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CHEMISTRY OF α- CYANOTHIOACETAMIDE

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Abstract - The methods of preparation, chemical properties and utility of α- cyanothioacetamide in the synthesis of sulphur and nitrogen heterocyclic compounds are reviewed.

I. INTRODUCTION

In the last few years we have been interested in surveying the recent developments in the chemistry of several classes of heterocyclic compounds[1-3]. During the preparation of our previous reviews we have noticed the growing value of α- cyanothioacetamide (CTAM, **1**) and its wide applications in the synthesis of several heterocyclic ring systems. Moreover, literature cites the use of this compound in different positions with no homogenity of the results of its reactions. The above findings prompted our interest to survey the chemistry of **1** as all the reviews dealing with the synthesis of heterocyclic compounds have ignored its importance in this field. One of the problems we faced during the preparation of this review was the contradicting results of the same reactions of **1** under nearly the same reaction conditions. As we know from our own practical experience with **1**, dealing with its chemistry must be taken in a sensitive manner as the characterized compound is. In most cases, however, our own opinion was reported and explained and at the same time the contradicted results are discussed in view of scientific facts. In some cases, reactions with derivatives of **1** were discussed in details and this seemed to us as a mandatory matter since this is the first time, from our point of view, that lights are shed in details on the chemistry of this highly active and important compound.

II. METHODS OF PREPARATION:

Several methods of preparation are reported for α- cyanothioacetamide (**1**) starting from different reactants.

1. From malononitrile:

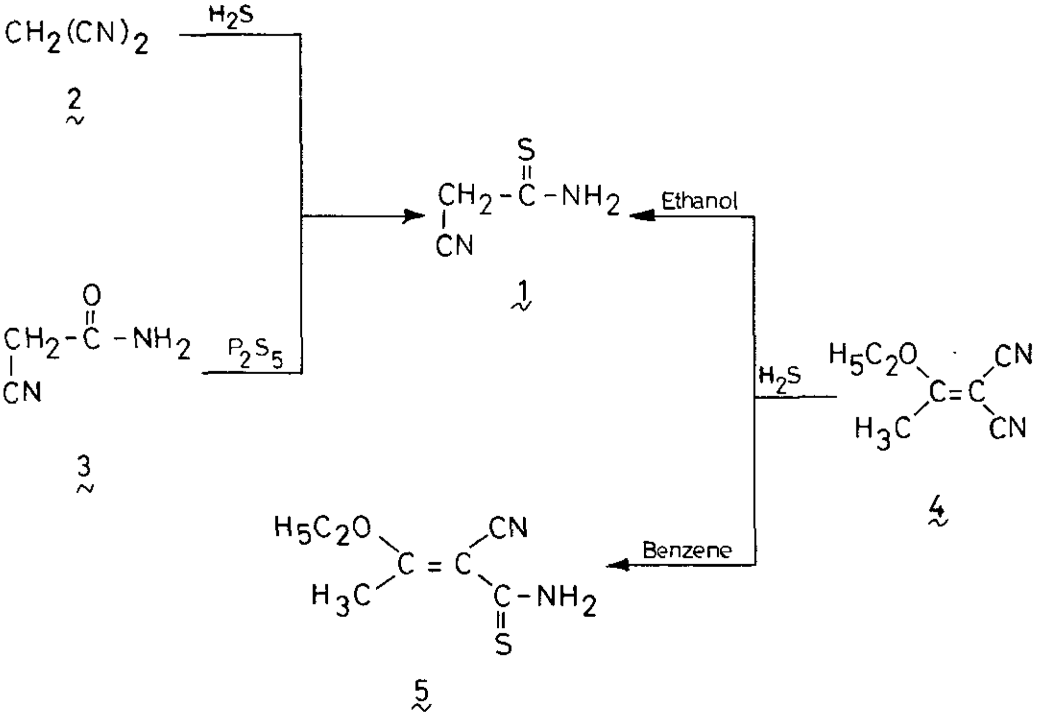
It has been reported that **1** could be prepared by the action of hydrogen sulphide on an alcoholic solution of malononitrile (**2**) in the presence of catalytic amounts of triethylamine[4-8] or triethanolamine[9,10].

2. From cyanoacetamide:

Low yields of **1** were obtained by the action of phosphorus pentasulphide on cyanoacetamide (**3**) in pyridine or ethyl acetoacetate[11-13].

3. From 1-ethoxyethylidenemalononitrile:

The product of the reaction of 1-ethoxyethylidenemalononitrile (**4**) with hydrogen sulphide was found to be dependent on the nature of the reaction solvent. Thus, when using ethanol as a solvent, the thioamide **1** was the sole reaction product. On the other hand, using benzene instead of ethanol afforded 2-cyano-3-ethoxythiocrotonamide (**5**) as the isolable reaction product[6].



A possible and logic mechanism accounting for the formation of 1 from the reaction of 4 and hydrogen sulphide in ethanol denotes that compound 5 is formed first as an intermediate. Since compound 5 is soluble in dry ethanol to the extent of 0.5% only at the reflux temperature, it could react then with hydrogen sulphide to give the postulated intermediate addition product 6. Compound 6 would then be cleaved under the reaction conditions to give the isolable reaction product 1 together with ethyl thioacetate (7). In support of the above mechanism[6], compound 5 reacted with hydrogen sulphide to give compounds 1, 7 and dithiomalonamide (8)[14,15] (cf. Chart 1).

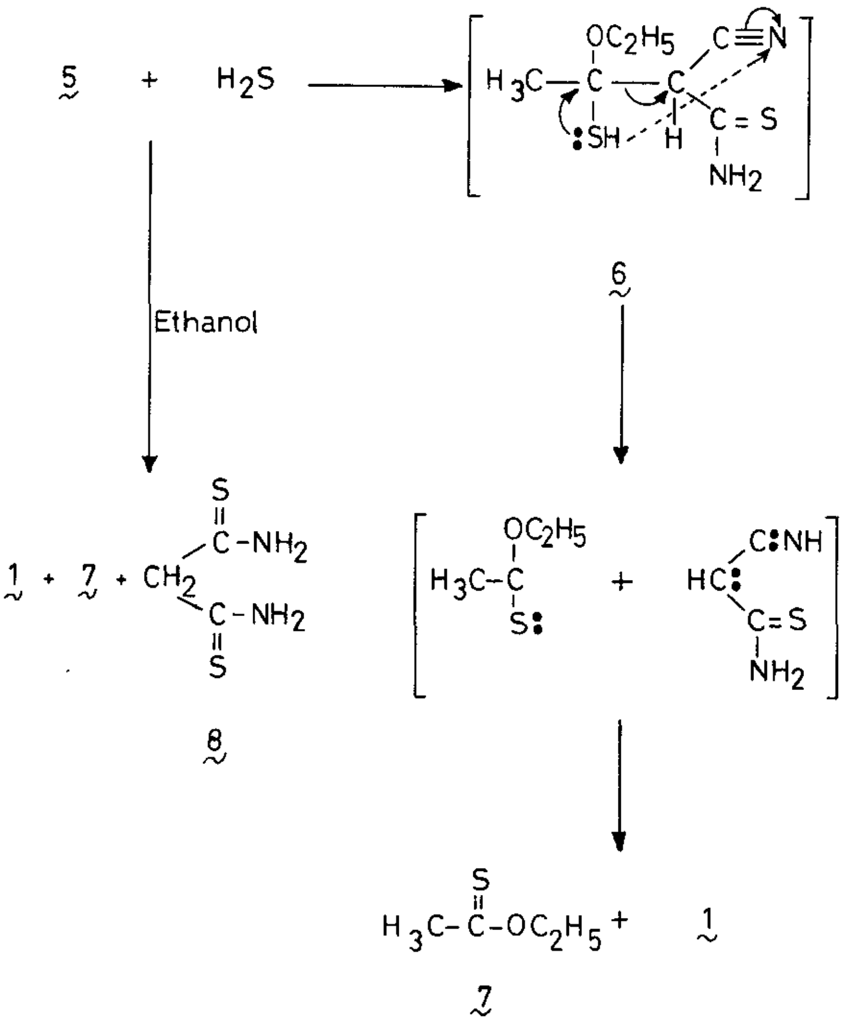


Chart 1

III. PHYSICAL PROPERTIES:

α-Cyanothioacetamide (**1**) is an almost colourless solid compound which can be crystallized from ethanol or benzene and darkens on long standing. Different melting points are reported for **1** among which may be mentioned:

118-121°C	(Reference No. 5)
114-120°C	(Reference No. 6)
115-117°C	(Reference No. 6)
119°C	(Reference No. 7)
121-123°C	(Reference No. 9) and
118-120°C	(Reference No. 10)

It must be pointed out, however, that it is advisable to use freshly prepared **1** as long standing may cause different results for the same reaction under the same experimental conditions. The internal coordinates of **1** (*Figure 1*)[11] are of interest and are reported here as a guide for structural elucidations.

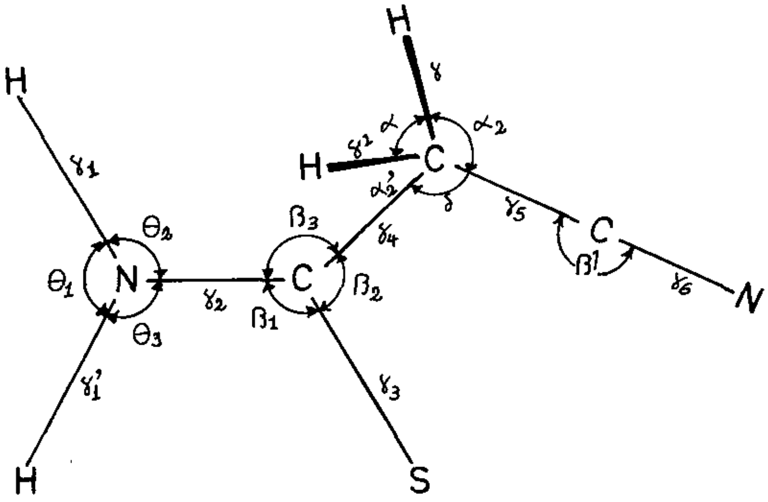


Figure 1: Internal coordinates of **1**

The IR spectral data of **1** are reported (Table 1) as they represent a model for *comparison of the IR spectral data of the reaction products starting with* **1**.

Table 1: IR spectral data of 1

Frequencies (cm^{-1})	Assignments	Frequencies (cm^{-1})	Assignments
3375	$\nu(NH)$	1260	$\nu(CC) + \delta(NCS) + \nu(CS)$
3295	$\nu(NH)$	1001	$\rho(NH_2) + \nu(CC) + \delta(CCC)$
2898	$\nu(CH)$	955	$\nu(CC)$
2268	$\nu(C\equiv N)$	760	$\nu(CS) + \delta(CC\equiv N)$
1630	$\delta(NH_2) + \nu(CN)$	630	$\nu(CC) + \delta(CC\equiv N) + \delta(NCS)$
1460	$\nu(CN) + w(CH_2)$	421	$\delta(NCS) + \delta(CC\equiv N)$
1415	$\delta(CH_2)$	335	$\delta(CCS) + \delta(CC\equiv N) + \delta(CCC)$
1385	$w(CH_2) + \nu(CN)$	105	$\delta(CCS) + \delta(CCC) + \delta(CC\equiv N)$

IV. CHEMICAL REACTIONS:

1. Condensation with aromatic aldehydes:

Aromatic aldehydes condense with 1 in the presence of basic catalysts to afford the corresponding 3-aryl-2-cyanothioacrylamide derivatives (9). Several examples of 9 were reported in literature to be synthesised via this route[6,12,13]. The structure of 9 was established via synthesis through other routes either by the action of phosphorus pentasulphide in pyridine on the corresponding amides[13](10) or by the action of hydrogen sulphide on the corresponding ylidene malononitriles (11) in dry benzene in the presence of catalytic amounts of triethylamine[6] (cf. Chart 2).

Brunskill et al.[5] reported that the products obtained by the action of aromatic aldehydes on 1 had the correct elemental composition and where appropriate had melting temperatures in agreement with literature values. The thioacrylamide structure (9) was in accord with the NMR spectra for compounds derived from heterocyclic aldehydes and 2- and 4- substituted benzaldehydes. However, for the reactions with benzaldehyde, 4-bromobenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde the reaction products had more complex spectra. These products were formulated as the 2,4-diaryl derivatives of 6-amino-3,5-dicyano-3,4-dihydro-2H-thiopyran-3-thiocarboxamide (12). Compounds 12 were assumed to be formed via the Diels-Alder self condensation reaction of the corresponding thioacrylamide derivatives (**9**) (cf. Chart 2).

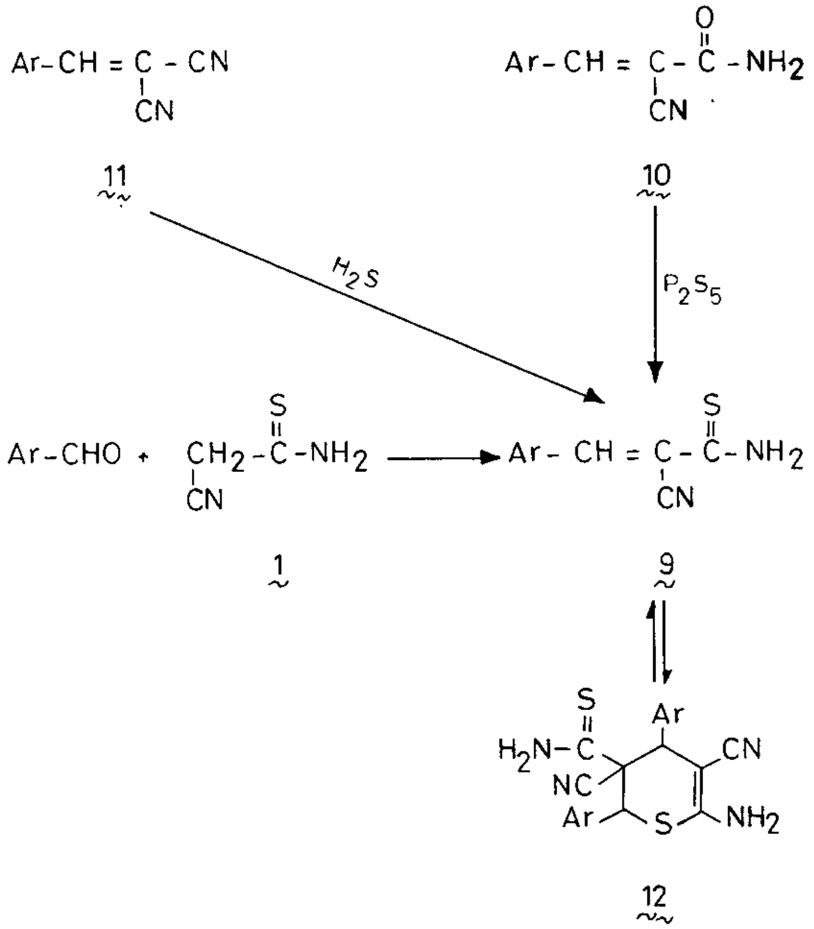
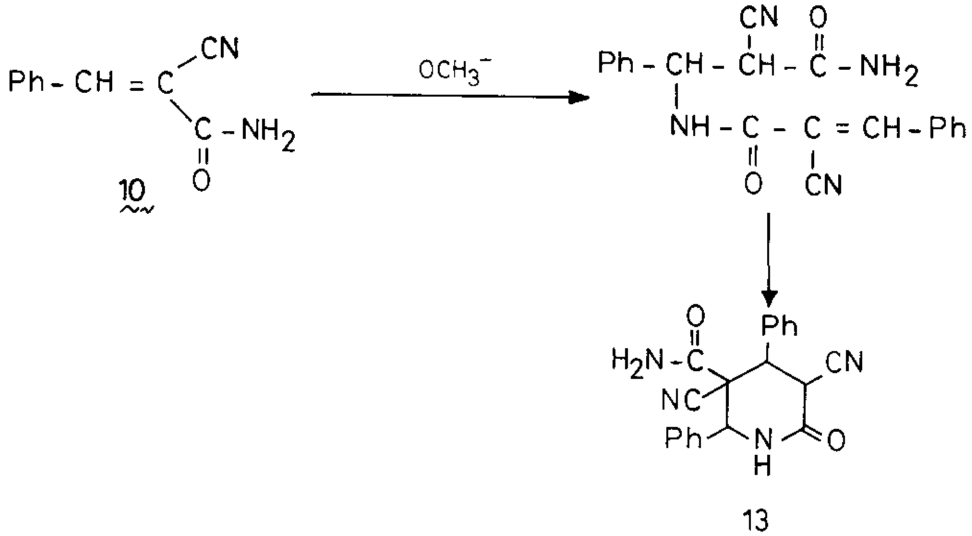


Chart 2

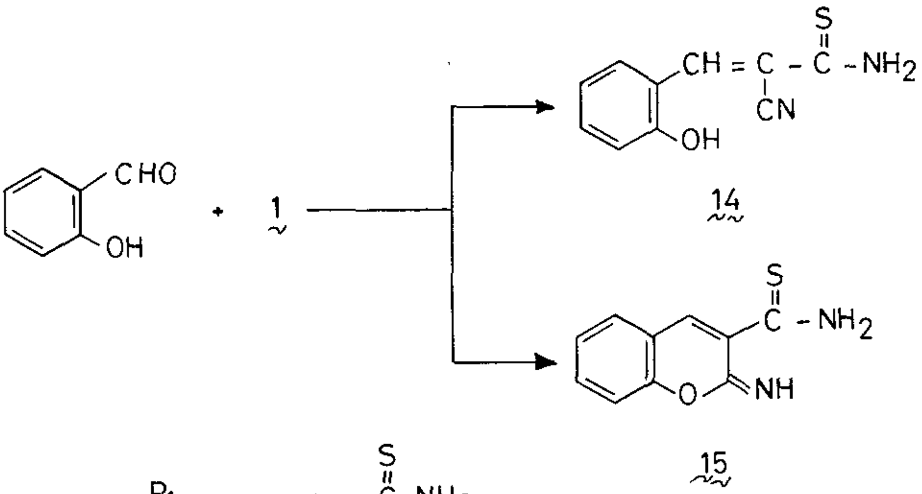
The IR spectra of **12** had an extra band in the region of the NH group (3400-3500 cm^{-1}) and a broadened CN band. Mass spectral studies showed no species of greater mass than the parent ion of the monomeric compound, presumably indicating the dissociation at the proper temperature.

Conclusive evidence for the correctness of the structure **12** was proved by the NMR spectra (in DMSO) of **9** and **12** at higher temperatures. At 100°C all the synthesised compounds had the spectral characteristics of the monomeric thioacrylamides (**9**). At low temperatures the spectra indicated the presence of a mixture of the monomeric (9) and the dimeric (12) forms for those cases which were initially pure dimeric forms (12). Even at 29°C the thiopyran (12) slowly dissociated to an equilibrium mixture of 9 and 12. The dissociation was completely reversible and could be achieved also starting from either the thioacrylamide (9) or the thiopyran (12). For the system where Ar=Ph, the equilibrium constant at 22°C was found to be 0.244 mol^{-1} (from its NMR spectrum) corresponding to ΔG_{295}= 3.46 kJ mol^{-1}. These results are entirely in accord with a reversible Diels-Alder heterodiene cycloaddition reaction[16].

In contrast to the above findings, dimerization has been reported[17] for 2-cyanocinnamide (10, Ar=Ph; the oxygen analogue of 9, Ar=Ph) but this is not a thermal pericyclic reaction. The proposed mechanism involves a base-catalyzed Michael condensation reaction followed by cyclization to the piperidone (13) rather than the pyran analogous of 12.



Grinstein and Serina[12] reported that the base catalyzed condensation reaction of salicylaldehyde with 1 afforded 2-cyano-3-(2-hydroxyphenyl)-thioacrylamide (14). On the other hand, Brunskill et al.[18] repeated the same reaction and claimed that they obtained a crystalline material with the same melting point as that for the reaction product obtained by Grinstein and Serina[12]. Brunskill et al.[18] formulated their reaction product as the imino derivative 15 on the basis of its IR and ^{1}H NMR spectral studies although this compound (15) could not be obtained in an analytically pure state even after repeated crystallizations from various solvents. It is remarkable to note here that similar erroneous reports on Knoevenagel condensation of o-hydroxyaldehydes are not uncommon[19]. However, warming the imino deriva-



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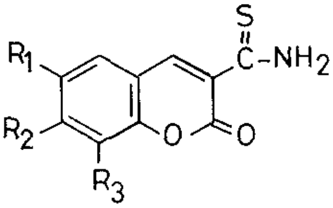
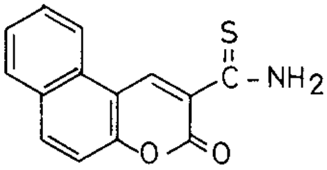


16a, $R_1=R_2=R_3=H$
b, $R_1=R_3=H; R_2=OH$
c, $R_2=R_3=H; R_1=OH$
d, $R_1=R_2=H; R_3=OCH_3$
e, $R_1=R_3=H; R_2=OCH_3$
f, $R_2=R_3=H; R_1=OCH_3$
g, $R_2=R_3=H; R_1=Br$

tive 15 with dilute hydrochloric acid afforded the corresponding coumarin derivative 16a which was easily purified by crystallization from ethanol. The structure of 16a was confirmed by elemental analysis and spectroscopic data studies[18]. The above condensation reaction was also extended to synthesise a variety of substituted coumarin derivatives (16b–g) utilizing the appropriate benzaldehyde derivatives. On the other hand, the use of 2-hydroxy-1-naphthaldehyde and 5-hydroxybenzo[b]thiophene-4-carboxaldehyde[20-22] resulted in the formation of the coumarin derivatives 17 and 18 respectively[18, 23].

The above condensation reaction constitutes an easy and facile route for the synthesis of thiocarboxamide derivatives. Other alternative syntheses necessitate the



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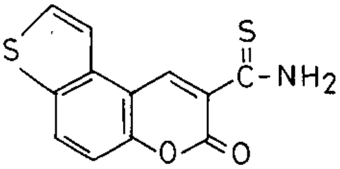

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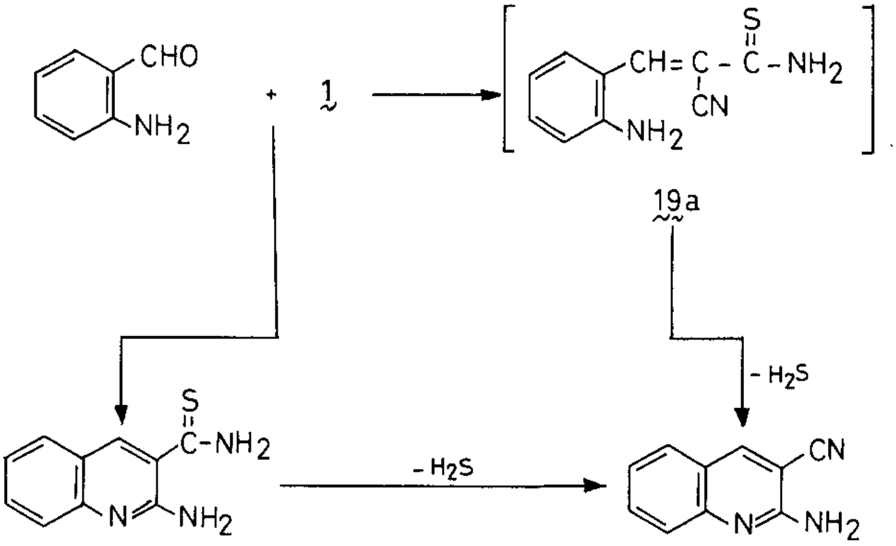
first formation of the corresponding carboxamides then their subsequent transformation into the corresponding thiocarboxamides by the action of phosphorus pentasulphide. However, in addition to the fact that the synthesis of carboxamides is too long[19], treatment with phosphorus pentasulphide under standard conditions[24] is so far unsuccessful[18].

The base-catalyzed condensation reaction of o-aminobenzaldehyde with 1 under similar conditions[18] afforded 2-amino-3-cyanoquinoline (20)[25] formed via the inter-



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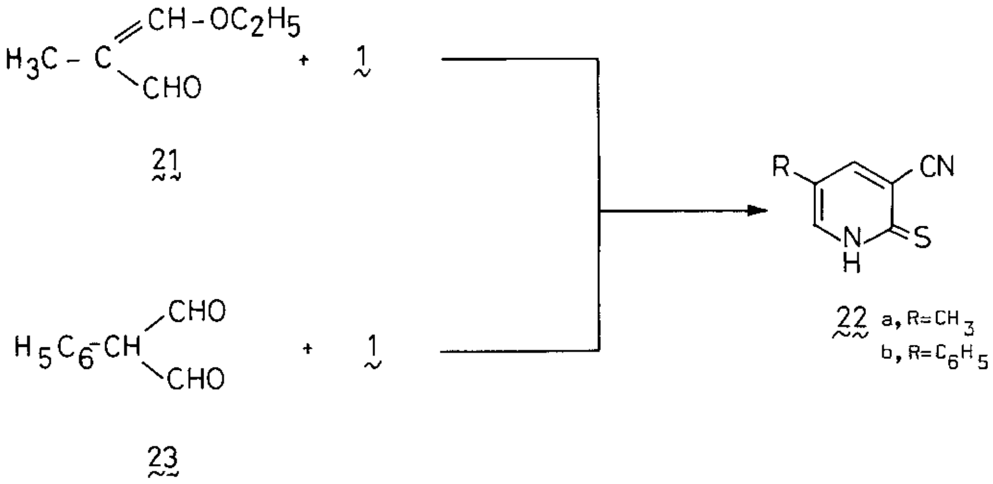
20

mediacy of 2-aminoquinoline-3-thiocarboxamide (19) which rapidly lost one molecule of hydrogen sulphide to give the final isolable 20. In our opinion, however, the formation of 20 in the reaction of 1 and o-aminobenzaldehyde proceeds via the intermediacy of the condensation product 19a which loses hydrogen sulphide to give directly compound 20. This explanation finds support from the fact that the thioamides, like 19, are reported by the same authors[18] to be highly stable (cf.

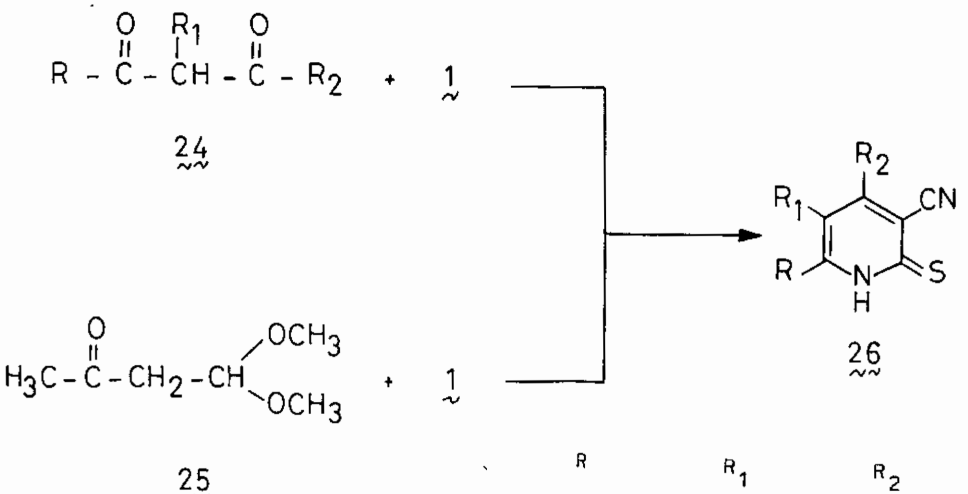
structures 15-18).

2-Methyl-3-ethoxyacrolein (21, a methylmalondialdehyde equivalent) condensed with 1 to give an excellent yield of 3-cyano-5-methyl-2(1H)-pyridinethione (22a)[26,27]. On the other hand, 2-phenylmalondialdehyde (23)[28,29] reacted with 1 in the presence of β-diethylaminoethanol to afford the 5-phenyl derivative (22b)[30].



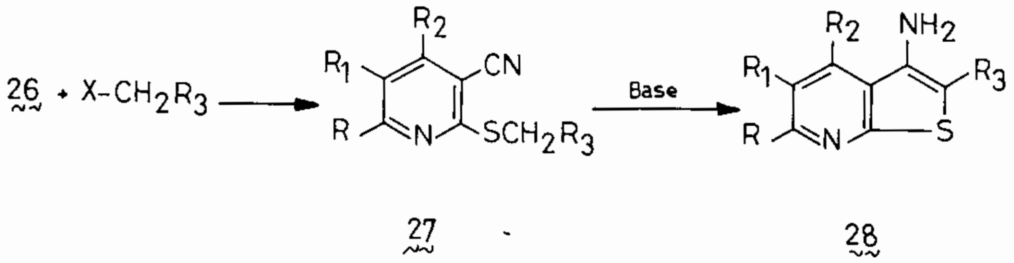
2. Reactions with β-dicarbonyl compounds:

The reaction of β-dicarbonyl compounds with 1 was found to be an easy and direct route for the synthesis of several 3-cyano-2-pyridinethione derivatives (26)[7,29,31-33]. Thus, compound 1 reacted with acetylacetone (24a), benzoylacetone (24b), ethyl acetonoxalate (24c), ethyl acetophenonoxalate (24d), 3-acetoxyacetylacetone (24e), 3-acetamino-acetylacetone (24f), ethyl acetoacetate (24g) and β-ketobutyraldehyde dimethylacetal (25) to yield 4,6-dimethyl-, 4-methyl-6-phenyl-, 6-methyl-4-ethoxycarbonyl-, 6-phenyl-4-ethoxycarbonyl-, 4,6-dimethyl-5-acetoxy-, 4,6-dimethyl-5-acetylamino-, 6-hydroxy-4-methyl- and 6-methyl-3-cyano-2-pyridinethione derivatives (26a-h) respectively in good yields.

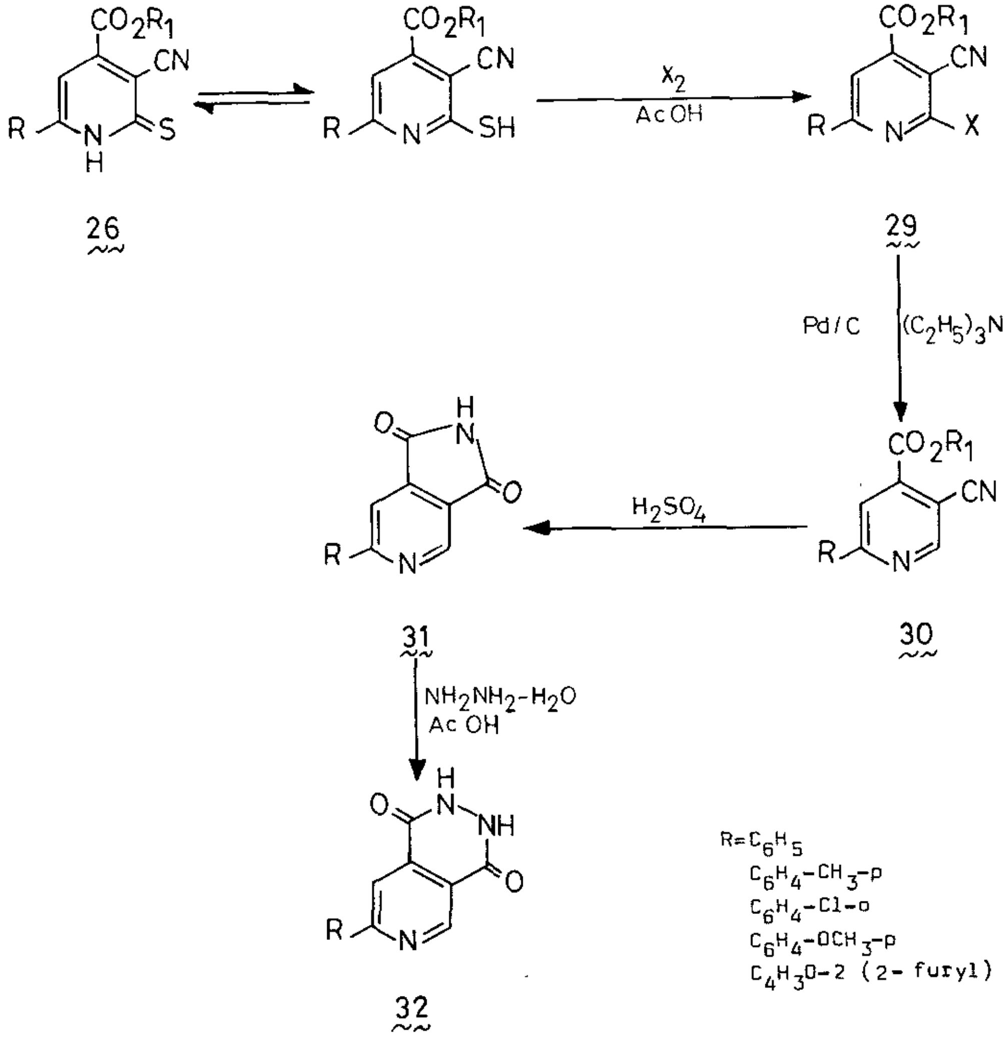


	R	R_1	R_2
24 and 26 a,	CH_3	H	CH_3
b,	C_6H_5	H	CH_3
c,	CH_3	H	$CO_2C_2H_5$
d,	C_6H_5	H	$CO_2C_2H_5$
e,	CH_3	CH_3CO_2	CH_3
f,	CH_3	CH_3CONH	CH_3
24 g,	OC_2H_5	H	CH_3
26 g,	OH	H	CH_3
26 h,	CH_3	H	H

The pyridinethione derivatives (26) are very important starting materials for the synthesis of 3-aminothieno[2,3-b]pyridines. Thus, thirty six thienopyridine derivatives (28, R=H, CH_3 or C_6H_5; R_1=H or NO_2; R_2=H, CH_3 or $CO_2C_2H_5$ and R_3= e.g. $COCH_3$, $CO_2C_2H_5$, CO_2CH_3, CN or NO_2) were prepared by cyclization of the in situ formed 27 in the presence of a base such as sodium ethoxide or potassium carbonate at reflux temperatures[34].



Moreover, Oka et al.[35] utilized the above pyridinethione derivatives (**26**) as the starting materials for the synthesis of several pyridopyridazine derivatives via a series of reactions. Thus, treatment of **26** with a halogen in acetic acid gave the corresponding 2-halogeno derivatives **29**. Reduction of **29** using palladium over carbon in the presence of triethylamine yielded the pyridine derivatives **30** which could be hydrolyzed then cyclized by the action of concentrated sulphuric acid to afford the pyrrolopyridines **31**. Compounds **31** reacted with hydrazine hydrate in acetic acid to furnish the finally isolable pyrido[3,4-d]pyridazine derivatives **32** in good yields (cf. Chart 3).



R=C_6H_5
C_6H_4-CH_3-p
C_6H_4-Cl-o
C_6H_4-OCH_3-p
C_4H_3O-2 (2- furyl)

Chart 3

3. Reactions with α,β- unsaturated ketones and nitriles:

Daboun et al.[36] and Soto et al.[4,37,38] reported independently, and almost simultaneously, a novel method for the synthesis of pyridine-2(1H)-thiones other than the few methods known in literature[7,39-44]. The method of Daboun et al.[36] involves the reaction of 1 with the α- benzoylcinnamonitrile derivatives (33, X=CN) in boiling ethanol in the presence of catalytic amounts of triethylamine to bring about a conjugate addition followed by a cyclization step (involving the amino group in 1 and the carbonyl group in 33) and spontaneous aromatization to yield the thiopyridone derivatives 34. On the other hand, Soto et al.[3,37,38] reacted 1 with each of the arylidene-acetophenones (chalcones, 33, X=H) and the α- benzoylcinnamonitriles (33, X=CN) at room temperature to afford the thiopyridone derivatives 34 together with the disulphides 35. The disulphides 35 were assumed to be formed via an oxidative dimerization of 34 under the applied reaction conditions. However, the dimerization reaction leading to the formation of 35 was prevented when the reaction was carried out in the presence of 2-mercaptoethanol and only 34 were the reaction products. It was found also that the addition of an oxidizing agent, such as iodine-potassium iodide[45,46], leads to the formation of the disulphides 35 as the only isolable reaction products (cf. Chart 4).

In an investigation of the same reaction, Krauze et al.[47] reported that the thioamide 1 reacted with the arylidene-acetophenones (33, X=H) to give the 3-cyano-4,6-diaryl-3,4-dihydropyridine-2-thiones (34a) as the sole reaction products.

Very recently, Elnagdi et al.[48] studied the reaction of 1 with 33 (X=CN, Ar=2-furyl) in boiling ethanol in the presence of piperidine and reported that the reaction product was formulated as the 5-(2-furylmethylene)pyridinethione derivative 36. On the other hand, the use of the 2-thienyl analogue 33 (X=CN, Ar=2-thienyl) resulted in the formation of the ylidene group exchange product 9 (Ar=2-thienyl). It is remarkable to note here that the melting point of 9 (Ar=2-thienyl) reported by Elnagdi et al.[48] is far-away from that previosly reported in literature[5,6] for the same compound (cf. Chart 4).

The reaction of 1 with the arylidenemalononitriles 11 was investigated by several authors[36,48,49]. Daboun et al.[36] reported that 1 reacted with 11 in boiling absolute ethanol in the presence of catalytic amounts of triethylamine to give 1:1 adducts. Several isomeric structures (37-39) were thus proposed for the reaction products. The authors[36], however, established structure 39 for the reaction products based on elemental analyses, IR and ^{1}H NMR spectral data studies.

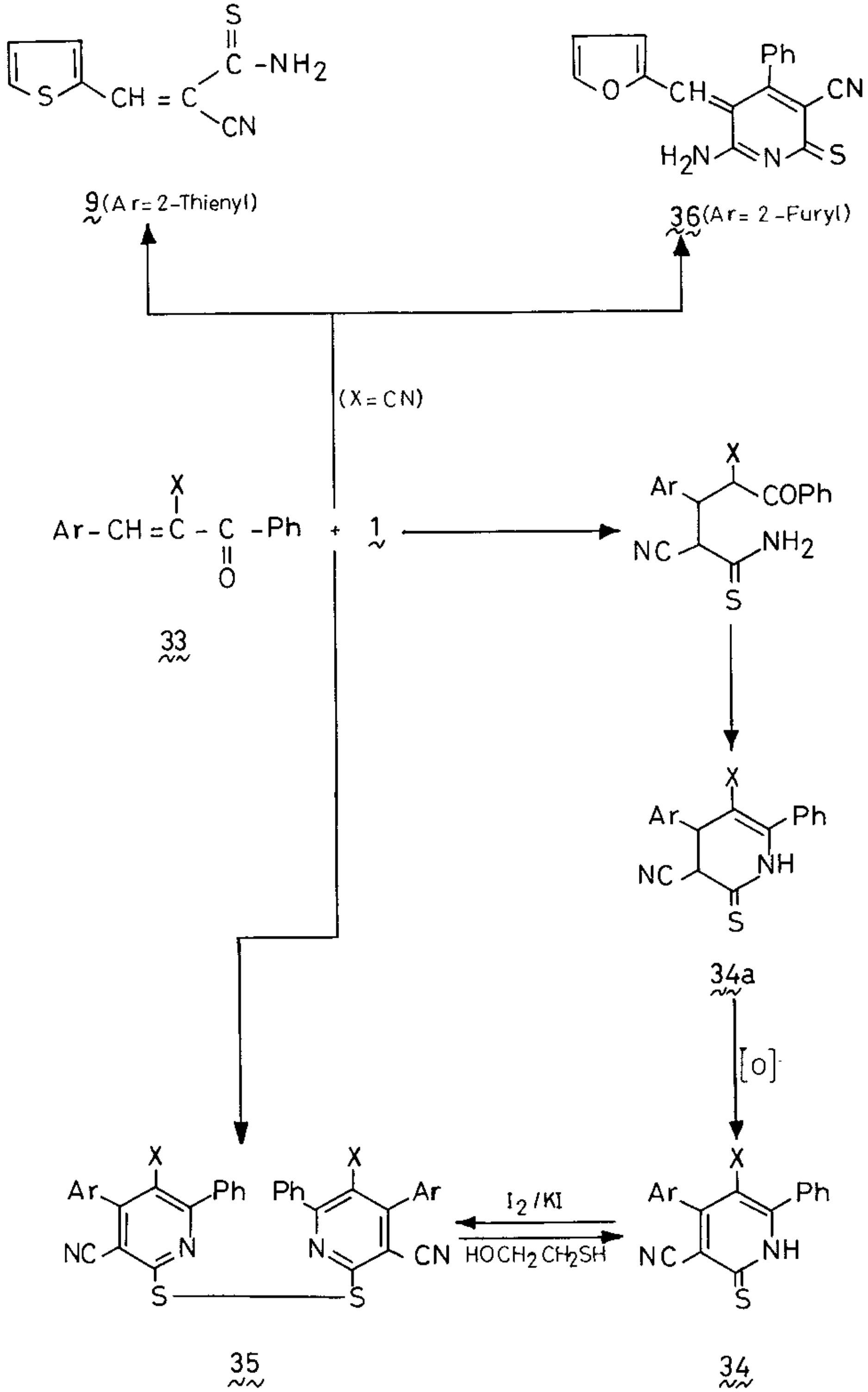


Chart 4

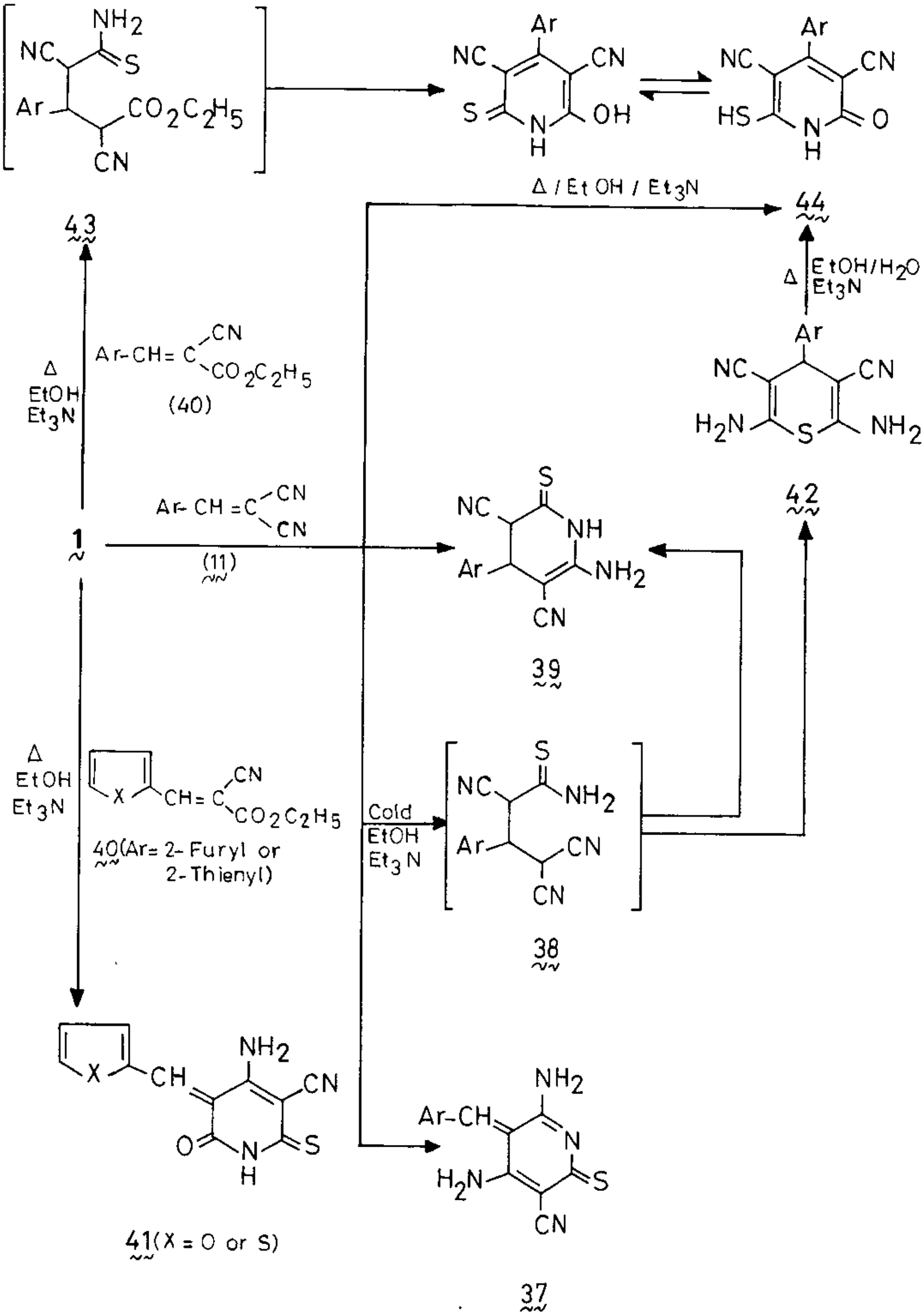

43
44
Δ / Et OH / Et3N
Δ
EtOH/H2O
Et3N
Δ
EtOH
Et3N
Ar-CH= C(CN)CO2C2H5
(40)
Ar- CH =C(CN)CN
(11)
1
42
39
Δ
EtOH
Et3N
40(Ar= 2-Furyl or 2-Thienyl)
Cold
EtOH
Et3N
38
41(X = O or S)
37

Chart 5

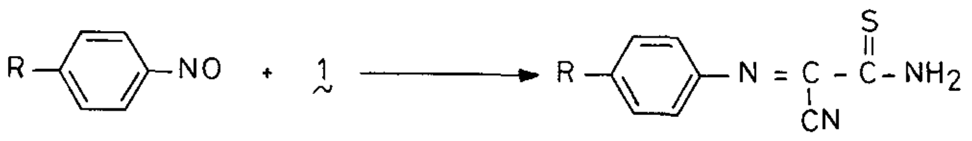
Fahmy and Mohareb[49] reported recently that the thioamide **1** condensed with benzalmalononitrile (**11**, Ar=Ph) in sodium ethoxide to yield the 5-benzylidene derivative **37** (Ar=Ph).

Elnagdi et al.[48], however, extended their study to involve the reaction of **1** with the ylidenemalononitriles **11** (Ar=2-furyl or 2-thienyl). Thus, the authors[48] reported that **1** reacted with **11** (Ar=2-furyl or 2-thienyl) in boiling ethanol in the presence of catyltic amounts of piperidine to afford the 5-ylidenepyridinethione derivatives **37** (Ar=2-furyl or 2-thienyl). This finding is in agreement with the results and structure proposed by Fahmy et al.[49] Furthermore, the same authors[48] reported also that the 5-ylidenepyridin-6-one-2-thione derivatives **41** (X=O or S) could be synthesized by reacting **1** with the correspoding ylidenes **40** (Ar=2-furyl or 2-thienyl) under the same experimental conditions (cf. Chart 5).

In a next communication, Elnagdi et al[50] reported that the reaction of the ylidene malononitriles **11** with **1** in cold ethanolic triethylamine solutions afforded the thiopyran derivatives **42** most likely formed via the intermediacy of the acyclic **38**. On the other hand, the reaction of the cinnamonitrile derivatives **40**, in boiling ethanolic triethylamine solutions, yielded the dihydropyridine derivatives **44** formed via the intermediacy of the acyclic **43**. The authors[50] reported also that compounds **44** could also be prepared either by boiling ethanolic aqueous triethylamine solutions of the thiopyrans **42** or conducting the reaction of **1** and **11** in boiling ethanolic triethylamine solutions (cf. Chart 5). The mechanism of Elnagdi et al.[50] accounting for the identity of the products of reaction of **1** with either **11** or **40** involves the loss of one molecule of ammonia from **42**, which was not mentioned at all in any step of the reported mechanism.

4. Reaction with nitroso compounds:

The thioamide **1** condensed with nitrosobenzene and its derivatives (**45**) to yield the corresponding azomethane derivatives (**46**)[12].



45 **46**

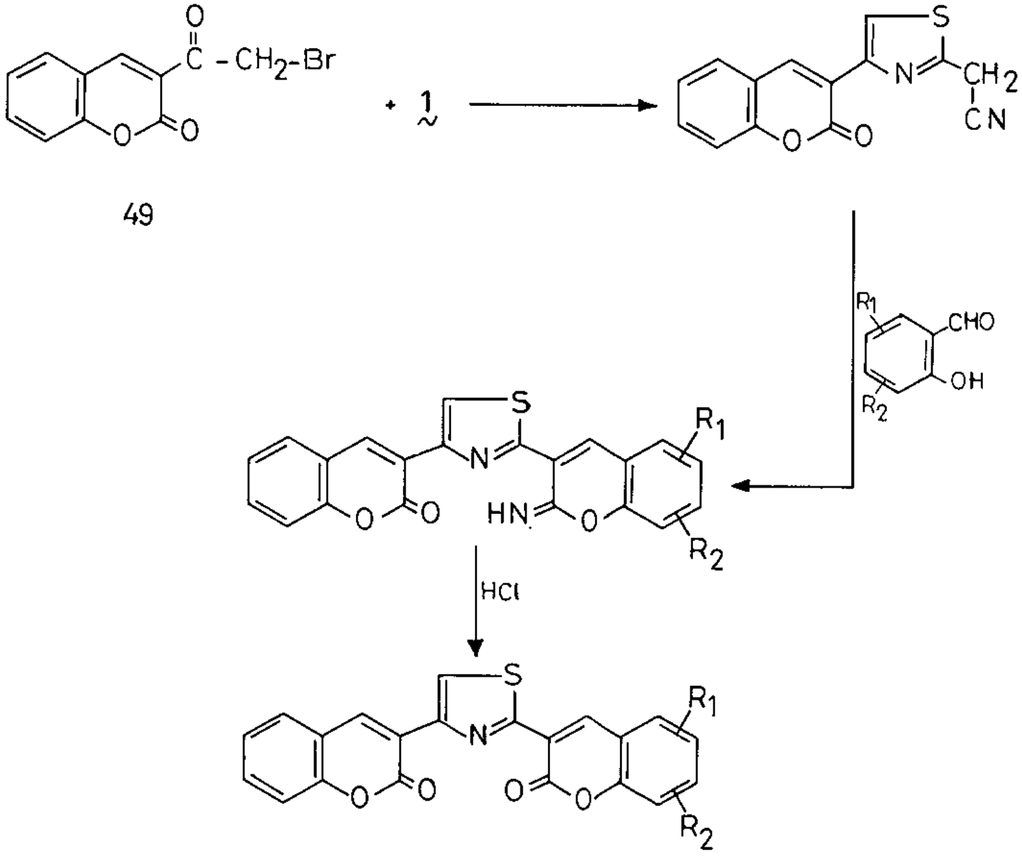
5. Reactions with halogenated compounds:

The halogenated ketones 47 were reported by Schäfer et al.[51] to react with 1 to yield the 2-thiazolylacetonitrile derivatives 48.

47

48 (R=H, CH_3 and Ph)

Different thiazolylcoumarin derivatives (50) could be synthesized similarly[52] via the reaction of 3-bromoacetylcoumarin (49) with 1 in a series of steps represented by the following equations:



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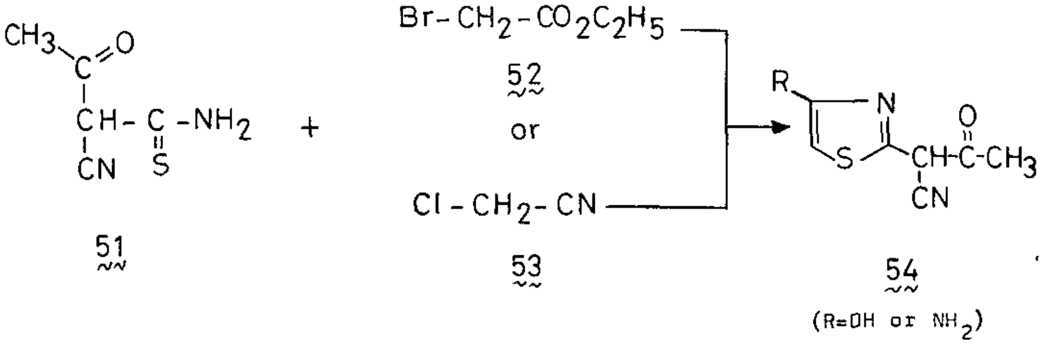
It has been reported that α- acetyl-α- cyanothioacetamide (51), obtained by acetylation of 1, could be cyclized via the reaction with ethyl α- bromoacetate (52) to give the thiazole derivative 54 in a good yield[53]. The same compound 54 could also be obtained by using α- chloroacetonitrile (53) instead of 52 in the above reaction[53].



On the other hand, Tornetta et al.[31] reported that the product of the reaction of 1 with ethyl bromopyruvate (55) was found to be highly dependent on the solvent used in the reaction. Thus, 1 and 55 reacted in a mixture of pyridine and acetic acid to afford 2-amino-3-cyano-4-ethoxycarbonylthiophene (56). When dimethylformamide was used as a solvent, 2-cyanomethyl-4-ethoxycarbonylthiazole (57) was the only isolable reaction product. Compound 57 condensed with 4-chlorobenzaldehyde to give the 4-chlorobenzal derivative 58. Compound 58 could be in turn synthesised via another route by the reaction of 4-chlorobenzal-α- cyanothioacetamide 9 (Ar=C$_6$H$_4$-Cl-p) with ethyl bromopyruvate (55) (cf. Chart 6).

Compound 1 reacted also with ethyl β-chloroacetonoxalate (59) in the presence of a mixture of pyridine and acetic acid to afford 5-acetyl-2-amino-3-cyano-4-ethoxycarbonylthiophene (60) and 2-acetyl-3-amino-5-chloro-4-ethoxycarbonyl-6-methylthieno[2,3-b]pyridine (64). Compound 64 is assumed to be formed via the intermediacy of the pyridine derivatives 62 and 63[31] (cf. Chart 7).

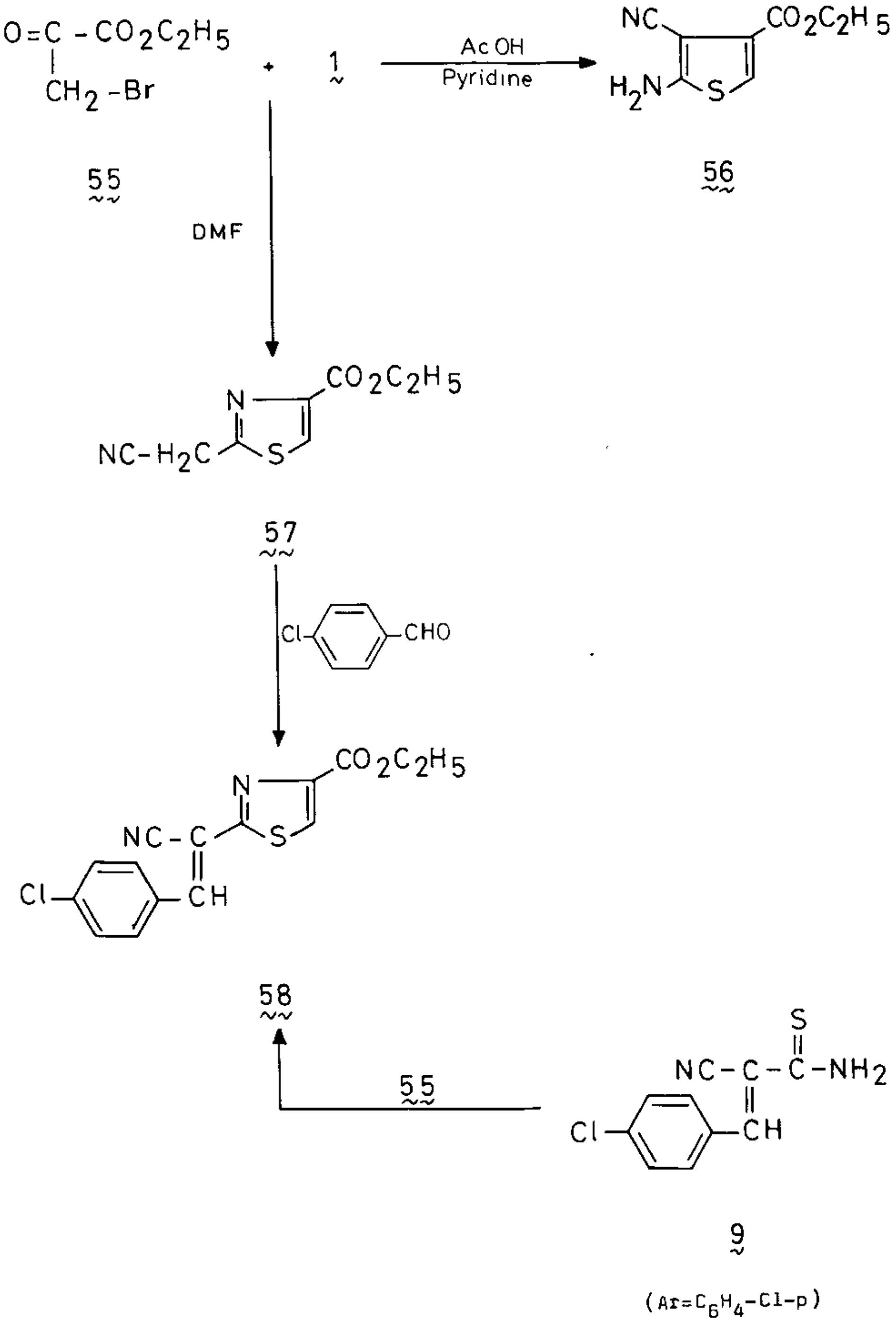


Chart 6

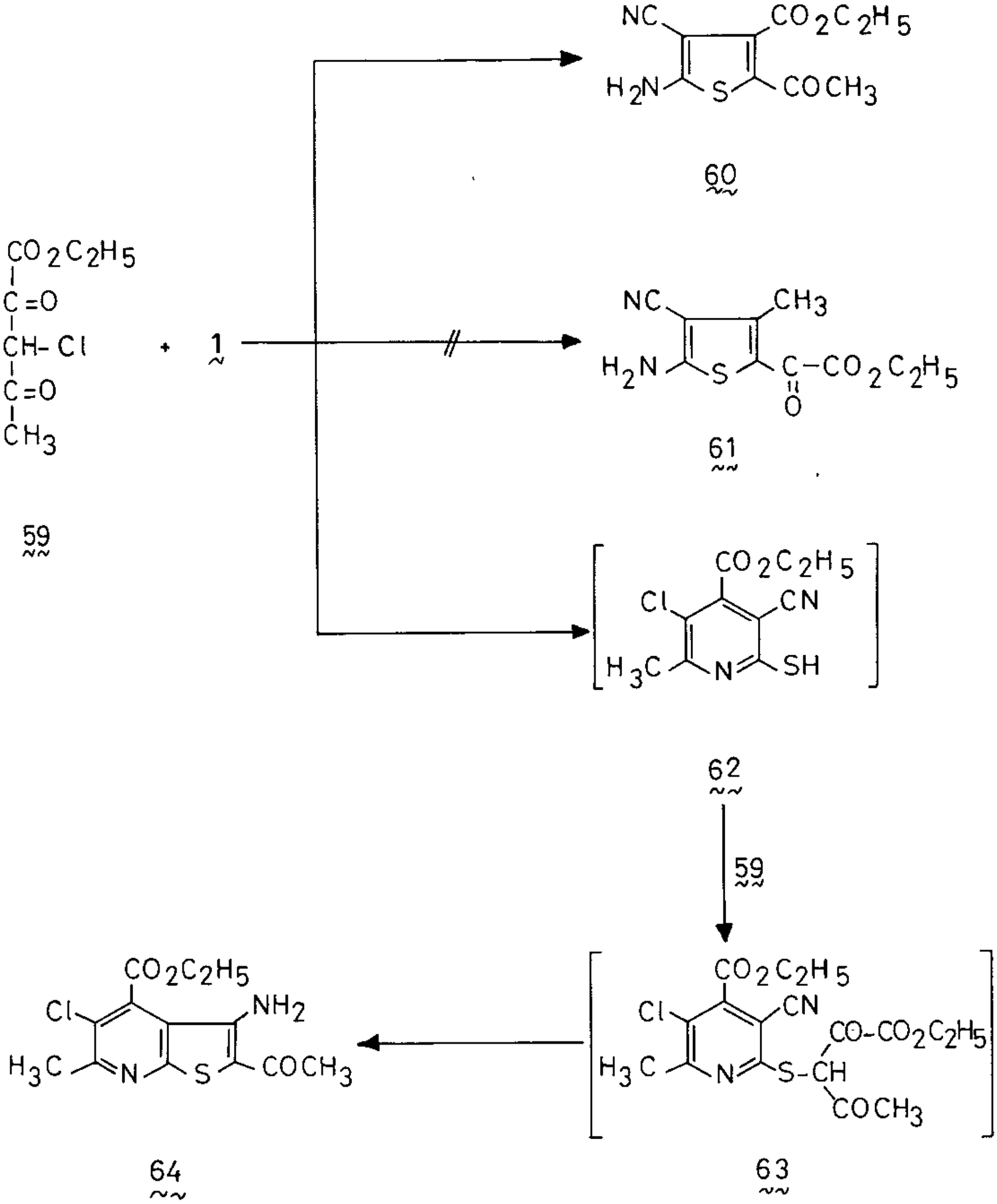

NC
CO2C2H5
H2N
S
COCH3
60
CO2C2H5
C=O
CH-Cl
C=O
CH3
59
+ 1
NC
CH3
H2N
S
C-CO2C2H5
O
61
CO2C2H5
Cl
CN
H3C
N
SH
62
59
CO2C2H5
Cl
CN
CO-CO2C2H5
H3C
N
S-CH
COCH3
63
CO2C2H5
Cl
NH2
H3C
N
S
COCH3
64

Chart 7

6. Action of bases:

Fahmy and Mohareb[49] reported very recently that when 1 was treated with a boiling ethanolic sodium ethoxide solution, a single product of molecular formula $C_6H_6N_4S$ was obtained. Several isomeric structures were thus considered for the reaction product (cf. structures 65-68). Structures 65-67 were ruled out and structure 68 was established for the reaction product based on IR and ^1H NMR spectral data studies. Moreover, compound 68 could be synthesised via another route by the reaction of 1 with malononitrile (2) in ethanol in the presence of catalytic amounts of triethylamine (cf. Chart 8).

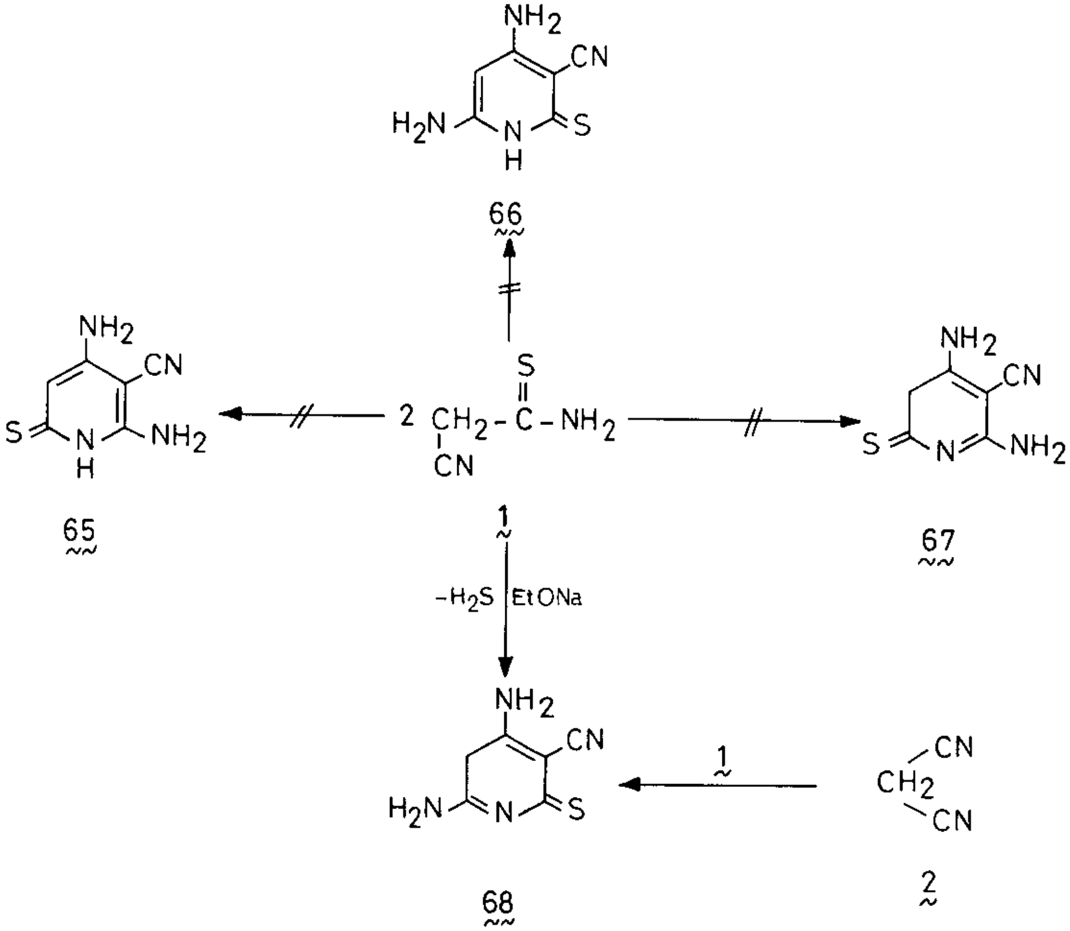


Chart 8

In an another communication, Mohareb and Fahmy[33] reported that 1 underwent self dimerization with ethanolic triethylamine solution at room temperature to give a product of molecular formula $C_6H_8N_4S_2$ which was formulated as the pyridine derivative 69 or the acyclic dithioamide 70. However, structure 70 was established for the reaction product based on IR and ^{1}H NMR spectral data. Moreover, compound 70 could be coupled with benzenediazonium chloride in the presence of sodium hydroxide to give the pyridazine derivative 72 most likely formed via the intermediacy of the non-isolable hydrazone derivative 71 (cf. Chart 9).

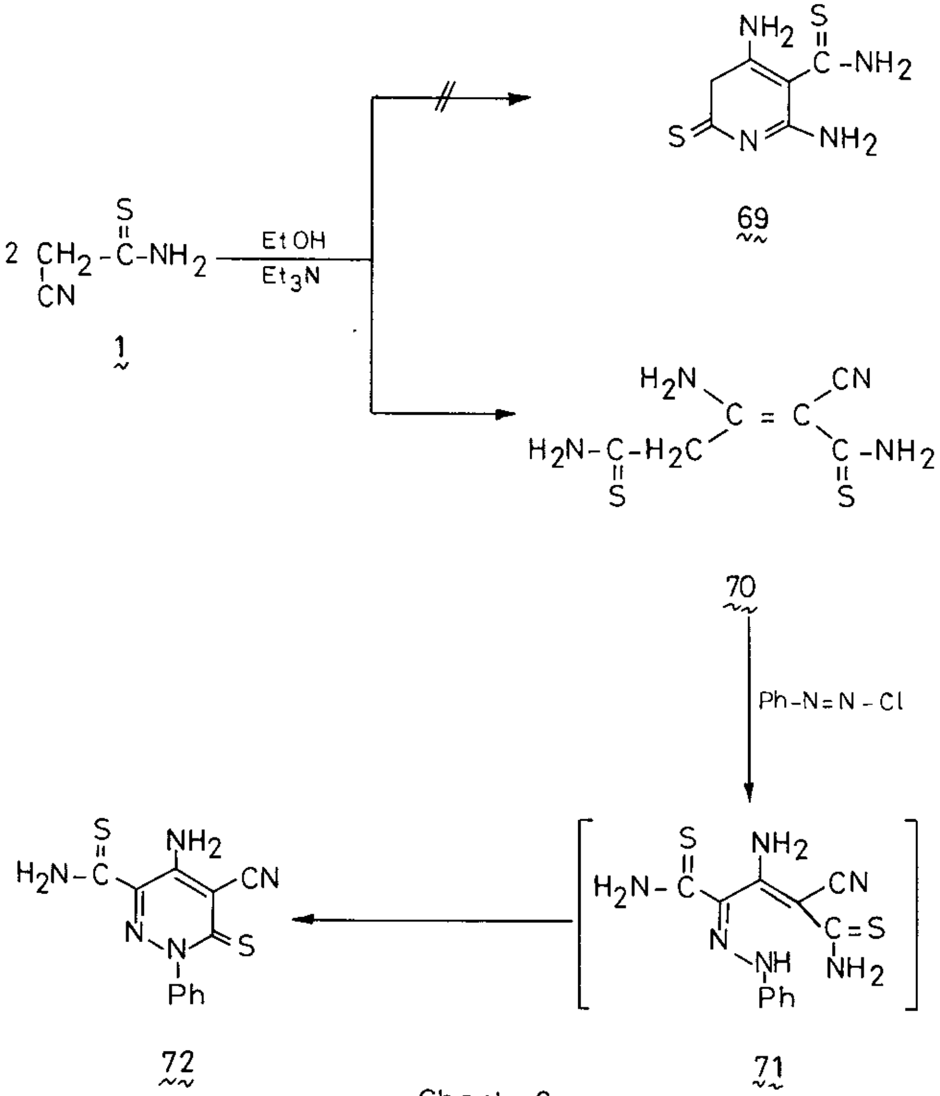
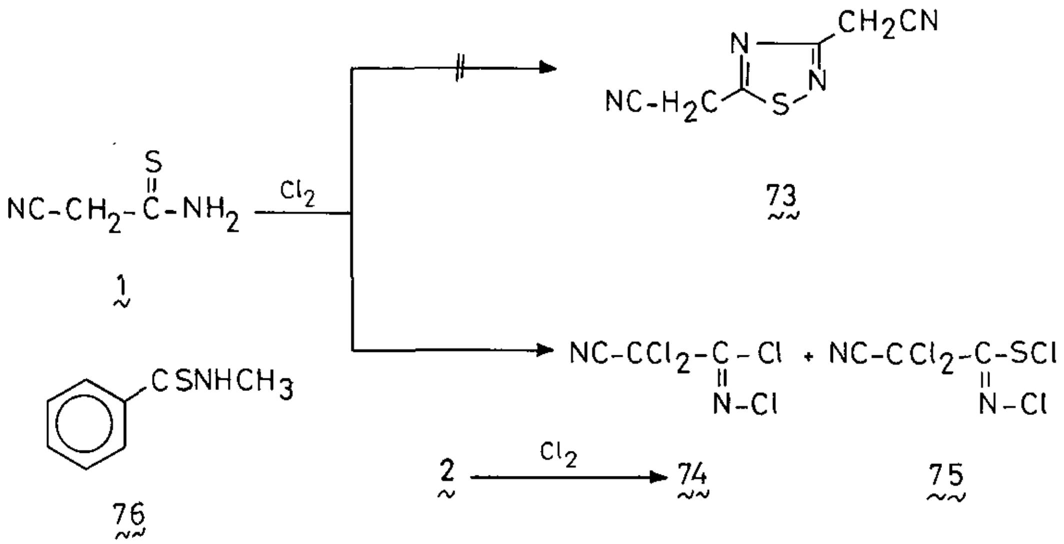


Chart 9

7 Reactions with halogens:

In an attempt to synthesise 3,5-di(cyanomethyl)-1,2,4-thiadiazole (73) by chlorination of 1 in carbon tetrachloride, two unexpected products were isolated[54]. These were N,2,2-trichlorocyanoacetimidoyl chloride (74) and N,2,2-trichlorocyanoacetimidoylsulphenyl chloride (75). This represents an unusual course of reaction for the treatment of N-unsubstituted thionamides with chlorine since the normal reaction products should be 1,2,4-thiadiazole derivatives[55]. However, the formation of an imidoyl chloride is known in the chlorination of N-methylthionbenzamide (76)[56].



73

1

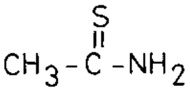
76

74

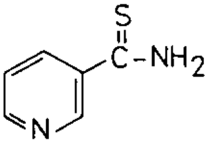
75

Proof that the lower boiling material possessed structure 74 resulted from comparison of its properties with those of an authentic sample prepared by chlorination of malononitrile (2)[57]. Structure 75 was assigned to the higher boiling material on the basis of microanalytical results and mass spectrum.

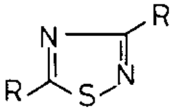
It was reported[54] also that the type of the reaction product of 1 with chlorine is dependent on the reaction temperature. Thus, low reaction temperature favours formation of 75 whereas room temperature favours formation of compound 74. The anomalous course of the reaction allowed the speculation that perhaps reaction conditions were discovered which might permit the synthesis of N-chloroimidoyl chlorides and N-chloroimidoylsulphenyl chlorides from other N-unsubstituted thionamides. This was disproved when, under the same conditions, thioacetamide (77) and thionicotinamide (78) yielded 3,5-dimethyl-1,2,4-thiadiazole (79a) and 3,5-di(3-pyridyl)-1,2,4-thiadiazole (79b) respectively.



77

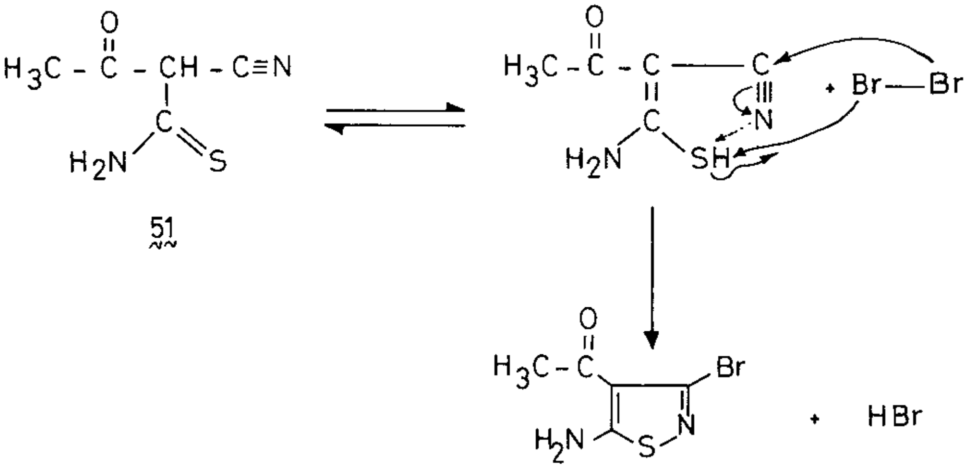


78



79 a, R=CH_3
b, R= 3-pyridyl

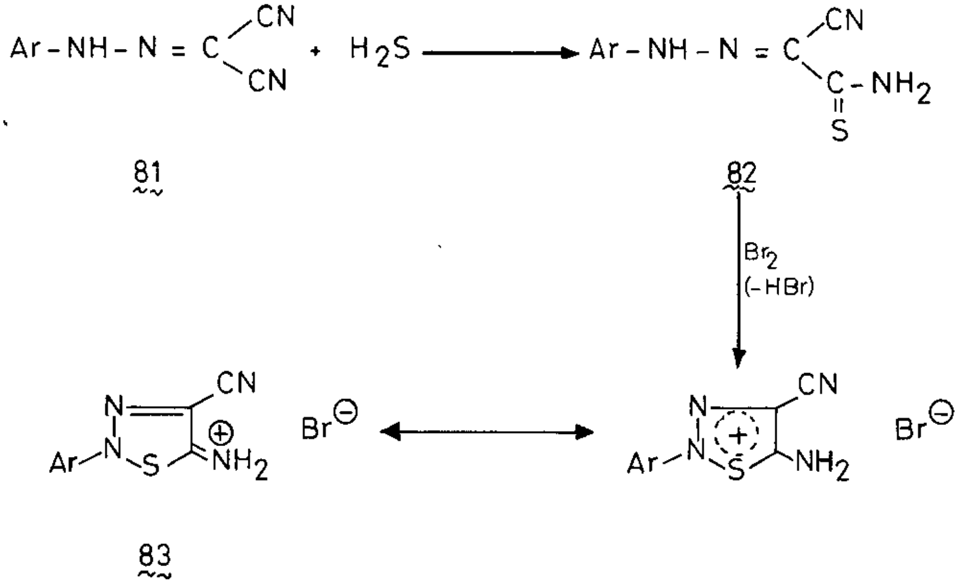
The course of halogenation was also extended to investigate halogenation of cyanothioacetamide derivatives. Thus, it has been found[53] that bromination of α- cyano-α- acetylthioacetamide (51) has resulted in the formation of the isothiazole derivative 80 in a good yield.



51

80

When α- arylhydrazono-α- cyanothioacetamide (82, prepared by the action of H_2S on arylazomalononitrile, 81) was reacted with bromine in ethyl acetate, oxidation occurred and 5-amino-2-phenyl-4-cyano-1,2,3-thiadiazolium bromide derivatives (83) were thus obtained[58].



8. Reaction with formamide acetals:

α- Cyanothioacetamide (1) possesses two nucleophilic centers susceptible to the attack by electrophilic reagents. Therefore, and by analogy to the known reactions of acetamide with acetals^{59}, Knoll et al.^{60} recently reported that 1 reacted with the substituted formamide dimethylacetal 84 in two successive steps to yield the N-(2-cyano-3-morpholinothioacryloyl)-formamidine derivative 86. Compound 86 is assumed to be formed via the intermediacy of 2-cyano-3-morpholinothioacrylamide (85). The formation of 86 goes with no difficulties in the presence of an excess of the acetal 84^{61}. It was observed also that the use of two equivalents of the acetal 84 resulted in the formation of a mixture of products containing only a small amount of 86. Under these conditions, the main product of the reaction was the acrylamide derivative 85. Compound 85 could either be transformed into 86, by the action of an another molecule of 84, or used in the synthesis of other formamidine derivatives. Thus, for example, N-(2-cyano-3-morpholinothioacryloyl)-N',N'-tetramethyleneformamide (88) could be synthesised via the reaction of 85 with N,N-tetramethyleneformamidine dimethylacetal (87) in the presence of methanol (cf. Chart 10).

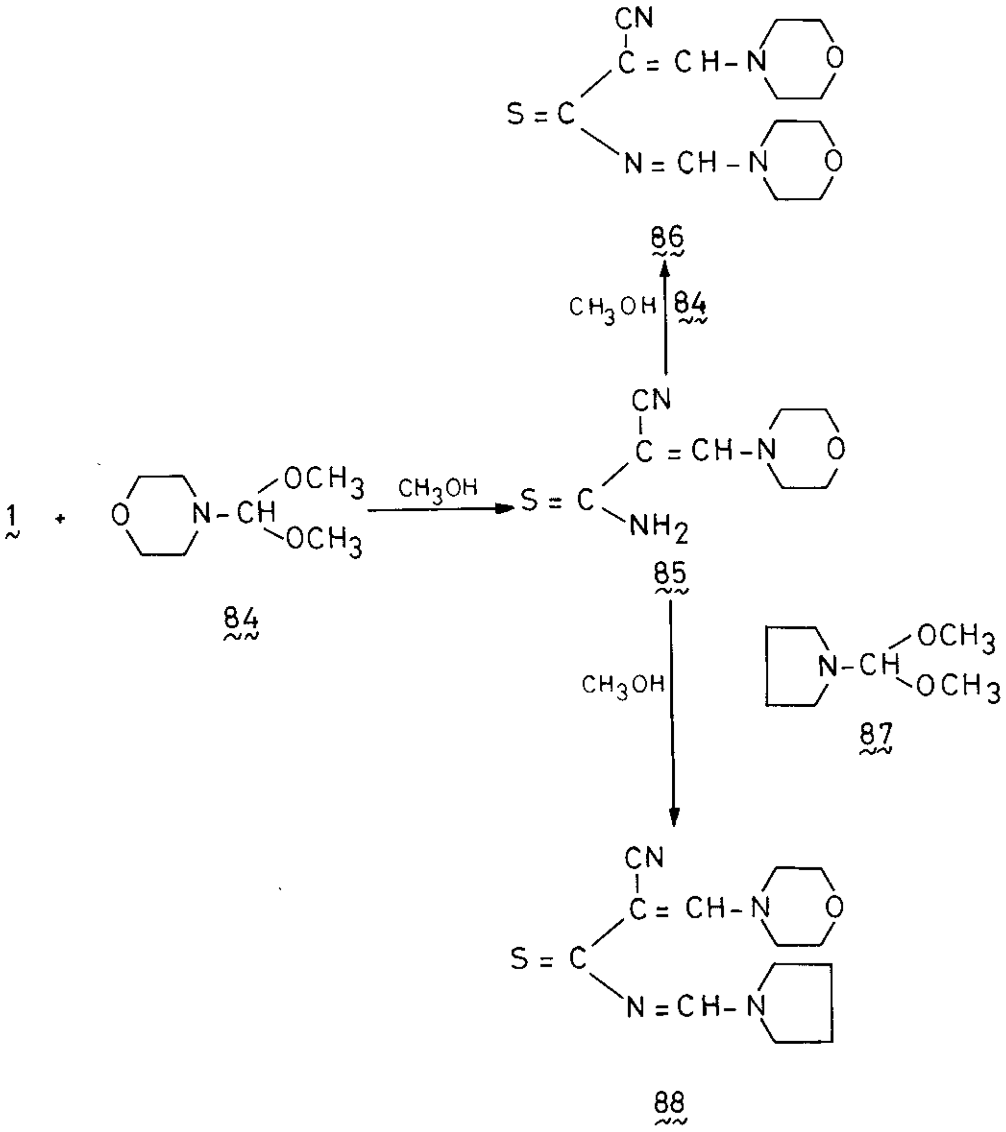
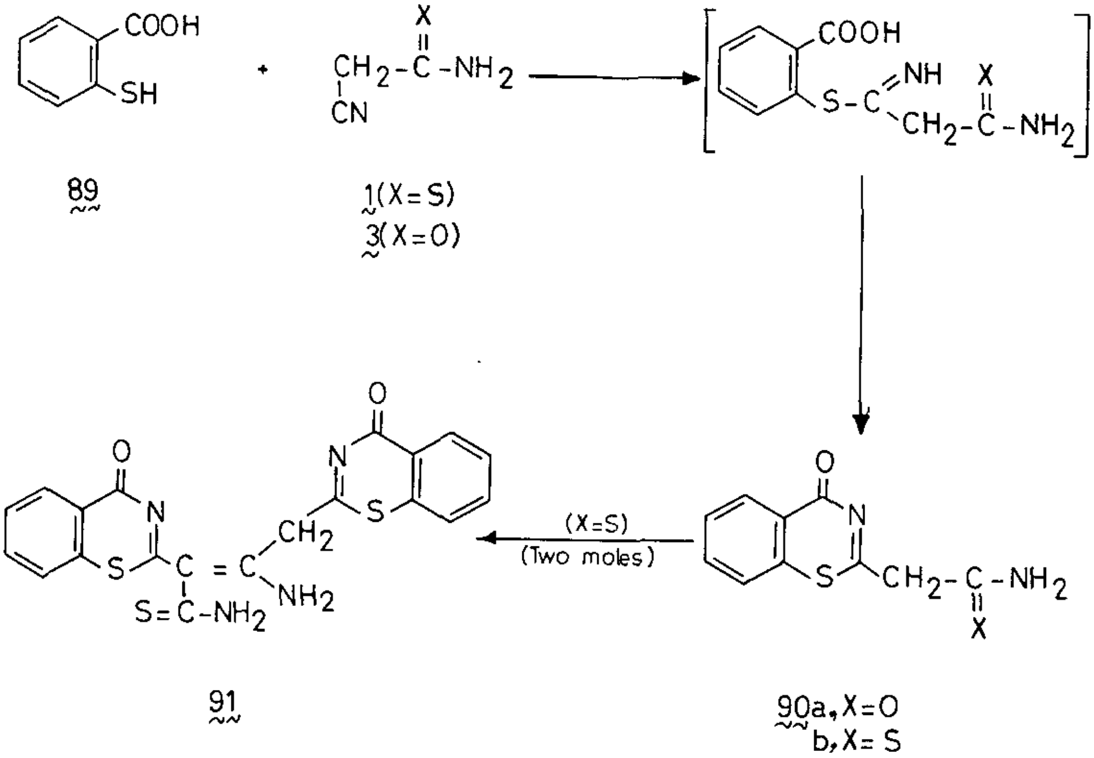


Chart 10

9. Reaction with thiosalicylic acid:

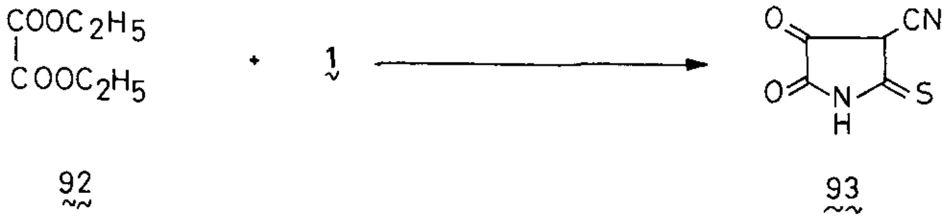
Ibrahim et al.[62] reported recently that cyanoacetamide (3) reacted with thiosalicylic acid (89) to afford the thiazinone derivative (90a). In contrast to this finding, the same authors[62] reported also that when equimolecular amounts of 1 and 89 were refluxed in pyridine under the same conditions, the bithiazinone der-



ivative 91 was the only isolable reaction product. Compound 91 is assumed to be formed via the self-condensation of the intermediate thiazinone derivative 90b under the applied reaction conditions. The authors[62] elucidated structure 91 on the basis of IR and ^1H NMR spectral data and similarity to condensation reactions of active methylene reagents with thioamides previously reported in literature[63].

10. Reaction with diethyl oxalate:

Compound 1 condensed with diethyl oxalate (92) in ethanolic sodium ethoxide solution to afford 4-cyano-2,3-dioxo-5-thionopyrrolidine (93) which was crystallized from hot water as the monohydrate derivative[9,10].



11. Reaction with dithiolylium perchlorates:

3-Aryl-1,2-dithiolylium perchlorates (94) condensed with 1 in ethanol to give the 3-cyanothiopyranthione derivative (95)[64,65]. Compounds 95 were converted into the thiopyranone derivatives 96 by treatment with mercuric acetate[64]. 95 reacted also with triethyloxonium tetrafluoroborate (97) to give the 2-ethylthiothiopyrylium derivatives 98 which could be hydrolyzed to give 96[65]. The thiopyrylium derivatives 98 reacted with the active methylene reagents such as malononitrile (2), benzoylacetonitrile (99a) and 1,3-indanedione (99b) to yield the thiopyran derivatives 100[65] (cf. Chart 11).

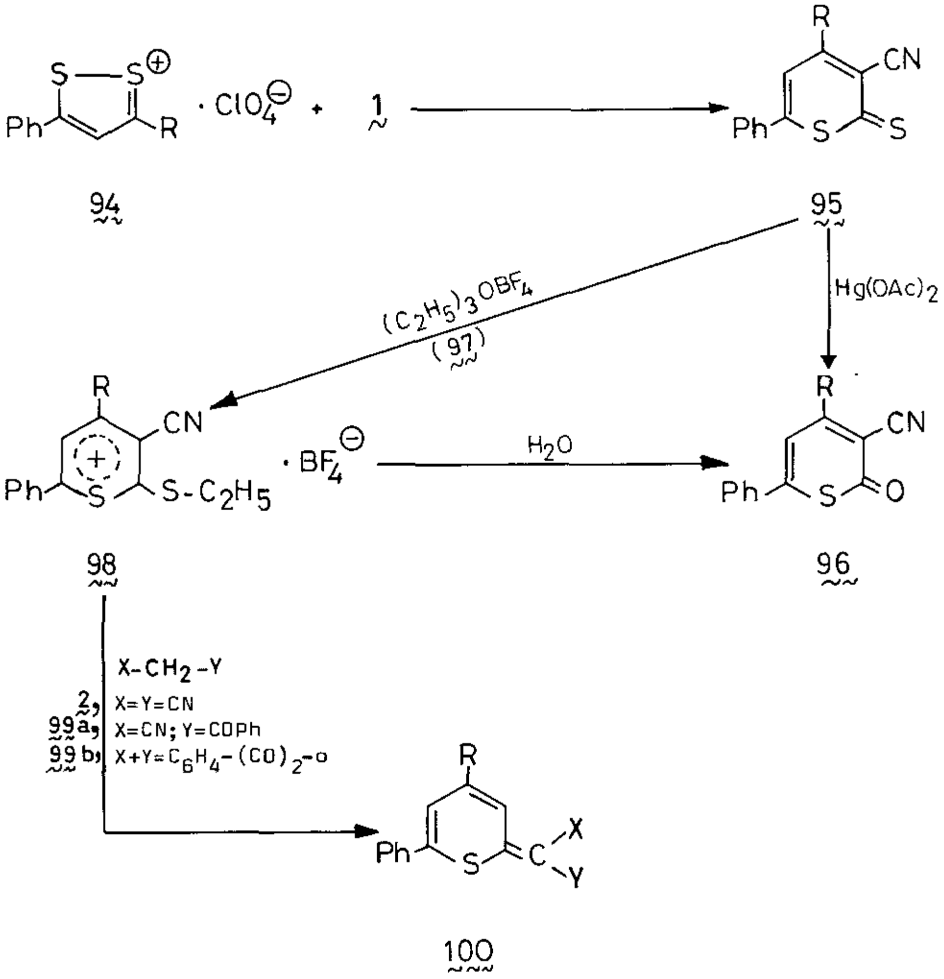


Chart 11

12. Reaction with ethyl dithioacetate:

The reaction of 1 with ethyl dithioacetate (101) was utilized as a route for the synthesis of some acyclic thioamides, isothiazoles and dithiolium salts[66]. Thus, 101 condensed with 1 in ethanolic potassium ethoxide to give the acyclic thioamide 102. Compound 102 reacted with hydrochloric acid to give the thiolothioamide 103 and with methyl iodide to afford the S-methylthioamide 104. 103 could also be converted into 104 by the action of diazomethane. On the other hand, both 102 and 103 were oxidized using a mixture of iodine, hydrogen peroxide and perchloric acid to give the dithiolium salts 105a,b respectively. Moreover, 104 could be cyclized by the action of ammonia followed by hydrogen peroxide to yield the isothiazole derivative 106 (cf. Chart 12).

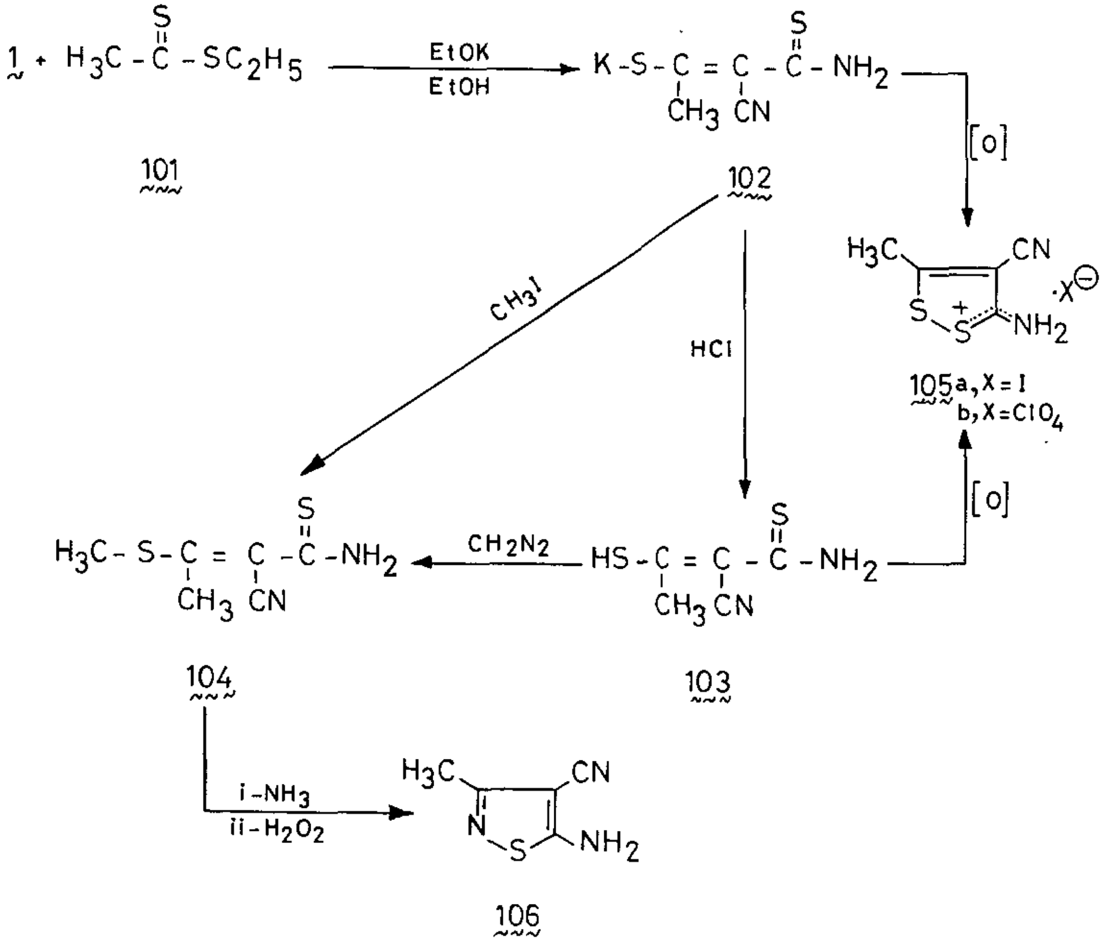
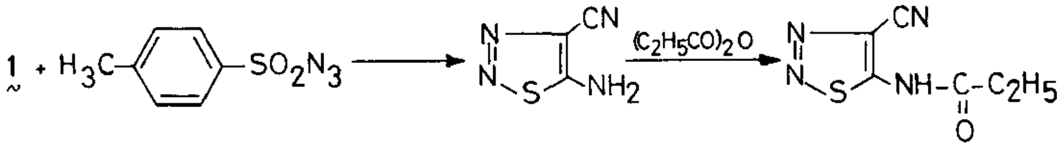


Chart 12

13. Reaction with p-toluenesulphonyl azide:

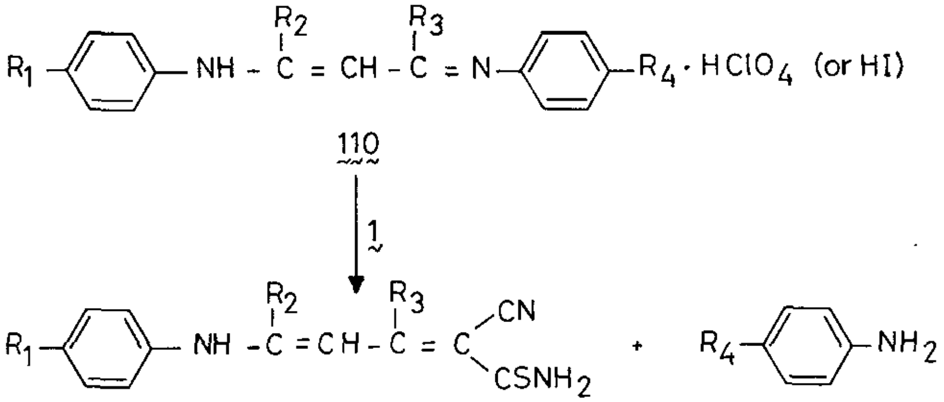
p-Toluenesulphonyl azide (107) reacted with 1 to give 5-amino-4-cyano-1,2,3-thiadiazole (108). Compound 108 reacted with propionic anhydride to give N-(4-cyano-1,2,3-thiadiazol-5-yl)-propionamide (109)[67].



107 108 109

14. Reaction with Schiff bases:

Compound 1 reacted with Schiff bases of the general formula 110 with selective replacement of the amino groups to give the cyanothioamide derivatives 111[68,69].

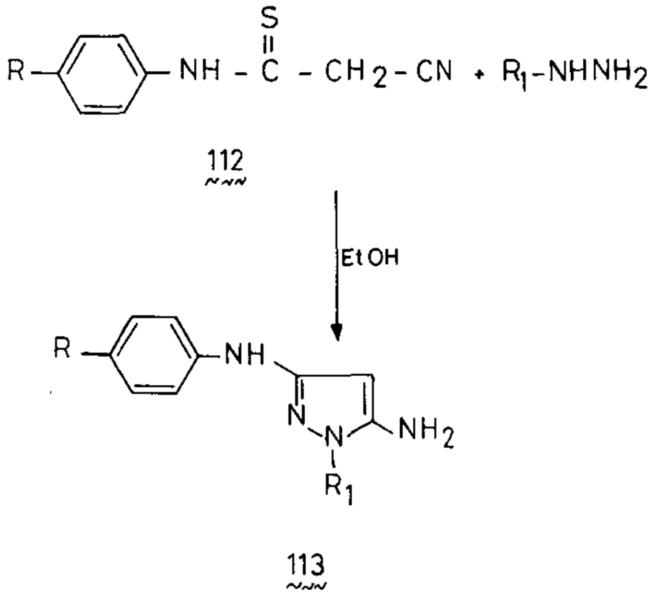


110

111

15. Reaction with hydrazines:

Although α-cyanothioacetamide (1) itself is not reported to react with hydrazines, yet N-arylcyanothioacetamides (112) react with hydrazines in ethanol to give the aminopyrazole derivatives 113[70].



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