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NEW SYNTHESIS OF 2,3-DIHYDRO-THIAZOLO[3,2-*a*]BENZIMIDAZOLES

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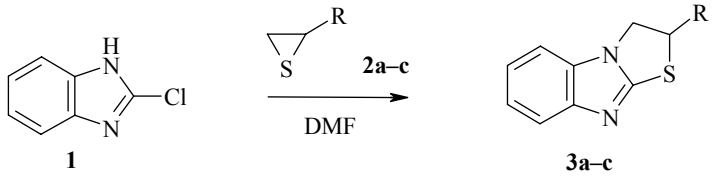
Several methods have been developed for synthesis of the 2,3-dihyhdrothiazolo[3,2-*a*]benzimidazole system: 1) Alkylation of 2-mercaptobenzimidazoles by 1,2-dihaloethanes [1]; 2) cyclization of 1-(2-hydroxyalkyl)-2-mercaptobenzimidazoles by dehydrating reagents [2], and 3) reaction of 2-methylsulfonyl-1-(thiiranyl-2-methyl)benzimidazoles with nucleophilic reagents [3].

We now propose a new one-step method for the preparation of 2,3-dihydrothiazolo[3,2-*a*]benzimidazole derivatives using the reaction of 2-chlorobenzimidazole (**1**) with thiiranes **2a-c**.

2,3-Dihydrothiazolo[3,2-*a*]benzimidazoles **3a-c** are formed in moderate yields upon heating benzimidazole **1** with an equimolar amount of thiiranes **2a-c** in the presence of bases in DMF.



a R = H, **b** R = CH_2OMe, **c** R = CH_2N

The characteristics of 2,3-dihydrothiazolo[3,2-*a*]benzimidazole **3a** correspond to the results reported by Suru et al. [1]. The use of asymmetric thiiranes **2b** and **2c** leads to 2-substituted dihydrothiazolobenzimidazoles **3b** and **3c**. The structure of these compounds was confirmed by the convergent synthesis of 2-(1-piperidinylmethyl)-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (**3c**) by the reaction of 2-methylsulfonyl-1-(thiiranyl-2-methyl)benzimidazole with piperidine [3]. The characteristics of samples of benzimidazole **3c** prepared by different methods were identical, which confirms opening of the thiirane ring according to the Krasusskii rule [4].

The ^{1}H NMR spectra of dihydrothiazolobenzimidazoles **3a-c** have signals for the dihydrothiazole ring protons, multiplets for the aromatic protons of the benzimidazole residue, and signals for the substituents at C-2.

The ^{13}C NMR spectra of **3b** and **3c** contain signals for the carbon atoms of the dihydrothiazole ring at 46.0-47.1 (C-3) and 50.7-51.7 ppm (C-2) as well as signals for the carbon atoms of the benzimidazole residue and substituents at C-2.

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The ^1H and ^{13}C NMR spectra were taken on a Bruker AM-300 spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$. The solvent signals served as the internal chemical shift reference. We used a commercial sample of thiirane **2a** obtained from Aldrich, while thiirane **2b** was prepared according to Schuets [5] and thiirane **2c** was prepared according to Stewart [6].

2,3-Dihydrothiazolo[3,2-*a*]benzimidazole (3a). A solution of 2-chlorobenzimidazole **1** (1.52 g, 10 mmol), NaOH (0.40 g, 10 mmol), and thiirane **2a** (0.60 g, 10 mmol) in DMF (30 ml) was heated at 45-50°C for 1 h and then at reflux for 1 h. The mixture was diluted with a 10-fold amount of water and extracted with two 50 ml portions of ethyl acetate. Then, the ethyl acetate was evaporated off to give 0.73 g (41%) compound **3a**, mp 98-99°C (hexane). ^1H NMR spectrum, δ, ppm: 3.88-4.00 (2H, m, SCH_2); 4.23-4.35 (2H, m, NCH_2); 7.17-7.31 (3H, m, 3CH benzimidazole); 7.60-7.68 (1H, m, CH benzimidazole). Found, %: C 61.52; H 4.68; N 15.64. $C_9H_8N_2S$. Calculated, %: C 61.33; H 4.58; N 15.90.

2-(Methoxymethyl)-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (3b). A solution of 2-chlorobenzimidazole **1** (1.52 g, 10 mmol), KOH (0.56 g, 10 mmol) and thiirane **2b** (1.04 g, 10 mmol) in DMF (30 ml) was heated at reflux for 1 h and then diluted with a five-fold amount of water. The mixture was extracted with two 50 ml portions of ether. Then, the ether was evaporated off to give 0.79 g (36%) compound **3b**, mp 64-66°C (ether). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.41 (3H, s, OCH_3); 3.64 (2H, d, $^3J = 7.2$, 2-CH_2); 4.24 (2H, d, $^3J = 5.8$, NCH_2); 4.46-4.56 (1H, m, SCH); 7.10-7.25 (3H, m, 3CH benzimidazole); 7.57-7.62 (1H, m, CH benzimidazole). ^{13}C NMR spectrum, δ, ppm: 45.96 (C-3); 50.68 (C-2); 59.19 (OCH_3); 74.09 (2-CH_2); 108.79 (C-5); 118.78 (C-8); 121.89 (C-6, C-7); 133.94 (C-4a); 149.28 (C-8a); 157.63 (C-9a). Found, %: C 59.91; H 5.58; N 12.88. $C_{11}H_{12}N_2OS$. Calculated, %: C 59.97; H 5.49; N 12.72.

2-(1-Piperidinylmethyl)-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (3c) was obtained analogously to compound **3b** using thiirane **2c** (1.57 g, 10 mmol). Water was added until a precipitate formed. The precipitate was filtered off, washed with water, and dried to give 1.34 g (49%) compound **3c**, mp 138-139°C (hexane). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.38-1.50 (2H, m, CCH_2); 1.52-1.62 (4H, m, $2CCH_2$); 2.35-2.50 (4H, m, $N(CH_2)_2$); 2.65 (1H, dd, $^3J = 7.7$, $^2J = 12.7$, 2-CH_2); 2.70 (1H, dd, $^3J = 7.9$, $^2J = 12.7$, 2-CH_2); 4.08 (1H, dd, $^3J = 6.3$, $^2J = 10.4$, NCH_2); 4.22 (1H, dd, $^3J = 7.3$, $^2J = 10.4$, NCH_2); 4.50-4.60 (1H, m, SCH); 7.08-7.20 (3H, m, 3CH benzimidazole); 7.55-7.60 (1H, m, CH benzimidazole). ^{13}C NMR spectrum, δ, ppm: 24.15 (CH_2); 25.86 ($2CH_2$); 47.12 (C-3); 50.61 (C-2); 54.78 ($N(CH_2)_2$); 62.69 (2-CH_2); 108.72 (C-5); 118.49 (C-8); 121.64 (C-7); 121.88 (C-6); 133.80 (C-4a); 148.91 (C-8a); 158.21 (C-9a). Found, %: C 65.78; H 6.93; H 15.53. $C_{15}H_{19}N_3S$. Calculated, %: C 65.90; H 7.00; N 15.37.

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