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Synthesis and structure of benzimidazo[1,2-*c*][1,2,3]thiadiazoles: first examples of a novel ring system

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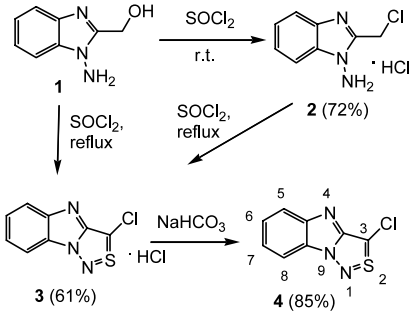
Abstract—(1-Amino-1*H*-benzimidazol-2-yl)methanol **1** with thionyl chloride at reflux afforded 3-chlorobenzimidazo[1,2-*c*][1,2,3]thiadiazole **4**, which reacted with various nucleophiles to give different products depending on the nature of the solvent. The structures of **4** and di(benzimidazo[1,2-*c*][1,2,3]thiadiazol-3-yl)sulfide **8** were confirmed by single-crystal X-ray analysis.

Various benzimidazole derivatives are of interest for pharmaceutical use[1] as well as useful intermediates in the synthesis of fused heterocyclic systems.[1d,2] In the course of our research work aimed toward the synthesis of benzimidazole derivatives with potential pharmaceutical activity we report herein our findings on the reaction of (1-amino-1*H*-benzimidazol-2-yl)methanol[3] **1** with thionyl chloride and subsequent reactions of the product obtained with various nucleophiles.

Compound **1** reacted with thionyl chloride at room temperature to give product **2** in good yield.[4] Surprisingly, reaction of **1** with thionyl chloride at reflux led to formation of 3-chlorobenzimidazo[1,2-*c*][1,2,3]thiadiazolium chloride **3**.[5] Compound **3** was also formed when **2** was refluxed with an excess of thionyl chloride. Evidently, the formation of 3-chlorobenzimidazo[1,2-*c*][1,2,3]thiadiazolium chloride **3** occurs through the initial chlorination reaction of the hydroxymethyl group of **1**. Treatment of the salt **3** with sodium hydrogen carbonate gave thiadiazole **4**[6] (Scheme 1). To the best of our knowledge, the obtained benzimidazo[1,2-*c*][1,2,3]thiadiazole represents a previously unreported tricyclic ring system as well as the first example of a 'c' fused 1,2,3-thiadiazole.

The transformation of **2** into **3** can be explained using as a mechanistic model, the Hurd–Mori reaction,[7] which usually leads to 1,2,3-thiadiazoles when *N*-acyl- or *N*-tosylhydrazones bearing an adjacent α-methyl or α-methylene group are treated with thionyl chloride.[7–9] Thus, the first step is probably cyclisation of **2** with thionyl chloride to the thiadiazole *S*-oxide **5** (Scheme 2). Then a Pummerer-like rearrangement initiated by the attack of thionyl chloride on the O atom of the S=O group followed by subsequent elimination of hydrogen chloride leads to the thiadiazolium chloride **3**, which upon treatment with sodium hydrogen carbonate affords thiadiazole **4**.

Structure **4** was confirmed by X-ray crystallography[10] (Fig. 1) and is compatible with the ^{1}H and ^{13}C NMR spectra. Signals in the ^{13}C NMR spectra of compounds **3** and **4** were assigned by comparison of experimental chemical shifts with those calculated using the VAMP[11] program using geometries of **3**,**4** optimised with the semiempirical PM3 method.[12] It should be noted that the numbering system used for the ORTEP figure is different from that in Scheme 1. Inspection of the bond



Scheme 1.

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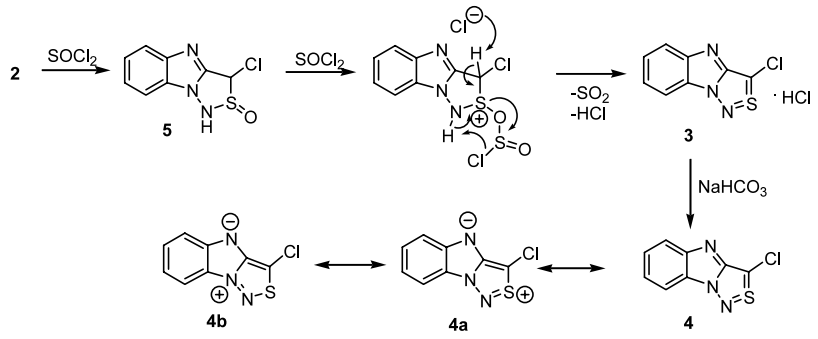


Scheme 2.

lengths shown in Figure 1, reveals that this ring system should not be represented by a single resonance contributor, and that there are important contributions from resonance structures **4**–**4a**,**b**.

1,2,3-Thiadiazoles are attractive because of their use in medicinal chemistry for the treatment of thromboses,[13a] as antibacterials[13b,c,d] or platelet-activating factors[13e] or in agricultural chemistry as plant activators or inducers of systemic acquired resistance (SAR) in plants.[13f,g] 1,2,3-Thiadiazoles are also valuable as synthetic intermediates for substituted acetylenes,[14a,b,c] thioamides,[14d] 5-aryloxy(thio)-1,2,3-thiadiazoles[8e] or other heterocyclic systems.[9] Therefore, it was of interest to study the interactions of **4** with various nucleophiles.

We have found that the products from chlorine substitution can be obtained using aprotic solvents such as DMF and toluene. The latter was found to be an even better solvent for the synthesis of the desired 3-substituted products (Scheme 3). Thus, the substitution reaction with 2-mercaptobenzimidazole in DMF proceeded at room temperature to give 3-(benzimidazol-2-yl)thiobenzimidazo[1,2-*c*][1,2,3]thiadiazole **6a**.[15] Reaction of **4** with aniline in toluene occurred to give **6b** when the reaction mixture was refluxed for 10 h.[16] The analogous reaction with potassium *tert*-butoxide gave the corresponding 3-*tert*-butoxy derivative **6c** after stirring of the reaction mixture at room temperature for 1 h.[17] However, performing reactions of **4** with the same reagents in methanol gave unexpected results. The reaction with potassium *tert*-butoxide in *tert*-butanol afforded 3-thioxoderivative **7**.[18] Reactions of **4** with sodium hydrogen sulfide or sodium sulfide in methanol led to formation of sulfide **8**. Compound **8** was also formed when **4** reacted with various *N*-nucleophiles in alcohols with the exception of sodium azide, which caused the formation of **8** in DMSO.[19] Only the reaction with morpholine in methanol afforded the substitution product **9**.[20] The structure of **8** as a solvate with chloroform was unambiguously established by X-ray crystallography[21] (Fig. 2). Although a more detailed investigation on the formation of sulfides **7** and **8** is currently underway, it can be concluded that molecule **4** is a source of sulfur in these reactions.

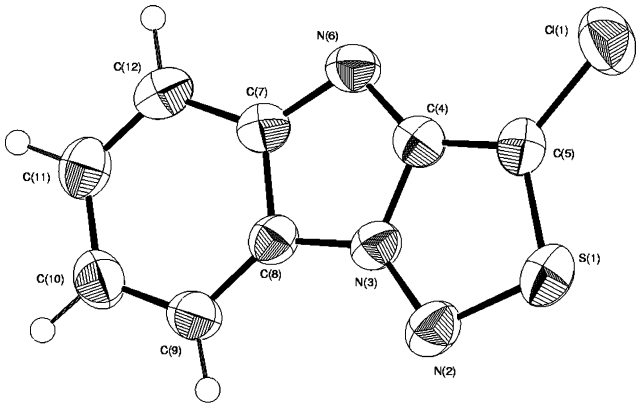
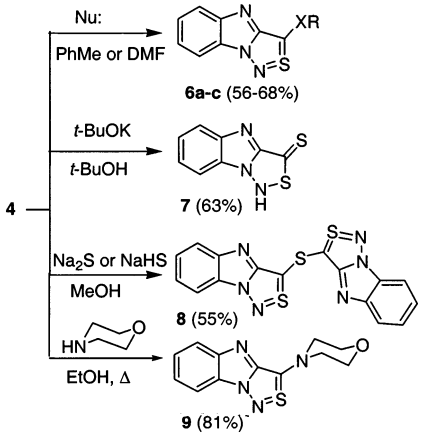


Figure 1. ORTEP drawing of compound **4**. Selected bond distances (Å): N(2)–S(1) 1.636(3); N(2)–N(3) 1.349(4); S(1)–C(5) 1.685(4); C(5)–C(4) 1.388(5); C(5)–Cl(1) 1.693(4); N(3)–C(4) 1.391(5); N(3)–C(8) 1.386(4); N(6)–C(4) 1.326(5); N(6)–C(7) 1.374(5); C(7)–C(8) 1.414(5).



Scheme 3.

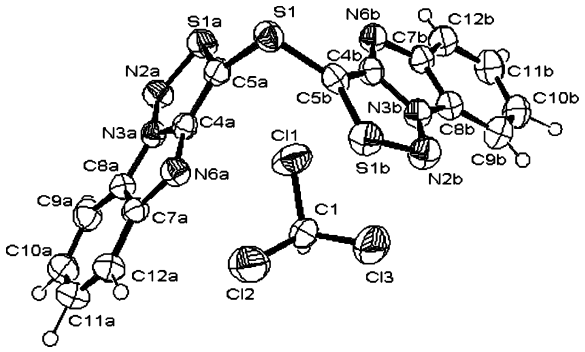


Figure 2. ORTEP drawing of compound **8**.

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4. Procedure and physico-chemical data for compound **2**. Compound **1** (2 g, 1.18 mmol) was dissolved in thionyl chloride (20 ml) and kept at room temperature for 0.5 h. The excess thionyl chloride was removed in vacuo without heating. The residue was triturated with ethanol, the precipitate was filtered off, washed with toluene and recrystallised to give 1.9 g (72%) of **2**, mp 107–109°C (from EtOH). IR (Nujol) ν_{max}/cm^{-1} 3251, 3114 (NH_2); δ_H (DMSO-d_6): 5.29 (2H, br. s, CH_2), 5.83 (2H, br. s, NH_2), 7.41–7.65 and 7.79–7.98 (4H, m, aromatic prot.) (Found: C, 44.4; H, 4.2; N, 19.5. $C_8H_9Cl_2N_3$ requires: C, 44.1; H, 4.2; N, 19.3%).
5. Procedure and physico-chemical data for compound **3**. A mixture of **1** (1.63 g, 10 mmol) or **2** (0.3 g, 1.8 mmol) and thionyl chloride (10 ml) was refluxed for 0.5 h and evaporated to dryness in vacuo. The residue was triturated with toluene, the precipitate was filtered off and recrystallised to give 1.05 g (50% from **1**) or 0.28 g (61% from **2**) of **3**, mp 236–239°C (from EtOH). δ_H (DMSO-D_6): 7.56 (1H, t, $J=5.5$ Hz, 6-H), 7.80 (1H, t, $J=5.5$ Hz, 7-H), 7.92 (1H, d, $J=5.5$ Hz, 5-H) 8.39 (1H, d, $J=5.5$ Hz, 8-H); δ_C (DMSO-D_6, D_2O): 115.20 (C-8 or C-5), 116.74 (C-5 or C-8), 125.20 (C-7), 127.50 (C-4a or C-8a), 129.30 (C-8a or C-4a), 132.60 (C-6), 142.10 (C-3), 147.7 (C-3a); MS (EI, 70 eV) m/z (%) 211 (17), 209 (M^+–HCl, 50), 146 (80), 81 (33), 79 (100). (Found: C, 39.3; H, 1.7; N, 17.4. $C_8H_5Cl_2N_3S$ requires C, 39.0; H, 2.05; N 17.1%).
6. Procedure and physico-chemical data for compound **4**. To a solution of **3** (1 g, 4 mmol) in water (40 ml) $NaHCO_3$ was added to pH >7. The precipitate was filtered off, washed with water and recrystallised to give 0.71 g (85%) of **4**, mp 132–133°C (from octane). δ_H (DMSO-d_6): 7.46 (1H, t, $J=5.5$ Hz, 6-H), 7.67 (1H, t, $J=5.5$ Hz, 7-H), 7.96 (1H, d, $J=5.5$ Hz, 5-H), 8.26 (1H, d, $J=5.5$ Hz, 8-H); δ_C (DMSO-d_6, D_2O): 113.51 (C-8), 121.20 (C-5 or C-7), 121.98 (C-7 or C-5), 125.59 (C-6), 129.27 (C-3), 155.07 (C-4a or C-8a), 157.33 (C-8a or C-4a), 160.82 (C-3a). (Found: C, 45.5; H, 2.1; N, 20.25. $C_8H_4N_3ClS$ requires C, 45.8; H, 1.9; N, 20.0%).
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10. Crystal data for compound **4**. $C_8H_4ClN_3S$, M_w 209.66, monoclinic, space group $P2_1/c$; $Z=4$, $a=7.3028(3)$, $b=9.9528(5)$, $c=11.4938(8)$ Å, $\alpha=90.0$, $\beta=94.440(2)$, $\gamma=90.0°$; $V=832.90(8)$ Å^3, $F(000)=400$; $D_x=1.576$ g/cm^3; $2\theta_{max}=55°$ (CCD area detector, Mo Kα radiation), $R=0.050$ (1134 data with $I>3\sigma I$). Crystallographic data for structure **4** have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 209359).
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15. Procedure and physico-chemical data for compound **6a**. To a mixture of **4** (0.3 g, 1.43 mmol) and 2-mercaptobenzimidazole (0.25 g, 1.67 mmol) in DMF (5 ml), triethylamine (0.17 g, 1.68 mmol) was added. The reaction mixture was stirred at room temperature for 7 days. The precipitate was filtered off and recrystallised to give 0.3 g (65%) of **6a**, mp 239–240°C (from DMSO). IR (Nujol) ν_{max}/cm^{-1} 3260 (NH); δ_H (DMSO-d_6): 3.25 (1H, br s, NH), 7.21–7.92 (7H, m, aromat. prot.), 8.20 (1H, d, $J=5.5$ Hz, 8-H); (Found: C, 55.6; H, 3.0; N, 21.4. $C_{15}H_9N_5S_2$ requires C, 55.7; H, 2.8; N, 21.7%).

16. Procedure and physico-chemical data for compound **6b**. A mixture of **4** (0.1 g, 0.47 mmol), aniline (0.09 g, 0.94 mmol) and anhydrous toluene (20 ml) was refluxed for 10 h. Then toluene was evaporated under reduced pressure, the residue was triturated with 2-propanol, the precipitate was filtered off and recrystallised to give 0.07 g (56%) of **6b**, mp 168–170°C (from chloroform). IR (Nujol) ν_{max}/cm^{-1} 3254 (NH); δ_H (DMSO-d_6): 7.2–8.2 (8H, m, aromat. prot.), 8.20 (1H, d, $J=5.5$ Hz, 8-H); 12.25 (1H, br s, NH). (Found: C, 63.25; H, 3.6; N, 21.2. $C_{14}H_{10}N_4S$ requires C, 63.1; H, 3.8; N, 21.0%).
17. Procedure and physico-chemical data for compound **6c**. Compound **6c** was obtained at room temperature according to the procedure described for **6b**, from **4** (0.2 g, 0.95 mmol) and KO*t*-Bu (0.32 g, 2.85 mmol). The reaction time was 1 h. Yield 0.16 g (68%), mp 43°C (from ethanol). δ_H (DMSO-d_6): 1.63 (9H, s, Me), 7.25 (1H, t, $J=5.5$ Hz, 6-H), 7.5 (1H, t, $J=5.5$ Hz, 7-H), 7.8 (1H, d, $J=5.5$ Hz, 5-H), 8.2 (1H, d, $J=5.5$ Hz, 8-H), (Found: C, 58.6; H, 5.45; N, 16.8. $C_{12}H_{13}N_3OS$ requires C, 58.3; H, 5.3; N, 17.0%).
18. Procedure and physico-chemical data for compound **7**. To a solution of **4** (0.05 g, 0.24 mmol) in *t*-BuOH (10 ml), KO*t*-Bu (0.08 g, 0.72 mmol) was added portionwise. The reaction mixture was stirred at 40°C for 1 h, then filtered and the filtrate was evaporated under reduced pressure. The precipitate was dissolved in water and acidified with acetic acid to pH 5. The precipitate was filtered off and recrystallised to give 0.01 g (63%) of **7**, mp 172–173°C (from DMSO). IR (Nujol) ν_{max}/cm^{-1} 3115 (NH), 1193 (C=S); δ_H (DMSO-d_6): 7.2–7.8 (3H, m, aromat. prot.), 8.2 (1H, d, $J=5.5$ Hz, 8-H); 13.47 (1H, br s, NH). MS (EI, 70 eV) m/z (%) 207 (M^+, 75). (Found: C, 46.6; H, 2.2, N, 20.1 $C_8H_5N_3S_2$ requires C, 46.4; H, 2.4; N, 20.3%).
19. Procedure and physico-chemical data for compound **8**. To a solution of sodium hydrogen sulfide (0.1 g 1.9 mmol) in ethanol (10 ml) was added compound **4** (0.2 g, 0.95 mmol) portionwise. The reaction mixture was stirred at room temperature for 4 h. The precipitate was filtered off and recrystallised to give 0.10 g (55%) of **8**, mp 188–190°C (from chloroform). δ_H (DMSO-d_6): 7.31 (2H, t, $J=5.5$ Hz, 6- and 6′-H), 7.68 (2H, t, $J=5.5$ Hz, 7- and 7′-H), 7.78 (2H, d, $J=5.5$ Hz, 5- and 5′-H), 8.17 (2H, d, $J=5.5$ Hz, 8- and 8′-H). (Found: C, 50.2; H, 2.3; N, 21.8. $C_{16}H_8N_6S_3$ requires C, 50.5; H, 2.1; N, 22.1%). Compound **8** was also obtained using the following reagents and reaction conditions: Na_2S, EtOH, rt, 5 h (yield 46%); NH_3, MeOH, reflux, 9 h (yield 40%); N_2H_4, MeOH, rt, 18 h (yield 72%); NaN_3, DMSO, rt, 18 h (yield 45%).
20. Procedure and physico-chemical data for compound **9**. A mixture of **4** (0.1 g, 0.48 mmol), morpholine (0.083 g, 0.95 mmol) and ethanol (20 ml) was refluxed for 5 h and cooled to room temperature. The precipitate was filtered off, washed with cold water and recrystallised to give 0.1 g (81%) of **9**, mp 189–190°C (from water). δ_H (DMSO-d_6): 3.86 (8H, m, 2NCH$_2$, 2OCH$_2$), 7.20 (1H, t, $J=5.5$ Hz, 6-H), 7.46 (1H, t, $J=5.5$ Hz, 7-H), 7.68 (1H, d, $J=5.5$ Hz, 5-H), 8.00 (1H, d, $J=5.5$ Hz, 8-H). (Found: C, 55.6; H, 4.9; N, 21.8. $C_{12}H_{12}N_4OS$ requires C, 55.4; H, 4.6; N, 21.5%).
21. Crystal data for compound **8**: $C_{16}H_8N_6S_3{\cdot}CHCl_3$, M_w 499.85, triclinic, space group $P\bar{1}$; $Z=2$, $a=7.6532$ (2), $b=8.3355(2)$, $c=17.3280(6)$ Å, $\alpha=101.3496(13)$, $\beta=93.3369(13)$, $\gamma=111.007(2)°$; $V=1001.70(5)$ Å^3, $F(000)=424$; $D_x=1.657$ g/cm^3; $2\theta_{max}=55°$ (CCD area detector, Mo Kα radiation), $R=0.0520$ (2985 data with $I>3\sigma I$). Crystallographic data for structure **8** have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 209360).