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Nano indium oxide catalyzed tandem cyclization of amidine with nitroolefin

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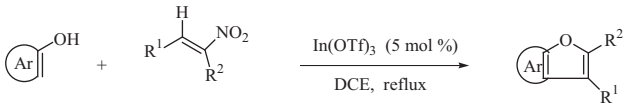
ABSTRACT

A tandem cyclization of amidine with nitroolefin has been described using nano In_2O_3 as an efficient catalyst. The reaction is effective for the preparation of 4,5-unsymmetrically substituted 1-*H* imidazole in moderate to good yields. The catalyst was successfully reused for four consecutive cycles with similar catalytic activities.

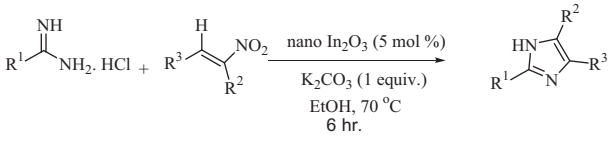
Recently metal nano catalysts have received considerable importance in organic synthesis due to their better catalytic properties and selectivity compared to their bulk counterparts.[1] In the context of green chemistry they have earned more significance due to their effective reusability as well as greater efficiency because of their higher surface area.[2] Indium metal and its salts have attracted attention of the synthetic community due to their wide applications in the field of organic synthesis.[3] Our group has been actively engaged in utilizing indium metal and its salts for useful reactions for more than a decade.[4] It is significant to note that the application of nano In_2O_3 as catalyst has not been well studied.[5a,b] Our recently reported work[5c,d] with nano In_2O_3 inspired us to explore its catalytic activity for useful transformations and preparation of important organic compounds.

Nitroolefins are easily prepared[6a] and considered as a useful substrate in many synthetic strategies like Michael addition,[6b] cycloaddition,[6c–e] Morita–Baylis–Hillman reaction,[6f] and two component coupling reaction.[7] Previous work by our group[7] on the synthesis of arenofurans has demonstrated an important use to nitroolefins (Scheme 1). It has been established that *N*-arylamidines serve as precursors to the synthesis of biologically important heterocycles.[8] We have used nitroolefins as starting material for the synthesis of 4,5-unsymmetrically substituted 1-*H* imidazoles (Scheme 1). Attempts made for the synthesis of imidazoles stem from the broad range of their applications in biological[9] as well as synthetic fields.[10] The traditional methods for the preparation of both 2,4,5-substituted and 1,2,4,5-substituted imidazoles are based on the multicomponent reaction using 1,2-dicarbonyl compounds, different aldehydes, and a nitrogen source.[11] There are a number of methods in the literature following this strategy[11] with variation of parameters and catalysts.[12] Most of these traditional methods involved the synthesis of symmetrically substituted imidazole at 4,5-position. This is due to the lesser availability of unsymmetric 1,2-diketones. Accordingly, a methodology for the synthesis of 4,5-unsymmetrically substituted imidazoles using a simple two-component one-pot reaction is highly desirable. Herein, we report a method for the synthesis of 4,5-unsymmetrically substituted 1-*H* imidazoles using nano In_2O_3 as catalyst, K_2CO_3 as base, and ethanol as solvent (Scheme 1).

Our previous work : Coupling between nitroolefin and phenol/napthols[7]



Present work : Tandem cyclization between amidine and nitroolefin



Scheme 1.

Being encouraged by our previous results,[7] we initiated our study taking amidine hydrochloride, nitroolefin, and $In(OTf)_3$ as

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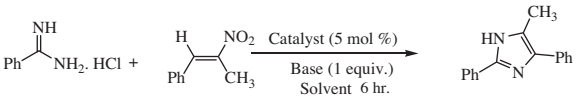
Table 1
Optimization of the reaction conditions

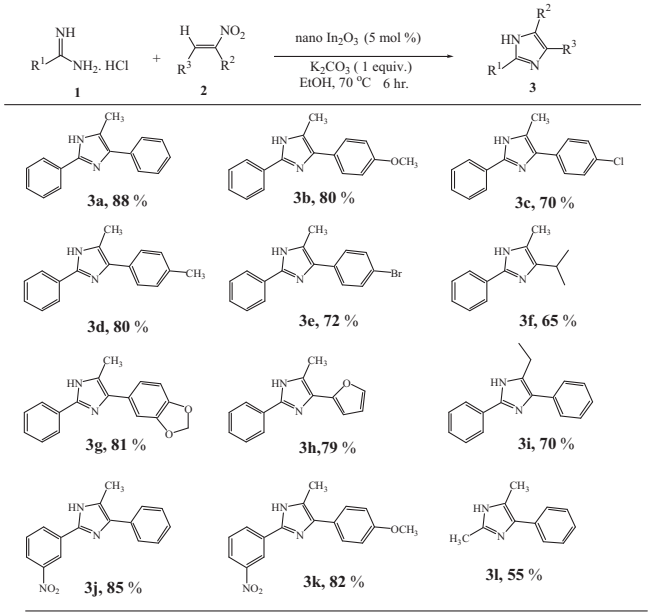


Entry	Catalyst	Base	Solvent	Temp (°C)	Yield[a] (%)
1	$In(OTf)_3$	K_2CO_3	EtOH	70	86
2	$In(OTf)_3$	K_2CO_3	DCB	70	40
3	$In(OTf)_3$	K_2CO_3	1,2-DCE	70	80
4	$In(OTf)_3$	K_2CO_3	CH_3CN	70	62
5	$In(OTf)_3$	K_2CO_3	DMSO	70	43
6	$In(OTf)_3$	K_2CO_3	DMF	70	40
7	$In(OTf)_3$	K_2CO_3	PEG400	70	51
8	$In(OTf)_3$	K_2CO_3	Toluene	70	72
9	$In(OTf)_3$	K_2CO_3	H_2O	70	56
10	$In(OTf)_3$	K_2CO_3	EtOH	70	59
11	$In(OTf)_3$	Cs_2CO_3	EtOH	70	71
12	$In(OTf)_3$	KOH	EtOH	70	72
13	$In(OTf)_3$	KOAc	EtOH	70	52
14	$In(OTf)_3$	DABCO	EtOH	70	58
15	$In(OTf)_3$	Et_3N	EtOH	70	78
16	$In(OTf)_3$	—	EtOH	70	—
17	$InCl_3$	K_2CO_3	EtOH	70	81
18	Powder In_2O_3	K_2CO_3	EtOH	70	70
19	**Nano In_2O_3**	**K_2CO_3**	**EtOH**	**70**	**88**
20	Nano ZnO	K_2CO_3	EtOH	70	74
21	Nano CuO	K_2CO_3	EtOH	70	70
22	Nano In_2O_3	K_2CO_3	1,2-DCE	70	<5
23	Nano In_2O_3	K_2CO_3	CH_3CN	70	58
24	Nano In_2O_3	K_2CO_3	PEG 400	70	53
25[b]	Nano In_2O_3	K_2CO_3	EtOH	70	90
26	Nano In_2O_3	K_2CO_3	EtOH	Reflux	89
27[c]	Nano In_2O_3	K_2CO_3	EtOH	70	78

[a] Isolated yield.
[b] 10 mol % catalyst used.
[c] 3 mol % catalyst used.

catalysts using 1,2-DCE as solvent and K_2CO_3 as base (Table 1, entry 3) and were able to synthesize the desired imidazole in 80% yield. Other solvents like DCB, CH_3CN, DMSO, DMF, dioxane, PEG-400, toluene, and H_2O (entries 2–10) gave lower yields. However, EtOH (Table 1, entry 1) was found as the best solvent increasing the product yield to a good extent (86%). We varied the bases like Cs_2CO_3, KOH, and KOAc (Table 1, entries 11–13) instead of K_2CO_3 but no enhancement of yield was observed. Application of organic bases like DABCO and Et_3N (Table 1, entries 14 and 15) furnished 58% and 78% yields, respectively. The reaction did not proceed at all, in the absence of base (Table 1, entry 16). Therefore, the choice of base has important role in the reaction path and is probably required to free the amidine hydrochloride. Indium chloride was also able to perform the reaction with good yields (81%, Table 1, entry 17). Motivated by this result, we then used powder In_2O_3 (Table 1, entry 18) and nano In_2O_3 (Table 1, entry 19) and obtained very good yields, 70% and 88%, respectively. To investigate the effect on the choice of catalyst, we have used different nano metal oxides like ZnO and CuO, (Table 1, entries 20 and 21), but no enhancement of yield has been observed. Thus we have found that nano In_2O_3 is an effective catalyst under the reaction conditions. Further, the efficiency of different solvents for nano In_2O_3-catalyzed reaction (Table 1, entries 22–24) has been examined and no promising result was found. Next, with EtOH as the solvent we tested the catalyst loading and observed that no considerable improvement was made on increasing the amount of catalyst or increasing the temperature from 70 °C to reflux (Table 1, entries 25 and 26). On lowering the amount of catalyst (3 mol %) yield of the reaction was reduced (Table 1, entry 27). The detailed optimization is summarized in Table 1.

Table 2
Scope of substrates



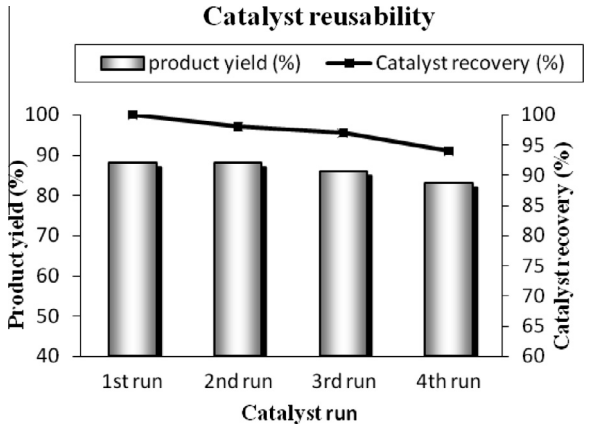
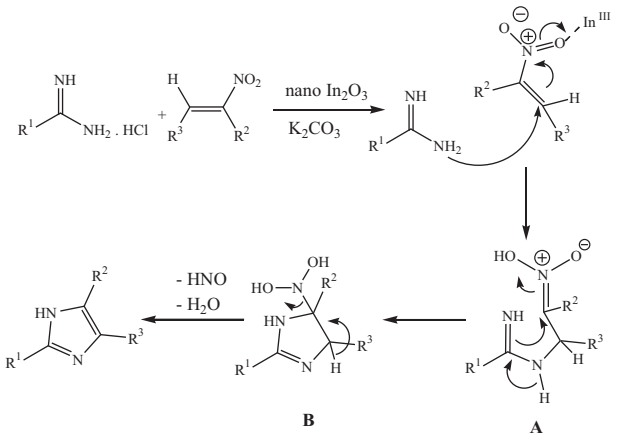


Figure 1. Reusability of the catalyst.

The substrate scope and limitations of our method were investigated and are summarized in Table 2. The reaction of (2-nitropropenyl)-benzene with benzamidine was very clean giving 88% yield (**3a**). We have performed the reactions varying the amidines with a wide range of structurally diverse nitroolefins and isolated the desired products in good yields. As it is evident from Table 2, this procedure is uniformly effective for nitroolefins with different substituents on the benzene ring as well as for aliphatic nitroolefin (**3f**). Nitroolefins with a methylenedioxy group on the aromatic moiety underwent smooth reaction with 81% yield (**3g**). The heterocyclic moiety (**3h**) remains unaffected under the present reaction conditions and furnished good yield (79%). However, using acetamidine (**31**) over benzamidine resulted in a lower yield (55%). The reaction did not proceed for (2-nitro-vinyl)-benzene with acetamidine or benzamidine under the present reaction conditions.

To check the reusability of the catalyst, the catalyst after each run, the latter was centrifuged and washed with ethanol and water followed by drying at 110 °C. The recovered catalyst was reused for four subsequent runs without any significant deactivation of the catalytic activity (Fig. 1).



Scheme 2. Plausible mechanism for the synthesis of 2,4,5-trisubstituted imidazole.

Based on our previous results,[7] a likely mechanistic pathway for the reaction is described in Scheme 2. Michael addition of amidine–nitroolefin forms the Michael adduct **A**. It is possible that the indium (III) catalyst promotes this addition by activating the double bond. Then the intermediate **A** undergoes cyclization to give the five membered cyclic intermediate **B**. Removal of HNO and H_2O from the latter leads to aromatization providing the desired product.[7,13,14]

In conclusion, we have explored the use of nano In_2O_3 as an effective and versatile catalyst for the synthesis of 4,5-unsymmetrically substituted 1-*H* imidazoles. The use of an environmentally friendly and inexpensive base and solvent, along with reusability of the catalyst provides a good example of a competitive, alternative synthetic methodology for these compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.050.

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14. During preparation of our manuscript for submission a very closely related work has been published. But analysis of their method proved that our mechanistic path is totally different. Ref. Tang, D.; Wu, P.; Liu, X.; Chen,; Y.-X.; Guo, S.-B.; Chen, W.-L.; Li, J.-G.; Chen, B.-H. *J. Org. Chem.* **2013**, *78*, 2746.
Typical procedure for the synthesis of *5-Methyl-2,4-diphenyl-1H-imidazole* (Table 2, **3a**): In an oven dried 10 mL round bottom flask, benzamidine hydrochloride (78 mg, 0.5 mmol), (2-nitro-propenyl)-benzene (81 mg, 0.5 mmol), nano In_2O_3 (7 mg, 5 mol %), K_2CO_3 (69 mg, 1 equiv), and dry EtOH (2 mL) were added and stirred for 6 h at 70 °C. The progress of the reaction was monitored by TLC. After completion of the reaction the excess EtOH was evaporated in a rotary evaporator and the crude reaction mixture was diluted with water (3 mL), and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography (hexane/ethyl acetate as eluent) to afford the analytically pure product as a white solid (103 mg, 88%). mp 180–184 °C. IR (KBr) 3357, 3076, 2692, 2584, 1872, 1735, 1598, 1492, 1456, 1406, 1278, 1126, 975 cm^{-1}; δ ^1H NMR (400 MHz, DMSO-d_6): δ 8.15 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 7.2 Hz, 2H), 7.54–7.45 (m, 5H), 7.34 (t, J = 7.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 143.4, 132.1, 131.5, 129.9, 129.3, 129.0, 127.6, 127.3, 127.0, 126.1, 11.5; Anal. Calcd for $C_{16}H_4N_2$: C, 82.02; H, 6.02; N, 11.96%. Found: C, 82.17; H, 6.10; N, 12.02%.
4-(4-Methoxy-phenyl)-5-methyl-2-phenyl-1H-imidazole (**3b**). White solid (80% yield): mp 176–178 °C; IR (KBr) 3431, 3045, 2912, 2769, 2644, 1641, 1606, 1253, 1186, 1012, 840, 821, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.58–7.50 (m, 3H), 7.07 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3, 142.7, 131.0, 130.5, 129.4, 129.0, 126.4, 126.0, 122.7, 114.5, 55.6, 11.1; Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60%. Found: C, 77.28; H, 6.14; N, 10.62%.
4-(4-Chloro-phenyl)-5-methyl-2-phenyl-1H-imidazole (**3c**). Pale yellow solid (70% yield): mp 164–166 °C; IR (KBr) 3276, 3240, 3045, 2964, 2852, 1909, 1596, 1517, 1494, 1361, 1255, 1164, 1091, 1014, 833, 682 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.47–7.43 (m, 4H), 7.34 (t, J = 7.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.3, 133.8, 130.7, 130.6, 129.3, 129.1, 128.7, 128.3, 128.0, 125.1, 12.2; Anal. Calcd for $C_{16}H_{13}N_2Cl$: C, 71.51; H, 4.88; N, 10.42%. Found: C, 71.62; H, 4.96; N, 10.53%.
5-Methyl-2-phenyl-4-p-tolyl-1H-imidazole (**3d**). White solid (80% yield): mp 179 °C; IR (KBr) 3353, 3043, 2966, 2927, 2852, 1676, 1598, 1517, 1369, 1172, 1116, 1029, 767, 700, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 6.8 Hz, 2H), 7.23 (d, J = 6.8 Hz, 2H), 7.17–7.16 (m, 3H), 7.00 (d, J = 6.8 Hz, 2H), 2.19 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.1, 131.3, 129.2, 129.1, 128.6, 127.5, 127.1, 126.9, 125.9, 21.1, 11.0; Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28%. Found: C, 82.30; H, 6.68; N, 11.37%.
4-(4-Bromo-phenyl)-5-methyl-2-phenyl-1H-imidazole (**3e**). White solid (72% yield): mp 168–169 °C; IR (KBr) 3429, 3153, 3043, 2912, 2759, 2634, 2439, 2318, 1907, 1641, 1477, 1936, 1317, 1072, 823, 688 cm^{-1}; ^1H NMR (400 MHz,

DMSO-d_6) δ 7.98 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 144.3, 131.6, 130.7, 129.1, 128.6, 128.4, 128.3, 127.9, 125.1, 119.0, 12.2; Anal. Calcd for $C_{16}H_{13}BrN_2$: C, 61.36; H, 4.18; N, 8.94%. Found: C, 61.46; H, 4.26; N, 9.06%.

4-Isopropyl-5-methyl-2-phenyl-1H-imidazole (**3f**). White solid (65% yield): mp 180–182 °C; IR (KBr) 3195, 3076, 3041, 2966, 2810, 2694, 2626, 2551, 1865, 1598, 1492, 1456, 1404, 1375, 1276, 1126, 1070, 975, 921, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.18–7.12 (m, 3H), 2.96–2.85 (m, 1H), 2.08 (s, 3H), 1.12 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 136.4, 131.0, 128.3, 127.1, 125.2, 25.3, 22.3, 10.9; Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99%. Found: C, 78.10; H, 8.16; N, 14.14%.

4-Benzo[1,3]dioxol-5-yl-5-methyl-2-phenyl-1H-imidazole (**3g**). White solid (81% yield): mp 184–186 °C; IR (KBr) 3434, 3355, 3276, 3199, 3122, 2927, 2547, 1865, 1735, 1693, 1602, 1525, 1346, 1249, 1124, 1041, 939, 815, 688.54 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.27–7.26 (m, 1H), 7.17–7.15 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.04 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3, 147.8, 145.9, 143.8, 130.8, 129.0, 128.8, 128.2, 127.9, 125.1, 120.0, 108.7, 107.2, 101.2, 12.3; Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07%. Found: C, 73.39; H, 5.10; N, 10.10%.

4-Furan-2-yl-5-methyl-2-phenyl-1H-imidazole (**3h**). White solid (79% yield): mp 172–174 °C; IR (KBr) 3355, 3151, 3078, 2927, 2852, 2646, 2397, 2310, 2231, 1895, 1745, 1728, 1604, 1448, 1267, 1159, 1012, 844, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 7.6 Hz, 2H), 7.89 (s, 1H), 7.63–7.60 (m, 3H), 7.16 (s, 1H), 6.71–6.70 (m, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.0, 143.1, 131.8, 129.6, 127.2, 126.6, 124.2, 122.2, 112.3, 109.3, 10.6; Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49%. Found: C, 75.03; H, 5.43; N, 12.54%.

5-Ethyl-2,4-diphenyl-1H-imidazole (**3i**). Pale yellow solid (70% yield): mp 188–189 °C; IR (KBr) 3373, 3076, 2964, 2738, 2694, 2549, 1595, 1490, 1454, 1398, 1122, 939, 698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 7.2 Hz, 2H), 7.41 (d, J = 7.2 Hz, 2H), 7.23–7.16 (m, 4H), 7.09 (t, J = 7.2 Hz, 1H), 2.57 (q, J = 7.6 Hz, 2H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 144.4, 135.1, 131.0, 129.1, 129.0, 128.8, 128.2, 126.8, 126.4, 125.2, 14.7, 11.0; Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28%. Found: C, 82.34; H, 6.58; N, 11.39%.

5-Methyl-2-(3-nitro-phenyl)-4-phenyl-1H-imidazole (**3j**). Yellow solid (85% yield): mp 210–213 °C; IR (KBr) 3512, 3082, 3047, 2854, 2347, 1731, 1591, 1525, 1438, 1348, 1265, 1091, 923, 889, 730, 690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.40 (d, J = 7.2 Hz, 1H), 8.14 (d, J = 7.26 Hz, 1H), 7.74–7.69 (m, 3H), 7.43 (t, J = 7.2 Hz, 2H), 7.27 (t, J = 6.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.7, 141.9, 135.5, 134.1, 132.2, 131.0, 130.7, 128.8, 126.6, 123.8, 122.5, 119.3, 12.4; Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05%. Found: C, 68.84; H, 4.76, N, 15.08%.

4-(4-Methoxy-phenyl)-5-methyl-2-(3-nitro-phenyl)-1H-imidazole (**3k**). Yellow solid (82% yield): mp 242–243 °C; IR (KBr) 3388, 3184, 3082, 2912, 2744, 2638, 1643, 1608, 1525, 1346, 1253, 842 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 148.3, 141.0, 135.2, 130.9, 130.5, 129.4, 127.8, 126.6, 122.6, 119.2, 114.3, 114.0, 55.1, 11.8; Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58%. Found: C, 66.08; H, 4.92; N, 13.60%.

2,5-Dimethyl-4-phenyl-1H-imidazole (**3l**). Yellowish liquid (55% yield): IR (KBr) 3487, 3043, 2665, 2590, 1893, 1818, 1596, 1444, 1390, 1271, 1170, 1095, 923, 781 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 2.33 (s, 3H) 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.6, 130.4, 129.1, 129.0, 128.7, 127.4, 116.6, 11.5, 10.7; Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27%. Found: C, 76.78; H, 7.04; N, 16.30%.