SHORT PAPER

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Behaviour of 2,3-dihydro-1H-benzo[d]imidazole-2-thione towards amines under Mannich-type condition†

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2,3-Dihydro-1H-benzo[d]imidazole-2-thione (**1**) was subjected to a Mannich reaction with either dimethylamine, urotropine, morpholine, thiomorpholine, (±) 3,3,5 trimethylhexahydroazepine, piperazine or *p*-bromoaniline and formalin in different molar ratios to afford the Mannich bases. The reactivity of the Mannich base **5a** towards indole was also investigated. In addition the condensation of hydroxymethyl derivative **10** with morpholine, benzimidazole, *p*-bromoaniline, tryptamine and aminiothiazole was achieved.

Thiol functionalized heterocyclic compounds frequently display bacteriostatic and antibilharizial activity.[1,2] Accordingly, considerable attention has been focused on the synthesis of benzimidazole-2-thione derivatives, in particular those having a basic side chain.

In as much as the incorporation of Mannich bases into heterocyclic moieties is known to improve their pharmacological properties,[3–6] it seemed interesting to prepare the Mannich bases of 2,3-dihydro-1H-benzo[d]imidazole-2-thione (**1**), and to investigate their synthetic potentialities.

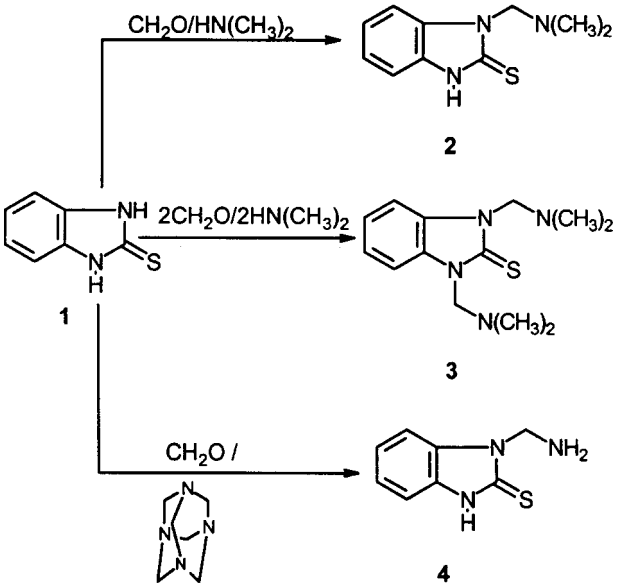
Thus, in continuation of our studies[7,8] on Mannich reaction, treatment of 2,3-dihydro-1H-benzo[d]imidazole-2-thione (**1**) with dimethylamine and formalin in ethyl acetate in a molar ratio of (1:1:1) gave the Mannich base **2**. The ^{1}H-NMR of **2** showed signals at δ 5(s, 2H, NC$\underline{H}_2$N) and 2.3 ppm (s, 6H, N(C$\underline{H}_3$)$_2$). On the other hand, treatment of **1** with formalin and dimethylamine in molar ratio of (1:2:2) afforded the bis-base **3**.

The primary base, 1-aminomethyl-2,3-dihydro-1H-benzo[d]imidazole-2-thione (**4**) was prepared through the reaction of **1** with formalin and urotropine in acidic medium. However, compound **4** cannot be obtained if ammonia is used in lieu of urotropine. Formation of **4** is in line with the reported Mannich type reaction using aminals.[9]

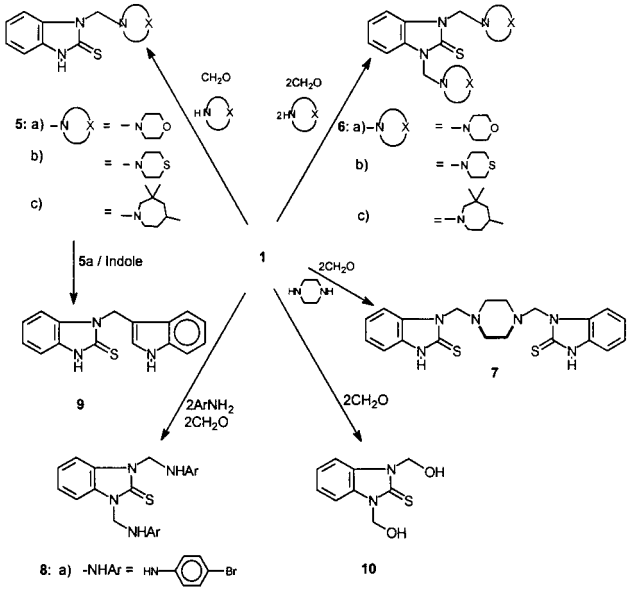
In addition, compound **1** was subjected to a Mannich reaction with morpholine, thiomorpholine or (±) 3,3,5-trimethylhexahydroazepine and formalin in a molar ratio of (1:1:1) to afford mono-Mannich bases of 2,3-dihydro-1H-benzo[d] imidazole-2-thiones (**5a-c**). On the other hand, the same reactants in a molar ratio of (1:2:2) gave the 1,3-bis Mannich bases of 2,3-dihydro-1H-benzo[d]imidazole-2-thiones (**6a-c**). On using piperazine in such a reaction, N,N′-bis(2,3-dihydro-1H-benzo[d]imidazole-2-thione)piperazine (**7**) was obtained. Treatment of **1** with primary amines such as *p*-bromoaniline and formalin in a molar ratio of (1:2:2) gave the secondary bis-base **8a**, (c.f. Scheme 2).

In addition, based on the evidence that enamines have been C-alkylated by Mannich bases,[10,11] (compound **5a** was treated with indole as a route to synthesize 2,3-dihydro-1H-benzo[d]imidazole-2-thione having a skatyl residue **9**.

In an extension to the present work, compound 1 was treated with formalin in ethanol to give the 1,3-dihydroxymethyl derivative **10** in high yield. On heating the 1,3-dihydroxymethyl derivative **10** with morpholine or benzo[d]imidazole in alcoholic solution compounds **6a** and **d** were obtained. It has been reported that benzimidazoles exhibit biological activity as inhibitor for the growth of certain yeasts and bacteria.[12]



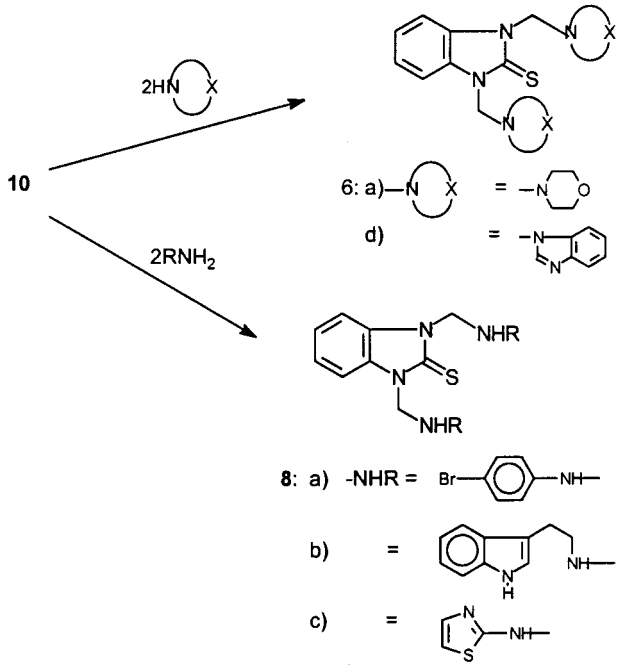
Scheme 1



Scheme 2

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 3

In addition, compound **10** was proved to be an important precursor for the synthesis of the secondary bis-base **8a-c** through its treatment with *p*-bromoaniline, tryptamine or 2-aminothiazole respectively (c.f. Scheme 3). This is in line with the reported[13] aminomethylation of thiourea either directly or by condensation of its N-hydroxymethyl derivative with alkylamines.

Experimental

Melting points (uncorrected) were taken in an open capillary tubes by the use of Gallenkamp electric melting point apparatus. Infraared spectra were recorded on Mattson 5000 FTIR spectrometer (England) using KBr wafer technique. ^{1}H-NMR spectra were obtained in DMSO=d_6 on Varian-Gemini 200 MHz. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane. Mass spectra were determined on GC-MSHP Model 5988 (German/USA), (±) 3,3,5-trimethylhexahydroazepine from Aldrich Chemical Company Inc. Milwaukee WIS 53233 (U.S.A.).

1-(Dimethylaminomethyl)-2,3-dihydro-1H-benzo[d]imidazole-2-thione (**2**): A solution of 2,3-dihydro-1H-benzo[d]imidazole-2-thione (**1**) (0.01 mol), formalin (40%; 0.01 mol) and dimethylamine (0.01 mol) in ethyl acetate (40 ml) was heated for 0.5 h on a steam bath. The reaction mixture was left to stand for two weeks at room temperature, then evaporated under vacuum. The product that separated on cooling was filtered off and recrystallized from ethylacetate to give the Mannich base **2** (54%); mp 235°C; IR: 3145 (NH), 2910 (CH_2str.), 1454 (C-N str.), 1347 (tert. amine) and 1189 cm^{-1} (CS); ^{1}H NMR (DMSO-d_6): δ 2.3 (s, 6H, N(C<u>H</u>$_3$)$_2$), 5.0 (s, 2H, N-C<u>H</u>$_2$-N), 7.1 (t, 2H, aromatic H-5,6), 7.2 (d, 2H, aromatic at H-4,7) and 12.5 ppm (s, 1H, NH); MS (*m/z*, %): 207 (M$^+$, 3.36), 150 (base peak, 100); Anal. Calcd. for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.32; N, 20.27. Found: C, 57.77; H, 6.25; N, 20.21%.

1,3-Di[(dimethylamino)methyl-2,3-dihydro-1H-benzo[d]imidazole-2-thione (**3**): A solution of **1** (0.01 mol), formalin (40%, 0.02 mol) and dimethylamine (0.02 mol) in ethyl acetate (40 ml) was subjected to react as the above method described for the preparation of compound **2**, whereby the semi solid obtained was treated with ether. The solid product that formed was crystallized from ethylacetate/ether to give **3**[6b] as white powder (51%) mp 80°C [lit. 80°C]. IR: 2880 (CH_2 str.), 1454 (CN str.), 1347 cm^{-1} (tert N); ^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 12H, 2(C<u>H</u>$_3$)$_2$N), 5.02 (s, 4H, N-C<u>H</u>$_2$N), 7.2 (t, 2H aromatic at H-5,6) and 7.4 ppm (d, 2H, aromatic at H-4,7); MS (*m/z*, %): 264 (M$^+$, 1.73), 150 (benzo[d]imidazole-2-thione, 8.85) and 58 (base peak, 100).

1-Aminomethyl-2,3-dihydro-1H-benzo[d]imidazole-2-thione (**4**): A solution of **1** (0.01 mol) in ethyl acetate (30 ml) was added to a mixture of powdered hexamethylenetetraamine (0.01 mol), ethyl acetate (20 ml) in one portion while stirring. The reaction mixture was heated at 50°C for 8 h, left at room temperature for 48 h, then filtered. The filter cake was stirred with ethanol (40 ml) then concentrated hydrochloric acid (2 ml) was added. The resulting suspension was stirred at room temperature for 4 h. The crystalline product, which consists of the amine hydrochloride and ammonium chloride, was stirred with water (10 ml) then filtered. The product was dried and then purified by boiling several times with ethanol to give pure analytical sample of **4** as white powder (56%); mp 257°C; IR: 3371 (NH_2), 3172 (NH), 1615 (NH, bend.), 1333 (tert. amine) and 1156 cm^{-1} (CS); Anal. Calcd. for $C_8H_9N_3S$: C, 53.61; H, 5.06; N, 23.44. Found: C, 53.58; H, 5.0; N 23.38%, MS (*m/z, %*), 179 (M$^+$, 4), 150 (base peak, 100).

*1-(Morpholinomethyl)-2,3-dihydro-1H-benzo[d]imidazole-2-thione (***5a***), 1-(Thiomorpholinomethyl)-2,3-dihydro-1H-benzo[d]imidazole-2-thione (***5b***), 1-((±) 3,3,5-Trimethylhexahydroazepine)-2,3-dihydro-1H-benzo[d]imidazole-2-thione (***5c***) and N,N′-bis(2,3-dihydro-1H-benzo[d]imidazole-1-methyl-2-thione)piperazine* (**7**): A solution of **1** (0.01 mol), formalin (40%; 0.01 mol) and morpholine, thiomorpholine, (±) 3,3,5-trimethylhexahydroazepine (0.01 mol) or piperazine (0.005 mol) in ethyl acetate (40 ml) was heated for 0.5 h on a steam bath. The reaction mixture was left for 2 weeks at room temperature, then evaporated under vacuum. The solid obtained after cooling, was filtered off and recrystallized from dilute ethanol to give **5a–c** and **7** respectively. IR **5a–c** and **7**: 3145 (NH), 2910 (CH_2 str.), 1532-1480 (C-N str.), 1357-1330 (tert. amine) and 1189 cm^{-1} (CS).

Compound **5a**: (80%); mp 205°C; ^{1}H-NMR (DMSO-d_6): δ 2.67 (t, 4H, C<u>H</u>$_2$NC<u>H</u>$_2$), 3.54 (t, 4H, C<u>H</u>$_2$OC<u>H</u>$_2$), 5.1 (dd, 2H, NC<u>H</u>$_2$N), 7.1 (t, 2H, aromatic at H-5,6) and 7.2 ppm (d, 2H, aromatic at H-4,7); Anal. Calcd. for $C_{12}H_{15}N_3OS$: C, 57.80; H, 6.06; N, 16.85. Found: C, 57.75; H, 5.97; N, 16.73%.

Compound **5b**: (88%); mp 180°C; Anal. Calcd. for $C_{12}H_{15}N_3S_2$: C, 54.31; H, 5.70; H, 15.83. Found: C, 54.29; N, 5.65; N, 15.76%.

Compound **5c**: (63%); mp 110°C; Anal. Calcd. for $C_{17}H_{25}N_3S$: C, 67.28; H, 8.31; N, 13.85. Found: C, 67.19; H, 8.24; N, 13.75%.

Compound **7**: (44%); mp 246°C. Anal. Calcd. for $C_{20}H_{22}N_6S_2$: C, 58.51; H, 5.40; N, 20.47. Found: C, 55.36; H, 5.33; N, 20.36%.

1,3-Di(substituted aminomethyl)-2,3-dihydro-1H-benzo[d]imidazole-2-thione **6a–c** and **8a**: These compounds were obtained using the same method as described above, but using a mixture of **1** (0.01 mol), formalin (40%, 0.02 mol) and morpholine, thiomorpholine, (±)-3,3,5-trimethylhexahydroazepine or p-bromoaniline (0.02 mol) in ethyl acetate (40 ml). The product was crystallized from dil.ethanol to give **6a–c** or from pet. ether to give **8a** respectively. IR **6a–c**: 2849–2816 (CH_2 str.), 1452–1445 (CN str.), 1340–1345 (tert N) and 1187–1179 cm^{-1} (CS).

Compound **6a**: (62%); mp 135°C [lit. 213-14°C]; ^{1}H-NMR(DMSO-d_6): δ 2.67 (t, 8H, 2C<u>H</u>$_2$NC<u>H</u>$_2$), 3.54 (t, 8H, 2C<u>H</u>$_2$-O-C<u>H</u>$_2$), 5.1 (dd, 4H, 2NC<u>H</u>$_2$N), 7.1 (t, 2H aromatic at H-5,6), and 7.2 ppm (d, 2H aromatic at H-4,7); MS (*m/z*, %) 348 (M$^+$, 0.08), 150 (14.42) and 100 (base peak, 100); Anal. Calcd. for $C_{17}H_{24}N_4O_2S$: C, 58.59; H, 6.94; N, 16.08. Found: C, 58.45; H, 6.87; N, 16.00%.

Compound **6b**: (74%); mp 150°C; Anal. Calcd. for $C_{17}H_{24}N_4S_3$: C, 53.65; H, 6.36; N, 14.72. Found: C, 53.53; H, 6.19; N, 14.61%.

Compound **6c**: (29%); mp 224°C; Anal. Calcd for $C_{27}H_{44}N_4S$: C, 70.99; H, 9.71; N, 12.27. Found: C, 70.85; H, 9.68; N, 12.13%.

Compound **8a**: (14%); mp 200°C; IR: 3319 (NH), 2856 (CH_2 str.), 1490 (aromatic), 1449 (CN str.), 1340 (tert N) and 1175 (CS) and 747 cm^{-1} (CBr); MS (*m/z*, %): 517 (M$^+$-1, 0.1), 171 (base peak, 100) and 150 (benzo[d]imidazole-2-thione, 43.31). Anal. Calcd for $C_{21}H_{18}N_4SBr_2$: C, 48.66; H, 3.5; N, 10.81. Found: C, 48.49; H, 3.39; N, 10.68%.

1,3-Di(hydroxymethyl)-2,3-dihydro-1H-benzo[d]imidazole-2-thione (**10**): A solution of (**1**) (0.01 mol), formalin (40%, 0.4 mol), in ethanol was heated for 30 min on a steam bath. It was kept overnight at room temperature, then diluted with water (60 ml). The precipitated product was filtered off and recrystallized from ethanol to give **10**[6b] as white powder (92%); mp 160°C [lit.[6b] mp 160–2°C]; IR: 3452 (OH), 2953 (CH_2 str.), 1465 (CN str.), 1346 (tert. amine) and 1142 cm^{-1} (CS); ^{1}H-NMR (DMSO-d_6): δ 5.8 (dd, 4H, 2CH_2O), 7.2 (t, 2H, aromatic at H-5,6), 7.4 (d, 2H, aromatic at H-4,7), 12.5 (s, 1H, OH) and 12.78 ppm (s, 1H, OH); MS: (*m/z*, %) 210 (M$^+$, 0.53), 209 (M$^+$-1, 0.37), 208 (M-2, 0.56), 180 (M-CH_2O, 5.12) and 150 (base peak, 100); Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.33. Found: C, 51.34; H, 4.68; N, 13.23%.

Reaction of **10** *with amines: formation of* ***6a*** *and* **d** *and* **8a–c**: A mixture of **10** (0.01 mol) and the appropriate amine (0.02 mol) in ethanol (40 ml) was heated for 4 h on a steam bath. The reaction

mixture was left overnight at room temperature, then evaporated under vacuum. The products obtained were recrystallized from the appropriate solvent to give **6a** and **d** and **8a–c**.

Compound **6a**: (63%; ethanol); mp 135°C.

Compound **6d**: (85%, pet. ether/ether); mp 270°C; IR: 2910 (CH_2 str.), 1615 (C=C, C=N), 1350 (tert. amine) and 1228 cm^{-1} (CS); MS (*m/z*, %): 410 (M^+, 0.26), 313 (M^+-imidazolylmethyl, 0.39), 150 (start, 9.8) and 118 (base peak, 100). Anal. Calcd. for $C_{22}H_{18}N_6S$: C, 67.29; H, 4.42; N, 20.48. Found C, 67.18; H, 4.38; N, 20.34%.

Compound **8a**: (50%, pet. ether); mp 200°C; IR for **9**a-c: 3435–3287 (NH), 2939–2878 (CH_2 str.), 1637 (C=C), 1605 (aromatic), 1314 (tert. amine) and 1171 cm^{-1} (CS).

Compound **8b**: (97%, pet. ether/ether); mp 245°C; ^{1}H-NMR ($DMSO_4$, d_6): 2.8 (t, 4H, two, $CHC\underline{H}_2$-indole) 4.3 (s, 2H, two CH_2-$NHC\underline{H}_2$), 4.8-5.2 (complex m, 8H, two N-$C\underline{H}_2$ and two N-CH_2-N), 6.9 (s, 2H, h-2 of indole) and 7-7.4 (m, 14H, aromatic); MS (*m/z*, %) 494 (M^+, 0.04), 150 (benzimidazole-2-thione, 0.14) and 143 (base peak, 100). Anal. Calcd for $C_{29}H_{30}N_6S$: C, 70.41; H, 6.11; N, 16.99. Found: C, 70.28; H, 6.03; N, 16.87%.

Compound **8c**: (42%, pet. ether/ether); mp 235°C (decomp.); Anal. Calcd for $C_{15}H_{14}N_6S_3$: C, 48.10; H, 3.77; N, 22.44. Found C, 48.03; H, 3.74; N, 22.41%.

1-(3′-Indolymethyl)-2,3-dihydro-1H-benzo[d]imidazole-2-thione (**9**): A mixture of 1-morpholinomethyl-2,3-dihydro-1H-benzo[d]imidazole-2-thione (**5a**)[6a] (0.01 mol) and indole (0.01 mol) in xylene was refluxed for 2 h, then left overnight and the precipitate formed was filtered off. The precipitate was dissolved in cold ethanol, then filtered. The filtrate was evaporated at room temperature to give **9**. The residue was dissolved in hot ethanol and left to cool whereby the crystal that separated was filtered off to give the starting benzimidazole-2-thione (**1**).

Compound **9**: (20%); mp 265°C; IR: 3435 (NH indole), 3155 (NH), 2878 (CH_2 str.), 1512 (C=C), 1464 (Cn str.), 1356 (tert. amine) and 1177 cm^{-1} (CS); MS (*m/z*, %): 279 (M^+, 0.76), 150 (base peak, 100), 117 (indole, 1.54); Anal. Calcd. for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N, 15.04; Found C, 68.65; H, 4.58; N, 15.0%.

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