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A novel bioglycerol-based recyclable carbon catalyst for an efficient one-pot synthesis of highly substituted imidazoles

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ABSTRACT

The new bioglycerol-based carbon catalyst acts as an efficient, readily available, and reusable catalyst for the synthesis of 2,4,5-trisubstituted imidazoles/1,2,4,5-tetrasubstituted imidazoles, when aromatic aldehyde, ammonium acetate/amine, and 1,2-diketone are reacted in acetonitrile.

Multi-component reactions[1] (MCRs) are one-pot processes, which emerged as important tools for drug discovery,[2] having advantages such as high atom economy and high selectivity.[3] Imidazole represents an important class of compounds in pharmaceutical chemistry with potential biological activity and is the core structural skeleton in many important biological molecules like histidine, histamine, and biotin as well as several drug moieties[4] such as Trifenagrel, Eprosartan, and Losartan (Fig. 1). Numerous methods have been reported for the synthesis of highly substituted imidazoles by using various catalytic systems such as L-proline,[5] $ZrCl_4$,[6] $InCl_3{\cdot}3H_2O$,[7] $HClO_4$–SiO_2,[8] BF_3SiO_2,[9] $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[10] heteropolyacids,[11] silica gel or Zeolite HY,[12] silica gel/$NaHSO_4$,[13] molecular iodine,[14] silica sulfuric acid,[15] microwave irradiation,[16] ionic liquids,[17] $NiCl_2{\cdot}6H_2O/Al_2O_3$,[18] and CAN.[19] However, the above mentioned methods suffer from one or more disadvantages such as the use of hazardous organic solvents, expensive moisture-sensitive catalysts, tedious workup conditions, longer reaction times, or large volumes of catalyst loadings. In recent years carbon-based solid acid catalysts[20] have gained prominence due to their significant advantages over homogeneous liquid phase mineral acids such as increased activity, selectivity, longer catalyst life, negligible equipment corrosion, ease of product separation, and reusability. Cellulose sulfuric acid is one such bio-supported recyclable solid acid catalyst, effectively used for the synthesis of various imidazole derivatives.[21,22] Mercapto propylsilica (MPS), a carbon-based heterogeneous solid catalyst has been reported to catalyze the synthesis of tri-, tetra-substituted imidazoles.[23] DABCO, another carbon-based catalyst has also been utilized as a mild and efficient catalyst for the synthesis of highly substituted imidazoles using a multi component strategy.[24] Prabhavathi Devi et al. reported obtaining similar sulfonic acid-functionalized polycyclic aromatic carbon catalyst from bioglycerol (biodiesel by-product) and also from glycerol-pitch (waste from fat splitting industry) by in situ partial carbonization and sulfonation in a single pot.[25] These carbon catalysts were demonstrated for their effectiveness for the esterification and THP protection and deprotection of alcohols and phenols, respectively.[26] Although other solid-supported acid catalysts like polymer-supported sulfonic acid or silica-supported sulfonic acid, etc., share similarities like ease of catalyst separation and product isolation, the present bio glycerol-based acid catalyst can easily be prepared in the laboratory,[27] and is economically viable since the starting material is readily available.

In continuation of our efforts toward exploring the development of novel environment friendly methodologies[28] which include the synthesis of heterocyclic compounds, herein, we report a mild and efficient one-pot protocol for the synthesis of highly

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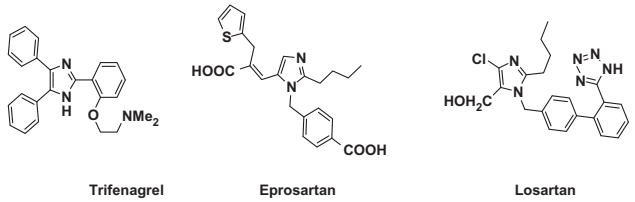
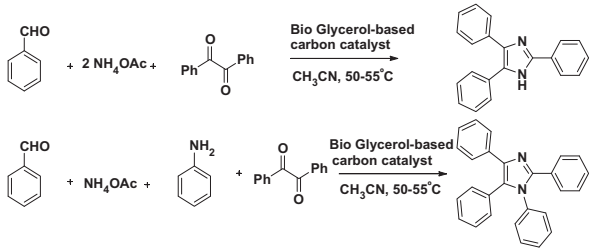


Figure 1. Bio active compounds with imidazole skeleton.



Scheme 1. Synthesis of highly substituted imidazoles.

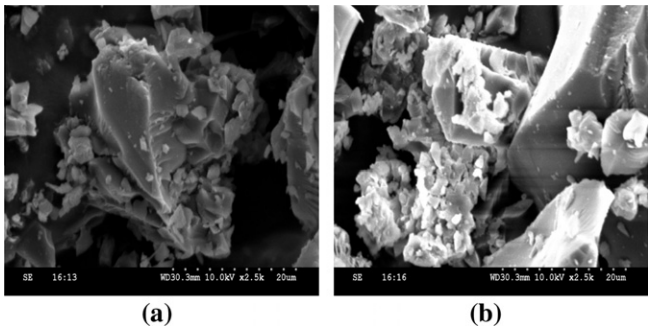


Figure 2. SEM images of (a) fresh bioglycerol-based carbon catalyst and (b) bio glycerol-based carbon catalyst after the fourth cycle.

Table 1
Optimization conditions for the synthesis of 2,4,5-triphenyl-1*H*-imidazole[a]

Entry	Solvent	*T* (°C)	Yield[b] (%)
2	CH_3CN	rt	52
2	CH_3CN	50–55	84
1	Toluene	60–65	48
3	Ethanol	60–65	42
4	Methanol	50–55	28
5	DMSO	80–85	41

[a] Reaction conditions: aldehydes (1.0 mmol), NH_4OAc (2.0 mmol), 1,2-diketone (1.0 mmol), catalyst (10 wt %), solvent (10 mL).
[b] Isolated yield.

Table 2
Recyclability of glycerol-based carbon catalyst

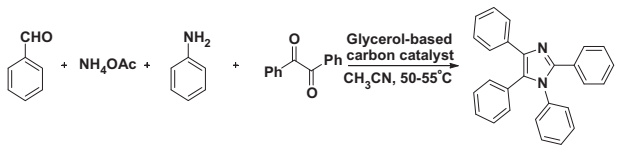
Cycles	Yield (%)	Catalyst recovered (%)
Native	84	88
1	83	86
2	82	85
3	81	83

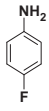
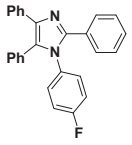
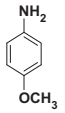
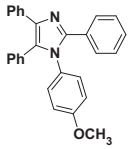
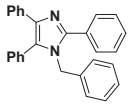
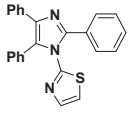
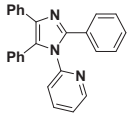
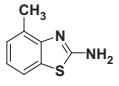
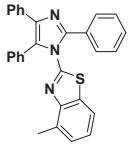
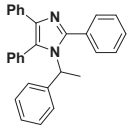
substituted imidazole derivatives for the first time by a multi-component reaction involving 1,2-diketone, aldehydes, NH_4OAc, and amine using a novel and recyclable bioglycerol-based carbon catalyst in acetonitrile (Scheme 1). SEM images of bioglycerol-based carbon catalyst are provided in Figure 2.

In continuation of exploring the possible applications for the carbon-based solid acid catalyst, here we report a facile and efficient one-pot synthesis of highly substituted imidazoles for the first time (Scheme 1).

In our initial studies toward the development of this methodology, 1,2-diketone (1.0 mmol) was reacted with aldehyde (1.0 mmol) and NH_4OAc (2.0 mmol) in acetonitrile and it was found that no reaction was observed and only starting materials were recovered. It was observed that the same reaction proceeded efficiently when bioglycerol-based carbon catalyst was used as a catalyst in acetonitrile at room temperature yielding the corresponding substituted imidazole in a 52% yield after 8 h. When the same reaction was attempted in acetonitrile at 50–55 °C the reaction proceeded to completion within 7 h and yielded the corresponding imidazole derivative in a 84% yield. While evaluating the influence of different solvent systems for bioglycerol-based carbon-catalyzed

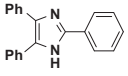
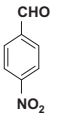
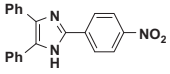
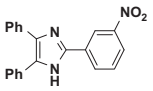
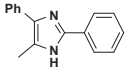
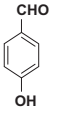
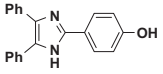
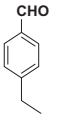
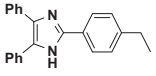
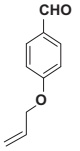
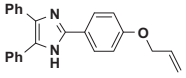
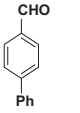
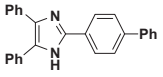
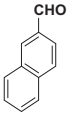
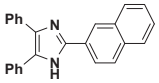
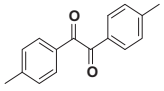
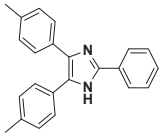
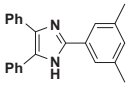
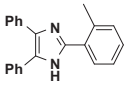
Table 3
Synthesis of 1,2,4,5-substituted imidazoles[a]



Entry	Aldehyde	Amine	Amine	1,2-Diketone	Product	Yield[b] (%)
1		NH_4OAc				82
2		NH_4OAc				82
3		NH_4OAc				74
4		NH_4OAc				77
5		NH_4OAc				73
6		NH_4OAc				72
7		NH_4OAc				70

[a] Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), NH_4OAc (1.0 mmol), 1,2-diketone (1.0 mmol), catalyst (10 wt %), CH_3CN (10 mL), at 50–55 °C.
[b] Isolated yield.

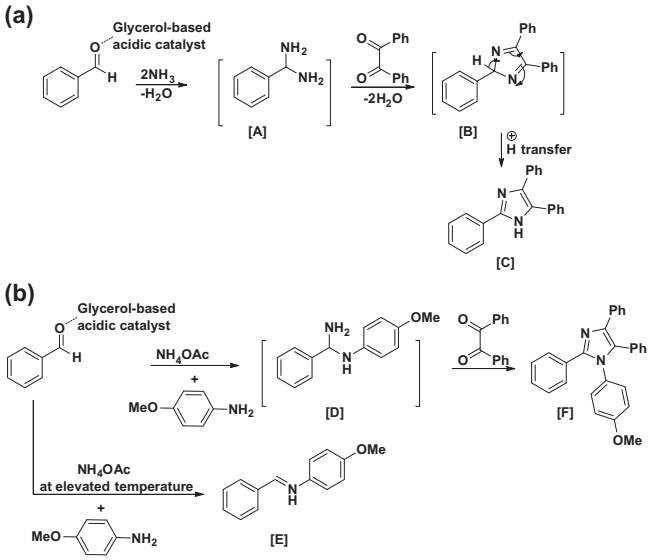
Table 4
Synthesis of 2,4,5-substituted imidazoles[a]

Entry	Aldehyde	Amine source	1,2-Diketone	Product	Yield[b] (%)
1		NH_4OAc			84
2		NH_4OAc			85
3		NH_4OAc			84
4		NH_4OAc			81
5		NH_4OAc			80
6		NH_4OAc			81
7		NH_4OAc			80
8		NH_4OAc			80
9		NH_4OAc			81
10		NH_4OAc			81
11		NH_4OAc			81
12		NH_4OAc			84

[a] Reaction conditions: aldehyde (1.0 mmol), NH_4OAc (2.0 mmol), 1,2-diketone (1.0 mmol), catalyst (10 wt %), CH_3CN (10 mL), at 50–55 °C.
[b] Isolated yield.

synthesis of highly substituted imidazoles, the role of different solvents like CH_3CN, toluene, ethanol, methanol, and DMSO was examined. Among these, only CH_3CN was found to be the best medium for attaining optimum yields (Table 1). Several examples illustrating this simple and practical methodology are summarized in Table 3 and 4. All the products were characterized by ^1H, ^{13}C NMR, IR, and mass spectra and compared with authentic samples.[29–31]

In all these reactions the glycerol-based carbon catalyst can be recovered and reused. After the reaction, the reaction mass was cooled to room temperature and the catalyst was filtered and



Scheme 2. Plausible mechanistic pathway for the synthesis of highly substituted imidazoles using bioglycerol-based carbon catalyst.

washed with ice-cold methanol and dried. The recovered catalyst was further used in the reaction with the same substrates and checked for the yields and catalytic activity of the recovered catalyst, as shown in Table 2. It was observed that the yields of highly substituted imidazoles diminished slightly after two to three recycles. The plausible mechanism for the synthesis of highly substituted imidazoles in the presence of bioglycerol-based carbon catalyst can be explained as shown in Scheme 2. In the case of 2,4,5-trisubstituted imidazole the reaction proceeds via diamine intermediate [A], which is formed by the activation of aldehydic carbonyl group by the acidic bioglycerol-based carbon catalyst through intermolecular hydrogen bonding, and condensation of diamine with 1,2-diketone followed by dehydration to form the imino intermediate [B], which rearranges to form the desired product [C]. In the case of tetra substituted imidazoles the reaction proceeds in the same fashion. Various reactions were conducted to establish the mechanism of this reaction changing the reactants and their molar ratios. In the case of the reaction of benzaldehyde with equimolar amounts of ammonium acetate and 4-methoxy aniline the intermediate [D] was isolated as an intermediate, which further reacted with 1,2-dicarbonyl compound to yield the expected product [F]. When the same reaction was conducted at elevated temperatures the imino intermediate [E] was also isolated as a side product (Scheme 2).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.092.

References and notes

1. (a) Eilbracht, P.; Barfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schimdt, A. *Chem. Rev.* **1999**, *99*, 3329; (b) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435.
2. (a) Weber, L. *Drug Discovery Today* **2002**, *7*, 143; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51; (c) Tempest, P. A. *Curr. Opin. Drug Discov. Dev.* **2005**, *8*,

776; (d) Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synlett* **2008**, 4007.
3. (a) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. and references cited therein; (b)For a monograph, see: *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; (c) Domling, A. *Chem. Rev.* **2006**, *106*, 17; (d) D'Souza, D. M.; Mueller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 3169; (e) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *73*, 9762.
4. (a) Koike, H.; Konse, T.; Sada, T.; Ikeda, T.; Hyogo, A.; Hinman, D.; Saito, H.; Yanagisawa *Ann. Rep. Sankyo Res. Lab.* **2003**, *55*, 1; (b) Abrahams, S. L.; Hazen, R. J.; Batson, A. G.; Phillips, A. P. J. *Pharmacol. Exp. Ther.* **1989**, *249*, 359; (c) Leister, C.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453.
5. Samai, S.; Nandi, G. C.; Singh, P.; Singh, M. S. *Tetrahedron* **2009**, *65*, 10155.
6. Sharma, G. V. M.; Jyothi, Y.; Lakshmi, P. S. *Synth. Commun.* **2006**, *36*, 2991.
7. Sharma, S. D.; Hazarika, P.; Konwar, D. *Tetrahedron Lett.* **2008**, *49*, 2216.
8. Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L. *J. Mol. Catal. A: Chem.* **2007**, *266*, 109.
9. Sadeghi, B.; Mirjalili, B. B. F.; Hashemi, M. M. *Tetrahedron Lett.* **2008**, *49*, 2575.
10. Nagarapu, L.; Apuri, S.; Kantevari, S. *J. Mol. Catal. A: Chem.* **2007**, *266*, 104.
11. Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. *J. Mol. Catal. A: Chem.* **2007**, *263*, 112.
12. Balalaei, S.; Arabanian, A. *Green Chem.* **2000**, *2*, 274.
13. Karimi, A. R.; Alimohammadi, Z.; Azizian, J.; Mohammadi, A. A.; Mohmm adizadeh, M. R. *Catal. Commun.* **2006**, *7*, 728.
14. Kidwai, M.; Mothsra, P.; Bansal, V.; Somvanshi, R. K.; Ethayathulla, A. S.; Dey, S.; Singh, T. P. *J. Mol. Catal. A: Chem.* **2007**, *265*, 177.
15. (a) Shaabani, A.; Rahmati, A. *J. Mol. Catal. A: Chem.* **2006**, *249*, 246; (b) Shaabani, A.; Rahmati, A.; Farhangi, E.; Badri, Z. *Catal. Commun.* **2007**, *8*, 1149.
16. (a) Usyatinsky, A. Y.; Khemelnitsky, Y. L. *Tetrahedron Lett.* **2000**, *41*, 5031; (b) Balalaie, S.; Hashemi, M. M.; Akhbari, M. *Tetrahedron Lett.* **2003**, *44*, 1709; (c) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453; (d) Sparks, R. B.; Combs, A. P. *Org. Lett.* **2004**, *6*, 2473; (e) Oskooie, H. A.; Alimohammadi, Z.; Heravi, M. M. *Heteroat. Chem.* **2006**, *17*, 699; (f) Santosh, V. N.; Mohan, B. K.; Vijay, S. P.; Sidhanath, V. B.; Satish, U. D.; Rajendra, P. P. *Open Catal. J.* **2010**, *3*, 58.
17. (a) Siddiqui, S. A.; Narkhede, U. C.; Palimkar, S. S.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2005**, *61*, 3539; (b) Hasaninejad, A.; Zare, A.; Shekouhy, M.; Ameri Rad, J. *J. Comb. Chem.* **2010**, *12*, 844.
18. Heravi, M. M.; Bakhtiari, K.; Oskooie, H. A.; Taheri, S. *J. Mol. Catal. A: Chem.* **2007**, *263*, 279.
19. Sangshetti, J. N.; Kokare, N. D.; Kotharkara, S. A.; Shinde, D. B. *J. Chem. Sci.* **2008**, *5*, 463.
20. (a) Hara, M.; Yoshida, T.; Takagaki, A.; Takata, T.; Kondo, J. N.; Hayashi, D. K. *Angew. Chem.* **2004**, *116*, 3015; (b) Toda, M.; Takagaki, A.; Okamura, M.; Kondo, J. N.; Hayashi, S.; Domen, K.; Hara, M. *Nature* **2005**, *438*, 178; (c) Takagaki, A.; Toda, M.; Okamura, M.; Kondo, J. N.; Hayashi, S.; Domen, K.; Hara, M. *Catal. Today* **2006**, *116*, 157; (d) Zong, M. H.; Duan, Z. Q.; Lou, W. Y.; Smith, T. J.; Wu, H. *Green Chem.* **2007**, *9*, 434.
21. Shelke, K. F.; Sapkal, S. B.; Kakade, G. K.; Shingate, B. B.; Shingare, M. S. *Green Chem. Lett. Rev.* **2010**, *3*, 27.
22. Suresh Kumar, B.; Venu Madhav, J.; Rajitha, B.; Thirupathi Reddy, Y.; Narsimha Reddy, P.; Crooks, P. A. *Synth. Commun.* **2011**, *41*, 662.
23. Mukhopadhyay, C.; Pradip Kumar, T.; Drew, M. G. B. *Tetrahedron Lett.* **2010**, *51*, 3944.
24. Murthy, S. N.; Madhav, B.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 5252.
25. Prabhavathi Devi, B. L. A.; Gangadhar, K. N.; Sai Prasad, P. S.; Jagannadh, B.; Prasad, R. B. N. *ChemSusChem* **2009**, *2*, 617.
26. Prabhavathi Devi, B. L. A.; Gangadhar, K. N.; Siva Kumar, K. L. N.; Shiva Shanker, K.; Prasad, R. B. N.; Sai Prasad, P. S. *J. Mol. Catal. A: Chem.* **2011**, *345*, 96.
27. *General procedure for the synthesis of bio glycerol-based carbon catalyst*: A mixture of glycerol (10 g) and concentrated sulfuric acid (30 g) was heated at 180 °C for 20 min, facilitating in situ partial carbonization and sulfonation. The reaction mixture was allowed to remain at that temperature for about 20 min (until foaming ceased) resulting in a polycyclic aromatic carbon product. The compound was cooled to ambient temperature and washed with hot water until the washings indicated a neutral pH value. The partially crystalline product was filtered and dried till it was moisture-free to get bio glycerol-based carbon catalyst (4.65 g).
28. (a) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Helv. Chim. Acta* **2009**, *92*, 2118; (b) Murthy, S. N.; Madhav, B.; Kumar, A. V.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron* **2009**, *65*, 5251; (c) Madhav, B.; Murthy, S. N.; Reddy, V. P.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2009**, *50*, 6025; (d) Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3649; (e) Shankar, J.; Karnakar, K.; Srinivas, B.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3938; (f) Ramesh, K.; Murthy, S. N.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2362; (g) Anil Kumar, B. S. P.; Madhav, B.; Harsha Vardhan Reddy, K.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2011**, *52*, 2862.
29. *General procedure for the synthesis of 2,4,5-substituted imidazole derivatives*: To a stirred solution of acetonitrile (10 mL), aldehyde (1.0 mmol) and bioglycerol-based carbon catalyst (10 wt %) were added and stirred for 10 min. To this ammonium acetate (2.0 mmol) followed by 1,2-diketone (1.0 mmol) were added, after which the reaction mixture was heated at 50–55 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to room temperature and catalyst was filtered, the solvent was removed by rotary evaporator. The crude residue was extracted with ethyl acetate (3×10 mL). The combined organic layers were extracted with water, saturated brine solution, and dried over anhydrous Na_2SO_4. The organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate and hexane (7:3) as eluent to give the corresponding substituted imidazole derivative in 78–85% yield. The identity as well as purity of the product was confirmed by ^1H, ^{13}C NMR, and mass spectra.
30. *General procedure for the synthesis of 1,2,4,5- substituted imidazole derivatives*: To a stirred solution of acetonitrile (10 mL), aldehyde (1.0 mmol) and bioglycerol-based carbon catalyst (10 wt %) were added and stirred for 10 min. To this ammonium acetate (1.0 mmol) and amine (1.0 mmol) followed by 1,2-diketone (1.0 mmol) were added, after which the reaction mixture was heated at 50–55 °C until completion of the reaction as indicated by TLC. The reaction mixture was cooled to room temperature and catalyst was filtered, the solvent was removed by rotary evaporator. The crude residue was extracted with ethyl acetate (3×10 mL). The combined organic layers were extracted with water, saturated brine solution, and dried over anhydrous Na_2SO_4. The organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography by using ethyl acetate and hexane (7:3) as eluent to give the corresponding substituted imidazole derivative in 70–82% yield. The identity as well as purity of the product was confirmed by ^1H, ^{13}C NMR, and mass spectra.
31. Spectral data of representative examples: 1-(4-fluorophenyl)-2,4,5-triphenyl-1*H*-imidazole (Table 3, entry 1): ^1H NMR (DMSO-d_6, 300 MHz): δ 7.54 (d, J = 6.7 Hz, 1H), 7.46–7.37 (m, 2H), 7.26–7.16 (m, 10H), 7.03–6.91 (m, 6H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ 131.0, 129.1, 128.9, 128.6, 128.2, 127.5, 126.9, 114.2.; ESI-MS (m/z): $(M+H)^+$.