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Journal of Fluorine Chemistry 108 (2001) 211–214

JOURNAL OF FLUORINE CHEMISTRY

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Unusual difluoromethylation of 2-mercaptoazoles

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Received 29 November 2000; accepted 25 January 2001

Abstract

The conditions for difluoromethylation of 2-mercaptobenzimidazoles with difluorocarbene ($CHClF_2$ in alkaline medium) at the sulfur atom or at two reaction centres — sulfur and nitrogen or two nitrogen atoms — were found. In the similar reaction, 2-mercapto-4(5)-(4-nitrophenyl)imidazole gives the product of bis(difluoromethylation) at the sulfur and nitrogen atoms. Benzimidazoles with two fluorinated alkyl substituents at the two nitrogen atoms were prepared for the first time. The *N*-difluoromethyl derivative of benzothiazole-2-thione was obtained by this procedure. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: 2-Mercaptoazoles; Difluorocarbene; 1,3-Bis(difluoromethyl)benzimidazole-2-thione

1. Introduction

Difluoromethylation reactions of phenols and thiophenols with chlorodifluoromethane in an alkaline medium are well-studied [1]. Similar difluoromethylation at nitrogen atom is also known for some heterocyclic bases [2,3] and dithiocarbamates, the ambident systems containing reactive nitrogen and sulfur atoms [4].

In the present work, we investigated the interaction of difluorocarbene, formed from $CHClF_2$ in alkaline medium, with 2-mercaptoazoles having two reaction centres, the thiol and the less nucleophilic heterocyclic nitrogen atom.

2. Results and discussion

It was found that the difluoromethylation of 2-mercapto-4(5)-(4-nitrophenyl)imidazole **1** occurred simultaneously at the two reaction centres. Only one of the two heterocyclic nitrogen atoms was involved in the reaction with the formation of compound **2**. The alternative isomer **3** was not formed presumably due to steric and electron-withdrawing effects of the 4-nitrophenyl substituent (Scheme 1).

2-Mercaptobenzimidazole **4** is difluoromethylated under the conditions indicated above, mainly at the sulfur atom to afford compound **5**. Difluorocarbene very slowly reacts with the secondary nitrogen atom of the benzimidazole ring as its nucleophilicity is decreased by the electron-withdrawing $SCHF_2$ group. The bis(difluoromethylation) product **6** was isolated from the reaction mixture in a low yield of 5% (Scheme 2).

An electron-donor ethoxy substituent in the aromatic ring enhances the nucleophilicity of the nitrogen atom and makes possible the difluoromethylation of 5(6)-ethoxy-2-mercapto-benzimidazole (**7**) at the two reaction centres. The reaction furnishes a difficult-to-separate 1:1 mixture of isomers **8** and **9** together with the product of difluoromethylation at the sulfur atom **10** (Scheme 3).

In order to effect difluoromethylation of 2-mercaptobenzimidazole simultaneously at the two reaction centres we used more severe reaction conditions, i.e. solid potassium hydroxide in anhydrous dimethylformamide. The reaction proceeded with strong evolution of heat to give the products of difluoromethylation at the sulfur and nitrogen atoms simultaneously (**6**) and at the sulfur atom only (**5**) together with unexpected product, 1,3-bis-(difluoromethyl)benzimidazole-2-thione **11** (Scheme 4).

Benzimidazole derivatives with fluorinated alkyl substituents at the two nitrogen atoms of the heterocycle were previously unknown.

It is likely that in a strongly alkaline medium 2-mercaptobenzimidazole **4** gives the dianion **12** which is attacked by difluorocarbenes on the two reaction centres and is transformed into the dianion **13**. The presence of two negative charges in the latter increases the electron density at the second nitrogen atom. This makes possible the interaction of the electrophilic difluorocarbene with this atom and the formation of the intermediate **14** which is stabilised by elimination of the: CF_2 group either from the nitrogen or

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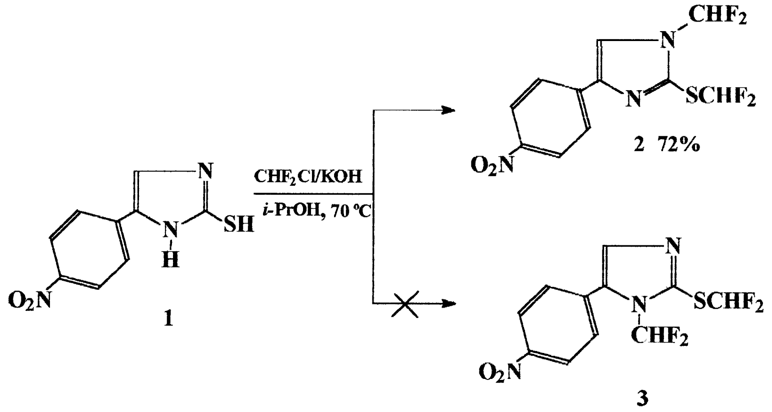
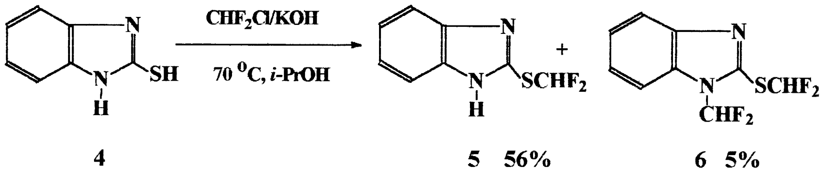
PII: S0022-1139(01)00350-5



Scheme 1.



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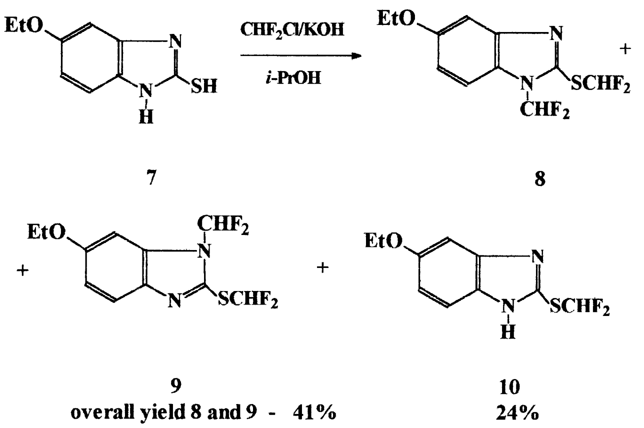

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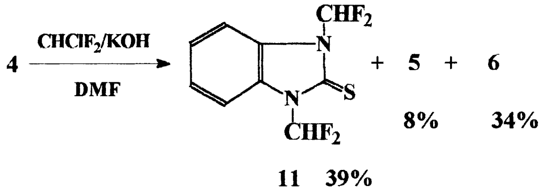
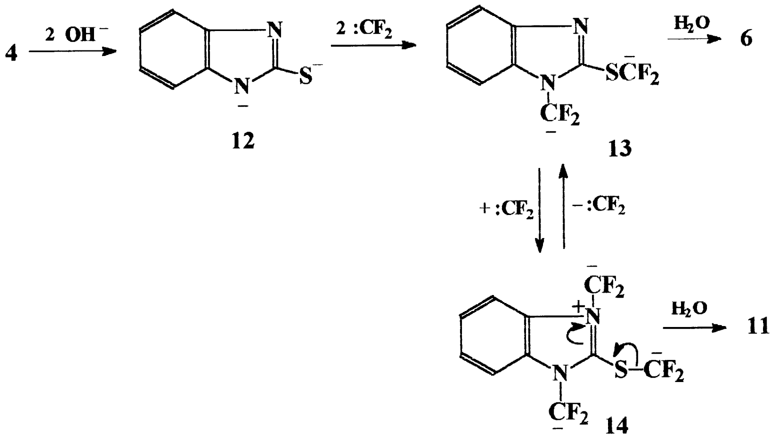


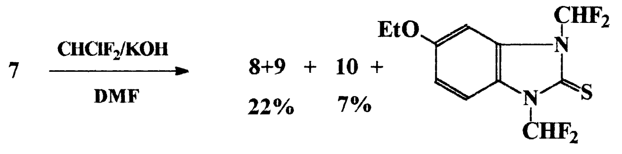
Scheme 4.

from the sulfur atom to give bis(difluoromethylated) products **6** and **11** (Scheme 5).

It was shown that, on heating compound **6** with solid KOH in DMF in the absence of $CHClF_2$, there occurred the abstraction of the difluoromethyl group from the nitrogen atom and the formation of 2-difluoromethylthiobenzimida-



Scheme 5.



15 25%

Scheme 6.

zole **5**. This finding indicates that the rearrangement via migration of the: CF_2 group from the sulfur to nitrogen atom in the formation of **11** is unlikely.

5(6)-Ethoxy-2-mercapto-benzimidazole **7** reacts with $CHClF_2$ and solid KOH in DMF in much the same fashion as 2-mercaptobenzimidazole **4** to give 1,3-bis(difluoromethyl)-5-ethoxybenzimidazole-2-thione (**15**) in about 25% yield and the products of difluoromethylation at the nitrogen and sulfur atoms **8–10** (Scheme 6).

On difluoromethylation of 2-mercaptobenzothiazole **16** under the same conditions as above, besides the previously described difluoromethylthio derivative **17** [5,6], there was isolated the *N*-difluoromethylated product **18** in 16% yield. The low yield of **18** is probably accounted for by lower electron density on the nitrogen atom of the anion derived from 2-mercaptobenzothiazole compared to the dianion **12** (Scheme 7).

Thus, we have found the reaction conditions for preparation of bis(difluoromethylated) benzimidazoles with CHF_2 groups at the sulfur and one nitrogen atom or at two nitrogen atoms and the *N*-difluoromethyl derivative of benzothiazole-2-thione.

3. Experimental

3.1. General

Boiling and melting points are uncorrected. ^1H NMR: Varian VXR-300 (300 MHz, TMS as internal standard). ^{19}F NMR: Varian VXR-300 (288 MHz, CCl_3F as internal standard). IR spectra were measured on an UR-20 spectrophotometer in CCl_4 solutions.

3.1.1. 1-Difluoromethyl-2-difluoromethylthio-4-(4-nitrophenyl)imidazole (2)

Through a vigorously stirred suspension of **1** (5 g, 0.0225 mol) in a mixture of 2-propanol (30 ml), water (30 ml) and KOH (16.8 g, 0.3 mol) $CHClF_2$ gas was bubbled for 3 h at a temperature of 70–75°C. After keeping the reaction mixture at 0°C for 12 h, the precipitate formed was filtered off, washed with water (3 × 50 ml), dried at 50°C, and crystallised from 2-propanol. Yield 5.30 g (72%), mp 126–127°C ^1H NMR (DMSO-d_6): $\delta = 7.58$ (t, $J_{H-F} = 55$ Hz, 1H); 7.89 (t, $J_{H-F} = 59$ Hz, 1H); 8.13–8.17, 8.27–8.31 (m, 4H); 8.75 (s, 1H). ^{19}F NMR ($CDCl_3$): $\delta = -93.66$ (d, $J_{F-H} = 59$ Hz, 2F); -91.65 (d, $J_{F-H} = 55$ Hz, 2F). Found: C 40.95; H 2.24; N 12.94, calculated for $C_{11}H_7F_4N_3O_2S$: C 41.12; H 2.20; N 13.08%.

3.1.2. 2-Difluoromethylthiobenzimidazole (5)

Through a stirred solution of **4** (2 g, 0.013 mol) in a mixture of 2-propanol (10 ml), water (10 ml) and KOH (7.8 g, 0.14 mol) $CHClF_2$ gas was bubbled for 4 h at 70–75°C. Absorption of the gas was observed only during the first 20 min. The reaction mixture was filtered, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 ml). The combined organic solutions were washed with water (3 × 30 ml) and dried ($MgSO_4$, 12 h). The combined aqueous solutions were neutralised to pH 8 with 10% aq. HCl and the white precipitate (crude **5**) was filtered and dried.

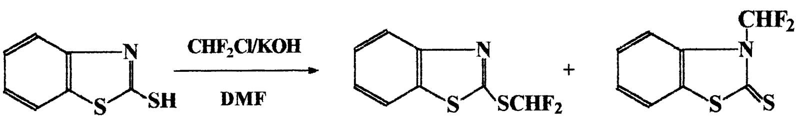
The organic extracts were evaporated. Hexane (10 ml) was added to the residue and the mixture was stirred for 5 min. The undissolved residue was filtered off and combined with the crude **5**, which was crystallised from 2-propanol to give pure **5**. Yield 1.50 g (56%), mp 206–208°C. ^1H NMR (acetone-D_6): $\delta = 7.30$–7.35 (m, 2H); 7.36 (t, $J_{H-F} = 55$ Hz, 1H); 7.40–7.46 (m, 2H); 9.60 (br.s, 1H). ^{19}F NMR (acetone-D_6): $\delta = -92.05$ (d, $J_{F-H} = 55$ Hz, 2F). IR: 3480 cm^{-1} (NH). Found: N 14.18; S 16.17, calculated for $C_8H_6F_2N_2S$: N 13.99; S 16.02%.

The hexane extract was evaporated to leave crude **6** (>80% purity shown by ^{19}F NMR spectra). Yield 0.17 g (5%).

3.1.3. 1-Difluoromethyl-2-difluoromethylthio-5 and 6-ethoxybenzimidazoles (8 and 9) and 2-difluoromethylthio-5(6)-ethoxybenzimidazole (10)

The reaction was carried out as above by using **7** (0.97 g, 0.005 mol), KOH (2.8 g, 0.05 mol), water (5 ml) and 2-propanol (5 ml).

The products **8** and **9** were isolated as a semisolid mass by vacuum distillation. Yield 0.6 g (41%), bp 146–150°C



16 **17** 50% **18** 16%

Scheme 7.

(0.02 Torr). ^{1}H NMR (CD_3CN): $\delta = 1.34$ (t, 3H); 1.35 (t, 3H); 3.98 (q, 2H); 4.01 (q, 2H); 7.00–7.15 (m, 2H); 7.20–7.27 (m, 2H); 7.34 (t, $J_{H-F} = 55$ Hz, 1H); 7.41 (t, $J_{H-F} = 55$ Hz, 1H); 7.60–7.67 (m, 2H); 7.68 (t, $J_{H-F} = 59$ Hz, 1H); 7.71 (t, $J_{H-F} = 59$ Hz, 1H). ^{19}F NMR ($CDCl_3$): $\delta = -96.73$ (d, $J_{F-H} = 59$ Hz, 2F); -96.06 (d, $J_{F-H} = 59$ Hz, 2F); -91.60 (d, $J_{F-H} = 55$ Hz, 4F). Found: N 9.93; S 10.77, calculated for $C_{11}H_{10}F_4N_2$ OS: N 9.52; S 10.89%.

Product **10** was crystallised from 2-propanol. Yield 0.29 g (24%), mp 136–137°C. ^{1}H NMR (DMSO-d_6): $\delta = 1.34$ (t, 3H); 4.01 (q, 2H); 7.10–7.40 (m, 3H); 7.74 (t, $J_{H-F} = 55$ Hz, 1H); 12.95 (br.s, 1H). ^{19}F NMR (DMSO-d_6): $\delta = -91.40$ (d, $J_{F-H} = 55$ Hz, 2F). IR: 3480 cm^{-1} (NH). Found: N 11.25; S 13.32, calculated for $C_{10}H_{10}F_2N_2$ OS: N 11.47; S 13.13%.

*3.1.4. 1,3-Bis(difluoromethyl)benzimidazole-2-thione (**11**) and 1-difluoromethyl-2-difluoromethylthiobenzimidazole (**6**)*

To a vigorously stirred solution of **4** (4.5 g, 0.03 mol) in anhydrous DMF (20 ml) was added finely crushed KOH (3.8 g, 0.067 mol) in one portion and an intense stream of $CHClF_2$ was bubbled through the suspension until the rate of absorption decreased (3–4 min). The temperature rose therewith to 50–60°C. Then, with stirring and intense bubbling, a second portion of KOH (9.3 g, 0.165 mol) was added. The reaction mixture turned greenish-blue and the temperature rose to 110–120°C in 1–2 min. After 5 min the absorption of the gas stopped and the colour disappeared. The reaction mixture was cooled and poured into water (150 ml). The precipitated solid was filtered to separate it from the oil, washed with cold hexane (10 ml), dried at 30°C, and crystallised from hexane with a silica gel additive to give pure **11** as long colourless needles. Yield 2.15 g (28%), mp 121–122°C. ^{1}H NMR (CD_3CN): $\delta = 7.40$–7.50 (m, 2H); 7.58–7.68 (m, 2H); 8.02 (t, $J_{H-F} = 58$ Hz, 2H). ^{19}F NMR (CD_3CN): $\delta = -104.32$ (d, $J_{F-H} = 58$ Hz, 4F). Found: N 11.34; S 12.62, calculated for $C_9H_6F_4N_2S$: N 11.20; S 12.81%.

The oil separated from crude **11** was extracted with hexane (3 × 40 ml). The extract was dried ($MgSO_4$, 12 h) and combined with the mother liquor from crystallisation of **11**. The solvent was evaporated and the residue was chromatographed on a silica gel column (MN-Kieselgel-60, eluent CCl_4) to give an additional portion of **11** (0.75 g, 11%, $R_f = 0.8$; overall yield 39%) and **6** ($R_f = 0.3$) as a yellow oil which solidified into colourless crystals after vacuum distillation. Yield 2.58 g (34%), bp 80–81°C (0.07 Torr), mp 55–57°C (from hexane). ^{1}H NMR (acetone-D_6): $\delta = 7.15$–7.25 (m, 1H); 7.40–7.50 (m, 2H); 7.51 (t, $J_{H-F} = 55$ Hz, 1H); 7.76 (t, $J_{H-F} = 59$ Hz, 1H); 7.80–7.85 (m, 1H). ^{19}F NMR (acetone-D_6): $\delta = -96.03$ (d, $J_{F-H} = 59$ Hz, 2F); -92.42 (d, $J_{F-H} = 55$ Hz, 2F). Found: N 11.24; S 12.87, calculated for $C_9H_6F_4N_2S$: N 11.20; S 12.81%.

The water solution left after extraction with hexane was neutralised to pH 8 with 10% aq. HCl and precipitated **5** was filtered off, dried, and crystallised from 2-propanol. Yield 0.53 g (8%).

*3.1.5. 1,3-Bis(difluoromethyl)-5-ethoxybenzimidazole-2-thione (**15**)*

The reaction was carried out as above by using **7** (0.97 g, 0.005 mol), KOH (2 g, 0.035 mol) and DMF (4 ml). After pouring into water, the mixture of products was extracted with diethyl ether, dried ($MgSO_4$, 12 h), and chromatographed on a silica gel (MN-Kieselgel-60, eluent CCl_4) to give 0.36 g (24%) of 15 as white crystals, $R_f = 0.7$, mp 117–118°C (from hexane). ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (t, 3H); 4.00 (q, 2H); 7.00–7.30 (m, 3H); 7.86 (t, $J_{H-F} = 58$ Hz, 1H); 7.90 (t, $J_{H-F} = 58$ Hz, 1H). ^{19}F NMR ($CDCl_3$): $\delta = -104.48$ (d, $J_{F-H} = 58\,Hz$, 2F); -103.59 (d, $J_{F-H} = 59$ Hz, 2F). Found: N 9.73; S 10.51, calculated for $C_{11}H_{10}F_4N_2OS$: N 9.52; S 10.89%.

The mixture of **8** and **9** was also separated by chromatography (MN-Kieselgel-60, eluent CCl_4). Yield 0.33 g (22%). Compound **10** was isolated from aqueous solution. Yield 0.085 g (7%).

*3.1.6. 2-Difluoromethylthiobenzothiazole (**17**) and 1-difluoromethylbenzothiazole-2-thione (**18**)*

To a vigorously stirred solution of 16 (8.3 g, 0.05 mol) in DMF (25 ml) finely crushed KOH (14.2 g, 0.25 mol) was added in one portion and an intense stream of $CHClF_2$ was bubbled through the suspension. The temperature rose to 60°C in 1–2 min. The reaction mixture was heated to 110°C and, after stirring with bubbling for 10 min, it was cooled and poured into water. The oil formed was extracted with diethyl ether (3 × 50 ml). The extract was dried ($MgSO_4$) and, after evaporation of the solvent, **17** and **18** were separated by column chromatography (MN-Kieselgel-60, eluent CCl_4).

17: Yellow oil, solidified after vacuum distillation, $R_f = 0.55$, yield 5.34 g (50%), bp 78–80°C (0.5 Torr); lit.: 70°C (0.2 Torr) [5], mp 35°C (from hexane); lit.: 34–35°C [6].

18: Colourless crystals, $R_f = 0.8$, yield 1.76 g (16%), mp 51–52°C (from hexane). ^{1}H NMR ($CDCl_3$): $\delta = 7.32$–7.48 (m, 3H); 7.64–7.68 (m, 1H); 8.15 (t, $J_{H-F} = 58$ Hz, 1H). ^{19}F NMR ($CDCl_3$): $\delta = -107.17$ (d, $J_{F-H} = 58$ Hz, 2F). Found: N 6.60; S 30.18, calculated for $C_8H_5F_2NS_2$: N 6.45; S 29.52%.

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