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Reactions of 2-mercaptobenzimidazole with bromotrifluoroethylene and 2-bromo-1,1-difluoroethylene

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Abstract

The cyclization reactions of 2-mercaptobenzimidazole with bromotrifluoroethylene and 2-bromo-1,1-difluoroethylene have been studied. New heterocycles, halogenated derivatives of 2,3-dihydrobenzimidazo[4,5b]thiazole-1,3, were isolated. The structures of the obtained compounds were supported by single-crystal X-ray diffraction analysis.

Introduction

The reaction of perhaloolefins with nucleophiles to form adducts or substitution products is widely known. These reactions are well studied for substrates with a single nucleophilic centre, such as alcohols, phenols, thiophenols, and heterocyclic systems [1,2]. However, the interactions of perfluoroolefins with the heterocycles having multiple nucleophilic centers like N-C-S or N-C-C are less studied. Some adducts of tetrafluoroethylene (TFE) with 2-mercaptoimidazole derivatives to the sulfur atom possess a high biological activity and they were described as potential antiinflammatory drugs [3,4]. A few publications describe some adducts of 2-mercaptoazoles with chlorotrifluoroethylene (CTFE) [5,6] and S-perfluoroalkylation of 2-mercaptoazoles under irradiation [7,8]. However, such reactions could lead to the formation of new five-membered fluorinated heterocycles if a 1,3-dinucleophilic system and perhaloethane or perhaloethene react. The cyclization of 2-mercaptoazoles with hexafluoropropene oxide is known so far [9]. Recently, we have set the task to study the behavior of perfluoroolefins in such reactions. Our previous studies were devoted to the interaction of 2-mercaptobenzimidazole (**1**) with tetrafluoroethylene (TFE) and chlorotrifluoroethylene [10]. Unexpected “reverse” cyclization took place, and in addition to the expected products of polyfluoroalkylation at the sulfur atom and at the sulfur and nitrogen atoms simultaneously (**2** and **3**), a new heterocycle, namely 2-chloro-2,3,3-trifluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (**4**) was synthesized (scheme 1).

Continuing our research in this area, we decided to study the reaction of bromine-containing polydifluoroolefins, namely bromotrifluoroethylene and 2-bromo-1,1-difluoroethylene, with **1** under conditions similar to those studied previously.

The reaction of the starting compound **1** with bromotrifluoroethylene was carried out under conditions similar to those described previously for chlorotrifluoroethylene [10], namely, in DMF in the presence of an excess of base (potash). The reaction was quite intense, accompanied by significant exothermic heating of the reaction mixture (up to 60-70 °C) when loaded with 5 g of **1**. As a result, a mixture of products was obtained in high yield (over 80%), the main ones being two heterocycles: 2-bromo-2,3,3-trifluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (**5**) and 2,2,3-trifluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (**6**), isolated with 45 and 27% yields, respectively (scheme 2).

Heterocycles were separated chromatographically. Compounds **5** and **6** are solid crystalline substances; their structure was proven by X-ray diffraction study (Fig. 1).

Figure 1. Molecular structure of compounds **5** (left) and **6** (right) according to X-ray diffraction data. Thermal ellipsoids of non-hydrogen atoms are shown at 50 % probability level.

Compound **5** was expected based on our previous studies. The formation of compound **5** can be explained in the same way as the formation of a similar chlorine-containing heterocycle during the reaction of **1** with chlorotrifluoroethylene (via an intermediate disulfide or thiirane ring). Heterocycle **6**, which does not contain a bromine atom, is apparently formed after the addition of bromotrifluoroethylene at the sulfur atom, followed by closure at the nitrogen atom with the elimination of the bromide ion. Such closure was not observed during the reaction of **1** with chlorotrifluoroethylene, even in trace amounts. Apparently, the bromine atom is significantly more mobile than the chlorine atom and is more readily subject to nucleophilic substitution. For the same reason, unlike in the study of the reaction of 1 with chlorotrifluoroethylene, we did not observe monosubstitution products at the sulfur atom. Very small amounts of the nitrogen and sulfur disubstitution product (**7**) (yield approximately 5%) were isolated from the reaction mixture. Product **7** was obtained as an oil and exhibited very complex ^{19}F and ^{13}C NMR spectra. It turned out to be difficult to unambiguously determine the coupling constants. The nature of product **7** was finally confirmed by mass spectra (a molecular ion was detected) and elemental analysis (bromine value).

In addition, three signals (doublets) were present in the NMR ^{19}F spectra, very similar in their constants to the signals of compound **5**, which could be responsible for 3-bromo-2,2,3-trifluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (**8**), but we were unable to isolate this product in pure form due to its small amount. Chromatographic separation allowed us to isolate a fraction containing, according to NMR spectra, approximately 70% of the presumed product in an amount of approximately 150 mg.

The interaction of compound **1** with 2-bromo-1,1-difluoroethylene, under these conditions, in contrast to the previous case, is accompanied by a significant formation of polymeric products of unknown structure. The yield of target products after chromatographic separation from resinous masses was approximately 35%. Two heterocycles, 3,3-difluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (**9**) and 2,2-difluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (**10**), were isolated in 28 and 7% yields (scheme 3), respectively and their structure was confirmed by X-ray diffraction study (Fig. 2). The formation of two different heterocycles can be explained by two competing reactions at the more nucleophilic center – the sulfur atom. If nucleophilic substitution at the bromine atom occurs initially, then subsequent closure at the difluoromethylene group at the nitrogen atom leads to the formation of compound **9**. If addition at the difluoromethylene group at the sulfur atom occurs initially, then subsequent closure with nucleophilic substitution with bromide-ion elimination at the nitrogen atom leads to the formation of compound **10**.

Scheme 3. Reactions of 2-mercaptobenzimidazole with 2-bromo-1,1-difluoroethylene

Figure 2. Molecular structure of compounds **9** (left) and **10** (right) according to X-ray diffraction data. Thermal ellipsoids of non-hydrogen atoms are shown at 50 % probability level.

Thus, we studied the cyclization reactions of 2-bromo-1,1-difluoroethylene and bromotrifluoroethylene with the model compound **2**, mercaptobenzimidazole. New heterocycles were obtained, and their fundamental difference from similar reactions of chlorotrifluoroethylene was demonstrated.

Experimental

Melting points were measured in an open capillary and are given uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR300 spectrometer (300 MHz), using TMS as an internal standard. ^{19}F NMR-spectra were recorded on a Varian VXR-200 spectrometer (188 MHz) using CCl_3F as an internal standard. ^{13}C NMR spectra were recorded on a Bruker AvanceDXR-500 spectrometer (125 MHz). Mass spectra were recorded on an Agilent 1100 LS/ MSD SL instrument with Rapid Resolution HT Cartridge 30 mm, 1.8mm Zorbax SB-C18 column.

General synthetic experimental procedure

A solution of 6.0 g (0.04 mol) of **1** in 50 mL of dry DMF was added to a stirred mixture of 30 g (0.21 mol) of calcined K_2CO_3 in 25 mL of dry DMF. The reaction vessel was evacuated and filled with the appropriate gas from the rubber balloon (approx. 0.1 mol of the reagent in the balloon). Until the mixture was agitated, the gas was absorbed, with some exothermic effect. The temperature spontaneously rose to 40–45 °C. The reaction mixture was stirred at this temperature for 1 h. Water (250 mL) was added, and after 5 min of stirring, the products were extracted with hexane (3 × 100 mL), washed with water (3 × 100 mL), and dried over $MgSO_4$. After evaporation, the solvent products were separated by column chromatography.

X-Ray diffraction studies were performed on an automatic “Bruker APEX II” diffractometer (graphite monochromatic MoKα radiation, CCD-detector, φ- and ω-scanning). The structures were solved using the OLEX2 [11] package with SHELXT [12] and SHELXL modules [13]. Positions of the hydrogen atoms were located from electron density difference maps and refined by a “riding” model with $U_{iso} = 1.2U_{eq}$ of the carrier atom. The crystallographic data and experimental parameters are listed in Table S1. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). The deposition numbers are given in Table S1.

2-Bromo-2,3,3-trifluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (5)

Colorless crystals. Yield 5.60 g (45%) m.p 52-54 °C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.27-7.33 (2H, m, H Ar); 7.51-7.54 (1H, m, H Ar); 7.65-7.72 (1H, m, H Ar). ^{19}F NMR spectrum (188 MHz, $CDCl_3$), δ, ppm (J, Hz): −72.5 (1F d, *J* = 200, CF_2); −82.3 (1F d, *J* = 8, CFBr); −107.6 (1F, dd, $^{2}J_{F\text{-}F}$ = 200, $^{3}J_{F\text{-}F}$ = 8, CF_2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: (*J*, Hz): 105,5 (ddd, $^{1}J_{C\text{-}F}$ = 304, $^{2}J_{C\text{-}F}$ = 25, $^{2}J'_{C\text{-}F}$ = 25); 110.3 (C Ar); 115.6 (dt, $^{1}J_{C\text{-}F}$ = 262, $^{2}J_{C\text{-}F}$ = 48); 120.3 (C Ar); 124.6 (C Ar); 124.9 (C Ar); 131.2 (C Ar);

148.0 (C Ar); 148.4 (C Ar). Mass spectrum m/z (I_{rel}, %) 310 $[M+H]^+$ (57), 308 $[M+H]^+$ (46), 229 $[M - Br]^+$ (100). Found, % C 34.91; H 1.27; Br 25.59. $C_9H_7BrF_3N_2S$. Calculated, % C 34.97; H 1.30; Br 25.85.

2,2,3-Trifluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (6),

Colorless crystals. Yield 2.49 g (27%) m.p 57-59 °C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 6.42 (1H, dd, $^2J_{H-F}$ = 65, $^3J_{H-F}$ = 7, CFH); 7.26-7.35 (2H, m, H Ar); 7.40-7.44 (1H, m, H Ar); 7.67-7.75 (1H, m, H Ar). ^{19}F NMR spectrum (188 MHz, $CDCl_3$), δ, ppm (*J*, Hz): −71.5 (1F d, *J* = 193, CF_2); −85.9 (1F d, *J* = 193, CF_2); −143.3 (1F, d, *J* = 65, CFH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: (*J*, Hz): 91,5 (ddd, $^1J_{C-F}$ = 228, $^2J_{C-F}$ = 25, $^2J_{C-F}$ = 25); 109.5 (C Ar); 120.0 (C Ar); 124.3 (C Ar); 132.5 (C Ar); 133.9 (dt, $^1J_{C-F}$ = 287, $^2J_{C-F}$ = 27); 146.9 (C Ar). Mass spectrum m/z (I_{rel}, %) 231 $[M+H]^+$ (100). Found, % C 45.01; H 2.27; F 25.11. $C_9H_5F_3N_2S$. Calculated, % C 46.97; H 2.19; F 24.76.

1-(2-Bromo-1,1,2-trifluoromethyl)-2-(2-bromo-1,1,2-trifluoromethylthio)-benzimidazile (7)

Colorless oil. Yield 0.79 g (5%). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 6.90 (1H, dt, $^2J_{H-F}$ = 47, $^3J_{H-F}$ = 9, CFBrH); 7.35-7.45 (2H, m, H Ar); 7.52 (1H, dm, CFBrH); 7.55-7.60 (1H, m, H Ar); 7.75-7.80 (1H, m, H Ar). ^{19}F NMR spectrum (188 MHz, $CDCl_3$), δ, ppm (*J*, Hz): −81.5-−90 (4F m, CF_2); −152.9 (1F m, CFBrH); −155.3 (1F, m, CFBrH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: (*J*, Hz): 85.9-91,5 (m); 109.5 (C Ar); 112.0 (C Ar); 120.3 (C Ar); 124.2 (C Ar); 125.6 (C, Ar); 133.3 (C Ar); 142.4 (C Ar). Mass spectrum m/z (I_{rel}, %) 473 $[M+H]^+$ (8), 472 $[M+H]^+$ (12), 471 $[M+H]^+$ (8), 312 $[M - 2Br]^+$ (100). Found, % C 28.09; H 1.17; Br 33.69. $C_{11}H_6Br_2F_6N_2S$. Calculated, % C 27.99; H 1.28; Br 33.88.

3-Bromo-2,2,3-trifluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (8)

^{19}F NMR spectrum (188 MHz, $CDCl_3$), δ, ppm (*J*, Hz): −65.2 (1F d, *J* = 195, CF_2); −73.8 (1F d, *J* = 8, CFBr); −87.6 (1F, dd, $^2J_{F-F}$ = 195, $^3J_{F-F}$ = 8, CF_2). Mass spectrum m/z (I_{rel}, %) 310 $[M+H]^+$ (33), 308 $[M+H]^+$ (47), 229 $[M - Br]^+$ (100).

3,3-difluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (9)

Colorless crystals. Yield 2.31 g (28%) m.p 78-89 °C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.25 (1H, t, *J* = 12); 7.26-7.31 (2H, m, H Ar); 7.50-7.52 (1H, m, H Ar); 7.60-7.63 (1H, m, H Ar). ^{19}F NMR spectrum (188 MHz, $CDCl_3$), δ, ppm (*J*, Hz): −73.7 (1F t, *J* = 12, CF_2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: (*J*, Hz): 41.5 (t, *J* = 15, CH_2); 109.9 (C Ar); 119.4 (C Ar); 121.1 (t, *J* = 126, CF_2); 123.3 (C Ar) 124.3 (C Ar); 130.5 (C Ar); 149.6 (C Ar); 153.9 (C Ar). Mass spectrum m/z (I_{rel}, %) 213 $[M+H]^+$ (100). Found, % C 51.04; H 2.87; F 18.11. $C_9H_6F_2N_2S$. Calculated, % C 50.94; H 2.85; F 17.90.

2,2-difluoro-2,3-dihydro-benzimidazo[4,5b]thiazole-1,3 (10)

Colorless crystals. Yield 0.59 g (7%) m.p 128-130 °C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.59 (1H, t, *J* = 12); 7.27-7.32 (2H, m, H Ar); 7.51-7.3 (1H, m, H Ar); 7.61-7.64 (1H, m, H Ar). ^{19}F NMR spectrum (188 MHz, $CDCl_3$), δ, ppm (*J*, Hz): −62.7 (1F t, *J* = 12, CF_2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: (*J*, Hz): 54.4 (t, *J* = 15, CH_2); 108.9 (C Ar); 122.2 (C Ar); 122.9 (C Ar); 132.8 (C Ar); 137.5 (t, J = 126, CF_2); 146.6 (C Ar) 151.1 (C Ar). Mass spectrum m/z (I_{rel}, %) 213 $[M+H]^+$ (100). Found, % C 51.21; H 2.76; F 18.04. $C_9H_6F_2N_2S$. Calculated, % C 50.94; H 2.85; F 17.90.

Declarations

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Consent to Publish declaration. Not applicable.

Data availability declaration. All data supporting the findings of this study are available within the paper and its Supplementary Information.

Ethics and Consent to Participate declarations. Not applicable.

Competing interests declarations. The authors declare that they have no competing interests as defined by Springer, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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Schemes

Schemes 1-3 are available in the Supplementary Files section.

Figures

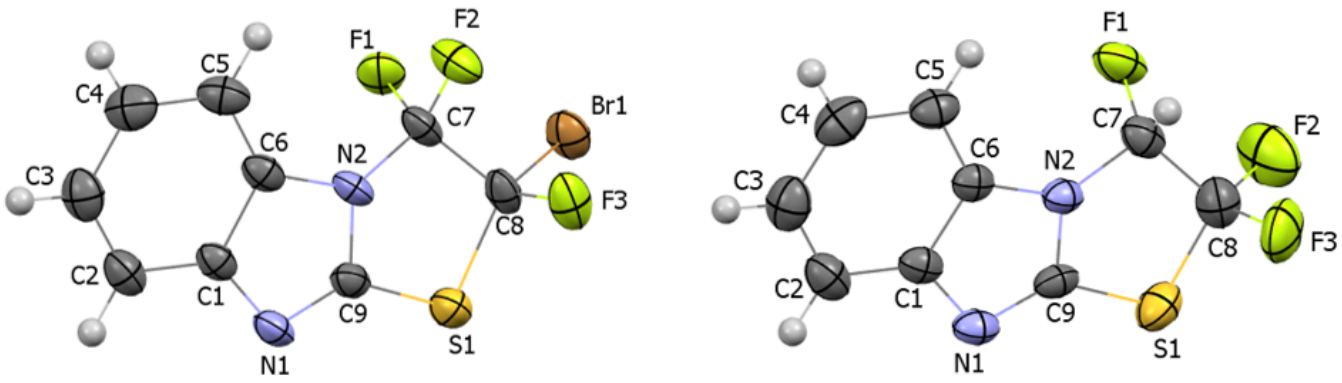


Figure 1

Molecular structure of compounds **5** (left) and **6** (right) according to X-ray diffraction data. Thermal ellipsoids of non-hydrogen atoms are shown at 50 % probability level.

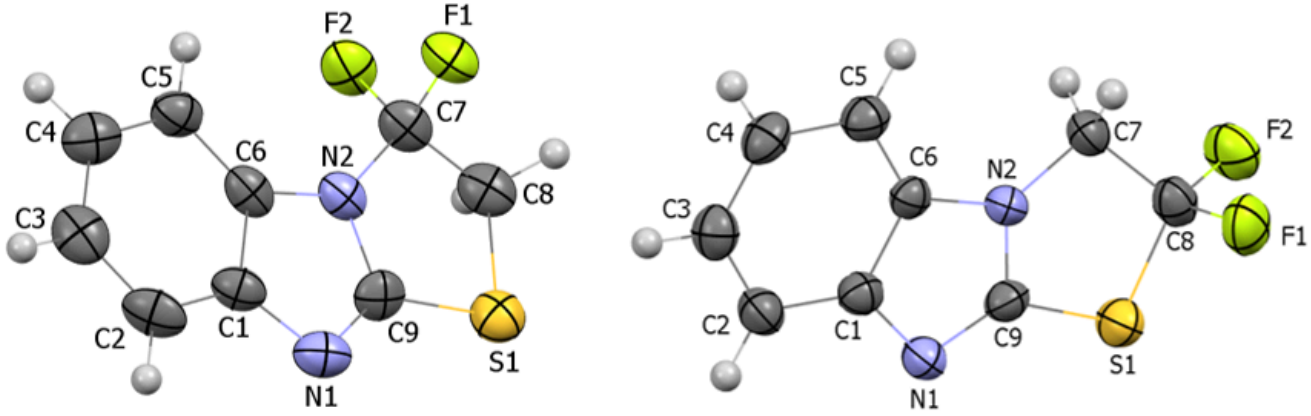


Figure 2

Molecular structure of compounds **9** (left) and **10** (right) according to X-ray diffraction data. Thermal ellipsoids of non-hydrogen atoms are shown at 50 % probability level.

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