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One-Pot Synthesis of Imidazole Derivatives Under Solvent-Free Condition

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A convenient and environment-friendly solvent-free procedure has been developed for one-pot synthesis of imidazole derivatives. On comparing the new method with the classical reaction condition, this new synthetic method shows many advantages such as high yields, easy set-up and mild reaction conditions. This method opens a new way for synthesizing highly efficient imidazole derivatives for green chemistry applications.

Key Words: One-pot synthesis, Imidazole derivatives, *o*-Phenylenediamines, Solvent-free.

INTRODUCTION

The imidazole and its derivatives are extensively studied as important moieties owing to existing in most of natural products and pharmacologically active compounds[1]. Furthermore, substituted imidazole derivatives have been found applications as diverse therapeutic agents, including antiulcers, antihypertensive, antiviral, antifungal, anticancer and antihistaminic[2,3]. In view of their importance, the synthesis of substituted imidazole has been one focus of organic synthetic chemistry. Many methods have been reported for the synthesis of imidazole derivatives such as solvent-assistant synthesis, transition metal catalyzed synthesis and so on[4,5]. However, most of these methods suffer from several disadvantages with longer reaction times, excess of organic solvent, lower product yields or harsh refluxing conditions. Therefore, the development of simple and efficient synthetic methods for the synthesis of imidazole derivatives is considered as an important work in the organic synthesis.

In recent years, solvent-free organic reactions have been attracting great interests due to their advantages, including high efficiency and selectivity, easy separation and purification, mild reaction conditions, reduction in waste production and friendly environment. Therefore, Many studies with solvent-free have been extensively used to Grignard reaction[6], Reformatsky reaction[7], Aldol condensation[8], Dieckmann condensation[9], Phenol coupling reaction[10], reduction reaction[11] and other reactions[12]. Interestingly, in this paper we firstly reported an efficient and facile one-pot method for the synthesis of imidazole derivatives under solvent-free condition.

EXPERIMENTAL

Aromatic aldehyde, benzil, ammonium acetate and benzene-1,2-diamine were purchased from TCI. The other reagents were obtained from Guangzhou chemical reagent company. The solvents were used as received from commercial sources, unless otherwise stated. Melting points were determined on XT-5 microscopic melting-point spectrometer and the thermometer was uncorrected. FTIR spectra were recorded on a FT IR-8101 spectrometer. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 or $CDCl_3$ with Me_4Si as internal standard using a Bruker-400 spectrometer. EI-Ms spectra were performed with a FINNIGAN Trace DSQ mass spectrometer at 70 eV using a direct inlet system.

General procedure for the synthesis of imidazole derivatives: Aromatic *o*-phenylenediamines **1** or benzyl **5** (2 mmol), aromatic aldehyde **2** (2 mmol) and ammonium acetate **3** (5 mmol) were put in a reaction flask and react under 70 ºC *ca.* 1 h. After completing the reaction, the reaction mixture was poured into water and then washed with water thoroughly. The product was filtered, dried and recrystallized from 95 % ethanol.

2-*p*-Tolyl-1*H*-benzo[d]imidazole (4a): m.p. 274-276 ºC. EI-MS (M^+): 208.28. ^{1}H NMR (DMSO-d_6) δ: 2.38 (s, 3H, CH_3), 7.19 (d, J = 5.2 Hz, 2H, ArH), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.51-7.63 (m, 2H, ArH), 8.07 (d, J = 8.0 Hz, 2H, ArH), 12.85 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3408, 3053, 2964, 2915, 2856, 1602, 1583, 1500, 1475, 1448, 1430, 1398, 1370, 1318, 1274, 1225.

2-(4-Chlorophenyl)-1*H*-benzo[d]imidazole (4b): m.p. 289-290 ºC. EI-MS (M^+): 228.28. ^{1}H NMR (DMSO-d_6) δ: 7.22 (t, *J* = 8.0 Hz, 2H, ArH), 7.54 (d, *J* = 8.0 Hz, 1H, ArH), 7.63-7.69 (m, 3H, ArH), 8.19 (d, *J* = 8.0 Hz, 2H, ArH), 12.98 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3408, 3051, 2909, 2850, 1602, 1491, 1472, 1449, 1430, 1397, 1371, 1320, 1274, 1225.

2-(4-Nitrophenyl)-1*H*-benzo[d]imidazole (4c): m.p. 261-263 ºC. EI-MS (M^+): 239.33. ^{1}H NMR (DMSO-d_6) δ: 7.20-7.30 (m, 2H, ArH), 7.58 (d, *J* = 8.0 Hz, 1H, ArH), 7.67 (d, *J* = 8.0 Hz, 1H, ArH), 7.74-7.78 (m, 1H, ArH), 7.85~7.89 (m, 1H, ArH), 7.97-8.04 (m, 2H, ArH), 13.07 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3412, 3063, 1608, 1562, 1526, 1446, 1417, 1378, 1348, 1278, 1226.

2-(4-Bromophenyl)-1*H*-benzo[d]imidazole (4d): m.p. 288-290 ºC. EI-MS (M^+): 272.07, 274.08. ^{1}H NMR (DMSO-d_6) δ: 7.22 (s, 2H, ArH), 7.55~7.66 (m, 2H, ArH), 7.77 (d, *J* = 8.4 Hz, 2H, ArH), 8.12 (d, *J* = 8.4 Hz, 2H, ArH), 13.00 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3405, 3051, 1598, 1564, 1503, 1469, 1446, 1427, 1319, 1274, 1231.

2-(3,4-Dichlorophenyl)-1*H*-benzo[d]imidazole (4e): m.p. 231-233 ºC. EI-MS (M^+): 262.26. ^{1}H NMR (DMSO-d_6) δ: 7.22-7.26 (m, 2H, ArH), 7.63 (s, 2H, ArH), 7.83 (d, *J* = 8.4 Hz, 1H, ArH), 8.15 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H, ArH), 8.40 (d, *J* = 2.0Hz, 1H, ArH), 13.09 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3409, 3054, 1612, 1592, 1510, 1465, 1445, 1427, 1317, 1287, 1228.

2-(2,4-Dichlorophenyl)-1*H*-benzo[d]imidazole (4f): m.p. 207-209 ºC. EI-MS (M^+): 262.18. ^{1}H NMR (DMSO-d_6) δ: 7.22-7.30 (m, 2H, ArH), 7.56-7.59 (m, 1H, ArH), 7.63 (d, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H, ArH), 7.71 (d, *J* = 8.0 Hz, 1H, ArH), 7.85 (d, *J* = 2.0 Hz, 1H, ArH), 7.95 (d, *J* = 8.4 Hz, 1H, ArH), 13.19 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 3415, 3058, 1604, 1593, 1556, 1487, 1465, 1441, 1422, 1396, 1360, 1281, 1223.

2-Phenyl-1*H*-benzo[d]imidazole (4h): m.p. 234-236 ºC. EI-MS (M^+): 194.11. ^{1}H NMR (DMSO-d_6) δ: 7.54 (m, 2 H), 7.75 (m, 3 H), 7.85 (m, 2 H), 8.3 (m, 2 H). IR (KBr, ν_{max}, cm^{-1}): 3248, 1683, 1648, 1580, 1523, 1302.

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (6a): m.p. 241-243 ºC. EI-MS (M^+): 326.23. ^{1}H NMR ($CDCl_3$) δ: 3.9 (s, 3 H), 7.32 (d, *J* = 8.1 Hz, 2H, ArH), 7.5-7.65 (m, 4H, ArH), 7.75 (m, 2H, ArH), 7.85-7.95 (m, 6H, ArH), 8.7 (br s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3415, 3017, 2985, 2903, 2874, 1601, 1574, 1498, 1441, 1394, 1309, 1281, 1216.

2-(4-Chlorophenyl)-4,5-diphenyl-1*H*-imidazole (6b): m.p. 262-264 ºC. EI-MS (M^+): 330.17. ^{1}H NMR ($CDCl_3$) δ: 7.5-7.65 (m, 6 H, ArH), 7.68-7.72 (m, 2 H, ArH), 7.9-8.0 (m, 6 H, ArH), 8.7 (br s, 1 H, NH). IR (KBr, ν_{max}, cm^{-1}): 3401, 3041, 2983, 2902, 2864, 1598, 1501, 1477, 1422, 1396, 1371, 1305, 1232.

2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (6c): m.p. 131-133 ºC. EI-MS (M^+): 341.29. ^{1}H NMR ($CDCl_3$) δ: 7.5-7.65 (m, 4 H, ArH), 7.68-7.72 (m, 4 H, ArH), 7.9-8.0 (m, 4 H, ArH), 8.25 (d, *J* = 8.1 Hz, 2 H, ArH), 8.9 (br s, 1 H, NH). IR (KBr, ν_{max}, cm^{-1}): 3421, 3023, 2973, 2945, 2884, 1601, 1597, 1498, 1447, 1410, 1320, 1214.

2-(4-Hydroxyphenyl)-4,5-diphenyl-1*H*-imidazole (6d): m.p. 256-257 ºC. EI-MS (M^+): 312.09. ^{1}H NMR ($CDCl_3$) δ: 5.3 (br s, 1H, OH), 7.55-7.60 (m, 6 H, ArH), 7.65-7.72 (m, 2 H, ArH), 7.9-8.0 (m, 6 H, ArH), 8.7 (br s, 1 H, NH). IR (KBr, ν_{max}, cm^{-1}): 3448, 3372, 3013, 2994, 2965, 1602, 1599, 1498, 1453, 1399, 1318, 1254, 1208.

2-[4-(Dimethylamino)phenyl]-4,5-diphenyl-1*H*-imidazole (6e): m.p. 259-260 ºC. EI-MS (M^+): 339.23. ^{1}H NMR ($CDCl_3$) δ: 2.9 (s, 6 H, 2CH_3), 7.1 (d, *J* = 8.2 Hz, 2H, ArH), 7.4-7.55 (m, 4 H, ArH), 7.65-7.7 (m, 2 H, ArH), 7.8-7.95 (m, 6 H, ArH), 8.7 (br s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3435, 3023, 2994, 2975, 1602, 1596, 1500, 1495, 1438, 1420, 1398, 1284, 1195.

2-(4-Fluorophenyl)-4,5-diphenyl-1H-imidazole (6f): m.p. 190-191 ºC. EI-MS (M^+): 314.17. ^{1}H NMR ($CDCl_3$) δ: 7.28-7.37 (t, *J* = 10.94 Hz, 6H, Ar), 7.40 (br.s, 1H, NH), 7.48-7.49 (t, *J* = 10.94 Hz, 6H, ArH), 7.57-7.59 (t, *J* = 9.38 Hz, 2H, ArH). IR (KBr, ν_{max}, cm^{-1}): 3425, 3035, 2973, 2891, 1601, 1596, 1493, 1420, 1395, 1294, 1213.

2,4,5-Triphenyl-1*H*-imidazole (6g): m.p. 276-277 ºC. EI-MS (M^+): 296.15. ^{1}H NMR ($CDCl_3$) δ: 7.55-7.68 (m, 6H, ArH), 7.72-7.75 (m, 3H, ArH), 7.9-7.95 (m, 6H, ArH), 8.8 (br s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3417, 3041, 2984, 2911, 2848, 1599, 1507, 1475, 1412, 1398, 1230.

2-Phenyl-1-propyl-1*H*-benzo[d]imidazole (8b): m.p. 244-246 ºC. EI-MS (M^+): 236.07. ^{1}H NMR ($CDCl_3$): δ: 8.46 (d, *J* = 8.2 Hz, 2H, ArH), 7.66-7.47 (m, 5H, ArH), 7.16 (d, *J* = 8.2 Hz, 2H, ArH), 4.16 (t, *J* = 3.6 Hz, 2H, CH_2), 1.86 (q, *J* = 3.6 Hz, 2H, CH_2), 1.08 (t, *J* = 3.6 Hz, 3H, CH_3). IR (KBr, ν_{max}, cm^{-1}): 3012, 2988, 2912, 2881, 1591, 1497, 1401, 1218.

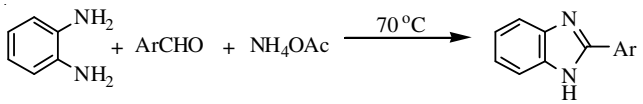
1-Benzyl-2-phenyl-1*H*-benzo[d]imidazole (8c): m.p. 283-285 ºC. EI-MS (M^+): 284.19. ^{1}H NMR ($CDCl_3$): δ: 8.24 (d, *J* = 8.4 Hz, 2H, ArH), 7.63-7.48 (m, 4H, ArH), 7.41-7.27 (m, 8H, ArH), 5.36 (s, 2H, CH_2). IR (KBr, ν_{max}, cm^{-1}): 3013, 2981, 2911, 2868, 1603, 1501, 1498, 1402, 1203.

1-(2-Phenyl-1*H*-benzo[d]imidazol-1-yl)propan-1-one (8d): m.p. 257-259 ºC. EI-MS (M^+): 250.39. ^{1}H NMR ($CDCl_3$): δ: 8.41 (d, *J* = 8.2 Hz, 2H, ArH), 7.74-7.36 (m, 5H, ArH), 7.13 (d, *J* = 8.2 Hz, 2H, ArH), 2.76 (q, *J* = 3.6 Hz, 2H, CH_2), 1.28 (t, *J* = 3.6 Hz, 3H, CH_3). IR (KBr, ν_{max}, cm^{-1}): 3017, 2973, 2908, 2874, 1698, 1601, 1507, 1494, 1408, 1209.

1,2-Diphenyl-1*H*-benzo[d]imidazole (8e): m.p. 293-295 ºC. EI-MS (M^+): 270.12. ^{1}H NMR ($CDCl_3$): δ: 8.64 (d, *J* = 8.24 Hz, 1H, ArH), 8.33 (d, *J* = 8.4 Hz, 2H, ArH), 7.68-7.40 (m, 9H, ArH), 7.18 (d, *J* = 7.8 Hz, 2H, ArH). IR (KBr, ν_{max}, cm^{-1}): 3077, 2998, 2933, 2889, 1593, 1500, 1495, 1403, 1394, 1214.

RESULTS AND DISCUSSION

In the preparation of the imidazole derivatives with one-pot and solvent-free method, the synthetic route was shown in **Scheme-I**. Firstly, benzene-1,2-diamine **1**, aromatic aldehyde **2** and ammonium acetate **3** were mixed equably together in a round-bottomed flask. Then, the mixture was heated slowly to *ca.* 70 ºC and the reaction was started. After *ca.* 1 h, the reaction was completed. The benzyl-substituted imidazole derivatives (**4**) were gained with high yields (Table-1).



1 **2** **3** **4**

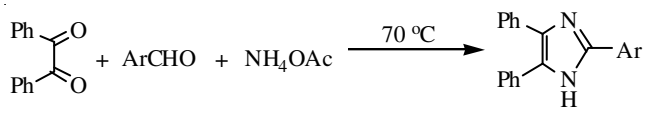
Scheme-I

TABLE-1
SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES

Entry	Ar	Product	Yields (%)
1	4-$CH_3C_6H_4$	**4a**	65
2	4-ClC_6H_4	**4b**	77
3	2-$NO_2C_6H_4$	**4c**	74
4	4-BrC_6H_4	**4d**	70
5	3,4-$Cl_2C_6H_3$	**4e**	74
6	2,4-$Cl_2C_6H_3$	**4f**	70
7	3-ClC_6H_4	**4g**	65
8	C_6H_5	**4h**	80

As shown in Table-1, it can be seen that aromatic aldehyde bearing either electron-withdrawing or electron-donating groups performs equally well in this reactions. All structures of **4** were confirmed by FTIR, MS and ^{1}H NMR.

In order to apply this reaction to a library synthesis, benzil **5** was chosen to react with aromatic aldehyde and ammonium acetate under the similar conditions of derivatives **4** as shown in **Scheme-II**. Interestingly, all the reactions could be continued smoothly and we can obtain the 2,4,5-triaryl-1*H*-imidazoles with high yields (Table-2).



5 **2** **3** **6**

Scheme-II

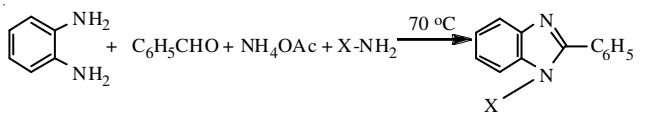
TABLE-2
SYNTHESIS OF 2-ARYL-4,5-DIPHENYL-1*H*-IMIDAZOLES

Entry	Ar	Product	Yields (%)
1	4-$CH_3OC_6H_4$	**6a**	90
2	4-ClC_6H_4	**6b**	85
3	4-$NO_2C_6H_4$	**6c**	83
4	4-HOC_6H_4	**6d**	87
5	4-$(CH_3)_2NC_6H_4$	**6e**	76
6	4-FC_6H_4	**6f**	93
7	C_6H_5	**6g**	89

Compared benzil **5** with *o*-phenylenediamines **1**, it was clear that benzil **5** showed a higher yields than those of *o*-phenylenediamines **1**, which was attributable to the strong nucleophilic activity of benzil **5**. The aromatic aldehyde with either electron-withdrawing or electron-donating groups displays different effects, which was very significant to improve their yields when aromatic aldehyde with electron-donating groups (Table-2).

Subsequently, we also explored the scope of this method to other substituted imidazole derivatives. Four component condensation of benzil, benzaldehyde derivatives was performed in present work using primary amines and ammonium acetate (**Scheme-III**).

As shown in Table-3, it could be found that substituted amine with electron-withdrawing and electron-donating groups performed obviously different yields in this reaction. Substituted amine bearing electron-withdrawing groups had low reaction activity, while substituted amine with electron-donating groups had high reaction activity. A series of multi-substituted imidazole derivatives were also prepared conveniently by this way with an efficient one-pot synthesis under solvent-free conditions.



1 **2** **3** **7** **8**

Scheme-III

TABLE-3
SYNTHESIS OF 1-X-2-ARYL-4,5-DIPHENYL IMIDAZOLES

Entry	X	Product	Yields (%)
1	OH	**8a**	trace
2	C_3H_7	**8b**	78
3	C_6H_5-CH_2	**8c**	84
4	C_2H_5CO	**8d**	39
5	C_6H_5	**8e**	61

Conclusion

In summary, we have developed an economical and environment-friendly procedure for the synthesis of imidazole derivatives with high yields under solvent-free conditions. As it is avoided to use toxic organic solvent, this new protocol has many advantages such as higher yield, lower cost, reduced environmental impact and convenient procedure. Our results open a new way for synthesizing highly efficient imidazole derivatives for green chemistry applications.

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