RECENT DEVELOPMENTS IN THE SYNTHESIS OF PYRAZOLE DERIVATIVES

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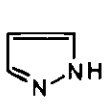
Abstract - The recently reported approaches for synthesis of pyrazoles are surveyed. Reactions of theoretical or practical importance are discussed in some detail.

INTRODUCTION

One of the most striking facts in organic chemistry is the excessive interest in pyrazole (1) derivatives as revealed from the enormous literature covering their chemistry. Although only very few naturally occurring pyrazole derivatives have been, till now, isolated, there is of course theoretical and practical reasons for the enormous interest in the chemistry of these heterocyclic derivatives. The early discovery of the analgesie and antipyratic properties of antipyrine (2), phenylbutanolidinone (3), the considerable biological activity of fused pyrazoles[1-22] and the excellent dying properties of pyrazolyl azo derivatives, e.g. tartazine (4)[23-31] have undoubtedly prompted interest in development of new procedures for the synthesis of pyrazoles and also synthesis of new pyrazole derivatives which might have better properties than these already marketed. The chemistry of pyrazole has been reviewed several times. The latest book of 1967[1] is now absolute. Although comprehensive heterocyclic chemistry recently published contained several chapters dealing with pyrazole chemistry, no trials were made to review efficiently all the recent syntheses of pyrazoles, many of which are of theoretical or practical importance. In the present chapter we report a comprehensive survey of recent synthetic approaches and routes to pyrazole derivatives. Emphasis will be placed on procedures that enabled synthesis of pyrazole derivatives that are difficulty accessible. It should be pointed out here, however,

that no trial to make encyclopedic scan of the subject was made.



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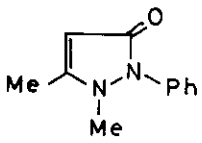

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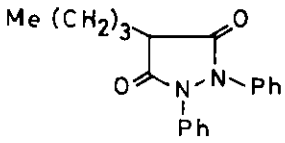

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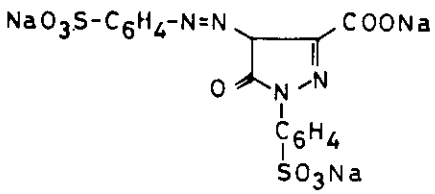

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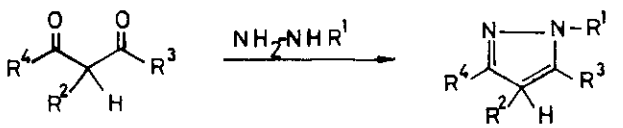
METHODS OF PREPARATION

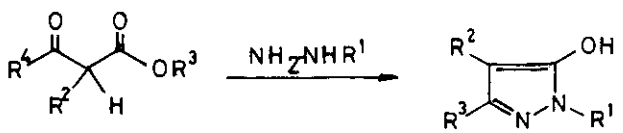
1. Synthesis via 3+2 condensation

(i) Reaction of hydrazines with β-bifunctional reagents:

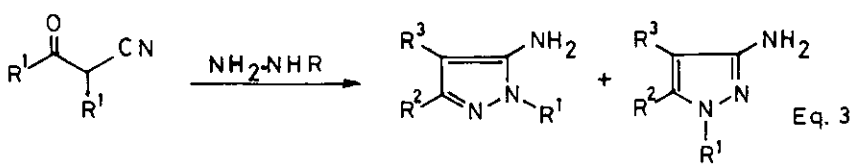
The most general approach for synthesis of pyrazoles is the condensation of a 3 carbon unit reagent with hydrazines, β-diketones, β-ketoesters and β-ketonitriles have since long been utilised as starting reagents for synthesis of pyrazoles[32-82] (cf. eq. 1-3).



Eq. 1

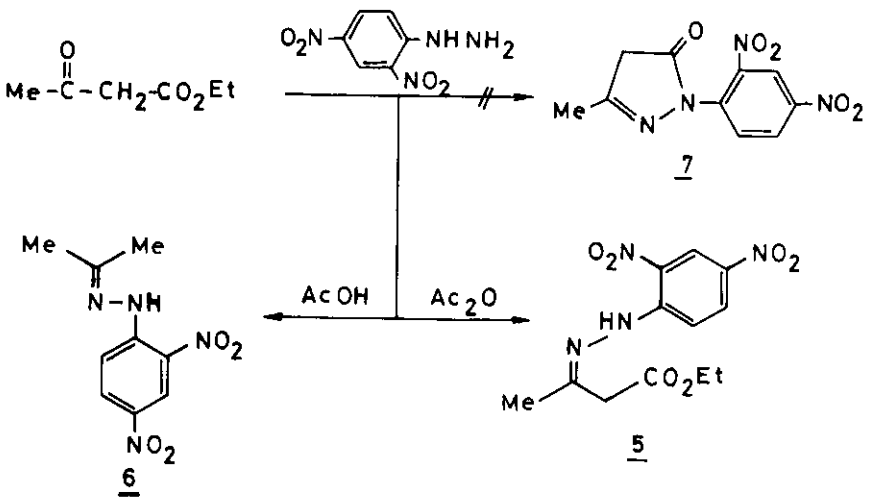


Eq. 2

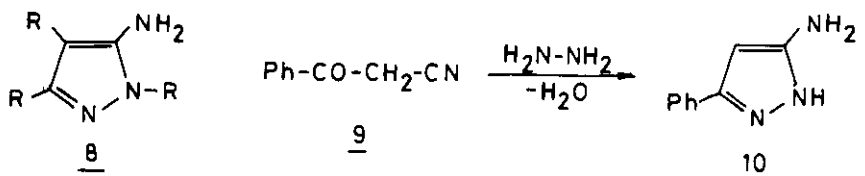


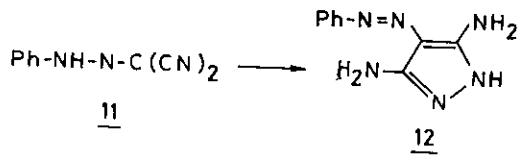
Eq. 3

The reactions reported above are not always simple and straightforward as they have always been treated. It is sufficient to report that in each case more than one isomeric pyrazole derivative is expected to be formed however in most cases only one isomer proved to be the reaction product. In some other cases the reactions failed to afford any pyrazole derivatives. For example, whereas β-keto-esters has been reported to afford 2-pyrazolin-5-ones on treatment with hydrazines, the reaction of 2,4-dinitrophenylhydrazine with ethyl acetoacetate has afforded only either the hydrazone (5) or (6) depending on reaction condition. Claimed formation of the pyrazole (7) from this reaction proved to be incorrect[83].



5-Aminopyrazoles (8) have been extensively synthesised via the reaction of hydrazines with β-functional nitriles[84-118]. A variety of β-functional nitriles have been utilised for the synthesis of 8. The reaction conditions utilised depend on the nature of the reacting nitrile and the utilised hydrazine. For example, whereas hydrazine hydrate reacts with benzoylacetonitrile (9) in refluxing ethanol to yield 5-amino-3-phenylpyrazole (10), it reacts with the arylhydrazone 11 at room temperature to give 3,5-diamino-4-arylazopyrazole (12)[106]. 1-Phenyl-4-phenylazo-3,5-diaminopyrazoles were formed on heating 11 with phenylhydrazine[113].





2-Substituted β-oxo, β-aldehyde and β-iminonitriles, also afforded 5-aminopyrazoles on reaction with hydrazine hydrate. It should be reported, here, that the exact experimental conditions described for the synthesis of these compounds should be strictly followed. The obtained products are always contaminated with pyrazolo[1,5-a]pyrimidine derivatives, resulting either from further reaction of the formed aminopyrazole with the β-functional nitrile or from formation of azines prior to cyclization into the aminopyrazole. The pyrazolo[1,5-a]pyrimidines become the major reaction products on slight change in the reaction conditions and also in case of the reaction of hydrazine with certain reagents. Specific examples are shown in Chart 1.

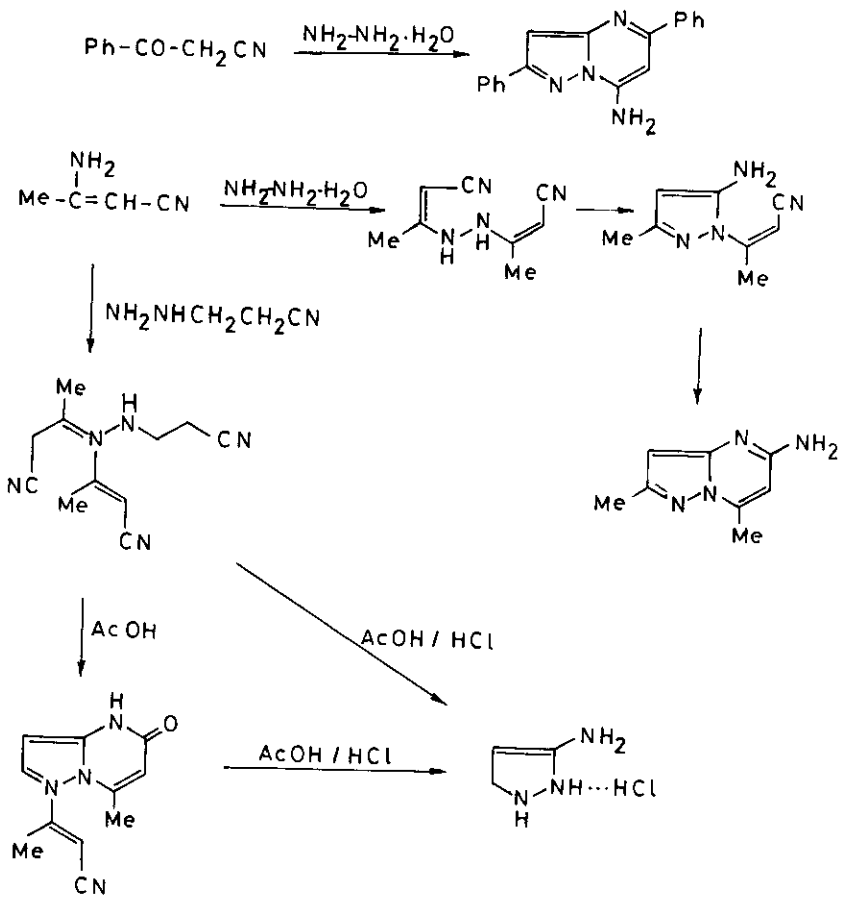
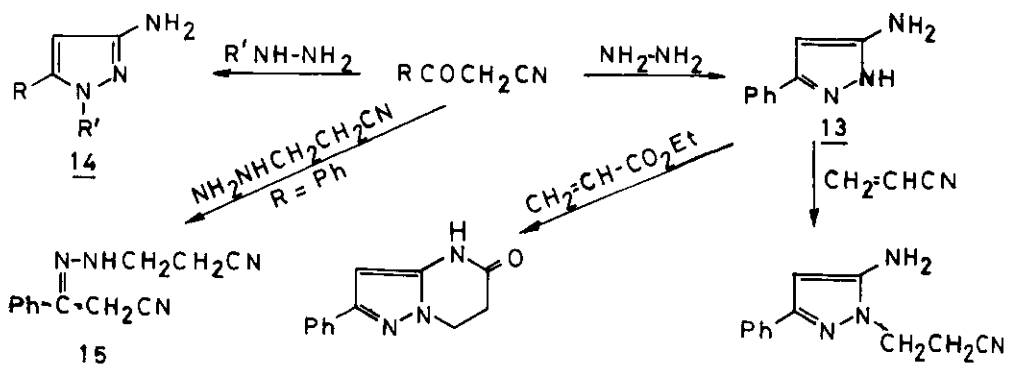
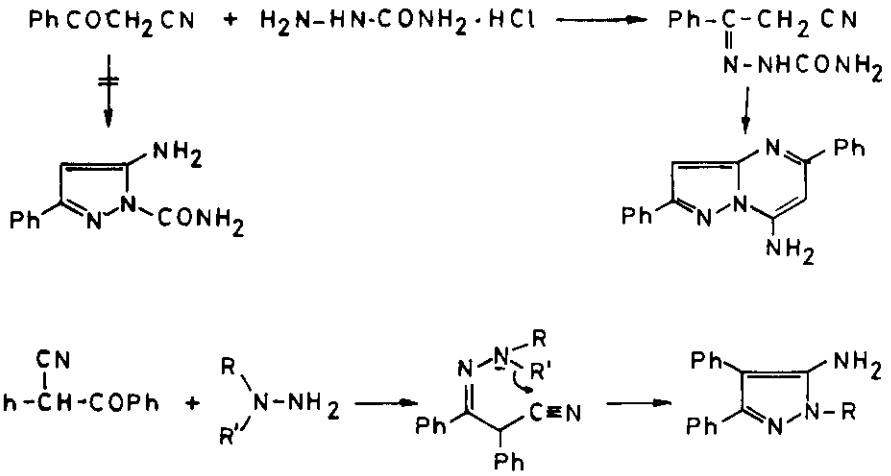


Chart (1)

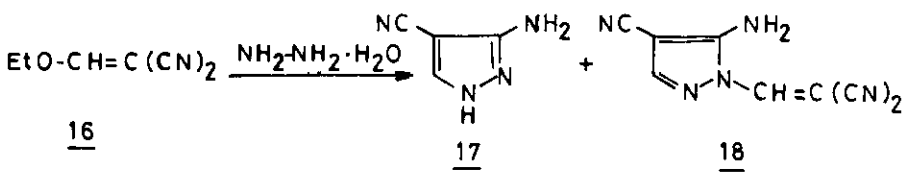
The reaction of substituted hydrazines with β-functional nitriles has been shown to afford 5-aminopyrazole, 3-amino-1-substituted pyrazoles (13) or isomeric (14). Generally aryl-substituted hydrazines afford derivatives of 13 whereas alkyl-substituted hydrazines afford the isomeric 14 on reaction with β-ketonitriles. Several intermediate hydrazones could be isolated in these reactions (see for example 15 in equations below) and could be readily cyclised into the final products. The statement reported above is an over simplification of the problem[118b]. Mixtures of derivatives of 13 and 14 could, in many cases, be separated. Also predominance of 14 in the reaction of alkyl hydrazines has been observed. For example, Elnagdi et al.[107] and Elguero et al.[110] both reported the isolation of 1-substituted alkylpyrazoles as major products in the reactions of benzoylacetonitrile with cyanoethylhydrazine and with β-hydroxyethylhydrazine. Elnagdi et al.[107] have recognised that a delicate balance exists between steric and relative reactivity of the hydrazine in reactions of β-functional nitriles with alkylhydrazines. Thus, whereas the substituted hydrazine moiety might be considered as the most active nucleophilic center and attack by this moiety at the carbonyl group should be expected, it is also the most hindered one. In some reactions steric factors play a major rule and 1-substituted 5-aminopyrazoles are isolated. Malononitrile has been reported, in old literature, to afford 3,5-diaminopyrazole[111] on the reaction with hydrazine hydrate. However, later work has established that the product which was actually formed is 3-amino-4-cyano-5-cyanomethylpyrazole. The formation of this product is assumed to proceed via the reaction of hydrazine with dimerized malononitrile which is formed via dimerisation of malononitrile in the presence of hydrazine[112].





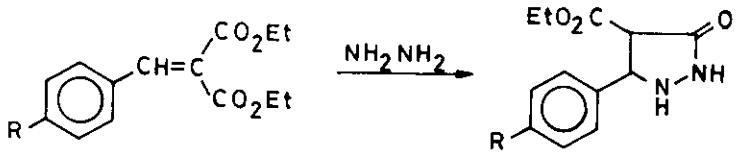
(ii) Reactions of hydrazines with α,β-unsaturated nitriles

An efficient route for the synthesis of 5-aminopyrazoles is the reaction of hydrazines with α,β-unsaturated nitriles. For example, 4-cyano-3-aminopyrazole (17) has been obtained, always contaminated with the 5-aminopyrazole derivative 18, by the reaction of hydrazine with ethoxymethylenemalononitrile (16). Reactions of this type have been recently reviewed and will not be discussed here any further[105].



Propynenitrile derivatives and allenic nitriles have recently been reported to afford aminopyrazoles on reaction with hydrazines[116,117].

The reaction of activated double bond systems with hydrazines has been also utilised as a general route for synthesis of pyrazoles. Old examples of this approach have been reviewed earlier, of interest among these synthesis is the reaction of arylidene diethyl malonate with hydrazines[119]. Although this reaction has been reported previously to afford malonohydrazine and the appropriate aldehyde azine[120], Callaghan[119] was able to obtain from the reaction of 19 with hydrazine at room temperature ethyl 5-aryl-3-oxopyrazoldine-4-carboxylate (20). However, the author has shown that the usefulness of this synthesis is limited by the occurrence of other reactions.



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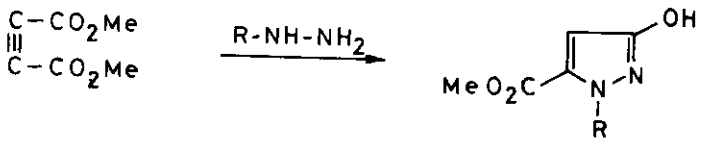
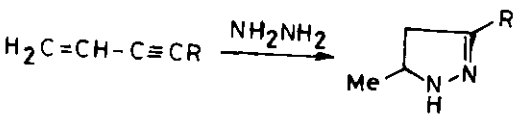
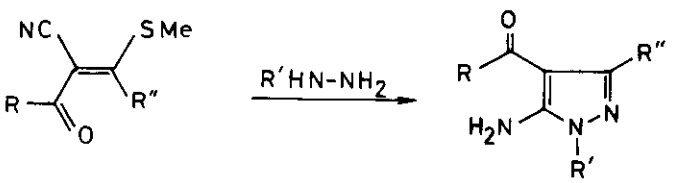
The reaction of hydrazines with dimethyl acetylenedicarboxylate has been reported to yield pyrazoles[121,122-125],

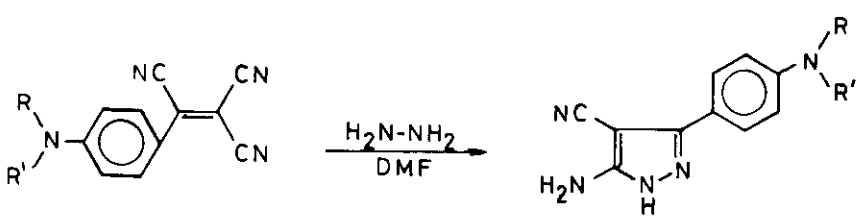


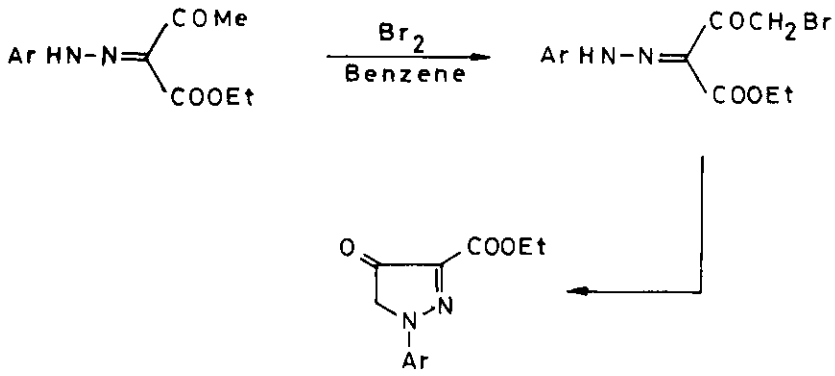
The reaction of hydrazines with diynes has been recently reported to yield pyrazole derivatives[126-129]. Similarly, hydrazidic halides reacted with allenes to yield pyrazoles[120].

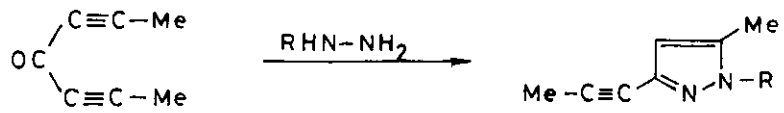


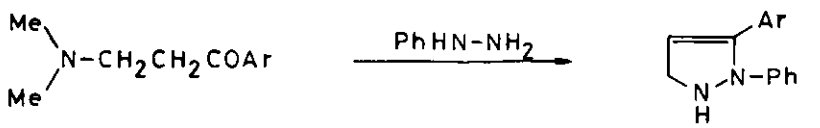
A variety of new pyrazole derivatives have been synthesised utilising the same idea of reacting β-functional reagents with hydrazines or acylated hydrazines. Examples for the most interesting of these syntheses are shown below[130-229].

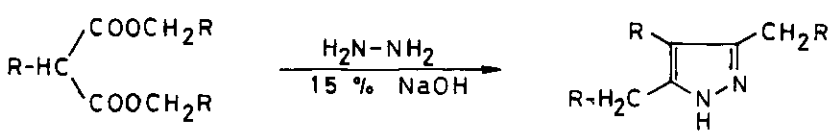


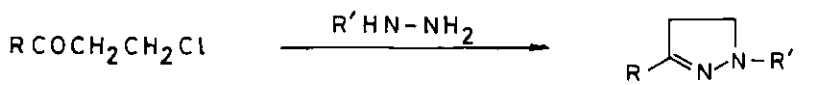




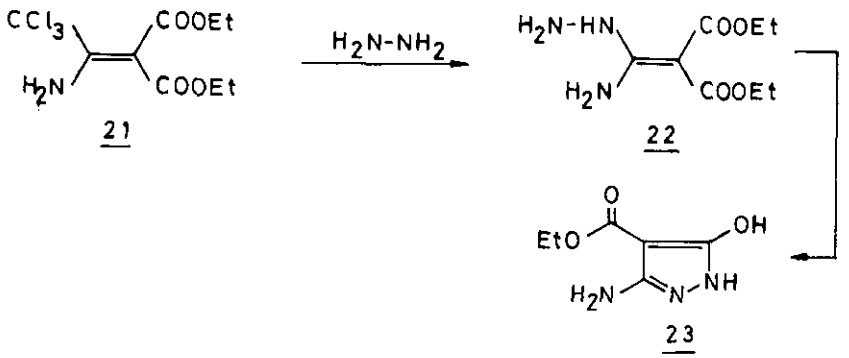


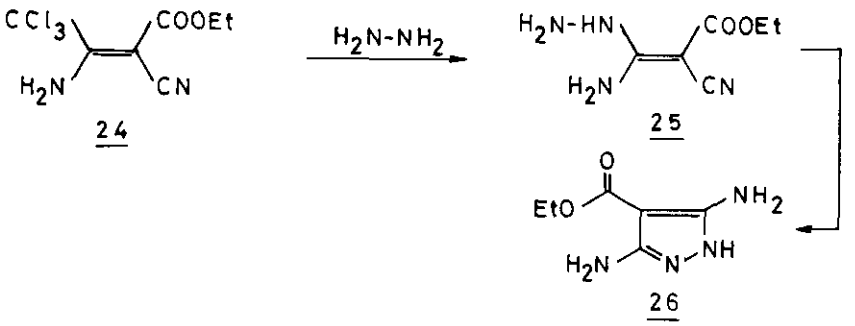


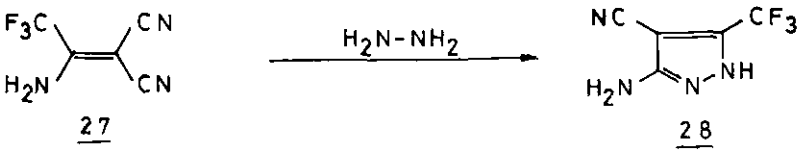




It has been shown that diethyl β-trichloromethyl-β-aminomethylenemalonate (21) and ethyl β-trichloromethyl-β-aminomethylenecyanoacetate (24) react with hydrazines to yield the aminopyrazole derivatives (23) and (26) via intermediate formation of the amidrazones (22) and (26) which could be isolated[230-234]. This is in contrast to the reported formation of 3-amino-4-cyano-5-trifluoromethylpyrazole (28) on treatment of β-trifluoromethyl-β-aminomethylenemalononitrile (27) with hydrazines[234].



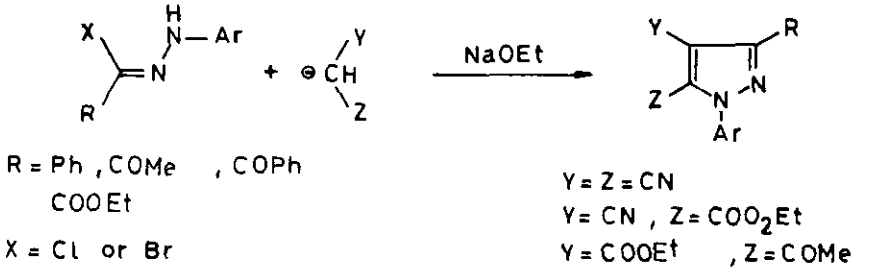


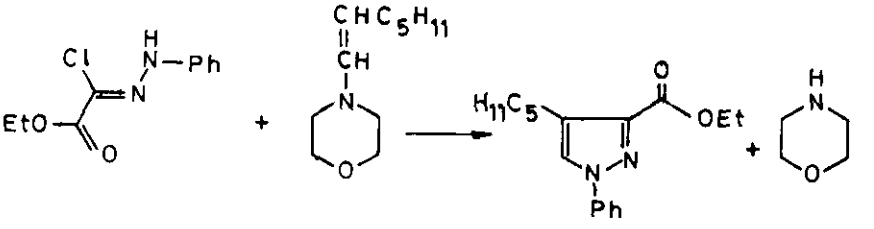


Synthesis from hydrazine derivatives:

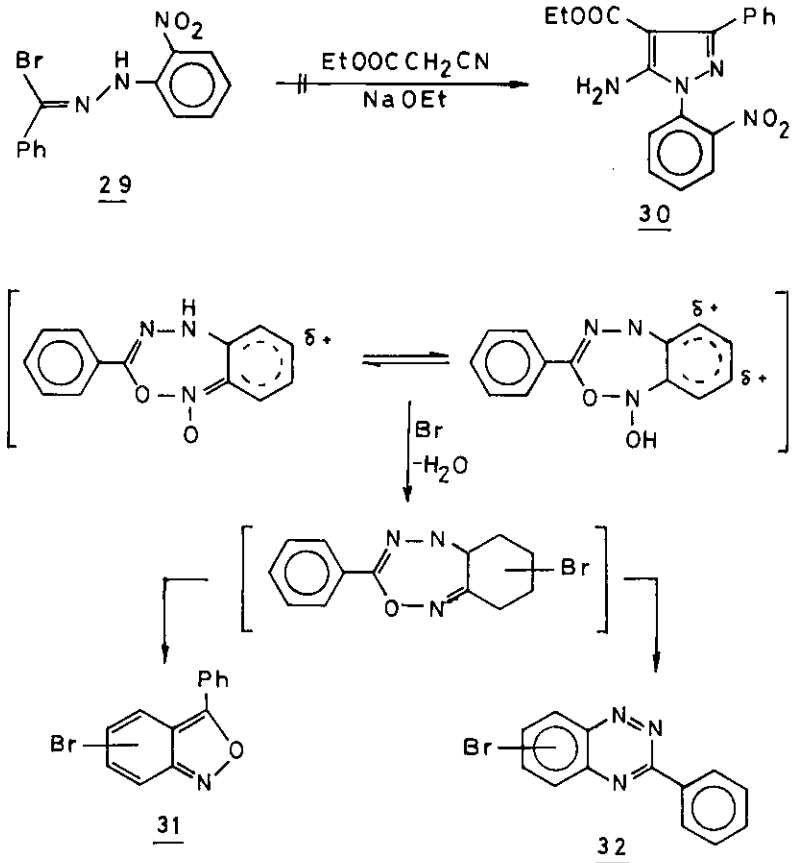
a) Hydrazonyl halides

The reaction of hydrazidic halides with active methylene reagents has been reported long ago to yield pyrazole derivatives. Similarly hydrazidic halides reacted with enamines, organomagnesium compounds and acetylenic compounds to yield pyrazoles[1]. These reactions have been rereported by Shawali et al.[235-241], it seems that the authors were not aware of old literature, however, they could add some new pyrazole derivatives. In contrast to reported formation of aminopyrazoles via this route.

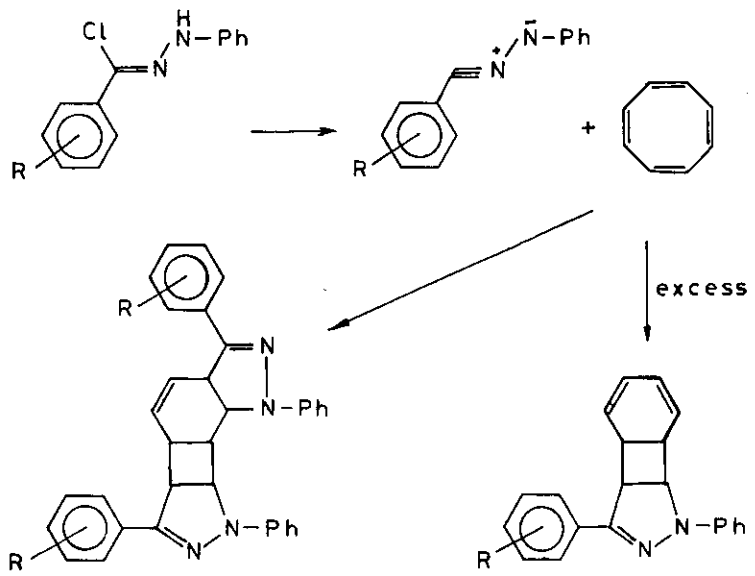




Beets and coworkers[242] were not able to isolate the expected pyrazole 30 on reacting 29 with ethyl cyanoacetate. A mixture of 6-bromo-3-phenyl-1,2,4-benzotriazine (32) and 5-bromo-2-phenylbenzoxazole (31) was instead obtained. A mechanism for the reaction is given below. In the light of these findings it seems quite odd that Shawali and coworkers[236-238] isolated aminopyrazoles from the reaction of ethyl cyanoacetate with the hydrazonyl chloride derivative.

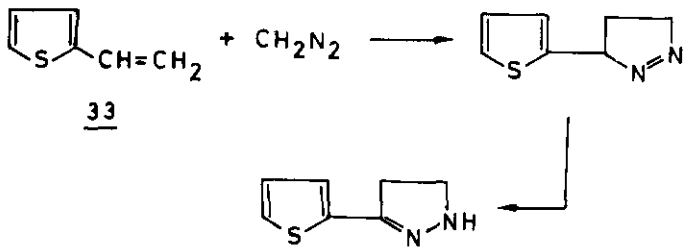


Nitrile imines, generated from hydrazonylhalides have been reported to add to cycloctatetraene to yield pyrazole derivatives. The nature of the product was shown to depend on molar ratio[243].



b) Diazo compounds:

The reaction of diazo compounds with olefins and acetylenes is a well established route for synthesis of pyrazole derivatives[1]. This route has been utilised extensively in recent literature for the synthesis of pyrazoles[244-270]. Thus, 2-vinylthiophene (33) reacted with diazomethane at -10°C to yield the pyrazole (34)[270].



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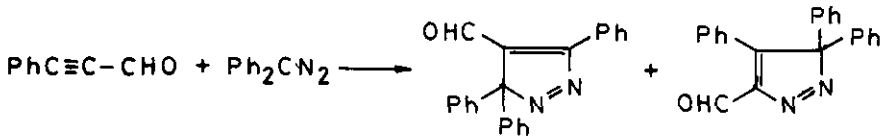
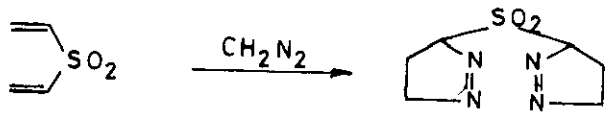
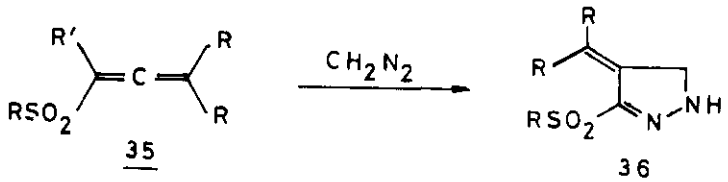
A variety of multiple bond systems has been employed in the same way, examples are presented below[245,249].





The reaction of allenes with diazomethane has been reported to yield pyrazole derivatives. For example compound 35 reacted with diazomethane to yield the pyrazole derivative 36[250].



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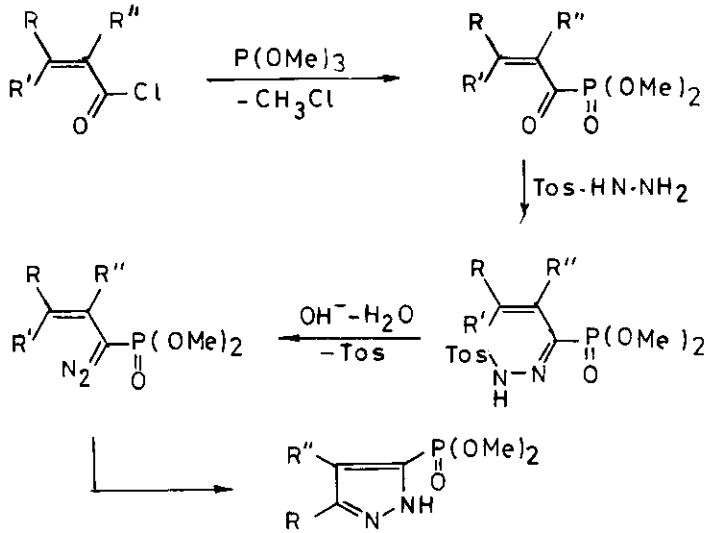
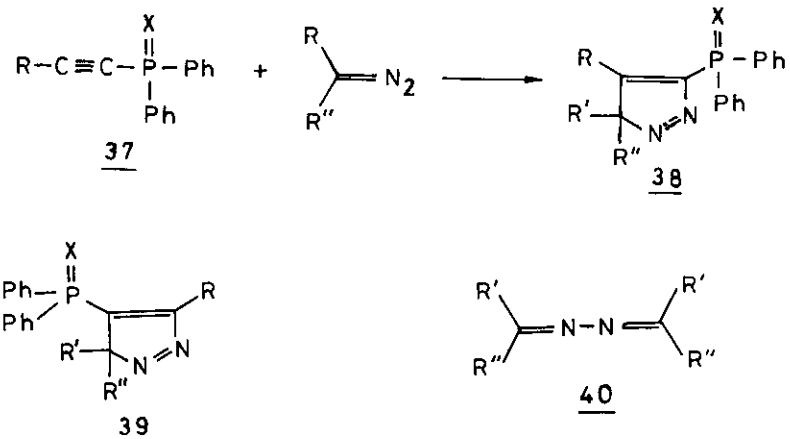
36

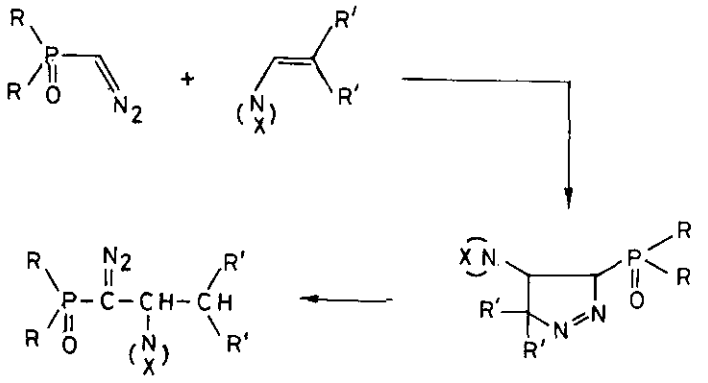
In the course of their investigations on the chemistry of diazoketones and phosphorylated diazo compounds Regitz and his group[254-262] have developed several interesting routes for the synthesis of phosphorylated pyrazoles. Thus, phosphoryl-vinyl-diazomethane having an aliphatic substituent on the double bond moiety, prepared via the route illustrated below[262], cyclised easily on standing into the corresponding pyrazole derivatives[259].



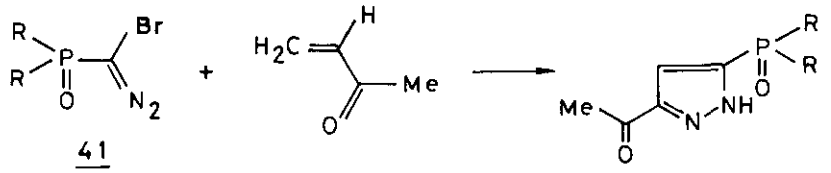
Alkynyl diphenylphosphenoxide (37; X=O) and sulphide (37; X=S) reacted with diazo compounds in ether/chloroform solution to yield the phosphorylated pyrazole 38[260]. The isomeric 39 and the azine 40 could be isolated in some cases.



In a similar way enamines reacted with phosphorylated diazo compounds to yield unstable pyrazole derivative which undergoes ready ring opening to yield α-diazo-β-aminophosphoryl derivatives[263].



The diazo compound 41 reacted with methyl vinyl ketone to yield the corresponding pyrazole 42[258].



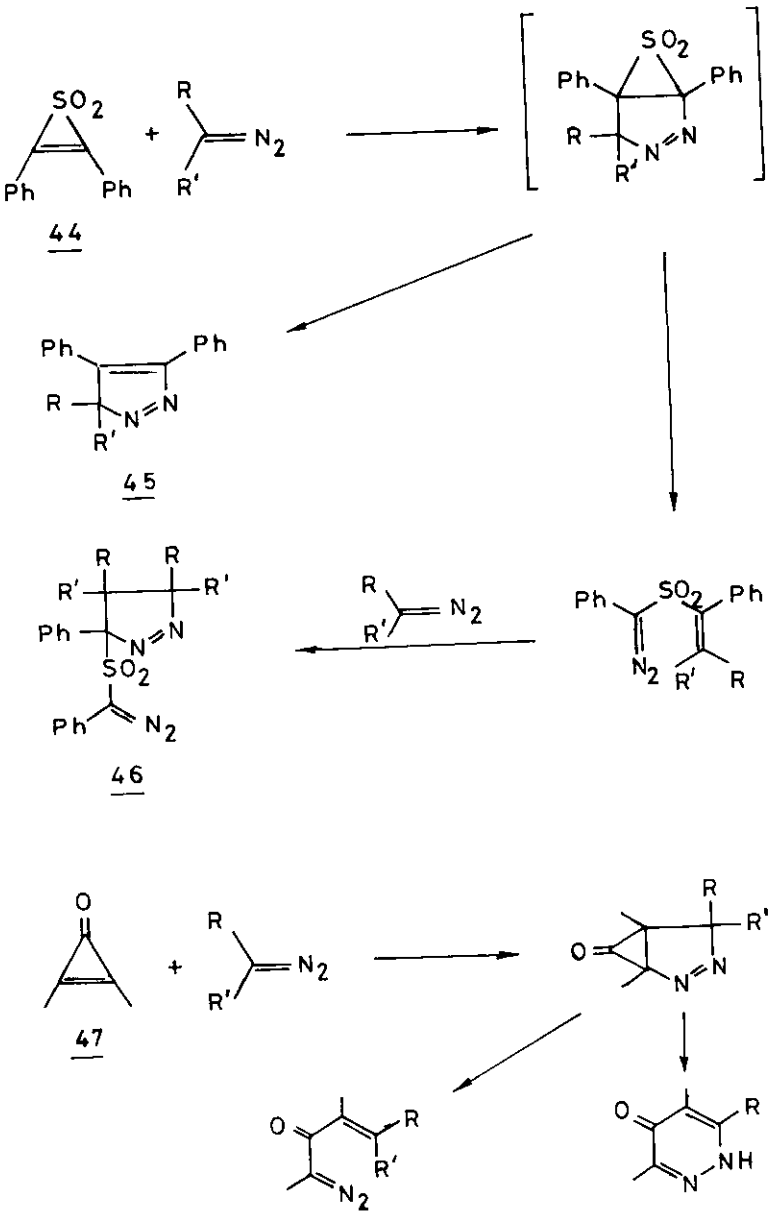
41 42

The reaction of yneamine with diethyl diazomalonate has been recently reported to yield the aminopyrazole 43[254].

43

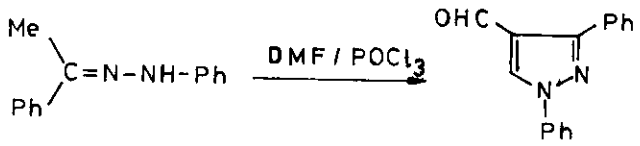
2,3-Diphenylthiaren-1,1-dioxide (44) reacted with diazomethane to yield α-diazo-benzylsulphonylpyrazoline (46) in 95% yield[255]. The reaction is assumed to proceed via addition of two molecules of the diazomethane to (44) as demonstrated in the next chart. This is in contrast to the reported formation of pyrazines on

treatment of the carbon analog of 44 (47) with diazomethane[254,265,266]. In contrast to the behaviour of 44 with diazomethane it reacted with 1-diazo-2-methoxyethane and with 2-diazopropane to yield compound 45 in addition to 46.

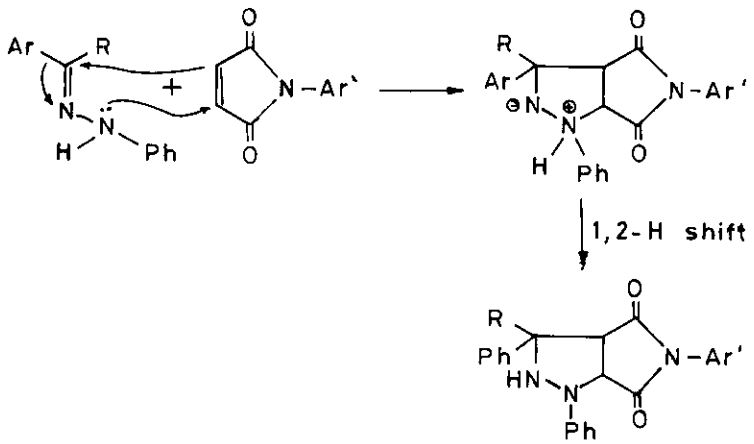


c) From hydrazones

Vilsmeier reaction with acetophenone phenylhydrazone has afforded pyrazole in good yields[270a].

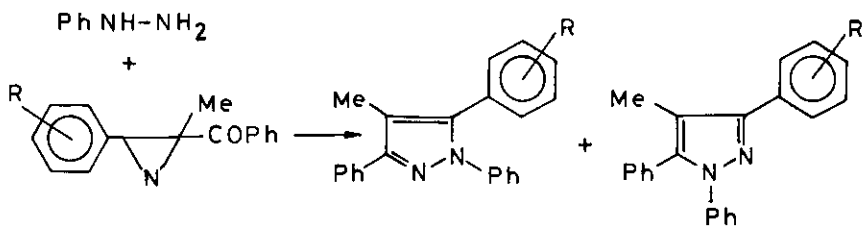


Fused pyrazoles have recently been prepared from reaction of aldehyde hydrazones with maleimides[270b].

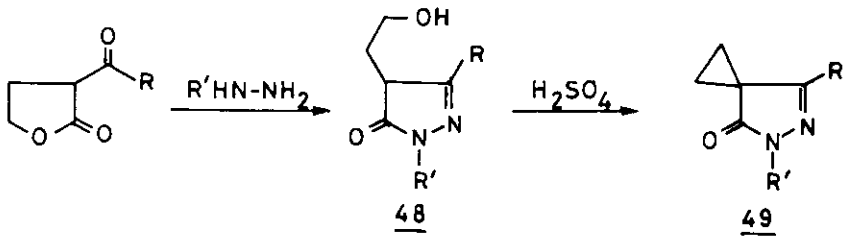


2. Synthesis via rearrangement of other heterocyclic compounds:

Several heterocyclic systems have been reported to rearrange into pyrazole derivatives. This type of molecular rearrangements have been previously reviewed in "Ring transformations of heterocycles"[267]. Consequently only recent reports in this area will be reviewed here. 2-Benzoyl-2-methyl-3-arylaziridine has been reported to afford a mixture of two isomeric pyrazoles on reaction with phenylhydrazine[267].

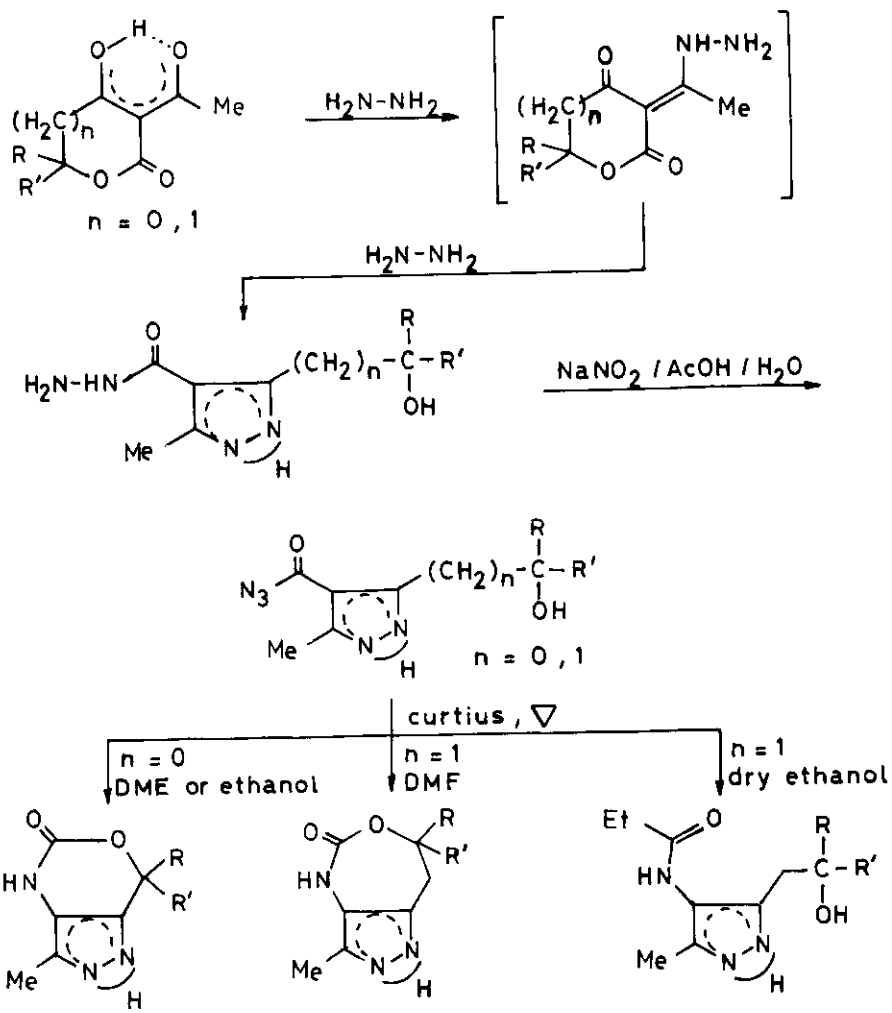


Treatment of α-acyl-γ-lactones with hydrazines affords good yields of the 4-(β-hydroxyethyl)-2-pyrazolin-5-one (48) which could be cyclised into the spiropyrazole derivative 49[268-269].

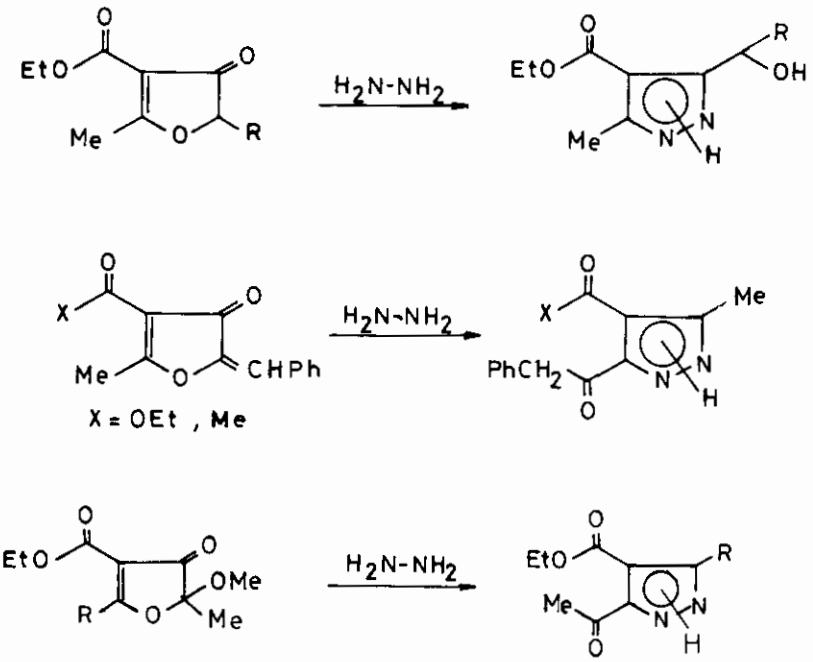


48 49

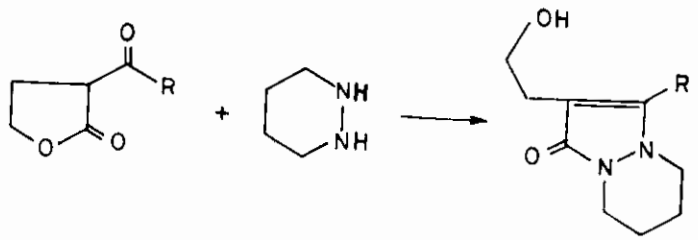
Very similar results have been recently reported by Chantegrel and Gelin[271] as summarised in equations below:



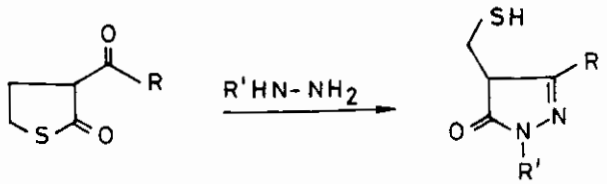
The rearrangement reaction of acylfuran derivatives into pyrazoles have been further investigated by the same french group and the most important achievements are summarized below[272-274].



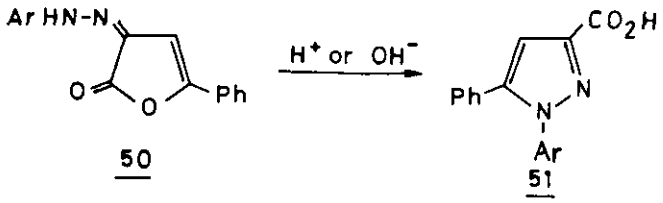
α-Acyl-γ-lactones have been reported to react with cyclic hydrazines to yield fused pyrazole derivatives[275,276].



α-Acyl-γ-thiolactones also rearranged into pyrazoles on similar treatment[277].

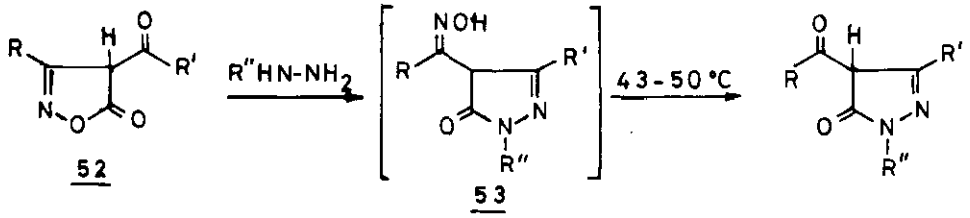


4-Arylhydrazono-2-phenyl-4,5-dihydrofuran-5-one (50) rearranged into 1-aryl-5-phenylpyrazole-3-carboxylate (51) on treatment with acid or alkali[278-279].



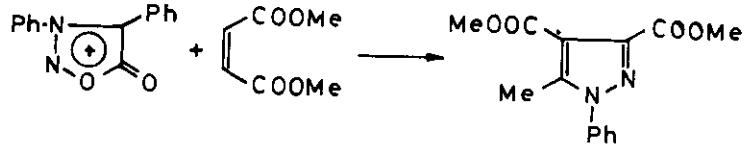
50 51

5-Oxo-1,2-oxazoles are known to rearrange into pyrazole derivatives on treatment with hydrazines[280]. Several reports have been published in this direction. Thus, Wamhoff, Schrann and Korte[281] have reported that 4-acyl-5-oxo-1,2-oxazolines (53) which eliminates the oxime moiety to yield the corresponding 4-acylpyrazolinones. This reaction makes possible the synthesis of acylated pyrazolones having a particular acyl group, the nature of the latter group is determined by that of substituent at the 3-position of the 1,2-oxazolin-5-one, whereas the substituent at the 3-position of the resulting pyrazole is dependent on the nature of the acyl group. At almost the same time, Harhash et al. have reported very similar results[282].



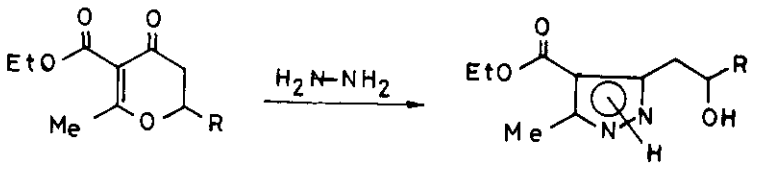
52 53

3,4-Diphenyl sydnone has been reported to afford pyrazoles on treatment with dimethyl acetylenedicarboxylate[283].

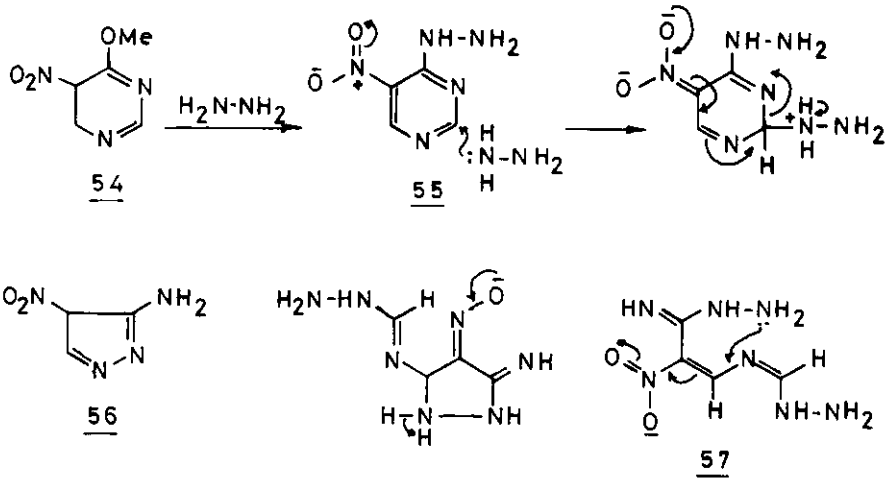


A variety of six-membered ring heterocyclic derivatives have been reported to yield pyrazoles on treatment with hydrazines, the rearrangements of coumarines and thiocoumarines into pyrazoles are well known[284].

Pyrones have been reported to react with hydrazines to yield pyrazoles[272].

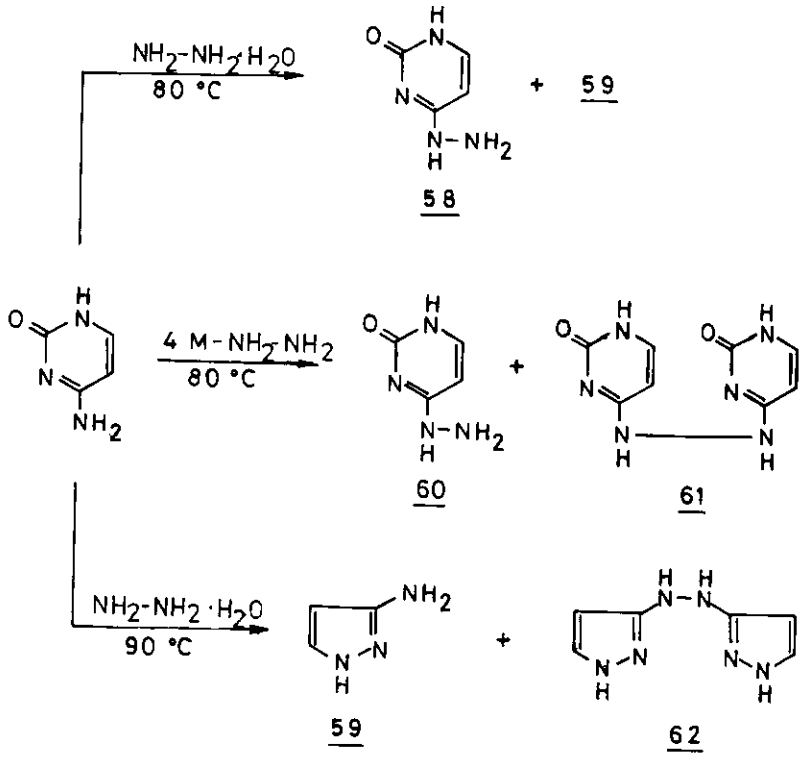


4-Methoxy-5-nitropyrimidine (54) interacted with ethanolic hydrazine hydrate below 0°C to give 4-hydrazino-5-nitropyrimidine (55) which was converted by an excess of hydrazine hydrate at 25°C into 3-amino-4-nitropyrazole (56). The author has acknowledged that this rearrangement reaction proceeds via nucleophilic attack by hydrazine on the 2-position of the hydrazinopyrimidine 58 with rupture of the 2,3-bond[285]. The resulting acyclic intermediate 57 is then thought to undergo intramolecular nucleophilic attack at the 6-position by the 4-hydrazine group with breaking of the 1,6-bond to give the aminopyrazole as shown below[285].



Another reaction in which pyrimidines have been converted into aminopyrazoles was reported by Hayes and Hayes-Baron[286]. These authors have shown that whereas uracil and thyamine and their related nucleotides and nucleosides are degraded quantitatively by treatment with hydrazine hydrate at 90°C to yield pyrazol-3-one and 5-methylpyrazolone together with, in the case of nucleosides and nucleotides, approximately quantitative yields of urea and sugar or sugar-phosphate hydrazone, sytosine and its derivative are degraded by hydrazine at 90°C to yield 3-amino-

pyrazole (59) and N,N´-di(3-pyrazolyl)-hydrazine (62). The above authors have also shown that the reaction of sytosine and derivatives with hydrazine hydrate at 80°C leads to the formation of (59) and 6-hydrazine-2,3-dihydropyrimidin-2-one (60). On the other hand, sytosine reacted with free hydrazine at 80°C to form a mixture of 60 and the bisdihydropyrimidine derivative (61) as shown in the next chart.



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