A facile and efficient synthesis of tri- and tetrasubstituted imidazoles with potassium hydrogen sulfate and DB18C6 in an aqueous medium

Chhanda Mukhopadhyay* and Pradip Kumar Tapaswi

Department of Chemistry, University of Calcutta, 92 APC Road, Kolkata 700009, India

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Potassium hydrogen sulfate in the presence of dibenzo-18-crown-6 (DB18C6) turns out to be a very efficient and effective catalyst for the facile synthesis of a wide variety of tri- and tetrasubstituted imidazoles in an aqueous medium at moderate temperature. The idea behind this is that the potassium ion, being trapped in the crown core, frees the hydrogen sulfate anion, which, because of its acidic nature, succeeds in the ready synthesis of the imidazoles.

Keywords: potassium hydrogen sulfate; DB18C6; tri- and tetrasubstituted imidazoles; aqueous medium; green reaction conditions

Introduction

The development of new methodologies to produce products of greater structural complexity from readily available simple starting materials with fewer synthetic steps but ensuring high yield under mild reaction conditions is the main challenge for the synthetic organic chemists (1, 2). Again, because of global environmental legislation on chemical process industries, aqueous environment has been currently receiving considerable attention in organic chemistry (3–5) because water is abundant in nature, has virtually no cost, and is safest among all available solvents, thus leading to environmentally benign chemical processes (6).

Synthesis of imidazole ring system and its derivatives occupies an important place in the realm of natural and synthetic organic chemistry as the imidazole moiety, being a part of the side chain in histidine, plays a major role in the biological activity of many peptides and proteins. Several functionalized imidazole derivatives express many pharmacological properties and play important roles in biochemical processes (7). The potency and wide applicability of the imidazole pharmacophore are largely because of its hydrogen-bond donor–acceptor capability as well as because of its high affinity for metals, which are present in many protein active sites (8) (e.g. Zn, Fe, Mg). Diverse substituted imidazoles act as inhibitors of p38 MAP kinase (9), B-Raf kinase (10), glucagon receptors (11), plant growth regulators (12), therapeutic agents (13), antibacterial (14), antitumor (15), and pesticides (16). Recent advancements in green chemistry and organometallic chemistry expand the utility of imidazoles as ionic liquids (17–19) and N-heterocyclic carbenes (20). Because of their widespread applications in various streams, there is an increasing interest in research on imidazoles.

2,4,5-Trisubstituted imidazoles are usually synthesized by a multicomponent reaction involving benzil (or a substituted benzil), an aldehyde, and ammonium acetate as an ammonia source (21), and many catalysts [silica/sulfuric acid (22, 23), Yb(OTf)3 (24), NiCl2·6H2O (25), oxalic acid (26), iodine (27), sulfanilic acid (28), tetrabutyl ammonium bromide (29), cerium ammonium nitrate (30), Zr(acac)4 (31), InCl3·3H2O (32)] as well as different activation modes [thermal activation, microwave irradiation (21, 33), or ultrasounds (30, 31)] have been used to get the

*Corresponding author. Email: cmukhop@yahoo.co.in

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desired imidazoles in high yields. Most of the earlier methodologies are performed either in solution [AcOH (21, 24), EtOH (25, 27), EtOH–H₂O (26, 34, 35)], under solventless conditions (22, 33, 36), or in ionic liquids (37, 38). But the synthesis of substituted imidazoles in an aqueous medium is rare. Actually there is only one report in this regard and that too under microwave irradiation at very high temperature (180–210°C) (39). Therefore, room for green methodologies for the rapid construction of substituted imidazoles in an aqueous medium at milder conditions still remains quite open.

Cyclic polyethers such as 18-crown-6 (18C6) and dibenzo-18-crown-6 (DB18C6) have some unique ability to bind metal cations and small neutral or ionic molecules selectively. Two kinds of binding forces for complexation of cyclic polyethers are well established: ion–dipole interaction and hydrogen bonding (40). Metal ions form complexes with crown ethers through ion–dipole electrostatic interactions, with the oxygen lone pairs being attracted to the cation positive charge (Scheme 1) and various organic molecules with acidic hydrogens binding to crown ethers via hydrogen bonding. Now, in the case of a salt, cyclic polyethers undergo complexation with the cations releasing the counter ion in the medium. Therefore, if the salt is an acid salt, say KHSO₄, K⁺ ion will be first trapped by the crown ether followed by the release of HSO₄⁻. Again, in the case of an aqueous medium, HSO₄⁻ will produce hydronium ion (H₃O⁺), thereby making the medium acidic (Scheme 1). We have very efficiently used this idea for the synthesis of various substituted imidazoles.

In continuation of our search for the synthesis of biologically important heterocycles (41–44), here we describe the synthesis of 2,4,5-trisubstituted imidazoles in an aqueous medium under moderate reaction condition.

**Results and discussion**

Initially, we started the condensation of benzil (1 mmol), benzaldehyde (1 mmol), and ammonium acetate (3 mmol) in water (5 mL) at room temperature for 24 h in the absence of catalyst but the desired product was not formed at all. Then the same reaction mixture was refluxed on an oil bath for an extended period of time (24 h) which led to very poor yield (15%) of 2,4,5-trisubstituted imidazole (Table 1, entry 2). Then, it was thought worthwhile to carry out the reaction in the presence of comparatively available crown ethers (18C6 and DB18C6) and acidic salts (KHSO₄ and NaHSO₄). After a thorough screening with the above-mentioned crown ethers and salts, it was revealed that heating the reaction mixture at 60°C for 4 h yields the best result (92% of isolated yield, Table 1, entry 6) in the presence of 15 mol% of both DB18C6 and KHSO₄. The details of the results obtained are given in Table 1.

Once the reaction was standardized, our first attempt was the synthesis of various 2,4,5-trisubstituted imidazoles with DB18C6 and KHSO₄ in water (Scheme 2), and the results are depicted in Table 2.

On examination of Table 2 we find that almost all of the 2,4,5-trisubstituted imidazoles were produced in high yields. A wide range of aromatic aldehydes bearing either electron donating or electron withdrawing substituents and different substituted benzils underwent this one-pot, three-component condensation to produce the products. Aliphatic aldehydes gave the corresponding imidazole in lower yield (52%) than did aromatic aldehydes while diacetyl gave lower yield of the product (65%) than that of other benzils. This is because of lower conjugation in the products than in the aromatic counterparts.

The same methodology was applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles via the one-pot, four-component condensation of an aldehyde, a benzil, a primary aromatic amine (as well as benzyl amine), and an ammonium acetate (Scheme 3), and the products were obtained in excellent yields in almost all cases except in the case of diacetyl where the yield is little lower (64%). The utility of this reaction was justified using various structurally different aldehydes and primary aromatic amines (Table 3).

The mechanism of the formation of trisubstituted imidazoles involves protonation of the aldehydic carbonyl, diamine intermediate [A] formation with two molecules of ammonia from ammonium acetate and condensation with one molecule of diketone compound to form intermediate [B] that subsequently aromatized to produce the final products. In the case of tetrasubstituted imidazoles, the mechanism proceeds through the formation of the imine of the

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**Scheme 1.** Potassium ion being trapped by the six oxygen atoms in the 18-crown-6 core and generation of hydronium ion in an aqueous medium.
aromatic aldehydes with aromatic amines (as it is more stable than the imine of aldehydes and ammonia). This imine subsequently forms the diamine intermediate with ammonia and the rest of the mechanism remains the same. Because of the formation of the more stable imine intermediate in the case of four-component reaction of benzil, ammonium acetate, aromatic aldehydes, and aromatic primary amines, 1,2,4,5-tetrasubstituted imidazoles are exclusively formed (in place of the mixture of tri- and tetrasubstituted imidazoles). The detail of the mechanism is given in Scheme 4.

After extraction by ethylacetate, the aqueous part containing DB18C6 and KHSO4 can be recycled at least six times for imidazole synthesis without substantial loss in the yield of the reaction. Therefore, the catalytic efficiency is quite high.

### Experimental

**General procedure for the trisubstituted imidazole formation**

To a mixture of aldehyde (1 mmol), benzil (1 mmol), and ammonium acetate (3 mmol) in water (5 mL) were added DB18C6 (15 mol%) and KHSO4 (15 mol%), and the mixture was stirred at room temperature for 15 min. The resulting mixture was heated on a water bath at 60°C for the stipulated time mentioned in Table 2. When the reaction was complete as monitored by TLC, the reaction mixture was extracted with EtOAc (3 × 10 mL) and dried over anhydrous Na2SO4. After removal of the solvent in vacuo, the pure products were obtained by direct crystallization from ethanol.

| Entry | Crown ether (mol%) | Salt (mol%) | Temperature (°C) | Time (h) | Yield (%) (isolated) |
|-------|-------------------|------------|-----------------|---------|----------------------|
| 1     | –                 | –          | 25              | 24      | Nil                  |
| 2     | –                 | –          | 100             | 24      | 15                   |
| 3     | 18C6 (15)         | KHSO4 (15) | 25              | 24      | Trace                |
| 4     | 18C6 (15)         | KHSO4 (15) | 60              | 6       | 75                   |
| 5     | DB18C6 (15)       | KHSO4 (15) | 25              | 24      | Trace                |
| 6     | DB18C6 (15)       | KHSO4 (15) | 60              | 4       | 92                   |
| 7     | DB18C6 (15)       | NaHSO4 (15)| 60              | 6       | 55                   |

After extraction by ethylacetate, the aqueous part containing DB18C6 and KHSO4 can be recycled at least six times for the imidazole synthesis. This recyclability of the catalyst increases its catalytic efficiency.

For large-scale preparation, aldehyde (10 mmol), benzil (10 mmol), ammonium acetate (30 mmol), water (20 mL), DB18C6 (15 mol%), and KHSO4 (15 mol%) were taken in a round-bottom flask (100 mL) and stirred at 60°C until the reaction was completed (monitored by TLC). After the completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 20 mL) and dried over anhydrous Na2SO4. After removal of the solvent in vacuo, the pure products were obtained by direct crystallization from ethanol.

**General procedure for the tetrasubstituted imidazole formation**

In the case of tetrasubstituted imidazoles, aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (1.5 mmol), aromatic primary amines (1 mmol), DB18C6 (15 mol%), and KHSO4 (15 mol%) were taken in water (5 mL), and the rest of the procedure remains the same. The final products were obtained by extraction with ethyl acetate, solvent removal in vacuo and crystallization from ethanol.

For large-scale preparation of tetrasubstituted imidazoles, aldehyde (10 mmol), benzil (10 mmol), primary amines (10 mmol), ammonium acetate (15 mmol), water (20 mL), DB18C6 (15 mol%), and KHSO4 (15 mol%) were taken in a round-bottom flask (100 mL) and stirred at room temperature for 30 min. The resulting mixture was heated on a water bath at 60°C until the reaction was completed (monitored by TLC). After the completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 20 mL) and dried over anhydrous Na2SO4. After removal of the solvent in vacuo, the pure products were obtained by direct crystallization from ethanol.
bath at 60°C until the reaction was complete (monitored by TLC). After the completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 20 mL) and dried over anhydrous Na2SO4. After removal of the solvent in vacuo, the pure products were obtained by direct crystallization from ethanol.

All the products gave satisfactory IR, 1H NMR, 13C NMR, and analytical data as given below.

4,5-Bis-(4-chlorophenyl)-2-(3′-nitrophenyl)-1H-imidazole (Table 2, entry 7)

The titled compound was obtained as a yellow solid (420 mg, 93%); Rf = 0.44 (25% ethylacetate/75% petroleum ether). M.P.: 314–316°C (MeOH); IR (KBr): 3342, 3129, 2933, 2372, 1597, 1491, 1442, 1405, 1329, 1176, 1131, 1087, 1022, 845, 772, and 702 cm−1. 1H NMR (300 MHz, CDCl3): 7.62 (d, J = 8.0, 1.5 Hz, 2H, C4′- and C5′-phenyl protons), 7.33–7.18 (m, 8H, C4-, C5-, C6-, and C7-phenyl protons), 6.99 (d, J = 8.4 Hz, 2H, C6′-, C5′-OMe). 13C NMR (75 MHz, CDCl3): 153.4 (C2), 140.5 (C3), 135.6 (C4), 135.5 (C1a), 133.7 (C2a), 133.2 (C4a), 130.9 (2C, C4′-, C5′-phenyl carbons), 130.2 (ipso to C4′, 129.4 (ipso to C3′, 128.5 (2C, C2′, C6′), 128.4 (2C, C2′, C5′), 128.3 (2C, C4′, C5′-phenyl carbons), 128.1 (C4′- or C5′-phenyl carbon), 127.8 (2C, C4′- or C5′-phenyl carbons), 126.6 (C4′- or C5′-phenyl carbons), 122.5 (C6′), 121.4 (C7), 114.3 (C2′), 112.0 (C5′), 55.8 (C5′-OMe). Anal. calcd. for C29H21N2O2Cl (%): C 74.25, H 4.67, N 5.99. Found (%): C 74.59, H 4.96, N 5.99. The titled compound was obtained as a white solid (429 mg, 92%); Rf = 0.75 (25% ethylacetate/75% petroleum ether). M.P.: 246–248°C (EtOAc); IR (KBr): 3341, 2936, 2372, 1584, 1441, 1221, 1178, 1045, and 694 cm−1. 1H NMR (300 MHz, CDCl3): 7.61 (dd, J = 7.5, 1.2 Hz, 2H, C4′- and C5′- phenyl protons), 7.33–7.20 (m, 8H, C4′-, C5′-phenyl protons), 7.18–7.11 (m, 3H, C3′a, C5′a, and C4′-H), 6.65 (d, J = 9.0, 1H, C3′-H), 3.82 (s, 3H, C2′-OMe), 3.32 (s, 3H, C5′-OMe). 13C NMR (75 MHz, CDCl3): 153.4 (C2), 150.9 (C3), 145.0 (C4), 137.8 (C5), 135.6 (C1a), 133.7 (C2a), 133.2 (C4a), 130.9 (2C, C4′-, C5′-phenyl carbons), 130.2 (ipso to C4′, 129.4 (ipso to C3′, 128.5 (2C, C2′, C6′), 128.4 (2C, C2′, C5′), 128.3 (2C, C4′, C5′-phenyl carbons), 128.1 (C4′- or C5′-phenyl carbon), 128.0 (2C, C4′-, C5′-phenyl carbons), 127.5 (2C, C4′- or C5′-phenyl carbons), 126.7 (C4′- or C5′-phenyl carbon), 119.8 (C7), 117.1 (C6′), 116.9 (C4′), 111.8 (C5′), 55.8 (C5′-OMe), and 55.0 (C4′-OMe). Anal. calcd. for C29H23N2O2Cl (%): C 74.59, H 4.96, N 5.99. Found (%): C 74.45, H 5.12, N 6.08.

1-(4a-Chlorophenyl)-2-(2′,5′-dimethoxyphenyl)-4,5-diphenyl-imidazole (Table 3, entry 1)

The titled compound was obtained as a white solid (420 mg, 93%); Rf = 0.54 (25% ethylacetate/75% petroleum ether). M.P.: 196–198°C (EtOAc); IR (KBr): 3411, 3058, 1600, 1490, 1438, 1380, 1272, 1228, 1090, 1027, and 698 cm−1. 1H NMR (300 MHz, CDCl3): 7.60 (dd, J = 8.0, 1.5 Hz, 2H, C4′- and C5′-phenyl protons), 7.33–7.18 (m, 8H, C4′-, C5′-phenyl protons), 7.13 (dd, J = 8.6, 1.5 Hz, 3H, C2′a, C6′a, and C2′-H), 6.99 (d, J = 8.4 Hz, 2H, C6′a, C5′-OMe). 13C NMR (75 MHz, CDCl3): [146.9, 146.5, 146.4 (C4′-, C5′-, and C2′)], 137.6 (C4′), 135.6 (C1a), 134.2 (C4a), 133.6 (C5′), 131.1 (2C, C4′- and C5′-phenyl carbons), [130.2, 130.1 (ipso to C4′ and C5′, respectively)], 129.6 (2C, C2′a, C6′a), 129.3 (2C, C2′a, C5′-OMe), 128.3 (2C, C4′- and C5′-phenyl carbons), 128.2 (C4′- or C5′-phenyl carbon), 127.5 (2C, C4′- or C5′-phenyl carbons), 126.8 (C4′- or C5′-phenyl carbons), 122.5 (C6′), 121.4 (C7), 114.3 (C2′), 112.0 (C5′), 55.8 (–OCH3). Anal. calcd. for C29H23N2O2Cl (%): C 74.59, H 4.96, N 5.99. Found (%): C 74.45, H 5.12, N 6.08.
Table 2. Synthesis of 2,4,5-trisubstituted imidazoles in an aqueous medium using DB18C6 and KHSO4 (15 mol%).

| Entry | Products | Time (h) | Yield (%) (isolated) | References |
|-------|----------|----------|----------------------|------------|
| 1     | ![Image1] | 4        | 92                   | 45         |
| 2     | ![Image2] | 4        | 90                   | 45         |
| 3     | ![Image3] | 5.5      | 87                   | 45         |
| 4     | ![Image4] | 6        | 82                   | 46         |
| 5     | ![Image5] | 4        | 92                   | 21         |
| 6     | ![Image6] | 5        | 90                   | 47         |
| 7     | ![Image7] | 6        | 89                   | –          |
| 8     | ![Image8] | 4        | 92                   | 21         |
| 9     | ![Image9] | 6        | 52                   | 47         |
| 10    | ![Image10] | 4        | 65                   | 43         |
Scheme 3. Synthesis of 1,2,4,5-tetrasubstituted imidazoles in an aqueous medium using DB18C6 and KHSO4 (15 mol%).

1-(4-Chlorophenyl)-2-(4'-hydroxyphenyl)-4,5-diphenyl-imidazole (Table 3, entry 4)
The titled compound was obtained as an off-white solid (397 mg, 94%); $R_f=0.37$ (25% ethylacetate/75% petroleum ether). M.P.: 290 $^\circ$C (MeOH); IR (KBr): 3034, 2935, 2593, 2490, 1604, 1521, 1488, 1398, 1276, 1165, 1094, and 698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 9.72 (brs, 1H, OH), 7.46 (d, $J=7.2$ Hz, 2H, C$_4$, C$_5$-phenyl protons), 7.33 (d, $J=8.7$ Hz, 2H, C$_2$-H and C$_6$-H), 7.27–7.25 (m, 3H, C$_3$$_a$-H, C$_5$$_a$-H, and one from either C$_4$ or C$_5$-phenyl protons), 7.21–7.11 (m, 9H, C$_3$$_a$-H, C$_5$$_a$-H, and seven from C$_4$ and C$_5$-phenyl protons). $^1$H NMR (300 MHz, CDCl$_3$): 157.8 (C$_4$), 146.7 (C$_2$), 136.7 (C$_4$), 135.9 (C$_3$), 134.5 (C$_1$$_a$), 131.3 (C$_4$$_a$), 131.2 (2C, C$_4$$_a$-phenyl carbons), 130.6 (2C, C$_2$$_a$ and C$_6$$_a$), 130.54 (ipsos to C$_4$), 130.50 (ipsos to C$_3$), 130.0 (2C, C$_3$$_a$ and C$_5$$_a$), 129.3 (2C, C$_4$$_a$-phenyl carbons), 128.6 (2C, C$_4$$_a$-phenyl carbons), 128.5 (2C, C$_4$ and C$_5$-phenyl carbons), 128.2 (2C, C$_4$$_a$-phenyl carbons), 126.4 (2C, C$_2$$_a$, C$_6$$_a$), 121.1 (C$_4$$_a$), 115.2 (C$_4$ and C$_5$). Anal. calcd. for C$_{29}$H$_{23}$N$_2$O$_2$Cl (%): C 74.59, H 4.96, N 6.00. Found (%): C 74.43, H 5.04, N 6.07.

1-(4a-Nitrophenyl)-2-(4'-N,N-dimethylaminophenyl)-4,5-diphenyl-imidazole (Table 3, entry 6)
The titled compound was obtained as a brick red solid (396 mg, 86%); $R_f=0.73$ (25% ethylacetate/75% petroleum ether). M.P.: 280–282°C (EtOAc); IR (KBr): 3436, 3071, 2853, 2797, 2369, 1606, 1521, 1488, 1346, 1198, and 697 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): 8.11 (d, $J=8.7$ Hz, 2H, C$_4$- and C$_5$-phenyl protons), 7.33 (d, $J=7.8$ Hz, 2H, C$_2$-H and C$_6$-H), 7.27–7.25 (m, 3H, C$_3$$_a$-H, C$_5$$_a$-H, and one from either C$_4$ or C$_5$-phenyl protons), 7.21–7.11 (m, 9H, C$_3$$_a$-H, C$_5$$_a$-H, and seven from C$_4$ and C$_5$-phenyl protons). $^1$H NMR (300 MHz, CDCl$_3$): 157.8 (C$_4$), 146.7 (C$_2$), 136.7 (C$_4$), 135.9 (C$_3$), 134.5 (C$_1$$_a$), 131.3 (C$_4$$_a$), 131.2 (2C, C$_4$$_a$-phenyl carbons), 130.6 (2C, C$_2$$_a$ and C$_6$$_a$), 130.54 (ipsos to C$_4$), 130.50 (ipsos to C$_3$), 130.0 (2C, C$_3$$_a$ and C$_5$$_a$), 129.3 (2C, C$_4$$_a$-phenyl carbons), 128.6 (2C, C$_4$$_a$-phenyl carbons), 128.5 (2C, C$_4$ and C$_5$-phenyl carbons), 128.2 (2C, C$_4$$_a$-phenyl carbons), 126.4 (2C, C$_2$$_a$, C$_6$$_a$), 121.1 (C$_4$$_a$), 115.2 (C$_4$ and C$_5$). Anal. calcd. for C$_{27}$H$_{19}$N$_3$O$_2$Cl (%): C 76.68, H 4.53, N 6.62. Found (%): C 76.79, H 4.66, N 6.51.
Table 3. Synthesis of 1,2,4,5-tetrasubstituted imidazoles in an aqueous medium using DB18C6 and KHSO$_4$ (15 mol%).

| Entry | Products | Time (h) | Yields (%) (isolated) | References |
|-------|----------|----------|-----------------------|------------|
| 1     | ![Product 1](image1.png) | 7        | 93                    | –          |
| 2     | ![Product 2](image2.png) | 6        | 92                    | –          |
| 3     | ![Product 3](image3.png) | 6        | 86                    | –          |
| 4     | ![Product 4](image4.png) | 7        | 94                    | –          |
| 5     | ![Product 5](image5.png) | 8        | 95                    | –          |
| 6     | ![Product 6](image6.png) | 7        | 86                    | –          |
| 7     | ![Product 7](image7.png) | 6        | 83                    | –          |
| Entry | Products | Time (h) | Yields (%) (isolated) | References |
|-------|----------|----------|-----------------------|------------|
| 8     | ![Product 8](image) | 6        | 93                    | –          |
| 9     | ![Product 9](image) | 6        | 87                    | –          |
| 10    | ![Product 10](image) | 7        | 89                    | –          |
| 11    | ![Product 11](image) | 6        | 92                    | –          |
| 12    | ![Product 12](image) | 6        | 93                    | –          |
| 13    | ![Product 13](image) | 8        | 84                    | –          |
| 14    | ![Product 14](image) | 7        | 85                    | 34         |
129.4) (ipso to C₄ and C₅), 129.3 (2C, C₂a and C₆a), 128.7 (2C, C₄⁻, C₅-phenyl carbons), 128.5 (C₄⁻ or C₅-phenyl carbon), 128.2 (2C, C₄⁻ or C₅-phenyl carbons), 127.5 (2C, C₄⁻, C₅-phenyl carbons), 127.0 (C₄⁻ or C₅-phenyl carbon), 124.4 (2C, C₃a and C₅a), 116.4 (C₁⁻), 111.6 (2C, C₃⁻ and C₅⁻), 40.1 [2C, -N(CH₃)₂]. Anal. calcd. for Cₑ₂₉H₂₄N₄O₂ (%): C 75.64, H 5.25, N 12.17. Found (%): C 75.51, H 5.33, N 12.29.

The titled compound was obtained as a yellow solid (396 mg, 83%); Rᵣ = 0.64 (25% ethylacetate/75% petroleum ether). M.P.: 208–210°C (EtOAc); IR (KBr): 3426, 2940, 2375, 1598, 1522, 1492, 1347, 1223, 1040, and 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 8.02 (d, J = 9.0 Hz, 2H, C₃a-H and C₅a-H), 7.61 (d, J = 6.9 Hz, 2H, C₃a⁻H and C₅a⁻H), 6.92 (s, 4H, C₂⁻ and C₆⁻ phenyl protons), 7.20 (t, J = 7.8 Hz, 4H, 2C, C₄⁻ and C₅⁻ phenyl protons), 2.39 (s, 6H, 2C, -NH₂). 

**Table 3 (Continued)**

| Entry | Products | Time (h) | Yields (%) | References |
|-------|----------|----------|------------|------------|
| 15    | ![Imidazole Structure](image1.png) | 6        | 92         | 34         |
| 16    | ![Imidazole Structure](image2.png) | 7        | 64         | 43         |
| 17    | ![Imidazole Structure](image3.png) | 6        | 84         | 47         |

2-(2', 5'-Dimethoxyphenyl)-1-(4a-nitrophenyl)-4,5-diphenyl-imidazole (Table 3, entry 7)

Scheme 4. Proposed mechanism for the DB18C6-KHSO₄ catalyzed synthesis of substituted imidazoles formation.
7.36–7.20 (m, 6H, C4-, C5-phenyl protons), 7.16 (brd, J = 5.7 Hz, 3H, C2a-H, and two other protons from C4- and C5-phenyl protons), 7.08 (d, J = 9.0 Hz, 2H, C2a-H and C6a-H), 6.93 (dd, J = 9.0 and 3.0 Hz, 1H, C4a-H), 6.64 (d, J = 9.0 Hz, 1H, C3'-H), 3.83 (s, 3H, C2-OCH3), 3.26 (s, 3H, C3'-OCH3). 13C NMR (75 MHz, CDCl3): 153.7 (C2'), 150.5 (C5'), 146.3 (C6a), 145.0 (C2), 142.7 (C1a), 138.3 (C4), 133.3 (C3), 130.9 (2C, C4- and C5-phenyl carbons), 129.7 (2C, C4- and C5-phenyl carbons), 127.7 (2C, C4- and C5-phenyl carbons), 127.0 (C4' or C5'-phenyl carbons), 126.3 (2C, C3a, C5a), 119.2 (C1'), 117.3 (C6'), 117.1 (C4), 111.9 (C3'), 55.8 (C2'-OCH3), 54.9 (C5'-OCH3). Anal. calcd. for C29H23N3O4 (%): C 72.95, H 4.85, N 9.39. Found (%): C 73.00, H 4.89, N 9.40.

2-(3',4'-Dimethoxyphenyl)-1-(4a-methoxyphenyl)-4,5-diphenylimidazole (Table 3, entry 8)
The titled compound was obtained as a white solid (387 mg, 87%); Rf = 0.29 (25% ethylacetate/75% petroleum ether). M.P.: 174–176°C (EtOAc); IR (KBr): 3431, 2932, 2370, 1599, 1516, 1488, 1445, 1257, 1226, 1131, 1019, and 770 cm−1. 1H NMR (300 MHz, CDCl3): 7.64 (d, J = 8.7 Hz, 2H, C3a-H and C5a-H), 6.85 (d, J = 8.7 Hz, 2H, C3a-H and C6a-H), 6.58 (d, J = 8.7 Hz, 2H, C3-H and C5'-H), 3.76 (s, 3H, C4a-OCH3), 2.93 [s, 3H, C5'-OCH3]. 13C NMR (75 MHz, CDCl3): 158.9 (C4a), 150.1 (C4), 147.7 (C3), 137.5 (C4), 134.7 (C5), 131.2 (2C, C4- and C5-phenyl carbons), 131.1 (C1a), 130.3, and 130.2 (C4' and C5-ipso carbons), 129.8 (2C, C2'), 129.6 (2C, C2a, C6a), 128.2 (2C, C2' and C5'-phenyl carbons), 127.6 (C4' or C5-phenyl carbon), 127.4 (2C, from C4' and C5'-phenyl carbons), 126.3 (C4' or C5-phenyl-imidazole (Table 3, entry 10)
The titled compound was obtained as a yellow solid (398 mg, 89%); Rf = 0.85 (25% ethylacetate/75% petroleum ether). M.P.: 198°C (EtOAc); IR (KBr): 3436, 2932, 2378, 1597, 1511, 1336, 1247, 853, and 699 cm−1. 1H NMR (300 MHz, CDCl3): 8.11 (d, J = 8.7 Hz, 2H, C3a-H and C5a-H), 7.65 (d, J = 9.0 Hz, 2H, C3-H and C5'-H), 7.59 (dd, J = 8.1 and 1.5 Hz, 2H, C4', C5'-phenyl protons), 7.32–7.13 (m, 8H, 4,5-phenyl protons), 7.03 (d, J = 8.7 Hz, 2H, C2a-H and C6a-H), 6.82 (d, J = 8.7 Hz, 2H, C3a-H and C5a-H), 3.80 (s, 3H, C4a-OCH3), 3.71 and 3.68 [2s, 6H, C4'-OCH3 and C4'-OCH3]. 13C NMR (75 MHz, CDCl3): 159.7 (C4a), 148.9 (C2a), 148.2 (C3'), 146.7 (C2), 137.6 (C4), 134.4 (C5), 131.0 (2C, C4', C5-phenyl carbons), 130.3, 129.7 (3C, C1a, C4 and C3 ipso carbons), 129.4 (2C, C2a, C6a), 128.1 (2C, C4', C5-phenyl carbons), 127.9 (2C, C4', C5-phenyl carbons), 127.6 (2C, C4'- and C5'-phenyl carbons), 126.8 (C4' or C5-phenyl carbons), 126.3 (C4' or C5-phenyl carbons), 126.3 (C4' or C5-phenyl carbons), 126.3 (C4' or C5-phenyl carbons), 123.1 (C1'), 121.5 (C6'), 114.0 (2C, C3a, C5a), 111.3 (C2'), 110.6 (C5), 55.6 (C4a-OCH3), 55.5 (C4'-OMe), and 55.2 (C3'-OMe). Anal. calcd. for C30H27N3O (%): C 75.16, H 4.85, N 9.02. Found (%): C 75.03, H 4.89, N 9.44.

2-(3',4'-Dimethoxyphenyl)-1-(4a-ethylphenyl)-4,5-diphenylimidazole (Table 3, entry 9)
The titled compound was obtained as an off-white solid (410 mg, 92%); Rf = 0.54 (25% ethylacetate/75% petroleum ether). M.P.: 162–164°C (EtOAc); IR (KBr): 3431, 3032, 2944, 2370, 1599, 1516, 1488, 1445, 1257, 1226, 1131, 1019, 770, and 699 cm−1. 1H NMR (300 MHz, CDCl3): 7.64 (d, J = 7.2 Hz, 2H from C4', C5-phenyl protons), 7.27–7.15 (m, 8H from C4', C5-phenyl protons), 7.07–7.02 (m, 4H, C2a-H, C6a-H, C2'-H, and C6'-H), 6.95 (d, J = 8.4 Hz, 2H,
2-(4′-N,N-Dimethylaminophenyl)-1-(4a-
methylphenyl)-4,5-diphenyl-imidazole (Table 3, entry 12)

The titled compound was obtained as a white solid (399 mg, 93%; \( R_f = 0.95 \) (25% ethylacetate/75% petroleum ether). M.P.: 234–236°C (EtOAc); IR (KBr): 2902, 1894, 1608, 1484, 1365, 1198, 816, 776, and 698 cm\(^{-1}\). \(^1^\)H NMR (300 MHz, CDCl\(_3\)): 7.62 (d, \( J = 7.0 \) Hz, 2H, C\(_4\)-, C\(_5\)-phenyl protons), 7.34 (d, \( J = 8.9 \) Hz, 2H, C\(_2\)-H and C\(_6\)-H), 7.30–7.13 (m, 8H, C\(_4\)-, C\(_5\)-phenyl protons), 7.07 (d, \( J = 8.1 \) Hz, 2H, C\(_2\)-H and C\(_5\)-H), 6.96 (d, \( J = 8.2 \) Hz, 2H, C\(_3\)-H and C\(_5\)-H), 6.59 (d, \( J = 8.9 \) Hz, 2H, C\(_3\)-H and C\(_2\)-H), 2.95 [s, 6H, \(-\text{N}(\text{CH}_3)\text{2}\)], 2.34 (s, 3H, C\(_4\text{a}\)-CH\(_3\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 150.1 (C\(_3\)), 147.6 (C\(_2\)), 137.8 (C\(_{4\text{a}}\)), 137.5 (C\(_4\)), 134.8 (C\(_{1\text{a}}\)), 134.6 (C\(_5\)), 131.2 (2C, C\(_4\)-, C\(_5\)-phenyl carbons), 131.0 (ipso to C\(_4\)), 129.8 (2C, C\(_2\)- and C\(_6\)-), 129.6 (2C, C\(_2\text{a}\) and C\(_5\text{a}\)), 128.2 (2C, C\(_3\text{a}\) and C\(_5\text{a}\)), 128.2 (2C, C\(_4\)- and C\(_5\)-phenyl carbons), 128.0 (2C, C\(_4\)-, C\(_5\)-phenyl carbons), 127.6 (C\(_{4\text{a}}\) or C\(_{5\text{a}}\)-phenyl carbon), 127.4 (C\(_4\)- or C\(_5\)-phenyl carbon), 126.3 (C\(_4\)- or C\(_5\)-phenyl carbon), 118.2 (C\(_1\)), 111.5 (2C, C\(_3\)- and C\(_2\)-), 40.1 [2C, \(-\text{N}(\text{CH}_3)\text{2}\)], 21.1 (C\(_4\text{a}\)-\text{CH}_3). Anal. calcd. for C\(_{30}\text{H}_{28}\text{N}_{3}\): C 83.88, H 6.34, N 9.78. Found (%): C 83.75, H 6.51, N 9.89.

1-(4a-Aminophenyl)-2-(4′-chlorophenyl)-4,5-diphenyl-imidazole (Table 3, entry 13)

The titled compound was obtained as a grey solid (379 mg, 90%); \( R_f = 0.64 \) (25% ethylacetate/75% petroleum ether). M.P.: 236–238°C (EtOAc); IR (KBr): 3382, 3051, 2275, 1623, 1515, 1293, 1092, 834, and 699 cm\(^{-1}\). \(^1^H\) NMR (300 MHz, CDCl\(_3\)): 7.41 (dd, \( J = 8.1 \) and 1.8 Hz, 2H, C\(_4\)-, C\(_5\)-phenyl protons), 7.27 (dd, \( J = 6.9 \) and 1.8 Hz, 2H, C\(_2\)-H and C\(_6\)-H), 7.14–6.90 (m, 10H, C\(_3\)-H, C\(_5\)-H, and eight protons from C\(_4\)- and C\(_5\)-phenyl protons), 6.62 (dd, \( J = 6.8 \) and 2.1 Hz, 2H, C\(_2\text{a}\)-H and C\(_6\text{a}\)-H), 6.34 (dd, \( J = 6.8 \) and 2.4 Hz, 2H, C\(_3\text{a}\)-H and C\(_5\text{a}\)-H), 3.84 (s, 2H, \(-\text{N}2\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 146.7 and 145.5 (2C, C\(_4\text{a}\), C\(_5\)), 137.3 (2C, C\(_4\), C\(_5\)), 134.5 and 133.4 (2C, C\(_1\), C\(_2\)), 131.5 (2C, ipso to C\(_4\), C\(_5\)), 131.1 (2C, C\(_4\)-, C\(_5\)-phenyl carbons), 130.1 (2C, C\(_2\)-, C\(_6\)-), 129.0, and 128.3 (6C, C\(_2\text{a}\), C\(_6\text{a}\), C\(_5\), C\(_6\), and two from C\(_4\)- and C\(_5\)-phenyl carbons), 128.2 (2C, C\(_4\)-, C\(_5\)-phenyl carbons), 128.1 (C\(_4\)- or C\(_5\)-phenyl carbon), 127.4 (2C, C\(_4\)-, C\(_5\)-phenyl carbons), 126.9 (C\(_4\)- or C\(_5\)-phenyl carbons), 126.8 (C\(_1\)), 115.1 (2C, C\(_3\text{a}\), C\(_5\text{a}\)). Anal. calcd. for C\(_{30}\text{H}_{28}\text{N}_{3}\text{Cl}\): C 76.86, H 4.78, N 9.96. Found (%): C 76.75, H 4.91, N 9.82.

Conclusion

We have for the first time utilized potassium hydrogen sulfate in the presence of dibenzo-18-crown-6 (DB18C6) as an efficient and highly effective catalyst for the facile synthesis of a wide variety of tri- and tetrasubstituted imidazoles in an aqueous medium at moderate temperature. Mild reaction conditions, easy work-up procedure, excellent overall yield, and use of water as the green reaction medium are the major advantages of this methodology.

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