UTILITY OF CYANOACETAMIDE AND CYANOTHIOACETAMIDE IN HETEROCYCLIC SYNTHESIS

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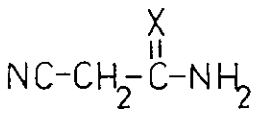
Abstract- The preparation and utility of cyanoacetamide and cyanothioacetamide in heterocyclic synthesis are reviewed.

INTRODUCTION

The chemistry of organic cyano compounds is now very rapidly developing[1]. Plenty of papers dealing with the synthesis and utilities of organic cyano compounds have been published in the last decade. Several new reactions for this class of compounds were also reported[1]. In order to update chemists knowledge in cyano group chemistry, several books[2-4] and review articles[5-8] have been recently reported. In conjunction to the previous effort aimed at exploring the rapidly expanding knowledge on the utility of organic cyano compounds in heterocyclic synthesis[5-8], we report the literature scanning the utility of cyanoacetic acid derivatives (1) in heterocycle synthesis. We hope that such review article will be of value for both researchers and instructors of heterocyclic chemistry.

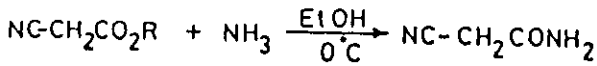


1a; X=O
b; X=S

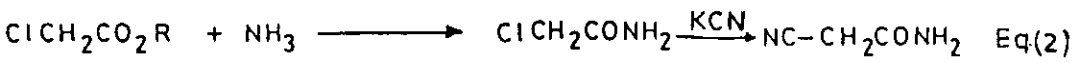
PREPARATION

The most commonly utilised derivatives of (1) are cyanoacetamide (1a; X=O) and cyanothioacetamide (1b; X = S). Cyanoacetamide is easily obtainable via routes

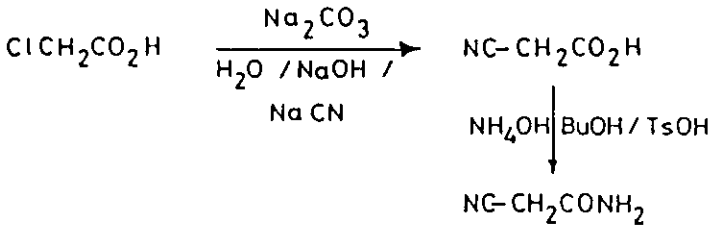
outlined in equations 1-3 (cf. Eq. 1-3)[9-13].



Eq.(1)

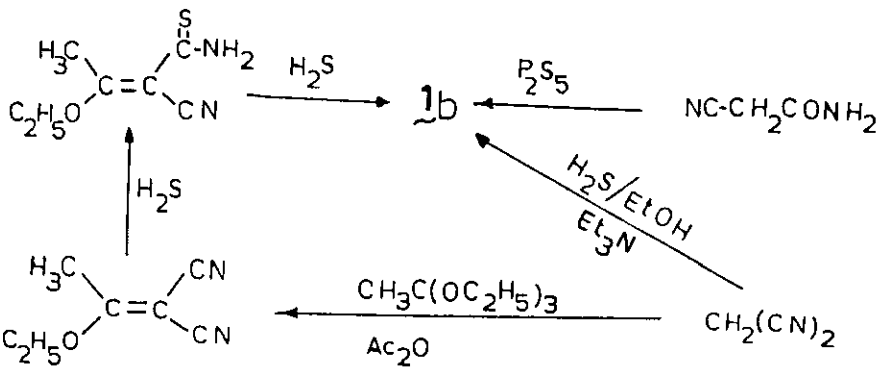


Eq.(2)



Eq.(3)

On the other hand, the synthetic approaches for cyanothioacetamide are outlined in Scheme 1 (cf. Scheme 1)[14-17].



Scheme 1

UTILITY IN HETEROCYCLIC SYNTHESIS:

A variety of functionally substituted heterocycles, not readily accessible, are reported utilising (1; X = O or S) as a starting material. In the following, reactions leading to heterocycles are categorised.

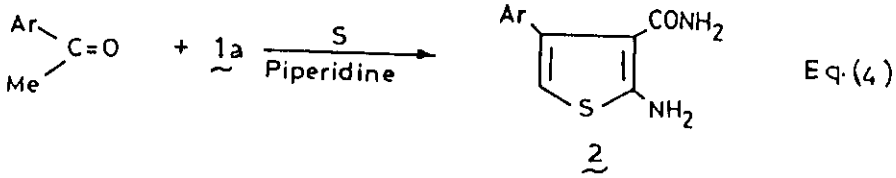
i) Synthesis of Five-Membered Heterocycles:

1. Synthesis of Five-Membered Rings with one Hetero-Atom:

a. Synthesis of Thiophenes and Fused Thiophenes:

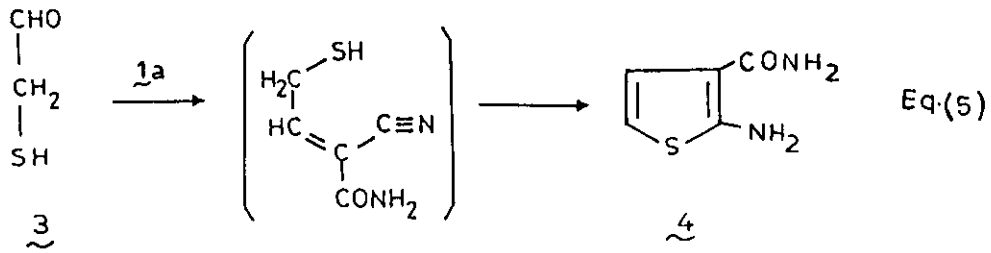
The Gewald thiophene synthesis utilising (1a; X = O) as a starting material has enabled synthesis of several 2-amino-3-carboxamidothiophene derivatives (2)[18-20]

(cf. Eq.4). The latter were usually utilised for the synthesis of thienopyrimidines utilising the Robein pyrimidine synthesis[21].



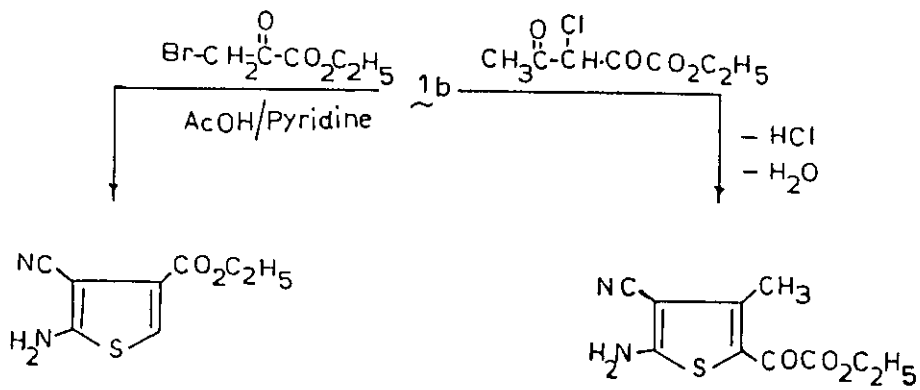
2 Eq.(4)

Another approach for the synthesis of aminothiophene (4) is the reaction of mercaptoacetaldehyde (3) with (1a). The reaction is believed to proceed as shown below (cf. Eq. 5)[22].



3 4 Eq.(5)

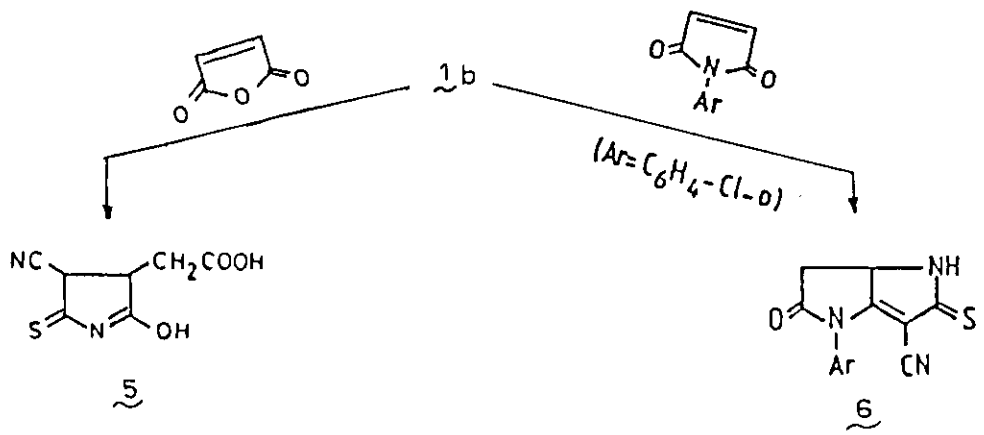
Also thiophene derivatives are synthesised via the reaction of cyanothioacetamide (1b) with ethyl 3-chloro-3,4-dioxopentanoate[23] and the reaction of (1b) with ethyl 3-bromo-2-oxopropanoate in acetic acid-pyridine mixture (cf. Scheme 2)[24].



Scheme 2

b. Synthesis of Pyrroles :

The reaction of cyanothioacetamide (1b) with maleic anhydride and N-(o-chlorophenyl)malimide has afforded the pyrrole derivative (5) and the pyrrolo[3,2-b]-pyrrole derivative (6) respectively (cf. Scheme 3)[25].

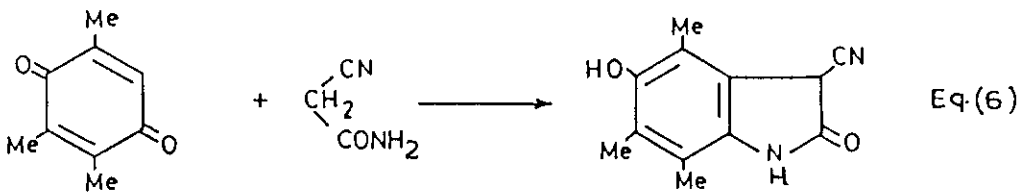


5 6

Scheme 3

c. Synthesis of Indoles:

The reaction of the substituted benzoquinone (7) with cyanoacetamide is reported to afford 3-cyanoindoxyl derivative (8) in good yield (cf. Eq. 6)[26,27].

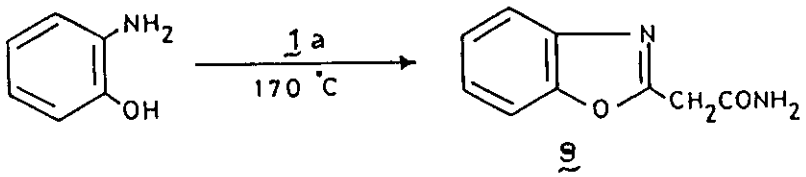


7 8

2. Synthesis of Five-Membered Rings with Two Hetero-Atoms:

a. Synthesis of Fused Oxazoles:

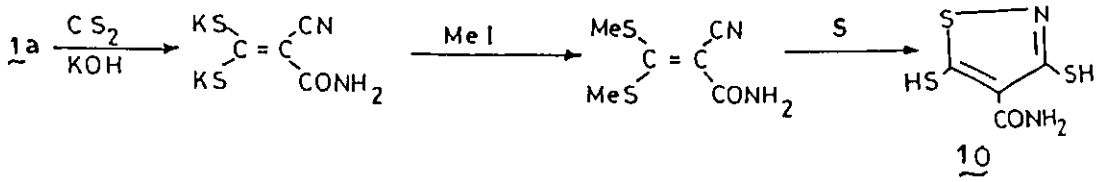
To our knowledge, only one report on the utility of cyanoacetamide (1a) for the synthesis of the oxazole derivative (9) is appeared (cf. Eq. 7)[28]. The formation of the reaction product is assumed to proceed via addition of the phenolic group to the cyano function in (1a) and cyclization via ammonia elimination.



9 Eq.(7)

b. Synthesis of Isothiazoles, Thiazoles and Fused Thiazoles:

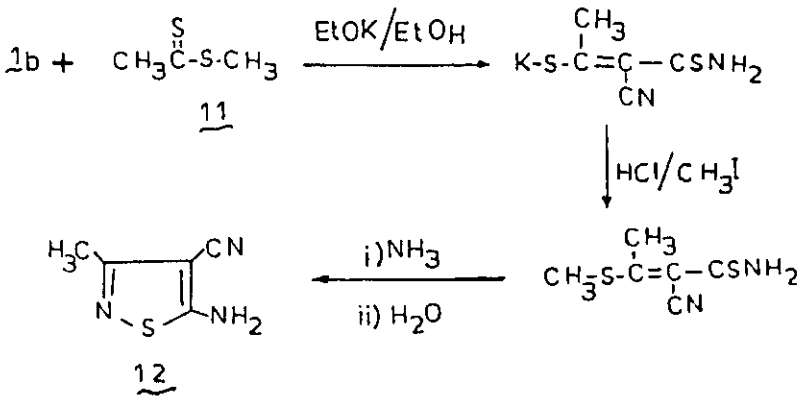
3,5-Dimercaptoisothiazole (10) is prepared utilizing cyanoacetamide (1a) as a starting material following the procedure outlined in the Scheme below (cf. Scheme 4)[29].



10

Scheme 4

Also 3-methyl-4-cyano-5-aminoisothiazole (12) can be synthesised via the reaction of cyanothioacetamide (1b) with (11) following the sequence outlined below (cf. Scheme 5)[30].

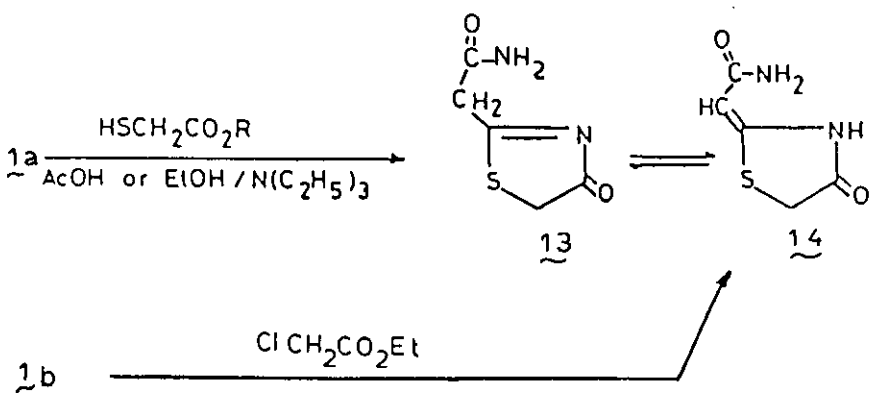


12

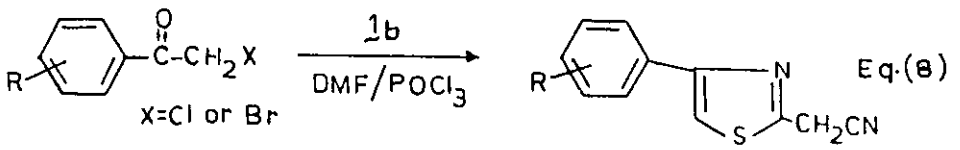
Scheme 5

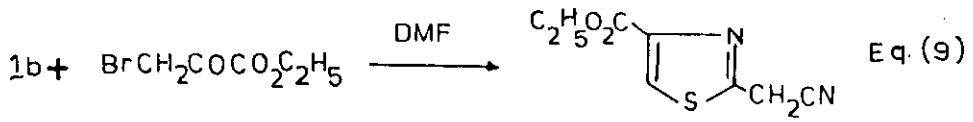
The reaction of cyanoacetamide (1a) with thioglycollic acid or thioglycollic acid esters affords 2-carboxamidomethyl-4-oxo-2-thiazolone (13) which is also formulated as the tautomeric (14) (cf. Scheme 6)[31,32].

The thiazolone (13) is also synthesised via the reaction of cyanothioacetamide (1b) with ethyl chloroacetate[33]. Similar thiazole derivatives are reported utilizing (1b) as a starting material (cf. Eq. 8,9)[34-37].

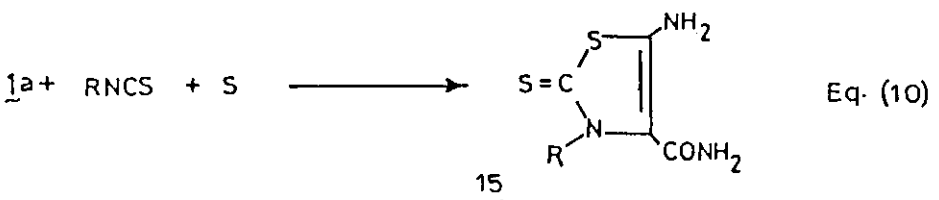


Scheme 6

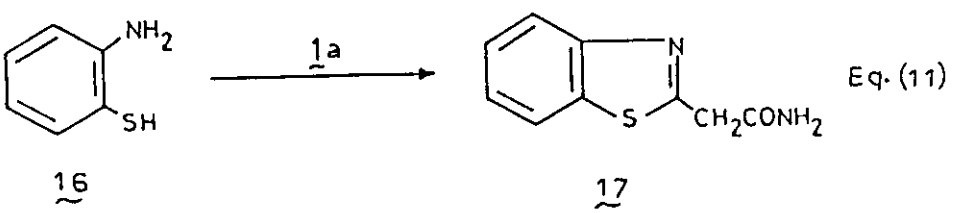




The reaction of cyanoacetamide (1a) with organic isothiocyanates in presence of elemental sulphur affords the corresponding 2-thiazolin-2-thione derivatives (15) (cf. Eq. 10)[38].

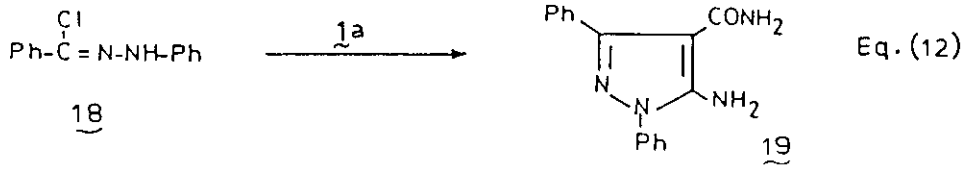


2-Cyanomethylbenzothiazole (17) is obtained in good yield via the reaction of (1a) with 2-mercaptoaniline (16) (cf. Eq. 11)[39].



c. Synthesis of Pyrazoles:

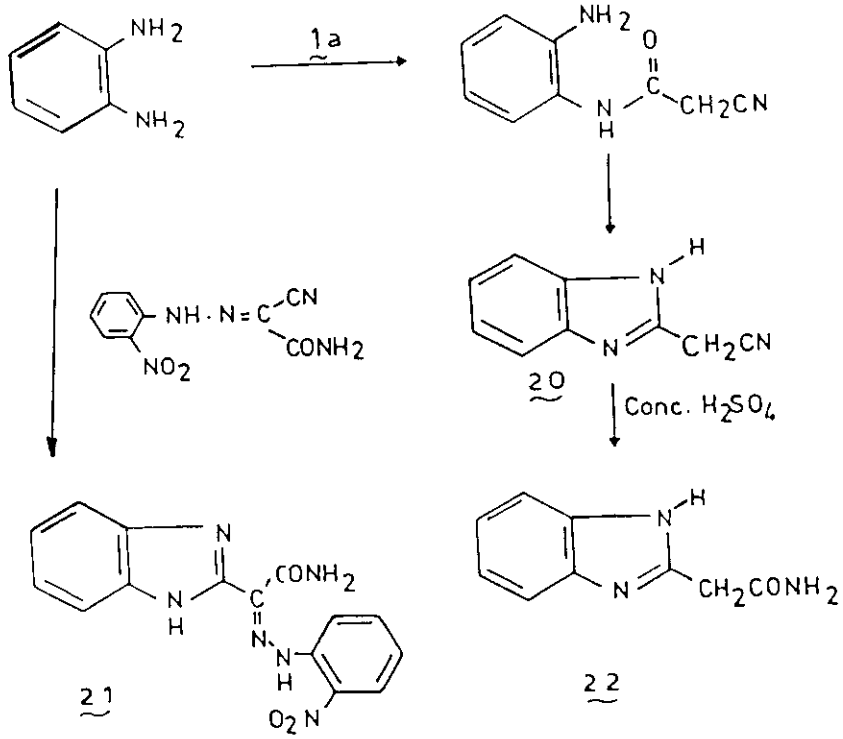
The only reported pyrazole synthesis utilizing (1a) and (18) as a starting materials is shown below (cf. Eq. 12)[40].



18 19 Eq. (12)

d. Synthesis of Imidazoles and Fused Imidazoles:

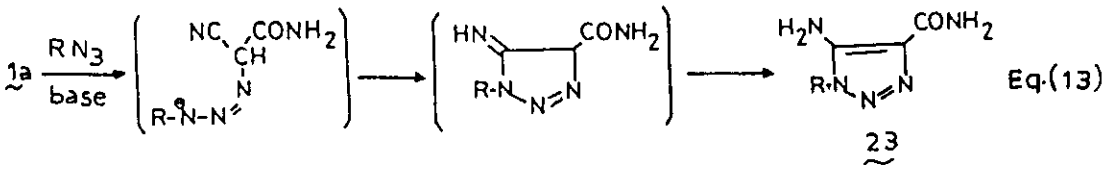
The reaction of cyanoacetamide (1a) with o-phenylenediamine affords 2-cyanomethylbenzimidazole (20) in good yield[41]. However, the 2-nitrophenylhydrazo derivative of (1a) affords the hydrazone (21) when reacts with o-phenylenediamine under similar conditions[42]. When o-phenylenediamine and (1a) are condensed at 40-50°C in presence of conc. H_2SO_4, the carbamido derivative (22) is isolated most likely via hydrolysis of 2-cyanomethylbenzimidazole (20) (cf. Scheme 7)[43,44].



Scheme 7

3. Synthesis of Five-Membered Rings with Three Hetero-Atoms:

Alkyl, aromatic and heterocyclic azides react with (1a) in presence of a catalytic amount of base to afford 1,2,3-triazoles (23) via attack at the active methylene group and subsequent addition to the cyano group (cf. Eq. 13)[45-48]. To our knowledge, this type of reactions is the only reported synthesis of five membered heterocycles with more than two hetero-atoms utilizing (1a,b) as a starting components.



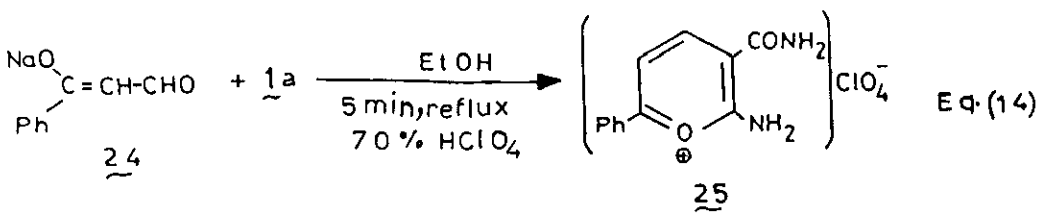
23 Eq.(13)

ii) Synthesis of Six-Membered Heterocycles:

1. Synthesis of Six-Membered Rings with One Hetero-Atom:

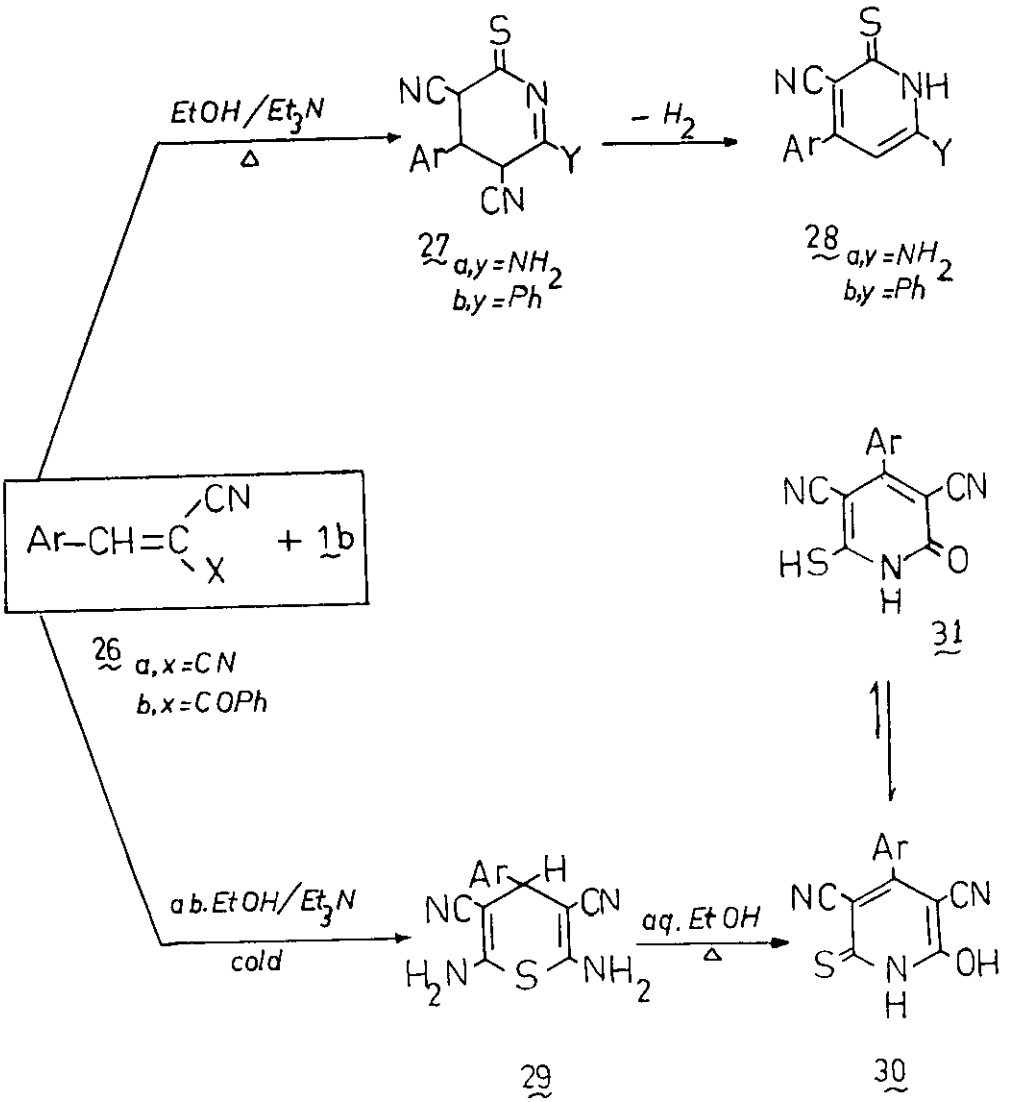
a. Synthesis of Pyrans, Thiopyrans and Selenopyrans:

The pyrylium salt (25) is synthesised via refluxing cyanoacetamide (1a) with the aldehyde (14) (cf. Eq. 14)[49]. The so-formed pyrylium salt rearranges into pyridine derivative upon treatment with strong acid[49].



24 25 Eq.(14)

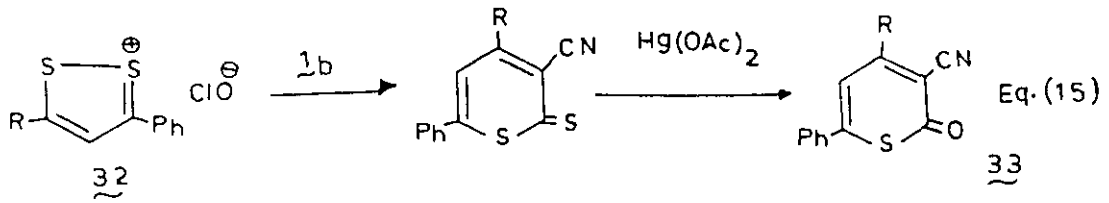
Conflecting results are reported for the reaction of cyanothioacetamide (1b) with cinnamonitrile derivatives (26a,b). Thus, Daboun and Riad[50] reported that the dihydropyridines (27a) are isolated from the reaction of (1b) with (26a). On the other hand Soto et al.[51] reported that the pyridines (28b) are the isolable products from the reaction of (26b) with (1b). (cf. Scheme 8)[52,53].



Scheme 8

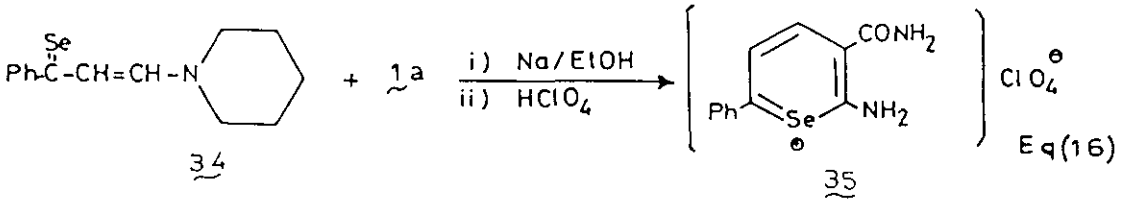
Recently it could be shown that the thiopyrans (29) are the products of the kinetically controlled reactions of (26a) with (1b) (cf. Scheme 8)[54]. These products rearrange on heating in aqueous ethanol into the thermodynamically stable dihydropyridines (30)[54]. Observed dependency of the products of reactions of active methylene reagents with cinnamonitrile derivatives on the nature of reactants and reaction conditions has been reported[55-64].

Another route for the synthesis of thiopyranone derivatives (33) is the reaction of cyanothioacetamide (1b) with (32) (cf. Eq. 15)[65].



32 33 Eq. (15)

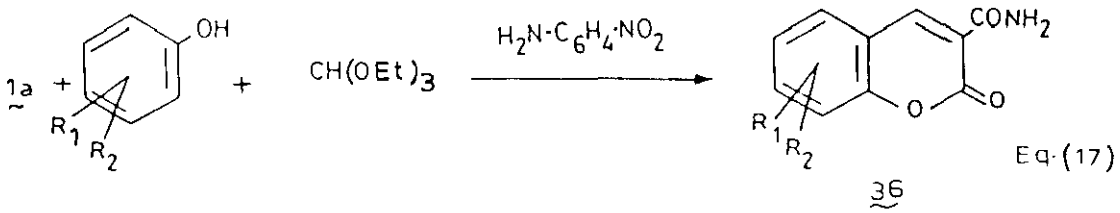
The selenopyran derivative (35) is isolated on heating cyanoacetamide (1a) with the enamine (34) (cf. Eq. 16)[66].



34 35 Eq (16)

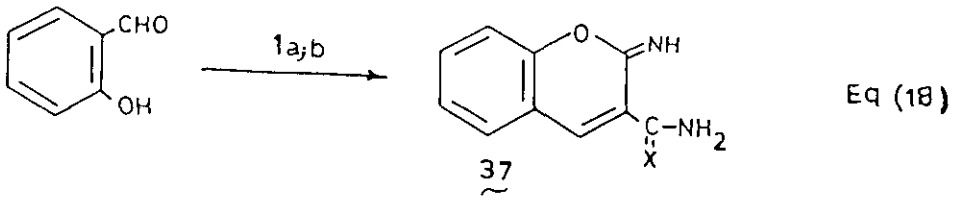
b. Synthesis of Coumarins and Thiocoumarins:

Coumarins (36) are synthesised via condensation of phenols with cyanoacetamide (1a) in presence of ethyl orthoformate and nitroanilines (cf. Eq. 17)[67].

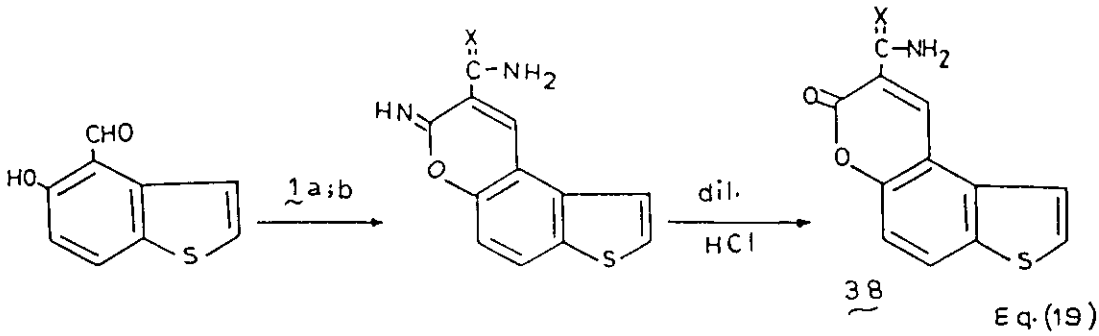


36 Eq. (17)

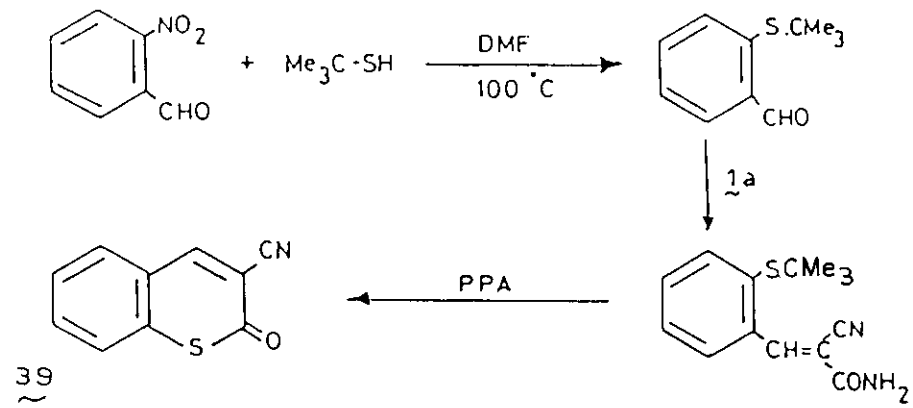
Generally, coumarin derivatives (37,38) are synthesised on condensing cyanoacetamide (1a) or cyanothioacetamide (1b) with o-hydroxyaldehydes. Examples are shown below (cf. Eq. 18,19)[68-71].



37 Eq (18)



Otto and Brian[72] reported the synthesis of the thiocoumarin (39) via the route outlined in the Scheme below.

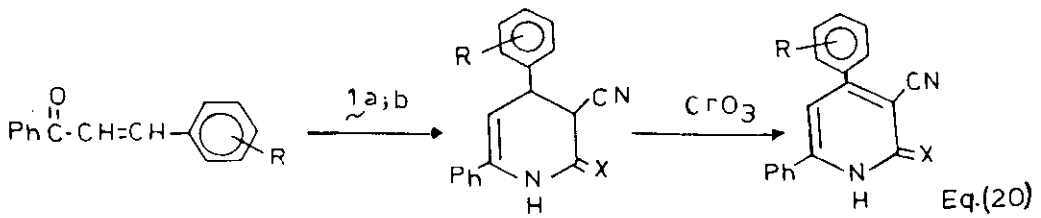


Scheme 9

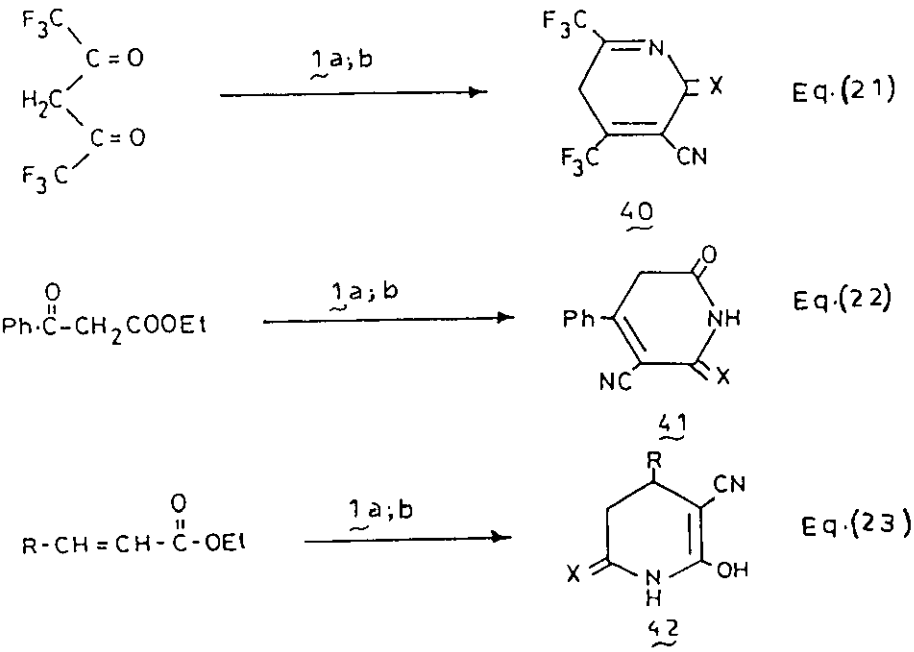
c. Synthesis of Pyridines:

Both cyanoacetamide (1a) and cyanothioacetamide (1b) are extensively utilized for the synthesis of pyridine derivatives. Literature reports before 1970 on pyridines synthesis has been efficiently reviewed by Meyers and Sircar[73], thus these reports will be neglected in our review.

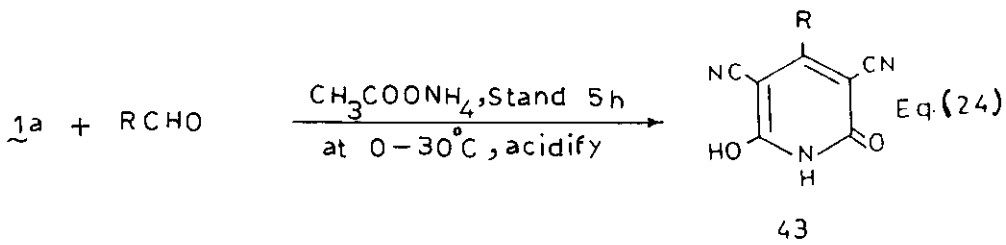
Pyridines are synthesised via the reaction of (1a) or (1b) with α,β-unsaturated ketones or their functional derivatives[74-80]. The reaction proceeds via a primary Michael addition followed by cyclization into pyridines via water elimination. Simple cyclic and heterocyclic $\alpha\beta$-unsaturated ketones were utilized and the intermediate Michael adducts are isolated in several cases (cf. Eq. 20).



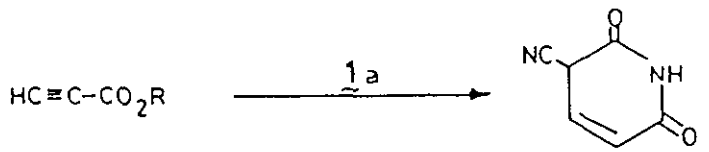
The condensation of β-diketones[80-82], β-ketoesters[83-86] and α,β-unsaturated esters[87-91] with cyanoacetamide (1a) and cyanothiacetamide (1b) affords the pyridines (40-42) in good yields (cf. Eq. 21-23).



Similar to the well known pyridine synthesis from the reaction of aldehydes with active methylenes in presence of ammonium acetate[92], the aromatic and heterocyclic aldehydes react with cyanoacetamide (1a) to yield the hydroxypyridinone (43) (cf. Eq. 24)[93].

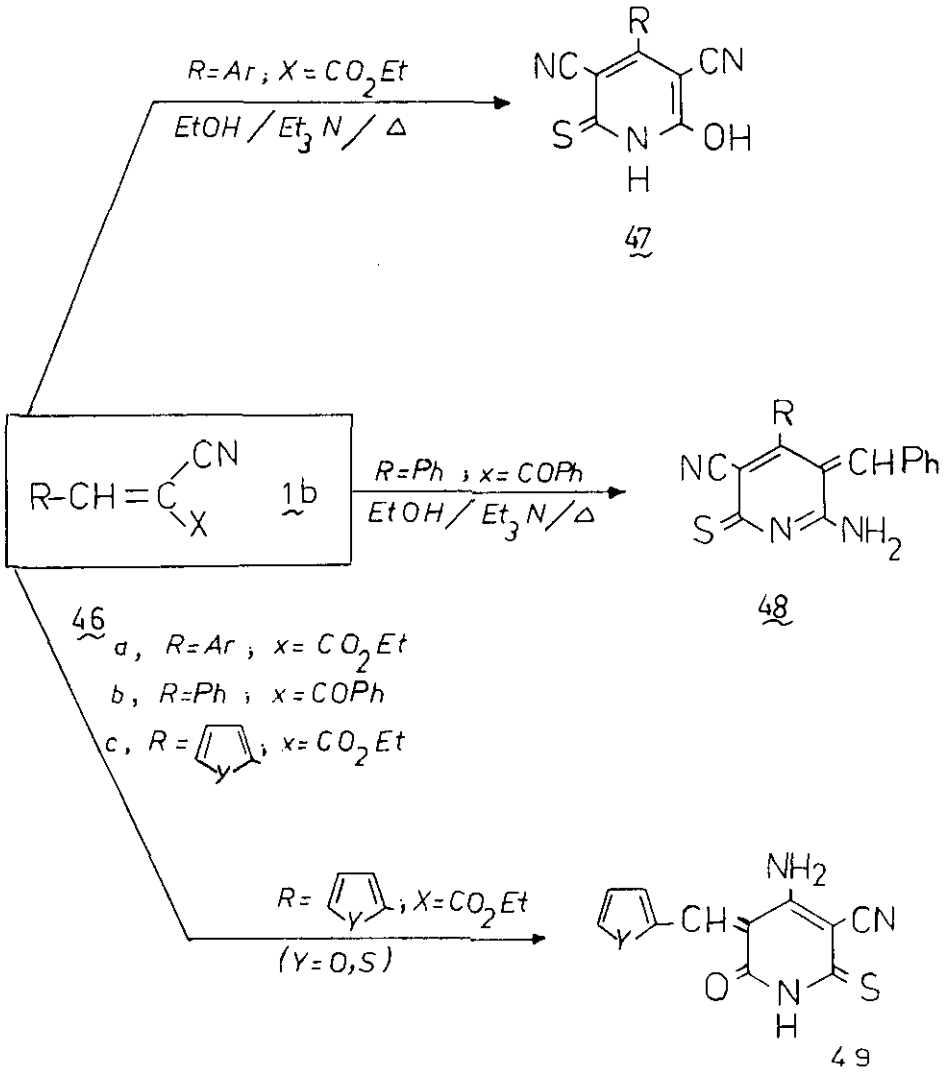


Quite similar to the above mentioned approach is the synthesis of the pyridinone (45) from (1a) and alkyl propiolate (44) (cf. Eq. 25)[94].

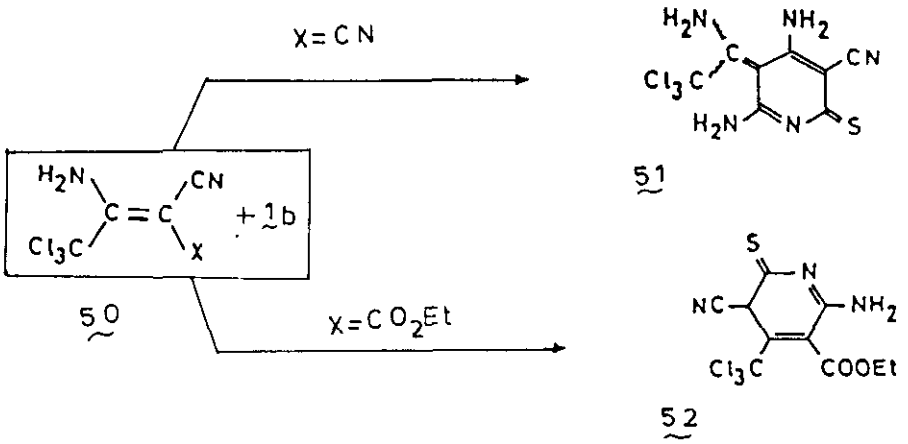


44 45 Eq.(25)

Pyridine derivatives (47-49, 51 and 52) are successfully synthesised via condensation of cyanothioacetamide (1b) with the cinnamonitrile derivatives (46) or the acrylonitrile derivatives (50) (cf. Scheme 10, 11)[54,95].

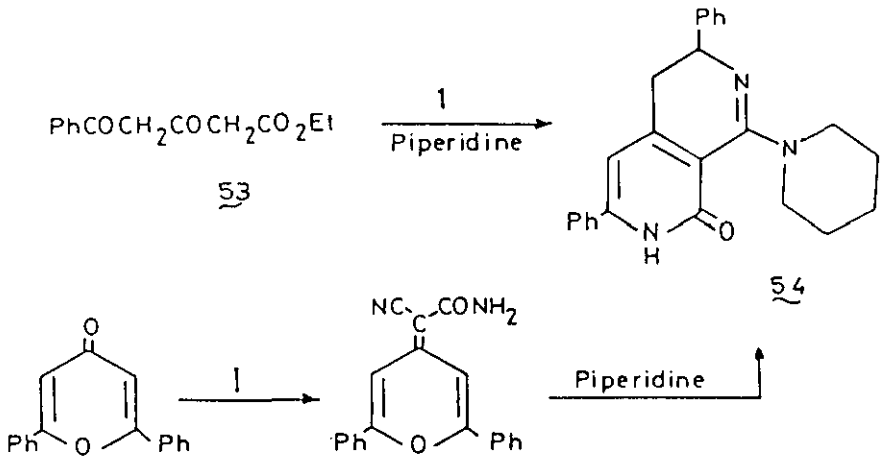


Scheme 10



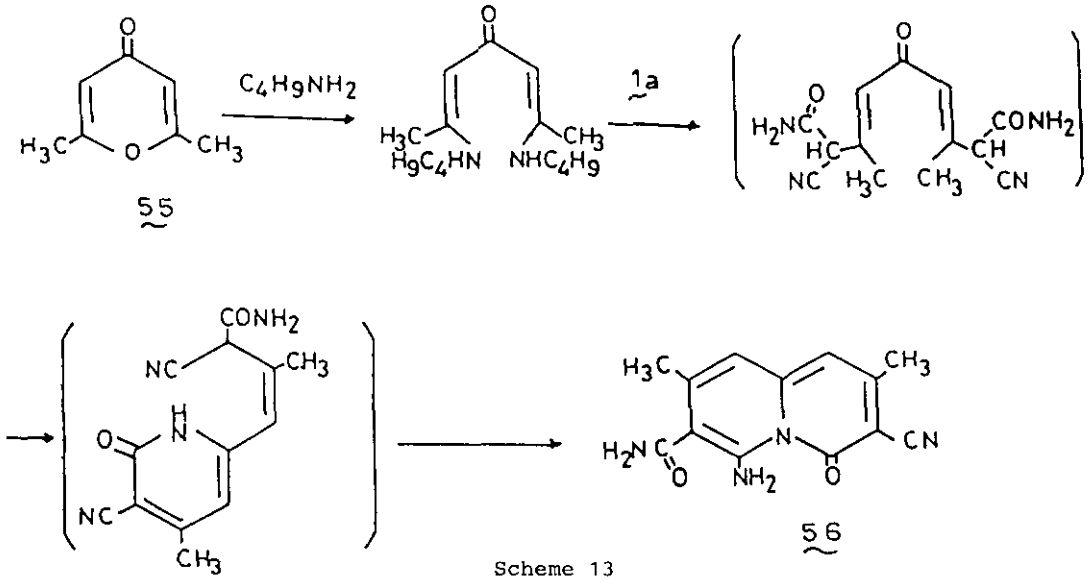
Scheme 11

Allan et al.[96] reported synthesis of the pyrido[3,4-c]pyridine (54) via the reaction of 3,5-dioxo-ester (53) with cyanoacetamide (1a) (cf. Scheme 12).



Scheme 12

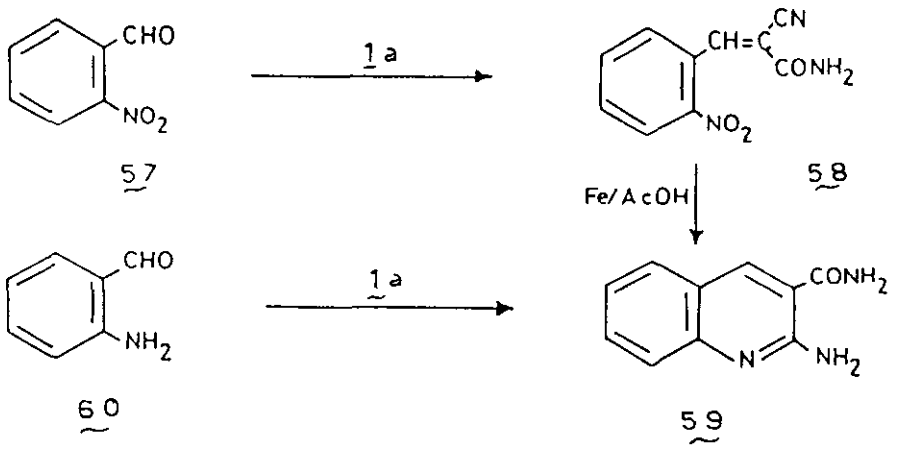
Similarly, rearrangement of the pyrone (55) on reacting with (1a) in presence of amine into the pyrido[1,2-a]pyridine derivative (56) is reported (cf. Scheme 13)[97]. Formation of (56) from (55) is believed to proceed via sequence shown in Scheme 13.



Scheme 13

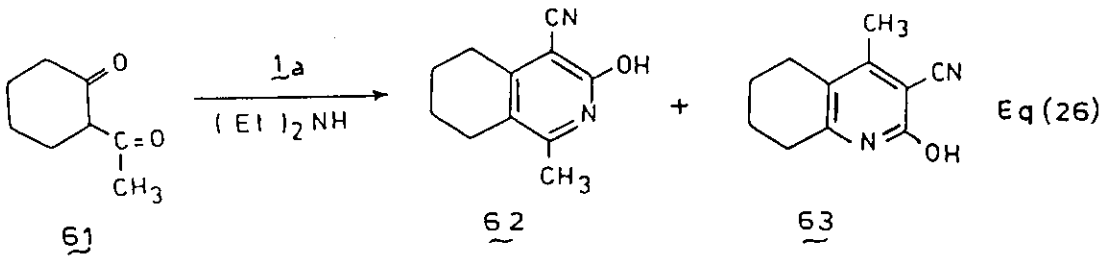
d. Synthesis of Quinolines and Isoquinolines:

The reaction of cyanoacetamide (1a) with o-nitroaldehydes and o-aminoaldehydes is extensively utilised for the synthesis of quinolines. For example, condensation of o-nitrobenzaldehyde (57) with (1a) affords the ylidene derivative (58) which on reduction with Fe/HAc gives 2-amino-3-carboxamidoquinoline derivative (59)[98]. The latter could be directly prepared via condensation of o-aminobenzaldehyde (60) with (1a) (cf. Scheme 14)[98].



Scheme 14

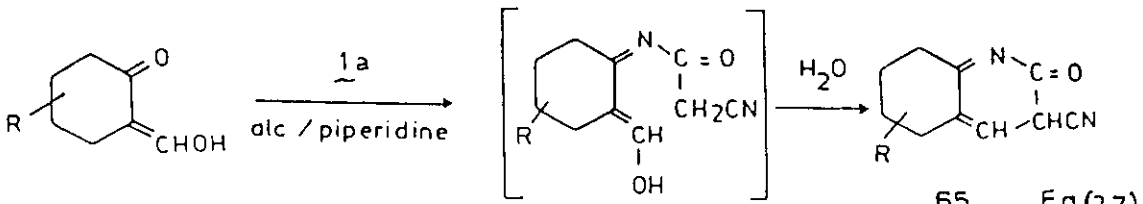
Sen et al.[99] reported that condensation of 2-acetylcyclohexanone (61) and (1a) in presence of diethylamine results in the formation of a mixture of the isoquinoline derivative (62) and the quinoline derivative (63) (cf. Eq. 26).



61 62 63 Eq (26)

Later Freeman et al.[100,101] have concluded, on the basis of spectral data and degradation studies, that the above condensation reaction results in the exclusive formation of the isoquinoline derivative (62). Whereas Sen et al.[99] used equimolecular quantities of 2-acetylcyclohexanone and cyanoacetamide, Freeman et al.[100,101] have used only half mole of cyanoacetamide for one mole of 2-acetylcyclohexanone. However, Kasturi et al.[102] have been able to show conclusively that under both conditions a mixture of the isoquinoline derivative (62) (major product) and the quinoline derivative (63) (minor product) is indeed formed.

In a similar manner 2-formylcyclohexanone (64) condensed with (1a) to yield only quinolin-2-one derivatives (65) (cf. Eq. 27)[103-105].

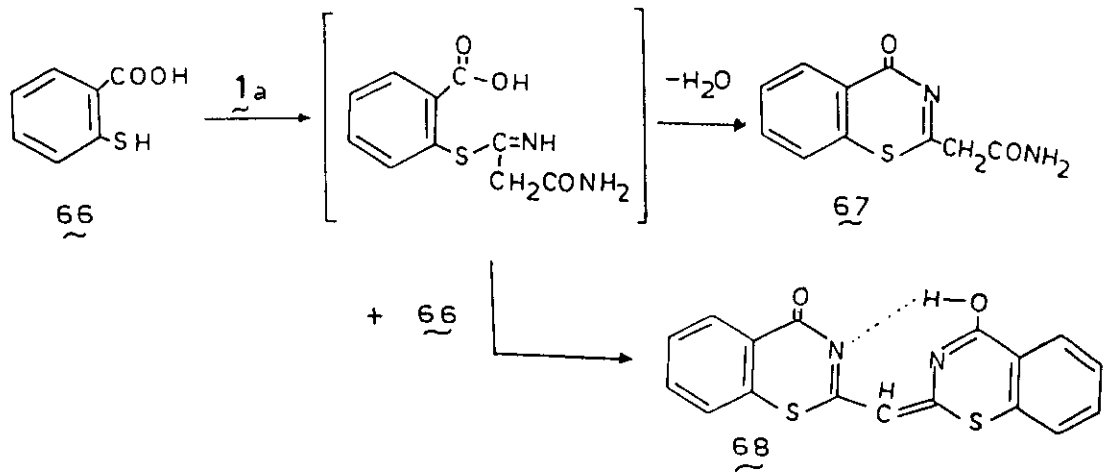


64 65 Eq.(27)

2. Synthesis of Six-Membered Rings with Two Hetero-Atoms:

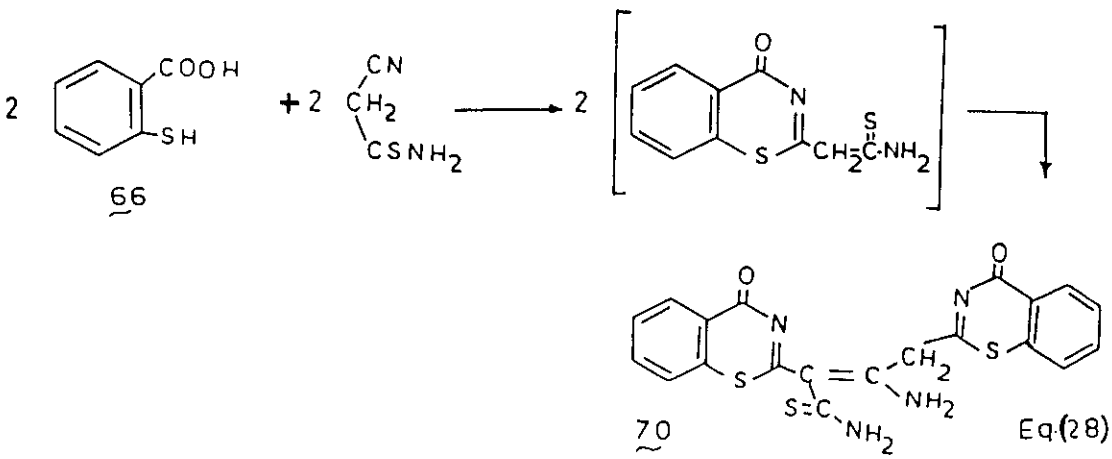
a. Synthesis of Thiazines and Bithiazines:

The reaction of cyanoacetamide (1a) with thiosalicyclic acid (66) in refluxing pyridine affords the thiazine derivative (67) (cf. Scheme 15)[106]. Moreover, the bithiazine derivative (68) is isolated when only half mole of cyanoacetamide reacts with one mole of thiosalicyclic acid (cf. Scheme 15)[106]. The hydrogen bonding proposed by the authors in (68) seems least likely since bond distances and bond angles make such bonding quite difficult.



Scheme 15

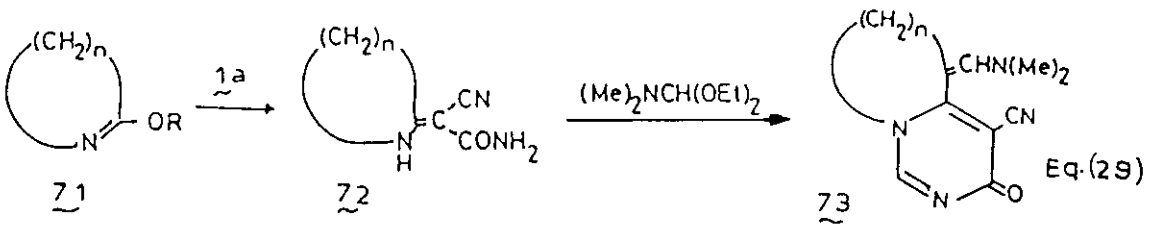
Similarly, cyanothioacetamide (1b) reacts with thiosalicyclic acid in refluxing pyridine to yield the bithiazine derivative (70) (cf. Eq. 28)[106]. This is assumed to be formed via self condensation of the intermediate thiazine derivative (69)[106].



Eq.(28)

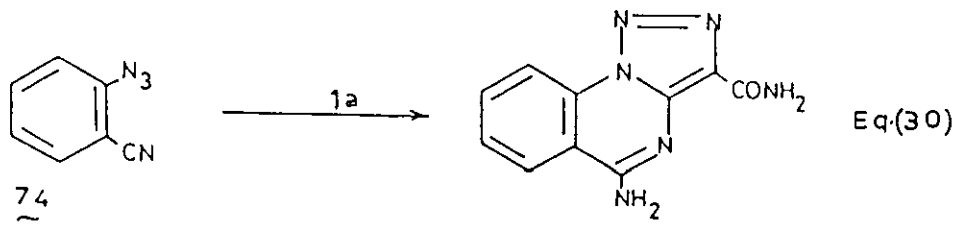
b. Synthesis of Pyrimidines and Fused Pyrimidines:

Several pyrimidine derivatives are synthesised utilising cyanoacetamide (1a) as a precursor. Two synthetic procedures seem to be of broad spectrum. The first one is the condensation of (1a) with cyclic iminoethers (71) to yield the ylidenes of general formula (72). These react readily with orthoesters to yield the bridgehead pyrimidines (73) (cf. Eq. 29)[107,108].



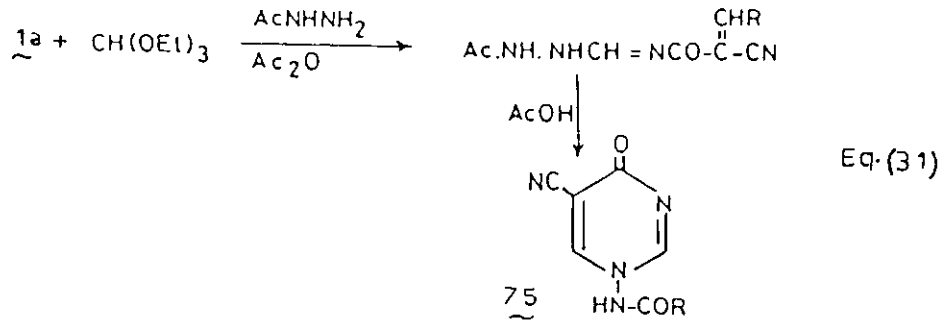
71 72 73

The other which implies the reaction of (1a) with o-azidonitriles (74), although interesting, leads either to fused pyrimidines or other products. An example for this approach is shown below (cf. Eq. 30)[109,110].



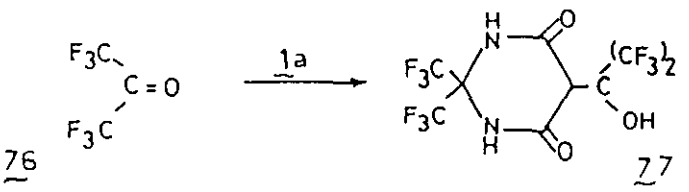
74

N-Acylaminopyrimidines (75) are synthesised from cyanoacetamide (1a) and triethyl orthoformate utilizing the route outlined in the equation below (cf. Eq. 31)[111].



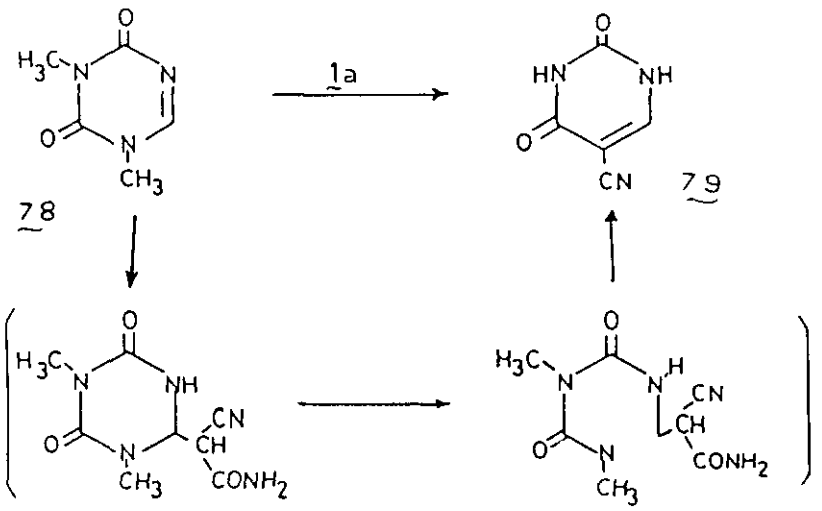
75

Cyanoacetamide (1a) reacts with hexafluroacetone (76) to yield the pyrimidine derivative (77) (cf. Eq. 32)[112,113].



Eq. (32)

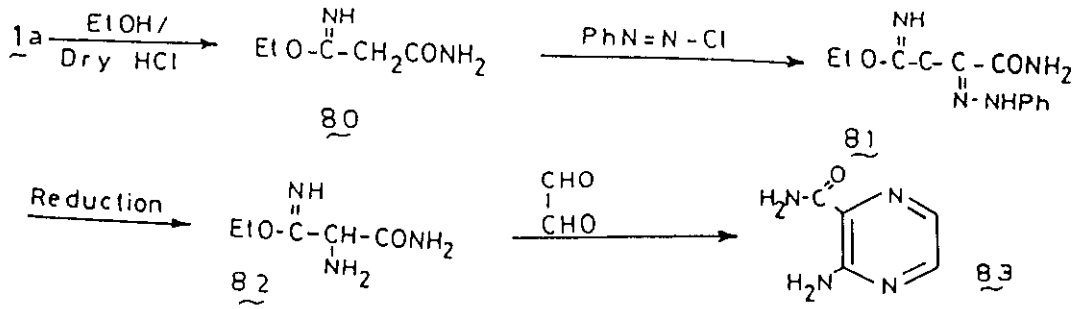
The uracil derivative (78) is rearranged on treatments with cyanoacetamide (1a) into the pyrimidine derivative (79) (cf. Scheme 16)[114].



Scheme 16

c. Synthesis of Pyrazines:

The pyrazine derivative (83) is synthesised via reacting cyanoacetamide (1a) with ethanol/dry HCl to yield the iminoether (80) which couples with benzenediazonium chloride to yield the corresponding arylhydrazone derivative (81). The latter on reduction affords (82) which condense with glyoxal to yield 2-amino-3-carboxamido-pyrazine (83) (cf. Scheme 17)[115].

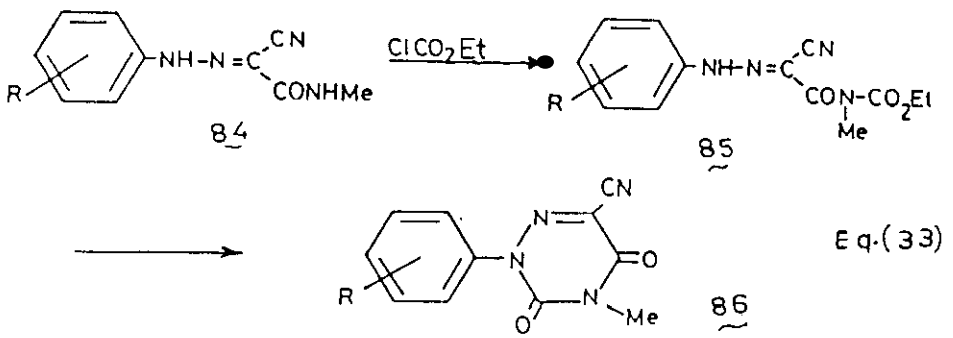


Scheme 17

3. Synthesis of Six-Membered Rings with Three Hetero-Atoms:

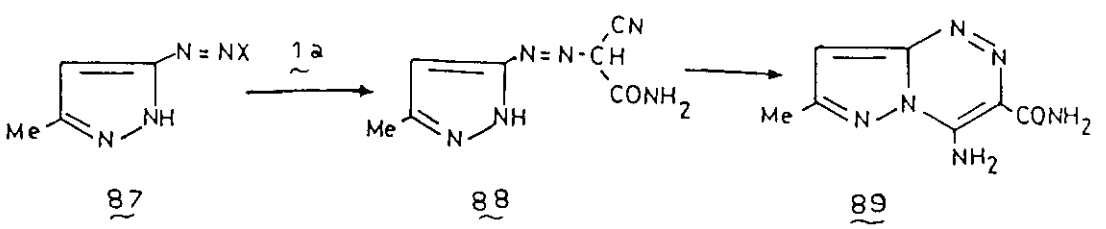
a. Synthesis of Triazines:

Slouka and Budkiora[116] reported synthesis of the triazine (86) via condensing the arylhydrazones (84) with ethyl chloroformate and subsequent cyclization of the resulting product (cf. Eq. 33).



Eq.(33)

The pyrazolo[3,2-c]triazine derivative (89) is synthesised via coupling 3-methyl-pyrazolo-5-diazonium chloride (87) with cyanoacetamide (1a) and cyclization of the coupling product (88) (cf. Scheme 18)[117]. This approach seems to be of value since it can be extended for synthesis of other azolotriazines by utilising the appropriate diazonium salt.



Scheme 18

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