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REVIEW

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Recent developments in chemical reactivity of *N,N*-dimethylenamino ketones as synthons for various heterocycles

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The current review presents recent progress in the utility of *N,N*-dimethyl enaminones as building blocks for a diverse range of acyclic, carbocyclic, five- and six-membered heterocyclic a broad range of heterocyclic and fused heterocyclic derivatives. Most importantly, these *N,N*-dimethyl analogues have proven to be of biological interest and provide an access to new class of biologically active heterocyclic compounds for biomedical applications. All of these topics are drawn from the recent literature till 2016.

1. Introduction

β-Aminovinyl ketones are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones. As can be rationalized, these systems have "enamine" character, and can act as building blocks for the synthesis of various heterocycles such as pyridine, pyrimidine, and pyrrole derivatives.[1] In addition, they also have "enone" character, and may act as acceptors in both 1,2- and 1,4-additions. In this way, β-aminovinyl ketones serve as scaffolds for annulation, and can provide access to systems such as pyrroles, indolizidines, quinolizidines, and perhydroindoles, all of which are common motifs in alkaloid structures.[1,2]

N,N-Dimethyl derivatives of β-aminovinyl ketones are chemical compounds consisting of an amino group linked through a carbon–carbon double bond to a keto group.[6] They are typical push–pull ethylenes in which the amine group pushes and the carbonyl pulls electron density. The chemistry of the enamino carbonyl group (1) is potentially an area of considerable scope when one considers that there are present in this moiety two electron-deficient centres (*i.e.* two electrophilic sites) at C-1 and C-3, while the C-2, carbonyl oxygen and amino functions are electron

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Hatem Moustafa Gaber was born in November 1969 in Menoufia and obtained his education in Cairo, Egypt. He graduated with B.Sc. degree in chemistry from Helwan University, Cairo in 1991 with general grade of "Very Good". After getting his M.Sc. degree in organic chemistry in 1995, he had a permanent position as a Senior Research Assistant at the National Organization for Drug Control and Research (NODCAR) in Cairo. He earned a Ph.D. degree in organic chemistry from Cairo University in 1999. He was promoted to the rank of a Researcher in organic chemistry in 1999 and an Associate Professor in 2006, before taking up his current position as a Professor of organic chemistry at NODCAR in 2011. Also, he was awarded three Postdoctoral Research Fellowships from several institutions, including an Egyptian Government Scholarship in the USA, working as a Visiting Fellow with Professor Dr C. Parkanyi at Florida Atlantic University in Florida to do research in the area of open-chain nucleoside chemistry with a grant from the General Egyptian Administration for Scholarships in Egypt (2001–2002); then a World Laboratory Scholarship in Denmark taken at Nucleic Acid Center at the University of Southern Denmark in Odense for the period of one year (2003–2004) under the direction of Professor Dr E. Pedersen in the field of nucleotide/oligonucleotide chemistry with support from ICSC–World Laboratory grant in Switzerland; moreover, a Research Fellowship in the UK at Cardiff University in Cardiff for the period of three years (2009–2009), working with Professor Dr M. Bagley on synthetic approaches towards new anti-cancer and antibiotic agents in addition to the synthesis and properties of anticonvulsant enaminones. In 2012, Dr Gaber was appointed Head of the Organic Chemistry Department at NODCAR, then Head of the General Pharmaceutical Chemistry Division (Dean) in 2014. His research interests include heterocyclic and medicinal chemistry with emphasis on the design and synthesis of novel bioactive heterocycles and the study of their biomedical applications with the aim of developing new therapeutic agents.

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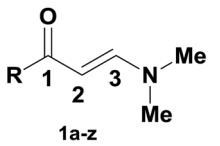
rich (*i.e.* three nucleophilic sites) (Fig. 1).[3,4] They can thus function both as nucleophiles and as electrophiles, their versatility in either case being extended by their ability to show ambident reactivity.[2] Accordingly, these β-acyl enamines proved to be suitable for a number of further synthetic transformations, mainly; hydrolysis to diones, reduction and condensation to fused heterocycles.

A few review articles, describing the chemistry of β-aminovinyl ketones, have appeared in the literature,[1,3,5,6] although hitherto with little emphasis on the reactivity of the corresponding *N*,*N*-dimethyl derivatives of β-aminovinyl ketones. Since a large number of developments in the use of these *N*,*N*-dimethyl derivatives in heterocyclic and medicinal chemistry have been reported recently, and in conjunction with our long-term continuing interest in exploring the synthetic applications of biologically active enamino compounds,[7–19] the current review presents firstly recent progress in the utility of *N*,*N*-dimethyl enaminones as building blocks for a diverse range of acyclic, carbocyclic, five- and six-membered heterocyclic as well as condensed heterocyclic compounds, with particular emphasis on the useful chemical transformations of this class of *N*,*N*-disubstituted enaminones to the structurally related α-(arylhydrazono)-β-ketoaldehydes. Structural investigation for these aldehydes and some of other products has also been made. This is finally followed by a consideration of the ever-increasing chemotherapeutic potentials of these *N*,*N*-dimethyl derivatives and their biomedical applications as valuable synthons on the way to a variety of bioactive heterocyclic compounds. All of these topics are drawn from the recent literature till 2016.



1a-z

1	R	1	R
a	Me	n	1-naphthyl
b	Et	o	2-naphthyl
c	t-Bu	p	2-thienyl
d	Ph	q	2-furyl
e	4-MeC_6H_4	r	2-pyrrolyl
f	4-$MeOC_6H_4$	s	2-pyridinyl
g	4-ClC_6H_4	t	4-pyridinyl
h	4-$NO_2C_6H_4$	u	3-pyridinyl
i	3-$NO_2C_6H_4$	v	2-piprazinyl
j	2-$NO_2C_6H_4$	x	2-pyrazolyl
k	2-OHC_6H_4	y	3-pyranyl
l	4-BrC_6H_4	z	3-coumainyl
m	4-$MeCOC_6H_4$		

Fig. 1 General formula of *N*,*N*-dimethyl enaminone derivatives.

Mark C. Bagley was educated at the University of Oxford (BA 1991; DPhil 1994 with Prof. L M Harwood), with post-doctoral studies at the Université de Genève (with Prof. W Oppolzer), Loughborough and Exeter (with Prof. C J Moody), before being appointed as a Lecturer in Organic Chemistry at Cardiff University in 1999. He stayed at Cardiff for 13 years, being promoted to a Senior lectureship in Organic Chemistry in 2004 and a Reader in 2006, before taking up his current position as Professor of Organic Chemistry at the University of Sussex in February 2012.

Zeinab A. Muhammad was born in Cairo, Egypt. She graduated from B.Sc, then she carried out his M.Sc. and Ph.D. studies in 2012 and 2015, respectively in the field of organic synthesis. Work at National Organization for Drug Control and Research (NODCAR), P.O. Box 29, Cairo, Egypt. She joined the scientific school of Prof. A. S. Shawali in 2009 and she has published scientific papers and reviews all in international journals in the fields of physical organic chemistry, chemistry of hydrazonoyl halides and bioactive heterocyclic chemistry.

2. Synthetic applications of *N*,*N*-dimethylenamino ketones

2.1. Preparation of acyclic compounds

2.1.1. Preparation of α-(arylhydrazono)-β-ketoaldehydes. One of the main route to α-(arylhydrazono)-β-ketoaldehydes is the coupling of arenediazonium salts with aminovinyl ketones.[20–23] However, anomalous behavior has been reported

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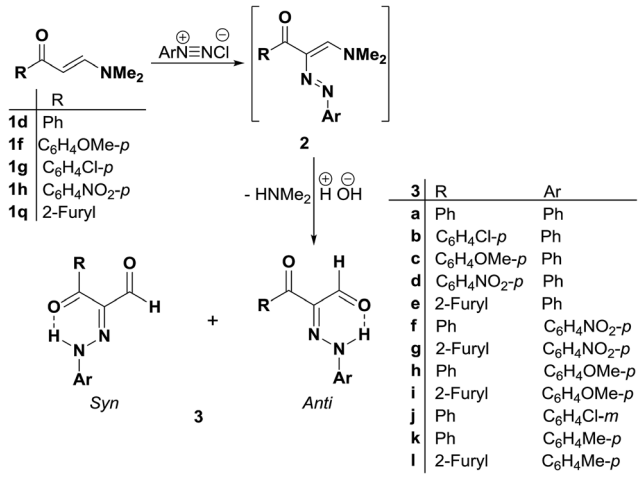
for reactions of cyclic aminovinyl ketones and aminovinyl esters with arenediazonium salts.[24,25] The structure and chemistry of these β-ketoaldehydes has attracted much attention with plenty of uses for these compounds, in heterocyclic synthesis, being reported recently.[26–31] It has been noted that in DMSO these molecules exist as a mixture of two conformers *E* and *Z*.[22,27,28]

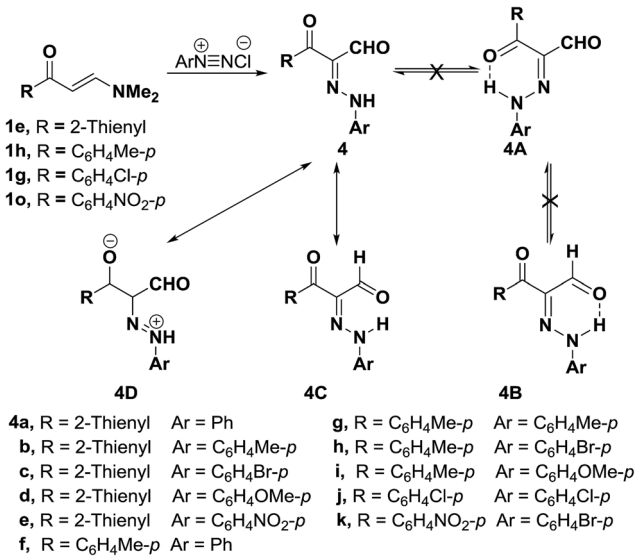
Coupling[21,22,32–34] of diazotized aromatic amines with the aminovinyl ketones **1d,f,g,h** and **1q** resulted in products of coupling and hydrolysis of the dimethylamine moiety. These products were shown, based on ^{1}H NMR and ^{13}C NMR, to exist as a mixture of *anti* and *syn* hydrazones with the *anti* form always prevailing.[22] It is assumed that initially formed arylazo intermediates **2a–k** are hydrolyzed, by the action of the aqueous base existing in the medium, into the arylhydrazonoaldehydes **3a–k** (Scheme 1).

In addition, 3-(thiophen-2-yl)- or 3-aryl-propionaldehydes **4a–k** were prepared *via* coupling of aminovinyl ketones **1p** and **1e,g,h** with aromatic diazonium salts.[28] It is believed that assumed fixation of hydrazones by hydrogen bonding in DMSO solution is least likely although it was observed in almost every case of aroyl derivatives the presence of two NH signals integrating for a total of one proton with varying intensity in each case depending upon the nature of the substituent at the carbonyl moiety (Scheme 2). This may point to the existence of an equilibrium between the two forms **4C** and **4D** in DMSO solution.[28]

Furthermore, it was found that diazotized anthranilonitrile (**5a**) or diazotized methyl anthranilate (**5b**) couples readily with the aminovinyl ketones **1a**, **1d**, **1p–s** to yield products of coupling and hydrolysis of dimethylamino moiety. The coupling products can thus be formulated as the hydrazone forms **8A,B** or potential tautomeric enol azo forms **7,8C** or a mixture of one or more of these forms. The hydrazone structure **8A,B** was established for all these products and the *E*-form **8A** is believed to be the predominant form except for the product of coupling 1-methyl-3-dimethylaminoprop-2-enone (**1a**) with diazotized anthranilonitrile (**5a**) (Scheme 3). ^{1}H NMR of this product show that it exists in DMSO as an equilibrium mixture of *E*-form **8A**, *Z*-form **8B** and the enol azo form **8C**, as ^{1}H NMR revealed three signals for a total of one proton, and it is



Scheme 1



Scheme 2

interesting to note that the *E*-form was the major constituent in this equilibrium mixture (70%). All these forms are stabilized by hydrogen bonding.[27,35]

Similarly, coupling of aminovinyl ketones either **1d,p** with benzonitrile diazonium chloride (**9**), following recently reported procedure,[21] produced the corresponding acyclic β-ketoaldehydes **10a,b** (Scheme 4).[36]

Also, 3-oxo-2-(arylhydrazono)pentanal **11a–h** were obtained in 50–80% yields *via* coupling *N*,*N*-dimethyl enaminones either **1b** or **1m** with aromatic diazonium salts. ^{1}H NMR of the products indicated that they exist at least in DMSO solution as mixtures of the *anti*-form **11** and *syn*-form **12** (Scheme 5). The *anti*-from generally predominated.[29]

The diazotized 2-aminocyclohexenethiophene (**13**) coupled readily with *N*,*N*-dimethylenamino ketones **1a,d,p–r** to yield the corresponding hydrazonopropanals **14a–e**, respectively (Scheme 6).[27]

It has been found that 5-methylisoxazole-3-diazonium chloride (**15a**) coupled readily with β-acyl enamines **1q,u** to produce the expected β-ketoaldehydes **16a,b**.[33] However, a similar treatment of ketoenamines **1d** and **1q** resulted in the cyclization into pyrazolo[5,1-*c*][1,2,4]triazines **18a,b** *via* the assumed intermediacy of acyclic aldehydes **17a,b** (Scheme 7).[33]

Elnagdi *et al.*[37] reported on the reaction of 1-dimethylamino-5-arylpenta-1,4-diene-3-one **19a–c** with diazonium ions in aqueous ethanol, where the dimethylamino group was substituted by the hydroxyl group and thus the corresponding 5-aryl-2-arylhydrazono-3-oxopent-4-enals **20a–c** were isolated. Compounds **20a–c** were presumably formed by hydrolysis of the enamine primary products. The ^{1}H NMR indicated the presence of a mixture of both *E* and *Z* forms of these pentenals in approximately equivalent ratios (Scheme 8).[37]

Also, enaminophthalimidoacetone derivative **21** readily underwent coupling with aromatic diazonium salts in the presence of sodium hydroxide to yield the analogous aldehydes **22a–d** in acceptable yields (Scheme 9).[38]

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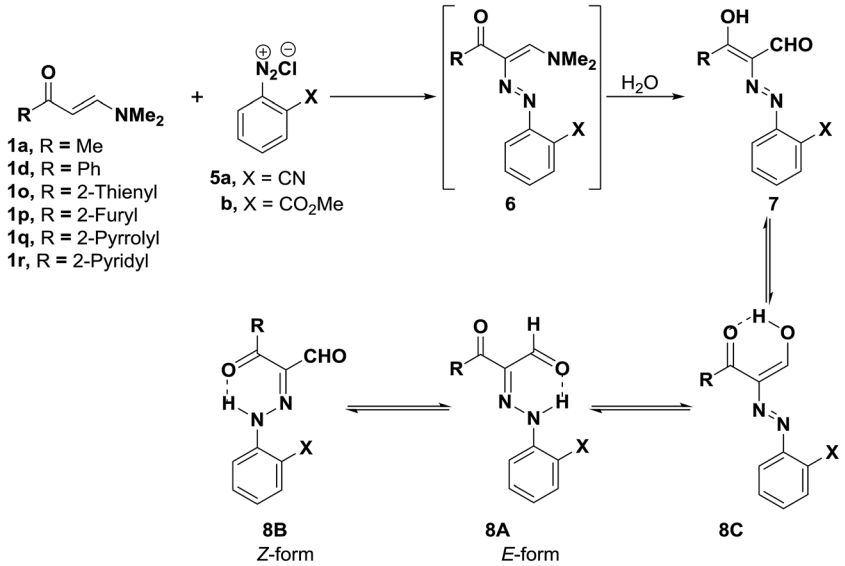
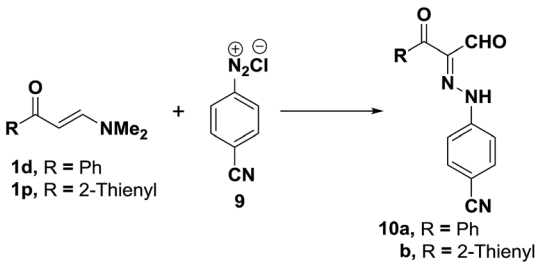


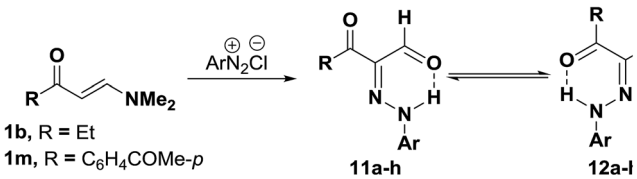
8a, R = Me	X = CN	**h**, R = Ph	X = CO_2Me
b, R = Me	X = CO_2Me	**i**, R = C_6H_4Cl-*p*	X = CO_2Me
c, R = Ph	X = CN	**j**, R = 2-Thienyl	X = CO_2Me
d, R = 2-Thienyl	X = CN	**k**, R = 2-Furyl	X = CO_2Me
e, R = 2-Furyl	X = CN	**l**, R = 2-Pyrrolyl	X = CO_2Me
f, R = 2-Pyrrolyl	X = CN	**m**, R = 2-Pyridyl	X = CO_2Me
g, R = 2-Pyridyl	X = CN		

Scheme 3



Scheme 4

Compounds **24a,b** were obtained in the same way as aldehydes **22** where the *N*,*N*-dimethylenamino ketone **21** coupled with heterocyclic diazonium salts **23a,b** to give rise to the corresponding hydrazones **24a,b** in good yields (Scheme 10).[38]



11,12a, R = Et; Ar = Ph	**e**, R = C_6H_4COMe-*p*; Ar = Ph
b, R = Et; Ar = C_6H_4Me-*p*	**f**, R = C_6H_4COMe-*p*; Ar = C_6H_4
c, R = Et; Ar = $C_6H_4NO_2$-*p*	**g**, R = C_6H_4COMe-*p*; Ar = C_6H_4
d, R = Et; Ar = C_6H_4OMe-*p*	**h**, R = C_6H_4COMe-*p*; Ar = C_6H_4

Scheme 5

As recently reported by our research group,[7] pyrazole enaminone derivative **1v** also coupled with *p*-chlorobenzenediazonium chloride to provide the pyrazoloylhydrazone derivative **25**, in 82% yield (Scheme 11).

Trials to couple enaminone of the coumarin **1z** with benzenediazonium chloride failed. However, *p*-nitrobenzenediazonium chloride coupled readily with **1z** to yield the respective arylhydrazonopropanals that proved to exist as an equilibrium mixture of the *anti*-form **26A** and the *syn*-form **26B** (Scheme 12).[25]

An interesting synthesis of arylhydrazonals is the formation of **27a–e**[39] on coupling of enaminal **27a** or enaminoester **27b** with various aromatic diazonium salts. Compounds **28a–e** were assigned the indicated hydrazone structure in preference to a potentially tautomeric enolazo structure. This assignment is based on ^{1}H NMR and ^{13}C NMR spectra which revealed signals for two formyl protons and carbons in **28a–d** and one such signal in the spectra of **28e** (Scheme 13).[40]

On the other hand, when dimethylaminomethylene derivative **29** was coupled with benzenediazonium chloride, the phenylhydrazone **32** was formed. It is believed that, as a result of nitrogen lone pair donation to enamine β-carbon, the latter becomes sufficiently nucleophilic and intermediate diazonium salt **30** is initially formed. This then readily hydrolyses into the azo derivative **31** that then undergoes Japp–Klingemann cleavage to yield the final isolated product **32** (Scheme 14).[41]

2.1.2. Preparation of *N*-monosubstituted enaminones and related compounds. Dimethylaminomethylidene derivatives **1d** and **1q** reacted with aniline in ethanol at reflux for three hours to yield products of addition and dimethylamine elimination.

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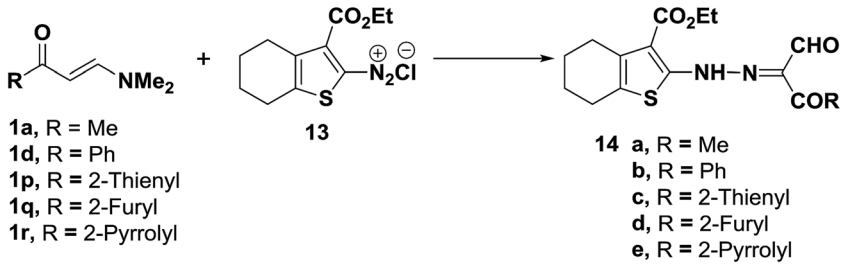
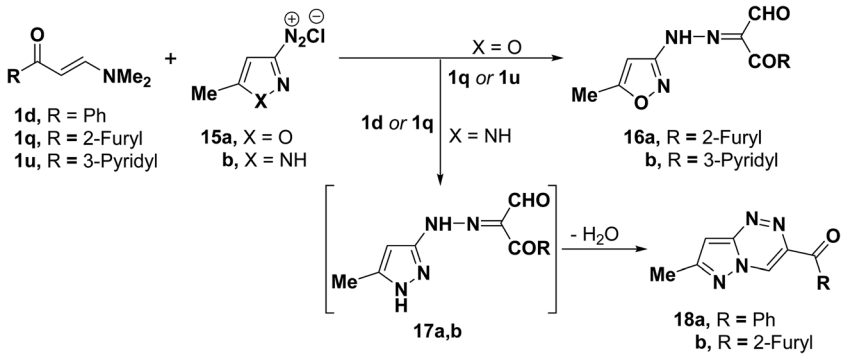
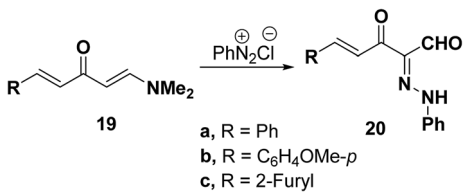


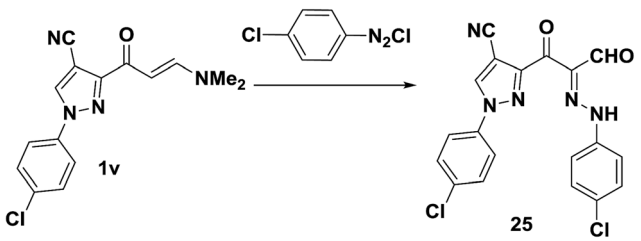
Scheme 6



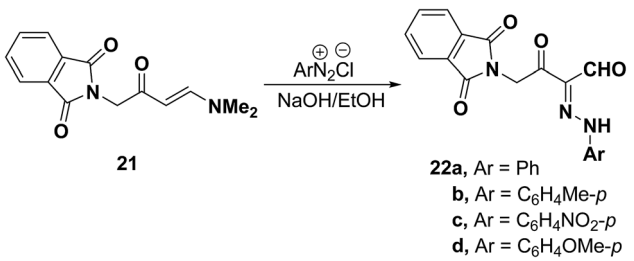
Scheme 7



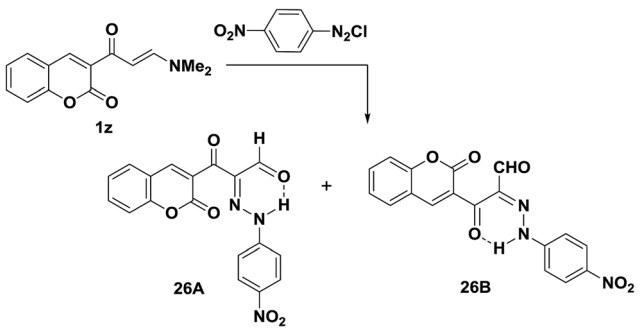
Scheme 8



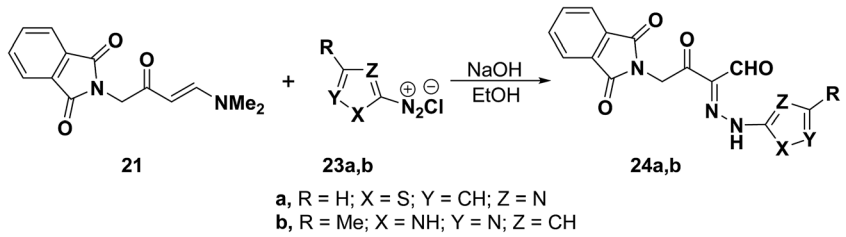
Scheme 11



Scheme 9



Scheme 12



Scheme 10

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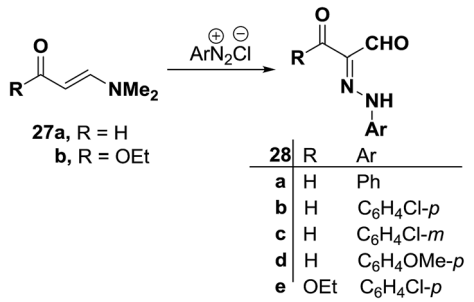
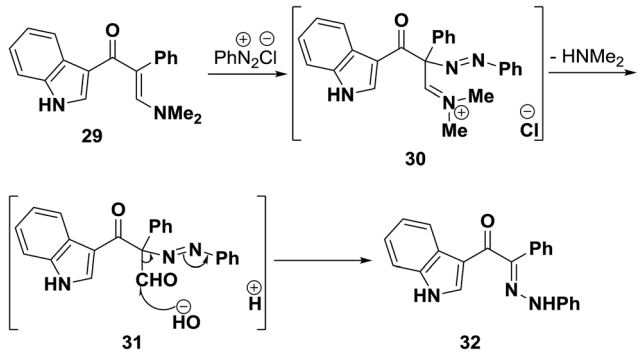


Scheme 13



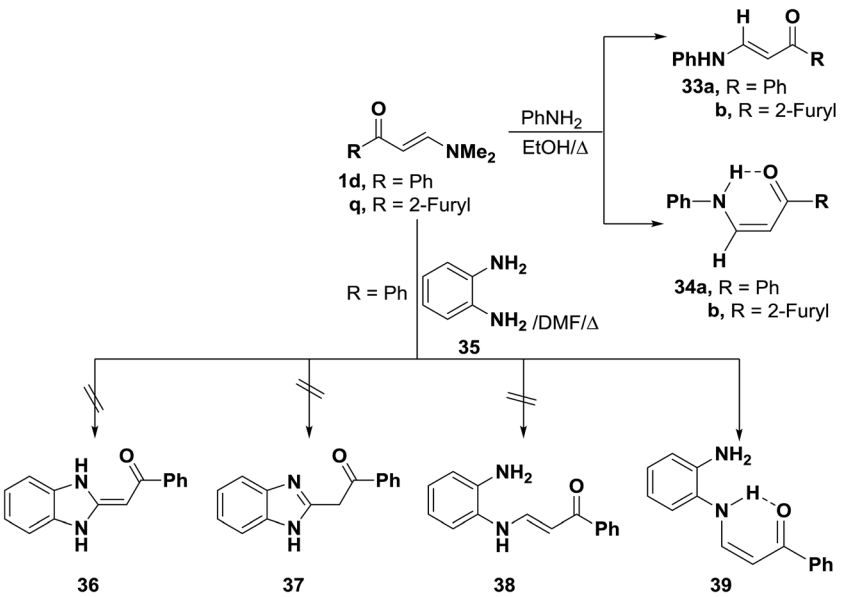
Scheme 14

The formed anilino derivatives proved to be *cis* products **34a,b** and the *trans*-form **33a,b** was completely excluded, since olefinic protons appeared, in each case, as a doublet with $J = 7$ Hz typical for such *cis* olefinic protons. The predominance of the *cis*-form is attributed to fixation through hydrogen bonding.[42] On the other hand, compound **1d** reacted with *o*-phenylenediamine (**35**) to afford a product that may be formulated as *cis* enaminone **39a** or stereoisomeric **38** or cyclic products **36** or **37**. Structure **39a** was established through ^{1}H NMR and ^{13}C NMR spectra (Scheme 15).[42,43]

In accordance with the previous observation,[42] β-aminovinyl ketones **1e,f** reacted with *o*-phenylenediamine (**36**) to afford products of condensation *via* dimethylamine elimination. These were assigned *cis* structure **41** rather than *trans* structure **40** based on ^{1}H NMR, which revealed signals for *cis* olefinic protons in their proper positions with $J = 9$ Hz. The predominance of this form may be due to fixation by hydrogen bonding.[43] In contrast to this observation, it has been found that a similar treatment of ketones **1d–f** with benzotriazole (**42**), instead of *o*-phenylenediamine (**36**), led to the formation of *trans* enaminones **43**, which were also obtained from the diazotization of *cis* enaminones **41** with sodium nitrite in acetic acid under stirring at room temperature (Scheme 16).[43]

On the other hand, tertiary enaminone **1y** reacted with methylamine, ethylamine and aniline in acetic acid under stirring at room temperature to yield the corresponding secondary enaminones, which were found to exist, in each case, as a mixture of the *E*- and *Z*-forms **44a–c** and **45a–c**. The existence of *Z*-form for these compounds is in contrast to the observed predominance of *E*-form for the starting **1y**. This is attributed to the stabilization of *Z*-form for those compounds through hydrogen bonding.[44] Interestingly, when compound **1y** was similarly treated with 2-aminothiazole (**46**) in acetic acid under stirring for three hours at room temperature, only the acyclic *Z*-enaminone **47** was formed in exclusively based on considering *J* value for olefinic protons ($J = 9$ Hz). While bicyclic pyridine derivative **48** was isolated upon heating of **1y** with **46** under reflux in acetic acid for two hours (Scheme 17).[44]

Tertiary amines **49a,b** were converted into the corresponding secondary amines **50a,b** when heated at reflux with equivalent amount of aniline in ethanol for two hours in yields of 53% and 37%, respectively.[45] Also, it has been found that a much better



Scheme 15

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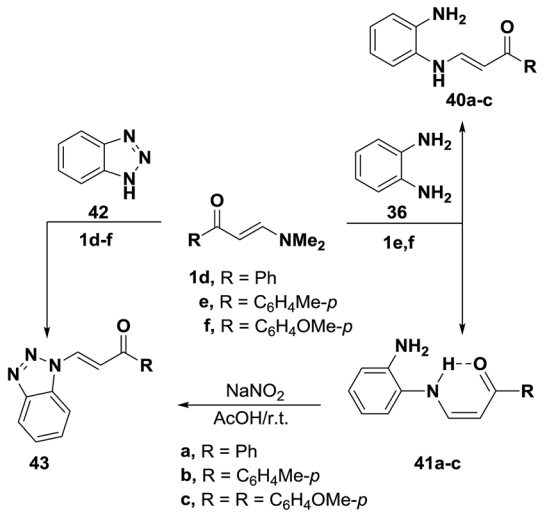
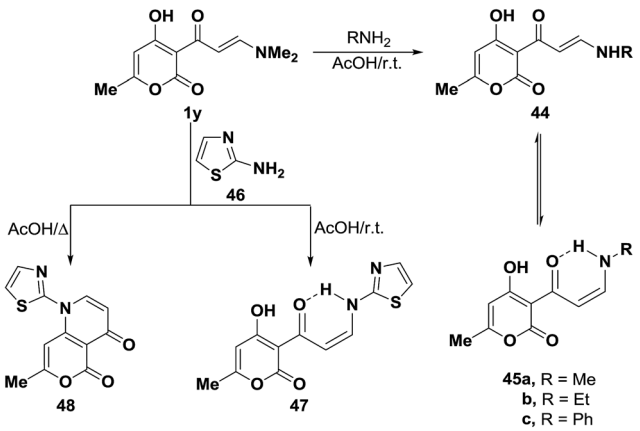
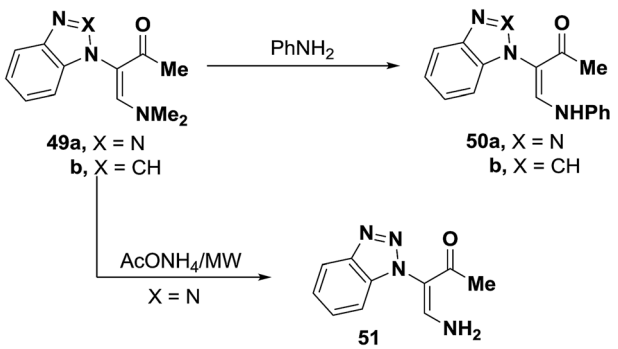


Scheme 16

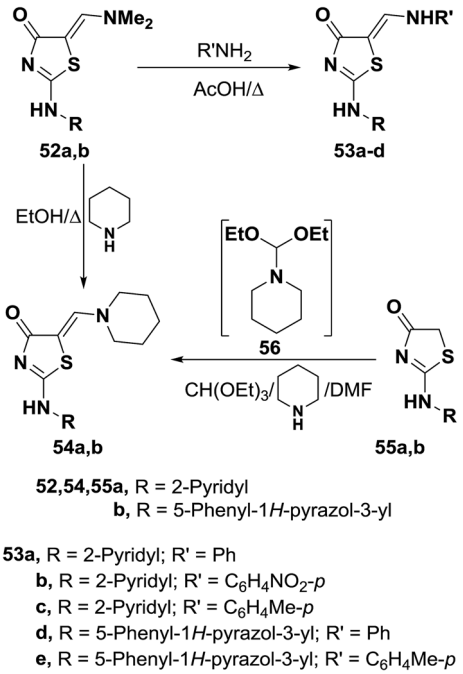


Scheme 17

yield (71%) of product **50a** could be obtained on microwave heating of **49** with equimolar amount of aniline in a domestic microwave oven at full power for two minutes.[45] On the other hand, microwave heating of **49** with ammonium acetate for two minutes in a domestic microwave oven at full power produced the primary amine **51** in yield of 91%. The authors[46] failed to



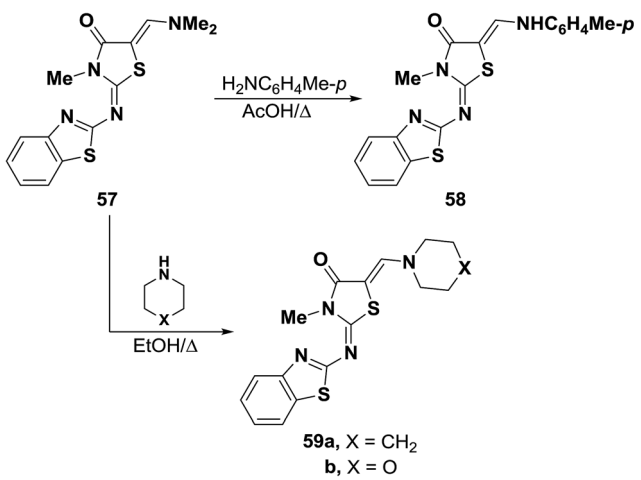
Scheme 18



Scheme 19

obtain **51** by conventional heating with ammonium acetate in acetic acid (Scheme 18).

Dimethylaminomethylene thiazolones **52a,b** reacted with equivalent amounts of aromatic amines with reflux in acetic acid for one hour to yield the corresponding secondary amines **53a–e**, respectively.[47] Similar treatment with piperidine in refluxing ethanol for seven hours afforded the piperidino derivatives **54a,b**, which were also obtained on reacting thiazolinones **55a,b** directly with triethyl orthoformate and piperidine in DMF.[47] Utilization of triethyl orthoformate and piperidine in DMF solution was found more economic and safer than using DMFDMA. It is believed that piperidine reacts with acetal forming non-isolable intermediate **56** which then condensed with **52** to give the final isolable products as depicted in Scheme 19.[47,48]



Scheme 20

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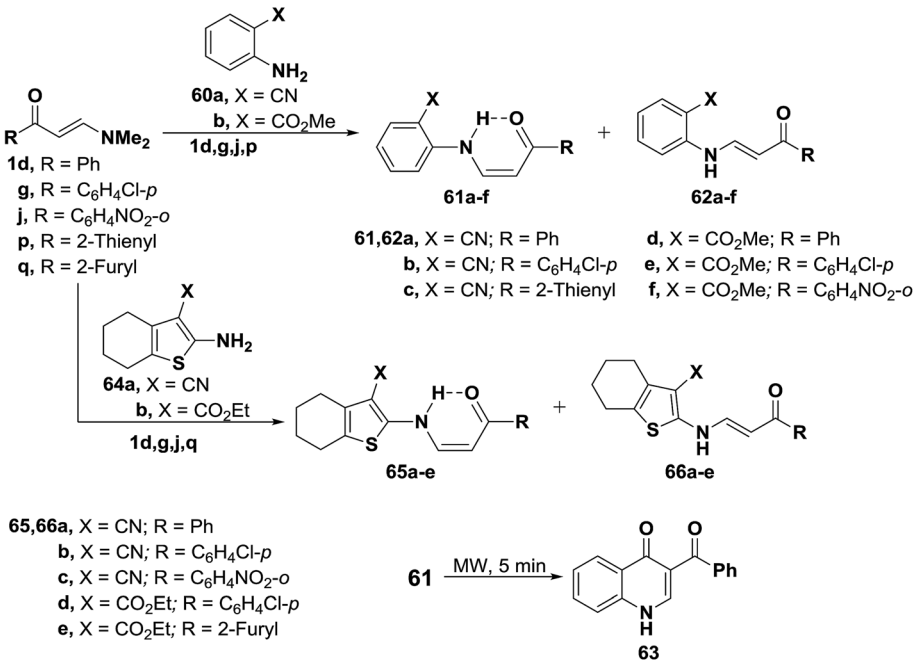
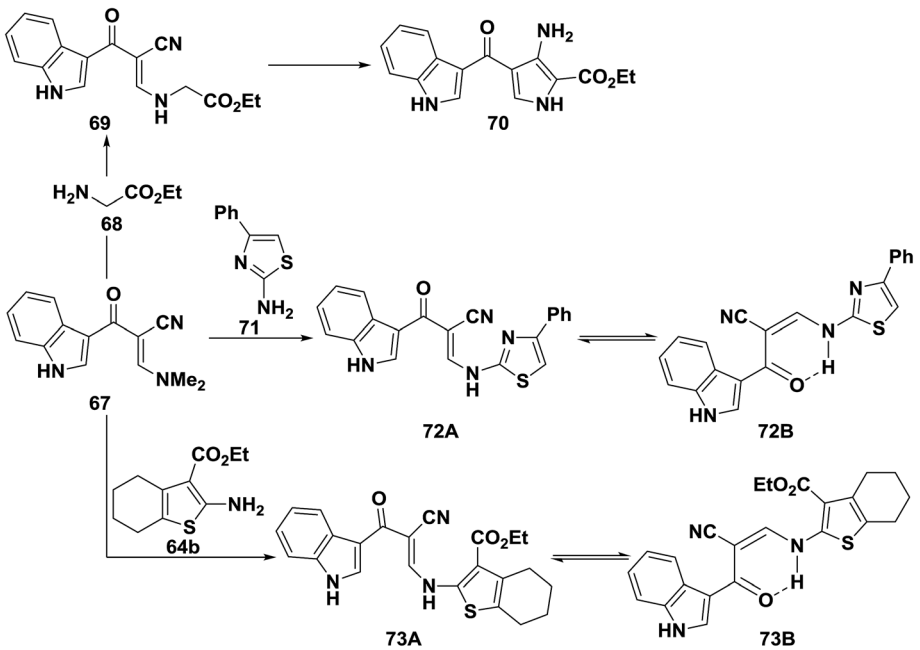


Scheme 21

Table 1 Relative concentration of *cis*- and *trans*-forms of enaminones **61**, **65** as indicated from ^{1}H NMR

Compounds	*cis*-Form	*trans*-Form
61b	7	1
61e	4	1
61f	4.2	1
65a	6.5	1
65c	6	1
65	4	1

Dimethylaminomethylene thiazolone **57** could be converted into the enamine **58** on treatment with *p*-toluidine in refluxing acetic acid for one hour.[47] Nucleophilic displacement of the active dimethylamino group of **57** by cycloaliphatic amines, in refluxing ethanol for seven hours, resulted in the formation of the corresponding derivatives of piperidino and morpholino **59a,b**, respectively. Structure **59b** was confirmed by X-ray crystal determination (Scheme 20).[47]



Scheme 22

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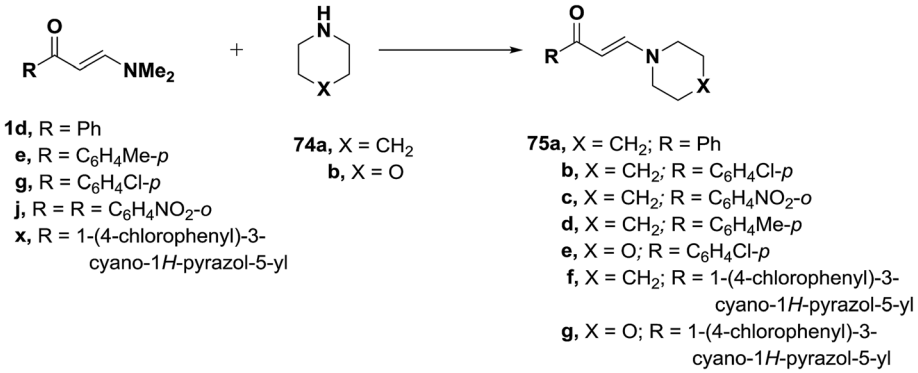
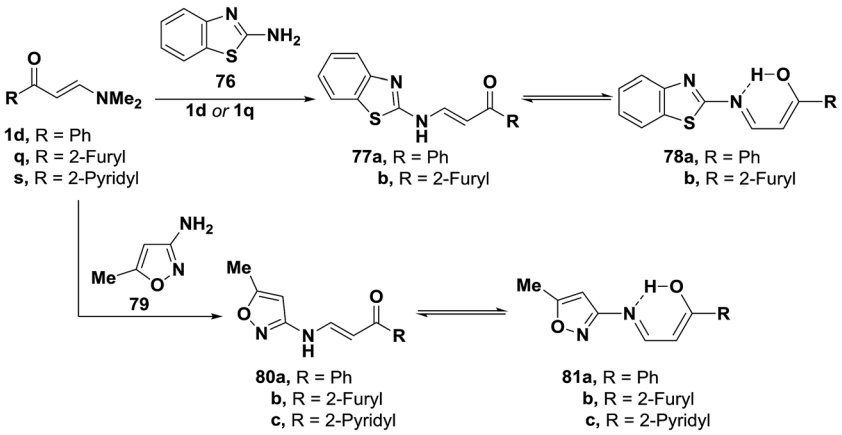


Scheme 23

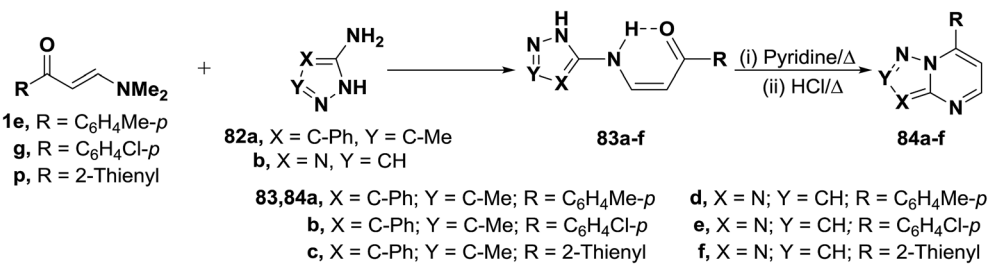


Scheme 24

In addition, interaction of dimethylaminomethylidenes **1d,g,j** and **1p** with anthranilonitrile (**60a**) or methylanthranilate (**60b**) yielded the *cis* enaminones **61a–f**, respectively (Scheme 21). Attempted cyclization of **61a–c** into the corresponding quinolines failed. Successful cyclization of **61d** into the quinolinone **63** could be affected, on heating for five minutes in domestic microwave oven at full power. When compounds **1d,g,j** and **1q** were similarly treated with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**64a**) or its 3-carboxylate derivative **64b**, the corresponding *cis* enaminones **65a–e** were obtained. Again, ^{1}H NMR indicated the predominance of the *cis*-form (*c.f.* Table 1).[49]

Reacting enaminonitrile **67** with ethyl glycinate **68** in ethanol/potassium carbonate solution yielded the analogous ethyl ester **69**, which could not be cyclized into the pyrrole derivative **70** under a variety of conditions.[41] Also, compound **67** reacted with aminothiazole derivative **71** and with aminothiophene derivative **64b** to afford the secondary amines **72B** and **73B**, respectively. Although **72B**, **73B** may also exist as **72A** or **73A**, the hydrogen bonded form **72B** and **73B** seems more stable (Scheme 22).[50]

On the other hand, when compounds **1d,e,g,j,x** were similarly treated with piperidine (**74a**), only the *E*-enaminones **75a–d**, respectively, were formed in exclusively as indicated from the coupling constant values for olefinic doublets. No trace of *Z*-form was observed in this reaction. Analogously, compounds **75f,g** were formed from the reaction of **1d,x** with morpholine (**74b**) (Scheme 23).[49,51–53]



Scheme 25

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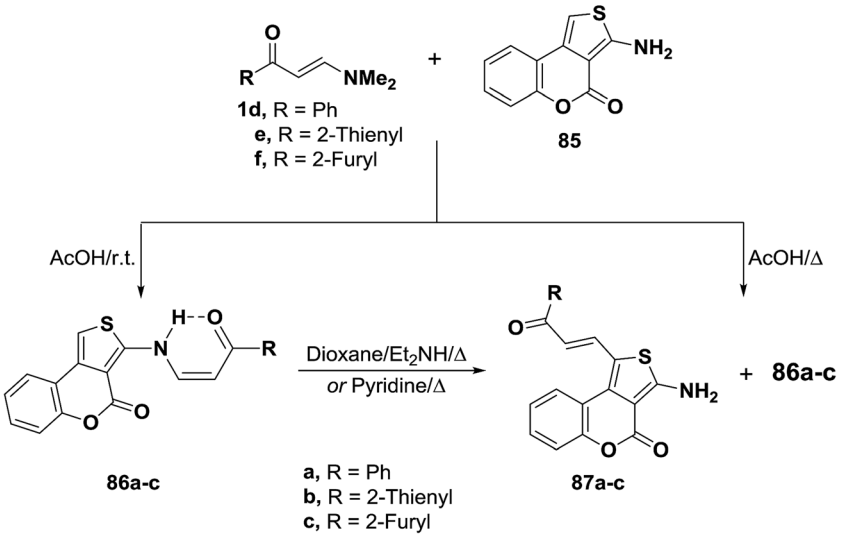
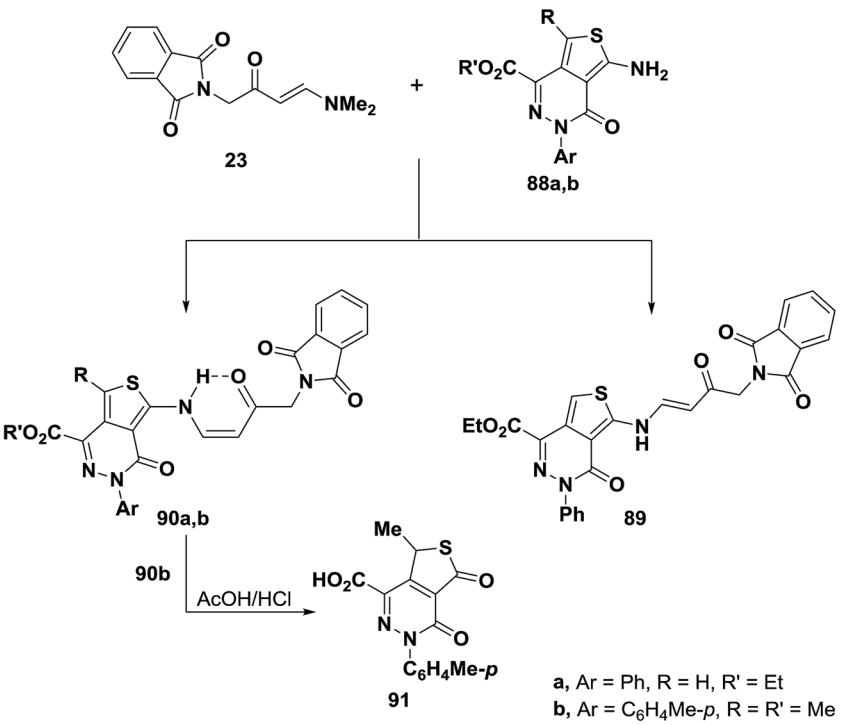


Scheme 26

Interaction of 2-aminobenzothiazole (**76**) with aminovinyl ketones **1d** and **1q** provided the heteroaromatic aminoenones **77a,b**. Similarly, compounds **1d** and **1q,s** were transformed to the corresponding acyclic aminoenones **80a–c** by treatment with 3-amino-5-methylisoxazole (**79**) (Scheme 24). These products **77a,b** and **80a–c** are believed to exist in equilibrium with enols **78a,b** and **81a–c**, which are stabilized through hydrogen bonding.[54]

N,*N*-Dimethylenamino ketones **1e,g** and **1p** reacted with aminopyrazoles **82a,b** to yield the acyclic enaminones **83a–f**. The structure of which proved to exist in the *cis*-form based on considering *J* values for olefinic protons ($J = 9$ Hz).[49] Compound **83a–f** readily cyclized into the bicyclic pyrimidines **84a–f** on reflux in pyridine solution in the presence of concentrated hydrochloric acid (Scheme 25).[49]

Treatment of *N*,*N*-dimethylamino derivatives **1d–f** with thienocoumarin **85** in acetic acid at room temperature furnished products of addition and dimethylamine elimination in 80–85% yields. IR and ^{1}H MNR spectra of these products indicated involvement of the amino function in this reaction. Therefore, structure **86a–c** was suggested for those products. On the other hand, when the reaction of **1d–f** with **85** was



Scheme 27

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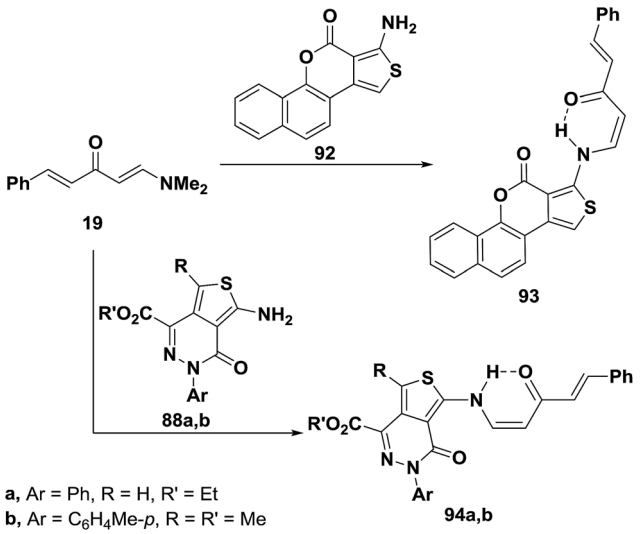
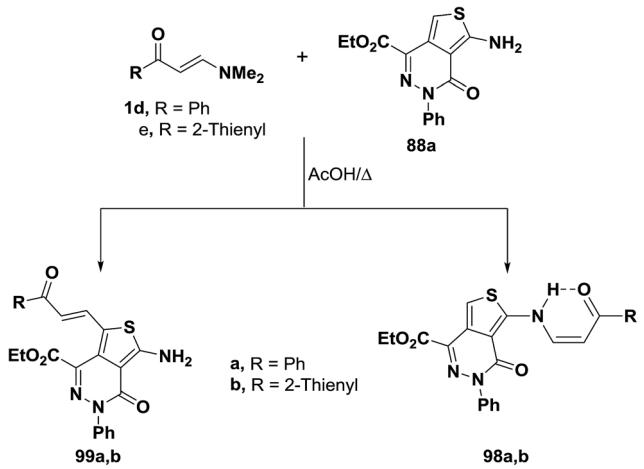


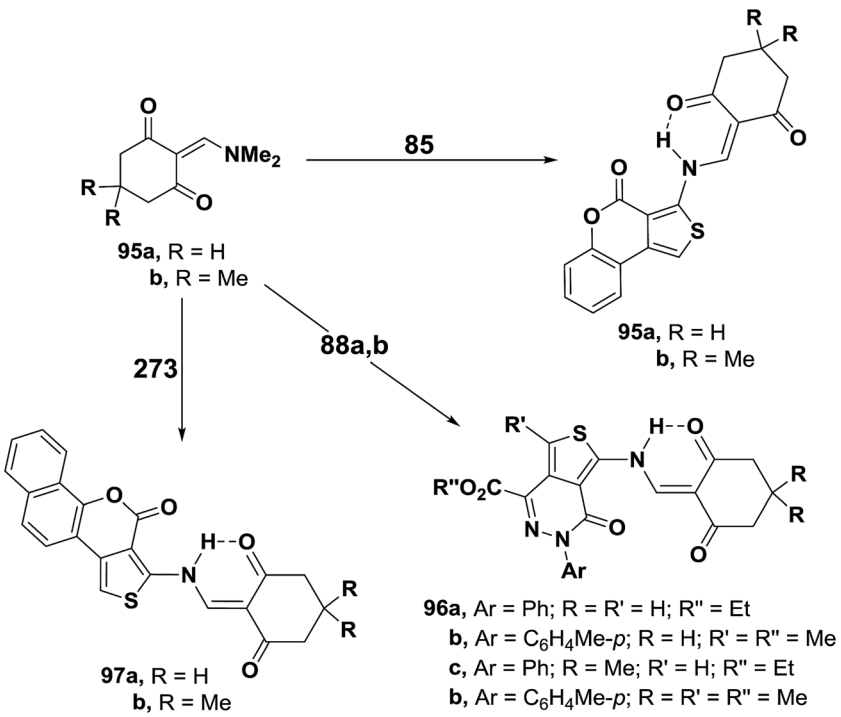
Scheme 28



Scheme 30

conducted in refluxing acetic acid, solid products **86a–c** were isolated by filtering the hot solution in 33–43% yields. When the mother liquor was left to stand at room temperature, the C-1 alkylation products **87a–c** were isolated in 32–36% yields. These products were found to be isomeric with **86a–c**. Both IR and ^{1}H NMR indicated that the amino function was not involved into the reaction.[53] Compounds **86a–c** rearranged into the corresponding α,β-unsaturated ketones **87a–c** on prolonged boiling under reflux in dioxane solution in the presence of diethylamine or in pyridine in 60–70% yields. Better conversion yields could not be achieved under a variety of conditions. It is thus believed that products **266** are kinetic products, while **71** are the thermodynamic ones. Conversion of **86** into **87** in basic media is believed to proceed *via* base addition across the double bond and elimination of **85**, thus allowing more of the thermodynamic product to be formed (Scheme 26).[55]

An interesting reaction leading to *cis*-enaminone is the condensation of aminothienopyridazines (**88a,b**) with aminovinyl ketone **23** to yield products of condensation *via* dimethylamine elimination for which structures **89** or **90** seemed possible. Structure **90** was established for those products based on the ^{1}H NMR and IR spectral data that revealed involvement of amino function in the reaction. Typical for secondary enaminone, compounds **90a,b** existed solely in *Z*-form as this



Scheme 29

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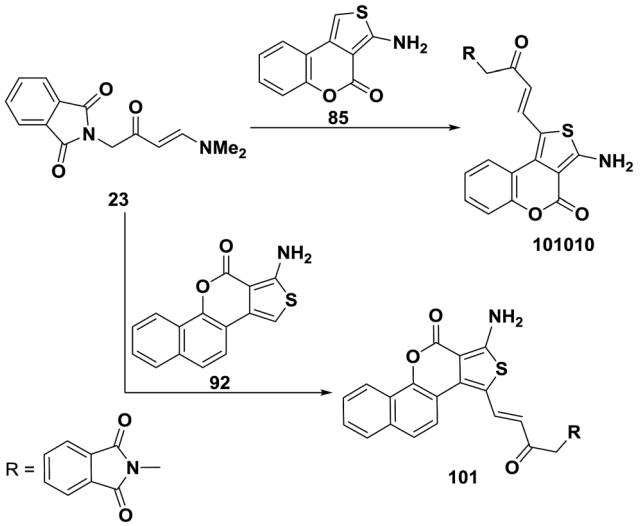
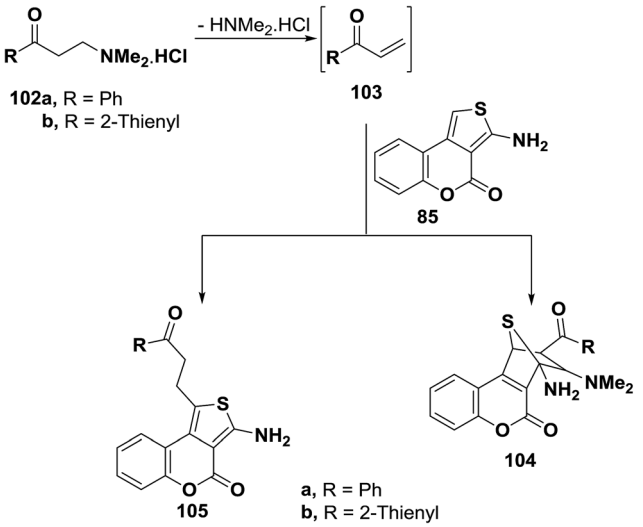
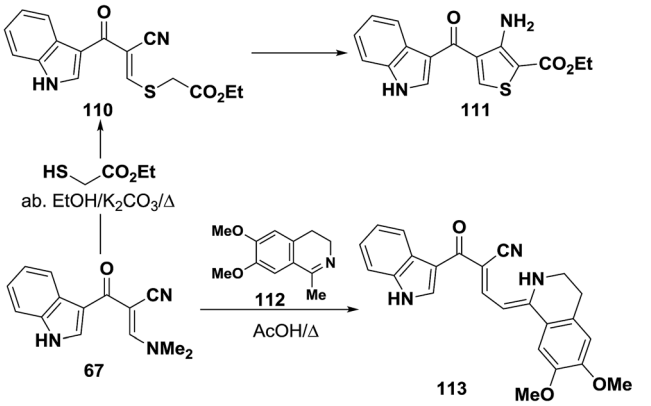


Scheme 31



Scheme 32



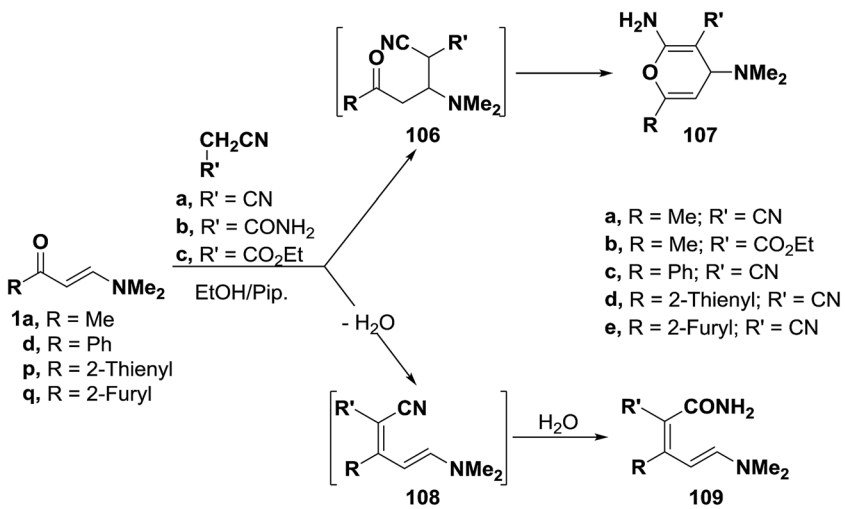
Scheme 34

form is fixed by hydrogen bond and this preferred over sterically and stereoelectronically fixed *E*-form.[54] Further confirmation of this structure assignment was obtained *via* successful conversion of **90b** into the thiophene **91** through hydrolysis of the alkylated amino moiety (Scheme 27).[56]

Dienone **19** underwent analogous reactions with aminothienopyridazines **88a,b** in a microwave oven at 560 W for 90 seconds to give rise to the expected *N*-alkylated products **92a,b**.[56] A similar treatment of **6a** with benzothienocoumarin **93** led to the corresponding enaminone **94** (Scheme 28).[56]

Aminothiophene derivatives **85**, **88a,b** and **93** reacted with the *N*,*N*-dimethylenamino ketones **95a,b** in a similar fashion yielding the corresponding secondary enaminones **95a,b**, **96a–d** and **97a,b** (Scheme 29).[56]

In contrast to the behavior of aminothiophene toward *N*,*N*-dimethylenamino ketones, interaction[55] of compounds **1d,e** with **88a** in acetic acid at reflux for three hours gave C-1 alkylation products **99a,b** instead of the *N*-alkylated derivatives **98a,b** that would be expected by analogy with the other reports[42,56] on the reactivity of nitrogen nucleophiles toward electron poor olefins (Scheme 30).



Scheme 33

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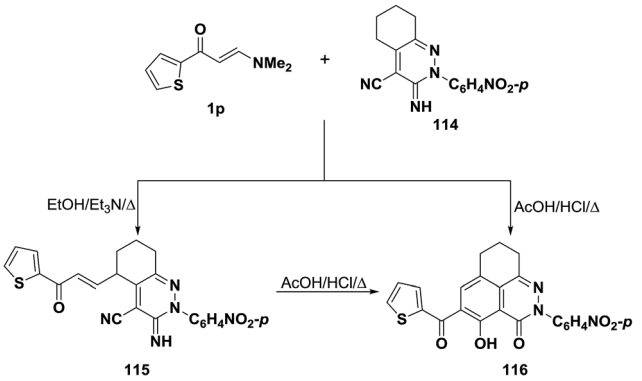
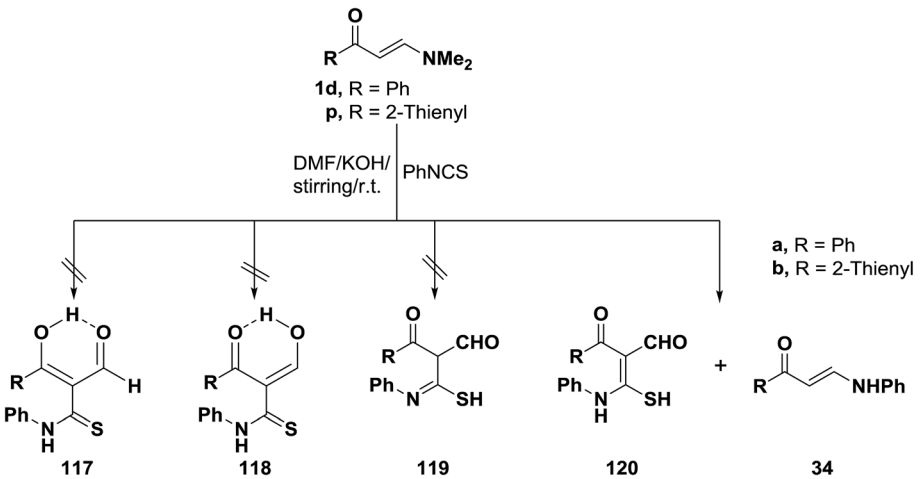


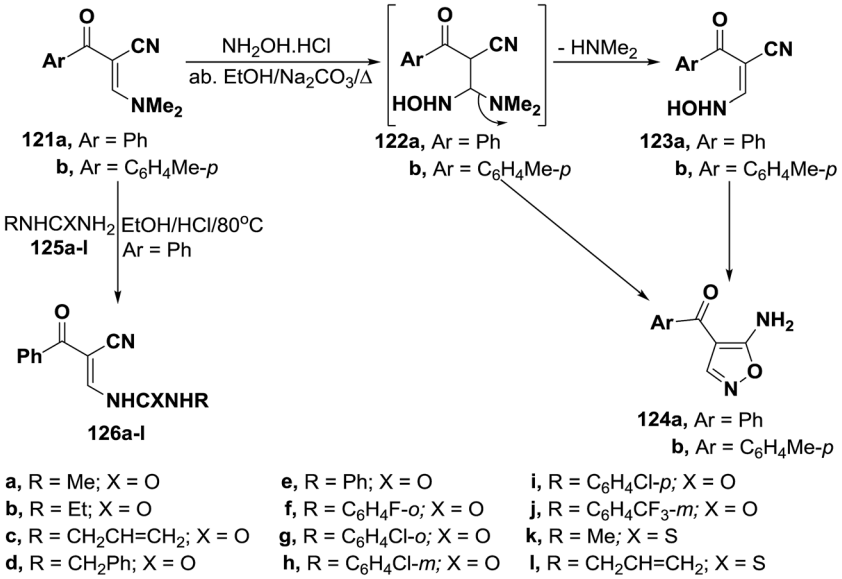
Scheme 35

Similar to the behavior of **73a** toward **1d,e** enaminoketone **23** reacted with thienocoumarin **85** under microwave heating in the presence of few drops of acetic acid to produce only the C-1 alkylation product **100**. This approach was also suitable for the preparation of another C-1 alkylation product **81**, where reaction of **23** with benzothienocoumarin **92** under the same reaction conditions led to the corresponding α,β-unsaturated ketone **101** (Scheme 31).[56]

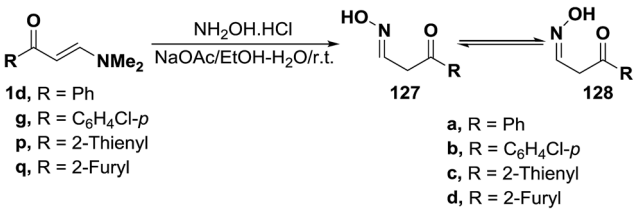
Also, compound **85** reacted with aryl vinyl ketones **103a,b**, generated *in situ* from corresponding dimethylaminopropanone hydrochlorides **102a,b**, in acetic acid/ethanol mixture at reflux for three hours to yield 1 : 1 adducts. These were stable on reflux in protic solvents and thus possible formation of cycloadducts similar to **104** was ruled out (Scheme 32). Moreover, ^{13}C NMR of the reaction products indicated presence of only two sp^3 carbons while in cycloadducts **104** four such carbons should have been



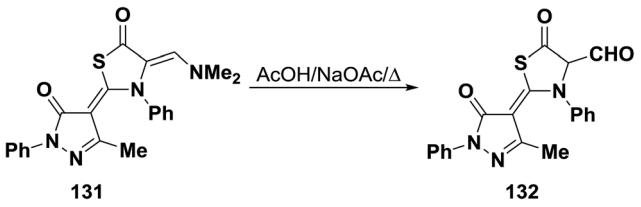
Scheme 36



Scheme 37



Scheme 38



Scheme 40

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observed. Therefore, the products for this reaction could be assigned structure **105**.[55]

It can thus be concluded that outcome of reactions of amines with electron poor olefins are dependent on nature of reagents used. Amino function, C-1 as well as the diene system are all possible sites of attack.[56]

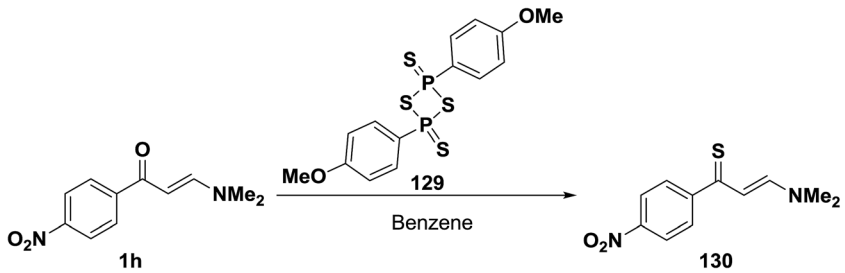
2.1.3. Miscellaneous. Aminovinyl ketones **1a**, **1d**, **1p,q** reacted with malononitrile or ethylcyanoacetate in ethanol and in the presence of a base, affording 1 : 1 adducts. These products could be formulated as pyran structure **107** or enamine structure **109**. However, structure **109** was assigned on the basis of ^{1}H NMR spectra, in which two olefinic doublets with a *J* value of 13 Hz were observed indicating that the *trans* olefinic moiety has not been involved in the reaction and hence this excluded completely the possibility of pyran structure **107** for this reaction products. Consequently, formation of **109** is assumed to occur *via* the addition of the active methylene reagents to carbonyl groups in **1a**, **1d** or **1p,q** and subsequent water elimination to furnish α,β-unsaturated nitriles **108**. Water eliminated in this process then hydrolyses the cyano group in the intermediates **108** affording the final isolated products **109**.[57,58] This structure was also confirmed by preparing the same reaction products **109c–e** *via* condensation of cyanoacetamide with **1d** or **1p,q** under the same reaction conditions (Scheme 33).[58]

Interaction of enaminonitrile **67b** with ethyl thioglycolate in ethanol/potassium carbonate solution yielded the ethyl ester **110**. Trials to effect cyclization of **110** into **111** under a variety of conditions failed. In protic medium **110** decomposed and in aprotic medium **100** was recovered unreacted (Scheme 34).[41] Moreover, compound **109** reacted also with 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**112**) in refluxing acetic acid to provide the respective dihydroisoquinolinylbutenenitrile derivative **113**. The authors[50] indicated that free donation around the single bond would allow for a *trans*-form that should in theory experience less steric interaction.

Also, interaction of enaminocarbonyl compound **1p** with pyridazine-3-imine derivative **114** in refluxing ethanol containing a few drops of triethylamine led to the acyclic compound **115** *via* loss of a dimethylamine molecule, while on being heated in a mixture of aqueous acetic acid and hydrochloric acid these afforded the tricyclic product **116** (Scheme 35). The latter could be also obtained *via* cyclization of α,β-unsaturated compound **115** into **116** on boiling in aqueous acetic acid/hydrochloric acid mixture.[59]

Interestingly, reaction of *N*,*N*-dimethylamino derivatives **1d** and **1p** with phenylisothiocyanate in DMF in the presence of potassium hydroxide afforded after acidification with hydrochloric acid two products, the major of which were found to be of molecular formulae corresponding to structure **120** or its tautomeric forms **117–119**. However, thiol structure **120** better agreed with the obtained spectral data for these compounds, thus thione structures **117** and **118** could be ruled out. Structure **119** was also excluded on the basis of ^{13}C NMR spectra of the isolated products, which revealed the absence of any sp^3-hybridized carbon atoms. These results strongly support structure **120** for the major products. The minor products for this reaction were assigned structure **34** based on the elemental analyses and spectral data of the isolated reaction products (Scheme 36).[60]

Unexpectedly, α-(dimethylamino)methylene-β-oxo nitriles **121a,b** reacted with hydroxylamine hydrochloride in absolute ethanol in the presence of anhydrous sodium carbonate under reflux to give the acyclic hydroxylaminopropenonitriles **123a,b**, in excellent yields, based on elemental analyses and spectral data of the isolated reaction products. It is of value to report here that all trials to convert compounds **123a,b** into the corresponding isoxazoles **124** were unsuccessful. This can be attributed to the fact that compounds **123a,b** are mainly existing in the *anti*-form as indicated from their ^{1}H NMR spectra.[61]



Scheme 39

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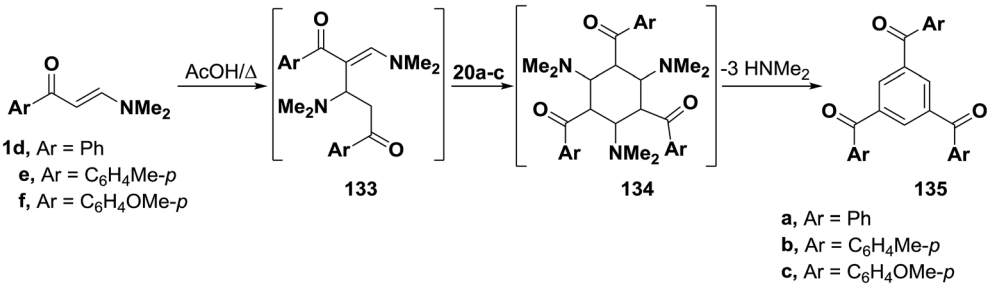
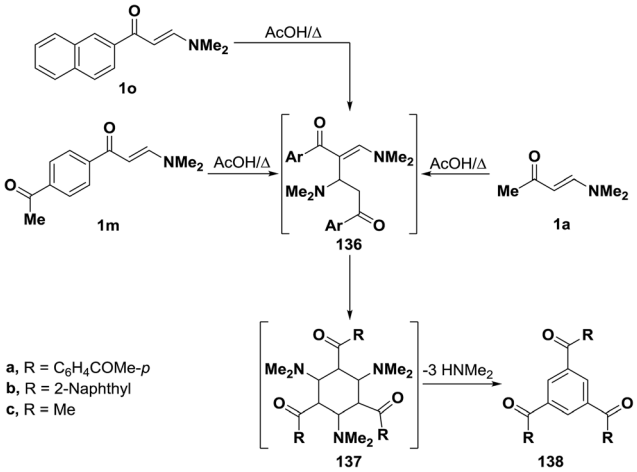


Scheme 41



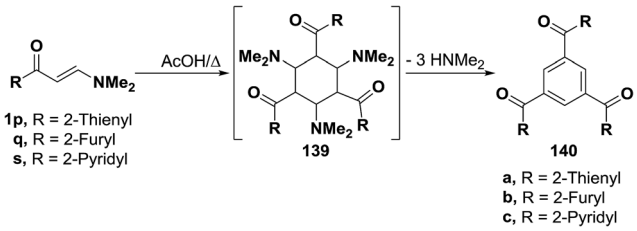
Scheme 42

On the other hand, reaction of 3-dimethylamino-2-benzoylpropenenitrile (**121a**) with *N*-substituted ureas or thioureas **125a–l** in acidic medium yielded ureidopropenenitriles **126a–l**, respectively (Scheme 37).[62]

Reacting enaminoketones **1d,g** and **1p,q** with hydroxylamine hydrochloride in ethanolic sodium acetate at room temperature resulted in the formation of products of condensation *via* dimethylamine elimination. These products were found to exist, in each case, as an equilibrium mixture of the hydroxylamino *E*- and *Z*-forms (**127** or **128**). Assignment of these forms were based on their ^{1}H NMR spectra, where two doublets for CH_2 protons and other two triplets for oxime CH were detected (Scheme 38).[63]

When *N*,*N*-dimethyl enaminone **1h** was allowed to react with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, Lawesson's Reagent (LR), in benzene at room temperature, the enaminothione **129** was produced in a high yield (Scheme 39).[64]

N,*N*-Dimethyl enamine **131** underwent hydrolysis upon boiling in acetic acid containing sodium acetate to give the bifunctional thiazolidinone-α-carboxaldehyde derivative **132** (Scheme 40).[65]



Scheme 43

2.2. Preparation of carbocyclic compounds

As mentioned earlier in this review, β-aminovinyl ketones **1d–f** underwent self-condensation on reflux in acetic acid yielding the 1,3,5-trisubstituted benzene derivatives **135a–c**.[43,66,67] The electron rich C-2 in one molecule of **1d**, **1e** or **1f** adds to the electron deficient C-3 in another molecule, forming the intermediates **133a–c**. It is most likely that these intermediates **133** reacted, in each case, swiftly with a third molecule of **1**, yielding the intermediates **134** that lose three molecules of dimethylamine, leading eventually to the triaroylbenzene derivatives **135**. It is believed that acidity of the reaction mixture has prompted such trimerization of enaminones into triaroylbenzenes (Scheme 41).

By using the synthetic sequence as was suggested for the synthesis of **135a–c**, the trisubstituted benzene derivatives **138a–c** were formed from aminovinyl ketones **1m**, **1o** and **1a**, respectively.[66–68] Formation of intermediates **136** and **137** is suggested although direct concerted 2 + 2 + 2 cycloaddition leading directly to **137** can not be overlooked (Scheme 42).[49]

This approach was also suitable for the preparation of the 1,3,5-trisubstituted benzenes **140a–c**, where reaction of the enaminone-derived heterocycles, such as thieno, furo and pyrido enaminones **1p,q,s** in refluxing acetic acid led to the corresponding trisubstituted derivatives **140a–c**. The reaction takes place by condensation of three moles of each enaminone **1p,q** or **1r** to form the corresponding intermediate **139** which loses, in each case, 3 moles of dimethylamine, aromatizes and affords the final isolated product **140a**, **140b** or **140c** (Scheme 43).[49,67]

Furthermore, it has been found that heating a mixture of **141** and an excess of an aryl ethynyl ketone **142** (~8 equivalents) in toluene resulted in smooth trimerization to afford the linked 1,3,5-triaroylbenzenes **143a–d** in good isolated yields, especially given the fact that six new C–C bonds are formed during the course of the reaction. Both electron rich (X = OMe) and electron deficient (R = NO_2) aryl ethynyl ketones proved to be suitable reactants, although nitro-substituted linked triaroylbenzenes were isolated in slightly lower yields (Scheme 44).[69]

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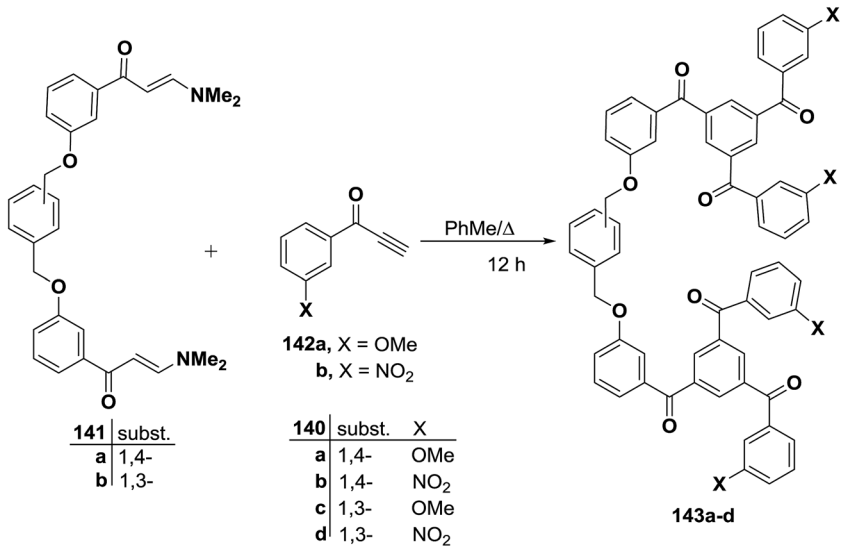
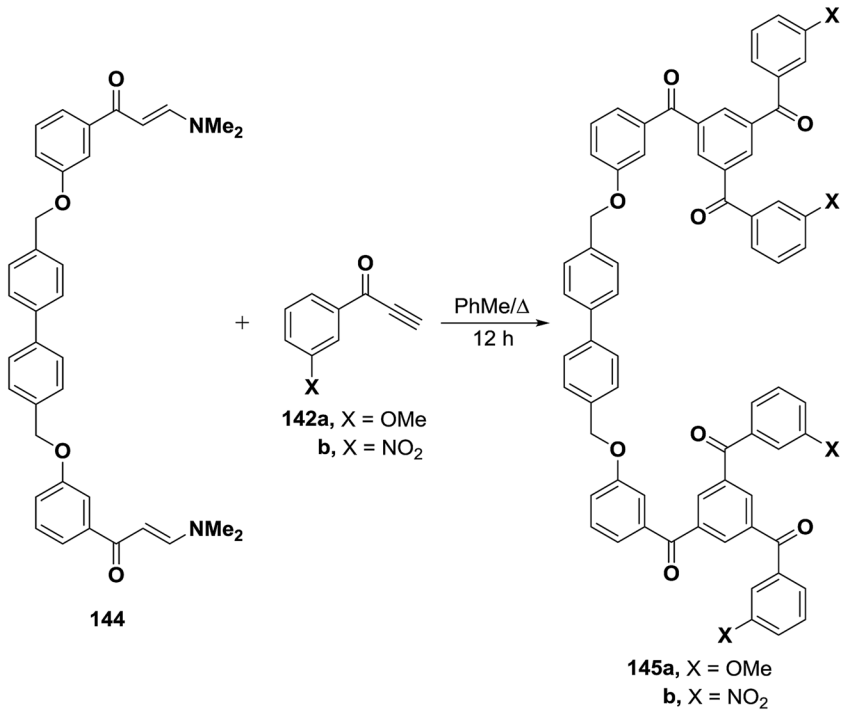


Scheme 44



Scheme 45

A similar treatment of the bis(enaminone) **144** with aryl ethynyl ketones **142a,b** resulted in the formation of the corresponding 1,3,5-triaroylbenzenes **145a,b** (Scheme 45).[69]

This protocol was also suitable for the preparation of tris(1,3,5-triaroylbenzene) derivative **147** in which the individual cyclotrimers are connected *via* a 1,3,5-trisubstituted phenyl ring (Scheme 46).[69]

Reaction of 3-dimethylaminoacrylaldehyde (**28a**) with aminothienocoumarin **85** in DMF at reflux for four hours gave a product of cycloaddition and dimethylamine elimination for which structure **148** was established. Similarly, condensed aminothiophene **91** reacted with 3-dimethylaminoacrylaldehyde (**28a**) under the same applied reaction conditions to afford the analogous cycloaddition product **149**.[56] Structures **138** and **149** were confirmed by preparing the same reaction products *via* alternative synthetic routes involving the reaction of acrylaldehyde (**150**) with condensed aminothiophenes **85** and **92**, respectively, under the same reaction conditions (Scheme 47).[56]

Lewis acid-catalyzed [3 + 2] cycloaddition of donor–acceptor cyclopropanes **151** and enamines **1d,o** in methylene chloride in presence of MgI_2 yielded nitrogen-functionalized cyclopentane derivatives **152** in good yields (Scheme 48).[70]

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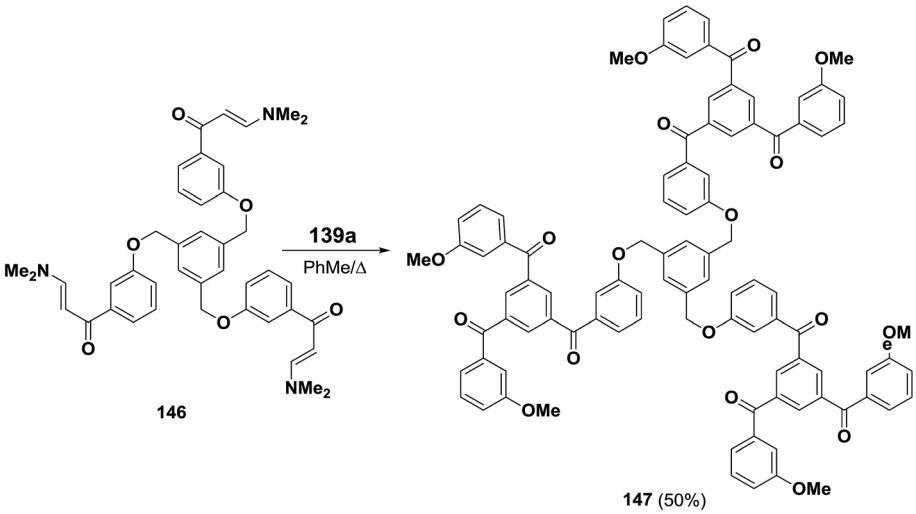
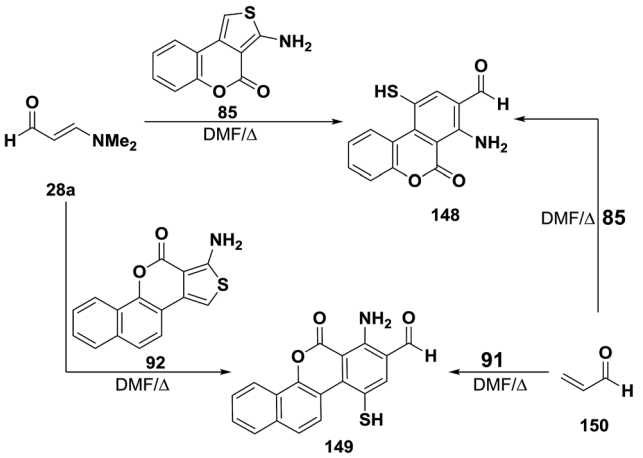


Scheme 46



Scheme 47

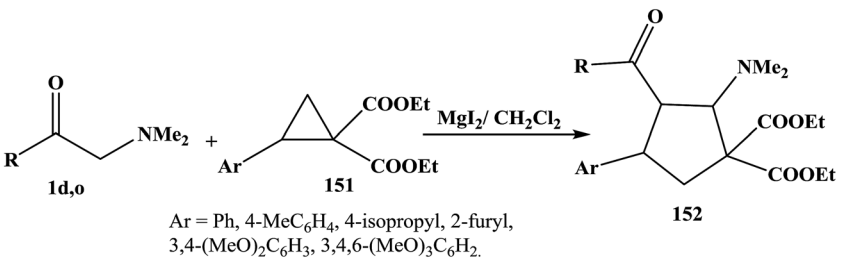
The use of enaminones as effective synthons for a directed C–H functionalization is reported. Proof-of-concept protocols have been developed for the Rh III-catalyzed synthesis of naphthalenes, based on the coupling of enaminones **1** with either alkynes **153** or α-diazo-β-ketoesters **154**. Two inherently reactive functionalities (hydroxy and aldehyde groups) are integrated into the newly formed cyclic framework and a broad range of substituents are tolerated, rendering target products **155**, **156** readily available for further elaboration (Scheme 49).[71]

2.3. Preparation of heteroaromatic compounds

β-Aminovinyl ketones are important synthetic intermediates, particularly in heterocyclic chemistry.[6,72] Heterocycles prepared from those ketones include carbazolequinone alkaloids,[73] tricyclic benzo[*a*]quinolizines,[74] pyrroles,[75] benzodizepines,[76] pyrimidines,[77] pyridines,[78] isoxazoles,[79] quinolines,[80,81] 1,3-thiazines,[82] furans,[83] benzothiazoles,[84] pyrazoles,[14,85–87] triazole,[88] isochromanes,[89] and 1,4-diazepines.[90] In this regard, many other recent examples are herewith provided including the preparation of five and six membered heterocycles and some of their condensed derivatives.

2.3.1. Preparation of five membered rings

2.3.1.1. Preparation of furans. Interaction of β-aminovinyl ketones with quinones represents an interesting approach to furan ring system. Many scientific publications in this area of investigation have been found. Thus, *e.g.*, treating vinyl ketone **1b** with *p*-benzoquinone, in acetic acid with stirring at room temperature, yielded a product of addition *via* dimethylamine and water elimination, this product can thus be formulated as **161** or isomeric **162**. However, the benzofuran-3-al structure **162** was assigned for that product on the basis of its elemental analysis and spectra data. Formation of **162**, as illustrated in



Scheme 48

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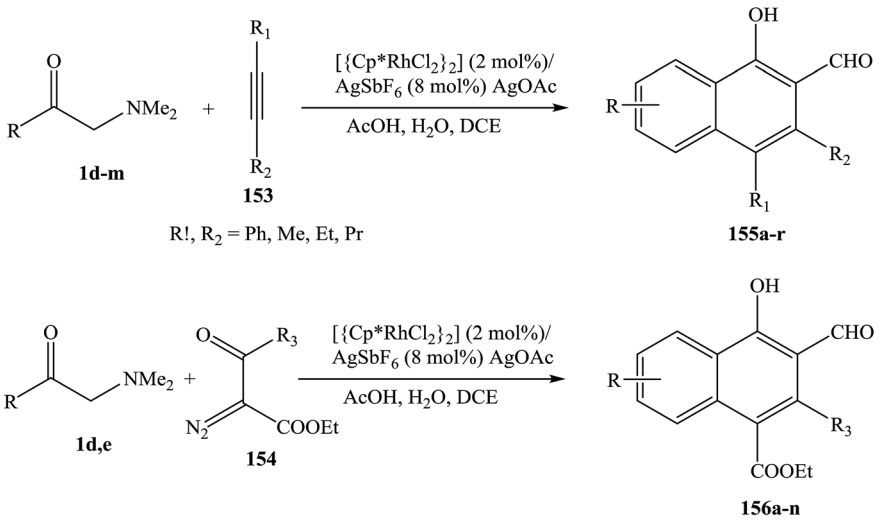
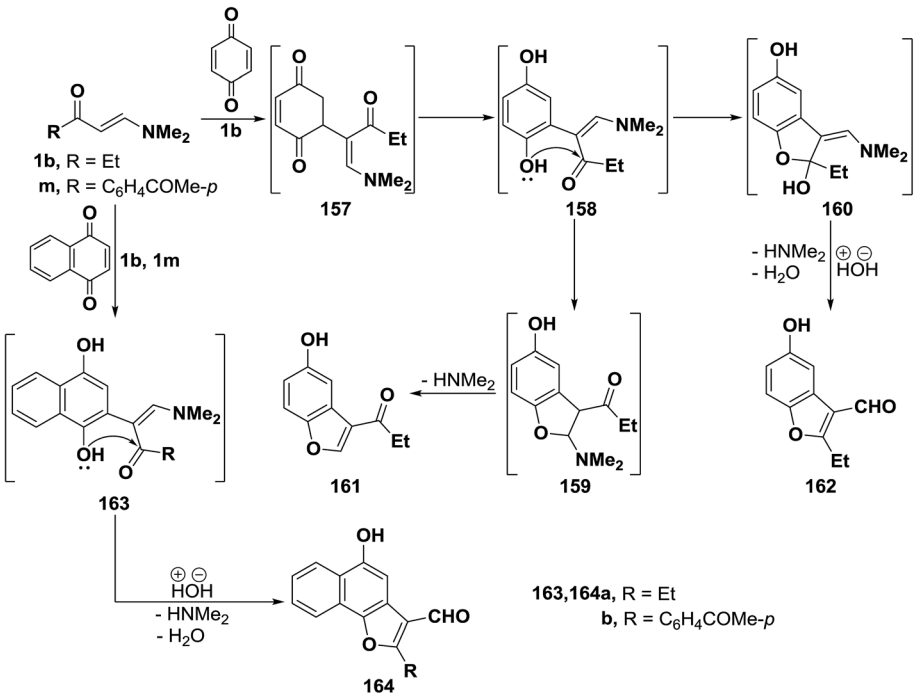


Scheme 49



Scheme 50

Scheme 111, may be explained to occur *via* initial addition of electron rich C-2 in the enaminone **1b** to the electron-deficient quinone carbon, forming the non-isolable acyclic adduct **157**, followed by subsequent enolization would take place, affording the dihydroxy intermediate **158**. The latter underwent intramolecular ionic heterocyclization at room temperature *via* nucleophilic attack by the OH function on the carbonyl carbon rather than the methylene CH, yielding the *N*,*N*-dimethylaminomethylidene intermediate **160**, accompanied by hydrolysis with the release of dimethylamine and water, leading eventually to the final isolable benzofuranal derivative **162**.[68]

Similar to the behavior of β-aminovinyl ketone **1b** toward *p*-benzoquinone, compounds **1b** and **1p** also reacted with 1,4-naphthoquinone to produce the corresponding furanals **164a,b** through the intermediate Michael adducts **163a,b** (Scheme 50).[68]

In addition, dienones **19a–c** reacted with *p*-benzoquinone, in acetic acid with stirring at room temperature, to yield products of addition *via* dimethylamine and water elimination, for which structure **167a–c** was considered as indicated from ^{1}H NMR spectra where a formyl-H was observed, in each case, at δ 9.0 (1H), δ 9.21 (1H) or δ 9.17 (1H) ppm. It is thus believed that *p*-benzoquinone initially adds to electron rich C-2, yielding acyclic

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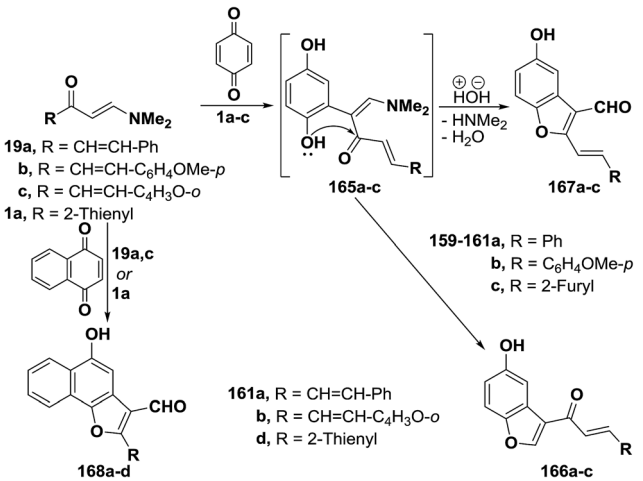
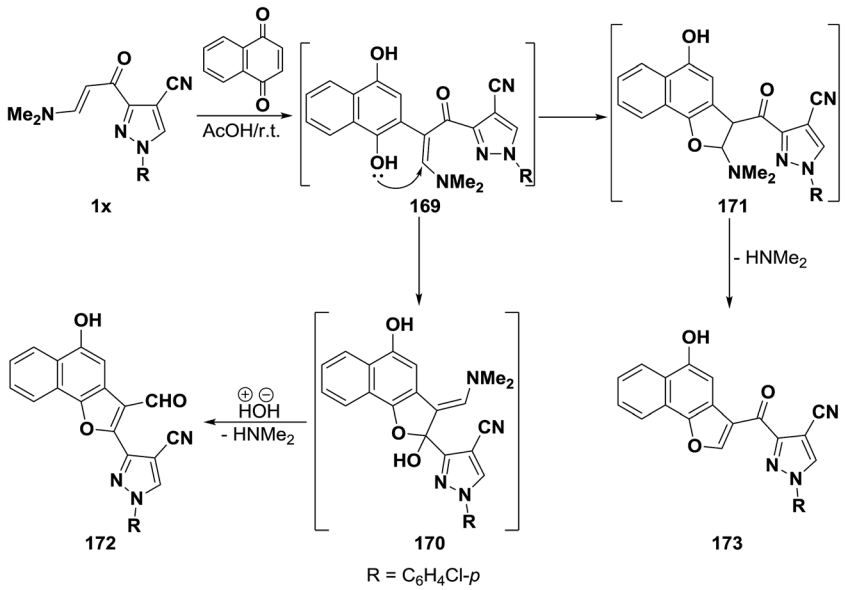


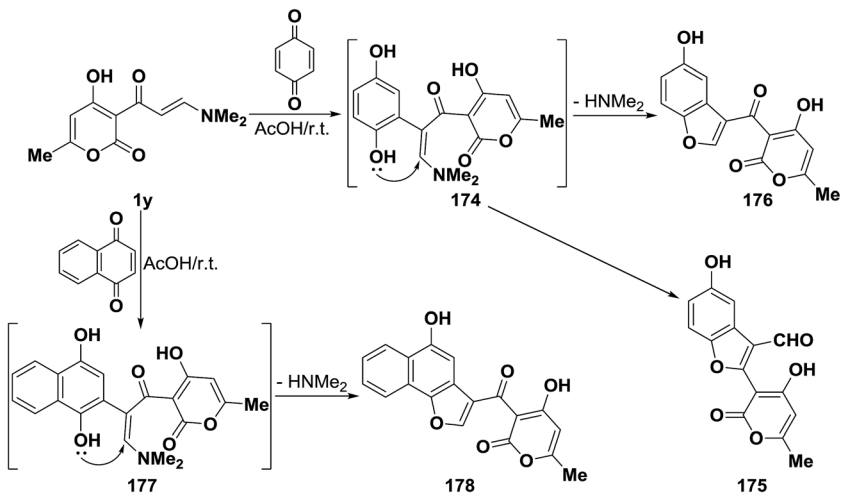
Scheme 51

dihydroxy intermediates **165a–c** which then cyclize exclusively into benzofuranals **167a–c** rather than the isomeric **160a–c**. Although cyclization into **160** seems to be kinetically more favored, products **167** are apparently thermodynamically more stable because of their extended conjugated double bond system.[37] By using the synthetic sequence as was suggested for the synthesis of **167a–c**, the naphthofuran-3-al derivatives **168a–d** were formed from 1,4-naphthoquinone (Scheme 51).[37,60]

In contrast to the observed formation of 3-formyl derivatives on reacting β-aminovinyl ketones with quinones, our research group reported[8] that pyrazolo enaminone **1x** reacted with 1,4-naphthoquinone to yield a product of addition and dimethylamine elimination. The naphthofuranoylpyrazole structure **173** was established for that product on the basis of its elemental analysis and spectra data. Formation of **173**, as illustrated in Scheme 50, may be rationalized *via* initial addition of electron rich C-2 in the enaminone **1x** to the active double bond of 1,4-



Scheme 52



Scheme 53

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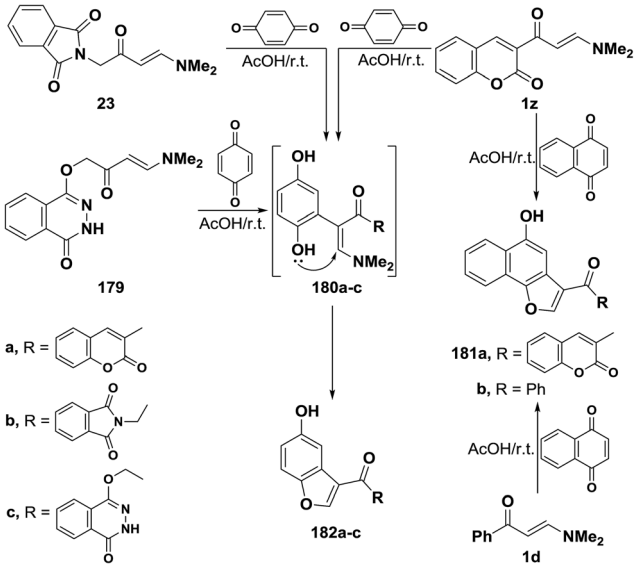
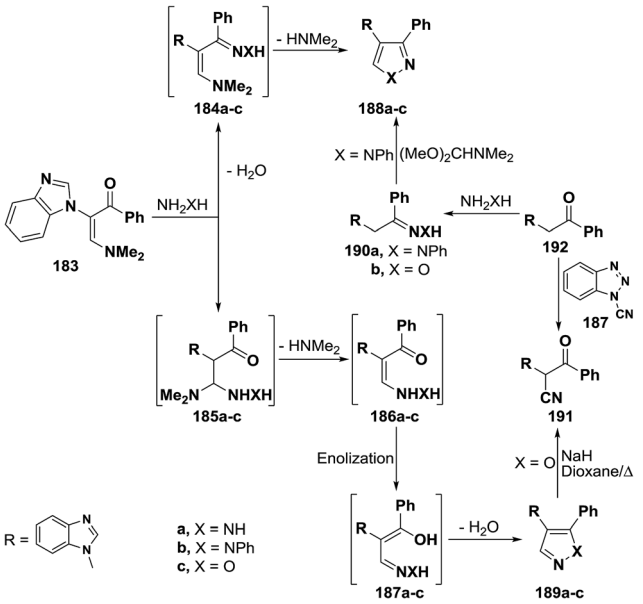
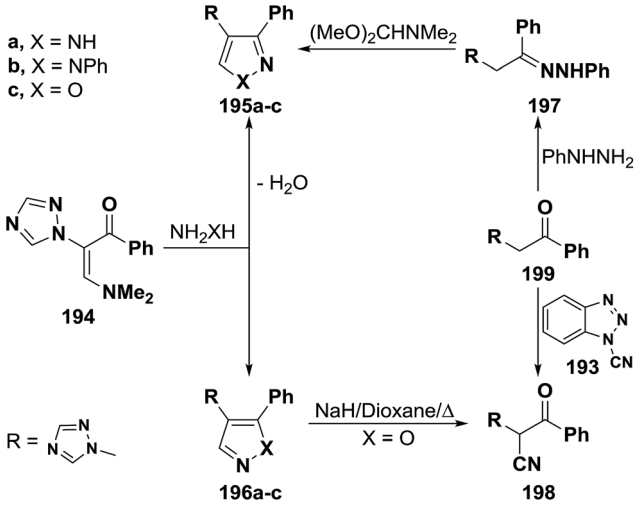


Scheme 54



Scheme 55



Scheme 56

naphthoquinone, followed by subsequent enolization would take place, forming the non-isolable acyclic dihydroxy intermediate **169**. The latter underwent intramolecular ionic heterocyclization at room temperature *via* nucleophilic attack by the OH function on the methylene CH rather than the carbonyl carbon, yielding the dihydronaphthofuran intermediate **171**, accompanied by 1,2-elimination with the release of dimethylamine, leading eventually to the final isolable 2-unsubstituted naphthofuran derivative **173** as described in our earlier report.[7] It seemed that our approach was not suitable for the synthesis of the naphthofuranal derivative **172** that would be expected by analogy with the aforesaid reports[37,60,68] on the reactivity of β-aminovinyl ketones toward quinones (Scheme 52).

In support of this view, pyrano enaminone **1y** also reacted with *p*-benzoquinone to give the corresponding pyranyl benzofuryl ketone **175** and not the pyranylbenzofuran-3-carboxaldehyde derivative **148**. Furthermore, reacting **1y** with 1,4-naphthoquinone afforded naphthofuryl ketone **177**. The formation of **175** and **177** from **1y**, is assumed to occur *via* initial addition of the aminovinyl ketone, of electron rich C-2, to the active double bond in quinones, forming the intermediate phenolic adducts **175** and **176**, that cyclize *via* loss of dimethylamine to yield the final isolable products (Scheme 53).[44]

In accordance with the previous observations reported by us[7] and by others,[44] β-ketoenamines **1z**, **23** and **179** reacted with *p*-benzoquinone to furnish the corresponding benzofuryl ketones **181a–c**, *via* the intermediacy of dihydroxy compounds **180a–c**.[90,91] The exact structure of products in these reactions has been firmly established on the basis of Heteronuclear Multiple Quantum Coherence spectroscopy (HMQC). Thus, HMQC of compound **181b**, as a representative example, indicated that carbonyl group at δ 188.9 ppm is not bonded to any hydrogen atoms. This fully supported the proposed structure **181**. A similar treatment of the *N*,*N*-dimethylamino derivatives of coumarin **1z** and of benzene **1d** with 1,4-naphthoquinone led to the naphthofuryl ketones **182a**[90] and **182b**,[42] respectively (Scheme 54).

2.3.1.2. Preparation of pyrazoles and isoxazoles. One of the common route to pyrazole and isoxazole ring systems is the interaction of β-aminovinyl ketones with N-nucleophiles. Several contributions have been made to this area of research. Thus, *e.g.*, treatment of vinyl ketone **183b** with hydrazine hydrate and with phenylhydrazine in absolute ethanol at reflux temperature for four hours gave rise to pyrazole products for which two possible structures **188** or **189** can be formulated. However, structure **189a,b** could be established for these products based on the non-identity of reaction product, obtained by reacting **183b** with phenylhyrazine, with a sample of **188b** prepared *via* initial condensation of acetophenone derivative **182b** with phenylhydrazine in refluxing absolute ethanol

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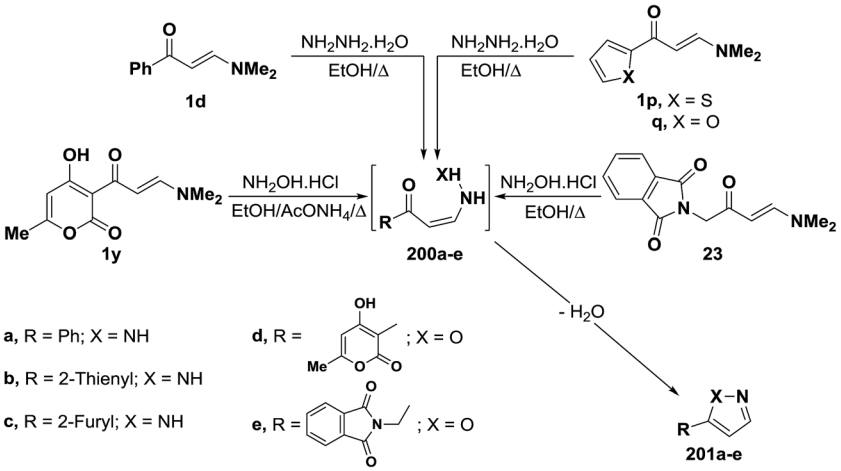
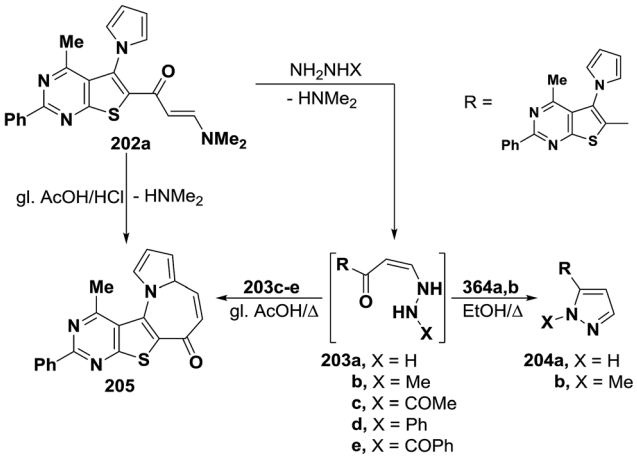


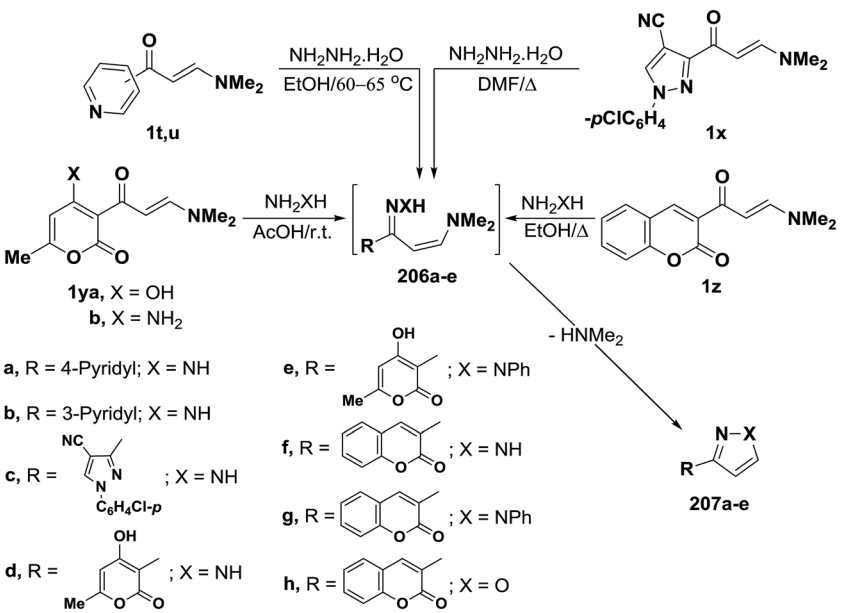
Scheme 57



Scheme 58

in the presence of acetic acid and subsequent treatment of the formed phenylhydrazone **190a** with DMFDMA (Scheme 55).[92] Compound **183b** also reacted with hydroxylamine hydrochloride, in absolute ethanol in the presence of fused sodium acetate under reflux for five hours, to yield a product that may be also formulated as **188c** or **189c**. Attempt to prepare a sample of **188c** from reaction of oxime **190b** with DMFDMA failed. However, structure **189c** could be established for the reaction product based on the fact that this reaction product readily converted, under basic reaction conditions, into the nitrile **191**, which was also prepared *via* direct cyanation of **192b** with *N*-cyanobenzotriazole **193** as an efficient *C*-cyanating reagent.[92,93]

A similar treatment of β-acylated enamine **194** with hydrazines led to 3-unsubstituted derivatives of pyrazole and isoxazole **196a–c** on treatment with hydrazines and hydroxylamine. The isomeric 5-unsubstituted pyrazole **195b** could be prepared



Scheme 59

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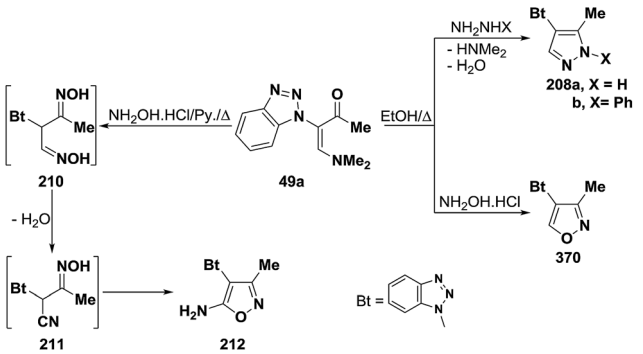
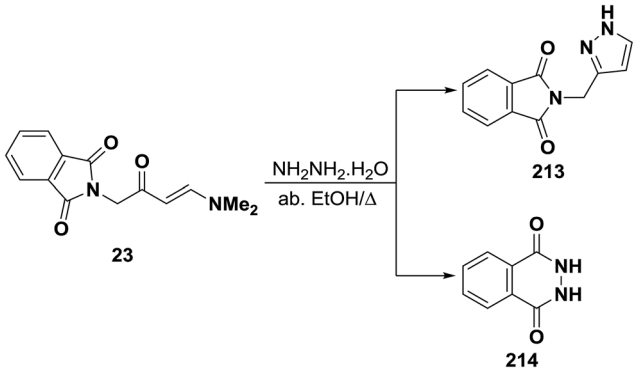
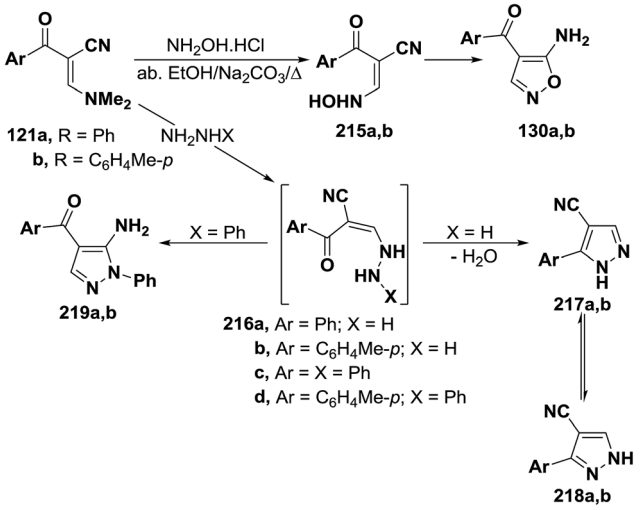


Scheme 60

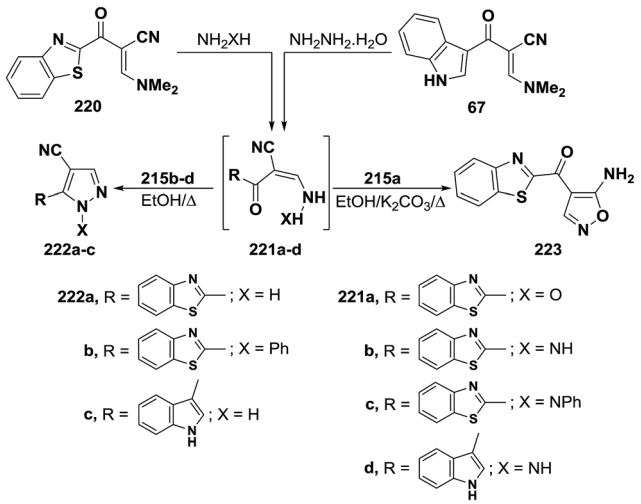
by condensing active methylene compound **199** with phenylhydrazine and subsequent condensation of the formed phenylhyrazone **197** with DMFDMA. On the other hand, the 5-unsubstituted isoxazole **196c** was converted into the α-cyanoketone **198** on reacting with a little excess of sodium hydride in refluxing dioxane. Alternatively, compound **198** was directly prepared from reaction of **199** with **193** (Scheme 56).[92]



Scheme 61



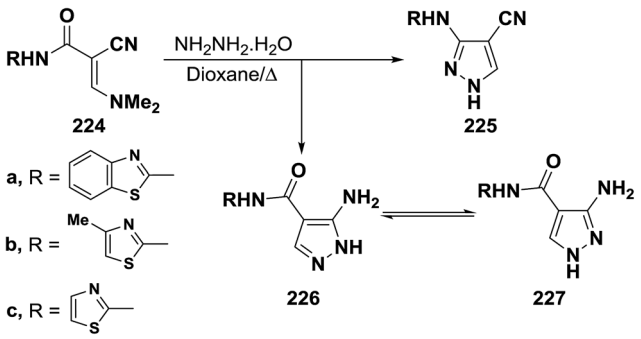
Scheme 62



Scheme 63

In accordance with the observed formation of 3-unsubstituted heterocyclic compounds, enaminoketones **1d** and **1p,q** reacted with hydrazine hydrate in refluxing ethanol to give the corresponding pyrazoles **201a–c**, respectively. It is believed that hydrazine adds, in each case, reversibly across the α,β-unsaturated moiety in **1d** or **1p,q** affording non-isolable intermediates **200a–c**. This is followed by deamination and dehydration, leading eventually to the final isolable pyrazoles **201a–c**.[55,94] In a similar manner, treatment of *N*,*N*-dimethylaminomethylene derivatives **1y** and **23** with hydroxylamine hydrochloride led to the isoxazoles **201d,e**, respectively (Scheme 57).[44,95,96]

In addition, heterocyclic enaminone **202** also reacted with each of hyrazine hydrate and methylhydrazine in refluxing ethanol to furnish the anticipated pyrazoles **204a,b**, *via* the intermediacy of **203a,b**. On the other hand, when the reaction of compound **202** with acetyl-, phenyl- and benzoyl-derivatives of hydrazine, was conducted in refluxing glacial acetic acid, in all cases, a single tetracyclic product was isolate for which structure **205** was established as indicated from spectral data of that reaction product. Formation of the tetracyclic azepine **205** would involve an initial formation of intermediates **203c–e** which underwent nucleophilic cyclization with loss of hydrazine molecules to afford the final single product **205**. The same



Scheme 64

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compound **205** was also obtained by refluxing enaminone **202** in a mixture of glacial acetic acid and hydrochloric acid (1 : 1) for four hours (Scheme 58).[97]

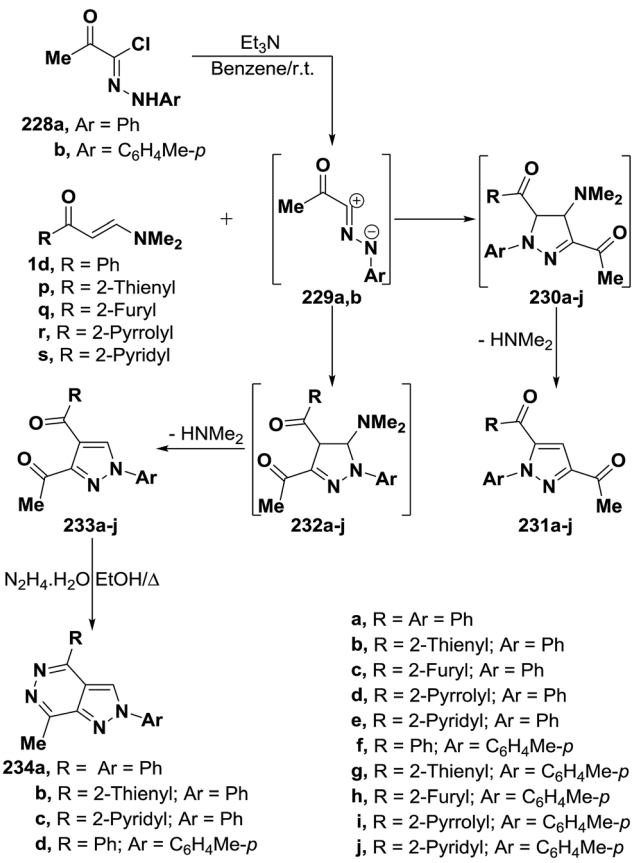
In contrast to the observed formation of 3-unsubstituted heterocycles, 5-unsubstituted pyrazoles **207a,b** were obtained upon heating of *N*,*N*-dimethylamino derivatives of pyridine **1t,u** to 60–65 °C under stirring, with hydrazine hydrate through the intermediate formation of acyclic condensation products **206a,b**.[98] *N*,*N*-Dimethylamino derivative of pyrazole **1x** underwent analogous reaction in refluxing DMF to yield the respective pyrazolylpyrazole derivative **207c** as described by us in a previous communication.[7] Compounds **1y** also reacted with hydrazine and with phenylhydrazine in acetic acid at room temperature to afford the pyranylpyrazoles **207d,e**.[44] When compound **1z** reacted with hydrazines in refluxing ethanol, the pyrazoles **207f,g** were isolated, while the isoxazole **207h** was obtained upon heating of **1z** with hydroxylamine hydrochloride in ethanol in the presence of anhydrous sodium acetate at reflux for six hours.[90] Compound **207f** was also obtained in yield of 60%, when the reaction of **1z** with hydrazine was carried out under microwave heating for five minutes (Scheme 59).[99]

An interesting reaction leading to 3-unsubstituted pyrazoles is the interaction of 3-(*N*,*N*-dimethylamino)-methylene derivatives **49a** with hydrazines in refluxing ethanol to give the pyrazoles **208a–d**.[100,101] On the contrary, compound **49a** reacted with hydroxylamine hydrochloride in refluxing ethanol to yield a product that was assigned 5-unsubstituted isoxazole structure **209** based on ^{1}H and ^{13}C NMR spectra.[101] Interestingly, it has been found that interaction of **49a** with an excess of hydroxylamine hydrochloride, in pyridine at reflux temperature for two hours, led to the 5-aminoisoxazole derivative **212**, which is assumed to proceed by reaction of the vinyl ketone **49a** with two molecules of hydroxylamine, affording the dioxime **210**, that then loses a molecule of water, yielding the α-cyano oxime **211**, followed by spontaneous cyclization to the final isolable aminoisoxazole **212** (Scheme 60).[100,102]

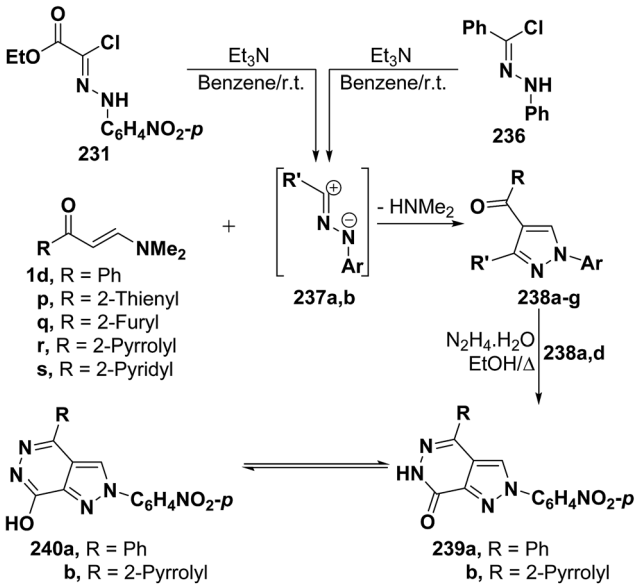
Unexpectedly, treatment of aminovinyl ketone **23** with hydrazine hydrate in refluxing absolute ethanol in an attempted to obtain the pyrazole derivative **213** was unsuccessful (Scheme 61). The isolated product was identified as 2,3-dihydrophthalazine-1,4-dione (**214**) identical to that reported in the literature.[95,103]

Interestingly, it has been found that enaminonitriles underwent somewhat different reactions with N-nucleophiles, providing access to cyano or amino heterocyclic compounds, depending on the applied reaction conditions. In the first step of those reactions, the dimethylamino group was substituted by hydrazines or by hydroxylamine. The final products were obtained by ring closure to the carbon atoms either of the carbonyl group, affording cyano compounds, or of the nitrile group, yielding amino analogues. Several data have been reported on this area of study (Scheme 62).

As previously indicated in this review, interaction of enaminonitriles **127a,b** with hydroxylamine hydrochloride did not



Scheme 65



238	R	R'	Ar
a	Ph	CO_2Et	$C_6H_4NO_2$-*p*
b	2-Thienyl	CO_2Et	$C_6H_4NO_2$-*p*
c	2-Furyl	CO_2Et	$C_6H_4NO_2$-*p*
d	2-Pyrrolyl	CO_2Et	$C_6H_4NO_2$-*p*
e	2-Pyridyl	CO_2Et	$C_6H_4NO_2$-*p*
f	Ph	Ph	Ph
g	2-Thienyl	Ph	Ph

Scheme 66

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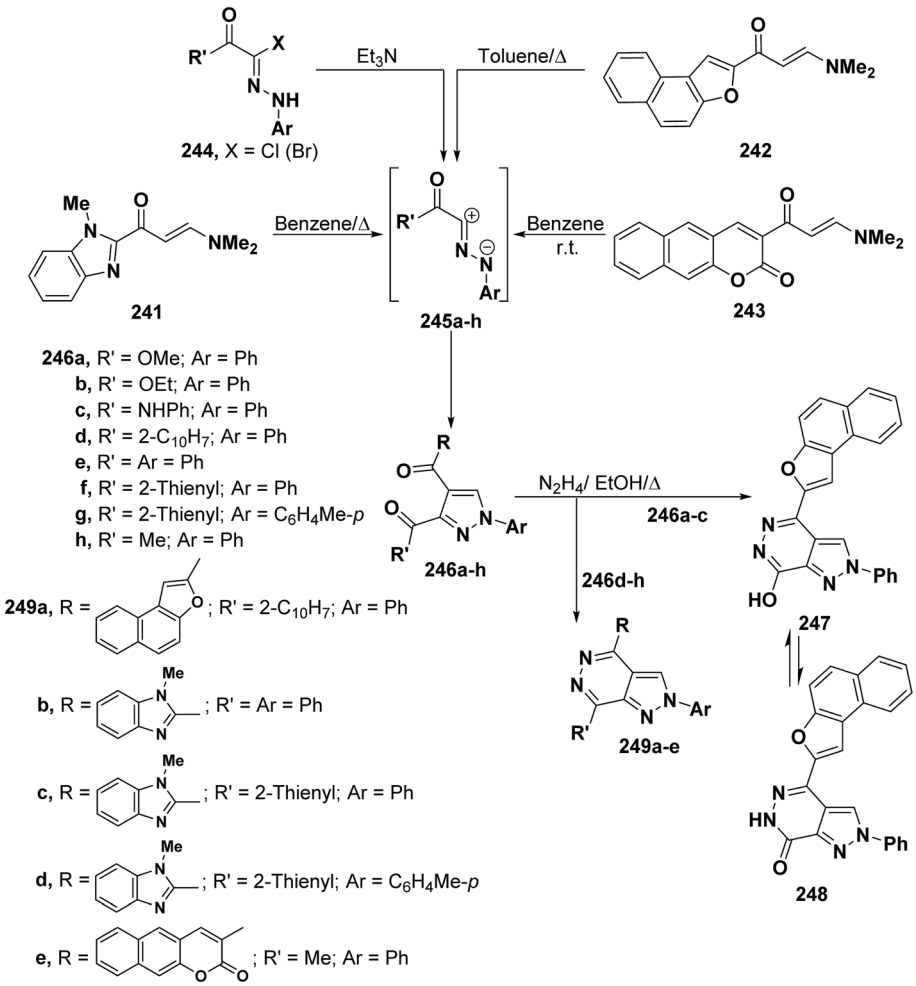
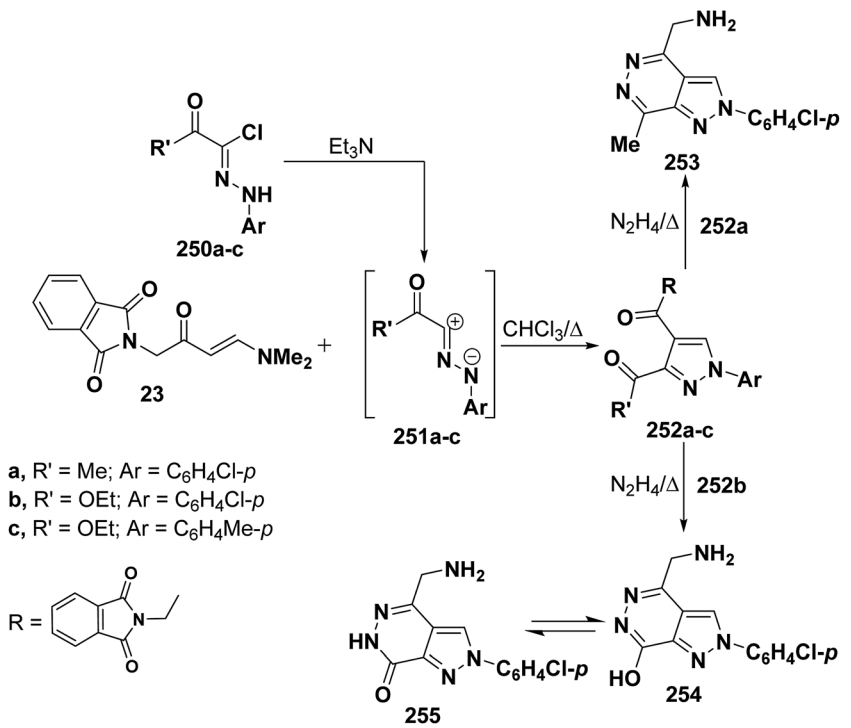


Scheme 67



Scheme 68

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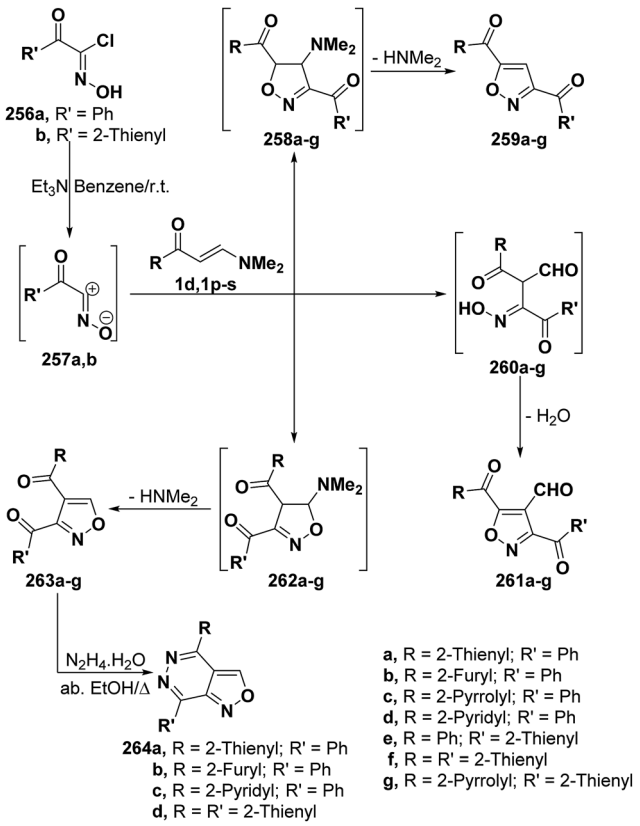
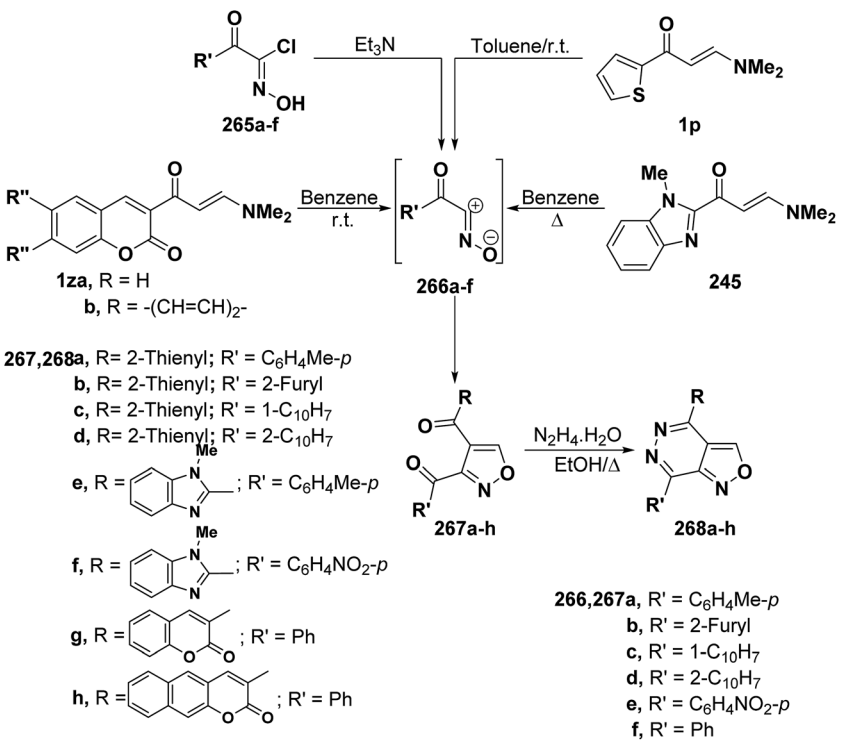


Scheme 69

give expected isoxazoles **130a,b**, but instead afforded the acyclic hydroxylaminomethylenes **215a,b**, that could not be cyclized into **130a,b** under a variety of reaction conditions.[61] In contrast, compounds **126a,b** reacted, on one hand, with hydrazine hydrate in refluxing absolute ethanol for six hours to yield the cyanopyrazoles **217a,b** and, on the other, with phenylhydrazine under the same experimental conditions to produce the aminopyrazoles **219a,b**. It is believed that compounds **127a,b** react initially with both hydrazines to provide the non-isolable acyclic hydrazino derivatives **216a–d**. The intermediates **216a,b** cyclize readily *via* water elimination, leading to pyrazoles **217a,b**.[61] No traces of the other possible regioisomers **218a,b** could be isolated, since the ^{1}H NMR spectra of the obtained products showed, in each case, the presence of pyrazole H-3 proton as a singlet at δ 7.9 ppm and this disagree with the tautomeric **218a,b** in which the corresponding pyrazole H-5 protons would appear as doublets.[104,105] Similar cyclization of **216c,d** into **219a,b** is sterically hindered as it could produce pyrazoles with two adjacent bulky substituents. Consequently, intermediates **216c,d** cyclize *via* nucleophilic addition to cyano group, yielding the aminopyrazole derivatives **218a,b** as confirmed by elemental analyses and spectral data (Scheme 63).

In contrast to the observed formation of acyclic products **129a,b**, enaminonitrile **220** reacted with hydroxylamine hydrochloride in absolute ethanol in the presence of potassium carbonate anhydrous at reflux temperature to give the aminoisoxazole derivative **223** as confirmed by elemental and spectral data. Compound **223** is assumed to be formed *via* a Michael type addition of the amino group of hydroxylamine to the enamine double bond in **220** with loss of dimethylamine



Scheme 70

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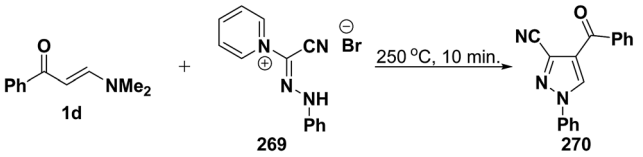
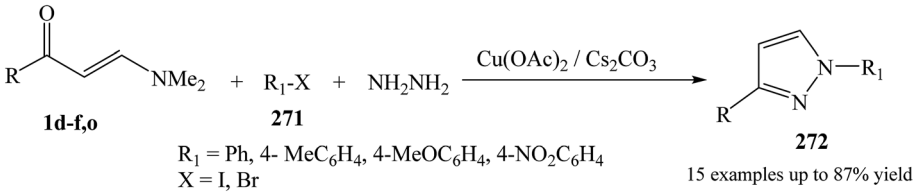
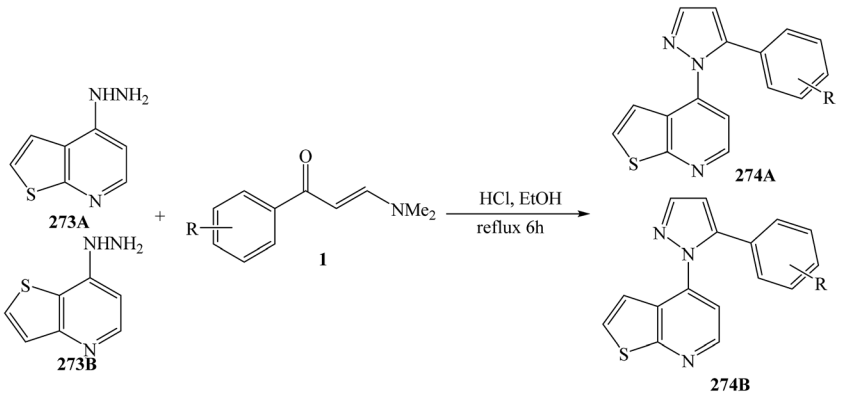


Scheme 71

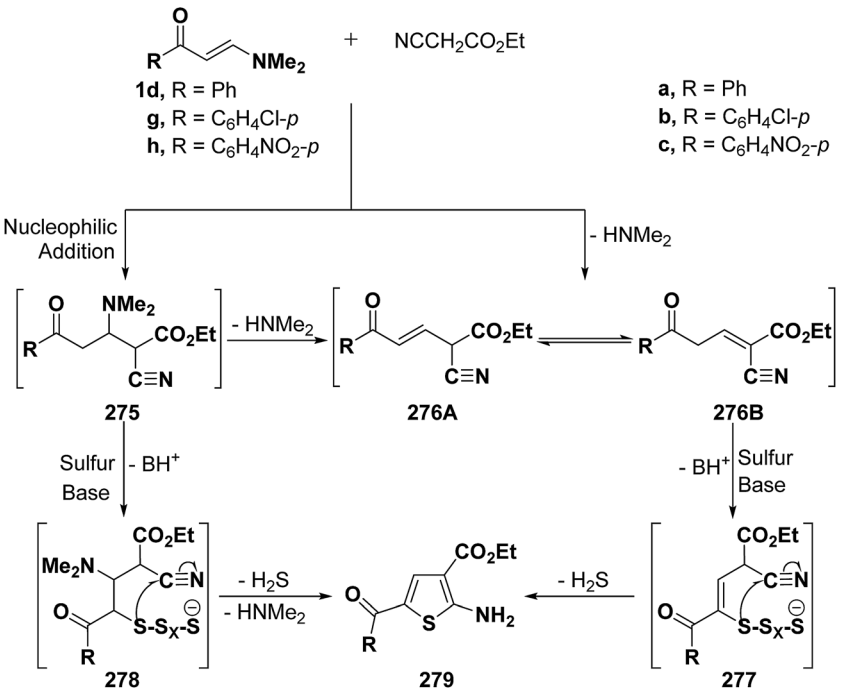
molecule, forming acyclic intermediate **221a**, which cyclized into the final amino derivative **223** *via* nucleophilic addition to cyano group.[106] On the other hand, it has been found that reacting enaminonitriles **67** and **220** with hyrazines in refluxing ethanol led to the cyanopyrazoles **223a–c**, respectively, which is a contradiction to the behavior of compound **220** toward hydroxylamine. The spectral data of the isolated products were



Scheme 72



Scheme 73



Scheme 74

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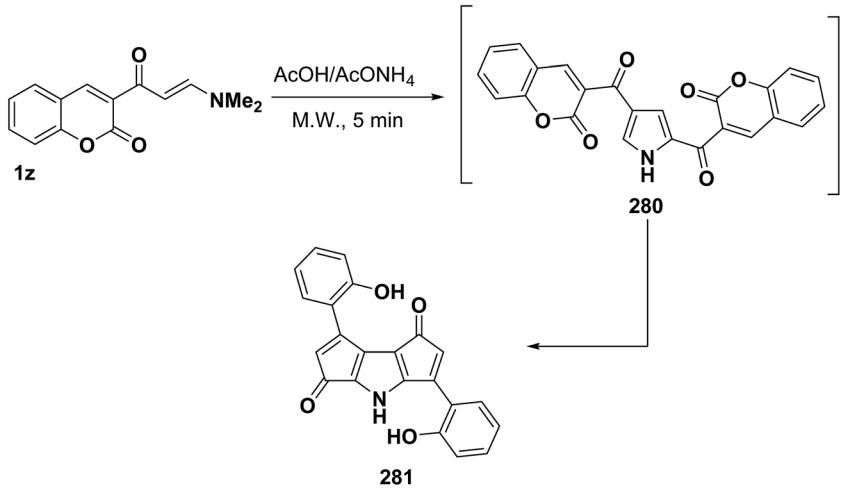


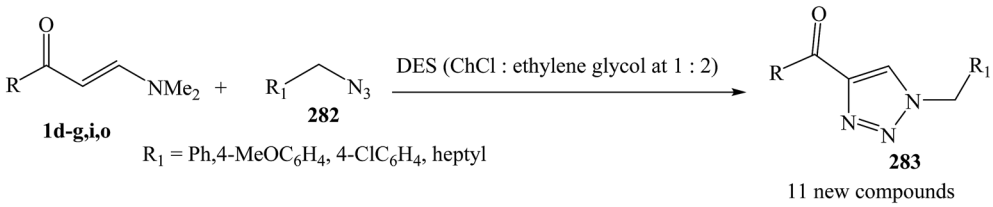
Scheme 75

in complete agreement with structure **222a–c**. Consequently, the acyclic hydrazino intermediates **221b–d**, formed in this process, are not subjected to nucleophilic addition, but are stabilized by the evolution of water molecules (Scheme 64).[50,106]

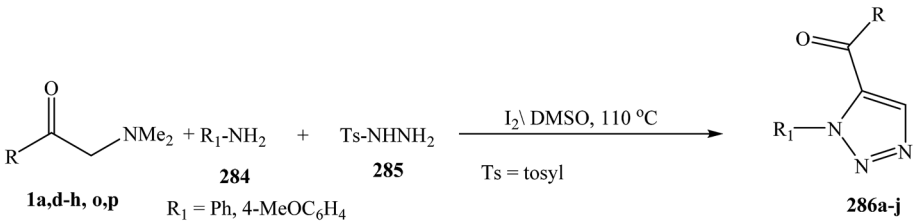
An interesting reaction leading to aminopyrazoles is the interaction of enaminonitriles **224a–c** with hydrazine hydrate in refluxing dioxane for three hours to furnish the aminopyrazoles **226** and not the cyanopyrazoles **225**. Inspection of ^{1}H NMR spectrum enabled establishing structure **226** for these pyrazole derivatives since the pyrazole H-3 appeared as a singlet at δ 8.0–8.3 ppm, the authors could not trace in the ^{1}H NMR any signals for the tautomeric **227** as this would reveal pyrazole H-5 as doublet (Scheme 64).[104]

It is worthwhile to report here that interaction of β-aminovinyl ketones with hydrazonoyl halides in the presence of bases also provides access to pyrazole ring system. Many examples have been reported on this interesting area of research.

Al-Zaydi and co-workers[107] reported that treatment of vinyl ketones **1d** and **1p–s** with nitrilimines **229a,b** (liberated *in situ* from the corresponding hydrazonoyl halides **228a,b** by the action of triethylamine in dry benzene solutions at room temperature) led to, in each case, the formation of only one isolable product as tested by TLC analysis. The reaction products were identified as the 5-unsubstituted pyrazole structure **233a–j** (Scheme 65) that are assumed to be formed *via* 1,3-dipolar cycloaddition of the nitrilimines **229a,b** to the activated double bond in the vinyl ketones **1d** and **1p–s** to afford the non-isolable dihydropyrazole intermediates **232a–j** followed by elimination of dimethylamine yielding the final pyrazole derivatives **233a–j**.[94,107–109] The other possible regioisomers **231a–j** are not observed through out the reaction course and were excluded on the basis of the spectral data of the isolated products. This conclusion was further confirmed chemically *via* reacting some examples of the isolated products **233a,b,e,f** with



Scheme 76



Scheme 77

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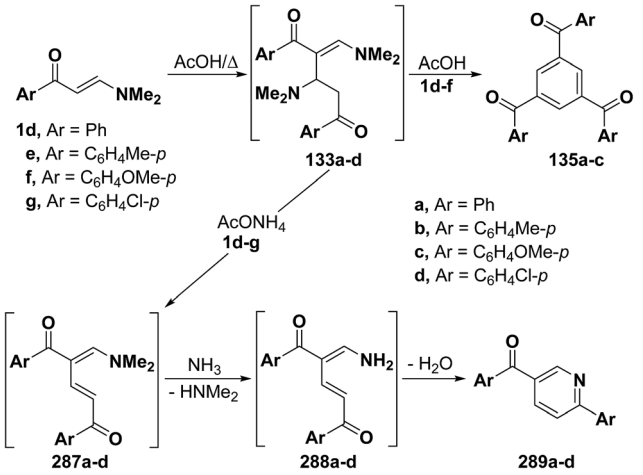
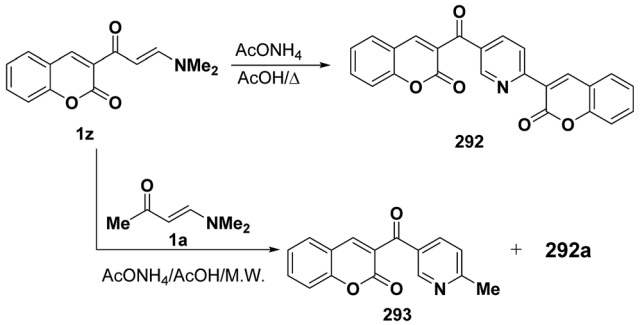


Scheme 78



Scheme 80

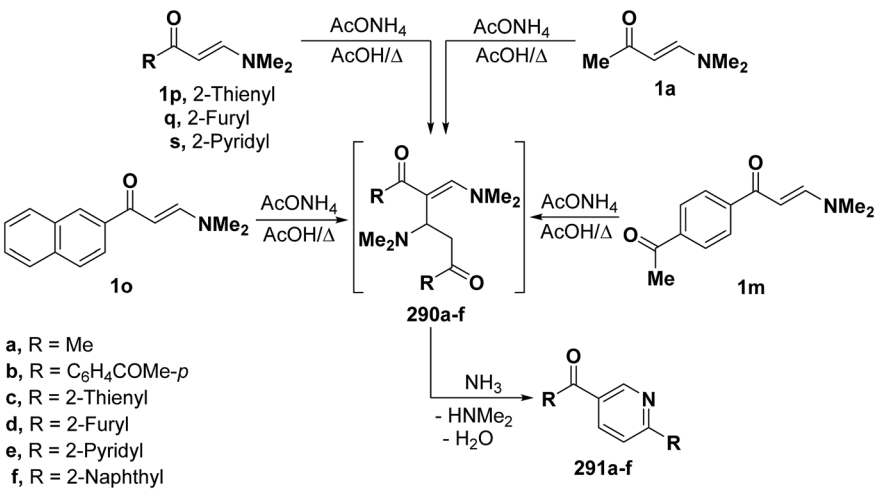
hydrazine hydrate in ethanol under reflux to afford the pyrazolo[3,4-*d*]pyridazine derivatives **234a–d** in almost quantitative yields. It is of importance to report here that compounds **234a–d** can not be prepared by the action of hydrazine on the other possible regioisomers **234a–j** under the same experimental conditions as shown in (Scheme 65).

By using the synthetic sequence as was suggested for the synthesis of **233a–j**, the 5-unsubstituted pyrazole derivatives **237a,b** were formed from nitrilimines **237a,b** that generated by the action of triethylamine on hydrazonoyl halides **235** and **236**, respectively, under the same experimental conditions.[107] Further confirmation of the proposed structure **238** comes from reacting the isolated products **237a,d** with hydrazine hydrate in ethanol under reflux to give products that were formulated as the pyrazolo[3,4-*d*]pyridazinones **239a,b** rather than the corresponding hydroxy derivatives **240a,b** as confirmed by the spectroscopic data of the isolated products (Scheme 66).[107]

In accordance with the observed formation of 5-unsubstituted pyrazoles, aminomethylene derivatives **241**, **242** and **243** reacted with nitrilimines **245a–h** (generated from hydrazonoyl halides **244a–k** and triethylamine) to furnish the corresponding pyrazole derivatives **246a–k** by cycloaddition and dimethylamine elimination.[4,99,110,111] Structure **246** was further established based on conversion of the isolated products **246a–e** with hydrazine hydrate into the corresponding pyrazolo[3,4-*d*]pyridazines **247** and **249a–e**, respectively. Clearly, these products can only be obtained from 5-unsubstituted isomer. It is worth mentioning herein that treatment of pyrazoles **246d–h** with hydrazine hydrate under reflux in ethanol led to the expected pyrazolopyridazines **249a–e**, respectively.[4,99,110] Similar hyrazinolysis of pyrazoles **246a–c**, in refluxing ethanol for two hours, resulted in the formation of only one isolable product. This product was identified as the 7-hydroxypyrazolopyridazine structure **247** that is formed *via* loss of a molecule of methanol, ethanol or aniline (Scheme 67).[110]

Also, it has been found that reaction of enaminone **23** with nitrilimines **250a–c** gave rise to the pyrazoles **251a–c**. Refluxing compound **251a,b** with hydrazine hydrate for five minutes led to the formation of 4-(aminomethyl)pyrazolopyridazines **253** and **254**, respectively, that are assumed to be formed as a result of hydrolysis accompanied by the release of phthalic acid (Scheme 68).[112]

By analogy with hydrazonoyl chlorides, hydroximoyl chlorides **256** also reacted with vinyl ketones **1d** and **1p–s** in the



Scheme 79

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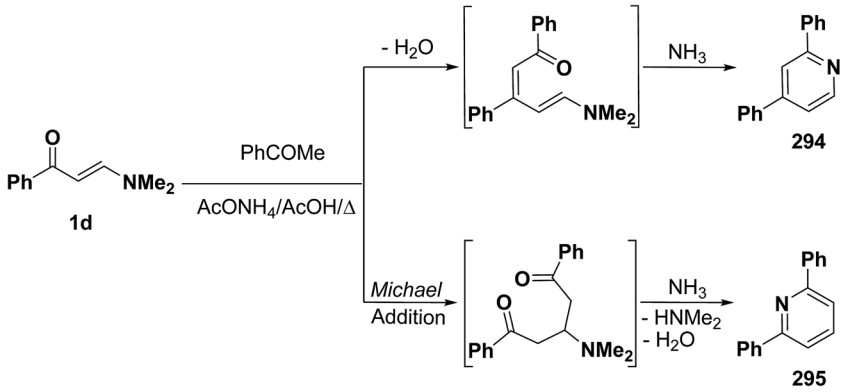
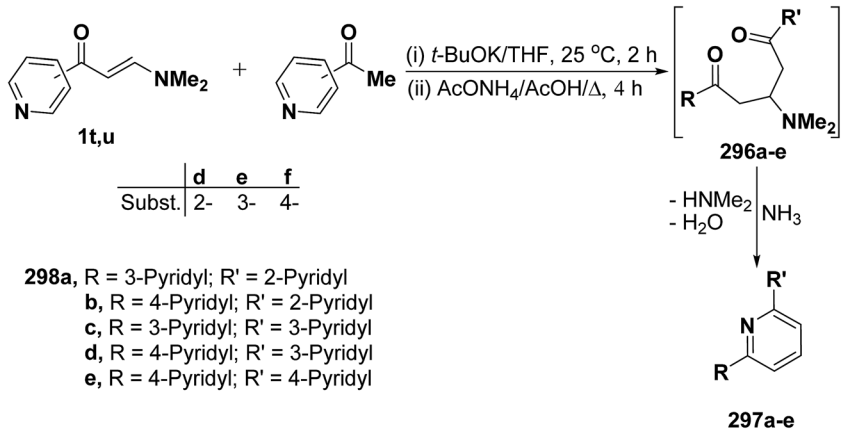


Scheme 81



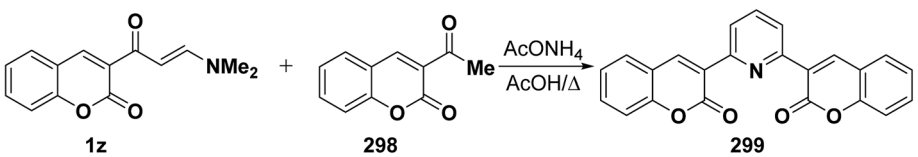
Scheme 82

presence of triethylamine to produce products of condensation *via* dimethylamine hydrochloride elimination for which three isomeric structures are possible. However, the structure of isolated products was considered to be 5-unsubstituted isoxazole structure **257** rather than other potential isomeric structures **259** and **261** based on spectral data and on the fact that the reaction products **263a,b,d,f** were readily converted into the corresponding isoxazolo[3,4-*d*]pyridazines **264a–d**, respectively, upon treating with hyrazine hydrate in refluxing absolute ethanol for 3–4 hours. It is believed that **256a,b** initially generate nitrile oxides **257a,b** *in situ* and these then undergo 1,3-dipolar cycloaddition to vinyl ketones **1d** and **1p–s** yielding intermediate cycloadducts **262a–g** that aromatize *via* dimethylamine elimination (Scheme 69).[107,108]

In a similar way, aminomethylene derivatives **1p**, **239** and **1z** underwent analogous reactions with a variety of nitrile oxides **266a–f** (generated from hydroximoyl chlorides **265a–f** and triethylamine) to give the expected isoxazole derivatives **267a–h** by cycloaddition and dimethylamine elimination in a straightforward manner (Scheme 70).[4,99,108] Spectral data as well as chemical behavior of the formed isoxazoles indicated that they are the 5-unsubstituted isomeric structure **267a–h** and this agrees with an already established trend in the behavior of β-aminovinyl ketones toward both nitrilimines and nitrile oxides.

An interesting synthesis of 5-unsubstituted pyrazole is the formation of **270** upon fusion of aminomethylene derivative **1d** with phenylhydrazonylpyridinium bromide **269** (Scheme 71).[113]

The synthesis of 1,3-disubstituted pyrazole derivative **272** was initiated with enaminone **1d–f,o**, hydrazine hydrate, and aryl halide derivatives **271** in the presence of presence of Cs_2CO_3 and Cu catalyst in DMF at elevated temperature (Scheme 72).[114]



Scheme 83

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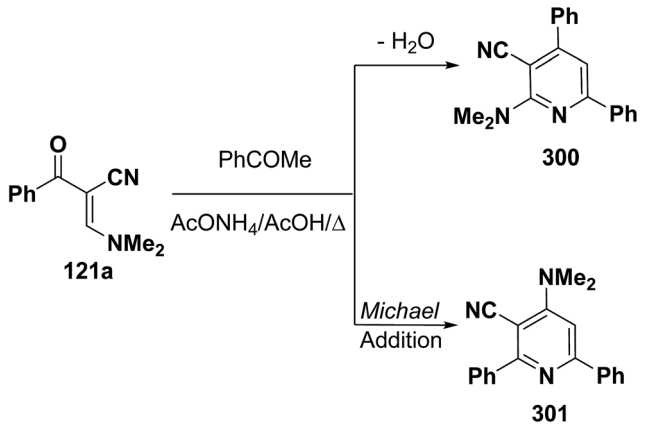


Scheme 84

4-Hydrazinothienopyrimidine **273A** or **273B** and the appropriate (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**1**) were mixed in ethanol containing HCl, and the mixture was heated to 70 °C for 6 h, yielded 4-(5-aryl-1*H*-pyrazol-1-yl)thieno[2,3-*d*] pyrimidine **274A** and 4-(5-aryl-1*H*-pyrazol-1-yl)thieno[3,2-*d*] pyrimidine **274B**, respectively (Scheme 73).[115]

2.3.1.3. Miscellaneous. It is also of value to report here that reactions with β-aminovinyl ketones allow an easy access to some other five membered heterocycles such as thiophenes and pyrroles. Some recent reports on this area have been published.

Elnagdi *et al.*[116] reported on the utility of vinyl ketones as aldehyde equivalents in Gewald reactions. It has been found that ketones **1d,g,h** reacted smoothly with elemental sulfur and ethyl cyanoacetate in the presence of equivalent amounts of piperidine, under reflux in dry DMF for 6–8 hours, to yield 4-unsubstituted-2-aminothiophenes **279a–c** in good yields. It is believed that the initial step in the reaction sequence would be the nucleophilic addition of an active methylene nitrile to the α,β-unsaturated moiety in ketones **1d,g,h** with subsequent elimination of dimethylamine to yield **276A** or **276B**. Alternatively, reaction of adducts **275** with sulfur in the presence of an equivalent amount of piperidine would yield **278** that would cyclize and aromatize to yield **279** *via* loss of hydrogen sulfide and dimethylamine molecules during the reaction course. This sequence is quite similar to the general mechanism of the Gewald reaction.[117] In either case, the reactivity of methylene moiety in either **275** or **276** is essential for the success of reaction (Scheme 74). Consequently, vinyl ketones **1d,g,h** proved to fulfill this prerequisite as they contain electron attracting substituents.[116]

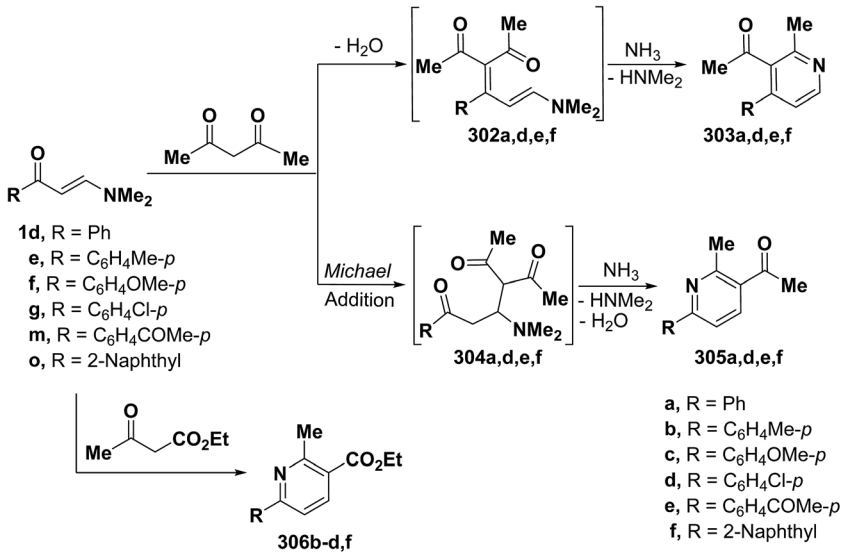
In addition, Al-Zaydi *et al.*[99] reported on the formation of pyrrole derivatives **281** upon treatment with acetic acid and ammonium acetate in a domestic microwave oven at full power. It is assumed that initially formed 2,4-dicoumarinoylpyrroles **280** undergo a Nenitzescu like cyclization[118] and decarbonylation; thus yielding the final products **281**, respectively (Scheme 75).

Martins and *et al.* evaluated the effect of type III DES in a reaction between β-enaminones **1d–g,i,o** and organic azide **282** for the synthesis of 4-acyl-1-substituted-1,2,3-triazoles **283** *via* 1,3-dipolar cycloaddition. The products were obtained in high selectivity and good yields (70–84%). The advantages of the method include easy work-up, metal-free conditions, inexpensiveness, and the ability to be used four times without a loss in yield (Scheme 76).[119]

1,5-Disubstituted 1,2,3-triazole derivatives **286** were prepared *via* the three-component reactions enaminone **1**, amine **284**, and tosylhydrazine **285**. This metal- and azide-free, regioselective synthetic method proceeds in the presence of only molecular iodine (Scheme 77).[120]

2.3.2. Preparation of six membered rings

2.3.2.1. Preparation of pyridines and related compounds. As mentioned earlier in this review, refluxing β-aminovinyl ketones **1d–f** in acetic acid alone resulted in the formation of 1,3,5-triaroylbenzene derivatives **135a–c** by a self condensation-elimination route.[43,66,67] In contrast, on being heated in acetic



Scheme 85

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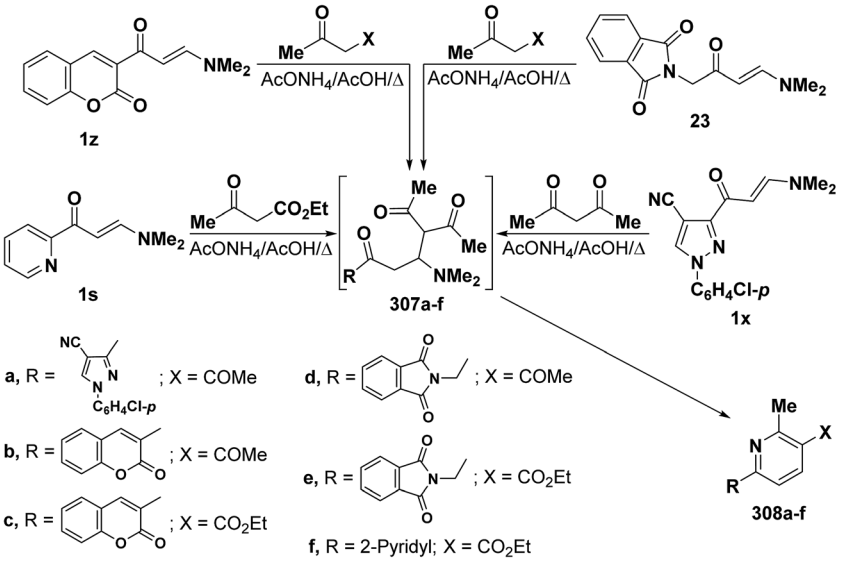
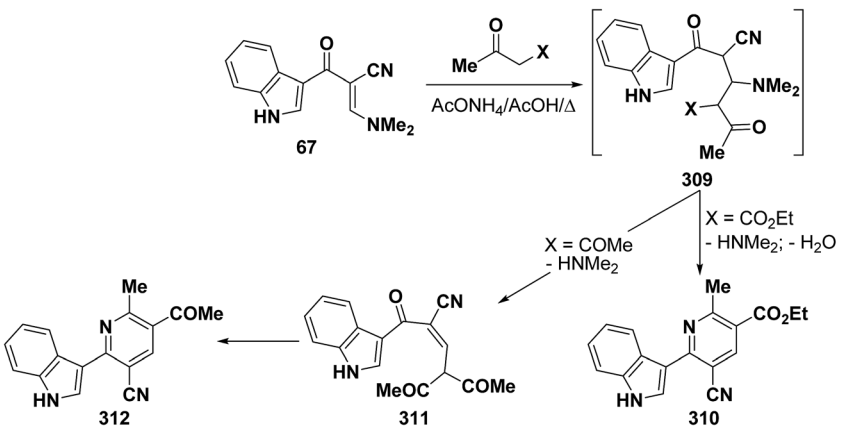
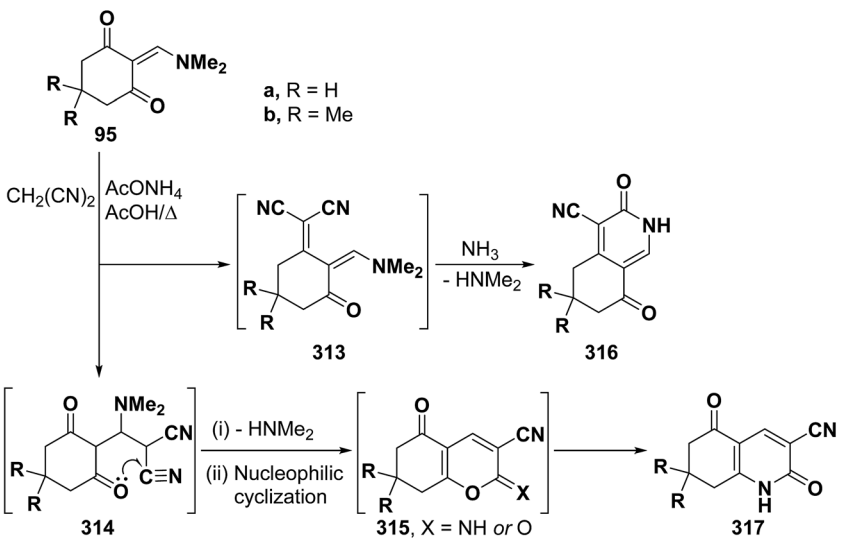


Scheme 86



Scheme 87



Scheme 88

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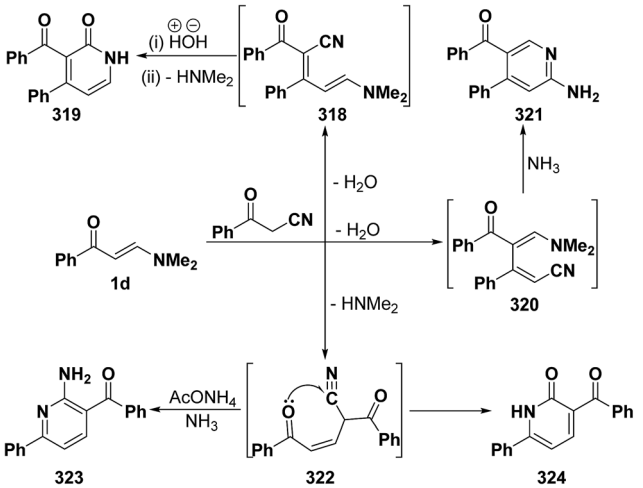


Scheme 89

acid in the presence of ammonium acetate, those ketones **1d–g** afforded 6-substituted-3-aroylpyridines **289a–d**, respectively.[66,67] The electron rich C-2 in one molecule of **1** adds to the electron deficient C-3 of another molecule, followed by dimethylamine elimination, forming the intermediates **21** and **287**, respectively. The latter intermediates **287** cyclizes by the action of ammonia into the final isolable products **289**, through the intermediacy of **288** (Scheme 78).

By using the synthetic sequence as was suggested for the synthesis of **289**, the 6-substituted-3-aroylpyridines **291a–f** were formed from dimethylaminomethylene compounds **1a**, **1m**, **1o** and **1p,q,s** respectively, by self cyclocondensation through the intermediate formation of **290a–f** (Scheme 79).[66–68]

Also, treating vinyl ketones **1z** in acetic acid/ammonium acetate afforded the corresponding pyridines **277** (ref. 78 and 99) while interaction of **1z** with enamino carbonyl compound **1a** in a microwave oven in the presence of ammonium acetate and acetic acid for two minutes gave a mixture of **292** and methylpyridine derivative **293** (Scheme 80).[99]

It is of value to report here that reaction of β-aminovinyl ketones with acetyl derivatives also provide access to pyridines. Lots of recent reports on this area have been found. Thus, *e.g.*, reacting aminovinyl ketone **1d** with acetophenone in refluxing acetic acid in the presence of ammonium acetate yielded a product that may be formulated as **294** or isomeric **295**. The cyclization reaction may proceed by two possible mechanisms, which differ in their sequential nucleophilic attack/amine exchange reaction. While initial condensation of the methyl function with the carbonyl group of the vinyl ketone **1d** and subsequent cyclization could lead to structure **294**, initial Michael addition of the methyl ketone across the activated double bond in **1d** and subsequent cyclization might afford compound **295** (Scheme 81).[121]

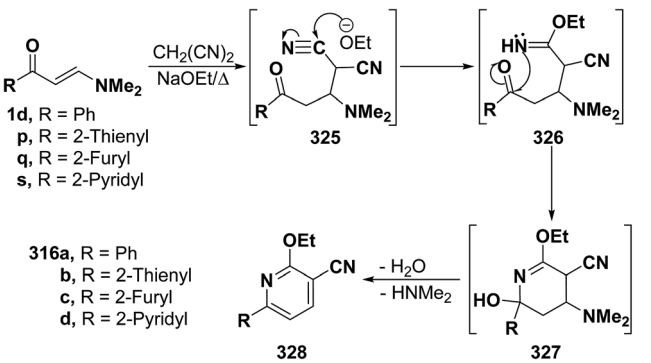
In a similar way, pyridine enaminones **1t,u** reacted with acetylpyridines in anhydrous tetrahydrofuran in the presence of potassium *t*-butoxide under stirring followed by refluxing in glacial acetic acid in the presence of ammonium acetate to afford the terpyridines **297a–e** in 25.8–29.7% yields through the intermediate formation of Michael adducts **296a–e** (Scheme 82).[122]

Analogously, aminovinyl ketone **1z** reacted with acetyl derivative **298** in refluxing acetic acid in the presence of ammonium acetate to produce the corresponding pyridine derivative **299** (Scheme 83).[78]

An interesting reaction leading to pyridine ring system is the interaction of enaminonitrile **121a** with acetophenone to give a sole isolable reaction product that was assigned structure **301** rather than isomeric **300** based on NOE difference NMR experiments where irradiation of pyridine 3-H at δ 7.37 ppm enhanced the dimethylamino signal (Scheme 84).[121]

It is also worthwhile to report here that interaction of β-aminovinyl ketones with active methylenes allows an interesting access to pyridine ring system. Intensive research work on this area of studies have been described. Elnagdi *et al.*[42,66,68,121] reported that reaction of aryl enaminones **1d,g**, **1m** with acetylacetone in refluxing acetic acid in the presence of ammonium acetate afforded pyridine derivatives. Two pathways can be envisioned for formation of these final products (Scheme 85). Thus, initial addition of active methylene moiety to α,β-unsaturated double bond in enaminones would afford Michael adducts **304a,d–f** that in the presence of ammonium ion condensed, in each case, with acetylcarbonyl group yielding an enamine that cyclizes into 6-arylpyridines **305a,d–f**. In contrast, initial condensation of active methylene moiety with carbonyl function would yield **302a,d–f** that in the presence of ammonium acetate cyclizes into the alternative 4-aryl analogues **303**. Structure **305** was preferred over possible isomeric structure **303** on the basis of ^{1}H NMR spectra.[7,42,66] A similar treatment of the aromatic enaminones **1e–g** and **1o** with ethyl acetoacetate led to the corresponding 4,5-unsubstituted pyridines **306b–d,f** as confirmed by the ^{1}H NMR spectra, which indicated pyridine protons with J = 8.0–8.2 Hz, that is characteristic for pyridine H-5 and H-4.[66]

In addition, heterocyclic enaminones **1s**, **1x**, **1z** and **23** also underwent analogous reactions with either acetylacetone or ethyl acetoacetate to yield the expected 6-heterocyclylpyridine derivatives **308a–f**, respectively, as the sole isolable products (Scheme 86). Formation of these compounds would involve an initial formation of Michael adducts **307a–f**, followed by intramolecular cyclization to give the final products **306a–f**.[7,25,91,121] 6-



Scheme 90

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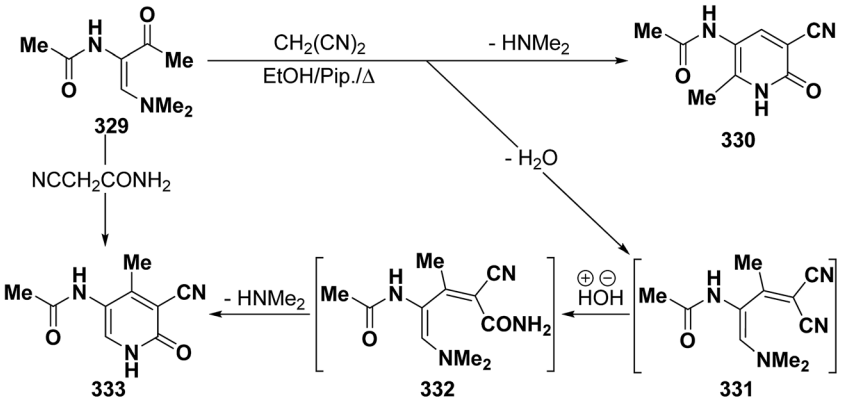
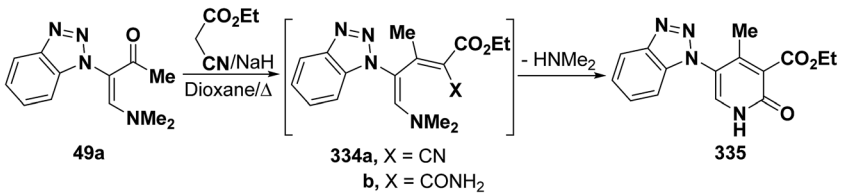


Scheme 91



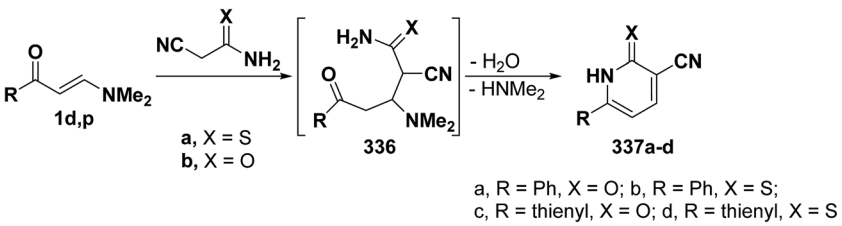
Scheme 92

Substituted pyridine structure **308a–f** was assigned for those products based on the presence of pyridyl ring protons, in each case, as doublets with $J = 8$ Hz as reported by us[7] and by others.[25,79,121]

In accordance with the observed formation of 6-heterocyclylpyridine derivatives **308**, enaminonitrile **67** reacted with ethyl acetoacetate in refluxing acetic acid in the presence of ammonium acetate to provide the expected pyridine derivative **310**. In contrast, treating compound **67** with acetylacetone under the same experimental conditions resulted in the formation of an acyclic product **310** that could not be cyclized into the anticipated pyridine derivative **312** (Scheme 87).[50]

Similar to the behavior of β-aminovinyl ketones toward acetylmethylene compounds, those vinyl ketones also reacted with cyanomethylene compounds to furnish pyridines. Thus, reaction of vinyl ketones **95a,b** with malononitrile in refluxing acetic acid and in presence of ammonium acetate yielded products of condensation *via* dimethylamine elimination. These may thus be formulated as **313–316**. Initial Michael addition to the α,β-unsaturated linkage can afford **314** that would then lose dimethylamine and cyclize into **315** or isomerize into **317** (Scheme 88). Alternatively, condensation of the carbonyl group in **95a,b** with the active methylene moiety would afford **313** that can then cyclize into **316**.[25]

An interesting reaction leading also to pyridine ring system is the interaction of phenyl enaminone **1a** with benzoylacetonitrile in refluxing acetic acid in the presence of ammonium acetate to furnish a mixture of two products. One of the products was assigned structure **323** and is assumed to be formed *via* initial addition of the active methylene moiety in benzoylacetonitrile to the enaminone C-3 and subsequent elimination of the dimethylamine yielding the acyclic Michael adduct **322**, that would react with ammonia to yield aminopyridine derivative **323** (Scheme 89). Several isomeric structures seemed possible for the other product, depending on the reaction route, namely; the pyridone structure **319** resulting from initial condensation of the active methylene moiety with the enaminone carbonyl function, forming **318**, followed by hydrolysis and subsequent cyclization, or an isomeric pyridone structure **321** resulting from initial condensation of the benzoylacetonitrile carbonyl function with the enaminone C-2, affording **320** and subsequent cyclization. Both structures **319** and **321** were excluded



Scheme 93

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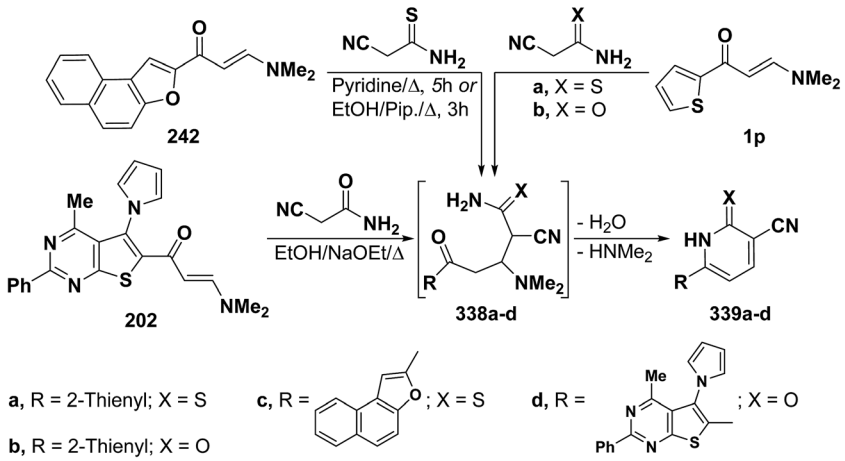
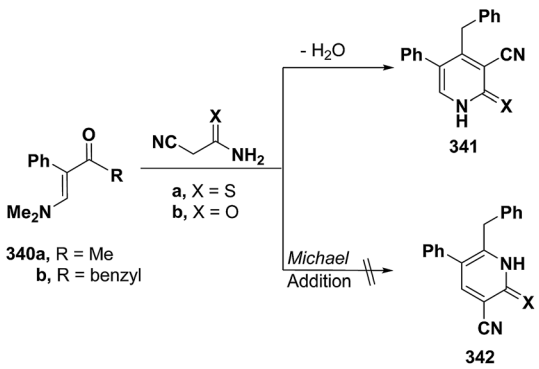


Scheme 94

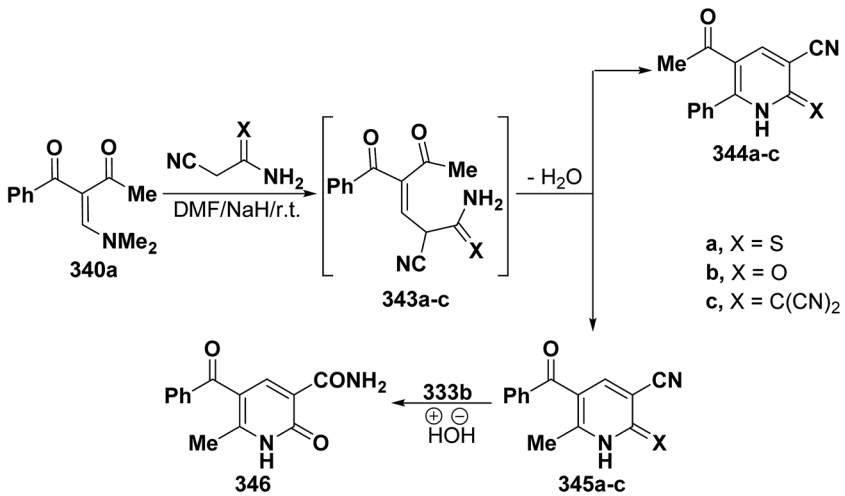


Scheme 95

based on the absence of a low field (δ > 8.5 ppm) pyridine 6-H signal. Consequently, the pyridone structure **324** was considered for the second reaction product that showed its stability on reflux in acetic acid or mineral acid, confirming structure **324**.[121]

In a similar way, β-aminovinyl ketones **1d** and **1p,q,s** reacted with malononitrile in refluxing ethanolic sodium ethoxide to yield the ethoxypyridines **327a–d**. Initial addition of carbanion of malononitrile across the activated double bond in vinyl ketones would yield the Michael adducts **325a–d**. Subsequent addition of ethoxide anion to one of the cyano groups would give the iminoethers **326a–d**, which would be cyclized *via* a nucleophilic attack of an NH group on a cyano carbon, affording the intermediates **327a–d**. This would be finally followed by deamination and dehydration, leading to the isolated ethoxypyridine products **328a–d** (Scheme 90).[94]

In contrast to the behavior of β-aminovinyl ketones toward cyanomethylene reagents, vinyl ketone **329** was treated with malononitrile, in ethanol in the presence of a catalytic amount of piperidine at reflux temperature to give a condensation product for which 6-unsubstituted pyridone structure **333** was considered rather than the alternative 4-unsubstituted structure **330** as indicated from spectral and chemical evidence.[116] In support of the proposed structure, compound **333** was also formed on treating **329** with cyanoacetamide in refluxing pyridine. Based on the above findings, the initial step in the reaction involves condensation of the carbonyl function in **329** with



Scheme 96

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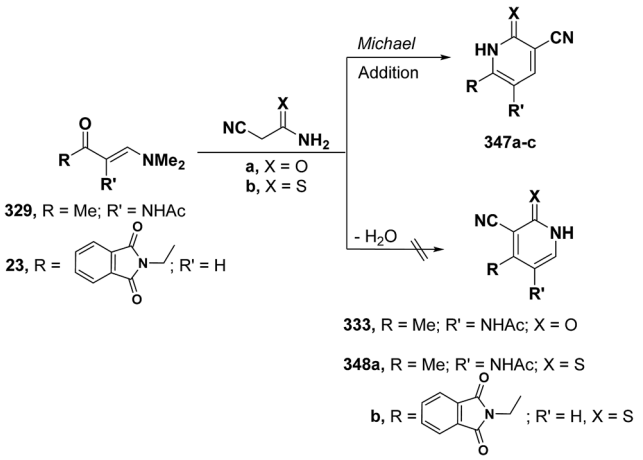
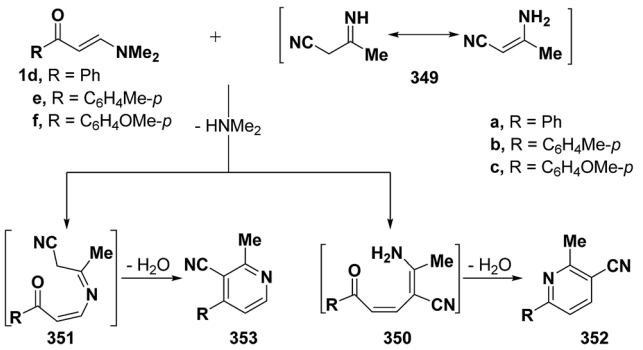
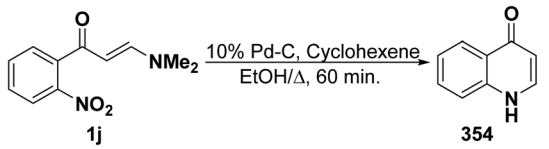


Scheme 97



Scheme 98



Scheme 99

malononitrile, yielding the diene **331** which is hydrolysed to an intermediate amide **332** and then cyclizes to **333** with the loss of dimethylamine molecule (Scheme 91).[123]

In a similar manner, vinyl ketone **49a** reacted with ethyl cyanoacetate in refluxing dioxane in the presence of sodium hydride to yield 6-unsubstituted pyridone derivative **335** *via* the intermediacy of the dienes **334a,b** (Scheme 92).[45]

One of the main route to 3-cyanopyridine-2-thiones and -2-ones is the interaction of β-aminovinyl ketones with cyanothioacetamide and with cyanoacetamide. Several data on this research area have been published. For instance, 3-cyanopyridines **337a–d** were prepared by treating enaminone **1d,p** with cyanothioacetamide in refluxing acetic acid in the presence of ammonium acetate for 1.5 hours, or with cyanoacetamide in sodium ethoxide solution at reflux, yielding the target molecule *via* the intermediacy of Michael adduct **336** (Scheme 93).[42,58,109,124,125]

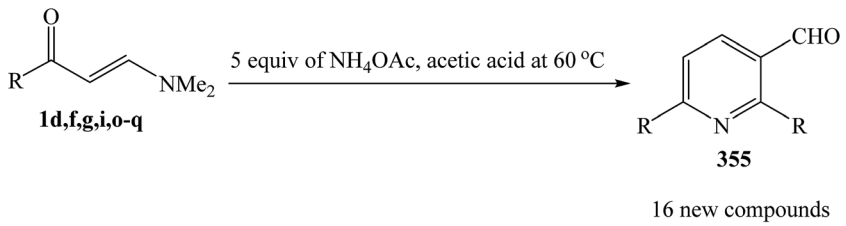
In accordance with the observed formation of 4,5-unsubstituted pyridines, heterocyclic enaminones **1p**, **242** and **202** reacted with cyanothioacetamide or cyanoacetamide to give the corresponding pyridines **339a–d**, respectively, *via* the intermediacy of Michael adducts **338a–d** (Scheme 94).[67,108,110,126]

Also, aminovinyl ketone **340b** condensed with cyanothioacetamide and with cyanoacetamide *via* dimethylamine elimination to yield the 3-cyanopyridines that were formulated as **341a,b** rather than isomeric **342a,b** as indicated from the ^{1}H NMR spectra for the reaction products. In case of X = S, ^{1}H NMR spectrum showed the pyridine ring CH as singlet at δ 7.76 ppm. This may suggest a favorable reaction product **342a** formed *via* initial addition of the active methylene moiety in cyanothioacetamide across the activated double bond in **340b** and subsequent cyclization and aromatization *via* dimethylamine elimination (Scheme 95). The alternative structure **341a** which could have resulted from initial condensation of the active methylene with the carbonyl function, should display a doublet for the pyridine ring CH.[127]

Treatment of dimethylaminomethylene compound **228a** with cyanothioacetamide, cyanoacetamide or anion of malononitrile dimer in dry DMF and sodium hydride led to 5-benzoylpyridines **345a–c** rather than isomeric **344a–c** based on the mass spectra (MS) of the isolated products. Additionally, the IR spectrum showed the disappearance of the cyano group so that structure **345b** became **346** upon hydrolysis (Scheme 96).[128]

Quite surprisingly, interaction of vinyl ketones **329** and **23** with cyanoacetamide or cyanothioacetamide gave, in each case, a sole isolable reaction product that was assigned 4-substituted pyridine structure **333** or **348a,b** rather than isomeric **347a–c**. Structure **333** or **348**, in this case, resulted from initial condensation of the active methylene in cyanoacetamide or cyanothioacetamide with carbonyl function in **329** or **23** and subsequent cyclization and aromatization *via* dimethylamine elimination (Scheme 97).[95,123]

On the other hand, it has been found that interaction of vinyl ketones **1d–f** with 3-aminocrotononitrile **349** afforded the 5,6-



Scheme 100

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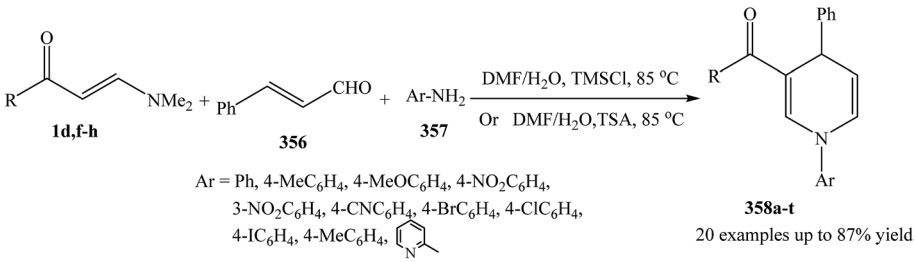
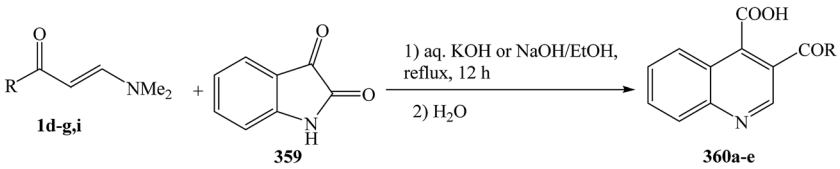
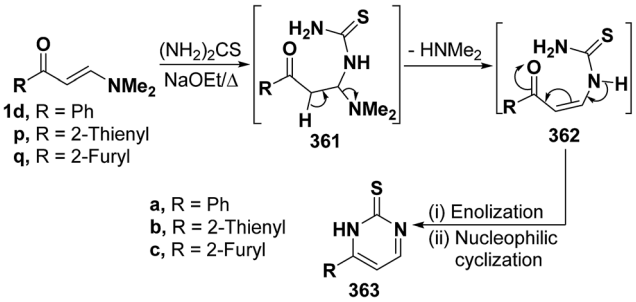


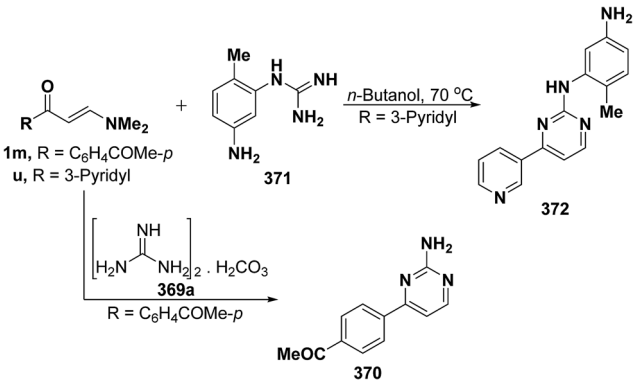
Scheme 101



Scheme 102



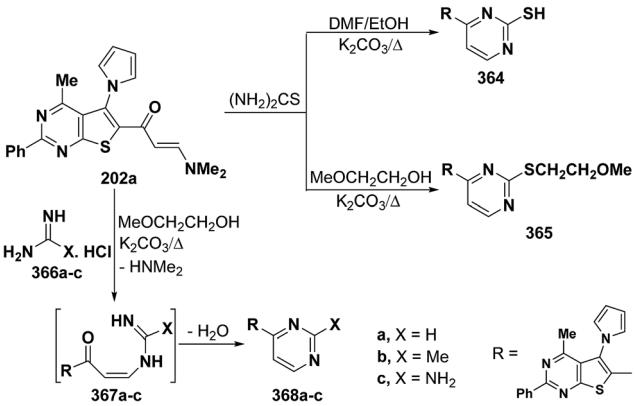
Scheme 103



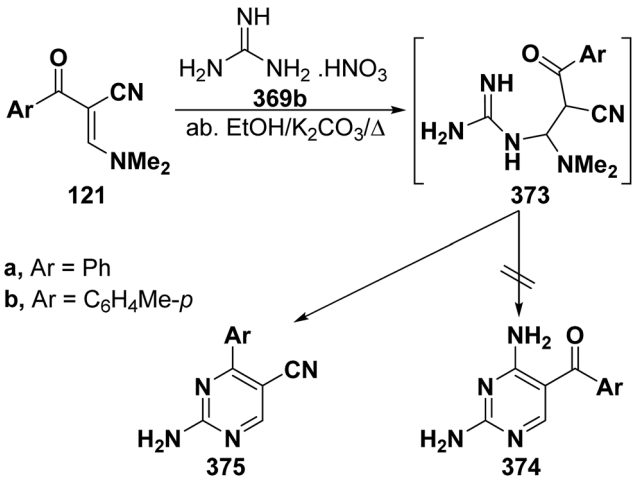
Scheme 105

unsubstituted pyridine derivative **353** *via* the intermediates **351**, but not **350** (Scheme 98).[43] Although this reaction can afford 4,5-unsubstituted analogue **352** as well, structure **353** is established based on H-5,6 coupling of pyridine which showed a value of 4 Hz, if the reaction product is **352** those protons would be expected to have a much higher value ($J \sim 9$ Hz).[7,42,43,66]

An interesting synthesis of quinolones is the formation of **354** on refluxing aminovinyl ketone **1j** in ethanol for 60 minutes under catalytic transfer hydrogenation conditions (CTH) using



Scheme 104



Scheme 106

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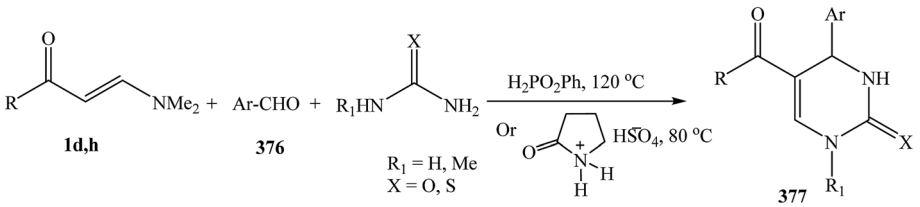
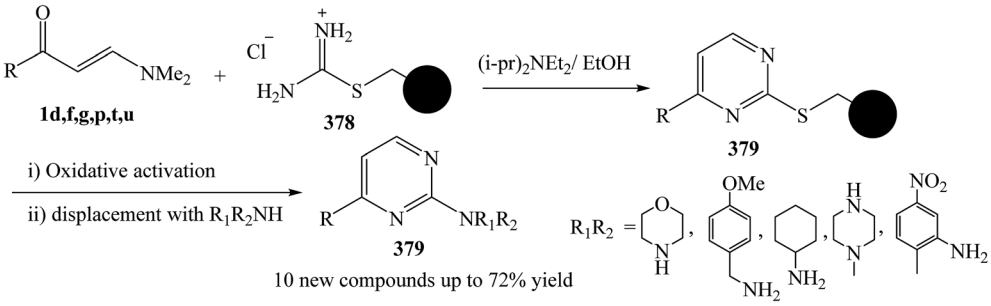
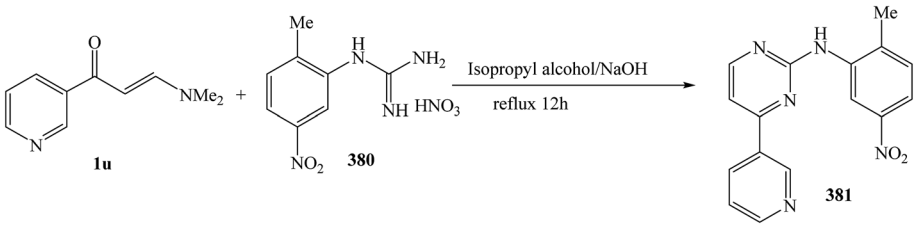


Scheme 107



Scheme 108



Scheme 109

cyclohexene as hydrogen source and 10% Pd–C as catalyst (Scheme 99).[129]

Shankaraiah and *et al.* was reported a clean, convenient, and highly efficient method for the rapid construction of pyridine 2,6-diarylnicotinaldehydes **355** by an unexpected self condensation of enaminoketones **1** in the presence of NH_4OAc in acetic acid under conventional conditions and also under microwave irradiation (Scheme 100).[130]

The three-component sequential reaction of enaminones **1d,f–h**, cinnamaldehyde **356** and the appropriate amines **357**, proceeded smoothly to give 1,3,4-trisubstituted 1,4-dihydropyridines **358a–t** in aqueous DMF (Scheme 101).[131,132]

Enaminones **1d–g,i** was heated at reflux with isatin **359** in the presence of an aqueous solution of KOH or NaOH, followed by subsequent acidification with dilute hydrochloric acid to give the quinoline-4-carboxylic acids **360a–e** in good to excellent yields (75–90%) (Scheme 102).[133]

2.3.2.2. Preparation of pyrimidines. One of the major routes to pyrimidines is the ring closure of β-aminovinyl ketones by bifunctional reagents. This one-pot cyclization involves both the carbonyl and the dimethylamino groups, leading eventually to the target pyrimidines. Some representative examples have been provided herewith. Thus, treatment of vinyl ketones **1d** and **1p,q** with thiourea in refluxing sodium ethoxide yielded the pyrimidine-2-thiones **363a–c**, respectively. Formation of these products would involve, in each case, an initial Michael addition of the amino group in thiourea to the activated double bond in **1d** or **1p,q** yielding Michael adduct **361a**, **361b** or **361c**. This is followed by deamination to form the acyclic non-isolable intermediates **362a–c**, which then undergo enolization and subsequent nucleophilic cyclization *via* loss of water, affording the final products **363a–c**. A plausible mechanism for the formation of pyrimidines **363a–c** is depicted in scheme **163** (Scheme 103).[94]

In a similar manner, heterocyclic enaminone **202** reacted with thiourea in refluxing DMF/ethanol in the presence of excess anhydrous potassium carbonate to afford the pyrimidine **364**, while the *S*-alkylated product **365** was obtained under similar reaction conditions, except that DMF/ethanol was replaced by methyl glycol.[97] On the other hand, treating **202** with guanidine compounds **366a–c** in refluxing methyl glycol in

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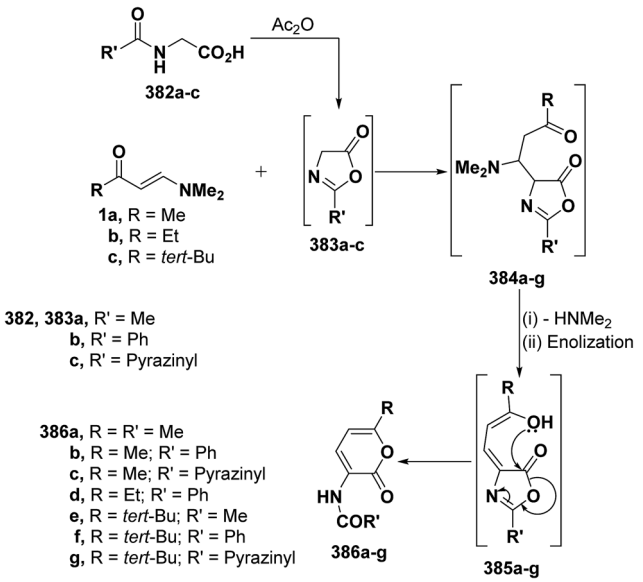


Scheme 110

the presence of excess anhydrous potassium carbonate resulted in the formation of the corresponding pyrimidines **368a–c**, respectively, *via* the intermediate formation of acyclic secondary enaminones **367a–c** (Scheme 104).[97]

In addition, reaction of aryl enaminone **1m** with guanidine carbonate (**369**) in refluxing ethanolic sodium ethoxide solution for sixteen hours resulted in the formation of 2-aminopyrimidine derivative **370**,[68] whereas pyrimidine derivative **372** was isolated on treatment of 3-pyridyl enaminone **1u** with guanidine derivative **371** *via* loss of dimethylamine and water molecules (Scheme 105).[134]

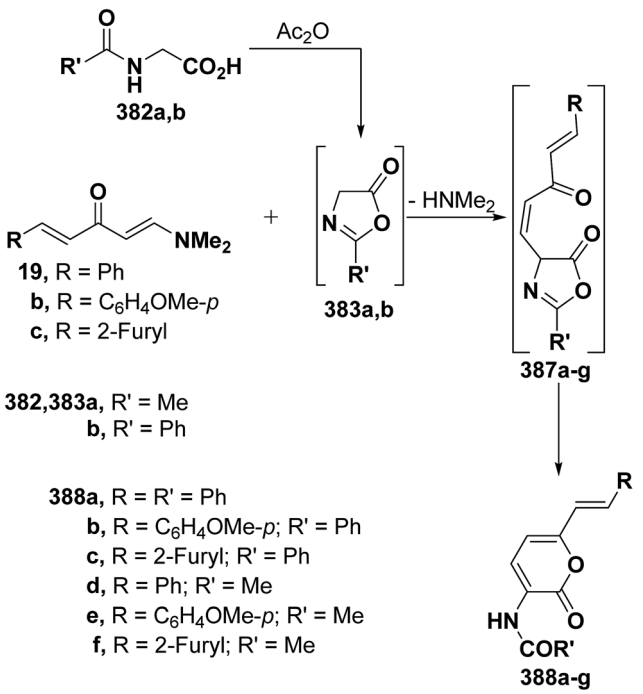
Interestingly, reaction of enaminonitriles **121a,b** with guanidine nitrate (**369**) in absolute ethanol in the presence of excess anhydrous potassium carbonate at reflux temperature furnished the pyrimidine-5-carbonitriles **375a,b**, *via* the intermediacy of Michael adducts **373a,b**, rather than the 5-aroyl analogues **374a,b** as proven from spectral data of the isolated products (Scheme 106).[61]

Recently, Alinezhad and *et al.* reported that phenylphosphinic acid or 2-pyrrolidonium bisulphate are found to catalyze the three-component condensation of an enaminone **1d,h**, aldehyde **376**, and urea or thiourea to afford the corresponding 6-unsubstituted dihydropyrimidinones **377** in high to excellent yields. This methodology is simple and fast synthetic route for the preparation of interesting class of heterocycles (Scheme 107).[135,136]

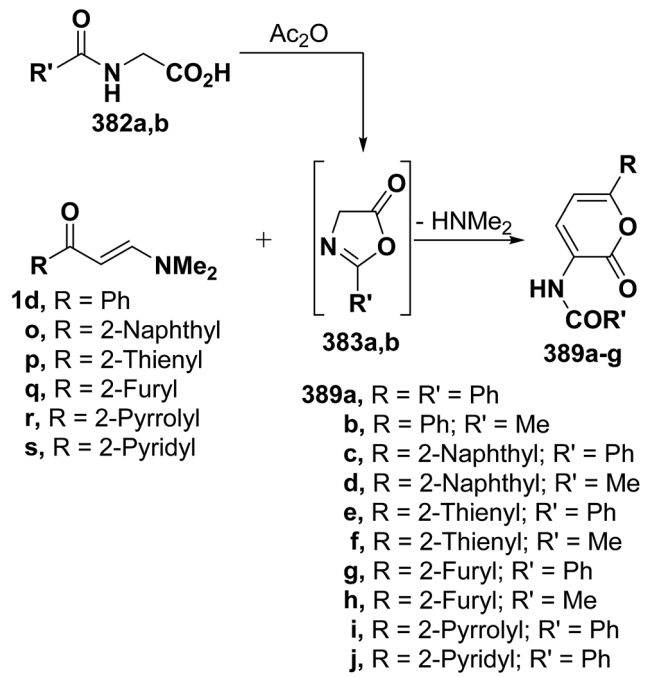
Ingham and *et al.*[137] was reported the development of a monolith-supported synthetic procedure of enaminone **1** in the presence of Huunig's base, taking advantage of flow processing and the superior flow characteristics of monolithic reagents over gel-phase beads, to allow facile access to an important family of 2-aminopyrimidine derivatives **379** through formation of thioether derivative **378**. The process has been successfully applied to a key precursor on route to Imatinib (Ar = 3-pyridyl, R_1 = 2-methyl-5-nitrobenzyl, R_2 = H) (Scheme 108).

The refluxing reaction of (*E*)-3-(dimethylamino)-1-(pyridin-3-yl) prop-2-en-1-one (**1u**) with 1-(2-methyl-5-nitrophenyl)guanidine nitrate **380** was processed in isopropyl alcohol for 12 h, to give *N*-(2-methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine **381** in 82% (Scheme 109).[138]

2.3.2.3. Preparation of pyrans. Recently, Kepe *et al.*[139,140] reported on an one-pot synthesis of different 2*H*-pyran-2-one derivatives *via* interaction of either monoactivated methyl



Scheme 111



Scheme 112

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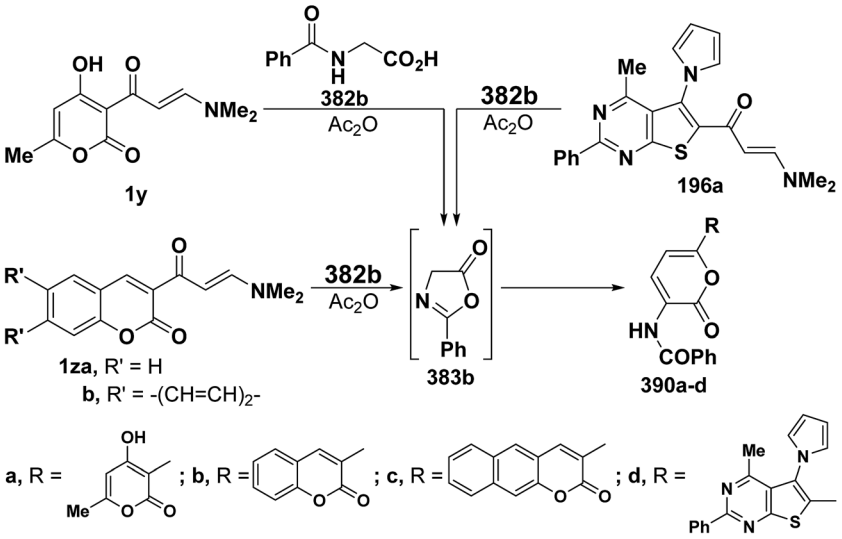
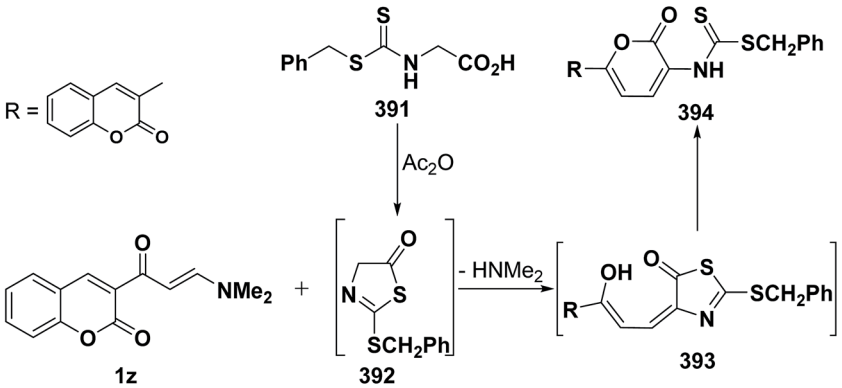


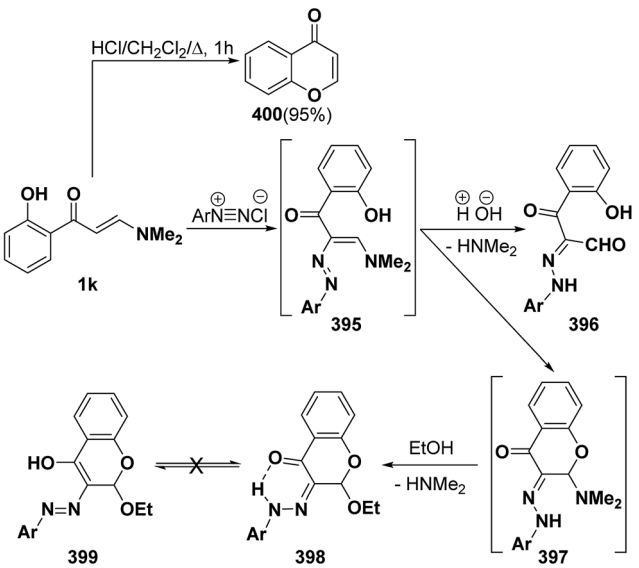
Scheme 113



Scheme 114

ketones or 1,3-dicarbonyl compounds with DMFDMA and *N*-acylglycines in acetic anhydride. More recently, the general nature of Kepe's pyranone synthesis was extended to reaction of *N*-substituted glycines with various β-aminovinyl ketones, with especial emphasis on ketones incorporating heterocyclic moieties. Thus, treating aliphatic enaminones **1a–c** with *N*-acetylglycine (**382a**), hippuric acid (**382b**) or *N*-pyrazinylcarbonylglycine (**382c**) in acetic anhydride led to the corresponding pyranones **386a–g**, respectively. It is believed that *N*-acylglycines **382a–c** are first cyclized to the corresponding oxazolones **383a–g** and subsequent reaction of the latter with enaminones **1a–c** yielded initially Michael adducts **384a–g**. These adducts undergo deamination and enolization to afford the non-isolable enols **385a–g** that rearrange into the final isolable products **386a–g**, respectively, *via* an attack of hydroxyl function on the oxazolone ring (Scheme 110).[68,141]

As an extension to the Kepe acylaminopyranone synthesis,[141,142] dienones **19a–c** reacted with *N*-acetyl- and *N*-benzoyl-glycines **382a,b** in acetic anhydride to yield products assumed to be the pyranones **388a–f** rather than the isomeric **389a–f**. It is thus assumed that *in situ* generated oxazolones



Scheme 115

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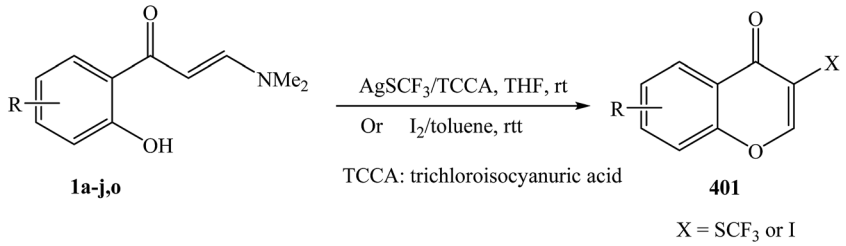
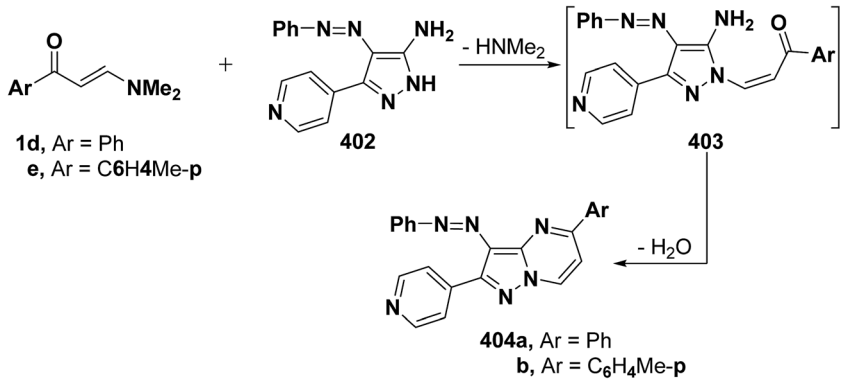


Scheme 116



Scheme 117

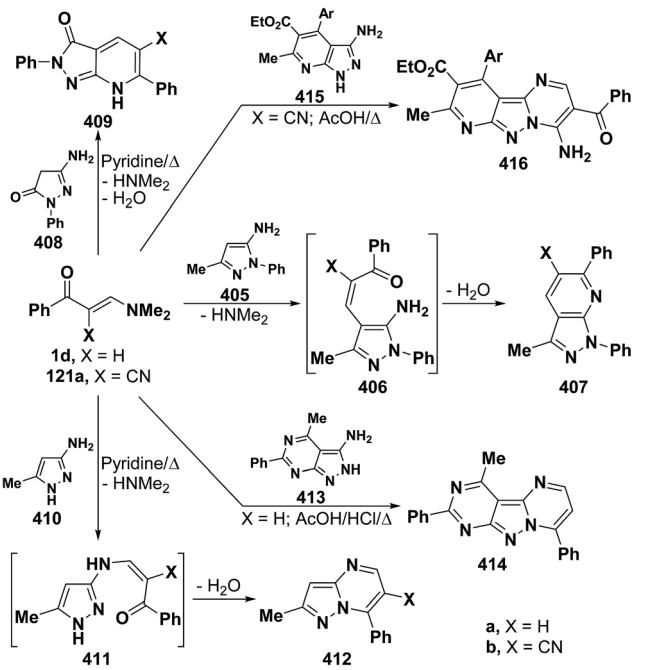
383a,b react with **19a–c** *via* initial addition of the active methylene in **383a,b** to the enaminone moiety at C-3, yielding intermediates **387a–g** that further rearrange into the final isolable products **388a–f** (Scheme 111).[37]

Similar reactions of **382a,b** with either aromatic enaminones **1d** and **1o** or with simple heterocyclic enaminones **1p–s** in acetic anhydride resulted in the formation of the corresponding acylaminopyranones **389a–j**, respectively (Scheme 112).[58]

In accordance with the observed formation of pyranones, heterocyclic enaminones **1y**, **1z** and **196** reacted with hippuric acid (**382b**) to give the desired pyranones **390a–d**, respectively (Scheme 113).[44,77,99,126] The formation of compounds **390a–d** starting from the corresponding heterocyclic enaminones and **382b** can thus be considered as an extension to the Kepe pyranone synthesis[141,142] to enable the synthesis of 6-heteroarylpyran-2-ones.

An interesting reaction leading to the formation of a pyranone ring system[78] is the interaction of aminovinyl ketone **1z** with dithiocarboxylic acid **391**, affording the pyranone derivative **394** *via* the intermediate formation of **392** and **393**, respectively, in a manner similar to that suggested to account for formation of pyranone **390b** from reaction of hippuric acid (**382b**) with the same vinyl ketone **1z**.[78] This is also a new extension to the Kepe acylaminopyranone synthesis (Scheme 114).[141,142]

Unexpectedly, interaction of aminovinyl ketone **1k** with aromatic diazonium salts did not give the anticipated arylhydrazonals **396a–c**, instead cyclic *N*,*O*-acetals **398a–c** were formed in good yields. It is believed that the formed enazo compounds **395a–c** were initially cyclized into **397a–c** that reacted with ethanol to yield the final isolable chromones (4*H*-benzopyran-4-ones, **398a–c**). Both ^{1}H and ^{13}C NMR spectra of the reaction products fit completely with the proposed structure. Additionally, the X-ray crystal structure determination of **398a** confirmed the existence of the hydrazono-chromone form **398** rather than the alternative possible enol azo form **399**.[141] Furthermore, the *o*-hydroxy substituted derivative **1k** showed an additional reactivity when treated with acids: it underwent intramolecular ring



Scheme 118

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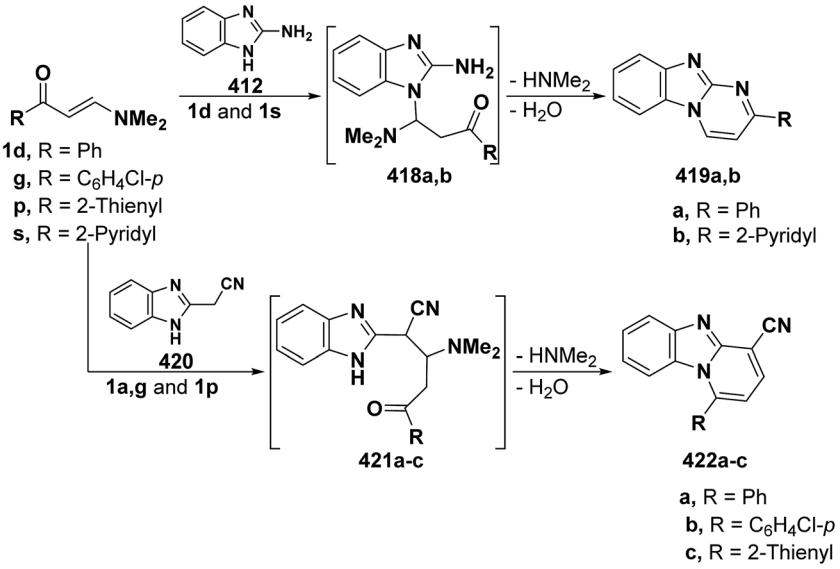


Scheme 119

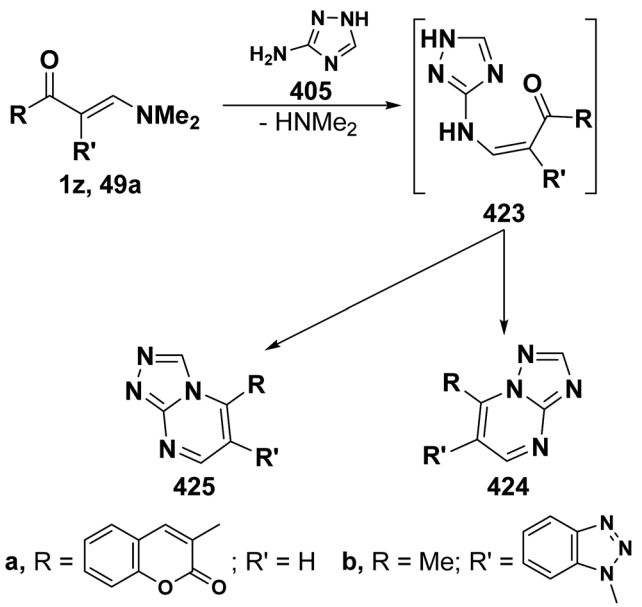
closure wherein the aromatic hydroxy group attacked the aminopropenone side chain, leading to chromone **400** in quantitative yield (Scheme 115).[142]

A facile and efficient synthetic strategy to 3-((trifluoromethyl) thio)-4*H*-chromen-4-one **401** was developed. $AgSCF_3$ and trichloroisocyanuric acid (TCCA) were employed here to generate active electrophilic trifluoromethylthio species *in situ*.[143] Or by using iodine in toluene.[144] This reactions could proceed under mild conditions in a short reaction time and be insensitive to air and moisture (Scheme 116).

2.3.3. Preparation of condensed heterocycles. Interaction of β-aminovinyl ketones **1d,e** with 4-substituted 5(3)-aminopyrazole derivative **402** in refluxing mixture of equivalent amounts of ethanol and acetic acid produced the pyrazolo[1,5-*a*]pyrimidine derivatives **404a,b** (Scheme 117). Formation of the latter products, as shown in Scheme 104, may be explained to occur *via* initial nucleophilic attack by the endocyclic nitrogen on the electron deficient C-3 in **1d,e** forming intermediates **403a,b** with loss of dimethylamine, followed by subsequent nucleophilic cyclization with the release of water.[145]

On the other hand, reaction of vinyl ketones **1d** and **121a** with 4-unsubstituted aminopyrazole **305** in the presence of zinc chloride and pyridine, respectively, yielded addition products with elimination of dimethylamine and water for which structure **407** was established. Additionally, when compounds **1d** and **405** were refluxed in ethanol, compound **406a** was isolated in a good yield. It could then be cyclized into **407a** on fusion with zinc chloride.[146] Likewise, treating vinyl ketones **1d** and **121a** with aminopyrazolone **408** in refluxing pyridine for three hours led to the corresponding pyrazolo[3,4-*b*]pyridines **409a,b** (Scheme 105).[144] In contrast to the observed formation of pyrazolopyridines,[146,147] the same ketones **1d** and **121a** reacted with 4-unsubstituted aminopyrazole **410** in refluxing pyridine to give the pyrazolo[1,5-*a*]pyrimidines **412a,b** as confirmed by the spectral data of the reaction products. Accordingly, formation of compounds **412a,b**, in this case, may be rationalized *via* initial nucleophilic attack by the exocyclic nitrogen on the electron deficient C-3 of enaminone moiety in **1d** and **121a** with subsequent elimination of dimethylamine, yielding intermediates **411a,b**. These undergo intramolecular cyclization *via* loss of water, affording the final products **412a,b** (Scheme 105).[54,148]

Similar to the previously described[52] behavior of vinyl ketone **1d** toward aminopyrazole **410**, compound **1d** reacted with 3-aminopyrazolo[3,4-*d*]pyrimidine derivative **413** in refluxing glacial acetic/hydrochloric (1 : 1) mixture for ten hours to give the respective pyrimido[2,3 : 4,3]pyrazolo[1,5-*a*]pyrimidine derivative **414** (Scheme 105).[149] In contrast to the reported[146] behavior of enaminonitrile **121a** toward aminopyrazole **410**, compound **121a** reacted with 3-amino-1*H*-pyrazolo[3,4-*b*]



Scheme 120

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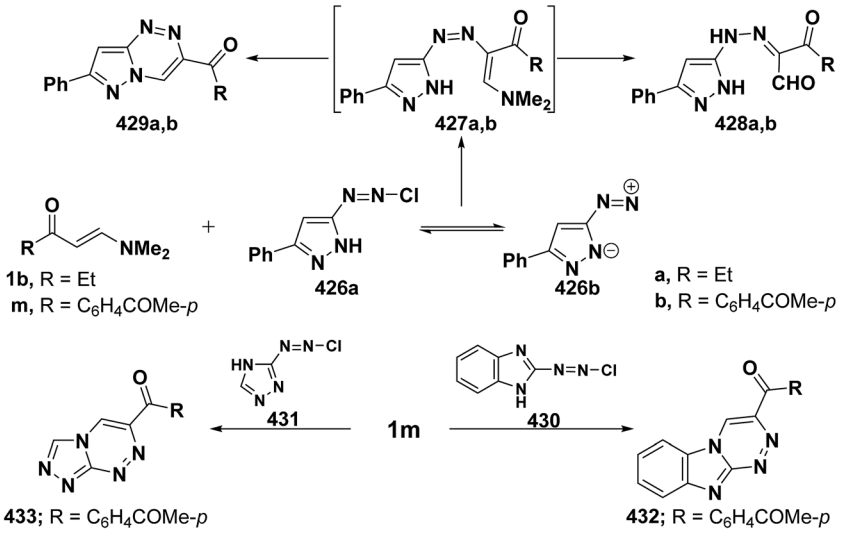
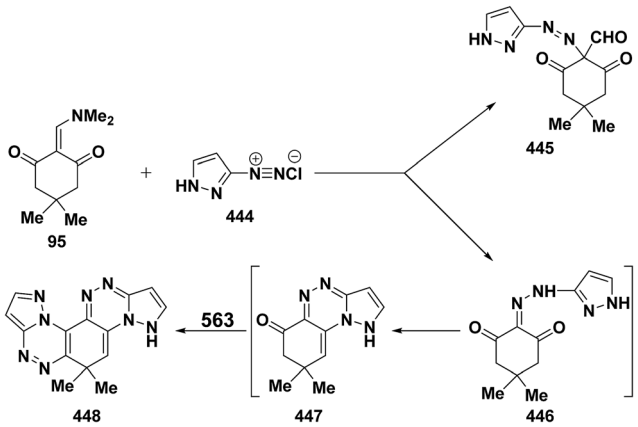


Scheme 121

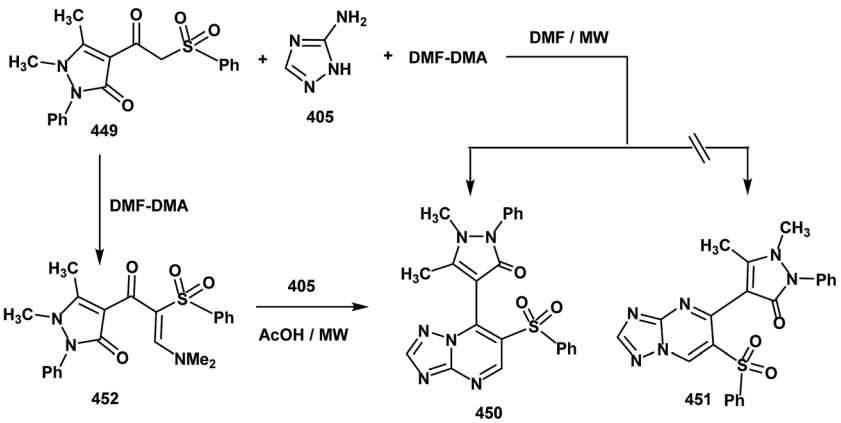


Scheme 122

pyridine derivative **415** in glacial acetic acid at reflux temperature for three hours to furnish the tricyclic pyrimidine derivative **416** (Scheme 118).[150]

Refluxing vinyl ketone **1d** or **1d** with 2-aminobenzimidazole (**417**) in pyridine solution afforded the 4-substituted pyrimido[1,2-*a*]benzimidazoles **419a,b**,[54] while 1-substituted 4-cyanobenzimidazo[1,2-*a*]pyridines **422a–c** were obtained on treatment of vinyl ketones **1d,g** or **1p** with 2-cyanomethylbenzimidazole (**420**) in refluxing ethanol containing a catalytic amount of piperidine.[23] Formation of compounds **419a,b** is thus formed *via* addition of the ring nitrogen to the activated double bond in **1d** and **1s** yielding Michael adducts **418a,b** which then cyclize by elimination of water and aromatize *via* loss of dimethylamine, affording the isolable products **419a,b**.[54] On the contrary, compounds **422a–c** are formed *via* addition of active methylene to the activated double bond, leading eventually to the final products through the intermediate formation of **421a–c** (Scheme 119).[23]

Moreover, heterocyclic enaminones **1z** and **49a** reacted with 3-amino-1,2,4-triazole (**405**) to yield products that may be formulated as **424** or the isomeric **425**.[45,90] However, structure **425** was established for the reaction products based on ^{1}H NMR data and NOE experiments (Scheme 120).



Scheme 123

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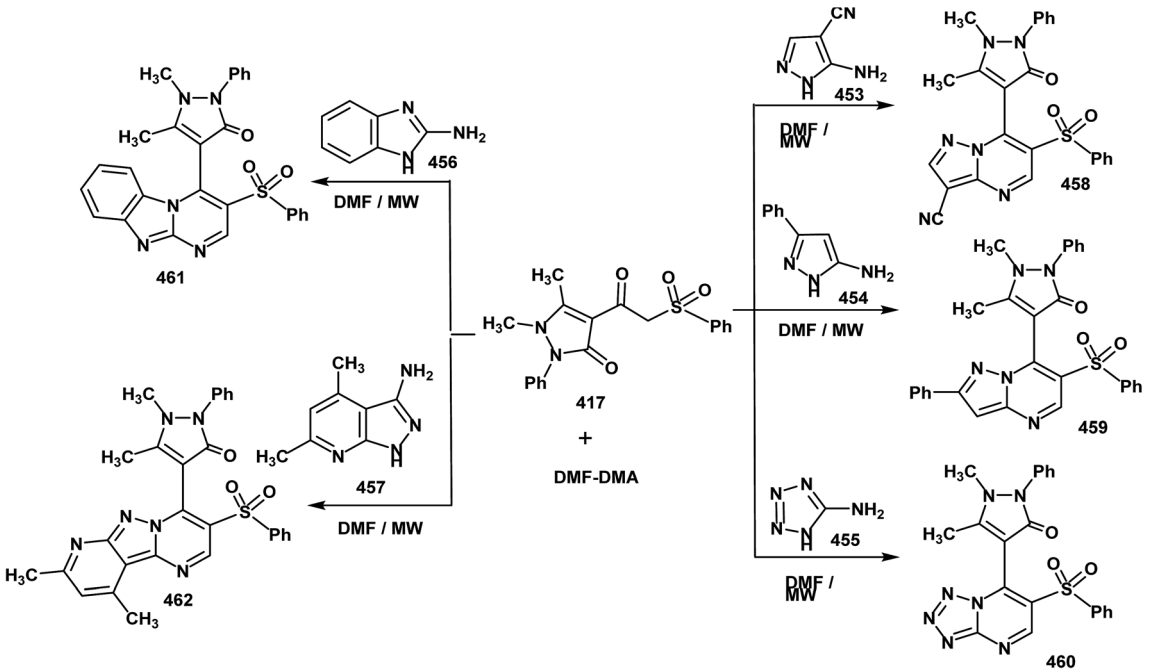
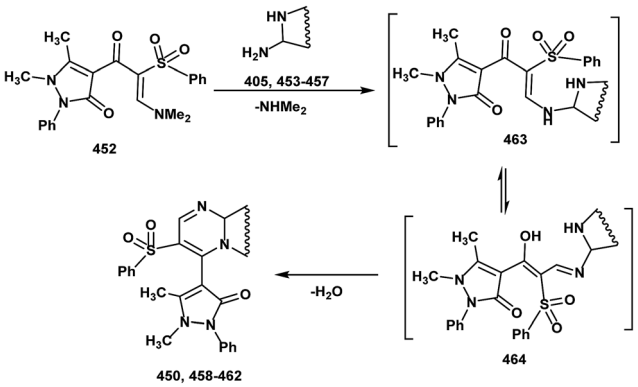


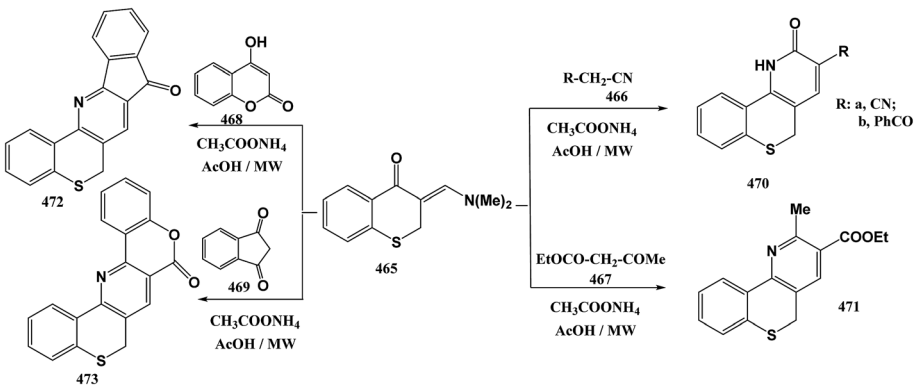
Scheme 124



Scheme 125

It has been reported[68] that vinyl ketones **1b** and **1m** coupled with the diazotized 5(3)-amino-3(5)-phenylpyrazole (**426a**), which exists in equilibrium with an isolable diazobetaine **426b**, to give azolotriazines **429a,b** rather than the expected acyclic α-hydrazono-β-ketoaldehydes **428a,b**. Thus, the inability to isolate the target hydrazones **428a,b** from this reaction may indicate that the reagents react *via* a direct 4 + 2 cycloaddition mechanism to the activated double bond in **1b** and **1m** leading to the isolated products **429a,b** (Scheme 121). Likewise, coupling compound **1m** with diazotized 2-aminobenzimidazole **430** and with diazotized 3-amino-1*H*-1,2,4-triazole **431** afforded the analogous [1,2,4]triazino[4,3-*a*]benzimidazole derivative **432** and triazolo[3,4-*c*][1,2,4]triazine derivative **433**, respectively, *via* direct 4 + 2 cycloaddition.[68]

Interestingly, the behavior of cyclic enaminone **95b** toward diazotized heterocyclic amine **444** differs also from the well



Scheme 126

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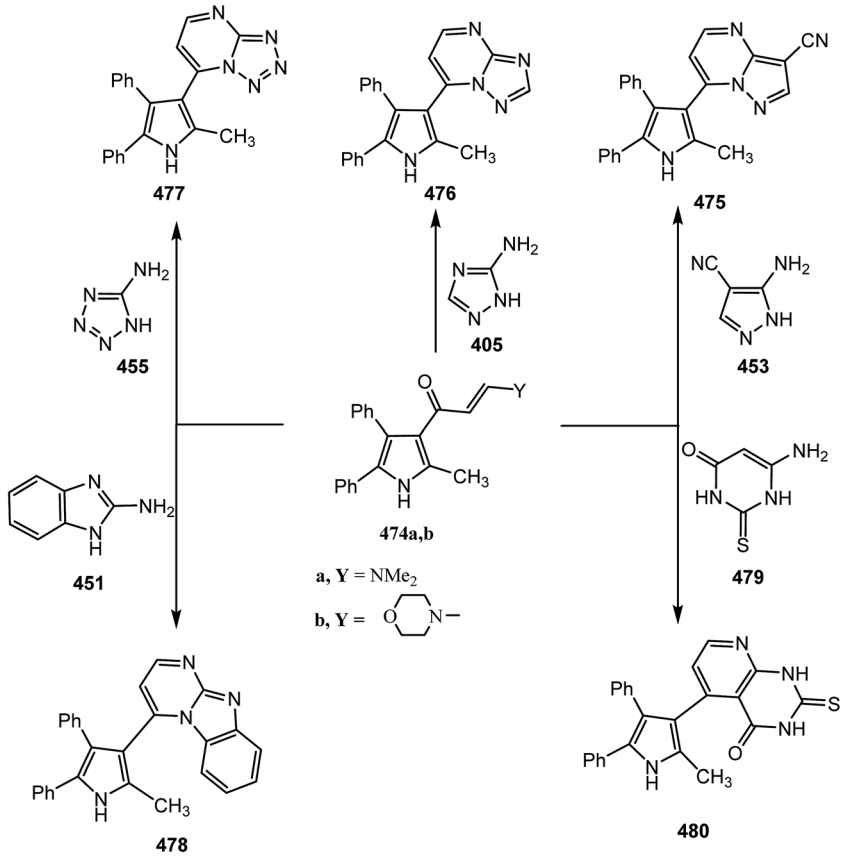


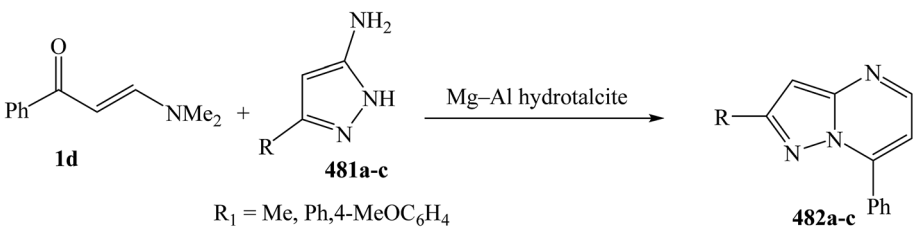
Scheme 127

established behavior of acyclic enaminones toward arenediazonium salts, where formation of 2-heteroylhydrazonopropanal **445** has not been observed, but instead a biscoupling product **448** has been obtained. This product is assumed to be formed *via* initial Japp Klingemann type cleavage of the dimethylaminomethylene moiety in **95b**, yielding **446** that cyclizes into **447** and then couples further with **444** to yield a hydrazone that cyclizes into the final isolable product **448** (Scheme 122).[25]

Multi-component reaction of sulphone **449**, 3-aminotriazole **405** and dimethylformamide–dimethylacetal (DMF–DMA) in DMF under microwave irradiation at 150 °C for 10 min. Afforded compound **450** rather than its isomeric structure **451** (Scheme 110). The conformation of compound **450** was established on the bases of spectral data (MS, IR, ^{1}H NMR) and elemental analyses. Furthermore, alternative synthesis of compound **452** was achieved *via* condensation of sulphone **1** with dimethylformamide dimethylacetal (DMF–DMF) to give compound **452**, and treatment of the product **5** with 3-aminotriazole **305** under the same reaction condition to yield authentic product **450** (Scheme 123).[151]

With this result in hand, the scope of such multi-component protocol were expanded and derivatives **453–457** were synthesized; sulphone **452** and dimethylformamide–dimethylacetal (DMF–DMA), under the same reaction conditions, afforded, in each case, the corresponding heterocyclic ring systems **458–462**, respectively (Scheme 124).[151]

To account for the formation of the products **450** and **458–462**, it was suggested that the studied reactions started with Michael-type addition of the exocyclic amino group of each the amines used to the activated double bond of **5** followed by *in*



Scheme 128

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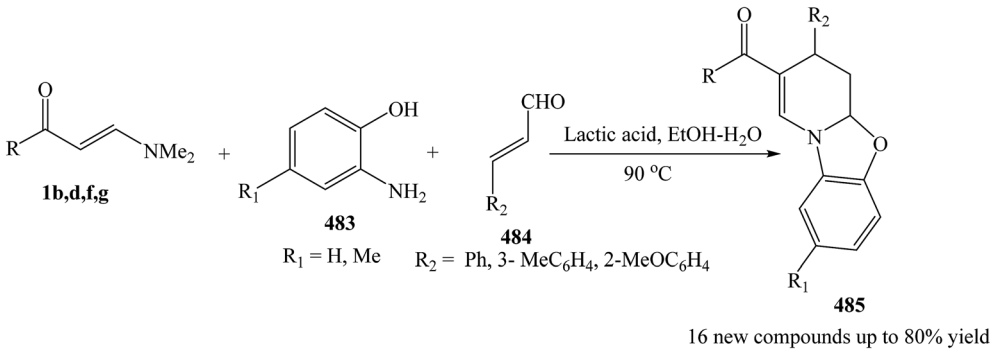
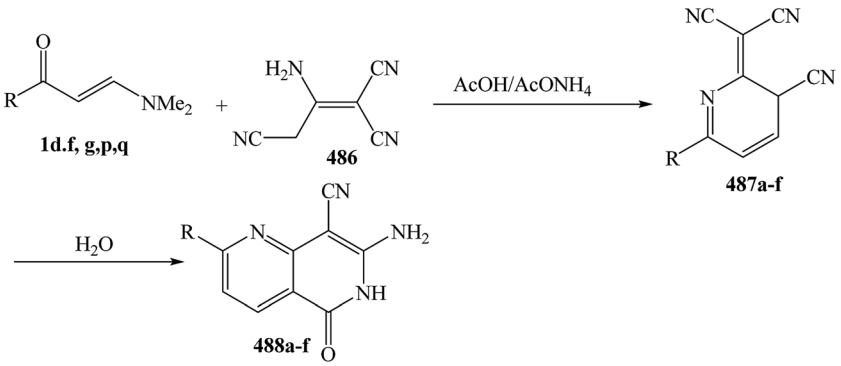
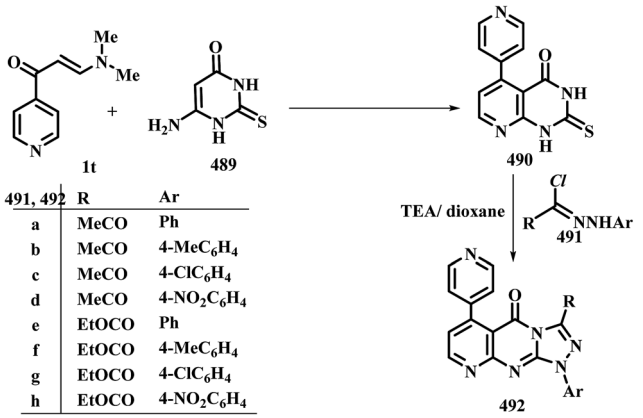


Scheme 129



Scheme 130



Scheme 131

situ tandem elimination of dimethylamine and dehydrative cyclization (Scheme 125).[151]

Also, the reaction of enaminone **465** with active methylene under microwave irradiation. Reaction of enaminone **465** with active methylene derivatives **466–469** gave in glacial acetic acid in the presence of ammonium acetate gave poly-heterocyclic ring systems **470–473**, respectively (Scheme 126). The structure of the products was assigned based on the spectral data and elemental analyses.[152]

The reactivity of the enaminone **474a** or the morpholinyl derivative **474b** towards some heterocyclic amines were also examined. Thus, reaction of **474a** or **474b** with 5-amino-1*H*-pyrazole-4-carbonitrile **453** in acetic acid under reflux yielded the respective pyrazolo[1,5-*a*]pyrimidine derivative **475** (Scheme 114). Similar treatment of **474a** or **474b** with 5-amino-1,2,4-triazole (**405**), 5-amino-1*H*-tetrazole (**455**), 2-amino-benzimidazole (**451**) and 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**479**) under the same reaction conditions afforded the respective 1,2,4-triazolo[1,5-*a*]pyrimidine **441**, tetrazolo[1,5-*a*]pyrimidine **477**, benzimidazo[1,2-*a*]pyrimidine **478** and 2,3-dihydropyrido[2,3-*d*]pyrimidinone **480** derivatives, respectively (Scheme 127).[51]

The catalytic activity of the as-synthesized and activated hydrotalcites towards the aza-Michael addition reaction was evaluated. Thus, the reaction of an enaminone **1d** with the 5-amino-1*H*-pyrazole derivatives **481a–c** in the presence hydrotalcite catalysts was carried out without solvent under microwave irradiation, to obtain only one isolable product in each case, (as examined by TLC) which were identified as pyrazolo[1,5-*a*]pyrimidine derivatives **482a–c** (Scheme 128).[153]

An environmentally benign multicomponent synthetic method has been realized for the diastereoselective construction of fused tetrahydropyridines **485** from reaction of enaminone **1b,d,f,g**, *o*-aminophenol **483**, and cinnamaldehyde **484** in the presence of lactic acid in water–ethanol media (Scheme 129).[154]

A mixture of enaminone **1d,g,p,q** and 3-amino-2-cyanopent-2-enedinitrile (**486**) in AcOH/NH_4OAc was heated under reflux for 2 h to give 7-amino-5-oxo-2-(thienyl)-5,6-dihydro-1,6-naphthyridine-8-carbonitriles **487a–d** (Scheme 130).[155]

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The reaction of enaminone **1t** with 6-amino-2-thioxo-(1*H*)-pyrimidin-4-one (**489**) produced 5-(pyridin-4-yl)-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**490**) (Scheme 2). Treatment of thione **490** with hydrazonoyl halides **491a–h** in dioxane, in the presence of triethylamine under reflux gave in each case a single product consistent with structure **492** (Scheme 2) based on spectroscopic data (IR, ^{1}H NMR and MS) and elemental analyses (Scheme 131).[16]

3. Conclusions and future directions

The data considered in this review clearly demonstrate the high synthetic applications of *N*,*N*-dimethylenamino ketones in the preparation of acyclic and carbocyclic compounds as well as a broad range of heterocyclic and fused heterocyclic derivatives. Most importantly, these *N*,*N*-dimethyl analogues have proven to be of biological interest and provide an access to new class of biologically active heterocyclic compounds for biomedical screening. Presently, the great interest of researchers worldwide in such ketones is confirmed by the fact that most of the articles cited in this review are dated in the last two decades. We are sure that they will generate new and innovative applications with future generations of compounds, and thus providing a valuable adjunct to therapy. Further studies in this direction are currently underway and the results of this research will be reported elsewhere.

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