A Task-Specific Ionic-Liquid-Mediated Solvent-Free Protocol for Direct Access to Dimethyl Acetal Protected Benzimidazole 2-Carboxaldehydes

Barnali Deb a
Ankita Chakraborty a
Jewel Hossain b
Swapan Majumdar a*

a Department of Chemistry, Tripura University, Suryamaninagar, 799 022, India
b Department of Chemistry, Ram Thakur College, Agartala 799 003, India

Abstract A robust and straightforward protocol has been developed for the synthesis of a diverse array of dimethyl acetal protected benzimidazole-2-carboxaldehydes by reacting various 2-amino aniline derivatives with methyl 4,4-dimethoxy-3-oxobutanoate using the task-specific imidazolium ionic liquid (HBIm·TFA) as a promoter for N-C/C-N annulation processes. The present protocol offers several advantages over existing protocols, such as single-step process, short reaction times, very mild reaction conditions, high yields, ease of purification, recovery and reusability of the catalyst, and scale-up of the reaction.

Key words benzimidazole carboxaldehydes, dimethyl acetal, C–C bond cleavage, task-specific ionic liquid

In drug discovery programs and for identifying biological leads, nitrogen-containing fused heterocyclic molecules play an important role as molecular templates. Among them, benzimidazole-containing heterocycles are of importance because of their broad spectrum of biological and therapeutic potentialities, making them one of the more widely investigated heterocyclic scaffolds. In addition to their biological potential, they are important intermediates in many synthetic organic and inorganic reactions, in dye and polymer synthesis, in fluorescence, chemosensing, crystal engineering, and corrosion science. They also act as ligands in the synthesis of transition-metal complexes of structural and biological interest. Therefore, their synthesis has received considerable attention and this has led to the development of several methods for the synthesis of benzimidazoles. These include the condensation of aromatic 1,2-diamines with carboxylic acids or their derivatives, generally under harsh conditions, oxidative cyclocondensation with aldehydes, or copper(I) catalysed coupling of o-haloacetanilides with amines or amidines, while very recently we and others also developed a benzimidazole synthesis by reaction with 1,2-diaminobenzene derivatives with active methylene compounds using a range of activators. In addition to these methods, rearrangement of quinoxalines or quinoxalone derivatives under different conditions to form benzimidazole derivatives have been documented. Derivatives of benzimidazole-2-carboxaldehyde have found applications in diverse therapeutic areas, as well as in chalcone preparation, generation of Schiff’s bases, and for the creation of a library of fused polyheterocycles. Unfortunately no straightforward synthesis of functionalized benzimidazole-2-carboxaldehydes has been reported to date. They can be synthesized via multi-step pathways (such as pathways 1–5 in Scheme 1): (1) condensation of o-phenylenediamine with tartaric acid followed by cleavage of the diol with NaIO 4; (2) condensation of 1,2-diaminobenzene with glycolic acid and then oxidation with MnO 2; (3) oxidation of 2-methyl benzimidazole with SeO 2; (4) direct and/or directed lithiation at the 2-position of benzimidazole followed by trapping with DMF; and (5) condensation of 1,2-diamino enzene with ethyl diethoxyacetate in Na/EtOH followed by hydrolytic cleavage.
To optimize the reaction conditions, \( \alpha \)-phenylenediamine (1a) and methyl 4,4-dimethoxy-3-oxobutanoate (2) were chosen for the model reaction under different reaction conditions. Previously we have reported\(^{22,24} \) that the neutral ionic liquid [BMIm]Br or basic ionic liquid [BMIm]OH (10 mol%) could be utilised as activators for the synthesis of benzimidazoles by reaction of \( \alpha \)-phenylenediamines with \( \beta \)-keto esters or amides at 115–120 °C, with the reaction proceeding through formation of a seven-membered benzodiazepinone intermediate. Unfortunately our initial attempts with these ionic liquid activators failed to produce the desired product in satisfactory yield on heating 1a with 2 at 80 °C for 4 or 12 hours, respectively (Table 1, entries 1 and 2), and further increasing the temperature did not improve the yield, probably due to decomposition of 2. However, heating the reaction mixture at 80 °C in the presence of 5 mol% of protic ionic liquid (HBIm·TFA) for 15 min produced the desired benzimidazole 2-carboxaldehyde dimethyl acetal 3a in 95% yield (entry 3), although reactions at room temperature or without catalyst were not successful (entries 4 and 5). The appearance of two singlets at \( \delta = 5.70 \) ppm (1H) and 3.46 ppm (6H) in the \( \text{H}^1 \) NMR spectrum and \( \delta = 98.4 \) and 53.6 ppm in the \( \text{C}^{13} \) NMR spectra of 3a corroborated the presence of the dimethyl acetal group (see Supporting Information). A molecular ion at \( m/z \) 193 further supported the structure of 3a. We also carried out the

### Table 1 Screening of Catalysts for Optimisation of Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activator</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[BMIm]Br(^{b} )</td>
<td>80</td>
<td>4 h</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>[BMIm]OH(^{b} )</td>
<td>80</td>
<td>12 h</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>[HBIm][TFA](^b )</td>
<td>80</td>
<td>15 min</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>[HBIm][TFA](^b )</td>
<td>rt</td>
<td>2 h</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>none</td>
<td>80</td>
<td>2 h</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>[Et,NH][TFA](^b )</td>
<td>80</td>
<td>2 h</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>SiO(_2)-H(_2)SO(_4)</td>
<td>80</td>
<td>2 h</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>SiO(_2)-HClO(_4)</td>
<td>80</td>
<td>2 h</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>SiO(_2)-H(_2)SO(_4)</td>
<td>80</td>
<td>3 h</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>FeCl(_3)-SiO(_2)</td>
<td>80</td>
<td>90 min</td>
<td>87</td>
</tr>
<tr>
<td>11</td>
<td>Nano TS 1</td>
<td>80</td>
<td>50 min</td>
<td>83</td>
</tr>
<tr>
<td>12</td>
<td>Amberlite IR120H(^{+} )</td>
<td>80</td>
<td>2 h</td>
<td>78</td>
</tr>
<tr>
<td>13</td>
<td>Amberlyst 15</td>
<td>80</td>
<td>90 min</td>
<td>73</td>
</tr>
<tr>
<td>14</td>
<td>[HBIm][TFA]</td>
<td>80</td>
<td>30 min</td>
<td>92(^{c} )</td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated yield on 1 mmol scale.
\(^{b}\) 5 mol% was used.
\(^{c}\) 10 mmol scale.

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**Scheme 1** General strategies involved in the synthesis of benzimidazole 2-carboxaldehydes

**Scheme 2** Prootic ionic liquid promoted synthesis of benzimidazole 2-carboxaldehyde dimethylacets
reaction with triethyl ammonium trifluoroacetate ([Et₃NH][TFA]), prepared from an equimolar mixture of triethylamine and trifluoroacetic acid under identical reaction conditions (entry 6) but no product was detected. We also screened some silica supported acidic reagents such as SiO₂·KHSO₄ (40 mg, 10% KHSO₄), SiO₂·HClO₃ (40 mg, 10% w/v), SiO₂·H₂SO₄ (40 mg, 10% w/v), SiO₂·FeCl₃ (32 mg containing ca. 10% FeCl₃), and nano titania-silica (TS1). These supported reagents also afforded 2-(1,1-dimethoxy)methyl benzimidazole (3a) in 80, 80, 82, 87, and 83% yield, respectively (entries 7–11). The reaction was also investigated using commercially available sulfonic acid resins Amberlyst-15 and Amberlite IR 120H⁺ (entries 12 and 13). The resin-based catalysts resulted in lower yields compared to the silica supported reagents. No reaction was observed when the model reaction was conducted using 5 mol% of neat trifluoroacetic acid (results not shown). These control experiments indicated that both a proton and imidazolium cation are essential to produce 3a in high yield.

From the results presented in Table 1, the protic ionic liquid (HBImTFA) showed the best catalytic activity for the synthesis of 3a with respect to both reaction time and yield. The reaction could also be scaled up to 10 mmol scale with very little decrease of the yield using the same mol% of ionic liquid (entry 14). It is noteworthy that the high yield of 3a indicates its stability in the mildly acidic reaction medium. Another important feature of the present protocol is the recyclability of the ionic liquid for five cycles without significant loss of catalytic efficiency (95–88%). Since most of the benzimidazole product solidified after completion of reaction, the product could be collected by filtration and the mother liquor containing the ionic liquid recycled after evaporation of solvent.

Having optimized the reaction conditions, the scope of the reaction with various o-phenylenediamines with methyl 4,4-dimethoxy-3-oxobutanoate was subsequently explored; the results are summarized in Figure 1. A wide range of aromatic diamines with electron-withdrawing or electron-donating groups at different positions of the aromatic ring, reacted smoothly in the presence of protic ionic liquid ([HBIm][TFA]) to afford benzimidazole-2-carboxaldehyde dimethyl acetals 3b–e and 3g–l in good to excellent yields within two hours. In contrast, 4-nitro-1,2-diaminobenzene afforded a different type of benzimidazole by C–C bond cleavage due to the presence of the strongly electron-withdrawing group in the aromatic ring depleting the negative charge on the nitrogen in intermediate D (see Scheme 3 below), with methoxy-directed oxidative cleavage resulting in 6-nitro-1H-benzo[d]imidazole-2-yl acetate (3f) in 35% yield with concomitant formation of many other unidentified products. All the synthesized products 3a–l were characterized by spectroscopic analyses. Unfortunately, 2,3-diaminopyridine failed to give the corresponding pyridoimidazole derivative; rather, it produced the seven-membered heterocycle 3m, as an inseparable mixture of tautomers, in 75% yield. A similar trend was observed in the case of 2-aminothiophenol, which yielded benzothiazepinone 3n as the sole product. Attempted reaction of 2-aminophenol yielded a mixture of unidentified products, probably due to the lower nucleophilicity of the phenolic OH group, meaning that the cyclisation step is not favourable.

Considering the mechanism of the reaction, we anticipated that both the imidazolium cation and N-H proton are indispensable for catalytic activity as neither the imidazolium cation (entries 1 and 2) nor proton alone (entries 6, 12 and 13) provide the optimum yield of product, but N-butyl imidazolium trifluoroacetate provided the best yield in the shortest reaction time. Thus, we speculate that dual activation of the ketone oxygen of the ketone and the oxygens of the acetal group of reagent 2 (A in Scheme 3) by both the proton and imidazolium cation activates the ketone carbonyl, thereby making it more susceptible to nucleophilic attack by the amino group of the o-phenylenediamine.
The resulting imine C undergoes ring-closure onto the second amino group to form aminal D followed by hydrogen-bond-assisted C–C bond cleavage to give the benzimidazole (Scheme 3). Although the possibility of simultaneous activation of both carbonyls of 2, leading to B, cannot be overlooked; in such a situation, the benzodiazepinone may result from attack by the two amino groups on both activated carbonyls.

1H and 13C NMR spectra were recorded with a Bruker Ascend 400 spectrometer (400 MHz for 1H and 100 MHz for 13C). Chemical shifts are reported in parts per million with tetramethylsilane internal reference, and coupling constants are reported in Hertz. Proton multiplicities are represented as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). Infrared spectra were recorded with a Fourier transform infrared (FT-IR, Model: Spectrum 100) spectrophotometer as KBr pellets or in thin films. The reported melting points are uncorrected. High-resolution mass spectrometric (HR-MS) data were acquired by electrospray ionization with a Q-ToF-micro quadrupole mass spectrometer.

All commercial reagents were used without further purification, unless otherwise specified. Ethyl acetate and petroleum ether (60–80 °C) were distilled before use. Column chromatography was performed on silica gel (60–120 mesh, 0.12–0.25 mm). Analytical thin-layer chromatography was performed on 0.25 mm silica gel plates with a UV254 fluorescent indicator.

**General Procedure**

The requisite o-phenylenediamine (108 mg, 1 mmol) and methyl 4,4-dimethoxy-3-oxobutanoate (194 mg, 1.1 mmol) were taken in a cone-shaped (10 mL) flask equipped with a magnetic stirrer. HBIm·TFA (12 mg, 0.05 mmol) was then added to the mixture, which was heated at 80 °C without solvent until the disappearance of the o-phenylenediamine (TLC). After completion of reaction, the solid mass was washed several times with water to remove the ionic liquid catalyst. Finally, the product was purified by crystallization using ethyl acetate over silica gel, eluting with 10–50% ethyl acetate in hexane.

2-(Dimethoxymethyl)-1H-benzimidazole (3a)

Yield: 182 mg (95%); colourless solid; mp 180 °C.

IR (neat): 2938, 2835, 1679, 1417, 1191, 1055 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.66–7.64 (dd, J = 5.6, 3.2 Hz, 2 H), 7.30–7.28 (dd, J = 6.0, 3.2 Hz, 2 H), 5.70 (s, 1 H), 3.46 (s, 6 H).

13C NMR (100 MHz, CDCl3): δ = 150.3, 137.9, 122.9, 115.6, 98.4, 53.6.


2-(Dimethoxymethyl)-6-methyl-1H-benzimidazole (3b)

Yield: 187 mg (91%); thick liquid.

IR (neat): 2927, 2826, 1692, 1442, 1325, 1107, 1055 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.53 (dd, J = 8 Hz, 1 H), 7.40 (s, 1 H), 7.10 (d, J = 7.6 Hz, 1 H), 5.67 (s, 1 H), 3.44 (s, 6 H), 2.47 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 150.0, 138.5, 124.4, 115.2, 98.5, 53.5, 21.6.


2-(Dimethoxymethyl)-5,6-dimethyl-1H-benzimidazole (3c)

Yield: 209 mg (95%); colourless solid; mp 100 °C.

IR (neat): 2926, 1691, 1516, 1449, 1192, 1062 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.39 (s, 2 H), 5.66 (s, 1 H), 3.43 (s, 6 H), 2.36 (s, 6 H).

13C NMR (100 MHz, CDCl3): δ = 149.4, 131.9, 115.7, 98.6, 77.0, 53.5, 20.3.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C12H16N2O2: 221.1250; found: 221.1250.

6-Chloro-2-(dimethoxymethyl)-1H-benzimidazole (3d)

Yield: 203 mg (90%); colourless solid; mp 140 °C.

IR (neat): 2920, 1421, 1321, 1105, 1055 cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.63 (s, 1 H), 7.55 (s, 1 H), 7.25 (s, 1 H), 5.66 (s, 1 H), 3.46 (s, 6 H).

13C NMR (100 MHz, CDCl3): δ = 151.3, 128.6, 123.6, 98.3, 77.0, 53.7.


2-(Dimethoxymethyl)-1H-benzimidazole-5-carboxylic Acid (3e)

Yield: 200 mg (85%); yellowish solid; mp 70 °C.

IR (neat): 2938, 2835, 1679, 1417, 1191, 1055 cm–1.

1H NMR (400 MHz, DMSO-d6): δ = 12.87 (s, 1 H), 12.74 (s, 1 H), 8.21 (s, 0.5 H), 8.08 (s, 0.5 H), 7.82 (s, 1 H), 7.67 (s, 0.5 H), 7.52 (s, 0.5 H), 5.65 (s, 1 H), 3.38 (s, 6 H).
$^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ (two tautomers) = 168.2, 153.8, 152.9, 146.4, 142.7, 137.6, 133.9, 125.4, 124.7, 124.4, 123.1, 121.5, 119.2, 114.1, 112.0, 98.9, 55.1, 53.9.

HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for C$_14$H$_{20}$N$_2$O$_2$: 249.1603; found: 252.1009.

1-Allyl-2-(dimethoxymethyl)-1H-benzimidazole (3i)

Yield: 246 mg (89%); yellowish sticky solid.

IR (neat): 2929, 2964, 2931, 2833, 1694, 1516, 1461, 1336, 1067 cm$^{-1}$.

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.26–8.24 (dd, $J = 8.2$, 1.2 Hz, 1 H), 7.15 (t, $J = 7.2$ Hz, 1 H), 7.01–6.99 (dd, $J = 11.6$, 2.0 Hz, 1 H), 5.60 (s, 1 H), 5.39 (dd, $J = 5.7$, 2.0 Hz, 1 H), 3.48 (s, 3 H), 1.88–1.80 (m, 2 H), 1.41–1.32 (m, 6 H), 0.90 (t, $J = 7.2$ Hz, 3 H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 149.2, 140.2, 135.6, 132.1, 122.1, 120.4, 110.0, 54.7, 44.3, 31.4, 29.6, 22.5, 14.0.

HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for C$_{16}$H$_{24}$N$_2$O$_2$: 277.1916; found: 277.1915.
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Supporting Information

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References


