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UTILITY OF α,β-UNSATURATED NITRILES IN HETEROCYCLIC SYNTHESIS

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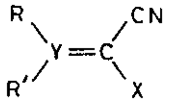
Abstract - New approaches for synthesis of different mono and polyheterocyclic derivatives utilising α,β-unsaturated nitriles are surveyed. The scope and limitation of the most important of these approaches are demonstrated.

INTRODUCTION:

α,β-Unsaturated nitriles (1) are versatile reagents which have been extensively utilised in heterocyclic synthesis. In spite of enormous number of reports on the utility of these compounds in synthesis of heterocycles, up to our knowledge, this subject has never been surveyed. The utility of acrylonitrile in heterocyclic synthesis has been surveyed by Bruson[1] in a chapter on cyanoethylation. However, this survey is now obsolete. The utility of tetracyanoethylene in heterocyclic synthesis has been reported previously by Meyers and Sircar[2] and as a part of a book on chemistry of cyano group. It was thus decided to demonstrate in this review only reactions of tetracyanoethylene that have not been surveyed in this reference. Reactions of α,β-unsaturated nitriles affording heterocyclic derivatives that have been recently reviewed by Freeman[3] will not be further discussed here.



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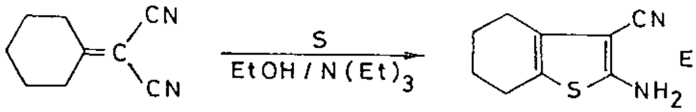
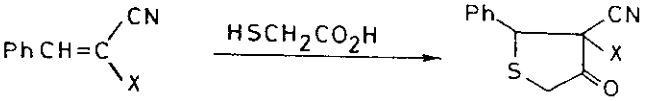
I- FIVE-MEMBERED RINGS FROM α,β-UNSATURATED NITRILES:

(A) Five-membered rings with one hetero-atom:

α,β-Unsaturated nitriles were thiolated into thiophen derivatives. For example, the arylidene derivative of cyclohexanone (2) was converted into the enaminothiophen derivative (3) on treatment with elemental sulphur.[4] The enamines can also be formed on heating mixtures of the ketone, the activated nitrile and elemental sulphur in the presence of a basic catalyst (cf. Eq. 1).

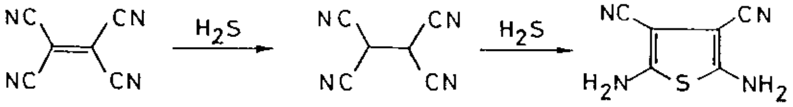

2 3 Eq. 1

Recently, the formation of thiophens from the reaction of α,β-unsaturated nitriles with thioglycollic acid has been reported.[5,6] The reaction may be thus considered as an extension of the Fiesselmann[7] thiophen synthesis (cf. Eq. 2).


$X = -CN$
$X = -CO_2C_2H_5$
$X = -COPh$

Eq. 2

Tetracyanoethylene (4) has been reported to react with hydrogen sulphide to yield the thiophen derivative (5).[8,9]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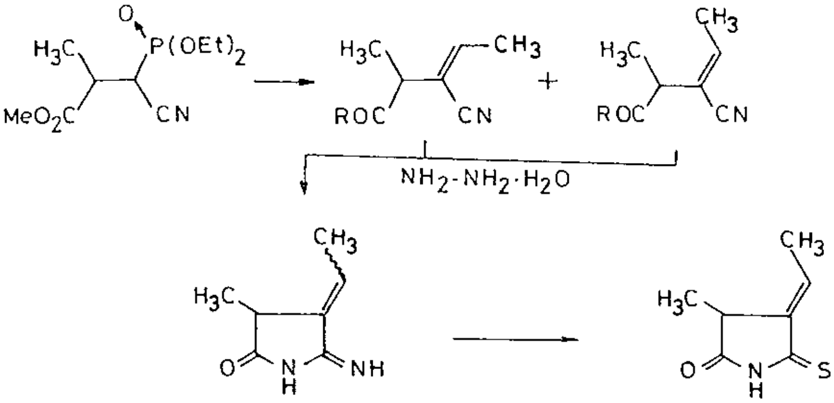
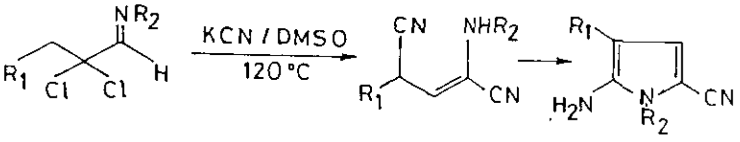
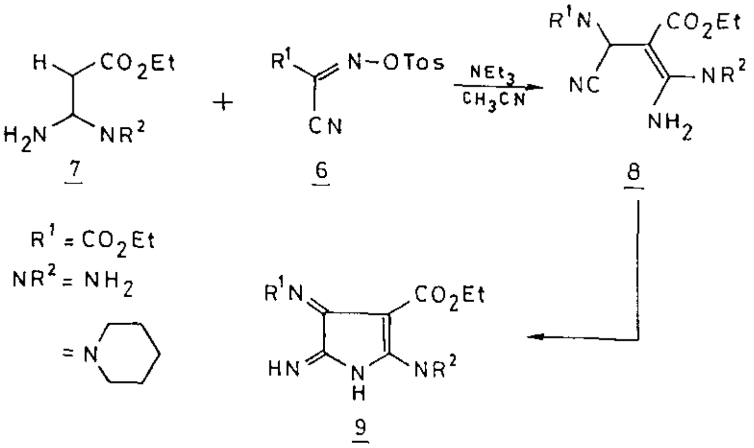
Several syntheses of pyrrole derivatives from α,β-unsaturated nitriles have recently been reported and are shown in equations 3 and 4.[10-12]


Eq. 3



Eq. 4

Recently an interesting pyrrole synthesis from the reaction of oximinonitriles (6) with enaminoesters (7) has been reported. The reaction is assumed to proceed via intermediacy of the acyclic (8) which then cyclise into the final isolable product (9).[13]



Nucleocides pyrrole derivative has also been synthesised utilising α,β-unsaturated nitriles.[14] Example is shown in chart 1.

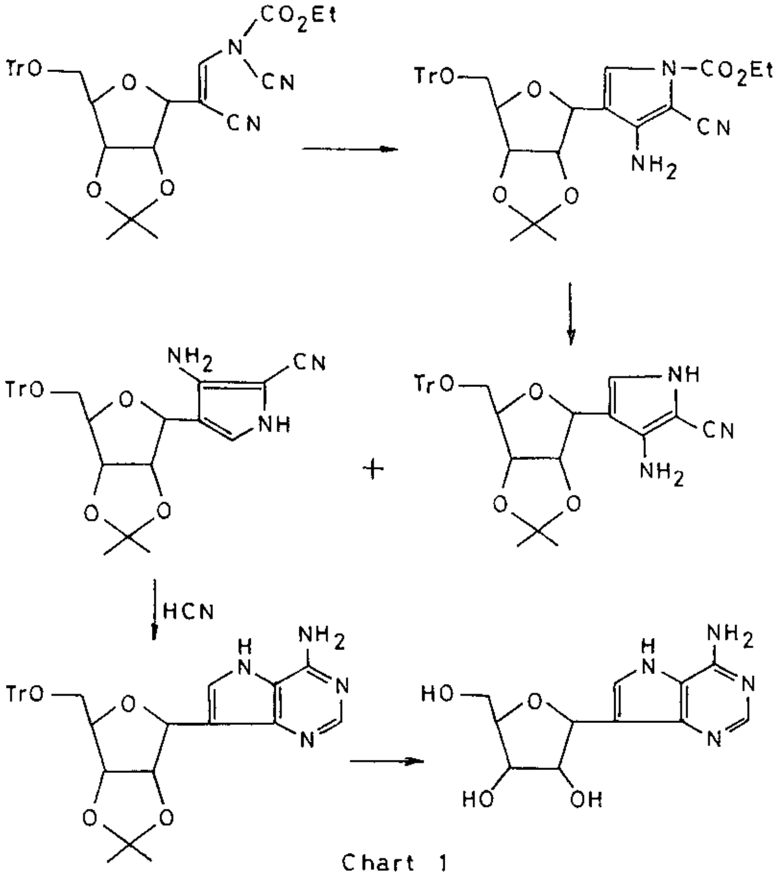
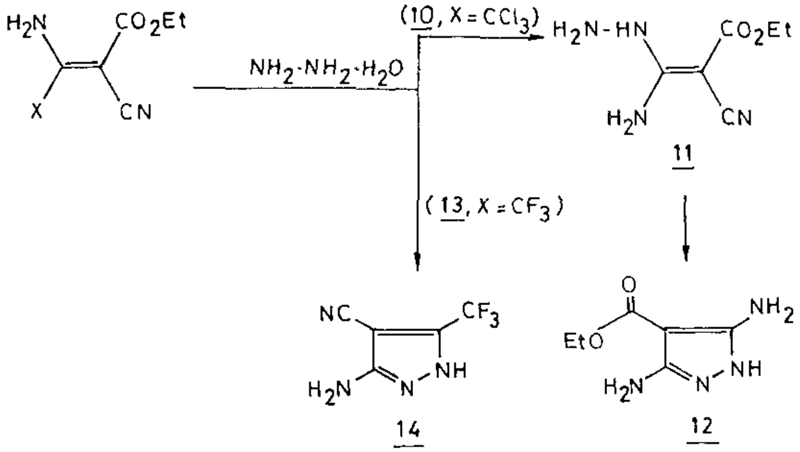


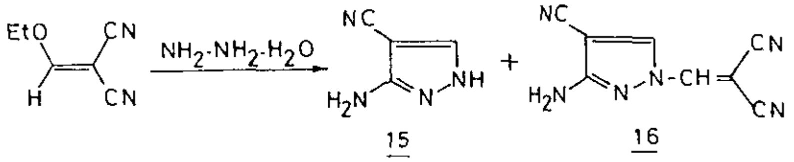
Chart 1

(B) Five-membered rings with two hetero-atoms:

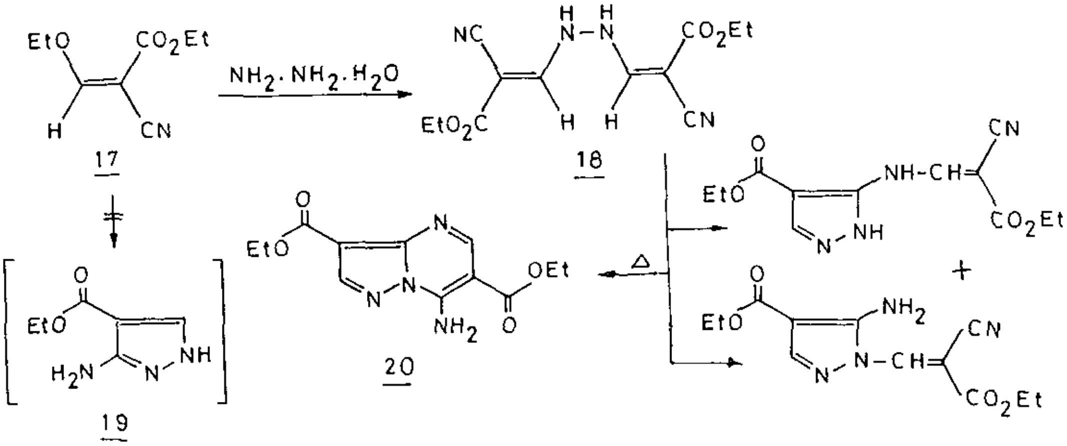
It has been shown that ethyl β-trichloromethyl-β-aminomethylenecyanoacetate (10, X=CCl_3), reacts with hydrazine hydrate to yield the aminopyrazole derivative (12) via intermediate formation of the amidrazone (11) which could be isolated.[15-19] This is in contrast to the reported formation of 3-amino-4-cyano-5-trifluoromethylpyrazole (14) on treatment of β-trifluoromethyl-β-aminomethylenemalononitrile (13, X=CF_3) with hydrazine hydrate.[19] Synthesis of pyrazoles via similar routes has been recently reported.[20-21]



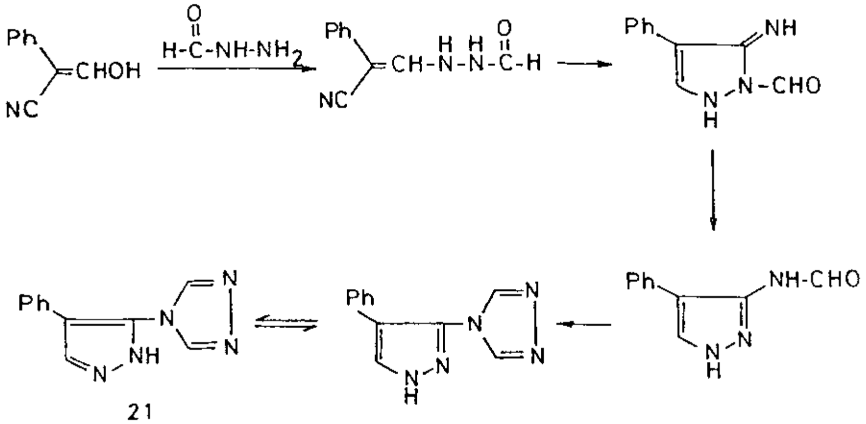
Ethoxymethylenemalononitrile reacted with hydrazine hydrate to yield the pyrazole derivatives (15) and (16).[22]



In an attempt to synthesis 3-amino-4-ethoxycarbonylpyrazole (19) via reacting (17) 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[23,24] have obtained instead of the expected pyrazole derivative (19) the pyrazolo[1,5-a]pyrimidine derivative (20). The formation of this product is expected to proceed via intermediate formation of (18).



4-(4-Phenyl-3-pyrazolyl)-4H-1,2,4-triazole (21) was recently prepared by the action of formylhydrazine on α-phenyl-α-cyanoacetaldehyde.[25]



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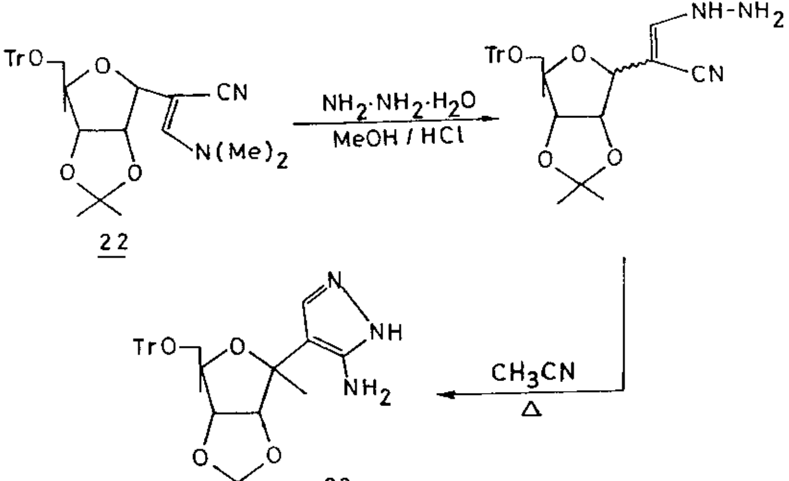
β-Dimethylamino-α-(2-ribosyl) acrylonitrile (22) reacted with hydrazine hydrate to yield the aminopyrazole derivative (23). This opened a new route for the synthesis of formycone and formycine analogues.[26]



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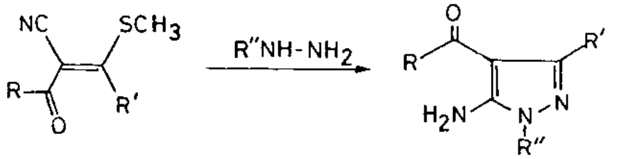
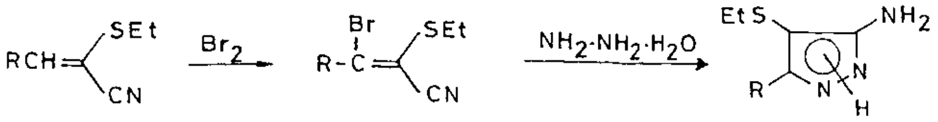
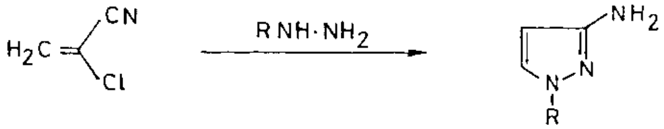
23

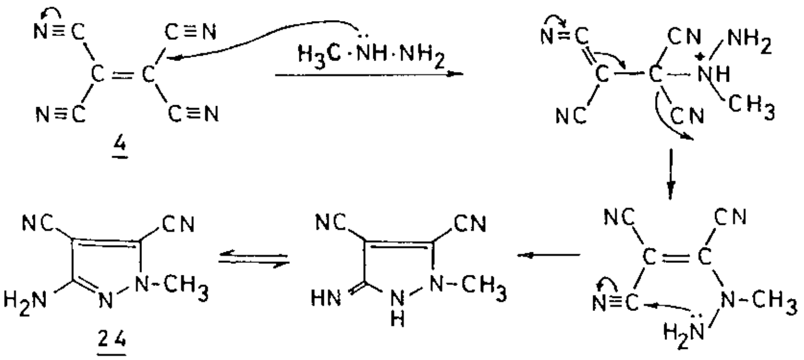
A variety of new pyrazole derivatives have been synthesed utilising the same idea of reacting α,β-unsaturated nitriles with hydrazine or acylated hydrazines Examples for the most interesting of these syntheses are shown below.[27-50]



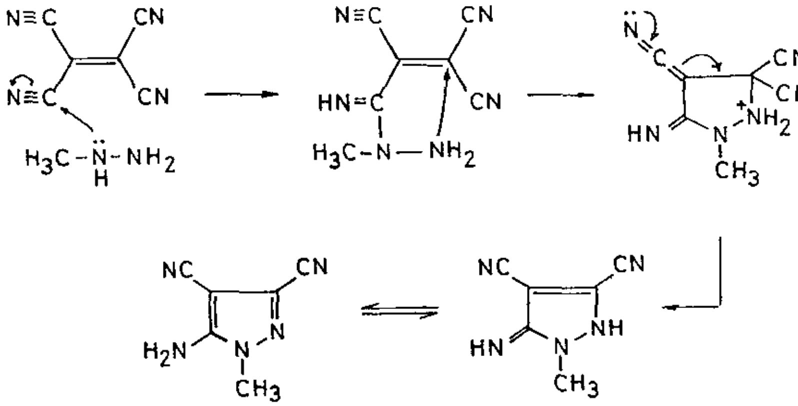




3,4-Dicyano-5-aminopyrazoles are synthesised by taking the advantage of the propensity of tetracyanoethylene (4) for Michael addition. Thus, aryl- and alkylhydrazones as well as hydrazides, semicarbazides and thiosemicarbazides have been reported to react with tetracyanoethylene (4) to afford 1-substituted 4,5-dicyano-3-aminopyrazoles.[46] The structure assigned for the reaction product of tetracyanoethylene (4) with methylhydrazine was reinvestigated by Hecht et al[47] and Earl et al[48] in two separate contributions. It has been shown by Hecht et al[47] 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 (4). Thus, one might for example, envision formation of the 1-methyl-4,5-dicyano-3-aminopyrazole (24) by conjugate addition of the more nucleophilic substituted nitrogen of methylhydrazine to tetracyanoethylene (4) 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:



Both authors on reconducting the above reaction have shown that it affords a mixture of two isomeric pyrazoles (53% and 27%[47], 47% and 8%[48]). These authors have shown on the basis 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 1-methyl-3,4-dicyano-5-aminopyrazole.

2,3-Diaminofumaronitrile has recently been utilised for the synthesis of imidazole derivatives[50] (cf. Chart 2).

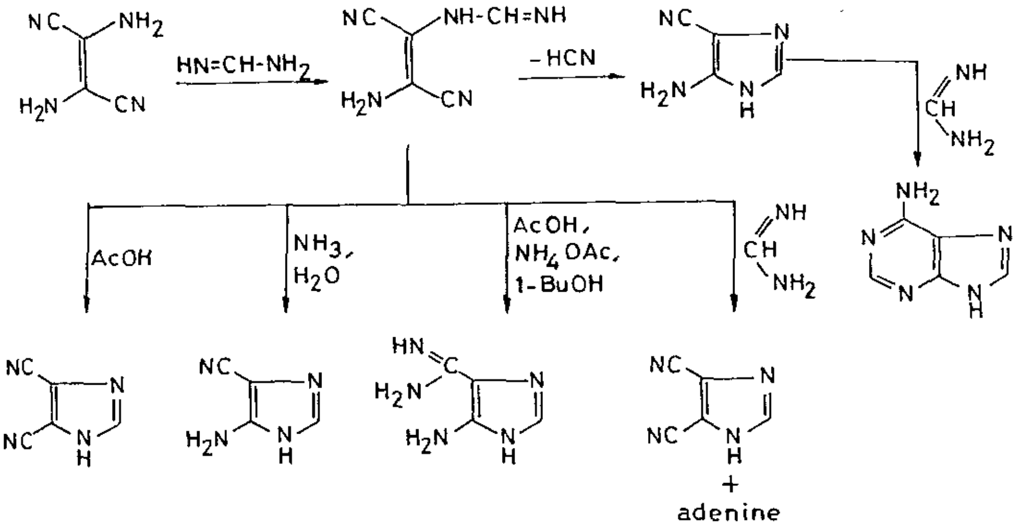
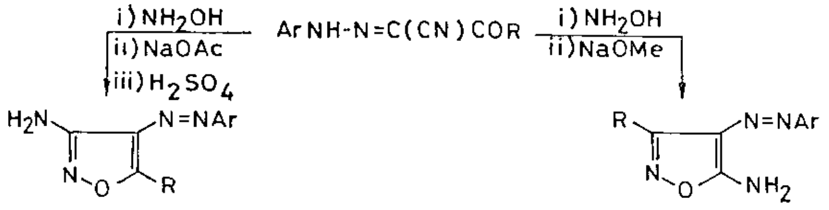
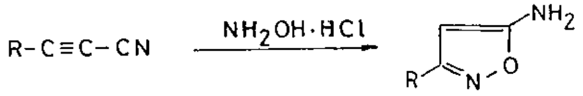


Chart 2

α,β-Unsaturated nitriles have been extensively utilised for the synthesis of amino-1,2-oxazoles[51-53] (cf. Eqs. 5 and 6).



Eq. 5



Eq. 6

When the salt of dimercaptomethylenemalononitrile[54] (25) is treated with sulphur in refluxing methanol, the isothiazole derivative (28) was obtained in a good yield. The existance of intermediates (26) and (27) has been envisioned. The former arises from nucleophilic attack by mercaptide ion on sulphur, whereas the latter involves a second nucleophilic attack on the nitrile with expulsion of the sulphur moiety by the nitrogen. Another example of this reaction involving the mononitrile derivative (29) has been described, which presumably proceeds through the same path, leading to the isothiazole derivative 30 (cf. Chart 3).

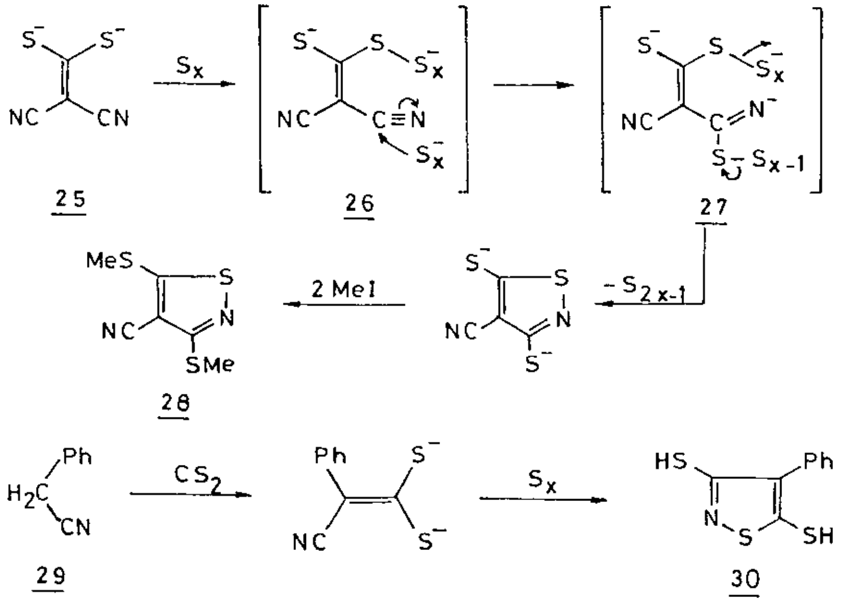
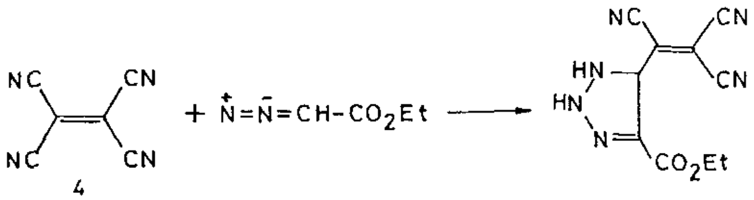


Chart 3

(C) Five-membered rings with three hetero-atoms:

Tetracyanoethylene (4) reacts with ethyl diazoacetate to yield 1,2,3-triazoles.[55]



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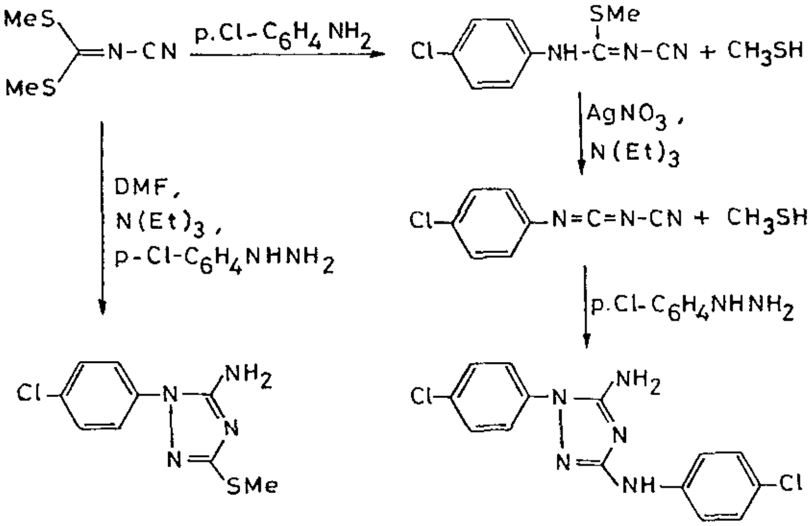
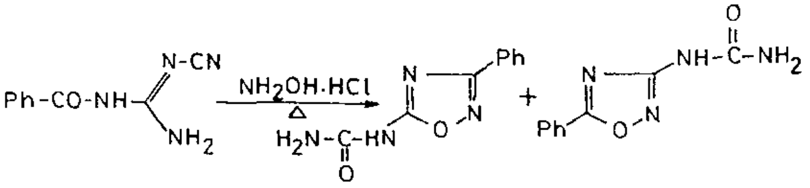
Cyanamide derivatives have been extensively utilised for the synthesis of 1,2,4-triazoles.[56-59] One interesting example for the utility of these reactions is shown below:

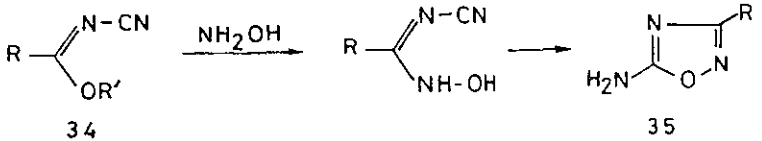


Cyanamide derivatives have been utilised for the synthesis of oxadiazoles.[60] For example, benzoyldicyandiamide (31) affords a mixture of the urido-1,2,4-oxadiazole derivatives (32) and (33) on treatment with hydroxylamine, the first predominating.[57,60]



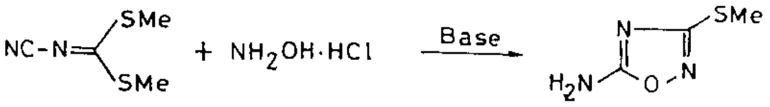
31 32 33

Similarly, the iminoether (34) affords the amino-oxadiazole derivative (35) on reaction with hydroxylamine.[61]



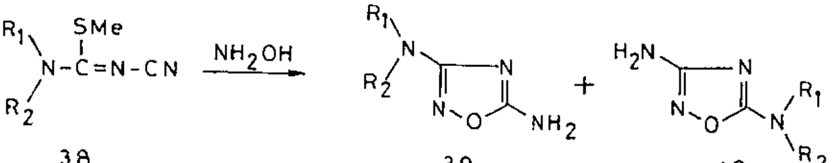
34 35

Also the cyanamide (36) reacted with hydroxylamine to yield 1,2,4-oxadiazole derivative (37).[62]



36 37

1-Substituted-3-cyano-isothioureas (38), gave mixture of the 5-amino 3-substituted-amino-1,2,4-oxadiazoles (39) and the isomeric 3-amino-5-substitutedamino-1,2,4-oxadiazoles (40) on reaction with hydroxylamine, compound (39) usually predominated.[63]



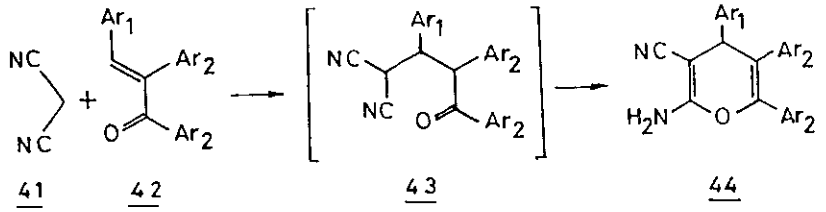
38 39 40

II- SIX-MEMBERED RINGS FROM α,β-UNSATURATED NITRILES:

Synthesis of vast number of heterocyclic six membered derivatives utilising α,β-unsaturated nitriles as starting materials has been reported.[64-86] Many of these synthetic approaches were surveyed by Taylor,[64] Freeman[3] and Meyers and Sircar.[2] These routes are not going to be discussed further and we are going to report only recent contributions in this area or contributions so related to our area of interest that its ignorance seems unlikely.

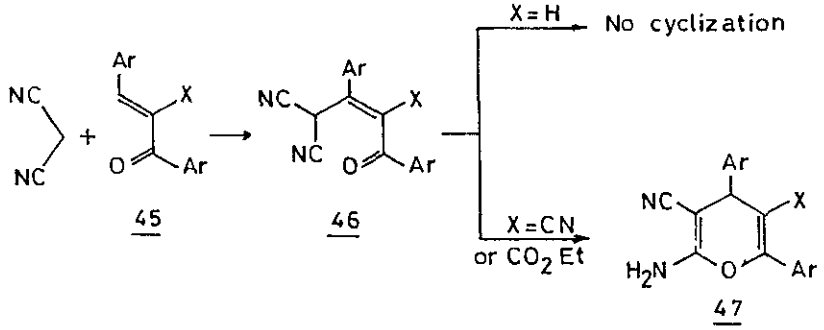
(A) Six-membered rings with one hetero-atom:

The spontaneous cyclization of the δ-cyanoketone (43), resulting from the addition of malononitrile (41) to benzylidenedeoxibenzoine (42), affords a 2-amino-4H-pyran ring 44.[68]



The reaction of a series of substituted benzylideneoxibenzoines with malononitrile in ethanol at room temperature with a trace of a basic catalyst has allowed the preparation of a series of 2-amino-3-cyano-4,5,6-triaryl-4H-pyrans (44) in high yields (70 90%).

It must be pointed out that the presence of the aryl group at position 5 in the resulting adduct is important for the cyclization. When malononitrile reacts with the chalkone (45, X=H), the cyclization does not take place and the adduct (46, X=H) is the product isolated from the reaction. On the other hand, the reaction of malononitrile with α-benzoylcinnamonitrile (45, X=CN) or ethyl α-benzoylcinnamate (45, X=CO_2Et) leads to pyrans (47).



Junek[87] has reported that salicylaldehyde reacts with 2-amino-1,1,3-tricyano-pent-2-ene (48) to yield the benzopyrano-[3,4-c]pyridine derivative (50). Substituted salicylaldehyde have been reported[87] to afford the iminocoumarin derivative (49). In a recent paper,[88] however, salicylaldehyde reacted with (48) to yield (51). Similarly, diethyl 3-amino-2-cyanopent-2-ene 1,5-dicarboxylate (52) has been reported to react with salicylaldehyde to yield (53). The same compound has been claimed to be obtained directly from reaction of salicylaldehyde with ethyl cyanoacetate[89] (cf. Chart 4).

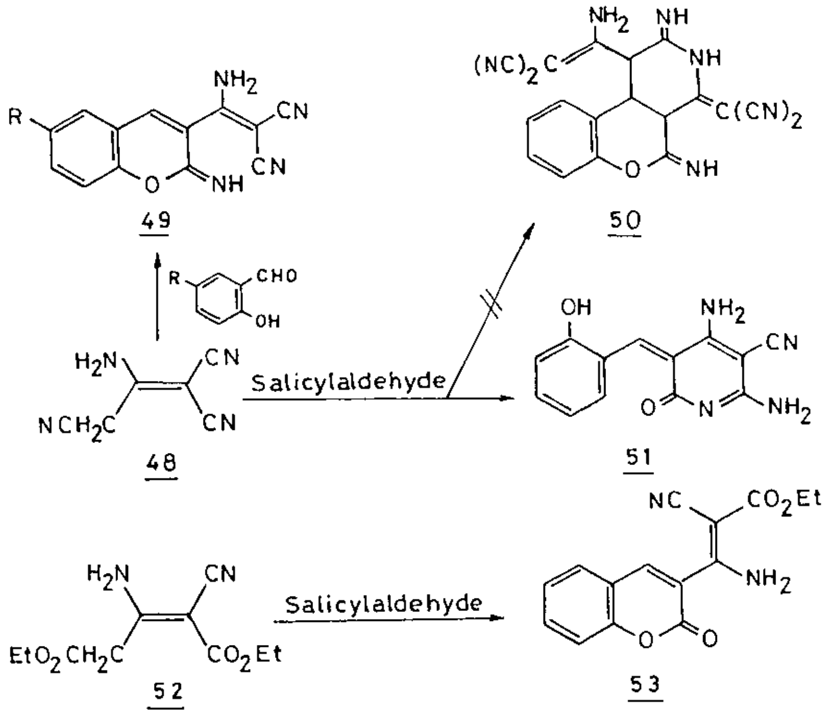
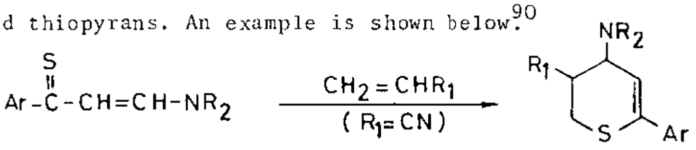


Chart 4

The reaction of acrylonitrile with α,β-unsaturated thioketones has been recently reported to afford thiopyrans. An example is shown below.[90]



Midorikawa et al[91] have shown that the reaction of substituted amines with ylidenemalononitriles affords pyridine derivatives (cf. Chart 5).

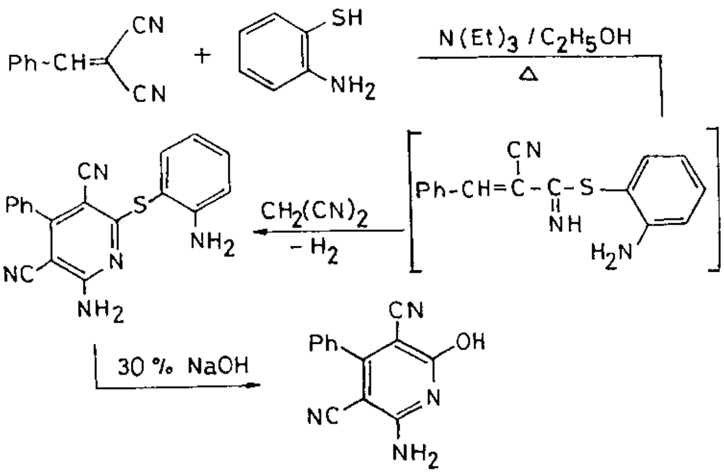


Chart 5

Conversion of 4-acetyloxazoles into pyridine derivatives via reaction with malononitrile has been reported. The reaction proceeds via formation of the yiledenemalononitrile derivative 54[92] (cf. Chart 6).

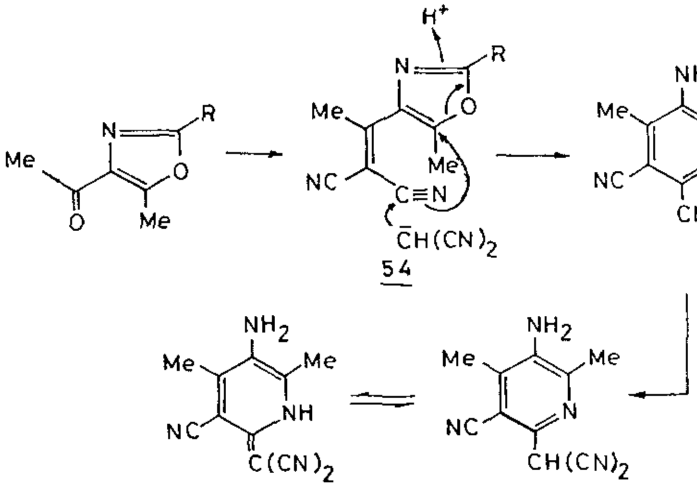
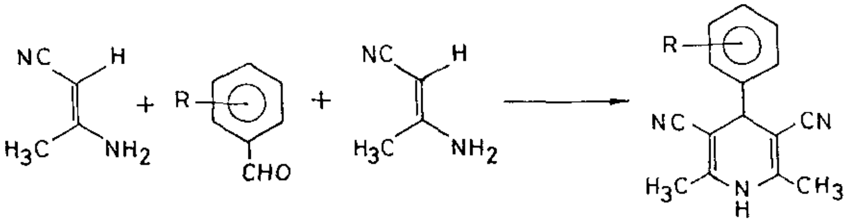


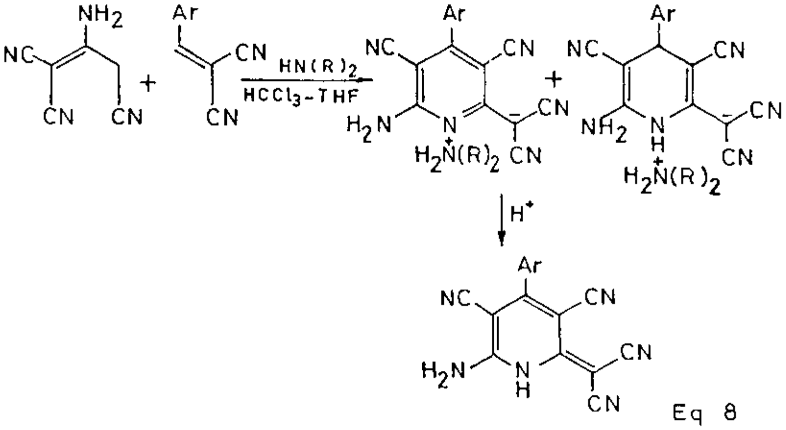
Chart 6

Several other pyridine syntheses from activated α,β-unsaturated nitriles are already available in literature, a very old example is the reaction of 2-aminocrotononitrile with aromatic aldehyde to yield a pyridine derivative[93] (cf. Eq. 7).

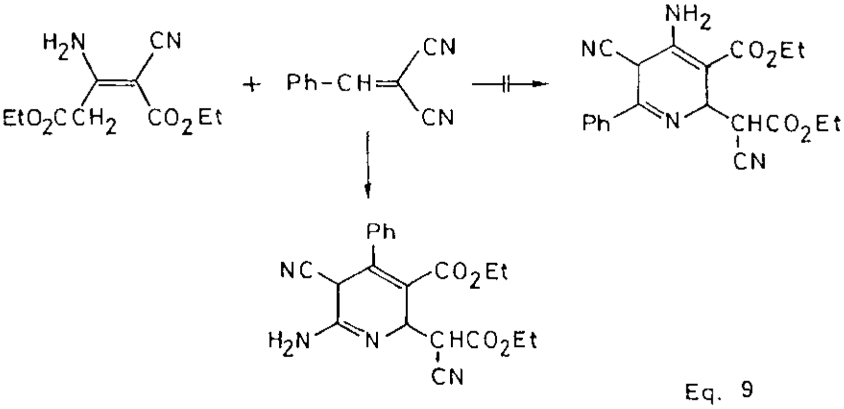


Eq. 7

Other interesting examples for the application of similar ideas have appeared in recent literature. For example, 2-amino-1,1,3-tricyanopent-2-ene (48) has been reported to react with benzalmalononitrile to yield pyridines.[94] Similarly, diethyl 3-amino-2-cyanopent-2-ene 1,5-dicarboxylate (52) has been reported to yield pyridines utilising almost the same idea[69] (cf. Eqs. 8 and 9).

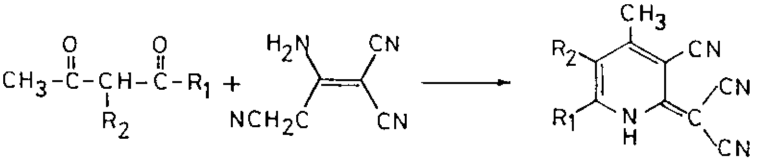


Eq 8

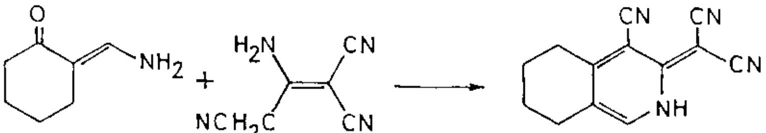


Eq. 9

2-Amino-1,1,3-tricyanopent-2-ene (48) has been reported to condense with β-diketones and β-aminoenones to yield pyridine derivatives[95-97] (cf. Eqs. 10,11).



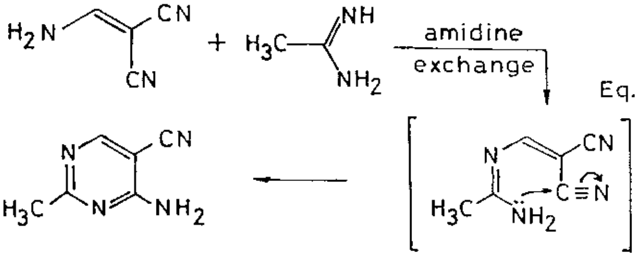
Eq. 10



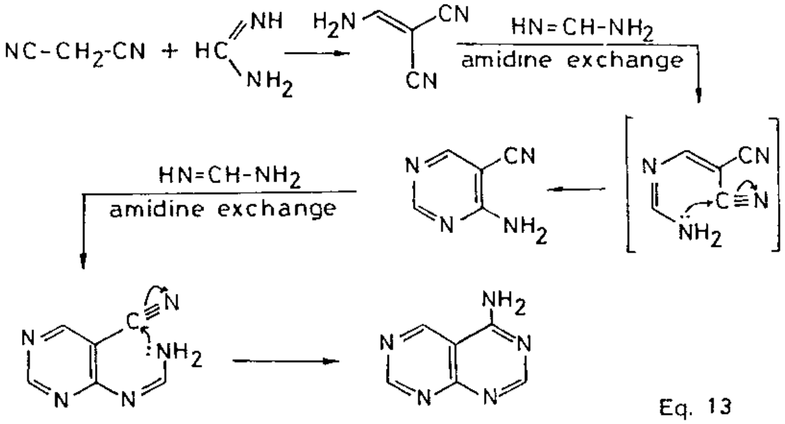
Eq. 11

(B) Six-membered rings with two hetero-atoms:

α,β-Unsaturated nitriles have been extensively utilised for the synthesis of pyrimidines. Taylor et al[64,98] have summarised all literature in this area in more than one reference. One of the interesting recent examples of the utility of α,β-unsaturated nitriles for pyrimidine synthesis is the reported reaction of 2-aminomethylenemalononitrile with acetamidine to yield pyrimidines[98] (cf. Eq. 12). Other important contribution in this area is shown in equation 13.[64] Recently, cyanoethylation of guanidine has been reported to afford pyrimidines.[99] Thus, cyanoethylation of cyanoguanidine in presence of lithium hydride has been reported to yield pyrimidines (cf. Chart 7).



Eq. 12



Eq. 13

Several interesting pyridazine syntheses utilising α,β-unsaturated nitriles as starting materials have been reported. Thus, compound (55) readily cyclised in protic media to yield the pyridazine derivative 56[100] (cf. Eq. 14).

55 56

Eq. 14

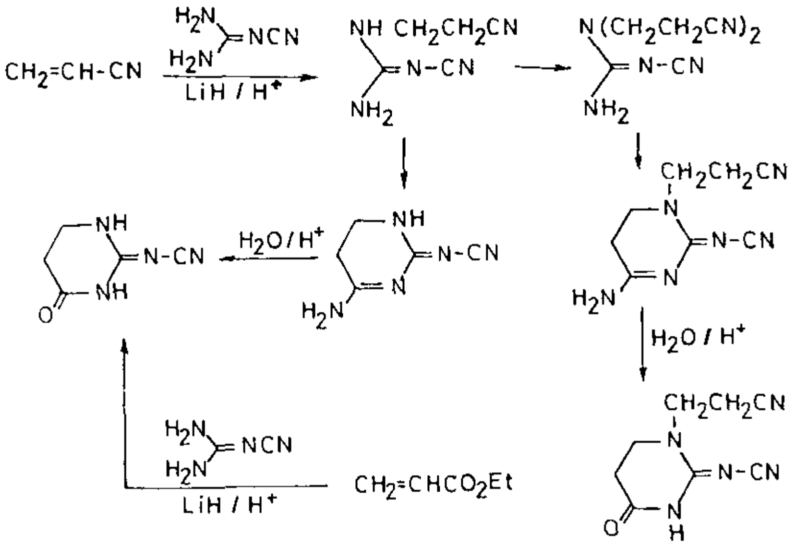


Chart 7

A very similar synthesis of pyridazines has been reported via coupling of 2-amino-1,1,3-tricyanopent-2-ene (48) with aryldiazonium salts and subsequent cyclization of the coupling products. The same pyridazine derivatives could be alternatively synthesised via treatment of arylhydrazono-methoxazolonitrile derivatives with malononitrile, a reaction that proceeds almost certainly via the intermediacy of the hydrazone 57[101] (cf. Chart 8).

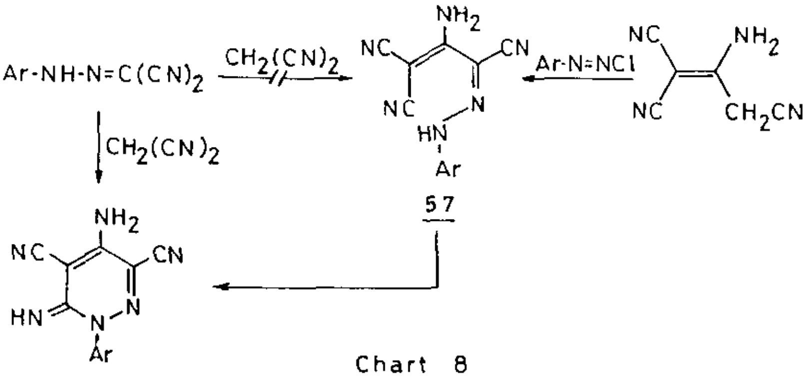
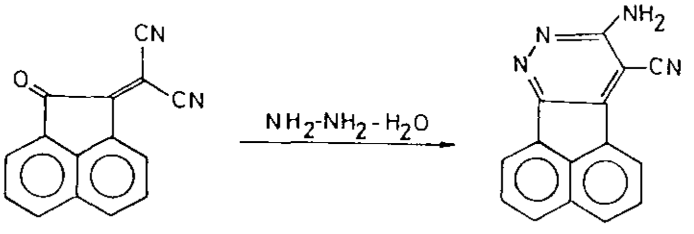


Chart 8

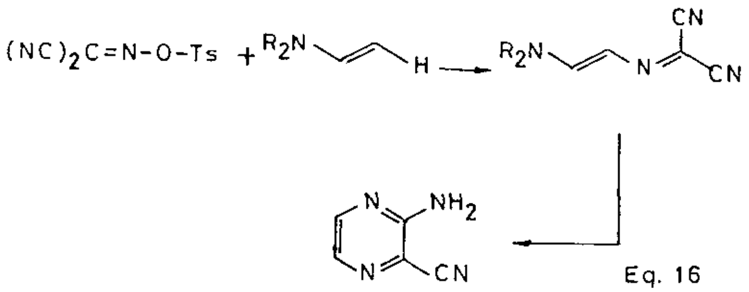
Similar synthesis of pyridazine derivatives utilising diethyl 3-amino-2 cyano-pent-2-ene 1,5-dicarboxylate has been reported.[102]

Acenaphthenoquinones readily condense with malononitrile to yield the corresponding yiledenemalononitrile which reacts readily with hydrazine hydrate to yield aminopyridazine derivative[103] (cf. Eq. 15).



Eq. 15

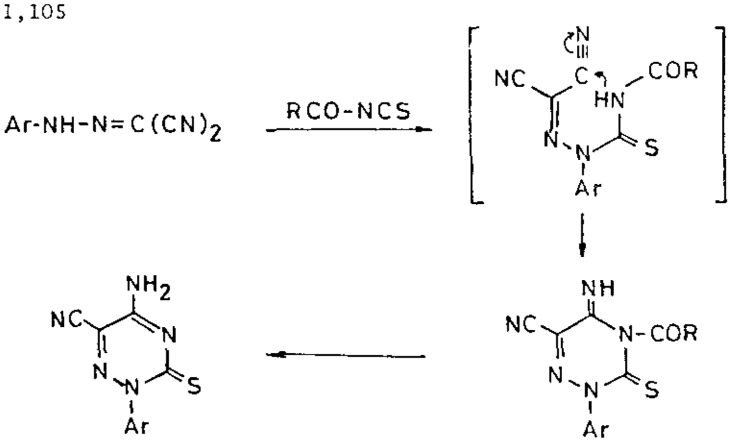
The utilization of o-tosylisonitroso-malononitrile or analogous derivatives for the synthesis of pyrazines is briefly described, following the general scheme[101,104] (cf. Eq. 16).



Eq. 16

(C) Six-membered rings with three hetero-atoms:

Several triazine syntheses starting from α,β-unsaturated nitriles have appeared in recent literature. An interesting recent example of these syntheses is shown in equation 17.[101,105]



a, Ar = C_6H_5
b, Ar = C_6H_4-Cl-p

Eq. 17

III- FUSED HETEROCYCLIC RINGS FROM α,β-UNSATURATED NITRILES:

Cyanoethylation has been extensively utilised to build up fused heterocycles. This is usually accomplished via cyanoethylation of a heterocyclic compound in a position adjacent to which a reactive center is suitably located to permit further reaction of the functional group in the obtained alkylated derivative to condense further with such reactive center to form either a new cyclic or heterocyclic ring. For example, phenoxazine (58a) or its sulphur analogue (58b) reacted smoothly and rapidly with acrylonitrile to yield the corresponding N-β-cyanoethylated products. These were readily hydrolysed into the corresponding acids which on treatment with phosphorus pentoxide afforded a mixture of 2,3-dihydro-3-keto-1H-pyrido[2,1-g]phenoxazine (59a) and its dehydro derivative (60a) or their thioanalogues (59b) and (60b) respectively[106] (cf. Chart 9).

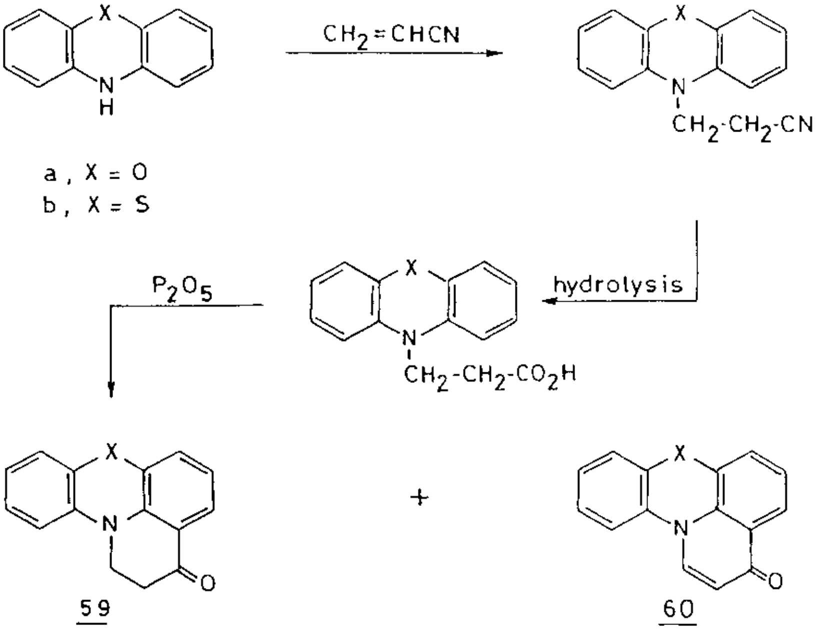


Chart 9

Quite similar to this is the reported cyanoethylation of 7-hydroxycoumarin (61) to yield the corresponding o-cyanoethylated derivative (62) which could be hydrolysed to the corresponding acid (63). The latter on cyclization with polyphosphoric acid has afforded a mixture of (64) and (65). In analogy with the behaviour of (61), 6-amino-7-methylcoumarin (66) reacted with acrylonitrile to yield (67) which readily cyclised into the pyridocoumarin derivative (68) on hydrolysis[107,108] (cf. Chart 10).

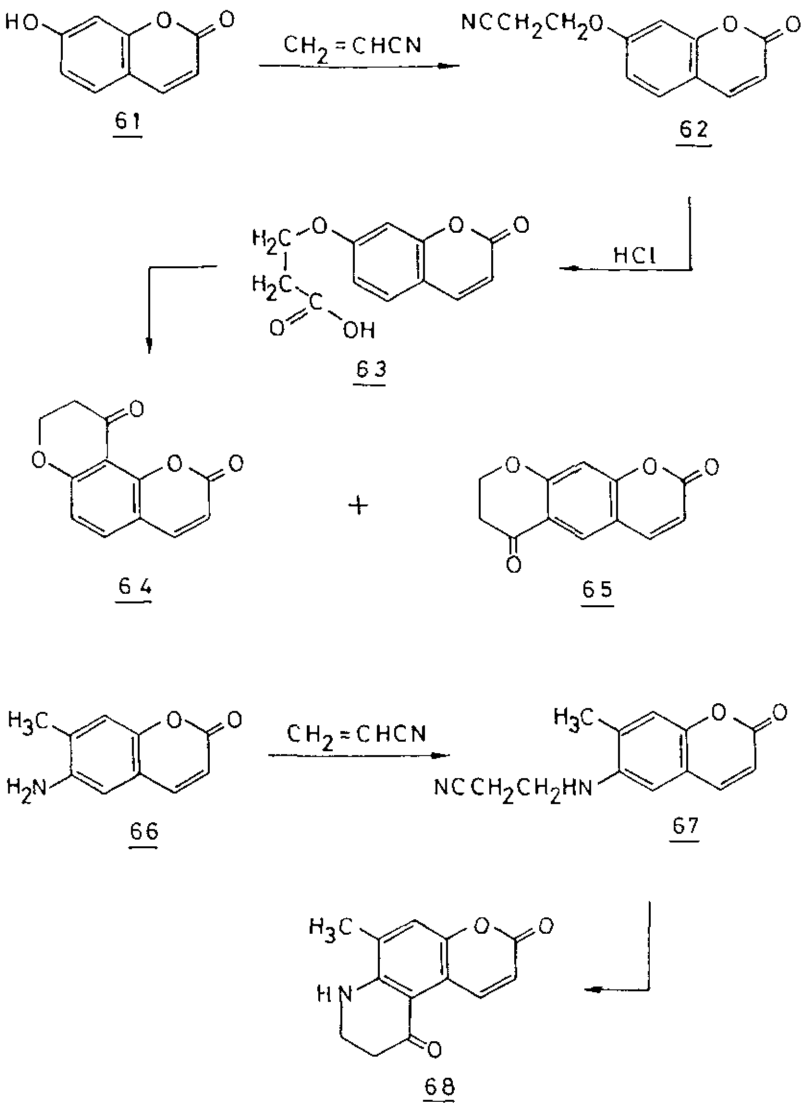


Chart 10

Aminopyrazole and aminoisoxazole derivatives have also been reported to react with acrylonitrile to yield either fused pyrimidines or ring N-cyanoethylated products, which readily cyclised to fused pyrimidines[109-119] (cf. Chart 11).

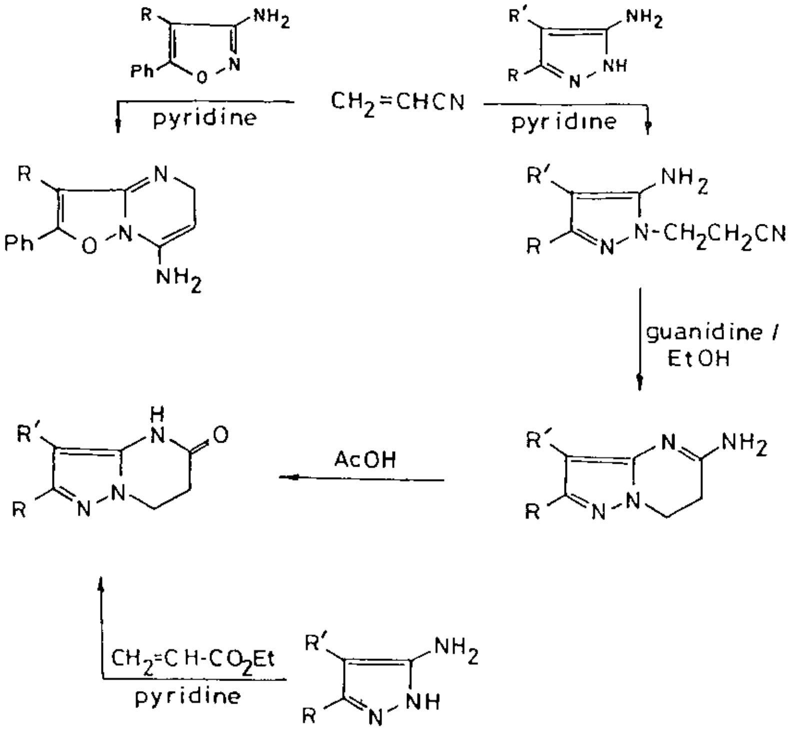


Chart 11

A recent interesting pyrimidine synthesis has been reported from our laboratories and is shown in Chart 12. The utility of the resulting cyanopyrimidines for building up fused heterocycles has also been reported[20].

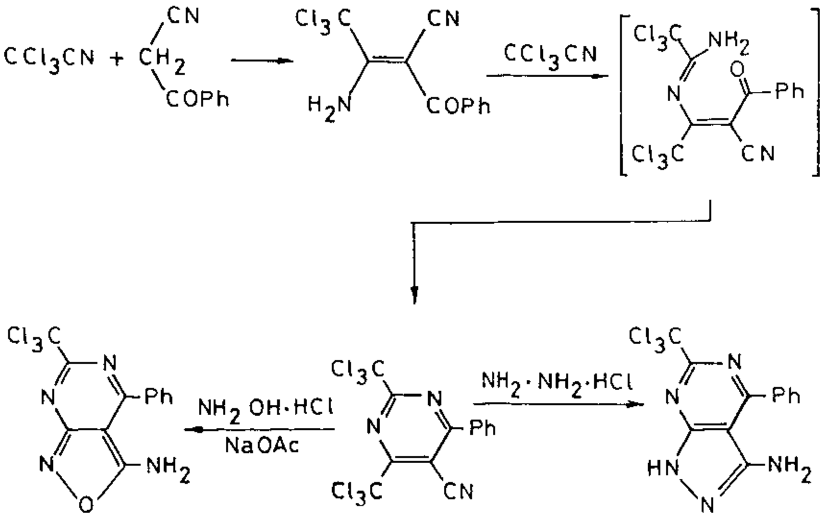


Chart 12

Recently, the enaminonitrile (69) was utilised for synthesis of several new fused pyrimidine derivatives[120] (cf. Chart 13).

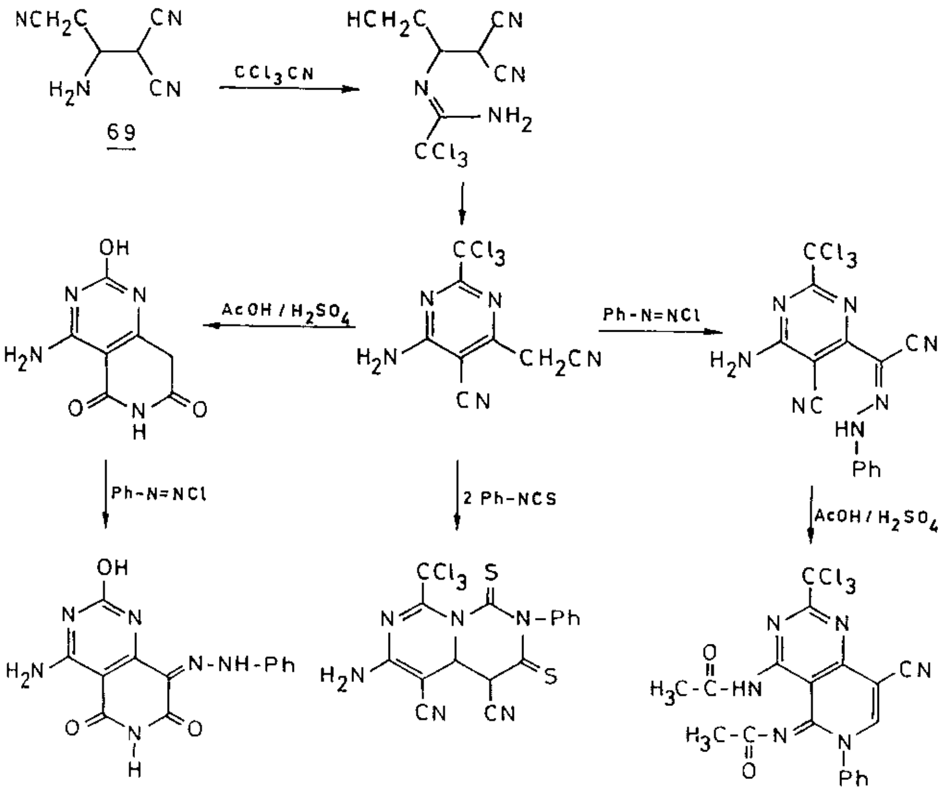


Chart 13

Synthesis of several new ring system derived from pyrazolo[1,5-a]pyrimidines and 1,2,4-triazolo[3,4-a]pyrimidines has been recently reported via the reaction of enaminonitrile (70) with cyclic amidines. The mechanism of the reaction involved was discussed[121] (cf. Chart 14).

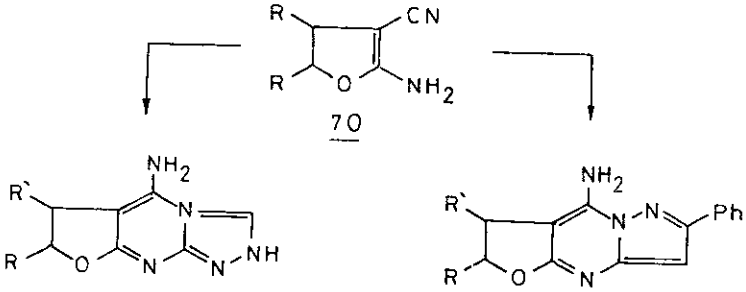
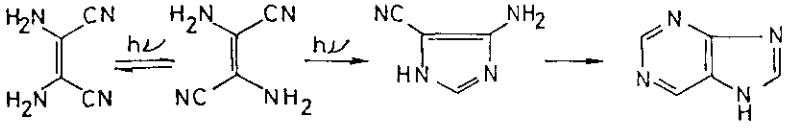
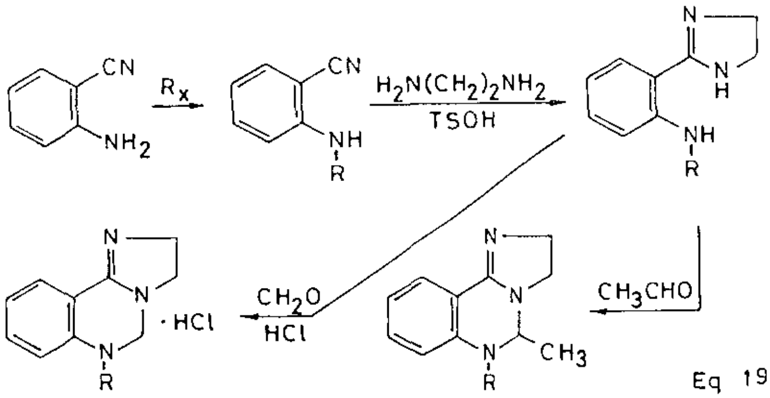


Chart 14

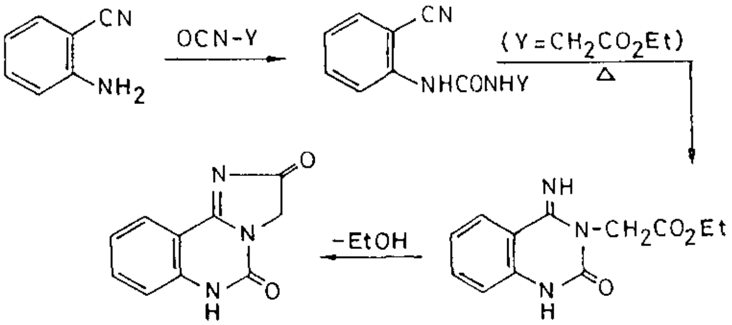
Several other syntheses of fused pyrimidines from enaminonitriles are shown below[122-127] (cf. Eqs. 18-20).



Eq. 18

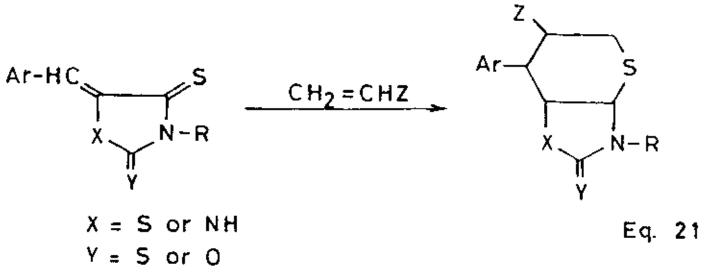


Eq 19



Eq. 20

The arylidene derivatives of isorhodanine and thiorhodanine have been reported to undergo 1,4-cycloaddition reaction with acrylonitrile, ethyl acrylate, α-nitrostyrene, styrylethyl ketone and N-aryl-maleimides, leading to substituted tetrahydrothiopyrano-7H[2,3-d]thiazol-2-ones and 2-thiones. The reaction products with acrylonitrile or with ethyl acrylate are shown in equation 21.[128-131]



Eq. 21

Almost simultaneously and independantly, Elnagdi et al[132] and Midorikawa et al[91] have reported a novel synthesis of thiazolo[2,3-a]pyridines. Elnagdi et al[132] have utilised 2-substitutedmethyl-2-thiazolin-4-ones and cinnamonitriles as starting materials, whereas Midorikawa and his group[91] utilised cinnamonitriles and ethyl thioglycollate as starting materials. However, the latter authors[91] have acknowledged the intermediacy of substitutedmethyl-2-thiazolin-4-ones in their reaction sequence (cf. Chart 15).

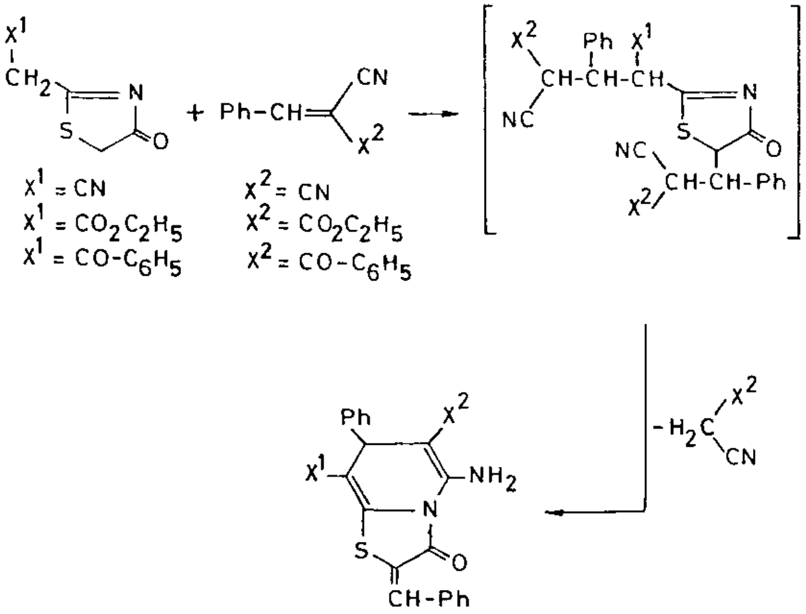


Chart 15

Several new syntheses of azolopyranes and pyrazoloazoles from yiledenemalononitrile derivatives have been recently reported[133,134] (cf. Charts 16 and 17).

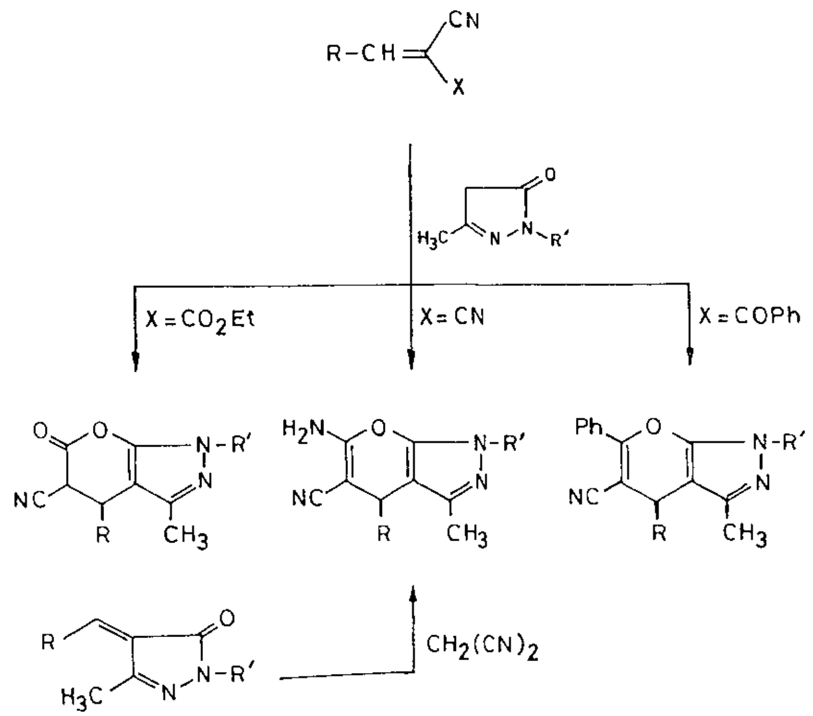


Chart 16

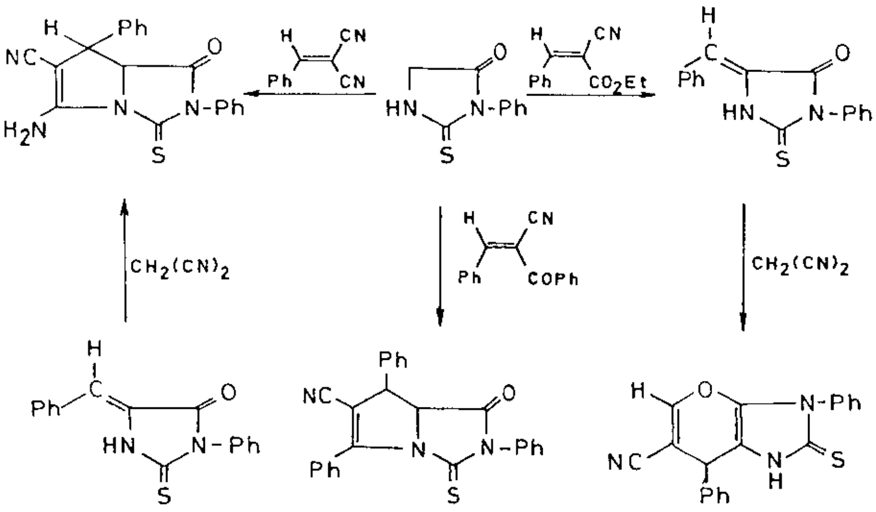
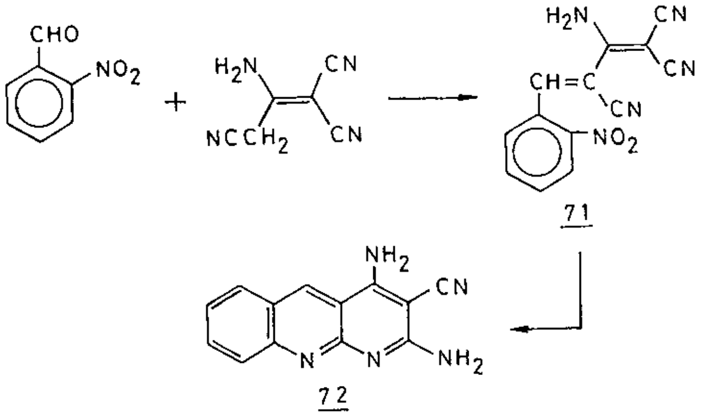


Chart 17

o-Nitrobenzaldehyde reacted with 2-amino-1,1,3-tricyanopent-2-ene (48) to yield the condensation product (71) which could be readily cyclised into 27.[87]



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