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# A Sustainable Green Route for Aqueous-Phase Synthesis of Substituted Imidazole

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**Abstract:** ***The development of environmentally benign and sustainable synthetic protocols for pharmaceutically relevant heterocycles is a pressing need in modern organic chemistry. Imidazole derivatives are an important class of compounds exhibiting diverse biological activities, yet their synthesis often involves hazardous reagents, harsh conditions, and organic solvents. Herein, we report a green, efficient, and catalyst-free aqueous phase synthesis of substituted imidazoles via a one-pot multicomponent reaction of α-diketones, aldehydes, and ammonium acetate. The reaction proceeds in water under mild conditions, affording imidazole derivatives in good to excellent yields. The protocol features several green metrics: water as a solvent, an environmentally benign catalyst, no hazardous by-products, and simple workup. The reaction scope is broad, tolerating various functional groups, and the products are obtained with high purity. Mechanistic insights suggest an in situ generated α-amino ketone intermediate drives the cyclocondensation. This green approach aligns with principles of green chemistry, offering a sustainable alternative to conventional imidazole synthesis, attractive for academic research and potential scale-up.***

**Keywords:** Heterocycle, Phase Transfer Catalyst, Aqueous Organic Synthesis, Green Protocol, MCR

## 1. Introduction

The imidazole structural unit is one of the most important nucleus found in a large number of natural products and pharmacologically active molecules[1-5] and the members of this family are known to possess NO synthase inhibition and antifungal, antimycotic, antibiotic, antiulcerative, antitumor, antibacterial and CB1 receptor antagonistic activities.[6,7] Various substituted imidazoles act as inhibitors of p38 MAP kinase[8] and B-Raf kinase,[9] glucagon receptors,[10] plant growth regulators,[11] therapeutic agents,[12] and pesticides.[13] Following that, several synthetic methods appeared in the literature for the construction of this important structural core. Recently, multicomponent reactions (MCRs) have attracted much attention to chemists since they are performed without isolation of the intermediate and, in turn, save both energy and raw materials coupled with reduction in time.[14]

Radziszewski and Japp reported the first synthesis of highly substituted imidazoles from a 1,2-dicarbonyl compound, different aldehydes, and ammonia. [15, 16] Since then, quite a good number of methods have been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles and 2,4,5-trisubstituted imidazoles. The 1,2,4,5-tetrasubstituted imidazoles are carried out by four- component condensation involving 1,2-diketone/α-hydroxyketone, an aldehyde, primary amine, and ammonium acetate using various catalysts in different conditions. S. Balalaie et al[17] synthesized tetrasubstituted imidazoles using a four-component condensation of benzil, aromatic aldehydes, primary amines, and ammonium acetate catalyzed by zeolite HY and silica gel without any solvent under microwave irradiation, leading to tetrasubstituted imidazoles in high yields and purity. Kidwai et. al reported the synthesis of the substituted imidazoles using molecular iodine [18] as the catalyst in refluxing ethanol. In the same year, Kantevari et. al [19] reported the synthesis of tetrasubstituted imidazoles under thermal conditions using $HClO_4$ supported on $SiO_2$ as the catalyst with a catalyst load of as low as 1%. This synthesis was capable of reducing the reaction time to a great extent. There had also been reports on the synthesis of substituted imidazoles employing the catalysts such as heteropolyacid [20,21] and silica gel/$NaHSO_4$ [22].

In the year 2009, Samai et. al [23] reported a simple and efficient one-pot multicomponent methodology for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles catalyzed by 15 mol % L-proline in refluxing methanol. This synthetic approach exploited the amphoteric behavior of the amino acid as well as eliminated the use of a hazardous toxic catalyst in the synthetic protocol. Synthesis of highly substituted imidazoles using acidic catalysts like $FeCl_3.6H_2O$,[24] $BF_3.SiO_2$,[25] mercaptopropyl silica [26] and silica-supported Wells-Dawson acid [27] have also been reported.

Apart from such a conventional retrosynthetic approach, S. Balalaie et. al reported the synthesis [28] by the condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation. Reports are also available in the literature for the synthesis of imidazole structural core employing hetero-Cope rearrangement [29] and by N-alkylation of trisubstituted imidazole.[30] Three-component cyclocondensation leading to 2,4,5-trisubstituted imidazoles are achieved through the involvement of 1,2-diketone/α-hydroxyketone, an aldehyde and ammonia source under microwave-assisted conditions.[31-35] Usyatinsky et al reported the solvent-free microwave-assisted synthesis of 2,4,5-substituted and 1,2,4,5-substituted imidazoles by microwave-assisted condensation of a 1,2-dicarbonyl compound with an aldehyde and an amine using acidic alumina impregnated with ammonium acetate as the

solid support. Other methodologies of the synthesis using acidic catalysts included acetic acid [36-38], silica-sulphuric acid [39], and oxalic acid.40 While other catalysts successfully administered for this multi-component condensation reaction are $NiCl_2.6H_2O/Al_2O_3$, [41] $ZrCl_4$, [42] ionic liquids, [43] ceric ammonium nitrate [44] and $InCl_3.3H_2O$.[45] In recent times, Narayana Murthy et al [46] synthesized tri- and tetrasubstituted imidazoles using a multi-component reaction of 1,2-diketone, amine source, and aldehyde using DABCO as a base in $^tBuOH$ as the solvent.

A solvent-less synthetic approach to the substituted imidazoles catalyzed by Sodium dihydrogen phosphate was reported in the same year by Jaberi et al. [47]. The method has applicability for the synthesis of both 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles. These methods, however, apply to certain synthetic conditions, but the limitations include the use of expensive reagents, demand longer reaction times, a tedious work-up procedure, offer low selectivity and high catalyst loading during operation, and eventually produce large amounts of toxic waste along with the desired product.

In the past two decades, the principles of green chemistry have influenced organic synthesis. Based on this, the synthesis processes including organic compounds have been considered for waste prevention, safer solvents, design for high energy efficiency, creation of atom economy, and use of renewable raw materials. [48] Minimizing the number of reactants (e.g., starting materials, solvents, catalysts, and auxiliaries) which do not become part of the desired product is the first and most important principle of green chemistry. Accordingly, the solvents used for chemical reactions and in the separation and purification steps are the main sources of waste.[49]

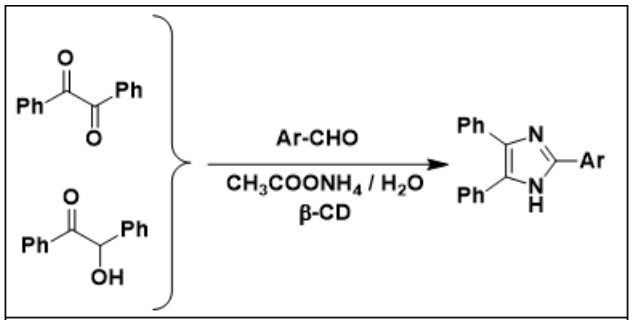
It has become clear that chemical and related industries, such as pharmaceuticals, are facing serious environmental and health concerns. Many classical synthetic methods with a wide range of applications generate a large amount of waste. [50]

Thus, there is a need for developing facile, efficient, and non-polluting synthetic procedures that reduce or eliminate the use of organic solvents and hazardous substances. Nowadays, searching for reaction media to replace volatile, flammable, and toxic solvents that are usually employed in organic synthesis has become a priority for the expansion of green chemical processes. [51, 52] This green and sustainable approach includes the identification of alternative chemical reactions to achieve environmental and economic advantages. [53, 54] Therefore, the synthetic value of MCRs will definitely increase when they are carried out in an aqueous medium.

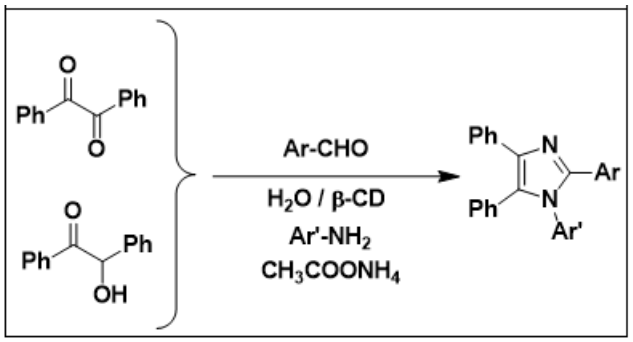
From both economic and environmental points of view, water has appeared as the medium of choice for carrying out organic reactions, because it is the safest, most environmentally acceptable, and most abundant solvent. [55,56] In addition, water generally facilitates the work-up procedures, because most organic compounds are easily separated from aqueous media due to their lipophilicity. Also, many organic reactions that occur in water exhibit significant rate enhancements. [57] Finally, water can create unique reactivity and selectivity with new solvation processes.58 Considering these advantages, efforts to design one-pot multicomponent reactions in aqueous media for the synthesis of diverse and functionalized heterocyclic scaffolds have become an attractive research area.

## 2. Experimental

Here, we would like to present a novel, mild, and highly efficient green method for the synthesis of tri- and tetra-substituted imidazoles in aqueous medium in the presence of β-CD as the phase transfer catalyst (Scheme 1 and 2).




**Scheme 1:** Synthesis of Triaryl Imidazole




**Scheme 2:** Synthesis of Tetraaryl Imidazole

To the best of our knowledge, highly substituted imidazole molecules have never been reported in aqueous medium in the presence of an efficient phase transfer catalyst (PTC). However, in recent times β-CD has emerged as an efficient phase transfer catalyst for carrying out many MCRs in aqueous medium, as the use of the PTC helped in overcoming the issue of solubility of the starting materials in water, which is the most crucial constraint during carrying out organic reactions. [59]

## 3. Results and Discussions

Here, we would like to present a novel, mild, and highly efficient green method for the synthesis of tri- and tetra-substituted imidazoles in aqueous medium in the presence of β-CD as the phase transfer catalyst (Scheme 1 and 2).

### *A. Synthesis:*

The typical procedure for 2,4,5-trisubstituted imidazoles involves the reaction of 1 mmol of Benzil, 1 mmol of 4-nitrobenzaldehyde, and 2.5 mmol of ammonium acetate in various solvents in the presence or absence of catalysts.

**Table 1:** Synthesis of 2,4,5-triaryl imidazole[a] using different experimental conditions

| Sl. | Catalyst | Solvent | Temp. (ºC) | Time (min) | Reaction conditions | Yield b (%) |
|---|---|---|---|---|---|---|
| 1 | - | EtOH | 80 ºC | 120 | Reflux | 45 |
| 2 | DBU (20mol %) | EtOH | 80 ºC | 60 | Reflux | 70 |
| 3 | $KH_2PO_4$ (10mol %) | EtOH | 80 ºC | 60 | Reflux | 75 |
| 4 | - | H2O | 100 ºC | 30 | Reflux | 70 |
| 5 | Silica gel (2.5g) | H2O | 100 ºC | 30 | Reflux | 75 |
| 6 | Alumina (20 mol %) | H2O | 100 ºC | 30 | Reflux | 78 |
| 7 | Urotropine (20 mol %) | H2O | 100 ºC | 30 | Reflux | 81 |
| 8 | $KH_2PO_4$ (10 mol %) | H2O | 100 ºC | 30 | reflux | 83 |
| 9 | β-CD (10 mol %) | H2O | RT | 15 | - | 85 |
| 10 | β-CD (20 mol %) | H2O | RT | 5 | - | 95 |

[a] Reagents used: 4-nitrobenzaldehyde (1mmol), benzil (1mmol), ammonium acetate (2.5 mmol), solvent 10 mL
[b] Yields refer to isolated yield of pure products.

These experiments clearly indicated that the β-CD-catalyzed approach is the most effective reaction condition for carrying out the three-component cyclocondensation reaction. In order to evaluate the applicability and tolerance level of the protocol, synthesis of 2, 4, 5-trisubstituted imidazoles 1a-c was carried out (Table 2).

**Preparation of 2,4,5- triaryl imidazoles (1a-1c):** In a 25 mL round-bottomed glass stoppered flask containing Benzil or benzoin (1 mmol), aldehyde (1 mmol), ammonium acetate (2.5 mmol), and 20 mol % of β-CD were suspended in 10 mL water and stirred at room temperature for the stipulated time(Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the crude product from the reaction mixture was washed with 3 portions of water (10 mL each). The solid was then crystallized from ethanol. Being a homogeneous catalyst and environmentally benign, there was no attempt to recover and reuse the catalyst.

**Table 2:** β-CD mediated photochemical synthesis of 2,4,5-trisubstituted imidazoles

| Entry | Product | R1 | Reaction Time (min) | | Yield (%) b,c | |
|---|---|---|---|---|---|---|
| | | | Benzil | Benzoin | Benzil | Benzoin |
| 2 | 1a | 4-OMe | 5 | 7 | 88 | 86 |
| 3 | 1b | 4-F | 5 | 7 | 92 | 90 |
| 4 | 1c | - | 5 | 7 | 90 | 88 |

[a] Aldehyde (1 mmol), benzil/benzoin (1 mmol), ammonium acetate (2.5 mmol) and 20 mol % of β-CD suspended in 10 mL water were stirred for the stipulated time
[b] Yields refer to pure isolated products
[c] The products were characterized by m.p., spectral (IR, $^1$H, $^{13}$C and HRMS) data

To extend the applicability of this method, the same reaction conditions were applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles 2a-e via a similar one-pot, four-component condensation of 1,2-diketone (1 mmol), aldehyde (1 mmol), amine (1 mmol) and ammonium acetate (1.25 mmol) in the presence of a catalytic amount of β-CD, as depicted in Scheme 2. Generally, the synthetic procedure employed was similar to that of trisubstituted imidazoles. The yields obtained were in the range of 70-95% (Table 3). There was no remarkable difference in yields and reaction time between aryl aldehydes with electron-donating groups and those with electron-withdrawing groups. Moreover, aromatic and heteroaromatic amines both responded well to this reaction. Benzoin gave comparable yields to those of benzil, but longer reaction times were required. The structures of compounds 2a- 2e were established from their IR, 1H-NMR, 13C-NMR and mass spectral data. The four-component condensation was also performed in the absence of the phase transfer catalyst; the yield of 2a was low (~ 45%), which indicates the formation of hydrophilic pockets in the presence of β-CD in water is essential for the contact of the reacting molecules, which facilitates the reaction.

**Preparation of 1,2,4,5-tetraaryl imidazoles (2a-2e):** In a 25 mL round-bottomed glass stoppered flask containing Benzil or benzoin (1 mmol), aldehyde (1 mmol), amine (1mmol), ammonium acetate (1.25 mmol), and 20 mol % of β-CD were suspended in 10 mL water and stirred at room temperature for the stipulated time(Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the crude product from the reaction mixture was washed with 3 portions of water (10 mL each). The solid was then crystallized from ethanol. Being a homogeneous catalyst and environmentally benign, there was no attempt to recover and reuse the catalyst.

**Table 3:** β-CD mediated photochemical synthesis of 1,2,4,5-tetrasubstituted imidazoles.

| Entry | Product | **$R^2$** | **Ar** | Reaction Time (min) | | **Yield (%)[b,c]** | |
|---|---|---|---|---|---|---|---|
| | | | | Benzil | Benzoin | Benzil | Benzoin |
| 1 | 2a | H | Ph | 9 | 10 | 92 | 90 |
| 2 | 2b | H | 4-Cl-Ph | 10 | 12 | 88 | 82 |
| 3 | 2c | 4-$NO_2$ | Ph | 7 | 9 | 95 | 92 |
| 4 | 2d | 4-$NO_2$ | 2-OMe-Ph | 8 | 10 | 90 | 87 |
| 5 | 2e | H | Thiophene- 2-methyl | 10 | 12 | 88 | 85 |

[a] Aldehyde (1 mmol), benzil/benzoin (1 mmol), amine (1 mmol), ammonium acetate (1.25 mmol) and 20 mol % of β-CD suspended in 10 mL water were stirred for the stipulated time
[b]Yields refer to pure isolated solid products
[c] Characterized by spectral (IR, $^1$H-NMR, $^{13}$C-NMR and HRMS) data

## 4. Conclusion

To summarize, we have achieved a convenient and efficient procedure for the synthesis of tri and tetra-substituted imidazoles through the one-pot cyclocondensation reaction using β-CD phase transfer catalyst in water in environmentally benign condition. The simple procedure combined with easy work-up involving highly economic and non-hazardous reagent combination will surely attract the chemist towards the synthesis of biologically and medicinally important tri- and tetra-substituted imidazoles.

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