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].

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].

| Compounds | X | R           | R’   | Ar       | Yield% |
|-----------|---|-------------|------|----------|--------|
| 2a        | S | C6H5CH2     | C6H5 | C6H5     | 80     |
| 2b        | S | C6H5CH2     | C6H5 | o-CH3C6H4| 65     |
| 2c        | S | C6H5CH2     | C6H5 | NH       | 73     |
| 3a        | S | –           | CH3  | C6H5     | 80     |
| 3b        | S | –           | CH3  | o-CH3C6H4| 78     |
| 3c        | S | –           | Piperidino | C6H5    | 85     |

Scheme 1. Rearrangements of compounds 1 and 4.

Table 1. Yields of compounds 2a–c and 3a–c.
Scheme 2. Syntheses of pyridazines 7.

Scheme 3. Syntheses of compounds 8a-d and 9.
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-alpyridines could be synthesized via reactions of arylidene-1H-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-alpyrimidines 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].

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

| Compounds | Ar        | Yield% |
|-----------|-----------|--------|
| 8a        | C₆H₅      | 85     |
| 8b        | p-BrC₆H₄  | 82     |
| 8c        | p-CH₃OC₆H₄| 88     |
| 8d        | m-O₂NC₆H₄| 82     |
| 9a        | C₆H₅      | 90     |
| 9b        | p-CH₃OC₆H₄| 92     |
| 9c        | m-O₂NC₆H₄| 87     |

### Scheme 4. Syntheses of compounds 11 and 15.
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-aminoproponitrile with nitro olefins under controlled microwave irradiation conditions. Thus, when equimolar

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

| Compounds | R   | Ar     | X     | Yield% |
|-----------|-----|--------|-------|--------|
| 17a       | H   | C6H5   | CONH2 | 80     |
| 17b       | H   | p-CH3OC6H4 | CONH2 | 82     |
| 17c       | C6H5 | C6H5  | NO2   | 88     |
| 17d       | C6H5 | p-CH3OC6H4 | NO2   | 90     |
| 19a       | –   | C6H5   | –     | 85     |
| 19b       | –   | p-CH3OC6H4 | –     | 88     |

![Scheme 6](image6.png)

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).

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![Scheme 7](image7.png)

Scheme 7. Syntheses of compounds 25a–d and 26a–b.
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 1H NMR and 13C 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 Elmagdi’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.](image-url)
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 pyridine, 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.

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

![Scheme 9. Syntheses of compounds 32a–e and 36.](image-url)
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].

Table 7. Yields of compounds 39a–f.

| Compounds | Ar       | Yield% |
|-----------|----------|--------|
| 39a       | C₆H₅     | 73     |
| 39b       | p-ClC₆H₄ | 70     |
| 39c       | p-CH₃OC₆H₄| 72     |
| 39d       | m-NO₂C₆H₄| 70     |
| 39e       | 2-Furyl  | 72     |
| 39f       | 3,4-Cl₂C₆H₃| 70   |

Scheme 10. Synthesis of compound 39a–f.

Scheme 11. Syntheses of compounds 45 and 46.
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(1H)-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].

| Compounds | R     | Ar                      | Yield% |
|-----------|-------|-------------------------|--------|
| 52a       | Butyl | o-MeO₂CC₆H₄             | 84     |
| 52b       | Hexyl | o-MeO₂CC₆H₄             | 88     |
| 52c       | Cyclohexyl | o-MeO₂CC₆H₄         | 89     |
| 52d       | Benzyl | o-MeO₂CC₆H₄             | 87     |

Table 9. Yields of compounds 56a–d.

| Compounds | X     | Ar                      | Yield% |
|-----------|-------|-------------------------|--------|
| 56a       | CN    | C₆H₅                    | 93     |
| 56b       | CN    | p-CH₃OC₆H₄              | 94     |
| 56c       | CN    | p-ClC₆H₄                | 88     |
| 56d       | CN    | p-NO₂C₆H₄               | 85     |
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
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 dimesone 63, aromatic aldehydes, ethyl acetoacetate 64, and ammonium acetate employing solar heating (Scheme 16 and Table 11) [40].

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,

Table 11. Yields of compounds 65a–g.

| Compounds | Ar     | Yield% |
|-----------|--------|--------|
| 65a       | C₆H₅   | 92     |
| 65b       | p-CH₃OC₆H₄ | 92    |
| 65c       | 1-Naphthyl | 88    |
| 65d       | p-ClC₆H₄ | 87     |
| 65e       | 2-Furyl  | 90     |
| 65f       | p-CH₃C₆H₄ | 88    |
| 65g       | m-O₂NC₆H₄ | 83    |

Table 12. Yields of compounds 70a–f.

| Compounds | R¹     | R²     | X           | Yield% |
|-----------|--------|--------|-------------|--------|
| 70a       | CH₃    | CO₂C₂H₅ | CN          | 72     |
| 70b       | CH₃    | CO₂C₂H₅ | CO₂C₂H₅     | 70     |
| 70c       | Cyclohexyl | CH₃    | CN          | 88     |
| 70d       |        |        | CO₂C₂H₅     | 75     |
| 70e       | CH₃    | CH₃    | CN          | 73     |
| 70f       |        |        | CO₂C₂H₅     | 75     |
aromatic aldehydes, aromatic amines 72, and ammonium acetate in dichloromethane in the presence of catalytic amount of high surface area SiO₂ 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.](image)

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

| Compounds | Ar       | R          | Yield% |
|-----------|----------|------------|--------|
| 73a       | C₆H₅     | C₆H₅      | 88     |
| 73b       | C₆H₅     | C₆H₅CH₂   | 80     |
| 73c       | p-ClC₆H₄ | C₆H₅      | 93     |
| 73d       | p-CH₃C₆H₄ | C₆H₅     | 90     |
| 73e       | m-O₂NC₆H₄ | p-CH₃C₆H₄ | 89     |
| 73f       | p-ClC₆H₄ | p-ClC₆H₄  | 84     |

![Scheme 19. Syntheses of compounds 76a-f.](image)
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 diphenylnitron 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 cinnamionitrites 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, thiyopyrans 79, benzopyrans 80, naphthopyrans 81, pyranoazoles 82, thiazolopyridines 83, phthaloazinones 84, and cinnoelines 85. Several of the compounds synthesized in this effort showed interesting biological activities, which have been reported in the literature [57,58] and

| Compounds | Ar                  | Yield% |
|-----------|---------------------|--------|
| 76a       | C₆H₅                | 63     |
| 76b       | p-CH₃OC₆H₄          | 73     |
| 76c       | p-O₂NC₆H₄           | 69     |
| 76d       | o-O₂NC₆H₄           | 65     |
| 76e       | p-Me₂NC₆H₄          | 66     |
| 76f       | 2-Thienyl           | 54     |
| 76g       | 2-Furyl             | 52     |

Scheme 20. Syntheses of compounds 78–86.
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

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

| Compounds | Ar  | X or Y | Yields% |
|-----------|-----|--------|---------|
| 80        | C₆H₅ CN | 74     |
| 81        | C₆H₅ CN | 76     |
| 83        | C₆H₅ CN | 96     |

Table 16. Yields of compounds 90a–c.

| Compounds | R    | Yield% |
|-----------|------|--------|
| 90a       | C₆H₅ | 72     |
| 90b       | 2-Furyl | 75     |
| 90c       | 2-Thinyl | 72     |

Scheme 21. Syntheses of compounds 90a–c.
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 = CO₂Et) 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 enamnone 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 ¹⁵N 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].

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 22. Syntheses of compounds 95a–d.

Table 17. Yields of compounds 95a–d.

| Compounds | Ar     | R   | X     | Yield% |
|-----------|--------|-----|-------|--------|
| 95a       | C₆H₅   | H   | CN    | 84     |
| 95b       | C₆H₅   | CH₃ | CN    | 82     |
| 95c       | m-O₂NC₆H₄ | H   | CN    | 85     |
| 95d       | p-CIC₅H₄ | H   | CN    | 80     |

Scheme 23. Syntheses of compounds 97, 99, 101, and 102.
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 InCl3 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 24. Synthesis of compound 105.

Scheme 25. Syntheses of compounds 108, 109, and 111–114.
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). 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-arylthiazoles 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-1H-benzimidazoles. The second process is a 1:2 condensation that generates 2-aryl-1-arylmethyl-1H-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      | C₆H₅          | 75      |
| 116b      | p-CH₃OC₆H₄    | 78      |
| 116c      | 1,4-C₆H₄(OCH₃)₂ | 77      |
| 116d      | m-O₂NC₆H₄     | 88      |
| 116e      | o-CI₂C₆H₄     | 89      |
| 116f      | o-CH₃OC₆H₄    | 80      |
| 116g      | p-O₂NC₆H₄     | 87      |
| 116h      | 2-Thienyl     | 79      |

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

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-CH3OC6H4          | 90     |
| 118b      | 7,4-C6H3-OC6H4      | 89     |
| 118c      | m-O2NC6H4           | 15     |
| 119a      | o-O2NC6H4           | 55     |
| 119b      | p-ClC6H4            | 70     |

Scheme 28. Syntheses of compounds 122a–g.
$N,N$-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.](image)

Table 20. Yields of compounds 122a–g.

| Compounds | X | Ar          | Yields% |
|-----------|---|-------------|---------|
| 122a      | O | C$_6$H$_5$  | 90      |
| 122b      | O | $p$-CH$_3$OC$_6$H$_4$ | 93      |
| 122c      | O | $m$-O$_2$NC$_6$H$_4$ | 96      |
| 122d      | O | $p$-ClC$_6$H$_4$  | 88      |
| 122e      | S | C$_6$H$_5$  | 94      |
| 122f      | S | $p$-CH$_3$OC$_6$H$_4$ | 92      |
| 122g      | S | $p$-$O_2$NC$_6$H$_4$ | 93      |

Table 21. Yields of compounds 124a–h.

| Compounds | Ar          | Yield% |
|-----------|-------------|--------|
| 124a      | C$_6$H$_5$  | 93     |
| 124b      | $p$-CH$_3$C$_6$H$_4$ | 94      |
| 124c      | $p$-CH$_3$OC$_6$H$_4$ | 95     |
| 124d      | $p$-$O_2$NC$_6$H$_4$ | 86     |
| 124e      | $o$-ClC$_6$H$_4$ | 88     |
| 124f      | $p$-ClC$_6$H$_4$ | 87     |
| 124g      | $p$-BrC$_6$H$_4$ | 88     |
| 124h      | 5-Methyl-3-yl | 88     |
|           | Pyrazole    | 88     |
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 NH₂OH 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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