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Green methodologies in organic synthesis: recent developments in our laboratories

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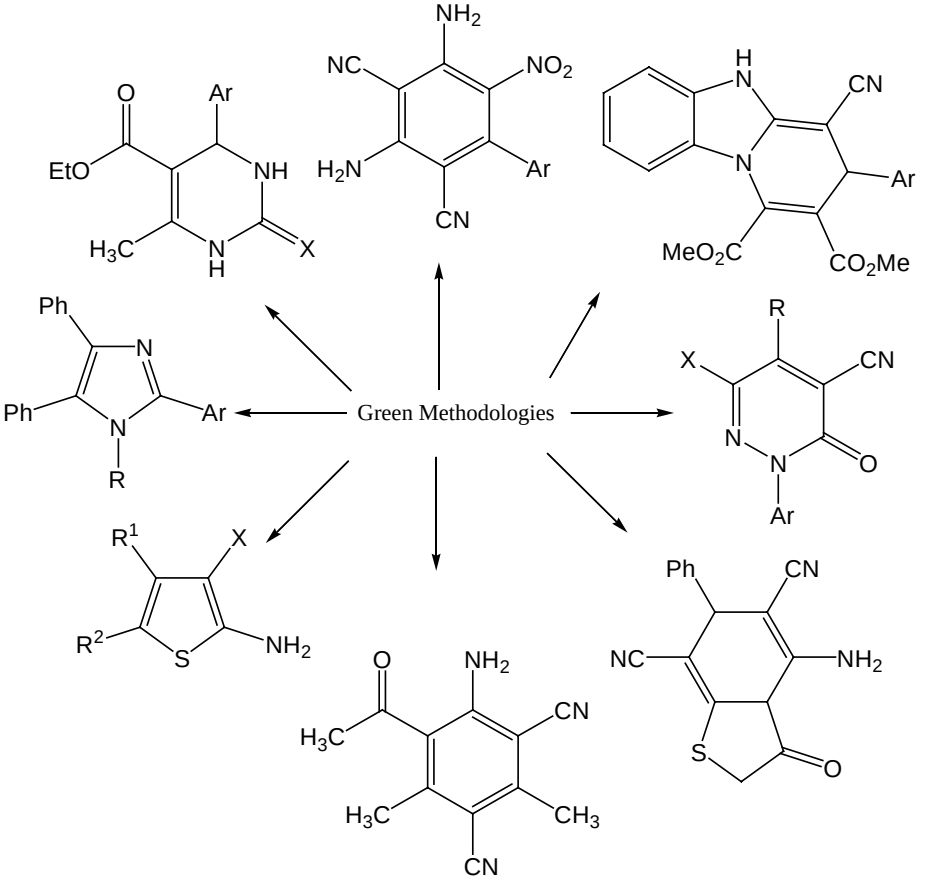
The results of the studies carried out in our laboratories during the last 15 years, aimed at developing green methodologies for the synthesis of polyfunctionalized heteroaromatic substances, are surveyed. The results of the investigations demonstrate that green methodologies are not only less hazard than classical preparative methods but they also are more efficient and economical. For example, short reaction times and higher yields are observed for reactions in which conventional heating is replaced by microwave or ultrasound irradiation. The implementation of multicomponent reactions in green preparative routes also reduces the cost of carrying out the reactions because multiple separation and crystallization steps are avoided. In general, by employing the new green methodologies we have been able to produce a large number of polyfunctional aromatic substances in a highly efficient manner.



Keywords: green methodologies; synthesis

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Introduction

As a result of pollution prevention legislation in the USA in 1990 [1], a green chemistry campaign was initiated so that organic substances could be produced in an environmentally clean manner. The basic principles guiding this new synthetic strategy are simply summarized in the following goals:

(1) Reducing potential waste production by utilizing atom economical processes, which minimize the use of solvents.
(2) Reducing the use of hazardous reagents or the production of hazardous by-products.
(3) Utilizing energy economically and looking at energy sources that do not rely on fossil fuel combustion.
(4) Minimizing time so that energy consumption is reduced.
(5) Maximizing yields by utilizing catalysts when appropriate.

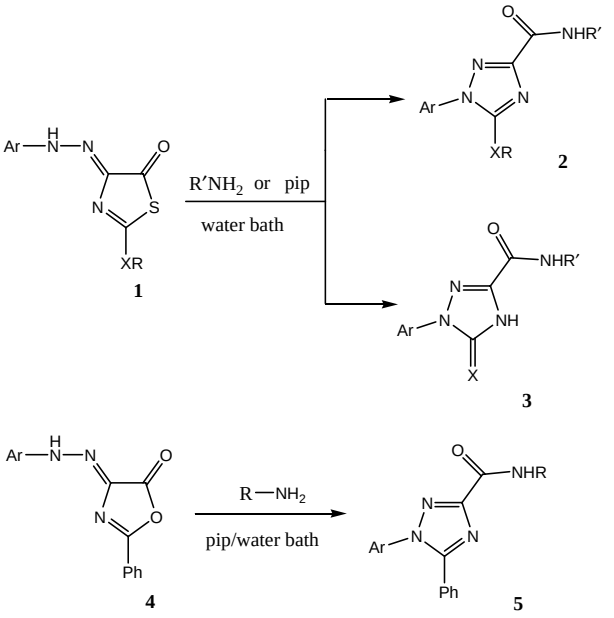
Owing to the fact that the 12 principles of green chemistry have been reviewed several times recently [2–5], they will not be elaborated in detail here. Instead, the review below focuses only studies carried out in our group that were targeted at developing green methodologies for the preparation of heterocyclic compounds.

Synthetic approaches

Solvent-free reactions

Long before the recognition and development of green chemistry concepts, we utilized methodologies employing solvent-free reactions for the production of 1,2,4-triazole carboxamides [6–8], recently patented as cannabinoid receptor blockers [9].

The goal of our more recent efforts was to design economical reactions. We observed that mixtures of **1** and a variety of amines when stirred in refluxing water yield either **2** or **3** depend on the nature of the amine utilized [6–8]. Recently we have also observed that **4** undergoes rearrangement to form **5** under these reaction conditions (Scheme 1 and Table 1) [10].



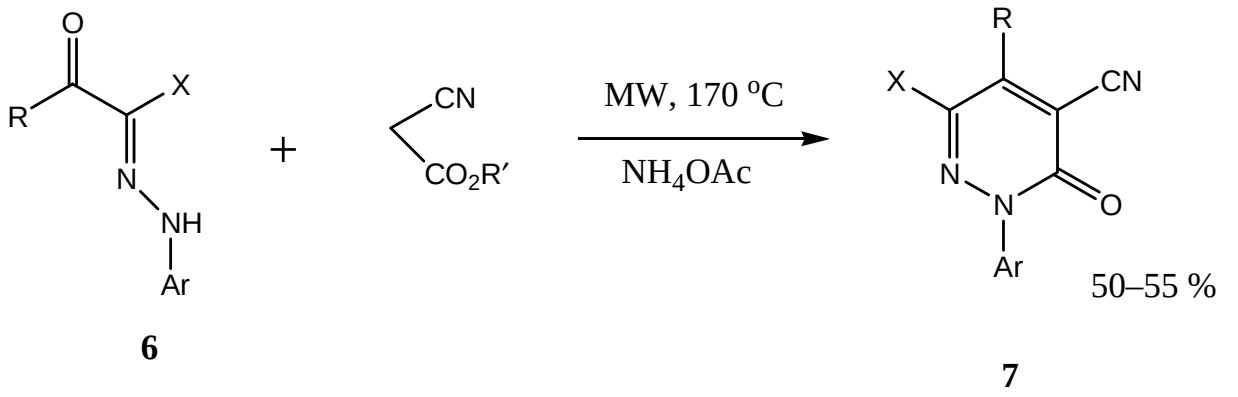
Scheme 1. Rearrangements of compounds **1** and **4**.

In the past decade, we have also described the conversion of **6** to **7** *via* reaction with ethyl cyanoacetate in the presence of a catalytic amount of both AcOH and ammonium acetate. This finding opens a new route in which **7** is employed as a precursor in generation of condensed pyridazines (Scheme 2) [11].

Recently, a green, highly efficient, three-component process for the synthesis of thiazolo[3,2-a]pyridine derivatives **8** and **9** was described. Accordingly, reactions were observed to occur between malononitrile, aromatic aldehydes, and 2-mercaptoacetic acid in respective molar ratios of 2:2:1.2 and 2:2:2.1 and in the presence of catalytic amounts of piperidine in the absence of solvent to produce **8** and **9** (Scheme 3 and Table 2) [12]. The structures of the products of these reactions were established using HMBC and heteronuclear multi-quantum correlation (HMQC) techniques. The findings contrast to the reported formation of pyronothiazoles **10** in similar reactions [13].

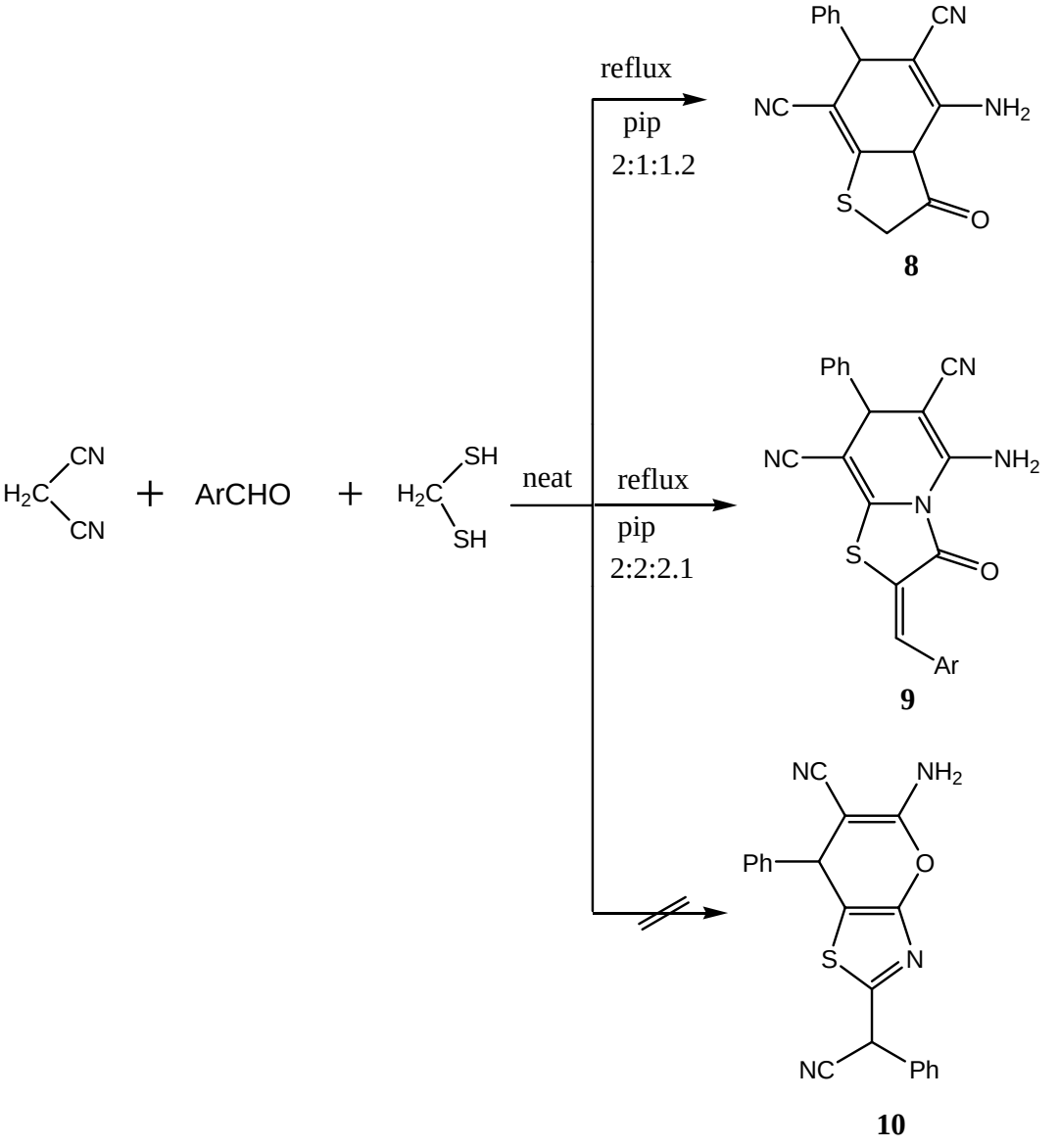
Table 1. Yields of compounds **2a**–**c** and **3a**–**c**.

Compounds	X	R	R′	Ar	Yield%
2a	S	$C_6H_5CH_2$	C_6H_5	C_6H_5	80
2b	S	$C_6H_5CH_2$	C_6H_5	*o*-$CH_3C_6H_4$	65
2c	S	$C_6H_5CH_2$	C_6H_5NH	C_6H_5	73
3a	S	–	CH_3	C_6H_5	80
3b	S	–	CH_3	*o*-$CH_3C_6H_4$	78
3c	S	–	Piperidino	C_6H_5	85



6 **7**

Scheme 2. Syntheses of pyridazines **7**.



8 **9** **10**

Scheme 3. Syntheses of compounds **8a**–**d** and **9**.

Table 2. Yields of compounds **8** and **9a–c**.

Compounds	Ar	Yield%
8a	C_6H_5	85
8b	*p*-BrC_6H_4	82
8c	*p*-$CH_3OC_6H_4$	88
8d	*m*-$O_2NC_6H_4$	82
9a	C_6H_5	90
9b	*p*-$CH_3OC_6H_4$	92
9c	*m*-$O_2NC_6H_4$	87

Enaminones **11** are produced *via* reactions of methyl ketones with dimethylformamide dimethylacetal (DMFDMA) [14] in refluxing toluene [15], but the yields of these processes are rather poor. Heating methyl ketones with DMFDMA in absence of solvent for 4–8 h, however, leads to the formation of **11** in much improved yields (Scheme 3) [14]. A similar methodology has been developed for the synthesis of **15** from **10**, triethylorthoformate and morpholine or piperidine **14a,b** (Scheme 4) [16].

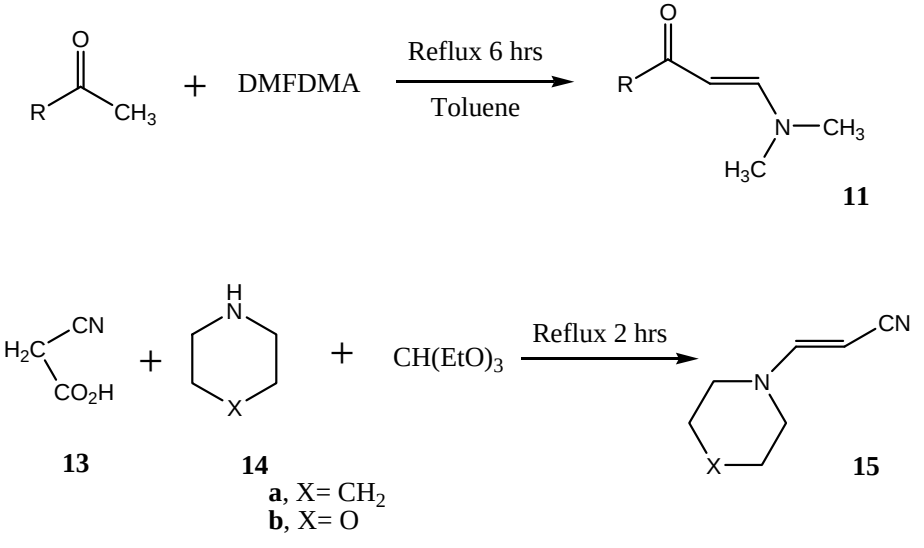
Utilization of microwaves and ultrasound as energy sources

Since Gidey and Gidey described [17] the utility of microwave irradiation produced in domestic ovens as an energy source for conducting organic reactions in short time periods, the utility of this technique in organic synthesis has gained great attention [17,18]. This is especially true when microwave ovens that are specially designed for chemical reactions were constructed.

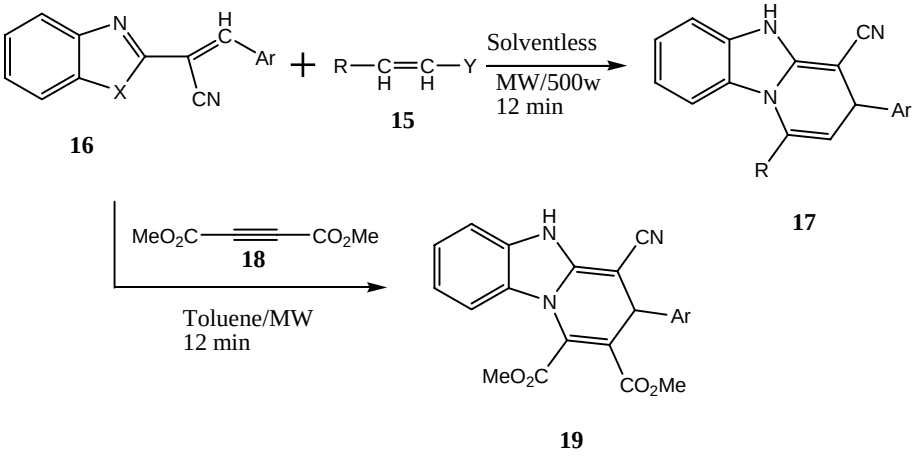
Our interest in adopting microwaves as energy sources started in 1997, when we observed that benzo[g]imidazo[1,2-a]pyridines could be synthesized *via* reactions of arylidene-1*H*-benzimidazole-2-acetonitriles **16** with different electron poor olefins and diethyl acetylenedicarboxylate under microwave heating (Scheme 5 and Table 3) [19]. In 2003, we reported the synthesis of **21** from the reaction of **20** and DMFDMA utilizing this technique [20] (Scheme 6).

In connection with our interest in applying green methodologies to the synthesis of condensed azines, we developed a novel and efficient route for the preparation of pyrimido[1,2-a]pyrimidines using microwave irradiation. Thus, subjecting equimolecular mixtures of 2-aminopyrimidine **22**, aromatic aldehydes **23**, and active nitriles **24** in the presence of piperidine as a catalyst to microwave irradiation leads to the formation of either 4-amino isomer **25** or 2-amino isomer **26** (Scheme 7 and Table 4) [21], depending on the active methylene compound employed. In this study, we employed the microwave organic reaction enhancement technology (MORE technology) [22] in a domestic oven. Moreover, we noted several difficulties with reproducing results and also hazards caused by solvent evaporation. Consequently, we instead began to utilize the controlled microwave heating technique.

We have described the syntheses of **7** from **6** in shorter times and improved yields using a microwave lab station. Also, we observed that **27** and **28** can be converted to **29** and **30**, respectively, by heating under controlled microwave conditions (Scheme 8 and Table 5) [20,[23–25].



Scheme 4. Syntheses of compounds **11** and **15**.

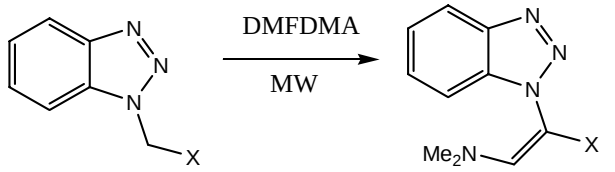


16 **15** **17** **18** **19**

Scheme 5. Syntheses of compounds **17a**–**d** and **19a**–**b**.

Table 3. Yields of compounds **17a**–**d** and **19a–b**.

Compounds	R	Ar	X	Yield%
17a	H	C_6H_5	$CONH_2$	80
17b	H	*p*-$CH_3OC_6H_4$	$CONH_2$	82
17c	C_6H_5	C_6H_5	NO_2	88
17d	C_6H_5	*p*-$CH_3OC_6H_4$	NO_2	90
19a	–	C_6H_5	–	85
19b	–	*p*-$CH_3OC_6H_4$	–	88



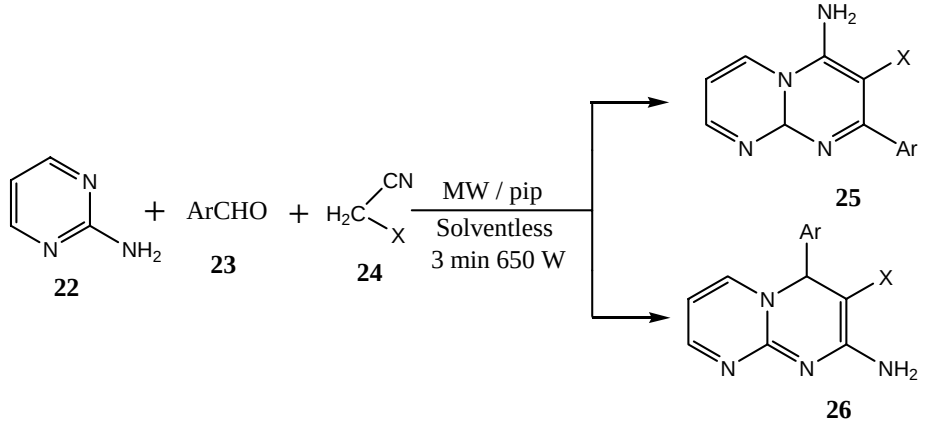
20 X = CN; $CO_2C_2H_5$; COC_6H_5 **21**

Scheme 6. Synthesis of compound **21**.

Benzoylacetonitrile **31** has long [26] been known to yield the self-tricondensation product **32** upon refluxing in pyridine. Abdelrazek and Michael [27] have subsequently reported that **33** is actually the reaction product.

Similarly, heating 3-aminocrotononitrile **34** in pyridine leads to the formation of the aniline derivative **35** that undergoes hydrolysis to afford **36** [26]. We reinvestigated this process and found that indeed **32** is the product formed. Moreover, instead of requiring the reaction to be carried out in refluxing pyridine for at least 5 h [26], we found that heating neat **19** in a microwave oven for 5 min afforded **32** [26] (Scheme 9 and Table 6).

Recently, a novel, simple, and efficient method for the synthesis of polysubstituted diaminobenzonitriles has been developed in our group. The process involves the reaction of 1,1,3-tricyano-2-aminopropionitrile with nitro olefins under controlled microwave irradiation conditions. Thus, when equimolar



22 **23** **24** **25** **26**

Scheme 7. Syntheses of compounds **25a**–**d** and **26a**–**b**.

Table 4. Yields of compounds **25a-d** and **26a-b**.

Compounds	X	Ar	Yield%
25a	CN	C_6H_5	85
25b	CN	*p*-ClC_6H_5	83
25c	$CO_2C_2H_5$	2-Furyle	81
25d	$CO_2C_2H_5$	*m*-$NO_2C_6H_4$	84
26a	C_5NH_2	*p*-$CH_3OC_6H_5$	82
26b	C_5NH_2	*m*-$NO_2C_6H_4$	83

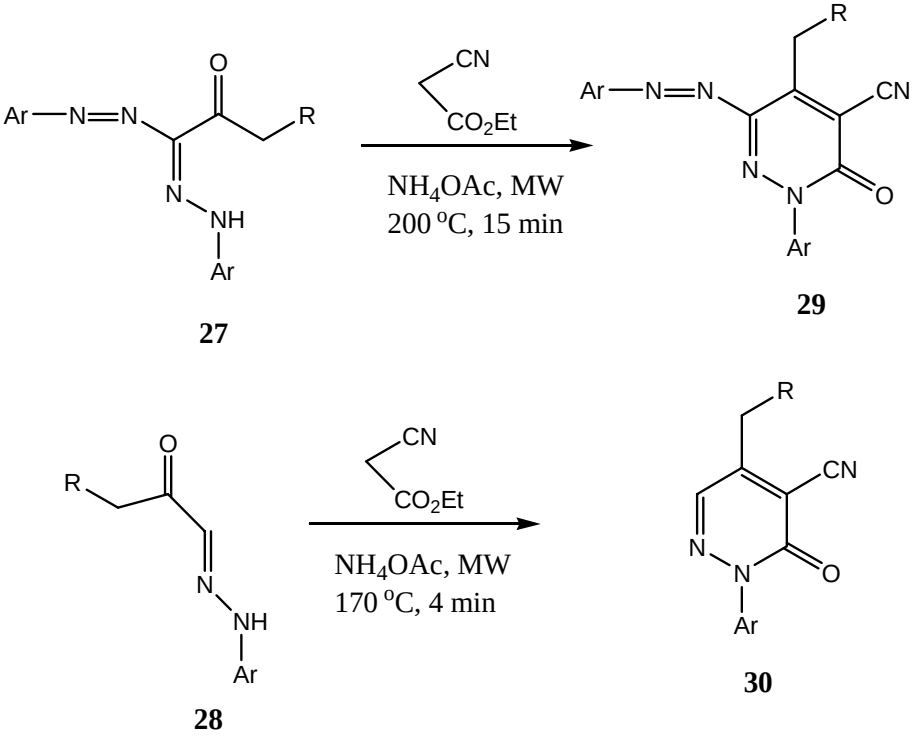
Table 5. Yields of compounds **29a**–**b** and **30**.

Compounds	R	Ar	Yield%
29a	H	C_6H_5	79
29b	CH_3	*p*-$CH_3C_6H_4$	64
30	C_2H_5	*p*-$CH_3C_6H_4$	64

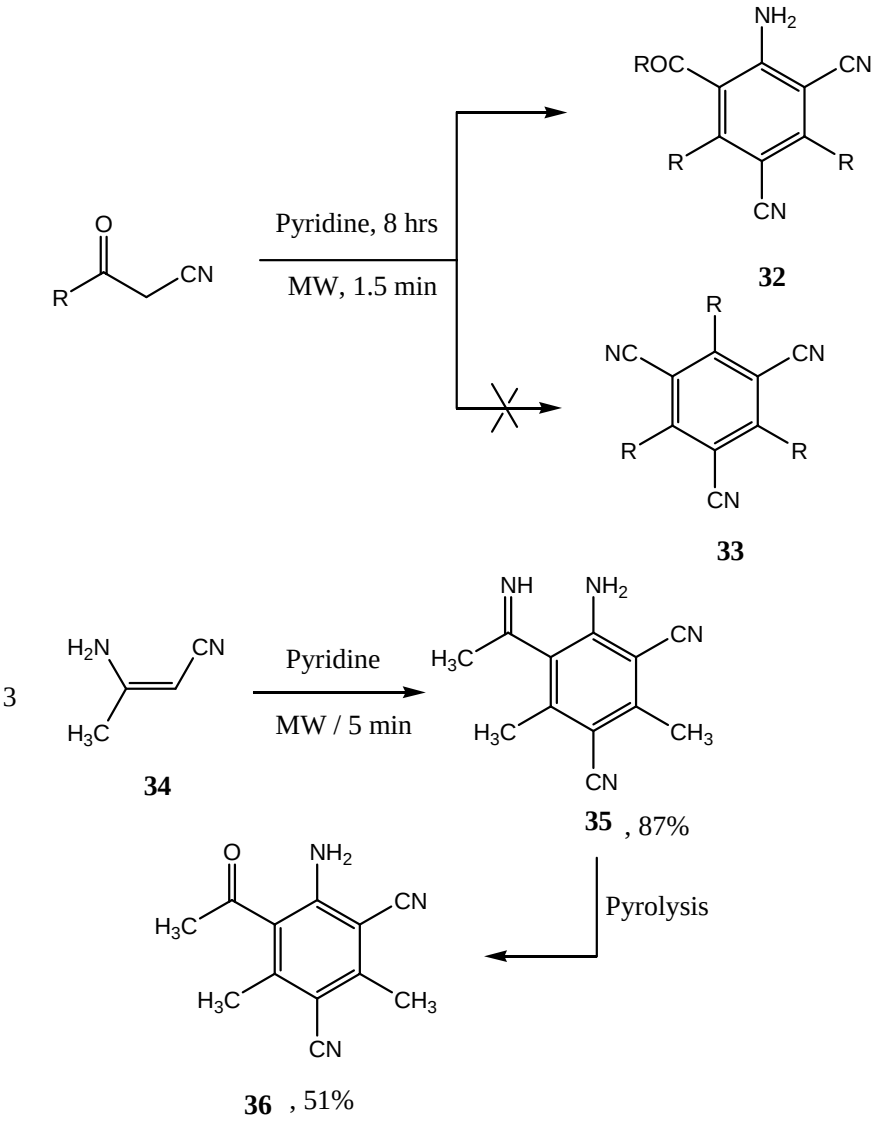
amounts of **37** and (E)-2-nitrophenylarenes **38** in dioxane are irradiated using a microwave lab station at 100 °C in the presence of piperidine (2 drops), the corresponding polysubstituted diaminobenzonitriles **39** are generated rather than the corresponding 2-cyanomethylpyridine derivatives **40**. The structures of **39** were established using ^{1}H NMR and ^{13}C NMR spectroscopic analysis (Scheme 10 and Table 7) [27].

Microwave promoted heating mixtures of 2-arylhydrazonals **41** with acrylonitrile **42a** or methyl vinylketone **42b** in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) for 5 min in the absence of solvent results in the formation of **45** *via* intermediates **43** and **44** that can be isolated in some cases (Scheme 7) [28,29]. Reactions **41** (X = COR) with hydroxylamine hydrochloride in acetic acid in presence of sodium acetate under microwave irradiation conditions afforded **46** [30], which is an ecofriendly route to this substance that serves as an alternative to Shawali et al.'s synthesis [31], which utilizes the reaction of **47** with cyanide ion, or the use of Elnagdi's coupling method of aroylacetonitrile with aryldiazonium salts [32] (Scheme 11). Notably, this reaction can be conducted on a 0.01 mol scale giving a reported yield of 93% for **45**.

Recently Al-Zaydi et al. [33] described a procedure for the formation of pyridines **48** that involves microwave or ultrasound irradiation of a mixture of **49** and an amine followed by treatment of the intermediate **50** with ethyl cyanoacetate also under



Scheme 8. Syntheses of compounds **29a**–**b** and **30**.



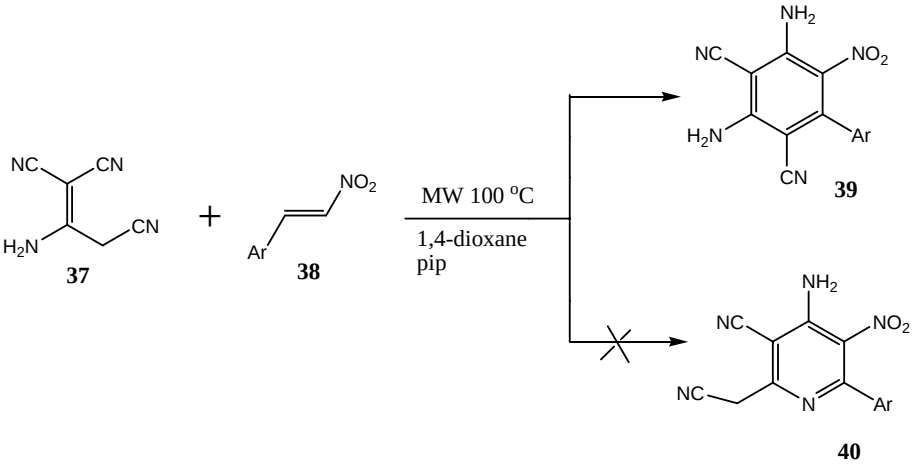
Scheme 9. Syntheses of compounds **32a**–**c** and **36**.

either microwave or ultrasound irradiation (Scheme 12). Generally, microwave irradiation proved to be more efficient in producing the desired pyridines in higher yields. Pyridones **48** couple with aromatic diazonium salts to yield arylhydrazones **51**, which react with elemental sulfur in the presence of piperidine, either under conventional heating or microwave or ultrasound irradiation conditions, to yield thienopyridines **52**. Again, the use of microwave and ultrasound irradiation requires less time to bring reactions to completion. Microwave reactions were observed to proceed faster than those promoted by ultrasound (Scheme 12 and Table 8) [33]. The structure of compound **52a** was assigned by using X-ray crystallography.

Table 6. Yields of compounds **32a**–**c**.

Compounds	R	Yield%
32a	C_6H_5	85
32b	*p*-ClC_6H4	87
32c	CH_3	27

Substituted 2-amino-2-chromenes **56** have received considerable attention owing to their importance as pigments, agrochemicals, and cosmetics

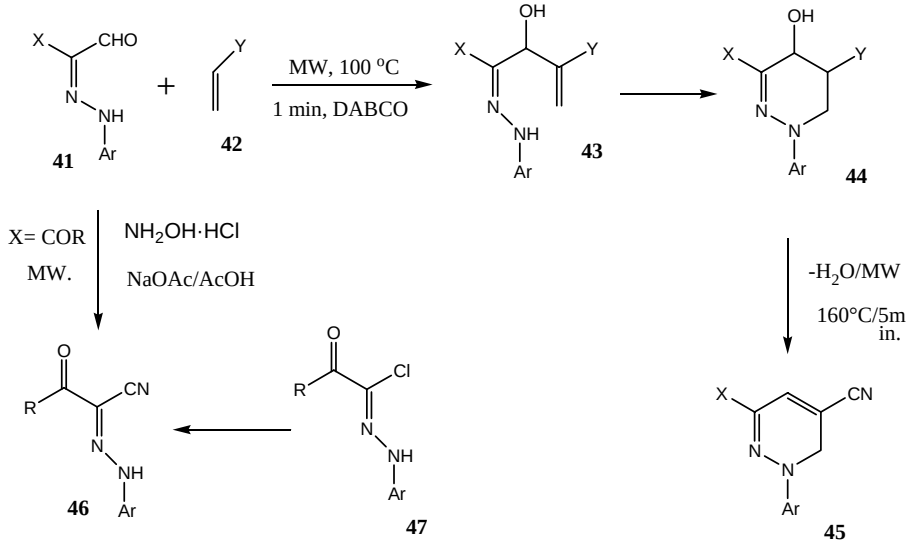


Scheme 10. Synthesis of compound **39a**–**f**.

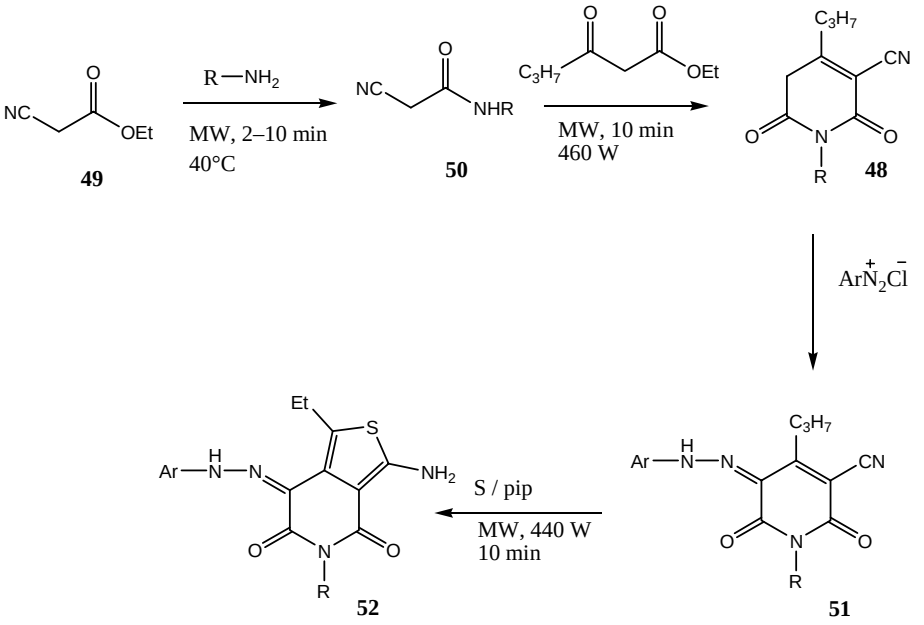
Table 7. Yields of compounds **39a**–**f**.

Compounds	Ar	Yield%
39a	C_6H_5	73
39b	*p*-ClC_6H_4	70
39c	*p*-$CH_3OC_6H_4$	72
39d	*m*-$NO_2C_6H_4$	70
39e	2-Furyl	72
39f	3,4-$Cl_2C_6H_3$	70

[34,35]. The synthesis of 2-amino-2-chromenes using conventional heating techniques requires prolonged times, and products are formed in only moderate yields. In contrast, an efficient, high-yielding three-component synthesis of these target molecules involves the utilization of controlled microwave heating of aldehydes with active methylene nitriles and α-naphthol **55** in ethanol containing a catalytic amount of piperidine at 80 °C for 5–8 min (Scheme 13 and Table 9) [36].



Scheme 11. Syntheses of compounds **45** and **46**.



Scheme 12. Syntheses of compounds **52a**–**d**.

We also developed a simple and efficient method for carrying out a one-pot three-component synthesis of the Biginelli 4-aryl-3,4-dihydropyrimidine-2(1*H*)-ones **58** through reaction of aldehydes, ethyl acetoacetate, and urea or thiourea under controlled microwave heating conditions (Scheme 14 and Table 10) [37].

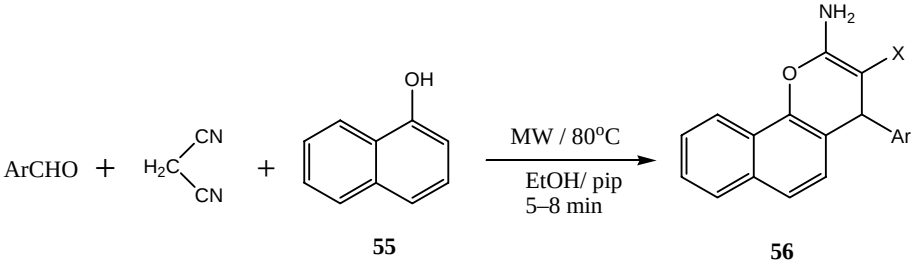
Under microwave irradiation conditions, **59** reacts to afford a mixture of **60** and **61**, of which the former undergoes self-condensation to yield **62** upon microwave irradiation in an acetic acid solution in the presence of acidic zeolite (Scheme 15) [38].

Table 8. Yields of compounds **52a**–**d**.

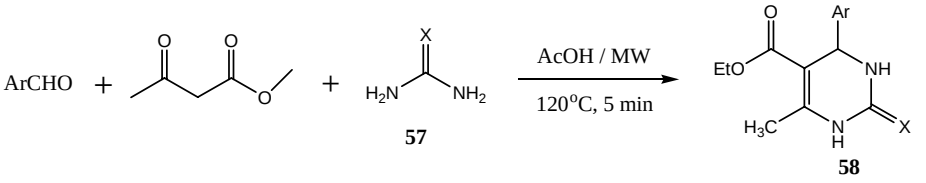
Compounds	R	Ar	Yield%
52a	Butyl	*o*-$MeO_2CC_6H_4$	84
52b	Hexyl	*o*-$MeO_2CC_6H_4$	88
52c	Cyclohexyl	*o*-$MeO_2CC_6H_4$	89
52d	Benzyl	*o*-$MeO_2CC_6H_4$	87

Table 9. Yields of compounds **56a**–**d**.

Compounds	X	Ar	Yield%
56a	CN	C_6H_5	93
56b	CN	*p*-$CH_3OC_6H_4$	94
56c	CN	*p*-ClC_6H_4	88
56d	CN	*p*-$NO_2C_6H_4$	85



Scheme 13. Syntheses of compounds **56a**–**d**.



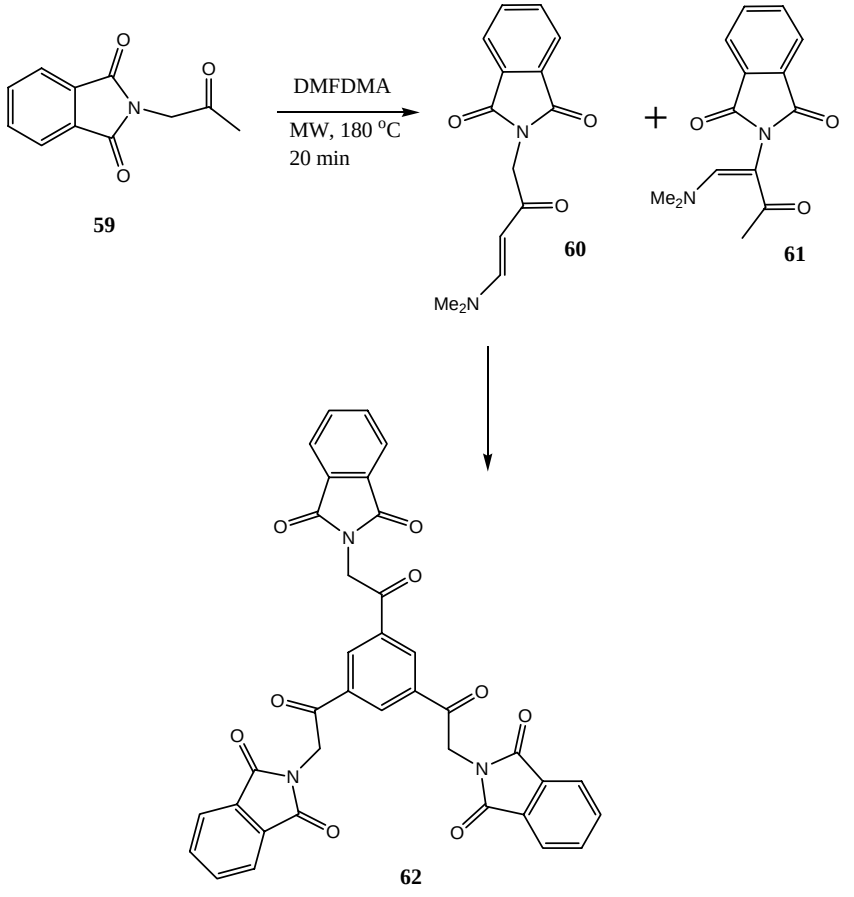
Scheme 14. Syntheses of compounds **58a**–**f**.

Table 10. Yields of compounds **58a**–**f**.

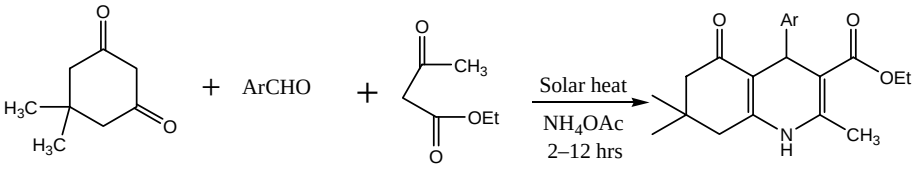
Compounds	X	Ar	Yield
58a	O	C_6H_5	90
58b	O	*p*-$CH_3OC_6H_4$	91
58c	O	*p*-ClC_6H_4	88
58d	O	*p*-$O_2NC_6H_4$	80
58e	S	C_6H_5	87
58f	S	*p*-$CH_3OC_6H_4$	88

Solar thermal energy as an energy source

A great demand now exists for alternative and freely available clean energy sources. An important indicator of the greenness of a chemical reaction is found in its energy efficiency (the cost and environmental friendliness of the energy, and its applicability on a large scale). Solar energy is essentially free and, because its use does not require raw materials, no pollutants are produced. Thus, solar energy can be



Scheme 15. Syntheses of compound **62**.



Scheme 16. Syntheses of compounds **65a**–**g**.

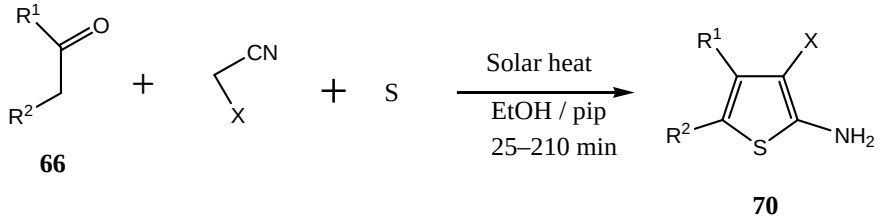
regarded as a clean reagent [39]. A description of our first utilization of solar thermochemical energy in organic synthesis was published in 2008. The process involved a four-component synthesis of polyhydroquinoline derivative **65** *via* the reaction of dimedone **63**, aromatic aldehydes, ethyl acetoacetate **64**, and ammonium acetate employing solar heating (Scheme 16 and Table 11) [40].

Table 11. Yields of compounds **65a**–**g**.

Compounds	Ar	Yield%
65a	C_6H_5	92
65b	*p*-$CH_3OC_6H_4$	92
65c	1-Naphthyl	88
65d	*p*-ClC_6H_4	87
65e	2-Furyl	90
65f	*p*-$CH_3C_6H_4$	88
65g	*m*-$O_2NC_6H_4$	83

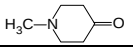
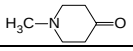
Green conditions have been developed for the synthesis of substituted 2-aminothiophenes **70**, employing multicomponent reactions of a ketone **66** with active methylene nitrile and elemental sulfur induced by solar thermal energy. The procedure proved to be efficient and simple in terms of conducting the reaction and isolating products (Scheme 17 and Table 12) [41].

The tetra-substituted imidazole scaffold is a core component of many biological systems as well as several natural products [42]. A number of synthetic approaches for the construction of this scaffold have been published, but all involve the use of high temperatures, expensive metal precursors, and catalysts that may be harmful to the environment. We observed that exposing a solution of benzoin **71**,



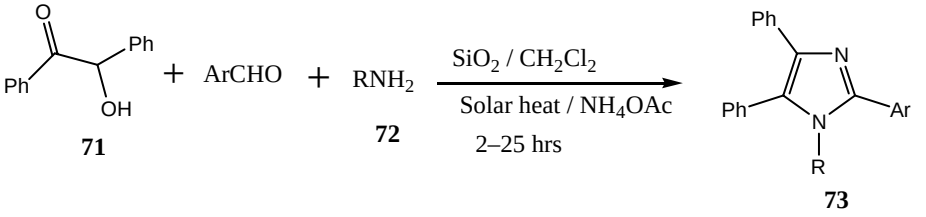
Scheme 17. Syntheses of compounds **70a**–**f**.

Table 12. Yields of compounds **70a**–**f**.

Compounds	R^1	R^2	X	Yield%
70a	CH_3	$CO_2C_2H_5$	CN	72
70b	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	70
70c	Cyclohexyl	CH_3	CN	88
70d			$CO_2C_2H_5$	75
70e	CH_3	CH_3	CN	73
70f			$CO_2C_2H_5$	75

aromatic aldehydes, aromatic amines **72**, and ammonium acetate in dichloromethane in the presence of catalytic amount of high surface area SiO_2 to direct sunlight for 2–25 h leads to the formation of the corresponding tetra-substituted imidazoles **73** in excellent yields (Scheme 18 and Table 13) [42].

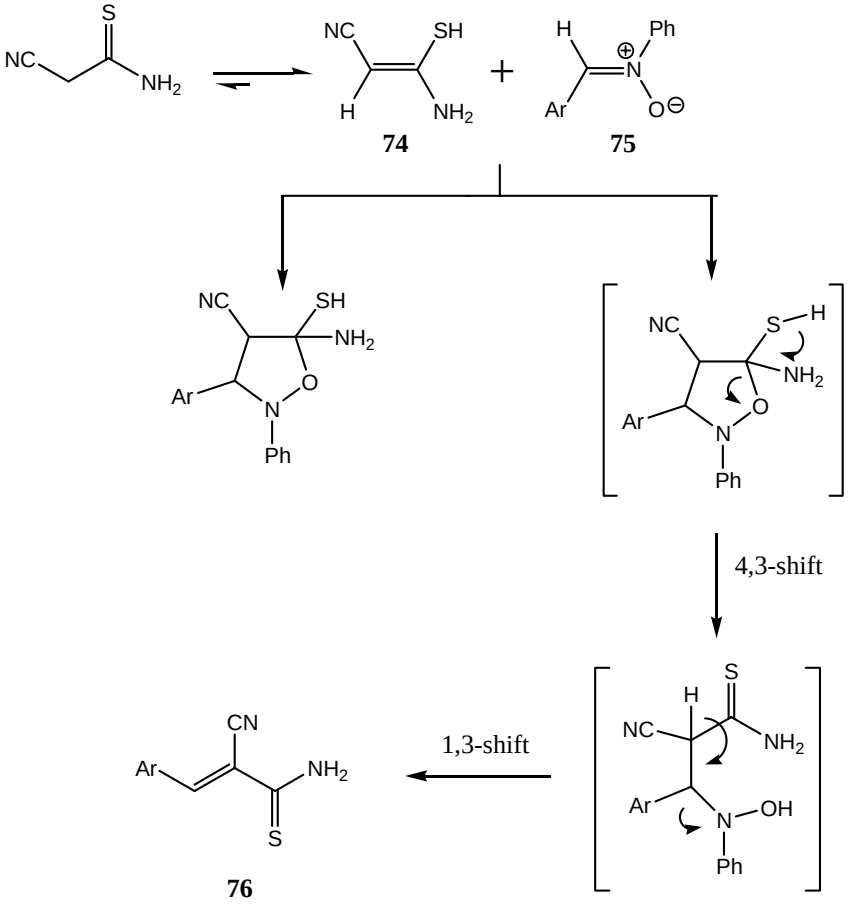
A novel synthesis of 2-cyano-3-aryl-2-enthioamides **76** has been recently developed in our laboratories. We



Scheme 18. Syntheses of compounds **73a**–**f**.

Table 13. Yields of compounds **73a**–**f**.

Compounds	Ar	R	Yield%
73a	C_6H_5	C_6H_5	88
73b	C_6H_5	$C_6H_5CH_2$	80
73c	*p*-ClC_6H_4	C_6H_5	93
73d	*p*-$CH_3C_6H_4$	C_6H_5	90
73e	*m*-$O_2NC_6H_4$	*p*-$CH_3C_6H_4$	89
73f	*p*-ClC_6H_4	*p*-ClC_6H_4	84



Scheme 19. Syntheses of compounds **76a**–**f**.

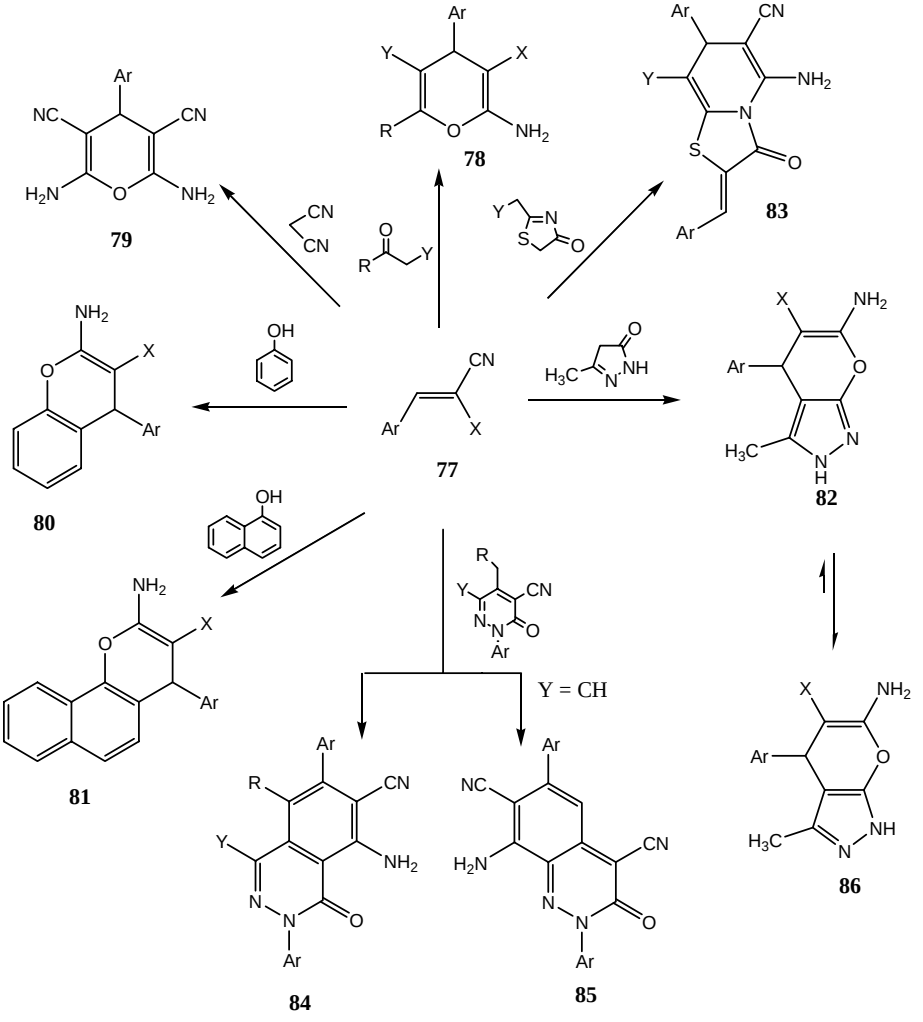
Table 14. Yields of compounds **76a–f**.

Compounds	Ar	Yield%
76a	C_6H_5	63
76b	*p*-$CH_3OC_6H_4$	73
76c	*p*-$O_2NC_6H_4$	69
76d	*o*-$O_2NC_6H_4$	65
76e	*p*-$Me_2NC_6H_4$	66
76f	2-Thienyl	54
76g	2-Furyl	52

observed that reactions of cyanothioacetamide **74** with nitrones **75** in EtOH under solar thermal energy conditions afford **76** in good yields. The reaction of **74** with diphenylnitrone furnished the corresponding 2-cyano-3-phenylprop-2-ene **76a**. It is worth mentioning that **76a** has not previously isolated as a solid product. A mechanism that accounts for the formation of **76** is presented in Scheme 19 (Table 14) [43].

Utility of heterogeneous acid and base catalysis to replace homogenous alternatives

In the 1970s and 1980s, we extensively investigated the reactivity of functionally substituted cinnamonitriles **77** toward active methylene compounds, electron rich aromatics, azolones, and alkyl heteroaromatic carbonitriles in the presence of homogeneous base catalysts, usually piperidine or pyridine [44–56]. This effort led to the preparation of a variety of pyrans **78**, thiopyrans **79**, benzopyrans **80**, naphthopyrans **81**, pyranoazoles **82**, thiazolopyridines **83**, phthaloazinones **84**, and cinnolines **85**. Several of the compounds synthesized in this effort showed interesting biological activities, which have been reported in the literature [57,58] and



Scheme 20. Syntheses of compounds **78**–**86**.

Table 15. Yields of compounds **80**, **81** and **83**.

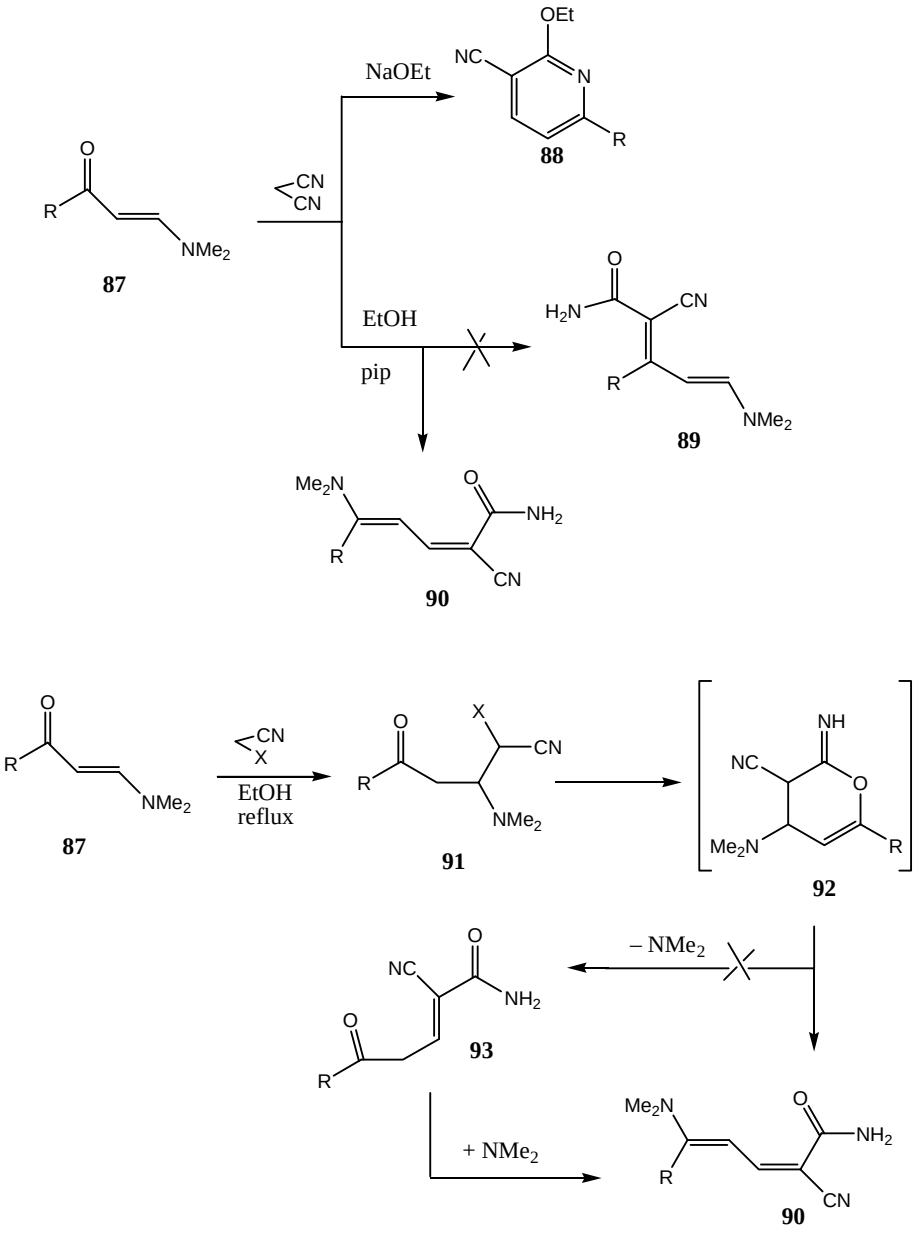
Compounds	Ar	X or Y	Yields%
80	C_6H_5	CN	74
81	C_6H_5	CN	76
83	C_6H_5	CN	96

Table 16. Yields of compounds **90a**–**c**.

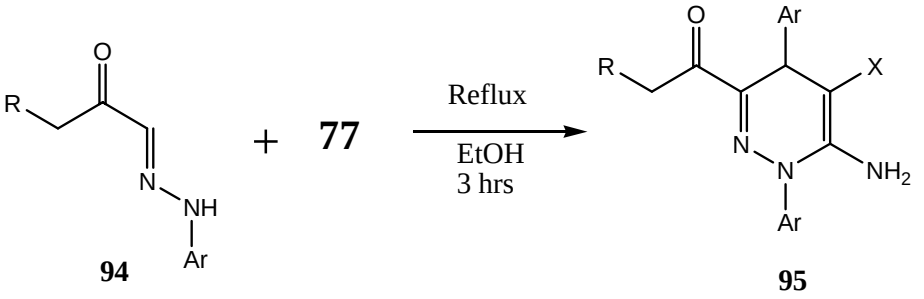
Compounds	R	Yield%
90a	C_6H_5	72
90b	2-Furyl	75
90c	2-Thinyl	72

described in patents [59,60]. As a consequence, synthetic approaches to these types of compounds have attracted much attention recently (Scheme 20) [61–64].

In 2008, we reported on utility of chitosan, a naturally occurring biopolymer obtained by treating chitin with strong alkali, as a heterogeneous catalyst for these reactions [65]. It occurred to us that it might be valuable to probe in detail the actual structures of some of these products, which have been questioned [67,68]. Chitosan is hydrophilic basic catalyst and, as such, it has been used successfully as a catalyst for Michael addition reactions (Scheme 20) [69]. It was



Scheme 21. Syntheses of compounds **90a**–**c**.



Scheme 22. Syntheses of compounds **95a**–**d**.

observed that reactions of **77** (X = CN) with acetoacetic ester and malononitrile in the presence of chitosan afford **78** and **79**, respectively, in almost the same yields described for reactions in the presence of piperidine.

Similarly, reactions of this substance with phenols, naphthols, and pyrazolone afforded the respective products **80**, **81**, and **82**. The latter product was incorrectly assigned as **86** earlier. The reaction of **77** with thiazolylacetonitriles and ethyl thiazolylacetate afforded **83** as expected despite claims to the contrary [67] (Table 15). Pyridazinylcarbonitriles (Y = CO_2Et) afforded **84** whereas when Y = CN **85** was formed (Scheme 20). All of the observed yields are similar to those given in the original reports [69].

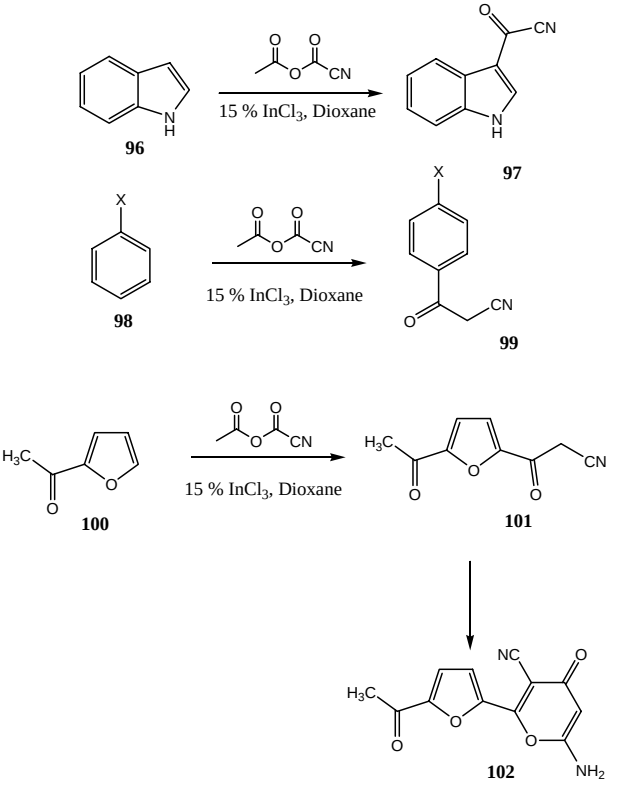
We have also utilized chitosan as base catalyst to promote addition reactions of malononitrile and ethyl cyanoacetate to form the enaminone **87**. Initially, Al-Omran et al. reported that **88** is the product of the reaction of these substances promoted by ethanolic sodium ethoxide, but suggested that **89** is produced when the reaction occurred in ethanolic piperidine (Scheme 21 and Table 16) [70]. Utilizing both ^{15}N NMR, HMBC NMR methods [71,72], and a subsequent X-ray crystal structural analysis, we demonstrated that the reaction product is really **90**. It is quite strange that the results of our work were available in open-access journals at least a year before the report of similar results by Abdelrazek et al. [68].

Table 17. Yields of compounds **95a**–**d**.

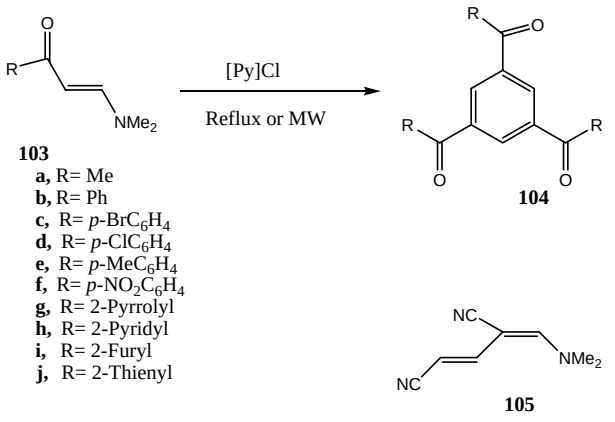
Compounds	Ar	R	X	Yield%
95a	C_6H_5	H	CN	84
95b	C_6H_5	CH_3	CN	82
95c	*m*-$O_2NC_6H_4$	H	CN	85
95d	*p*-ClC_6H_4	H	CN	80

We have recently found that **87** reacts not only with malononitrile but also with ethyl cyanoacetate and benzoylacetonitrile to yield dienamides, which are believed to be formed *via* intermediates **91**, **92**, and **93**. The possibility that formation of **92** takes place, which then reacts further by elimination of dimethylamine, was excluded based on experimental observations (Scheme 21) [73].

Chitosan has also been used as catalyst for the addition of **94** to **77** yielding **95**, thus replacing piperidine reported in the initial paper as the catalyst of choice (Scheme 22 and Table 17) [74,75].



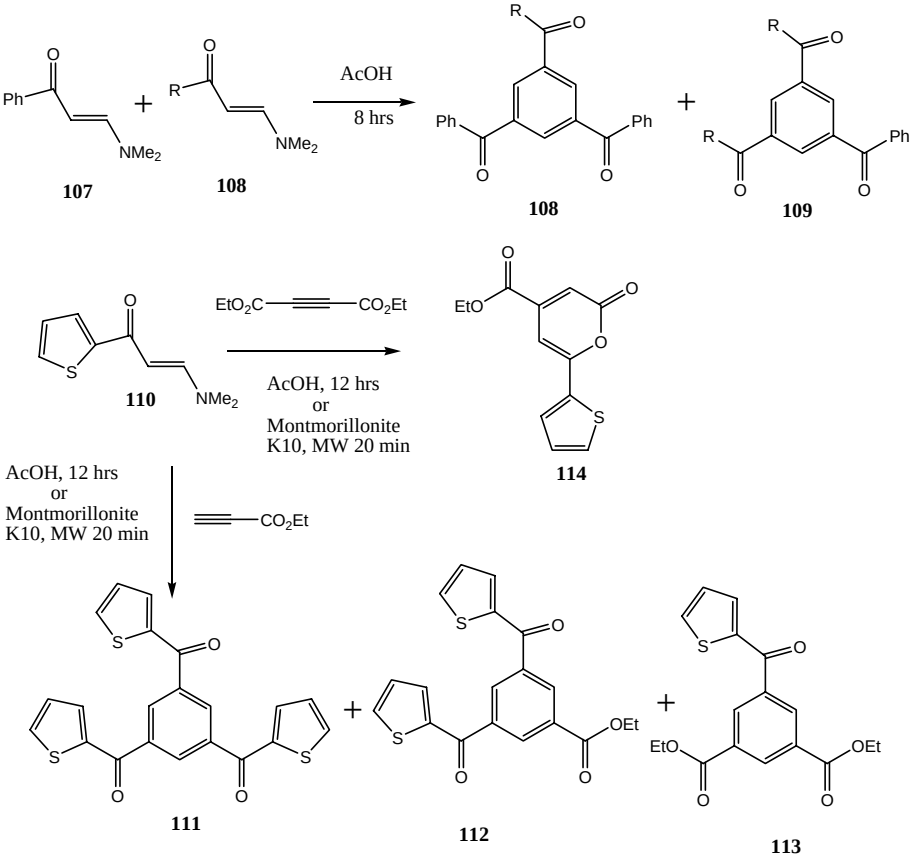
Scheme 23. Syntheses of compounds **97**, **99**, **101**, and **102**.



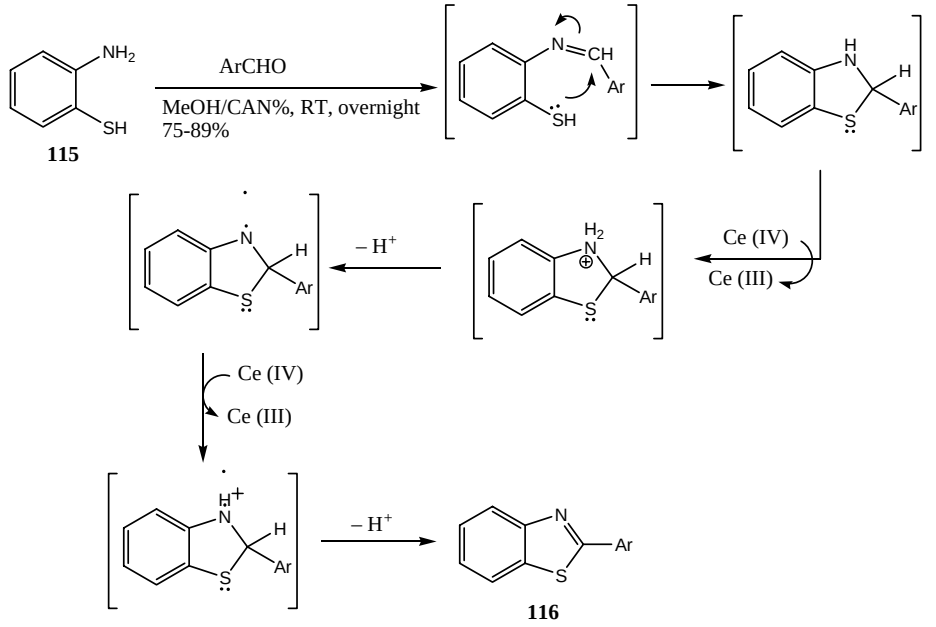
Scheme 24. Synthesis of compound **105**.

Eco-friendly, solid Lewis acid catalysts as well as ionic liquids have also been employed as replacement for their noneco-friendly counterparts. In 2007 we reported [76] the utilization of **97**, prepared by the reaction of indole **96** with cyanoacetic acid/acetic anhydride mixture following the procedure reported by Slatt et al. [77] as a building block for the synthesis of substituted indoles. This approach appeared to us to be an interesting route to 3-oxoalkanomitriles. However, less electron-rich aromatics failed to undergo the reaction employing the conditions developed. We envisioned that $InCl_3$ would act as an efficient catalyst for this condensation and, indeed, this catalyst did promote the reaction of **98** to form oxoalanonitriles **99**. Also, **101** and **102** have been produced from **100** in 70% yields (Scheme 23) [78].

Abdel-Khalik and Elnagdi [79] reported that enaminones **103a** are converted into 1,2,5-triaroylbenzenes **104a** in refluxing in acetic acid (Scheme 24). Subsequently Makhseed et al. [80] extended this approach to the synthesis of benzene-1,3,5-trials **104** (R = H) and triethylbenzene-1,3,5-tricarboxylates **104** (R = OH). Recently Al-Zaydi et al. were able to affect the conversion of **103d** to **104d** more efficiently using pyridine hydrochloride as an ionic liquid and MW as the energy source (Scheme 24) [81]. Although **103e** in



Scheme 25. Syntheses of compounds **108**, **109**, and **111**–**114**.



Scheme 26. Syntheses of compounds **116a**–**h**.

refluxing acetic acid reacts to generate **105** only, when the process is carried out in the presence of pyridinium hydrochloride **104e** is formed [81]. Very recently, Al-Mousawi et al. showed that these conversions can be affected by fusing enaminones in the presence of montmorillonite K10. Moreover, these workers provided evidence that the reaction takes place in a stepwise manner. Specifically, the results of crossover experiments showed that mixtures of **106** and **107** afford both **108** and **109**. In addition, the reaction of **110** with ethyl propiolate was shown to afford a mixture of **111–113** (Scheme 25) [14]. On heating with dimethyl acetylenedicarboxylate in the presence of montmorillonite K10, **110** is converted to **114** (Scheme 25).

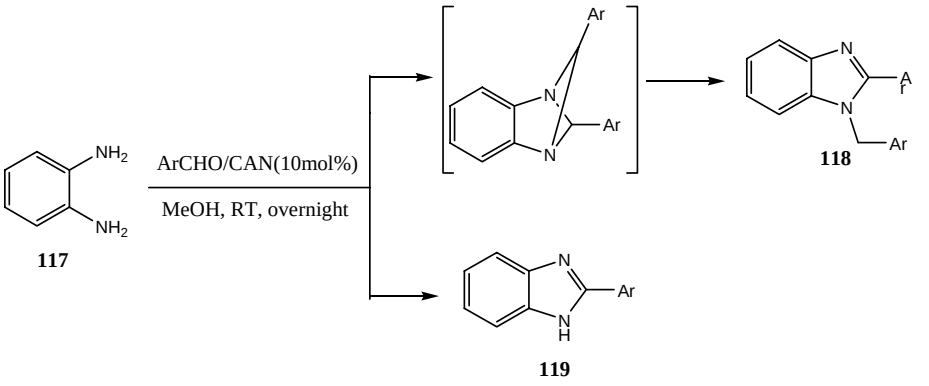
Ceric (IV) ammonium nitrate (CAN) is a convenient and widely used reagent for affecting a broad range of reactions owing to advantages that include solubility in water and various organic solvents, inexpensiveness, eco-friendly nature, uncomplicated handling, fast conversions, and convenient work up procedure. We have initiated a program aimed at exploring the potential of CAN in organic transformation. This effort led to the development of a one-pot CAN-catalyzed synthesis of 2-arylthiazoloes **116** from the reaction of 2-aminothiophenol **115** and aromatic aldehydes (Scheme 26 and Table 18) [82].

The reactions of *o*-phenylenediamine **117** with aromatic aldehydes in MeOH at room temperature, catalyzed by Cerium (IV) ammonium nitrate (CAN), afford either **118** and/or **119**. The results clearly show that this process proceeds mainly *via* two different routes. The first involves 1:1 condensation followed by oxidation to afford 2-aryl-1-substituted-1*H*-benzimidazoles. The second process is a 1:2 condensation that generates 2-aryl-1-arylmethyl-1*H*-benzimidazoles. Thus, in these reactions both of the expected products are obtained in ratios that depend on nature of the solvent. For example, in methanol both **118** and **119** are obtained (Scheme 27 and Table 19) [83].

Although extensively utilized as a one-electron oxidant [84], CAN's use as a Lewis acid catalyst in

Table 18. Yields of compounds **116a–h**.

Compounds	Ar	Yields%
116a	C_6H_5	75
116b	*p*-$CH_3OC_6H_4$	78
116c	1,4-$C_6H_9(OCH_3)_2$	77
116d	*m*-$O_2NC_6H_4$	88
116e	*o*-ClC_6H_4	89
116f	*o*-$CH_3OC_6H_4$	80
116g	*p*-$O_2NC_6H_4$	87
116h	2-Thienyl	79

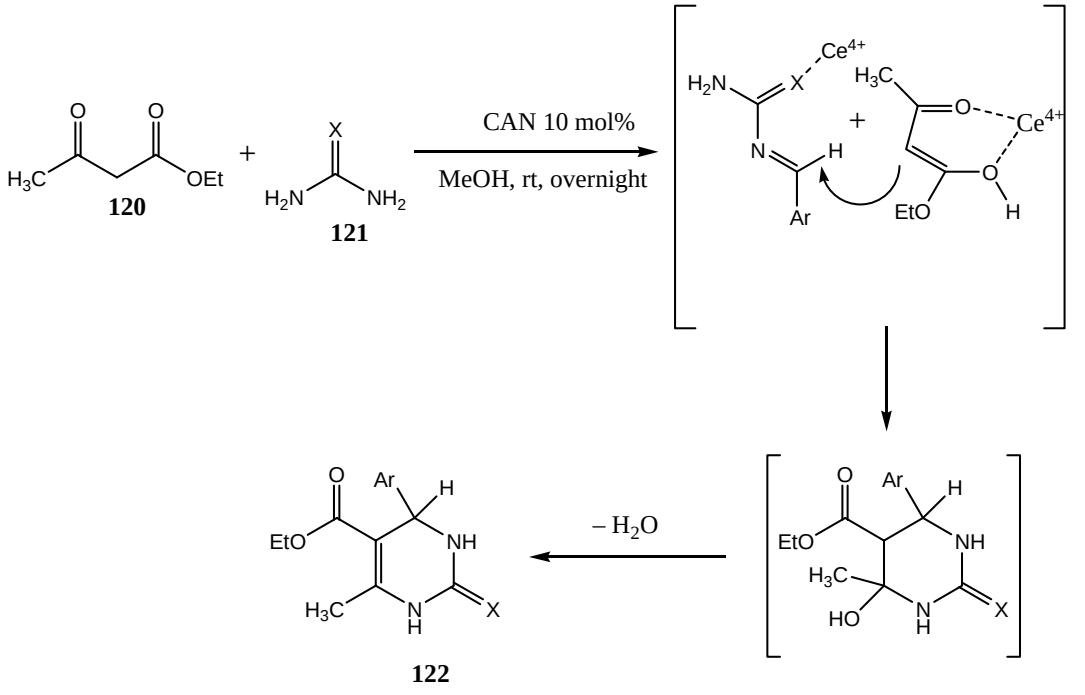


Scheme 27. Syntheses of compounds **118a**–**c** and **119a**–**b**.

Table 19. Yields of compounds **118a**–**c** and **119a**–**b**.

Compounds	Ar	Yield%
118a	*p*-$CH_3OC_6H_4$	90
118b	7,4-C_6H_3-OCH_3	89
118c	*m*-$O_2NC_6H_4$	15
119a	*o*-$O_2NC_6H_4$	55
119b	*p*-ClC_6H_4	70

C–N bond forming reactions leading to heterocyclic compounds is somehow limited [85]. We recently observed that a simple and highly efficient procedure for conducting the Biginelli condensation reaction of aldehydes, β-ketoesters **120**, urea, or thiourea **121a,b** at ambient temperature involves the use of CAN as a Lewis-acid catalyst. A mechanism to account for the formation of the products is shown in Scheme 28 (Table 20) [86].



122

Scheme 28. Syntheses of compounds **122a**–**g**.

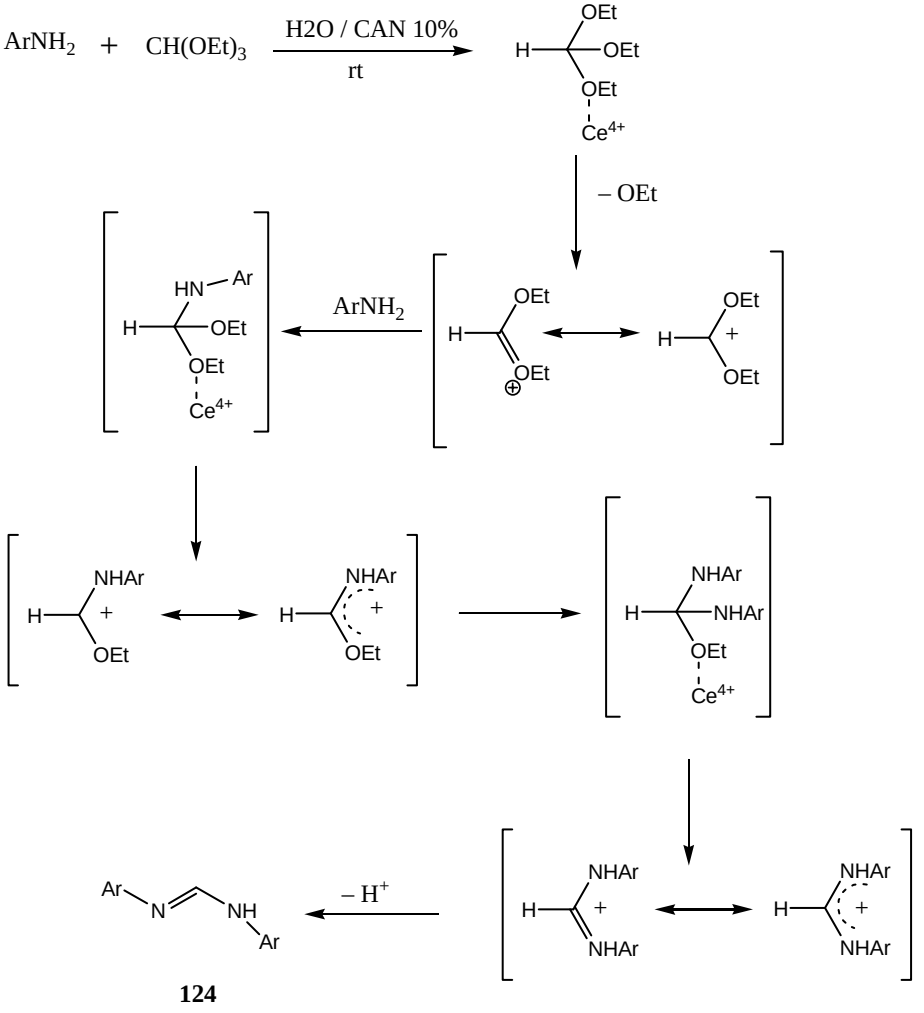
Table 20. Yields of compounds **122a**–**g**.

Compounds	X	Ar	Yields%
122a	O	C_6H_5	90
122b	O	p-$CH_3OC_6H_4$	93
122c	O	m-$O_2NC_6H_4$	96
122d	O	p-ClC_6H_4	88
122e	S	C_6H_5	94
122f	S	p-$CH_3OC_6H_4$	92
122g	S	p-$O_2NC_6H_4$	93

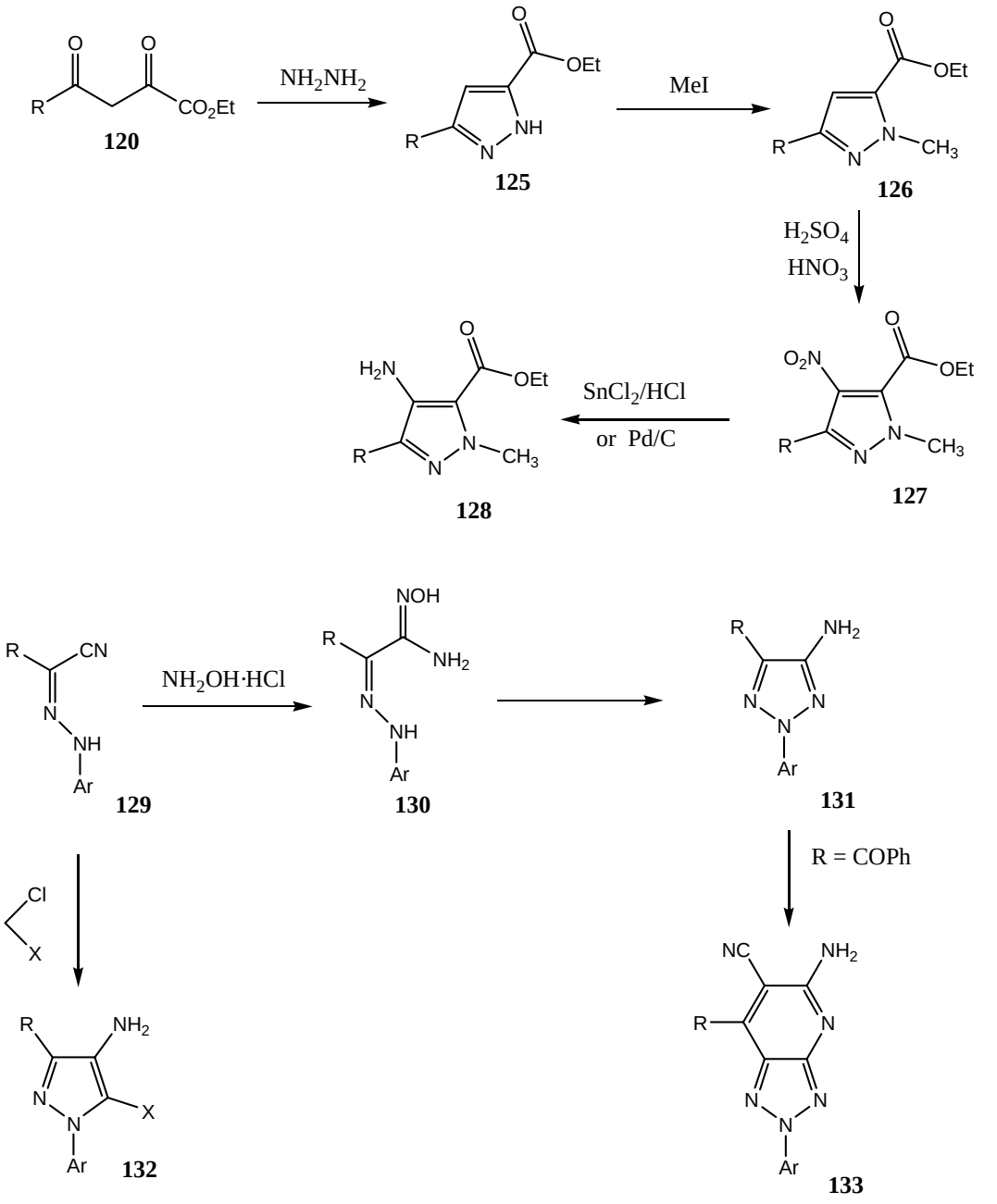
Table 21. Yields of compounds **124a**–**h**.

Compounds	Ar	Yield%
124a	C_6H_5	93
124b	p-$CH_3C_6H_4$	94
124c	p-$CH_3OC_6H_4$	95
124d	p-$O_2NC_6H_4$	86
124e	o-ClC_6H_4	88
124f	p-ClC_6H_4	87
124g	p-BrC_6H_4	88
124h	5-Methyl-3-yl	88
	Pyrazole	88

N,*N*-diaryl-formamidines are of considerable interest in fields related to organic and medicinal chemistry. Exchange reactions of *N*,*N* -dimethylformamidines or acetamidines by a variety of amines have been reported to be the most popular method for the synthesis of symmetrical and unsymmetrical formamidines. We have developed a simple and green route for the synthesis of *N*,*N*′-diaryl-formamidines **124** *via* the reaction of aromatic amines with triethylorthoformate **123** in water at room temperature catalyzed by CAN acting as a Lewis acid catalyst (Scheme 29 and Table 21) [87].



Scheme 29. Syntheses of compounds **124a**–**h**.



Scheme 30. Syntheses of compounds **128, 132**, and **133**.

Greener synthetic approaches

4-Aminopyrazoles-5-carboxylic acid derivatives are interesting intermediates in the synthesis of pharmaceuticals. Moreover, reported synthetic approaches to these substances are rather inefficient hazardous and/or nonconcise [88]. For example, **128**, a precursor of Viagra, is prepared using a multistep sequence that includes production of potentially explosive nitropyrazoles by employing a hazardous nitration reaction mixture followed by a heavy metal reduction. Recently we described a direct synthesis of **132** through the reaction of **129** with functionally substituted alkyl halides (Scheme 30). Similarly **129** was converted to a Zaperinsate analog *via* reaction with NH_4OH to yield intermediate **130** that then reacts with malononitrile to yield **133**.

Conclusion

In investigations carried out over a 48-year period, our group has made contributions to green methodologies by providing greener approaches to several

biologically interesting polyfunctional heteroaromatic compounds.

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