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A facile strategy for the synthesis of highly substituted imidazole using tetrabutyl ammoniumbromide as catalyst

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Abstract A simple and facile strategy for the synthesis of highly substituted imidazoles has been developed by multi-component condensation of 1,2-diketone, aldehyde, amine, and ammonium acetate in presence of tetrabutyl ammonium bromide as catalyst.

Keywords 1,2-Diketone · Aldehyde · Amine · Multi-component condensation · Tetrabutyl ammonium bromide · Ammonium acetate/ammonium formate

Introduction

The modern trend in synthetic organic chemistry is driving more towards multi-component reactions (MCRs) because of several advantages over linear reactions in synthesis of complex molecules in single step with high yields and simplified isolation procedures. The imidazole nucleus is present in large number of natural products and also in pharmacologically active compounds [1–5]. Therefore, the interest is continuously growing on synthesis of imidazole derivatives and a number of synthetic methods are available in literature. In 1882, Radziszewski reported the first synthesis of highly substituted imidazoles from 1,2-diketone, different aldehydes and ammonia [6, 7]. Specifically, synthesis of 1,2,4,5-tetrasubstituted imidazoles are accomplished by multi-component condensation of 1,2-diketone, aldehyde, primary amine and ammonium acetate using molecular iodine [8], $FeCl_3{\cdot}6H_2O$ [9], $BF_3.SiO_2$ [10], Silicagel/$NaHSO_4$ [11], Silicagel or zeolite HY [12], $HClO_4$-SiO_2 [13], Silica-supported acid [14], heteropolyacid [15], $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [16], L-proline [17],

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and microwaves [18]. Similarly, 2,4,5-trisubstituted imidazoles are made from three component condensation of 1,2-diketone, aldehyde and ammonium acetate using silica sulfuric acid [19], $NiCl_2{\cdot}6H_2O/Al_2O_3$ [20], CAN [21], $ZrCl_4$ [22], ionic liquids [23], acetic acid [24–26], and microwaves [27–30]. Metal nitrate over zeolite HY [31], and DABCO [32] was also used as catalysts for the synthesis of highly substituted imidazoles. All the methods cited above have disadvantages in terms of cost, hazardous nature, long reaction times, tedious isolation procedures and high loading of catalyst. In recent past, tetrabutyl ammonium bromide (TBABr) has emerged as mild, water-tolerant, inexpensive and environmentally compatible homogenous catalyst in various organic transformations [23, 33–35]. Biginelly-type compounds [36] and biscoumarine & 3,4-dihydropyrano[c]chromone derivatives [37] were also prepared by using TBABr as catalyst. To the best of our knowledge, quarternary ammonium salts more specifically tetrabutyl ammonium bromide (TBABr) is not been used as a catalyst for the synthesis of highly substituted imidazoles and attracted our attention to investigate the application of TBABr as a catalyst. Thus, a series of imidazole derivatives were synthesized by using TBABr as catalyst and found to be more efficient.

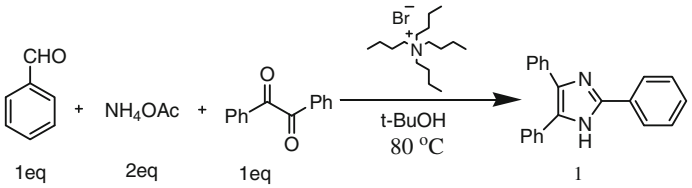
Results and discussion

In a typical reaction, benzaldehyde (1.0 mmol) was reacted with ammonium acetate (2.0 mmol) and 1,2-diketone (1.0 mmol) in *t*-BuOH (5 mL) using tetrabutyl ammonium bromide (TBABr, 10 mol%) as catalyst at 80 °C in 6–8 h and obtained 2,4,5-trisubstituted imidazole derivatives in high yield. Similar reaction was also conducted in presence of ammonium formate or ammonium trifluoroacetate in place of ammonium acetate and obtained imidazole products of marginally low yield. In order to find an alternate catalyst, tetraethyl ammonium bromide (TEABr) used as catalyst in 10 mol%, however, it was found to yield 80%. Further efforts were made to identify a suitable solvent. Thus, solvents like acetonitrile, THF, methanol, ethanol, isopropanol, *t*-BuOH and H_2O was screened for the same reaction and *t*-BuOH was found to be a good solvent with 95% yield (Table 1).

After having established the conditions with a choice of solvent, catalyst and ammonium acetate, the scope of present protocol was extended using diverse

Table 1 Effect of solvent on yield of product

Entry	Solvent	Time (h)	Yield (%)
1.	CH_3CN	8	30
2.	THF	8	45
3.	CH_3OH	8	65
4.	C_2H_5OH	8	72
5.	$(CH_3)_2CHOH$	8	89
6.	$(CH_3)_3COH$	8	95
7.	H_2O	10	No reaction



Scheme 1 Preparation of 2,4,5-trisubstituted imidazole derivatives

substituted aldehydes and obtained 2,4,5-trisubstituted imidazole derivatives in high yields. The reaction details are drawn in a Scheme 1 and tabulated in Table 2.

Table 2 Preparation of 2,4,5-trisubstituted imidazoles

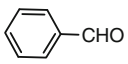
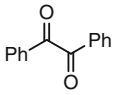
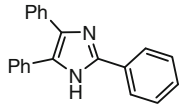
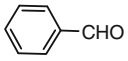
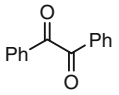
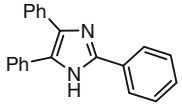
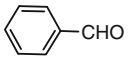
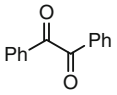
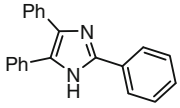
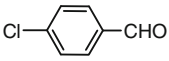
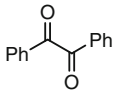
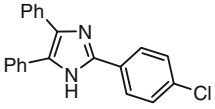
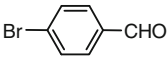
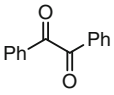
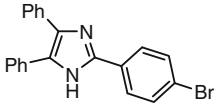
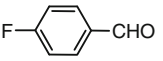
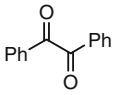
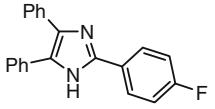
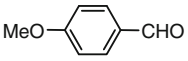
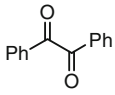
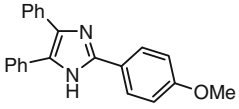
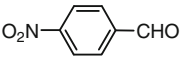
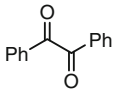
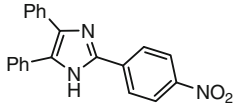
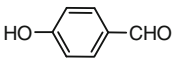
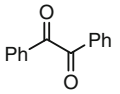
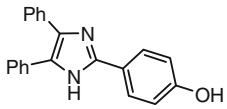
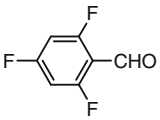
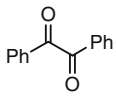
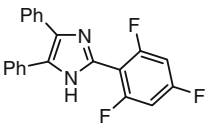
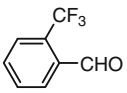
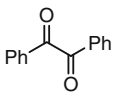
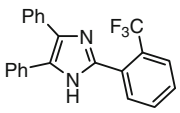
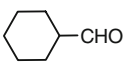
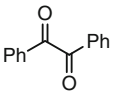
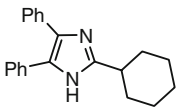
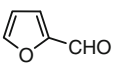
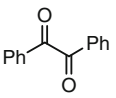
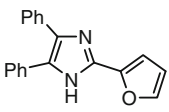
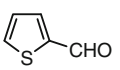
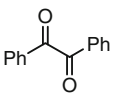
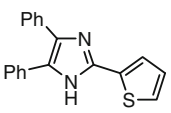
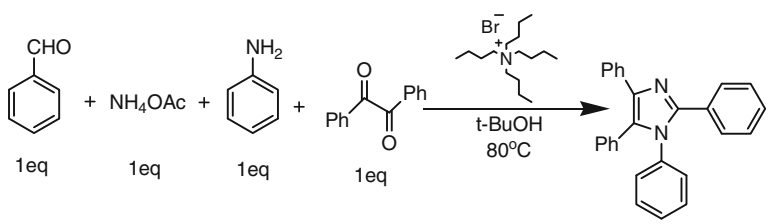
Entry	Aldehyde	Amine source	1,2-diketone	Product	Yield (%)
1.		NH_4OAc			95
2.		$HCOONH_4$			91
3.		CF_3COONH_4			85
4.		NH_4OAc			89
5.		NH_4OAc			88
6.		NH_4OAc			85
7.		NH_4OAc			90
8.		NH_4OAc			83

Table 2 continued

9.		NH_4OAc			87
10.		NH_4OAc			75
11.		NH_4OAc			92
12.		NH_4OAc			88
13.		NH_4OAc			89
14.		NH_4OAc			88

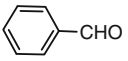
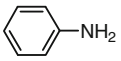
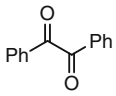
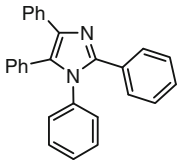
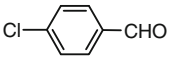
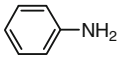
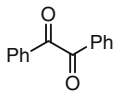
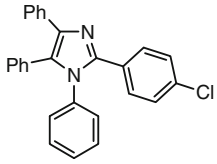
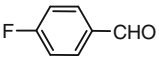
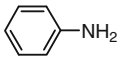
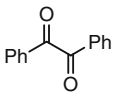
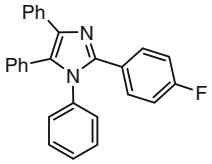
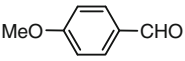
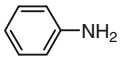
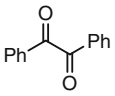
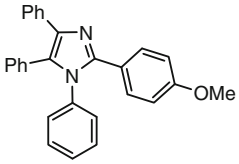
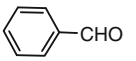
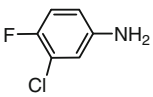
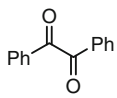
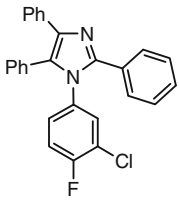
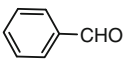
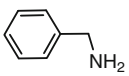
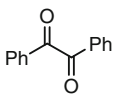
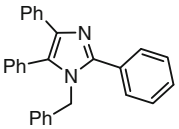


Scheme 2 Preparation of 1,2,4,5-tetrasubstituted imidazole derivatives

Similarly, 1,2,4,5-tetrasubstituted imidazoles were prepared by reaction of benzaldehyde (1.0 mmol) with ammonium acetate (1.0 mmol), aniline (1.0 mmol) and benzil (1.0 mmol) using TBABr (10 mol%) as catalyst in *t*-BuOH (5 mL) at 80 °C for 8 h and obtained the product. The same reaction was further extended with substituted benzaldehydes and established the conditions. The synthetic sequence is drawn in a Scheme 2 and products are tabulated in Table 3.

In conclusion, an efficient single pot strategy has been developed for the preparation of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives using tetrabutyl ammonium bromide as a catalyst. The method is established with

Table 3 Preparation of 1,2,4,5-tetrasubstituted imidazoles

Entry	Aldehyde	Amine(1)	Amine(2)	1,2-diketone	Product	Yield (%)
1.		NH_4OAc				87
2.		NH_4OAc				80
3.		NH_4OAc				81
4.		NH_4OAc				75
5.		NH_4OAc				78
6.		NH_4OAc				80

diverse functionalized aldehydes and applicable to the synthesis of desired functional imidazoles.

Experimental

IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Bruker AV 300 MHz in DMSO

using TMS as internal standard. Electron impact (EI) and chemical ionization mass spectra were recorded on a VG 7070 H instrument at 70 eV. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh); spots were visualized with UV light. Merck silica gel (60–120 mesh) was used for column chromatography. CHN analyses were recorded on a vario EL analyzer.

Synthesis of 2,4,5-tri substituted imidazole derinatives.

2,4,5-Triphenyl-1H-imidazole [32]

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole [31]

2-(4-Bromorophenyl)-4,5-diphenyl-1H-imidazole [32]

2-(4-Fluorophenyl)-4,5-diphenyl-1H-imidazole [32]

2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole [31]

2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole [31]

4-(4,5-Diphenyl-1H-imidazol-2-yl)phenol [32]

4,5-Diphenyl-2-(2,4,6-trifluorophenyl)-1*H*-imidazole.

I.R. (KBr, cm^{-1}): 3422 (-NH-), 1620, 1540; ^{1}H NMR (DMSO, 300 MHz): δ 7.09–7.18 (m, 1H, Ar–H), 7.23–7.35 (m, 6H, Ar–H), 7.49–7.55 (m, 4H, Ar–H), 7.99–8.08 (m, 1H, Ar–H), 12.62 (br-s, 1H, NH); MS (EI, 70 eV): m/z $M^{+\cdot}$, 350, 165; Anal. Calcd. for $C_{21}H_{13}F_3N_2$: C 71.99, H 3.74, N 8.00%. Found: C 71.45, H 3.52, N 8.11%.

4,5-Diphenyl-2-(2-(trifluoromethyl)phenyl)-1H-imidazole [38]

2-Cyclohexyl-4,5-diphenyl-1H-imidazole [39]

2-(Furan-2-yl)-4,5-diphenyl-1H-imidazole [31]

4,5-Diphenyl-2-(thiophen-2-yl)-1H-imidazole [39]

Synthesis of 1,2,4,5-tetra substituted imidazole derivatives

1,2,4,5-Tetraphenyl-1H-imidazole [32]

2-(4-Chlorophenyl)-1,4,5-triphenyl-1H-imidazole [31]

1-(3-Chloro-4-fluorophenyl)-2,4,5-triphenyl-1*H*-imidazole

I.R. (KBr, cm^{-1}): 1600, 1530; ^{1}H NMR (DMSO, 300 MHz): δ 6.88–6.93 (m, 1H, Ar–H), 7.02 (t, 1H, J = 8.49 Hz, Ar–H), 7.09–7.30 (m, 12H, Ar–H), 7.37–7.41 (m, 2H, Ar–H), 7.51 (d, 2H, J = 6.79 Hz, Ar–H); MS (EI, 70 eV): m/z $M^{+\cdot}$, 424, 165; Anal. Calcd. for $C_{27}H_{18}ClFN_2$: C 76.32, H 4.27, N 6.59%. Found: C 75.98, H 4.42, N 6.50%.

2-(4-Methoxyphenyl)-1,4,5-triphenyl-1H-imidazole [31]

2-(4-Fluorophenyl)-1,4,5-triphenyl-1*H*-imidazole

I.R. (KBr, cm^{-1}): 1598, 1495; ^{1}H NMR (DMSO, 300 MHz): δ 6.92 (t, 2H, J = 8.68 Hz, Ar–H), 7.03–7.12 (m, 4H, Ar–H), 7.17–7.30 (m, 9H, Ar–H), 7.35–7.40 (m, 2H, Ar–H), 7.51 (d, 2H, J = 6.79 Hz, Ar–H); MS (EI, 70 eV): m/z $M^{+\cdot}$, 390, 165; Anal. Calcd. for $C_{27}H_{19}FN_2$: C 83.05, H 4.90, N 7.17%. Found: C 82.71, H 4.72, N 7.05%.

1-Benzyl-2,4,5-triphenyl-1H-imidazole [32]

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