

Alkyl-substituted heteroaromatics as precursors to polycyclic heteroaromatics: recent developments

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Abstract

Recent developments in alkylheteroaromatics are surveyed with emphasis on our group's work aimed at developing efficient approaches to benzofused heteroaromatics.

Keywords: Alkylpyridazinyl carbonitriles, alkylcoumarinyl carbonitriles, phthalazines, azolopyridazines, pyridopyridazines, microwaves as energy source

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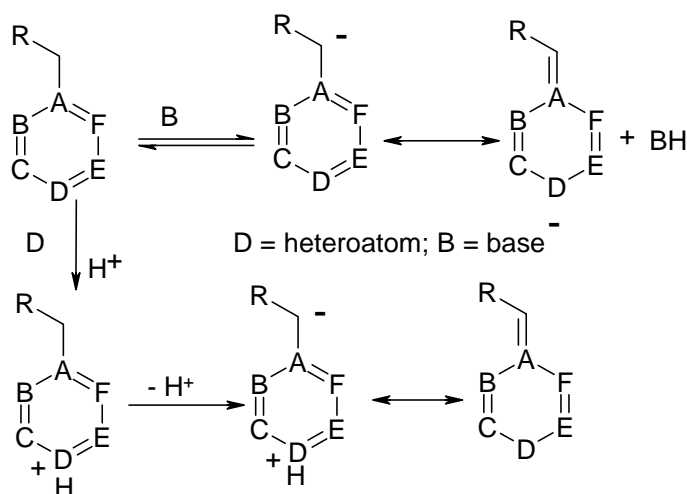
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Introduction

Alkyl groups linked to heteroaromatic π -deficient molecules are activated towards electrophiles both in acidic and basic media and in this way differ from alkyl aromatic hydrocarbons. Activity in basic media is attributed to ready formation of resonance stabilized carbanions. On the other hand, activity in an acidic medium is attributed to the formation of methylene heteroaromatics as a result of protonation and deprotonation (*cf.* Scheme 1).

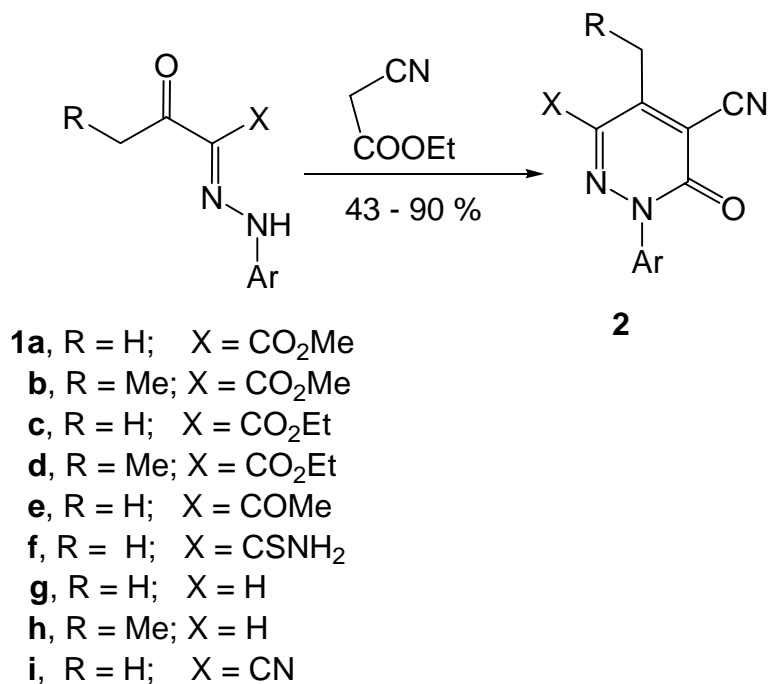


Scheme 1

In addition, alkyl functions linked to ring nitrogens in azines and polyazoles can also produce carbanions under mild conditions. Katritzky *et al.*¹⁻⁵ have utilized this activity extensively for the synthesis of a variety of systems. Alkyl-substituted heteroaromatics have been utilized extensively as building blocks in heterocyclic synthesis and their utility in synthesis has been surveyed by one of us on 1997.⁶ Alkyl π -deficient molecules with electron-withdrawing substituents in adjacent positions are more useful as building blocks for synthesis of condensed heteroaromatics. Their utility for synthesis of condensed pyridines has also been surveyed by Abou Shanab, Wakefield and Elnagdi.⁶ Some time ago Elnagdi *et al.* synthesised a variety of benzofused heteroaromatics and pyridofused heteroaromatics utilizing alkyl-substituted heteroaromatic carbonitriles as starting materials. Contributions in this area were surveyed by Elnagdi *et al.* 1994.⁷ Since the publication of that review, considerable progress in this area has been made and are highlighted in this short review. We review the literature in the period 1996-2006. Since 1997 Elnagdi, F. Al-Omran and N. Al-Awadi have reported several interesting reactivities of *N*-alkyl azoles and *N*-alkyl azines.

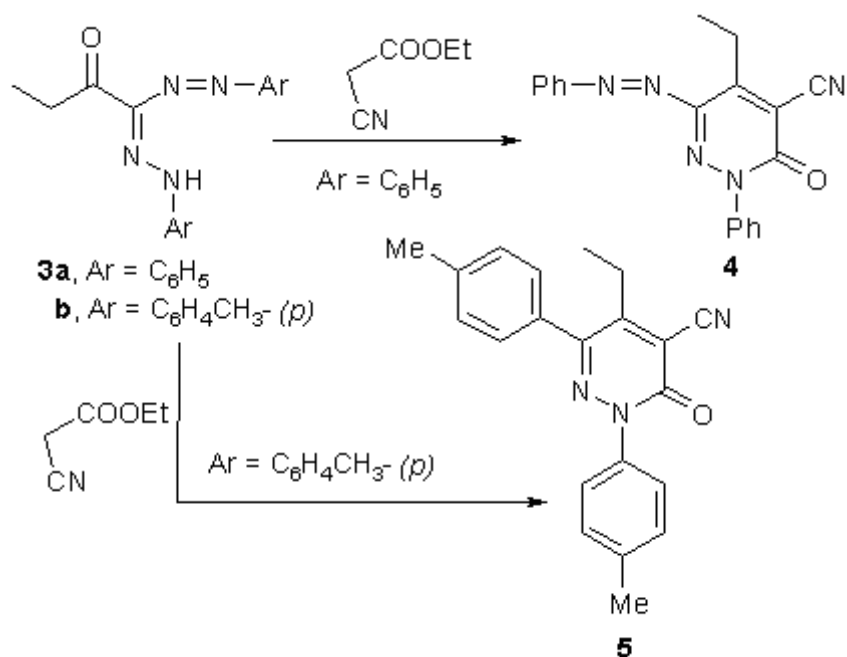
1. Synthesis of Alkyl-substituted Heteroaromatics: A Decade of Exploration of the Potential of the Basic Synthetic Route

Initially we synthesized pyridazinyl carbonitriles **2a-i** *via* condensation of the aryl hydrazones **1a-i** with ethyl cyanoacetate in the presence of ammonium acetate (Scheme 2).⁸⁻¹⁵ This synthesis can now be conducted by microwave heating in a much shorter time and with higher yields.¹²



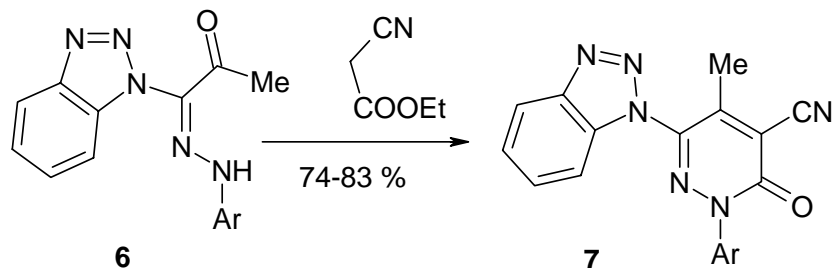
Scheme 2

Recently, it was found that condensation of formazone **3a** with ethyl cyanoacetate with microwave irradiation afforded pyridazinone **4**. However, quite unexpectedly, formazane **3b** gave compound **5** *via* nitrogen extrusion during the reaction. The structure of this product was established with certainty by an X-ray crystal structure determination.¹⁶



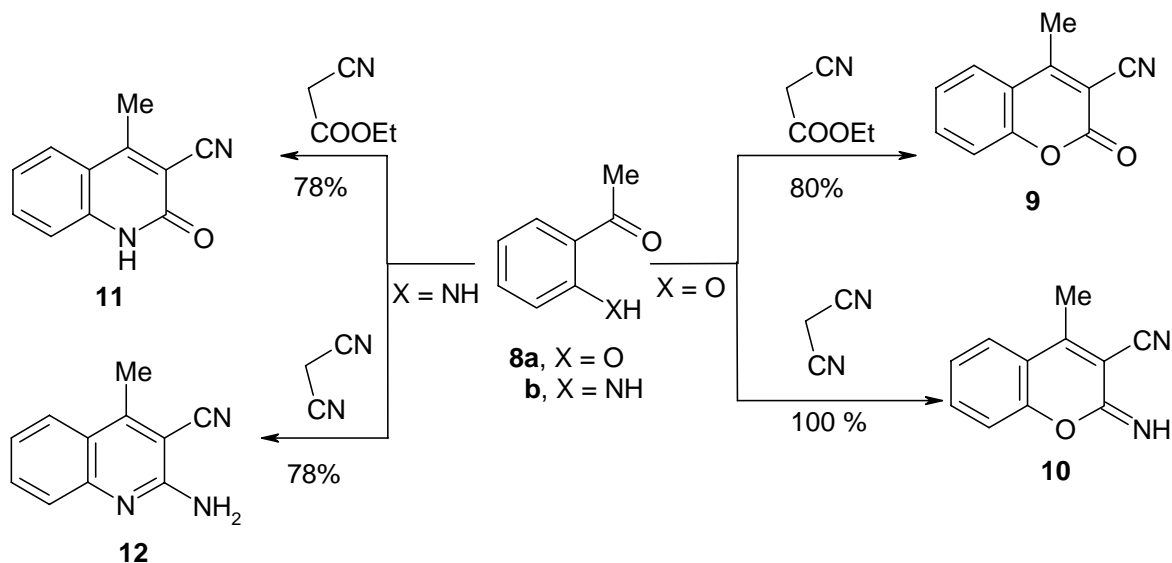
Scheme 3

Condensing the arylhydrazones **6** with ethyl cyanoacetate produced pyridazines **7** in good yields.¹⁷



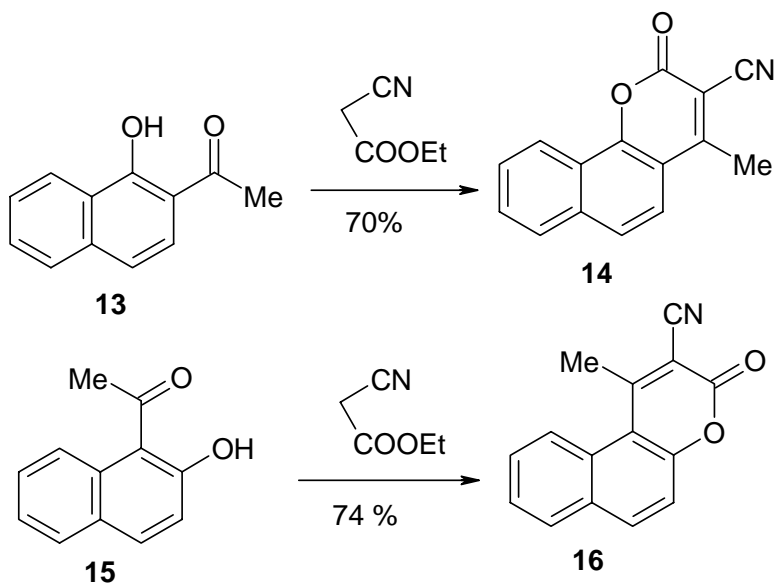
Scheme 4

Alkyl coumarinyl carbonitriles and alkyl quinolinyl carbonitriles were obtained based on the same idea. Condensing 2-hydroxyacetophenone **8a** with ethyl cyanoacetate and malononitrile gave coumarins **9** and **10**, respectively, while condensing 2-aminoacetophenone **8b** with ethyl cyanoacetate and malononitrile gave quinoline derivatives **11** and **12**, respectively.^{18,19}



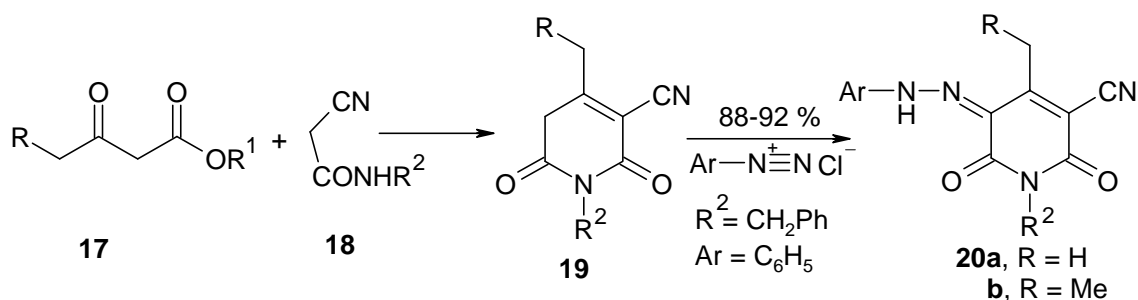
Scheme 5

In a similar way, 2-acetyl-1-naphthol **13** and 1-acetyl-2-naphthol **15** were condensed with ethyl cyanoacetate to yield naphthopyranones **14** and **16**, respectively.^{18,19}



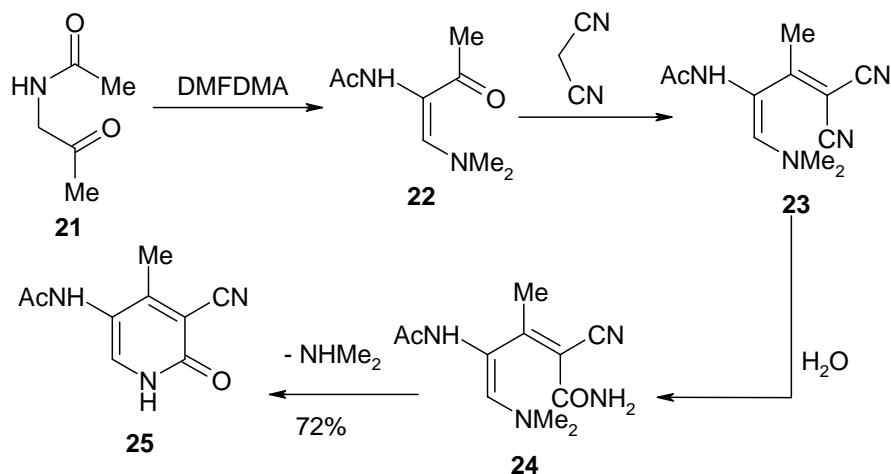
Scheme 6

Synthesis of alkyl pyridinyl carbonitriles *via* reacting β -ketoester **17** with cyanoacetamides **18** is a well-established, industrial synthesis, as pyridones **19** are important intermediates for synthesis of D2T2 printing dyes **20**. Recently, the synthesis of **20b** utilizing methyl propionylacetate as starting material was achieved.²⁰



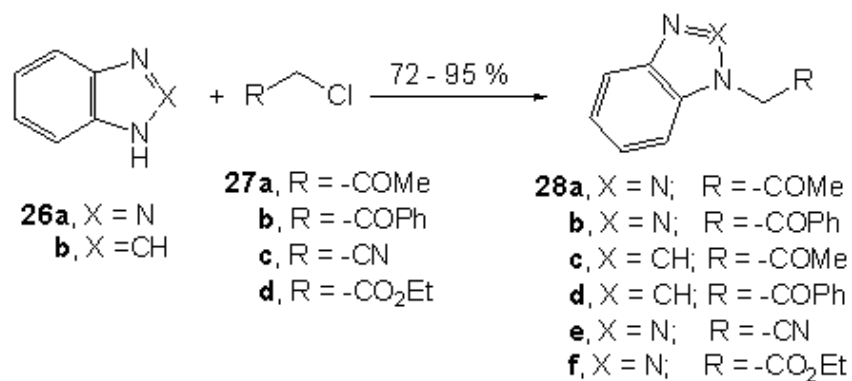
Scheme 7

Acetylaminoacetone **21** reacted with dimethylformamide dimethylacetal (DMFDMA) to yield **22** which, when condensed with malononitrile, yielded the diene **23**. Hydrolysis of the latter with subsequent cyclization afforded 5-acetylamino-4-methyl-2-oxopyridine-3-carbonitrile **25** via the intermediacy of **24**.²¹



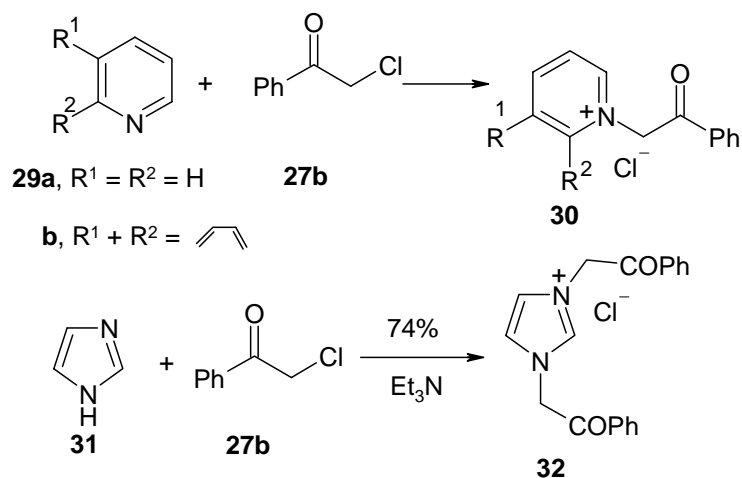
Scheme 8

Benzotriazole **26a**, and benzimidazole **26b** reacted with α -chloroketones **27a,b** in the presence of a base, yielding benzotriazolyl, and benzimidazolyl ketones **28a,b** and **28c,d**, respectively.²²⁻²⁸ Similarly, **26a** reacted with chloroacetonitrile **27c** or ethyl chloroacetate **27d** to give **28e** and **28f**, respectively.²⁹



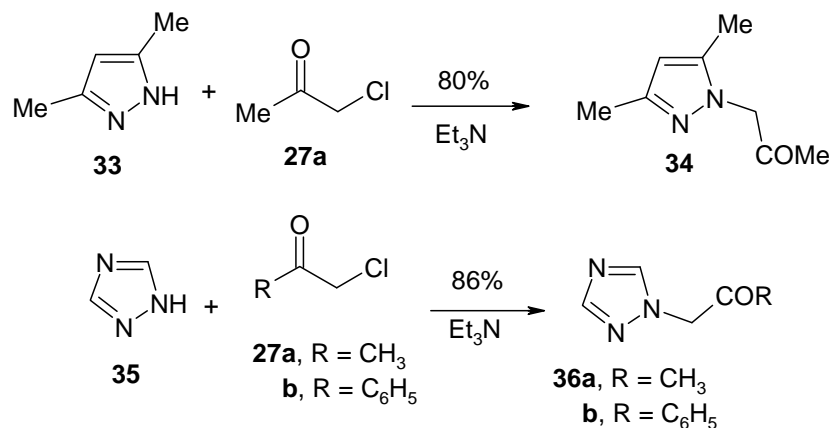
Scheme 9

Compounds **30** and **32** are prepared by reacting pyridines **29** or imidazole **31** with α -chloroacetophenone **27a,b**, respectively.^{26,28}



Scheme 10

3,5-Dimethylpyrazol-1-ylacetone **34** was prepared from 3,5-dimethylpyrazole **33** and chloroacetone **27a** in toluene in the presence of triethylamine in equivalent amount.³⁰ In a similar manner, 1,2,4-triazole **35** reacted with α -chloroacetones **27** to yield compounds **36**.²⁵



Scheme 11

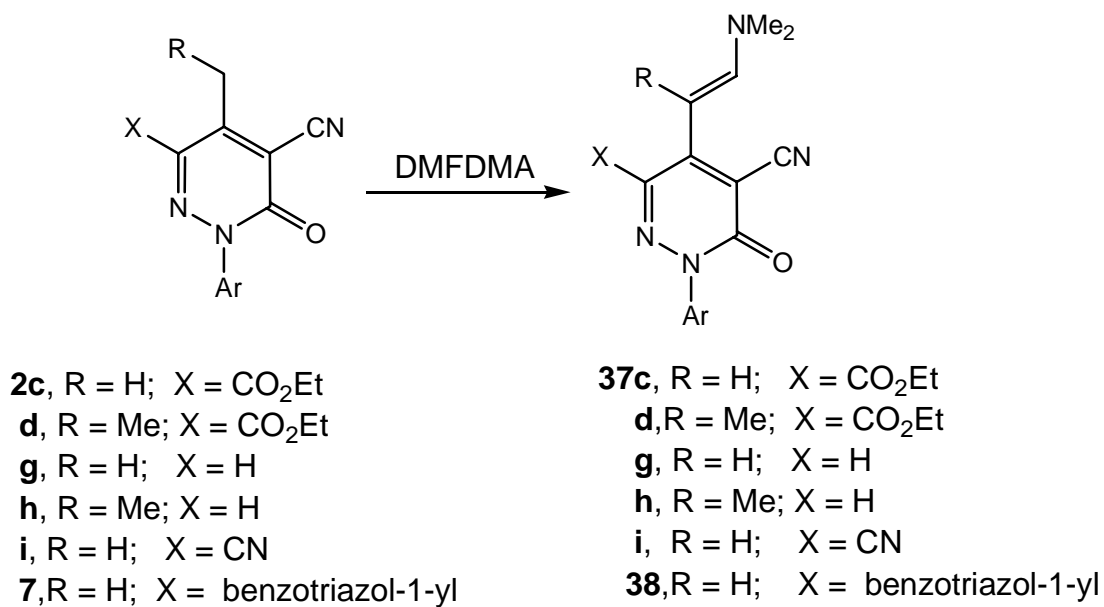
2. Chemical Reactivity of Alkyl-substituted Heteroaromatics

The most important aspect of the reactivity of these compounds is their reaction with electrophiles under mild conditions. Reactivity towards carbon, nitrogen and sulfur nucleophiles has been extensively investigated in our laboratories as reaction products could be subsequently utilized to build condensed polyfunctionally substituted heteroaromatics. Important achievements in this area will also be discussed.

2.1. Reactivity toward carbon electrophiles

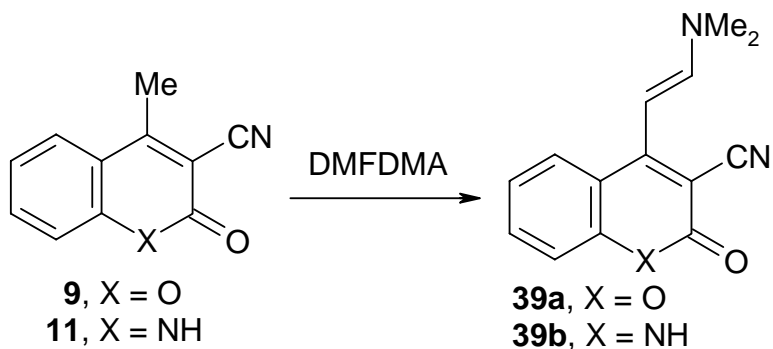
2.1.1. Reactivity of alkyl-substituted heteroaromatic carbonitriles towards amide acetals.

Alkyl groups in alkyl-substituted heteroaromatic carbonitriles readily condense with DMFDMA to yield enamines. Thus, pyridazinones **2** yielded *E*-dimethylaminoethylenes **37** in good yields. Compounds **37** were assigned the *E*-structure based on ¹H NMR studies which revealed alkene protons with *J* = 13 Hz.^{8,12, 31-33} Similarly, compound **7** condensed with DMFDMA to yield the enamine **38**.¹⁷



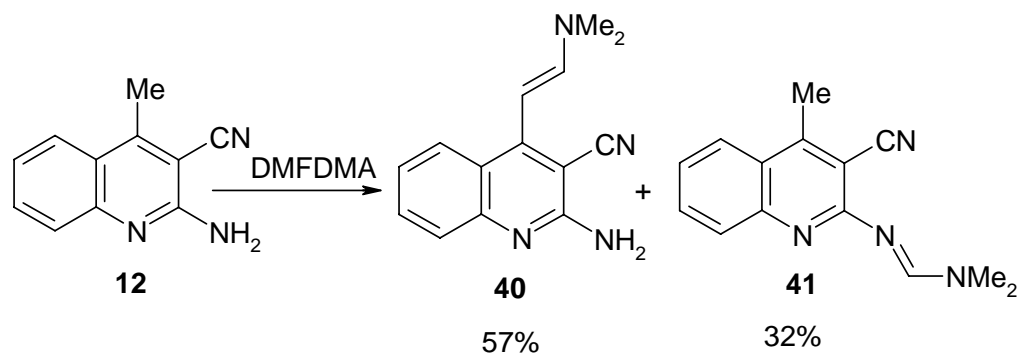
Scheme 12

Compounds **9** and **11** also condensed with DMFDMA to yield the enaminones **39a,b**.¹⁸



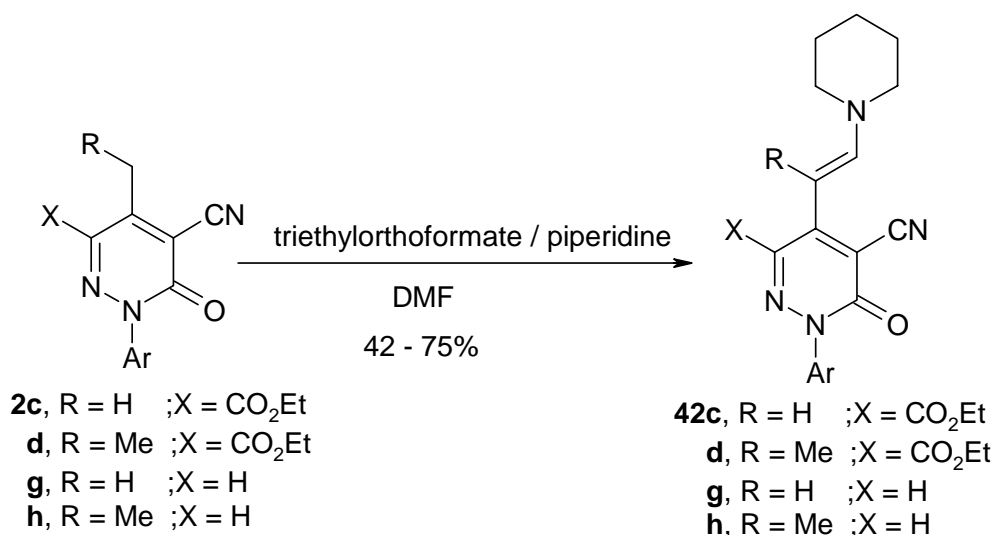
Scheme 13

On the other hand, the reaction of **12** with DMFDMA in refluxing xylene afforded a xylene-soluble product **40** and a xylene-insoluble product **41** in a ratio of 3:1.¹⁸



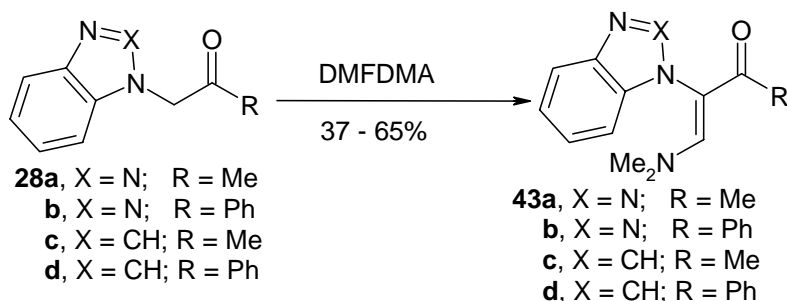
Scheme 14

Elnagdi *et al.*³⁴ condensed the pyridazinones **2** with triethyl orthoformate and piperidine in the presence of dimethylformamide (DMF) to yield the enamines **42** thus substituting expensive and toxic DMFDMA as a reagent for the synthesis of such enamines.



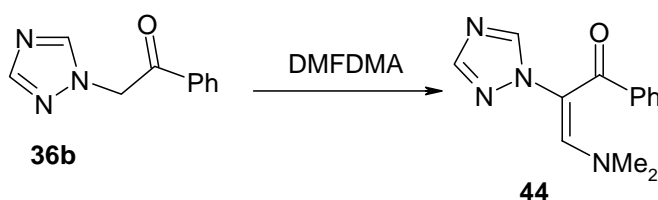
Scheme 15

2.1.2. Reactivity of N-alkyl functions linked to ring nitrogens towards amide acetals.
 Condensation of **28a-d** with DMFDMA afforded the enamines **43**.^{22,25,27,35}



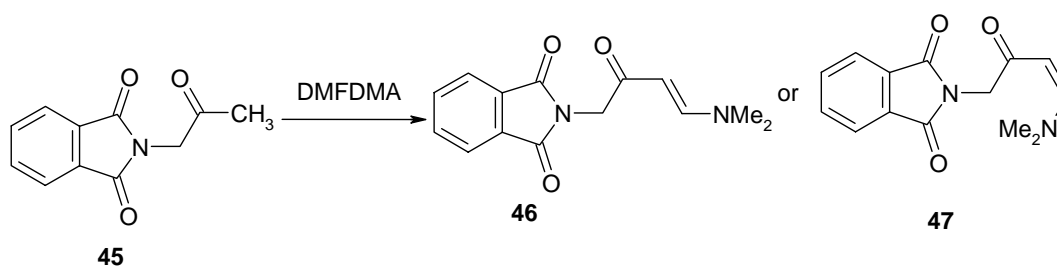
Scheme 16

Similarly, triazolylacetophenone **36b** condensed with DMFDMA to give the enaminone **44**.²⁵



Scheme 17

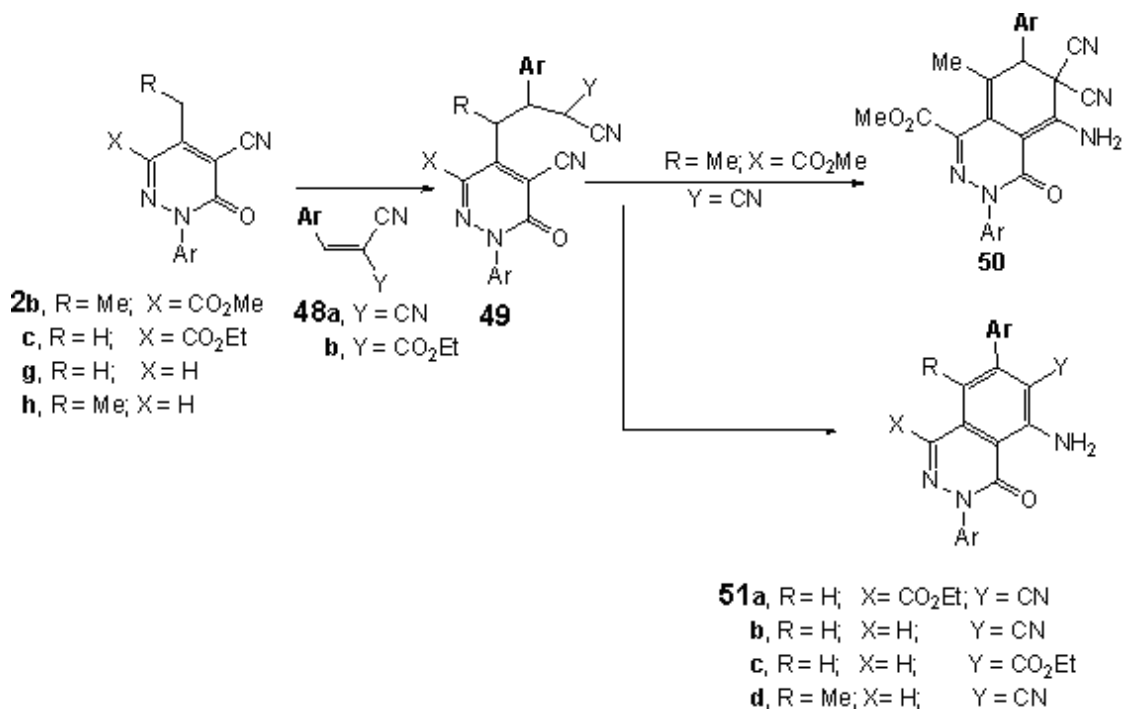
In contrast to this, Al-Mousawi *et al.* and Al-Omran *et al.*^{36a,b} reported that compound **45** condensed with DMFDMA to yield a product for which Al-Mousawi assigned a *trans* structure **46**, while Al-Omran assigned the *cis*-form **47**.



Scheme 18

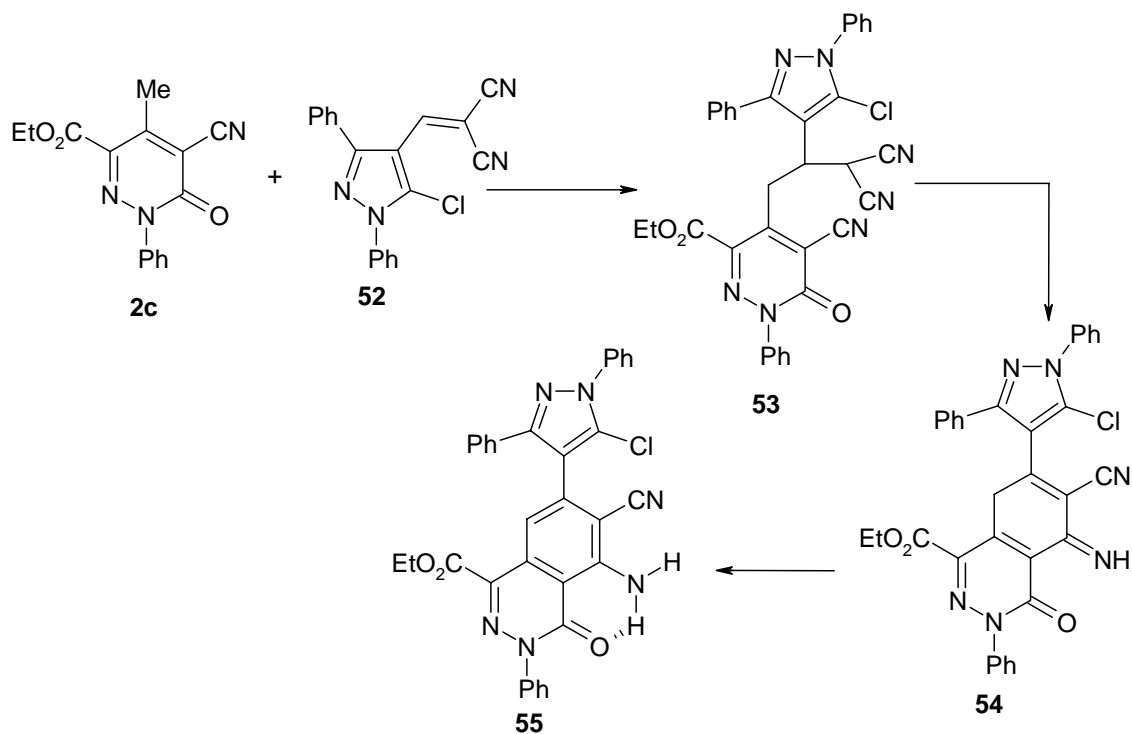
2.1.3. Reactivity of alkyl-substituted heteroaromatic carbonitriles towards α - β -unsaturated nitriles. This reaction can be used for synthesis of benzofused aminoheterocycles. Thus alkylpyridazinyl carbonitriles and alkylcoumarinyl carbonitriles add to α -substituted cinnamionitriles. The adducts cyclise and lose hydrogen cyanide to yield benzo-fused derivatives. This is an extension of our earlier synthesis of aromatic amines from crotononitriles. On several occasions, our co-workers⁸ isolated the non-aromatic dicyano compound although aromaticity of the final product is the driving force for hydrogen cyanide elimination. The structure of

tetrahydrophthalazine **50**, which is prepared from **2** with **48a**, was established by an ^1H NMR analysis that revealed the presence of an amino group and the absence of CH multiplets in the range of $\delta = 2\text{-}4$ ppm. Formation of **50** from **2** is assumed to occur *via* initial formation of Michael adducts **49**. On the other hand, reacting **2c,g,h** with **48a,b** resulted in the direct formation of phthalazine derivatives **51**.^{8,33,37-39}



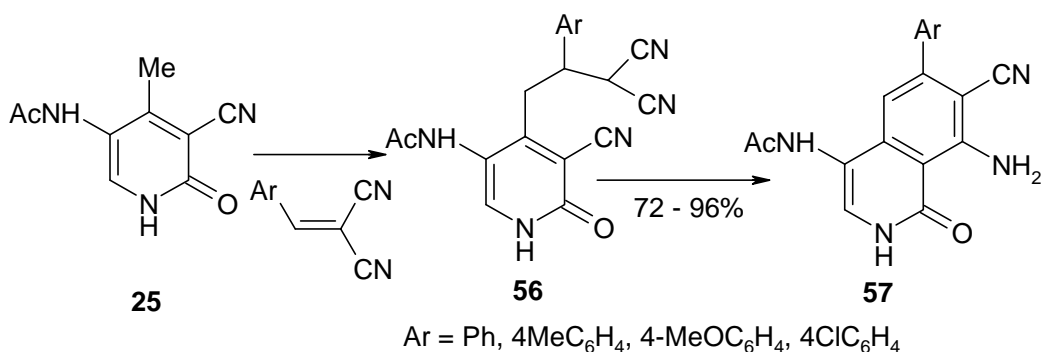
Scheme 19

Compound **2c** reacted with methylenemalononitrile **52** to yield phthalazinone **55** which is assumed to be formed *via* the intermediates **53** and **54**.⁴⁰ Recently, also pyrrolidine malononitrile was added to **2c** in a similar way to yield phthalazines.⁴¹



Scheme 20

On the other hand, reaction of 5-acetylamino-4-methyl-2-oxopyridine-3-carbonitrile **25** with arylidene malononitriles afforded **56** that cyclised to the diamino-isoquinolones **57**, most likely *via* the established reaction sequence for reaction of arylidene malononitriles with alkylazinyll carbonitriles.²¹

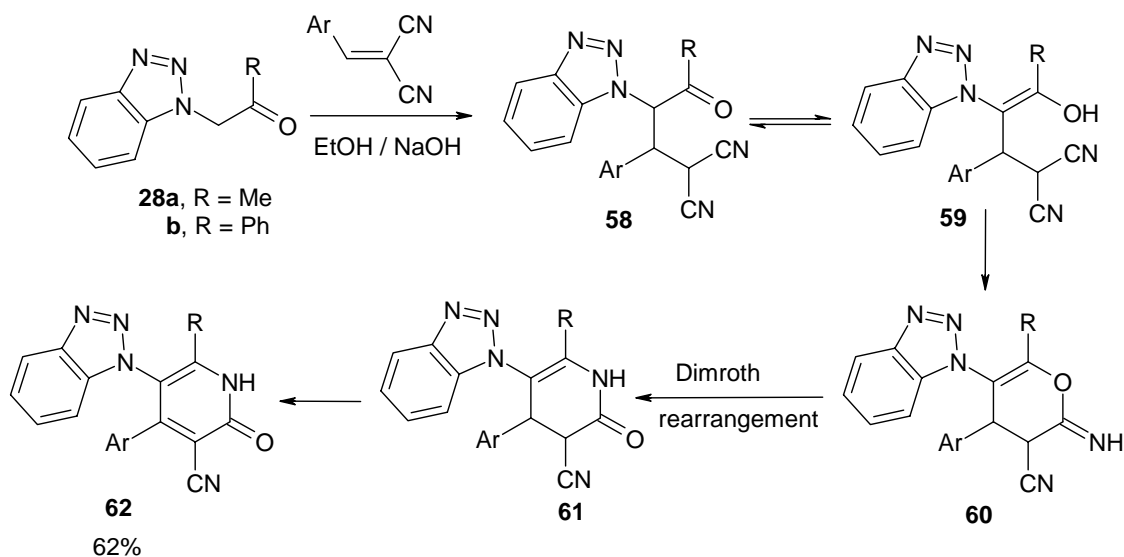


Scheme 21

2.1.4. Reaction of *N*-alkyl functions linked to ring nitrogens with α,β -unsaturated nitriles.

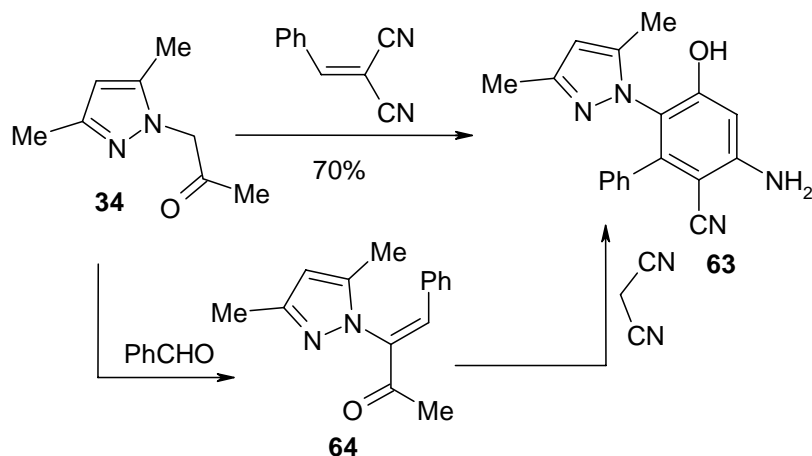
The triazolylacetone **28a** and triazolylacetophenone **28b** reacted with arylidene malononitrile in refluxing ethanol and in the presence of triethylamine to yield products that can be formulated as

62. The formation of **62** is assumed to proceed *via* initial addition of the active methylene of **28a,b** to the double bond in arylidenemalononitrile yielding Michael adduct **58** or **59** which then cyclises to **60** and undergoes a Dimroth type rearrangement to yield **61** which aromatizes to give the isolated product **62**.^{22, 35}



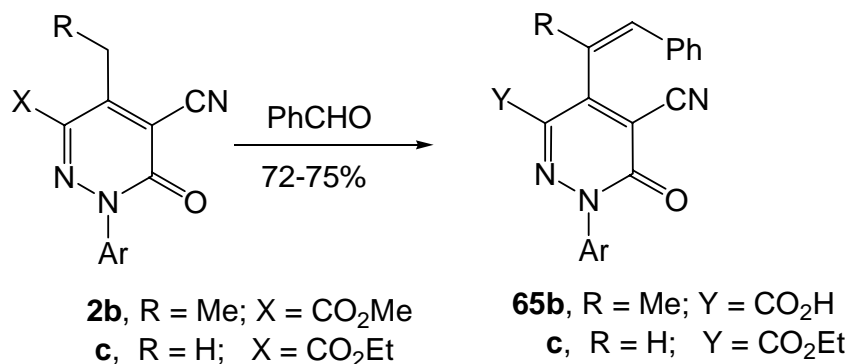
Scheme 22

On the other hand, the pyrazolylacetone **34** reacted with benzylidenemalononitrile to yield the addition product **63**. Structure **63** could be established *via* initial reaction of **34** with benzaldehyde and subsequent interaction of the formed arylidene **64** with malononitrile.³⁰



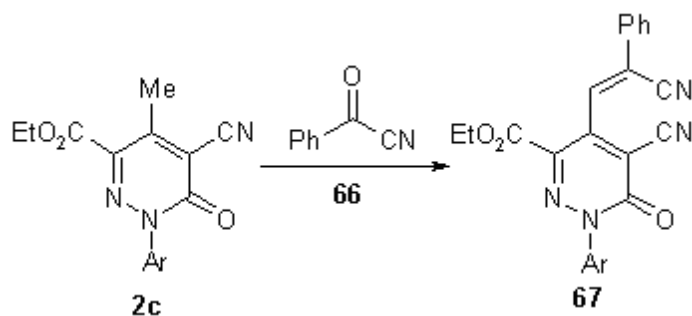
Scheme 23

2.1.5. Reactivity of alkyl-substituted heteroaromatic carbonitriles towards carbonyl compounds. Styryl derivative **65** was formed on reaction of **2b,c** with benzaldehyde; the water formed during the condensation affected hydrolysis of methyl ester.^{8,15}



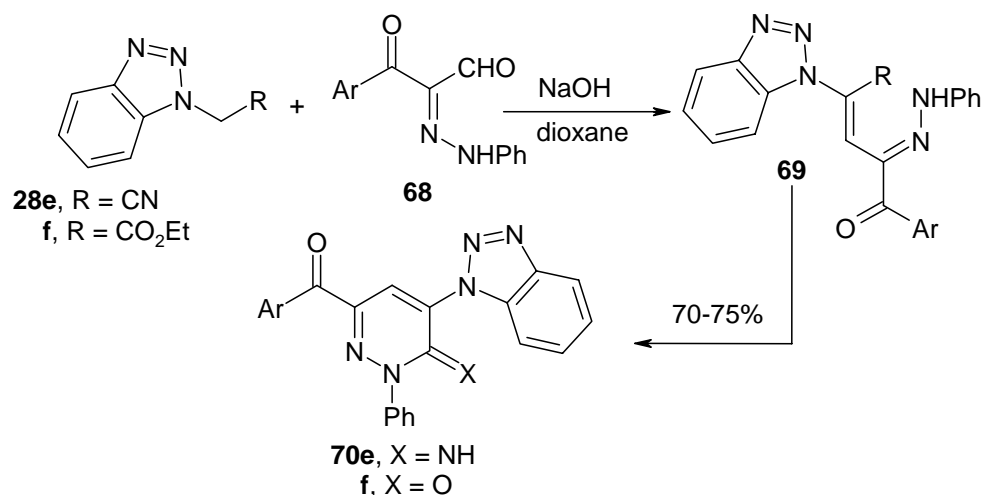
Scheme 24

Compound **2c** condensed with benzoyl cyanide **66** to yield the dicyanonitrile **67**.³²



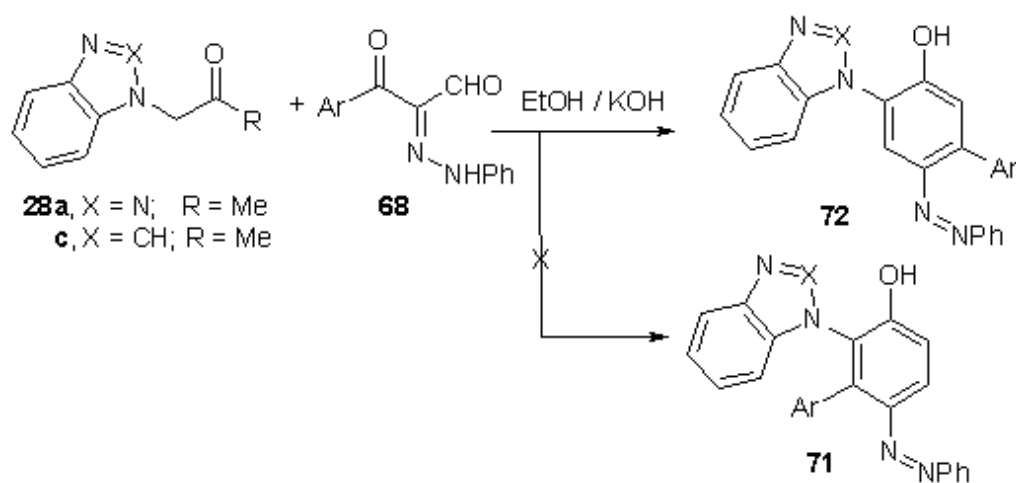
Scheme 25

2.1.6. Reactivity of N-alkyl functions linked to ring nitrogens with arylhydrazonals. Benzotriazolylacetone **28e** and ethyl benzotriazolylacetate **28f** condensed with arylhydrazone **68** and yielded **69** that cyclised to the benzotriazolylpyridazine derivatives **70e,f**.²⁹



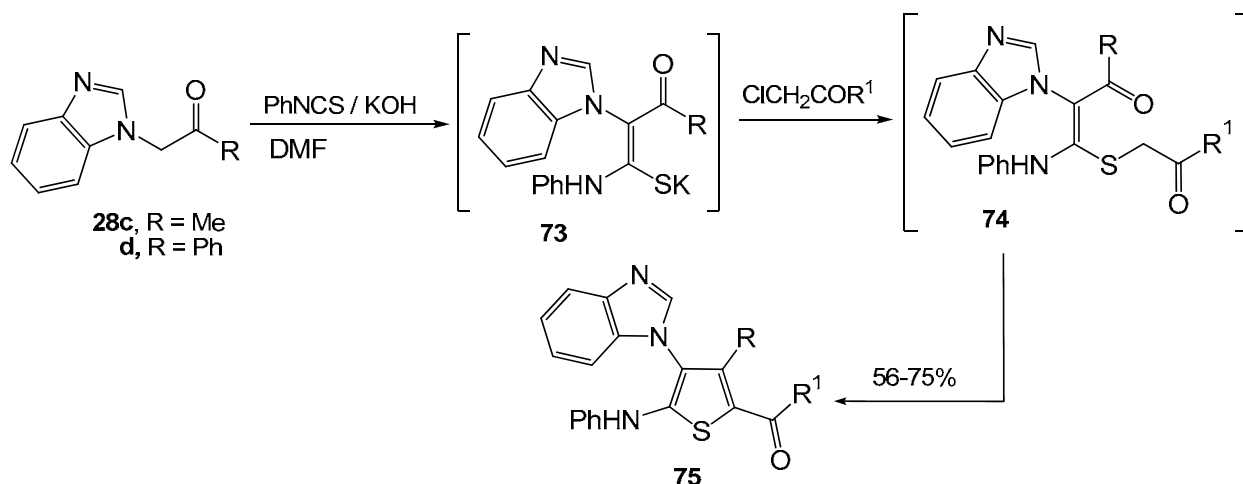
Scheme 26

Also it has been found that compound **28a,c** reacted with arylhydrazones **68** to yield products that can be formulated as **71** or its positional isomer **72**. Structure **72** was established based on ^1H NMR examination which revealed two aryl singlets at δ 7.76 and 8.34 ppm, thus excluding structure **71**.^[22]



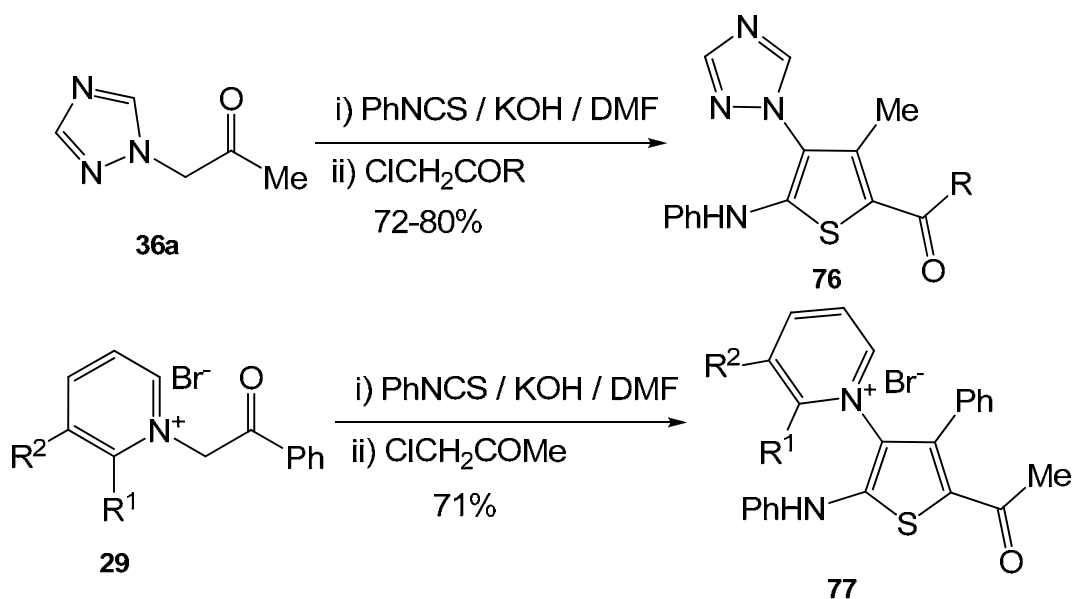
Scheme 27

2.1.7. Reactivity of N-alkyl functions linked to ring nitrogens towards phenylisothiocyanate. Compounds **28** reacted initially with phenylisothiocyanate in DMF in the presence of potassium hydroxide followed by α -haloketones to yield the azolythiophenes **75** via the intermediacy of **73** and **74**.^{22,26}



Scheme 28

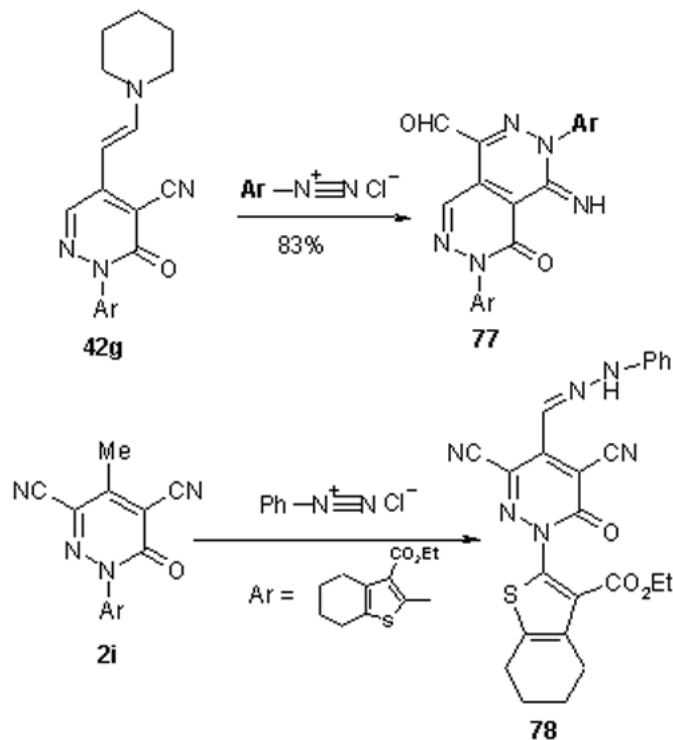
Similarly, compounds **36a** and **29** reacted with phenylisothiocyanate and α -haloketones under similar conditions to yield **75** and **76**,^{22,26} respectively.



Scheme 29

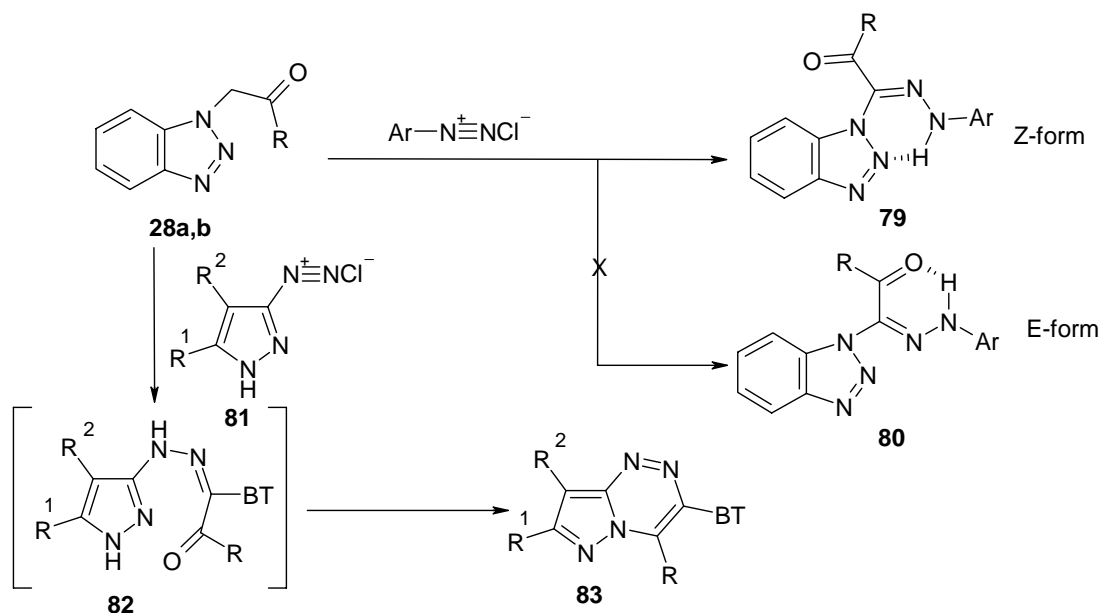
2.2. Reactivity towards nitrogen electrophiles

2.2.1. Coupling with aryldiazonium salts. It has been found that the enamine **42g** couples readily with aryldiazonium chloride to give the corresponding pyridazinopyridazine derivatives **78**.^{34,42} Mohreb *et al.*⁴² reported successful coupling of **2i** with phenyldiazonium chloride to yield **78** which could not be cyclised.



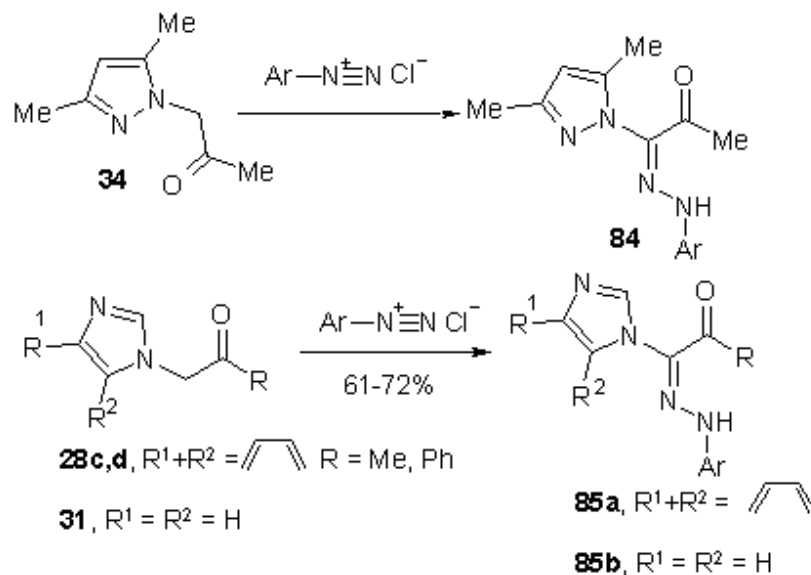
Scheme 30

Also, compounds **28a,b** coupled readily with aromatic diazonium salts to yield the corresponding arylhydrazones. Although these products can exist as two forms, *Z*-form **79** or *E*-forms **80**, only one form was detected by ^1H NMR inspection, most likely form **79**. Recent X-ray analyses of similar systems have established a preference for the *anti*-form due to stereoelectronic factors. Compounds **28a,b** also coupled with diazotized aminopyrazole **81** to yield the hydrazone **82** which cyclized spontaneously under the coupling conditions to give the pyrazolo[5,1-*c*]-1,2,4-triazine derivatives **83**.^{17,35}



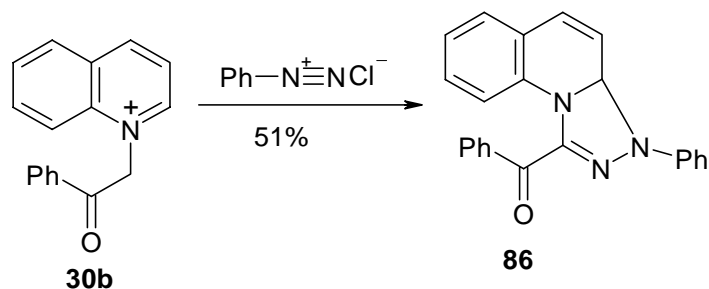
Scheme 31

Similarly, pyrazole **34**, benzimidazoles **28c,d** and imidazoles **31** coupled readily with aromatic diazonium salts to yield the hydrazones **84**³⁰, and **85a,b**^{25,26} respectively.



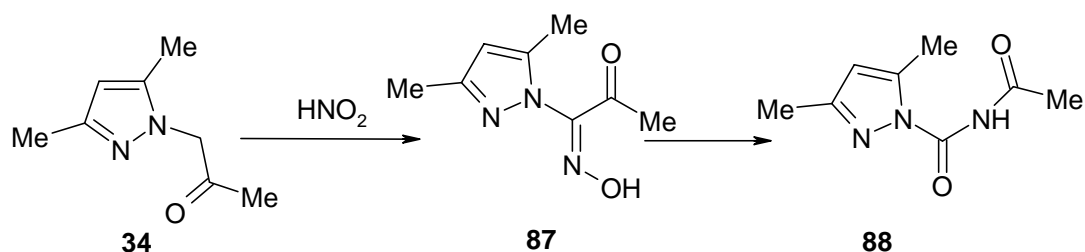
Scheme 32

On the other hand, reaction of **30b** with benzenediazonium chloride did not afford the expected arylhydrazones, instead the [1,2,4]triazolo[4,3-*d*]quinoline derivative **86** was formed.²⁶



Scheme 33

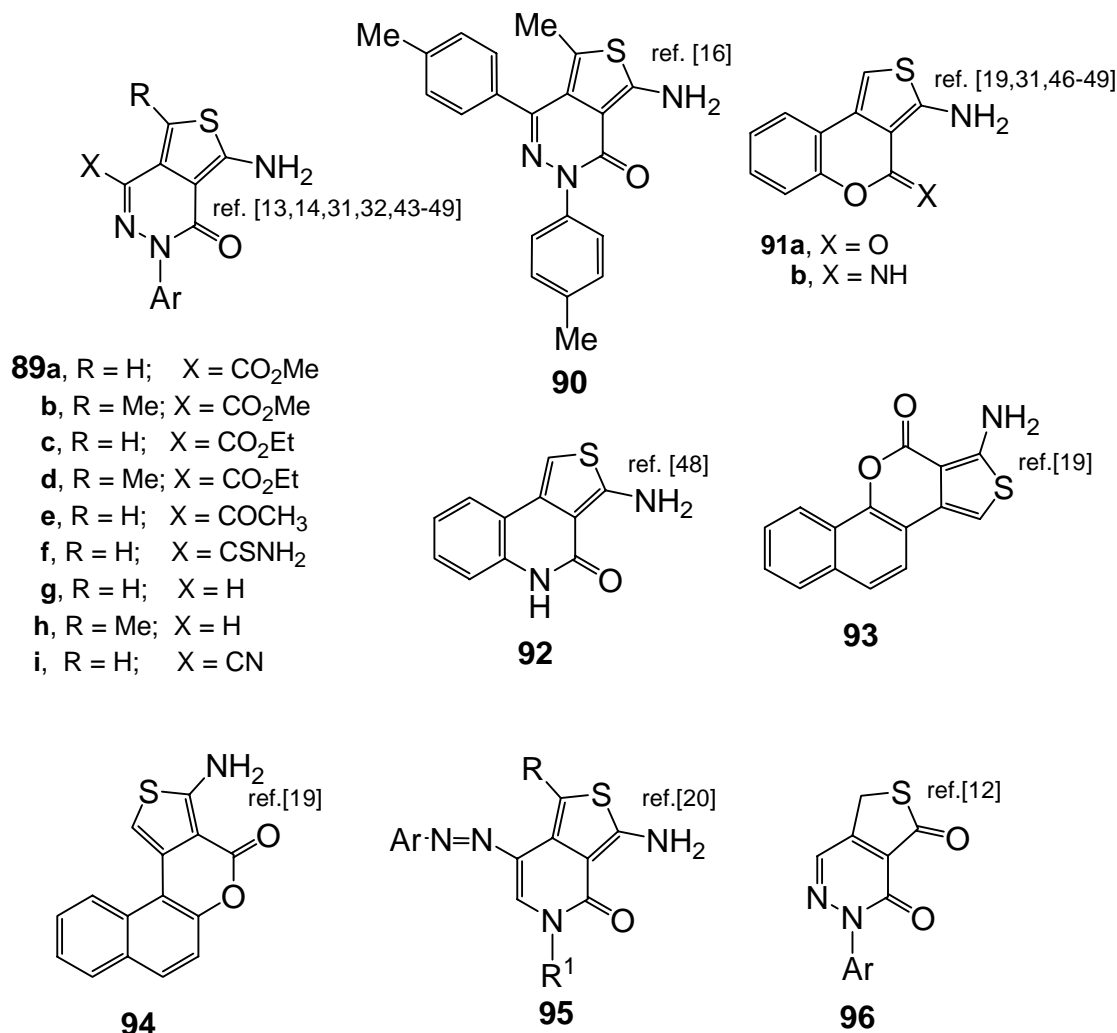
2.2.2. Reactivity towards nitrous acid. Compound **34** reacted with nitrous acid to yield a product that can be formulated as **87** or **88**. Structure **88** was established based on a ^{13}C NMR analysis that revealed the presence of two carbonyl carbons at δ 178.4 and 176.2 ppm.³⁰



Scheme 34

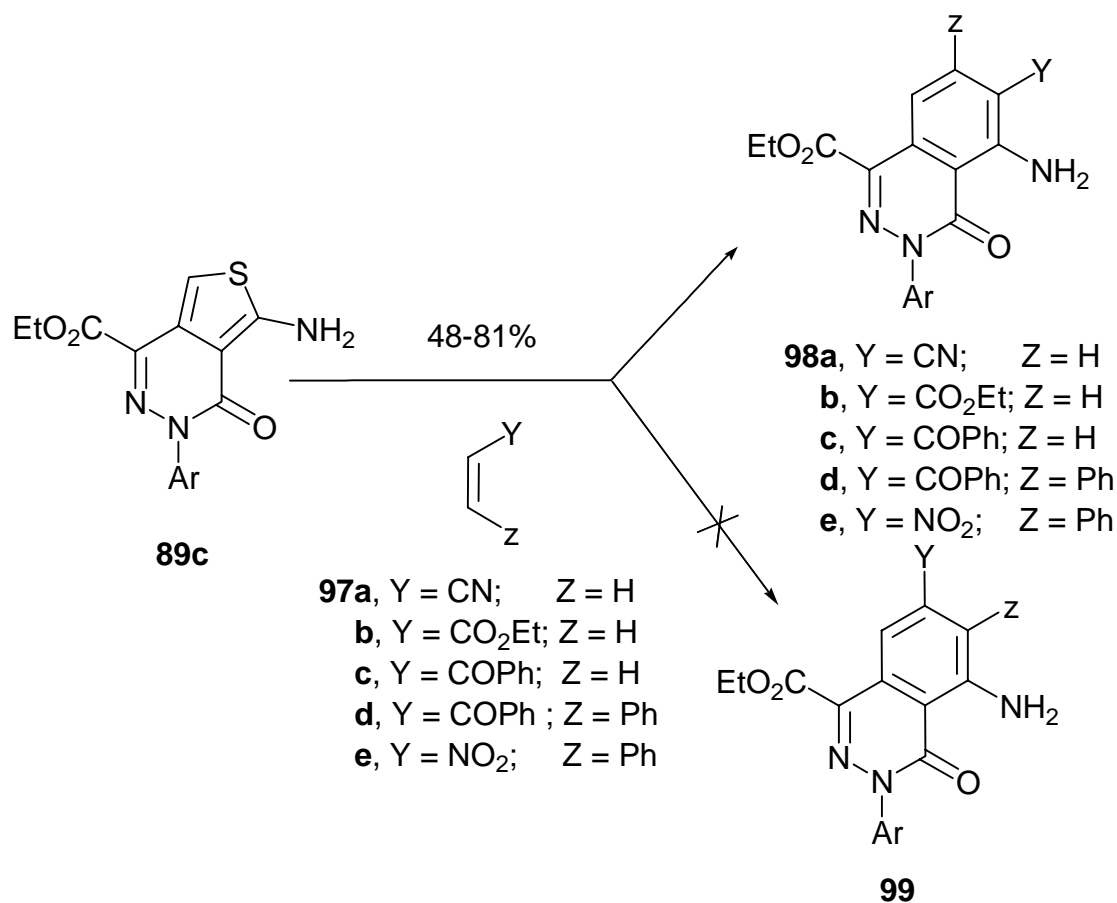
2.3. Synthesis and reactivity of condensed aminothiophenes

The fused thiophene derivatives **89-95** (Scheme 35)^{8,12,16,19,20,,32,43-49} were prepared by reacting the alkyl-substituted heteroaromatic carbonitriles, **2**, **5**, **9-11**, **14**, **16** and **20** respectively with elemental sulfur in the presence of a base. The formation of thiophenes in these reactions, rather than pyrrole thiols, has been established with certainty by X-ray crystal structure determination of compound **90**. Moreover, several aminothienopyridazines were hydrolysed in acid media to produce the corresponding thiophenones **96**.



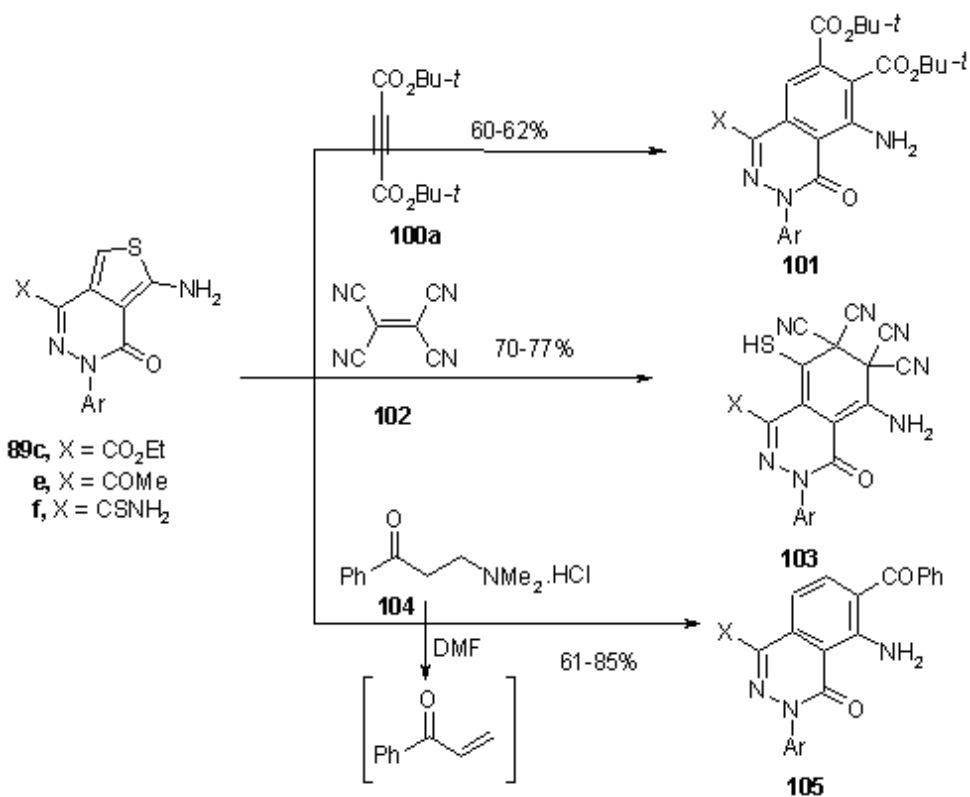
Scheme 35

The thienoheteroaromatics reported here have been extensively investigated as novel dienes in Diels–Alder reactions. In 1989 Elnagdi *et al.*⁴⁴ reported general syntheses of benzofused pyridazines. Initially, Elnagdi *et al.* investigated the reactivity of **89c** towards activated double bond systems. Thus, on treating **89c** with acrylonitrile **97a** and ethyl acrylate **97b** products that may be formulated as **98a,b** or **99a,b** were obtained through hydrogen sulfide elimination. The regioselectivity of addition was established based on ¹H NMR analysis of **98a** which revealed two doublets at δ 7.62, and 8.50 ppm with $J = 9$ Hz for *ortho* coupled protons, excluding completely possible structure **99**. Phthalazines **98c-e**⁴⁵ were produced from reaction of **89** with phenyl vinyl ketone **97c**, phenyl styryl ketone **97d** and ω -nitrostyrene **97e**, respectively.



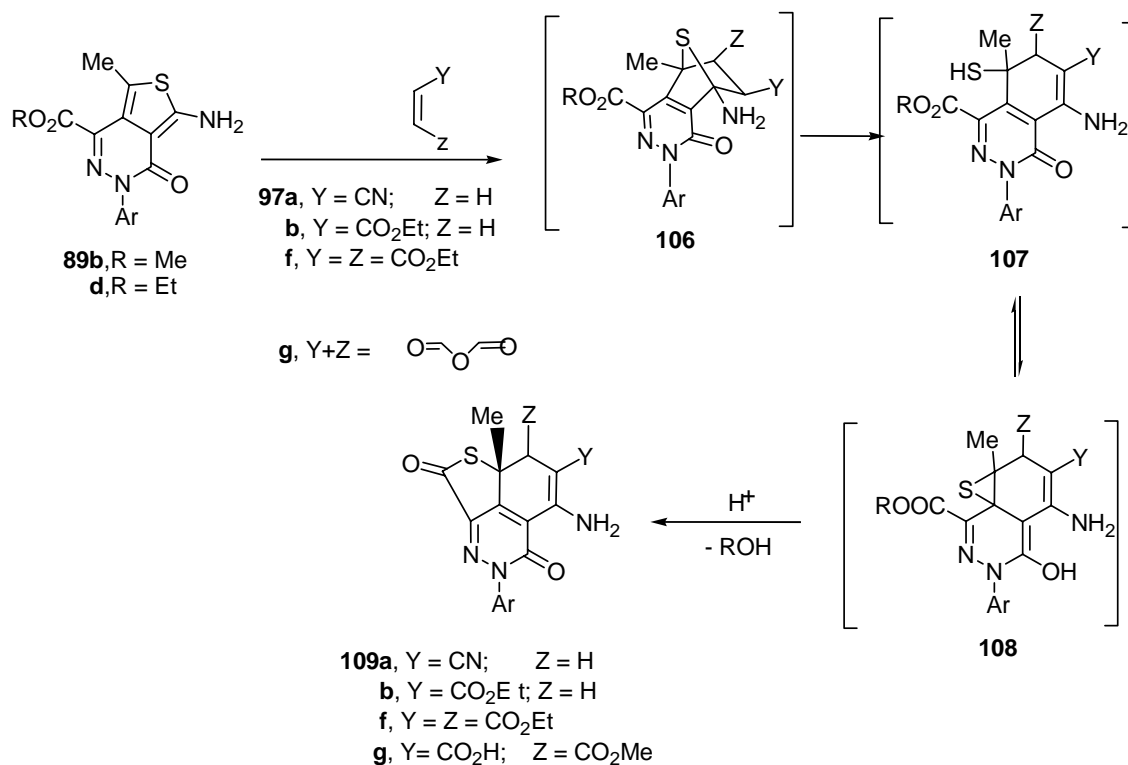
Scheme 36

Like the previously mentioned reactions, the pyridazines **89c,e,f** reacted with di-*t*-butyl acetylenedicarboxylate **100a**, tetracyanoethylene **102** and Mannich compound **104** to yield the compounds **101**, **103** and **105**, respectively.⁴⁵



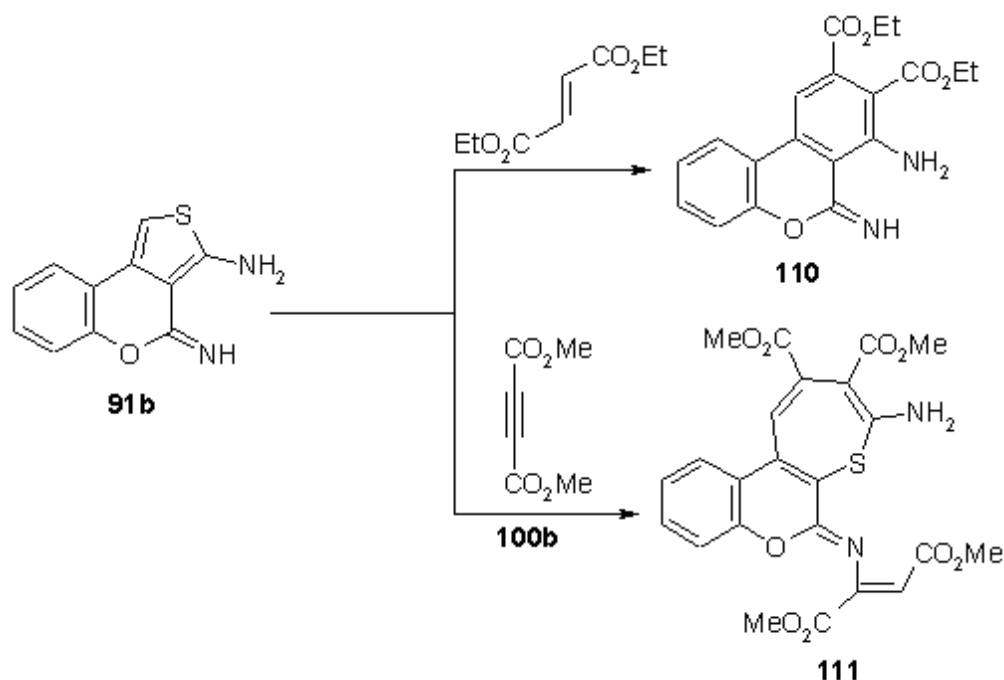
Scheme 37

These reactions proved to be general ones and many electron-poor olefins were successfully added to **89**. This is quite different from the reported behavior of **89b,d** towards **97a,b,f**, where **89b,d** reacted with acrylonitrile, ethyl acrylate, and diethyl maleate to yield products of addition and alcohol elimination. These are assigned structures **109** and assumed to be formed *via* rearrangement of initially formed cycloadducts **106-108**.^{8,47} In a similar manner the reaction of maleic anhydride **97g** with **89b** afforded **109g**. It is believed that the methanol lost during formation of **109g** affects opening of the anhydride ring.⁴⁷



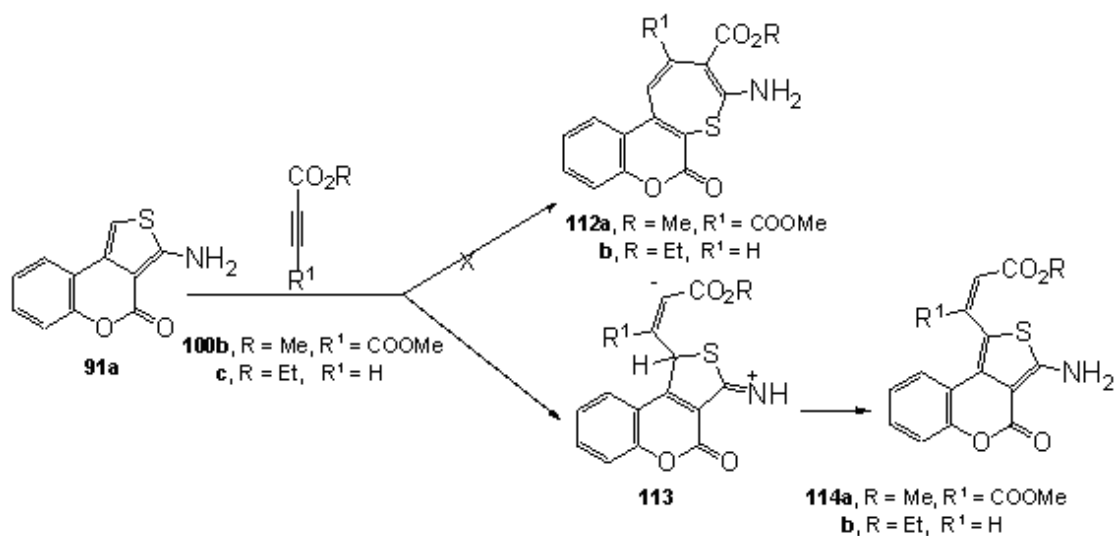
Scheme 38

Some time ago Dopp *et al.*⁵⁰ proposed the formation of thiepin **111** from reaction of thieno[3,4,3',4']benzo[*b*]pyranimine **91b** with dimethyl acetylenedicarboxylate (DMAD). While the cycloadduct produced from reaction of **91b** with diethyl fumarate decomposed in a manner similar to that observed earlier by Elnagdi *et al.* to give **110**. Later our group reported similar thiepins⁸ formed by reaction of condensed thiophenes **91a,b** and **92** with acetylenic esters. Al-Omran *et al.*^{51,52} also claimed the formation of thiepins on reaction of other condensed aminothiophenes and DMAD.



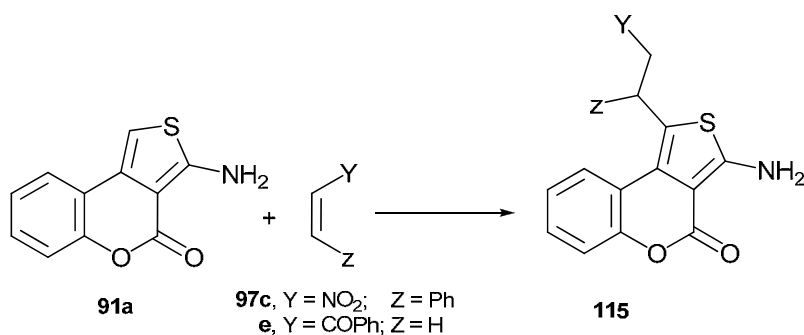
Scheme 39

In the light of well-accepted thermal instability of thiepins⁵⁰ and to see whether the rearrangement into thiepins is a general reaction, we decided to look further into the structure of thiepins claimed to be formed in the previous work.⁸ Elnagdi *et al.*⁴⁸ investigated the reaction of **91a** with ethyl propiolate in the cold to yield a 1:1 adduct that had been earlier assumed to be a thiepinochromone **112b**. High resolution ¹H NMR analysis of this product indicated the presence of two *trans* coupled olefinic protons at δ 5.90 and 8.23 ppm with $J = 13.7$ Hz. Clearly this is inconsistent with the *cis* protons of thiepin structure **112b**. Consequently a C-1 alkylation was established *via* a dipolar cycloaddition sequence leading to the formation of **114b**.⁴⁸ Compound **91a** reacted in the same way with DMAD **100b** to yield the C-1 alkylated product **114a**.



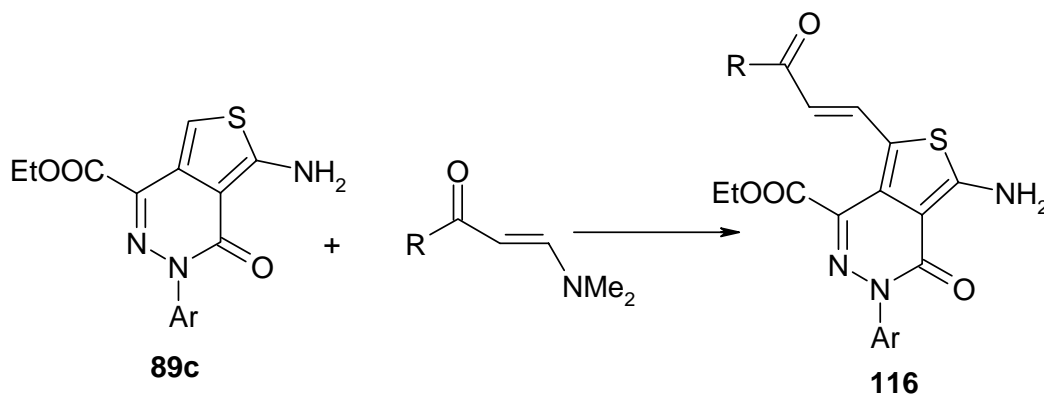
Scheme 40

In fact C-1 alkylation of aminothienocoumarins has been observed in our laboratories⁴⁶ on reacting ω -nitrostyrene, and aryl vinyl ketones, with **91a** to yield 1:1 adducts **115**.



Scheme 41

Similarly the pyridazine **89c** reacted with an enaminone to give the C-1 alkylation product **116**.⁴⁶



Scheme 42

Prof. Döpp, who was most likely unaware of our work, has come recently to the same conclusion.^{53,54}

Conclusions

Our work over the last decade clearly revealed the importance of alkylheteroaromatics as building blocks for heterocyclic systems. Many fused heteroaromatic amines that may find soon their way into the dye industry have been obtained based on these compounds *via* simple efficient procedures.

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Mohamed Hilmy Elnagdi was born in Egypt in September 1941. He graduated from the Faculty of Science at Cairo University in 1962; since that date, Prof. Elnagdi has worked at Cairo University, Faculty of Science, in the Chemistry Department. Prof. Elnagdi obtained his M.Sc. in 1966, Ph.D. in 1969, and D.Sc. in 1982. He has also been awarded a Diploma in Applied Chemistry from Tokyo Institute of Technology in 1973. Prof. Elnagdi has been professor of organic chemistry at Cairo University since 1980. He worked as professor of organic chemistry at Kuwait University from 1993 to 1999, then as visiting professor at the same university in 2003. Prof. Elnagdi has received fellowships from several institutions, including NTNF Norway taken at University of Oslon (1977); Visiting Associate Professor at the University of Utah in 1976 with Prof. L. B. Townsend; Alexander von Humboldt Fellowship at the University of Bonn with Profs. H. Wamhoff and R. Regitz. The Alexander von Humboldt Foundation has continually supported his activities in Germany, enabling him to cooperate with many German colleagues including Profs. K. Hafner, K. S. Hartki, M. Hoffmann, and H. H. Otto. Prof. Elnagdi has specialized in the synthesis of polyfunctional heterocycles and has published around 350 papers in this area as well as 15 review articles. In addition, he got several national and regional research awards and published several books.



Prof. Ghozlan is now Professor of organic chemistry in the Chemistry Department, Faculty of Science, Cairo University. He graduated with B.Sc. degree from the same university in 1974. He received his M.Sc. and Ph.D. degrees in 1977 and 1980, respectively, from Cairo University under supervision of Prof. M. H. Elnagdi. Prof. Ghozlan published more than 44 research papers in the area of heterocyclic chemistry.



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