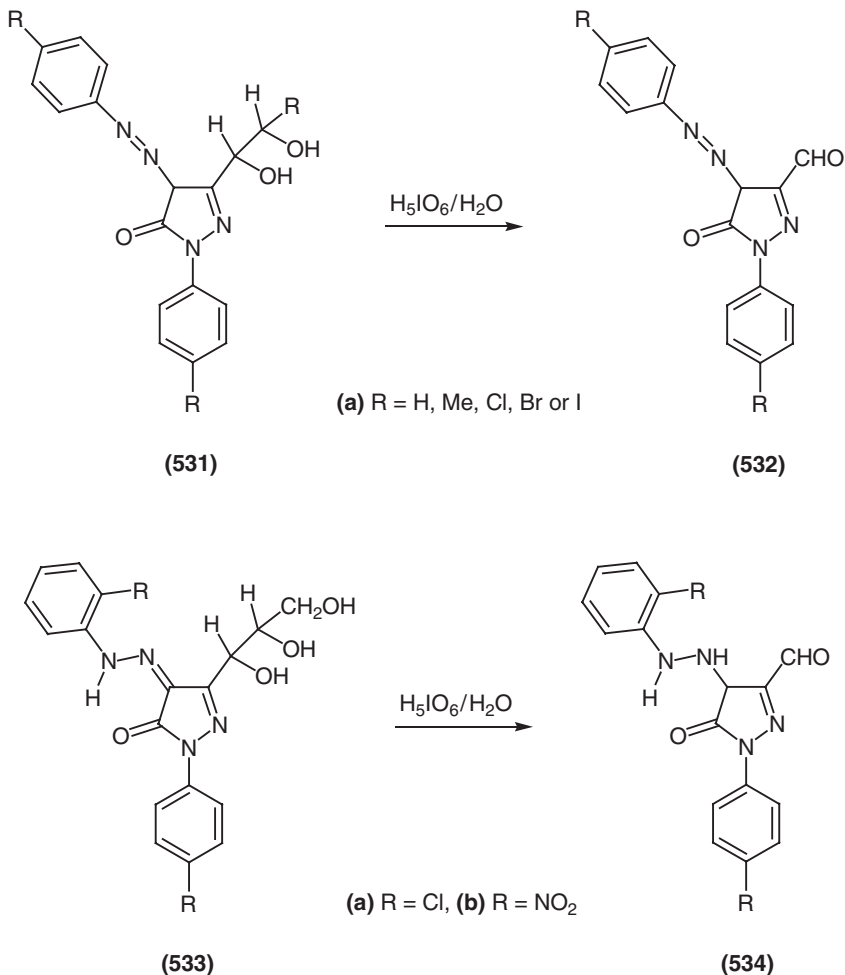
Sodium metaperiodate in aqueous methanol oxidatively cleaved pyrazol-3-ones **535a–d** into 2-(*N'*-acetyl-*N'*-methyl-*N*-phenyl-hydrazino)-*N*-(substituted)-2-oxoacetamides **536a–d**, in 64–98% yield. Under the same reaction conditions pyrazol-3-ones **537a–d** were cleaved to give acetic acid *N*-methyl-*N'*-(2-oxo substituted)-*N'*-phenylhydrazide **538f–h** and (*N'*-acetyl-*N'*-methyl-*N*-phenyl-hydrazino)oxoacetic acid **538i**, in 49–94% yield (88AP551) (Scheme 147).

H. WITH LEAD TETRAACETATE

Gillmann et al. (94SC2133) (Scheme 148) found a convenient method to prepare methyl 2-bromo-2,3-butadienoate **540** via oxidative ring cleavage of 4-bromopyrazol-3-one **539** using lead tetraacetate and boron trifluoride etherate in 59% yield. Compounds such as **540** are valuable building blocks for the synthesis of 2-aryl and 2-alkenyl substituted alka-2,3-dienoates via palladium-catalyzed cross-coupling reactions.

I. WITH POTASSIUM PERMANGANATE OR PYRIDINIUM CHROMATE

Oxidation of 4-formylpyrazol-3-one **113** with potassium permanganate in aqueous potassium hydroxide gave the pyrazol-3-one-4-carboxylic acid **541** (76PHA149) (Scheme 149), whereas 5-(α -hydroxybenzyl)pyrazol-3-one **542** and 5-benzylpyrazol-3-one **543** were oxidized by pyridinium chromate to 5-benzoylpyrazol-3-one **544** (81JCS(P1)1371).



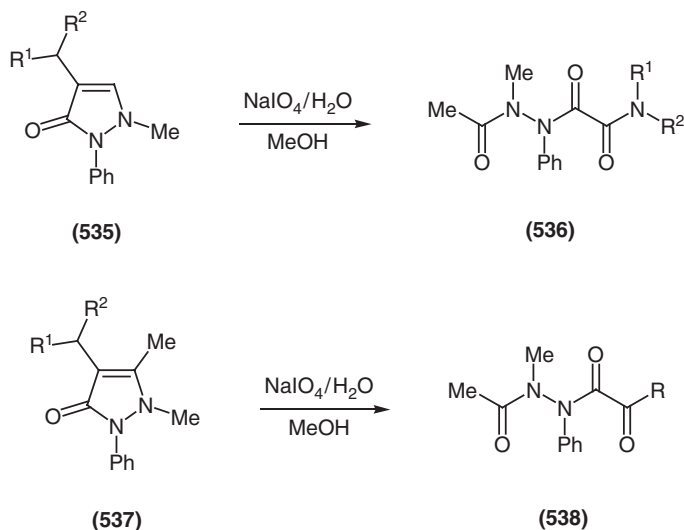
Scheme 146

XV. Reduction

The reduction of functional groups such as aldehyde, nitro, nitroso, alkene and imino as well as deamination of amines and cleavage of amides has been accomplished by various reducing agents without affecting the pyrazol-3-one ring.

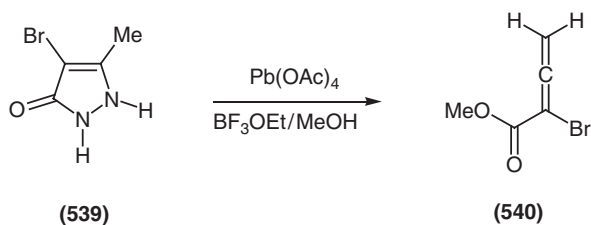
A. BY CATALYTIC HYDROGENATION

The best method by far to reduce 4-nitropyrazol-3-ones is by catalytic hydrogenation at three atmospheres in the presence of 5% or 10% palladium on carbon. The reduction can be done in methanol with a few drops of concentrated hydrochloric acid



(a) $R^1 = R^2 = H$, (b) $R^1 = H, R^2 = Me$, (c) $R^1 = R^2 = Me$, (d) $R^1 = H, R^2 = i\text{-Pr}$
 (e) $R = H$, (f) $R = Me$, (g) $R = Et$, (h) $R = i\text{-Pr}$, (i) $R = OH$

Scheme 147



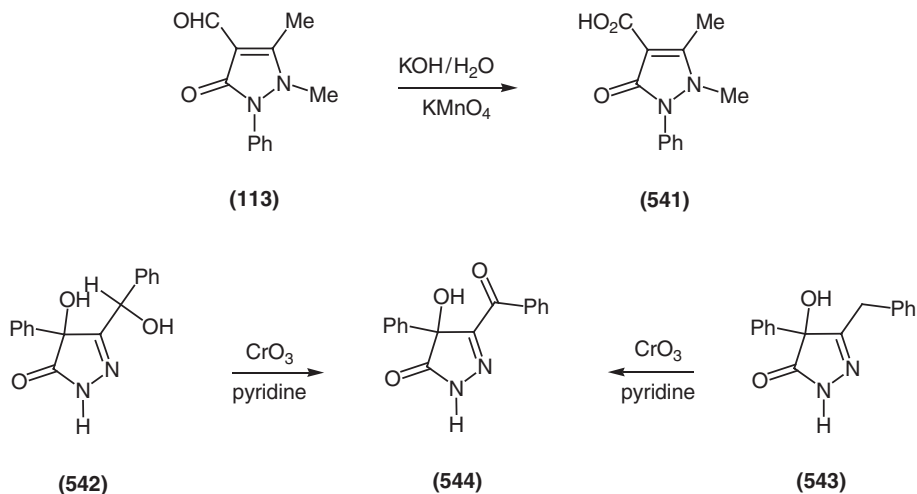
Scheme 148

or in methanol alone. Thus, nitro compounds **545a–f** were reduced to 4-aminopyrazol-3-ones **546a–f** in 49–82% yield (87EJM239, 01JHC1065) (Scheme 150).

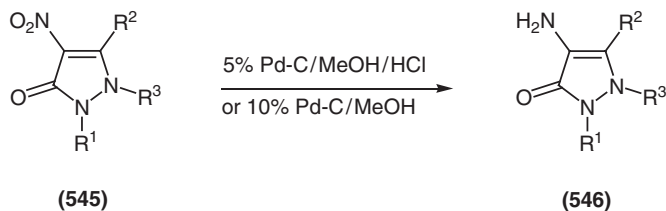
Catalytic hydrogenation of 1,2-dihydropyrazol-3-one **547** with 10% palladium on carbon in ethanol selectively reduced the α,β -unsaturated bond of the 4-hydroxycyclopent-2-en-1-yl substituent and gave 4-(3-hydroxycyclopentyl)pyrazol-3-one **548** in near quantitative yield (97JHC233) (Scheme 151).

B. WITH IRON, ZINC OR STANNOUS CHLORIDE

4-Bromo-5-(2-nitrophenylsulfonylmethyl)pyrazol-3-one **549** was both reduced and debrominated by treatment with tin(II) chloride to afford the amino derivative **550** (70CPB2058) (Scheme 152). In a patent by Buckland and Gourley (89EUP347136)

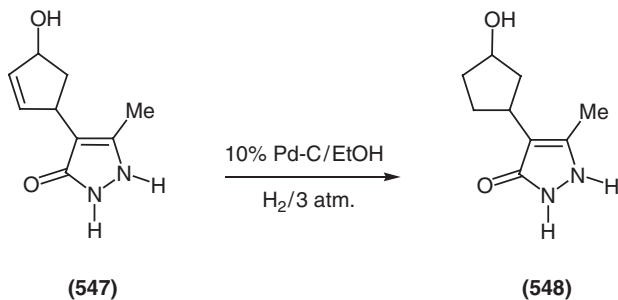


Scheme 149

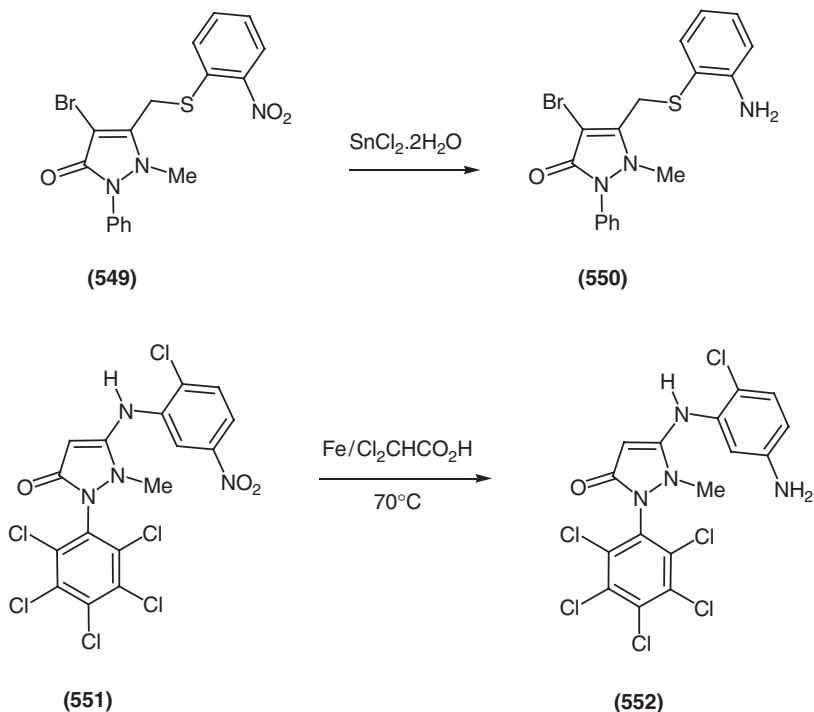


(a) $R^1 = R^3 = \text{H}$, $R^2 = 2\text{-HOC}_6\text{H}_4$, (b) $R^1 = \text{Me}$, $R^2 = 2\text{-HOC}_6\text{H}_4$, $R^3 = \text{H}$, (c) $R^1 = \text{H}$, $R^2 = 2\text{-HOC}_6\text{H}_4$, $R^3 = \text{Me}$, (d) $R^1 = \text{Ph}$, $R^2 = 4\text{-NO}_2\text{C}_6\text{H}_4$, $R^3 = \text{Me}$, (e) $R^1 = \text{Ph}$, $R^2 = 4\text{-NH}_2\text{C}_6\text{H}_4$, $R^3 = \text{Me}$, (f) $R^1 = 4\text{-NO}_2\text{C}_6\text{H}_4$, $R^2 = \text{Ph}$, $R^3 = \text{Me}$,

Scheme 150



Scheme 151



Scheme 152

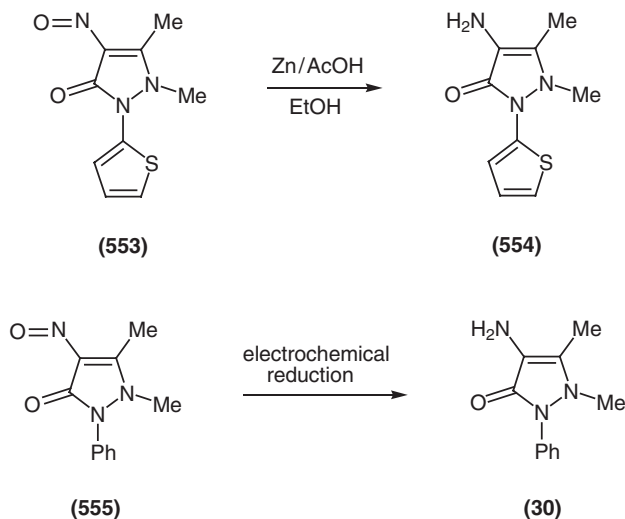
the reaction of 5-(2-chloro-5-nitroanilino)pyrazol-3-one **551** with iron powder in dichloroacetic acid at 70 °C was reported to give the corresponding amino derivative **552** in 91% yield.

4-Nitrosopyrazol-3-one **553** has been reduced to the corresponding amine **554** with zinc and acetic acid in ethanol at 5 °C. The amine was not isolated but condensed further with benzaldehyde (**79AP853**) (**Scheme 153**). Arkhipova et al. (**84EL1123**) prepared 4-aminopyrazol-3-one **30**, in 67–92% yield, by electrochemical reduction of 4-nitrosoantipyrene **555** using a variety of cathodes in 0.15–1.1 M HCl with Cd 5.6 Å/dm² at 22 °C. The yield of the amine increased with changing cathodes in the order Al < Sn < Pd.

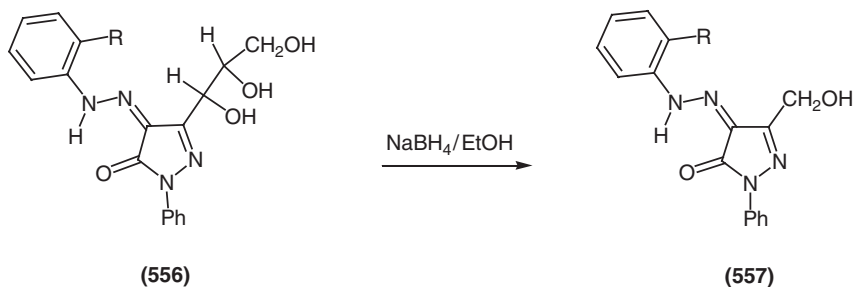
C. WITH SODIUM BOROHYDRIDE

Treatment of hydrazonotrihydroxypropylpyrazol-3-ones **556a,b** with sodium borohydride in ethanol caused reductive cleavage of the dihydroxyethyl chain without affecting the hydrazone group to give hydroxymethylhydrazonopyrazol-3-ones **557a,b** (**88PHA77**) (**Scheme 154**).

The alkene function of 4-[(2-nitrophenyl)methylidene]pyrazol-3-ones **558a–c** was selectively reduced with sodium borohydride in 1,4-dioxane to give 4-(2-nitrobenzyl)pyrazol-3-ones **559a–c**. Reduction of the nitro group was accomplished by treatment with sodium borohydride in dilute sodium hydroxide containing 10%



Scheme 153

(a) R = Cl, (b) R = NO₂

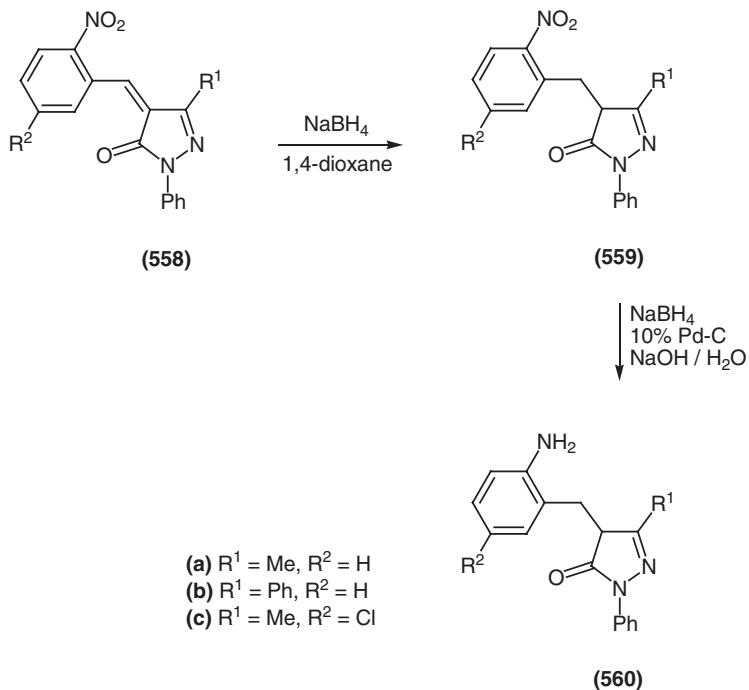
Scheme 154

palladium on carbon to afford 4-(2-aminobenzyl)pyrazol-3-ones **560a–c** (75CJC3637) (Scheme 155).

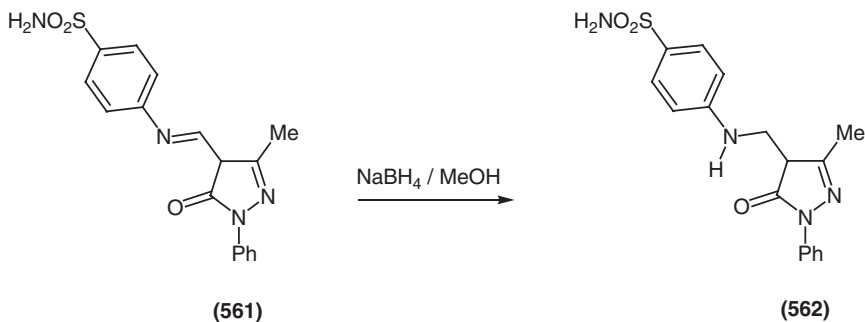
The imino group of the 4-methyleneaminobenzene sulfonamide substituent of pyrazol-3-one **561** was selectively reduced by sodium borohydride in methanol to give 4-methylaminopyrazol-3-one **562** in 70% yield (75PHA582) (Scheme 156).

Sodium borohydride in methanol cleaved the tertiary amide bond of the 4-substituent of pyrazol-3-ones **563a–e**. 4-Anilinympyrazol-3-one **564a** derived from amides **563a–d** and 4-(4-methoxyanilino)pyrazol-3-one **564e** obtained from amide **563e** were isolated in moderate yields (82H2309) (Scheme 157).

Coutts et al. (75CJC3637) and Wrzeciono et al. (78PHA264) (Scheme 158) reduced the respective 4-[(2-nitrophenyl)methylidene]pyrazol-3-ones **565a–c** and 4-[(2-furfuryl)methylidene]pyrazol-3-ones **565d–i** with sodium borohydride in 1,4-dioxane and obtained the corresponding pyrazol-3-ones **566a–i** in moderate to good yields.



Scheme 155

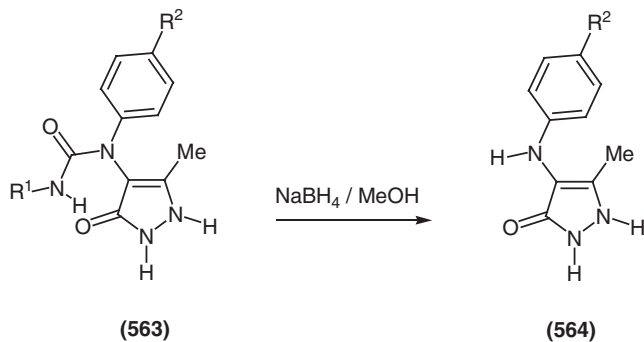


Scheme 156

Compounds **566d–i** exhibited significant anti-bacterial action against *Escherichia coli* K12.J5, *Salmonella panama* Nr.73 and *Staphylococcus aureus* 209P strains.

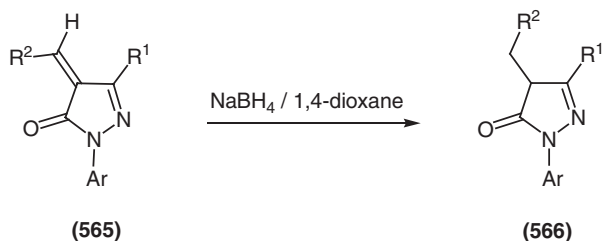
D. WITH TRIALKYL PHOSPHITES

Reduction of 4-arylmethylidenepyrazol-3-ones **567a,b** with triethyl phosphite and triisopropyl phosphite, respectively, afforded the corresponding 4-arylmethylidene derivatives **568a,b** in 48% and 31% yield as the only products (73JCS(P1)1606) (Scheme 159).



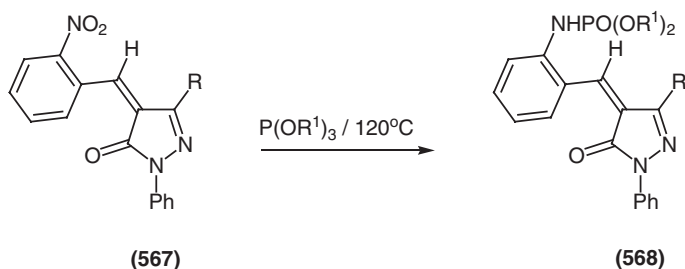
(a) R¹ = Me, R² = H, (b) R¹ = Et, R² = H, (c) R¹ = H₂C=CHCH₂, R² = H
 (d) R¹ = *n*-C₄H₉, R² = H, (e) R¹ = Me, R² = MeO

Scheme 157



(a) R¹ = Me, R² = 2-NO₂C₆H₄, Ar = Ph, (b) R¹ = Ar = Ph, R² = 2-NO₂C₆H₄
 (c) R¹ = Me, Ar = Ph, R² = 2-NO₂-5-ClC₆H₃, (d) R¹ = Me, R² = furfur-2-yl, Ar = 2-ClC₆H₄, (e) R¹ = Me, R² = furfur-2-yl, Ar = 3-ClC₆H₄, (f) R¹ = Me, R² = furfur-2-yl, Ar = 4-ClC₆H₄, (g) R¹ = Me, R² = 5-NO₂furfur-2-yl, Ar = 2-ClC₆H₄, (h) R¹ = Me, R² = 5-NO₂furfur-2-yl, Ar = 3-ClC₆H₄, (i) R¹ = Me, R² = 5-NO₂furfur-2-yl, Ar = 4-ClC₆H₄.

Scheme 158



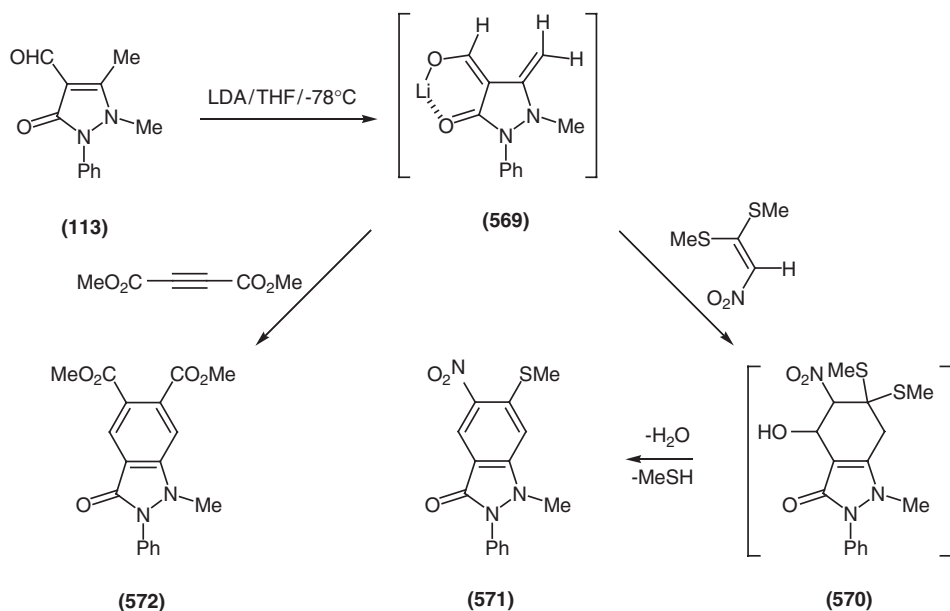
(a) R = H, R¹ = Et, (b) R = Me, R¹ = *i*-Pr

Scheme 159

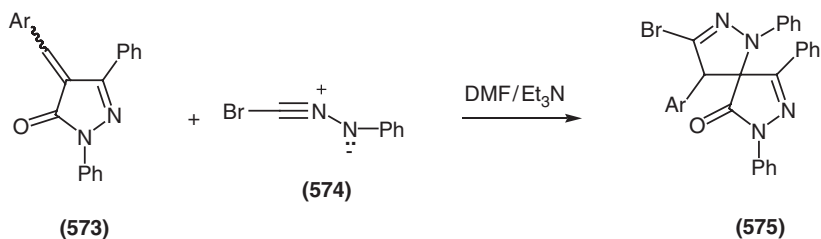
XVI. Cycloaddition

A. OF ENOLATE OF 1,5-DIMETHYL-3-OXO-2-PHENYLPYRAZOLE-4-CARBALDEHYDE

Substituents on the pyrazol-3-one ring have taken part in both Diels–Alder and 1,3-dipolar cycloaddition reactions. Stabilized dihydropyrazol-3-one enolate **569** generated by deprotonation of pyrazol-3-one **113** with LDA in tetrahydrofuran has undergone facile cycloaddition with 1,1-bismethylsulfonyl-2-nitroethene and yielded directly the indazol-3-one **571** (99JCS(P1)3001) (Scheme 160). It is proposed that the



Scheme 160



(a) Ar = Ph, (b) Ar = 4-MeC₆H₄, (c) Ar = 4-MeOC₆H₄, (d) Ar = 2-ClC₆H₄, (e) Ar = 4-ClC₆H₄

Scheme 161

initially formed adduct **570** undergoes *in situ* aromatization via dehydration and elimination of methanethiol anion. Cycloaddition of enolate **569** with dimethyl acetylene dicarboxylate afforded dimethylindazole-5,6-dicarboxylate **572** in 72% yield.

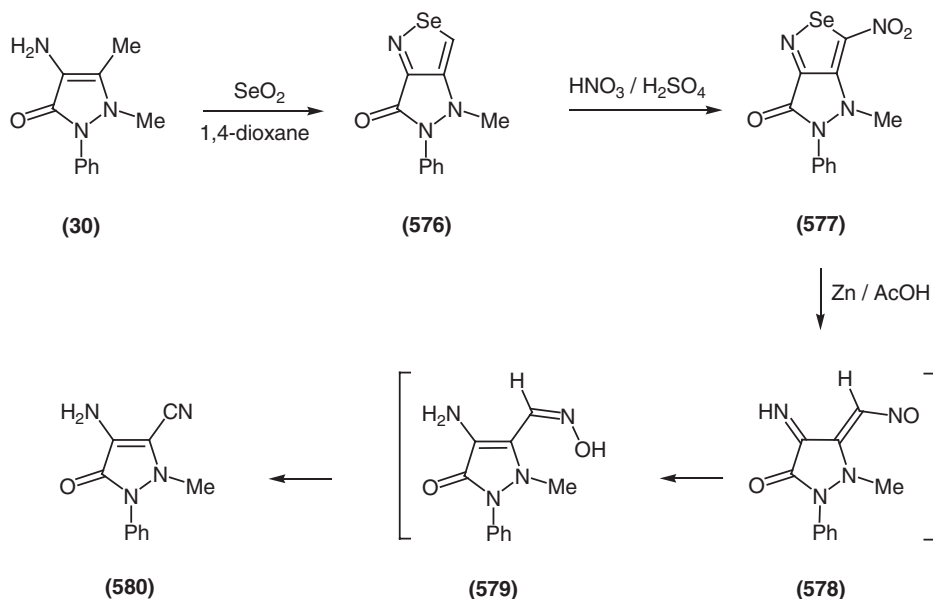
B. C-BROMO-N-PHENYLNITRILE IMIDE TO ARYLIDENEPYRAZO-3-ONES

1,3-Dipolar cycloaddition of C-bromo-N-phenylnitrile imide **574** to arylidenepyrazol-3-ones **573a–e** in DMF containing triethylamine gave the spiropyrazol-3-ones **575a–e** in good yields (01HCA3313) (Scheme 161).

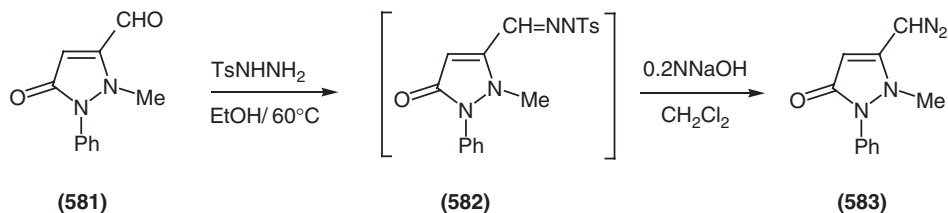
XVII. Miscellaneous Reactions

A. TRANSFORMATION OF FUNCTIONAL GROUPS

Sakakibara and co-workers (84TL4579) (Scheme 162) reported the facile conversion of the 5-methyl group of pyrazol-3-one **30** into a cyano group via fused isoselenazole ring formation followed by nitration and reduction. Thus, pyrazol-3-one **30** with selenium dioxide in dioxane gave pyrazolo[4,3-*c*]isoselenazol-6-one **576**. Treatment of **576** with nitric acid in the presence of sulfuric acid gave 3-nitropyrazolo[4,3-*c*]isoselenazol-6-one **577**. Reduction of the latter with zinc in acetic acid gave the 4-amino-5-cyanopyrazol-3-one **580**. The mechanism of this reaction was



Scheme 162



Scheme 163

envisaged to proceed by reduction of the nitro group of **577** to a nitroso derivative and then ring opening along with reductive deselenation to give 4-imino-5-(nitrosomethylidene)pyrazol-3-one **578**, followed by further reduction to 4-amino-3-oxopyrazolecarbaldehyde oxime **579** and finally dehydration to pyrazol-3-one **580**.

Pyrazol-3-one **581** was reacted with tosylhydrazide in hot ethanol to give tosylhydrazone derivative **582**. The latter was not isolated but after the solvent was removed it was treated with aqueous sodium hydroxide in dichloromethane to afford 5-diazomethylpyrazol-3-one **583**, 69% overall yield (88JHC1681) (Scheme 163).

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Recent Progress in 1,2,4-Triazolo[1,5-a]pyrimidine Chemistry

GUNTHER FISCHER

Geibelstraße 15, D-04129 Leipzig, Germany

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I. Introduction

A. GENERAL SURVEY

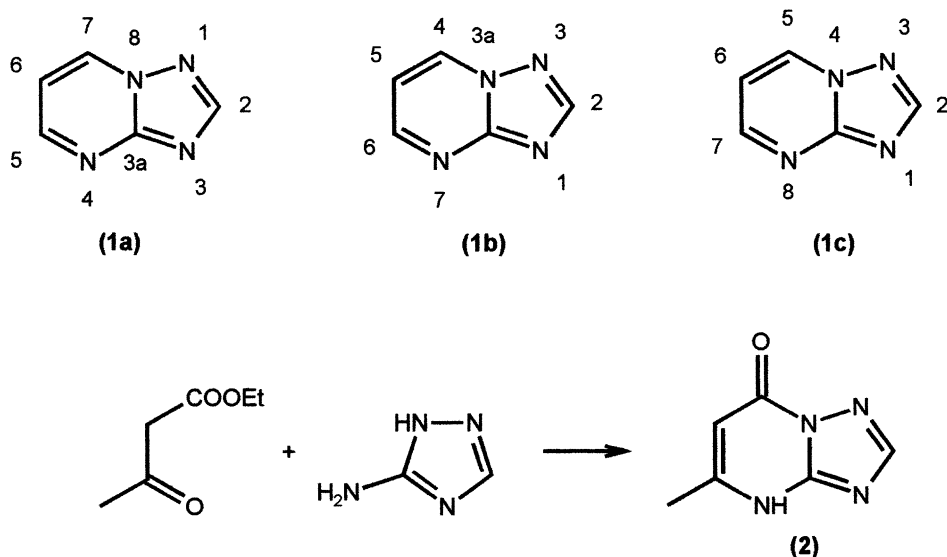
1,2,4-Triazolo[1,5-a]pyrimidines (TPs) continue to play an important role in pharmaceuticals, agrochemistry, photography, and other fields. They likewise attract attention in synthetic, analytical, and theoretical chemistry.

Since the preceding review (93AHC(57)81) about 250 chemical articles were published by the groups of Desenko, Elnagdi, Reiter (*cf.* 98MI1), Rusinov, Stanovnik, and Yang (*cf.* 03MI6), and by numerous other authors. Several handbook contributions (84CHEC(5)847, 87CH(47), 88MI1, 92CH(47II), 96CHECII(8)417) and a short review (97MI8) dealing with TPs in a wider context deserve mentioning. Further, there is a partially overlapping review treating all four nitrogen-bridgehead triazolopyrimidine structures (98AHC(72)127).

B. SCOPE AND LIMITATION

This review is based on the present author's earlier compilation (93AHC(57)81) and covers the literature to the end of 2005 together with some 2006 work. The organization of the material follows that of the 1993 review as far as possible. Patents are included provided they reveal important aspects of synthesis or application.

Tricyclic derivatives are dealt with when the additional ring is a carbocyclic one. Isomeric 1,2,4-triazolo[4,3-*a*]pyrimidines (Section II,C) and partially reduced TPs (Sections II,A,6 and IV,D) are mentioned only when they are precursors, potential intermediates, or reaction products of TPs.



Scheme 1

C. NOMENCLATURE

1,2,4-Triazolo[1,5-a]pyrimidines are numbered as in formula **1a** (Scheme 1). The common name in the photographic literature is *1,3,3a,7-tetraazaindenes* with different numbering (**1b**) (cf. 04MI10, p. 16). A third kind of numbering TPs (the *indolizin* numbering **1c**) is preferred by Reiter's group (93JHC1325 and further articles) and some other authors (93MI4, 06AX(E)01252).

Among tautomerizable derivatives, 7-hydroxy compounds have been confirmed to exist largely in the 4H-7-oxo form (e.g., **2**; cf. Section III,E,1) that, therefore, will be used in this review. For other hydroxy as well as mercapto and amino TPs, when the exact position of tautomeric equilibria is uncertain, the most probable or the respective authors' form will be depicted.

II. Syntheses

A. 5-AMINO-1,2,4-TRIAZOLES AND 1,3-BIFUNCTIONAL SYNTHONS

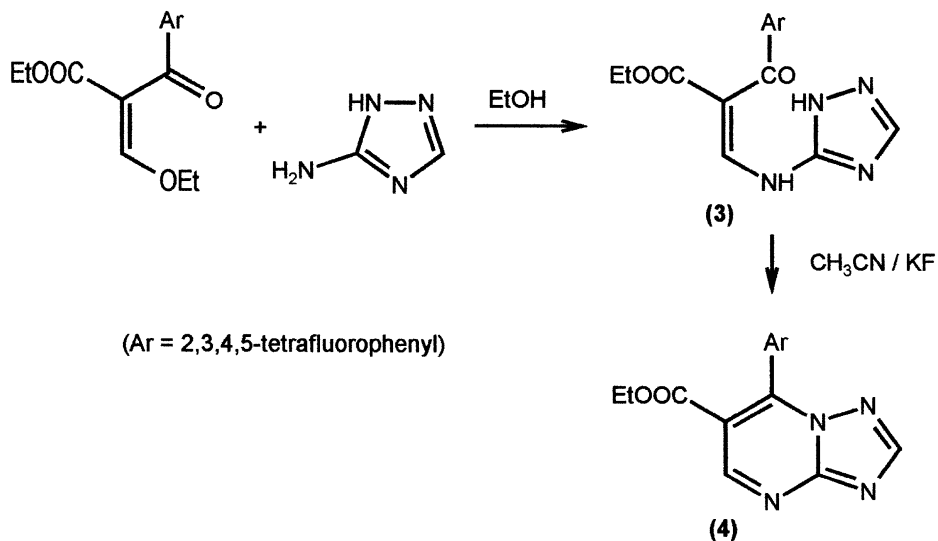
1. Principle and Conditions

By far the most TP syntheses are condensations of dinucleophilic 5-amino-1,2,4-triazoles (ATs) with 1,3-bifunctional synthons as shown in the formation of TP **2**. A general review covers corresponding reactions of acetoacetic ester with aryl- and heteroarylamines (97CHE499). To the earlier reported list of relevant functionalities described up to 1991 (93AHC(57)81, p. 85) may be added $=\text{CHSO}_2\text{R}$ (02S901) and tautomeric $=\text{C}(\text{SH})\text{NHR}$ (92JSC165).

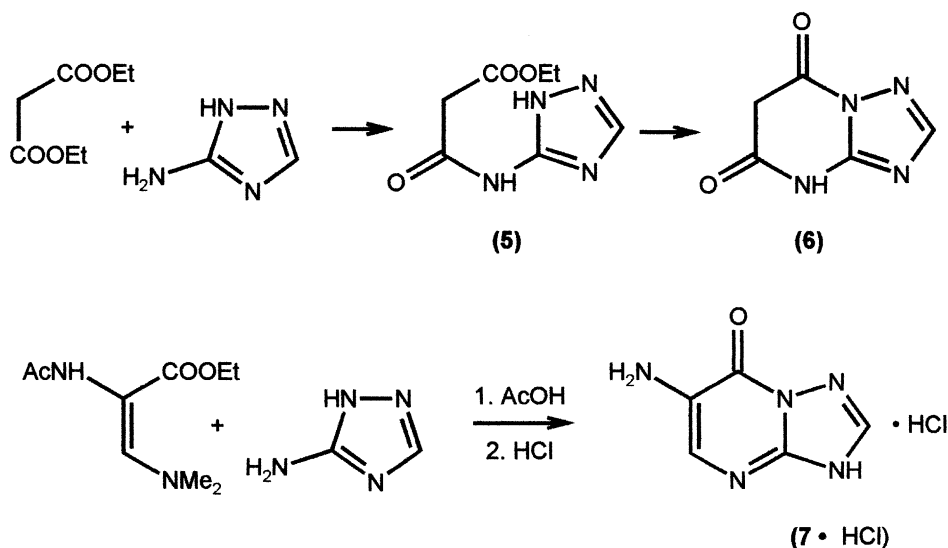
New synthetic conditions recently described involve melting under microwave irradiation, a reaction that is environmental friendly and gives higher yields than conventional heating in solvent (04JCR174; cf. 03MI4). Furthermore, certain lithium 1,3-diketonates have proven to be better synthons than the corresponding diketones (03RCB1190).

Previous mechanistic conclusions have been confirmed by isolating stable intermediate AT derivatives such as enamine **3** (Scheme 2) on reacting ATs with 3-ketovinyl ethers (01RJOC570), 3-ketoenamines (03HAC491), 3-ketoaldehydes (03MI4), enamine-2-carboxylic esters (91CPB1099), or ethoxymethylene malonates (93MI2, 99MCR277). That means, the overall reaction starts with the interaction of the AT amino group and the enolic (or analogous) functionality of the three-carbon synthon. In the two-step examples, just mentioned, the first step proceeds under milder conditions (sometimes just in ethanol at room temperature), but the final cyclization (or the one-step reaction, if the intermediate is not trapped) requires stronger means (e.g., PPA or boiling acetic acid). Under extreme conditions, triazolylamide **5** was subject to flash vacuum pyrolysis between 300 and 450 °C to give about 50% TP **6** (Scheme 3) (03ARK(is.10)262).

Libraries of fused 3-aminopyrimidin-4-ones (such as TP **7**) and other compounds were just recently prepared by the solid-phase and by the solution-phase parallel



Scheme 2

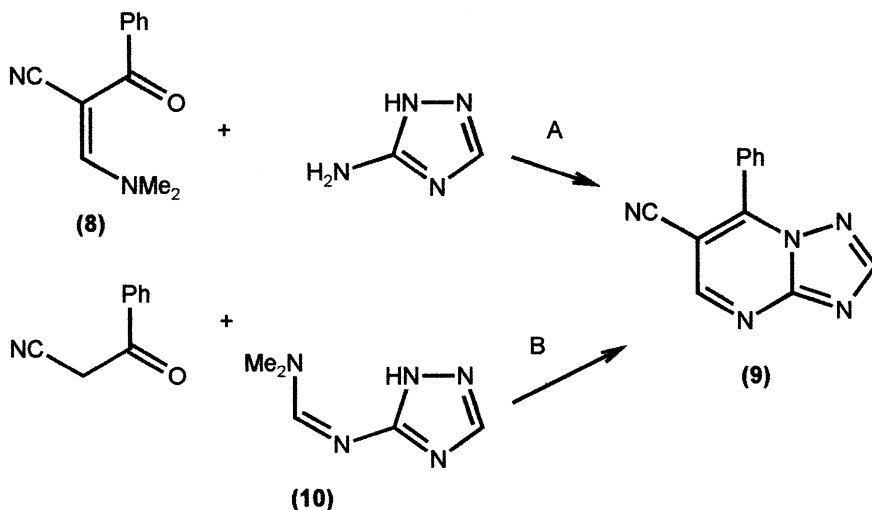


Scheme 3

synthesis (06MI2). The latter method turned out to be advantageous with respect to yield and purity.

2. Use of Modified 5-Amino-1,2,4-triazoles

Scheme 4 shows two parallel paths of pyrimidine ring annulation: the conventional method (A) and a route B using a reactive AT derivative (00JCR(S)13). Amidine **10**,



formed from AT and DMF dimethylacetal, can be regarded as the result of incorporating one carbon of the three-carbon synthon **8** into the AT molecule; condensation with a reactive two-carbon component leads to target TP **9**. Path B also serves in confirming the structure of product **9**. Similar syntheses of 7-aryl and 7-heterocyclyl TPs have been described (99JCR(S)88, 00SC1985, 03HAC491), for example, that of an antipyrine derivative (02MI1).

3. The Diversity of 1,3-Bifunctional Synthons

Examples of TP syntheses published in the relevant period are listed in Table 1, arranged according to the bifunctional synthons used and to the substituents entering the positions 5 and 7. TPs are included in reviews dealing with heterocyclic synthesis by the use of enamines (98AHC(72)283), enamine-2-carboxylic esters (93PHC34, 99JHC1581), and ketene mercaptals (91MI3).

In recent years, 3-ketoenamines have growing interest as building blocks for 7-aryl TPs (*cf.* Scheme 4, Path A) (01JHC1119, 04WOP108729). They also serve to synthesize 7-heterocyclyl TPs (04JHC381, 04MI6). In addition to usual *N,N*-dimethyl compounds (**8**-type) also analogs having a free amino group can be used as in the synthesis of 7-trifluoromethyl derivatives (03RCB1190). Enaminones can be formed *in situ*, for instance, from dimedone and DMF dimethylacetal (05RCB2903).

In the course of the cyclization of the stable tetrafluorobenzoyl derivative **11a** (Scheme 5) fluorine at the *o*-position is involved in the reaction and is replaced to give trifluorobenzo TP **11b** (05RJOC1071). Acetylonyl is introduced as substituent into the 7-position by the use of triketone heptan-2,4,6-trione (95JHC407).

The electron acceptor tetracyanoethylene on interaction with AT first forms a charge transfer complex that after loss of hydrocyanic acid is transformed into

Table 1. Syntheses of TPs from 1,3-bifunctional synthons and ATs

Bifunctional synthon ^a	R-5 ^b	R-7 ^b	References
1,3-Dialdehyde	H	H	06WOP18725
2-Formylacetal	H	H	93RCB1921, 94RCB1884
1,3-Diacetal	H	H	99JCS(P1)1527
2-Formylvinyl ether	H	H	02MI6, 06WOP18725
2-Formylvinylchloride	H	R	94T12113, 02MI2
3-Iminiovinylchloride	H	R	94T12113
2-Formylenamine	H	R	94T12113, 06S59
3-Iminioenamine	H	R	94T12113, 95H(40)729
3-Ketoaldehyde	R	H	97MI2, 04JHC647
3-Ketoacetal	R	H	92MI3, 96MI1
3-Ketovinyl ether	H	R	01RJOC570, 05T5379
3-Ketovinyl sulfone	R	H	02S901 ^c
3-Ketoenamine	H	R	04JCR174, 04JHC267, 04WOP108729
1,3-Diketone	R	R'	92MI4, 99MI1
3-Ketoalkyne	R ^d	H	05ZN(B)1175
2-Formylcarboxylate	R	OH	99CPB928
2-Alkoxyacetylacetal	OH	H	04MI2
Enamine-2-carboxylate	H	OH	93JHC1253, 97JHC247
Acetylenedicarboxylate	COOMe	OH	99MI2
3-Ketocarboxylate	R	OH	92MI2
3-Alkoxyacrylate	OH	R	99EUP947516
Alkoxyalkylene malonate	R	OH	93MI2
2-Chloroacrylate	OH	R	00CHE1329
Malonic ester	OH	OH	92MI2, 97JST(415)285
Malonyl chloride	OH	OH	93JHC169
2-Acylketene mercaptal	SR	R'	92MI4, 05WOP54246
2-Cyanoketene mercaptal	SR	NH ₂	02WOP40485
Alkoxyalkylene cyanoacetate	R	NH ₂	97BMCL1087
Alkoxyalkylene malonitrile	R	NH ₂	95IJC(B)209
2-Formylnitrile	H	NH ₂	01HEC485
2-Cyanoenamine	H	NH ₂	02MI7
Malonitrile	NH ₂	NH ₂	95JCR(S)290
2-Thiocarbamylcarboxylate	NHR	OH	92JSC165

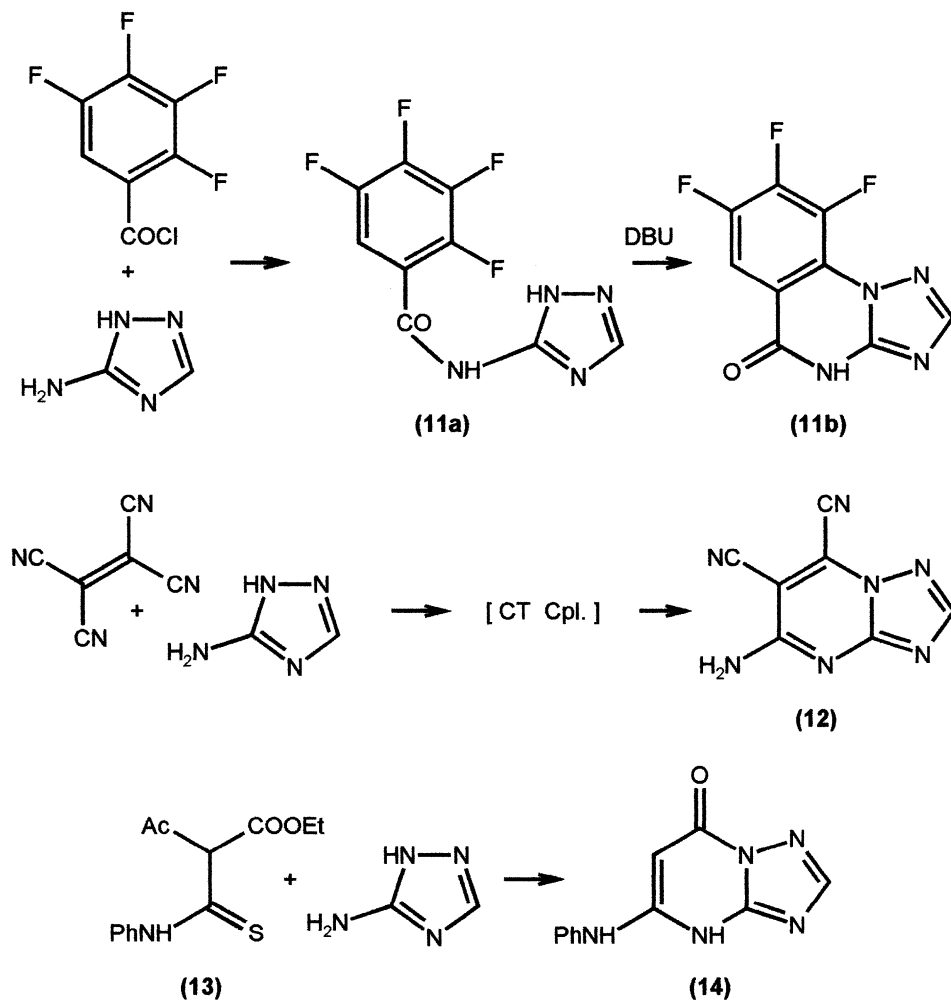
^aOr tautomeric form.

^bSubstituents on C-5 and C-7, respectively; R and R' mean (possibly substituted) alkyl, aryl, heterocyclyl, and H; OH means hydroxy or tautomeric oxo form.

^cAnd regioisomeric 7-R compound.

^dDeoxyaltrose derivative [relating C-glycosides *cf.* 98AHC(70)163].

dicyano TP **12** (97PHA23). Fusion of 1,4-naphthoquinone or indenone onto TP can in a similar way be performed by the use of 2,3-dicyano-1,4-naphthoquinone or dicyanomethylene indane-1,3-dione, respectively. (Another indeno TP is accessible from triketone 2-acetyllindane-1,3-dione (93IJC(B)440).) On the other hand, acetoacetic ester **13** with AT suffers ester group cleavage to form anilino TP **14** (92JSC165).

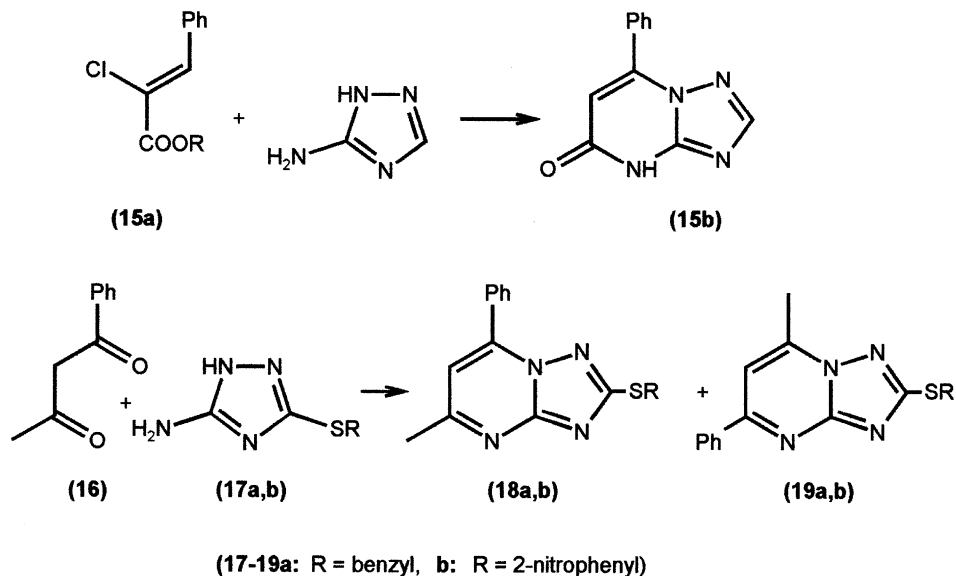


Scheme 5

4. Regioselectivity

3-Ketocarboxylic esters condense with AT, as a rule, to give exclusively 7-oxo derivatives (see Scheme 1); an exception is that of a side reaction in a special case (93JHC1325). Esters having instead a 3-acetal or 3-enolether functionality, however, are known to tend to reverse reactivity (e.g., 99EUP947516, 04MI2). 2-Chlorocinnamic acid (**15a**, Scheme 6) or its ester remarkably also behave so (00CHE1329).

Herbicide chemists have continued to report studies on regioselectivity involving the reactions of unsymmetrical 1,3-diketones and AT derivatives (92MI1, 92MI4). Benzoylacetone (**16**), trifluoroacetylacetone, and 2-acetylcyclopentanone, for example, in an acidic medium combine with ATs (e.g., **17a**) to form preferentially 5-methyl TPs (70–97%) such as **18a** and to a minor extent 7-methyl isomers (e.g., **19a**); the



Scheme 6

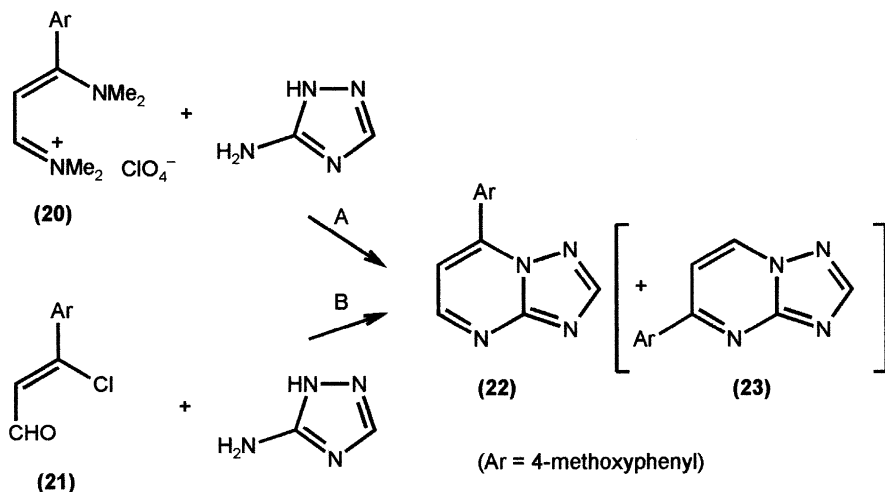
ratio of **18a** and **19a** is 82:18. Reiter and coworkers contributed further examples (95JHC407) and concluded from the results that these reactions are more influenced by steric than by electronic factors.

Changing the pH value changes the situation (00MI1): Whereas the isomers **18b** and **19b** in acetic acid are similarly obtained in a ratio of 81:19, this ratio is reversed in the presence of sodium ethylate (26:74 at 25 °C). Increasing temperature decreases the regioselectivity (ratio 49:51 at 60 °C in the latter medium). Mixtures of isomers were also obtained from several triketones and 2-methylthio AT (95JHC407).

Reactions of 1-aryl-3-iminioenamines (such as **20**) and AT (Scheme 7, Path A) in the presence of sodium hydride (DMF, 100 °C) proceed under regiochemical control; only 7-aryl TPs (e.g., **22**) can be isolated (94T12113). The same results are obtained with the corresponding 2-formylvinylchloride (**21**, Path B), 3-iminiovinylchloride, 2-formylenamine, and 3-ketoenamine.

Other conditions yield admixtures including the isomeric 5-aryl compound (**23**), thus from enamine **20** (with NaH) at higher temperatures or from vinylchloride **21** in a neutral medium. In the respective authors' opinion Path A is the better route to pure 7-aryl TPs while Path B provides better yields of 5-aryl TPs from the mixtures. Analogous reactions via Path A lead exclusively to 7-heterocyclyl TPs (98H(47)689).

Scheme 8 shows the behavior of 2-acylvinyldisulfones, for example, **24** as a hydrate (02S901). In water or acetic acid (Path A) mixtures of isomers (e.g., **25** and **26**) are formed the composition of which depends on the C-2 substituent of the AT. In boiling acetonitrile, however, the 5-substituted regioisomer (**26**) is exclusively obtained. The same reaction at room temperature (Path B) stops at intermediate **27** that can be aromatized in boiling acetic acid to give isomer **26**.



Scheme 7

To add a synthesis chosen from the triazoloquinazoline series, the reaction of the activated aryl chloride 2,3-dichloro-6-nitrobenzonitrile and 3-methylthio AT leads to a mixture of isomeric triazolo[5,1-b]- and triazolo[1,5-a]quinazoline derivatives, though both in poor yields (95JHC1359).

One single example of the formation of a TP ring isomer was found among AT reactions during the relevant period: Under the hard conditions of pyrolysis, Meldrum's acid derivative **28** gives a mixture of oxo TP **29** and oxo-triazolo[4,3-a]pyrimidine **30**, the proportions changing from 36:64 to 69:31 between 400 and 700 °C (97JCS(P1)1799). They are regarded as thermodynamic and kinetic products, respectively.

5. Direct Introduction of Substituents onto Positions 2, 3, 4, and 6

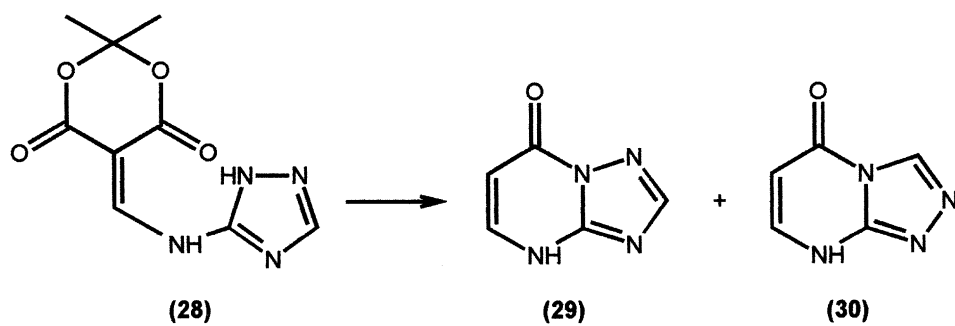
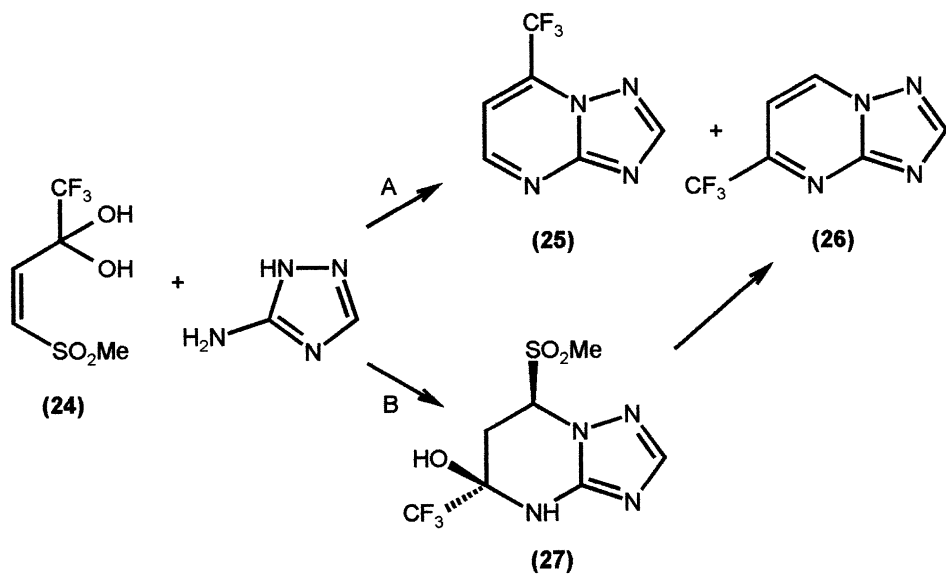
Triazolopyrimidines substituted at these sites are obtained from accordingly substituted synthons as exemplified by the synthesis of TP **31** (Scheme 9) (97JCR(M)2378). Further examples for the positions 2, 4, and 6 are listed in Table 2.

Application of AT 3-carboxylic acid under *standard conditions* of TP synthesis (boiling acetic acid) usually leads to decarboxylation. This can be avoided, in the reaction with sulfon **24**, by boiling the mixture in water (02S901).

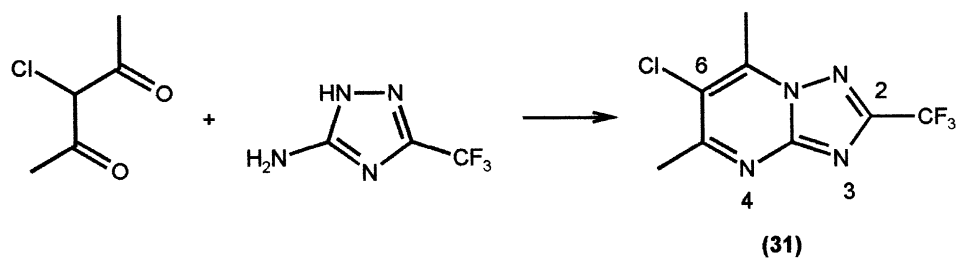
Condensations of 1,3-dicarbonyl synthons (99JCS(P1)1527) or equivalents (e.g., **33** or **34b**) (99CHE708) and 4-substituted ATs provide an approach to quaternary 1,2,4-triazolo[1,5-a]pyrimidinium salts substituted onto N-3, such as **32** and **35** (Scheme 10).

6. Syntheses via Dihydro Derivatives

Different from bromide **34b**, chalcones unsubstituted onto the double bond (e.g., **36**) when condensing with AT yield dihydro TPs (e.g., **37a**, Scheme 11)



Scheme 8



Scheme 9

Table 2. TPs substituted onto positions 2, 4, or 6 from direct synthesis

Position	Substituent ^a	References
2	Aryl	97RJOC1784
	SH	04ARK(is.5)77
	SR	92MI1, 95JHC407
	SR'	00MI1
	SO ₂ R	00RJGC1458
	SO ₂ NHR'	04MI4, 05MI6
	NH ₂	97RJOC1784
	NHR'	99JCS(P1)1527
	NR ₂	93MI2, 02JHC319
	NHSO ₂ R'	97BMCL1087
	N=CHR' ^b	03USP6570014
	NO ₂	97RJOC1784
	Fluoroalkyl	99JFC(96)51
	CH ₂ OH	97RJOC1784
	CH ₂ COOH	97RJOC1784
	COOH ^c	02S901
COOR	97RJOC1784	
Heterocyclyl	95IJC(B)209	
4	Alkyl	03USP6570014
6	Aryl ^d	95H(40)729
	SO ₂ R' ^d	95H(40)729
	NHCOR	97JHC247
	NHCOOCH ₂ Ph	99CCC177, 05JHC1167
	N=N-R'	95JCR(S)290, 97JCR(M)2378, 98MI2, 04JHC647, 04ZN(B)721
	Fluoroalkyl	05WOP87770
	CH ₂ CH ₂ OH ^e	93RCB1265
	Sugar derivative	02MI6, 05MI5
	CH ₂ COCH ₃	97RCB1178
	CN	99JCR(S)88, 02MI8
	COOEt	97BMCL1087, 05WOP54246
	Heterocyclyl	93JHC1253, 95H(40)729 ^d , 02MI7, 04T4601

^aR: alkyl, R': aryl.

^bProtected amino group.

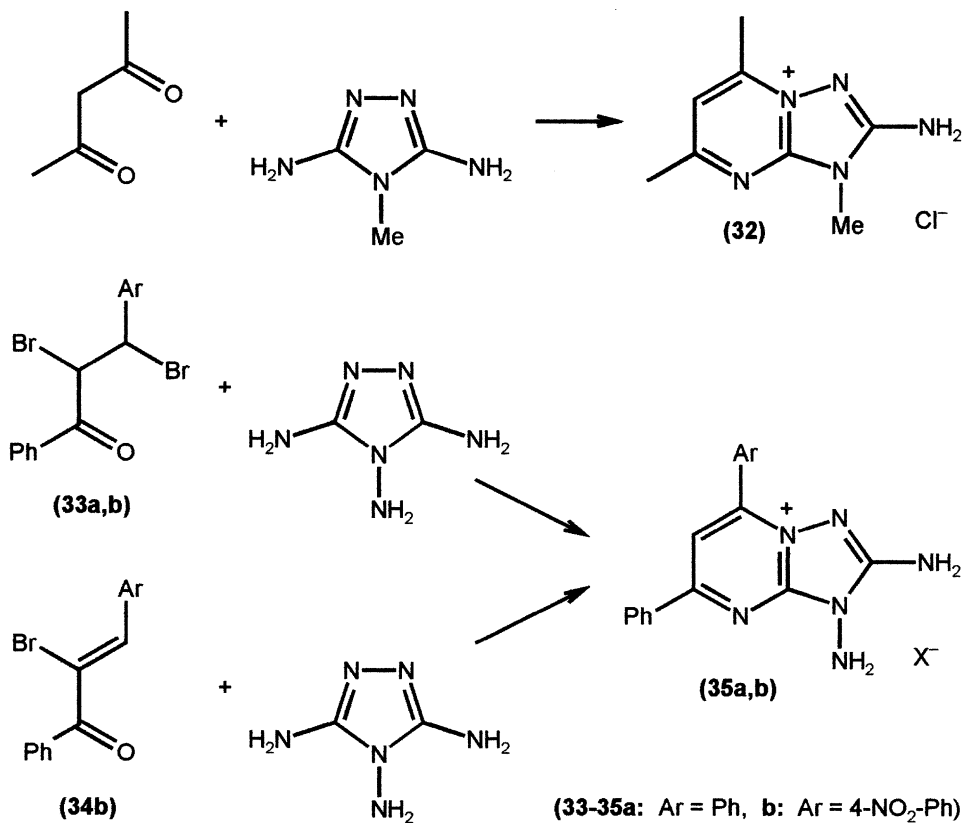
^cSee text.

^dFrom 2-substituted 3-iminioenamines.

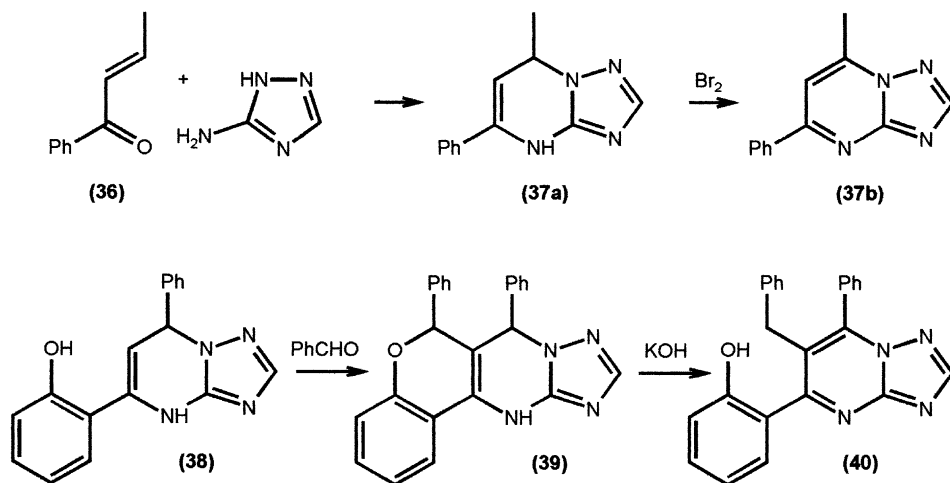
^eFrom 1,1-diacetyl cyclopropane.

(91CHE1242). Desenko's group has continued the work in this field (95CHE125). Dehydrogenation proceeds by means of bromine oxidation (91CHE88) or spontaneously by air (00CHE1329, 04MI1).

5-(2-Hydroxyphenyl)-dihydro TP (**38**) can merely aromatize in the presence of benzaldehyde in superbases media (KOH/DMF) (96CHE215), but the aldehyde can additionally be involved in the reaction to give tetracyclic pyran derivative **39**. The latter substance on heating in similar media undergoes aromatizing isomerization



Scheme 10



Scheme 11

that may occur via reductive opening of the pyran ring and concurrent dehydrogenation to yield TP **40**, alternatively hydroxide assisted elimination of phenoxide may be followed by aromatization (01CHE1312).

A three-component condensation of benzaldehyde and ketone (without isolating the chalkone) with AT leads to a mixture of dihydro and aromatic TP (93CHE406).

B. OTHER PYRIMIDINE RING SYNTHESSES

The annulation of pyrimidine onto the triazole ring can be accomplished by the use of heterocyclic precursors that can be regarded as masked 1,3-bifunctional reagents. This way, triacetic acid lactone (**41**, Scheme 12) reacts as a masked 1,3-diketone and transforms AT to TP **42** together with ring isomer **43** and decarboxylation product **44** (02CRC517).

Oxazolones play a similar part (93H(35)955, 94JCR(S)416, 94MI2). Thus, enol ether **45** behaves as a masked 3-ethoxyacrylate and yields, through intermediate **46**, benzamido TP **47** that, under harsher conditions, directly forms from compound **45**.

Condensation of acetophenone with AT in DMF and catalytic acetic acid (Scheme 13) leads to dihydro TP **49** and byproduct **50** that in the presence of hydrochloric or phosphoric acid becomes the main product (92DOK801). It seems to originate from the hypothetical intermediate **48** by reaction with the solvent DMF.

Finally, 5,6-benzo TP derivative **51** can be synthesized from anthranilic acid and the appropriate 1,2,4-triazolinethione derivative (93AQ621).

C. 2-HYDRAZINOPYRIMIDINES AND ONE-CARBON SYNTHONS

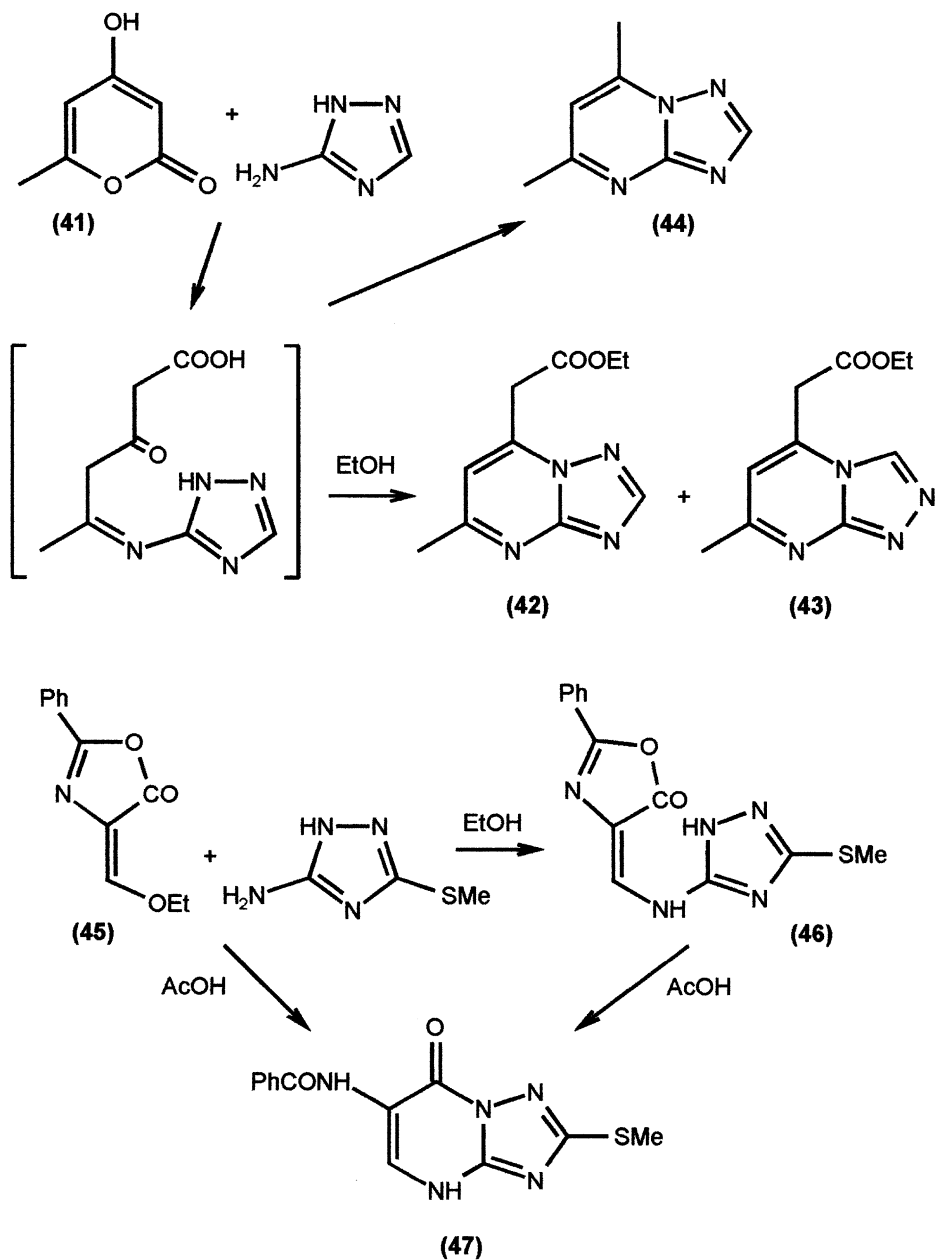
1. Principle

A second common TP synthesis consists in the condensation of a C₁-synthon with a 2-hydrazinopyrimidine (HP) derivative (e.g., **52**, Scheme 14). A triazolo[4,3-a]pyrimidine (e.g., **53**) initially forms that often can be isolated (98ZN(B)1203). Harsher conditions allow it to isomerize to the target TP **54** by Dimroth rearrangement. By contrast, TPs (e.g., **55**) can be obtained from HPs in a one-pot reaction (99JFC(96)51).

A review of triazole annulation is available (93CHE1369).

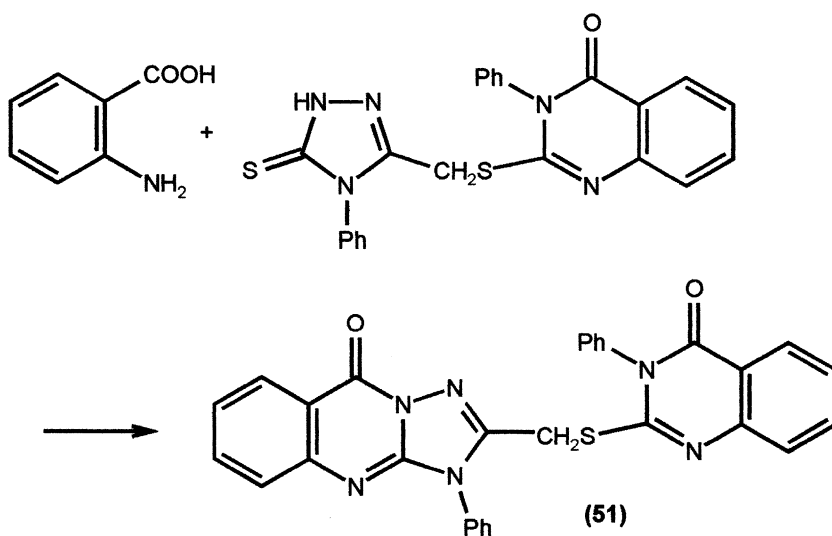
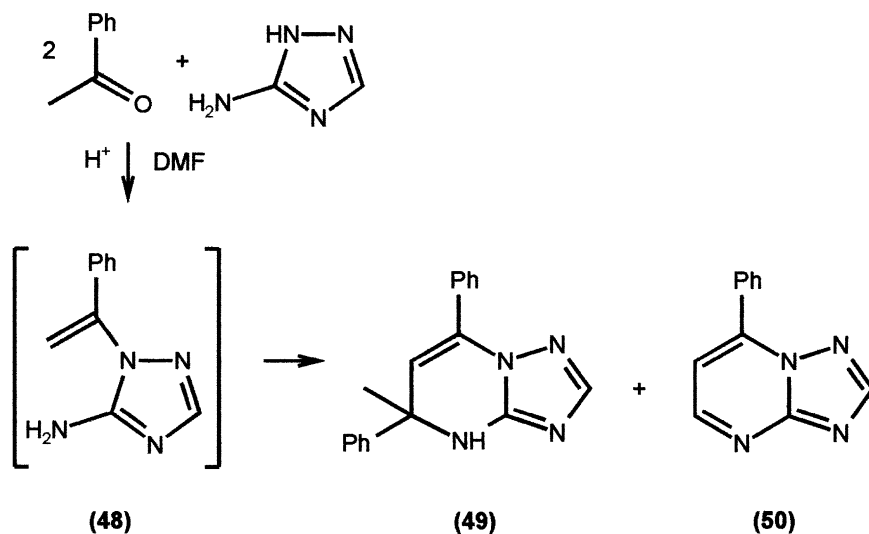
2. The Dimroth Rearrangement

This reaction was reviewed in the context of heterocycle chemistry (73CIM39, 99AHC(75)79) as well as in connection with the reactivity of 1,2,4-triazolo[4,3-a]pyrimidines (90AHC(49)277, 99AHC(73)131). New examples include those of the formation of the above-mentioned 5,7-dimethyl TP (**44**) by an alkaline rearrangement (94MI1) and of the synthesis of thioether **57** by benzylation of [4,3-a] compound **56** (Scheme 15) in strongly alkaline solution (whereas alkylation in acetone/potassium carbonate is not accompanied by isomerization) (04MI9).



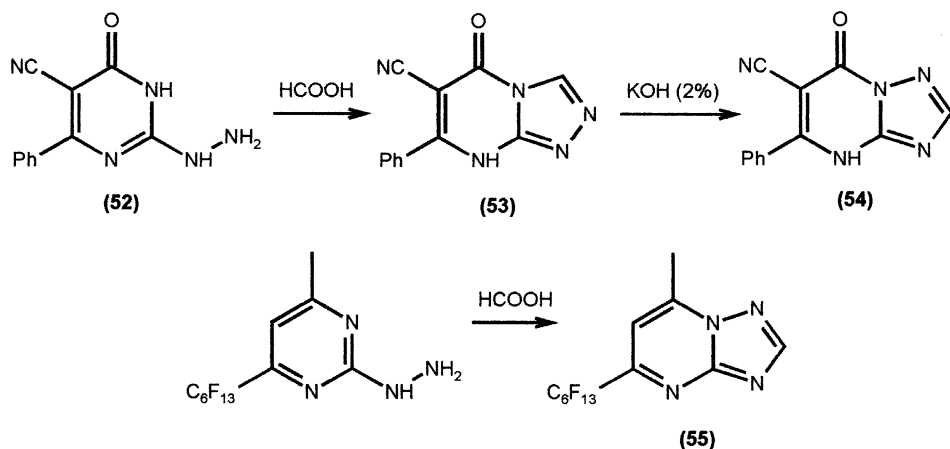
Scheme 12

Camphor derivative **58** falling into the [4,3-a] series isomerized to yield a mixture of the major *endo*-isomer **59** and the minor *exo*-isomer (02TA821). C-Glucosyl derivatives of the same series, in the presence of diazabicycloundecene (DBU), unexpectedly also gave the [1,5-a] ring isomers (94MI3; cf. 98AHC(72)127, pp. 165–168).

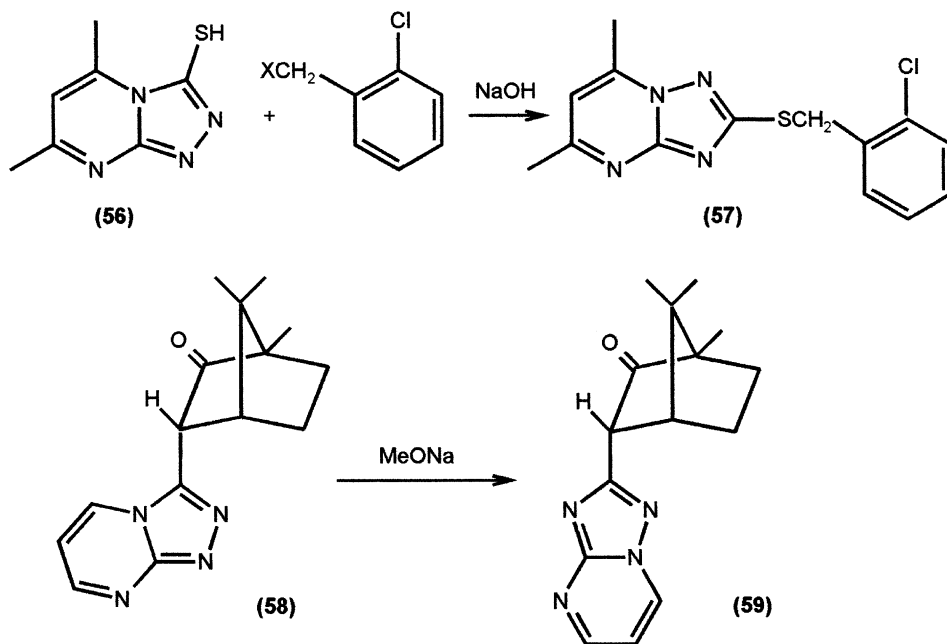


Scheme 13

Nitrile **53** mentioned above, under the influence of more concentrated alkali, suffers a Dimroth-like rearrangement involving the cyano group in the recyclization to form imine **60** (Scheme 16) (98Z_N(B)1203). When the pyrimidine NH group in hydrazine **52** is blocked as in methyl derivative **61** then a primary cyclization involves the pyrimidine N-1 atom (to give **62**) and isomerization affords N-methylated 5-oxo TP **63**.



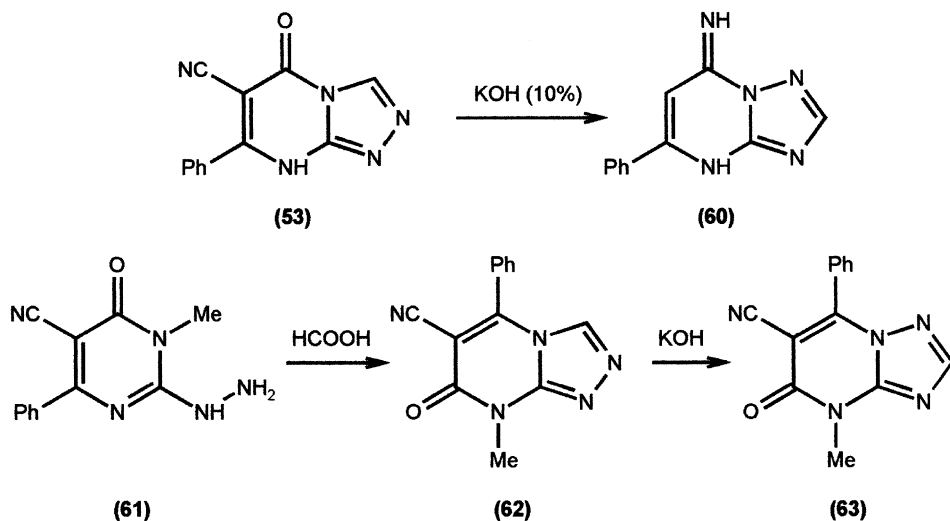
Scheme 14



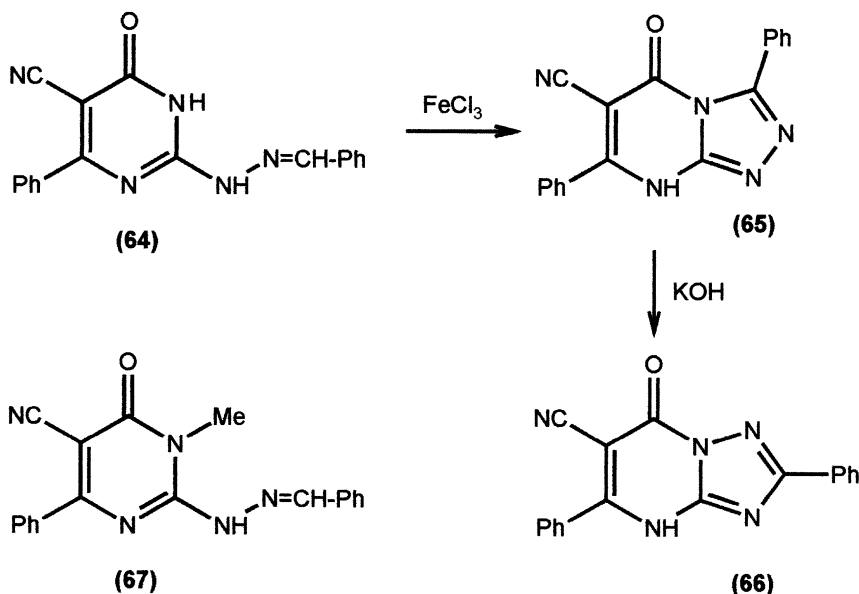
Scheme 15

3. Use of Modified 2-Hydrazinopyrimidines

In an additional step inserted before cyclization, a C₁-synthon can be incorporated in the hydrazinopyrimidine. Examples of frequently used modified HPs are those of hydrazides or (in the presence of oxidants) hydrazones. Thus precursor **53** of TP **54** is easily obtained from the N^β-formyl derivative of HP **52** by heating (98Z^N(B)1203).



Scheme 16



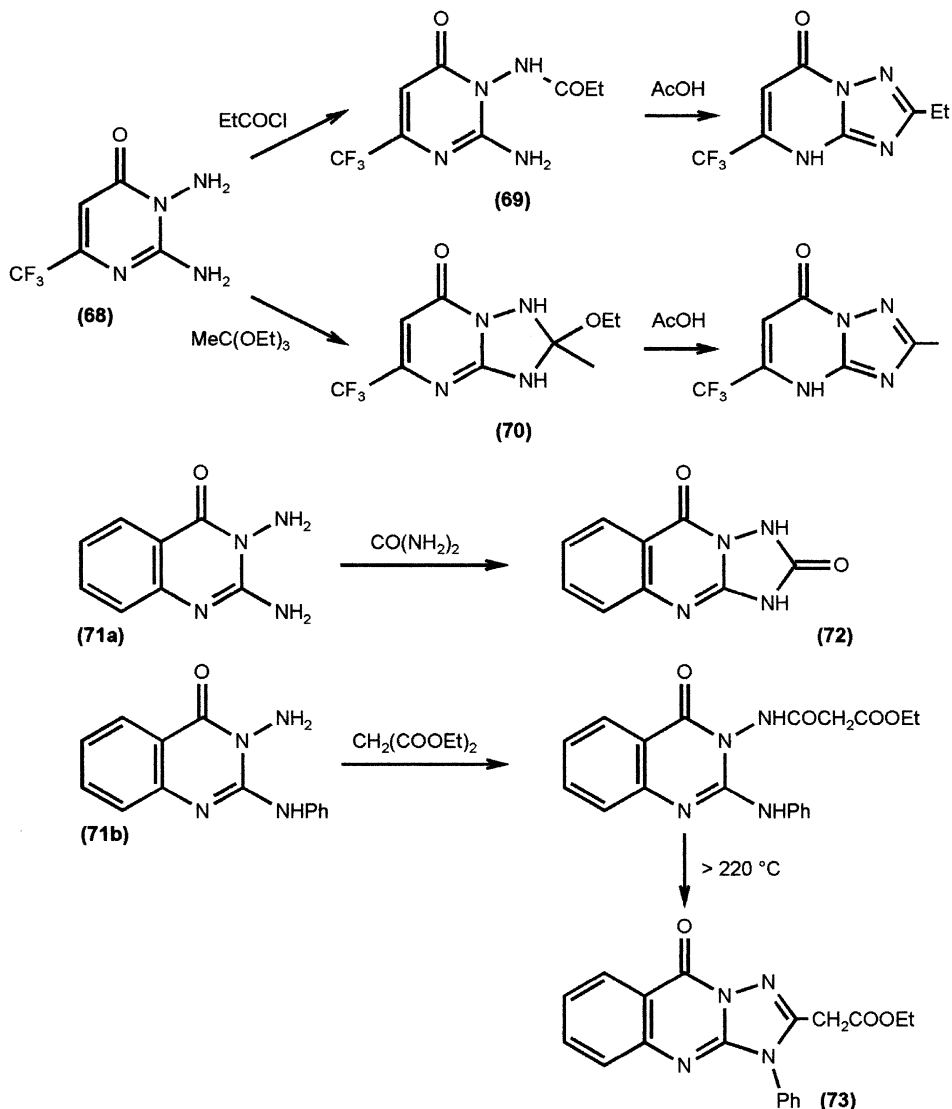
Scheme 17

On the other hand, hydrazone **64** (derived from hydrazine **52**) yields, analogously to phenyl compounds **53** and **54**, diphenyl derivatives **65** and **66** (Scheme 17). Its 3-methyl analog (**67**) reacts in the same way. Similar syntheses starting from the hydrazones of benzaldehyde (**93MI4**) or 3,3-dimethylbutyraldehyde (**96MI1**) were described as one-pot reactions skipping the stage of the [4,3-a] isomers.

D. OTHER TRIAZOLE RING SYNTHESSES

1. From 2,3-Diaminopyrimidines and One-Carbon Synthons

Most cyclizations of 2,3-diaminopyrimidones (e.g., **68**) (04JAP(K)107228) or corresponding quinazolones proceed with the participation of carboxylic acids or their derivatives (esters, anhydrides, chlorides, or orthoesters) as shown in Scheme 18.



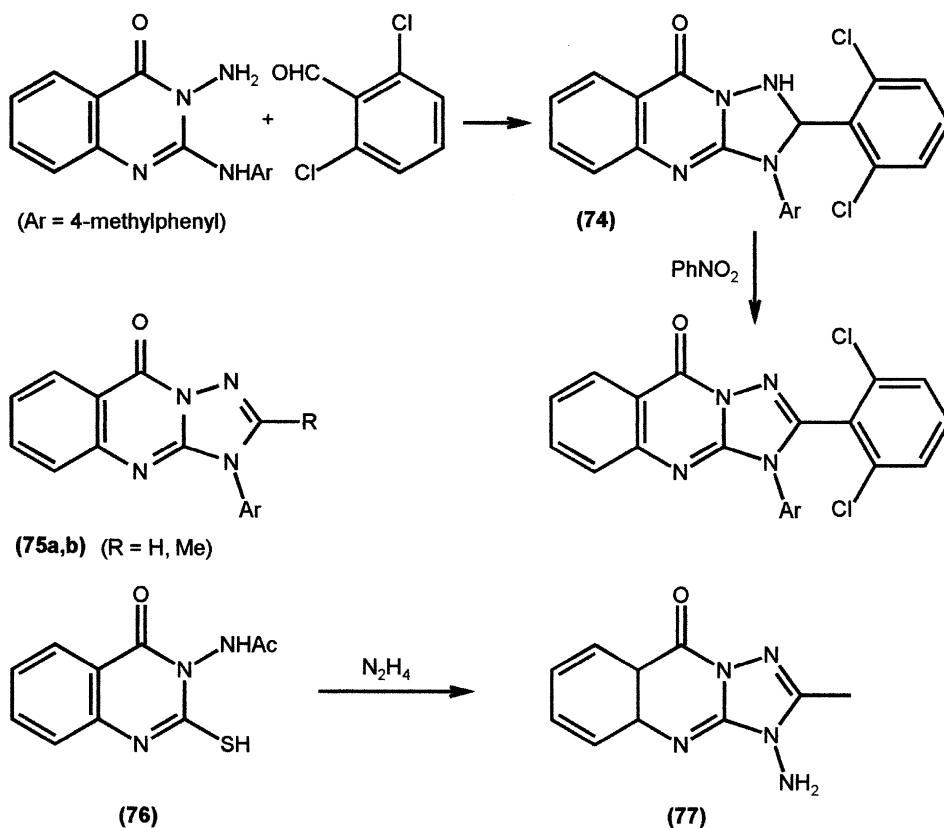
Scheme 18

Noncyclized or saturated intermediates (**69**, **70**) can frequently be found. Cyclizations of quinazolones (e.g., **71a**, **b**) by means of urea (85IJC(B)873) or malonic ester (97BCJ2209) yield triazoloquinazolones **72** and **73**, respectively, functionalized at C-2.

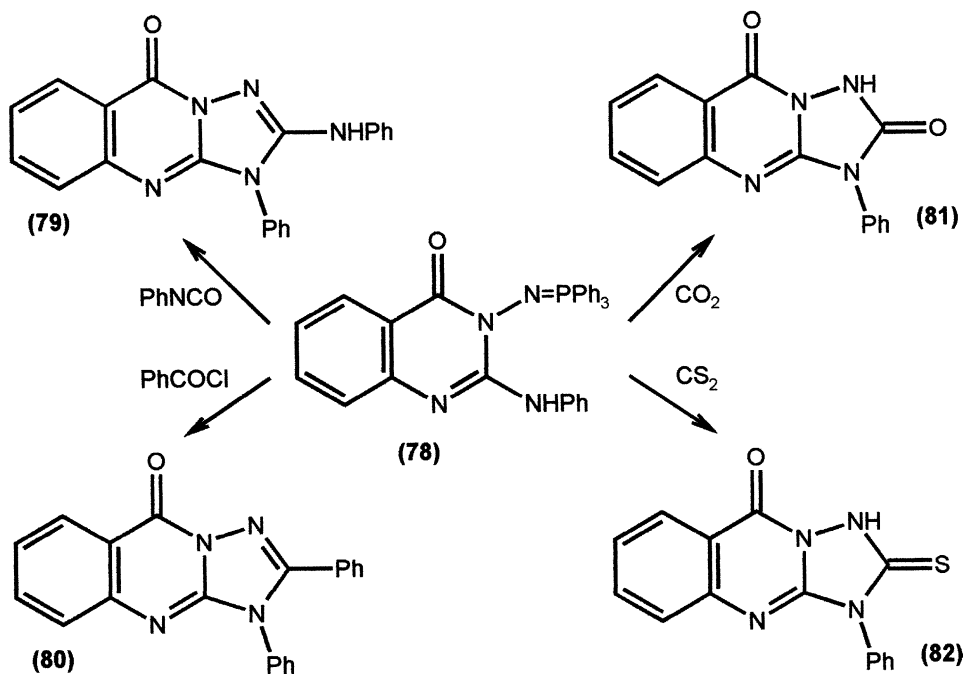
Application of aldehydes (Scheme 19, upper part) leads, through intermediate anils, to dihydro compounds (e.g., **74**) that can be dehydrogenated, for example, by nitrobenzene (01M1063). 2-Hydroxy-1-naphthaldehyde or acetylacetone suffer elimination of 2-naphthol or acetone, respectively, during the reactions; products **75a** and **b**, respectively, are obtained.

A hypothetical intermediate 2-hydrazinoquinazolone that without doubt forms from 2-mercapto compound **76** and hydrazine consequently cyclizes to give amine **77** (03JHC973).

Iminophosphorane **78** is easily synthesized from quinazolone **71b** (04EJOC3872). It undergoes, in the respective author's words, *tandem aza-Wittig/heterocumulene-mediated annulations* leading to products **79–82** (Scheme 20).



Scheme 19



Scheme 20

2. From Pyrimidin-2-ylcarbamidoximes

This synthetic route (*cf.* 86MI1) is illustrated by examples chosen from recent publications (Scheme 21) (00WOP56733, 02WOP36595, 04MI5). Several variants lead to TPs **83** and **84**.

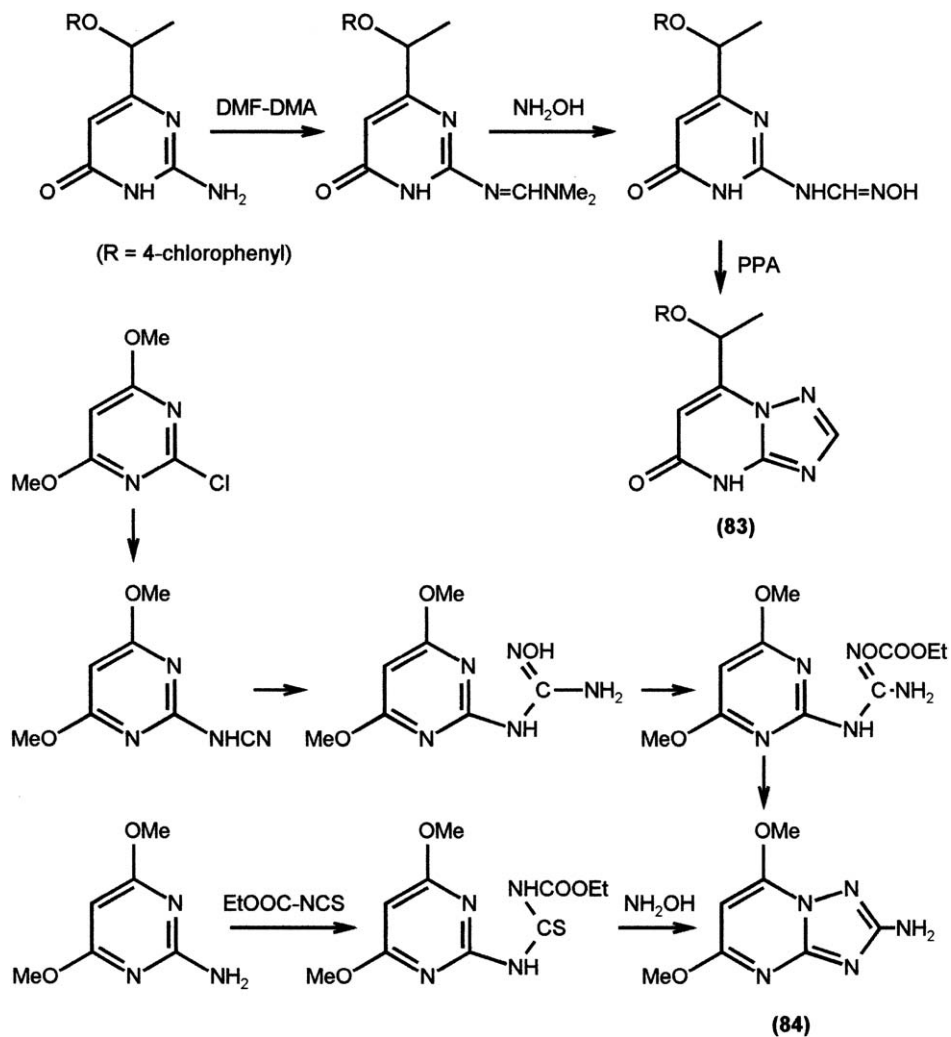
E. NONHETEROCYCLIC PRECURSORS

The reaction of 3-carene-derived 3-chlorovinylketone **85** with benzylidene aminoguanidine unexpectedly gave optically active TP **86** (Scheme 22) (02MC226).

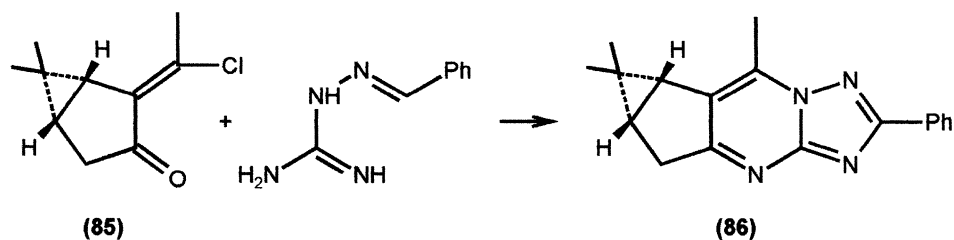
III. Structure

A. THEORETICAL METHODS

Quantum-chemical calculations on TPs, particularly oxo compounds, were performed by several groups. In this way, studies could be assisted and results could be corroborated with those fields of NMR spectroscopy (Sections III,C,1–3), tautomerism (Section III,E), protonation and coordination (Section IV,A), QSAR studies (Section V,B), and reactivity. To give an example, a reaction mechanism for



Scheme 21



Scheme 22

nucleophilic addition could be proposed on the basis of calculations (see Section IV,D) (93RJOC1582).

A new aromaticity index was calculated for heterocyclic compounds (87T4725). Comparison of the index of 2-ribosyl-5,7-dimethyl TP with that of the isomeric [4,3-a] compound suggests that the driving force for the Dimroth rearrangement of the latter substance (*cf.* Section II,C,2) is the increase in aromatic character.

B. MOLECULAR DIMENSIONS

1. X-ray Diffraction

X-ray structural analysis by single crystal or powder diffraction (Table 3) mainly serves in determining spatial or molecular structures. Thus, hydrogen-bonded chains and double chains in the crystal structures of 5-oxo TP (**106**, see below) and 7-oxo TP (**29**), respectively, were detected (00JST(519)165) and ring isomers were distinguished (02MC226, 03HAC607). The former substance was also included in a study on crystal structure prediction by calculations that involved 50 small molecules with rigid geometries (05MI2).

Further, X-ray studies give answers to questions about deprotonation (97JST(415)285), protonation, and coordination (99AX(C)1337); for instance, they enable comparison between a free and a coordinated ligand. In this connection many TP-metal complexes were prepared and investigated (see Section IV,A,2).

Finally, X-ray analysis helps to identify tautomers (93RJOC525) and was made the basis of QSAR investigations in the field of herbicides (97MI3, 98MI12).

2. Microwave Spectroscopy

The microwave spectrum of parent TP was reported (93JSP(161)136). The dipole moment was found to be 4.6 D.

C. MOLECULAR SPECTRA

1. ¹H-NMR Spectra

Chemical shifts of selected TPs without and with oxo substituents are listed in Tables 4 and 5, respectively. ¹H-NMR data often enable determination of the structures of substituted TPs. Thus, in pairs of isomeric aryl or alkyl TPs (**22**, **23**; **25**, **26**) 7- and 5-substituted compounds can be distinguished by the help of H,H coupling constants (94T12113, 02S901). In other cases the *Nuclear Overhauser Effect* was used (01JHC1119).

Chemical shifts of H-6 vary over a wider range than those of the other TP protons (see Table 4). Due to neighboring substituents such as phenyl or trifluoromethyl they are shifted downfield. In the spectra of 7-azolyl TPs remarkable changes of the chemical shifts (H-6 of TP and especially azole protons), compared with the

Table 3. X-ray diffraction of TPs

Substitution	Formula	References
5,7-di-Me	44	06AX(E)o1310
5,7-di-Ph	104b	99AX(C)1337
5,7-di-Me-2-OC ₆ H ₄ COOMe (<i>o</i>)		99MI5
5,7-di-Me-2-OC ₆ H ₄ COOEt (<i>o</i>)		05AX(E)o3842
5,7-di-Me-2-OC ₆ H ₄ COOiPr (<i>o</i>)		05AX(E)o2079
5-Me-7-CH ₂ COOEt	42	96AX(C)1031, 02CRC517
6-CN-7-Me		06AX(E)o1252
6-(N=NPh)-7-Et		04JHC647
5-Me-6-NO ₂ -7-C ₆ H ₄ NMe ₂ (<i>p</i>)	134b	92CHE1323
5-Me-6-NO ₂ -7-N(Me)C ₆ H ₄ OMe (<i>p</i>)	155	92CHE1323
5-Me-2-SCH ₂ Ph		99JHC183
2-SCH ₂ C ₆ H ₄ C(COOMe)=CHOMe (<i>o</i>)		05AX(E)o1992
5,7-di-Me-2-S[C ₆ H ₂ CF ₃ (<i>p</i>) (NO ₂) ₂ (<i>o,o'</i>)]		97MI5
5,7-di-Me-2-SCH ₂ CH ₂ CH ₂ SP(OiPr) ₂ =S		03HAC607
5-Me-2-SO ₂ NHC ₆ H ₃ F ₂ (<i>o,o'</i>) ^a	197	05AX(E)o2083
5,7-di-Me-2-SO ₂ NHC ₆ H ₄ Cl (<i>o</i>)		98MI9, 02MI9
5,7-di-Me-2-SO ₂ NHC ₆ H ₄ Me (<i>p</i>)	173a	97MI3
5,7-di-Me-2-SO ₂ NHC ₆ H ₃ Cl ₂ (<i>o,o'</i>)	173b	97MI3, 98MI12
5,6-(di-Me-bicyclohexeno)-7-Me-2-Ph	86	02MC226
C-2 camphor derivative	59	02TA821
5-oxo	106	00JST(519)165
5-oxo-7-NH ₂	7	99ZK517
7-oxo	29	00JST(519)165
5,7-dioxo (Na salt)	(6)	97JST(415)285
5-Me-6-NO ₂ -7-oxo	154	93RJOC525
5-Me-7-oxo-2-CF ₃ ^b		04AX(C)o733
5,7-di-Ph-6-oximino		93K275
5-Ph-7-C ₆ H ₄ NO ₂ (<i>p</i>)-2,3-di-NH ₂ ^c	35b	99CHE708
5-Ph-6-OH-7-C ₆ H ₄ NO ₂ (<i>p</i>)-2,3-di-NH ₂ ^d	99	01CHE338

^aAcetonitrile solvate.

^bAnd salt formed with 3-CF₃-AT (**164**-type, see below).

^cQuaternary salt (bromide), DMF solvate.

^dBetain.

single-ring parent substances, can be explained in terms of significant conjugation between both heterocyclic rings (00RJOC866).

In oxo-substituted TPs (Table 5) having no N-alkyl groups the NH signal is identified by deuterium oxide exchange. Their spectra are also used, together with ¹³C-NMR data, to define tautomeric equilibria, for instance, of 5,7-dioxo TP (**6**, see Section III,E,1) and the partition of isomers in the course of N-alkylation (93RJOC525, 01JHC237). ¹H-NMR data of certain benzo derivatives not integrated into Table 5 similarly show an NH signal (95JHC1359).

Table 4. $^1\text{H-NMR}$ chemical shifts of TPs without oxo substitution

Substitution	Formula	δ (ppm) ^a in positions				Solvent ^b	References ^c
		2	5	6	7		
–	1a	8.70	8.93	7.41	9.45	D	94MRC373
		8.89	9.13	7.70	9.16	T	
5-CF ₃	26	8.67	–	7.48	9.11	D	02S901
7-CF ₃	25	8.66	9.01	7.48	–	D	
7-(indol-3-yl)	159	9.12	8.83	7.87	–	D	99MC233
5,7-di-CF ₃		9.12	–	8.49	–	D	96MRC725
5,7-di-Ph	104b	8.73	–	8.17	–	D	
		8.49	–	7.61	–	F	02MRC529
5-Me-7-Cl		8.80	(2.70)	7.80	–	D	00RJOC866
5-Me-7-CF ₃		8.58	(2.84)	7.34	–	C	03RCB1190
5-Me-7-Ph		8.65	(2.70)	7.53	–	D	95JHC407
5-Ph-7-Me	37b	8.67	–	7.94	(2.85)	D	
5,6-cyclohexeno		8.45	–	–	9.10	D	97MI2
5-Me-7-CH ₂ COOMe		8.15	(2.45)	6.85	–	C	02CRC517
5-Me-7-(CH=CHNMe ₂)	182	8.26	(2.50)	6.46	–	C	96JHC465
7-C ₆ H ₄ NEtAc (<i>p</i>)		8.54	8.87	7.25	–	C	01JHC1119
6-CH ₂ COCH ₃		8.58	8.73	–	9.18	C	94RCB1884
6-COOEt-7-C ₆ HF ₄	4	8.80	9.40	–	–	D	01RJOC570
6-CN-7-Ph	9	8.59	9.05	–	–	C	00JCR(S)13
6-piperidino	157	8.46	8.95	–	8.75	D	99MC233
5-Me-6-NO ₂ -7-C ₆ H ₄ NMe ₂ (<i>p</i>)	134b	8.75	(2.65)	–	–	D	92CHE1323
6-(N=NPh)-7-Et		8.8	9.2	–	–	D	04JHC647
2-SMe-5-Me	179	–	(2.69)	6.89	8.55	C	99JHC1199
2,5-di-CF ₃ -7-Me		–	–	7.50	(2.96)	C	97JCR(M)2378
2-NHPh-5,7-di-Me		–	(2.57)	6.81	(2.72)	D	99JCS(P1)1527
2-SMe-5,7-di-Me		–	(2.56)	7.01	(2.70)	D	95JHC407
2-SMe-5-Me-7-Cl	148	–	(2.59)	7.55	–	C	97JHC1519
2-SMe-5-Me-6-Ac		–	(2.65)	–	9.88	D	95JHC407
2-SMe-6-Ac-7-Me		–	9.22	–	(2.72)	D	
2-SCH ₂ COOMe-5,7-di-Me		–	(2.57)	6.69	(2.66)	C	01MI6, <i>cf.</i> 01MI1

^aFigures in parentheses refer to methyl groups.

^bSolvents: C, CDCl₃; D, DMSO-*d*₆; F, DMF-*d*₇; T, TFA.

^cImmediately successive identical references are not repeated (in the following tables, too).

2. $^{13}\text{C-NMR}$ Spectra

Table 6 lists chemical shifts of typical TPs; data of a further 60 various 7-oxo TPs were compiled (95JST(355)273, 97JST(435)65). Several assignments were confirmed by *distortionless enhancement by polarization transfer (DEPT)* and *two-dimensional $^1\text{H-}^{13}\text{C}$ correlation (HETCOR)* experiments (93MI3, 01JHC1119). The assignments are used to distinguish TPs and isomeric 1,2,4-triazolo[4,3-*a*]pyrimidines or 3-alkyl and 4-alkyl derivatives (Scheme 23). Thus, differentiating pairs of isomeric oxo compounds **87** and **88** (93MI3) or **29** and **30** (97JCS(P1)1799) is possible.

Table 5. ¹H-NMR chemical shifts of TPs with oxo substitution

Substitution	Formula	δ (ppm) ^a in positions							Solvent ^b	References ^c
		1	2	3	4	5	6	7		
5-oxo	106	–	8.11	–	13.03	–	6.16	8.62	D	00JST(519)165
5-oxo-7-Ph	15b	–	8.26	–	13.0	–	6.47	–	F	00CHE1329
5,7-dioxo	6	–	8.3	–	12.3	–	5.1	–	D	97JST(415)285
2-CF ₃ -5,7-dioxo		–	–	–	12.72	–	6.48	–	D	97JCR(M)2378
7-oxo										
–	29	–	8.25	–	–	8.02	5.96	–	D	00JST(519)165
2-morpholino-5-COOMe	109	–	–	–	7.60	–	6.55	–	C	99MI2
2-morpholino-4-Me-5-COOMe	110	–	–	–	(3.40)	–	6.40	–	D	
2-SMe-4-Me-6-COOEt	162	–	–	–	(3.55)	8.60	–	–	D	
2-CF ₃ -5-Me		–	–	–	6.42	(2.36)	5.98	–	D	97JCR(M)2378
2-CH ₂ COOH-5-Me	189a	–	–	–	–	(2.35)	5.90	–	D	97RJOC1784
2-NO ₂ -5-Me		–	–	–	–	(2.40)	6.15	–	D	
2-(NMe-CH ₂ CH ₂ OH)-5-Me	188	–	–	–	12.8	(2.22)	5.64	–	D	02JHC319
6-NH ₂ · 2 HBr	174	–	8.25	–	–	8.52	–	–	D	05JHC1167
6-NHAc		–	8.28	–	9.48	8.62	–	–	D	97JHC247
6-(tetrazol-5-yl)		–	8.70	–	–	9.52	–	–	C/F	91CPB1099
3-Me-6-NO ₂		–	9.13	(3.80)	–	9.18	–	–		93RJOC525
4-Me-6-NO ₂		–	8.46	–	(3.97)	9.69	–	–		
3,5-di-Me-6-NO ₂	89	–	9.01	(3.71)	–	(2.50)	–	–		
4,5-di-Me-6-NO ₂	90	–	8.41	–	(3.89)	(2.60)	–	–		
1-Me-2-SMe-5,6-cyclohexeno	111	(4.20)	–	–	–	–	–	–	C	01JHC237
2-SBu-3,5-di-Me	112	–	–	(3.57)	–	(2.35)	6.08	–	C	
2-SMe-4,5-di-Me	113	–	–	–	(3.80)	(2.45)	5.85	–	C	

^{a-c}See Table 4 for footnotes (a–c).

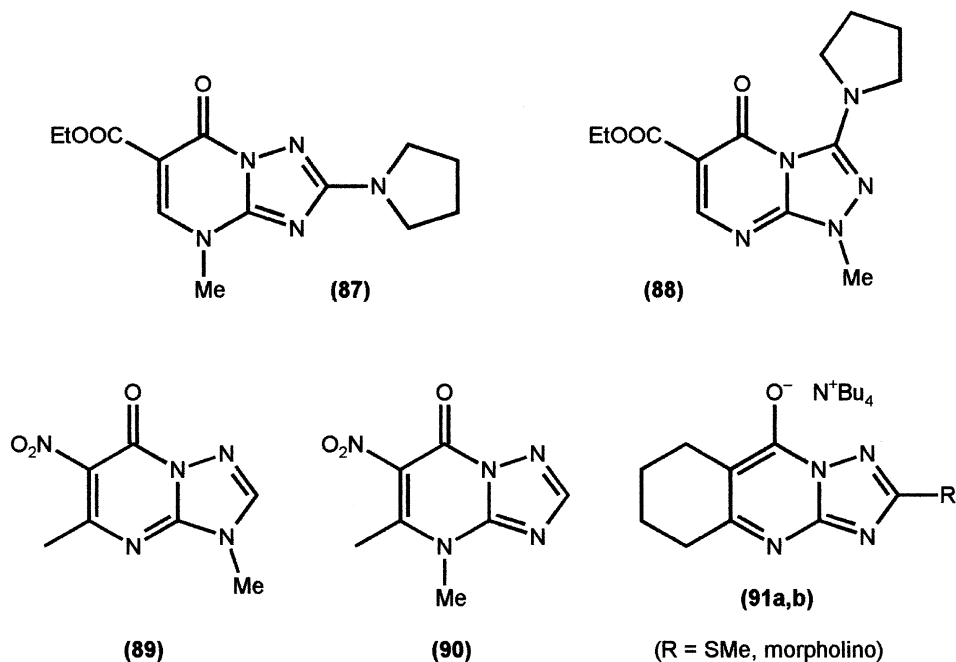
Table 6. ^{13}C -NMR chemical shifts of TPs

Substitution ^a	Formula	δ (ppm) in positions ^b					Solvent ^c	References
		2	3a	5	6	7		
–	1a	155.8	154.6	155.5	110.9	137.4	D	94MRC373
		144.8	146.3	161.4	122.1	139.0	T	
5,7-di- <i>t</i> -Bu	104a	154.5	155.3	174.9	103.7	156.9	D	96MRC725
5,7-di-CF ₃		158.3	154.8	151.0	106.3	136.5	D	
5,7-di-Ph	104b	156.0	155.8	160.7	106.8	147.5	D	
2-SMe-5-Me		169.2	155.6	165.1	110.1	133.7	C	99JHC1199
2-SMe-5,7-di-Me		166.9	155.4	164.0	110.1	146.0	D	95JHC407
2-SMe-5,7-di-CF ₃		174.4	155.6	150.9	103.2	135.5	C	03RCB1190
2-SMe-5-Me-7-CF ₃		156.5	148.0	164.8	107.6	133.7	C	
2-SMe-5-Me-6-Ac		169.7	154.6	164.7	120.1	139.0	D	95JHC407
6-CH ₂ COCH ₃		155.6	153.8	157.4	118.4	136.2	D	94RCB1884
6-[N=N-C ₆ H ₄ CN (<i>o</i>)]-7-Ph		147.9	150.1	151.8	144.2	158.2	D	04ZN(B)721
5-Me-7-SH		151.8	147.6	148.7	114.5	177.0	D	95JST(355)273
5-Me-7-NH ₂		154.2	148.4 ^d	163.1	89.9	155.5 ^d	D	
2-SMe-5,6-ch-7-OMe	147	167.6	156.2	165.7	106.8	151.5	C	01JHC237
5-oxo	106	152.6	150.0	161.0	108.0	136.9	D	00JST(519)165
5,7-dioxo	6	146.0	148.9	165.0	79.8	156.7	D	97JST(415)285
7-oxo								
–	29	151.8	151.0	141.0	99.1	156.6	D	00JST(519)165
5,6-ch		151.5	149.5	147.4	105.8	156.3	D	99JHC1199
3,5-di-Me-6-NO ₂	89	145.2	147.9	160.0	130.7	149.3	D	93RJOC525
4,5-di-Me-6-NO ₂	90	153.1	151.2	151.5	129.4	148.9	D	
2-pyrrolidino-4-Me-6-COOEt	87	150.0	151.8	144.8	105.1	163.0	C	93MI3
1-Me-2-SMe-5,6-ch	111	163.7	152.9	162.0	111.3	157.2	C	01JHC237
2-SBu-3,5-di-Me	112	153.4	149.5	163.7	103.0	156.2	C	
2-SMe-4,5-di-Me	113	164.2	152.2	150.5	100.4	154.2	C	

^ach: cyclohexeno.^bNumbering according to formula **1a**.^cSolvents: C, CDCl₃; D, DMSO-*d*₆; T, TFA.^dOr reversed.

^{13}C -NMR chemical shifts of a large number of 7-oxo and other TPs were measured and assigned by the use of a whole arsenal of 2D-NMR methods (95JST(355)273, 97JST(435)65) and were calculated as well by various *ab initio* methods (97MI7). Lactam–lactim tautomers studied in this way may be related to the corresponding N- and O-alkylation products. Thus, the structures of N-methyl compounds such as **89** and **90** were assigned and the ratios of isomers were directly determined using spectrometer data (93RJOC525). In another case examples of all four of the possible methyl derivatives (three N-methyl, one O-methyl) could be isolated and identified [*cf.* Table 6, compounds **111**–**113** and **147** (formulas see below)] (01JHC237).

In a series of 7-hydroxy TP tetrabutylammonium salts the coupling constants corroborate the conclusion that the 2-morpholino group in salt **91b** lacks coplanarity



Scheme 23

with the TP moiety, contrary to the smaller 2-methylthio group in salt **91a** (01JHC237).

3. ^{15}N -NMR Spectra

^{15}N -NMR spectra of TPs were rarely measured before the nineties but have received growing importance during the period under review. Typical examples can be found in Table 7; data of many other 7-oxo TPs were reported (95JST(355)273, 97JST(435)65). In TPs having no tautomerizable substituent in the 7-position generally N-3 is much more shielded than the other pyridine-type nitrogen atoms (00JCS(D)867).

Controversial assignment of ^{15}N signals in the literature (cf. 82OMR87, 89MI1) led to new investigations. By recording the ^{15}N - ^1H gradient heteronuclear multiple-quantum coherence (GHMQC) spectrum of the TP parent substance (**1a**) all signals could be unambiguously assigned (00POL965).

In the 7-oxo TP series ^{15}N -NMR resonances were assigned by the various possible N,H coupling constants. For many compounds two broadened higher-field resonances (N-3, N-4) were observed (95JST(355)273). In other cases of 2-substituted derivatives all four of the nitrogen atoms gave sharp lines (97JST(435)65). These experimental data and assisting quantum-chemical calculations (97MI7) served to elucidate the tautomerism of these compounds (see Section III,E,1).

Table 7. ^{15}N -NMR chemical shifts of TPs

Substitution	Formula	$-\delta$ (ppm) in positions ^a				Solvent ^b	References
		1	3	4	8		
—	1a	105.2	149.6	102.3	153.6	D	00POL965
		106.0	151.3	103.2	154.3	F	02MRC529
		107.2	154.7	107.2	154.7	S	00JCS(D)867
		106.0	227.2	118.0	159.4	T	94MRC373
5,7-di-Me	44	109.7	151.0	111.7	152.8	C	00JCS(D)867
		110.7	151.6	114.0	154.5	D	96MRC725
5,7-di- <i>t</i> -Bu	104a	106.4	155.1	114.2	157.5	C	00JCS(D)867
5,7-di-CF ₃	104b	104.5	144.7	98.7	158.8	D	96MRC725
5,7-di-Ph		110.1	150.2	120.3	158.6	D	
		108.3	151.2	120.7	155.3	S	00JCS(D)867
6-CH ₂ COCH ₃		105.6	150.1	104.1	154.3	D	94RCB1884
5-Me-7-NH ₂		120.4	156.6	173.4	148.6	D	95JST(355)273
5-Me-7-SH		102.4	173.1	230.5	142.6	D	
5-Me-7-oxo	2	110.6	165.4	252.3	155.0	D	
2-NH ₂ -5-Me-7-oxo		161.1	188.2	254.1	164.8	D	
5-Me-6-Cl-7-oxo		109.4	170.1	242.8	160.3	D	

^aNumbering according to formula **1a**.

^bSolvents: C, CDCl₃; D, DMSO-*d*₆; F, DMF-*d*₇; T, TFA; S, solid.

4. ^{19}F -NMR Spectra

^{19}F -NMR chemical shifts and coupling constants can be helpful for differentiating positional or ring isomers of fluoroalkyl (**03RCB1190**) and fluoroaryl triazolo-pyrimidines (**01RJOC570**).

5. Electronic Spectra

Some characteristic examples of UV spectroscopic data are compiled in **Table 8**. Thus, an intense band at 293–300 nm (as in **37b**) is typical for 5-aryl TPs (**91CHE1242**). The introduction of nitro or halo substituents onto position 6 of parent compound **1a** leads to a bathochromic shift (**00CHE714**).

In the 7-oxo TP series, the spectra of all four possible alkylation types [e.g., **111**, **112**, **113**, **147** (see below), alkylated at N-1, N-3, N-4, and O, respectively] are distinctly different from each other (**01JHC237**). Nonalkylated (tautomerizable) compound **188** (see below) fits remarkably well in with the 4-alkyl type.

The longest-wavelength band of **35**-type quaternary TP salts (forming yellow or orange crystals) is shifted into the 430–466 nm region (**99CHE708**) and in the case of **99**-type betains even to 468–477 nm (**01CHE338**). Fluorescence of quaternary salts (**99CHE708**) and of 5,6-fused 7-phenyl TPs (**91CHE88**), too, was studied.

Table 8. UV Spectra of TPs

Substitution ^a	Formula	λ_{\max} in nm ($\epsilon \times 10^{-3}$)		Solvent ^b	References
–	1a		272 (3.8)	EtOH	00CHE714
5-Ph-7-Me	37b	247 (22.2)	293 (15.3)	EtOH	91CHE1242
5-C ₆ H ₄ OH(<i>o</i>)-7-Ph		261 (23.4)	317 (18.6)	i-PrOH	96CHE215
6-Br	156	218 (31.0)	290 (4.0)	bu.	00CHE714
6-NO ₂	121	240 (3.8)	345 (4.9)	bu.	
5-Me-7-NEt ₂	195	221	271 (5.1)	MeOH	90PHA768
2-SPr(i)-5,6-ch-7-NHCH ₂ CH ₂ Cl		218 (18.4)	246 (36.0)	EtOH	02JHC703
2-SMe-5,6-ch-7-OMe	147	210 (28.0)	239 (33.6)	EtOH	01JHC237
2-SMe-5,6-ch-7-SH		254 (21.0)	294 (6.0)	EtOH	
5,7-dioxo	6	208 (26.9)	261 (15.8)	H ₂ O	97JST(415)285
7-oxo					
2-NMeCH ₂ CH ₂ OH-5-Me	188		230 (23.4)	EtOH	02JHC319
1-Me-2-SMe-5,6-ch	111	208 (17.4)	241 (20.1)		
			293 (9.7)	EtOH	01JHC237
2-SBu-3,5-di-Me	112		223 (24.6)	EtOH	
2-SMe-4,5-di-Me	113		233 (26.7)	EtOH	

^ach: cyclohexeno.^bbu.: buffer solution H₃PO₄ (pH 2.26).

The S_1 - S_0 electronic absorption of TP (**1a**) was assigned as a π^* - π transition by *rotational band contour analysis* (93JSP(158)399).

6. Infrared Spectra

Important TP bands of some non-oxo derivatives can be found in Table 9. These bands were usually denoted as C=N bands. Later the two most characteristic bands, named ν_{TP} (about 1610–1650 cm^{-1}) and ν_{PY} (about 1505–1550 cm^{-1}), were assigned to an overall triazolopyrimidine and pyrimidine ring mode vibrations, respectively (00JCS(D)867, 00POL965; cf. 06JOM693).

Table 10 shows IR bands of selected 5- and 7-oxo TPs, especially the NH and CO bands.

7. Mass Spectra

Mass spectrometric splitting of substituents and ring fragments from TPs is exemplified in Table 11. In a similar way fragmentation of tetrafluorophenyl TP carboxylic ester **4** mainly proceeds by elimination of fluorine, decomposition of the ester group, cleavage of tetrafluorophenyl, and elimination of hydrocyanic acid (01RJOC570).

Mass spectrometry allows differentiation between substitution onto C-5 and C-7: Thus, signal 103 (benzonitrile ion) can be obtained from thioether **19b** (5-phenyl) only and not from isomeric 7-phenyl compound **18b** (00MI1). Even prototropic tautomerism of 6-nitro-7-oxo TPs in the gas phase was elucidated (93RJOC525).

An example of practical applications is that of the qualitative and quantitative analysis of TP sulfonanilide herbicides Flumetsulam (**197**, see below, Scheme 51) and Metosulam (**198**) by *liquid chromatography coupled with tandem mass spectrometry*

Table 9. Selected IR-bands of TPs without oxo substitution

Substitution	Formula	Bands (cm^{-1} , KBr)		References
–	1a	1621	1534, 1515	00JCS(D)867
5,7-di-Me	44	1637	1550	
5,7-di- <i>t</i> -Bu	104a	1615	1530	
5,7-di-Ph	104b	1612	1543	
5,6-cyclohexeno		1628	1522	99JHC1199
5,6-cyclohexeno-7-Cl		1609	1515	
2-SMe-5,6-cyclohexeno		1620	1504	
2-SMe-5-Me	179	1622	1532	
2,5-bis-CF ₃ -7-Me		1647		97JCR(M)2378
5-NH ₂ -6,7-di-CN	12	1635		97PHA23
6-CN-7-Ph	9	1648		00JCR(M)173
2,3-di-NH ₂ -5-Ph-6-OH-7-C ₆ H ₄ NO ₂ (<i>p</i>), betain	99	1652	1629	01CHE338

Table 10. Selected IR bands of TPs with oxo substitution

Substitution/fusion ^a	Formula	TP bands (cm ⁻¹) ^b			References
		NH	C=O	C=N	
5-oxo	106		1737, 1683 ^c		05JOM4773
5-oxo-6-NHCOPh-7-Ph			1650	1635	94MI2
4-Me-5-oxo-6-CN-7-Ph	63		1674	1620	98ZN(B)1203
5,7-dioxo	6		1715 ^c		05JOM4773
2-CF ₃ -5,7-dioxo		3242	1674, 1645		97JCR(M)2378
7-oxo					
5-Me	2		1702 ^c		05JOM4773
2,5-bis-CF ₃		3309	1698		97JCR(M)2378
5,6-ch			1686		99JHC1199
1-Me-2-SMe-5,6-ch	111		1673	1582, 1530	01JHC237
2-SBu-3,5-di-Me	112		1693	1599, 1536	
2-SMe-4,5-di-Me	113		1709	1612, 1554	
2-morpholino-5-COOMe	109	3110	1640		99MI2
5-Ph-6-CN	54	3114	1671	1606	98ZN(B)1203
2,5-di-Ph-6-CN	66	3225	1666	1615	
2-oxo-3-Ph-5,6-benzo	81	3448	1735, 1698		04EJOC3872
2-thioxo-3-Ph-5,6-benzo	82	3423	1702		

^ach: cyclohexeno.^bKBr if not otherwise (°) stated.^cNujol and hexachlorobutadiene mulls.**Table 11.** MS fragmentation of TPs

Substitution	Formula	Selected assigned fragment ions (<i>I</i> _{rel} in %)	References
2-SMe-5-Ph-7-CF ₃		M-H (39), M-F (7), M-SMe (13)	03RCB1190
2-CF ₃ -5-Ph-7-CHF ₂		M-F (5), M-CHF ₂ (5), M-CF ₃ -CHF ₂ -Ph (5)	
5-Me-6-NO ₂ -7-C ₆ H ₄ NMe ₂ (<i>p</i>)	134b	M-OH (1), M-NO (1), M-NO ₂ (8)	92CHE1323
2,7-di-Ph-4-Me-5-oxo-6-CN		M-NMe (9), PhC≡C-CN (22), PhCN (43)	98ZN(B)1203
2,5-di-Ph-6-CN-7-oxo	66	M-CO (54), PhC≡C-CN (89)	
5-Ph-7-oxo		M-NH (7), M-CO (37), PhC≡CH (87)	95PHA33
2-Et-5-Me-6-NO ₂ -7-oxo		M-O (23), M-OH (69), M-OH-CO (19), M-NO ₂ (3), M-NO ₂ -CO (14)	93RJOC525

interfaced via a turbo ion spray (LC-TISP-MS-MS) (00ACA(415)41). Deprotonation of anilic nitrogen is followed by removal of the sulfonylic group.

Investigations of fragmentation reactions of molecular dications did not reveal any evidence for a TP parent compound dication, different from the situation with other aromatic nitrogen heterocycles (92OMS89).

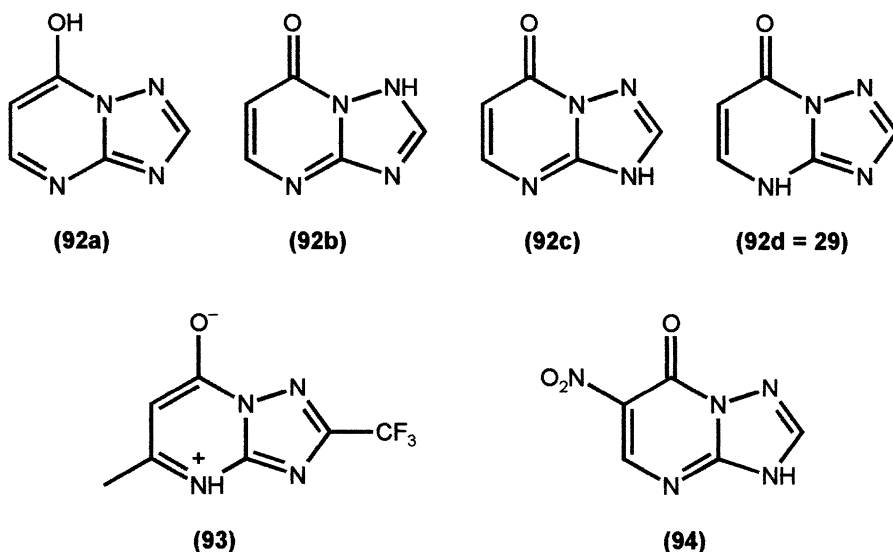
D. THERMODYNAMIC PROPERTIES

Density, vapor pressure, heat capacity, and standard molar enthalpies of formation, fusion, vaporization, and combustion of parent TP have been determined (97JCED1037). Calculated enthalpies of formation of TP and some 6-substituted derivatives have been published (00CHE714). The thermal behavior of 5-oxo TP (106) and 7-oxo TP (29) hemihydrate has been studied in a calorimeter and a thermobalance (00JST(519)165).

E. TAUTOMERISM

1. Prototropic Tautomerism of Oxo Derivatives

Many TP derivatives are subject to tautomerism. Thus substance **92** (Scheme 24) can be drawn in the form of one (vinylogous) lactim structure (92a) and three different (vinylogous) lactams (92b-d). Several tools have been used to establish the exact tautomeric structures, especially NMR, IR, and mass spectrometry, X-ray diffraction, alkylation reactions, and quantum-chemical calculations (*cf.* 01AHC(81)1).



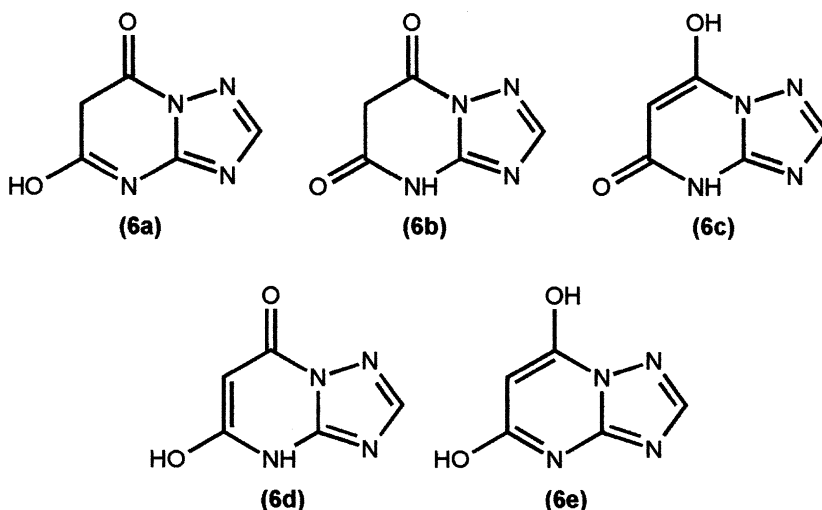
Scheme 24

Such calculations had precisely been the source of a controversy in 1980 (*cf.* 93AHC(57)81, p. 108). In the meantime, the problem has been solved with the help of NMR spectroscopy in favor of the 4H- and 3H-tautomers (**92d**- and **92c**-types, respectively) by Kleinpeter et al. (95JST(355)273, 97JST(435)65). Experimental and calculated ^{15}N -NMR resonances of a large variety of 7-oxo (and 7-thioxo) TPs proved that these substances exist as a quickly established equilibrium of the two tautomers or (in some cases of 2-substituted derivatives) as the 4H-form only. Further quantum-chemical calculations corroborate the results (97JST(401)1, 97MI7).

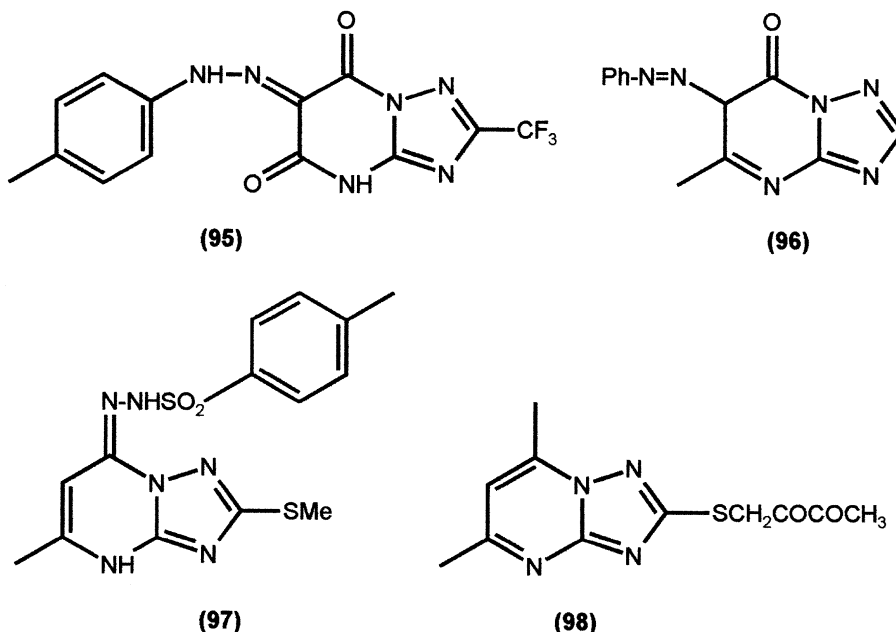
5-Oxo (**106**), 5-oxo-7-amino, and 7-oxo TP (**29**) exist as 4H-tautomers (00JCS(P2)1675, 00JST(519)165). Crystal data of 2-trifluoromethyl-5-methyl-7-oxo TP suggest a significant contribution of the polarized form **93** (04AX(C)o733).

By contrast 6-nitro compound **94** and some homologs were shown to be the 3H-tautomers in the solid state (by X-ray crystallography) and in the gas phase (by mass spectrometry) (93RJOC525). Certain 6-amino TP derivatives, too, were drawn by the respective authors in the 3H-forms (99CCCC177, 06MI2). Finally, unusual 1H-tautomers (93JHC1253, 93PHC34, 05JHC1167) and 6H-tautomers (such as **96**, see below, Scheme 26) were depicted.

5,7-Dioxo TP seems to exist as a mixture of all five possible pyrimidinedione tautomers (**6a–e**, Scheme 25) because the ^{13}C -NMR spectrum shows the signals of two CH_2 and three CH groups (03ARK(is.10)262). A broad ^1H -NMR signal, integrating for 0.8H, suggests the predominance of the three enolic forms **6c–e**. According to the MO-calculated heats of formation, the methylene form **6b** is the most stable in the gas phase (97JST(415)285).



Scheme 25



Scheme 26

2. Prototropic Tautomerism of Ring Substituents

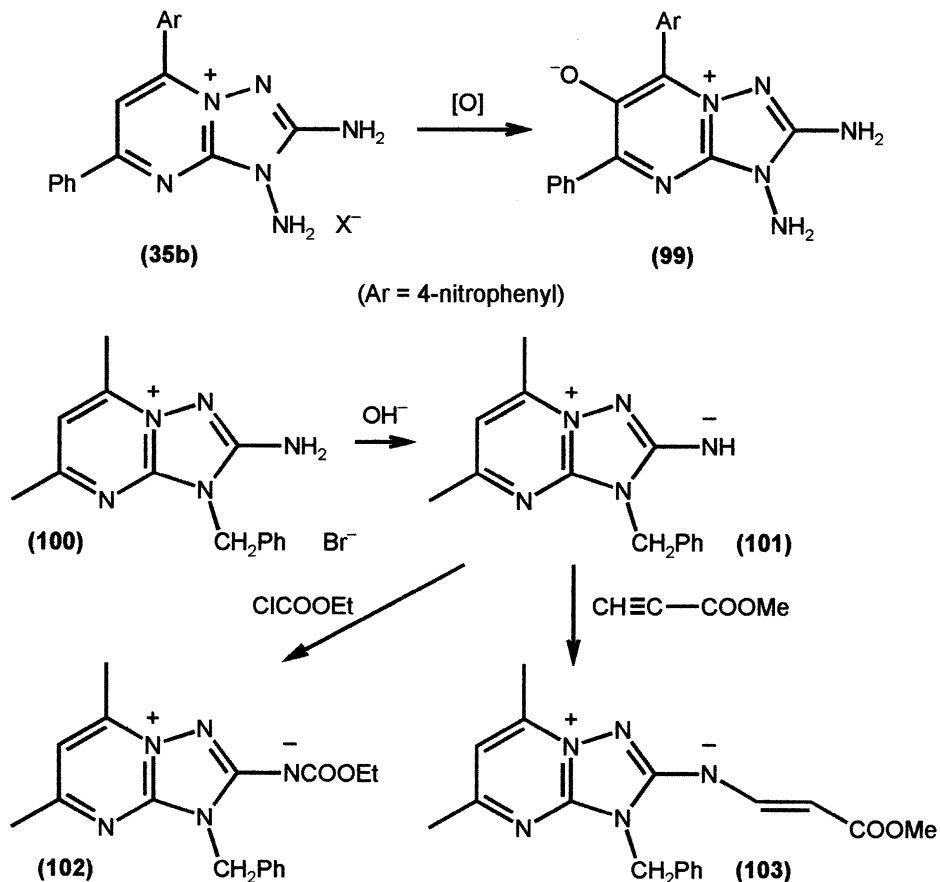
Triazolopyrimidines containing azo groups in the 6-position are depicted in different forms: Unlike the description of 6-aryldiazo TPs in the usual 4H-7-oxo form, some authors derive a 6-hydrazono structure **95** (97JCR(M)2378) or 6H-6-aryldiazo-7-oxo structures, such as **96** (92JSC165, 98MI2), from spectroscopic data (Scheme 26). For the same reason, 7-hydrazono form **97** is preferred to a possible 7-hydrazino structure (99JHC1199).

The solvent and temperature dependences of the keto-enol tautomerism of the diacetyl group in TP **98** have been reported (98MI3).

F. BETAIN AND MESOIONIC STRUCTURES

In the course of the synthesis of quaternary triazolopyrimidinium salts, such as **35** (Section II.A.5, Scheme 10), betains **99** are formed along with the salts by autoxidation (Scheme 27) (01CHE338). There are contributions of several 6-oxo resonance structures.

The treatment of 2-amino TP quaternary salts (type **100**) with Amberlite resin (OH form) or aqueous sodium hydroxide gave triazolopyrimidinylium aminides (type **101**) (99JCS(P1)1527). The 7-methyl resonances in the ¹H-NMR spectra of both species appear as doublets although H-6 exists as a broadened resonance. Mesoionic compound **101** was acylated to yield carbamate-like ester **102** whereas conjugate



addition occurred with propiolate (instead of the expected 1,3-dipolar cycloaddition) to give *trans*-acrylate **103**. All of these aminides are stable compounds.

IV. Reactivity

A. TRIAZOLOPYRIMIDINES AS BASES AND ACIDS

1. Protonation and Dissociation

In the TP parent substance (**1a**) the N-3 atom has been confirmed as the site of the largest negative atomic charge and of protonation by *magnet circular dichroism (MCD) spectra* (85JOC302; cf. 00AHC(77)1), NMR spectra (94MRC373), and calculations (99AX(C)1337, 02JST(605)33). Basicity constants for TP and 6-substituted derivatives were reported (00CHE714).

Oxo TPs are weak acids. The pK_a values of 5-oxo (**106**) and 7-oxo TP (**29**), determined by potentiometric titration (18 °C, water), are 5.9 and 5.7, respectively (00JST(519)165). The corresponding values of photographically important 7-oxo TPs and some analogs were compiled (04MI10, p. 33). Much interest was taken in TP sulfonanilide herbicides, such as Flumetsulam (**197**, see below, Scheme 51; pK_a 4.6) and Metosulam (**198**, pK_a 4.8) (00ACA(415)41) and a number of 5,7-dimethyl TP sulfonanilides (pK_a between 4.89 and 9.02) (98MI5, 99MI3).

6-Amino-7-oxo TP (**7**) was isolated as a hydrochloride (06MI2) or as a dihydrobromide (**174**, see below) (05JHC1167).

5,7-Dioxo TP (**6**) possesses a strongly acidic active methylene group (pK_{a1} 2.9) that loses one proton on forming the monoanion as detected by NMR and X-ray diffraction data of the sodium salt (97JST(415)285). The second ionization concerns N-4 (pK_{a2} 9.9). The IR spectra of the neutral substance, the mono-, and the di-anion show broad stretching vibration bands at 1715, 1679, and 1644 cm^{-1} , respectively (05JOM4773).

Acidic TP compounds are able to form isolable salts, for instance, with ethanolamine and piperidine (97RJOC1784), with AT and its derivatives (**164**-type, see below) (04AX(C)o733) or with tetraalkylammonium and -phosphonium cations (*cf.* **91**) (01JHC237).

2. Coordination

Metal complexes of TPs have been the target of intense research especially by Spanish, Dutch-Italian, and Polish groups. A review covering 1991–1998 was delivered by Salas et al. (99CCR(193–195)1119). It is now briefly updated by Table 12 (*cf.* Scheme 28).

Quantum-chemical calculations have been used to predict the complex-forming capacity of the ligands (e.g., 97JST(415)285, 00JCS(P2)1675, 00JST(519)165). The complexes have usually been characterized by X-ray diffraction, molecular spectra, magnetic, and thermometric measurements. Generally the ligands bind the metals at N-3.

B. RING ALKYLATION

1. Alkylation of Tautomerizing Triazolopyrimidines

N-Alkylation of oxo TPs by alkyl halides (often performed in the presence of *t*-BuOK or NaH) preferentially leads to 4-alkyl derivatives, for instance, to pharmaceutically useful products or intermediates **107** (04MI2) and **108** (95BMCL2071; *cf.* 99CPB928), respectively (Scheme 29). Other selective N-4 alkylations are those of ester **109** to form ester **110** (99MI2), of other esters (99MCR277) or nitriles **54** and **66** (98ZN(B)1203).

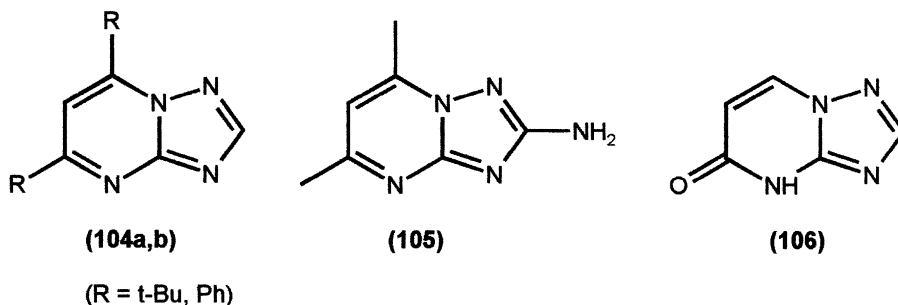
When 4-alkyl-7-oxo TPs are synthesized starting from AT enamines (see Section II,A,1, Scheme 2) by cyclization/alkylation in a one-pot reaction then the reaction is believed to proceed via alkylation of the enamine nitrogen and subsequent cyclization (93MI2). Acylation similarly attacks N-4 (93MI4).

Table 12. TP complexes

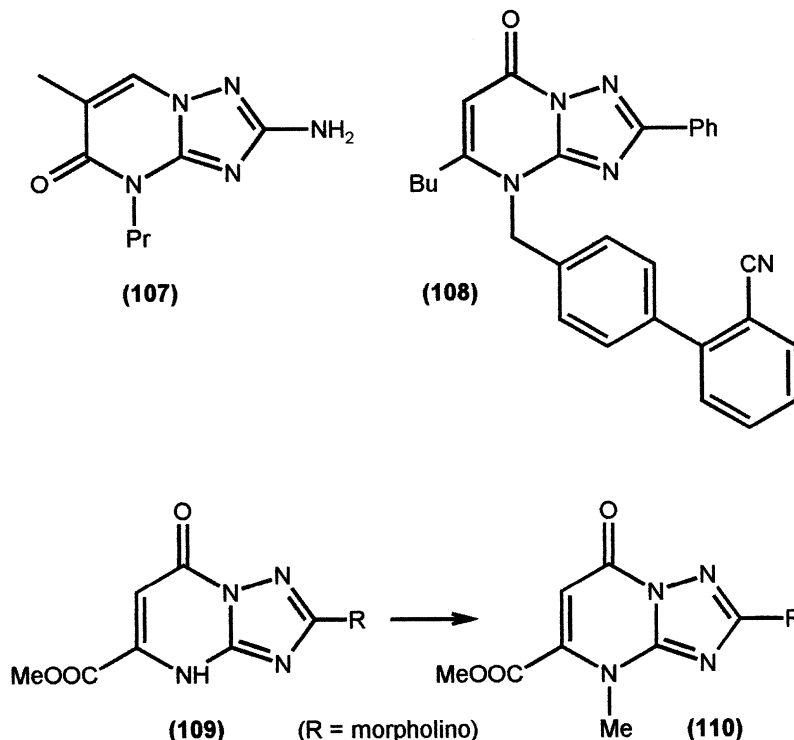
Metal M	Ligand L ^a	M:L relation	References
Cu	2	1:2	00MI2
	29	1:2	03AX(E)m903, 04JCX549
	106	1:2	02EJIC811
	44, 104b	1:1	99POL519
Cu, Zn, Cd, Mn, Fe, Co, Ni	29	1:2	04POL743
Ag	1a	1:1, 2:3	00MI2
	2	1:1, 3:2	04MI10 (pp. 35, 63) ^b
	29, 106	1:1	01JCS(D)1798
	44	1:1	98JPC(A)2443
Ag/Pt	29	1/1:2	01ICC254
Au	1a, 44, 104b	1:1	02MRC529
Zn	1a	1:2	00POL965
Zn, Co	44, 104ab	1:2	97ICA(260)145, 98PJC55
Hg	2	1:1, 2:3	73UP1, 97AQ(IE)55
Sn	1a, 44	1:1, 1:2	06JOM693
	2, 6, 106	1:1, 1:2	05JOM4773
	106	1:2	00AX(C)934
Ru	44	1:1, 1:2	98ICA(273)259, 01EJIC369, 04JMC1110
	105	1:2	99EJIC213
Ru, Pt	29, 106	1:2	01MI8
Pd	1a, 44, 104ab	1:2	00JCS(D)867
	2	1:1	00MI2
	106	1:1, 1:2	04POL2373
	29	1:1	02JCS(D)4740
Pd, Pt	29	1:1	02ICA(333)93, 02POL343, 04MI7
Pt	1a, 44, 104ab	1:1, 1:2	02ICA(333)93, 02POL343, 04MI7
	2	1:2	03MI1

^aTP ligands: **1a**, parent compound; **2**, 5-Me-7-oxo TP; **6**, 5,7-dioxo TP; **29**, 7-oxo TP; **44**, 5,7-di-Me TP; **104a**, 5,7-di-*t*-Bu TP; **104b**, 5,7-di-Ph TP; **105**, 2-NH₂-5,7-di-Me TP; **106**, 5-oxo TP.

^bDealing with the role of these salts and complexes in photographic silver halide emulsions.



Scheme 28



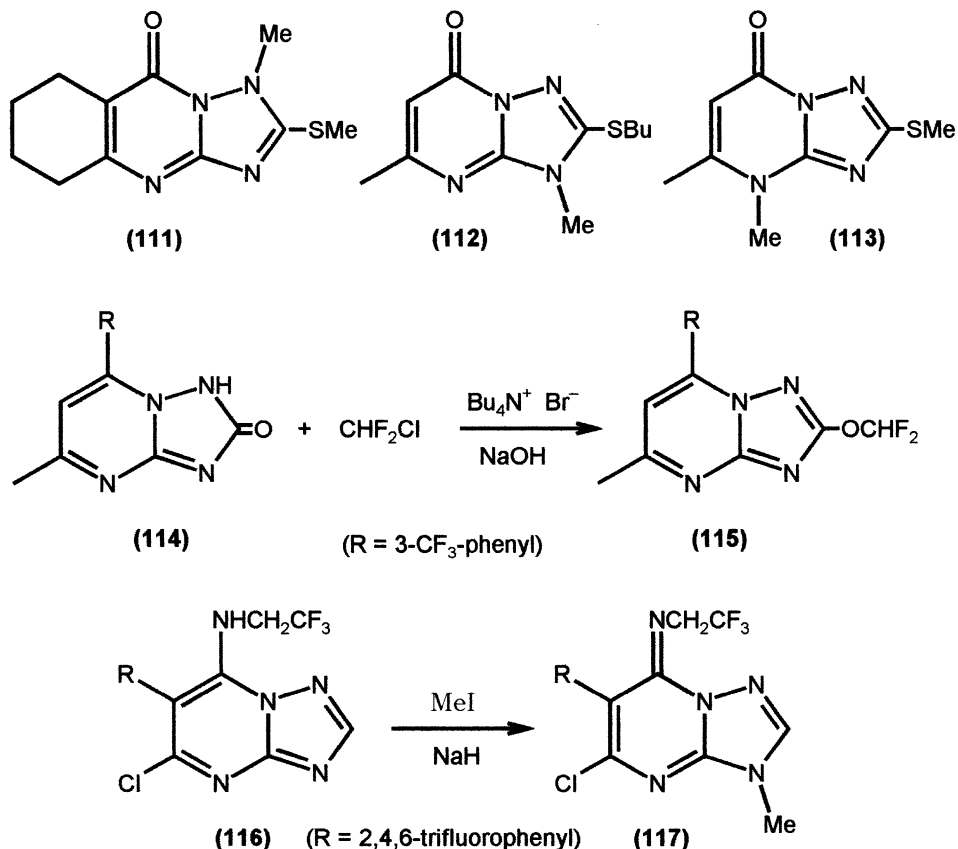
Scheme 29

On methylating 6-nitro-7-oxo TPs, preferably as sodium salts, commonly mixtures of 3- and 4-methyl isomers are obtained, for instance, compounds **89** and **90** in the ratio of 70:30 from the 5-methyl homolog ([93RJOC525](#)). The direction of the methylation is primarily determined by steric factors of the substituents in the 2- and especially in the 5-position.

Replacement of oxo TP sodium salts by tetraalkylammonium salts (e.g., **91**), particularly in the case of highly insoluble TPs, proved to be advantageous concerning conditions, yield, and accessibility of all possible alkyl (including 1-alkyl) derivatives ([01JHC237](#)). In this way 1-, 3-, and 4-alkyl TPs were unambiguously obtained for spectroscopic comparison, for instance N-methylated substances **111**, **112**, and **113**, respectively ([Scheme 30](#)).

1-Alkyl TPs, usually minor side products of the alkylation (yield 0.2–5%), are more abundant (yield 10–19%) in the reaction of 2-morpholino-7-oxo TP ammonium salts (e.g., **91b**). The large morpholino group may be twisted out of the TP plain, while the smaller methylthio group (in **91a**) is coplanar, and conjugation lowers the nucleophilicity of N-1.

For the sake of completeness, the fourth possibility of alkylating oxo TPs is worth mentioning: In rare cases a direct O-alkylation has been observed. Thus the reaction of 2-oxo TP **114** and difluorocarbene gives 2-alkoxy TP **115** together with a trace of the 1-alkyl derivative ([92MI4](#)). O-Alkylation has also been claimed in the reaction



Scheme 30

of TPs and chloroacetate (00MI4) and in the alkylation of TP **2** (in a test mixture together with nine other hydroxyazines and -azoles, polymer-bound to anion exchange resin) for a combinatorial library (96TL5257).

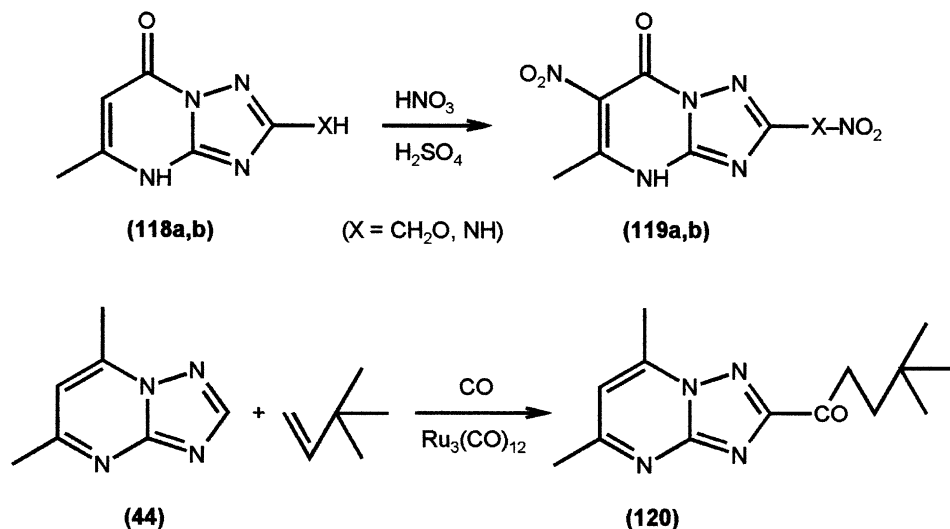
Ring alkylation of 7-amino TPs (e.g., **116**) leads to substitution in the 3-position (to give **117**) (05WOP30216) or in 3- and 4-positions (01WOP96341).

2. Quaternization

Alkylation of nontautomerizing TPs usually occurs in the 3-position and yields quaternary salts, for instance, 3-benzyl compound **100** (99JCS(P1)1527) and cephalosporin derivatives (92JAN721).

C. ELECTROPHILIC REACTIONS AT CARBON RING ATOMS

Electrophilic substitution of TPs occurs in the 6-position (02JST(605)33). Bromination (*cf.* 94AHC(59)245) and nitration of 7-oxo TP **2** and 2-substituted



Scheme 31

derivatives were optimized (97RJOC1784). Whereas most of these substances are selectively nitrated at C-6 (see also 93RJOC525), 2-hydroxymethyl (**118a**), 2-amino (**118b**), and 2-phenyl derivatives undergo dinitration, both 6-position and 2-substituent being attacked, unaffected by the conditions. Thus nitrate **119a**, nitramine **119b**, and a nitrophenyl derivative, respectively, are obtained (Scheme 31).

Azo coupling of aromatic or heteroaromatic diazonium salts with oxo TPs at the 6-position gives azo compounds (92JSC165) or tautomers (e.g., **95**) (97JCR(M)2378).

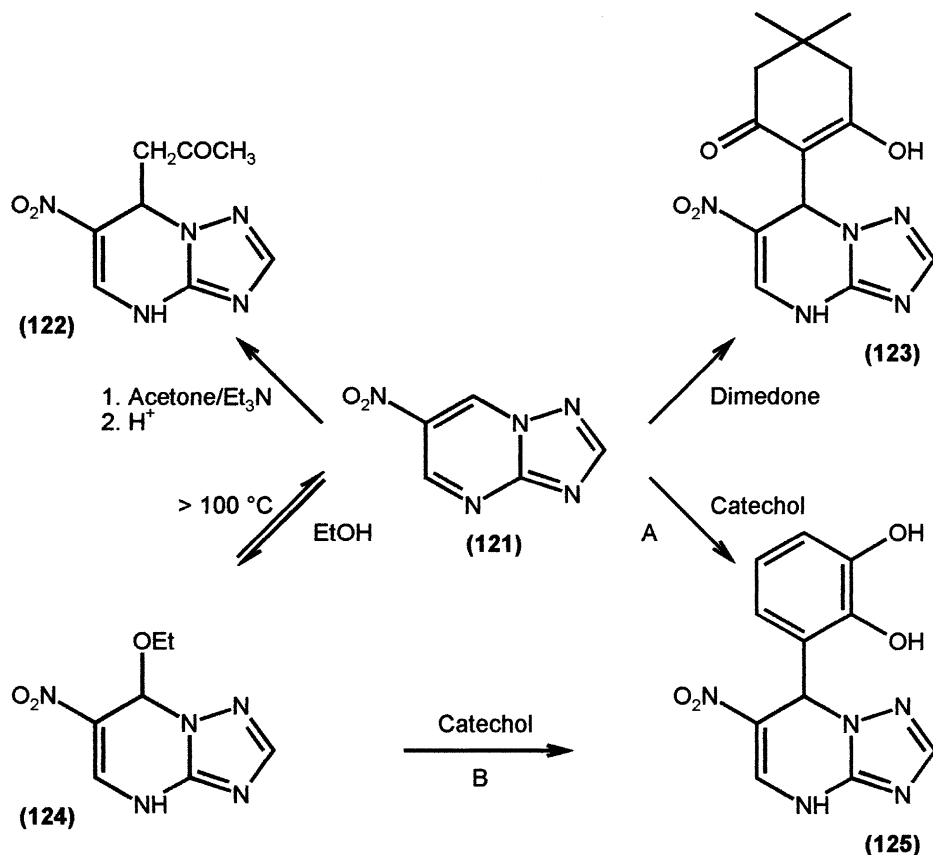
The combination of C–H activation and olefin insertion onto C-2 of TP **44**, catalyzed by ruthenium carbonyl (*cluster catalysis*), presents an opportunity for C–C bond formation to yield 2-acyl TP **120** (01AG222).

D. NUCLEOPHILIC ADDITION

The field of nucleophilic addition onto TPs has been dominated by Russian work done with TP derivatives that are activated by a nitro group in the 6-position (*cf.* 91MI2, 95CHE125, 95H(40)441). The reactivity of these compounds was assessed on the basis of quantum-chemical data (93CHE694). The center of nucleophilicity is C-7.

The addition of acetone onto 6-nitro TPs (e.g., **121**, Scheme 32), according to the same source, requires the presence of base to generate the acetone anion whereas all the other nucleophiles do not. An intermediate σ -adduct on acidification gives dihydro TP **122**. 1,3-Diketones such as dimedone or indane-1,3-dione are CH acids stronger than acetone and react without base activation to give, for instance, adduct **123** (93RJOC519).

Known addition reactions were reinvestigated to elucidate the pathway (93RJOC1582). Ethanol, methanol, or water form unstable adducts, such as **124**. Catechol adduct **125** (or the analogous adducts of pyrrole, indole, 4-dialkylamino-benzene) can be obtained both from nitro TP **121** (Path A) and from adduct **124** that



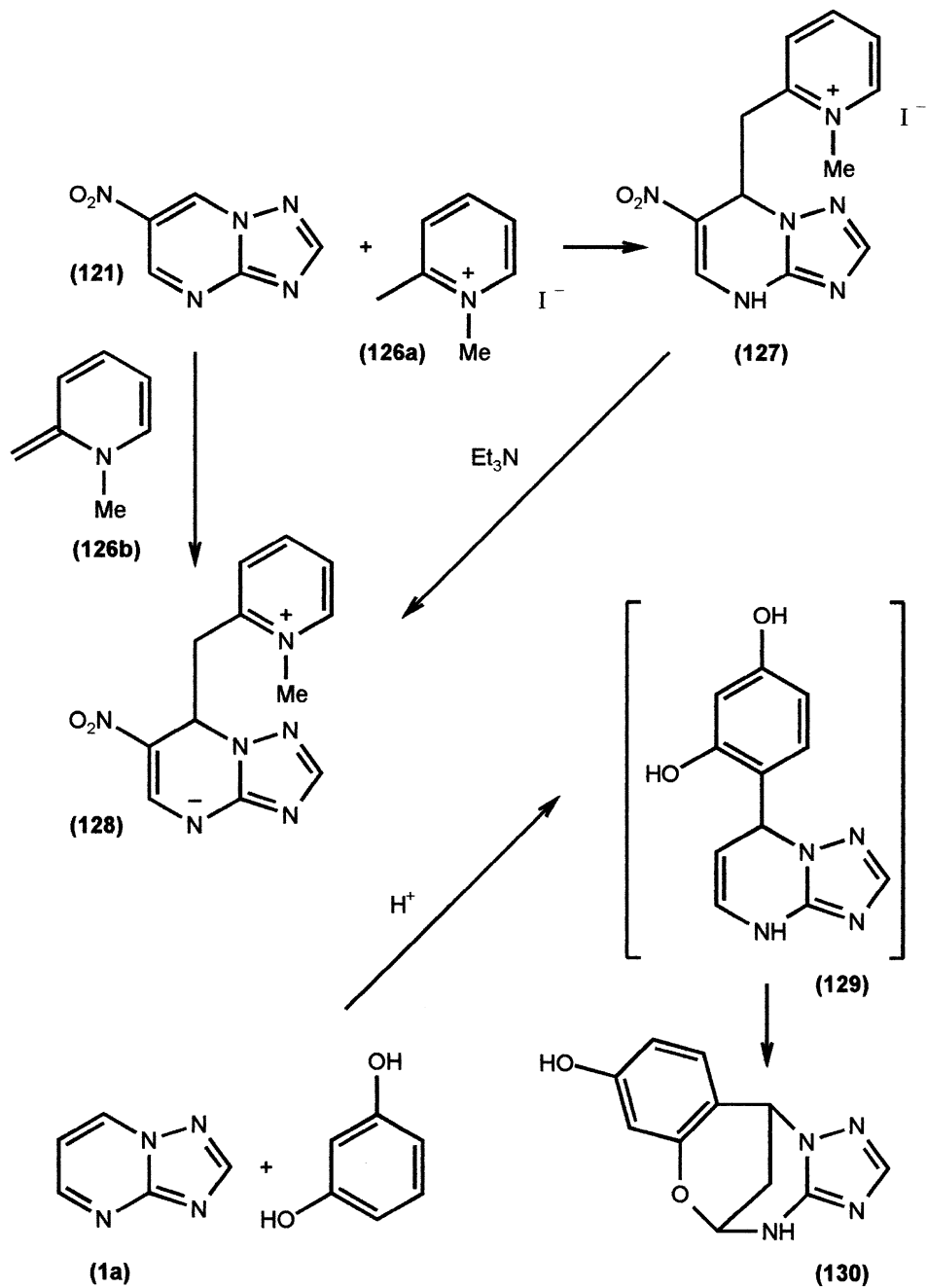
Scheme 32

appears when the reaction with catechol is conducted in ethanol (Path B). The question whether adduct **125** forms directly from TP **121** or through intermediate **124** (when ethanol is present) has been unequivocally decided in favor of direct Path A, on the basis of experimental and calculated results.

Finally, nitro TP **121** does not react with CH-active 2-methylbenzimidazole or methylazines unless these bases have been activated by quaternization (98RJOC263). Thus, picolinium salt **126a** gives adduct **127** that can be deprotonated to yield mesoionic compound **128** (Scheme 33). The same product is directly and easier obtained when salt **126a** has further been activated by generating the corresponding anhydrobase **126b** that can be prepared *in situ*.

On the other hand, TPs without nitro groups (e.g., parent compound **1a**) are able to react with resorcinol under acid conditions, the nonisolable intermediate **129** being cyclized to give oxadiazocine **130** as predicted by theoretical studies (99RCB1553).

Reduction or hydrogenation similarly occurs on the pyrimidine ring to yield 4,7-dihydro and 4,5,6,7-tetrahydro TP derivatives as exemplified by TP herbicide Flumetsulam (**197**, see Section V,B) (92MI6).



Scheme 33

E. RING CLEAVAGE

1. Cleavage of the Pyrimidine Ring

A systematic treatise on the reactions of ring cleavage is found in a review dealing with bridging-nitrogen azoloazines (95CHE1251).

TP derivatives strongly vary in their stability toward **hydrolytic** pyrimidine ring cleavage. Dione **6** in a retrosynthetic reaction decomposes to give triazole **131** (Scheme 34) just in water (97JST(415)285) and still faster in hydrochloric acid. Cupric chloride, when present, captures the final cleavage product AT as complex **132** that is also obtained from TP **2** copper complex on boiling in hydrochloric acid (04AX(E)m370). However, the TP moiety in tetrazole **133** resists even concentrated sulfuric acid; after some hours at 100 °C only the *tert*-butyl group had been lost (91CPB1099).

6-Nitro TP **134a** is cleaved in a neutral medium, homolog **134b** needs pH 11–12 (Path A) (92CHE1323). Isolated final products AT and 4-dimethylamino- ω -nitroacetophenone are consistent with the proposed mechanism.

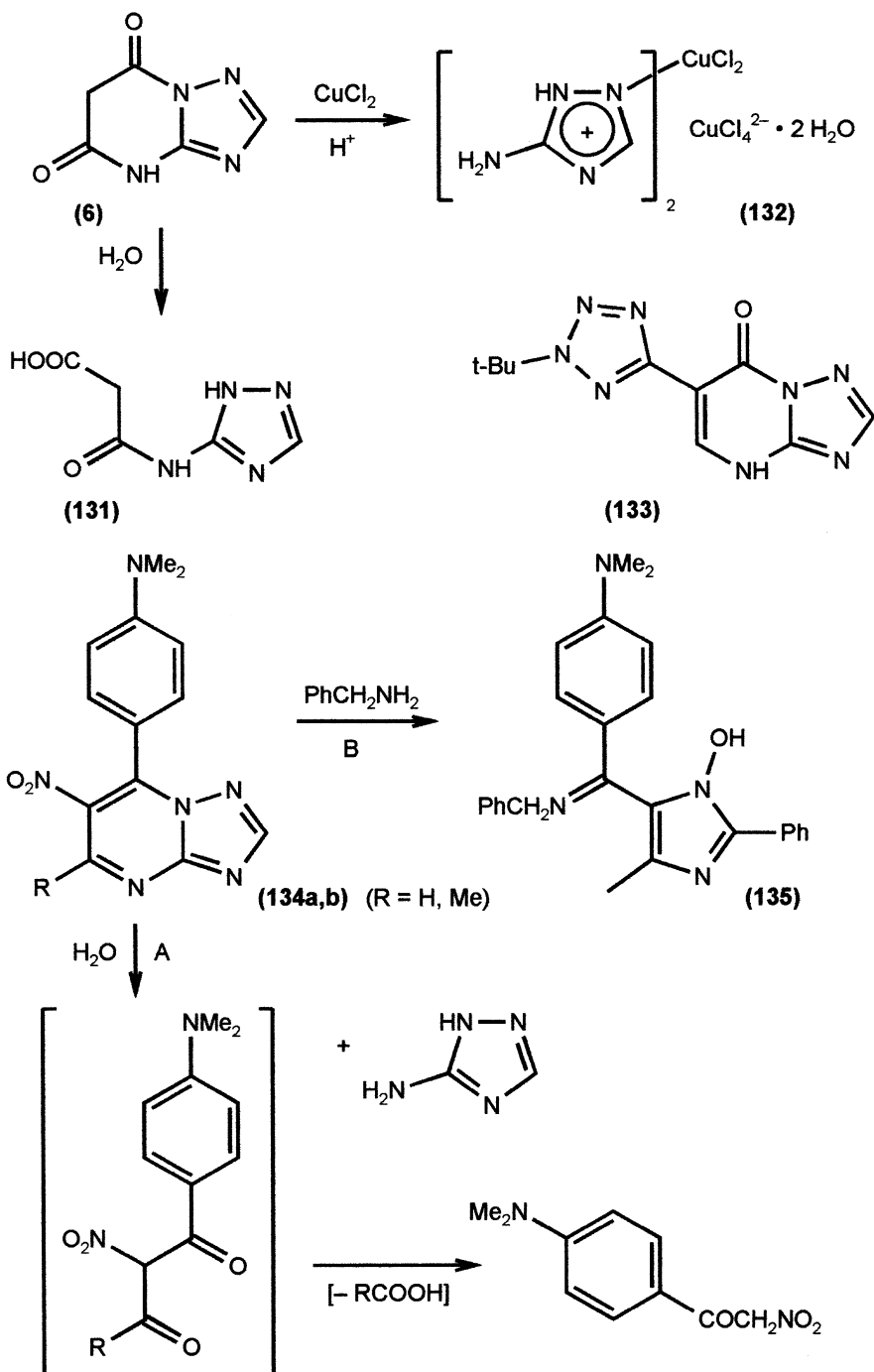
Decomposition of 6-nitro TP **134b** proceeds quite differently in the presence of the **N-nucleophile** benzylamine and leads unusually to 1-hydroxyimidazole **135** (Path B) (93MC213).

Cleavage of N-alkyl-6-nitro-7-oxo TPs by N-nucleophiles was thoroughly investigated (01RCB682). Pyrimidine-ring opening is controlled by the accessibility of C-5 for nucleophilic attack. Both an unsubstituted C-5 site and (in the case of 5-methyl substitution) the use of primary (sterically unhindered) amines favor this reaction and exclude an alternative cleavage of the triazole ring (see the following Section IV,E,2).

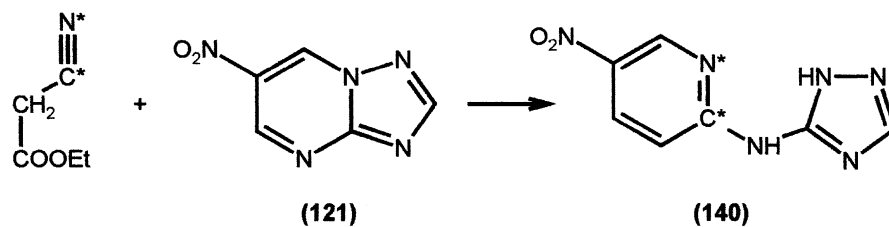
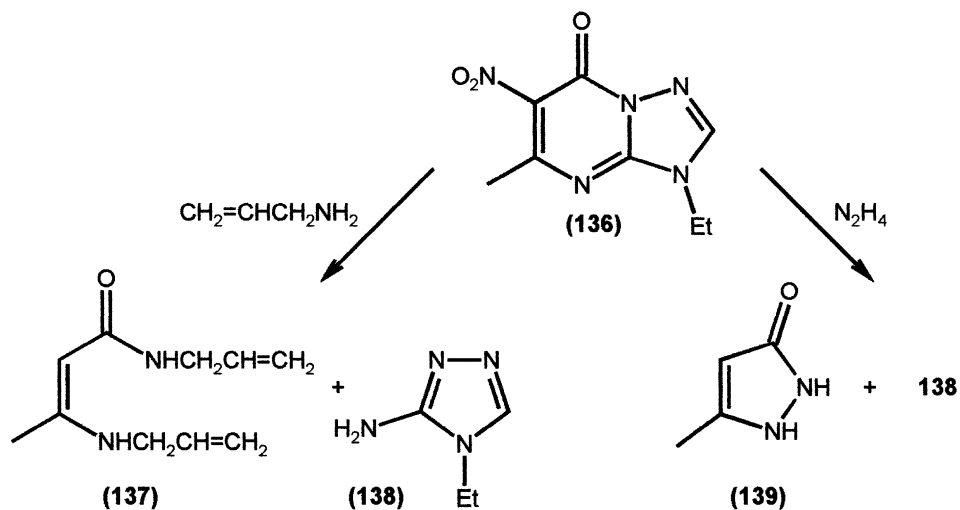
Thus, 5-methyl derivatives (e.g., **136**) on reaction with ammonia or primary amines (e.g., allylamine) release 3-aminocrotonamides (e.g., **137**) as the pyrimidine ring fragment (Scheme 35). The intact triazole ring appears in the form of 4-alkyl AT (e.g., **138**). 3- or 4-alkyl derivatives unsubstituted at C-5 similarly react with secondary amines to yield, together with 3-aminoacrylamides, AT **138** or 5-alkylaminotriazole, respectively. TPs such as **136** are degraded by hydrazine to give pyrazolones (e.g., **139**) and the corresponding AT derivatives.

A pyrimidine-to-pyridine ring transformation (*cf.* 03AHC(84)31) is exemplified by the reaction of 6-nitro TPs (e.g., **121**) with cyano **C-nucleophiles**, for example, cyanoacetates (93RJOC659, 94CHE213). Initial attack of the nucleophile at C-7, ring cleavage of the adduct, and incorporation of the C–C–N fragment into a new pyridine ring, as elucidated by NMR spectroscopy and stable-isotopic labeling (see marked atoms in Scheme 35), give rise to pyridylaminotriazole **140**.

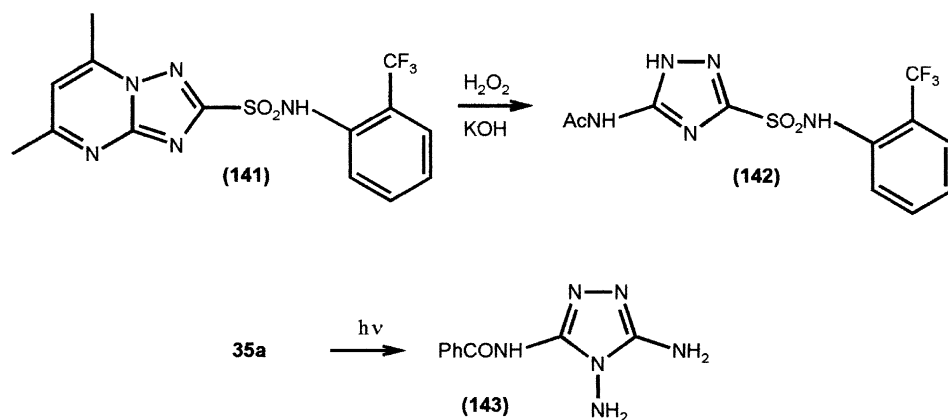
Ring cleavage of TP sulfonanilide **141** by **oxidation** leads to AT derivative **142** (Scheme 36) (92MI2), whereas quaternary salt **35a** suffers **photodecomposition** in sunlight to yield the analogous AT **143** (99CHE708). In both cases an acyl group derived from the pyrimidine fragment remains attached to the exocyclic amino group of AT.



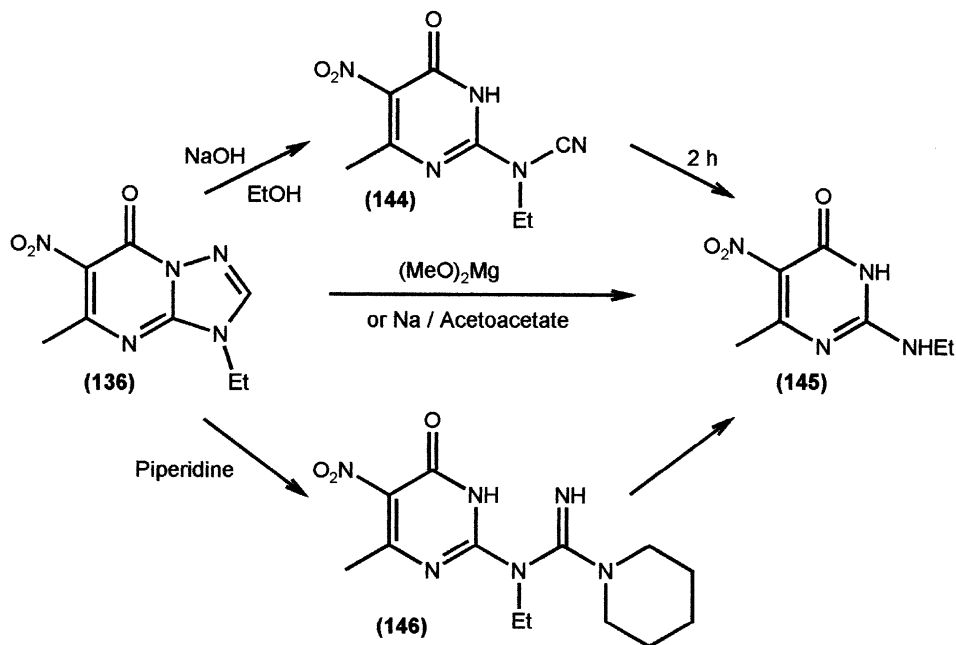
Scheme 34



Scheme 35



Scheme 36



Scheme 37

2. Cleavage of the Triazole Ring

This reaction (*cf.* 95CHE1251), earlier described as being dependent on unusual TP structures or extreme conditions, was now found to be predominant in the series of 3-alkyl-5-methyl-6-nitro-7-oxo TPs unsubstituted in the 2-position (e.g., **136**, Scheme 37) (01RCB682). The triazole ring is exclusively cleaved in the presence of strong bases or C-nucleophiles to obtain pyrimidones such as **145**. Under the influence of ethanolic alkali, after short reaction times, a mixture of intermediate cyanamide **144** and product **145** was obtained.

The course of reactions with N-nucleophiles depends on the structures of both reactants (see Section IV,E,1). Interaction of 5-methyl species **136** and sterically hindered secondary amines (e.g., piperidine) proceeds through guanidine **146** onto product **145**.

The triazole ring cleavage under the influence of sodium hydride serves to synthesize 2-cyanamido-4-amino-5-arylpymidines from TPs, such as imine **117** (05WOP30216).

F. NUCLEOPHILIC SUBSTITUTION OF FUNCTIONAL GROUPS AT THE RINGS

1. Reactivity of Halogen in Positions 5 and 7

The high reactivity of 5- and especially 7-halogen TPs make them the keynote substances for derivatization. A number of representative reactions are listed in Table 13.

Table 13. Nucleophilic substitution of chlorine (and bromine)

Position	New substituent ^{a,b}	Reagent ^b	References
5	OR	ROH/NaH	04WOP108136
	OR'	R'ONa	96MI1
	NR ₂	NHR ₂	93CPB1100, 04BMCL4831, 04JMC6218
5 or 7	Alkyl	R ₂ Zn/Ni complex	03WOP4465
	CH(COOR) ₂	CH ₂ (COOR) ₂ /NaH	06WOP34848
	OR	RONa	92MI2, 99JHC183
7	CN	R ₄ N ⁺ CN ⁻	05WOP95405, 06WOP34848
	OH	NaOH	02EUP1249452
	OR	ROH/K ₂ CO ₃	04WOP113341
	SH	CS(NH ₂) ₂	95PHA33
	SAr	ArSH	95IJC(B)209
	SR	RSH/K ₂ CO ₃	04WOP113341
	SR''	R''SH	92MI5, 95JAP(K)07/309872
	NH ₂	NH ₃ /MeOH	05WOP87770
	NHR	RNH ₂	99USP5986135 ^c , 02JHC703
	NHR'	R'NH ₂	95IJC(B)209
	NR ¹ R ²	R ¹ R ² NH/KHCO ₃	91EGP294487 ^d
	NHOH, NHOR	NH ₂ OH, NH ₂ OR	97JHC1519
	NHOR, NR ¹ SR ²	NH ₂ OR etc./Et ₃ N	02GEP10121101
	NHNH ₂	NH ₂ NH ₂	95PHA33
	NHNH ₂	NH ₂ NR ₂ /Et ₃ N	02GEP10121101
	NHNHTs	NH ₂ NHTs	99JHC1199
	Me	MeMgBr	92MI1
	C ₁₄ H ₂₉	C ₁₄ H ₂₉ MgBr	02JA13856 ^e
	Alkyl	RMgBr/ZnBr ₂	04WOP58765
	5 and 7	Azolyl	RLi
OR		Azole Na salt	00RJOC866
OR		RONa	93JHC169, 03MI3, 03MI7
SR		RSNa	03MI3

^aSH, NHOH, NHNH₂ or tautomeric thioxo, oxime, hydrazone groups, respectively.

^bR: alkyl (R¹, R²); R': alkyl, aryl; R'': alkyl, aryl, heterocyclyl.

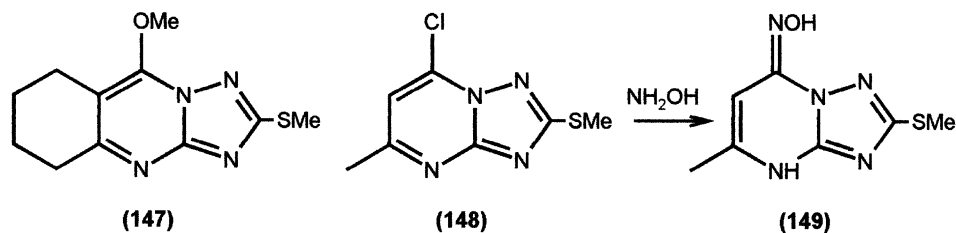
^cOptically pure (S)-amines.

^dChiral aminoalditols.

^eFe(acac)₃-catalyzed alkyl-heteroaryl cross-coupling reaction.

On studying oxo TP alkylation (see Sections III,C,5 and IV,B,1) a “fourth alkyl product” (e.g., **147**, Scheme 38) having an O-alkyl group can only indirectly be synthesized through the chloro compound (01JHC237). Similarly a direct oximation of 7-oxo TPs is not possible because of their amide character and must be replaced by a path via chlorides (e.g., **148**) to yield oxime **149** (97JHC1519).

The differentiated reactivity in the two positions of 5,7-dihalo TPs allows selective substitution in the 7-position (99USP5986135, 06WOP27170) or stepwise substitution first in the 7-, then, under harsher conditions, in the 5-position (04WOP108136).



Scheme 38

Some C–C linking reactions in addition to those listed in Table 13, are worth mentioning. 5,7-Dichloro TP **150** reacts selectively with an enamine to give dehydropiperidyl derivative **151** (Scheme 39) (99WOP41255). Palladium-catalyzed coupling of 7-iodo TP **152** to a propynol, accompanied by isomerization, yields chalcone **153** (91SL115). The intended chlorination of 7-oxo TP **154** in the 7-position by the action of phosphorus oxychloride in the presence of dimethylaniline resulted in the C–C coupling to the *p*-position of the aniline to give TP **134b** (92CHE1323). A blocked *p*-position as in dimethyl-*p*-anisidine, however, leads to an unusual demethylation yielding anisidine **155**.

2. Reactivity of Halogen in Positions 2 and 6

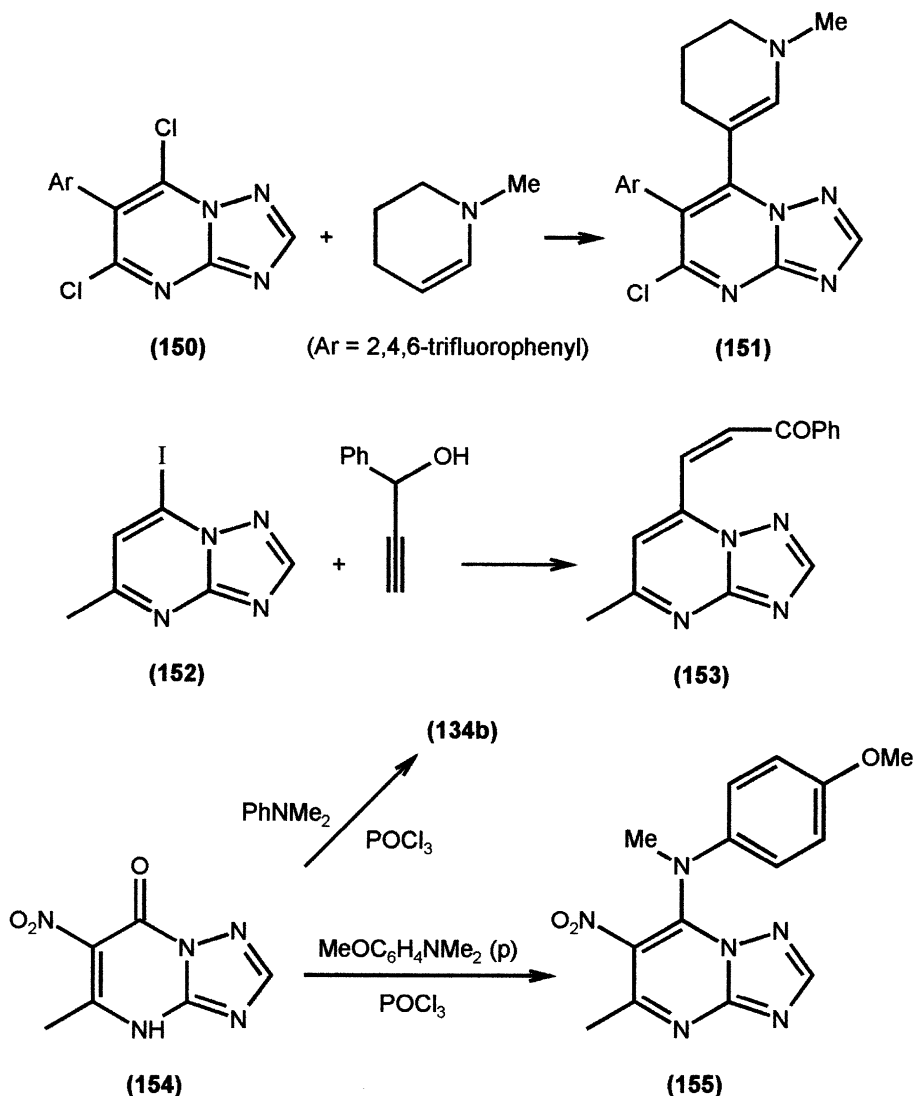
Transformation of 2-halo TP into 2-methoxy TP is an example of a rarely published substitution of 2-position halogen (92MI4). The most reactive chlorine atom in a 2,5,7-trichloro TP derivative is that in the 7-position (03WOP80614).

Reactions of 6-bromo TP (**156**) with N- and C-nucleophiles could be accomplished although Makisumi had regarded bromine in the 6-position as a weak nucleofugal group (*cf.* 93AHC(57)81, p. 119). Thus, piperidine **157** and, in a *cine*-substitution through the surprisingly stable intermediate **158**, indole **159** were obtained (Scheme 40) (99MC233).

3. Substitution of O-, S-, and N-Containing Functions

Reactions involving these leaving groups (see Table 14) generally follow the same rules as those for the halo compounds (Scheme 41). Thus, exchange of methoxy for methylthio or vice versa can selectively proceed at the 7-position as shown by the formation of compounds **160** and **161** (03MI3). 2-Alkylthio (e.g., **162**) and 2-alkanesulfonyl derivatives, owing to their good accessibility, frequently serve as precursors of otherwise 2-substituted TPs (e.g., **163**) (99MI2).

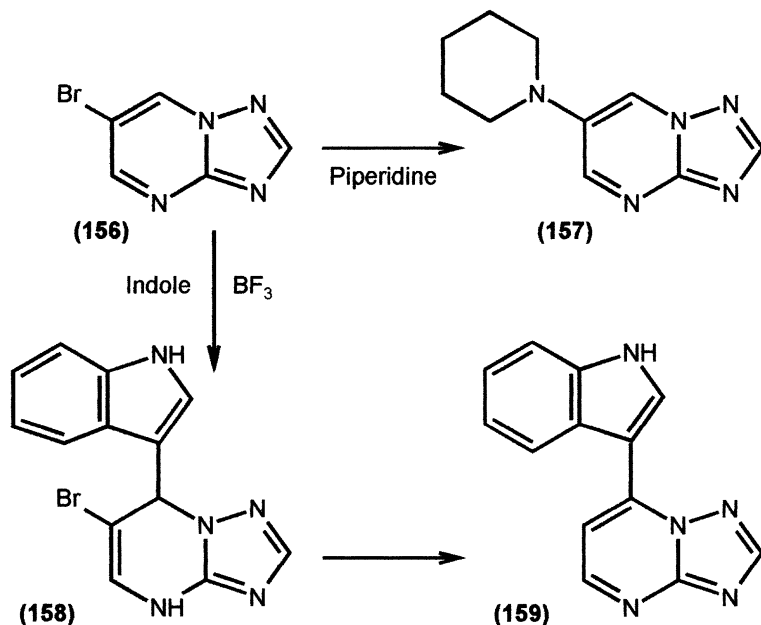
The replacement of the oxo functionality by chlorine (*cf.* 94AHC(59)245) has been the subject of many proposals attempting to improve the process of production (Scheme 42). Thus dichloro TP (**165a**) was claimed to be obtained in high yield when synthesized directly from the intermediate salt **164** (98USP5808066). Sulfonanilides



Scheme 39

165b were reported to form in a one-pot reaction from malonic acid, phosphorus oxychloride, and the appropriate AT derivative (**93JHC169**, **03MI7**). The latter reaction can proceed in a cyclic process (**95WOP11246**).

7-Amino compounds (such as **167**) can be made from oxo TPs (e.g., **166**) and amines without phosphorus oxychloride but instead with hexamethyldisilazane in a silylation-amination one-pot reaction (**02JHC703**).



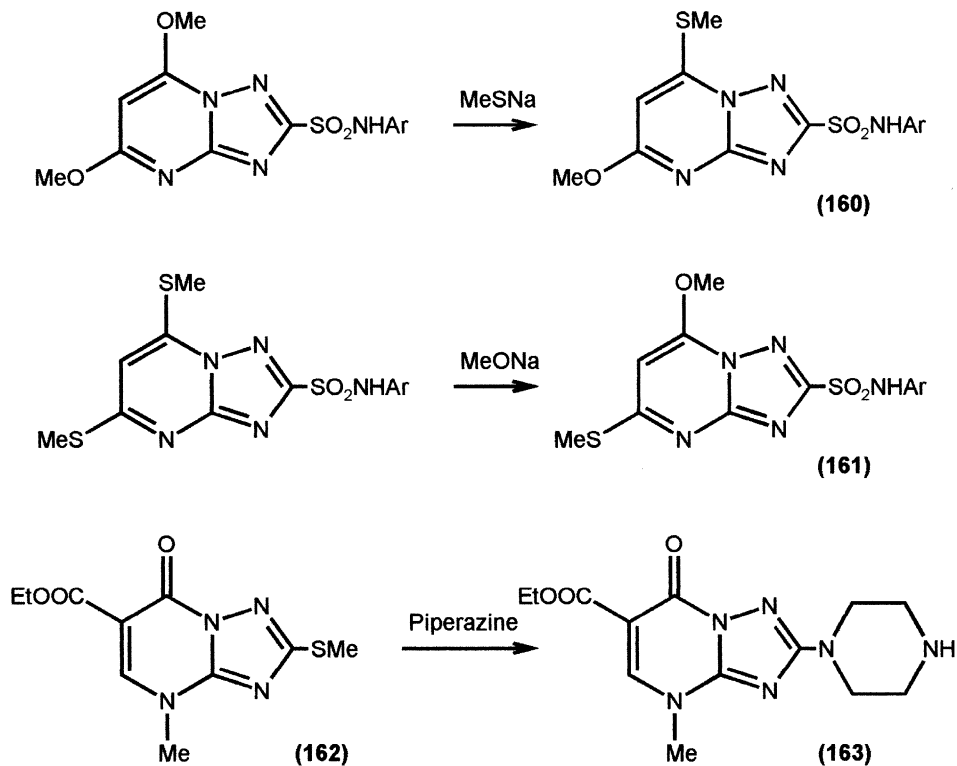
Scheme 40

Table 14. Nucleophilic substitution of O-, S-, and N-containing groups

Group ^{a,b}	Position	New substituent ^{a,b}	Reagent ^b	References
OH	5 or 7	Cl	POCl ₃	96MI1, 03JHC813
	5 and 7	Cl	POCl ₃	99JHC183
OR ¹	7	SR	RSNa	03MI3
SR ¹	2	NR ₂	R ₂ NH	99MI2
	5	OR	RONa	92MI4
SO ₂ R ¹		NR ₂	R ₂ NH	05WOP54246
	7	NHNH ₂	NH ₂ NH ₂	95PHA33
	2	OR	RONa	04WOP58765
		OR'	R'OH/NaH	03MI2, 05AX(E)o3842
		SH	(NH ₄) ₂ S or NaSH	04WOP46149
		SR'	R'SH/NaH	00MI1
		CN	R ₄ N ⁺ CN ⁻	04WOP58765
	OCHR'-PO(OR) ₂	HOCHR'-PO(OR) ₂ /NaH	00HAC313	
N ₃	7	OH	HCl or NaOH	92MI5
		S-SO ₃ Na	Na ₂ S ₂ O ₃	
CN	2	Me	MeMgX	06WOP34848

^aOH, NHNH₂ or tautomeric oxo, hydrazono group, respectively.

^bR: alkyl, R': aryl; R¹: other R in leaving group.



Scheme 41

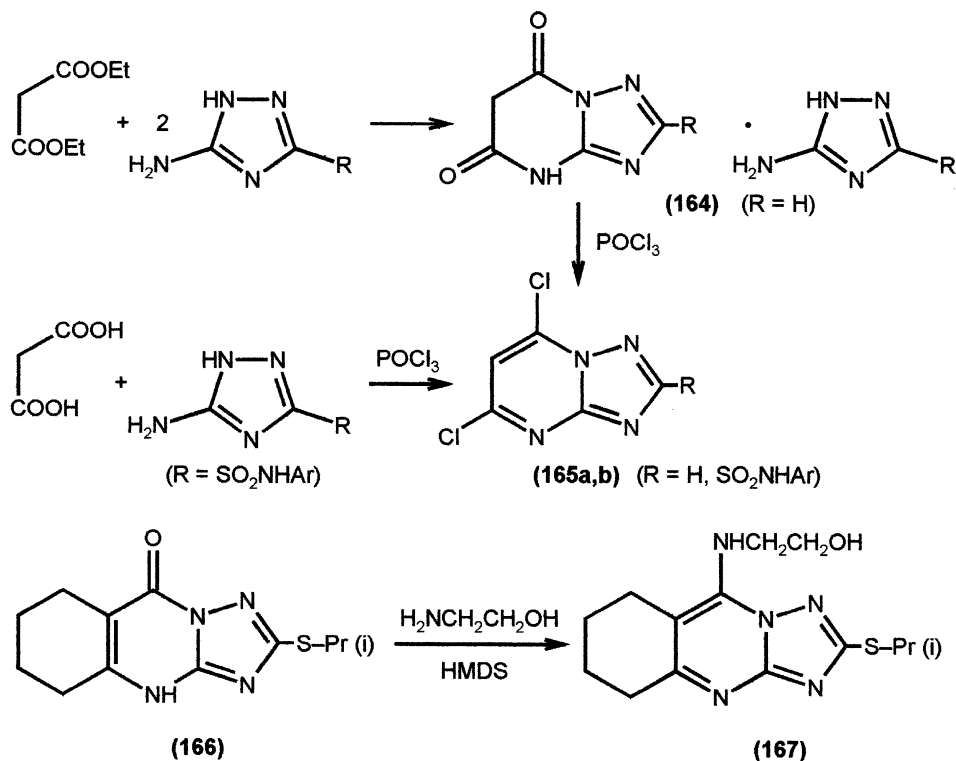
G. INTRODUCTION AND TRANSFORMATION OF INDIVIDUAL SUBSTITUENTS

1. Carboxylic Acid Derivatives

Along with esterification and ester hydrolysis (97RJOC1784, 02S901, 04JAP(K)107228) or deprotecting (hydrolysis of cephalosporin-analogous benzhydryl ester **168**, Scheme 43) (92BCJ3288) further reactions of esters, that is amidation and hydrazidation (99MCR277, 01JHC1119) or formation of hydrazinium salts (97RJOC1784) should be mentioned.

2. Sulfur-Containing Substituents

Reactions not fitting in with Section IV,F are listed in Table 15 (*cf.* Scheme 43). Additionally it should be noted that S-alkylation of 2-mercapto TPs (such as **170**) by benzylhalides gives higher yields and purer products when proceeding as a phase transfer reaction in ether-aqueous sodium hydroxide in the presence of benzyltrimethylammonium bromide (04MI9). TP **170** and α,α' -dichloroacetone react to yield a symmetrical bis-thioether (04MI3).



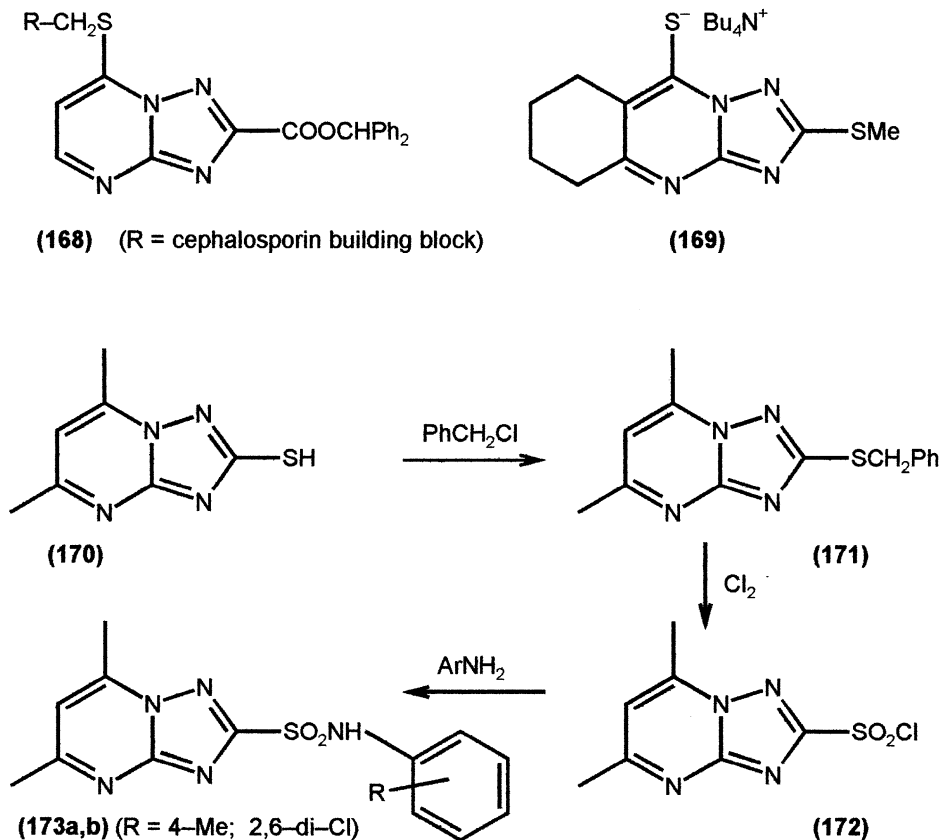
Scheme 42

The synthesis of herbicide-type TP 2-sulfonanilides (92MI1, 92MI2, 92MI3) or analogs (98MI8) is exemplified by the reaction of thiol **170** via benzylthioether **171** and sulfochloride **172** to obtain sulfonanilides **173** (97MI3).

3. Amines and Their Derivatives

Reactions not included in Section IV,F are compiled in Table 16. In addition, a Sandmeyer reaction allows 2-chloro or 2-bromo TPs to be obtained from 2-amino compounds (92MI4, 96GEP4434971). 6-Amino TP **174** (Scheme 44), however, on diazotation gives the stable diazo compound **175** that on heating in methanol suffers reduction (dediazonation) to yield 7-oxo TP (**29**) (05JHC1167). Desamination in the 3-position is observed when quaternary salts **35** are diazotized (**35b** to give **176b**) or acetylated (to give **177a,b**). In the case of diphenyl compound **35a** just heating in chloroform leads to TP **176a** (99CHE708).

Hydrolysis of tosylhydrazone **97** (Scheme 45) provides the 7-unsubstituted TP **179** (99JHC1199), according to a reaction type that "may be regarded essentially as the thermal decomposition of the hydrazide anion" (Albert, 1949). The reaction sequence starting from chloride **178** through hydrazone **97** to give TP **179**



Scheme 43

represents a noncatalytic dehalogenation method that is also applicable to structures sensitive to hydrogenation. The corresponding deuteration provides access to 7-deutero compounds, active hydrogen on other positions being simultaneously exchanged. Thus, hydrazone **97** yields a 1:1 mixture of polydeutero products **180a** and **b**.

4. Elimination by Direct Reduction

Different from the indirect reduction just mentioned (Scheme 45, substrate **178**), chlorine in 7-position can frequently be eliminated by catalytic hydrogenation (palladium/charcoal) (**96MI1**), by zinc (**02WOP64211**) or by the zinc-copper couple in the presence of acetic acid (**03MI3**). The latter method even works with sulfur-containing chlorides when catalytic hydrogenation or zinc reduction failed; for example, the 7-positioned chlorine of dichloride **181** is selectively removed (**99JHC183**).

Table 15. Sulfur-containing substituents

New group ^a	Position	Precursor ^{a,b}	Reagent ^a	References
SH	2	SCH ₂ Ph	AlCl ₃	04WOP46149
SR	2	SH	RX/NaOH	98MI10, 01HAC491, 01MI4, 01MI7, 02MI3, 02MI4, 02MI5
	7	SH (82)	RX/K ₂ CO ₃	04EJOC3872
		SH	RCl ^c	95BMCL2777, 00MI6
		S ⁻ Bu ₄ N ⁺ (169)	RX/AcONa	95PHA33
			RX	01JHC237
SAr	2	SH	ArCl	97MI1
SR'	2	SH	R'X	00MI5
SHet	2	SH	HetX	00MI3
SOMe	2	SMe	MCPA/0 °C	04WOP46149
SO ₂ Me	2	SMe	MCPA/20 °C	
			H ₂ O ₂ /AcOH	00HAC313, 00MI1
SO ₂ Cl	2	SH	Cl ₂	92MI1
		SCH ₂ Ph	Cl ₂	
SO ₂ NHAr	2	SO ₂ Cl	ArNH ₂	99BBR(258)797
			ArNHSiMe ₃	97MI6

^aR: alkyl; R': alkyl, aryl; Het: heterocyclyl; X: halo.

^bSH or tautomeric thioxo.

^cCephalosporin building block.

H. REACTIVITY OF SIDE CHAINS

1. Toward Electrophilic Reagents

Side-chain bromination of 5,7-dimethyl-6-aryl TPs (e.g., **187**, see below) by pyridinium tribromide can be restricted to the 7-positioned methyl (**06WOP34848**). The same regioselectivity rule governs the reaction of 5,7-dimethyl TP (**44**) with DMF dimethylacetal which yields enamine **182**, and, through oxime **183**, nitrile **184** (Scheme 46) (**96JHC465**).

Acylation of hydroxyalkyl TPs by aliphatic acids (**93RCB1265**) and by aromatic acids (**98EUP850902**) was described. The latter reaction proceeds as a *Mitsunobu reaction* (redox condensation) in the presence of azodicarboxylic ester and triphenylphosphine to give, for example, ester **185**.

Acetic acid (**02CRC517**) or malonic acid as TP substituents in 5- or 7-positions are easily decarboxylated. The overall process of introducing a methyl group into the 5-position (e.g., to give **187**) is depicted in Scheme 47 (**06WOP34848**). Partial degradation of the dialkyl malonate substituent in the 5-position yields an alkyl acetate group (**05WOP120233**).

The mild oxidation of 2-positioned hydroxymethyl to give TP 2-aldehydes was managed by means of DMSO, activated by oxalyl chloride (**03WOP93280**), or

Table 16. Amines and their derivatives

New group ^a	Position	Precursor ^a	Reagent ^a	References
NH ₂	2	N=CHPh	H ⁺	03USP6570014
		NHNO ₂	H ₂ SO ₄	97RJOC1784
	6	NHCOOCH ₂ Ph	HBr/AcOH ^b	05JHC1167
N(Me)dih. ^c	7	NHCH ₂ Ar	CF ₃ SO ₃ H	02WOP64211
	2	NHMe	3-diazo-dih. ^c	06WOP18725
NHSO ₂ Ar	2	NH ₂	ArSO ₂ Cl ^d	05USP215570
NHCOOAr	2	NH ₂	ArOCOCl	05JAP(K)139119
NHCONHR	2	NHCOOAr	RNH ₂	
NHCONHAr	2	NH ₂	ArNCO	04WOP108729
NHCSNHAr	3	NH ₂ (77)	ArNCS	03JHC973
NHCSNHCOAr	2	NH ₂	ArCONCS	01MI5
	7	NH ₂	ArCONCS	00PS(158)9
N ₃	7	NHNH ₂	HNO ₂	95PHA33
N=CHAR	3	NH ₂ (35a, 77)	ArCHO	99CHE708, 03JHC973
N=CHNMe ₂	7	NH ₂	DMF/POCl ₃	05WOP80396
N=CMeNH ₂	7	N ₃	MeCN	92MI5
N=CPhNMe ₂	2	NH ₂	PhCONMe ₂ /POCl ₃	00WOP9508
NHOCH ₂ Ph ^e	7	NHOH ^e	NaH/PhCH ₂ Cl	97JHC1519
NHNHAr	3	N=NR	SnCl ₂	03JHC973
NHNHCHO	7	NHNH ₂	HCOOH	92MI5
NHNHCOMe	7	NHNH ₂	AcOH	
NHN(COR') ₂	7	NHNH ₂	(R'CO) ₂ O	
NHNHSO ₂ Ar	7	NHNH ₂	ArSO ₂ Cl	
NHN=CHR'	7	NHNH ₂	R'CHO	92MI5, 95IJC(B)209, 95PHA33
		N ₃		
NHN=CMeOEt	7	NHNH ₂	CH ₃ C(OEt) ₃	92MI5
N=NAr	3	NH ₂ (77)	ArNO	03JHC973
Heterocyclyl	7	NHNH ₂		92MI5, 95PHA33
		N ₃		92MI5

^aR: alkyl; R': alkyl, aryl.

^bDeprotection of Cbo-protected amine.

^cdih.: dihydropyran-2,4-dion-3-yl.

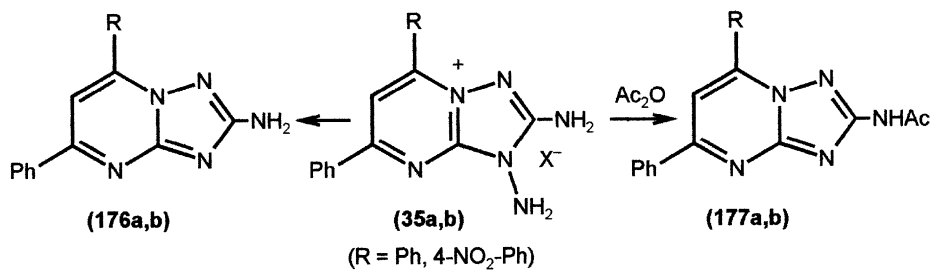
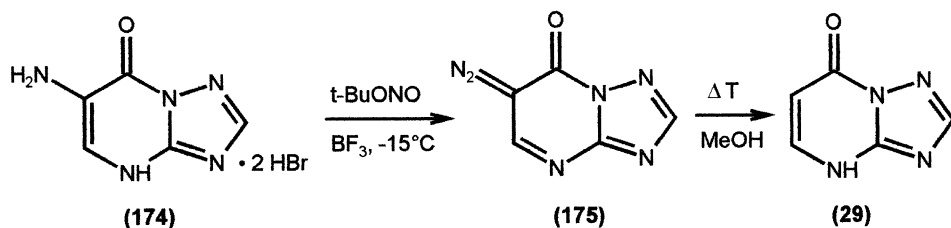
^dCatalysis by N-arylsulfilimines (e.g., TP-N=SMe₂) and 3-picoline.

^eHydroxylamine or tautomeric oxime structure.

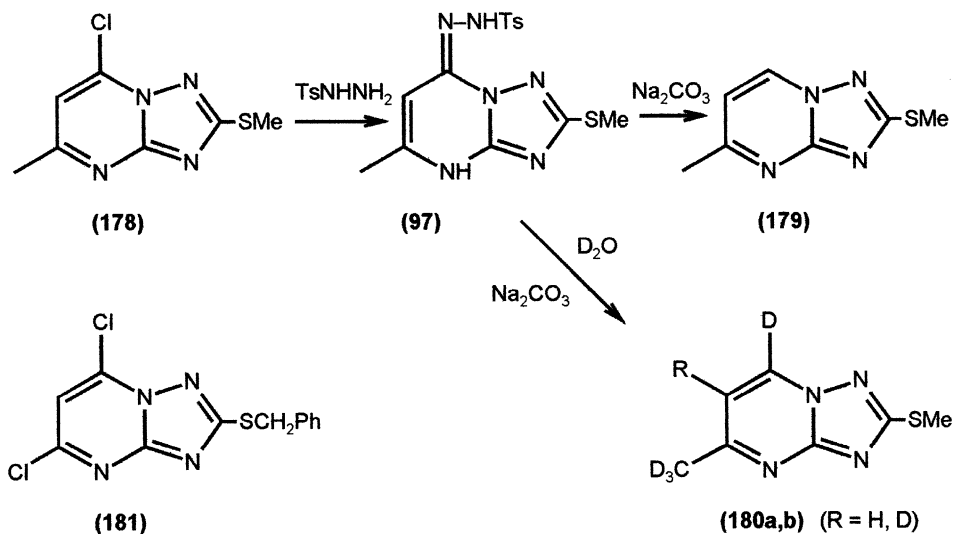
iodobenzene diacetate, catalyzed by 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (06MI3) whereas alkaline permanganate directly led to carboxylic acids (04JAP(K)107228).

2. Toward Nucleophilic Reagents

A typical reaction is the etherification of haloalkyl TPs by phenols in the presence of sodium hydride (95WOP10521). Fluorine can be replaced by O- or N-nucleophilic groups in 6-(fluorophenyl) TPs (05USP124635), 7-(fluorophenyl) TPs (e.g., 4)



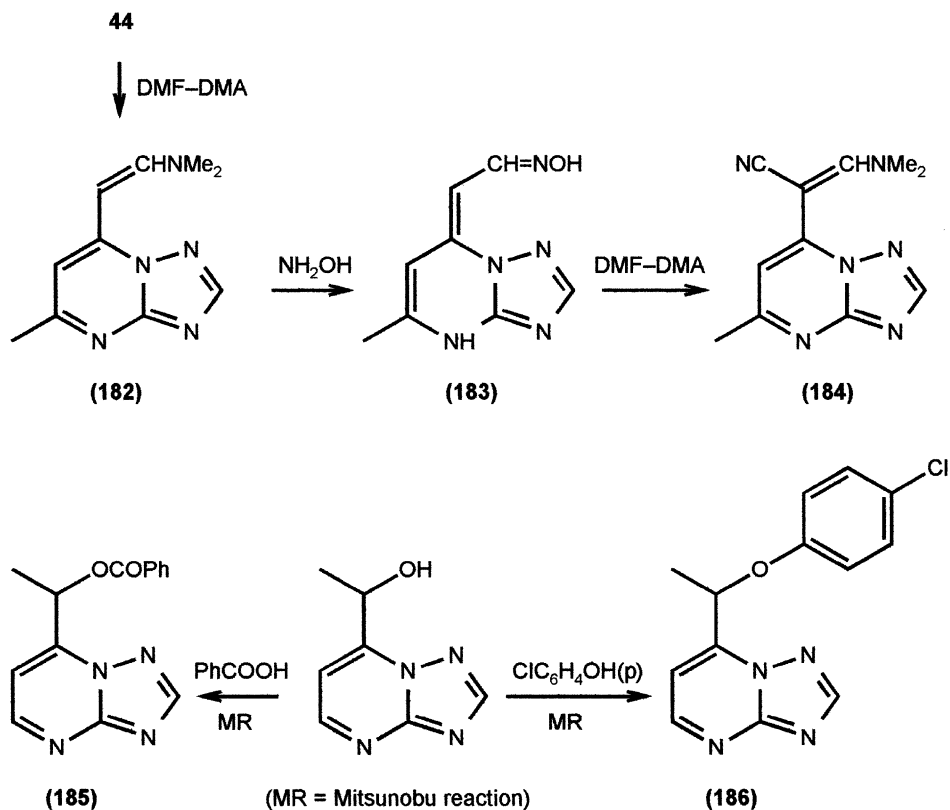
Scheme 44



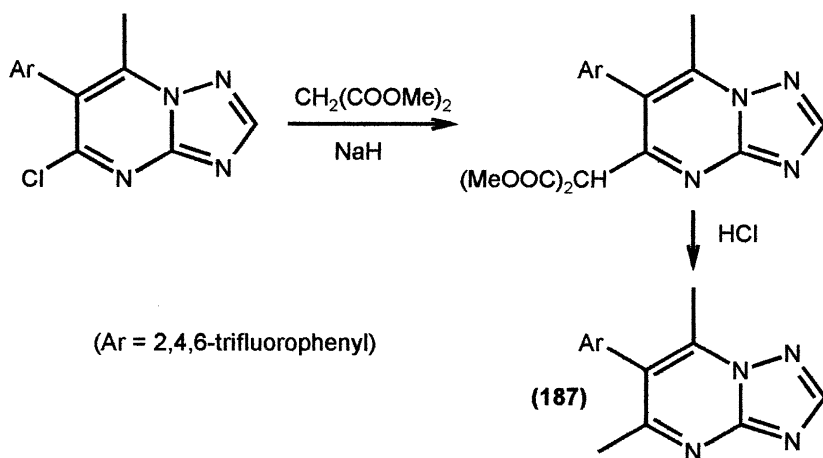
Scheme 45

(01RJOC570), and 6,7-(fluorobenzo) TPs (e.g., **11b**) (05RJOC1071). 2-(Chloromethyl) TPs condense with lithium benzenesulfinate derivatives to give sulfones (93EUP544166).

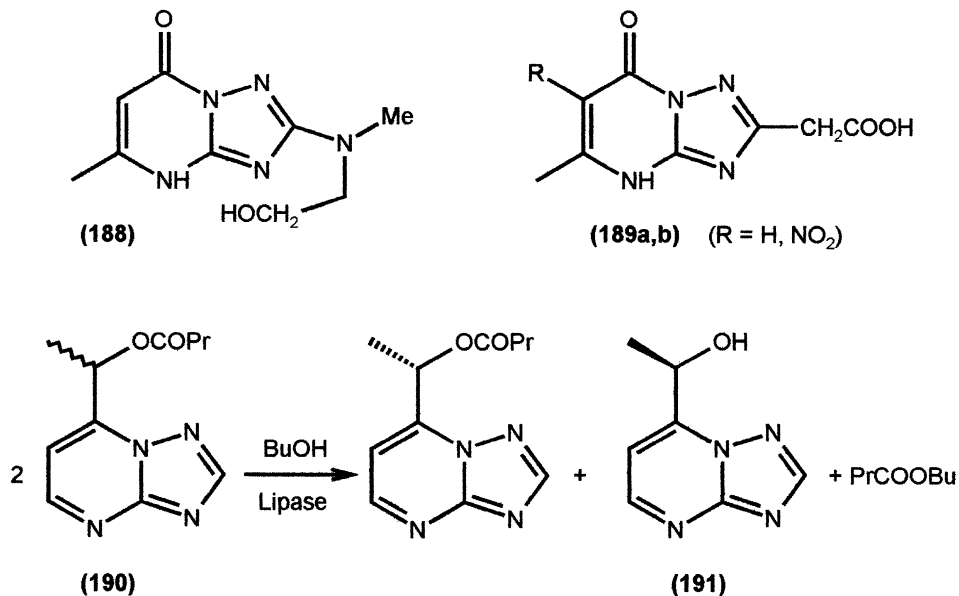
7-(Hydroxyalkyl) TPs and phenols react to yield phenol ethers (e.g., **186**, Scheme 46) by an application of the Mitsunobu reaction (see Section IV,H,1) (98WOP7724).



Scheme 46



Scheme 47



Scheme 48

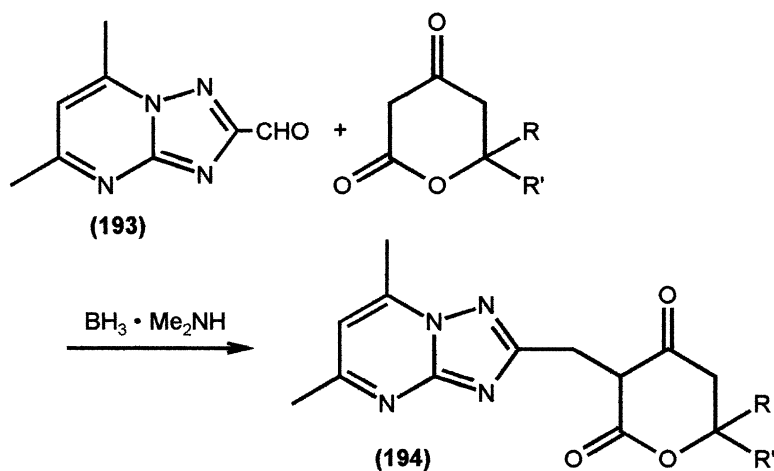
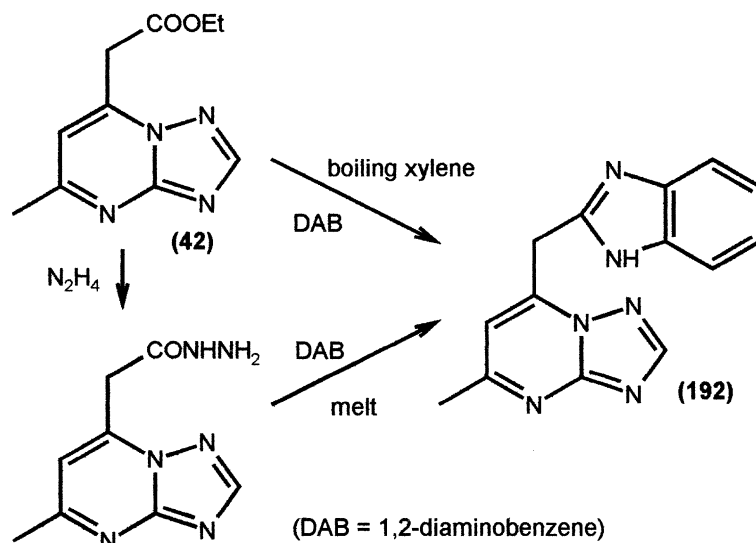
Hydroxyalkylamine **188** (Scheme 48) in an acid medium cyclizes to give two imidazolidino TP isomers (02JHC319). The ether bond of alkoxyalkyl TPs can be cleaved by hydrobromic acid (05WOP87770), that of similar benzyl ethers by catalyzed hydrogenation (04JAP(K)107228).

Aiming at mass spectrometric labeling, a 2-acyl TP derivative was transformed into a special O-substituted oxime (01AG222).

TP 2-acetic acid **189a** can be esterified through its acyl chloride or, more conveniently, in one step by reacting in ethanolic suspension with thionyl chloride (97RJOC1784). Nitro compound **189b** via its ethyl ester gives the hydrazide. Enantiomerically pure alcohols (e.g., **191**) are produced by selective transesterification, for instance by reacting racemic esters (e.g., **190**) with alcohols in the presence of an esterase or lipase (98GEP19706336).

Direct amidation of TP 5-acetic acid by aliphatic amines is performed in the presence of dicyclohexyl carbodiimide (98EUP838722). Ester **42** easily forms the respective hydrazide (Scheme 49); both substances each condenses with 1,2-diaminobenzene to give the 7-(benzimidazol-2-yl)-methyl compound **192** (02CRC517).

7-Acyl TPs can be reduced to form enantiomerically pure 7-(α -hydroxyalkyl) TPs, the reaction proceeding in the presence of a microorganism and a carbon source or in the presence of an enzyme and a reducing agent (98GEP19707008). Finally, reductive condensation of 2-formyl TPs (e.g., **193**) and dihydropyran-2,4-dione leads to TP derivatives **194** (06MI3).

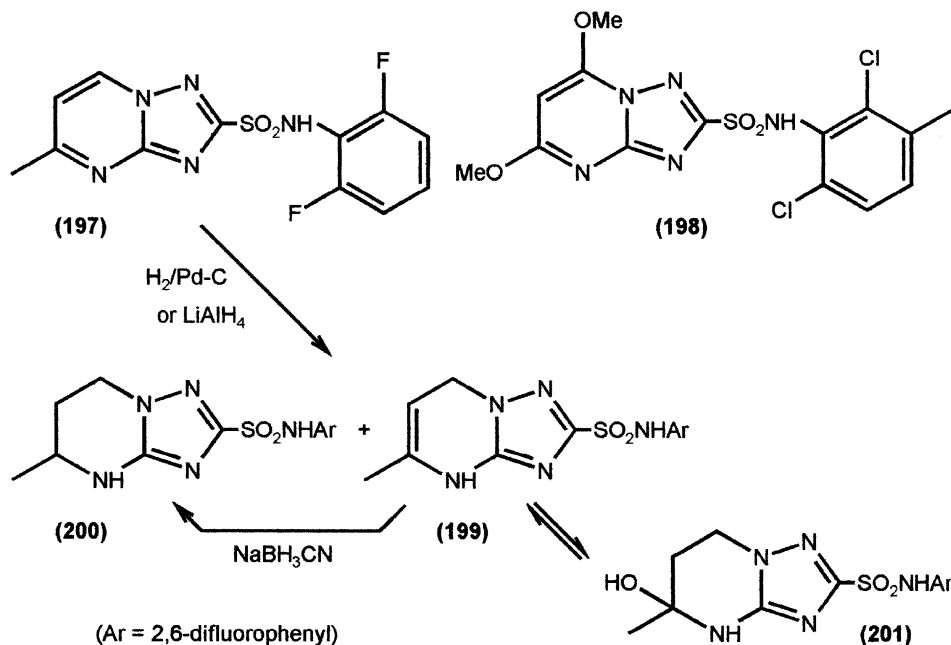


Scheme 49

V. Applications

A. PHARMACEUTICAL USES

Ts continue to attract much pharmaceutical interest. They have been the subjects of about 200 relevant patents (*cf.* 98AHC(72)127, p. 169) and numerous publications dealing with laboratory and clinical tests, analytics, and other topics. The most



Scheme 51

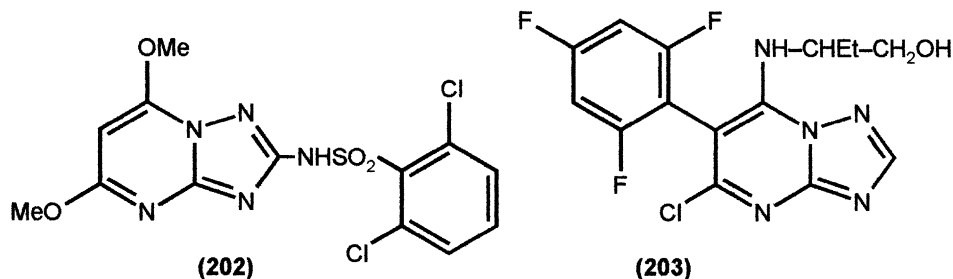
The mode of their action consists in the *acetolactate synthase (ALS)* inhibition and, as a result, in the inhibition of the branched-chain amino acid biosynthesis from acetolactate (90MI1, 92MI7, 98MI4). Results of QSAR studies were published (03MI3). Another approach was used to analyze a model of inhibition of photosystem II (96MI1).

Metosulam (198) was ^{14}C -radiolabeled in the 2-position or in the benzene ring by modified synthetic routes (97MI6). This way data on the pharmacokinetics in mammals could be provided (97MI4). Flumetsulam (197) was toxicologically examined (03MI5) and included in QSAR studies of herbicide toxicity (06BMC2779).

Metabolic investigations with Flumetsulam revealed the following paths of detoxification (tolerance mechanisms) in nonsensitive plants: mono- or dihydroxylation (to give 5-hydroxymethyl and/or 4'-hydroxy substitution) and glucose conjugation (to form O-glucosides) (92MI3, 93MI5, 03MI3). Other substances additionally undergo O-dealkylation and TP ring cleavage (94MI5).

The anaerobic aquatic degradation of Flumetsulam was studied to elucidate the metabolism in soil (92MI6). The most probable degradation product is *reduced Flumetsulam hydrate* (201), existing in an equilibrium mixture. The determination of this structure was assisted by chemically reducing Flumetsulam to yield dihydro and tetrahydro products 199 and 200, respectively.

The extensive analytical literature dealing with herbicides such as Flumetsulam and Metosulam includes, for instance, trace and ultra-trace analyzes in soil or foods



Scheme 52

using solid-phase extraction combined with chromatographic, spectrometric (UV, MS), and electrophoretic methods (95MI1, 05MI3, 05MI4). Flumetsulam is not sufficient thermally stable for gas chromatography unless N-methylated (99MI7).

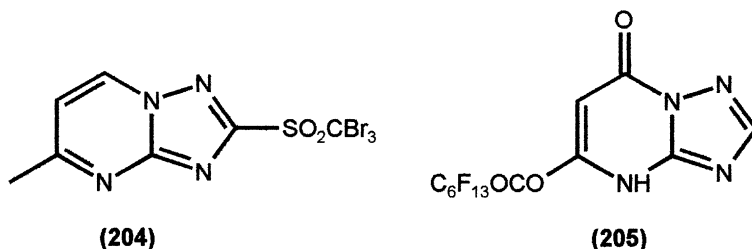
Much effort has targeted at discovering new TP herbicides in the groups of 2-thioethers (00MI5), phenyl derivatives (95MI2), 2-arenesulfonamides (type **202**, Scheme 52) (94MI4, 96MI2), and especially 2-sulfonanilides (type **173**) (97MI3, 98MI5, 98MI9, 98MI11, 98MI12, 99MI3, 99MI4, 99MI9). QSAR analysis has been based on electronic and steric factors, physicochemical properties, X-ray diffraction, quantum-chemical calculations, and (98MI7, 99MI8) *comparative molecular field analysis* (CoMFA).

The main foci among about 200 patents (*cf.* 98AHC(72)127, p. 167) have been, together with sulfonamides, 2-(arenesulfonylamino) TPs (e.g., **202**) (02WOP36595) and, as fungicides, 6-(halophenyl)-7-amino TPs (e.g., **203**) (06WOP27170). The bronchodilator **107** has been proposed as herbicide safener (92EUP467529). Platinum and ruthenium complexes of TPs are active agents against Trypanosoma forms (04MI8). Just recently new synthetic variations of the 5,7-dimethyl TP structure (**44**) have been published (05MI7, 05MI8, 06MI1).

C. USES IN INFORMATION RECORDING

The photographic application of TPs, centered around substance **2**, as stabilizers of photographic silver halide emulsions was recently thoroughly treated (04MI10). Acidity, adsorptivity of the silver salts, and redox properties of these compounds were dealt with as parameters governing the mechanism of stabilization. A neural network could be used to compute QSAR with derivatives of agent **2** on the basis of their stabilizing activity and ¹³C-NMR chemical shifts (99JPR449).

Photothermographic materials can be stabilized by polyhalomethyl derivatives (e.g., **204**, Scheme 53) (97JAP(K)09/319022) whereas TP 5,7-diones (e.g., **6**) were claimed as couplers for heat-developable diazo recording material (04JAP(K)142377). Other TPs (e.g., **2**) were found to improve lightfastness of ink-jet recorded images (00JAP(K)94829).



Scheme 53

D. OTHER USES

Owing to their anticorrosive properties TPs (e.g., **205**) serve as rust inhibitors in lubricants for magnetic recording materials (95JAP(K)07/65352) or in chemical-mechanical polishing systems (02JAP(K)134442).

By making use of the adsorbability of TPs semiconductor particles for photoelectrochemical cells are provided with an adsorbed mixture of dye and TP (e.g., **2**) (00JAP(K)228233). Finally, TP carboxylic acids can be contained in compositions for depositing silver layers (*plating*) (04USP40852).

List of Abbreviations

AT	5-amino-1,2,4-triazole
HP	2-hydrazinopyrimidine
TP	1,2,4-triazolo[1,5-a]pyrimidine

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Organometallic Chemistry of Polypyridine Ligands III

ALEXANDER P. SADIMENKO

Department of Chemistry, University of Fort Hare, Alice 5701, Republic of South Africa

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I. Introduction

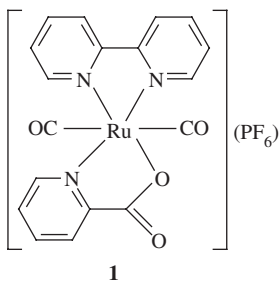
This chapter constitutes parts 11 and 12 in a series covering the organometallic chemistry of polypyridine ligands with non-transition and early transition metals (07AHC(93)185) and manganese group metals (07AHC(94)109). Organometallic compounds of polypyridine ligands with iron group metals attracted attention due to their unique photochemical and electrochemical properties, ability to form molecular assemblies and nanocrystallites, and to catalyze photo- and electrochemical reduction of carbon dioxide. Herein, we consider organoiron, organoruthenium, and organoosmium complexes of polypyridine ligands. As always in this series of chapters, emphasis will be on the synthetic and coordination aspects, as well as reactivity.

II. Organoiron, Organoruthenium, and Organoosmium Complexes

A. MONO-POLYPYRIDINE COMPLEXES

Reaction of $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$ with 2,2'-bipyridine or 4,4'-di(*i*-propoxycarbonyl)-2,2'-bipyridine (LL) gives a solution consisting of a mixture of $[\text{Ru}^{\text{II}}(\text{LL})(\text{CO})_2\text{Cl}_2]$ and $[\text{Ru}^{\text{III}}(\text{LL})(\text{CO})\text{Cl}_3]$ (91JEAC(319)347, 93JOM(444)191), but not the *cis*-isomer

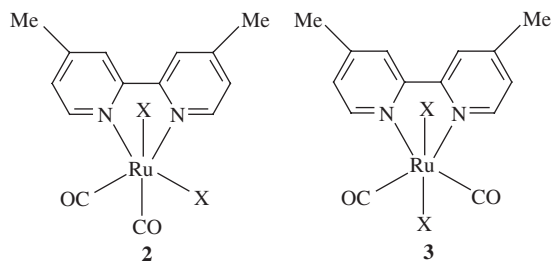
of $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$ as indicated earlier (64JCS3466, 66JCS(A)300). A pure *trans*(Cl)-isomer was claimed to result (82AJC2445, 82ICA(65)L75, 83POL409, 86SRIMC85, 89IS107, 00JEAC(490)62, 01CCC207). Refluxing this mixture of the 2,2'-bipyridine complex in water-methanol gives pure *trans*- $[\text{Ru}^{\text{II}}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ (82ICA(64)L75). Selectivity is determined by the conditions of the preparation of the ruthenium(II) polymeric precursor and the pH of the medium (97IC5384). $[\text{Ru}^{\text{III}}(\text{bpy})(\text{CO})\text{Cl}_3]$ can be reduced electrochemically to $(\text{Me}_4\text{N})[\text{Ru}^{\text{II}}(\text{bpy})(\text{CO})\text{Cl}_3]$ (91JEAC(319)347). Photolysis of the acetonitrile (AN) solutions of $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$ or $(\text{Me}_4\text{N})[\text{Ru}(\text{LL})(\text{CO})\text{Cl}_3]$ (LL = 2,2'-bipyridine or 4,4'-di(*i*-propoxycarbonyl)-2,2'-bipyridine) gives the photosubstitution products $[\text{Ru}(\text{LL})(\text{CO})(\text{AN})\text{Cl}_2]$, $[\text{Ru}(\text{LL})(\text{AN})_2\text{Cl}_2]$, and $[\text{Ru}(\text{LL})(\text{AN})_3\text{Cl}]^+$ (80IC860, 81ICA(53)L3, 84IC1440, 90JA9490, 93JOM(444)191, 93JPC5973). $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ and $[\text{Ru}(4,4'\text{-Me}_2\text{bpy})(\text{CO})_2\text{Cl}_2]$ were prepared similarly (86JCS(D)253). Photolysis of $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$ (LL = bpy, 4,4'-Me₂bpy) in acetonitrile gives various ligand-substitution products, among them are $[\text{Ru}(\text{bpy})(\text{CO})(\text{AN})\text{Cl}_2]$, $[\text{Ru}(\text{bpy})(\text{AN})_3\text{Cl}]^+$, and $[\text{Ru}(4,4'\text{-Me}_2\text{bpy})(\text{AN})_3\text{Cl}]^+$ (00OM163, 01PCCP1992, 03JCP81). Photolysis in methylene chloride gives $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ dimer. The tetrahydrofuran (THF)-substitution product $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}(\text{THF})]$ is labile functions as a ligand with respect to chromium, manganese, and ruthenium species to yield homo- and heterodinuclear complexes (78JOM(144)175, 80JOM(197)357, 93IC3789). Photolysis of $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ in methanol yields $[\text{Ru}(\text{bpy})(\text{CO})(\text{MeOH})\text{Cl}_2]$ (02EJI1169). Prolonged photolysis leads to the binuclear species $[(\text{bpy})\text{Cl}(\text{OC})\text{Ru}(\mu\text{-OMe})_2\text{RuCl}_2(\text{bpy})]$. Extended heating of 2,2'-bipyridine or 1,10-phenanthroline with $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ in formic acid gives ruthenium(III) complexes $[\text{RuCl}_3(\text{CO})(\text{LL})]$ (LL = bpy, phen) (99POL2091). $[\text{Ru}(\text{bpy})_2(\text{CO})_2\text{Cl}_2]$ reacts with 2-pyridylcarboxylic acid in aqueous silver nitrate and potassium hexafluorophosphate to yield **1** (03JOM(665)107).



Interaction of $[\{\text{Ru}(\text{CO})_3\text{Cl}_2\}_2]$ and 2,2'-bipyridine gives $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ (95OM825, 95OM5454, 96POL1571). The product reacts with an aqueous mixture of hydrochloric and nitric acids at elevated temperatures to yield nitrosyl or nitrido complexes $[\text{Ru}(\text{bpy})(\text{NO})\text{Cl}_3]$, $[(\text{H}_2\text{O})\text{Cl}_2(\text{bpy})\text{RuNRu}(\text{bpy})\text{Cl}_3]$, and $[\text{Cl}_3(\text{bpy})\text{RuNRu}(\text{bpy})\text{Cl}_3]^-$ (95IC2931). With aqueous hydrobromic or hydroiodic acid, the products of halogen exchange follow, $[\text{Ru}(\text{bpy})(\text{CO})_2\text{X}_2]$ (X = Br, I) (96JCS(D)1927, 04IC7380). When nitric acid was added, in both cases the nitrosyl complexes $[\text{Ru}(\text{bpy})(\text{NO})\text{X}_3]$ (X = Br, I) resulted. The reaction of $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}_2]$

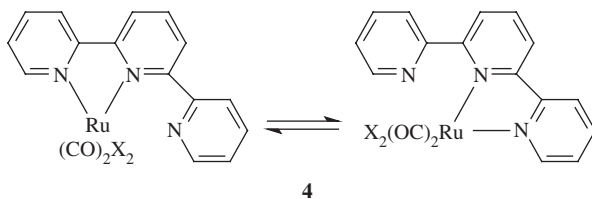
with an aqueous mixture of hydrofluoric and nitric acids leads to $[\text{Ru}(\text{bpy})(\text{NO})\text{Cl}_2\text{F}]$. Extended reaction with $\text{HBr}-\text{HNO}_3$ gives the binuclear complex $[(\text{H}_2\text{O})\text{Br}_2(\text{bpy})\text{RuNRu}(\text{bpy})\text{Br}_3]$. $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ with aqueous potassium thiocyanate gives the product of substitution of the chloride ligands, $[\text{Ru}(\text{bpy})(\text{CO})_2(\text{NCS})_2]$ (96OM4081). $[\{\text{Ru}(\text{CO})_3\text{Cl}_2\}_2]$ on reaction with 6,6'-dimethyl-2,2'-bipyridine (LL) in THF gives $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$. In ethylene glycol, the product is $[\text{Ru}(\text{LL})(\text{CO})_2(\text{Cl})\text{H}]$. With potassium thiocyanate, the Cl-substitution product, $[\text{Ru}(\text{LL})(\text{CO})_2(\text{SCN})\text{H}]$, results. Other examples of chemical modification of the coordination sphere of ruthenium(II) and polypyridine ligands are known (80JA5543, 93JA6382, 95JEAC(396)27, 97IC3794, 98JEAC(444)253, 98JOM(552)205, 99JEAC(466)187). $[\text{Ru}_3(\text{CO})_{12}]$ reacts with 2,2'-bipyridine-4,4'-dicarboxylic acid (LL) in the presence of aqueous hydrochloric acid to yield $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$ (00JCS(D)2745). $[\{\text{Ru}(\text{CO})_3\text{Cl}_2\}_2]$ reacts with a variety of 4,4'- R_2 -2,2'-bipyridines (LL; R = H, Me, *t*-Bu, NO_2 , H_2PO_3 , Cl, Br) to yield $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$ (01JCS(D)2649). 4,4'-Dimethoxycarbonyl-2,2'-bipyridine and 5,5'-dimethoxycarbonyl-2,2'-bipyridine (LL) react with $[\{\text{Ru}(\text{CO})_3\text{Cl}_2\}_2]$ to yield $[\text{RuCl}_2(\text{CO})_2(\text{LL})]$ (02JOM(654)8). The reaction of 6,6'-diethoxycarbonyl-2,2'-bipyridine and 6-methoxycarbonyl-6'-carboxylate-2,2'-bipyridine was conducted in methylene chloride.

Complex **2** (X = Cl) interacts with aqueous hydrobromic acid to yield the ligand-substitution complex in the same *cis*(Br)-isomeric form **2** (X = Br) (99EJ1101, 99IC3182). With aqueous hydroiodic acid, however, the sole product is the *trans*(I)-isomer **3** (X = I). Complex **3** (X = Cl) being in the *trans*(Cl)-configuration reacts with aqueous hydrobromic and hydroiodic acids as well as potassium thiocyanate to yield *trans*(X)-isomers **3** (X = Br, I, SCN). Species $[\text{M}(\text{SnR}_3)_2(\text{CO})_2(4,4'\text{-Me}_2\text{bpy})]$ (M = Ru, Os; R = Me, Ph) are known (00CCR(208)309, 01JCS(D)2587). Photolysis of $[\text{Os}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ in acetonitrile gives $[\text{Os}(\text{bpy})(\text{CO})(\text{AN})\text{Cl}_2]$ and electrochemical oxidation in acetonitrile gives $[\text{Os}(\text{bpy})(\text{CO})(\text{AN})\text{Cl}_2]^+$ (02EJ12850). Reaction of $[\text{Ru}(\text{CO})_2(\text{AN})_2](\text{PF}_6)_2$ with NO_2PF_6 in acetonitrile followed by 2,2'-bipyridine gives $[\text{Ru}(\text{bpy})(\text{CO})_2(\text{AN})_2](\text{PF}_6)_2$ (04JOM484).



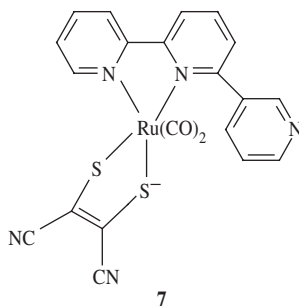
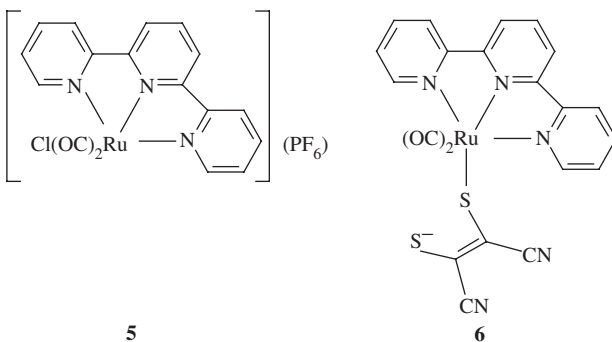
In *trans*- $[\text{Ru}(\text{trpy})(\text{CO})_2\text{X}_2]$ (X = Cl, Br, I), 2,2':6',2''-terpyridine is a bidentate ligand (67JCS(A)1238, 67JINC133, 82AJC2445, 84AJC929, 94JCS(D)111). $[\{\text{RuCl}_2(\text{CO})_2\}_n]$ reacts with LiX (X = Cl, Br, I) and then 2,2':6',2''-terpyridine to yield $[\text{RuX}_2(\text{CO})_2(\text{trpy})]$ (X = Cl, Br, I) (94JCS(D)111). Heating the products in tetrachloroethane leads to the decarbonylation products $[\text{RuX}_2(\text{CO})(\text{trpy})]$. NMR

data are in agreement with the dynamic behavior of complexes in solution described by the equilibrium **4**.



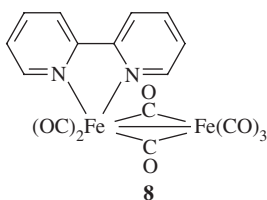
Photolysis of $[\text{Ru}(\text{CO})_2\text{X}_2(\text{bpy})]$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) in acetonitrile, methanol, or ethanol leads to the substitution of one carbonyl ligand by a solvent molecule (**00IC2777**, **04IC4380**, **05JPC(B)17538**). The same route is observed for the reaction of $[\text{Ru}(\text{CO})_2\text{Cl}_2(\text{bpy})]$ in dialkylcyanamide solutions, the products being $[\text{Ru}(\text{CO})\text{Cl}_2(\text{bpy})(\text{R}_2\text{NC}\equiv\text{N})]$ ($\text{R} = \text{Me}, \text{Et}$) (**06JOM2368**).

2,2':6',2''-Terpyridine reacts with $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$ in refluxing ethanol–water in the presence of ammonium hexafluorophosphate to yield **5** with tridentate coordination of the ligand (**97OM4421**). The product reacts with sodium formate in acetonitrile to yield the ligand-substitution product $[\text{Ru}(\text{trpy})(\text{CO})_2(\text{OCHO})](\text{PF}_6)$. Complex **5** reacts with $\text{Na}_2\text{S}_2\text{C}_2(\text{CN})_2$ in methanol. First, **6** was obtained and then it transformed gradually into **7** with bidentate coordination of the 2,2':6',2''-terpyridine ligand (**01JCS(D)57**). The reaction of **5** with 3,4-toluenedithiol occurs to the stage of the analog of **7** with bidentate coordination of the polypyridine ligand. The product with tridentate coordination was not found. The reaction of **5** with $\text{Cs}\{\text{PhC}(\text{S})\text{C}(\text{S})\text{Ph}\}$ in methanol proceeds differently and affords $[\text{Ru}(\text{CO})(\text{C}(\text{O})\text{OMe})(\text{SC}(\text{Ph})\text{C}(\text{Ph})\text{SC}(\text{O})\text{OMe})(\eta^3\text{-trpy})]$.



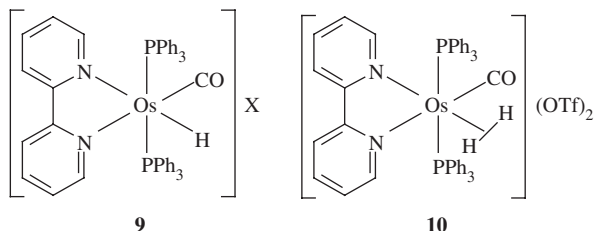
Complexes $[M(L_1)(L_2)(CO)_2(LL)]$ ($M = Ru, Os$) where L_1 and L_2 are various ligands and LL is a polypyridine ligand are interesting in terms of the possibility of tuning the excited-state properties of the polypyridine species (96CEJ1556, 02CCR(230)107). Syntheses of some representatives are outlined below. $[RuI_2(CO)_2(AN)_2]$ reacts with 4,4'-dimethyl-2,2'-bipyridine in diethyl ether under reflux to yield $[RuI_2(CO)_2(4,4'-Me_2bpy)]$ (01IC277). Other examples include $[Ru(L_1)(L_2)((CO)_2(bpy))]$ ($L_1 = Cl, I, OTf$; $L_2 = Me, Et$) (92OM3774, 94OM3279). $[OsCl_2(CO)_2(bpy)]$ enters photochemical CO-substitution reactions with acetonitrile (00CCR(200)933). $[OsCl_2(CO)_2]_n$ reacts with 4,4'-dimethyl-2,2'-bipyridine in *n*-propanol to yield $[OsCl_2(CO)_2(4,4'-Me_2bpy)]$. $[RuI_2(CO)_2(4,4'-Me_2bpy)]$ with $LiSnR_3$ ($R = Me, Ph$) in THF gives $[Ru(SnR_3)_2(CO)_2(4,4'-Me_2bpy)]$ ($R = Me, Ph$). $[OsCl_2(CO)_2(4,4'-Me_2bpy)]$ with $LiSnPh_3$ in THF gives $[Os(SnPh_3)_2(CO)_2(4,4'-Me_2bpy)]$. Another representative which can be prepared similarly is $[Ru(Me)(I)(CO)_2(bpy)]$ (87JOM(328)209, 94IC3212, 95IC3879, 95JA5579).

$[Fe(CO)_3(bpy)]$ (82CB1070, 83JCR(S)216) may be obtained from ferric chloride, sodium 2,2'-bipyridyl, and carbon monoxide (02JOM(662)137). $[Fe_3(CO)_{12}]$ with 2,2'-bipyridine, 4,4'-dimethyl-2,2'-bipyridine, 1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, or 2,9-dimethyl-1,10-phenanthroline (LL) in the presence of trimethylamine oxide in THF gives a mixture of mononuclear complexes $[Fe(CO)_3(LL)]$ and dinuclear products $[Fe_2(CO)_7(LL)]$, one of which is illustrated as **8** (03JOM(677)101). The same set of products follows from $[Fe_2(CO)_9]$ and $[Fe(CO)_5]$, while $[Fe(CO)_3(\text{benzylideneacetone})]$ forms exclusively mononuclear complexes. The reaction of $[Fe_5C(CO)_5]$ with 2,2'-bipyridine in THF yields $[Fe(bpy)_3][(\mu-H)Fe_4C(CO)_{123}]_2$. $[Ru(CO)_3(LL)]$ (90CCR(104)39) as well as $[Ru(bpy)(CO)Cl_3]^-$ are known (74JCS(D)1640, 90AX(C)312).

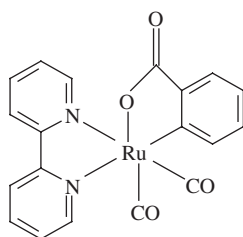


2,2'-Bipyridine with $[Ru(CO)_5]$ in methylene chloride gives unidentified polymeric insoluble complexes (97JCS(D)2997). 2,2':6',2''-terpyridine and 6-(2-thienyl)-2,2'-bipyridine (LL) in methylene chloride form $[RuCl_3(LL)]$ with tridentate *N,N,N*- and *N,N,S*-coordination, respectively.

Complexes $[OsH(LL)(CO)(PR_3)_2]^+$ ($LL = bpy, phen$) are known (83OM551, 84OM1241, 98IC127). Complex $[OsH_2(CO)(PPh_3)(bpy)]^{2+}$ is regarded as a dihydrogen complex (92IC1471). Reaction of $[Os(CO)(PPh_3)_3(Cl)H]$ with 2,2'-bipyridine gives **9** ($X = Cl$), which with ammonium triflate gives **9** ($X = OTf$) (96IC4396). The product enters reversible protonation with triflic acid to yield dihydrogen species **10**. $[Os(\eta^2-H_2)(bpy)(P(OEt)_3)]^{2+}$ reacts with carbon monoxide to yield $[Os(bpy)(CO)(P(OEt)_3)_3]^{2+}$ (04JOM1639).



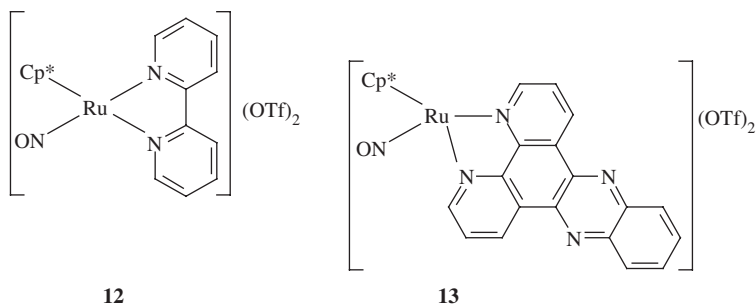
Carbonyl-carboxylato complexes of ruthenium(II) $[\text{Ru}(\text{CO})_2(\text{RCOO})_2(\text{LL})]$ (LL = bpy, phen) catalyze carbonylation and hydrogenation of organic substances (91JMOC(64)257, 97JOM(547)35). Refluxing of $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$ with 2,2'-bipyridine or 1,10-phenanthroline in the presence of sodium benzoate in methanol gives the mononuclear complexes containing the cyclometalated benzoate group. The structure of the 2,2'-bipyridine complex is illustrated as **11** (04IC683).



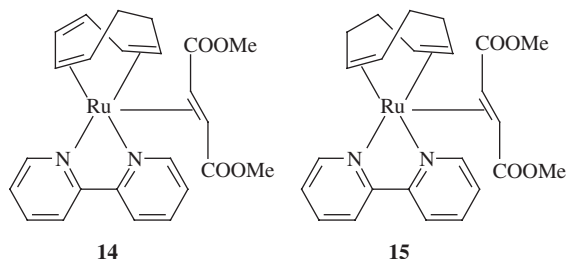
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Polymeric complex $[\{(\eta^4\text{-nbd})\text{RuCl}_2\}_n]$ reacts with various polypyridine ligands LL (bpy, phen, 5,6-Me₂phen, 4,7-Me₂phen, 3,4,7,8-Me₄phen) in acetone to yield $[(\eta^4\text{-nbd})\text{Ru}(\text{LL})\text{Cl}_2]$ (97POL3847). The reaction of $[(\eta^4\text{-nbd})\text{Ru}(\text{phen})\text{Cl}_2]$ with triphenylphosphine and silver hexafluorophosphate in methylene chloride gives the cationic complex $[(\eta^4\text{-nbd})\text{Ru}(\text{LL})\text{Cl}(\text{PPh}_3)](\text{PF}_6)$. Complexes are active catalysts of the water-gas shift reaction. 2,2'-Biquinoline, 3,3'-dimethylene-2,2'-biquinoline, or 3,3'-trimethylene-2,2'-biquinoline (LL) with $[\{(\eta^4\text{-nbd})\text{RuCl}_2\}_x]$ in THF/water yield complexes $[(\eta^4\text{-nbd})\text{RuCl}_2(\text{LL})]$ (06POL9).

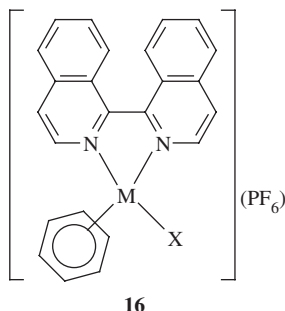
2,2'-Bipyridine reacts with $[(\eta^5\text{-Cp}^*)\text{Ru}(\text{NO})(\text{OTf})_2]$ in THF to yield the dicationic complex **12** (96IC4383). The same ruthenium precursor with dipyrido[3,2-a:2',3'-c]phenazine produces **13**. $[(\eta^5\text{-Cp})\text{Ru}(\eta^2\text{-dimethyl maleate})(\text{bpy})]^+$ is also described (92OM456).



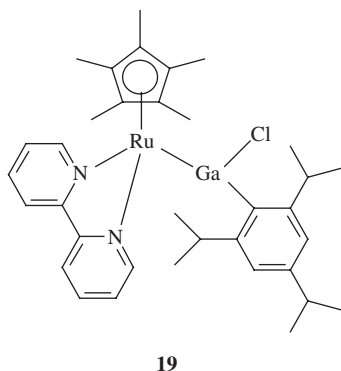
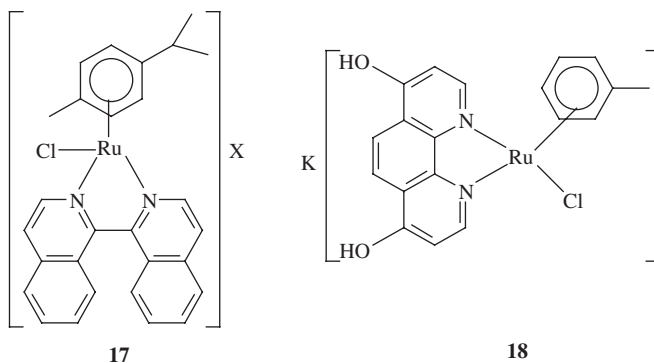
$[(\eta^6\text{-1,6-Cyclooctatriene})\text{Ru}(\eta^2\text{-dimethylfumarate})]$ reacts with 2,2'-bipyridine or 1,10-phenanthroline in diethyl ether to yield the ruthenium(0) products and the 2,2'-bipyridine complex is illustrated as **14** (99OM3671). Similar cyclooctadiene complexes **15** (for 2,2'-bipyridine) result from $[(\eta^6\text{-1,6-cyclooctadiene})\text{Ru}(\eta^4\text{-cod})]$, 2,2'-bipyridine or 1,10-phenanthroline, and dimethylfumarate in methylene chloride.



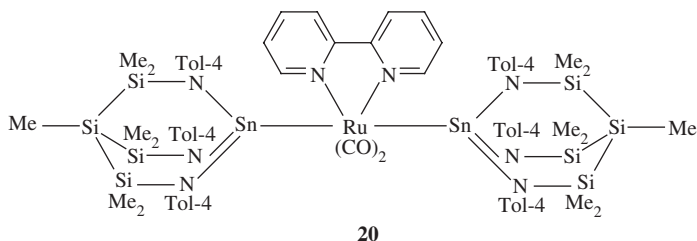
$[(\eta^6\text{-C}_6\text{H}_6)\text{RuX}_2]_2$ ($\text{X} = \text{Cl}, \text{I}$) and 1,1'-biisoquinoline in methanol in the presence of ammonium hexafluorophosphate yield **16** ($\text{M} = \text{Ru}, \text{X} = \text{Cl}, \text{I}$) (00OM547). $[(\eta^6\text{-C}_6\text{H}_6)\text{Os}(\text{AN})\text{X}_2]$ ($\text{X} = \text{Cl}, \text{I}$) under the same conditions gives **16** ($\text{M} = \text{Os}, \text{X} = \text{Cl}, \text{I}$). $[(\eta^6\text{-Toluene})\text{Fe}(\text{H})_2(\text{SiCl}_3)_2]$ on interaction with 2,2'-bipyridine forms $(\text{bpyH}_2)^{2+}$ (97IC2119). $\{[(\eta^6\text{-C}_6\text{H}_6)\text{RuCl}_2]_2\}$ and 2,2'-bipyridine in acetonitrile give $[(\eta^6\text{-C}_6\text{H}_6)\text{Ru}(\text{bpy})\text{Cl}]\text{Cl}$ (01IC5711). $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{bpy})(\text{H}_2\text{O})]^{2+}$ serves as a catalyst precursor in the transfer hydrogenation of ketones in solution (95IC306). If the source of protons is HCOONa , an intermediate could be a formate complex $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{bpy})(\text{HCOO})]^+$, and the catalytic action could be ascribed to $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{bpy})(\text{H})]^+$ (01CJC1002). 2,2'-Bipyridine reacts with $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{H}_2\text{O})_3](\text{SO}_4)$ in aqueous solution to yield $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{bpy})(\text{H}_2\text{O})](\text{SO}_4)$ (02OM2964, 04OM3047). The product reacts with sodium formate in an acidic medium to yield $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{bpy})(\text{HCOO})](\text{HCOO})$. In an alkaline medium and in the presence of sodium hexafluorophosphate, the product is $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{bpy})(\text{H})](\text{PF}_6)$. Similar complexes, $[(\eta^6\text{-C}_6\text{H}_6)\text{Ru}(\text{phen})\text{Cl}](\text{PF}_6)$, $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{phen})\text{Cl}](\text{PF}_6)$, $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(5\text{-R-phen})\text{Cl}](\text{PF}_6)$ ($\text{R} = \text{H}, \text{NO}_2, \text{NH}_2$), $[(\eta^6\text{-C}_6\text{H}_6)\text{Ru}(\text{phen})(\text{H}_2\text{O})](\text{PF}_6)_2$, $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{phen})(\text{H}_2\text{O})](\text{PF}_6)_2$, and $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(5\text{-R-phen})(\text{H}_2\text{O})](\text{PF}_6)_2$ ($\text{R} = \text{H}, \text{NO}_2, \text{NH}_2$) catalyze transfer hydrogenation of acetophenone (05JOM3202, 06ICA2369).



$[\{(\eta^6\text{-Cymene})\text{RuCl}\}_2]$ reacts with 1,1'-biisoquinoline in ethanol–benzene and gives **17** ($X = \text{Cl}$), which further enters a metathesis reaction with sodium tetraphenylborate to yield **17** ($X = \text{BPh}_4$) (03JOM(667)197). $[(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{bpy})\text{Cl}]\text{Cl}$ and **18** are the catalysts in the transfer hydrogenation of bicarbonate (03JMOC(195)95, 04OM1480). Complex $[(\eta^5\text{-Cp}^*)\text{Ru}(\text{bpy})\text{Cl}]$ (89JOM(362)383, 98CRV1439) with interesting catalytic properties (01JMAC267) can be reduced by KC_8 in THF to yield the potassium salt $\text{K}[(\eta^5\text{-Cp}^*)\text{Ru}(\text{bpy})]$ (04OM2855). A lithium salt follows from $\text{LiC}_{10}\text{H}_8$. The potassium salt reacts with methyl iodide or trimethylstannyl chloride to yield $[(\eta^5\text{-Cp}^*)\text{Ru}(\text{bpy})\text{R}]$ ($\text{R} = \text{Me}, \text{SnMe}_3$). With (2,4,6-tri-*i*-propylphenyl) $\text{GaCl}_2(\text{THF})$, the product is **19**.



1,10-Phenanthroline with $[(\text{OC})_3\text{Fe}(\mu\text{-SePh})_3\text{Fe}(\mu\text{-SePh})_3\text{Fe}(\text{CO})_3]$ gives $[\text{Fe}(\text{CO})_2(\text{phen})(\text{SePh})_2]$ (98JCS(D)353). Amidostannane $[\text{MeSi}\{\text{SiMe}_2\text{N}(4\text{-Tol})\}_3\text{Sn-Li}(\text{OEt}_2)]$ reacts with $[\text{RuCl}_2(\text{bpy})(\text{CO})_2]$ to yield **20** (01EJ13155).

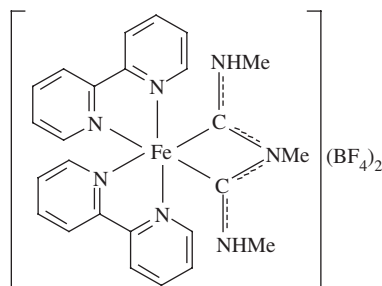


[Ru(4,4'-Me₂bpy)(PPh₃)₂(-C≡CR)Cl] (R = *t*-Bu, Ph, C₆H₄Me) are made from the dichloride precursors (04IC3492). In the same manner, [Ru(4,4'-Me₂bpy)(PPh₃)₂Cl₂] reacts with *p*-nitrophenylacetylene and thallium hexafluorophosphate in methylene chloride with further addition of potassium carbonate to yield [Ru(4,4'-Me₂bpy)(PPh₃)₂(-C≡CC₆H₄NO₂-*p*)Cl] (04JCS(D)4130). In a similar manner, the 4,4'-dibromo- and 4,4'-diiodobipyridine analogs were synthesized. Further substitution of the chloro-ligand in these complexes provided a series of [Ru(4,4'-R₂bpy)(PPh₃)₂(-C≡CC₆H₄NO₂-*p*)₂] (R = Me, Br, I). Reaction of [Ru(4,4'-Me₂bpy)(PPh₃)₂(-C≡CBu-*t*)Cl] with thallium hexafluorophosphate in nitrogen-saturated THF gives [Ru(4,4'-Me₂bipy)(PPh₃)₂(-C≡CBu-*t*)(N≡N)](PF₆). Another complex is [Ru(bpy)(PPh₃)₂(CO)(-C≡C(CH₂)₃Cl)](PF₆) (97OM3482).

[Ru(2-Ar-py)(AN)₄](PF₆) (Ar = Ph, *p*-Tol) react with 1,10-phenanthroline in acetonitrile and 2,2'-bipyridine in methylene chloride to yield [Ru(2-Arpy)(AN)₂(LL)](PF₆) (Ar = Ph, *p*-Tol; LL = bpy, phen) (05IC1626, 06ICA883).

B. BIS-POLYPYRIDINE COMPLEXES

[Fe(acac)₃] reacts with AlEt₂(OEt) and 2,2'-bipyridine to yield the ethyl complex [FeEt₂(bpy)₂] (65JA4652, 66JA5198, 66JOM(6)572, 99JCS(D)1027). [Fe(acac)₃] with AlMe₂(OMe) in ether gives [FeMe₂(bpy)₂]. [FeCl₂(bpy)₂] reacts with methyl lithium in toluene to yield [FeMe₂(bpy)₂] (02JOM(662)137). [FeEt₂(bpy)₂] decomposes with the loss of 2,2'-bipyridine, ethane, and ethylene (68JA1878, 72BCJ1104, 72BCJ1111). [FeR₂(bpy)₂] (R = Me, Et) reacts with carbon monoxide in THF to yield ketone R₂CO and diketone RC(O)C(O)R (R = Me, Et, *n*-Pr) (82OM155). In toluene, the products are [Fe(bpy)(CO)₃], R₂CO (R = Me, Et), and free 2,2'-bipyridine (02JOM(662)137). Homoleptic complexes [Fe(LL)₂](BF₄)₂ (LL = bpy, phen) react with isocyanides to yield [Fe(CNR)₂(LL)₂](BF₄)₂ (LL = bpy, phen; R = Me, *i*-Pr, *t*-Bu, Cy) (76JCS(D)12). Reaction of the products (LL = bpy, R = Me, *i*-Pr; L = phen, R = *i*-Pr) with methylamine gives dicarbene complexes illustrated as **21** for the case LL = bpy and R = Me.



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2,2'-Bipyridine on refluxing with RuCl₃ in dimethylformamide gives [Ru(CO)Cl(bpy)₂]Cl (80CC1213, 82JCS(D)1143). Photolysis of this complex produces carbon monoxide (80CC750). Thermolysis gives carbon monoxide and further photolysis

releases hydrogen. $[\text{Ru}(\text{CO})\text{Cl}(\text{LL})_2]\text{Cl}$ (LL = bpy, phen) reveal catalytic activity in the water–gas shift reaction (82JCS(D)1885).

A range of complexes $[\text{M}(\text{LL})_2(\text{CO})\text{R}](\text{PF}_6)$ (M = Ru, R = CH_2Ph ; Os; R = H, Me, Ph; LL = bpy, phen) is known (84OM1241). $[\text{Os}(\text{bpy})_2(\text{CO})(\text{OTf})](\text{OTf})$ (84OM1241) has interesting photochemical properties (86JPC2182, 88IC1787, 89JPC4511). With methylene chloride in the presence of dimethylaminopyridine, the product is $[\text{Os}(\text{bpy})_2(\text{CO})\text{Cl}](\text{OTf})$ (05ICA196). With bromoethane and iodomethane, $[\text{Os}(\text{bpy})_2(\text{CO})\text{X}](\text{OTf})$ (X = Br, I) are formed. $[\text{Ru}(\text{bpy})_2(\text{CO})\text{Cl}](\text{PF}_6)$ (86OM724) on refluxing with sodium nitrite in water–methanol solution gives $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{NO}_2)](\text{PF}_6)$ (92IC1971).

$[\text{Ru}(\text{bpy})_2(\text{CO})_2](\text{PF}_6)_2$ and $[\text{Ru}(4,4'\text{-Me}_2\text{bpy})_2(\text{CO})_2](\text{PF}_6)_2$ were also prepared (86JCS(D)253, 94ICA(226)247). $[\text{Ru}(4,4'\text{-Me}_2\text{bpy})(\text{CO})_2\text{Cl}_2]$ reacts with 2,2'-bipyridine and ammonium hexafluorophosphate to yield the mixed-ligand complex $[\text{Ru}(\text{bpy})(4,4'\text{-Me}_2\text{bipy})(\text{CO})_2](\text{PF}_6)_2$ (90JCS(D)2155). Refluxing $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ in formic acid followed by the reaction with 1,10-phenanthroline and further with ammonium hexafluorophosphate gives $[\text{Ru}(\text{phen})_2(\text{CO})_2](\text{PF}_6)_2$. Reaction of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$, 1,10-phenanthroline, and lithium chloride in dimethylformamide (DMF), and further dissolution of the crude product in formic acid in the presence of ammonium hexafluorophosphate gives $[\text{Ru}(\text{phen})_2(\text{CO})\text{Cl}](\text{PF}_6)$. $[\text{Ru}(\text{bpy})_2(\text{CO})_2](\text{PF}_6)_2$ reacts with excess NaBH_4 to yield $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{CHO})](\text{PF}_6)$ (95IC5399). Thermal decomposition of the product in methanol leads to $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{COOMe})](\text{PF}_6)$. Thermolysis in acetonitrile saturated with carbon dioxide produces HCOO^- and $[\text{Ru}(\text{bpy})_2(\text{CO})_2](\text{PF}_6)_2$.

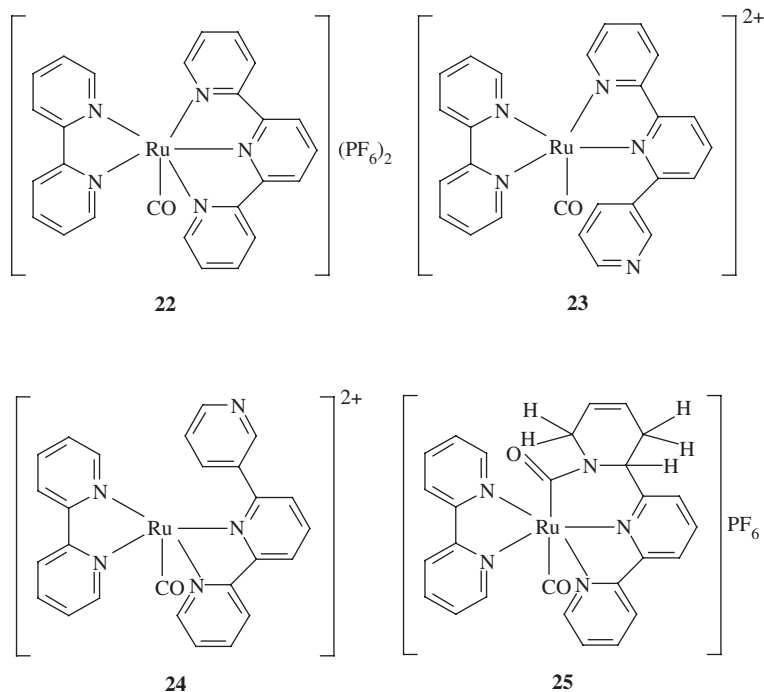
$[\text{Ru}(\text{bpy})_2(\text{CO})(\text{Me})]^+$ can be prepared through $[\text{Ru}(\text{bpy})_2(\text{OH}_2)_2]$ (90JOM(388)C13). The preparation of $[\text{Ru}(\text{bpy})_2(\text{CO})_2](\text{PF}_6)_2$, $[\text{Ru}(\text{bpy})_2(\text{CO})_3]$ is described in (78IC2211). $[\text{Ru}(\text{bpy})_2(\text{CO})_3]$ with HPF_6 in the presence of aqueous sodium hydroxide and further with trimethylsilyl acetylene gives $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{Me})](\text{PF}_6)$ (01JOM(619)299). $[\text{Ru}(\text{bpy})_2(\text{CO})_2](\text{PF}_6)_2$ reacts with sodium tetrahydroborate in methanol–acetone to yield $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{C}(\text{O})\text{H})](\text{PF}_6)$. $[\text{Ru}(\text{bpy})_2(\text{CO})_3]$ reacts with aqueous propionic acid and further with potassium hexafluorophosphate to afford $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{C}(\text{O})\text{Me})](\text{PF}_6)$. $[\text{Ru}(\text{bpy})_2(\text{CO})\text{X}]^+$ (X = CO_2 , COOH , CO , CHO , CH_2OH , Me , COOMe , COMe) are possible intermediates in the reduction of carbon dioxide (95OM5099).

Reaction of $[\{\text{Ru}(\text{bpy})(\text{CO})\text{Cl}_2\}_2]$ with 1,10-phenanthroline or $[\{\text{Ru}(\text{phen})(\text{CO})\text{Cl}_2\}_2]$ with 2,2'-bipyridine gives $[\text{Ru}(\text{bpy})(\text{phen})(\text{CO})\text{Cl}]^+$ (04IC2818).

Bubbling carbon monoxide through the ethylene glycol suspensions of *cis*- $[(\text{LL})_2\text{OsCl}_2 \cdot x\text{H}_2\text{O}]$ (LL = bpy, 4,4'-X₂-5,5'-Y₂bpy, X = OMe, Me, Cl, Y = H; X = H, Y = Me; X = Y = Me) in the presence of ammonium hexafluorophosphate gives *cis*- $[\text{Os}(\text{LL})_2(\text{CO})\text{Cl}](\text{PF}_6)$ (90IC2792). The complex with X = NMe₂ and Y = H was also prepared in an indirect procedure. 4,4'-Distyryl-2,2'-bipyridine (LL), $[(\text{LL})_2\text{MCl}_2] \cdot 2\text{H}_2\text{O}$ (M = Ru, Os) on refluxing in formic acid and further on addition of ammonium hexafluorophosphate give $[(\text{LL})_2\text{M}(\text{CO})\text{Cl}](\text{PF}_6)$ (M = Ru, Os) (87IC882).

Mixed-ligand species that combine two different bidentate ligands or a combination of a bidentate and a tridentate ligand are of interest (89IC3309, 90JCC119, 92IC3004, 95IC6145, 99IC2267). Thus, the synthesis of the series of

complexes $[\text{Ru}(\text{CO})(\text{LL})(\text{trpy})](\text{PF}_6)_2$ ($\text{LL} = \text{bpy}$, $4,4'\text{-Me}_2\text{bpy}$, phen , $4\text{-(2-}i\text{-Bu) bpy}$) illustrated as **22** for the 2,2'-bipyridine complex starts with $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$ according to (94JCS(D)3659). They react with triflic acid in dichloromethane to yield $[\text{Ru}(\text{LL})(\text{CO})_2(\text{OTf})_2]$ (98JCS(D)2293). Further refluxing with 2,2':6',2''-terpyridine in ethanol gives species with a bidentately coordinated trpy-ligand obtained as a mixture of two isomers, **23** and **24** (the 2,2'-bipyridine complex is illustrated). Finally, addition of Me_3NO and ammonium hexafluorophosphate produces the series of complexes **22**. The reaction of $[\text{Ru}(\text{bpy})(\eta^2\text{-trpy})(\text{CO})(\text{CHO})](\text{PF}_6)$ (01OM4956) with triflic acid in methanol gives $[\text{Ru}(\text{bpy})(\eta^2\text{-trpy})(\text{CO})(\text{CH}_2\text{OMe})](\text{PF}_6)$ (05OM5067). The minor product is **25** (06OM563).

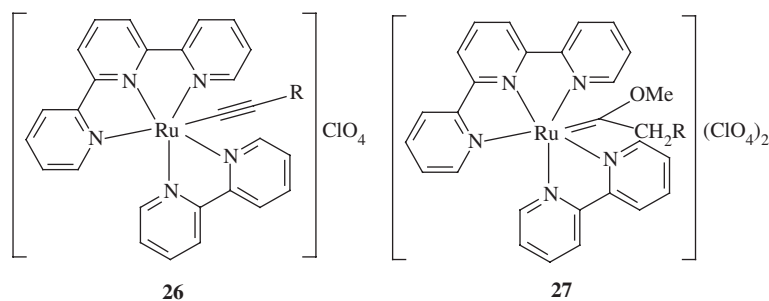


The general scheme for the preparation of the heteroleptic ruthenium(II) complexes of composition $[\text{Ru}(\text{L})(\text{L}^1)(\text{L}^2)]^{2+}$ where L, L^1 , and L^2 are various polypyridine ligands is based on $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$ (80TMC317, 94IC3863, 02JCS(D)3820). The first step involves transformation of $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$ to $[\text{Ru}(\text{L})(\text{CO})_2\text{Cl}_2]$ and the second a conversion of the product to $[\text{Ru}(\text{L})(\text{CO})_2(\text{OTf})_2]$ with further substitution of the triflate groups to yield $[\text{Ru}(\text{L})(\text{L}^1)(\text{CO})_2]^{2+}$. The last step is decarbonylation of the product in the presence of Me_3NO and the third polypyridine ligand to afford the heteroleptic complex containing three polypyridine ligands. An alternate route may include, after the formation of $[\text{Ru}(\text{L})(\text{CO})_2\text{Cl}_2]$ and then a photochemical transformation of the latter to the dinuclear complex $[\{\text{Ru}(\text{CO})\text{Cl}_2\}_2]$, reaction with the ligand L^1 in the presence of aqueous potassium hexafluorophosphate which gives $[\text{Ru}(\text{L})(\text{L}^1)(\text{CO})\text{Cl}](\text{PF}_6)$, this is followed by

decarbonylation in the presence of the third polypyridine ligand and Me_3NO to produce the desired heteroleptic ruthenium(II) complex of composition $[\text{Ru}(\text{L})(\text{L}^1)(\text{L}^2)](\text{PF}_6)_2$ (**04JCS(D)1766**). The range of polypyridine ligands includes 2,2'-bipyridine, 4,4'-dimethyl-2,2'-bipyridine, 5,5'-dimethyl-2,2'-bipyridine, 1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 5,6-dimethyl-1,10-phenanthroline, di(2-pyridyl)amine, di(2-pyridyl)ketone, and 2,2':6',2''-terpyridine in various combinations, with the requirement that all three ligands in the coordination sphere of the ruthenium(II) site are different. The products are widely applied for devising supramolecular systems (**06CCR1254**).

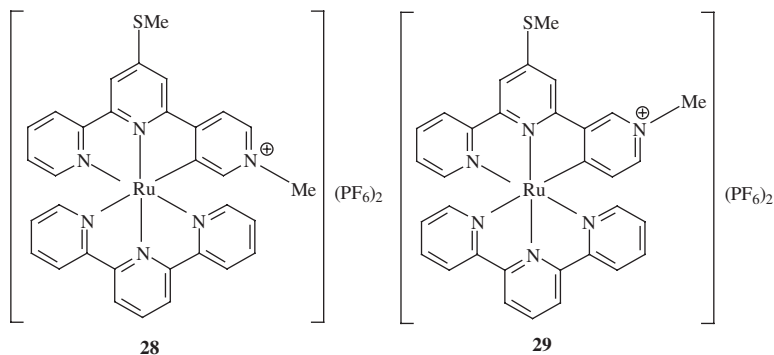
$[\text{Ru}(\text{trpy})(\text{CO})_2\text{Cl}](\text{PF}_6)$ reacts with silver tetrafluoroborate in acetone, then with acetonitrile followed by BF_4/PF_6 anion exchange to yield $[\text{Ru}(\text{trpy})(\text{CO})_2(\text{AN})](\text{PF}_6)_2$ (**01OM4956**). The product with 2,2'-bipyridine and 4,4'-dimethyl-2,2'-bipyridine (LL) gives the mixed-ligand complex $[\text{Ru}(\text{LL})(\eta^2\text{-trpy})(\text{CO})_2](\text{PF}_6)_2$ (LL = bpy, 4,4'- Me_2bpy). The products when treated with sodium tetrahydroborate in methanol give rise to $[\text{Ru}(\text{LL})(\eta^2\text{-trpy})(\text{CO})(\text{CHO})](\text{PF}_6)$ (LL = bpy, 4,4'- Me_2bpy). Bis-1,10-phenanthroline analogs of these (trpy)(LL)-compounds are known (**98OM5178**). $[\text{Ru}(\text{LL})(\eta^2\text{-trpy})(\text{CO})_2](\text{PF}_6)_2$ (LL = bpy, 4,4'- Me_2bpy) in AN/ H_2O when treated with sodium tetrahydroborate in diglyme afford hydroxymethyl complexes $[\text{Ru}(\text{LL})(\eta^2\text{-trpy})(\text{CO})(\text{CH}_2\text{OH})](\text{PF}_6)$ (LL = bpy, 4,4'- Me_2bpy).

Aqua-complex $[\text{Ru}(\eta^3\text{-trpy})(\eta^2\text{-bpy})(\text{H}_2\text{O})](\text{ClO}_4)_2$ reacts with acetylenes $\text{HC}\equiv\text{CR}$ (R = *t*-Bu, Ph, $\text{C}_6\text{H}_4\text{X-4}$; X = F, Cl, Me, OMe; R = $(\text{C}_6\text{H}_4\text{C}\equiv\text{C})_n\text{Ph}$; $n = 1, 2$) in the presence of triethylamine in acetone to yield **26** (**04OM2263**). Products **26** (R = *t*-Bu, $\text{C}_6\text{H}_4\text{OMe-4}$) when treated by triflic acid in methanol yielded the carbene complexes **27**. Complex $[\text{Ru}(\text{bpy})_2(\eta^1\text{-naphthyridine})(\text{CO})](\text{BF}_4)_2$ is known (**05AGE2229**).



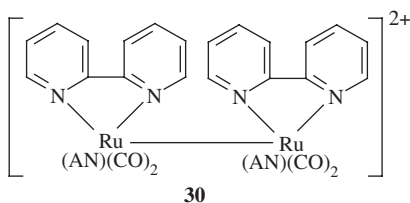
C. CYCLOMETALATION

Refluxing of $[\text{Ru}(\eta^3\text{-trpy})\text{Cl}_3]$ with *N*'-methyl-4''-methylthio-2,2':6',4''-terpyridinium hexafluorophosphate or *N*''-methyl-4'-methylthio-2,2':6',3''-terpyridinium hexafluorophosphate in ethanol gives **28** and **29**, respectively, with cyclometalated terpyridinium ligand (**03OM970**). Another representative is $[\text{Ru}(\eta^3(\text{N,N,C})\text{-N-methyl-2,2':6',2''-terpyridinium})(\eta^3\text{-terpyridine})]$ (**96JCS(D)873**).

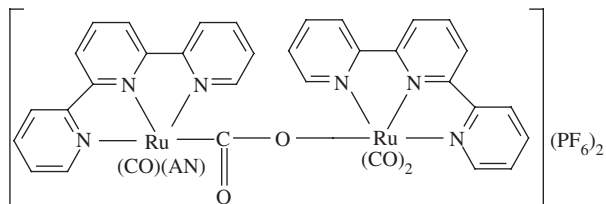


D. DINUCLEAR COMPLEXES

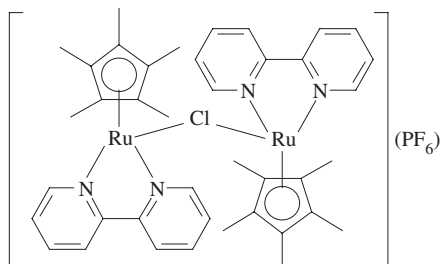
Photolysis of $[\text{Ru}(\text{LL})(\text{CO})_2\text{Cl}_2]$ ($\text{LL} = \text{bpy}, 4,4'\text{-Me}_2\text{bpy}, \text{phen}$) leads to decarbonylation and formation of the dinuclear complexes $[\text{Ru}(\text{LL})(\text{CO})\text{Cl}(\mu\text{-Cl})_2\text{Ru}(\text{LL})(\text{CO})\text{Cl}]$ not containing the ruthenium–ruthenium bond (99JCS(D)275). $[\text{Ru}(\text{CO})_2(\text{AN})_2](\text{PF}_6)_2$ with excess 2,2'-bipyridine in acetonitrile gives the binuclear complex **30** (01OM1668) containing the ruthenium–ruthenium bond. Under steady-state irradiation such bridges may be cleaved in acetonitrile or methanol (95JPP99).



Reaction of the terdentately coordinated complex $[\text{Ru}(\text{trpy})(\text{CO})_2\text{Cl}](\text{PF}_6)$ considered above with sodium carbonate in acetonitrile gives the bimetallic CO_2 -bridged dicationic **31** (97OM4421). On bubbling carbon monoxide into a methylene chloride solution, the ligand-substitution product $[(\text{trpy})_2(\text{OC})\text{Ru}(\mu\text{-CO}_2)\text{Ru}(\text{trpy})_2(\text{CO})](\text{PF}_6)_2$ resulted. Similar complex is $[(\text{bpy})_2(\text{OC})\text{Ru}(\mu\text{-CO}_2)\text{Ru}(\text{bpy})_2(\text{CO})](\text{PF}_6)_2$ (96CRV2063, 96JA11984). Reaction of $[\text{Ru}(\text{trpy})(\text{CO})_2\text{Cl}](\text{PF}_6)$ and $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{COOH})](\text{PF}_6)$ (96CL27) in acetonitrile gives the mixed-ligand product $[(\text{bpy})_2(\text{OC})\text{Ru}(\mu\text{-CO}_2)\text{Ru}(\text{trpy})(\text{CO})_2](\text{PF}_6)_2$ (97OM4421). $[\text{Fe}_2(\text{bpy})(\text{CO})_7]$ (74JA1233) and $[\text{Fe}_2(\text{bpy})(\text{PBU-}n_3)(\text{CO})_7]$ are known (87OM1665). 2,2'-Bipyridine reacts with $[(\eta^5\text{-Cp}^*)\text{ClRu}(\mu\text{-Cl})\text{RuCl}(\eta^5\text{-Cp}^*)]$ in the presence of sodium hexafluorophosphate to give the dinuclear product **32** (06ICA978).

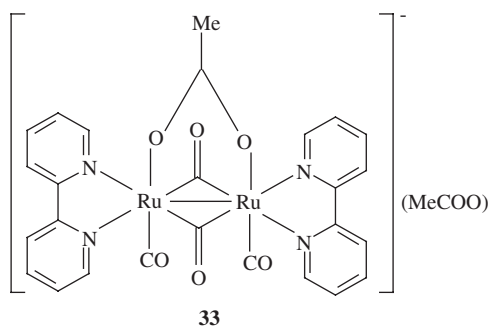


31

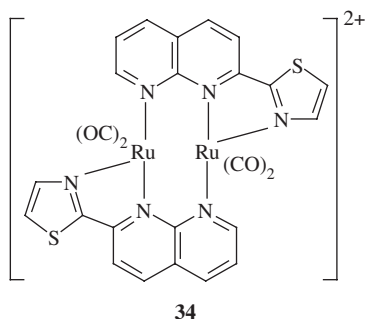


32

2,2'-Bipyridine, 1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 5,6-dimethyl-1,10-phenanthroline, and 4,4'-dimethyl-2,2'-bipyridine (LL) react with $[\{\text{Ru}_2(\text{CO})_4(\text{MeCOO})_2\}_n]$ in ethanol and then with sodium tetraphenylborate to yield dinuclear complexes $[\text{Ru}_2(\text{CO})_4(\text{MeCOO})(\text{LL})_2](\text{BPh}_4)$ (88AX(C)1722, 93JOM(463)187, 96OM2979). Another approach is based on preliminary conversion of $[\{\text{Ru}(\text{CO})_2(\text{MeCOO})\}_n]$ to $[\text{Ru}(\text{CO})_2(\text{MeCOO})(\text{AN})]_2$ (88OM1663). In the absence of NaBPh_4 , the acetate complexes $[\text{Ru}_2(\text{CO})_4(\text{MeCOO})(\text{LL})_2](\text{MeCOO})$ were prepared. The structure of the products is shown as **33**, using the 2,2'-bipyridine acetato complex as an example. An identical complex with 1,1'-biisoquinoline can be prepared similarly (03JOM(667)197). Such complexes where 2,2'-bipyridine and 1,10-phenanthroline are ligands catalyze carbonylation and hydrogenation of organic compounds (91JMOC(64)257, 97JOM(547)35, 03ICA(351)225). Another synthetic approach involves the reaction of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ with a mixture $\text{HCOOH}/(\text{HCHO})_2$ on heating that yields $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$. 4,4'-Dimethyl-2,2'-bipyridine reacts with the mixture of this ruthenium(II) precursor and sodium acetate to yield the dinuclear complex **33**, $[\text{Ru}_2(\text{MeCOO})_2(\text{CO})_4(4,4'\text{-Me}_2\text{bpy})_2]^+$ isolated as a hexafluorophosphate salt (04IC683). In the case of 5,5'-dimethylpyridine and 5,6-dimethyl-1,10-phenanthroline (LL), however, a mixture of the mononuclear ruthenium(II) species, $[\text{Ru}(\text{MeCOO})_2(\text{CO})_2(\text{LL})]$ and cationic dinuclear product of type **33** resulted. $[\text{Ru}_2(\text{CO})_4(\mu\text{-OOCR})_2(\text{py})_2]$ (R = Me, Ph) with 2,2'-bipyridine and 1,10-phenanthroline (LL) yield $[(\text{LL})_2\text{Ru}_2(\text{CO})_2(\mu\text{-CO})_2(\mu\text{-OOCR})]$. Similarly, $[\text{Ru}_2(\text{CO})_4(\mu, \eta^2\text{-OOCFc})_2(\text{py})_2]$ with 2,2'-bipyridine, 4,4'-dimethyl-2,2'-bipyridine, 1,10-phenanthroline, 5-nitro-1,10-phenanthroline, or 5-amino-1,10-phenanthroline (LL) give products similar to **33**, $[(\text{LL})_2\text{Ru}_2(\text{CO})_2(\mu\text{-CO})_2(\mu\text{-OOCFc})]^+$ obtained as hexafluorophosphates and tetrafluoroborates (07JOM755).



2-(2-Hetaryl)-1,8-naphthyridine (hetaryl = furyl, thiazolyl, pyridyl) with $[\text{Ru}_2(\text{CO})_4(\text{AN})_6](\text{BF}_4)_2$ give products exemplified by the 2-thiazolyl derivative **34** (06IC4007). Similar reaction of 2-*i*-propyl-1,8-naphthyridine (LL) in the presence of *n*-Bu₄NOTf gives $[\text{Ru}_2(\text{LL})_2(\text{CO})_4(\text{OTf})_2]$ (06JOM4779).

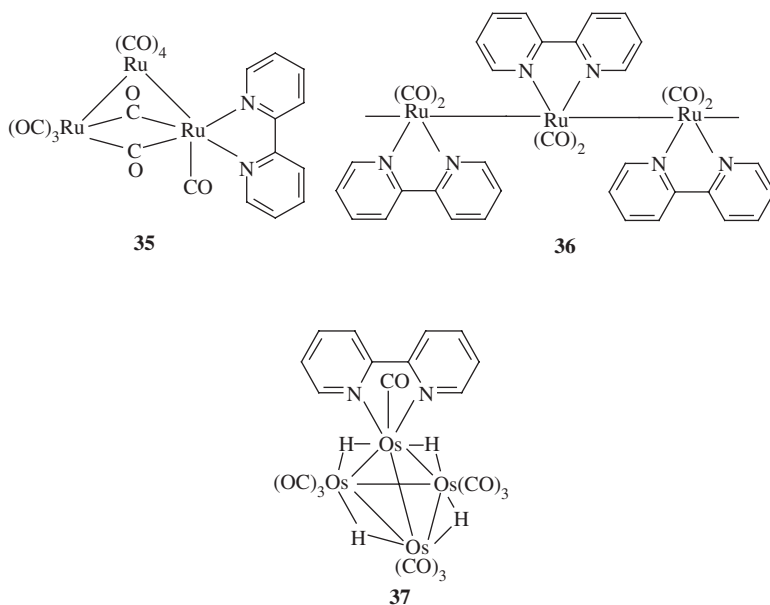


E. POLYNUCLEAR COMPLEXES AND CLUSTERS

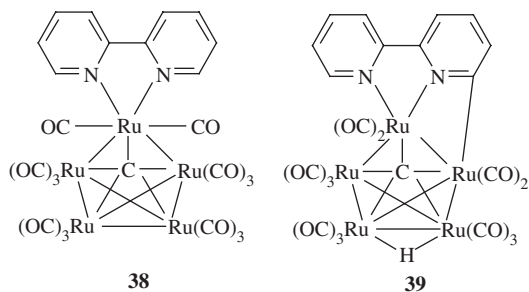
Polynuclear ruthenium complexes are interesting because of their photoluminescent and redox properties (96CRV759). Cluster $[\text{Os}_3(\text{CO})_{10}(\text{bpy})]$ (97JCS(D)2511) has interesting photochemical (95IC6312, 98IC661, 99JOM(572)271, 99OM4380) and redox (99JOM(573)121) properties, and the proximity of the metal-to-ligand charge transfer (MLCT) excited state (98CCR(171)93, 98CCR(177)127) as claimed by theoretical computations (01EJI223). $[\text{Os}_3(\text{CO})_{10}(4,4'\text{-Me}_2\text{bpy})]$ is known (02ICA(327)126).

On refluxing in hexane (85CC1348) or cyclohexane (86JOM(314)311), 2,2'-bipyridine and $[\text{Ru}_3(\text{CO})_{12}]$ at earlier stages yield cluster **35** (85JOM(294)123). A further reaction route involves consecutive substitution of the carbon monoxide ligands by 2,2'-bipyridine molecules, and the final product can be possibly **36**. 2,2'-Bipyridine with $[\text{Ru}_4(\mu\text{-H})_4(\text{CO})_{12}]$ gives the substitution product $[\text{Ru}_4(\mu\text{-H})_4(\text{CO})_{10}(\text{bpy})]$, and the process goes through the stage of the $\eta^1(N)$ -coordinated 2,2'-bipyridine $[\text{Ru}_4(\mu\text{-H})_4(\text{CO})_{11}(\eta^1\text{-bpy})]$ (98JCS(D)2625). 2,2'-Bipyridine,

4,4'-diphenyl-2,2'-bipyridine, 1,10-phenanthroline, 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, and dipyrido[3,2-a:2',3'-c]phenazine react with $[\text{Os}_4(\mu\text{-H})_4(\text{CO})_{11}(\text{AN})]$ to yield disubstitution products of type **37** illustrated for the 2,2'-bipyridine complex (**99JOM(573)189**).

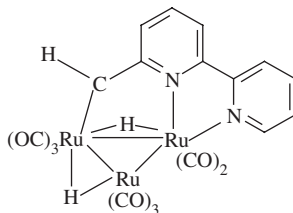


Cluster $[\text{Ru}_5\text{C}(\text{CO})_{15}]$ reacts with 2,2'-bipyridine and 1,10-phenanthroline in the presence of Me_3NO to yield the major monosubstitution products **38** and the orthometalated complexes **39** in minor amount (both structures illustrate the 2,2'-bipyridine complexes) (**97JCS(D)2705**).



6,6'-Dimethyl-2,2'-bipyridine reacts with $[\text{Ru}_3(\text{CO})_{12}]$ in THF under reflux to yield the product of C–H activation of one of the methyl groups **40** (**04AGE3464**). Product **40** further reacts with $[\text{Ru}_3(\text{CO})_{12}]$ under reflux in chlorobenzene to afford more complicated clusters, $[\text{Ru}_6(\mu_3\text{-H})(\mu_5\text{-CbipyMe})(\mu\text{-CO})_3(\text{CO})_{13}]$, a hexanuclear cluster with a carbyne-type carbon atom originating from one of the methyl groups of the polypyridine ligand, $[\text{Ru}_7(\mu_3\text{-H})(\mu_5\text{-CbipyMe})(\mu\text{-CO})_2(\text{CO})_{16}]$, a heptanuclear cluster

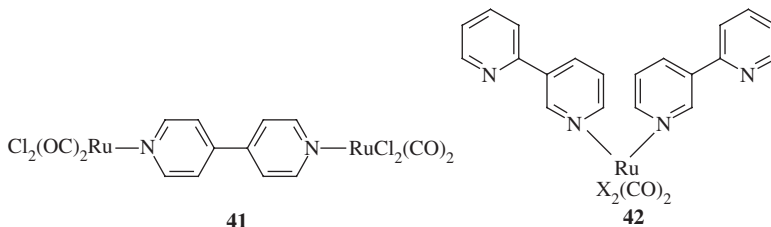
with a carbyne-type carbon atom, and $[\text{Ru}_5(\mu\text{-H})(\mu_5\text{-C})(\mu\text{-bpyMe})(\text{CO})_{13}]$, a pentanuclear where the carbide ligand is present and arises from one of the methyl groups of the starting ligand. Monomethyl-2,2'-bipyridine ligand constitutes another bridging ligand in this cluster.



40

F. 4,4'-BIPYRIDINE COMPLEXES

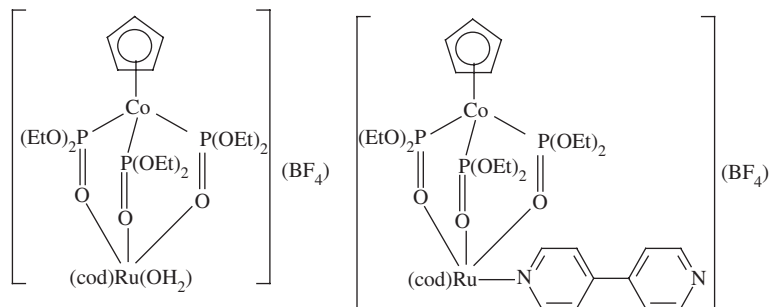
4,4'-Bipyridine reacts with $[\{\text{Ru}(\text{CO})_3\text{Cl}_2\}_2]$ in ethanol to yield the binuclear product **41** (02JOM(655)31). 2,4'-Bipyridine under the same conditions forms the mononuclear complex **42** (X = Cl) with the monodentate coordination of the ligand, which on ligand exchange with potassium iodide gives **42** (X = I).



41

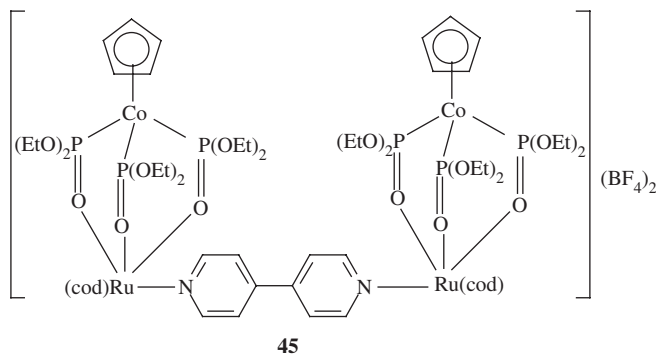
42

Complex **43** reacts with 4,4'-bipyridine to yield **44** with monodentate coordination of 4,4'-bipyridine ligand (99IC136). Further interaction of **43** and **44** gives **45** where 4,4'-bipyridine fulfills its bridging role. Reaction of $[\text{Ru}_3(\mu_3\text{-O})(\mu\text{-MeCOO})_6(\text{CO})(\text{L})(\text{H}_2\text{O})]$ (L = py, 4-NMe₂py, 4-CNpy) with $[\text{Ru}_3(\mu_3\text{-O})(\mu\text{-MeCOO})_6(\text{CO})(\text{L})(\eta^1\text{-4,4'-bipy})]$ gives clusters with the bridging 4,4'-bipyridine ligand, $[\text{Ru}_3(\mu_3\text{-O})(\mu\text{-MeCOO})_6(\text{CO})(\text{L})(\mu\text{-4,4'-bpy})\text{Ru}_3(\mu_3\text{-O})(\mu\text{-MeCOO})_6(\text{CO})(\text{L})]$ (99JA4625).

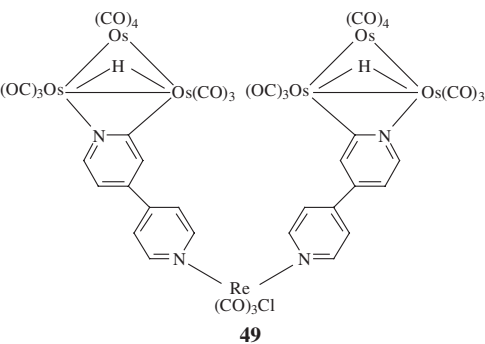
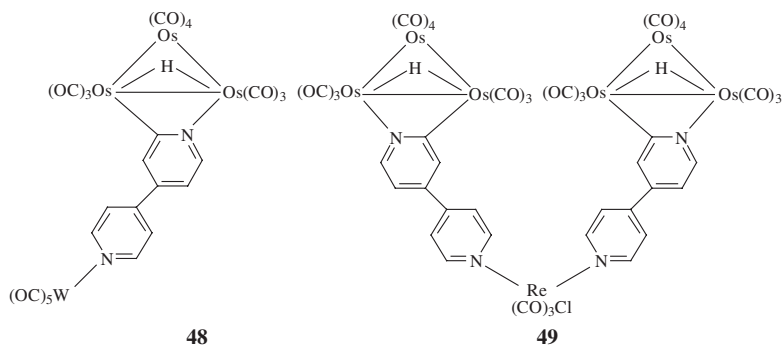
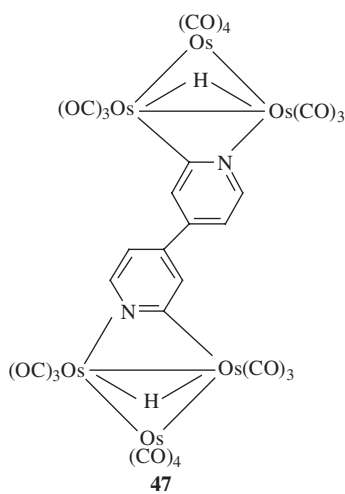
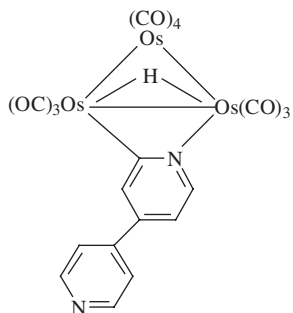


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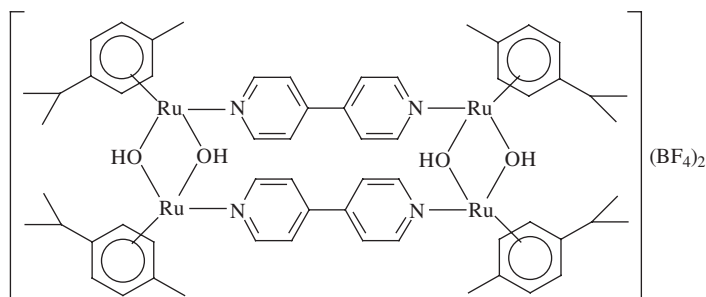
44



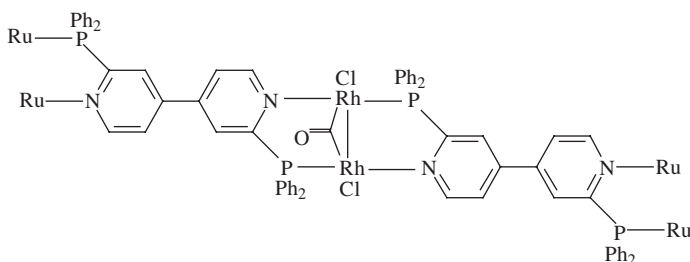
4,4'-Bipyridine oxidatively adds to $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$ to yield **46** and **47** (O2JOM(655)39). Complex **46** reacts with $[\text{W}(\text{CO})_5(\text{THF})]$ in THF to yield **48** and with $[\text{ReCl}(\text{CO})_5]$ in benzene to yield **49**.



4,4'-Bipyridine reacts with $[\{(\eta^6\text{-cymene})\text{Ru}\}_2(\mu\text{-OH})_3](\text{BF}_4)$ to yield the tetranuclear complex **50** (06ICA978). The dinuclear complex with oxalate and 4,4'-bipyridine bridges has the composition $[\{(\eta^6\text{-cymene})\text{Ru}\}_2(\mu\text{-C}_2\text{O}_4)_2(4,4'\text{-bpy})_2(\text{OTf})_4$ (97JCS(D)4345).

**50**

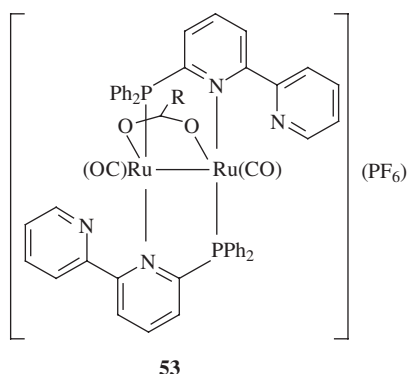
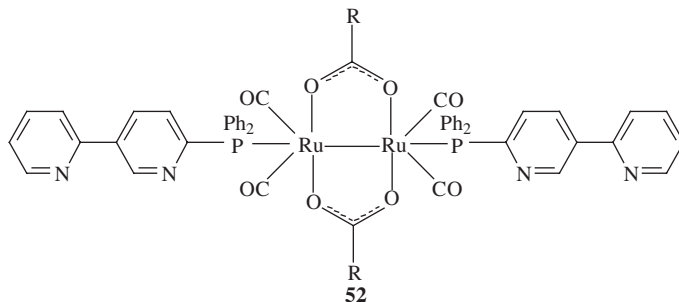
2,2'-Bis(diphenylphosphino)-4,4'-bipyridine (LL) with $[\text{Ru}_6\text{C}(\text{CO})_{17}]$ forms $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\text{LL})]$ and with excess of $[\text{Ru}_6\text{C}(\text{CO})_{17}]$ it provides $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\mu\text{-LL})\{\text{Ru}_6\text{C}(\text{CO})_{15}\}]$ (05OM3516). Coordination involves the pyridine nitrogen atom and phosphine phosphorus atom. $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\text{LL})]$ with $[\text{Rh}_6(\text{CO})_{15}(\text{AN})]$ gives the heterodinuclear product $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\mu\text{-LL})\{\text{Rh}_6(\text{CO})_{14}\}]$. With $[\text{Rh}_2(\text{CO})_4\text{Cl}_2]$ the heterotetranuclear **51** can be prepared. $[\text{Ir}_4(\text{CO})_{11}\text{Br}]^-$ in this type of reaction gives heterodinuclear species $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\mu\text{-LL})\{\text{Ir}_4(\text{CO})_{10}\}]$. If the ruthenium complex $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\text{LL})]$ is in excess, the resulting cluster is $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\mu\text{-LL})\{\text{Ir}_4(\text{CO})_{10}\}(\mu\text{-LL})\{\text{Ru}_6\text{C}(\text{CO})_{15}\}]$, which can be decarbonylated on refluxing. The decarbonylation product may further react with $[\{\text{Ru}_6\text{C}(\text{CO})_{15}\}(\text{LL})]$ to yield $[\{\text{Ru}_6\text{C}(\text{CO})_{15}(\text{L-L})\}_3\{\text{Ir}_4(\text{CO})_8\}]$.

**51**

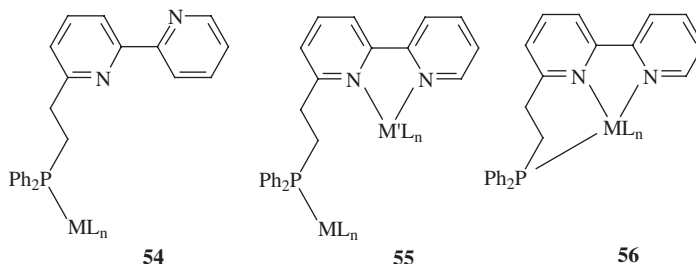
G. POLYPYRIDYLPHOSPHINES

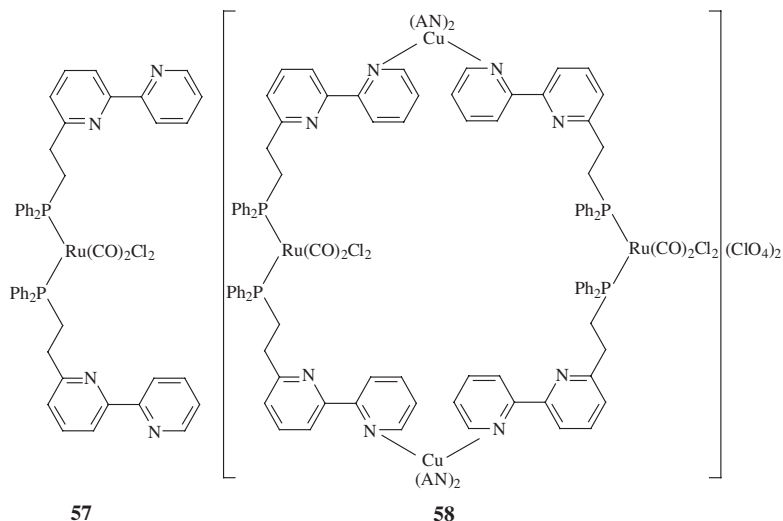
Refluxing the polymeric carboxylate precursor $[\{\text{Ru}_2(\mu, \eta^2\text{-OC}(\text{R})\text{O})_2(\text{CO})_4\}_n]$ or $[\{\text{Ru}_2(\mu, \eta^2\text{-OC}(\text{R})\text{O})_2(\text{CO})_4(\text{AN})_2\}_n]$ ($\text{R} = \text{H, Me, Et}$) with 6-diphenylphosphino-2,2'-bipyridine in ethanol or toluene gives **52** (97JCS(D)2843). If the reaction is run

under reflux in toluene in the presence of ammonium hexafluorophosphate, the product is **53**, where the ligand fulfills its *P,N,N*-chelate function.



Bipyridylphosphines combine chelating properties of the bipyridine unit and coordinating properties of the P(III) center (85NJC225, 89TL463). Three coordination modes may be envisaged for 6-(2-diphenylphosphinoethyl)-2,2'-bipyridine (95CC2033). In mode **54**, the ligand fulfills monodentate P-coordination due to the phosphine counterpart. In mode **55**, the ligand functions as a bridge between two metal centers. Mode **56** illustrates the formation of fully chelated *P,N,N*-complex. Reaction of this ligand with an equimolar amount of $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$ in methanol in the presence of triethylamine gives **56** ($\text{ML}_n = \text{Ru}(\text{CO})\text{Cl}_2$) (97JCS(D)3777). If half of the amount of $[\{\text{Ru}(\text{CO})_2\text{Cl}_2\}_n]$ is applied in the absence of triethylamine, the product is the *P,P*-coordinated **57**. This complex has ligand properties and on interaction with $[\text{Cu}(\text{AN})_4](\text{ClO}_4)$ forms the macrocyclic product **58**.

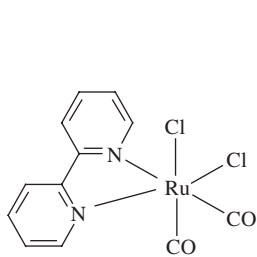
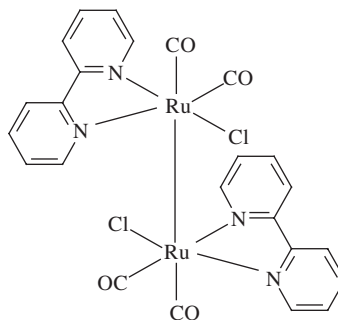
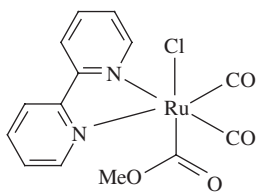
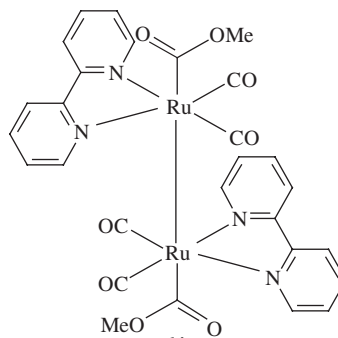
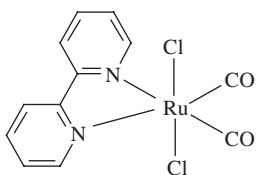
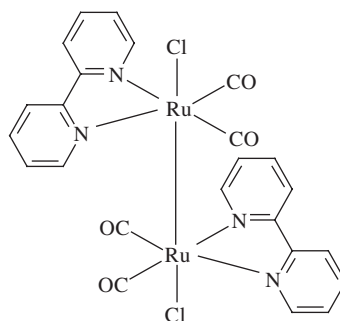


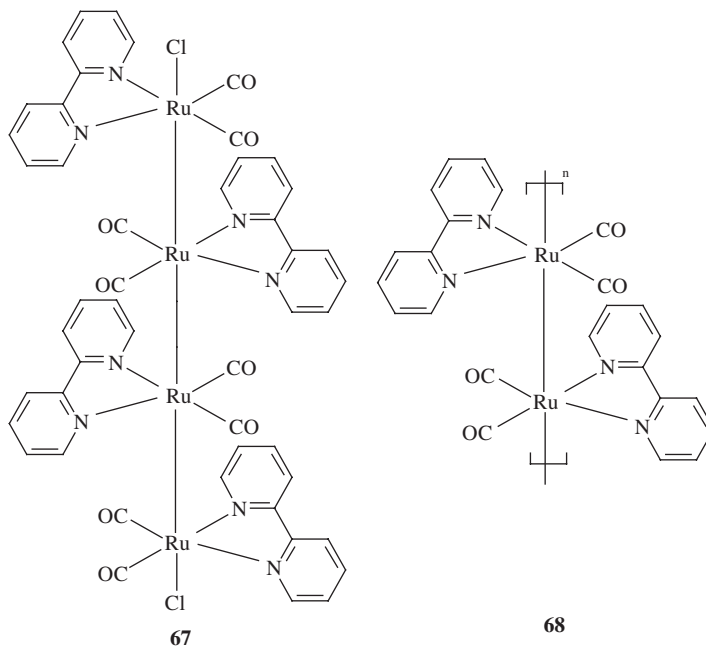


H. CATALYTIC ASPECTS

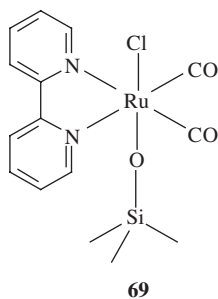
Ruthenium polypyridine complexes have remarkable redox properties and MLCT energies (88CCR(84)85). Mononuclear ruthenium polypyridine complexes catalyze electrochemical (87CL597, 87OM901, 91IC86, 92OM3172, 93CIC1, 94JOM(476)7, 95JOM(498)187, 98CCR(168)233) and photochemical (87CL1035, 90JOM(382)157, 92MI1, 93MI1, 95IC1830, 95JPC12797, 96IC303, 96NJC759, 98MI1) reduction of carbon monoxide as well as the water-gas shift reaction (79JA5922, 82AGE628, 82IC1704, 85JA585, 86IC4140, 86OM724, 93JOM(457)121, 98JMOC(136)127, 99AC157), and photoredox water splitting (82CCR(46)159). They serve as sensitizers for photovoltaic solar cells (95CCR(95)49). Complex $[\text{Os}(\text{CO})\text{Cl}(\text{phen})_2](\text{PF}_6)$ is of interest as a photocatalyst in solar energy conversion schemes (84IC875). One of the catalysts of CO_2 -reduction is $[\text{Ru}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ (94CC189, 94IC2961). The catalytic system $[\text{Ru}_3(\text{CO})_{12}]$ -2,2'-bipyridine is postulated to consist of mononuclear ruthenium units containing one 2,2'-bipyridine molecule (86JOM(314)C49, 91JMOC(64)163, 94JCA(148)722, 94JMOC(91)145). In the electrochemical reduction of CO_2 , $[\text{Ru}(\text{bpy})(\text{trpy})(\eta^1\text{-C-CO}_2)]$ can be readily converted to $[\text{Ru}(\text{bpy})(\text{trpy})(\text{CO})]^{2+}$, which is then reduced to $[\text{Ru}(\text{bpy})(\text{trpy})(\text{CHO})]^+$ and $[\text{Ru}(\text{bpy})(\text{trpy})(\text{CH}_2\text{OH})]$ affording the products HCHO, CH_3OH , HOOCCHO , and $\text{HOOC-CH}_2\text{OH}$ (93CL955, 94IC3415). The route to the C_2 -products in the case of $[\text{Ru}(\text{bpy})(\eta^3\text{-trpy})(\text{CO})](\text{PF}_6)_2$ acting as a catalyst of the electrochemical reduction of carbon dioxide is the generation of $[\text{Ru}(\text{bpy})(\eta^2\text{-trpy})(\text{CO})_2](\text{PF}_6)_2$ on interaction with CO_2 (88ADOC139, 00CRV439). $[\text{Ru}(\text{bpy})_2(\text{CO})(\eta^1\text{-C-CO}_2)]$ can be reversibly transformed to $[\text{Ru}(\text{bpy})_2(\text{CO})_2]^{2+}$ through the stage of $[\text{Ru}(\text{bpy})_2(\text{CO})(\text{COOH})]^+$ in aqueous but not organic media (83CL901, 92OM1450, 93IC1508, 96CL27). This compound is amphoteric, which is important in the reversible transformation of carbon monoxide to carbon dioxide (95AIC409, 96TIC145, 98BCJ17). $[\text{Ru}(\text{bpy})_2$

$[\text{RuCl}_2(\text{bpy})(\text{CO})_2]$ does not stop at the stage of dimer **66**, but gradually produces a ruthenium(I)–ruthenium(II) tetramer **67** and then ruthenium(II) polymer **68** as described by X-ray powder diffractometry (02OM4009). The same effects could happen in the preparation of ruthenium(II)–polypyridine catalysts on solid supports (94JMOC(91)335, 95JMOC(102)79). $[\{\text{Os}(\text{bpy})_2(\text{CO})_2\}_n]$ can also be prepared by electrochemical methods (01EJ1613) from *trans*-(Cl)- $[\text{Os}(\text{bpy})(\text{CO})_2\text{Cl}_2]$ (97JCS(D)153) prepared from $[\{\text{Os}(\text{CO})_2\text{Cl}_2\}_n]$ and 2,2'-bipyridine on refluxing in *n*-propanol. Polymers $[\text{M}(\text{bpy})(\text{CO})_2\text{Cl}_2]_n$ (M = Ru, Os) are reduced electrochemically to the metal(0) species $[\text{M}(\text{bpy})(\text{CO})_2]_n$ (01JEAC(506)115, 03ACS141, 04IC7250).

**61****62****63****64****65****66**



The catalytic system $[\text{Ru}_3(\text{CO})_{12}]/2,2'$ -bipyridine/ SiO_2 is attractive for the water-gas shift reaction (90JMOC(59)33, 94JCA(148)722) and hydroformylation of 1-hexene (93JMOC(84)145, 94JCA(148)315). Possibly, one of the surface structures of this catalytic systems is **69** (96JOM(509)163). However, oligomeric and polymeric formations cannot be excluded.



III. Conclusions

1. Polypyridine complexes of the iron group typically contain chelated (η^2 -coordinated) ligands that occur in different variations in the mononuclear complexes with one or two such ligands. Many of the existing complexes are

postulated as active forms in the catalyzed electro- and photochemical reduction of carbon dioxide, water-gas shift, and other reactions. They tend to form dinuclear complexes, and many of them play a significant role in the catalytic reactions. The pyridylphosphine ligand is a versatile ligand combining the $\eta^2(N_1, N'_1)$ - and $\eta^1(P)$ -coordination modes.

2. Organoruthenium and organoosmium compounds of polypyridine ligands offer alternative coordination modes of these ligands. In the cyclometalated complexes the $\eta^2(N_1, C'_2)$ coordination mode occurs. In some clusters the $\eta^2(N_1, C_2)$ donor function is manifested. The latter becomes possible in clusters of 4,4'-bipyridine ligands, which otherwise play their traditional bridging function.

List of Abbreviations

acac	acetylacetonato
AN	acetonitrile
Ar	aryl
bpy	2,2'-bipyridine
Bu	butyl
cod	cyclooctadiene-1,4
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
Fc	ferrocenyl
Me	methyl
MLCT	metal-to-ligand charge transfer
nbd	norbornadiene-2,5
OTf	triflate
Ph	phenyl
phen	1,10-phenanthroline
Pr	propyl
py	pyridine
qu	quinoline
trpy	2,2':6',2''-terpyridine
THF	tetrahydrofuran
Tol	tolyl

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