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Novel access to 1-substituted-benzimidazoles via benzotriazole-mediated synthesis

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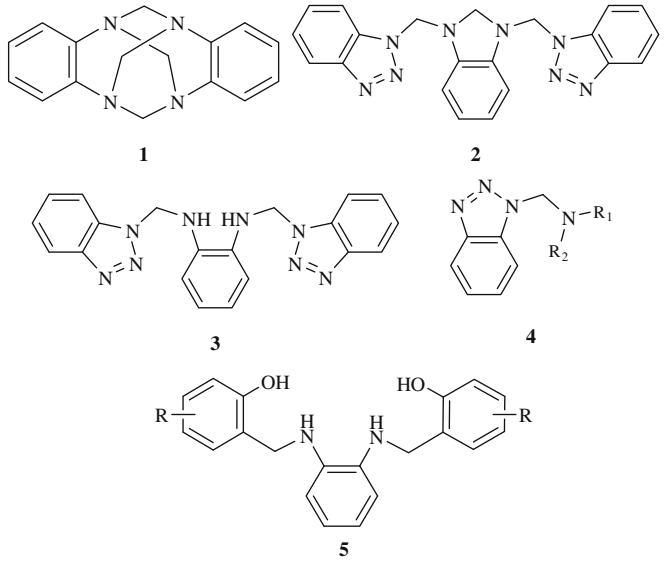
ABSTRACT

A one-pot good-yielding synthesis of 1-(alcoxymethyl)-1*H*-benzimidazoles and 1-((1*H*-benzimidazol-1-yl)methyl)-1*H*-benzotriazole from N^1,N^2-bis((1*H*-benzotriazol-1-yl)methyl)benzene-1,2-diamine (**3**) and alcohols is described. The synthesis of **3** from macrocyclic aminal 6*H*,13*H*-5:12,7:14-dimethanedibenzo-[*d*,*i*][1,3,6,8]tetraazecine (DMDBTA, **1**) and benzotriazole is also described. Both these methods are simple, isolation of the products from the reaction mixtures is easy, and the yields are good.

6*H*,13*H*-5:12,7:14-Dimethanedibenzo[*d*,*i*][1,3,6,8]tetraazecine (DMDBTA, **1**), which was prepared for the first time by the end of the 19th-century by condensation of *o*-phenylenediamine with formaldehyde,[1] belongs to a class of nitrogen-containing heterocycles having a cage-adamanzanes-type structure. Now, it is worth pointing out that during our continuous research program about the reactivity of **1**,[2–4] the reaction between **1** and benzotriazole in dioxane yielding bis-1,3(benzotriazol-yl-methyl)-2,3-dihydrobenzil imidazole (**2**) resulted in moderate yield.[4] In order to improve the yield of **2** we used ethyl acetate as a solvent instead of dioxane due to the major stability of **1** in this solvent. Under these conditions an unexpected compound called N^1,N^2-bis((1*H*-benzotriazol-1-yl)methyl)benzene-1,2-diamine (**3**) was obtained in good yields.[5] It should be noted that **3** is an interesting compound because it possesses two benzotriazolyl groups, and it is structurally related to compounds such as *N*-(α-amino substituted)-benzotriazoles (**4**) which constitute an interesting class of aminals that react by nucleophilic substitution of the benzotriazolyl group with a variety of O-, S-, and C-nucleophiles.[6]

The molecular structure of **3**, which to the best of our knowledge is previously unreported, became evident from NMR spectral measurements in DMSO-d_6. The ^{1}H NMR spectrum of **3**[5] showed two set of signals for the aromatic protons which were unequivocally assigned to protons of the benzotriazolyl and *o*-phenylenediamine rings, based on their chemical shifts and correlation in the 2D-COSY spectrum.

An X-ray analysis confirmed the structure of **3**.[7] The molecular diagram is shown in Figure 1, and relevant bond lengths and angles are given in Table 1.



Single-crystal X-ray diffraction analysis[7] revealed that **3** is composed of discrete monomeric molecules with the two benzotriazolyl moieties arranged in a face-to-face manner. The bond angles around the benzylic carbon are close to normal tetrahedral bond angles. The bond angles around atoms N4 and N5 are close to sp^2-hybridization [$\sum\alpha \cong 360°$]. Interestingly, the two benzotriazolyl–methylene bonds are different (C20–N3 and C19–N6, Table 1). This observation is explained in terms of a strong anomeric effect of the $n_{N5} \rightarrow \sigma^*_{C19-N6}$. Such stereoelectronic interactions might cause a lengthening of the C19–N6 bond.[8]

Next, our attention was initially focused on the presumption that **3** can undergo double amino-alkylation with phenols to give the corresponding di-Mannich bases **5**. However, attempts to prepare target compounds **5** by treating **3** with phenols in 2-propanol

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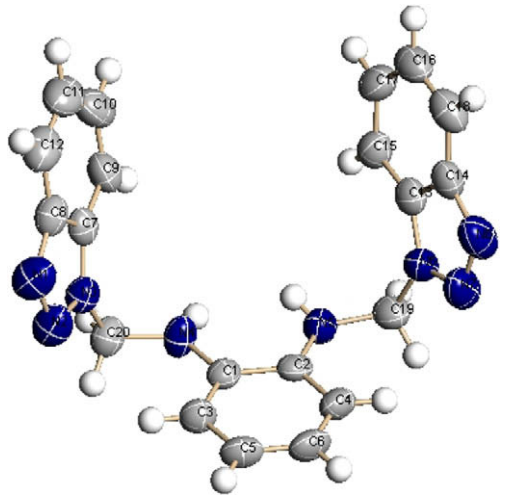


Figure 1. The molecular structure of **3**. Displacement ellipsoids are drawn at the 50% probability level, and H atoms are shown as small spheres.

Table 1
Selected bond lengths (Å) and bond angles (°) for **3**

Bond lengths		Bond angles	
C1–N4	1.404(3)	N5–C19–N6	115.0(2)
C20–N4	1.417(4)	N4–C20–N3	113.9(2)
C20–N3	1.458(4)		
C2–N5	1.402(3)		
C19–N5	1.429(4)		
C19–N6	1.478(4)		

as the solvent according to known procedures[9,10] were unsuccessful. The only substances that could be isolated from this reaction were the starting phenol and the unexpected products 1-(isopropoxymethyl)-1*H*-benzimidazole (**6c**) and 1-methyl-benzimidazole (**7**). It is noteworthy that parallel reactions carried out in the absence of phenol always gave compounds **6c** (yield 16.7%) and **7** (yield 68.4%). On the basis of these interesting results, we decided

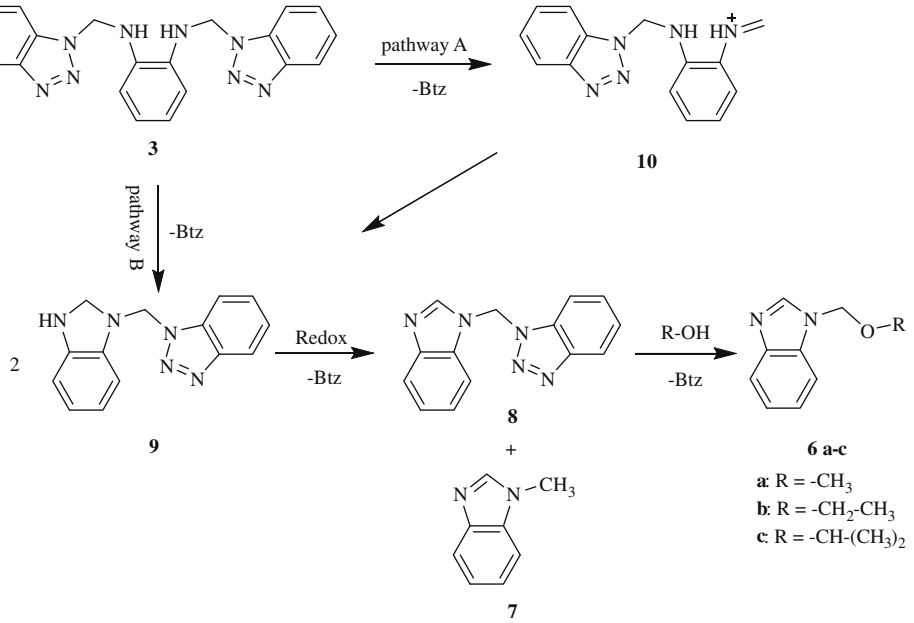
Table 2
Reactions of compound **3** with alcohols a–h

Entry	Alcohol	Time (h)	Yield (%)		
			6a–c	**8**	**7**
a	MeOH	36	64.2	—	19.7
b	EtOH	34	49.0	—	22.4
c	*i*-PrOH	26	16.7	—	68.4
d	PrOH	30	—	24.8	59.1
e	ButOH	24	—	29.6	48.6
f	PentOH	9	—	49.0	21.8
g	HexOH	5	—	41.6	45.1
h	*t*-BuOH	26	—	38.2	51.3

to explore the scope and generality of this reaction using alcohols of different sizes (Scheme 1).[11] During the work, however, we found unexpected results; with the smaller-sized alcohols such as methanol and ethanol, the respective 1-(alcoxy methyl)-1*H*-benzimidazoles (**6a–b**) were obtained in yields of 64.2% and 49.0%, respectively (Table 2, entries a and b), but with propanol, butanol, pentanol, hexanol, and 1,1-dimethyl-ethanol, none of the 1-(alcoxymethyl)-1*H*-benzimidazoles (**6**) were produced as stated by TLC, and the reactions instead afforded benzotriazole, **7** and the compound 1-((1*H*-benzimidazol-1-yl)methyl)-1*H*-benzotriazole (**8**) in good yields (see Table 2).

The structures of the compounds **6a–c** and **8** were established through rigorous spectroscopic analysis.[11] The structure of **8** was initially determined using an array of NMR experiments. These NMR data, together with LR–MS (*m*/*z* 249.0 [M^+]) confirmed the suggested structure of compound **8**. Satisfactory elemental analyses were obtained for compounds **6a–c** and **8**.[11]

This singular behavior of **3** was attributed to the strong tendency of **3** to undergo a ring-closing reaction to yield **8**, due to the presence of a strong anomeric effect, which assisted the facile loss of the one benzotriazole moiety,[8] and the additional stability of benzimidazole ring (**8**) over the expected product. Although a more in-depth study of the reaction mechanism is required, the results provide evidence that **3** undergoes a rearrangement process under the given reaction conditions, followed by fast oxidation of the resulting 1-((2,3-dihydro-1*H*-benzimidazol-1-yl)methyl)-1*H*-benzotriazole (**9**) with atmospheric oxygen to form 1-((*1H*-ben-



Scheme 1. Proposed pathways to the formation of **6a–c**, **7**, and **8**.

zimidazol-1-yl)methyl)-1*H*-benzotriazole (**8**) (Scheme 1), which has been reported for the preparation of benzimidazole derivatives.[12,13]

There are two plausible reaction pathways that would explain the selective elimination of one benzotriazolyl moiety (Btz) of **3** to produce **8**. The first one (pathway **A** in Scheme 1) involves a stepwise mechanism with a rate-limiting expulsion of the benzotriazolate leaving group to give the cationic intermediate (**10**), which undergoes an intramolecular cyclization. The second proposed pathway (**B** in Scheme 1) may be explained by the presumption that the preferred conformation of the molecule acts as an organic template which induces pre-organization to favor its subsequent cyclization to the benzimidazole ring, involving a concerted mechanism with simultaneous bond formation and fission in which the leaving group is expelled as an anion.

Finally, in order to investigate the reaction mechanism, we used density functional theory (DFT) calculations to analyze the transformation of **3**–**8**. The structure of **3**, the transition states, and intermediates were further optimized using density functional theory (DFT) at the B3LYP level and a 6-31G(d) basis set.[14] Both transition states were characterized with vibrational frequency analyses performed at the same theoretical level, which showed only one imaginary frequency in each transition state.[15] All the calculations were carried out using the GAUSSIAN 98W program package.[16] The gas-phase energy barrier at the B3LYP/6-31G* level for the bimolecular mechanism is only 1.4 kcal/mol higher in energy than unimolecular mechanism. However, inclusion of the solvent effect, performed through single-point calculations on the gas-phase optimized structures using the polarizable continuum model (PCM),[17–19] increases the free-energy barrier for the unimolecular mechanism by 13.6 kcal mol^{-1}, which indicates that the formation of pentacoordinated transition state is thermodynamically favored.

Due to the relatively low nucleophilicity of alcohols compared to amines and the tendency of **3** to undergo spontaneous cyclization to afford 1-((1*H*-benzimidazol-1-yl)methyl)-1*H*-benzotriazole (**8**) (Scheme 1), we believe that **8** would be an obvious precursor to **6a–c**. Thus, the intermediate **8**, formed by oxidation, reacts by subsequent nucleophilic substitution by small alcohols (Scheme 1), whereas the observed unreactivity of the other alcohols (Table 2, entries d–h) was expected on the basis of the mechanistic hypothesis due to the lower nucleophilicity of these bulky alcohols.[20] To confirm the latter, we carried out the reactions between **8** and the cited alcohols, but the results were similar to those previously obtained with **3**, thus we concluded that **8** was the compound undergoing the substitution reaction. Further investigations on the synthetic applications of N^1,N^2-bis((1*H*-benzotriazol-1-yl)-methyl)-benzene-1,2-diamine (**3**) and 1-((1*H*-benzimidazol-1-yl)-methyl)-1*H*-benzotriazole (**8**) are in progress.

In this Letter, we introduce N^1,N^2-bis((1*H*-benzotriazol-1-yl)methyl)benzene-1,2-diamine (**3**) as a new starting material for the synthesis of 1-substituted-1*H*-benzo[*d*]imidazoles. This methodology represents a valid alternative to the existing procedures especially for 1-alkylsubstituted benzimidazoles.

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5. *Preparation of N^1,N^2-bis((1H-benzotriazol-1-yl)methyl)-benzene-1,2-diamine* (**3**): A mixture of 1 g (3.79 mmol) of DMDBTA and 0.9 g (7.58 mmol) of benzotriazole in 5 mL of ethyl acetate was stirred for 12 h at room temperature. The precipitated solid was collected by filtration and was washed with ethyl acetate and dried in vacuo: yield 85%, mp 156–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.17 (d, J = 6.84 Hz, 4H), 6.51 (t, J = 6.84 Hz, 2H, –NH), 6.48 (m, 2H), 6.75 (m, 2H), 7.34 (t, J = 7.88 Hz, 2H, Bt), 7.47 (t, J = 7.88 Hz, 2H), 7.98 (d, J = 7.88 Hz, 4H).^{13}C NMR (100 MHz, DMSO-d_6) δ: 57.3, 111.0, 112.5, 119.0, 119.2, 123.9, 127.1, 132.2, 133.1, 145.4.
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7. Crystal data for compound **3**, $C_{20}H_{18}N_8$, were collected using a Siemens Smart CCD diffractometer, M = 370.42, monoclinic, $P2(1)/c$, a = 10.302(1), b = 17.565(2), c = 10.662(1) Å, V = 1816.4(4) Å^3, Z = 4, D_{calcd} = 1.355 g/cm^{-3}, X-ray source Mo Kα (radiation), λ = 0.71073 Å, F(0 0 0) = 776, colorless prism 0.50 × 0.29 × 0.25 mm. The structure solution was obtained by direct methods and was refined with anisotropic thermal parameters using full-matrix least squares procedures on F^2 to give R = 0.064, wR = 0.220 for 5303 independent observed reflections and 261 parameters. Crystallographic data (excluding structure factors) for the given structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 745159. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223 336033 or email: deposit@ccdc.cam.ac.uk).
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11. *Reaction of N^1,N^2-bis((1H-benzotriazol-1-yl)methyl)-benzene-1,2-diamine with alcohols:* In a typical reaction, the appropriate alcohol and N^1,N^2-bis((1*H*-benzotriazol-1-yl)methyl)-benzene-1,2-diamine were heated to reflux for different times, ranging from 5 to 36 h. The solution was concentrated by rotary-evaporator, and the residue was purified by column chromatography on silica gel (eluted with benzene/ethyl acetate, 8:2) to afford: *1-(methoxymethyl)-1H-benzimidazole (6a):* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.28 (s, 3H), 5.49 (s, 2H), 7.33 (m, 2H), 7.52 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.3, 76.0, 110.2, 120.4, 122.8, 123.6, 133.6, 143.1, 144.0 (CG–MS) m/z 162 (M^+). Elemental Anal. Calcd for $C_9H_{10}N_2O$: C, 66.6 7; H, 6.17; N, 17.28. Found: C, 66.59; H, 6.21; N, 17.24. *1-(Ethoxymethyl)-1H-benzimidazole (6b):* ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7 Hz, 3H), 3.43 (q, J = 7 Hz, 2H), 5.53 (s, 2H), 7.31 (t, J = 6 Hz, 2H,), 7.53 (d, J = 6.2 Hz, 1H), 7.80 (d, J = 6.5 Hz, 1H), 7.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 64.3, 75.5, 110.1, 120.3, 122.6, 123.4, 133.6, 143.0, 143.9 (CG–MS) m/z 176 (M^+). Elemental Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.82; N, 15.91. Found: C, 68.13; H, 6.86; N, 115.87. *1-(Isopropoxymethyl)-1H-benzimidazole (6c):* ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, J = 6.4 Hz, 6H), 3.66 (h, J = 6.4 Hz, 6H), 5.57 (s, 2H), 7.31 (t, J = 6.2 Hz, 2H), 7.54 (d, J = 6.2 Hz, 1H), 7.81 (d, J = 6.2 Hz, 1H), 7.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 69.8, 72.4, 110.3, 120.4, 122.7, 123.4, 133.4, 142.8, 142.8 (CG–MS) m/z 190 (M^+). Elemental Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.37; N, 14.74. Found: C, 69.42; H, 7.41; N, 14.71. *1-(1H-Benzimidazol-1-yl-methyl)-1H-1,2,3-benzotriazole (8):* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.50 (d, J = 8.1 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 2H), 8.08 (d, J = 8.1 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.7, 108.6, 110.0, 120.7, 120.8, 123.4, 124.3, 124.7, 128.7, 131.9, 132.9, 142.2, 143.9, 146.4 (CG–MS) m/z 249 (M^+). Elemental Anal. Calcd for $C_{14}H_{11}N_5$: C, 67.47; H, 4.42; N, 28.08. Found: C, 67.41; H, 4.46; N, 28.03.
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