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Efficient (bromodimethyl)sulfonium bromide mediated synthesis of benzimidazoles☆

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Abstract—Benzimidazoles have been efficiently synthesized in high yields by treatment of 1,2-phenylenediamine with aldehydes using (bromodimethyl)sulfonium bromide at room temperature.

1. Introduction

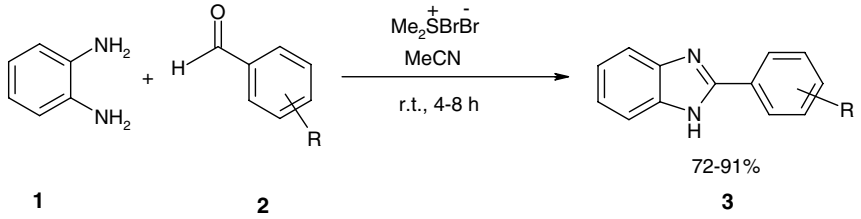
The benzimidazole moiety is found in various bioactive compounds having antiviral, antiulcer, antihypertension and anticancer properties.[1] General methods for the synthesis of benzimidazoles involve treatment of 1,2-phenylenediamines with carboxylic acids or various derivatives under strongly acidic conditions or with aldehydes followed by oxidation.[2,3]

2. Results and discussion

In continuation of our work[4] on the development of useful synthetic methodologies, we have observed that benzimidazoles can be synthesized efficiently by treatment of 1,2-phenylenediamine with aldehydes using (bromodimethyl)sulfonium bromide at room temperature (Scheme 1).

Several aldehydes (aromatic, heteroaromatic and aliphatic) underwent the above conversion to form a series of benzimidazoles (Table 1). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked well. Aliphatic α,β-unsaturated aldehydes (Table 1, entry **3m**) also afforded the desired products in high yields. The method is suitable for the preparation of benzimidazoles from an acid sensitive aldehyde such as furfuraldehyde (entry **3n**) and the sterically hindered aldehyde 2-naphthaldehyde (entry **3o**). The reaction conditions are mild and the experimental procedure is simple. The products were formed in high yields (72–91%). The structures of the products were determined from their spectral (^{1}H NMR, IR and MS) data.

(Bromodimethyl)sulfonium bromide is an inexpensive reagent. It has been used mainly as a catalyst but its scope has not been fully explored.[5] Here it has been applied for oxidative dehydrogenation of the cyclic



Scheme 1.

Keywords: Aldehyde; Diamine; (Bromodimethyl)sulfonium bromide; Benzimidazole.
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Table 1. Synthesis of benzimidazoles using (bromodimethyl)sulfonium bromide[a]

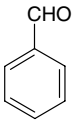
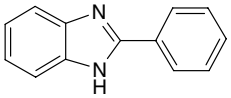
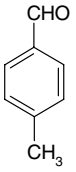
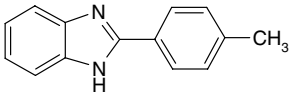
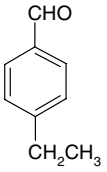
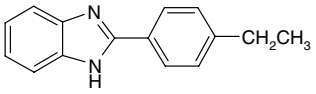
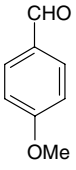
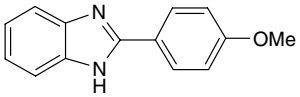
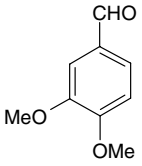
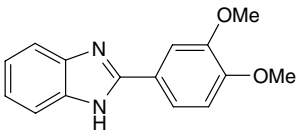
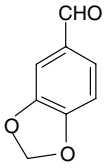
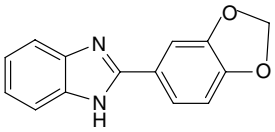
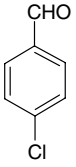
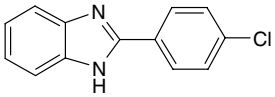
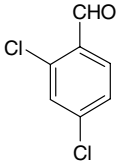
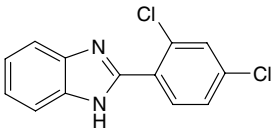
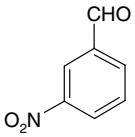
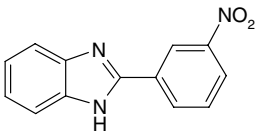
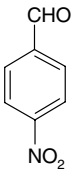
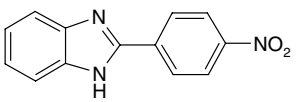
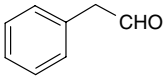
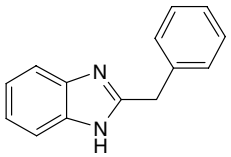
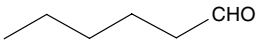
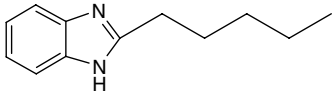
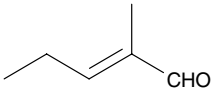
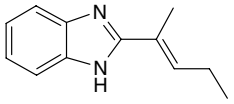
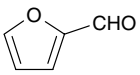
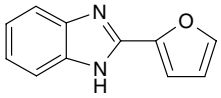
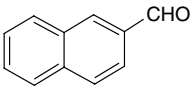
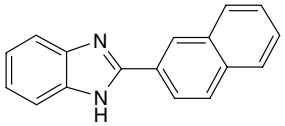
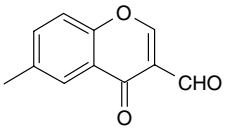
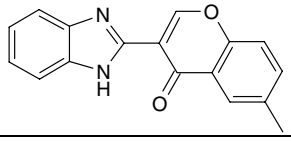
Entry	Aldehyde	Product	Time (h)	Isolated yield (%)
3a			5	85
3b			6	78
3c			6	74
3d			6	80
3e			8	72
3f			8	75
3g			5	82
3h			5	84
3i			4	81
3j			4	86

Table 1 (*continued*)

Entry	Aldehyde	Product	Time (h)	Isolated yield (%)
3k			6	84
3l			8	78
3m			8	91
3n			8	72
3o			6	74
3p			4	82

[a] The structures of the products were determined from their spectral (^{1}H NMR, IR and MS) data.

intermediates formed from the condensation of 1,2-phenylenediamine and aldehydes.

In conclusion, (bromodimethyl)sulfonium bromide has been employed here for the first time as a mild and efficient reagent for the convenient preparation of benzimidazoles in high yields from 1,2-phenylenediamine and a wide variety of aldehydes.

3. General experimental procedure

To a mixture of an aldehyde (0.5 mmol) and 1,2-phenylenediamine (0.6 mmol) in acetonitrile (5 mL) under a nitrogen atmosphere, (bromodimethyl)sulfonium bromide (0.5 mmol) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the solvent was evaporated and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3×10 mL) and the extract was dried and concentrated. The residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain the pure benzimidazole.

The spectral (^{1}H NMR, IR and MS) data of some representative benzimidazoles are given below.

3.1. Compound 3g

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 12.70 (1H, br s), 8.08 (2H, d, $J = 8.0$ Hz), 7.59 (1H, m), 7.26–7.20 (3H, m), 7.18–7.04 (2H, m); IR (KBr): ν 3188, 2981, 1624 cm^{-1}; FABMS: m/z 231 (^{37}Cl [M+H]$^+$), 229 (^{35}Cl [M+H]$^+$); Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.27; H, 3.94; N, 12.25. Found: C, 68.42; H, 3.86; N, 12.38.

3.2. Compound 3m

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 11.82 (1H, br s), 7.62–7.21 (2H, m), 7.18–7.01 (2H, m), 6.42 (1H, t, $J = 7.0$ Hz), 2.29–2.22 (2H, m), 2.16 (3H, s), 1.08 (3H, t, $J = 7.0$ Hz); IR (KBr): ν 3064, 2963, 2923, 1648 cm^{-1}; FABMS: m/z 187 [M+H]$^+$; Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.42; H, 7.53; N, 15.05. Found: C, 77.68; H, 7.64; N, 15.23.

3.3. Compound 3o

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 11.86 (1H, br s), 8.74 (1H, br s), 8.38 (1H, dd, $J = 8.0$, 2.0 Hz), 8.02–7.90 (3H, m), 7.69–7.52 (4H, m), 7.26–7.18 (2H, m); IR (KBr): ν 3056, 2924, 2853, 1624 cm^{-1}; FABMS: m/z 245 [M+H]$^+$; Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.61; H, 4.92; N, 11.47. Found: C, 83.87; H, 4.88; N, 11.61.

3.4. Compound 3p

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 11.79 (1H, br s), 9.28 (1H, s), 8.16 (1H, s), 7.68 (1H, m), 7.58–7.46 (2H, m), 7.24–7.20 (3H, m), 2.56 (3H, s); IR (KBr): ν 3308, 3048, 2923, 2854, 1639 cm^{-1}; FABMS: m/z 277 $[M+H]^+$; Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.91; H, 4.35; N, 10.14. Found: C, 73.98; H, 4.42; N, 10.23.

Acknowledgements

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