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PYRAZOLE 1-OXIDES, 1,2-DIOXIDES AND DERIVATIVES

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Abstract - Structure, syntheses, spectroscopic properties and the chemical reactivity of the N-oxides of the pyrazole nucleus are described.

CONTENTS

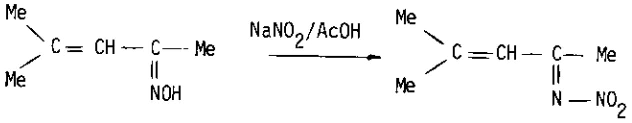
1.0. Introduction

Heterocyclic N-oxides have been the subject of extensive research over the past fifty years[1]. The advances made during this time have been bestowed upon them the right to be considered as a field in its own merit within the vast field of heterocyclic chemistry. Attention has been focussed mainly on the six-membered heterocyclic N-oxides relative to their five-membered counter-parts. Nevertheless, some aspects of the chemistry of the latter have been reviewed in a few cases[1]. An important member of this class of molecules is the N-oxides of the pyrazole ring and forms the subject of this review, which aims at presenting an integrated picture of their chemistry.

This article covers the literature available from the early encounters with this nucleus around 1900, until today. Aspects of the chemistry of this ring system have been earlier covered by Katritzky[1] in his book "Chemistry of the Heterocyclic N-Oxides". It is, therefore, merely for the sake of presentation and completeness of the present account that topics from that work are included.

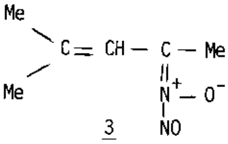
2.0. Structure - Historical Survey

In 1899 Harries reported[2] the nitrosation of mesityl oxide oxime 1, whithout specifying reagent conditions, to a white solid of composition $C_6H_{10}N_2O_2$, to which he assigned the nitrimine structure 2, based upon investigations of Scholl[3] on pernitroso compounds of the terpene series. This formulation was rejected by Fusco[4] in favour of structure 3 which contains the unique N-nitrosonitrone function.



1 2

Later investigators could not confirm or deny either structure until 1962 when Freeman[6] provided detailed spectral and chemical evidence to support and elucidate the actual structure as pyrazole-1,2-



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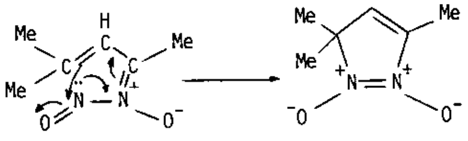
dioxide 4, possibly derived by a redistribution of the electrons in structure 3.



3 4

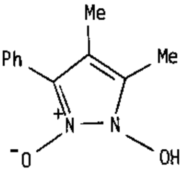
Similarly, a nitrimine structure 6a was initially proposed for the nitrosation product of the oxime 5a in 1904[6].

$$R^1-CH=C(R^2)-C(=NOH)-R^3 \longrightarrow R^1-CH=C(R^2)-C(=N-NO_2)-R^3$$

5 6

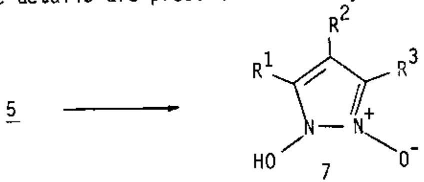
a: $R^1 = Ph$, $R^2 = R^3 = Me$

However, it was only much later, in 1968, that Freeman and Gannon proved[7] that the product structure was actually 7a.



7a

The nitrosation of the oxime 5is rather general and a series of compounds of the general type 7 was subsequently prepared. Specific details are presented in the synthesis section.



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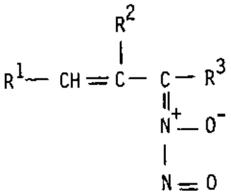
The assignement of structure 7 was based on physical, chemical and spectroscopic data, thus ruling out alternative structures as 6, 8 or 9.



$$R^1-CH=C(R^2)-C(=N^+(O^-)-N=O)-R^3$$

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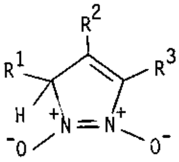

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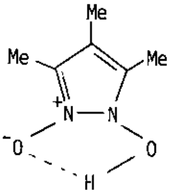
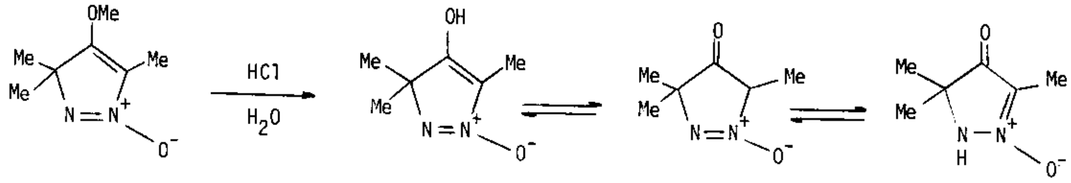
In particular the nmr spectrum of 1-hydroxy-3,4,5-trimethylpyrazole 2-oxide 7b consists of two sharp singlets at δ 1.95 (3H) and 2.20 (6H) in addition to a singlet at 15.8 (1H). The magnetic equivalence of two of the methyl groups constitutes additional evidence for the chelate structure 7b in which rapid tautomerism causes the 3- and 5- methyl groups to be equivalent. Even at -60 °C the spectrum does not change[6].



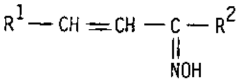
7b

Freeman also examined the product of the hydrolysis of 4-methoxy-3,5,5-trimethylisopyrazole 2-oxide 10, which was reported by Fusco and Trisoglio as a tautomeric mixture of 11, 12 and 13[6].



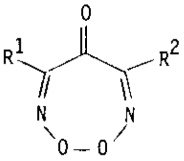
10 11 12 13

It was found that the hydrolysis product could be adequately described by structure 13 on the basis of its spectral data. Spectral data as well as chemical reactions are discussed in the appropriate sections. Besides, three structures 15, 16 and 17 were considered[9] for the compounds obtained from the nitrosation of the α,β-unsaturated oxime 14.



$R^1-CH=CH-\underset{\underset{NOH}{\|}}{C}-R^2$

14



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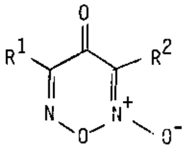

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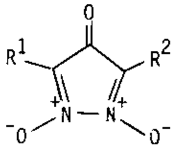


17

Structures 15 and 16 were considered earlier[9,10] and structure 15 was favoured. Wieland[11], independently, suggested structure 16 based upon his work on furoxans but presented no experimental support. However, the six-membered ring structure 16 was ruled out later, according to spectral data provided by Freeman and his co-workers[9,10]. The nmr spectrum of the symmetrical structure 17g (R^1=R^2=R^3=Me) shows only one sharp signal at 2.12 ppm indicating that both methyl groups are in identical environments. Thus, a different isomeric structure was not possible[9]. Furthermore, the bright yellow to orange-red colours of these compounds could not be explained by the seven-membered ring structure 15 nor is the thermal stability of these compounds compatible with the peroxide structure. Finally, reduction leads to pyrazole derivatives, which are directly related to structure 17 and two of the compounds of structure 17 have been synthesized from a five-membered ring precursor.

3.0. Synthesis

From the two major approaches employed in the formation of the pyrazole-N-oxides the cyclisation of suitably substituted precursors (see below 3.1.- 3.3.) has prevailed. The alternative N-oxidation of the pyrazole nucleus (see below 3.4.-3.5.) has found limited use as is, generally, the case with heterocyclic N-oxides[1].

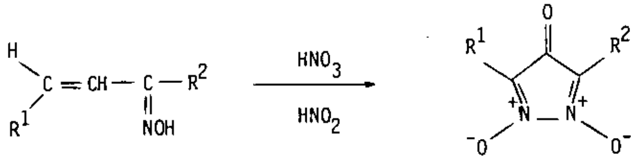
The following literature methods have been reported :

3.1. Oxidative Cyclisation of β-Alkyl- or Aryl-α,β-unsaturated Oximes

β-Alkyl or aryl-α,β-unsaturated oximes are converted into 4-oxo-4H-pyrazole 1,2-dioxides 17 and/or the corresponding oximino derivatives 18 upon nitrosation.

Thus, the oximes 14 with a dilute mixture of nitrous and nitric acids yielded the heterocyclic N-oxides 17 in low yields[9,12,13]. The yield of 17 could be increased by carrying out the reaction in the presence of molecular oxygen. The actual effect of the oxygen is not understood but 17 could be obtained in up to 40 % yield in its presence. In addition, small amounts of other products were obtained, i.e the parent unsaturated ketone, pyrazoles, isoxazoles and isoxazoline derivatives.

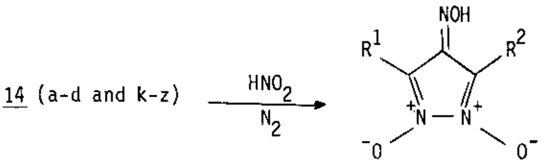
Attempts to prepare the monosubstituted analogue R^1=H, R^2=Ph of 17 by nitrosation of the oximes of either cinnamaldehyde or acrylophenone were unsuccessful[14].



14 17

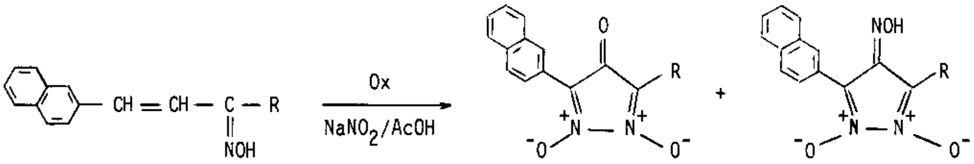
a: R^1=Ph, R^2=Me; b: R^1=Ph, R^2=Et; c: R^1=Ph, R^2=Pr; d: R^1=Ph, R^2=n-Bu; e: R^1=Ph, R^2=t-Bu; f: R^1=R^2=Ph; g: R^1=R^2=Me; h: R^1=R^2=COOEt; j: R^1=R^2=COOMe; i: R^1=Ph, R^2=COOEt; k: R^1=p-MeOC_6H_4, R^2=Me; l: R^1=p-MeC_6H_4, R^2=Me; m: R^1=p-(i-Pr)C_6H_4, R^2=Et; n: R^1=furyl-2, R^2=Me; o: R^1=thienyl-2, R^2=Me; p: R^1=p-MeOC_6H_4, R^2=Ph; q: R^1=p-MeC_6H_4, R^2=Ph; v: R^1=p-BrC_6H_4, R^2=Ph; r: R^1=Ph, R^2=p-MeOC_6H_4; s: R^1=Ph, R^2=p-MeC_6H_4 ; t: R^1=Ph, R^2=p-BrC_6H_4; u: R^1=R^2=p-MeC_6H_4 ; w: R^1=R^2=p-MeOC_6H_4; x: R^1=R^2=t-Bu; y: R^1=C_6D_5, R^2=t-Bu ; z: R^1=R^2=C_6D_5

However nitrosation of 14 under nitrogen gives rise to the oximino derivative 18[12].



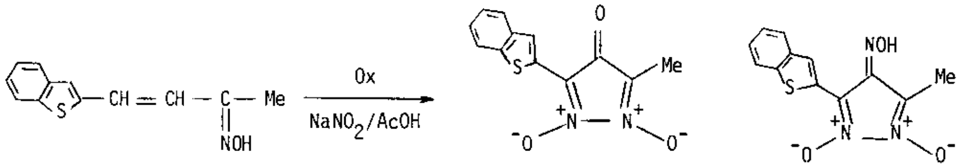
18

Attempts to convert 17 into 18 with hydroxylamine leads to reduction of the heterocyclic ring[9]. Recently, Unterhalt and his coworkers[15] have reported the oxidative nitrosation of β-naphthyl- and β-benzothienyl α,β-unsaturated oximes 14a'-d' to yield a mixture of compounds, which appears to be the N-oxides 17a'-d' and 18a'-d'.



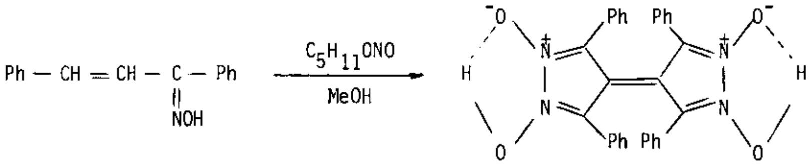
14 17a'-c' 18a'-c'

a': R=Me ; b': R=Et; c': R=Pr



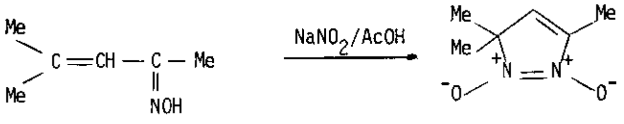
14d' 17d' 18d'

Interestingly, benzylideneacetophenone oxime 14f, with isopentyl nitrite in methanol, is converted into an N,N'-dihydroxybipyrazolyl-N,N'-oxide 19 in 45 % yield[16].

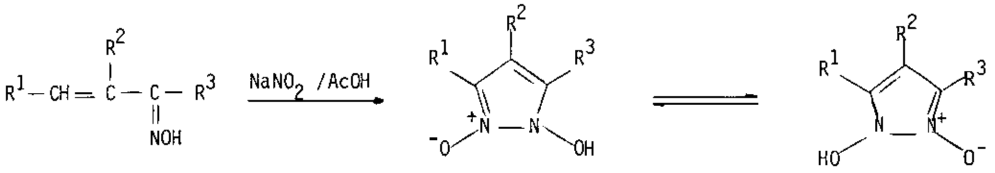


14f 19

Freeman[5] reported the preparation of 4 by nitrosation of mesityl oxide oxime 1 as early as 1962. Freeman's reaction was later generalized and a series of derivatives of 4, i.e the 1-hydroxypyrazole 2-oxides 7 were prepared in high yields[14].



1 4

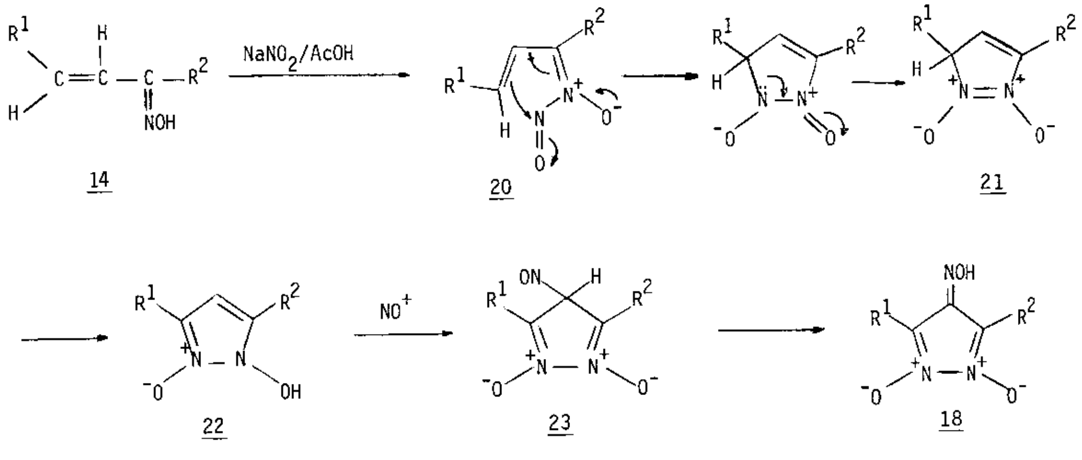


5 7

a: $R^1=R^2=R^3=Ph$; b: $R^1=R^2=R^3=Me$; c: $R^1=R^2=Me$, $R^3=Ph$; d: $R^1=R^3=Ph$, $R^2=Me$

It is not known whether the tautomers 7 are inter- or intra-molecularly hydrogen bonded, but in either case rapid proton exchange would interconvert one into the other. A similar situation exists with pyrazoles themselves.

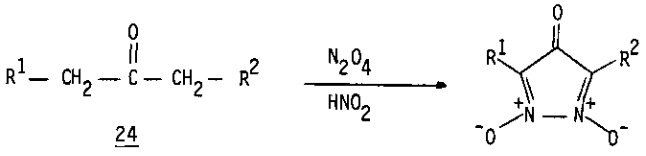
A common reaction path has been proposed[9] for at least the early stages of nitrosation reactions of α,β-unsaturated oximes and this is shown below for 14.



Thus, 14 undergoes initial N-nitrosation to 20 followed by ring closure to 21 and tautomerization to 22. The latter intermediate in the presence of excess nitrous acid under nitrogen apparently suffers electrophilic substitution to 23 ultimately leading to 18. Oxime formation is almost precluded when there is no excess of nitrous acid under oxygen, and the ketone 17 is the predominant product. The proposed steps through 21 and 22 were validated by the isolation of analogous intermediates (4 and 7 in the reaction of 1 and 5 respectively). It should be noted that the steps leading to 17 from 14, under the conditions mentioned, are not known, but since it has not been possible to obtain 17 from 18 under the conditions of the reaction, it is believed that 17 arises by a separate series of reactions, which may involve free-radical intermediates.

3.2. Oxidative Cyclisation of Dialkylketones

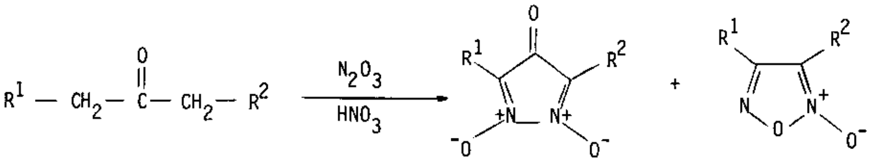
An alternative approach to the formation of some derivatives of 17 was discovered by Henry and von Pechman[17] using the oxidative nitrosation of dialkyl ketones 24[10]. The reaction presumably involves initial formation of the corresponding 1,3-dioxime followed by oxidative ring closure to 17.
The N-oxides 17 also may be obtained by treatment of 14 with nitric acid in the presence of a catalytic quantity of sodium nitrate or with a mixture of nitric and acetic acid.



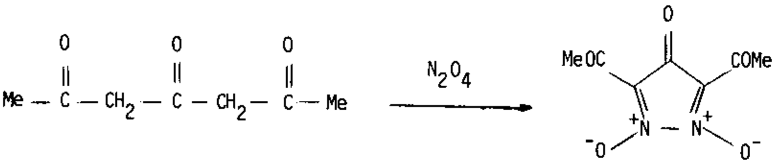
24 17

a: R^1=Ph, R^2=COOEt; b: R^1=R^2=COOEt;
c: R^1=R^2=COOMe; d: R^1=R^2=Ph

Unterhalt and Pindur[18] found that 24b,c,e and f react with dinitrogen trioxide / nitric acid to give the crystalline 3,5-dialkoxycarbonyl-4-oxo-4H-pyrazole 1,2-dioxides 17 and the oily dialkoxycarbonylfuroxans 25 while compounds 24g,h, under the same reaction conditions, gave 25 as the sole product. These researchers also reported the formation of 27 by the reaction of 1,3-diacetylacetone 26 with dinitrogen tetroxide.



24 17 25



26 27

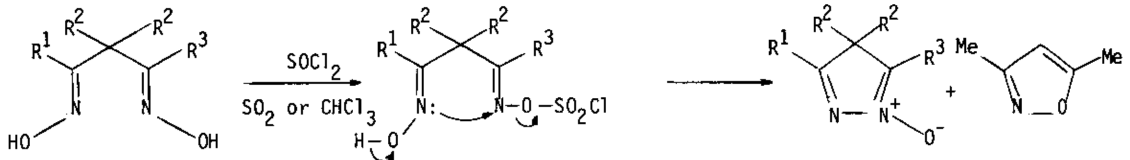
3.3. Oxidative Cyclisation of 1,3-Dioximes

There exist a number of reports on the synthesis of pyrazole 1,2-dioxides that include oxidative cyclisation of 1,3-dioximes with a variety of oxidizing agents[14,19-25]. The nature of the latter as well as the reaction conditions are obviously of paramount importance to the reaction course.

Gnichtel and co-workers[14], in 1966, reported the reaction of 1,3-dioximes 28b and 28c with thionyl chloride in liquid sulphur dioxide at -60 °C. The main products were the pyrazole 1-oxides 30b and 30c, respectively, along with minor yields of the parent pyrazoles as by-products.

Much later, in 1980, Gnichtel et al.[19] found that a much cleaner reaction is obtained when the 1,3-dioximes 28 are treated with thionyl chloride in chloroform at room temperature and the N-oxides 30 are the sole products. The significance of substitution at the 2-position of the dioximes was demonstrated by the isolation of isoxazole 31a as the sole product, instead of the desired N-oxide, when this position is unsubstituted as in 28a, evidently owing to tautomerization of the latter.

The reacting configuration of the 1,3-dioximes 28 was determined by spectroscopic methods[19] to be 1E,3E.

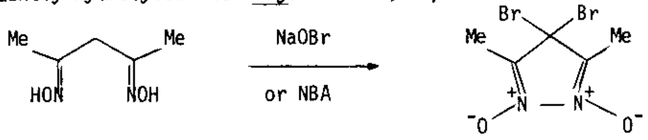


28 29 30 31a

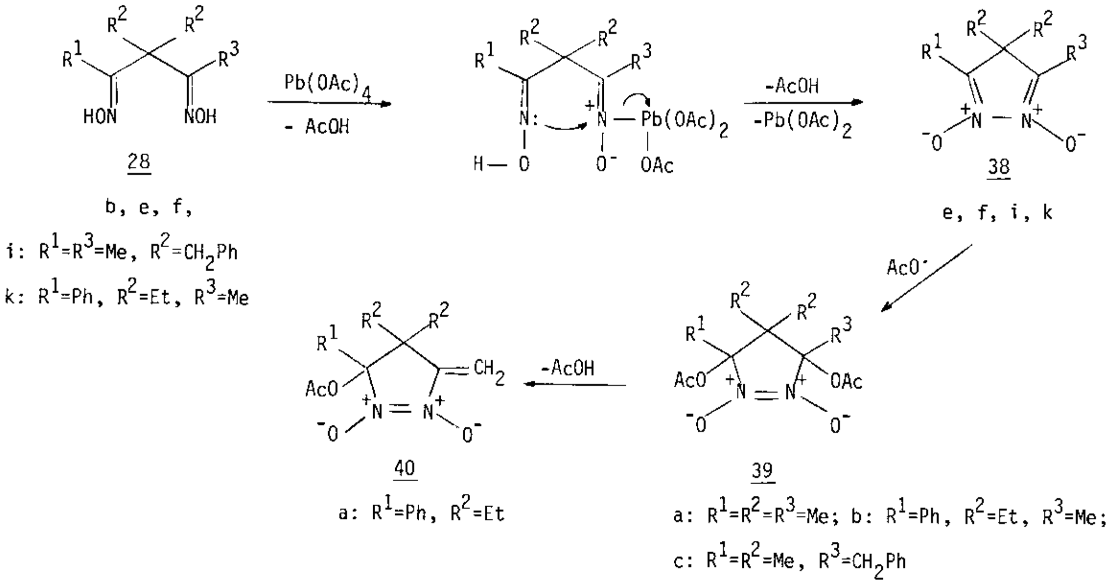
a: R^1=R^3=Me, R^2=H; b: R^1=R^2=R^3=Me; c: R^1=R^3=Me, R^2=Ph; d: R^1=R^3=Ph, R^2=Et; e: R^1=Ph, R^2=R^3=Me;
f: R^1=R^3=Ph, R^2=Me

Other oxidative cyclisation methods of 1,3-dioximes leading to pyrazole N-oxides include the use of sodium hypobromite[20], phenyliodine(III)bistrifluoroacetate (PIT)[21], lead tetraacetate (LTA)[22,23] and sodium hypochlorite[24].

Oxidation of the dioxime 28a by NaOBr gave an initially moderate yield of the heterocyclic N-oxide 32a, which was subsequently hydrolysed into 17g. However, superior results were realized when the reaction was modified by using N-bromoacetamide (NBA) in place of NaOBr[25]. The dioximes 28a, 28g and 28h on treatment[21] with PIT lead to the formation of 4-oxo-2H-pyrazole 1,2-dioxides 17g, 17a and 17f respectively and the corresponding 3,5-disubstituted isoxazoles 31.



28a 32a



28 b, e, f,

i: $R^1=R^3=Me$, $R^2=CH_2Ph$

k: $R^1=Ph$, $R^2=Et$, $R^3=Me$

38 e, f, i, k

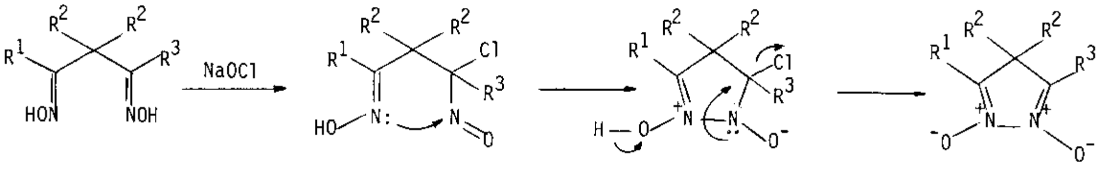
40 a: $R^1=Ph$, $R^2=Et$

39 a: $R^1=R^2=R^3=Me$; b: $R^1=Ph$, $R^2=Et$, $R^3=Me$; c: $R^1=R^2=Me$, $R^3=CH_2Ph$

The formation of the N-oxides 38 is thought of as an intermediate step in the acetoxylation, which results from the presence of acetoxyl radicals produced from LTA in the course of the reaction. It is envisaged that product 40 results from the elimination of a molecule of acetic acid from 39. Recently, the reaction conditions and the yields of the heterocycles 38 were optimized using commercially available sodium hypochlorite solution[26]. The use of this oxidant is advantageous in that it requires simple and mild reaction conditions, easy work-up and gives rather respectable yields of 38. The low cost of the reagent adds to the synthetic value of the method.

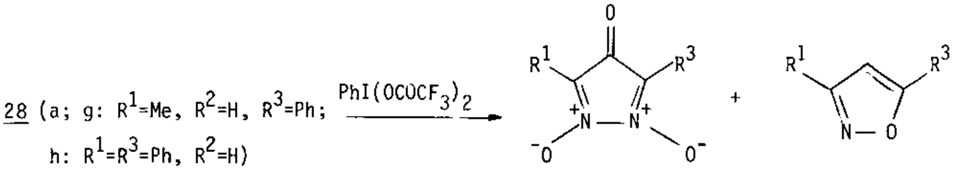
A plausible reaction pathway that portrays the oxidative cyclisation of 28 is delineated below.

A transient green colouration of the reaction mixture may be indicative of a nitroso-oxime intermediate 41, which subsequently undergoes cyclisation and dehydrochlorination to 38[24].



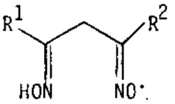
28 41 42 38

Furthermore, a few pyrazole-N-oxides, such as 45 or 46, have been obtained from LTA oxidation of some alicyclic 1,3-dioximes[22]. It is quite likely that the LTA oxidation mechanism proposed for the aliphatic 1,3-dioximes is also operative in cases where the =NOH is attached to a carbocyclic ring.



17 31

Several possibilities have been proposed with regard to the mechanism of the above reaction, e.g. the dioxime may first be transformed into an iminoxy radical 33 by abstraction of H· or give an iodine-(III)derivative 34, or a gem-nitroso-trifluoroacetate 35. Such intermediates are known to be formed[21] from simple oximes by eventual release of iodobenzene and trifluoroacetic acid. These may further be converted into 36, which reacts with more PIT and gives the bistrifluoroacetoxy derivative 37, which is finally hydrolysed, probably during work-up.



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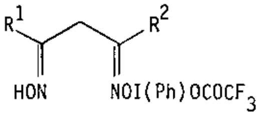

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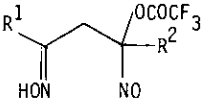

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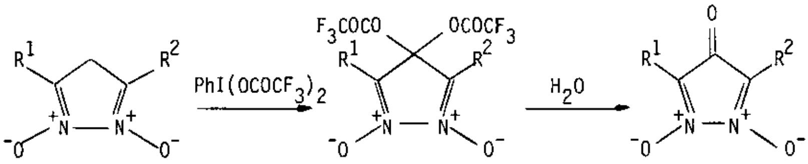


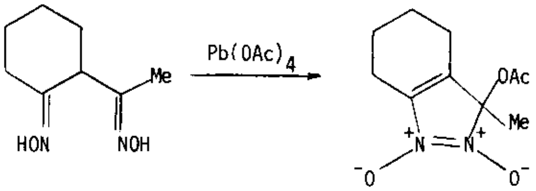
36 37 17

All the above described methods, lead to N-oxides having an oxo-, oxime- or halo- group at the 4-position of the pyrazole nucleus, i.e. a functionality with an appreciable interference in the electronic structure of the ring.

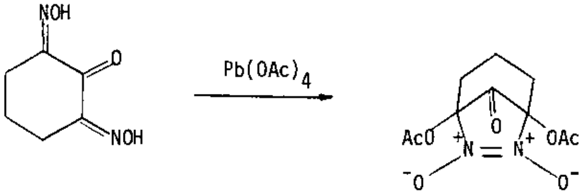
In contrast there are only a few known 4H-pyrazole 1,2-dioxides dialkylated at the 4-position. These have been prepared by the oxidative cyclisation of the corresponding 1,3-dioximes with LTA[22,23] or NaOCl[24].

Oxidation of 28 with LTA[22,23] resulted mainly in pyrazole dioxides 38. In most cases acetoxylated pyrazoline 1,2-dioxides 39 and 40 were also produced in substantial quantities, along with a number of side products. Although the reasons for the preferential formation of pyrazole 1,2-dioxides rather than the acetoxylated compounds are uncertain, it appears that the substituents R^2 influence the progress of the reaction. Furthermore, influence is also exercised by alkyl or aryl groups adjacent to the =NOH moiety.

A plausible mechanism[22] has been proposed to explain the formation of the N-oxides 38-40 as shown.



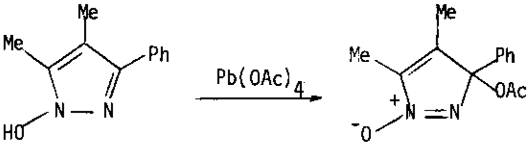
43 45



44 46

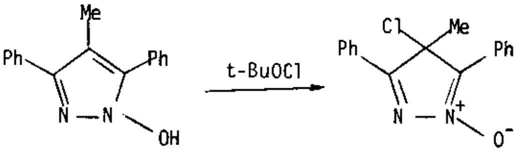
3.4. Oxidation of N-Hydroxypyrazoles

The N-hydroxypyrazole 47a is oxidized[7] with lead tetraacetate to yield the pyrazole-N-oxide 48a.



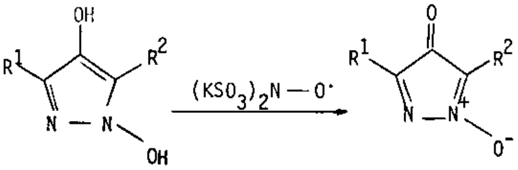
47a 48a

Besides treatment of 47b with t-butyl hypochlorite yields[26] the 4-chloro-4-methyl-3,5-diphenylpyrazolenine 1-oxide 49a.



47b 49a

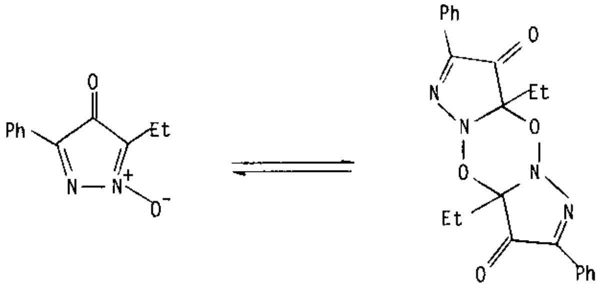
Freeman in 1969 reported[9] the synthesis of 1,4-dihydroxypyrazoles 50 , which were readily oxidized by dipotassium nitrosodisulphonate (Fremy's salt) to the N-oxides 51.



50 51

a: $R^1=R^2=Ph$; b: $R^1=Me$, $R^2=Ph$; c: $R^1=Et$, $R^2=Ph$; d: $R^1=R^2=Me$

The structure of the unsymmetrical derivatives 51 has not been unequivocally established, but some inferential evidence is available, such as the fact that during purification of 51c a new compound was isolated, which was assighed structure 52 on the basis of spectral data[9]. 52 reverted to 51 upon heating or dissolution.

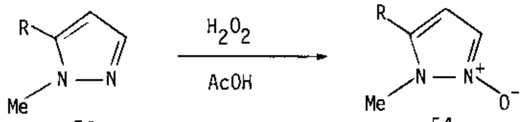


51c

52

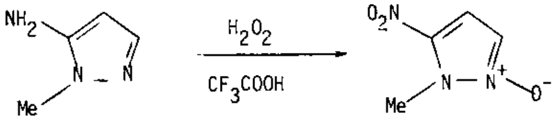
3.5. Nuclear Oxidation of the Pyrazole Ring

Simple pyrazoles generally do not react with peracids[28,29]. There are only two examples of successful results, i.e. oxidation of 1-methylpyrazole 53 to 1-methylpyrazole 2-oxide 54 by peracetic acid in moderate yield and 5-amino-1-methylpyrazole 55 to 1-methyl-5-nitropyrazole 2-oxide 56 by pertrifluoroacetic acid.



53

54

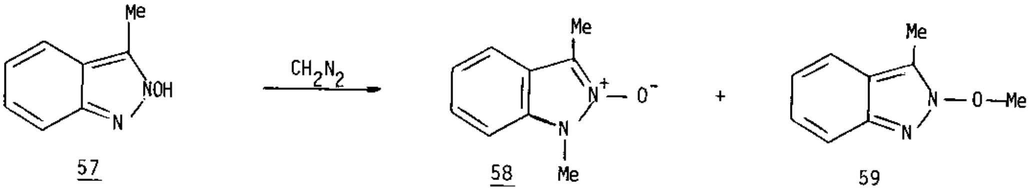


55

56

3.6. Other Methods

There exist a few reports on the synthesis of benzo-fused pyrazole-N-oxides[30,31]. Thus, the reaction of 2-hydroxyindazole 57 with diazomethane affords the N-oxide 58 along with the O-methylated product 59[30].



57 58 59

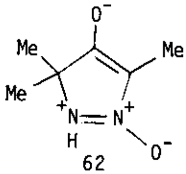
Furthermore, a well-known method in indazoles, and very rare in pyrazoles, is the creation of the N-N bond as the last step of the ring synthesis. Accordingly, the indazole 1-oxides 61 are formed from the nitro-derivative 60 in basic medium[31].

60 61

4.0. Spectroscopic Properties

4.1. Infrared Spectra

The ir spectra of pyrazole N-oxides are characterized by the presence of an absorption at 1200-1350 cm^{-1}, generally attributed to the $=\underset{|}{N}^{+}-O^{-}$ functionality in heterocyclic N-oxides[1], whose position and intensity depend on substitution[19,22,25]. The ir spectrum of 7 shows no distinctive band associated with O-H stretching but is characterized by a broad diffuse absorption between 2500 and 1670 cm^{-1}. At longer wavelengths the bands were sharp and distinguishable[6,7]. In compound 13 a carbonyl band is clearly present, although it is lower than that of ordinary cyclopentanones[8]. This lowering may be ascribed to hydrogen bonding and to interaction with the $=\underset{|}{N}^{+}-O^{-}$ group or with the unshared electrons of the amino group. An interaction of the latter type leads to the ionic structure 62 whose contribution to the ground state of the molecule would account for the lack of reactivity of the carbonyl group of 13.



62

The ir spectrum of 17 shows a strong band at 780 cm^{-1}. This band was present in all the compounds of this series, regardless of whether an aromatic ring was present and Freeman suggested that it is due to an N-O vibration[10].

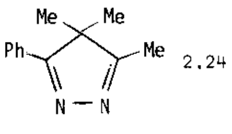
4.2. Ultraviolet Spectra

The uv spectra of some N-oxides have been reported[6,8,11,13,28,29].

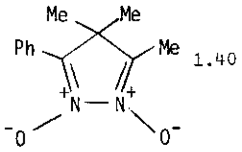
Comparison of the uv absorptions of the N-oxides 30 with their corresponding pyrazoles shows[19] an hypsochromic shift in the range of 31-38 nm, due to the extended conjugation within the ring. Furthermore, the uv absorption of 30 in various solvents shows an hypsochromic shift with increasing solvent polarity[14]. The dipole moment of 30b (in benzene) is 6.8 D while that of pyridine-N-oxide is 4.19 D and that of N-phenyl-sydnone 6.5 D[14].

4.3. Nuclear Magnetic Resonance Spectra

The chemical shifts of the substituents at the 3- and 5- positions of the pyrazole-N-oxides are influenced by the diamagnetic shielding exerted by the exocyclic oxygen of the $=\underset{|}{\overset{+}{N}}-O^{-}$ group and subsequently are more upfield than those of the corresponding pyrazoles[22]. An example is given below.

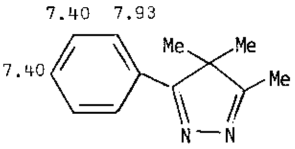


63a

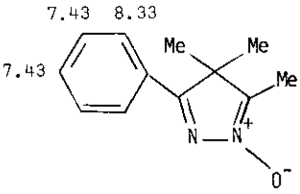


38e

This shielding effect has been well-established in a number of heterocyclic N-oxides[32]. Furthermore, the o-protons of a phenyl group present at the 3- or 5- positions of the pyrazole ring are the most strongly affected as expected[19]. An example is given below.



63a



30e

4.4. Mass Spectra

There exist a couple of reports[33,34] on the fragmentation features of pyrazole-N-oxides.

A consistent fragmentation pattern is obsrved in the spectra of compounds 17 and 51. In all cases scission of the ring occurs by a process, which involves cleavage of the N-N bond and one of the bonds to the carbonyl carbon. However, there is no report of a $M\text{-}30^{\rceil+}$fragment while loss of CO or oxygen directly from the molecular ion is not involved to any significant extent[34].

Furthermore, the primary fragmentation of 38-40, 44 and 45, which is common to all of these compounds, is characterized by the presence of peaks at m/z $M^{\rceil+}$,$M\text{-}16^{\rceil+}$ and $M\text{-}30^{\rceil+}$ owing to the molecular ion, and to the loss of an oxygen atom and a nitroso group from the molecular ion, respectively. The intensity of the $M\text{-}16^{\rceil+}$ fragment is very low, but this fragment has been observed in the spectra of other heterocyclic N-oxides[35,36] and is of diagnostic value in the characterization of such compounds. A similar pattern has been observed in the furazan N-oxides[35] and 1,2-benzisoxazole N-oxides[36], which tend to favour the loss of a nitroso group rather than an oxygen atom.

An alternative fragmentation route proceeds via ring scission through cleavage of the N-N and C-C bonds[34].

No loss of N_2 was evident in either ring, in contrast with the previously reported extrusion of this fragment in the spectra of pyrazoles[34].

4.5. Electron Paramagnetic Resonance Spectra

A series of anion radicals of substituted 4-oxo-pyrazole-1,2-dioxides 17 and 1-oxides 51 were generated via low temperature potassium metal reduction in tetrahydrofuran[37].

The epr coupling constants in conjugation with INDO spin density calculations indicate that the spin and charge densities are nearly equally distributed between the ring system and the carbonyl oxygen[37].

The stability of the anion radicals is attributed to the formation of tight ion pairs with the potassium cation. This tight ion association splits the degeneracy of the four nitrogens in the anion radical of 2,2',5,5'-tetraphenyl-3,3',4,4'-tetraazafulvalene 3,3',4,4'-tetraoxide. The anion radical of 2,5-diphenyl-4-oxopyrazole-1,2-dioxide loses an oxygen atom upon warming, leaving the anion radical of the corresponding N-oxide[37].

4.6. Mössbauer Studies

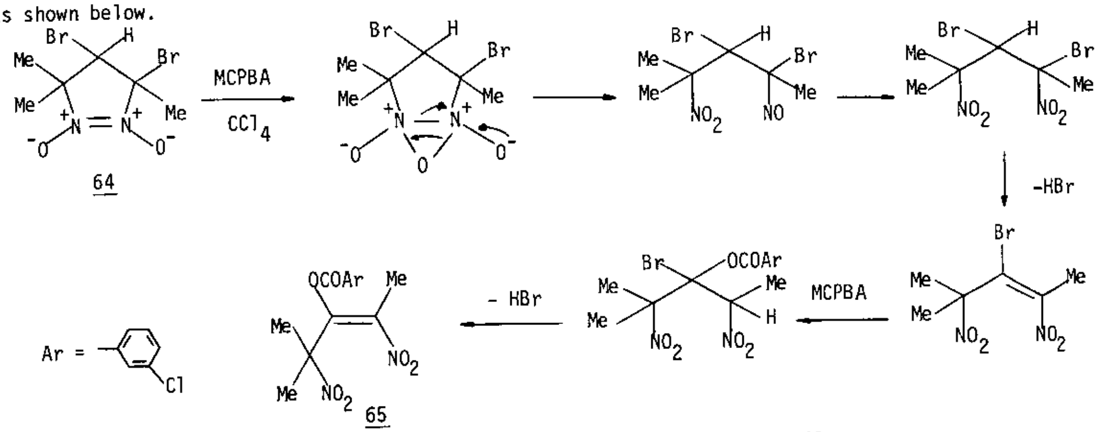
Mössbauer parameters have been reported for tin(IV) complexes with anions of 3,5-diphenyl-4-methyl-1-hydroxy-2-pyrazole-N-oxide 7a[38]. The isomer shifts obtained for the dihalotin$(Ph_2pyzo_2)_2$ complexes are significantly larger than those reported for other corresponding $X_2Sn(<^{O}_{O})_2$ complexes, indicating that the ligand effects the largest electron density at the tin nucleus[38].

5.0. Chemical Reactivity

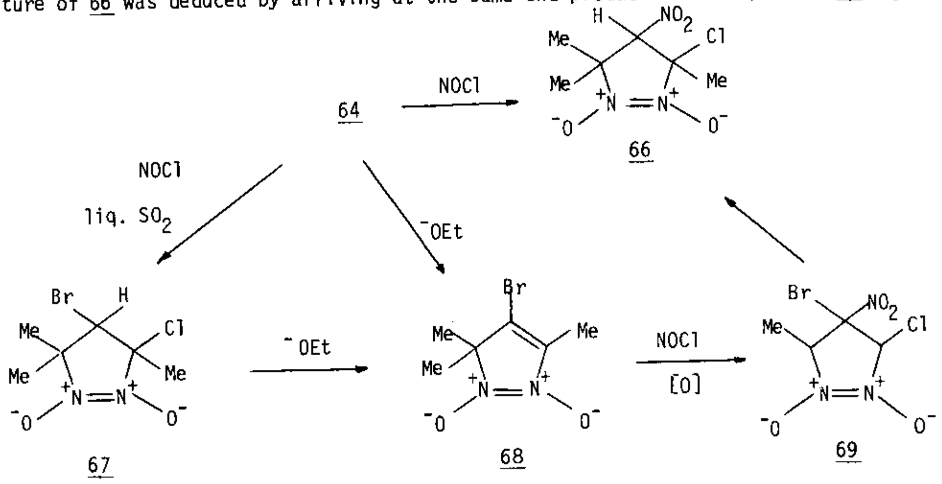
5.1. Ring Reactions

5.1.1. Oxidation

3,5,5-Trimethyl-4,4-dibromopyrazoline-1,2-dioxide 64 was oxidized directly to a dinitro product 65 with m-chloroperbenzoic acid (MCPBA)[39]. The transformation of 64 to 65 has been suggested to proceed as shown below.

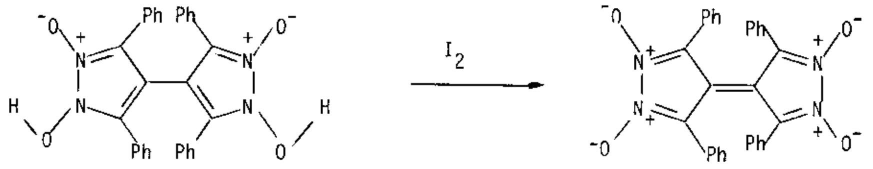


The reaction of 64 with nitrosyl chloride was also studied. It was found[39] that in a sealed tube nitrosyl chloride does not oxidize the nitroso groups but instead gives an anomalous product 66. The structure of 66 was deduced by arriving at the same end-product via the pathway 64 → 67 → 68 → 69.



In liquid sulfur dioxide, nitrosyl chloride replaces the tertiary bromine in 64 to give 67. Base dehydrohalogenates 64 or 67 to 68. Nitrosyl chloride then adds and oxidizes 68 to 69 and finally the latter is hydrolyzed in the work-up.

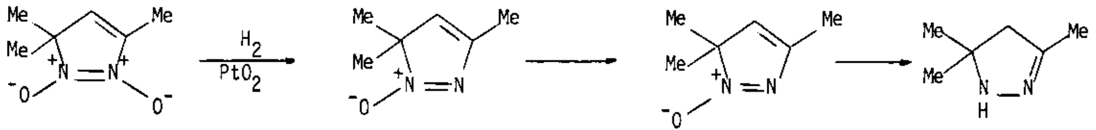
Besides, 19 was found to produce the heterocyclic N-oxide 70 upon oxidation with I_2[16].



19 70

5.1.2. Reduction

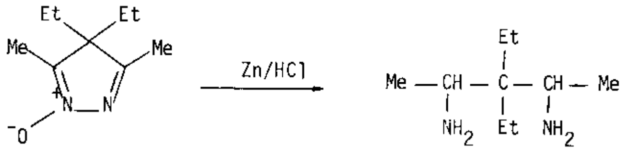
Pernitrosomesityl oxide 4 was reduced to 73[5]. Catalytic hydrogenation proceeded stepwise and could be controlled. The first reduction product was 71. If the catalytic hydrogenation was interrupted after approximately two-thirds of the hydrogen uptake has occurred, it was occasionally possible to isolate the product 72. Apparently, the production of the latter is dependent upon the activity of the catalyst but no detailed study was made. Complete reduction of 4 yielded 73.



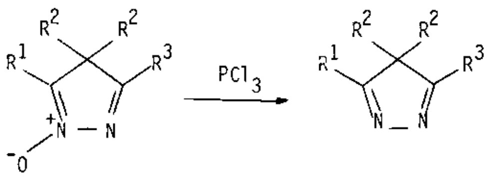
4 71 72 73

It was possible to reduce 4 to 73 by using potassium borohydride in boiling ethanol, but the procedure was complicated by side reactions[5]. Lithium aluminium hydride (LAH) caused[5] complete reduction to the trimethylpyrazoline 73.

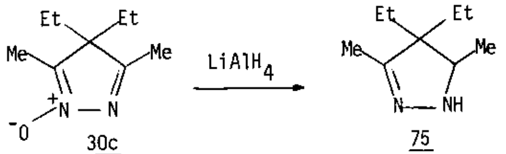
Furthermore, reduction of 30c with zinc in hydrochloric acid at room temperature leads[14] to the primary diamine 74 whereas reduction of 30b and 30c with PCl_3 yielded[14] the corresponding pyrazoles 63. The N-oxide 30c with $LiAlH_4$ resulted[14] in pyrazoline 75.



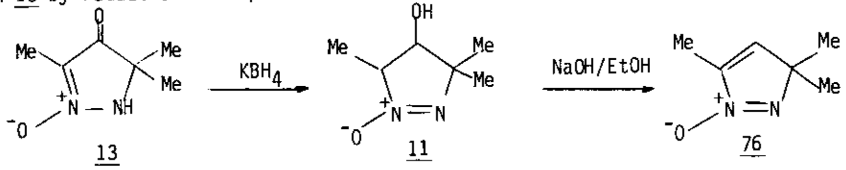
30c 74



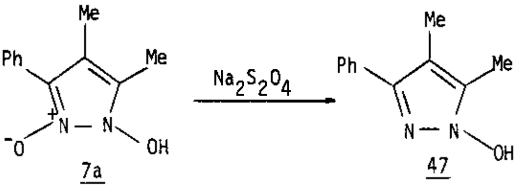
30 63



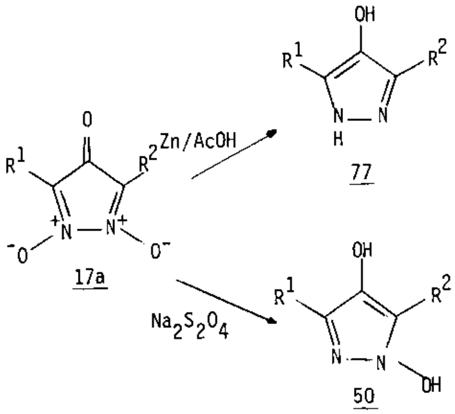
Reduction of 13 with potassium borohydride at 25 °C yielded 11, which was converted to 76 upon treatment with alkali[6]. Chromic acid oxidation of N-oxide 76 regenerates 13. Compound 76 could be obtained directly from 13 by reduction with potassium borohydride at 75 °C.



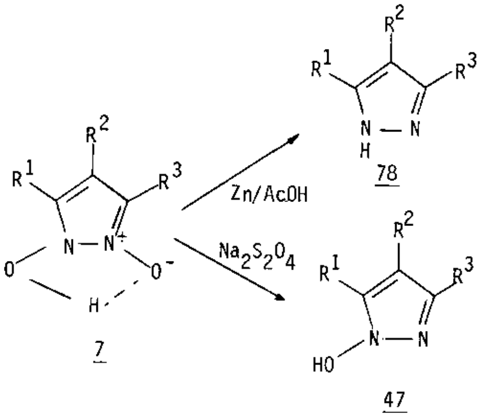
Reduction of 7a with aqueous sodium hydrosulfite produced[7] 47.



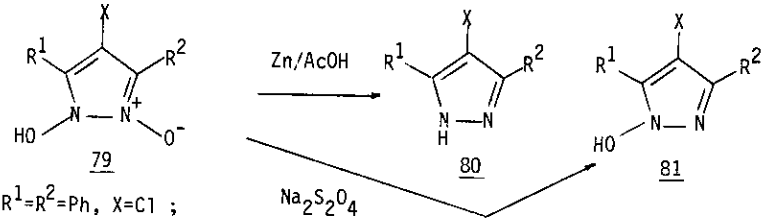
Reduction of 17 with zinc and acetic acid resulted in the 4-hydroxypyrazoles 77, while with sodium hydrosulfite yielded the corresponding 1,4-dihydroxypyrazoles 50[9].



Furthermore, the N-hydroxypyrazole-N-oxides 7 were easily reduced[6] by zinc and acetic acid to the parent pyrazoles 78 at reflux temperature for 4 h. Under mild conditions (1 h at room temperature) the same reagents yielded the corresponding N-hydroxypyrazoles 47. In practice sodium dithionite proved to be a more useful reagent for effecting selective reduction to 47[6].

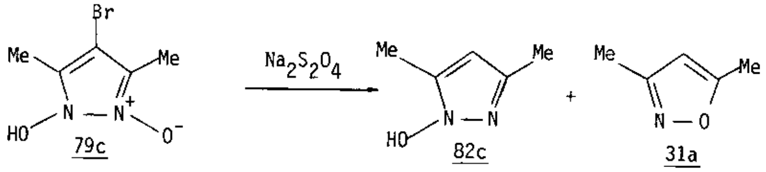


Reduction of 79 with zinc and acetic acid gave the 4-chloropyrazoles 80, while with sodium dithionite gave the 4-chloro-1-hydroxypyrazoles 81[25]. Dithionite reduction of 79c gave a low yield of 82c, while the major product of the reaction was the 3,5-dimethylisoxazole 31a[25]. The formation of the latter has also been observed for other azole N-oxides[40].

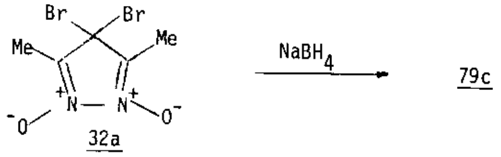


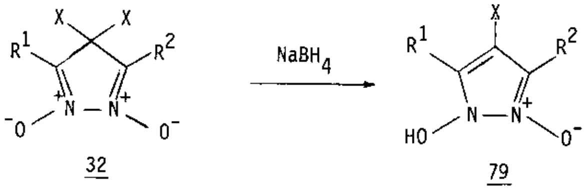
a: $R^1=R^2=Ph$, X=Cl ;

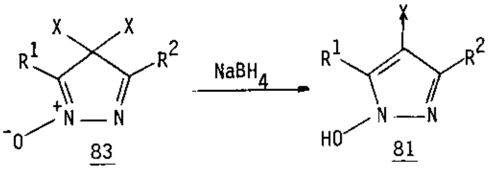
b: $R^1=Me$, $R^2=Ph$, X=Cl



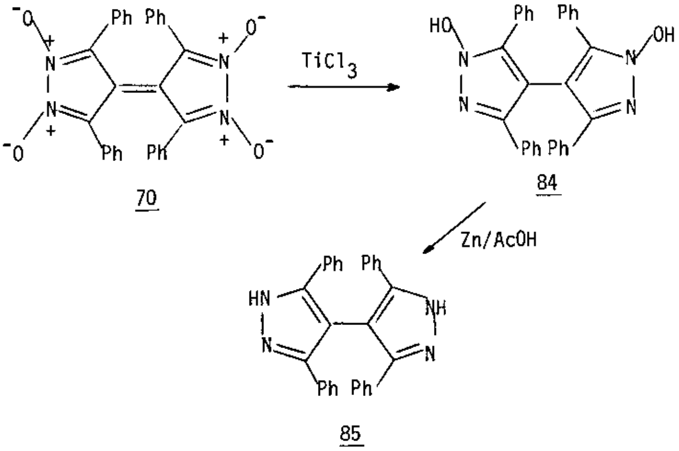
79c was obtained by reduction of 32a with $NaBH_4$. This reaction, general for gem-halides, permits the reduction of 32 and 83 to 79 and 81 respectively in nearly quantitative yield[25]. No overreduction was observed, even with large excess of sodium borohydride and prolonged reaction times[25].





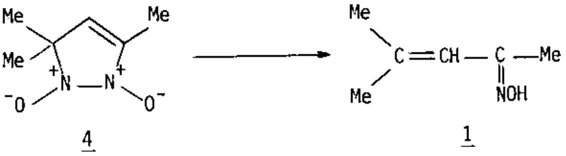


Reduction of 70 with $TiCl_3$ produced 84[16], further reduction of which yielded the bipyrazole 85[16].

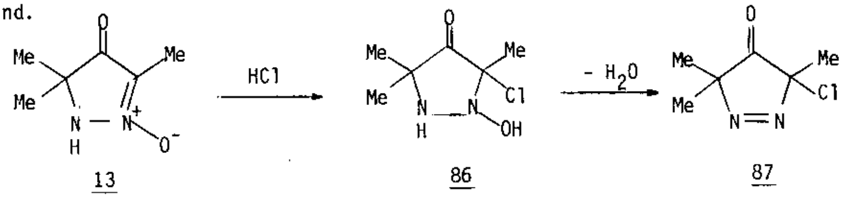


5.1.3. Hydrolysis

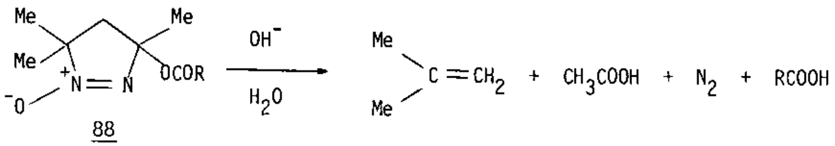
Hydrolysis of 4 resulted in the mesityl oxide oxime 1 and a nitrite ion[5].



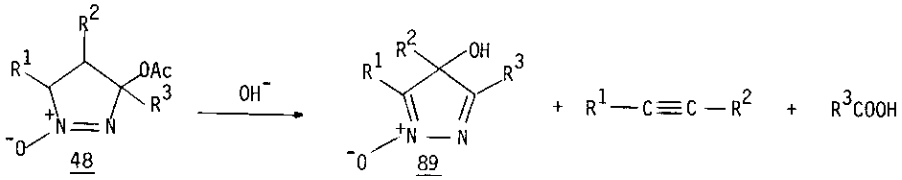
When the N-oxide 13 is treated with hydrocloric acid, it is converted to 87[8]. Nitrones are known[8] to react with halogen acids to form hydroxylamines. In this case dehydration may occur to form an azo compound.



The pyrazoline I-oxide 88, upon hydrolysis, produces alkenes, acids and nitrogen[41].



On the other hand the hydrolysis of 3-acetoxy-3H-pyrazole 1-oxides 48 produced acetylenes and acids.

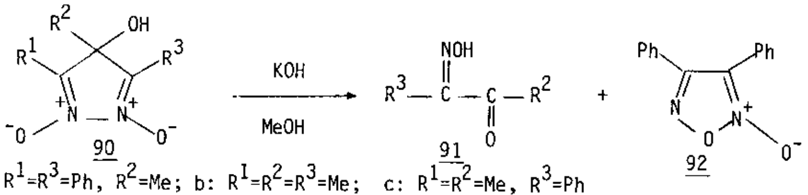


a: $R^1=R^2=Me$, $R^3=Ph$;

b: $R^1=R^3=Ph$, $R^2=Me$

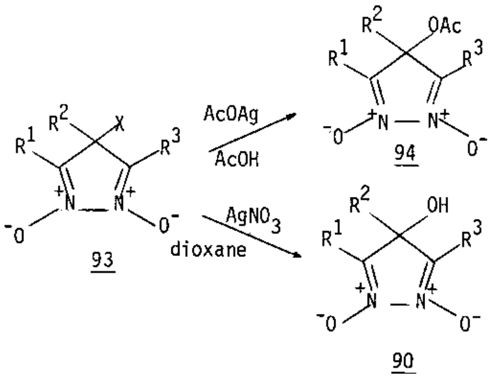
However, these hydrolyses were not completely straight forward, since some 4-hydroxy-4-methyl-3,5-diphenyl-4H-pyrazole 1-oxide 89b (c.a. 20 %) was obtained from the hydrolysis of 48b. Hydrolysis of acetate 48a produced 1-phenylpropyne rather than the expected 2-butyne[41].

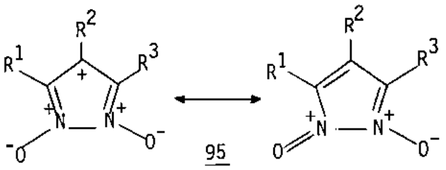
Furthermore, when carbinol 90 was heated with aqueous methanolic potassium hydroxide, it was converted to 1-phenyl-1-oximinoacetone 91a and diphenylfuroxan 92a. The latter presumably arises from dimerization of the benzonitrile oxide formed during the reaction. The unsymmetrical carbinol 90c gave a mixture of the two possible monoximes[41].



a: $R^1=R^3=Ph$, $R^2=Me$; b: $R^1=R^2=R^3=Me$; c: $R^1=R^2=Me$, $R^3=Ph$

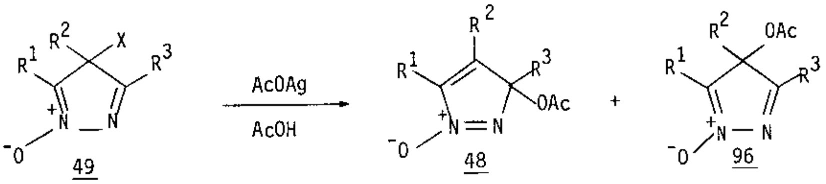
The 4-chloro-4H-pyrazole 1,2-dioxides 93 (X=Cl) reacted in a straightforward manner with both silver acetate in acetic acid and silver nitrate in aqueous dioxane to produce the 4-acetoxy 94 and 4-hydroxy- 90 derivatives respectively[41] It has been proposed that a cationic intermediate 95 is involved[41].





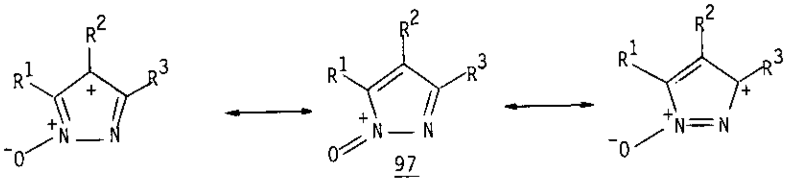
95

The 4-chloro-4H-pyrazole 1-oxides 49 (X=Cl) reacted in a completely different way. Treatment of these compounds with silver acetate in acetic acid produced[41] principally the 3-acetoxy-3H-pyrazoles 48 accompanied, in some instances, by the expected derivative 96.



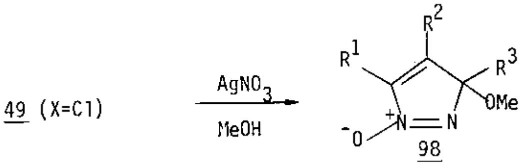
49 48 96

Although it has been determined[26] that the 3-acetates 48 can be thermally isomerized to the 4-acetates 96, it is likely that the 4-acetates were direct products of the substitution reaction since the temperatures employed (10 °C) were much lower than those required for isomerization (100 °C). The involvement of the resonance stabilized cationic intermediate 97 analogous to 95 has also been proposed[41].



97

This intermediate is unsymmetrical and its electrophilic character is shared by positions 3- and 4-. Analogous 3-methoxy derivatives 98 were obtained when the reactions were carried out with silver nitrate in methanol, a result also suggestive an ionic intermediate[41].



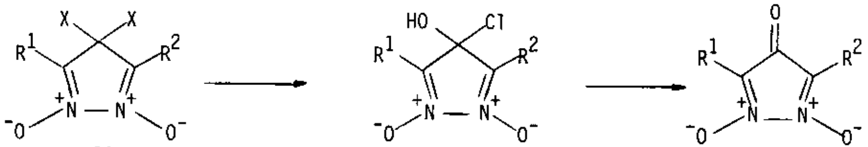
49 (X=Cl) 98

Reaction of the 4-chloro-monoxides 49 with aqueous silver nitrate was more complex since it was accompanied by complete destruction of the heterocycle. The products were acetylenes, carboxylic acids and nitrogen[41].

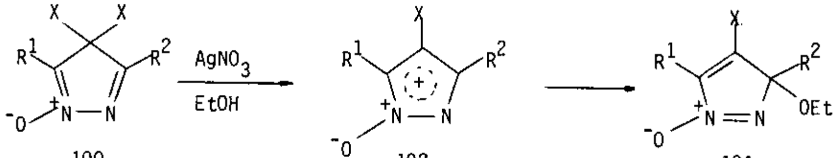
$$\underline{49}\ (X{=}Cl)\ \xrightarrow[H_2O]{AgNO_3}\ R^1COOH + R^2{-}C{\equiv}C{-}R^3 + N_2$$

The 4,4-dihalo-4H-pyrazole N-oxides undergo silver ion promoted solvolysis reactions, which are similar to those reported above. Thus, compounds 32 are converted to the 4-oxo-4H-pyrazole 1,2-dioxides 17 by reaction with aqueous ethanolic silver nitrate, probably through the intermediate substitution product 99[25]. This transformation is not surprising, since the conversion of 32e to the corresponding pyrazole 1,2-dioxide 17 has been reported to occur upon heating in ethanol, even in the absence of silver ion[25].

The pyrazole 1-oxides 100 react in a different manner with ethanolic silver nitrate, undergoing ethanolysis with rearrangement to the 4-chloro-3-ethoxy-3H-pyrazole 1-oxides 101. The possible intermediacy of a species such as 102 has been suggested to explain similar rearrangements in the solvolysis of 4-chloro-4H-pyrazole 1-oxides[25].



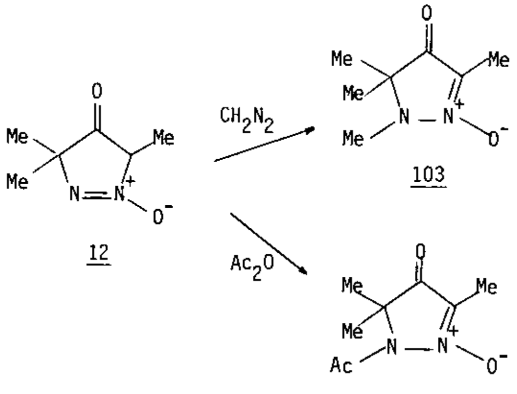
32 99 17



100 102 101

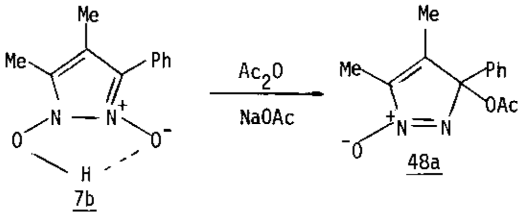
5.1.4. Electrophilic Substitution

Methylation of 12 with diazomethane and acetylation with acetic anhydride produced the corresponding N-substituted compounds 103 and 104 respectively[8].

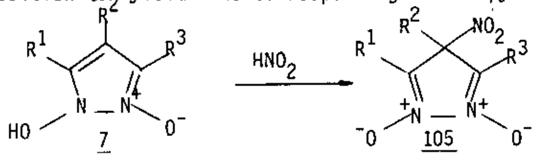


12 103 104

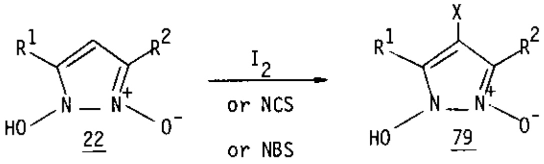
Treatment of the hydroxypyrazole N-oxides 7 with either acetic anhydride - sodium acetate or p-nitrobenzoyl chloride in pyridine produced[6] acyl derivatives of rearranged structure. For example, treatment of 7b with acetic anhydride yielded 48a.



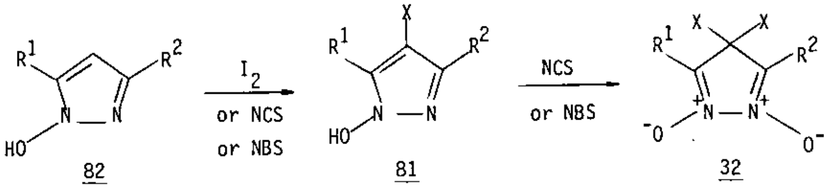
Besides, hydroxypyrazole N-oxides bearing alkyl groups in the 4-position undergo nitrosation followed by oxidation at that position to yield[6] the corresponding 4-nitropyrazolenine 1,2-dioxides 105.

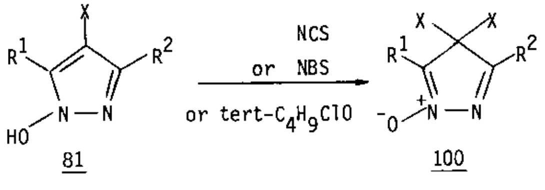


Reaction of some hydroxypyrazole N-oxides 22 with iodine or with N-chloro- or N-bromosuccinimide (NCS or NBS) in a 1/1 ratio gives[25] high yields of the 4-halo derivatives 79.

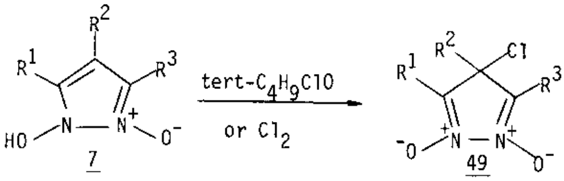


Treatment of 82 with one or two equivalents of NBS or NCS produced 81 or 32 respectively[25]. The compounds 32 could be prepared from 79 or 22 by using one or two equivalents of tert-butyl hypochlorite respectively.





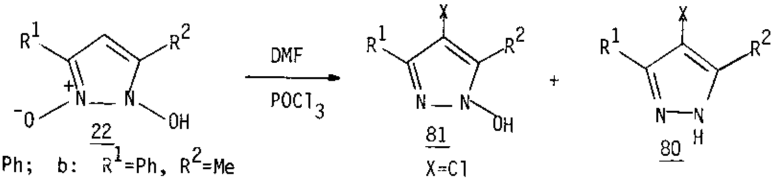
Chlorination of 7 with tert-butyl hypochlorite or gaseous chlorine produced the pyrazole 1,2-dioxides 49 in good yields[41].



5.1.5. Vilsmeier Reaction

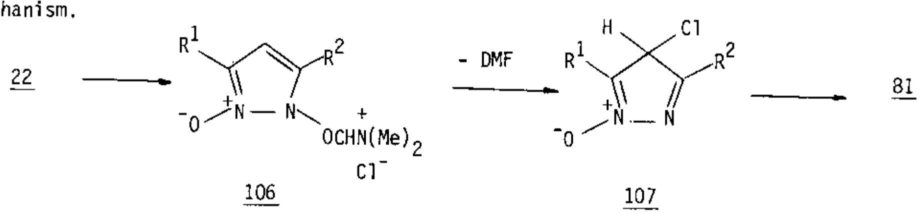
The N-oxides 22 react readily with the Vilsmeier reagent, but instead of formylation, they undergo deoxygenation and chlorination to give 4-chloropyrazole derivatives[42].

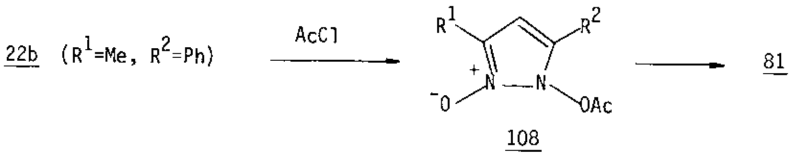
Reaction of 22 under the Vilsmeier conditions produced readily two products identified as 80 and 81.



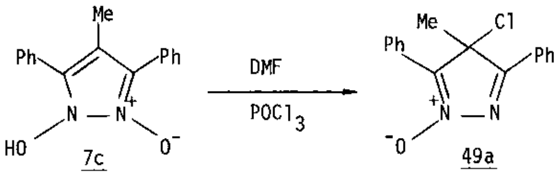
a: $R^1=R^2=Ph$; b: $R^1=Ph$, $R^2=Me$

A plausible mechanism for the conversion of 22 to 81 has been proposed[42] through intermediates 106 and 107. The overall process appears to be analogous to the rearrangement of 1-acetoxypyrazole 2-oxides to 4-acetoxy-4H-pyrazoles reported by Freeman[26]. The formation of 81 by reaction of 22 with acetyl chloride, a process, which almost certainly involves the acetate 108 lent support to the above mechanism.



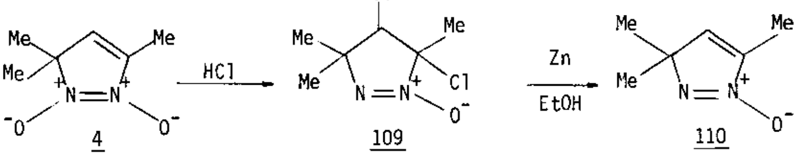


Careful monitoring of the reaction of 22b led to isolation of a compound, which in fact, appears to be the intermediate 108b. This compound was relatively stable, when stored in the cold, but it rearranged over a few days in the solid state at room temperature, or more rapidly in solution to give 81b. Furthermore, the N-oxide 49a was also obtained from the Vilsmeier reaction on 7c[42].

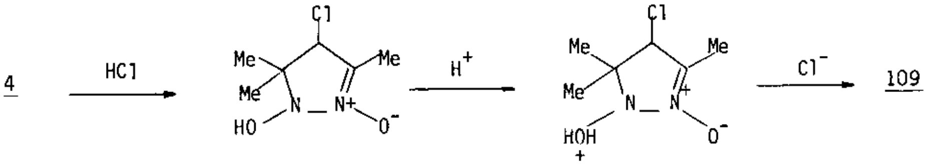


5.1.6. Addition Reactions

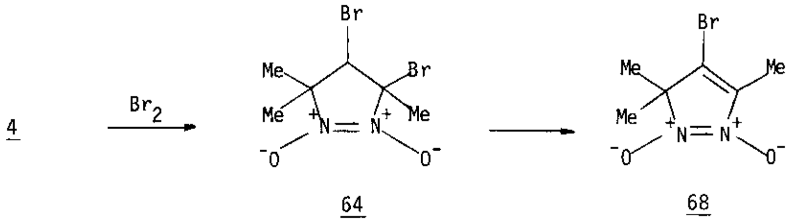
Treatment of 4 with concentrated hydrochloric acid produced[5] 109, which on further reaction with zinc and ethanol yielded 110.

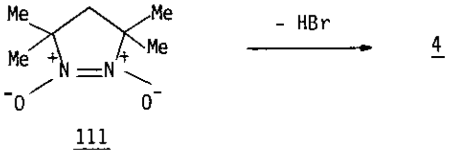


The conversion of 4 to 109 has been explained by the following reaction pathway.



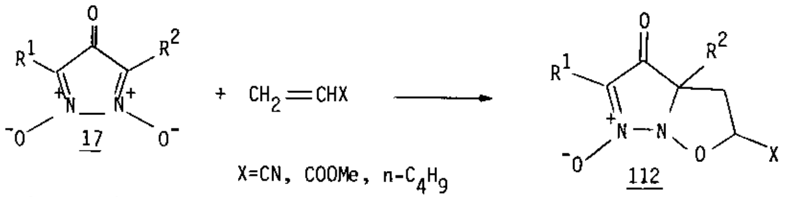
4 reacts with bromine to form 64, which, upon treatment with base, is transformed to 68[8]. Besides, dehydrobromination of 111 gave 4 in 62 % yield[20]. In the formation of either 63 or 4 no reagents and conditions are specified by the authors.



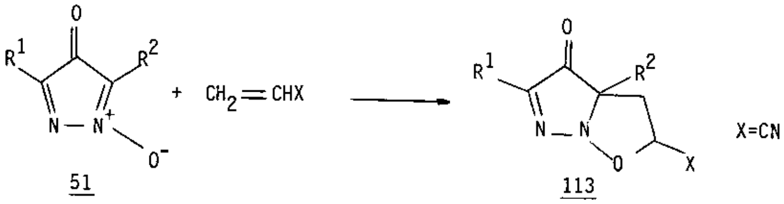


5.1.7. Cycloadditions

Condensation of 17 with acrylonitrile, methyl acrylate and butyl vinyl ether yielded 1/1 cycloadducts[43] 112. All of these compounds resulted from the same regiospecific cycloaddition in which

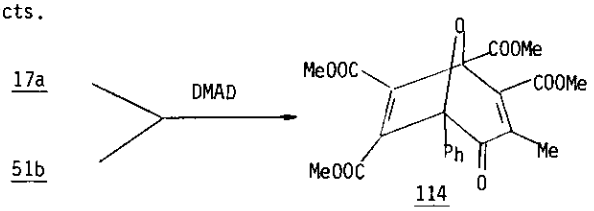


the exocyclic oxygen is attached to the carbon atom of the olefin, which bears the functional group. In all cases examined, addition took place exclusively at the aliphatic $=\overset{+}{\underset{|}{N}}-O^-$ group. Furthermore, the pyrazole 1-oxides 55 undergo cycloaddition with olefins to produce the heterocycles 117. The cycloaddition of 51 follows the same pattern i.e. 51 → 113.

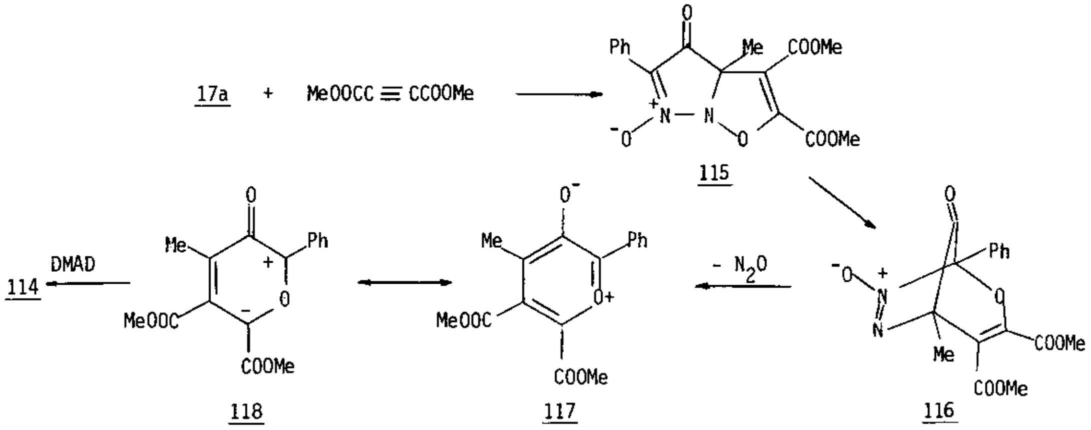


No description of the stereochemistry of the cycloadducts 112 and 113 has been reported. The structure of the heterocycles 112 and 113 was identified by spectroscopic data and some reactions such as hydrolysis and hydrogenolysis[43]..

An interesting reaction has been reported[44] about the dioxide 17a and the monooxide 51b with dimethyl acetylene dicarboxylate (DMAD). The product obtained from these reactions was nitrogen-free, derived from two or one equivalents of the ester and one equivalent of the dioxide or monooxide respectively. Dinitrogen monooxide was evolved during the reaction. Structure 114 was proposed for the adduct. Proof of the structure of these derivatives was based upon spectroscopic studies and a variety of oxidation and reduction products.



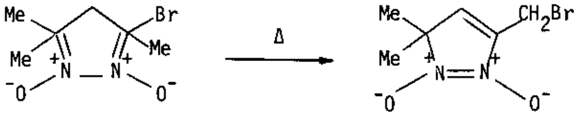
A possible route from the pyrazole 1,2-dioxide 17a to compound 114 is delineated below. The formation of adducts analogous to 115 has been postulated in other nitrone-acetylene cycloadditions. The rearrangement of 115 to 117 might be anticipated on the basis of the reported instability of the 4-isoxazoline nucleus[43]. Compounds similar to 118 have been postulated as responsible for the colour produced upon heating epoxycyclopentadienones[43]. In one case, such a compound was trapped by DMAD to give a derivative analogous to 114. As this mechanism would suggest, compound 114 was also obtained from the reaction of the mono-N-oxide 51b with DMAD.



17a 115 116 117 118 114

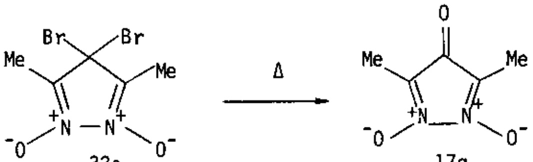
5.1.8. Thermal and Photochemical Rearrangements

Boiling of 111 in benzene gave[20] 9 % of a bromomethyl derivative, which was dehydrogenated to give 119 in 80 % yield[20].



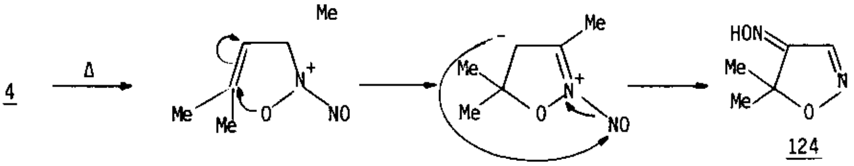
111 119

32a on heating gave 17g in 52 % yield



32a 17g

Thermal rearrangement of 4 proceeded readily in boiling acetonitrile to 120[5].



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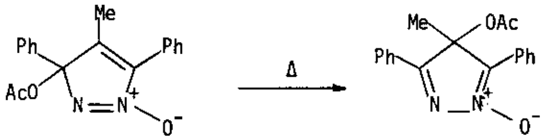
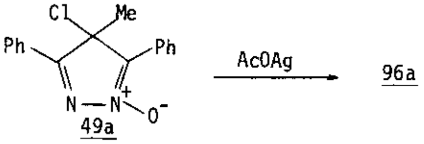
Upon heating in aqueous dioxane 48b rearranges[26] to acetate 96a.



48b 96a

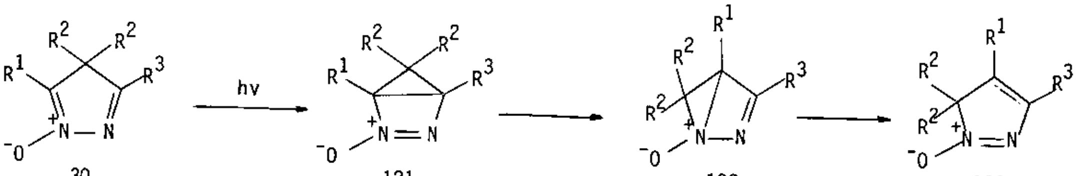
However, it was found that 49a reacts readily with silver acetate to 96a. This reaction appears to proceed without rearrangement as it is likely that a carbonium ion intermediate is involved[26].



49a

96a

Irradiation of 30 affords[44] the pyrazolenine N-oxides 123. Bicyclic intermediates 121 and 122 are believed to be implicated in this reaction[45]. The final step is similar to that reported from studies of the valence bond isomerization of pyrazolenines[46].

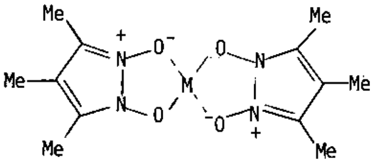


30 121 122 123

5.1.9. Complex Formation

Freeman and Gannon, in 1969, reported[6] that addition of an aqueous solution of the sodium salt of 7 to aqueous solutions of a variety of metal ions Cu(II), Co(II), Ni(II), Cd(II) resulted in the precipitation of highly coloured, flocculent precipitates, which are highly insoluble in all solvents. Elemental analyses indicated 2:1 complexes.

The chelate character of these materials was inferred from their colours and the appearance of metal-ligand streching frequencies in the far infrared region at 500-550 cm^{-1}, a typical region for metal-oxygen bonds[6]. The structure of these chelates presumably resembles those of β-diketones.



Later in 1977, West and his co-workers[47-49] reported several papers about transition metal ion complexes of the conjugate base of 7b, 22a and 22b as well as some lanthanide complexes of 22a.

Of interest in the transition metal ion complexes of 22a was the inability of the trivalent metal ions i.e. Cr(III) and Fe(III) to form the tris complexes with all ligands bound in a bidentate manner.

Furthermore, the Cr(III) complex yielded electrolytic solutions in solvents such as acetonitrile and dimethylformamide. It was suggested that there was evidently a steric factor, which did not allow all the three ligands to be bound in a bidentate fashion[47].

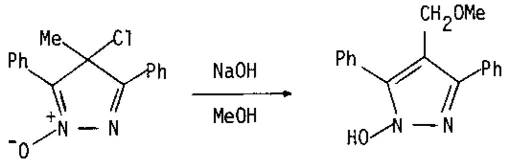
The existence of aquo ligands in the coordination spheres of some of the metal ions of the transition metal ion complexes of 7b was established[48] by thermogravimetric experiments. Spectral information indicated that Cr(III) and Fe(III) have only two of the di-N-oxide ligands bound in a bidentate manner. The Co(III) and Ni(II) complexes appear to be five-coordinate with two bidentate di-N-oxides[49].

All the transition metal ion complexes of the conjugate bases 22b are non-electrolytes and the ligand based on the ir results acts as a bidentate in all compounds[49]. The Cr(III), Co(II) and Ni(II) compounds show approximately octahedral symmetry and ligand field parameters have been calculated from the electronic spectra. The Fe(III) solid possesses a strong ligand-to-metal charge transfer band at 20.20 kK and epr studies show the Cu(II) complex to be dimeric[49].

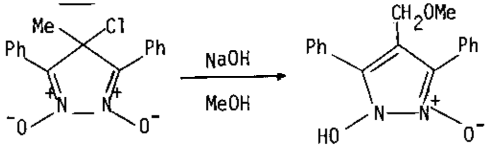
5.2. Reactions of the Substituents

3,5-Diphenyl-4-methylchloropyrazole 1-oxide 49a and its 1,2-dioxide 93a react with methanolic sodium hydroxide to produce 47f and 7d respectively in yields 80-95 %[50].

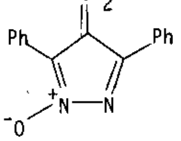
It seems likely that these reactions proceed by an elimination-addition mechanism with the pyrazole 1-oxide 124 and 1,2-dioxide 125 as intermediates.



49a 47f



93a 7d



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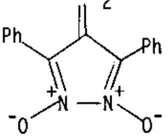
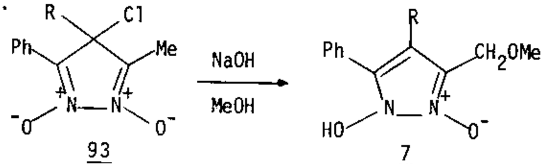


125

In a somewhat more unusual reaction, treatment of chlorides 93b and 93c in the same manner led to side-chain substitution in the 3-methyl group yielding compounds 7e and 7f respectively. This result suggests an enhanced acidity of these methyl groups leading to the formation of teh 3-methylene derivatives 126 in these two examples and it is apparent that other destructive base-catalyzed reactions operate concurrently[50].

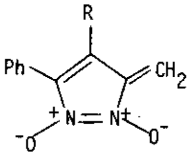


93

b: R=CH_2Ph; c: R=Ph

7

e, f



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REFERENCES

1. A.R.Katritzky and J.M.Lagowski, "Chemistry of the Heterocyclic N-Oxides" ed. by A.T.Blomquist, Acad. Press, London, 1971.
2. C.Harries and R.Gley, *Ber.*, 1899, 32, 1330.
3. R.Scholl, *Ann.*, 1906, 345, 363.
4. R.Fusco and G.Trisoglio, *Attiacad. Italia, Rend. classe sci. fis. mat. nat.*, 1941, **7**, 618.
5. J.P.Freeman *J.Org. Chem.*, 1962, **27**, 1309.
6. J.P.Freeman and J.J.Gannon, *J. Org. Chem.*, 1969, **34**, 194.
7. J.P.Freeman and J.J.Gannon, *J. Heterocycl. Chem.*, 1966, **3**, 544.
8. J.P.Freeman, *J. Org. Chem.*, 1962, **27**, 2881.
9. J.P.Freeman, J.J.Gannon, and D.L.Surbey, *J. Org. Chem.*, 1969, **34**, 187.
10. J.P.Freeman and D.L.Surbey, *Tet. Lett.*, 1967, 4917.
11. H.Wieland, *Ann.*, 1921, **424**, 112.
12. B.Unterhalt, *Arch. Pharm.*, 1967, **300**, 822.
13. B.Unterhalt, *Tet. Lett.*, 1968, 1841.
14. H.Gnichtel and H.J.Schönherr, *Chem. Ber.*, 1966, **99**, 618.

15.B.Unterhalt and U.Pindur, Arch. Pharm., 1985, 318, 956.

16.J.P.Freeman and J.F.Hansen, J. Chem. Soc. Chem. Comm., 1972, 961.

17.P.Henry and H. von Pechmann, Ber., 1893, 26, 997.

18.B.Unterhalt and U.Pindur, Arch. Pharm., 1976, 309, 781.

19.H.Gnichtel and U.Boehringer, Chem. Ber., 1980, 113, 1507.

20.L.B.Volodorski and L.A.Tikhonova, Khim. Geterotsikl. Soedin, 1977, 248 ; Chem. Abstr., 1977, 87, 23135h.

21.S.Spyroudis and A.Varvoglis, Chim. Chron. New Series, 1982, 11, 173.

22.A.Kotali and V.P.Papageorgiou, J. Chem. Soc. Perkin Trans 1, 1985, 2083.

23.J.Stephanidou-Stephanatou, J. Heterocycl. Chem., 1985, 22, 293.

24.A.Kotali, V.P.Papageorgiou,and P.G.Tsoungas, Chim. Chron. New Series, in press.

25.J.F.Hansen, Y.I.Kim, L.J.Griswold, G.W.Hoelle, D.L.Taylor,and D.E.Vietti, J. Org. Chem., 1980, 45, 76.

26.J.P.Freeman and E.Janiga, J. Org. Chem., 1974, 39, 2663.

27.A.R.Katritzky and C.W.Rees, "Comprehensive Heterocyclic Chemistry", Vol. 5, ed. K.T.Potts, Pergamon Press, p. 234.

28.K.Schofield, M.R.Grimmett,and B.T.R.Keene, "Heteroaromatic Nitrogen Compounds : The Azoles", Cambridge University Press, Cambridge, 1976.

29.I.J.Ferguson, K.Schofield, J.W.Barnett, and M.R.Grimmett, J. Chem. Soc. Perkin Trans 1, 1977, 672.

30.A.J.Boulton, Bull. Soc. Chim. Belg., 1981, 90, 645.

31.L.C.Behr, R.Fusco, and C.H.Jarboe, Chem. Heterocycl. Comp., 1967, 22, 1.

32.P.G.Tsoungas and B.F.De Costa, Magn. Reson. Chem., 1988, 26, 8.

33.J.F.Hansen and M.J.O'Hare, J. Heterocycl. Chem., 1976, 13, 985.

34.A.Kotali, V.P.Papageorgiou, and P.G.Tsoungas, Org. Mass Spectrom., 1986, 21, 435.

35.H.E.Ungnade and E.D.Longhram, J. Heterocycl. Chem., 1964, 1, 61.

36.C.Tsiamis and P.G.Tsoungas, J. Heterocycl. Chem., 1985, 22, 687.

37.G.R.Stevenson, J.F.Hansen, G.Clark, and J.P.Freeman, J. Org. Chem., 1979, 44, 3211.

38.D.Petridis, T.Lockwood, M.O'Rourke, D.V.Naik, F.P.Mullins, and C.Curran, Inorg. Chim. Acta, 1979, 33, 107.

39.E.C.Bozzi and L.B.Clapp, J. Heterocycl. Chem., 1978, 15, 1525.

40.J.L.Pinkus, G.G.Woodyard, and T.Cohen, J. Org. Chem., 1965, 30, 1104; R.A.Y.Jones and N.Sadighi, J. Chem. Soc. Perkin Trans 1, 1976, 2259.

41.J.P.Freeman, E.R.Janiga, and J.F.Lorenc, J. Org. Chem., 1977, 42, 3721.

42.J.F.Hansen, Y.I.Kim, and K.A.Merrigan, J. Org. Chem., 1979, 44, 4438.

43.J.P.Freeman and M.L.Hoare, J. Org. Chem., 1971, **36**, 19.

44.W.R.Dolzier, J. Chem. Soc. Chem. Comm., 1970, 289.

45.R.Paredes and W.R.Dolbier, Rev. Latinoamer. Quim., 1975, **6**, 29.

46.Reference 29, p. 252.

47.J.F.Hansen, S.P.McCormick, and D.X.West, J. Inorg. Nucl. Chem., 1977, **39**, 2083; ibid, 1977, **39**, 2086.

48.D.X.West and M.A.Vanek, J. Inorg. Nucl. Chem., 1978, **40**, 1027.

49.D.X.West and A.D.Johnson, J. Inorg. Nucl. Chem., 1979, **41**, 1101.

50.J.P.Freeman and J.F.Lorenc, J. Org. Chem., 1977, **42**, 178.

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