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One-pot synthesis of benzimidazoles from *gem*-dibromomethylarenes using *o*-diaminoarenes

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ABSTRACT

A one-pot synthesis of benzimidazoles from *gem*-dibromomethylarenes is described. The reaction shows the method to prepare a variety of benzimidazole analogues with excellent yield.

The benzimidazole nucleus is the key building block for a variety of compounds that play crucial role in the activity of a number of biologically important molecules.[1] Benzimidazole derivatives have several therapeutic applications such as antiulcer,[2] antihelminthic (Thiabendazole),[3] antihypertensive (BIBR277),[4] anticoagulant (Chlorothiophene benzimidazole),[5] antiallergic,[6] analgesic,[7] anti-inflammatory,[8] antimicrobial,[9] antiviral,[10] antiparasitic[11], and anticancer (Hoechst 33258)[12] (see Fig. 1).

It is also reported that the benzimidazole nucleus is an essential part of many antineoplastic derivatives[13] (TREANDA)® (bendamustine hydrochloride) containing alkylating group and benzimidazole component has been used for the treatment of chronic lymphocytic leukemia.

Several methods have been reported for the synthesis of benzimidazoles.[14] The most common one involves the cyclization of *o*-diaminoarenes with carboxylic acids or their derivatives under acidic condition.[15] Benzimidazoles can also be prepared by the coupling of aldehydes with *o*-diaminoarene under oxidative conditions[16] or with 2-nitroanilines under reductive conditions.[17] More recently, transition metal-catalyzed amination followed by condensation has been reported for the preparation of various benzimidazoles.[18,19]

The substitution of the carboxylic acid or aldehyde component with an alternative functional group has not been reported so far. Therefore, the development of a simple and stable substitute for these aromatic acids or aldehydes by using inexpensive and readily available reagents would extend the scope of the reaction in organic synthesis. Recently, *gem*-dihalomethylarenes have received considerable attention due to their application in the preparation of aldehydes.[20] To our knowledge, the use of *gem*-dihalomethylarenes is limited to the synthesis of aldehydes and α,β-unsaturated carboxylic acids,[21] there is no published report on their use to synthesize biologically active molecules like benzimidazoles. Herein, we report a new, rapid, and efficient method for the synthesis of benzimidazole through the reaction between *gem*-dibromomethylarenes and different *o*-diaminoarenes.

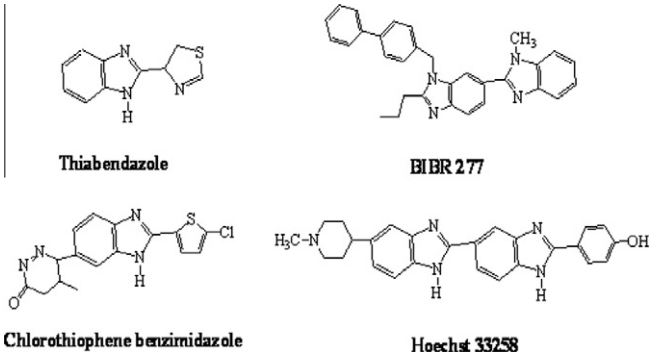

Figure 1. Selected drugs containing benzimidazole substructure.

The synthetic approach starting from the corresponding commercially available methyl analogues using radical bromination was documented.[22] Our approach was initiated using a mixture of benzal bromide (*gem*-1,3-bis (dibromomethyl) benzene)**1a**

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Table 1
Synthesis of benzimidazoles from *gem*-dibromomethylarenes using different *o*-diaminoarenes

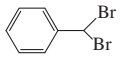
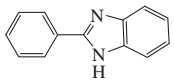
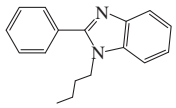
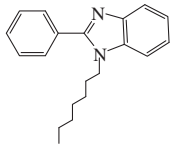
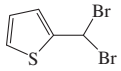
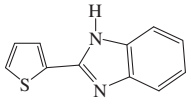
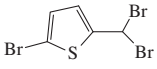
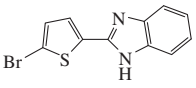
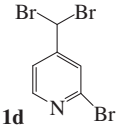
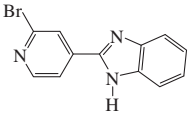
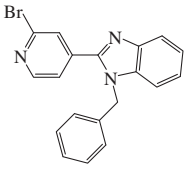
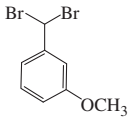
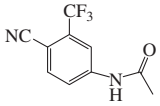
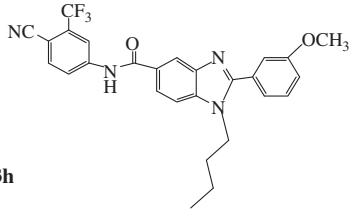
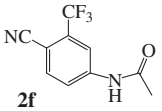
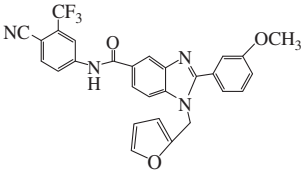
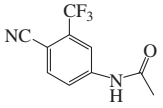
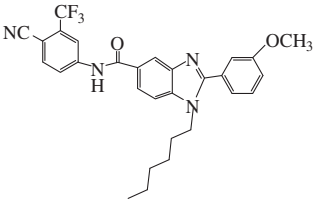
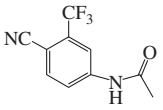
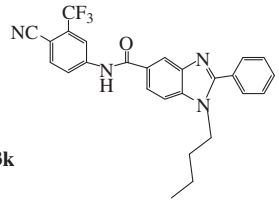
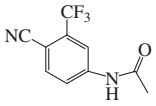
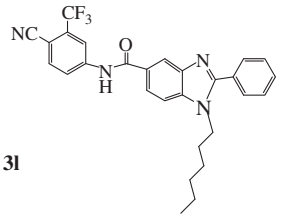
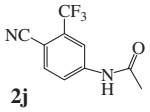
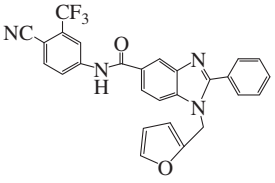
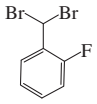
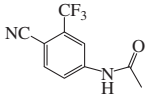
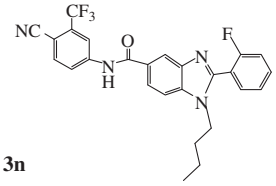
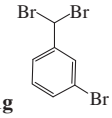
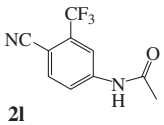
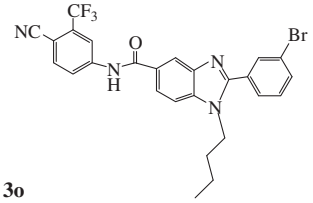
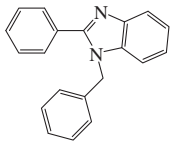
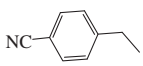
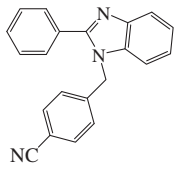
Entry	Substrate[a]	Different *o*-diaminoarenes (R and R^1)	Product	Time (h)	Yield[b] (%)
1	 **1a**	R = –H R^1 = –H **2a**	 **3a**	2	90
2	**1a**	R = *n*-butyl R^1 = –H **2b**	 **3b**	2	89
3	**1a**	R = *n*-heptyl R^1 = –H **2c**	 **3c**	2	88
4	 **1b**	R = –H R^1 = –H **2a**	 **3d**	2	79
5	 **1c**	R = –H R^1 = –H **2a**	 **3e**	2	84
6	 **1d**	R = –H R^1 = –H **2a**	 **3f**	2	90
7	**1d**	R = Benzyl R^1 = –H **2d**	 **3g**	2	91
8	 **1e**	R = n-Butyl R^1=  **2e**	 **3h**	2	90
9	**1c**	R =  R^1=  **2f**	 **3i**	2	94
10	**1e**	R = n-hexyl R^1= **2g** 	 **3j**	2	93

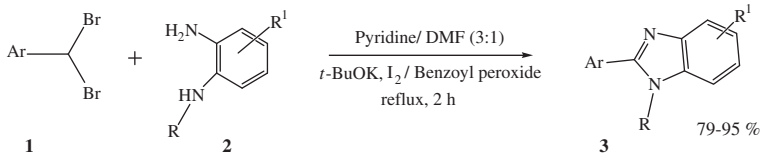
Table 1 (*continued*)

Entry	Substrate[a]	Different *o*-diaminoarenes (R and R^1)	Product	Time (h)	Yield[b] (%)
11	**1a**	R = n-Butyl R^1=  **2h**	 **3k**	2	95
12	**1a**	R = n-hexyl R^1=  **2i**	 **3l**	2	92
13	**1a**	R =  R^1=  **2j**	 **3m**	2	89
14	 **1f**	R = n-Butyl R^1=  **2k**	 **3n**	2	88
15	 **1g**	R = n-Butyl R^1=  **2l**	 **3o**	2	89
16	**1a**	R = Benzyl R^1 = H **2m**	 **3p**	2	91
17	**1a**	R=  R^1= H **2n**	 **3q**	2	90

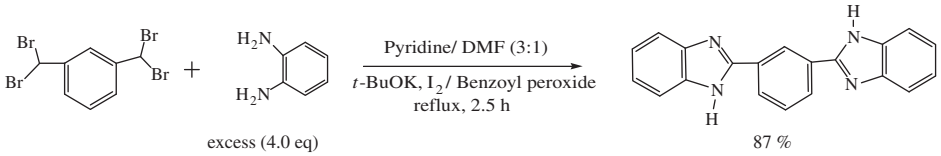
[a] Substrates are prepared from the commercial methyl analogues by radical bromination.
[b] Isolated yields.

(1.0 equiv) and *o*-diaminobenzene **2a** (2.0 equiv) with anhydrous pyridine/DMF(3:1) in the presence of a catalytic quantity (0.2 equiv) of potassium tertiary butoxide (*t*-BuOK) followed by the addition of iodine (0.4 equiv) and catalytic amount of benzoyl peroxide (0.2 equiv) and refluxed for 2 h. The starting material was consumed in 2 h as indicated by TLC analysis and the obtained benzimidazole **3a** was isolated with 90% yield. Use of 2.0 equiv of *o*-diaminobenzene was found to be optimal for the complete conversion of **1a** to **3a**. Various base catalysts such as DBU, triethylamine, *N*-ethyldiisopropylamine, DABCO, K_2CO_3, $CsCO_3$,and morpholine were screened. While piperidine, pyrrolidine, DBU, and morpholine catalyzed the reaction to give quantitative yield in 3–5 h, the other bases did not promote this reaction. Encouraged by this success, the other *gem*-dibromomethylarenes **3(a–q)** were subjected to cyclization reaction with different *o*-diaminoarenes to yield the corresponding benzimidazoles in excellent yield. The results are depicted in Table 1.

The reaction was further probed by treating *gem*-1,3-bis (dibromomethyl)benzene with excess of *o*-diaminobenzene (4 equiv) using the same procedure as described in Scheme 1 to



Scheme 1. General approach to synthesis of benzimidazoles.



Scheme 2. Synthesis of 2-(3-(1*H*-benzoimidazol-2-yl)phenyl)-1*H*-benzoimidazole.

obtain 2-(3-(1*H*-benzoimidazol-2-yl)phenyl)-1*H*-benzoimidazole (Scheme 2) in 87% yield.[23–25]

gem-Dibromomethylarenes being stable and readily accessible substitutes for noncommercial and some of the unstable aldehydes, this transformation would extend the scope in organic synthesis. In addition, it is worthy to note that both aromatic and heteroaromatic *gem*-dibromomethylarenes bearing various functionalities such as amide, halogen, cyano, trifluoro methyl and methoxy groups survived the reaction and provided high yield of corresponding benzimidazoles.

In conclusion, we have demonstrated a general methodology wherein *gem*-dibromomethylarenes could be employed for the first time in the cyclization protocol for the direct synthesis of biologically important benzimidazoles. As this reaction provides benzimidazoles in a single step from *gem*-dibromomethylarenes, this approach provides one of the easiest pathways for accessing this class of valuable compounds from easily available starting materials, and a wide range of multisubstituted benzimidazoles could be generated accordingly for chemical library construction. We believe that this transformation would have many potential applications in synthetic chemistry.

Acknowledgment

The authors are grateful to UGC, Govt. of India for the financial support to K.S.R. under the projects vide No. F. 31-143/2005(SR).

Supplementary data

Supplementary data (^{1}H NMR, ^{13}C NMR of **3(a–h)** and **3(p–q)**) and mass spectra of all the synthesized compounds described in schemes (**1**–**2**)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.080.

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23. Condensation of pyridinium cations with active methylene compounds has been documented but has not been applied to bis-pyridinium cations: Richard H. Kline, US3989738; Appl. No. 597803, 1976.
24. Representative procedure for the synthesis of benzimidazoles analogues **3**(**a**–**q**) (Scheme 1):
To a mixture of benzal bromide **1a** (1 g, 0.004 mol) and *o*-diaminobenzene **2a** (0.86 g, 0.008 mol) in pyridine (3 ml)/DMF (1 ml) was added *t*-BuOK (0.179 g, 0.0016 mol) then followed by addition of I_2 (0.2 g, 0.0016 mol) and benzoyl peroxide (0.19 g, 0.0008 mol), and the reaction mixture was refluxed for 2 h. The completion of reaction was confirmed by TLC. The black reaction mixture was concentrated and the obtained residue was dissolved in water, then extracted with ethyl acetate (2 × 30 ml), the combined organic phase was washed with water and brine solution, dried over anhydrous sodium sulfate. The organic phase was evaporated and the crude product was purified by column chromatography using silica gel (60/120 mesh) with petroleum ether/ethyl acetate (9/1) to afford 0.7 g (90%) of benzimidazole **3a** as a off white solid.
Selected spectral data:
Compound **3d**: 0.31 g of compound was isolated as brownish solid; R_f (10% EtOAc/hexane) 0.70; mp: 203–205 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.9–7.92 (1H, d, J = 8.2 Hz, Ar-H), 7.82–7.8 (1H, d, J = 7.8 Hz, Ar-H), 7.72–7.0 (1H, d,

J = 7.4 Hz, Ar-H), 7.62–7.58 (1H, m, Ar-H), 7.5–7.46 (1H, m, Ar-H), 7.23–7.21 (1H, d, J = 8.0 Hz, Ar-H), 7.20–7.17 (1H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$), 146.9, 133.6, 132.7, 130.7, 129.2, 128.6, 128.4, 128.2, 126.6, 122.5, 111.1; IR ν_{max} (KBr, cm^{-1}): 3413, 2947, 1450, 1275, 1275, 1024, 969, 742; MS (ESI) $[M+H]^+$: 201.1.

Compound **3f**: 0.375 g of compound was isolated as pale brownish solid; R_f (10% EtOAc/hexane) 0.50; mp: 186–188 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.3 (1H, s, –NH), 8.58–8.56 (1H, d, J = 7.8 Hz, Ar-H), 8.34–8.33 (1H, s, Ar-H), 8.16–8.14 (1H, d, J = 7.6 Hz, Ar-H), 7.78–7.76 (1H, d, J = 8.0 Hz, Ar-H), 7.64–7.62 (1H, d, J = 7.8 Hz, Ar-H), 7.3–7.25 (2H, m, Ar-H); δ_C (100.6 MHz, DMSO-d_6), 156.5, 152.5, 148.7, 147.4, 145.5, 134.5, 133.7, 129.4, 127.7, 125.2, 124.9, 117.2; IR ν_{max} (KBr, cm^{-1}): 3179, 1601, 1445, 1137, 995, 738; MS (ESI) $[M+H]^+$: 274.2, $[M+2]^+$: 276.0.

Compound **3h**: 0.8 g of compound was isolated as off white solid; R_f (10% EtOAc/hexane) 0.45; mp: 241–243 °C; ^{1}H NMR (DMSO-d_6): δ: 10.95 (s, 1H, –CONH), 8.53–8.51 (1H, d, J = 8.4 Hz, Ar-H), 8.45–8.43 (1H, d, J = 8.2 Hz, Ar-H), 8.34–8.32 (1H, d, J = 7.6 Hz, Ar-H), 8.15–8.13 (1H, d, J = 7.2 Hz, Ar-H), 7.98–7.93 (1H, m, Ar-H), 7.88–7.86 (1H, d, J = 7.4 Hz, Ar-H), 7.55–7.53 (1H, d, J = 7.4 Hz, Ar-H), 7.35–7.30 (2H, m, Ar-H), 7.15–7.13 (1H, d, J = 7.0 Hz, Ar-H), 4.40–4.35 (2H, t, J = 12.0 Hz, $-NCH_2$), 3.93 (3H, s, $-OCH_3$), 1.63–1.50 (2H, m, $-CH_2$), 1.13–1.03 (2H, m, $-CH_2$), 0.7 (3H, t, J = 12.0 Hz, $-CH_3$); δ_C (100.6 MHz, DMSO-d_6), 165.9, 162.7, 148, 144.9, 137.1, 136.7, 136, 134.6, 132, 131.1, 130.9, 129.2, 129.1, 128.7, 128.6, 127.5, 122.8, 122.6, 122.1, 121.6, 110.3, 34.2, 31.8, 23.1, 22.7, 14.1; IR ν_{max} (KBr, cm^{-1}): 3386, 3121, 2228, 1684, 1321; MS (ESI+ion); m/z = 493.1 [M+H].

Compound **3q**: 0.56 g of compound was isolated as pale yellow solid; R_f (10% EtOAc/hexane) 0.50; mp: 219–221 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19–8.17 (1H, d, J = 8.0 Hz, Ar-H), 7.89–7.87 (1H, d, J = 8.0 Hz, Ar-H), 7.63–7.59 (4H, m, Ar-H), 7.48–7.44 (2H, m, Ar-H), 7.36–7.32 (1H, m, Ar-H), 7.29–7.25 (2H, m, Ar-H), 7.2–7.14 (2H, m, Ar-H), 5.5 (2H, S, $-CH_2$); δ_C (100.6 MHz, $CDCl_3$), 154, 143, 141.6, 135.6, 132.9, 132.5, 130.2, 129.6, 129.1, 126.7 123.4, 123.1, 120.2, 118.2, 112, 110, 48; IR ν_{max} (KBr, cm^{-1}): 2926, 2229, 1609, 1460, 829, 745; MS (ESI) $[M+1]^+$: 310.1.

25. Compound characterization data for: 2-(3-(1*H*-benzoimidazol-2-yl)phenyl)-1*H*-benzoimidazole (Scheme 2). 0.31 g (87%) of brownish red solid. R_f (20% EtOAc/hexane) 0.75; mp: 279–282 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.09 (2H, br s, –NH), 8.27–8.23 (2H, m, Ar-H), 7.94–7.92 (1H, d, J = 8.0 Hz, Ar-H), 7.61–7.55 (4H, m, Ar-H), 7.50–7.48 (2H, d, J = 8.1 Hz, Ar-H), 7.22–7.16 (4H, m, Ar-H); δ_C (100.6 MHz, DMSO-d_6), 154.1, 143.9, 135.8, 134.9, 131.1, 130.7, 129.8, 127.4, 122.2, 121.8, 111.4; IR ν_{max} (KBr, cm^{-1}): 3420, 1635, 1409, 1273, 1112, 959, 745; MS (ESI) $[M+H]^+$: 311.1.