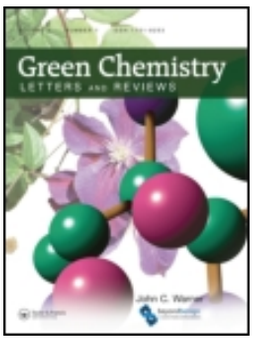

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RESEARCH LETTER

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

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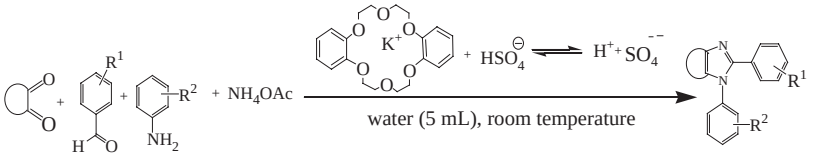
Potassium hydrogen sulfate in the presence of dibenzo-18-crown-6 (DB18C6) turns out to be a very efficient and effective catalyst for the facile synthesis of a wide variety of tri- and tetrasubstituted imidazoles in an aqueous medium at moderate temperature. The idea behind this is that the potassium 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*), $NiCl_2{\cdot}6H_2O$ (*25*), oxalic acid (*26*), iodine (*27*), sulfanilic acid (*28*), tetrabutyl ammonium bromide (*29*), cerium ammonium nitrate (*30*), $Zr(acac)_4$ (*31*), $InCl_3{\cdot}3H_2O$ (*32*)] as well as different activation modes [thermal activation, microwave irradiation (*21, 33*), or ultrasounds (*30, 31*)] have been used to get the

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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–H_2O (*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 $KHSO_4$, K^+ ion will be first trapped by the crown ether followed by the release of HSO_4^-. Again, in the case of an aqueous medium, HSO_4^- will produce hydronium ion (H_3O^+), 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-tri- and 1,2,4,5-tetrasubstituted imidazoles in an aqueous medium under moderate reaction condition.

Results and discussion

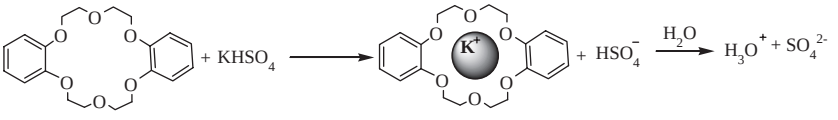
Initially, we started the condensation of benzil (1 mmol), benzaldehyde (1 mmol), and ammonium acetate (3 mmol) in water (5 mL) at room temperature for 24 h in the absence of catalyst but the desired product was not formed at all. Then the same reaction mixture was refluxed on an oil bath for an extended 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 ($KHSO_4$ and $NaHSO_4$). 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 $KHSO_4$. 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 $KHSO_4$ 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 cyclocondensation to produce the products. Aliphatic aldehydes gave the corresponding imidazole in lower yield (52%) than did aromatic aldehydes while diacetyls 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.

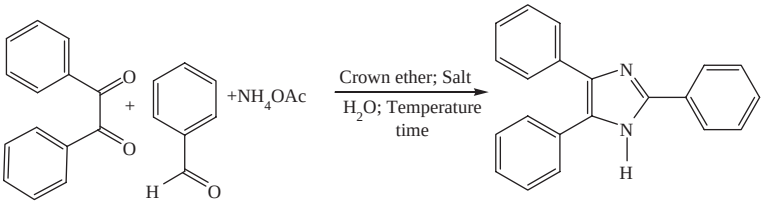
The same methodology was applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles via the one-pot, four-component condensation of an aldehyde, a benzil, a primary aromatic amine (as well as benzyl amine), and an ammonium acetate (Scheme 3), and the products were obtained in excellent yields in 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



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.

Table 1. Condensation of benzil, benzaldehyde, and ammonium acetate in the presence of crown ethers and salts in an aqueous medium.



Entry	Crown ether (mol%)	Salt (mol%)	Temperature (°C)	Time (h)	Yield (%) (isolated)
1	–	–	25	24	Nil
2	–	–	100	24	15
3	18C6 (15)	$KHSO_4$ (15)	25	24	Trace
4	18C6 (15)	$KHSO_4$ (15)	60	6	75
5	DB18C6 (15)	$KHSO_4$ (15)	25	24	Trace
6	DB18C6 (15)	$KHSO_4$ (15)	60	4	92
7	DB18C6 (15)	$NaHSO_4$ (15)	60	6	55

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 $KHSO_4$ 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 $KHSO_4$ (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 Na_2SO_4. After removal of the solvent in vacuo, the pure products were obtained by direct crystallization from ethanol.

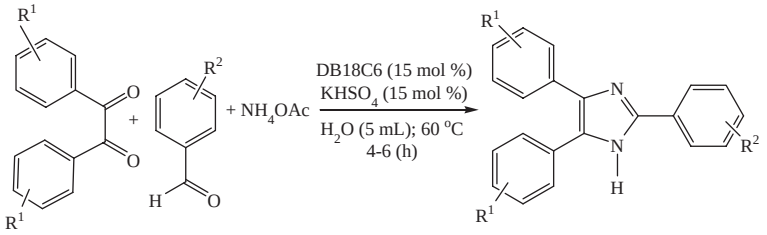
After extraction by ethylacetate, the aqueous part containing DB18C6 and $KHSO_4$ can be reused at least six times for the imidazole synthesis. This recyclability of the catalyst increases its catalytic efficiency.

For large-scale preparation, aldehyde (10 mmol), benzil (10 mmol), ammonium acetate (30 mmol), water (20 mL), DB18C6 (15 mol%), and $KHSO_4$ (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 Na_2SO_4. 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 $KHSO_4$ (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 $KHSO_4$ (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



Scheme 2. Synthesis of 2,4,5-trisubstituted imidazoles in an aqueous medium using DB18C6 and $KHSO_4$ (15 mol%).

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 Na_2SO_4. After removal of the solvent in vacuo, the pure products were obtained by direct crystallization from ethanol.

All the products gave satisfactory IR, ^{1}H NMR, ^{13}C 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%); $R_f = 0.44$ (25% ethylacetate/75% petroleum ether). M.P.: 314–315°C (MeOH); IR (KBr): 3072, 2964, 2376, 1527, 1348, 1091, and 834 cm^{-1}. ^{1}H NMR (300 MHz, d_6-DMSO): 12.84 (s, 1H), 8.65 (s, 1H), 8.21 (d, $J = 7.2$ Hz, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 7.40–7.10 (m, 8H). ^{13}C NMR (75 MHz, d_6-DMSO): 148.3, 143.9, 136.9, 133.5, 132.8, 131.6, 131.2, 130.3, 130.1, 129.3, 128.9, 128.4, 122.7, 119.5, 117.8. Anal. calcd. for $C_{21}H_{13}N_3O_2Cl_2$ (%): C 61.48, H 3.19, N 10.24. Found (%): C 61.36, H 3.27, N 10.28.

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

The titled compound was obtained as a white solid (420 mg, 93%); $R_f = 0.54$ (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}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.60 (dd, $J = 8.0$, 1.5 Hz, 2H, C_4- and C_5-phenyl protons), 7.33–7.18 (m, 8H, C_4-, C_5-phenyl protons), 7.13 (dd, $J = 8.6$, 1.5 Hz, 3H, C_{2a}-, C_{6a}-, $C_{2'}$–H), 6.99 (d, $J = 8.4$ Hz, 2H, C_{3a}-, C_{5a}–H), 6.77–6.70 (m, 2H, $C_{5'}$-, $C_{6'}$–H), 3.74 (s, 3H, $C_{3'}$–OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): [146.9, 146.5, 146.4 ($C_{4'}$-, $C_{3'}$-, and C_2)], 137.6 (C_4), 135.6 (C_{1a}), 134.2 (C_{4a}), 133.6 (C_5), 131.1 (2C, C_4- and C_5-phenyl carbons), [130.2, 130.1 (ipso to C_4- and C_5-, respectively)], 129.6 (2C, C_{2a}, C_{6a}), 129.3 (2C, C_{3a}, C_{5a}), 128.5 (2C, C_4-, and C_5-phenyl carbons), 128.2 (C_4- or C_5-phenyl carbon), 128.1 (2C, C_4- or C_5-phenyl carbons), 127.5 (2C, C_4- or C_5-phenyl carbons), 126.8 (C_4- or C_5-phenyl carbons), 122.5 ($C_{6'}$), 121.4 ($C_{1'}$), 114.3 ($C_{2'}$), 112.0 ($C_{5'}$), 55.8 (–OCH_3). Anal. calcd. for $C_{28}H_{21}N_2O_2Cl$ (%): C 74.25, H 4.67, N 6.19. Found (%): C 74.13, H 4.79, N 6.24.

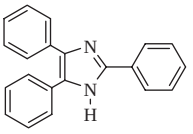
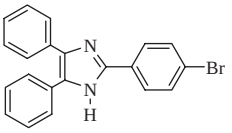
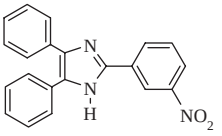
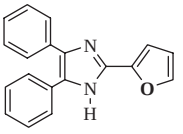
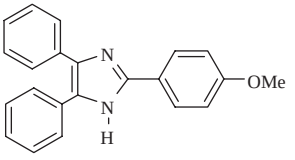
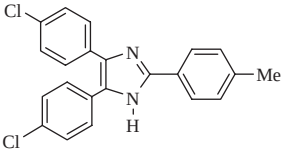
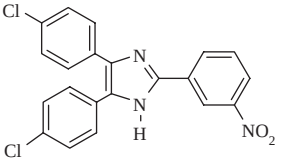
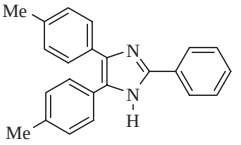
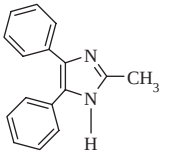
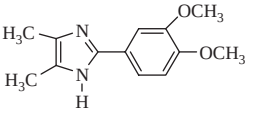
1-(4a-Chlorophenyl)-2-(2′,5′-dimethoxyphenyl)-4,5-diphenyl-imidazole (Table 3, entry 2)

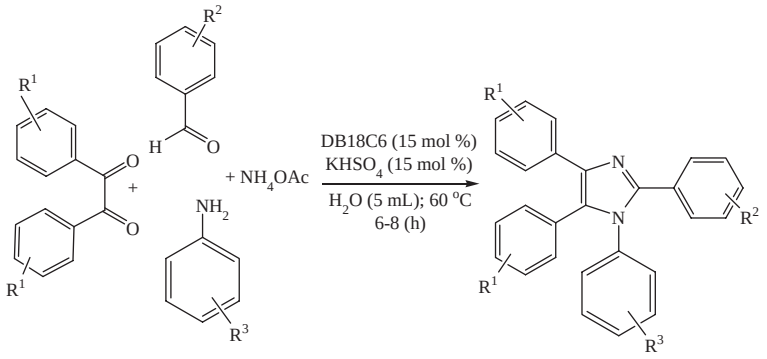
The titled compound was obtained as a white solid (429 mg, 92%); $R_f = 0.75$ (25% ethylacetate/75% petroleum ether). M.P.: 246–248°C (EtOAc); IR (KBr): 3341, 2936, 2372, 1602, 1522, 1484, 1441, 1221, 1178, 1045, and 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.61 (dd, $J = 7.5$, 1.2 Hz, 2H, C_4-, C_5-phenyl protons), 7.33–7.20 (m, 8H, C_4-, C_5-phenyl protons), 7.18–7.11 (m, 3H, C_{2a}, C_{6a}, and $C_{6'}$-H), 6.95–6.86 (m, 3H, C_{3a}, C_{5a}, and $C_{4'}$-H), 6.65 (d, $J = 9.0$, 1H, $C_{3'}$-H), 3.82 (s, 3H, $C_{2'}$-OMe), 3.32 (s, 3H, $C_{5'}$-OMe). ^{13}C NMR (75 MHz, $CDCl_3$): 153.4 ($C_{2'}$), 150.9 ($C_{5'}$), 145.0 (C_2), 137.8 (C_4), 135.6 (C_{1a}), 133.7 (C_5), 133.2 (C_{4a}), 130.9 (2C, C_4-, C_5-phenyl carbons), 130.2 (ipso to C_4), 129.4 (ipso to C_5), 128.5 (2C, C_{2a}, C_{6a}), 128.4 (2C, C_{3a}, C_{5a}), 128.3 (2C, C_4, C_5-phenyl carbons), 128.1 (C_4- or C_5-phenyl carbon), 128.0 (2C, C_4-, C_5-phenyl carbons), 127.5 (2C, C_4-, C_5-phenyl carbons), 126.7 (C_4- or C_5-phenyl carbon), 119.8 ($C_{1'}$), 117.1 ($C_{6'}$), 116.9 ($C_{4'}$), 111.8 ($C_{3'}$), 55.8 (C_2-OMe), and 55.0 (C_5-OMe). Anal. calcd. for $C_{29}H_{23}N_2O_2Cl$ (%): C 74.59, H 4.96, N 5.99. Found (%): C 74.45, H 5.12, N 6.08.

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

The titled compound was obtained as a white crystalline solid (401 mg, 86%); $R_f = 0.57$ (25% ethylacetate/75% petroleum ether). M.P.: 172°C (EtOAc); IR (KBr): 3432, 3053, 2933, 2375, 1597, 1491, 1442, 1405, 1329, 1176, 1131, 1087, 1022, 845, 772, and 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.62 (d, $J = 7.5$ Hz, 2H, C_4- and C_5-phenyl protons), 7.26–7.17 (m, 8H, C_4-, C_5-phenyl protons), 7.14 (brd, $J = 5.7$ Hz, 2H, C_{2a}-H and C_{6a}-H), 7.06 (s, 1H, $C_{2'}$-H), 7.00 (d,

Table 2. Synthesis of 2,4,5-trisubstituted imidazoles in an aqueous medium using DB18C6 and $KHSO_4$ (15 mol%).

Entry	Products	Time (h)	Yield (%) (isolated)	References
1		4	92	*45*
2		4	90	*45*
3		5.5	87	*45*
4		6	82	*46*
5		4	92	*21*
6		5	90	*47*
7		6	89	–
8		4	92	*21*
9		6	52	*47*
10		4	65	*43*



Scheme 3. Synthesis of 1,2,4,5-tetrasubstituted imidazoles in an aqueous medium using DB18C6 and $KHSO_4$ (15 mol%).

$J = 8.1$ Hz, 2H, C_{3a}-H and C_{5a}-H), 6.91 (d, $J = 8.4$ Hz, 1H, $C_{6'}$-H), 6.74 (d, $J = 8.4$ Hz, 1H, $C_{5'}$-H), 3.85 (s, 3H, $C_{4'}$-OCH_3), 3.74 (s, 3H, $C_{3'}$-OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 149.3 ($C_{4'}$), 148.4 ($C_{3'}$), 146.6 (C_2), 137.8 (C_4), 135.6 (C_{1a}), 134.0 (C_{4a}), 133.8 (C_5), 130.9 (2C, C_4-,C_5-phenyl carbons), 130.2 (ipso to C_4), 130.09 (ipso to C_5), 129.6 (2C, C_{2a}, C_{6a}), 129.2 (2C, C_{3a}, C_{5a}), 128.4 (2C, C_4-, C_5-phenyl carbons), 128.1 (C_4- or C_5-phenyl carbon), 128.0 (2C, C_4-, C_5-phenyl carbons), 127.2 (2C, C_4-, C_5-phenyl carbons), 126.6 (C_4- or C_5-phenyl carbon), 122.4 ($C_{1'}$), 121.7 ($C_{6'}$), 112.1 ($C_{2'}$), 110.6 ($C_{5'}$), (55.5 and 55.7) ($2 \times OCH_3$). Anal. calcd. for $C_{29}H_{23}N_2O_2Cl$ (%): C 74.59, H 4.96, N 6.00. Found (%): C 74.43, H 5.04, N 6.07.

1-(4a-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°C (MeOH); IR (KBr): 3034, 2935, 2593, 2490, 1604, 1488, 1440, 1398, 1276, 1165, 1094, 836, 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_{3a}-H, C_{5a}-H, and one from either C_4- or C_5-phenyl protons), 7.21–7.11 (m, 9H, $C_{3'}$-H, $C_{5'}$-H, and seven from C_4-, C_5-phenyl protons), 6.67 (d, $J = 8.7$H, 2H, C_{2a}-H and C_{6a}-H). ^{13}C NMR (75 MHz, $CDCl_3$): 157.8 ($C_{4'}$), 146.7 (C_2), 136.7 (C_4), 135.9 (C_5), 134.5 (C_{1a}), 133.1 (C_{4a}), 131.2 (2C, C_4-, C_5-phenyl carbons), 130.6 (2C, C_{2a}, C_{6a}), 130.54 (ipso to C_4), 130.50 (ipso to C_5), 130.0 (2C, C_{3a}, C_{5a}), 129.3 (2C, C_4-, C_5-phenyl carbons), 128.6 (2C, C_4-, C_5-phenyl carbons), 128.5 (2C, C_4-, C_5-phenyl carbons), 128.2 (2C, C_4-, C_5-phenyl carbons), 126.4 (2C, $C_{2'}$, $C_{6'}$), 121.1 ($C_{1'}$), 115.2 ($C_{3'}$, $C_{5'}$). Anal. calcd. for $C_{27}H_{19}N_2OCl$ (%): C 76.68, H 4.53, N 6.62. Found (%): C 76.79, H 4.66, N 6.51.

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

The titled compound was obtained as a yellow solid (428 mg, 95%); $R_f = 0.96$ (25% ethylacetate/75% petroleum ether). M.P.: 218°C (EtOAc); IR (KBr): 3432, 3066, 2365, 1597, 1521, 1492, 1412, 1345, 1095, 852, and 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 8.10 (d, $J = 8.7$ Hz, 2H, C_{3a}-H and C_{5a}-H), 7.56 (d, $J = 6.6$ Hz, 2H, C_4-, C_5-phenyl protons), 7.33–7.09 (m, 14H, eight from C_4-, C_5-phenyl protons, C_{2a}-, C_{6a}-, $C_{2'}$-, $C_{3'}$-, $C_{5'}$-, and $C_{6'}$-H). ^{13}C NMR (75 MHz, $CDCl_3$): 147.1 (C_{4a}), 145.6 (C_2), 142.0 (C_{1a}), 138.6 (C_4), 135.3 (C_5), 133.0 ($C_{4'}$), 131.0 (2C, C_4-, C_5-phenyl carbons), 130.6 (ipso to C_4), 130.3 (2C, $C_{2'}$, $C_{6'}$), 129.4 (ipso to C_5), 129.1 (2C, C_{2a}, C_{6a}), 128.8 (3C, $C_{3'}$, $C_{5'}$, and one carbon from either C_4- or C_5-phenyl carbon), 128.7 (2C, C_4-, C_5-phenyl carbons), 128.3 (2C, C_4-, C_5-phenyl carbons), 127.6 ($C_{1'}$), 127.3 (2C, C_4-, C_5-phenyl carbons), 127.2 (C_4- or C_5-phenyl carbon), 124.5 (2C, C_{3a} and C_{5a}). Anal. calcd. for $C_{27}H_{18}N_3O_2Cl$ (%): C 71.76, H 4.01, N 9.30. Found (%): C 71.85, H 4.23, N 9.21.

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_{3a}-H and C_{5a}-H), 7.60 (dd, $J = 7.8$ and 1.2 Hz, 2H, two protons from C_4-, C_5-phenyl protons), 7.33–7.21 (m, 8H, C_4-, C_5-phenyl protons), 7.18 (d, $J = 9.0$ Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.11 (dd, $J = 8.1$ and 1.8 Hz, 2H, C_{2a}-H and C_{6a}-H), 6.58 (d, $J = 9.0$ Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 2.96 [s, 6H, $-N(CH_3)_2$]. ^{13}C NMR (75 MHz, $CDCl_3$): 150.6 ($C_{4'}$), 147.7 (C_{4a}), 146.8 (C_2), 142.9 (C_{1a}), 138.1 (C_4), 133.5 (C_5), 131.1 (2C, C_4-, C_5-phenyl carbons), 130.2 (2C, $C_{2'}$ and $C_{6'}$), (123.0 and

Table 3. Synthesis of 1,2,4,5-tetrasubstituted imidazoles in an aqueous medium using DB18C6 and $KHSO_4$ (15 mol%).

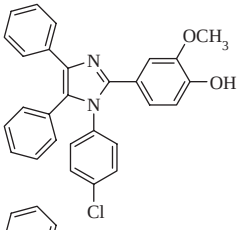
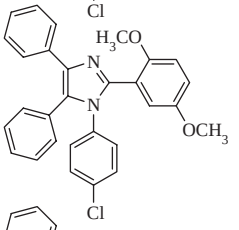
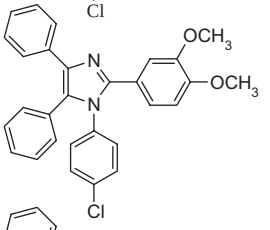
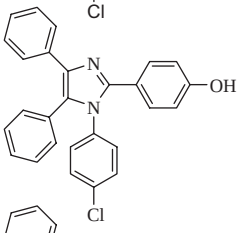
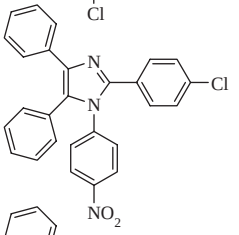
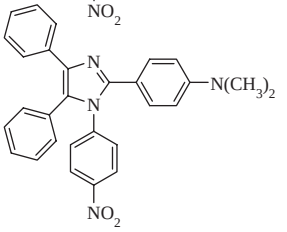
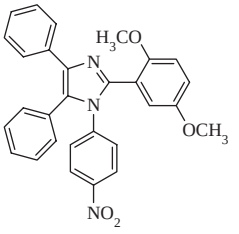
Entry	Products	Time (h)	Yields (%) (isolated)	References
1		7	93	–
2		6	92	–
3		6	86	–
4		7	94	–
5		8	95	–
6		7	86	–
7		6	83	–

Table 3 (*Continued*)

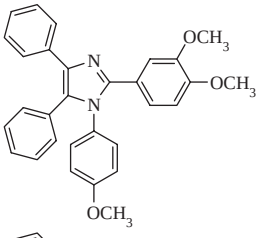
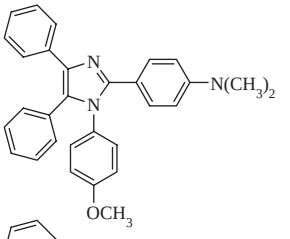
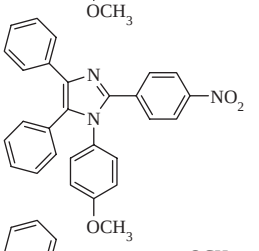
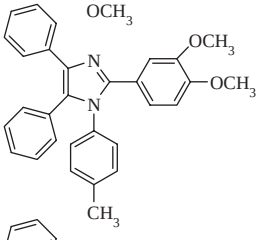
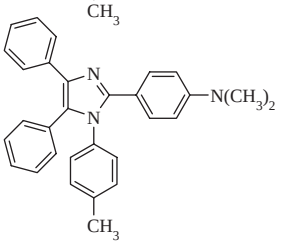
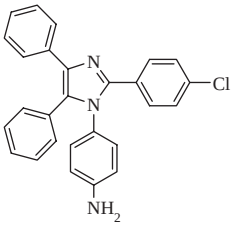
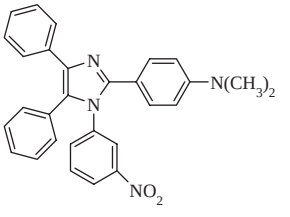
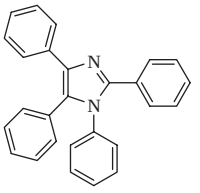
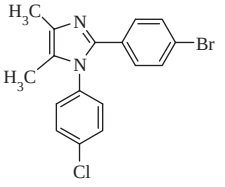
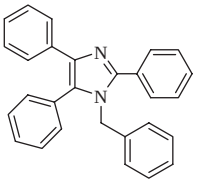
Entry	Products	Time (h)	Yields (%) (isolated)	References
8		6	93	–
9		6	87	–
10		7	89	–
11		6	92	–
12		6	93	–
13		8	84	–
14		7	85	*34*

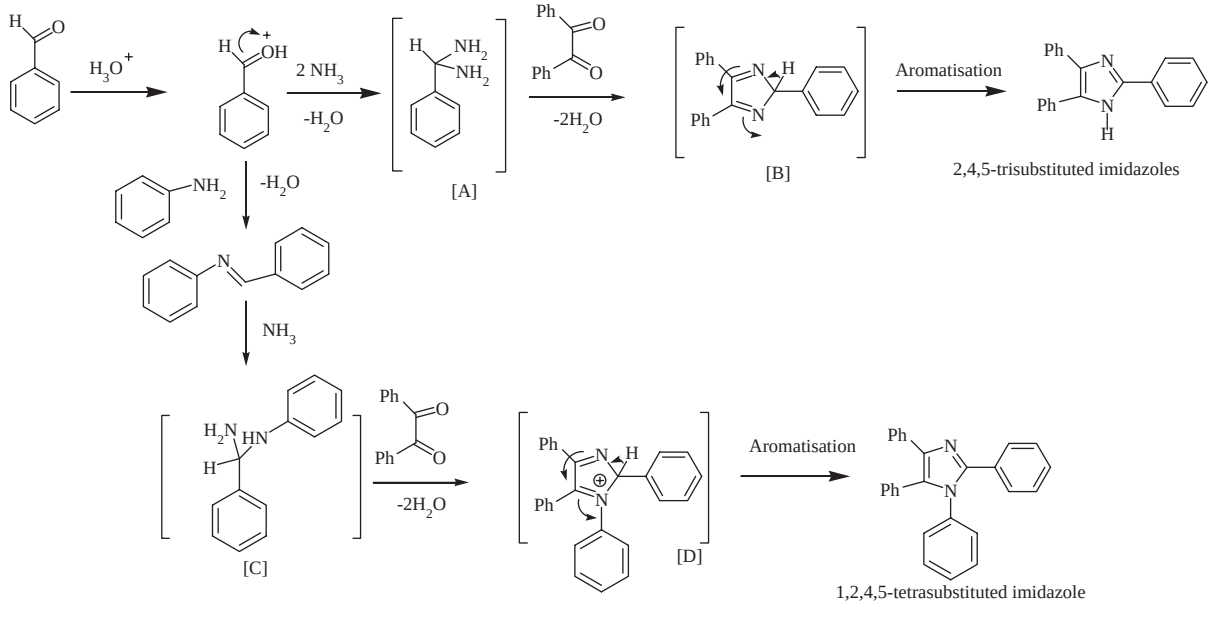
Table 3 (*Continued*)

Entry	Products	Time (h)	Yields (%) (isolated)	References
15		6	92	*34*
16		7	64	*43*
17		6	84	*47*

129.4) (ipso to C_4 and C_5), 129.3 (2C, C_{2a} and C_{6a}), 128.7 (2C, C_4-, C_5-phenyl carbons), 128.5 (C_4- or C_5-phenyl carbon), 128.2 (2C, C_4-, C_5-phenyl carbons), 127.5 (2C, C_4-, C_5-phenyl carbons), 127.0 (C_4- or C_5-phenyl carbon), 124.4 (2C, C_{3a} and C_{5a}), 116.4 ($C_{1'}$), 111.6 (2C, $C_{3'}$ and $C_{5'}$), 40.1 [2C, $-N(CH_3)_2$]. Anal. calcd. for $C_{29}H_{24}N_4O_2$ (%): C 75.64, H 5.25, N 12.17. Found (%): C 75.51, H 5.33, N 12.29.

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

The titled compound was obtained as a yellow solid (396 mg, 83%); $R_f = 0.64$ (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, $CDCl_3$): 8.02 (d, $J = 9.0$ Hz, 2H, C_{3a}-H and C_{5a}-H), 7.61 (d, $J = 6.9$ Hz, 2H, C_4-, C_5-phenyl protons),



Scheme 4. Proposed mechanism for the DB18C6-$KHSO_4$ catalyzed synthesis of substituted imidazoles formation.

7.36–7.20 (m, 6H, C_4-, C_5-phenyl protons), 7.16 (brd, $J = 5.7$ Hz, 3H, $C_{2'}$, and two other protons from C_4- and C_5-phenyl protons), 7.08 (d, $J = 9.0$ Hz, 2H, C_{2a}-H and C_{6a}-H), 6.93 (dd, $J = 9.0$ and 3.0 Hz, 1H, $C_{4'}$-H), 6.64 (d, $J = 9.0$ Hz, 1H, $C_{3'}$-H), 3.83 (s, 3H, C_2-OCH_3), 3.26 (s, 3H, $C_{5'}$-OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 153.7 ($C_{2'}$), 150.5 ($C_{5'}$), 146.3 (C_{4a}), 145.0 (C_2), 142.7 (C_{1a}), 138.3 (C_4), 133.3 (C_5), 130.9 (2C, C_4-, C_5-phenyl carbons), 129.7 (ipso to C_4), 129.2 (ipso to C_5), 128.8 (2C, C_{2a}, C_{6a}), 128.5 (C_4- or C_5-phenyl carbon), 128.1 (2C, C_4-, C_5-phenyl carbons), 127.7 (2C, C_4-, C_5-phenyl carbons), 127.5 (2C, C_4-, C_5-phenyl carbons), 127.0 (C_4- or C_5-phenyl carbon), 123.5 (2C, C_{3a}, C_{5a}), 119.2 ($C_{1'}$), 117.3 ($C_{6'}$), 117.1 ($C_{4'}$), 111.9 ($C_{3'}$), 55.8 ($C_{2'}$-OCH_3), 54.9 ($C_{5'}$-$O\bar{C}H_3$). Anal. calcd. for $C_{29}H_{23}N_3O_4$ (%): C 72.95, H 4.85, N 8.80. Found (%): C 72.83, H 4.97, N 8.95.

2-(3′,4′-Dimethoxyphenyl)-1-(4a-methoxyphenyl)-4,5-diphenylimidazole (Table 3, entry 8)

The titled compound was obtained as a white solid (430 mg, 93%); $R_f = 0.29$ (25% ethylacetate/75% petroleum ether). M.P.: 174–176°C (EtOAc); IR (KBr): 2945, 2834, 2374, 2040, 1601, 1515, 1471, 1442, 1247, 1026, and 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.60 (d, $J = 7.2$ Hz, 2H, C_4- and C_5-phenyl protons), 7.30–7.10 (m, 8H,C_4-, C_5-phenyl protons), 7.05 (brs, 1H, $C_{2'}$-H), 6.97 (d, $J = 8.4$ Hz, 3H, C_{2a}-H, C_{6a}-H, and $C_{6'}$-H), 6.76–6.69 (m, 3H, C_{3a}-H, C_{5a}-H, and $C_{5'}$-H), 3.80 (s, 3H, C_{4a}-OCH_3), 3.71 and 3.68 [2s, 6H, $C_{4'}$-OCH_3 and $C_{3'}$-OCH_3]. ^{13}C NMR (75 MHz, $CDCl_3$): 159.0 (C_{4a}), 148.9 ($C_{4'}$), 148.2 ($C_{3'}$), 146.7 (C_2), 137.6 (C_4), 134.4 (C_5), 131.0 (2C, C_4-, C_5-phenyl carbons), (130.7, 130.6, and 129.9) (3C, C_{1a}, C_4 and C_5 ipso carbons), 129.4 (2C, C_{2a}, C_{6a}), 128.1 (2C, C_4-, C_5-phenyl carbons), 127.9 (2C, C_4-, C_5-phenyl carbons),127.7 (C_4- or C_5-phenyl carbon), 127.2 (2C, C_4-, C_5-phenyl carbons), 126.3 (C_4- or C_5-phenyl carbon), 123.1 ($C_{1'}$), 121.5 ($C_{6'}$), 114.0 (2C, C_{3a}, C_{5a}), 111.3 ($C_{2'}$), 110.6 ($C_{5'}$), 55.6 (C_{4a}-O<u>Me</u>), 55.5 ($C_{4'}$-O<u>Me</u>), and 55.2 ($C_{3'}$-O<u>Me</u>). Anal. calcd. for $C_{30}H_{26}N_2O_3$ (%): C 77.90, H 5.67, N 6.06. Found (%): C 77.81, H 5.75, N 6.14.

2-(4′-N,N-Dimethylaminophenyl)-1-(4a-methoxyphenyl)-4,5-diphenyl-imidazole (Table 3, entry 9)

The titled compound was obtained as an off-white solid (387 mg, 87%); $R_f = 0.67$ (25% ethylacetate/75% petroleum ether). M.P.: 224°C (EtOAc); IR (KBr): 3436, 2899, 2375, 1610, 1510, 1441, 1365, 1248, 818, and 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.61 (d, $J = 7.5$ Hz, 2H, C_4-, C_5-phenyl protons), 7.33 (d, $J = 8.7$ Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.26–7.11 (m, 8H, C_4-, C_5-phenyl protons), 6.99 (d, $J = 8.7$ Hz, 2H, C_{2a}-H and C_{6a}-H), 6.76 (d, $J = 8.7$ Hz, 2H, C_{3a}-H and C_{5a}-H), 6.58 (d, $J = 8.7$ Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 3.76 (s, 3H, C_{4a}-OCH_3), 2.93 [s, 6H, $-N(CH_3)_2$]. ^{13}C NMR (75 MHz, $CDCl_3$): 158.9 (C_{4a}), 150.1 ($C_{4'}$), 147.7 (C_2), 137.5 (C_4), 134.7 (C_5), 131.2 (2C, C_4-, C_5-phenyl carbons), 131.1 (C_{1a}), 130.3, and 130.2 (C_4- and C_5-ipso carbons), 129.8 (2C, $C_{2'}$, $C_{6'}$), 129.6 (2C, C_{2a}, C_{6a}), 128.2 (2C, C_4- and C_5-phenyl carbons), 128.0 (2C, from C_4- and C_5-phenyl carbons), 127.6 (C_4- or C_5-phenyl carbon), 127.4 (2C, from C_4- and C_5-phenyl carbons), 126.3 (C_4- or C_5-phenyl carbon), 118.3 ($C_{1'}$), 114.1 (2C, C_{3a}, C_{5a}), 111.6 (2C, $C_{3'}$, $C_{5'}$), 55.3 (C_{4a}-$O\bar{C}H_3$), 40.2 [2C, $-N(CH_3)_2$]. Anal. calcd. for $C_{30}H_{27}N_3O$ (%): C 80.87, H 6.11, N 9.43. Found (%): C 80.74, H 6.22, N 9.52.

1-(4a-Methoxyphenyl)-2-(4′-nitrophenyl)-4,5-diphenyl-imidazole (Table 3, entry 10)

The titled compound was obtained as a yellow solid (398 mg, 89%); $R_f = 0.85$ (25% ethylacetate/75% petroleum ether). M.P.: 198°C (EtOAc); IR (KBr): 3436, 2932, 2378, 1597, 1511, 1336, 1247, 853, and 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.11 (d, $J = 8.7$ Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.65 (d, $J = 9.0$ Hz, 2H, $C_{2'}$-H and $C_{6'}$-H), 7.59 (dd, $J = 8.1$ and 1.5 Hz, 2H, C_4-, C_5-phenyl protons), 7.32–7.13 (m, 8H, 4,5-phenyl protons), 7.03 (d, $J = 8.7$ Hz, 2H, C_{2a}-H and C_{6a}-H), 6.82 (d, $J = 8.7$ Hz, 2H, C_{3a}-H and C_{5a}-H), 3.80 (s, 3H, C_{4a}-OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 159.7 (C_{4a}), 147.07 ($C_{4'}$), 144.3 (C_2), 138.9 (C_4), 136.2 ($C_{1'}$), 133.5 (C_5), 132.7 (C_{1a}), 131.0 (2C, C_4-, C_5-phenyl carbons), 129.8 (C_4- or C_5-ipso carbon), 129.3 (2C, $C_{2'}$, $C_{6'}$), 129.1 (2C, C_{2a}, C_{6a}), 129.0 (C_4- or C_5-ipso carbon), 128.5 (2C, C_4-, C_5-phenyl carbons), 128.4 (C_4- or C_5-phenyl carbon), 128.3 (2C, C_4-, C_5-phenyl carbons), 127.3 (2C, C_{2a}, C_{6a}), 127.1 (C_4- or C_5-phenyl carbon), 123.4 (2C, $C_{3'}$, $C_{5'}$), 114.6 (2C, C_{3a}, C_{5a}), 55.4 (C_{4a}–$O\bar{C}H_3$). Anal. calcd. for $C_{28}H_{21}N_3O_3$ (%): C 75.16, H 4.73, N 9.39. Found (%): C 75.03, H 4.89, N 9.44.

2-(3,4′-Dimethoxyphenyl)-1-(4a-methylphenyl)-4,5-diphenyl-imidazole (Table 3, entry 11)

The titled compound was obtained as a white solid (410 mg, 92%); $R_f = 0.54$ (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}.^{1}H NMR (300 MHz, $CDCl_3$): 7.64 (d, $J = 7.2$ Hz, 2H from C_4-, C_5-phenyl protons), 7.27–7.15 (m, 8H from C_4-, C_5-phenyl protons), 7.07–7.02 (m, 4H, C_{2a}-H, C_{6a}-H, $C_{2'}$-H, and $C_{6'}$-H), 6.95 (d, $J = 8.4$ Hz, 2H,

C_{3a}-H and C_{5a}-H), 6.72 (d, $J = 9.0$ Hz, 1H, $C_{5'}$-H), 3.81 (s, 3H, $C_{4'}$-OCH_3), 3.67 (s, 3H, $C_{3'}$-OCH_3), 2.29 (s, 3H, C_{4a}-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 148.9 ($C_{4'}$), 148.1 ($C_{3'}$), 146.5 (C_2), 137.9 (C_{4a}), 137.5 (C_4), 134.5 (C_{1a}), 134.2 (C_5), 130.9 (2C, C_4-, C_5-phenyl carbons), 130.5, and 130.4 (2C, ipso to C_4 and C_5), 129.5 (2C, C_{2a}, C_{6a}), 128.1 (2C, C_{3a}, C_{5a}), 128.0 (2C, C_4-, C_5-phenyl carbons), 127.9 (2C, C_4-, C_5-phenyl carbons), 127.7 (C_4- or C_5-phenyl carbon), 127.1 (2C, C_4-, C_5-phenyl carbons), 126.3 (C_4- or C_5-phenyl carbon), 123.0 ($C_{1'}$), 121.5 ($C_{2'}$), 111.9 ($C_{6'}$), 110.5 ($C_{5'}$), 55.5 ($C_{4'}$–O$\bar{C}H_3$), 55.3 ($C_{3'}$–O$\bar{C}H_3$), 20.8 (C_{4a}–$\bar{C}H_3$). Anal. calcd. for $C_{30}H_{26}N_2O_2$ (%): C 80.69, H 5.87, N 6.27. Found (%): C 80.54, H 5.99, N 6.35.

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_{2a}-H and C_{6a}-H), 6.96 (d, $J = 8.2$ Hz, 2H, C_{3a}-H and C_{5a}-H), 6.59 (d, $J = 8.9$ Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 2.95 [s, 6H, –$N(CH_3)_2$], 2.34 (s, 3H, C_{4a}-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 150.1 ($C_{4'}$), 147.6 (C_2), 137.8 (C_{4a}), 137.5 (C_4), 134.8 (C_{1a}), 134.6 (C_5), 131.2 (2C, C_4-, C_5-phenyl carbons), 131.0 (ipso to C_4), 130.1 (ipso to C_5), 129.8 (2C, $C_{2'}$ and $C_{6'}$), 129.6 (2C, C_{2a} and C_{6a}), 128.2 (2C, C_{3a} and C_{5a}), 128.2 (2C, C_4- and C_5-phenyl carbons), 128.0 (2C, C_4-, C_5-phenyl carbons), 127.6 (C_4- or C_5-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 $C_{5'}$), 40.1 [2C, –$N(CH_3)_2$], 21.1 (C_{4a}-$\bar{C}H_3$). Anal. calcd. for $C_{30}H_{27}N_3$ (%): 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_{2a}-H and C_{6a}-H), 6.34 (dd, $J = 6.8$ and 2.4 Hz, 2H, C_{3a}-H and C_{5a}-H), 3.84 (s, 2H, –NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): (146.7 and 145.5) (2C, C_{4a}, C_2), 137.3 (2C, C_4, C_5), (134.5 and 133.4 (2C, C_{1a}, $C_{4'}$), 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_{2a}, C_{6a}, $C_{3'}$, $C_{5'}$, 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_{3a}, C_{5a}). Anal. calcd. for $C_{27}H_{20}N_3Cl$ (%): 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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