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Synthesis of Some Benzimidazole-substituted Benzotriazoles

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ABSTRACT

2-Alkylsubstituted benzimidazoles (3a–h) were prepared from the acid-catalyzed reaction of 4-methyl-1,2-phenylenediamine with corresponding carboxylic acids. Addition of these benzimidazoles to N-chloromethylbenzotriazole in the presence of sodium amide under reflux conditions gave the novel benzimidazole-substituted benzotriazoles (5a–f). IR and ^{1}H NMR spectroscopy and elemental analysis were used for the identification of these compounds.

KEYWORDS

Phenylenediamine, benzimidazole, benzotriazole.

1. Introduction

Benzimidazoles are of special interest because of their diverse biological activity and clinical applications.[1] This heterocyclic system has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological activities. It is well documented that several benzimidazoles show chemotherapeutic[2–7] and biological[8–10] effects. Compounds containing a benzotriazole moiety[11–13] attached to a heterocyclic system are of wide interest because of their diverse biological activities. Several heterocycles containing a benzotriazole moiety have been reported in the literature.[11–17] However benzimidazole systems containing a benzotriazole moiety are not well represented. Preparation of the (benzimidazole)methylbenzotriazoles is often carried out using a three-component reaction of benzotriazole, formaldehyde and benzimidazole.[18,19] Instead, preparation of the (benzimidazole)methylbenzotriazoles using N-hydroxy-methylmethylbenzotriazole or N-chloromethylbenzotriazole is more convenient and eliminates the use of formaldehyde.[14,20]

As part of ongoing studies[17,21] to explore the versatile biological properties of benzotriazoles and benzimidazoles, we have modified and extended these methods in order to synthesize some novel benzimidazole-substituted benzotriazoles.

2. Experimental

All chemicals were of reagent grade quality and used without further purification. 1-Chloromethybenzotriazole was prepared by reaction of 1-hydroxymethyl-benzotriazole and thionyl chloride.[20] Melting points were determined on an Electrothermal digital melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded using Bruker 300 and 500 MHz spectrometers. IR spectra were recorded using a Galaxy 500 FTIR spectrophotometer. Microanalyses were performed on an Elemental Vario EL III elemental analyser at the University of Arak. Reaction progress was routinely monitored by thin layer chromatography (TLC) on silica gel plates. The structures of all novel compounds reported below were confirmed by spectroscopic methods and the corresponding elemental analyses are reported below. Compounds **3a**, **3b** and **3d** are known.[22,23]

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2.1. General Procedure for the Preparation of Benzimidazoles and Benzimidazole-substituted Benzotriazoles

For the preparation of substituted 5-methylbenzimidazoles (**3a–h**) a mixture of 4-methyl-1,2-phenylenediamine (1.0 mmol) and the corresponding carboxylic acid (1.0 and 0.5 mmol for monofunctional and bifunctional acids respectively) in hydrochloric acid (10 mL, 4 mol L^{-1}) was refluxed for 4 to 9 h. The mixture was cooled and neutralized slowly with NaOH (1 mol L^{-1}). The precipitate was filtered to give crude benzimidazoles **(3a–h)**, which were then recrystallized from a mixture of ethanol and water (50:50). Adipic acid and succinic acid were used as bifunctional acids for the syntheses of **3f** and **3g**, respectively. The reaction was monitored by TLC (n-hexane/ethyl acetate, 2:1).

For the preparation of benzimidazole-substituted benzotriazoles **(5a–f)** a mixture of sodium amide (1 mmol) and the corresponding synthesized benzimidazole **3** (1 mmol) in dry toluene (5 mL) was refluxed for 4 to 6 h. Chloromethylbenzotriazole (1 mmol) was added to the hot suspension and refluxed for 8 to 9 h. After cooling, crystals formed which were collected in a funnel. The crude product was recrystallized from water. The reaction was monitored by TLC (n-hexane/ethyl acetate, 2:1).

2.2. 2,5-Dimethyl-1H-1,3-benzimidazole (3a)

Cream crystals, yield 60%, m.p. 160–162 °C, ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.37 (s, 3H, $CH_{3phenyl}$), 2.44 (s, 3H, CH_3), 6.91–7.32 (m, 3H, phenyl), 12.01 ppm (bs, 1H, NH). IR (KBr) $\bar{\nu}$: 3038 (N-H), 2717, 2912 (C-$H_{aliphatic}$), 1030, 1224 (C-N), 858, 804 cm^{-1}.

2.3. 2-Ethyl-5-methyl-1H-1,3-benzimidazole (3b)

Brown crystals, yield 75%, m.p. 170–172 °C, ^{1}H NMR (DMSO d_6, 500 MHz), δ: 1.28–1.31 (t, 3H, J = 7.6 Hz, CH_{3ethyl}), 2.76–2.81 (q, 2H, J = 7.6 Hz, CH_{2ethyl}), 2.38 (s, 3H, $CH_{3phenyl}$), 6.91–7.32 (m, 3H, phenyl), 12.01 ppm (bs, 1H, NH). IR (KBr) $\bar{\nu}$: 3040 (N-H), 2727, 2846, 2974 (C-$H_{aliphatic}$), 1041 (C-N), 808 cm^{-1}.

2.4. 5-Methyl-2-(trichloromethyl)-1H-1,3-benzimidazole (3c)

Brown crystals, yield 75%, m.p. 187–189 °C, ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.31 (s, 3H, CH_3), 7.07–7.62 (m, 3H, phenyl), 13.33 ppm (bs, 1H, NH). IR (KBr) $\bar{\nu}$: 3043 (N-H), 2957

(C-$H_{aliphatic}$), 1029, 1132, 1190 (C-N), 833, 707 cm^{-1}. Anal. calcd. for $C_9H_7N_2Cl_3$: C, 43.32; H, 2.83; N, 11.23. Found: C, 43.51; H, 2.98; N, 10.88.

2.5. 5-Methyl-2-(2-pyridyl)-1H-1,3-benzimidazole (3d)

Grey crystals, yield 85%, m.p. 230–232 °C, ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.68 (s, 3H, CH_3), 6.67–8.67 (m, 7H, aromatic), 12.09 ppm (bs, 1H, NH). IR (KBr) $\bar{\nu}$: 3041 (N-H), 2950 (C-$H_{aliphatic}$), 1120 (C-N), 806, 700 cm^{-1}. Anal. calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.36; H, 5.56; N, 20.32.

2.6. 5-Methyl-2-(3-pyridyl)-1H-1,3-benzimidazole (3e)

Cream crystals, yield 80%, m.p. 240–242 °C, ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.29 (s, 3H, CH_3), 7.06–9.32 (m, 7H, aromatic), 12.99 ppm (bs, 1H, NH). IR (KBr) $\bar{\nu}$: 3047 (N-H), 2910 (C-$H_{aliphatic}$), 1132, 1229 (C-N), 812, 707 cm^{-1}. Anal. calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.87; H, 5.38; N, 20.24.

2.7. 5-Methyl-2-[4-(5-methyl-1H-1,3-benzimidazole-2-yl)butyl]-1H-1,3-benzimidazole (3f)

Red crystals, yield 70%, m.p. 270–271 °C, ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.81 (m, 4H, CH_2), 2.37 (s, 6H, CH_3), 2.82 (m, 4H, CH_2), 6.91–7.33 (m, 6H, phenyl), 12.00 ppm (s, 2H, NH). IR (KBr) $\bar{\nu}$: 3038 (N-H), 2756, 2870, 2933 (C-$H_{aliphatic}$), 1129 (C-N), 798 cm^{-1}. Anal. calcd. for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60. Found: C, 75.68; H, 6.69; N, 17.68.

2.8. 5-Methyl-2-[2-(5-methyl-1H-1,3-benzimidazole-2-yl)ethyl]-1H-1,3-benzimidazole (3g)

Pink crystals, yield 70%, m.p. 260–262 °C, ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.38 (s, 6H, CH_3), 3.06–3.07 (t, 4H, J = 4.6 Hz, CH_2), 6.90–7.40 (m, 6H, phenyl), 12.18 ppm (s, 2H, NH). IR (KBr) $\bar{\nu}$: 3063 (N-H), 2792, 2980, 2924 (C-$H_{aliphatic}$), 1024, 1151 (C-N), 794 cm^{-1}. Anal. calcd. for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25; N, 19.30. Found: C, 74.67; H, 6.11; N, 17.19.48.

2.9. 5-Methyl-2-(4-pyridyl)-1H-1,3-benzimidazole (3h)

Red crystals, yield 80%, m.p. 236–238 °C, ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 2.44 (s, 3H, CH_3), 7.06–8.75 (m, 7H, aromatic), 13.18 ppm (bs, 1H, NH). IR (KBr) $\bar{\nu}$: 3070 (N-H), 2970 (C-$H_{aliphatic}$), 1004 (C-N), 804, 696 cm^{-1}. Anal. calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.34; H, 5.02; N, 20.38.

2.10. 1-[(2,5-Dimethyl)-1H-1,3-benzimidazole-1-yl)methyl]-1H-1,2,3-benzotriazole (5a)

Cream crystals, yield 65%, m.p. 231–233 °C, ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.50 (s, 3H, $CH_{3phenyl}$), 6.83 (s, 2H, CH_2), 7.13–7.67 ppm (m, 7H, aromatic). IR (KBr) $\bar{\nu}$: 3052 (C-$H_{aromatic}$), 2981 (C-$H_{aliphatic}$), 1675 (C=C, C=N), 1445, 740 cm^{-1}. Anal. calcd. for $C_{16}H_{15}N_5$: C, 69.30; H, 5.45; N, 25.25. Found: C, 69.06; H, 5.18; N, 25.39.

2.11. 1-[(2-Ethyl-5-methyl)-1H-1,3-benzimidazole-1-yl)methyl]-1H-1,2,3-benzotriazole (5b)

Cream crystals, yield 60%, m.p. 245 °C, ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.17–2.19 (t, 3H, J = 4.5 Hz, CH_{3ethyl}), 2.51–2.53 (q, 2H, J = 5.7 Hz, CH_{2ethyl}), 2.47 (s, 3H, $CH_{3phenyl}$), 6.87 (s, 2H, CH_2), 7.11–7.65 ppm (m, 7H, aromatic). IR (KBr) $\bar{\nu}$: 3049 (C-$H_{aromatic}$), 2987 (C-$H_{aliphatic}$), 1610, 1679 (C=C, C=N), 1440, 840, 796 cm^{-1}. Anal. calcd. for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 70.21; H, 6.05; N, 23.81.

2.12. 1-{[5-Methyl-2-(trichloromethyl)-1H-1,3-benzimidazole-1-yl]methyl}-1H-1,2,3-benzotriazole (5c)

Cream crystals, yield 60%, m.p. 268 °C, ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.47 (s, 3H, CH_3), 7.08 (s, 2H, CH_2), 7.41–8.06 ppm (m, 7H, aromatic). IR (KBr) $\bar{\nu}$: 3019 (C-$H_{aromatic}$), 2793–2910 (C-$H_{aliphatic}$), 1670 (C=C, C=N), 1485, 810, 707 cm^{-1}. Anal. calcd. for $C_{16}H_{12}Cl_3N_5$: C, 50.48; H, 3.18; N, 18.39. Found: C, 50.17; H, 3.26; N, 18.69.

2.13. 1-{[5-Methyl-2-(2-pyridyl)-1H-1,3-benzimidazole-1-yl]methyl}-1H-1,2,3-benzotriazole (5d)

Grey crystals, yield 65%, m.p. 245 °C, ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.50 (s, 3H, CH_3), 7.15 (s, 2H, CH_2), 7.40–8.03 ppm (m, 11H, aromatic). IR (KBr) $\bar{\nu}$: 3030 (C-$H_{aromatic}$), 2849–2974 (C-$H_{aliphatic}$), 1646, 1690 (C=C, C=N), 1458, 806, 785 cm^{-1}. Anal. calcd. for $C_{20}H_{16}N_6$: C, 70.57; H, 4.74; N, 24.69. Found: C, 70.32; H, 4.98; N, 24.41.

2.14. 1-{[5-Methyl-2-(3-pyridyl)-1H-1,3-benzimidazole-1-yl]methyl}-1H-1,2,3-benzotriazole (5e)

Brown crystals, yield 65%, m.p. 255 °C, ^{1}H NMR (DMSO-d_6, 300 MHz), δ: 1.65 (s, 3H, CH_3), 7.05 (s, 2H, CH_2), 7.35, 9.33 ppm (m, 11H, aromatic). IR (KBr) $\bar{\nu}$: 3095 (C-$H_{aromatic}$), 2995 (C-$H_{aliphtic}$), 1665, 1689 (C=C, C=N), 1470, 623 cm^{-1}. Anal. calcd. for $C_{20}H_{16}N_6$: C, 70.57; H, 4.74; N, 24.69. Found: C, 70.65; H, 4.89; N, 24.91.

2.15. 1-({5-Methyl-2-[4-(5-methyl-1H-1,3-benzimidazole-2-yl)butyl]-1H-1,3-benzimidazole-1-yl}methyl)-1H-1,2,3-benzotriazole (5f)

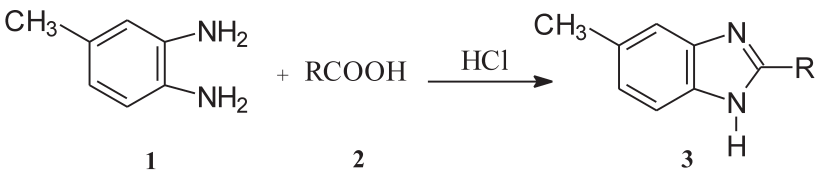
Red crystals, yield 60%, m.p. 280 °C, ^{1}H NMR (DMSO-d_6, 300 MHz), δ: 1.17–1.23 (m, 2H, CH_2), 1.80–1.88 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.72–2.82 (m, 2H, CH_2), 3.01–3.16 (m, 2H, CH_2), 6.91 (s, 2H, CH_2), 6.99–8.07 (m, 10H, aromatic), 12.05 ppm (bs, 1H, NH). IR (KBr) $\bar{\nu}$: 3150 (N-H), 2910, 2939 (C-$H_{aliphatic}$), 1618, 1690 (C=C, C=N), 1454, 1409, 742 cm^{-1}. Anal. calcd. for $C_{27}H_{27}N_7$: C, 72.14; H, 6.05; N, 21.81. Found: C, 72.41; H, 5.90; N, 21.63.

3. Results and Discussion

Benzimidazoles **(3a–h)** were prepared via an acid-catalyzed cyclization of 4-methyl-1,2-phenylenediamine **1** with the appropriate carboxylic acid **2** under reflux conditions (Scheme 1). The nucleophilic addition of benzimidazoles to 1-chloromethylbenzotriazole (**4**) in the presence of a strong base, $NaNH_2$, under reflux conditions afforded the novel benzimidazole-substituted benzotriazoles **(5a–f)**.

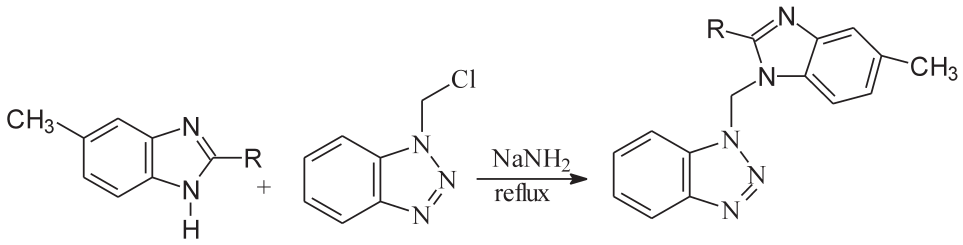
The ^{1}H NMR spectra of the synthesized compounds support the structures and the expected reactions. The ^{1}H NMR spectra of benzimidazoles **(3a–h)** exhibit the typical NH proton resonance as a broad singlet at δ 12.02–13.33 ppm. The chemical shifts of the aromatic protons appear at δ 6.67–9.32 ppm. The absorption peak for the characteristic methylene group between the benzimidazole and the benzotriazole ring for **(5a–f)** appears as a singlet in the δ 6.87–7.15 ppm region. The absence of the NH proton absorption around δ 6.67–9.32 ppm in the ^{1}H NMR spectra for the benzotriazoles in **(5a–f)** confirms the nucleophilic addition of benzimidazoles to 1-chloromethylbenzotriazole. However the ^{1}H NMR spectrum of **(5f)** shows a NH signal at δ 12.05 ppm, which means that one of the two NH groups of the corresponding side chain benzimidazoles of **(3f)** reacts with N-chloromethylbenzotriazole.

In conclusion, an easy procedure was developed for the preparation of bulky benzotriazoles from substituted benzimidazoles.



1 2 3

3a) R = methyl
3b) R = ethyl
3c) R = trichloromethyl
3d) R = 2-piridyl
3e) R = 3-pyridyl
3f) R = 4-(5-methyl-1H-1,3-benzimidazole-2-yl)butyl
3g) R = 2-(methyl-1H-1,3-benzimidazole-2-yl)ethyl
3h) R = 4-pyridyl



3 4 5

5a) R = methyl
5b) R = ethyl
5c) R = trichloromethyl
5d) R = 2-pyridyl
5e) R = 3-pyridyl
5f) R = 4-(5-methyl-1H-1,3-benzimidazole-2-yl)butyl

Scheme 1

The work-up procedures are very simple and the products are easily purified through recrystallization.

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