RECENT DEVELOPMENTS IN CHEMISTRY OF 3(5)-AMINOPYRAZOLES

*Mohamed H. Elnagdi**, *Fathy M. Abdel-Galil*, *Bahia Y. Riad*
Department of Chemistry, Faculty of Science, Cairo University,
Giza, A.R. Egypt and

Galal Eldin Hamza Elgemeie
Department of Chemistry, Faculty of Science, Minia University,
Minia, A.R. Egypt

Abstract - The methods of preparation, structure, chemical properties and synthetic potentiality of 3(5)-aminopyrazoles are reported.

INTRODUCTION

Perhaps one of the most unusual facts of the chemistry of heterocyclic compounds is the enormous literature reported for pyrazole derivatives.[1] Such a fact may not be surprising for those who are interested in the chemistry of this class of compounds as, of course, there are theoretical and practical reasons for this interest. The early discovery of the antipyretic properties of antipyrine as well as the interesting dyeing properties of many azopyrazole derivatives have definitely contributed to this unusual interest.

5-Aminopyrazoles (1) became of recent importance due to the reported anti-inflammatory and antipyretic properties of many of these derivatives. Moreover, in recent years, these derivatives have been extensively utilised as intermediates for synthesis of fused pyrazoles of potential biological activity.[2-21]

The chemistry of 5-aminopyrazoles has been reviewed in two books which were published in 1964[1] and in 1967.[22] The extensive literature that has been published since both books appeared made it mandatory to update knowledge in this area. Moreover, the chemistry of both has been described in the two books in a very brief way.

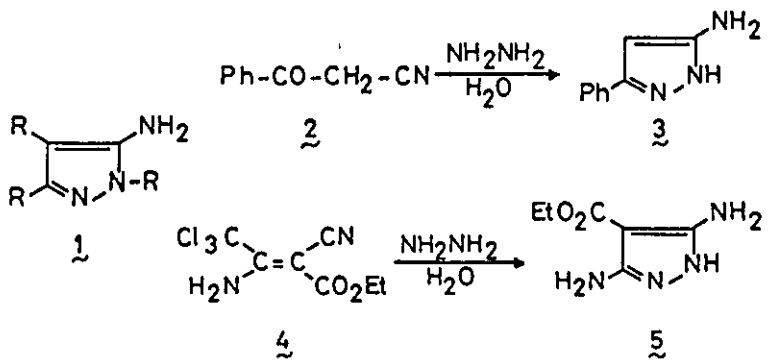
In the following a trial to make an up to date survey of the chemistry of these compounds was made. It should be, however, stated clearly here that it was not our plan at any time to make an encyclopedic scan of the subject. Some reports were not involved because they seemed to the authors as a mere repetition of the established and reviewed chemistry of these compounds. On the other hand,

some of the old literature is surveyed here either because it was not previously reviewed or because it seemed to us of vital importance in understanding the chemistry of this class of compounds.

I-METHODS OF PREPARATION

i-Reactions of β-functional nitriles with hydrazines

5-Aminopyrazoles (1) have been extensively synthesised via the reaction of hydrazines with β-functional nitriles.[23-48] A variety of β-functional nitriles have been utilised for the synthesis of 1. The reaction conditions utilised depend on the nature of the reacting nitrile and the utilised hydrazine. For example, whereas hydrazine hydrate reacts with benzoylacetonitrile (2) at room temperature to yield 5-amino-3-phenylpyrazole (3), it reacts with the enamino ester 4 to give 3,5-diamino-4-ethoxycarbonylpyrazole (5).[45]



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

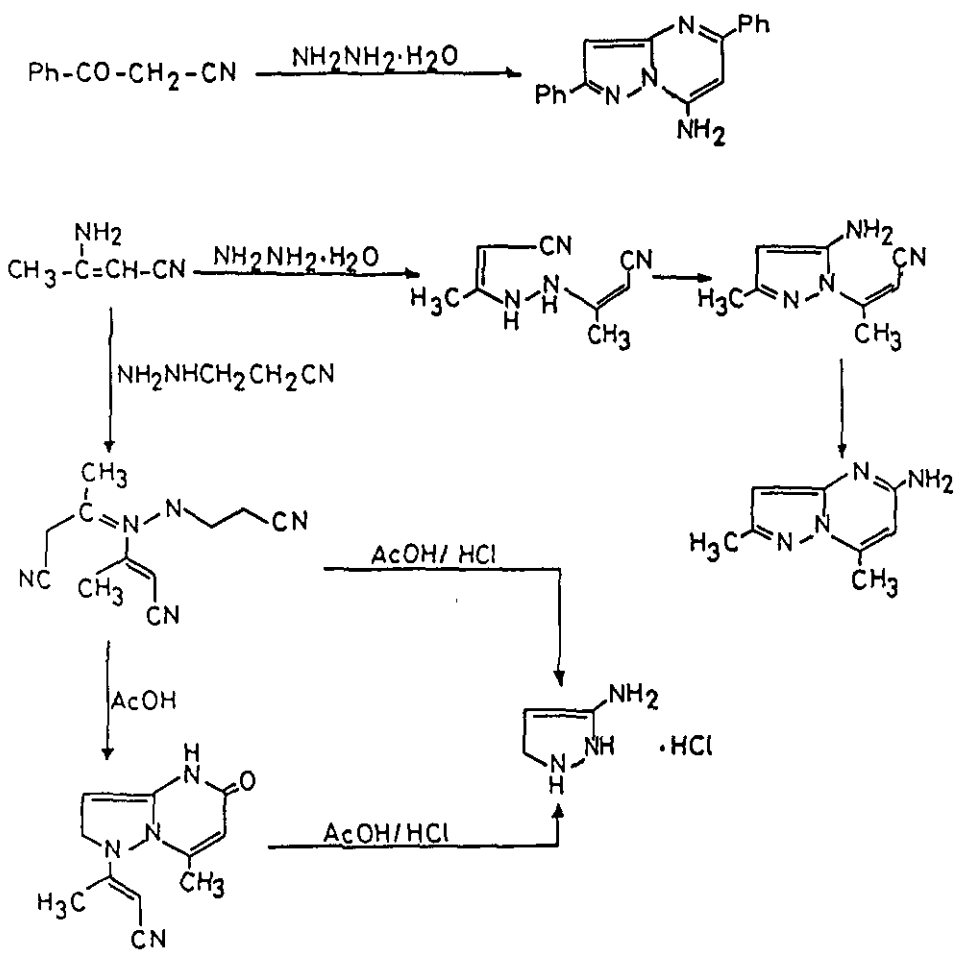
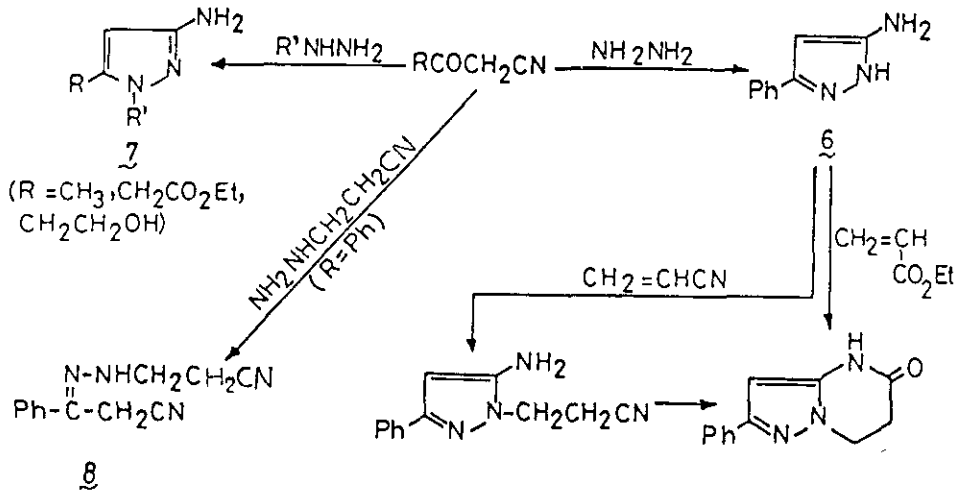
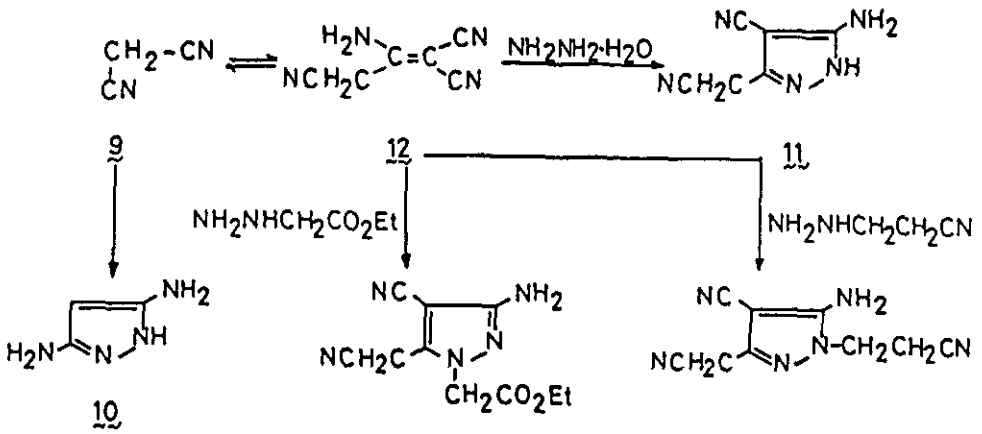


Chart 1

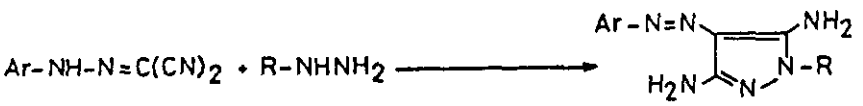
The reaction of substituted hydrazines with β-functional nitriles has been shown to afford 5-aminopyrazole derivatives. The reaction may theoretically afford either 3-amino-1-substituted pyrazoles (6) or isomeric (7). Generally arylsubstituted hydrazines afford derivatives of 6 whereas alkylsubstituted *hydrazines* afford the isomeric 7 on reaction with β-keto nitriles. Several intermediate hydrazones could be isolated in these reactions (see for example 8 in equations below) and could be readily cyclised into the final products. The statement reported above is though usually followed an over simplification of the problem.



Mixtures of derivatives of 6 and 7 could, in many cases, be separated. Also predominance of 7 in the reaction of alkyl hydrazines has been observed. For example, Elnagdi et al.[46] and Elguero et al.[49] both reported the isolation of 1-substituted alkylpyrazoles as major products in the reactions of benzoylacetonitrile with cyanoethylhydrazine and with β-hydroxyethylhydrazine. Elnagdi et al.[46] have recently recognised that a delicate balance exists between steric and relative reactivity of the hydrazine in the reactions of β-functional nitriles with alkyl hydrazines. Thus, whereas the substituted hydrazine moiety might be considered as the most active nucleophilic center and attack by this moiety at the carbonyl group should be expected, it is also the most hindered one. In some reactions steric factors play a major rule and 1-substituted 5-aminopyrazoles are isolated. Malononitrile (9) has been reported, in old literature, to afford 3,5-diaminopyrazole (10)[50] on the reaction with hydrazine hydrate. However, recent work has established that the product which was actually formed is 3-amino-4-cyano-5-cyanomethylpyrazole (11). The formation of this product is assumed to proceed via the reaction of hydrazine with dimerized malononitrile (12) which exists in equilibrium with malononitrile.[51]



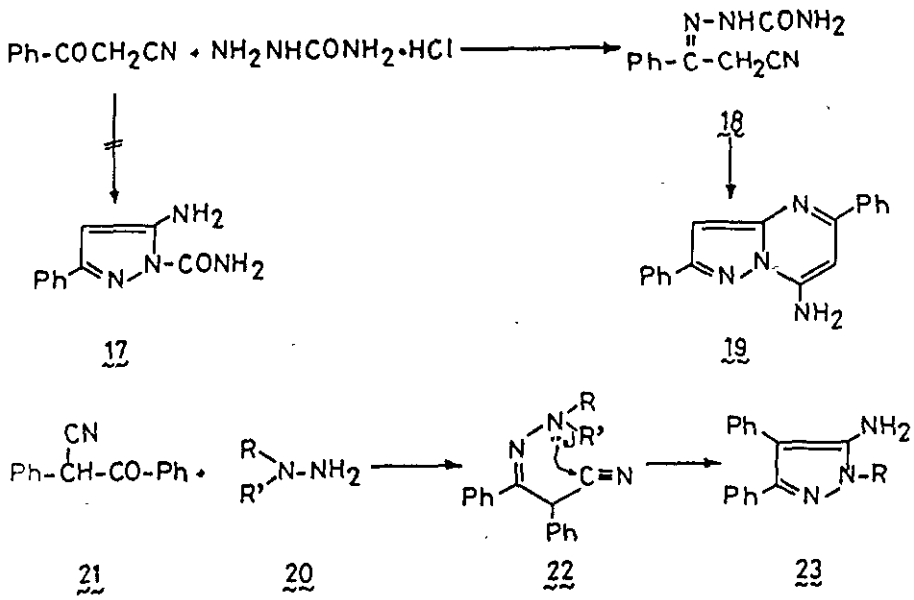
In contrast to the behaviour of malononitrile, substituted malononitrile derivatives have been shown to react smoothly with hydrazines to yield 3,5-diaminopyrazoles. Thus, Elnagdi et al.[51,52] have shown that arylhydrazonomesoxalonitriles (13) react with hydrazines to yield 3,5-diamino-4-arylazopyrazoles (14). Similarly very recently an Israeli group[53] reported that phenylmalononitrile (15) afforded 3,5-diamino-4-phenylpyrazole (16) when reacted with hydrazine hydrate.



13 14

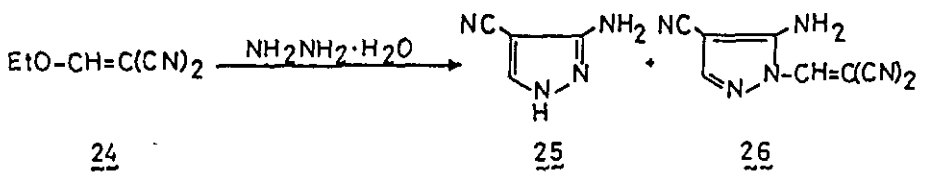
15 16

Spiro and Farba[54] have reinvestigated the reaction of benzoylacetonitrile with semicarbazide which was reported to yield the pyrazole derivative 17 and other unidentifiable product and could establish that the product which was previously assigned structure 17 is actually 3-phenyl-3-oxopropionitrile semicarbazone (18). The other product of mp 270°C was shown to be the pyrazolo[1,5-a]pyrimidine derivative (19). 1,1-Dialkylated hydrazines (20) have been reported to condense with β-ketonitriles (21) to afford the corresponding hydrazone derivatives (22). Cyclisation of 22 yields the aminopyrazoles 23 via dealkylation of the least strongly bonded alkyl group.[54,55]



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

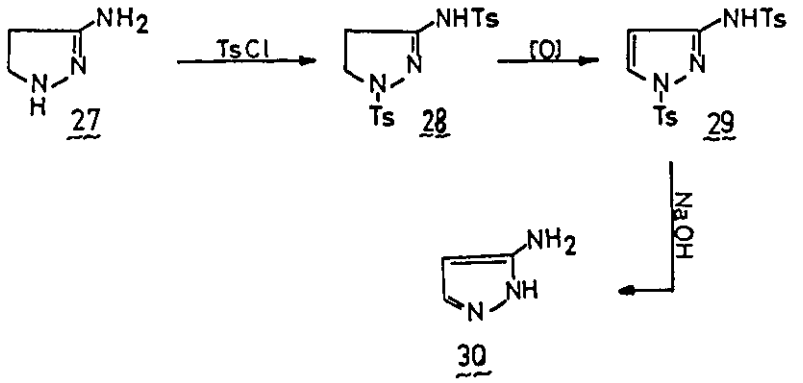
An efficient route for the synthesis of 5-aminopyrazoles is the reaction of hydrazines with α,β-unsaturated nitriles. For example, 4-cyano-3-aminopyrazole (25) has been obtained, always contaminated with the 5-aminopyrazole derivative 26, by the reaction of hydrazine with ethoxymethylenemalononitrile (24). Reactions of this type have been recently reviewed and will not be discussed here any further.[44]



Propynenitrile derivatives and allenic nitriles have recently been reported to afford aminopyrazoles on reaction with hydrazines.[56,57]

iii- Synthesis from heterocyclic derivatives

5-Aminopyrazoles have been also obtained from other pyrazole derivatives.[56-59] Thus, oxidation of 5-aminopyrazolines usually afford 5-aminopyrazole derivatives. 5-Amino-2-pyrazolines are usually converted into 5-aminopyrazoles via oxidation of the Schiff's bases, formed via the reactions of the formers with aromatic aldehydes, with potassium permanganate and hydrolysis of the resulting products. Usually the 5-amino-2-pyrazoline derivative 27 is converted to the tosylate 28, oxidation affords 29 and then hydrolysis of the resulting product affords 30.[59]



Several heterocyclic derivatives are known to be readily converted into aminopyrazole derivatives. Thus, 4-methoxy-5-nitropyrimidine (31) interacted with ethanolic hydrazine hydrate below 0°C to give 4-hydrazino-5-nitropyrimidine (32) which was converted by an excess of hydrazine hydrate at 25°C into 3-amino-4-nitropyrazole (34). The authors[60] have acknowledged that this rearrangement proceeds via nucleophilic attack by hydrazine on the 2-position of the hydrazinopyrimidine 32 with the rupture of the 2,3-bond. The resulting acyclic intermediate 33 then undergoes intramolecular nucleophilic attack at the 6-position by the 4-hydrazine group with breaking of the 1,6-bond to give 34 (cf. Chart 2).[60]

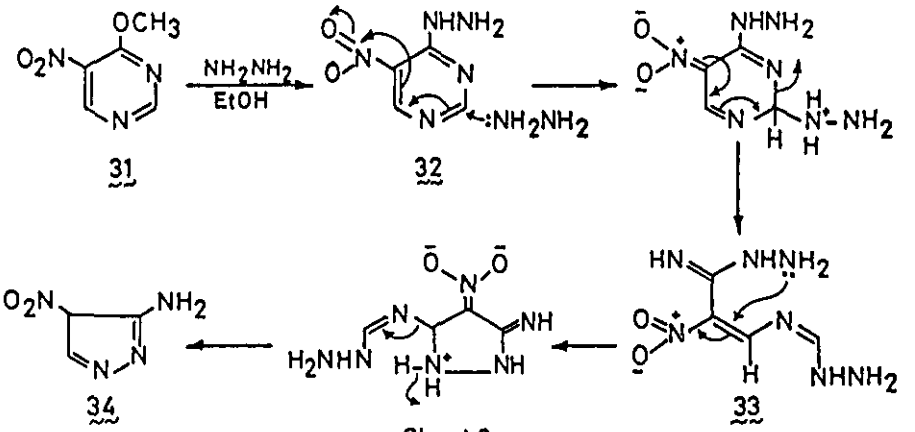
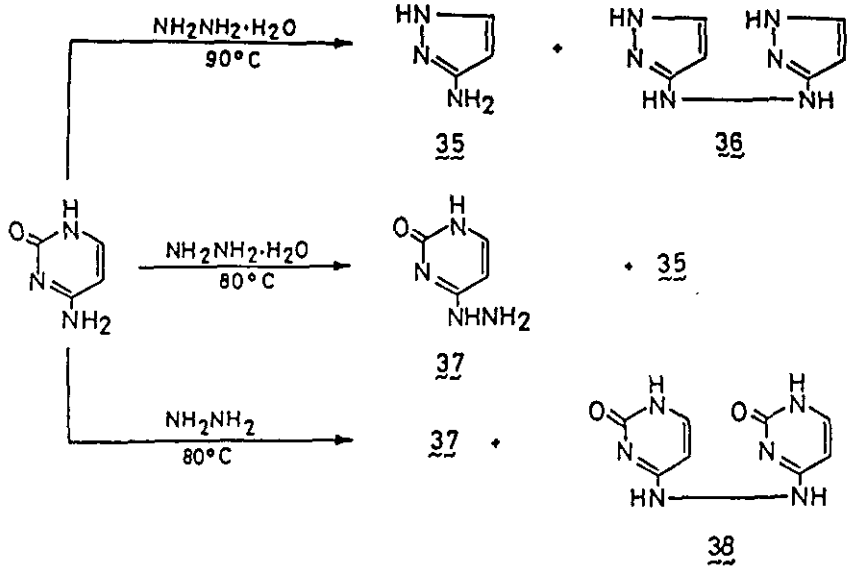


Chart 2

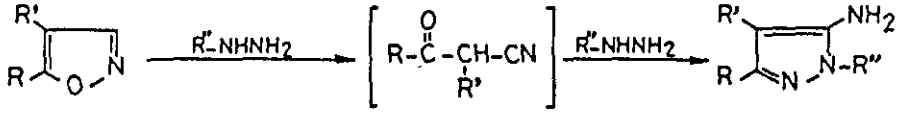
Another reaction in which pyrimidine is converted into aminopyrazole was reported by Hayes and Baron.[61] The authors have shown that whereas uracil and thymine and their related nucleotides and nucleosides are degraded quantitatively by treatment with hydrazine hydrate at 90°C to yield pyrazol-3-one and 3-methylpyr-

azol-3-one together with approximately quantitative yields of urea and sugar or sugar-phosphate hydrazone (in case of nucleotides and nucleosides), cytosine and its derivatives are degraded by hydrazine hydrate at 90°C to yield 3-aminopyrazole (35) and N,N'-di(3-pyrazolyl)-hydrazine (36). The same authors have also shown that the reaction of cytosine and its derivatives with hydrazine hydrate at 80°C leads to the formation of 35 and 6-hydrazino-2,3-dihydropyrimidin-2-one (37). On the other hand, cytosine reacted with ethanolic hydrazine at 80°C to yield a mixture of 37 and the bis-dihydropyrimidine derivative 38.



35 36 37 38

The conversion of isoxazoles 39 having no substituents at position 3 into aminopyrazoles has been reported to be a general reaction that proceeds also with a very high yield.[62,63]



39

II-STRUCTURE OF 3(5)-AMINOPYRAZOLES

3(5)-Aminopyrazoles (A) are tautomeric with 5-imino-2-pyrazolones (B). It is difficult to make a clear cut distinction between the two structures. It is usually necessary to consider both structures, as well as their resonance stabilized ionic hybrid structures, to rationalize for the chemical behaviour of these

compounds,[22] although it has been stated that in a superficial way it is more or less apparent that 3(5)-aminopyrazoles behave primarily as 3(5)-imines.[22] Such statement seems to be over simplified and it might even be wrong as the ultra violet absorption studies have indicated that 5-iminopyrazolones exist as such under the conditions of measurements. Recently, spectroscopic investigations using IR, UV, NMR and M.O. calculations have confirmed that these compounds exist mainly in the amino structure.[64,65]

(A) (B)

CHEMICAL PROPERTIES

Generally the chemical properties of 5-aminopyrazoles resemble those of the corr-esponding 5-hydroxy analoges (5-pyrazolones) except in the reactions taking place mainly with the amino group. Electrophilic substitution usually takes place at the 4-position. Coupling with diazonium salts, nitrosation, halogenation and nitration take place at this position. Acylation, sulphonylation, oxidation and hydrolysis have also been reported. These reactions were previously surveyed efficiently in references 1 and 22 and are summarised here in Chart 3. In the following review emphasis will be placed on the reactions leading to the formation of fused azoles as a great advance in the chemistry of aminopyrazoles in this direction has occurred since reference 66 appeared. In addition to the potential biological importance of fused pyrazoles the synthetic approaches to the latters might also be of interest to be extended to other amino heterocyclic derivatives thus promoting ideas in this field.[22]

THE SYNTHETIC POTENTIALITY OF 5-AMINOPYRAZOLES

A-Synthesis of pyrazolo[1,5-a]pyrimidines

1-Unsubstituted 5-aminopyrazoles (40) have been extensively utilised for the synthesis of pyrazolo[1,5-a]pyrimidines.[66-91] With only few exceptions all reported syntheses of pyrazolo[1,5-a]pyrimidines utilise the cyclocondensation reaction of 3(5)-aminopyrazole (40) with β-bifunctional reagents.[67-83] Thus, pyrazolo[1,5-a]-pyrimidines were isolated from the reactions of 40 with β-diketones, β-keto esters,

β-keto nitriles, malonic acid derivatives and malonaldehyde derivatives (Chart 4). Acyclic intermediates have been isolated from most of these cyclocondensation reactions. Although ring nitrogen in 40 is known to be the most nucleophilic center in the molecule acylamine acyclic intermediates have been always isolated. The formation of these acyclic intermediates may be assumed to proceed via intermediacy of ring acylated reaction products which then undergo rearrangement, via intermolecular acylation, into the final isolable products.

Although the reaction of asymmetric β-diketones with 40 may lead theoretically to the promotion of two isomeric derivatives in all the reported reactions of this type only one product could be isolated. Generally the reaction was assumed to proceed via the interaction of the most active carbonyl moiety of the diketone with the exocyclic amino function and cyclocondensation.

The reactions of β-keto esters with 40 can also lead either to 41 or 42. In old literature several authors have assigned structure 42 (or possible tautomers) to the cyclocondensation products. However, Sprio and Plescia[67] have reported that fusing 3(5)-amino-5(3)-phenylpyrazole (43) with ethyl benzoylacetate at 160°C for two hours, as reported by Checchi et al.,[92] afforded in addition to the previously isolated 4,7-dihydro-7-oxo-2,5-diphenylpyrazolo[1,5-a]pyrimidine (44) another product for which structure 45 was suggested on the basis of spectral data. By

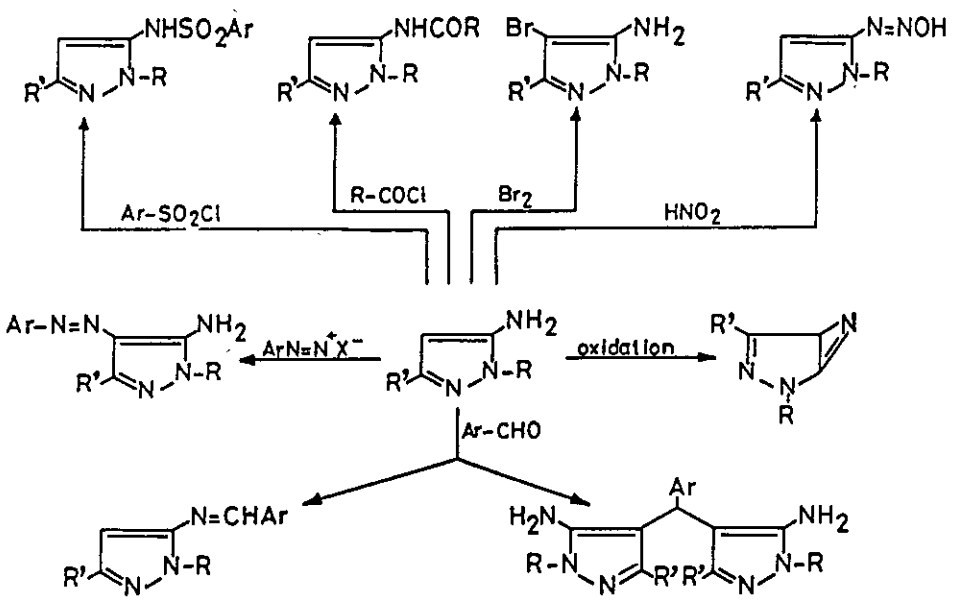


Chart 3

maintaining the reaction at 160°C for 10 minutes compound 45 was the main product. However, fusing 43 at 220°C for 10 minutes gave only the pyrazolo[1,5-a]pyrimidine derivative 44 which was also obtained by fusion of 45 at 220°C. When 45 was cyclised by ethanolic HCl the 5-oxo isomers 44 and 46 are formed. Compound 46 was also obtained by the action of ethyl phenylpropiolate on 43. These results lead the authors to conclude that cyclisation of 45 into 44 occurs due to the thermal rearrangement of the benzoylacetyl group in 45 and that the formation of 44 or 46 might be expected from the reactions of β-keto esters with 5-aminopyrazoles. It is interesting to report that the spectroscopic data of 44 and 46 reported by sprio and Plescia[67] are almost identical thus demonstrating the difficulty to discriminate both structures on the basis of IR and ^{1}H NMR data only (cf. Chart 5). In an investigation dealing with the behaviour of 5-amino-4-arylazopyrazoles (47) towards β-keto esters and ethyl phenylpropiolat, Elnagdi et al[70] have noted that the IR spectra of 48 differ from that of 49 which exist, as suggested by the authors, as such and not in the tautomeric structure 48a which is similar to that suggested by Sprio and Plescia.[67] Thus, whereas the IR spectra of 48 revealed a pyrimidine ring CO at 1700 cm^{-1} almost with no shift than that of the tetrahydropyrazolo[1,5-a]pyrimidines, the IR of 49 exhibited a large down shift in the frequency (1670 cm^{-1}) of the ring CO due to conjugation with the C=C in the ring. In an another investigation Elnagdi et al.[88] have also revealed, based on ^{1}H NMR data, that the reaction of 3,5-diaminopyrazole (50) with ethyl acetoacetate affords 51 and not the isomeric 52 (cf. Chart 5). Several pyrazolo[1,5-a]-pyrimidine derivatives have recently been synthesised via condensation of substituted aminopyrazoles with β-keto esters and their structures were identified based on spectroscopic data.[73,79]

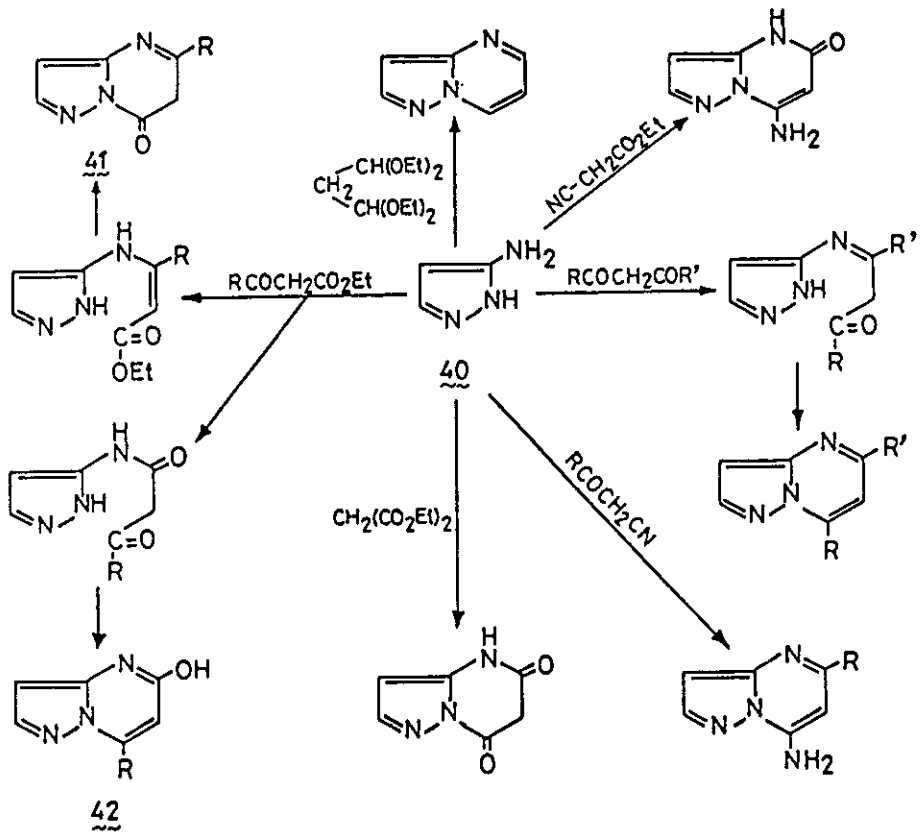
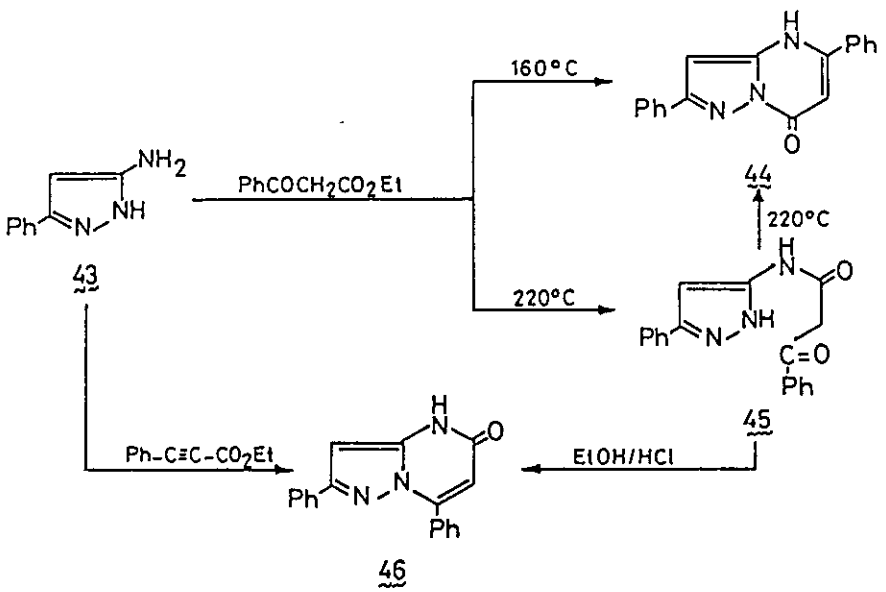

41
CH(OEt)2
CH2
CH(OEt)2
NC-CH2CO2Et
NH2
RCOCH2CO2Et
RCOCH2COR'
C=O
OEt
40
C=O
R
CH2(CO2Et)2
RCOCH2CN
OH
42

Chart 4


160°C
Ph
PhCOCH2CO2Et
NH2
43
44
220°C
220°C
C=O
Ph
45
Ph-C≡C-CO2Et
EtOH/HCl
46

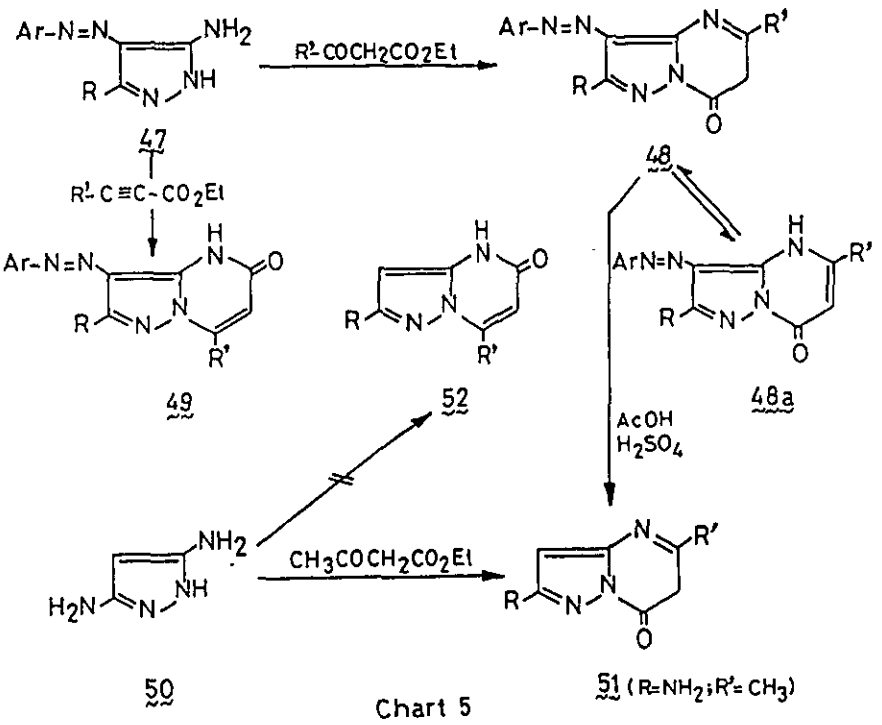


Chart 5

The addition of suitably substituted β-functional reagents to 40 has been extensively utilised as a route for the synthesis of pyrazolo[1,5-a]pyrimidines.[83-88] Thus, propiolic acid derivatives, acrylic acid derivatives, ethoxymethylenemalononitrile, ethyl ethoxymethylenecyanoacetate and diethyl ethoxymethylenemalonate have been reported to add readily to 40 to form pyrazolo[1,5-a]pyrimidine derivatives. Acyclic intermediates for all but the reaction with propiolic acid derivatives could be isolated and characterised (cf. Chart 6). Although most of these reaction intermediates were proved to be pyrazol-1-ylacrylic or β-functional ethylpyrazole derivatives, formed via Michael type addition to the unsaturated double bond, this does not neccessarily indicate the actual structure of the end product. Saito et al.[93] have shown that pyrazoloacrylic acid derivatives rearrange readily into pyrazol-5-ylaminoacrylic acids (cf. Chart 6). Thus, structural assignments based on similarity to literature in this area might be misleading and the suggested structures, in our opinion, should be well documented.

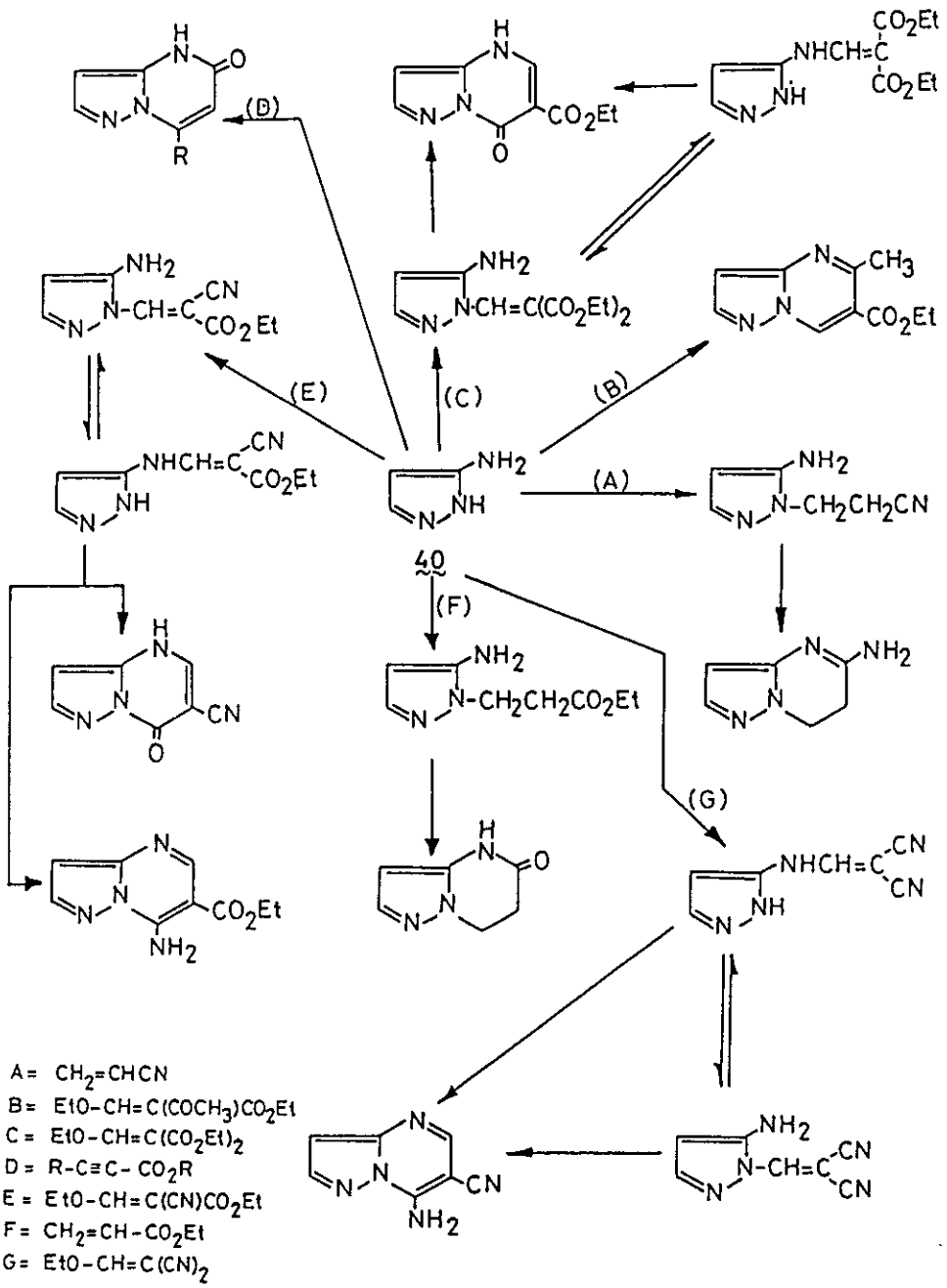

A= CH2=CHCN
B= EtO-CH=C(COCH3)CO2Et
C= EtO-CH=C(CO2Et)2
D= R-C≡C-CO2R
E= EtO-CH=C(CN)CO2Et
F= CH2=CH-CO2Et
G= EtO-CH=C(CN)2

Chart 6

5-Aminopyrazoles have also been reported to react with β-enamino nitriles and with β-enamino esters to yield pyrazolo[1,5-a]pyrimidines. The nature of the end product was proved to depend on the nature of the utilised β-enamino nitrile or enamino ester and the reaction conditions. Thus, Elnagdi et al.[89] have shown that diethyl β-amino-β-trichloromethylmethylenemalonate (53) reacts with aminopyrazoles to yield the pyrazolo[1,5-a]pyrimidine derivatives 54. The corresponding cyanoacetate derivatives 55 afforded either 56 or 57 on condensation with 5-aminopyrazoles depending on the reaction conditions (cf. Chart 7). The 5-amino-4-arylazopyrazoles (58) afforded the pyrazolo[1,5-a]pyrimidine derivatives 59 on similar treatment.

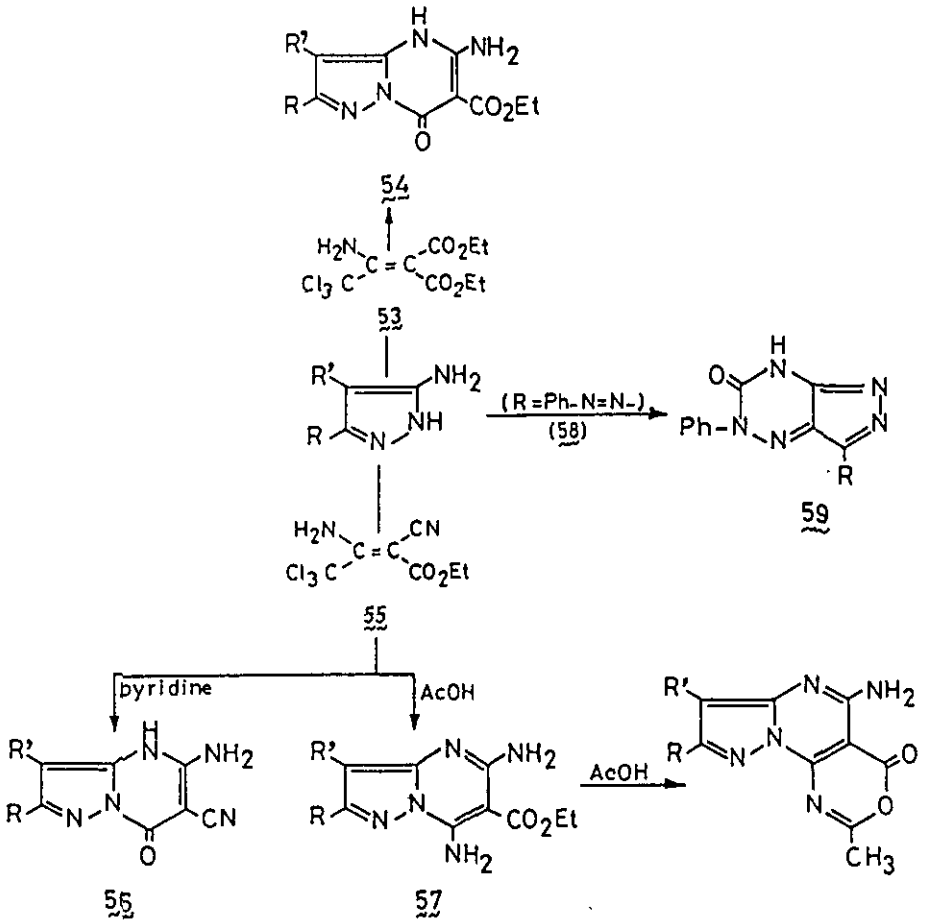


Chart 7

Recently, Elnagdi and Wamhoff[90,91] reported that 5-amino-3-phenylpyrazole reacts with the enamino furan derivatives 60 to yield the pyrazolo[1,5-a]pyrimidines 61. On the other hand, the enamino nitrile derivatives 62 afforded the furo[2,3:5,6]-pyrazolo[1,5-a]pyrimidines 63 on similar treatment. The mechanism of the formation of these products was discussed and is demonstrated in Chart 8.

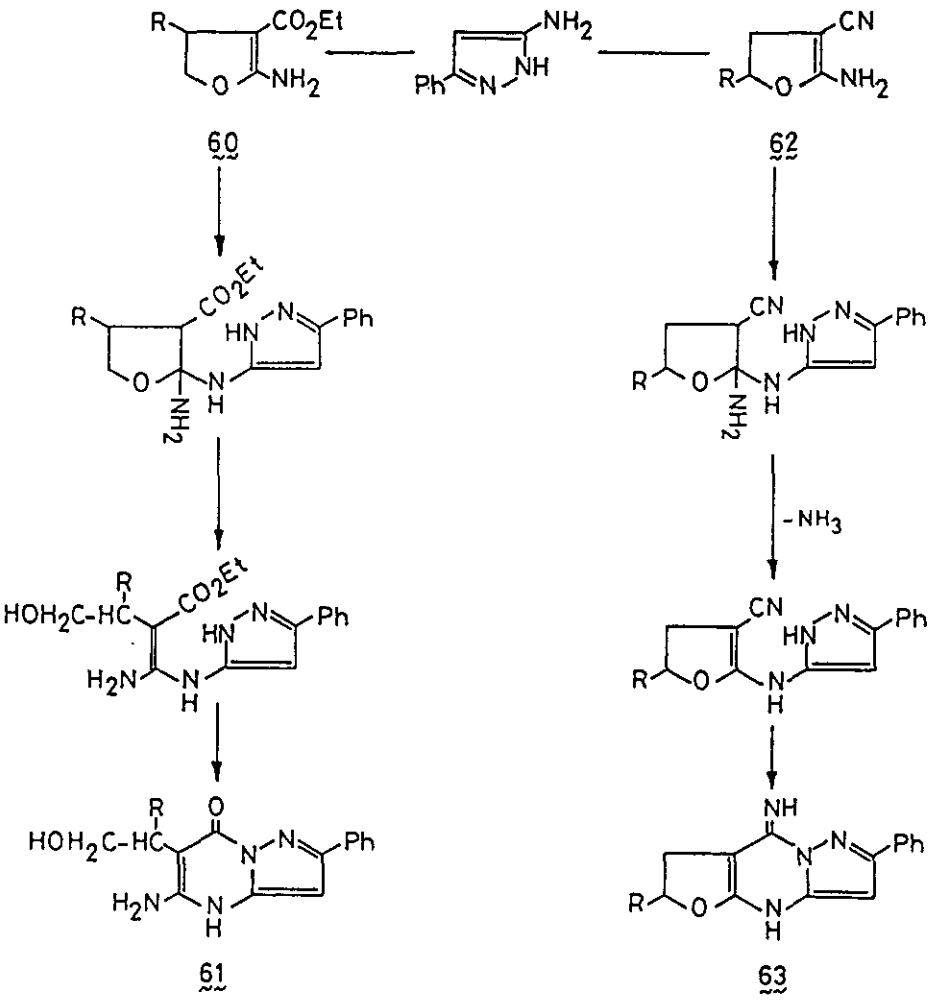


Chart 8

B-Synthesis of pyrazolo[3,4-d]pyrimidines

Taylor et al.[94-96] have extensively utilised 5-amino-4-cyanopyrazoles (64) as precursors to pyrazolo[3,4-d]pyrimidine derivatives. The authors have shown that treatment of 64 with carbon disulphide in pyridine solution afforded the pyrazolo-[3,4-d]pyrimidine-thione derivatives 65. The reaction was considered to proceed via the intermediate formation of the 4-imino-m-thiazine derivatives 66 which rearrange rapidly and irreversibly by a base catalysed (pyridine) ring-opening and ring closure sequence to yield the final products.[94,95]

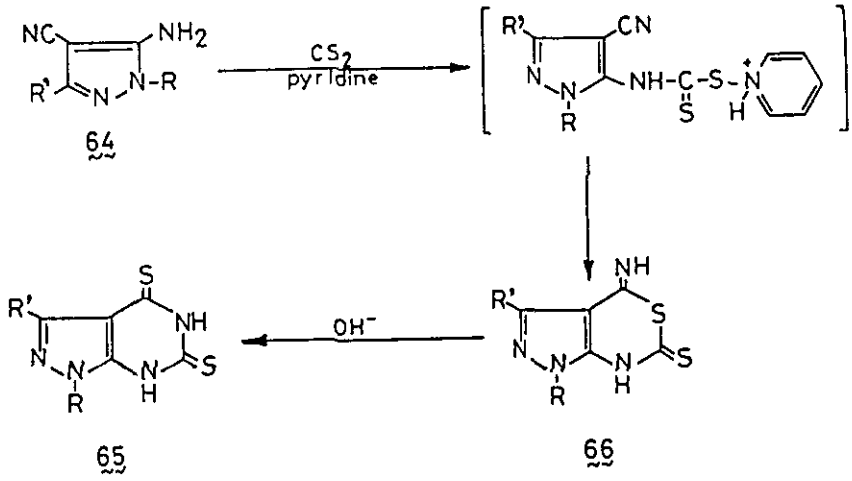


Chart 9

Simple nitriles were also reported to react with 64 to yield the pyrazolo[3,4-d]-pyrimidine derivatives 67. Another route for the synthesis of 67 starting from 5-aminopyrazoles has been reported by the same authors.[96] This route involves the reaction of 64 with ethyl orthoformate to afford the corresponding Schiff's bases 68 which were cyclised by ammonia, amines and guanidine to yield the final pyrimidine derivatives 69, 70 and 71 respectively. Quite similar to this is the reaction of 64 with diethyl oxalate to yield 72. Compound 72 could be converted into the pyrazolo[3,4-d]pyrimidine derivative 73 by the action of diazomethane followed by boiling in ethanolic ammonia.[96] Equations representing the above reactions are shown in Chart 10.

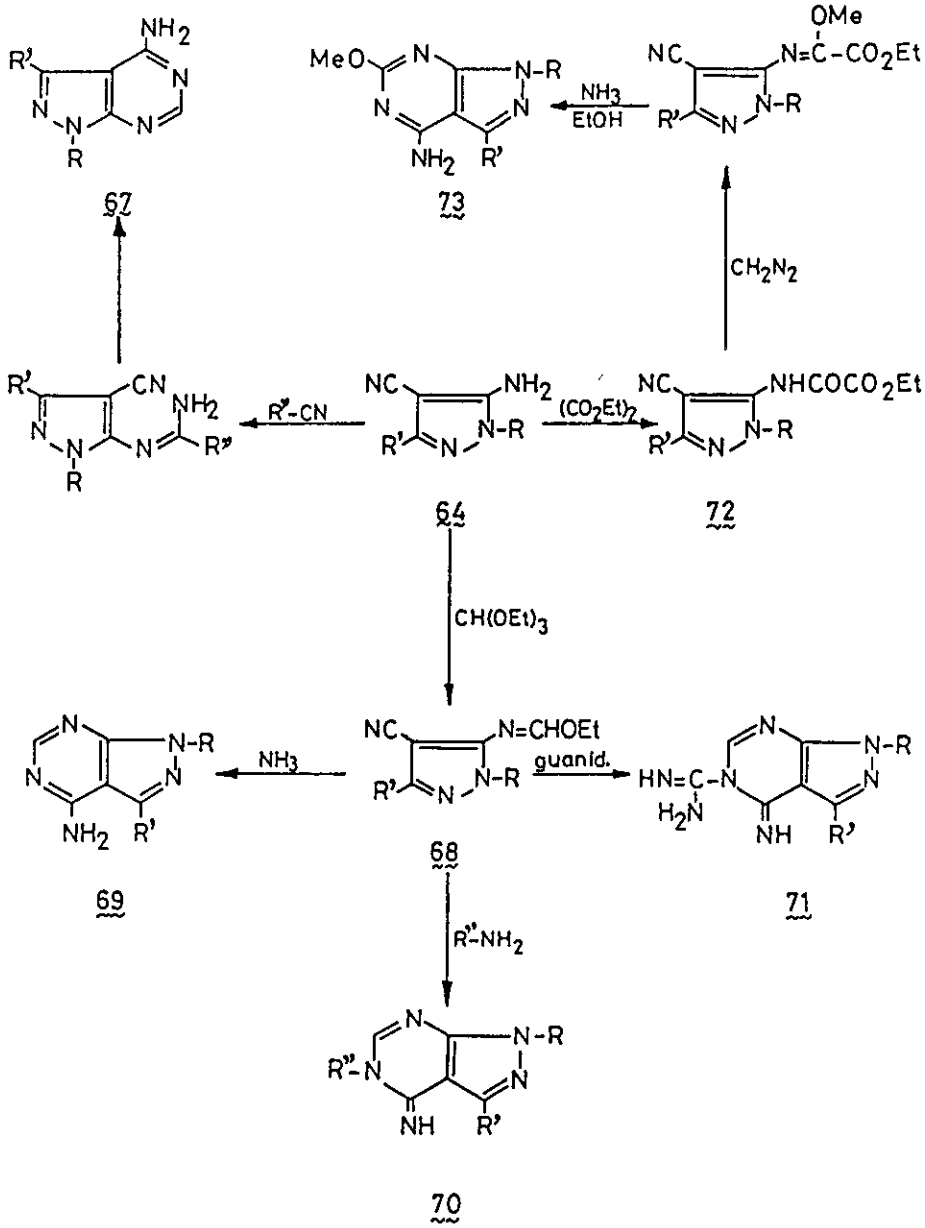
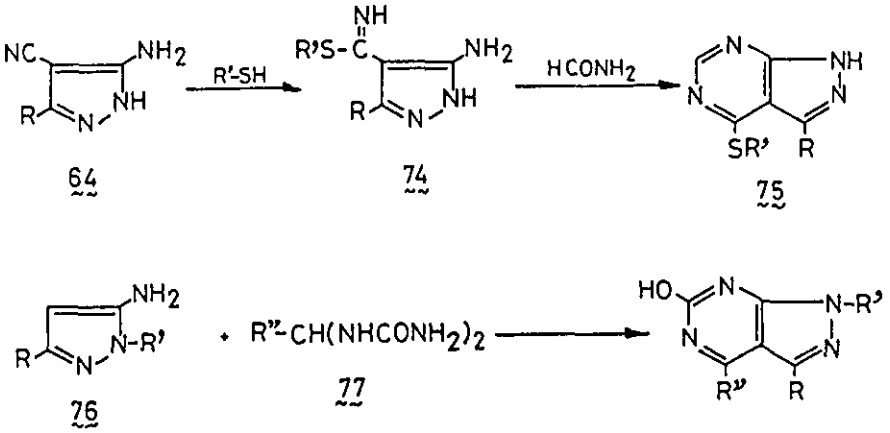

NH2
R'
N
N
N
R
67
MeO
N
N-R
NH2
R'
73
NH3
EtOH
NC
OMe
N=C-CO2Et
R'
N
N-R
CH2N2
R'
CN
NH2
N
N
N
R"
R
R"-CN
NC
NH2
R'
N
N-R
64
(CO2Et)2
NC
NHCOCO2Et
R'
N
N-R
72
CH(OEt)3
N
N-R
N
N
NH2
R'
69
NH3
NC
N=CHOEt
R'
N
N-R
68
guanid.
HN=C-N
H2N
N
N-R
N
NH
R'
71
R"-NH2
R"-N
N
N-R
N
NH
R'
70

Chart 10

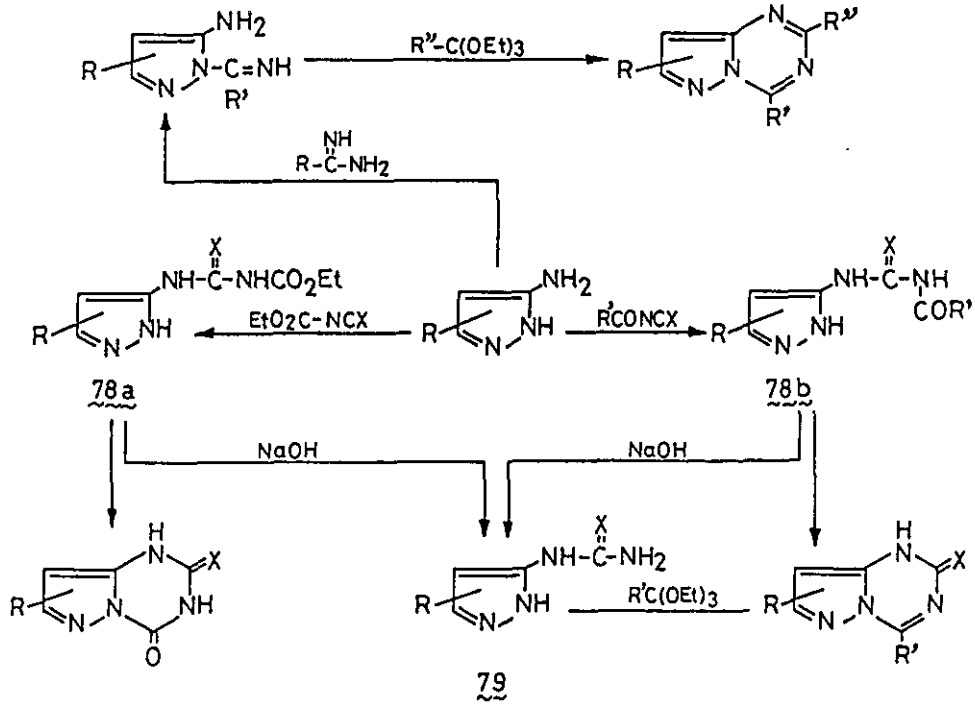
Because of their biological importance many recent methods for the synthesis of pyrazolo[3,4-d]pyrimidines have been described in literature.[97-112] Most of these methods utilised the readily available 5-aminopyrazoles as starting materials. Of interest among these methods is the reaction of 3-amino-4-cyanopyrazoles 64 with mercaptans[102] to yield the iminothioethers 74 which could be cyclised to the corresponding pyrazolo[3,4-d]pyrimidine derivatives 75 by refluxing in formamide solution.[108] Another method for the synthesis of this class of compounds involved the reaction of 1-substituted 5-aminopyrazoles 76 with the diuridomethane derivatives 77.



C-Synthesis of pyrazolo[1,5-a]-s-triazines

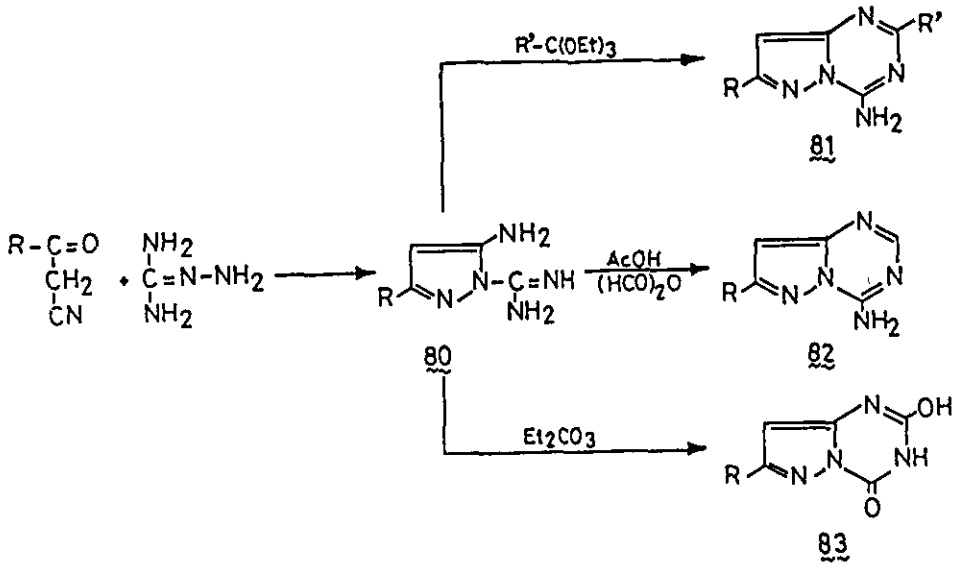
Recently, the interest in the synthesis of derivatives of this ring system has been revived.[43,112-115] It has been stated in several of the recent publications that derivatives of this ring system may be considered isomeric with the corresponding purines and might be expected to inhibit various nucleic acid-enzyme systems.[113,114] Moreover, anticancer activity has been reported for several pyrazolo[1,5-a]-1,3,5-triazines.[116] Pyrazolo[1,5-a]-1,3,5-triazines have been generally synthesised via the action of ethoxycarbonyl isocyanate or its thio analogue on 5-aminopyrazoles to yield the N-carbethoxy-N-(pyrazol-5-yl)-ureas (78a,b).[5,6,116] Compounds 78 were then either directly cyclised into the corresponding pyrazolo[1,5-a]-1,3,5-triazine derivatives or hydrolysed into the corresponding N-(pyrazol-5-yl)-urea derivatives 79. Cyclisation of 79 with triethyl orthoacetate gave the corresponding pyrazolo-[1,5-a]-1,3,5-triazine derivatives.[6,116] The synthetic potentialities of the

[1,5-a]-1,3,5-triazine derivatives[6,116] (cf. Chart 11). Novinson et al.[113] have developed a new general synthesis of this ring system which allows ready introduction of different alkyl groups at positions 2 and 4. The authors have shown that the reaction of 3-aminopyrazoles with amidate esters, such as ethyl acetamidate, affords ring N-1 acetamidate derivatives. Ring closure of these compounds with orthoesters afforded pyrazolo[1,5-a]-1,3,5-triazine derivatives. Another route for the synthesis of these compounds was reported by Vogel and Troxiler.[6] Thus, the 5-amino-1-carbamidinopyrazoles (80) were cyclised into the pyrazolo[1,5-a]-1,3,5-triazines 81-83 by the action of orthoesters, acetic-formic anhydride and diethyl carbonate respectively. The 4-amino group in compounds 81 and 82 could be converted by standard procedures to OH, SH, SCH_3, Cl and NRR' group. The reaction of the pyrazolo[1,5-a]-1,3,5-triazine derivatives 82 with electrophiles leads to the formation of derivatives which are substituted at position 7.



78a 78b 79

Chart 11



D-Synthesis of pyrazolo[1,5-c]-as-triazines

The diazotisation of 5-amino-3-phenylpyrazole and the reaction of this diazonium salt with a variety of active methylene reagents has been surveyed.[15,117] For example, as-triazines were the only products that isolated when the diazonium salt 84 reacted with ethyl acetoacetate or 3-aminocrotonitrile. On the other hand, the reaction with ethyl cyanoacetate and benzoylacetonitrile afforded, in acidic pH, hydrazones which were cyclised to pyrazolo[1,5-c]-as-triazine derivatives. The pyrazolo[1,5-c]-as-triazines were the only reaction products that formed in alkaline medium.

The formation of cyclic or acyclic products from the coupling reactions of active methylene compounds with the diazotised aminopyrazole 84 was explained by the mechanistic pathway for the reactions. Coupling with reagents which lead to the direct formation of cyclic products can take place with diazonium salts which exist in equilibrium with the diazobetaiene 85 via a dipolar cycloaddition. When the usual coupling takes place the hydrazones are formed.[118]

Diazo heterocyclic compounds were found to be active intermediates for the synthesis of fused rings through dipolar cycloaddition reactions. Thus, fused triazines were formed by the addition of 3-diazopyrazoles to a variety of dipolarophiles under mild reaction conditions[13,118-122] (cf. Chart 12).

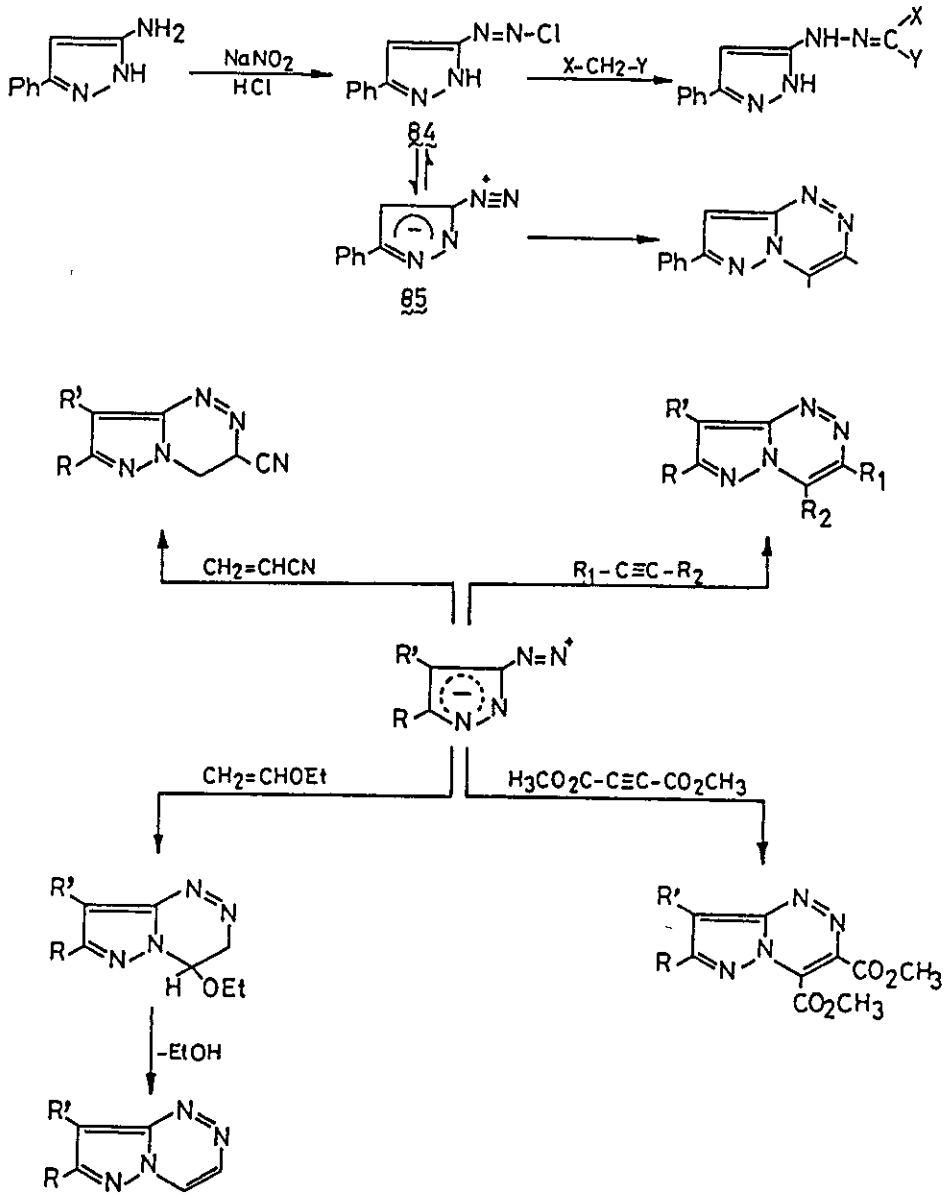

NaNO2
HCl
X-CH2-Y
84
85
CH2=CHCN
R1-C≡C-R2
CH2=CHOEt
H3CO2C-C≡C-CO2CH3
-EtOH

Chart 12

E-Synthesis of other pyrazolotriazines

It has been reported that the thiourea derivatives 86, obtained via the reaction of 5-amino-4-arylazopyrazoles with benzoyl or ethoxycarbonyl isothiocyanates, cyclise into the pyrazolo[4,3-d]-as-triazine derivatives 88 on treatment with pyridine.[118] The formation of these products was assumed to proceed via the sequence demonstrated in Chart 13. Evidence for the formation of the benzoylamino intermediates could be provided by the isolation and characterisation of the benzoylaminopyrazolo[4,3-d]-as-triazine derivatives 87.

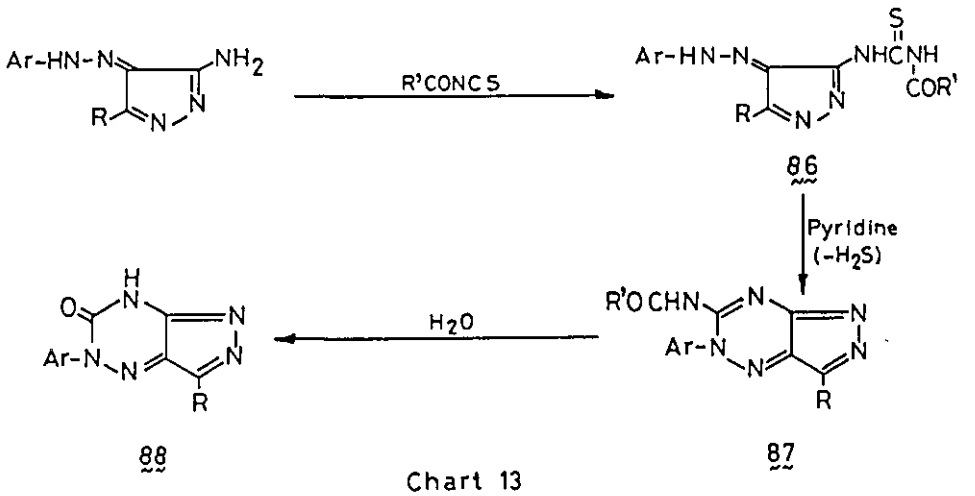


Chart 13

F-Synthesis of pyrazolo[3,4-b]pyridines

The reactions of 1-substituted and 4-unsubstituted 5-aminopyrazoles with β-bifunctional reagents have been shown to afford substituted aminopyrazole derivatives which can be cyclised under a variety of reaction conditions to yield pyrazolo-[3,4-b]pyridine derivatives.[123-125] Recently, Ratajazyk and Swett[126] showed that the reaction of 5-amino-1,3-dimethylpyrazole with ethyl acetoacetate yielded two isomeric pyrazolopyridones which were identified as their corresponding tetrahydropyrazolopyridine derivatives as well as by their IR, ^{1}H NMR and ^{13}C NMR spectral data. Additional proof was provided by a separate synthetic route involving the Friedlander's reaction (cf. Chart 14). Another route for the synthesis of pyrazolo[3,4-b]pyridines has been recently reported.[127] This includes the reaction of 5-aminopyrazoles with DMF-$POCl_3$ to yield the dimethylaminomethylene derivatives 89 which on hydrolysis afford the corresponding aldehydopyrazoles 90.

Compounds 90 could then be condensed with ethyl acetate to yield the pyrazolo[3,4-b]-pyridine derivatives 91 (Chart 14). Haufel and Breitmaier[128] have reported the synthesis of 90 (R_1=Ph;R_2=CH_3) via a similar route. The authors have shown that this new aldehyde opened a direct route for the synthesis of condensed heterocycles of the pyrazole series. Cyclocondensation of 90 with β-dicarbonyl compounds, ethyl cyanoacetate and formamide afforded the pyrazolo[3,4-b]pyridine derivatives 92 and 93 and the pyrazolo[3,4-d]pyrimidine derivatives 94, respectively (cf. Chart 15). The behaviour of 5-amino-3-hydroxypyrazoles toward the action of β-bifunctional reagents and α,β-unsaturated systems differs from that shown in Charts 14 and 15. The (CH_2) group at C-4 of these compounds is activated by both the amino and keto function (cf. possible tautomeric form in Chart 16). This increment in reactivity leads to participation of this moiety in the reactions with the above mentioned reagents.[84,85] In basic media this position is exclusively involved in the reactions. Thus, the nature of the reaction product of 5-amino-3-hydroxypyrazole with β-diketones and β-keto esters has been shown to depend on the applied reaction conditions. In acidic media the formation of the pyrazolo[1,5-a]pyrimidine derivatives 95 is favoured whereas in alkaline media the pyrazolo[3,4-b]pyridines 96 are the only obtainable reaction products (cf. Chart 16).

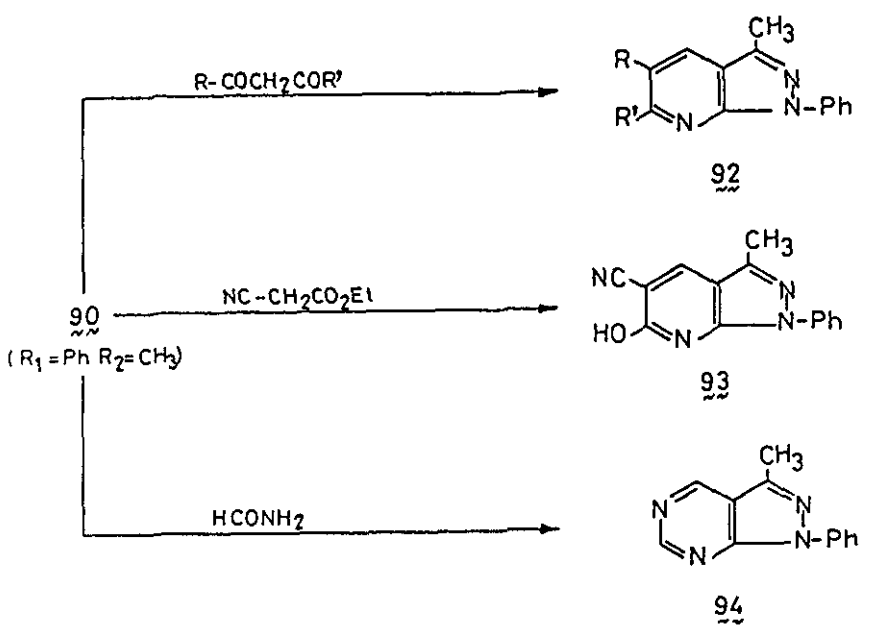


Chart 15

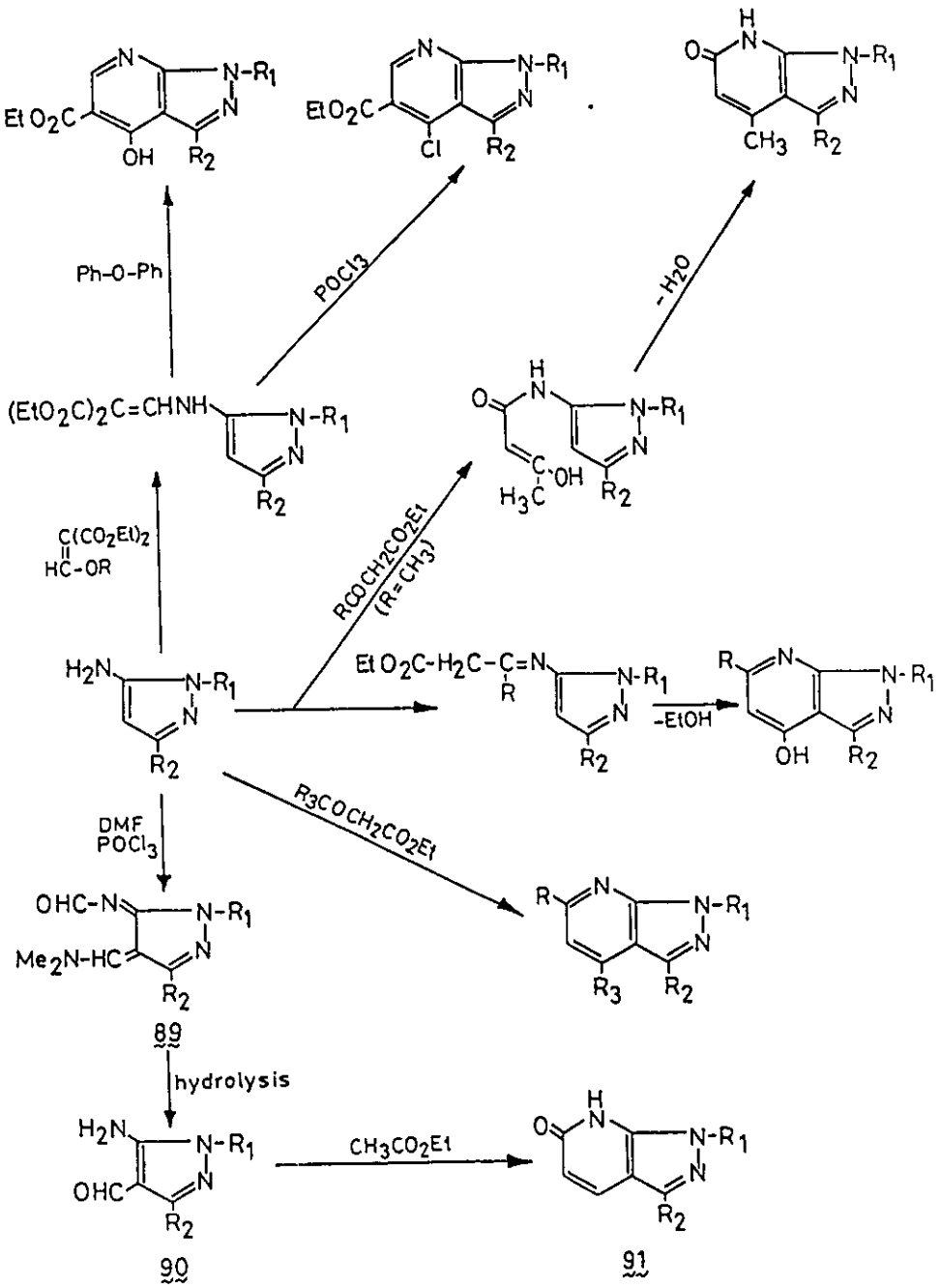

Ph-O-Ph
POCl3
-H2O
C(CO2Et)2
HC-OR
RCOCH2CO2Et
(R=CH3)
-EtOH
DMF
POCl3
R3COCH2CO2Et
hydrolysis
CH3CO2Et
89
90
91

Chart 14

Elnagdi and Ohta[86] reported that 3-amino-1-phenyl-5-hydroxypyrazole reacts with acrylonitrile and ethyl acrylate to yield the 4,4-dialkylated products 97 and 98. The reaction with crotonitrile was described by the same authors[86] to yield the pyrazolo[3,4-b]pyridine derivative 99 (cf. Chart 16).

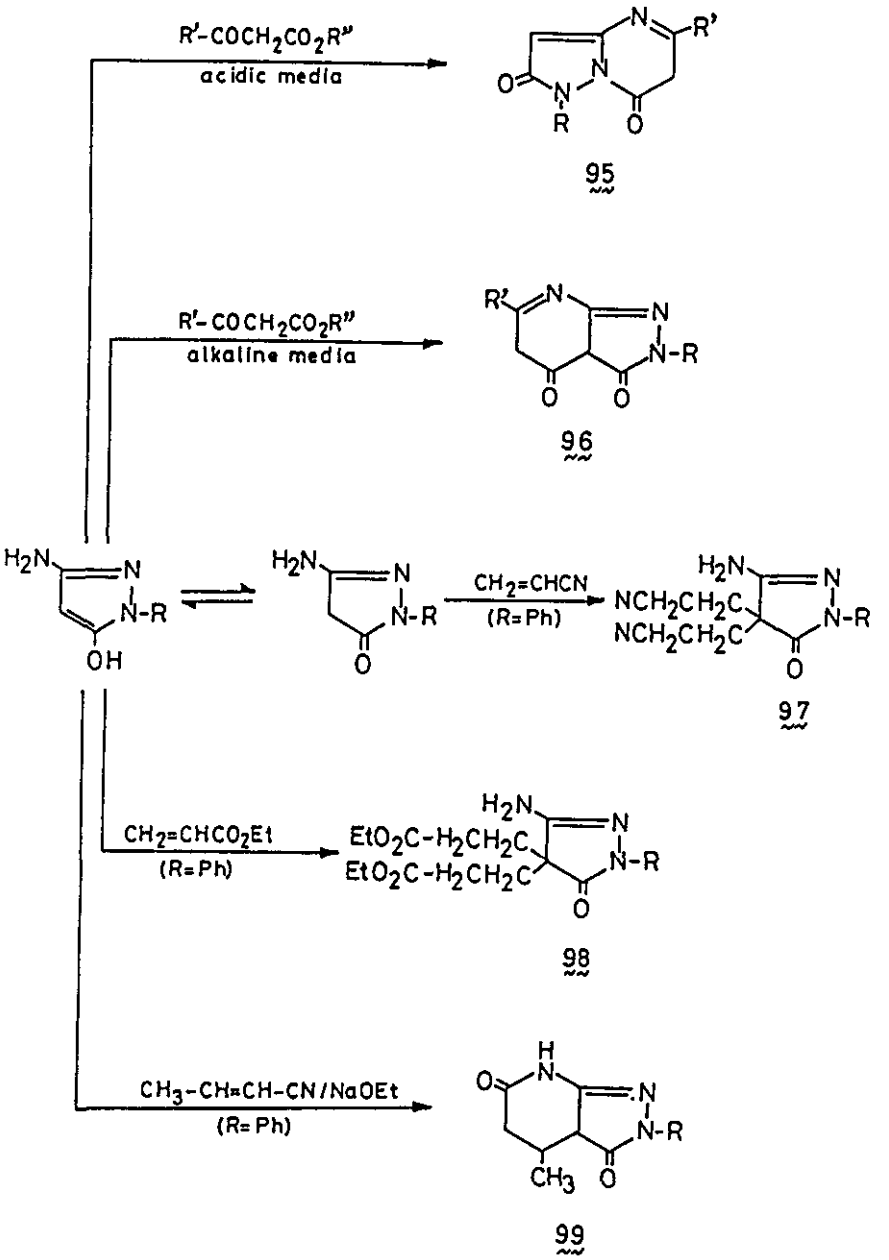


Chart 16

G-Synthesis of pyrazoloazoles

The reaction of 5-amino-4-bromopyrazole (100) with benzoyl isothiocyanate has been reported to afford the pyrazolo[4,5-d]thiazole derivatives 101 or 102 depending on the reaction conditions. On the other hand, compound 100 reacted with ethoxycarbonyl isothiocyanate to yield the thiocyanate pyrazole derivative 103. The latter compound could be readily cyclised into the pyrazolo[4,5-d]thiazole derivative 104.[129] (cf. Chart 17).

Several recent syntheses of imidazo[1,2-b]pyrazoles utilising 5-aminopyrazoles have been reported in literature[130,131] and are summarised in Chart 18. The synthesis of other pyrazoloazoles from 5-aminopyrazoles is also reported.[130,131]

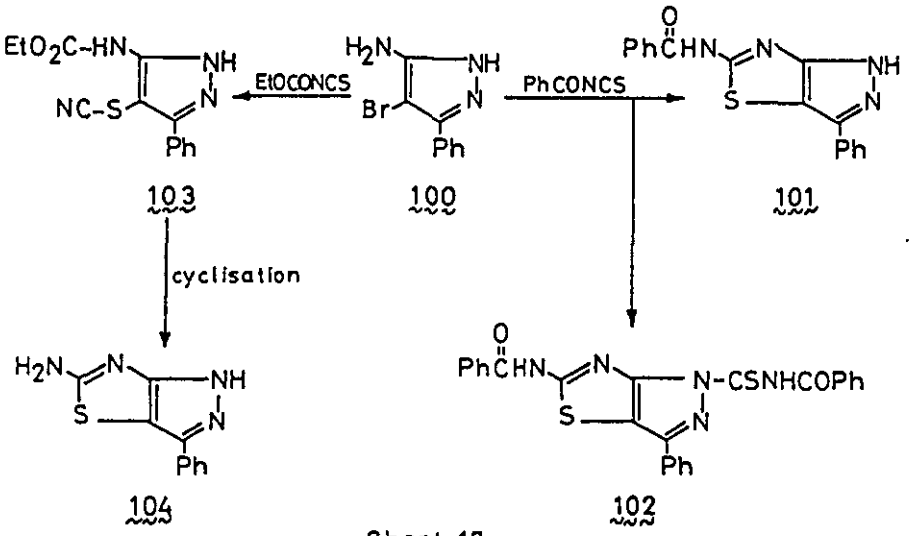


Chart 17

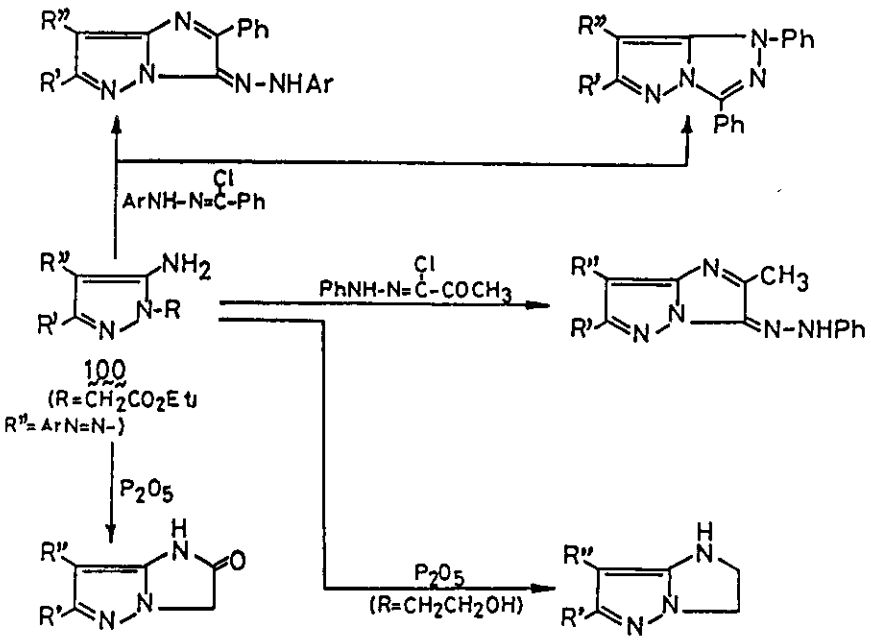


Chart 18

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