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A Simple and Convenient One-Pot Synthesis of Benzimidazole Derivatives Using Cobalt(II) Chloride Hexahydrate as Catalyst

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Abstract: A simple and efficient method for the convenient synthesis of 2-arylbenzimidazole has been described on reaction with *o*-phenylenediamine and various aromatic aldehydes using cobalt(II) chloride hexahydrate as a catalyst. The method is cost-effective, high-yielding, clean, and selective.

Keywords: Aldehydes, benzimidazole, catalysis, cobalt(II) chloride hexahydrate, *o*-phenylene diamine

INTRODUCTION

Benzimidazole and its derivatives have some significant importance in medicinal chemistry.[1] The synthesis of benzimidazole is carried out by the reaction of *o*-phenylenediamine and carboxylic acid or its derivatives (nitriles, amides, orthoesters) under harsh dehydrating conditions.[2–4] Another alternate approach is the condensation of *o*-phenylenediamine and aldehyde in the presence of oxidative reagents such as sodium metabisulfite,[5] $I_2/KI/K_2CO_3/H_2O$,[6] $Na_2S_2O_5$ under microwave irradiation,[7] silica sulfuric acid,[8] iodobenzene diacetate (IBD),[9]

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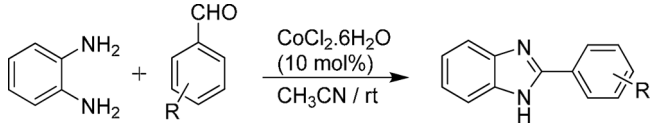


Scheme 1. Synthesis of 2-aryl benzimidazoles using cobalt(II) chloride hexahydrate as catalyst.

HCl/H_2O_2,[10] air in dioxane,[11] bromodimethylsulfonium bromide (BDMS),[12] and CAN/H_2O_2.[13] In continuation of our endeavor to develop new synthetic methodologies,[14] herein we report a simple and efficient method for the preparation of 2-arylbenzimidazole using cobalt(II) chloride hexahydrate as an effective catalyst (Scheme 1).

RESULTS AND DISCUSSION

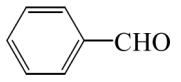
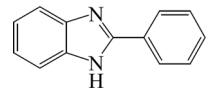
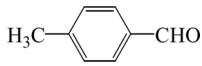
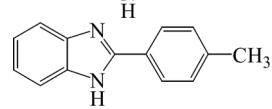
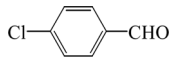
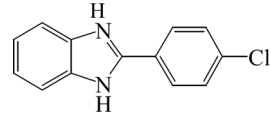
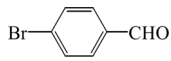
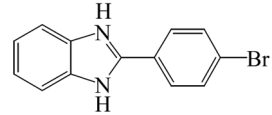
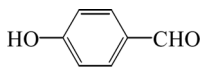
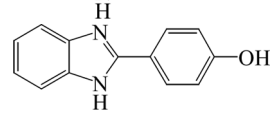
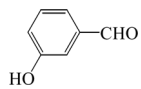
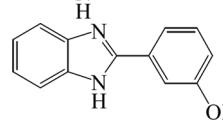
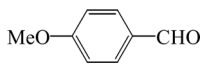
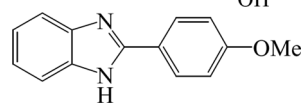
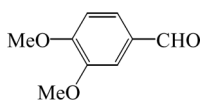
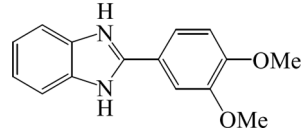
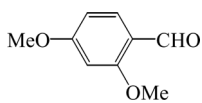
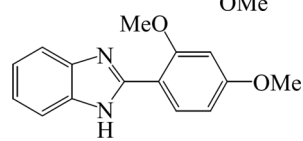
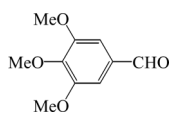
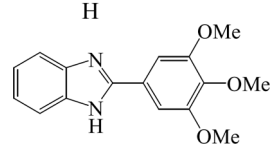
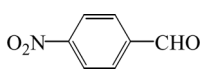
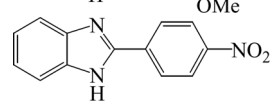
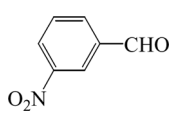
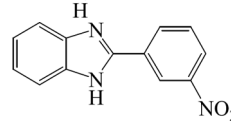
Initially, the reaction of 3,4,5-trimethoxybenzaldehyde with *o*-phenylenediamine was chosen as a model reaction to find a suitable catalyst and solvent for the preparation of 2-arylbenzimidazole derivatives. In the course of the study, several solvents including acetonitrile, dichloromethane, ethanol, and 1,4-dioxane were examined to obtain better yields. The best results with 88% yield and selectivity were obtained in acetonitrile. In the absence of catalyst, it gives only 38% yield of the desired product after 12 h.

A wide variety of aromatic aldehydes were treated with *o*-phenylenediamine in the presence of cobalt(II) chloride hexahydrate under similar experimental conditions. Notably, various aromatic aldehydes containing both electron-withdrawing and electron-donating groups underwent oxidative cyclization at room temperature in good yields. From the results of Table 1, it is quite clear that aromatic aldehydes with electron-donating groups such as hydroxyl and methoxy (entries **e–j**) provided the corresponding 2-arylbenzimidazole in good yields in less time than aldehydes tethered with withdrawing groups (entries **c, d, k, and l**). Similarly, terephthalaldehyde (entry **m**) reacts with two molecules of *o*-phenylenediamine and afforded the corresponding *bis*-2-arylbenzimidazole in good yields under the same experimental conditions.

EXPERIMENTAL

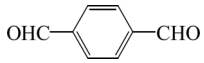
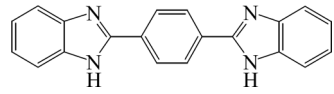
Melting points were recorded on a Büchi B-545 melting-point apparatus. Infrared (IR) spectra were recorded in KBr on a Nicolet Impact 410

Table 1. Cobalt(II) chloride hexahydrate–catalyzed synthesis of 2-aryl benzimidazole

Entry	Aldehydes **(1)**	Time (h)	Product[a] **(2)**	Yield (%) [ref.][b]
a		4		81[11]
b		3		83
c		6		80[12]
d		6		81[9]
e		3		82
f		3		83
g		3		85[9]
h		3		86
i		2		84
j		6		88
k		5		78
l		4		79

(*Continued*)

Table 1. Continued

Entry	Aldehydes **(1)**	Time (h)	Product[a] **(2)**	Yield (%) [ref.][b]
m		2		80

[a]Products were characterized by recording IR, ^{1}H NMR, and ^{13}C NMR spectra and elemental analysis.

[b]Isolated yield.

spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian 400-MHz spectrometer in dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as internal standard. Elemental analyses were carried out in a Perkin-Elmer 2400 automatic carbon, hydrogen, nitrogen, and sulfur analyzer.

Typical Experimental Procedure for Synthesis of 2-Aryl Benzimidazoles

Cobalt(II) chloride hexahydrate (0.1 mmol) was added to a mixture of an aldehyde (1.1 mmol) and *o*-phenylenediamine (1 mmol) in acetonitrile (5 mL). The mixture was stirred at room temperature, and the progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the solvent was evaporated, and the crude product was dissolved in 5 mL of hot ethanol and then treated with 0.2 mL of NH_4OH, followed by 5 ml of water. The mixture was heated, and after cooling, the solid was filtered and washed with a cold solvent mixture (ethanol + hexane) to get the pure benzimidazole derivative. All the products were fully characterized by the usual spectroscopic techniques.

Data

2-(4-Methylphenyl)benzimidazole (**2b**)

Mp 275°C (lit.[6] mp 277°C). IR (KBr): 1622 (C=N), 3446 (NH) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3 H), 7.18 (d, $J = 7.2$ Hz, 2 H), 7.34–7.37 (m, 2 H), 7.47–7.51 (m, 1 H), 7.60–7.63 (m, 1 H), 8.06 (d, $J = 8.0$ Hz, 2 H), 12.80 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0, 111.1, 118.7, 121.6, 122.3, 126.4, 127.4, 129.5, 139.6, 143.8, 151.4. Anal. calcd. for $C_{14}H_{12}N_2$(208.26): C, 80.74; H, 5.81; N, 13.45. Found: C, 80.60; H, 5.85; N, 13.59.

2-(4-Hydroxyphenyl)benzimidazole (**2e**)

Mp 256°C (lit.[7] mp 254–256°C). IR (KBr): 1612 (C=N), 3360 (NH), 3570 (OH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.90 (d, $J = 8.4$ Hz, 2 H), 7.12–7.16 (m, 2 H), 7.46 (d, $J = 6.8$ Hz, 1 H), 7.59 (d, $J = 7.6$ Hz, 1 H), 7.99 (d, $J = 8.8$ Hz, 2 H), 9.94 (bs, 1 H), 12.63 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.2, 115.4, 120.5, 121.4, 128.0, 138.8, 145.0, 158.9. Anal. calcd. for $C_{13}H_{10}N_2O$ (210.23): C, 74.27; H, 4.79; N, 13.33. Found: C, 74.17; H, 4.82; N, 13.51.

2-(3-Hydroxyphenyl)benzimidazole (**2f**)

Mp 277°C. IR (KBr): 1618 (C=N), 3447 (NH), 3565 (OH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 6.89 (d, $J = 7.6$ Hz, 1 H), 7.17–7.20 (m, 2 H), 7.33 (t, $J = 7.2$ Hz, 1 H), 7.48–7.51 (m, 1 H), 7.57–7.59 (m, 2 H), 7.62–7.66 (m, 1 H), 9.74 (s, 1 H), 12.81 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.1, 115.5, 117.6, 118.0, 122.6, 130.4, 131.7, 139.6, 152.2, 158.3. Anal. calcd. for $C_{13}H_{10}N_2O$ (210.23): C, 74.27; H, 4.79; N, 13.33. Found: C, 74.19; H, 4.83; N, 13.49.

2-(3,4-Dimethoxyphenyl)benzimidazole (**2h**)

Mp 282°C. IR (KBr): 1609 (C=N), 3445 (NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3 H), 3.85 (s, 3 H), 7.09 (d, $J = 8.4$ Hz, 1 H), 7.14–7.17 (m, 2 H), 7.49 (bs, 1 H), 7.59 (bs, 1 H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.73 (s, 1 H), 12.81 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.3, 110.5, 111.7, 112.5, 119.1, 119.9, 122.1, 122.8, 123.4, 135.7, 144.5, 149.6, 150.9, 152.2. Anal. calcd. for $C_{15}H_{14}N_2O_2$ (254.29): C, 70.85; H, 5.55; N, 11.02. Found: C, 70.72; H, 5.59; N, 11.13.

2-(2,4-Dimethoxyphenyl)benzimidazole (**2i**)

Mp 176°C. IR (KBr): 1619 (C=N), 3446 (NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3 H), 4.02 (s, 3 H), 6.72 (s, 1 H), 6.75 (d, $J = 8.8$ Hz, 1 H), 7.15–7.18 (m, 2 H), 7.57–7.60 (m, 2 H), 8.24 (d, $J = 8.0$ Hz, 1 H), 12.00 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.1, 56.6, 99.1, 103.4, 107.5, 113.8, 125.7, 131.1, 131.4, 146.4, 159.8, 165.2. Anal. calcd. for $C_{15}H_{14}N_2O_2$ (254.29): C, 70.85; H, 5.55; N, 11.02. Found: C, 70.70; H, 5.59; N, 11.12.

2-(3,4,5-Trimethoxyphenyl)benzimidazole (**2j**)

Mp 262°C. IR (KBr): 1620 (C=N), 3447 (NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 3.74 (s, 3 H), 3.91 (s, 6 H), 7.19–7.21 (m, 2 H), 7.51–7.54 (m, 3 H), 7.63–7.66 (m, 1 H), 12.85 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): 56.0, 60.2, 103.8, 111.2, 118.7, 121.7, 122.4, 125.5, 135.0, 138.9, 151.2, 153.2. Anal. calcd. for $C_{16}H_{16}N_2O_3$ (284.31): C, 67.59; H, 5.67; N, 9.85. Found: C, 67. 44; H, 5. 63; N. 9.99.

2-(4-Nitroyphenyl)benzimidazole (**2k**)

Mp 317°C (lit.[15] mp 316°C). IR (KBr): 1347, 1554 (NO_2), 1615 (C=N), 3446 (NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 7.19–7.22 (m, 2 H), 7.54–7.56 (m, 1 H), 7.65–7.67 (m, 1 H), 8.32 (d, $J = 8.0$ Hz, 2 H), 8.37 (d, $J = 8.8$ Hz, 2 H), 13.20 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): 120.0, 123.1, 124.4, 127.5, 129.6, 136.1, 147.9, 149.1. Anal. calcd. for $C_{13}H_9N_3O_2$ (239.23): C, 65.27; H, 3.79; N, 17.56. Found: C, 65.40; H, 3.83; N, 17.42.

2-(3-Nitrophenyl)benzimidazole (**2l**)

Mp 144 °C. IR (KBr): 1345, 1552 (NO_2), 1617 (C = N), 3346 (NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 7.25–7.27 (m, 2 H), 7.58–7.60 (m, 1 H), 7.69–7.72 (m, 1 H), 7.84–7.88 (m, 1 H), 8.32–8.35 (m, 1 H), 8.60–8.64 (m, 1 H), 9.02 (s, 1 H), 13.31 (bs, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): 121.0, 123.0, 124.4, 131.0, 131.7, 132.6, 148.5, 149.2. Anal. calcd. for $C_{13}H_9N_3O_2$(239.23): C, 65.27; H, 3.79; N, 17.56. Found: C, 65.41; H, 3.82; N, 17.44.

1′,4′-Di-(2-Phenylbenzimidazole)benzene (**2m**)

IR (KBr): 1623 (C=N) 3304 (NH) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 7.19–7.26 (m, 4 H), 7.57 (d, $J = 7.6$ Hz, 2 H), 7.70 (d, $J = 7.6$ Hz, 2 H), 8.35 (s, 4 H), 13.05 (s, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): 111.5, 119.0, 121.9, 122.9, 126.9, 131.2, 143.9, 150.6. Anal. calcd. for $C_{20}H_{14}N_4$ (310.36): C, 77.40; H, 4.55; N, 18.05. Found: C, 77.28; H, 4.52; N, 18.16.

CONCLUSION

In summary, we have devised a simple and efficient method for the facile synthesis of benzimidazole derivatives using a readily available and

cost-effective catalyst. The significant features of this method are good selectivity, good yields, and clean reactions, as well as avoidance of column chromatographic purifications. We believe this method is a useful contribution to the existing methodologies and a new addition of the catalytic activity of cobalt(II) chloride hexahydrate in the arsenal of organic synthesis.

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