Synthesis of 2-Substituted Benzimidazoles by Iodine-Mediated Condensation of Orthoesters with 1,2-Phenylenediamines

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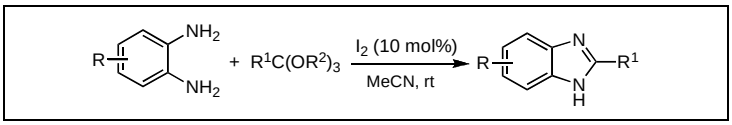

Iodine was found to be an efficient catalyst for the synthesis of 2-substituted benzimidazoles by the condensation of orthoesters and 1,2-phenylenediamines in good to excellent yields under mild reaction conditions.

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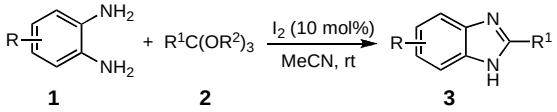
INTRODUCTION

The 2-substituted benzimidazole derivatives are important heterocyclic compounds, which exhibit a diverse range of biological properties such as antiviral, antitumour, antibacterial and anti-inflammatory activities [1]. They have also been used as ligands for asymmetric catalysis [2] and act as ligands to transition metals for modeling biological systems [3]. Therefore, the synthesis of this type of compounds has attracted considerable attention. Synthetic routes that are common to the preparation of these heterocycles typically involve the reaction of a carboxylic acid and its derivative with an appropriate 1,2-phenylenediamine in the presence of strong acid at elevated temperature [4]. Another alternative approach is the condensation of aldehydes with 1,2-phenylenediamine [5]. Some methods using transition metal catalyzed coupling reactions to construct the benzimidazole nucleus have also been reported. Those involved a palladium-catalyzed intramolecular *N*-arylation of (*o*-bromophenyl)amidine [6]. A method starting from 1,2-phenylenediamine and orthoester in the presence of KSF clay [7], Zeolite [8], or $Yb(OTf)_3$ [9] at high temperature has been developed for the synthesis of benzimidazole derivatives. However, many of these procedures are associated with several drawbacks such as expensive reagents, harsh reaction conditions, extended reaction times, occurrence of side products, unsatisfactory yields and complicated experimental procedure. Therefore, there is a need to develop a convenient, efficient and practically useful process for the synthesis 2-substituted benzimidazole derivatives

Recently, the use of molecular iodine as an inexpensive, nontoxic, readily available, environmentally benign catalyst for various organic transformations has received considerable attention [10-11]. As part of our ongoing program in developing various new synthetic transformations using cheap and eco-friendly materials as catalysts [12], we report herein a convenient and facile synthesis of 2-substituted benzimidazole derivatives from 1,2-phenylenediamine and orthoester using a catalytic amount of iodine at room temperature (Scheme I).

Scheme I



1 **2** **3**

RESULTS AND DISCUSSION

In preliminary study, we investigate the reaction of 1,2-phenylenediamines (1.0 mmol) and triethyl orthoformate (1.2 mmol) in CH_3CN in the presence of a catalytic amount of I_2 (10 mol%) at room temperature. To our delight, the product **3a** was formed and the complete conversion with 98% isolated yield was observed after 15 minutes. Further studies showed that CH_3CN was the best solvent among the solvents (MeOH, EtOH, THF, DMF, DMSO, CH_2Cl_2, $CHCl_3$, 2-methoxyethanol). Next, we examined the catalytic requirement of I_2 (5-20 mol%) for the reaction in CH_3CN. Gratifyingly, 10 mol% I_2 was sufficient to catalyzed the reaction. A rate enhancement with high yield was observed when higher molar ratios of I_2. However, no product formation was observed in the absence of I_2.

To evaluate the generality of this method, we next investigated the scope and limitation of this reaction under optimized conditions (CH_3CN, 10 mol% of I_2, r.t) and the results are summarized in Table 1. As shown in Table 1, a variety of structurally diverse 1,2-phenylene-diamines and orthoesters underwent the condensation reaction smoothly to afford the corresponding 2-substituted benzimidazole derivatives in high to excellent yields. The electronic property of the substituents on the aromatic ring of 1,2-phenylenediamines had an obvious effect on the yields under the current reaction conditions.

In general, when the R represented the electron-withdrawing groups such as chloro (Table 1, entries **m**-**o**) and nitro (Table 1, entries **p**-**s**), the yields and purities of the products were obviously worse, and long reaction times were required. All of the 2-substituted benzimidazole derivatives have been characterized by ^{1}H NMR, ^{13}C NMR, and IR spectra, and the known compounds were confirmed by comparison of their spectral data and melting points with those reported in the literature.

EXPERIMENTAL

Melting points were recorded on X-4 apparatus. IR spectra were obtained using Shimadzu FTIR-8900 spectrometer instrument. NMR spectra were taken with a varain Mercury Plus 400 spectrometer. Mass spectra were performed on a ThermoFinnigan LCQ Advantage instrument with an ESI source (4.5 KeV). Elemental analyses were carried out on Vario EL III CHNOS Elemental Analyzer.

Table 1
I_2-catalyzed Synthesis of 2-Substituted Benzimidazole Derivatives

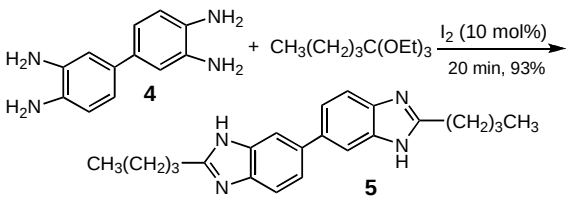
Entry	R	R^1	R^2	Time (min)	Yield (%)[a]	Mp (°C)	Lit. Mp (°C)	Ref.
a	H	H	CH_3CH_2	15	98	172-173	172-173	8
b	H	CH_3	CH_3	16	95	175-176	175-176	8
c	H	CH_3CH_2	CH_3CH_2	15	94	174-175	170-172	8
d	H	$CH_3(CH_2)_3$	CH_3	12	93	149-150	150	13
e	3-Me	H	CH_3CH_2	30	88	145-146		
f	3-Me	CH_3	CH_3	28	86	166-167		
g	4-Me	H	CH_3CH_2	20	93	114-115	115-116	9
h	4-Me	CH_3	CH_3	18	90	203-204	201-203	9
i	4-Me	CH_3CH_2	CH_3CH_2	15	92	164-165	163-164	9
j	4,5-Me_2	H	CH_3CH_2	40	93	201-202	203-205	7
k	4,5-Me_2	CH_3	CH_3	35	90	239-240	239-240	7
l	4,5-Me_2	$CH_3(CH_2)_3$	CH_3	30	92	115-116	116	14
m	4-Cl	H	CH_3CH_2	80	82	125-126	123-126	8
n	4-Cl	CH_3	CH_3	80	86	200-201	199-200	8
o	4-Cl	CH_3CH_2	CH_3CH_2	70	88	168-170	170-171	8
p	4-NO_2	H	CH_3CH_2	150	87	201-202	206-208	9
q	4-NO_2	CH_3	CH_3	120	86	227-228	218-221	9
r	4-NO_2	CH_3CH_2	CH_3CH_2	120	84	181-182	178-179	15
s	4-NO_2	$CH_3(CH_2)_3$	CH_3	120	88	138-140	139-141	16

[a] Isolated yields after coloumn chromatography.

This reaction was further explored for the synthesis of bis-benzimidazole compound **5** by the reaction of 3,3'-diaminobenzidine **4** and two equivalents of triethyl orthovalerate under similar conditions. Compound **5** was obtained in excellent yield (Scheme II).

In conclusion, we have developed a rapid, mild and efficient route for the synthesis of 2-substituted benzimidazole derivatives by condensation of various 1,2-phenylenediamines with orthoesters at room temperature using I_2 as a novel catalyst. The advantages of current protocol include high efficiency, good substrate generality, the use of inexpensive and environmentally benign catalyst under mild conditions, and experimentally operational ease.

Scheme II



General Procedure for the synthesis of 2-substituted benzimidazole derivatives (3). A mixture of 1,2-phenylenediamine (1 mmol), orthoester (1.2 mmol) and I_2 (0.1 mmol) in CH_3CN (2 ml) was stirred at room temperature. The completion of reaction was followed by TLC. After completion, water was added and the product was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure to afford the crude product. The crude product was subjected to column chromatography over silica gel using hexane/ethyl acetate as eluent to obtain pure product.

Benzimidazole (3a). This compound was obtained as pale yellow solid; ir (KBr): 3415, 1619, 1482, 1438, 1297, 1262, 1156, 1006, 882, 741 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ 7.30-7.33 (m, 2H), 7.68-7.71 (m, 2H), 8.18 (s, 1H); ESI-MS: 119 $(M+1)^+$.

2-Methylbenzimidazole (3b). This compound was obtained as pale yellow solid; ir (KBr): 3417, 2995, 1622, 1556, 1450, 1360, 1271, 1218, 1043, 1003, 834, 737 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 7.21-7.24 (m, 2H), 7.52-7.56 (m, 2H), 7.81 (s, 1H); ESI-MS: 133 $(M+1)^+$.

2-Ethylbenzimidazole (3c). This compound was obtained as pale yellow solid; ir (KBr): 3417, 2974, 1619, 1542, 1426, 1271, 1220, 1156, 1043, 965, 880, 742 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.6 Hz, 3H), 2.98 (q, J = 7.6 Hz, 2H), 7.20-7.25 (m, 2H), 7.54-7.56 (m, 2H), 9.97 (s, 1H); ESI-MS: 147 $(M+1)^+$.

2-Butylbenzimidazole (3d). This compound was obtained as pale yellow solid; ir (KBr): 3414, 2929, 1622, 1534, 1417, 1274, 1153, 1101, 1029, 930, 880, 751 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 1.39 (sext, J = 7.2 Hz, 2H), 1.83 (quin, J = 7.2 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H), 7.19-7.23 (m, 2H), 7.53-7.56 (m, 2H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.67, 22.41, 29.06, 30.43, 114.58, 122.07, 138.59, 155.62; ESI-MS: 175 $(M+1)^+$; *Anal.* Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.96; H, 8.31; N, 15.92.

4-Methylbenzimidazole (3e). This compound was obtained as pale yellow solid; ir (KBr): 3414, 2990, 2926, 1616, 1485, 1450, 1400, 1297, 1249, 1168, 948 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.02 (s, 3H), 7.10 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 10.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)): δ 17.39, 112.74, 123.26, 123.55, 126.18, 136.96, 137.86, 140.34; ESI-MS: 133 $(M+1)^+$; *Anal.* Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.98; H, 6.25; N, 21.05.

2-Ethyl-4-methylbenzimidazole (3f). This compound was obtained as pale yellow solid; ir (KBr): 3340, 2716, 2606, 1572, 1413, 1225, 1159, 1024, 865 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.6 Hz, 3H), 2.60 (s, 3H), 3.08 (q, J = 7.6 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)): δ 12.83, 17.37, 22.62, 112.12, 122.76, 123.36, 124.87, 137.45, 137.50, 155.75; ESI-MS: 161 $(M+1)^+$; *Anal.* Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 75.05; H, 7.68; N, 17.26.

5-Methylbenzimidazole (3g). This compound was obtained as pale yellow solid; ir (KBr): 3413, 3016, 2802, 1619, 1476, 1444, 1281, 1248, 1164, 1001, 880, 808 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 7.12 (d, J = 7.2 Hz, 1H), 7.44 (s, 1H), 7.56 (d, J = 7.2 Hz, 1H), 8.04 (s, 1H), 9.04 (s, 1H); ESI-MS: 133 $(M+1)^+$.

2,5-Dimethylbenzimidazole (3h). This compound was obtained as pale yellow solid; ir (KBr): 3417, 2913, 2774, 1630, 1553, 1483, 1401, 1281, 1143, 1029, 881, 804 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 2.61 (s, 3H), 7.03 (d, J = 8.4 Hz, 1H), 7.31 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 9.41 (s, 1H); ESI-MS: 147 $(M+1)^+$.

2-Ethyl-5-methylbenzimidazole (3i). This compound was obtained as pale yellow solid; ir (KBr): 3426, 2972, 2730, 1632, 1549, 1411, 1317, 1276, 1140, 1069, 1040, 971, 863, 807 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.6 Hz, 3H), 2.44 (s, 3H), 2.95 (q, J = 7.6 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 8.43 (s, 1H); ESI-MS: 161 $(M+1)^+$.

5,6-Dimethylbenzimidazole (3j). This compound was obtained as pale yellow solid; ir (KBr): 3467, 2758, 1712, 1470, 1445, 1406, 1335, 1304, 1268, 1157, 1025, 998, 961 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.37 (s, 6H), 7.42 (s, 2H), 7.95 (s, 1H), 8.23 (s, 1H); ESI-MS: 147 $(M+1)^+$.

2,5,6-Trimethylbenzimidazole (3k). This compound was obtained as pale yellow solid; ir (KBr): 3378, 2919, 1632, 1540, 1452, 1389, 1306, 1231, 1161, 1022, 1000, 854 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.31 (s, 6H), 2.68 (s, 3H), 7.35 (s, 2H); ESI-MS: 161 $(M+1)^+$.

2-Butyl-5,6-dimethylbenzimidazole (3l). This compound was obtained as pale yellow solid; ir (KBr): 3452, 2959, 2929, 1630, 1539, 1440, 1305, 1195, 1160, 1085, 1020, 997, 976, 847 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 0.86 (t, J = 7.6 Hz, 3H), 1.37 (sext, J = 7.6 Hz, 2H), 1.81 (quin, J = 7.6 Hz, 2H), 2.33 (s, 6H), 2.91 (t, J = 7.6 Hz, 2H), 7.32 (s, 2H), 10.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.93, 20.49, 22.64, 29.26, 30.71, 115.00, 130.99, 137.32, 154.90; ESI-MS: 203 $(M+1)^+$. *Anal.* Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.32; H, 9.05; N, 13.69.

4-Chlorobenzimidazole (3m). This compound was obtained as yellow solid; ir (KBr): 3442, 1626, 1582, 1461, 1287, 1150, 1056, 952, 908, 878, 799, 732 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 7.19 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 8.15 (s, 1H), 12.26 (s, 1H); ESI-MS: 153 $(M+1)^+$.

2-Methyl-5-chlorobenzimidazole (3n). This compound was obtained as yellow solid; ir (KBr): 3415, 2971, 1624, 1545, 1400, 1278, 1059, 921, 804 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.62 (s, 3H), 7.18 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 8.49 (s, 1H); ESI-MS: 167 $(M+1)^+$.

5-Nitrobenzimidazole (3o). This compound was obtained as yellow solid; ir (KBr): 3483, 2814, 1623,1590, 1513, 1464, 1408, 1374, 1300, 1263, 1240, 1067, 952, 896, 741 cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 7.78 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H), 8.58 (s, 1H); ESI-MS: 164 $(M+1)^+$.

2-Methyl-5-nitrobenzimidazole (3q). This compound was obtained as yellow solid; ir (KBr): 3561, 2923, 1684, 1627, 1593, 1516, 1471, 1356, 1216, 1065, 1022, 942, 879 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$): δ 2.70 (s, 3H), 7.78 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.48 (s, 1H); ESI-MS: 178 $(M+1)^+$.

2-Butyl-5-nitrobenzimidazole (3s). This compound was obtained as yellow solid; ir (KBr): 3354, 2959, 1627, 1594, 1513, 1471, 1410, 1342, 1066, 1008, 882 cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6): δ 0.89 (t, J = 7.2 Hz, 6H), 1.42 (sext, J = 7.2 Hz, 4H), 1.89 (quin, J = 7.2 Hz, 4H), 3.03 (t, J = 7.2 Hz, 4H), 7.59 (d, J = 8.4 Hz, 4H), 8.18 (d, J = 8.4 Hz, 4H), 8.48 (s, 2H), 11.02 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6)): δ 13.85, 22.62, 29.44, 30.29, 111.89, 114.38, 118.68, 138.46, 142.90, 143.64, 160.39; ESI-MS: 220 $(M+1)^+$. *Anal.* Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17; Found: C, 60.42; H, 6.05; N, 19.02.

2,2'-Dibutyl-1*H*,1'*H*-5,5-bibenzimidazolyl (5). This compound was obtained as colorless solid, mp 241-242°; ir (KBr): 3415, 2930, 1728, 1630, 1575, 1542, 1415, 1276, 1085, 1026, 810 cm^{-1}; ^1H nmr (400 MHz, CD_3OD): δ 0.97 (t, J = 7.2 Hz, 6H), 1.41 (sext, J = 7.2 Hz, 4H), 1.81 (quin, J = 7.2 Hz, 4H), 2.88 (t, J = 7.2 Hz, 4H), 7.47 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.69 (s, 2H); ^{13}C nmr (100 MHz, CD_3OH): δ 14.88, 22.19, 28.35, 30.24, 112.36, 114.44, 121.99, 136.71, 156.40; ESI-MS: 347 $(M+1)^+$; *Anal.* Calcd. for $C_{22}H_{26}N_4$: C, 76.27; H, 7.56; N, 16.17. Found: C, 76.08; H, 7.40; N, 16.36.

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