UTILITY OF HYDRAZINES AND HYDRAZINE DERIVATIVES IN HETEROCYCLIC SYNTHESIS

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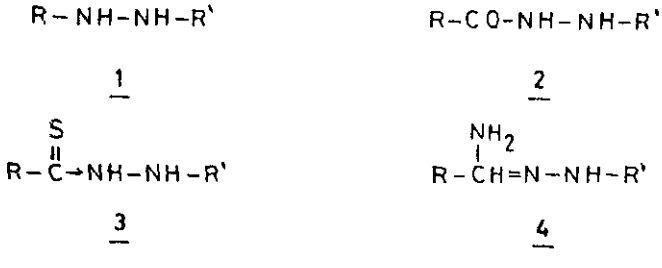
Abstract - Recent utilities of hydrazine and hydrazine derivatives in the synthesis of hydrazines and hydrzine derivatives for synthesis of heterocycles are surveyed. Several novel approaches for the synthesis of azoles, azines and azoloazines are reported.

Hydrazine and hydrazine derivatives have been extensively utilised in heterocyclic synthesis.[1-4] Perhaps one can state that today it is hardly to find any heterocyclic chemists who are not dealing with hydrazines and hydrazine derivatives during his work. It is a fact that every year hundreds of publications appears in the area and making a comprehensive review of the literature in this area is extremely difficult task because of the difficulty of dealing with such a very broad subject. We have decided to place emphasis only on recent developments in this area. It seemed that the old literature is well known for chemist, that it is no more useful to survey it. Hydrazine derivatives that are going to be dealt with are hydrazine and alkyl and aryl substituted hydrazines (1), aryl and aroyl hydrazines (2), thiohydrazines (3), amidrazones (4), hydrazidic halides (5), hydrazones (6), semicarbazides, thiosemicarbazides, amino guanidine (7), and diazo compounds (8).



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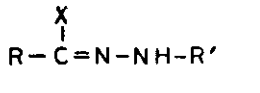

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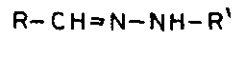

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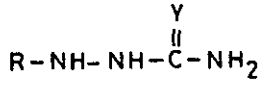
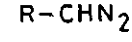


7 a , Y = O
b , Y = S
c , Y = NH



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R , R' = H alkyl and aryl
X = halogen

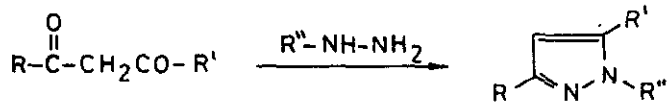
UTILITY OF HYDRAZINES IN HETEROCYCLIC SYNTHESIS:

Hydrazine hydrate, monosubstituted and disubstituted hydrazine derivatives have been extensively utilized for the synthesis of azoles, azines and larger ring systems.

I- Synthesis of Five Membered Heterocyclic Derivatives:

1. Synthesis of pyrazole derivatives

The reaction of hydrazine and substituted hydrazines is one of the general routes for synthesis of pyrazoles. The reaction of hydrazines with β-diketones or β-ketoesters constitutes one of the oldest general routes to pyrazoles[5,6]. Both unsubstituted, mono- and disubstituted hydrazines have been utilised in these reactions and a variety of experimental procedures have also been reported[7-20]. The general features of these reactions have been surveyed by Behr[5] and although hundreds of publications have been appeared dealing with the reactions of hydrazines with β-diketones and with β-ketoesters, these reports did not add much to basic knowledge in this area, (cf. Chart 1).



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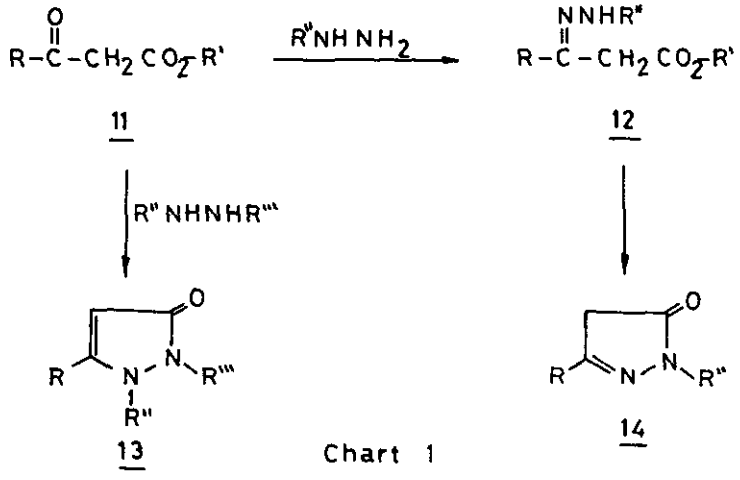
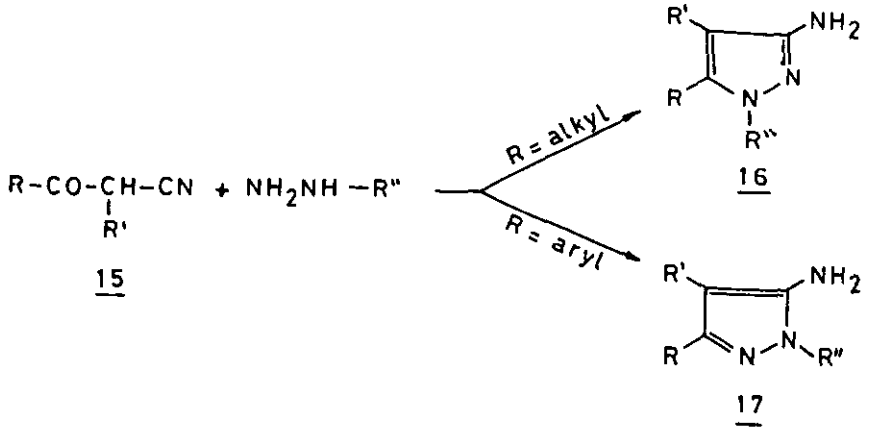


Chart 1

Hydrazines have long been known to react with 3-oxonitriles to afford heterocyclic derivatives[21-73]. Thus, the reaction of 3-oxonitriles with hydrazines has been reported to proceed under a variety of conditions leading usually to a high yield of amino pyrazoles. Both substituted and unsubstituted hydrazines have been used. 2-Substituted 3-oxonitriles (15) reacted with unsubstituted hydrazines to afford the corresponding 5-amino-pyrazole derivatives (16), R" = H[21]. On the other hand, 2-unsubstituted 3-oxonitriles usually afford pyrazolo[1,5-a]pyrimidine derivatives[18] when similarly treated with hydrazine hydrate (cf. Chart 2). Only very few 2-unsubstituted 3-oxonitriles have been reported to react with the former reagent to afford 5-aminopyrazole derivatives[21].



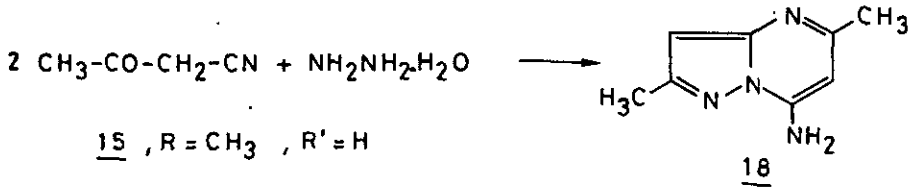
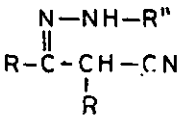


Chart 2

The reaction of substituted hydrazines with 3-oxonitriles may theoretically afford either the 3-aminopyrazole derivatives (16) or the isomeric 5-aminopyrazole derivative (17)[21]. Generally aryl and heterocyclic substituted hydrazines afford 1-substituted 5-aminopyrazoles, whereas alkyl substituted hydrazines afford, in most cases, a mixture of both (16) and (18). The intermediate aryl hydrazone derivative (19) have been isolated when aryl hydrazines react with 3-oxonitriles and could be readily cyclized into the corresponding aminopyrazole (17). The reaction of 3-oxonitriles with alkyl substituted hydrazines was shown to depend on the nature of the oxonitrile and the reaction conditions. A delicate equilibrium was shown to exist between steric considerations and relative reactivities[21].



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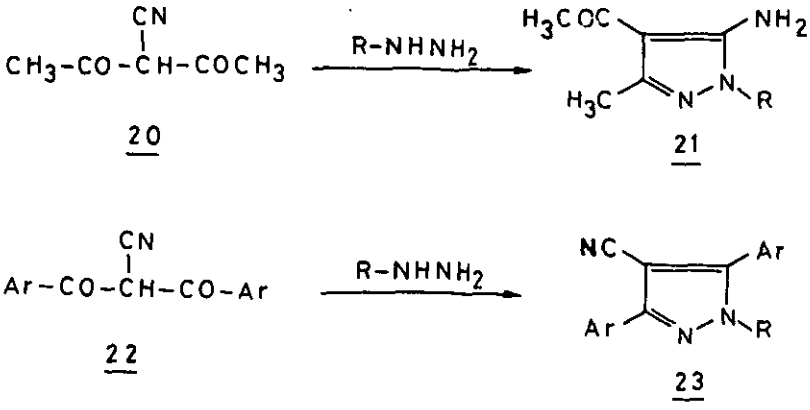
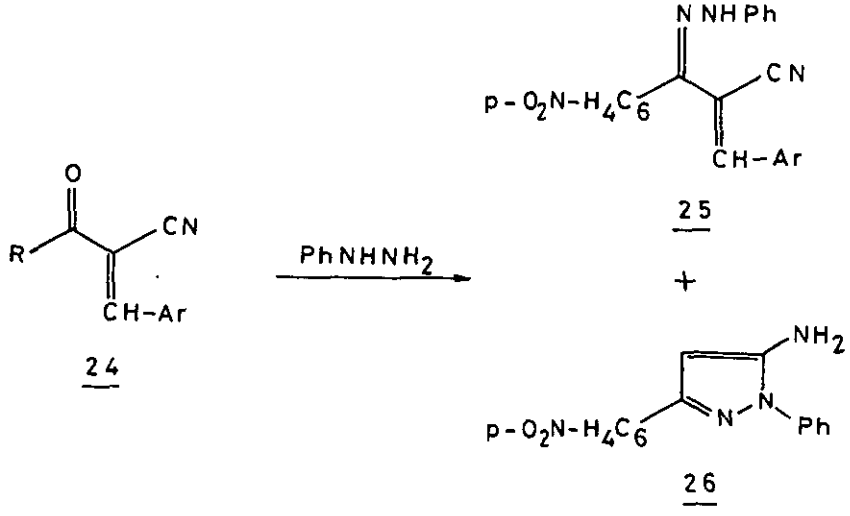
α-Cyanoacetylacetone (20) has been reported to react with substituted hydrazines to afford the corresponding 5-aminopyrazole derivatives (21). On the other hand, other 2-aryl-3-oxonitriles in which the two aryl substituents are strongly linked to the carbon atom, e.g. cyanodibenzoylmethane (22), reacted with the same reagent to yield 4-cyano-1-substituted 3,5-diarylpyrazole[74,75].



Whereas scission of the double bond in the arylidene derivatives of 3-oxo-nitriles was reported to take place by the action of hydrazines in basic media, the formation of 3,5-diaryl-3-pyrazolines was reported to take place in acid media[76-80].

The intermediate phenylhydrazone derivative (25) was isolated together with (26) on reaction of compound(24) (Ar = C_6H_4-NO_2-p) with phenylhydrazine. Elnagdi et al;[29-31] have reported that (24) (Ar = $C_6H_4N(CH_3)_2$-p) reacts with β-cyanoethylhydrazine to yield the hydrazone (27). The latter was cyclized to yield either (28) or (29) depending on the applied reaction conditions[29] (cf. Chart 3).



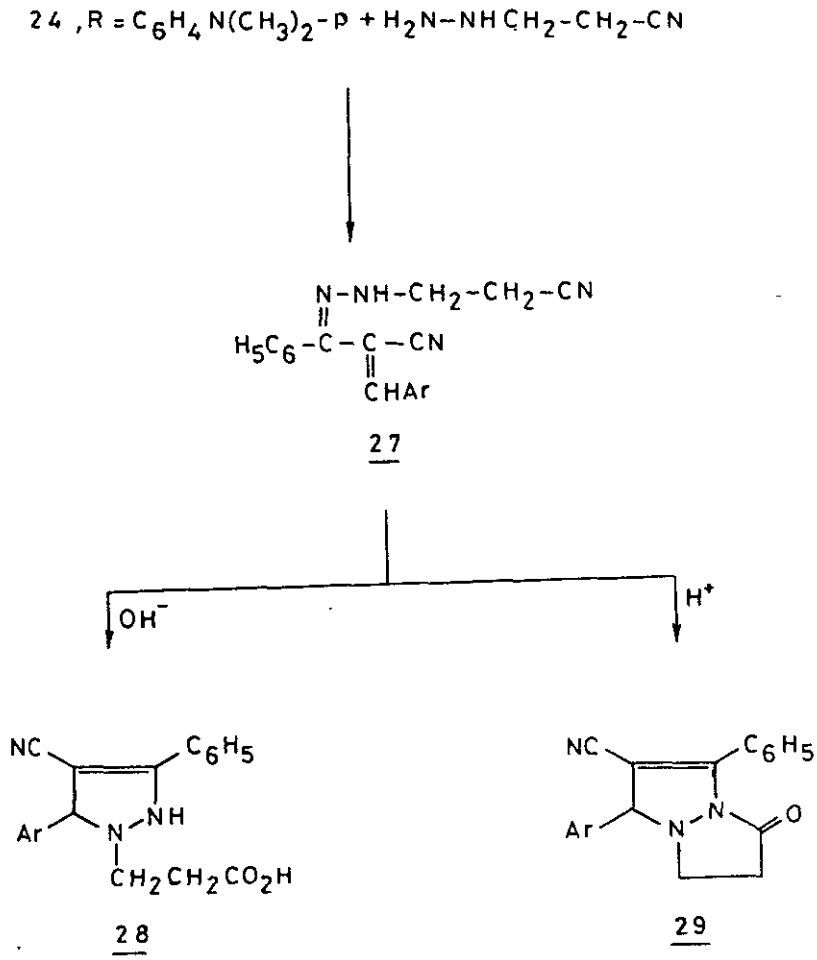


Chart 3

In the old literature malononitrile has been reported to react with hydrazine to yield 3,5-diaminopyrazole derivatives[81] (cf. Chart 4). Later, Taylor and Hartke[82] showed that the products previously claimed to be 3,5-diaminopyrazole, are really 5-amino-3-cyanomethylpyrazole derivatives (35) formed via dimerization of malononitrile prior to its reaction with hydrazine.[82-85] In contrast to malononitrile, substituted malononitrile has afforded 3,5-diaminopyrazoles in good yields.[30,85-87]. For example,

arylhydrazonomalononitrile derivatives (30) afforded the 3,5-aminopyrazoles (32) on reaction with hydrazines. Recently phenylmalononitrile (36) was reported[88] to afford 4-phenyl-3,5-diaminopyrazole derivatives (37) on reaction with hydrazines. The 3,5-diaminopyrazole derivatives (34) could be obtained from the reaction of hydrazines with the ethoxyimidate derivative (33).[88]

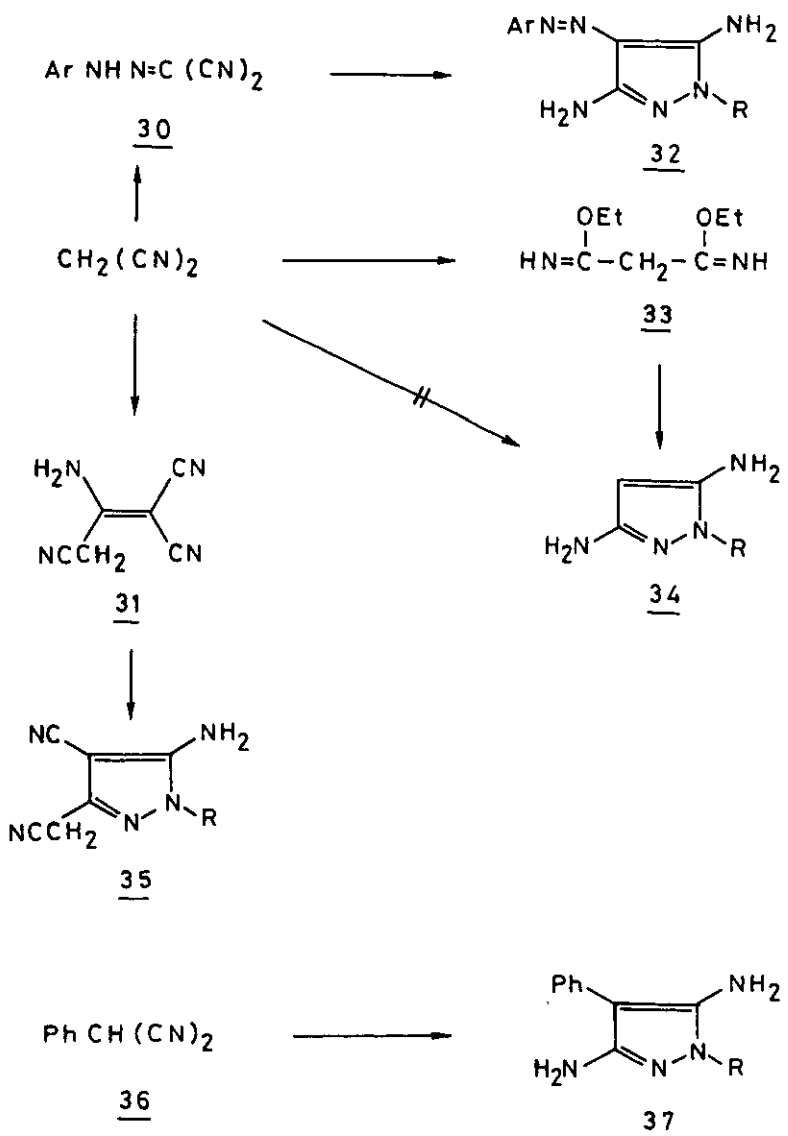


Chart 4

α,β-Unsaturated ketones have been shown to react with hydrazines to yield pyrazolines. The reaction is believed to proceed via addition to the double bond and subsequent cyclization. However, in some cases condensation with the oxo function prior to cyclization has been also suggested[89-94] (cf. Chart 5).

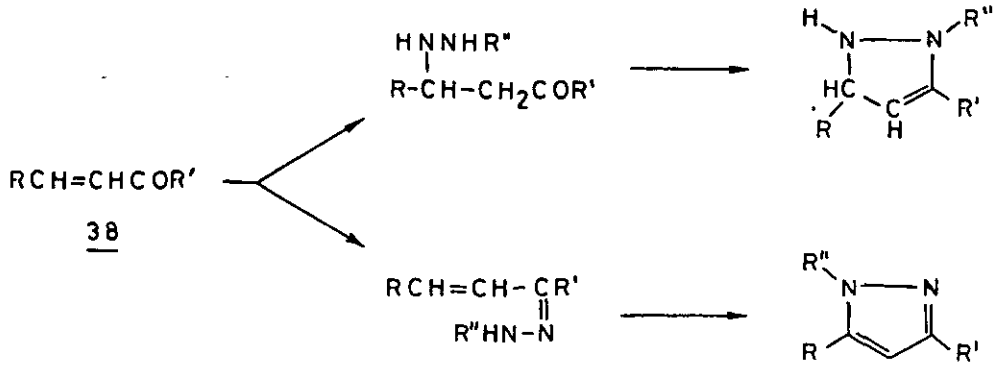


Chart 5

Acetylenic ketones and acetylenic esters are also known to react with hydrazines and substituted hydrazines to yield pyrazoles and pyrazolones. The mechanism of this reaction which is utilized for the synthesis of variety of substituted pyrazoles has recently been discussed.[95-109] Examples of this reaction are shown in Chart 6.

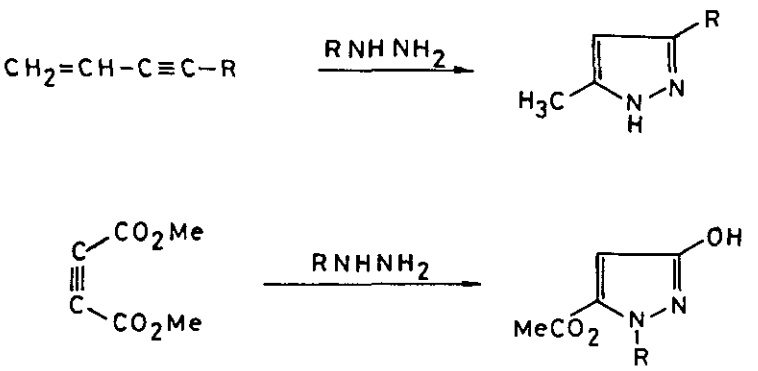
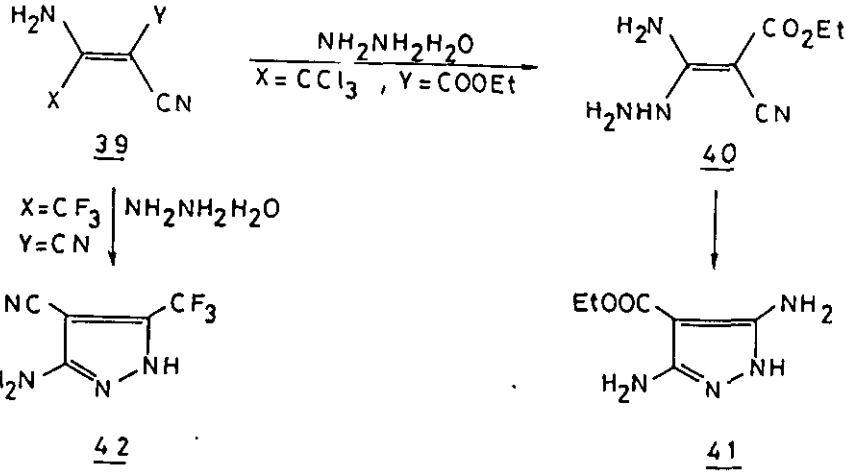
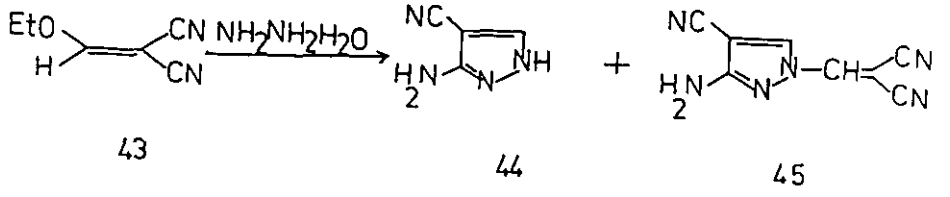


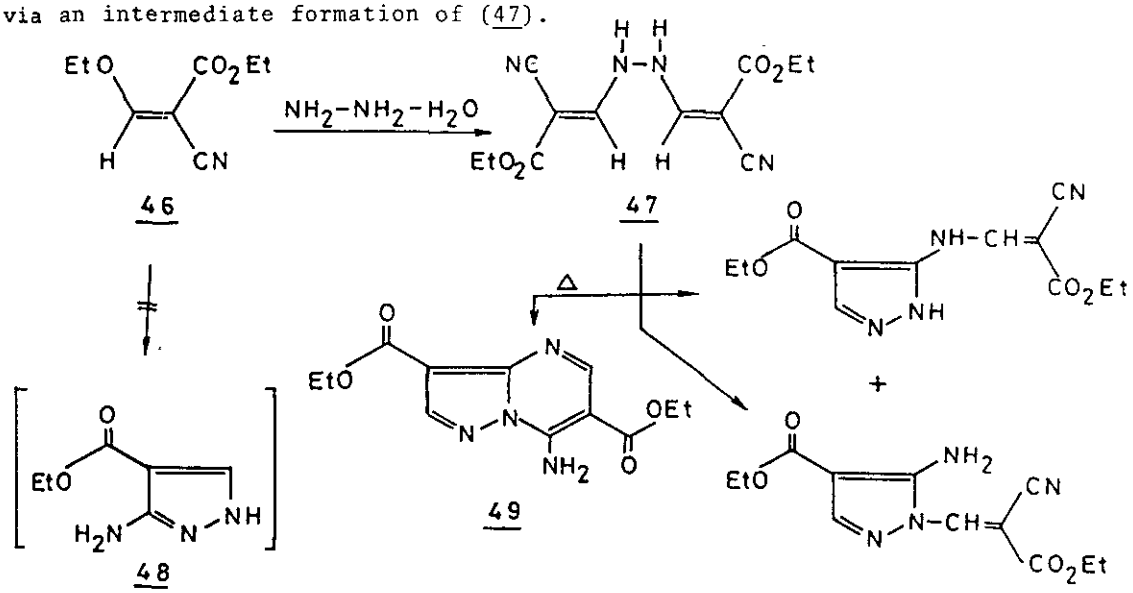
Chart 6

It has been shown that ethyl β-trichloromethylenecyanoacetate (39, X = CCl_3, Y = COOEt) reacts with hydrazine hydrate to yield the aminopyrazole derivative (41) via intermediate formation of the amidrazone (40) which could be isolated.[110-113] This is in contrast to the reported formation of 3-amino-4-cyano-5-trifluoromethylpyrazole (42) on treatment of β-trifluoromethyl-β-amino-methylenemalononitrile (39) (X = CF_3, Y = CN) with hydrazine hydrate.[114] Synthesis of pyrazoles via similar routes has been recently reported.[115-117] Ethoxymethylenemalononitrile (43) reacted with hydrazine hydrate to yield the pyrazole derivatives (44) and (45).[117]

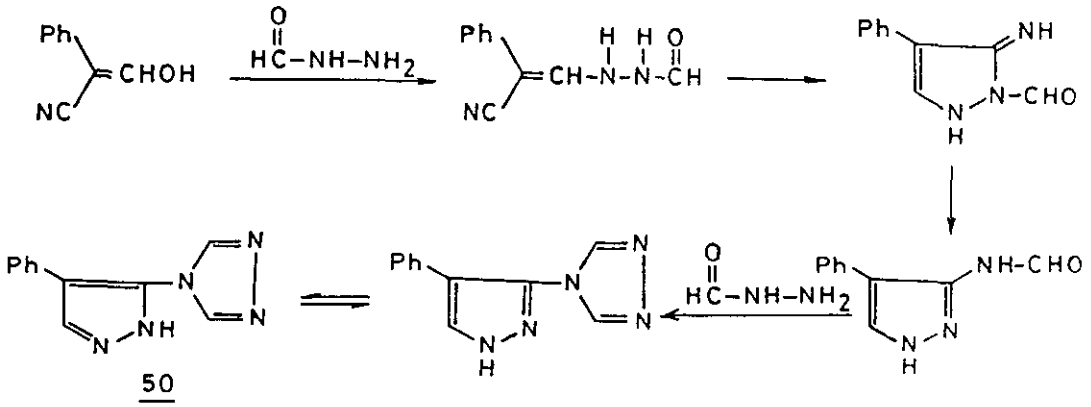




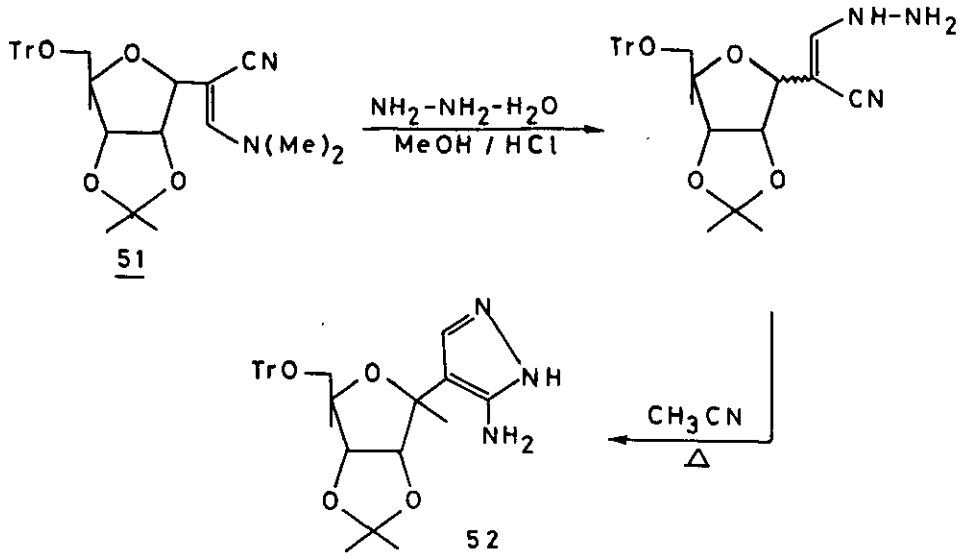
In an attempt to synthesis 3-amino-4-ethyoxycarbonylpyrazole (48) via the reaction of (46) with hydrazine hydrate in a manner similar to that reported for its reaction with phenylhydrazine which is established to afford pyrazole derivatives. Midorikawa et al.[118,119] have obtained instead of the expected pyrazole derivative (48), the pyrazolo[1,5-a]pyrimidine derivative (49). The formation of this product is expected to proceed via an intermediate formation of (47).



4-(4-Phenyl-3-pyrazolyl)-4H-1,2,4-triazole (50) was recently prepared by the action of formylhydrazine on α-phenyl-α-cyanoacetaldehyde[120] as shown below.

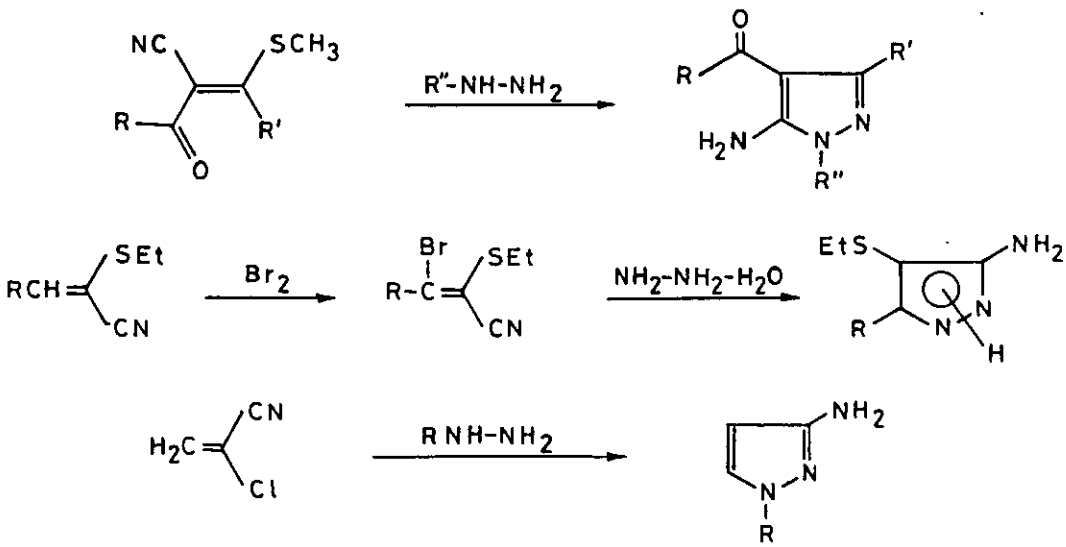


β-Dimethylamino-α-(2-ribosyl)-acrylonitrile (51) reacted with hydrazine hydrate to yield the aminopyrazole derivative (52). This opened a new route for the synthesis of formycin and formycin analogues[121].

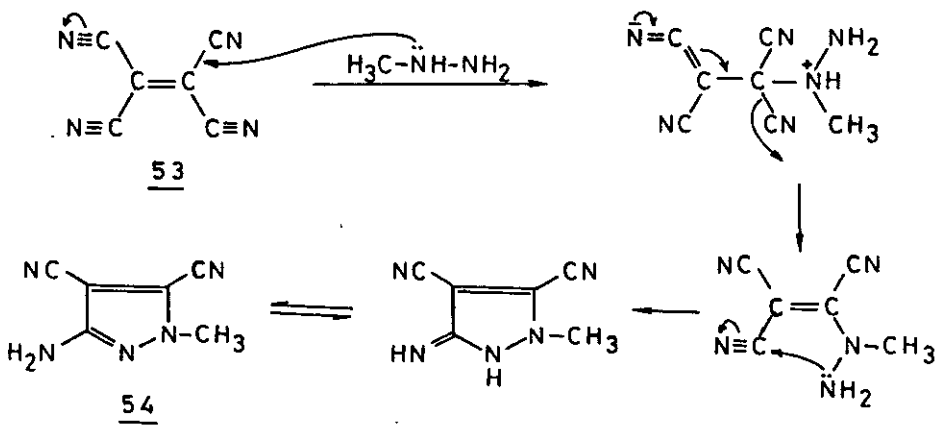


51 52

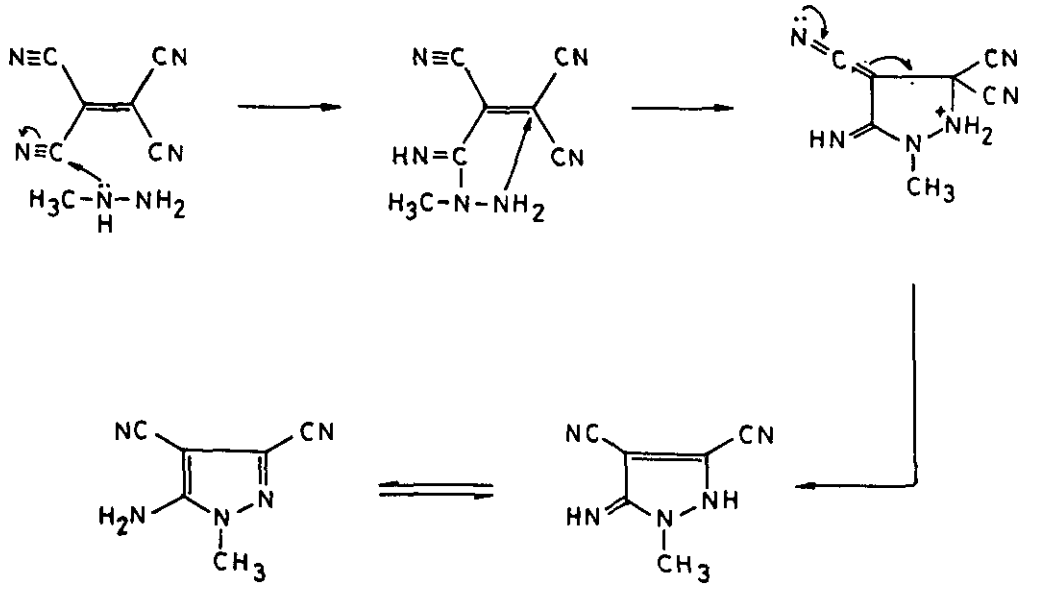
A variety of new pyrazole derivatives have been synthesized utilizing the same idea of reacting α,β-unsaturated nitriles with hydrazines or acylated hydrazines. Examples for the most interesting of these syntheses are shown below.[22,85,108,122-141]



3-Amino-4,5-dicyano-1-methylpyrazoles (54) are synthesized by taking the advantage of the propensity of tetracyanoethylene (53) for Michael addition. Thus, aryl- and alkylhydrazones as well as hydrazides, semicarbazides and thiosemicarbazides have been reported to react with tetracyanoethylene (53) to afford 1-substituted 4,5-dicyano-3-aminopyrazoles.[137] The structure assigned for the reaction product of tetracyanoethylene (53) with methylhydrazine was reinvestigated by Hecht et al.[138] and Earl et al.[139] in two separate contributions. It has been shown by Hecht et al.[138] that consideration of the mechanistic routes suggested in literature for this reaction illustrates the source of structural ambiguity in the formation of these products from methylhydrazine and tetracyanoethylene (53). Thus, one might, for example, envision the formation of the 1-methyl-4,5-dicyano-3-aminopyrazole (54) by conjugate addition of the more nucleophilic substituted nitrogen of methylhydrazine to tetracyanoethylene (53) followed by addition of unsubstituted hydrazine nitrogen of the hydrazine to a cyano group, affording the observed product according to the following scheme:

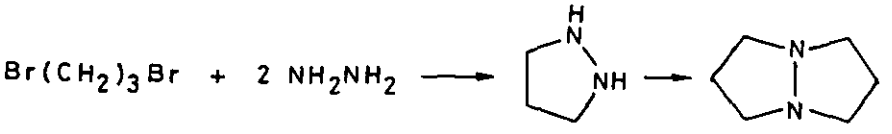


Alternatively, as has been previously suggested, addition of the substituted nitrogen of methylhydrazine to the cyano group might occur first and the reaction then proceeds as shown in the scheme below.[117]



Both authors on reconducting the above reaction have shown that it affords a mixture of two isomeric pyrazoles (35% and 27%[138], 47% and 8%.[139]) These authors have shown on the bases of chemical evidences as well as IR, UV and ^{13}C NMR spectra that the major product for which the 3-amino-4,5-dicyano-1-methylpyrazole structure was formally assigned is really 5-amino-3,4-dicyano-1-methylpyrazole.

When bifunctional alkylating agents reacted with hydrazines as shown below pyrazoles or fused pyrazole derivatives are formed.[142]



Several other reactions of hydrazines with multifunctional reagents leading to the formation of pyrazoles are show in Chart 7.[142-145]

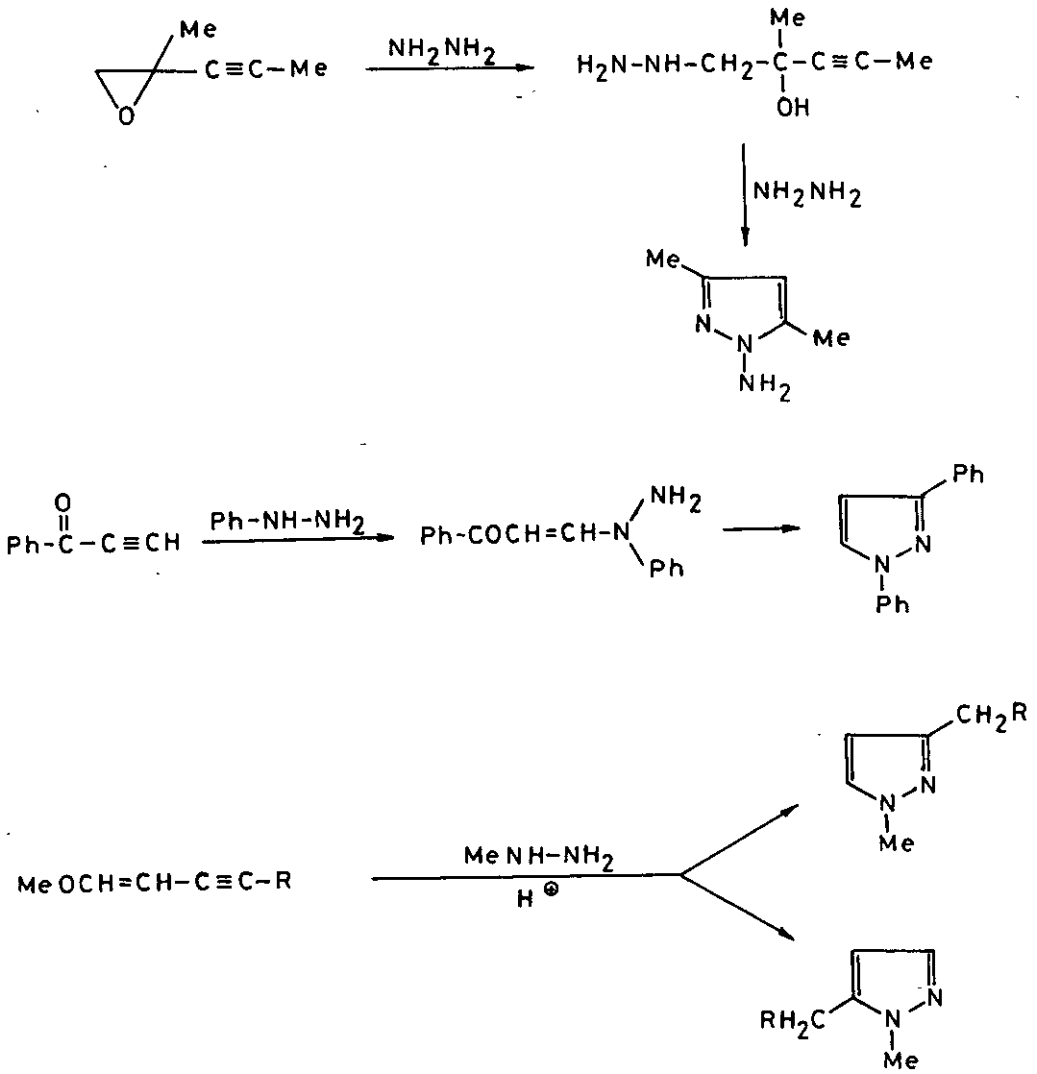


Chart 7

The conversion of isoxazoles into pyrazoles by the action of hydrazines has been reviewed.[146] Some interesting examples for this interconversion are shown in Charts (8 and 9).

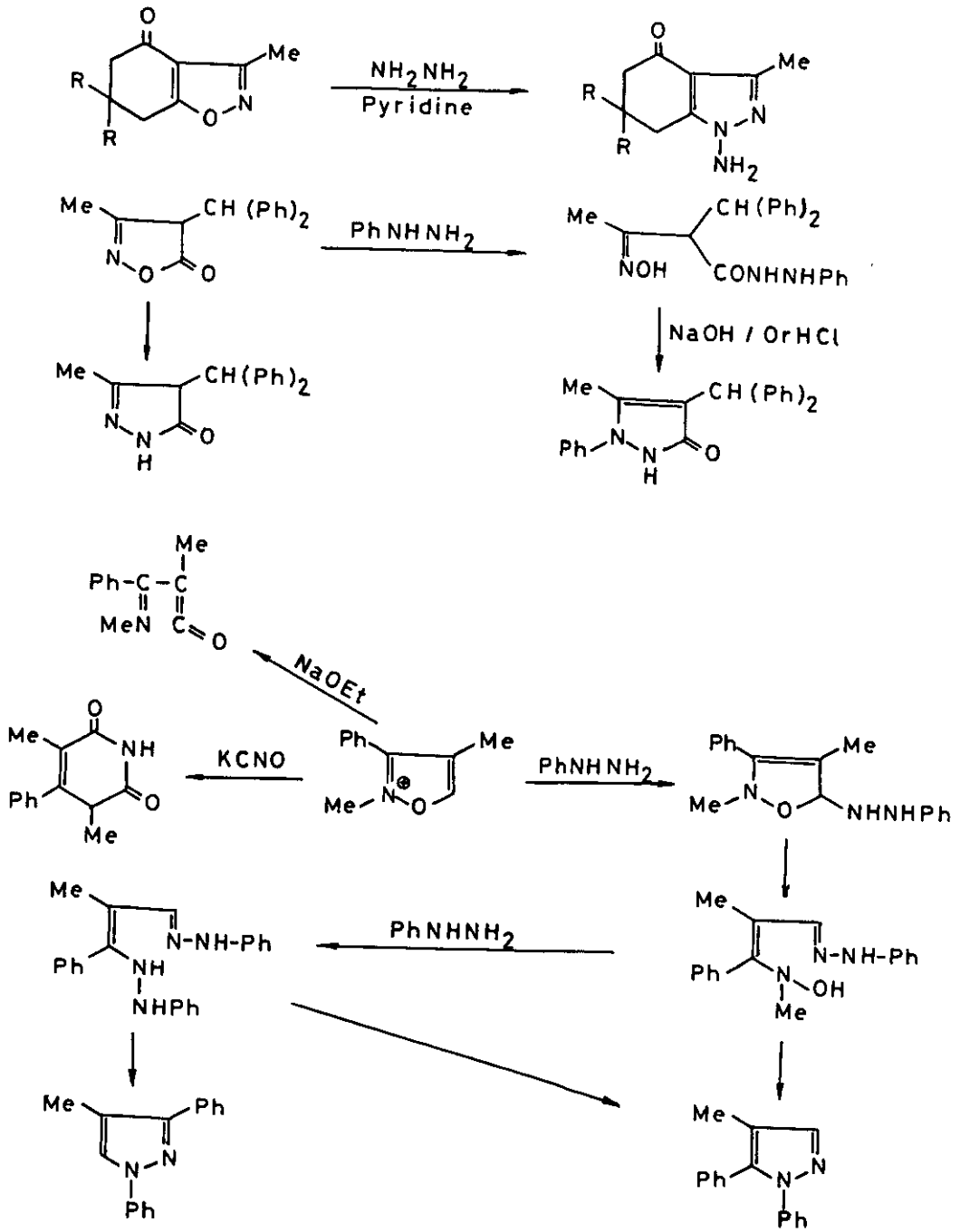


Chart 8

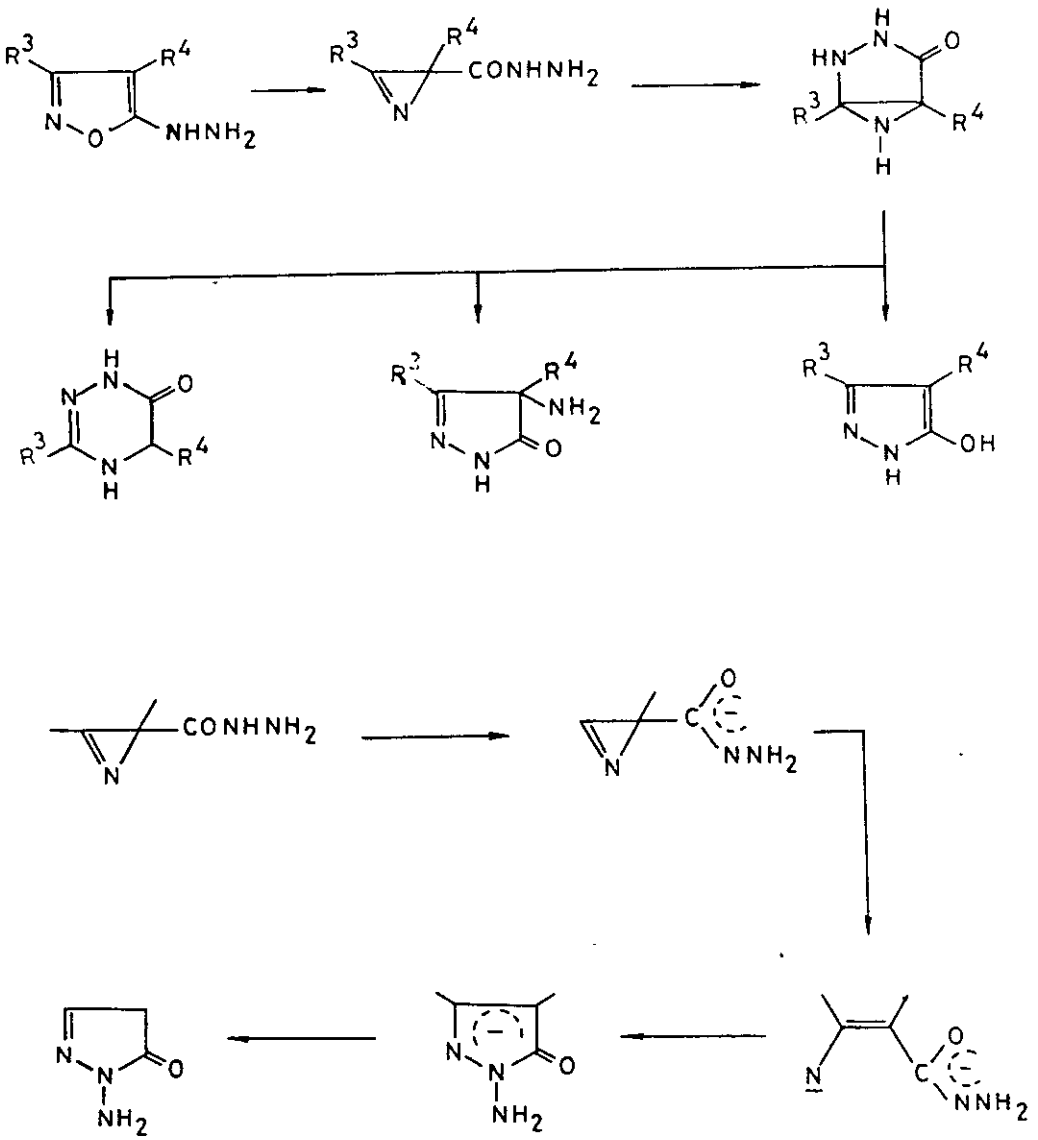


Chart 9

Other rearrangement of heterocyclic derivatives into pyrazoles has been reported.[147-151] Some typical examples of these rearrangement are shown in Charts 10 and 11.

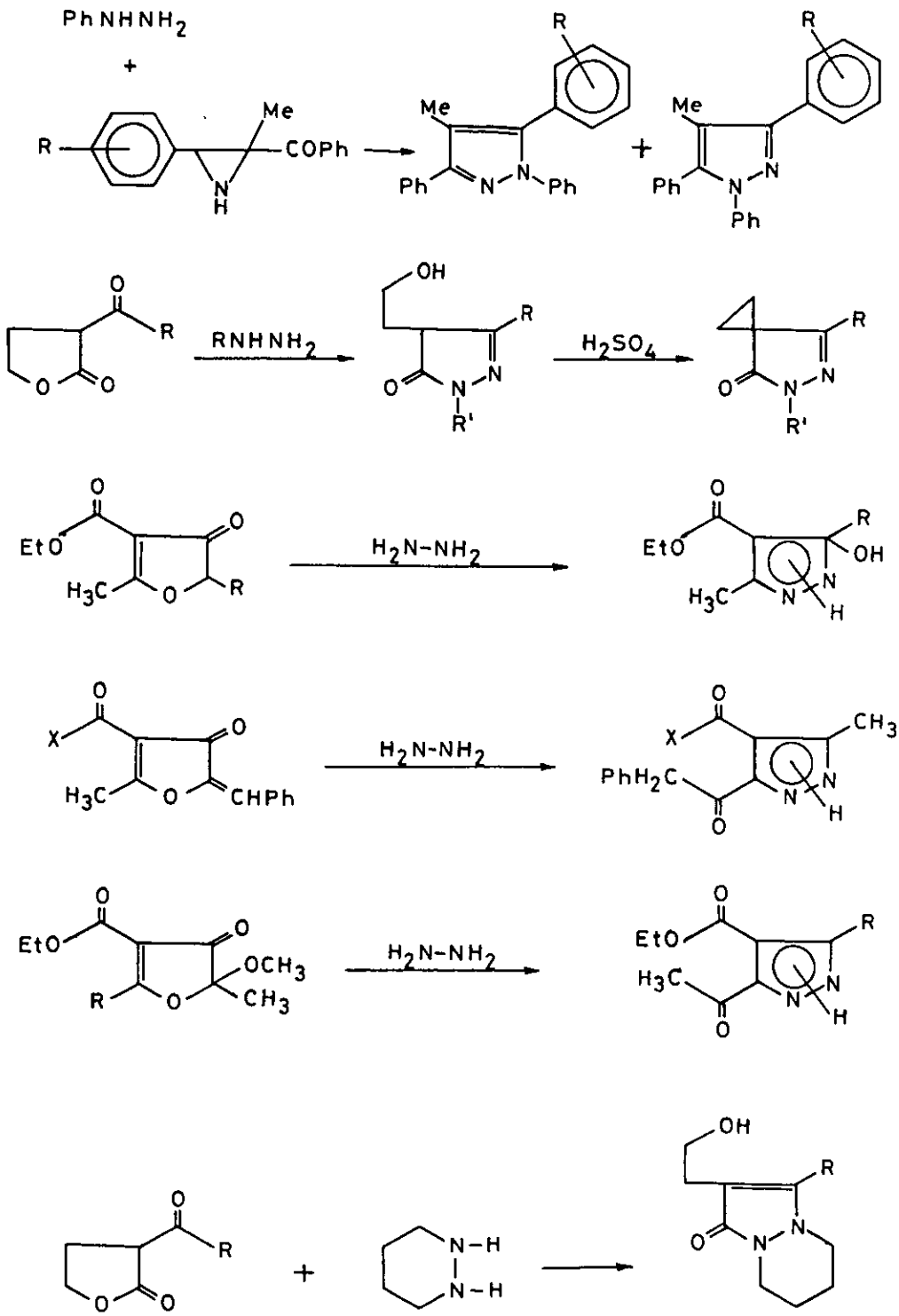


Chart 10

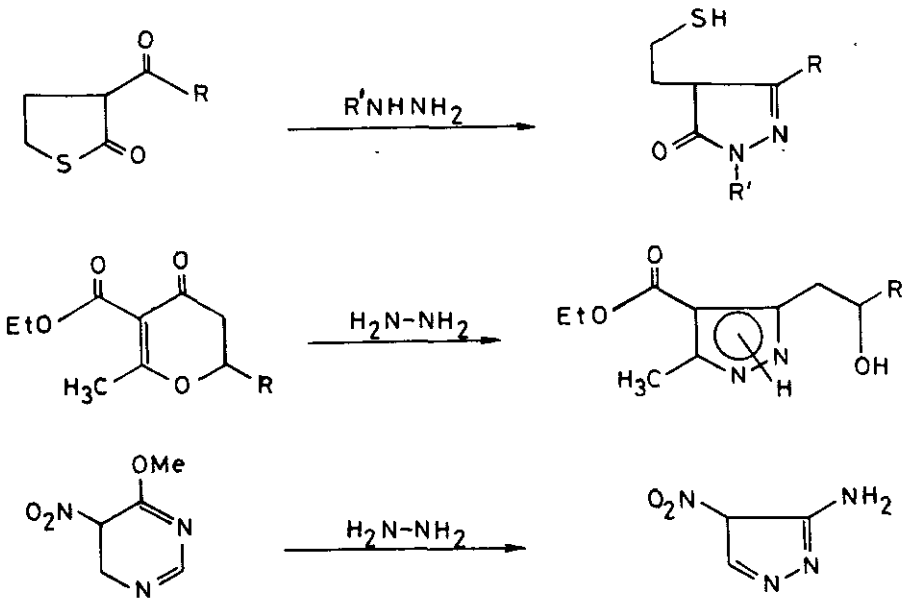
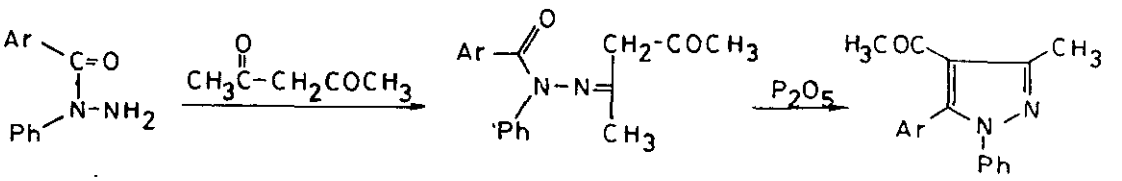


Chart 11

Acylhydrazines have also been reported to condense with β-diketones and ketoesters to yield pyrazole derivatives.[152-154] Recently β-ketonitriles could be condensed with hydrazines to yield pyrazoles (cf. equations below.)[155]



Diazo compounds have also been shown to afford pyrazole derivatives on reaction with a variety of double bonded and triple bonded systems.[156] Reactions of this type have been recently reviewed by Regitz et al.[156-158] some typical examples are shown in Charts 12 and 13.

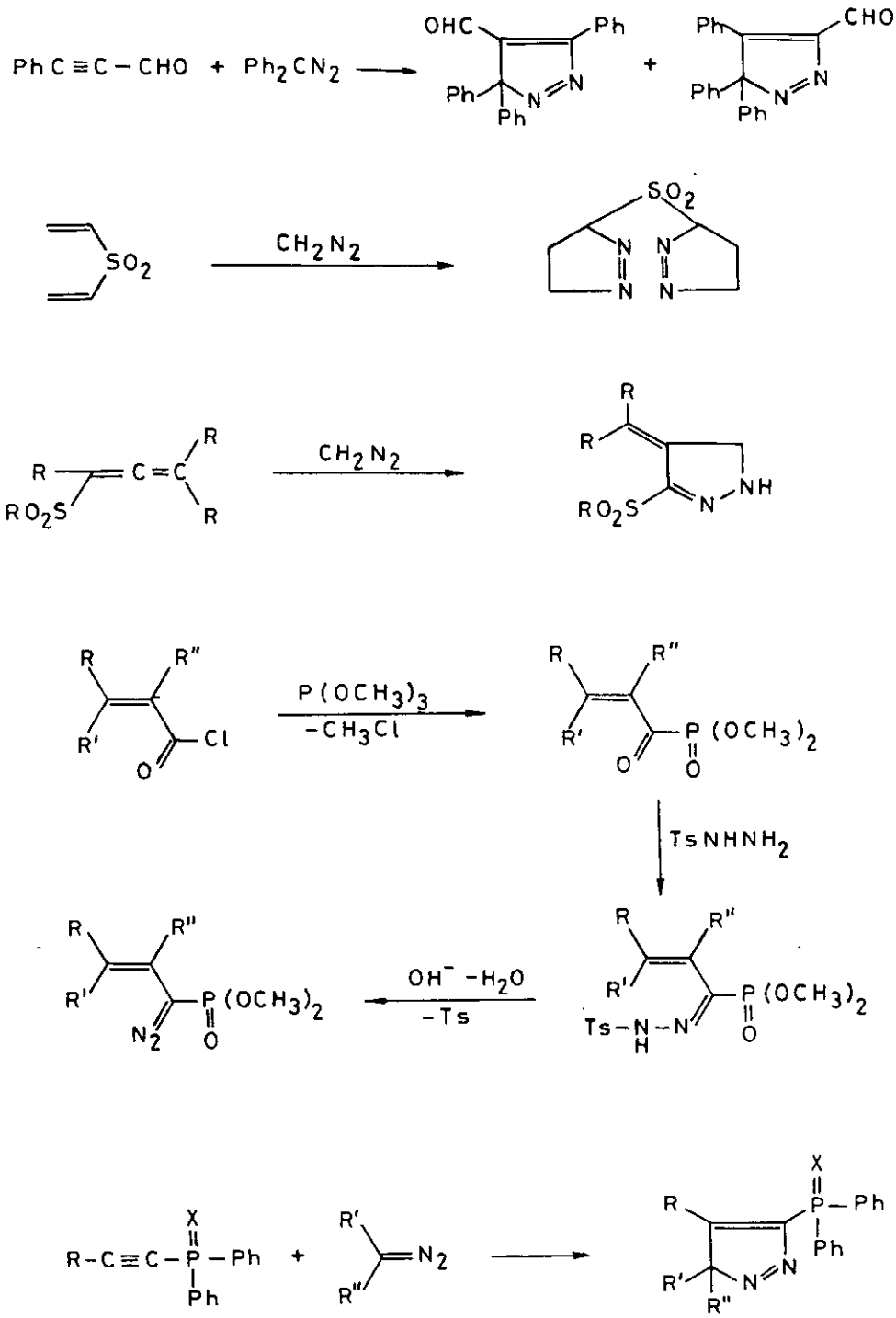


Chart 12

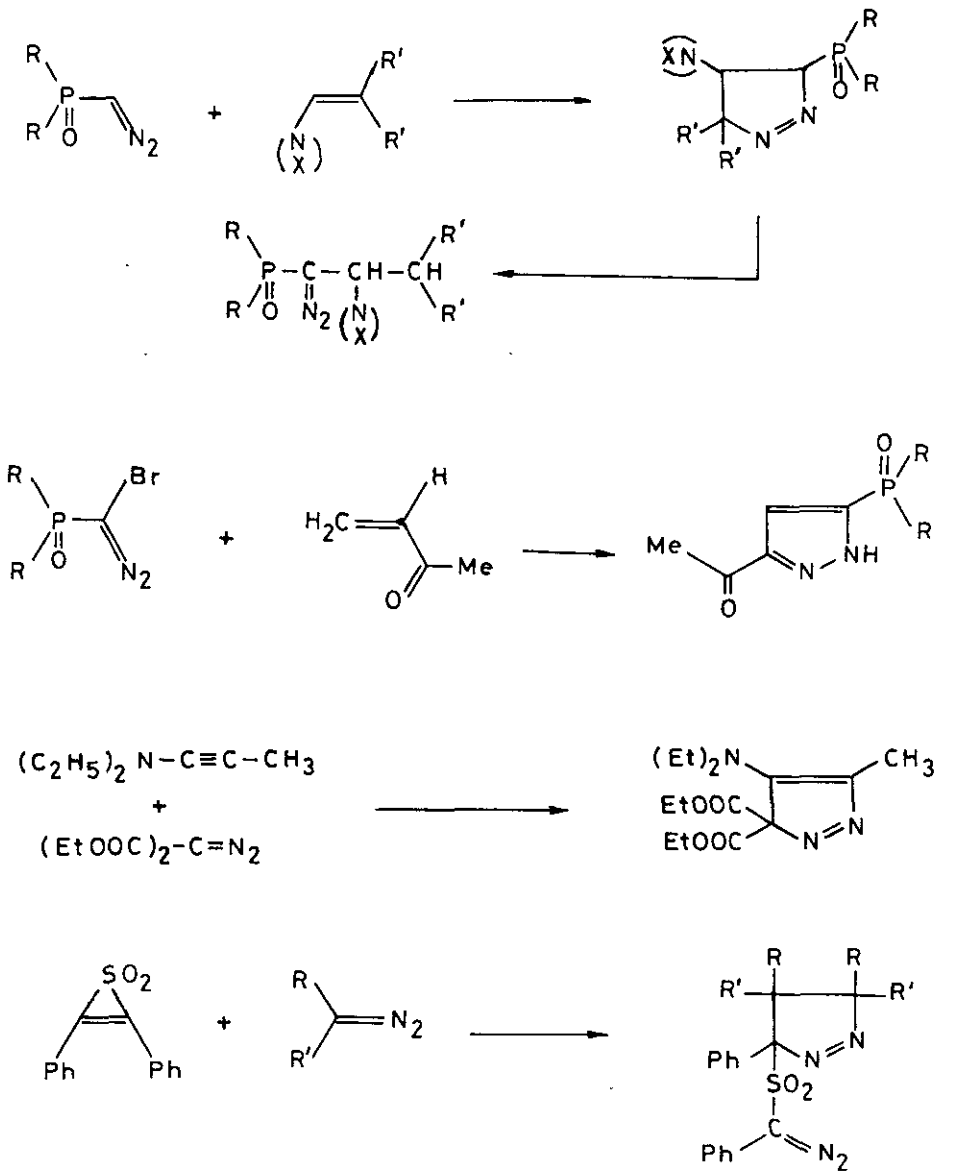
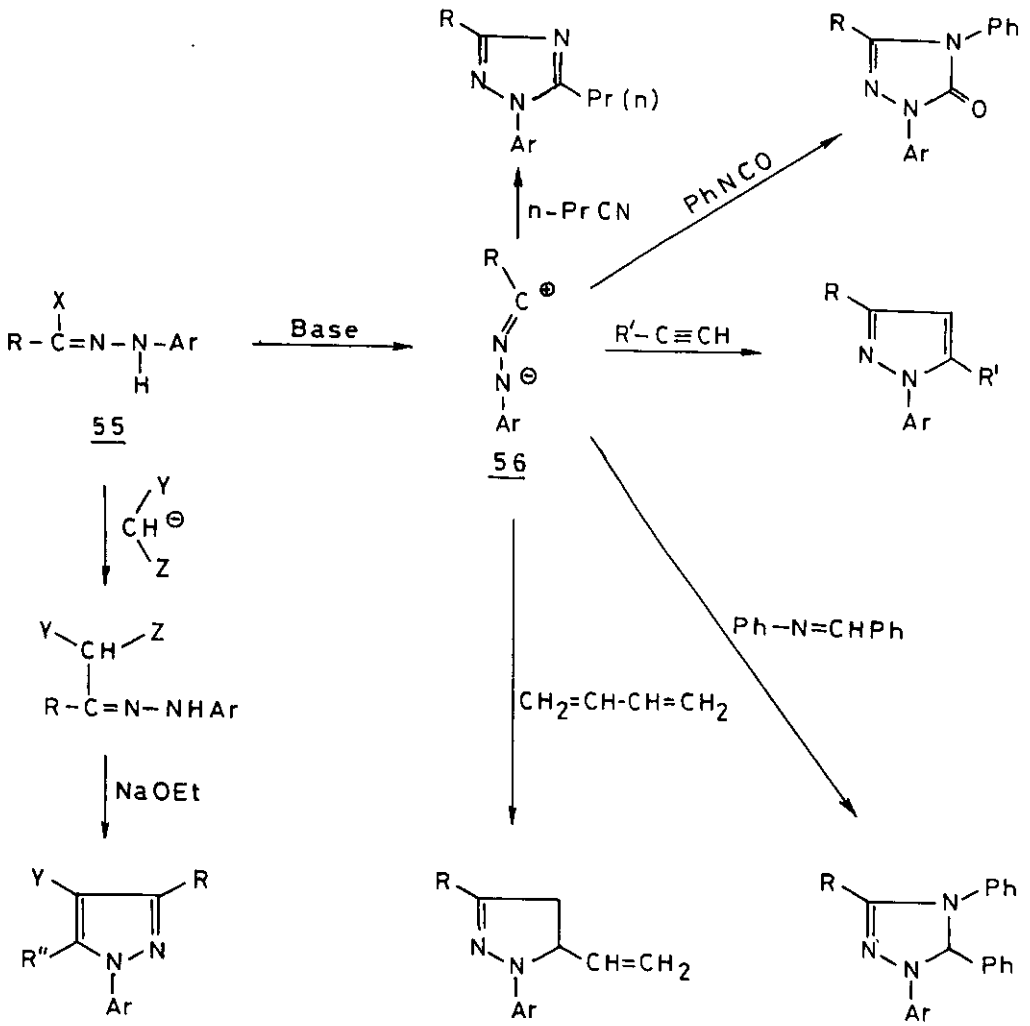


Chart 13

Hydrazonyl halides usually prepared by direct halogenation of hydrazones can readily undergo dehydrohalogenation to yield 1,3-dipoles.[159-164] This 1,3-dipolar ion undergoes cycloaddition with a large variety of compounds containing double and triple bond to form 1,3-diarylpyrazoline derivatives.[165] Examples for the formation of pyrazoles via this sequence are shown in Chart 14.[165]

Recently pyrazolylhydrazonyl halides (57) could be prepared and were converted into a variety of pyrazole derivative (cf. Chart 15).[166-170]

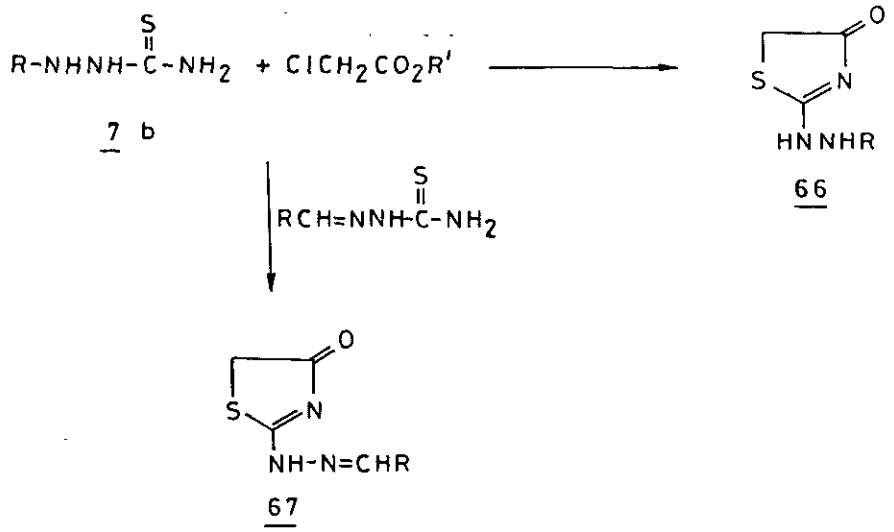


R = Ph, $COCH_3$, COPh, $COOC_2H_5$
X = Cl or Br
Y = Z = CN
Y = CN, Z = $COOC_2H_5$
Y = $COOC_2H_5$, Z = $COCH_3$

Chart 14

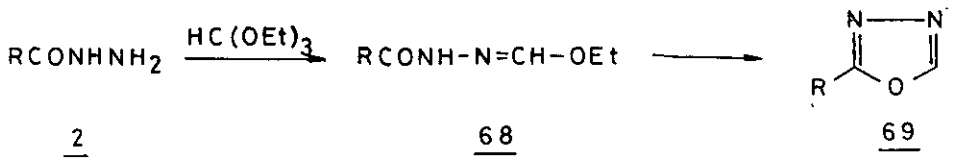
2- Synthesis of Thiazoles

A variety of thiazole derivatives have been synthesized via reaction of thiosemicarbazides and thiosemicarbazones with chloroacetic acid, chloroacetic esters and with α-haloketones.[171,172] Reactions of this type has been surveyed very recently by Metziger, but mucn details[171-180] were not described.



3- Synthesis of 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles and 1,2,4-Triazoles:

A variety of 1,3,4-oxadiazole and 1,3,4-thiadiazoles derivatives could be obtained from hydrazine derivatives.[181-212] A variety of reagents have been utilized to effect such cyclization reactions and some of these reactions leading to 1,3,4-oxadiazole or 1,3,4-thiadiazole has been reviewed.[193,213,214] Thus, acylhydrazines are reported to react with ethyl orthoformate to yield 1,3,4-oxadiazoles (69).[193,213,214]



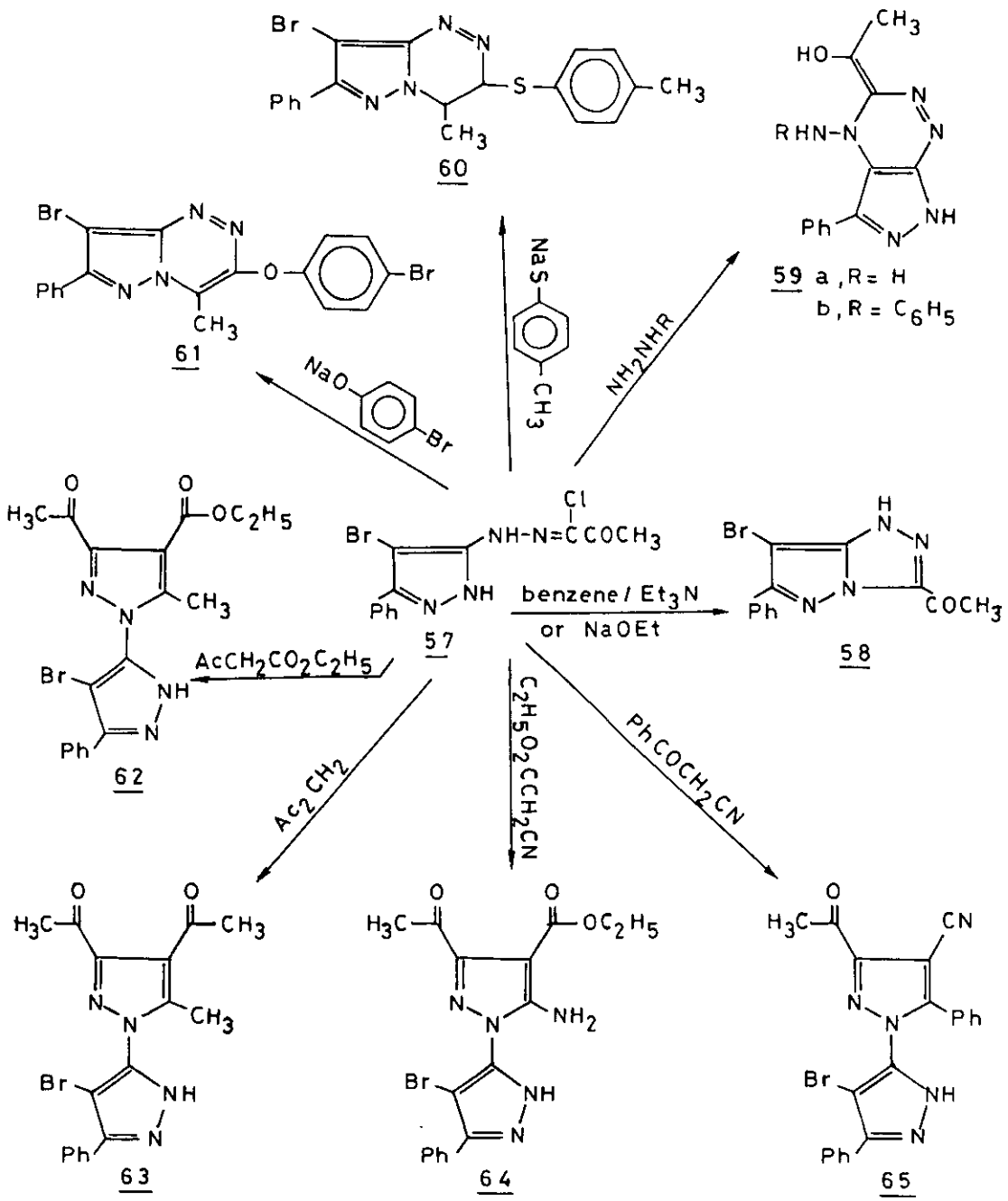


Chart 15

Alternatively, the acid hydrazide can be reacted with an imidate salt to yield 1,3-oxadiazoles.[215] The condensation is sensitive to pH. Condensation of imidates with hydrazones has been reported to yield a poly 1,2,4-triazole (cf. Chart 16).[216,217]

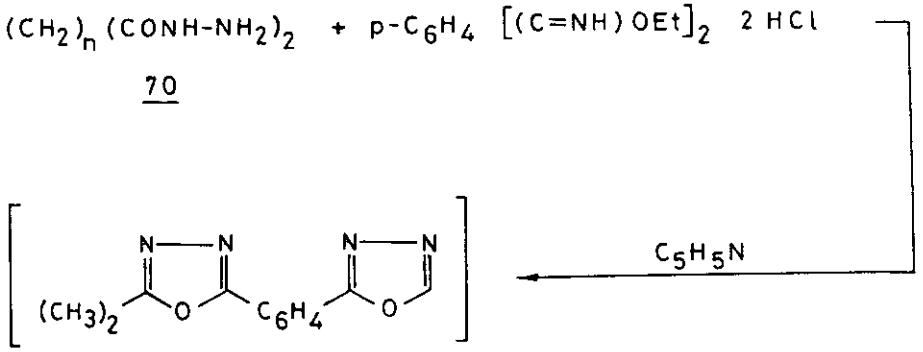
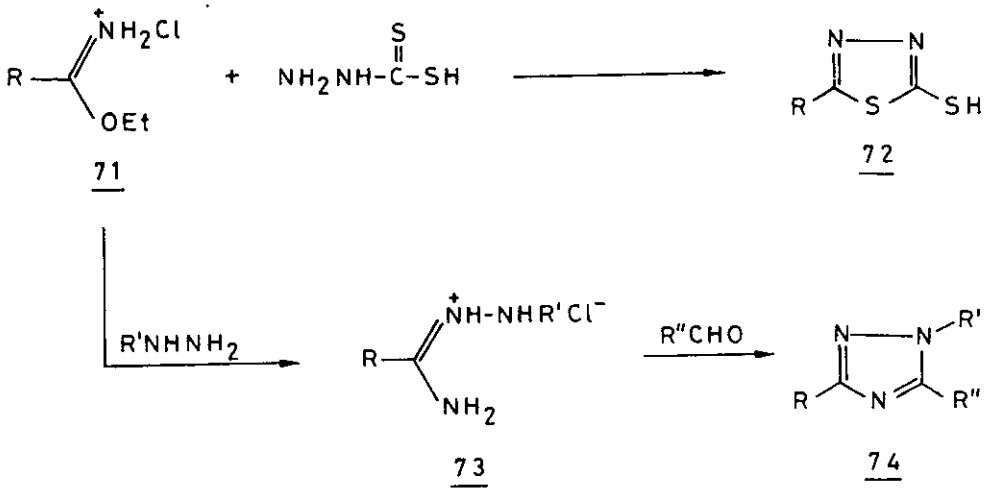


Chart 16

1,3,4-Thiadiazoles and 1,2,4-triazoles have also been similarly prepared as shown below.[218,219]



Thiohydrazides have been converted into 1,3,4-thiadiazole, under a variety of conditions[3] (cf. Chart 17).

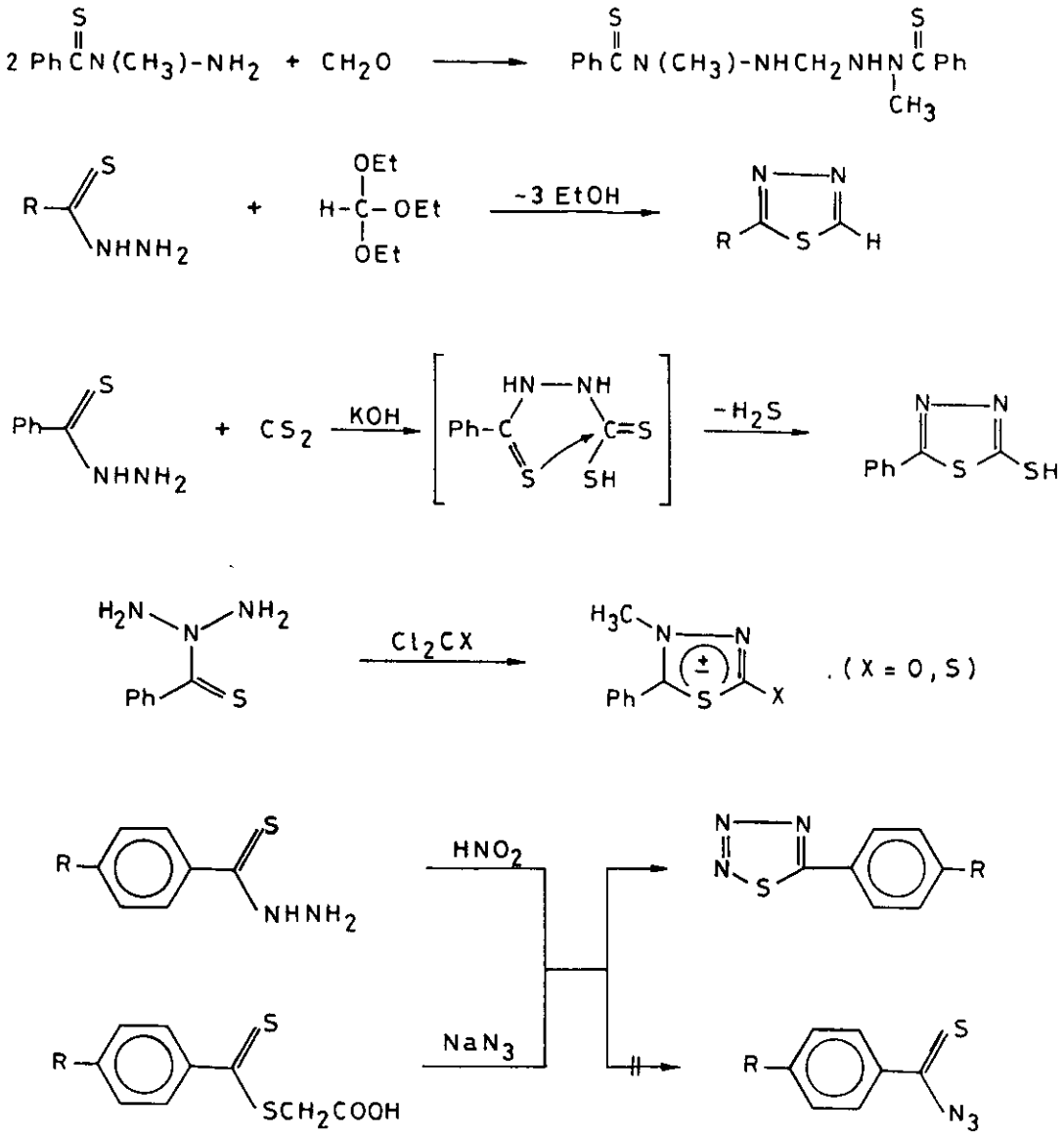
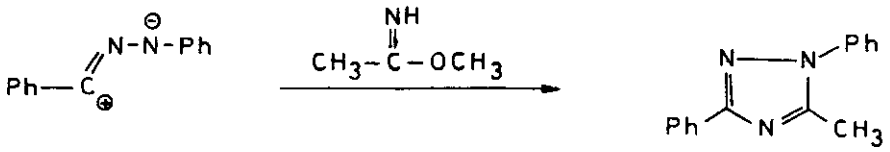


Chart 17

Cycloaddition reactions of imidates with nitrile imines have also been shown to yield a 1,2,4-triazole derivatives (75).[161]



56

R = Ar = C_6H_5

75

Several other examples for conversion of hydrazines and hydrazine derivatives into oxadiazoles, thiadiazoles and 1,2,4-triazoles are shown in Chart 18.[220-230]

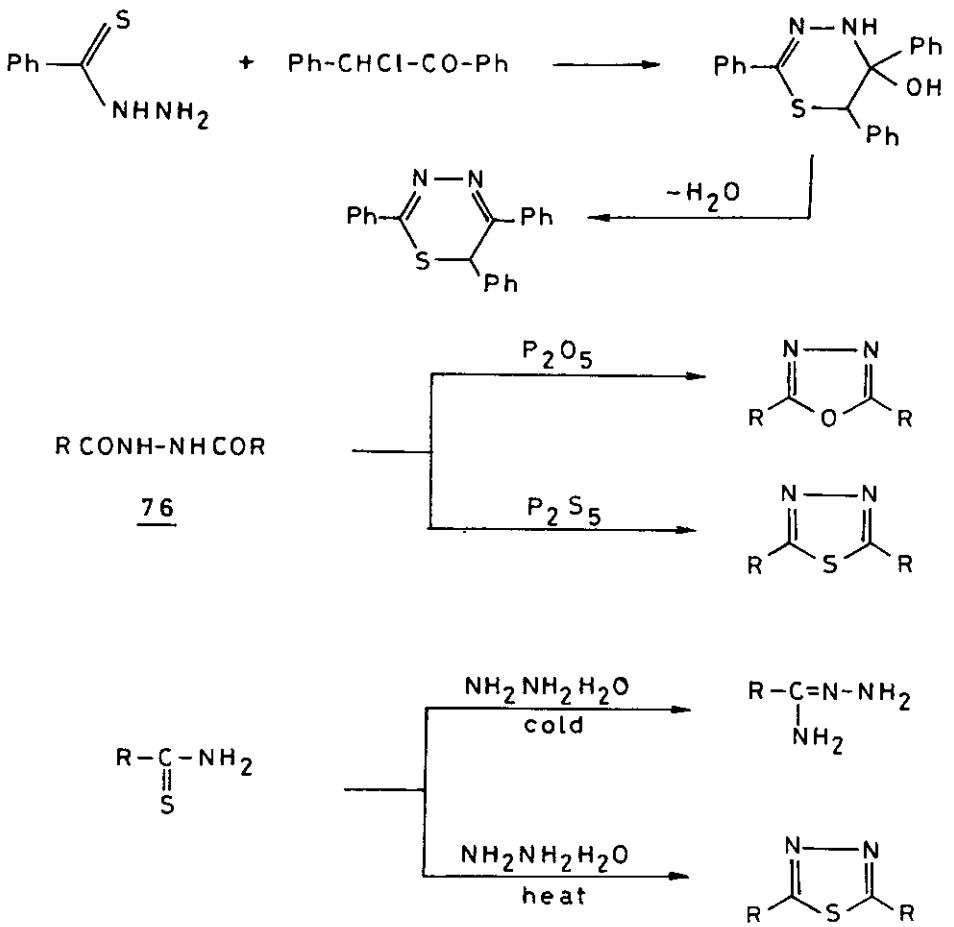


Chart 18

Heterocyclic hydrazines of the general type (77) reacted with orthoesters to yield fused 1,2,4-triazoles.[309]

On the other hand, the reaction of aldehydes afforded the hydrazones that could also be cyclized under a variety of reaction conditions into the corresponding 1,2,4-triazole derivatives, typical examples are shown in (Chart 19).[313,314] The reaction of carbonyl and 1,3-dicarbonyl compounds with cyclic amidrazones such as 2-hydrazinoquinoxalines (83) and 1-hydrazinoisoquinolines (86) have been studied.[309,313] The primary products of these reactions can be cyclized, either to pyrazoles (88), or to fused ring triazole systems (89).[309,313]

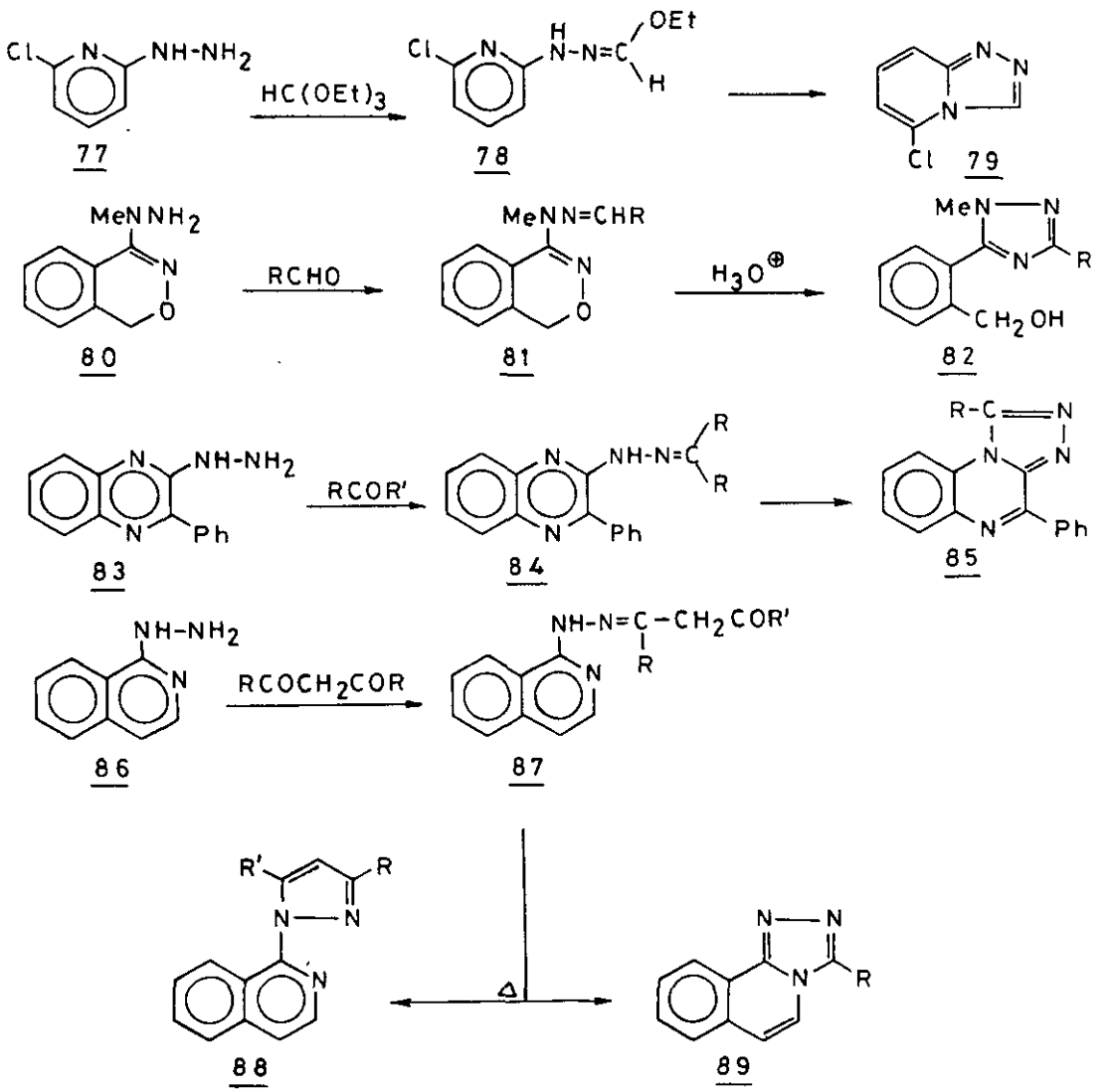


Chart 19

Acid chlorides, anhydrides, esters and even acids themselves all react with unsubstituted amidrazones. When acid chlorides are used, acylamidrazones are the usual products. These can lose water on heating to form the corresponding 1,2,4-triazoles.[231-240,308,309] Derivatives of carboxylic acids, such as diacid chlorides, or diesters, on reaction with amidrazones give access to compounds containing two triazole rings (cf. Chart 20).[241,242]

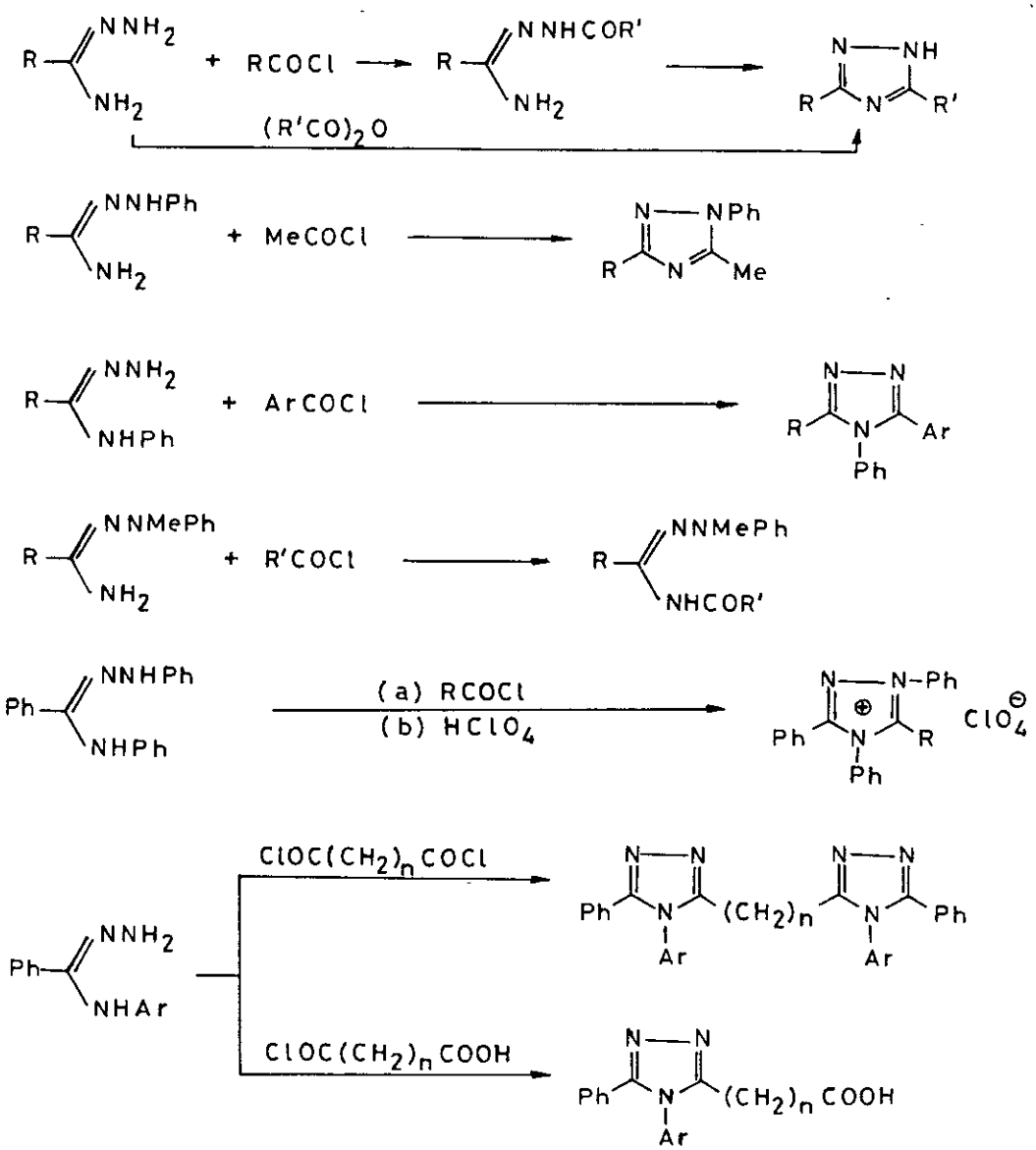
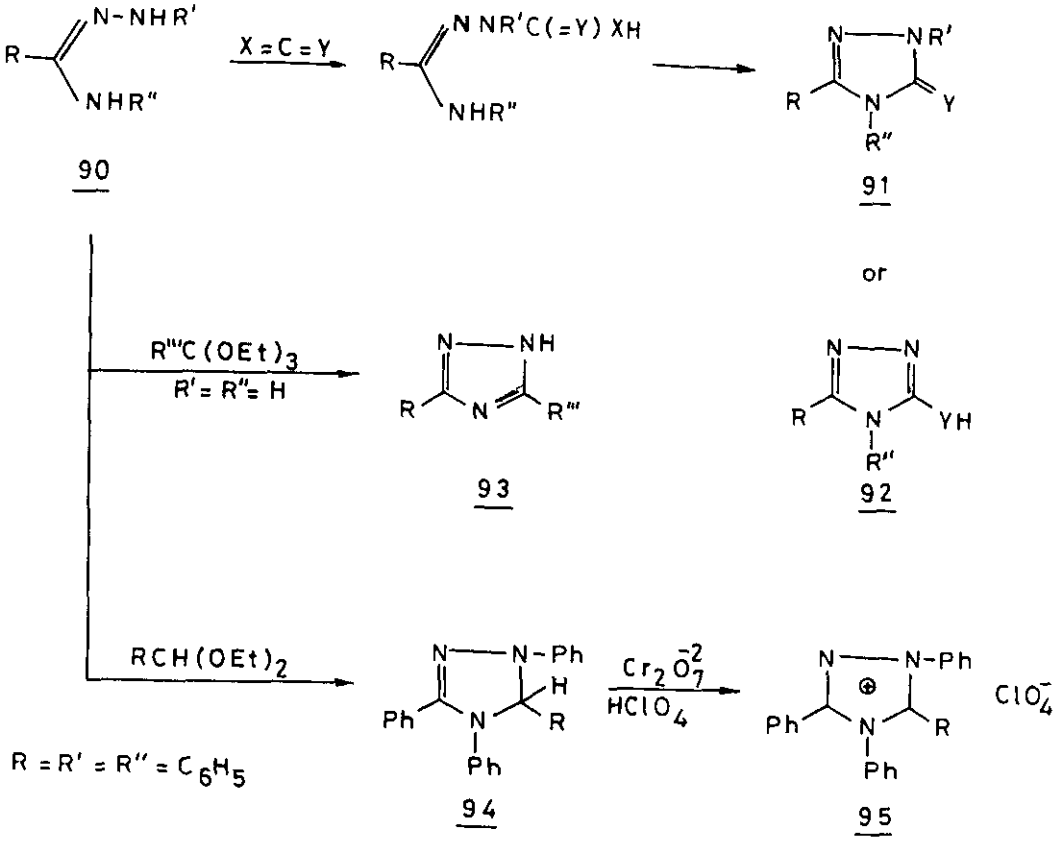


Chart 20

Compounds of the general structure X=C=Y react with amidrazones (90) to afford either 1,2,4-triazoline (91) or 1,2,4-triazole (92) derivatives.[234,243,309] Compound (90; R'=R"=H) reacted also with ethyl orthoformate to yield 1,2,4-triazole derivative (93).[243] On the other hand N^1, N^3-diphenyl benzamidrazone (90, R=R'=R"=C_6H_5) reacted with aldehyde acetals to afford triazoline (94) which, on oxidation, gave triazolium salts (95) (cf. Chart 21).[232]



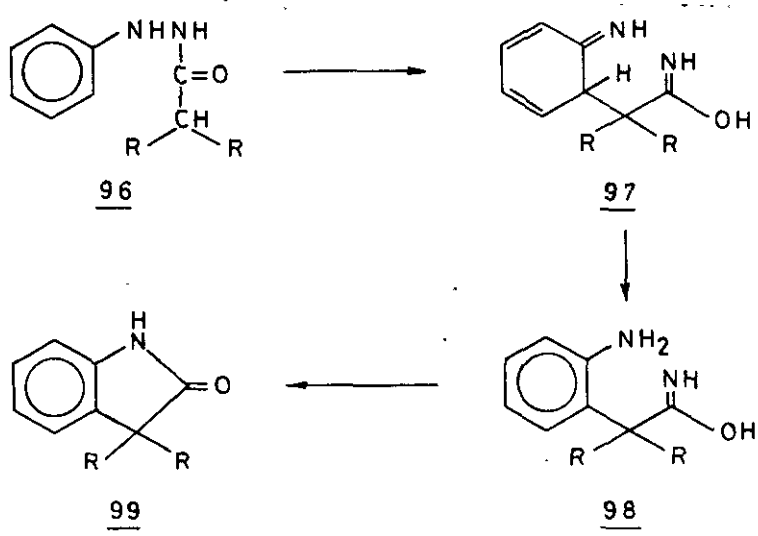
90 91 92 93 94 95

Chart 21

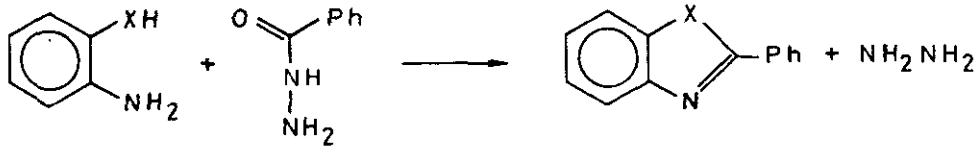
4- Other Five Membered Heterocyclic Derivatives:

A variety of other five membered heterocyclic derivatives could be prepared from hydrazine derivatives.[244-256] Whereas it seems to author completely impossible to survey here all syntheses of these type, every effort has been made to report here synthetic approaches that seemed in the eyes of the reviewer interesting or important.

The conversion of aryl hydrazones into indole derivatives is a well known reaction and Fischer indole synthesis is reported in every student book.[251-253] Similar to this synthesis, phenyl hydrazines can be cyclised with sodamide or calcium oxide at elevated temperatures to give indolones.[260,261] The course of the formation of (99) is explained via a mechanism similar to that suggested for the Fischer indole synthesis.



A reaction,in which hydrazine was not directly involved, leads to a useful synthesis have been reported (cf. equation below).[262]



A variety of synthesis of 1,2,3-triazoles and 1,2,3,4-tetrazoles utilizing hydrazines and hydrazine derivatives have been reported.[258,263] Since the chemistry of both ring systems have been surveyed in two recent[258,263] articles only representative examples of the most interesting reactions are reported here in Chart 22.[264,265]

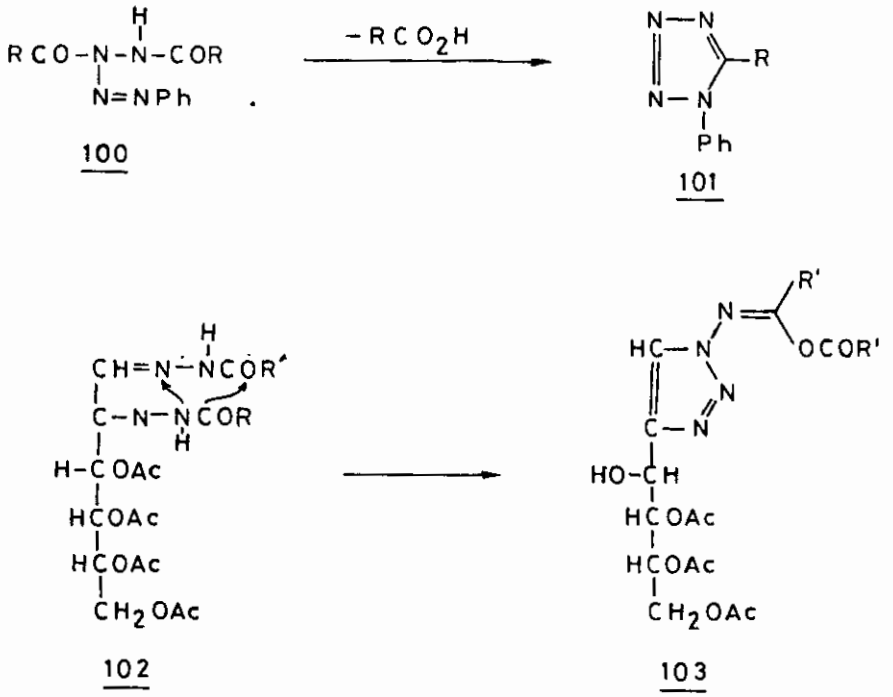
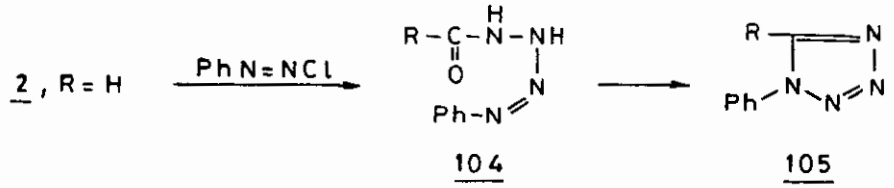


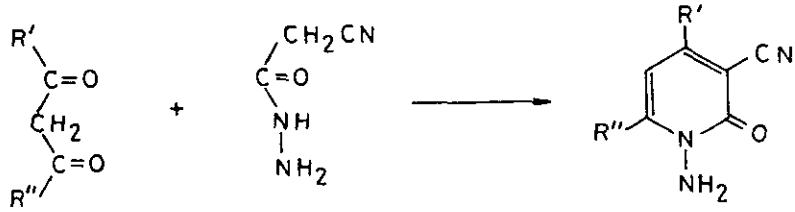
Chart 22

The coupling reaction of hydrazides with benzenediazonium salts has been reported to yield tetrazines which could be readily cyclized to tetrazoles.[266]

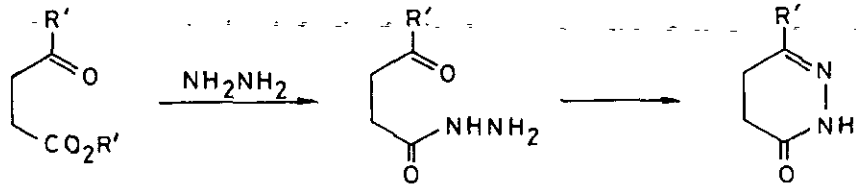


II- SYNTHESIS OF SIX MEMBERED HETEROCYCLIC DERIVATIVES:

Synthesis of pyridines,[267-278] pyridazines,[167,279-287] triazines[284] and tetrazines[282,286-291] utilizing hydrazines and hydrazine derivatives is one of the most general approaches for the synthesis of these ring systems. We are going here to report only recent synthetic utilities of hydrazine derivatives for the synthesis of these derivatives. Formation of pyridines from reaction of 2-cyanoethanoic acid hydrazide with β-dicarbonyl compounds has been reported by Ried et al. as shown below:[267]



The most general method for the preparation of pyridazines (108) involves the reaction of hydrazine with γ-oxobutyric acid derivatives,[117,167,279-285] to yield the intermediate (107) which then cyclizes to the final product (108).



106 107 108

An alternate to this procedure has been recently reported.[287] Thus coupling of malononitrile dimer (109; X=CN) and ethyl cyanoacetate dimer (109; X=$COOC_2H_5$) with aryl diazonium salts have been reported to afford hydrazones (110) (cf. Chart 23).[283,286,287]

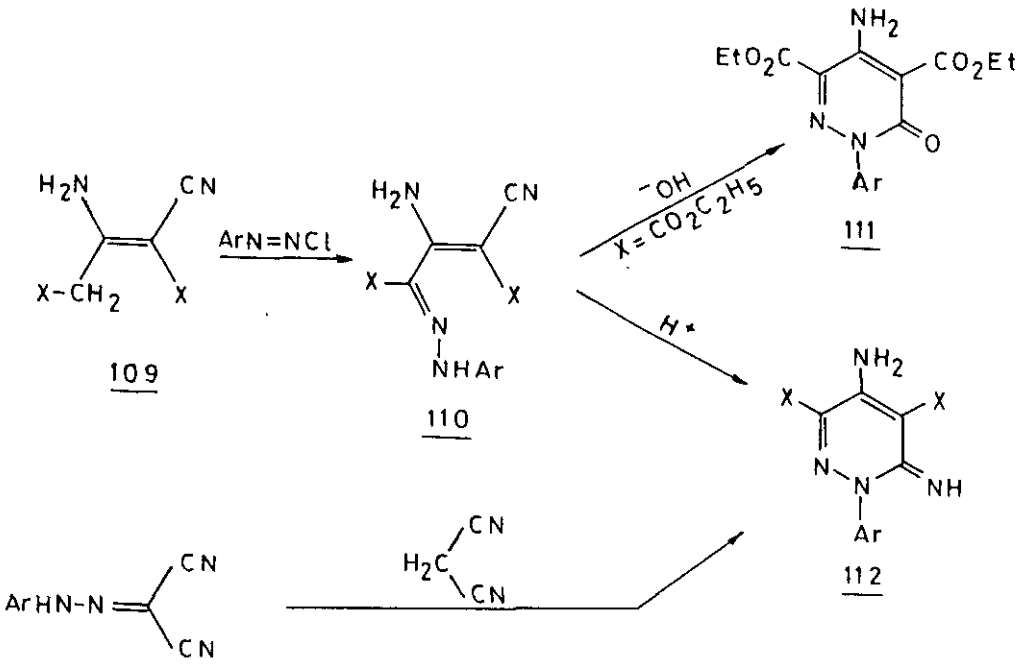


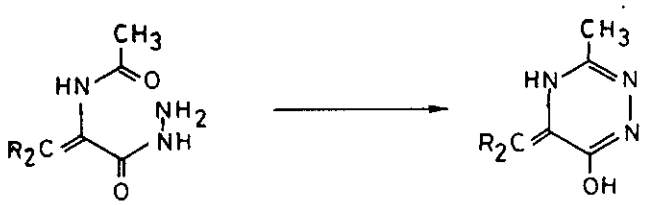
Chart 23

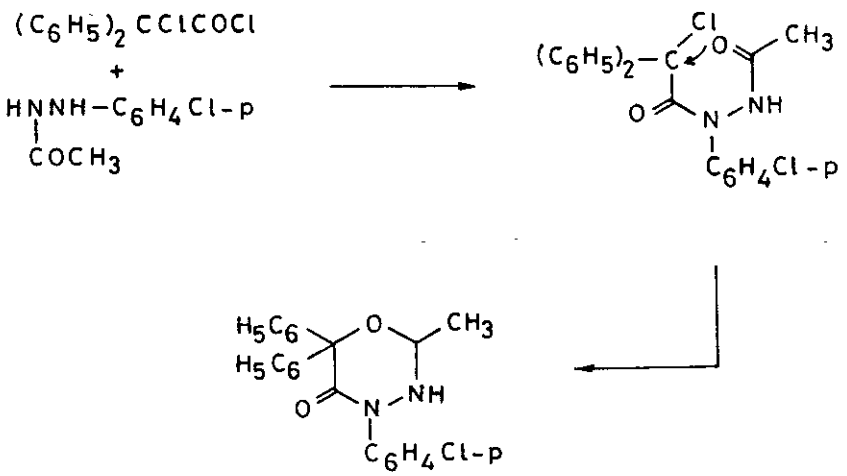
The latter cyclized either into pyridazinones (111) or pyridazin-6-imine (112) depending on cyclization conditions.

Quite similar to this synthesis is the reported cyclization of hydrazone into the pyridazine derivative (114).[283]

113 114

1,2,4-Triazines and 1,3,4-oxadiazines have been obtained via procedures which are in fact extension to these described above. Examples are shown in Chart 24.[288-296]





A variety of procedure for the synthesis of 1,2,4,5-tetrazines have been reported[297-301] in literature. These are shown in Charts 25 and 26.

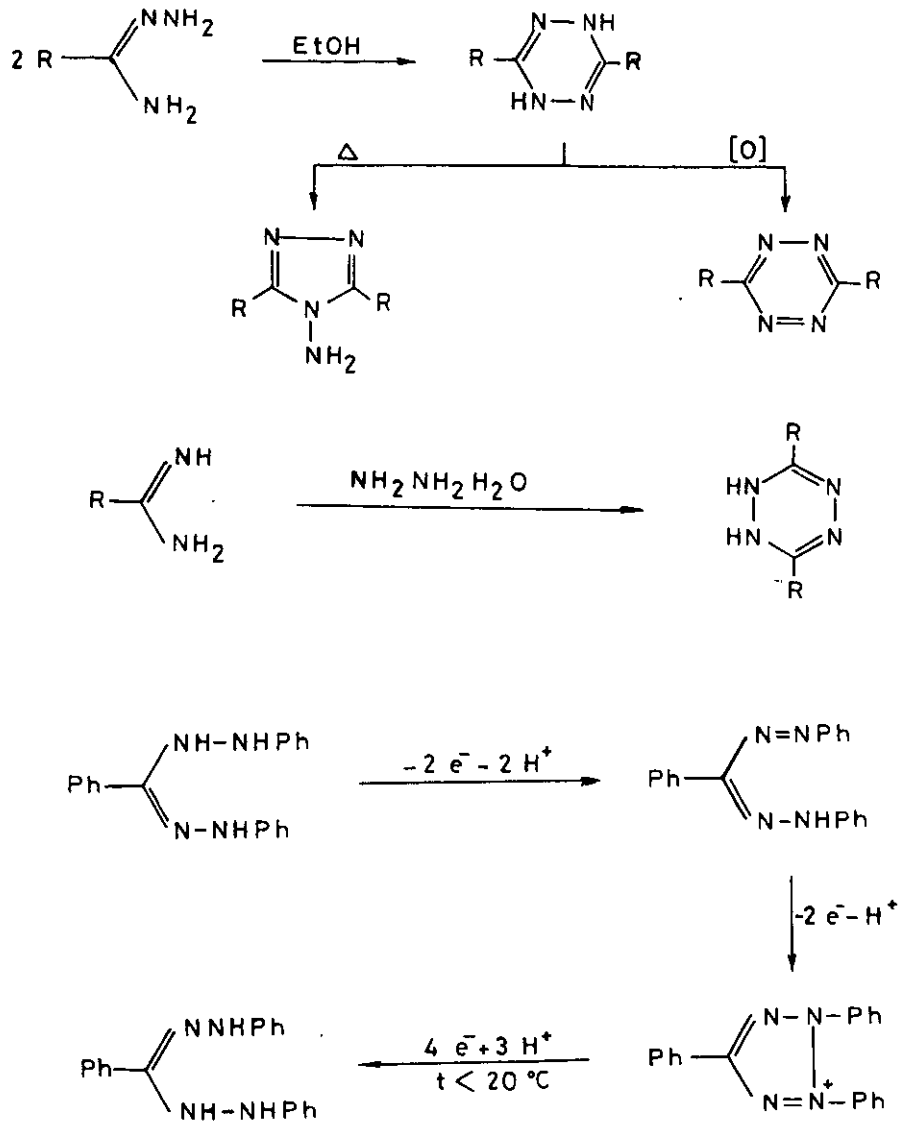


Chart 25

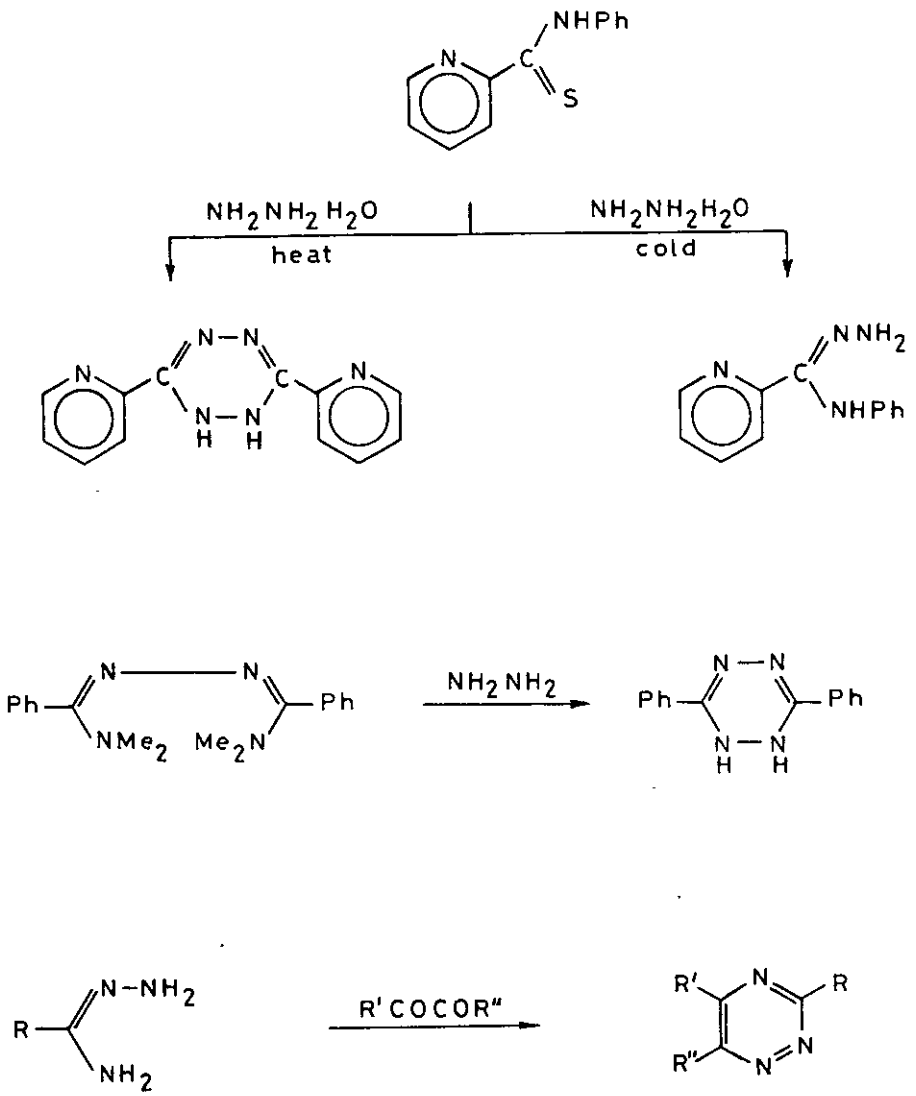
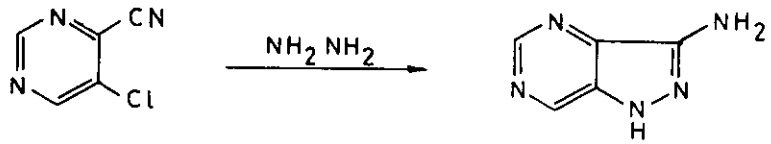


Chart 26

III- SYNTHESIS OF FUSED HETEROCYCLES:

Enormous number of fused heterocyclic derivatives have been described in literature in which hydrazines and hydrazine derivatives have been utilized as starting materials.[302-318] Surveying literature in this area

in a comprehensive thesis review article is completely impossible. Consequently we have decided to report here synthesis of only biheterocyclic systems in which the starting material is a derivative of ring system considered in the previous three chapters. Even this proved to be highly difficult task as thousand of papers should have been reviewed. Again it was decided to report here the general methods of synthesizing such fused heterocycles, perhaps the most common synthetic approach is the reaction of hydrazines with suitably located functional groups in a way enabling synthesis of fused heterocycles. Thus, 5-chloro-4-cyanopyrimidine (115) reacted with hydrazine to afford 3-amino-pyrazolo|4,5-d|pyrimidine (116).[318]



115 116

The corresponding esters were readily converted into pyrazolo|4,3-d|pyrimidines on treatment with hydrazines. Quite similarly is the reported formation of (118) from the reaction of (117) and hydrazines (cf. Chart 27).[115]

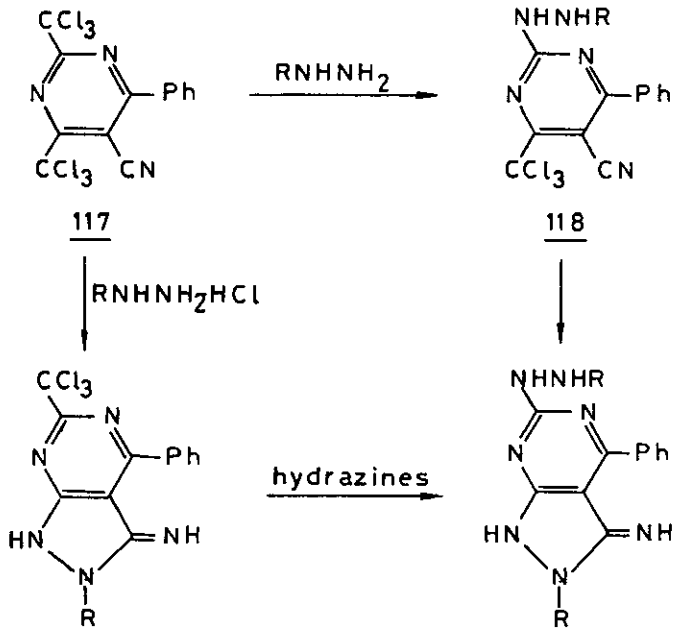
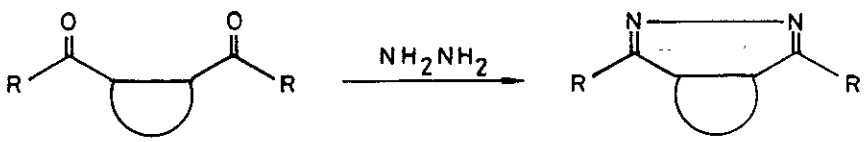


Chart 27

Fused pyrazolines have been synthesized via the reaction of O-difunctionally substituted azoles with hydrazines as shown below:[58,319]



Hydrazinoazoles having a 2-hydrazinopyrazole structure has been reported to afford fused triazoles.[168,169,320-326] A variety of reagents have been utilized and some of the interesting results are shown in Chart 28.

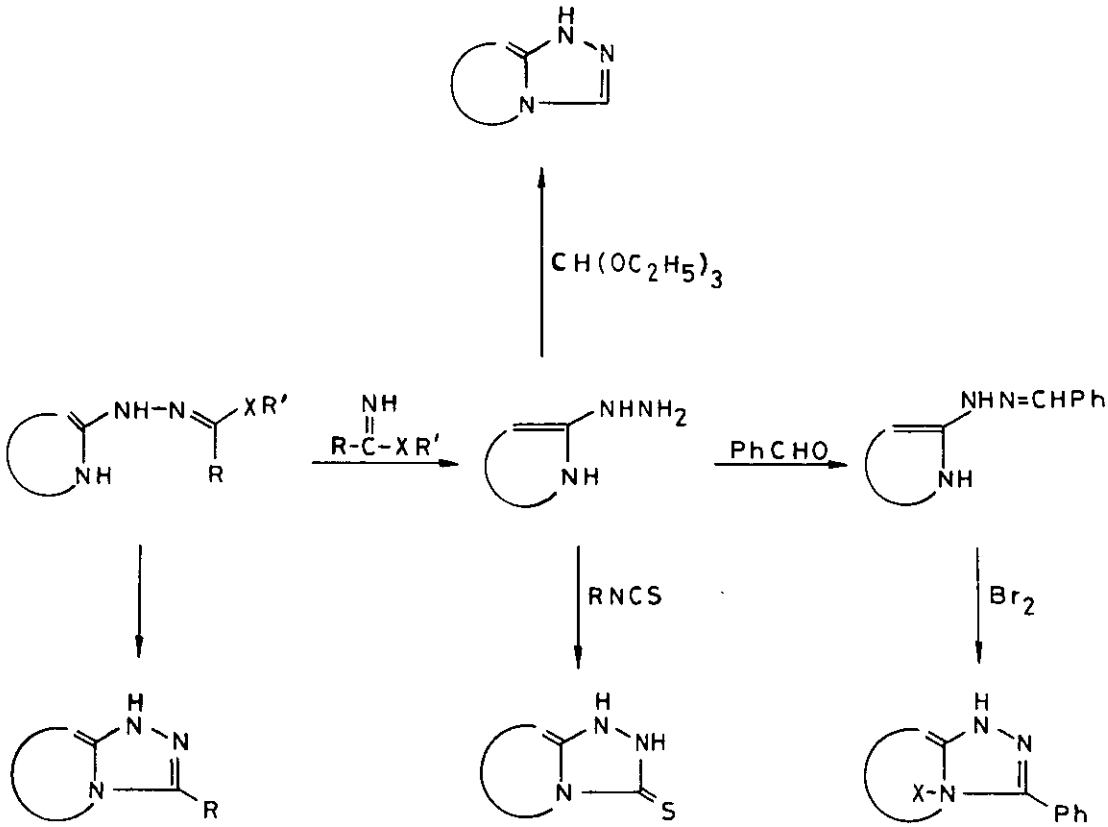


Chart 28

Heterocyclic diazonium compounds and heterocyclic diazo compounds have been extensively utilized for synthesis of fused heterocyclic derivatives, and reactions of this type have recently been surveyed by our group. The most interesting reactions of this type are reported.[168-170,321] (cf. Charts 29,30).

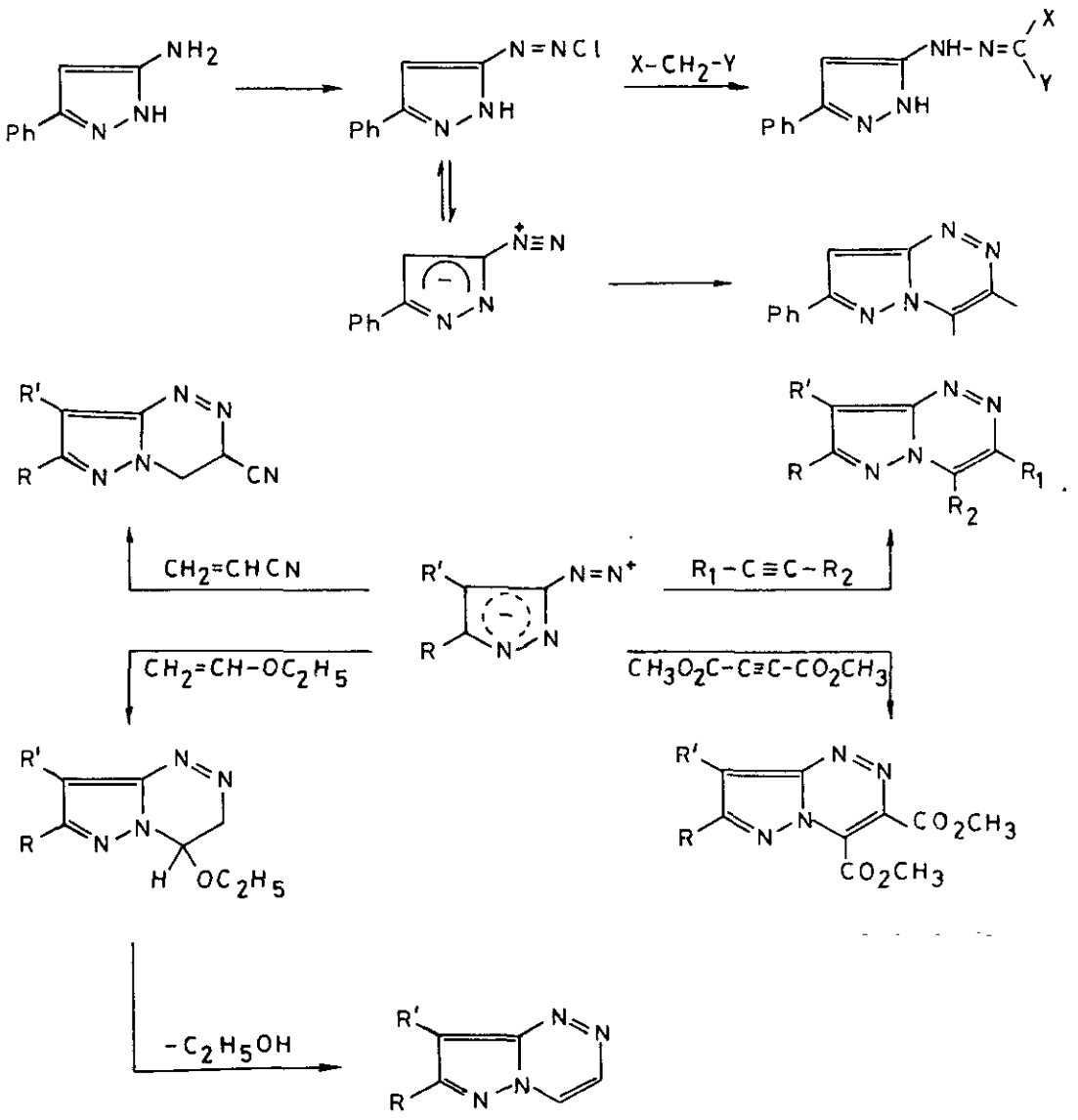


Chart 29

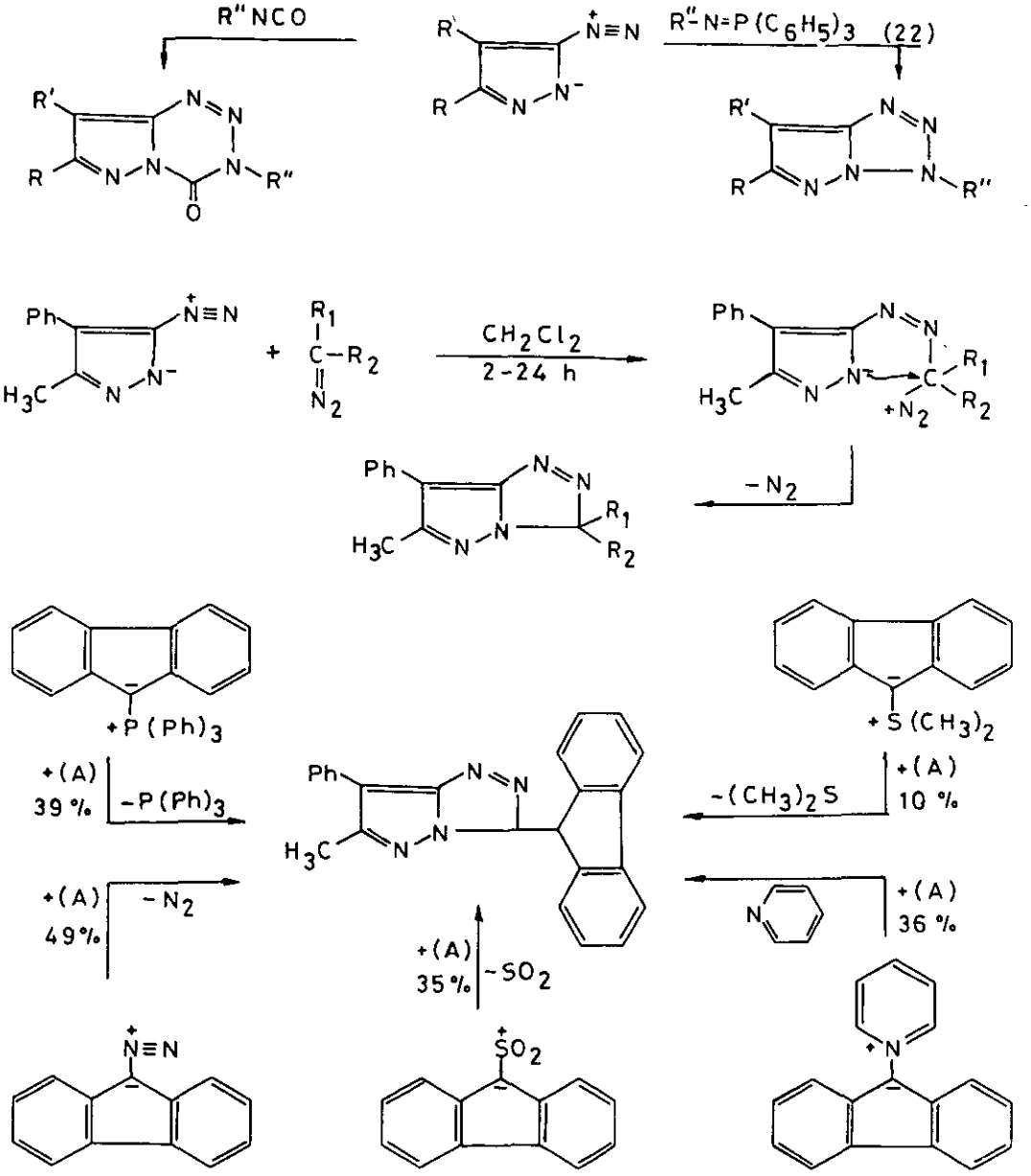


Chart 30

Hydrazine derivatives of heterocyclic compounds having suitable functional substituent at the hetero ring have also been utilized for synthesis of fused heterocycles. Some interesting examples are shown in Chart 31.[67,324,326]

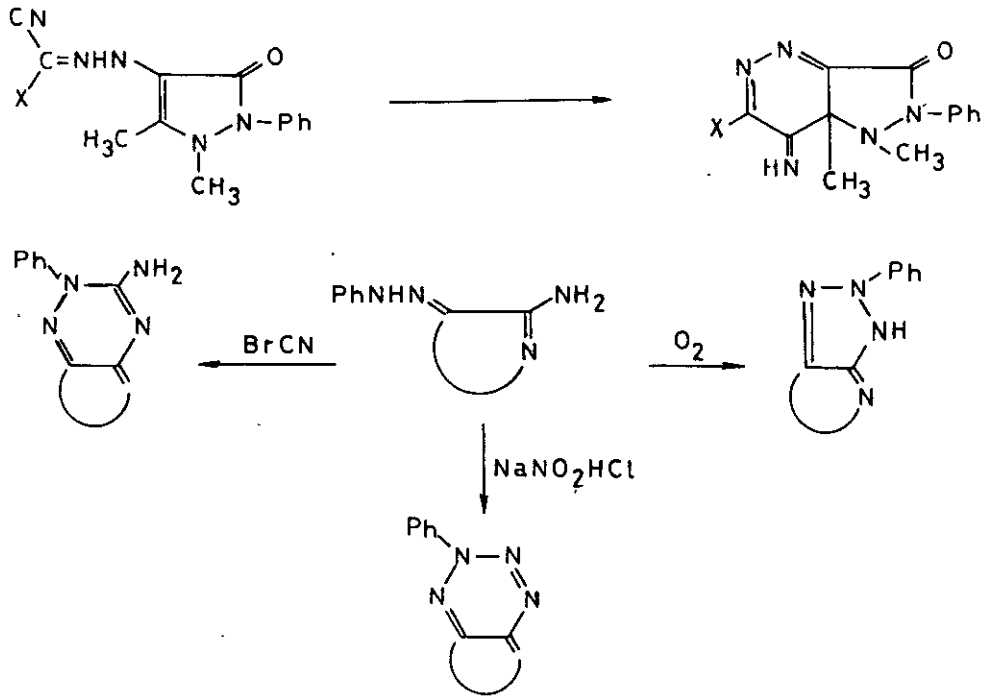
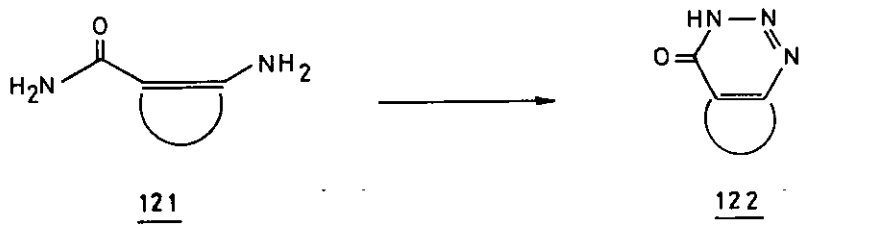
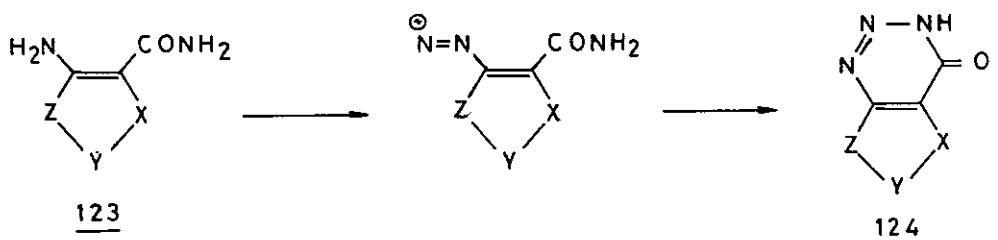


Chart 31

Diazotization of (121) affords usually 1,2,3-triazine derivative (122) via the self coupling with the amide nitrogen.[166]



121 122



123 124

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