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# Synthesis of *S*-difluoromethyl dithiocarbamates

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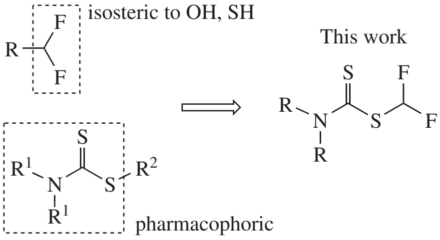
**A method for preparation of *S*-difluoromethyl dithiocarbamates has been developed, which involves the treatment of secondary amines with carbon disulfide in methanol followed by S-difluoromethylation of the intermediate dithiocarbamate anion with difluorocarbene generated from (bromodifluoromethyl)trimethylsilane.**

Organic compounds bearing fluorinated substituents play an important role in medicinal chemistry and related fields.[1] Though major emphasis has long been placed on the trifluoromethyl group,[2–4] partially fluorinated fragments are attracting increasing attention. In particular, the difluoromethyl group possesses a unique property of being isosteric to hydroxy and thiol ones due to hydrogen bond donor ability coupled with its increased metabolic stabilty.[5] Among various methods for the introduction of $CHF_2$ fragment (nucleophilic and radical difluoromethylation,[6] electrophilic difluoromethylation[7] and deoxofluorination[8]), reactions of acidic OH, SH, NH and CH functional groups with difluorocarbene are the most straightforward.[7]

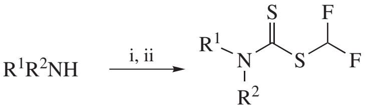
Dithiocarbamates constitute a class of pharmacophoric compounds exhibiting various types of biological activities[9] (Scheme 1). Correspondingly, several types of fluorine containing dithiocarbamates have been prepared.[10] At the same time, only one example of a dithiocarbamate substituted at sulfur with the $CHF_2$ group was described in the literature.[11]



**Scheme 1**

Herein, were report an efficient method for the synthesis of compounds of this type based on interaction of dithiocarbamate anion with difluorocarbene. As a key reagent, we employ (bromodifluoromethyl)trimethylsilane ($Me_3SiCF_2Br$), which was recently introduced as an efficient source of difluorocarbene.[7(*d*)] This compound is commercially available or can be readily obtained from (trifluoromethyl)trimethylsilane.[7(*d*),12–14] Important feature of $Me_3SiCF_2Br$ is that it can generate difluorocarbene under mildly basic conditions, whereas difluoromethylation of heteroatom groups is usually performed using strongly alkaline media,[7] which may be incompatible with S-difluoromethylated dithiocarbamate functionality.

Treatment of secondary amines **1a–h** with carbon disulfide in methanol in the presence of potassium carbonate resulted in rapid formation of dithiocarbamate salt. Subsequent addition of $Me_3SiCF_2Br$ and stirring for additional 10 min followed by work-up afforded dithiocarbamates **2** in good yields (Scheme 2).[†] Amines bearing unprotected hydroxy or carboxylic group also furnished the expected products **2g**,**h**. Dicyclohexyl amine gave expected product **2f** in lower yield, presumably, due to steric effects. A reaction of primary amine, *n*-butylamine, was unsuccessful. Molecular structures of compounds **2a**,**f** were confirmed by single crystal X-ray analysis (Figure 1).[‡]



**1a–h** **2a–h**

| | $R^1$ | $R^2$ | Isolated yield of **2** (%) |
|---|---|---|---|
| **a** | $-(CH_2)_4-$ | | 89 |
| **b** | $-(CH_2)_2O(CH_2)_2-$ | | 48 |
| **c** | Et | Et | 82 |
| **d** | Bn | Bn | 53 |
| **e** | All | All | 76 |
| **f** | cyclohexyl | cyclohexyl | 35 |
| **g** | Me | $(CH_2)_2OH$ | 66 |
| **h** | Me | $CH_2CO_2H$ | 55 |

**Scheme 2** *Reagents and conditions*: i, $CS_2$ (1.15 equiv.), $K_2CO_3$ (1.1 equiv.), MeOH, 0 °C to room temperature, 10 min; ii, $Me_3SiCF_2Br$ (1.5 equiv.), 0 °C to room temperature, 10 min. In the case of **2h**, 2.1 equiv. of $K_2CO_3$ was used.

In this process, dithiocarbamate anion likely serves as a Lewis basic activator towards the silicon reagent to generate

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[†] *General procedure for reactions of amines* **1a**–**g**. Amine **1a**–**g** (2.0 mmol) was added to a stirred suspension of $K_2CO_3$ (304 mg, 2.20 mmol, 1.10 equiv.) in dry methanol (2.0 ml), and the reaction flask was immersed into ice/water bath. Carbon disulfide (175 mg, 2.30 mmol, 1.15 equiv.) was added dropwise at 0 °C, and stirring was continued for 5 min, the ice/water bath was removed and the mixture was stirred for additional 5 min at room temperature. Then, the reaction mixture was cooled to 0 °C, $TMSCF_2Br$ (609 mg, 3.00 mmol, 1.50 equiv.) was added dropwise, the mixture was stirred for 5 min at 0 °C, and then at room temperature (for **1a**–**e**,**g**, 5 min; for **1f**, 60 min). For the workup, the mixture was diluted with ethyl acetate (4.0 ml) and water (6.0 ml), the aqueous layer was extracted with ethyl acetate (3×4 ml), the combined organic extracts were concentrated under vacuum, and the residue was passed through short pad of silica gel (~5 g) (for **2a**–**c**,**e**–**g**, eluting with $CH_2Cl_2$; for **2d**, eluting with $CCl_4$).

For characteristics of compounds **2a**–**h**, see Online Supplementary Materials.

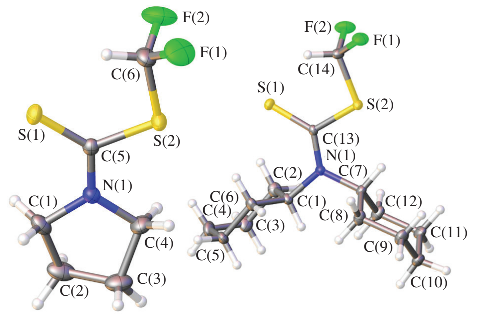
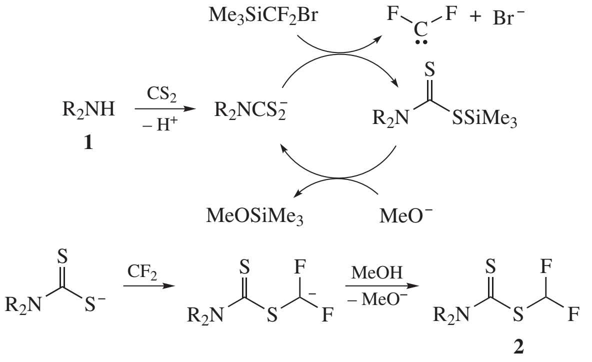


**Figure 1** Structures of **2a** (left) and **2f** (right).

difluorocarbene and an intermediate with S–Si bond[10(*a*)] (Scheme 3). S-Desilylation of the latter species would proceed rapidly to regenerate dithiocarbamate anion. It should be pointed out that in reaction of diallylamine **1e**, no products arising from double bond cyclopropantion were observed, suggesting very fast trapping of difluorocarbene with dithiocarbamate anion.[15] Alternatively, difluorocarbene can be generated by the interaction of the silane with methanol/$K_2CO_3$ system.



**Scheme 3**

In summary, a convenient and rapid protocol for the synthesis of $CHF_2$-substituted dithiocarbamates from secondary amines using (bromodifluoromethyl)trimethylsilane as a source of difluorocarbene has been developed.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.11.018.

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[‡] *Crystal data.* **2a**: crystals of $C_6H_9F_2NS_2$ ($M$ = 197.26) are orthorhombic, space group *Pnma* (no. 62), $a$ = 6.3986(3), $b$ = 7.2230(4) and $c$ = = 18.6156(10) Å, $V$ = 860.36(8) Å$^3$, $Z$ = 4, $\mu$(MoKα) = 0.586 mm$^{-1}$, $d_{calc}$ = = 1.523 g cm$^{-3}$, 21 311 reflections measured ($4.38° \leqslant 2\theta \leqslant 61.47°$), 1436 unique ($R_{int}$ = 0.0370, $R_\sigma$ = 0.0153) which were used in all calculations. The final $R_1$ = 0.0392 [$I > 2\sigma(I)$], $wR_2$ = 0.0819 and GOF = 1.340 (all data).

**2f**: crystals of $C_{14}H_{23}F_2NS_2$ ($M$ = 307.45) are monoclinic, space group $P2_1/c$ (no. 14), $a$ = 9.4569(5), $b$ = 12.2154(6) and $c$ = 13.4491(7) Å, $\beta$ = = 102.5814(10)°, $V$ = 1516.33(14) Å$^3$, $Z$ = 4, $\mu$(MoKα) = 0.359 mm$^{-1}$, $d_{calc}$ = 1.347 g cm$^{-3}$, 19989 reflections measured ($4.414° \leqslant 2\theta \leqslant 61.358°$), 4693 unique ($R_{int}$ = 0.0337, $R_\sigma$ = 0.0304) which were used in all calculations. The final $R_1$ = 0.0387 [$I > 2\sigma(I)$], $wR_2$ = 0.0827 and GOF = 1.108 (all data).

CCDC 1421539 and 1421540 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.