HETEROCYCLES, Vol. 69, 2006, pp. 351 - 364. © The Japan Institute of Heterocyclic Chemistry
Received, 20th July, 2006, Accepted, 21st September, 2006, Published online, 26th September, 2006. COM-06-S(O)43

# STRAINED 1-AZABICYCLO[1.1.0]BUTANES IN THE SYNTHESIS OF AZETIDINETHIOCARBOXYLATE DERIVATIVES

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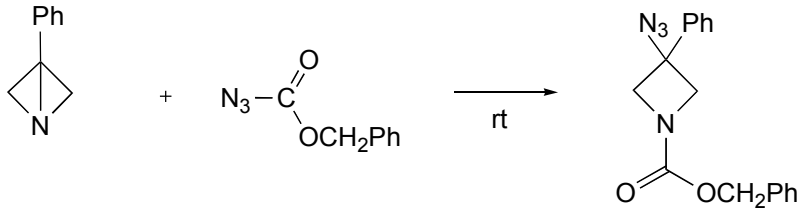
**Abstract** – The reaction of 3-phenyl-1-azabicyclo[1.1.0]butane (**1a**) with chlorodithio-formates (**5**) at room temperature yielded 3-chloro-3-phenylazetidine-1-carbodithioates (**6**). The same products were obtained in a two-step procedure by treatment of **1a** with thiophosgene to give azetidine-1-carbothioyl chloride (**7a**), followed by treatment with the corresponding sulfane. 3-Chloro-3-phenylazetidine-1-thiocarbamides (**8**) and the corresponding *O*-methyl 1-carbothioates (**9**) were prepared by the reaction of compounds (**7**) with amines and methanol, respectively. These reactions open a new access to derivatives of azetidine-1-carboxylic acid.

## INTRODUCTION

The smallest bicyclic systems containing one N-atom are 1- and 2-azabicyclo[1.1.0]butanes. Whereas the latter were postulated as unstable intermediates only, several representatives of the former have been described[2,3] (and refs. cited therein).[4] In the last two decades, numerous reactions were reported, in which 1-azabicyclo[1.1.0]butanes were explored as versatile reagents.[2,6] The most important reaction is the addition of electrophilic agents of type R-X (*e.g.* $(RCO)_2O$, $ClCO_2R$, $N_3CO_2R$, TsCl, $TsN_3$, HF, etc) across the weakest C-N bond to give azetidine derivatives. As an example, the addition of benzyl

azidoformate with 3-phenyl-1-azabicyclo[1.1.0]butane (**1a**) leading to 1-benzyloxyazetidine (**2**) is shown in *Scheme 1*.[7]

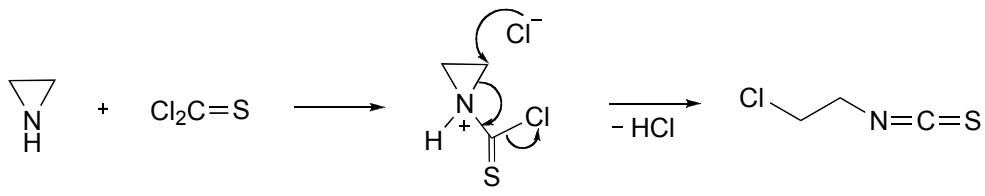
*Scheme 1*




**1a** **2**

Reactions of thiophosgene with primary or secondary amines are applied in the synthesis of thiocarbamoyl chlorides, which are useful intermediates for the preparation of thiocarbamates, dithiocarbamates and thioureas.[8-11] An alternative way to prepare dithiocarbamates is the reaction of amines with chlorodithioformates.[12-14] Cyclic secondary amines such as pyrrolidine and morpholine are known to react easily with thiophosgene to give either the corresponding thiocarbamoyl chlorides or thioureas.[15,16] However, in the case of the parent aziridine, the intermediate (**3**) undergoes a ring opening accompanied by elimination of HCl to give 2-chloroethyl isothiocyanate (**4,** *Scheme 2*).[17] The corresponding reaction with azetidine has not been reported. As thiocarbamoyl derivatives are of general interest with respect to their biological activity, we decided to elaborate a synthesis of such azetidine derivatives starting with 1-azabicyclo[1.1.0]butanes (**1**).

*Scheme 2*



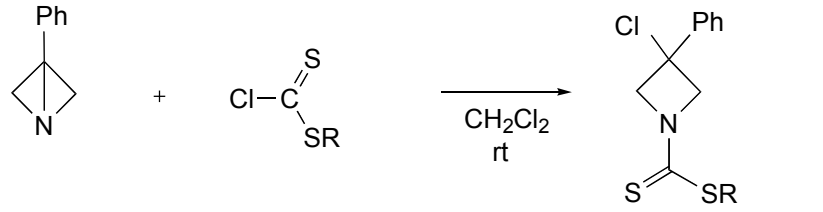

**3** **4**

## RESULTS AND DISCUSSION

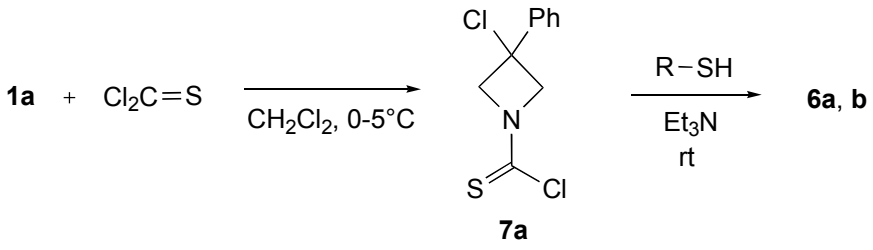
The reaction of **1a** with phenyl chlorodithioformate (**5a**) was carried out at room temperature in $CH_2Cl_2$. After 1 h (TLC control), the starting materials were consumed, the solvent was evaporated, and the product (**6a**) was isolated as a crystalline material by means of prep. TLC. In the $^1$H-NMR spectrum, the

signals of the two $CH_2$ groups appear as a complex multiplet (4.87–5.00 ppm); the corresponding $^{13}C$ absorptions are located at 69.4 and 70.3 ppm. These data indicate a hindered rotation within the thiocarbamoyl moiety.[18] The hindered rotation about the C–N bond in N,N-disubstituted thioamides is well documented.[19] On the other hand, symmetrically N,N-disubstituted dithiocarbamates have been reported to show only one signal for two equivalent atoms of the two N-substituents in the $^1H$-NMR spectrum.[20] Only recently, the NMR spectra of such compounds registered at 200 and 400 MHz evidenced small differences in chemical shifts of equivalent atoms in the $^1H$- as well as the $^{13}C$-NMR spectrum.[21] Both, MS and elemental analyses confirmed the formation of a 1:1-adduct of **1a** and **5a**, and finally, the molecular structure of **6a** was established by X-Ray crystallography (*Scheme 3, Figure*). The analogous reactions of **1a** with benzyl and propyl chlorodithioformate (**5b** and **5c**), yielded the azetidine derivatives (**6b**) and (**6c**), respectively (*Scheme 3*).

*Scheme 3*




**1a** **5a** R = Ph, **b** R = $PhCH_2$, **c** R = Pr **6a** R = Ph, **b** R = $PhCH_2$, **c** R = Pr




**7a**

The dithiocarbamates (**6a**) and (**6b**) have also been prepared by an alternative method using thiocarbamoyl chloride (**7a**), which was easily accessible by addition of thiophosgene and **1a** (*Scheme 3*). The reaction of thiophosgene with **1a** is exothermic, and the mixture had to be cooled. In the $^1H$-NMR spectrum of **7a**, the $CH_2$ groups appear as a multiplet at 4.78-5.28 ppm. The $^{13}C$-NMR spectrum shows a characteristic absorption for C=S at 172.6 ppm (*N*,*N*-dimethylthiocarbamoyl chloride: 187.3 ppm[21b] or 173.1 ppm[23]) as well as two triplets for $CH_2$ groups (70.0 and 71.3 ppm) and one singlet for the

quaternary C-atom (58.4 ppm) of the azetidine moiety. Without isolation, the solution of the crude **7a** was treated with two equivalents of benzenethiol and benzyl sulfane, respectively, in the presence of one equivalent of $Et_3N$. After 24 h and aqueous workup, **6a** and **6b** were isolated. The attempted reaction of **7a** with *tert*-butyl sulfane failed, and after 24 h the $^1$H-NMR spectrum revealed the presence of unconsumed **7a**.

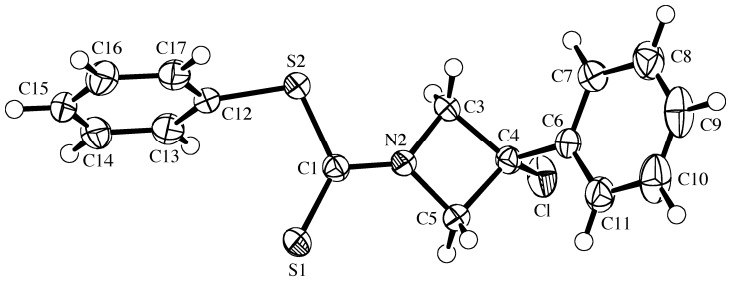
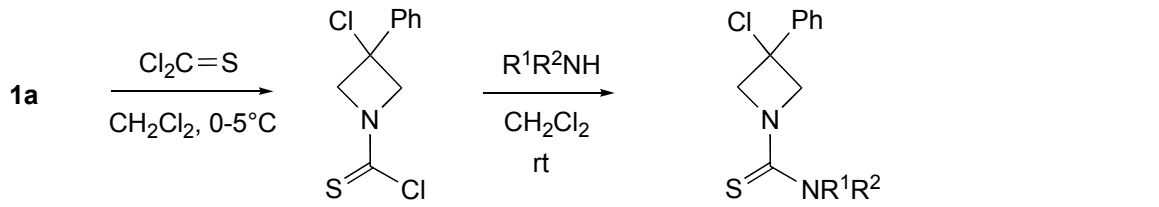



*Figure 1*. ORTEP plot[22] of the molecular structure of **6a** (50% probability ellipsoids; arbitrary numbering of atoms).

The *in situ* prepared **7a** was also treated with piperidine or morpholine (2 equiv.) to give, after 1 h at room temperature, the expected thioureas (**8a**) and (**8b**), respectively (*Scheme 4*). Similarly, the reaction with aniline led to **8c**. In contrast to dithiocarbamates of type **6**, the $^{13}$C-NMR spectra of thioureas (**8**) showed only one $CH_2$-absorption for the azetidine ring.

*Scheme 4*




**7a**

**8a** $R^1 - R^2 = -(CH_2)_5-$

**b** $R^1 - R^2 = -(CH_2)_2-O-(CH_2)_2-$

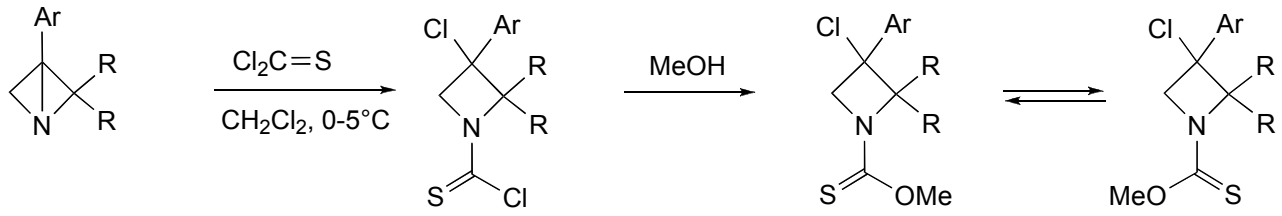
**c** $R^1$ = Ph, $R^2$ = H

Furthermore, the α- and β-C atoms of the piperidine and morpholine residues showed one signal for two $CH_2$ groups in each case. This phenomenon indicates that the rotation barrier for the CN bonds in the thiourea derivatives (**8**) is significantly lower than in the dithiocarbamates (**6**). This observation fits well with the reported low rotational barrier in tetrasubstituted thioureas.[24]

With the aim of preparing symmetrical thioureas bearing two azetidine rings, the reaction of **1a** with thiophosgene in the ratio of 2:1 was carried out. After addition of thiophosgene to the solution of **1a** in $CH_2Cl_2$ at 0–5°C and stirring of the mixture for 10 min, the solvent was evaporated, and a viscous oily residue was obtained, which was identified as **7a**. None of the expected thiourea could be detected.

In extension of the reactions of **7a** with thiols and amines, MeOH was used as an *O*-nucleophile. The crude **7a**, prepared in a typical manner (1:1 ratio of **1a** and $Cl_2C$=S), was dissolved in MeOH, and the solution was left at room temperature over night. A crystalline product was isolated and identified as thiocarbamate (**9a**) (*Scheme 5*). The MeO group of this product absorbs at 4.00 ($^1$H) and 58.0 ppm ($^{13}$C). In the $^{13}$C-NMR spectrum, the signal of the C=S group appears at 189.4 ppm, and two signals for the two $CH_2$ groups were found at 67.3 and 68.7 ppm. The quarternary azetidine C-atom absorbs at 61.0 ppm. In the case of 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (**1b**), the crude 1:1-adduct (**7b**) was obtained in almost quantitative yield. Its $^{13}$C-NMR spectrum shows two C=S signals at 174.7 and 173.1 ppm and two sets of two Me signals at 25.6/23.5 and 25.2/22.5 ppm, which indicates the presence of two rotamers in almost equal amounts. The reaction of this product with MeOH afforded **9b** as a crystalline material. On the basis of the $^1$H-NMR spectrum (signals at 1.83/1.08 and 2.03/1.32 ppm), the ratio of the two rotamers was determined to *ca*. 5:1.

*Scheme 5*



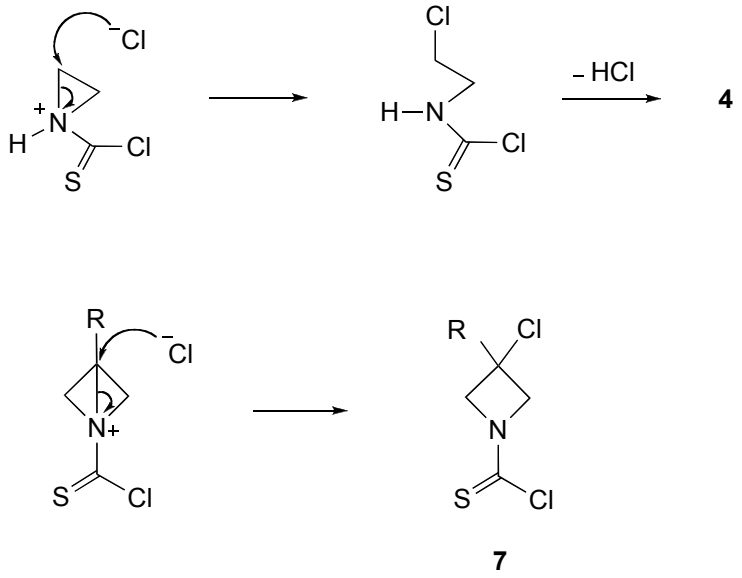

**1a** Ar = Ph, R = H
**b** Ar = Ph, R = Me
**c** Ar = 4-$FC_6H_4$, R = Me

**7a** Ar = Ph, R = H
**b** Ar = Ph, R = Me
**c** Ar = 4-$FC_6H_4$, R = Me

**9a** Ar = Ph, R = H
**b** Ar = Ph, R = Me
**c** Ar = 4-$FC_6H_4$, R = Me

In summary, the results described in this paper show that the reactions of 1-azabicyclo[1.1.0]butanes (**1**) with chlorodithioformates and thiophosgene, respectively, open straightforward access to the hitherto unknown thiocarbamoyl derivatives of azetidine. In contrast to the reaction of $Cl_2C$=S with the structurally related aziridine, which after ring opening and elimination of HCl leads to a chlorinated isothiocyanate (see *Scheme 2*), compounds (**1**) undergo conversion to the less strained and relatively stable adducts (**7**). In spite of this difference, the reaction mechanisms of these two transformations follow a similar pathway, typical for three-membered nitrogen heterocycles (*Scheme 6*).

*Scheme 6*




## EXPERIMENTAL

**General remarks**. Melting points (mp) were determined in capillary using a *Meltemp 2* apparatus and are uncorrected. IR spectra (KBr pellets or neat) were recorded with a *Nexus* spectrophotometer. $^{1}$H- and $^{13}$C-NMR spectra were registered with a *Tesla BS 687* instrument (80 MHz and 20 MHz, respectively) or a *Bruker 300* (300 MHz and 75 MHz, respectively) spectrometer using TMS ($\delta = 0$ ppm) as an internal standard. MS (CI) were recorded on a *Finnigan-Mat-90* or *Finnigan-SSQ-700* spectrometer. Elemental analyses were performed in the Analytical Laboratory of the University of Zurich or in the Laboratory of the Polish Academy of Sciences (CBMiM) in Lodz.

**Starting materials**. 3-Phenyl-1-azabicyclo[1.1.0]butane (**1a**), 2,2-dimethyl-3-phenyl-1-azabicyclo[1.1.0]butane (**1b**), and 2,2-dimethyl-3-(4-fluorophenyl)-1-azabicyclo[1.1.0]butane (**1c**) were prepared according to a known protocol from trimethylsulfonium iodide, butyllithium and the corresponding azirine.[25] Phenyl chlorodithioformate (**5a**), benzyl chlorodithioformate (**5b**), and propyl chlorodithioformate (**5c**) were synthesized from the corresponding sulfane and thiophosgene in $CHCl_3$/aq. NaOH (**5a**)[26] or in $CS_2$ (**5b**, **5c**).[27]

*2,2-Dimethyl-3-(4-fluorophenyl)-1-azabicyclo[1.1.0]butane* (**1c**). Yield: 3.20 g (65%). Colorless, thick oil distilled in a Kugelrohr at 80°C/0.2 Torr. IR (KBr): 1522*s*, 1223*s*, 833*s*, 607*m*, 553*s*. $^{1}$H-NMR ($CDCl_3$): 1.14, 1.18 (2*s*, 2 Me), 2.49, 2.62 (*AB*, $J = 1.6$ Hz, $CH_2N$), 6.90–7.46 (*m*, 4 arom. H). $^{13}$C-NMR ($CDCl_3$): 12.8, 22.8 (2 Me), 41.3 ($Me_2C$), 54.2 ($CH_2N$), 68.4 ($C_q$), 115.3 (*d*, $^{2}J_{C,F} = 21.7$ Hz, 2 arom. CH), 130.2 (*d*,

$^3J_{C,F}$ = 8.3 Hz, 2 arom. CH), 130.6 (*d*, $^4J_{C,F}$ = 2.9 Hz, arom. $C_q$), 162.5 (*d*, $^1J_{C,F}$ = 246.4 Hz, arom. $C_qF$). CI-MS: 179 (12), 178 (100, $[M+1]^+$).

**Reaction of 1a with chlorodithioformates (5). General procedure A** (GPA). A mixture of 1 mmol of **1a** and 1 mmol of the corresponding chlorodithioformate in 1 mL of $CH_2Cl_2$ was stirred magnetically for ca. 1 h. Then, the solvent was evaporated and the product was isolated after preparative layer chromatography using plates precoated with silica and hexane/$CH_2Cl_2$ 3:2 as the eluent. Analytically pure samples were obtained by crystallization from MeOH/$CH_2Cl_2$, $Et_2O$ and hexane, respectively.

**Reaction of 7a with thiophenol and benzyl sulfane. General procedure B** (GPB). A solution of the crude **7a** in 2 mL of $CH_2Cl_2$ was treated with a mixture of 101 mg (1 mmol) of $Et_3N$ and 2 mmol of the corresponding thiol in 1 mL of $CH_2Cl_2$ at rt. The mixture was stirred for 24 h, the solution was diluted with 7 mL of $CH_2Cl_2$ and washed first with a 2% aqueous solution of NaOH, then with a 2% aqueous solution of HCl, and finally with water. The organic phase was separated and dried over $MgSO_4$. Analytically pure samples were obtained after crystallization from a mixture of MeOH and $CH_2Cl_2$ (reaction with thiophenol) or after preparative layer chromatography using plates precoated with silica and hexane/$CH_2Cl_2$ 1:1 as the eluent and subsequent crystallization from diethyl ether.

*Phenyl 3-chloro-3-phenylazetidine-1-carbodithioate* (**6a**). Yield: 160 mg (50%; GPA) and 130 mg (41%; GPB). Colorless crystals; mp 142–145°C (MeOH/$CH_2Cl_2$). IR (KBr): 1467*s*, 1438*s*, 1176*s*, 982*m*, 748*m*, 699*m*. $^1$H-NMR ($CDCl_3$): 4.87–5.00 (*m*, 2 $CH_2N$), 7.38–7.52 (*m*, 10 arom. H). $^{13}$C-NMR ($CDCl_3$): 60.9 ($C_q$), 69.4, 70.3 (2 $CH_2N$), 125.6, 128.8, 129.0, 129.2, 130.2, 136.5 (10 arom. CH), 129.5, 140.6 (2 arom. $C_q$), 195.4 (C=S). CI-MS: 323 (7), 322 (38), 321 (17, $[M+1]^+$), 320 (100, $M^{+\cdot}$). Anal. Calcd for $C_{16}H_{14}NClS_2$: C, 60.08; H, 4.41; N, 4.38; S, 20.05. Found: C, 60.03; H, 4.44; N, 4.36; S, 19.83.

*Benzyl 3-chloro-3-phenylazetidine-1-carbodithioate* (**6b**). Yield: 240 mg (72%; GPA) and 120 mg (36%; GPB). Colorless crystals; mp 52–54°C ($Et_2O$). IR (KBr): 1479*s*, 1440*s*, 1171*s*, 979*s*, 725*m*, 695*s*, 614*m*. $^1$H-NMR ($CDCl_3$): 4.56 (*s*, $CH_2S$), 4.76, 4.82 (*AB*, *J* = 11.1 Hz, $CH_2N$), 4.88, 4.97 (*AB*, *J* = 12.1 Hz, $CH_2N$), 7.25–7.42 (*m*, 10 arom. H). $^{13}$C-NMR ($CDCl_3$): 40.7 ($CH_2S$), 61.1 ($C_q$), 68.8, 70.2 (2 $CH_2N$), 125.5, 127.5, 128.6, 128.8, 128.9, 129.1 (10 arom. CH), 136.1, 140.6 (2 arom. $C_q$), 195.2 (C=S). CI-MS: 336 (42), 334 (100, $M^{+\cdot}$), 300 (26), 178 (23). Anal. Calcd for $C_{17}H_{16}NClS_2$: C, 61.15; H, 4.83; N, 4.19; S, 19.2. Found: C, 60.16; H, 4.85; N, 4.02; S, 18.30.

*Propyl 3-chloro-3-phenylazetidine-1-carbodithioate* (**6c**). Yield: 220 mg (77%; GPA). Colorless crystals; mp 46–48°C (hexane). IR (KBr): 1485*vs*, 1448*s*, 1436*s*, 1422*m*, 1172*vs*, 977*s*, 718*m*, 693*s*, 619*m*, 524*m*.

$^1$H-NMR ($CDCl_3$): 1.02 (*t*, *J* = 7.4 Hz, *Me*$CH_2$), 1.67–1.79 (m, MeC*H*$_2$$CH_2$), 3.26 (*t*, *J* = 7.5 Hz, $CH_2S$), 4.76–4.97 (*m*, 2 $CH_2N$), 7.33–7.43 (*m*, 10 arom. H). $^{13}$C-NMR ($CDCl_3$): 13.3 (*Me*$CH_2$), 22.4 (Me*C*$H_2$$CH_2S$), 38.0 (MeCH$_2$*C*$H_2S$), 61.1 ($C_q$), 68.8, 70.0 (2 $CH_2N$), 125.6, 128.7, 128.9 (5 arom. CH), 140.7 (arom. $C_q$), 196.2 (C=S). CI-MS: 288 (40), 287 (16, $[M+1]^+$), 286 (100, $M^{+\cdot}$), 252 (28). Anal. Calcd for $C_{13}H_{16}NClS_2$: C, 54.62; H, 5.64; N, 4.90; S, 22.44. Found: C, 54.67, H, 5.69, N, 4.85, S, 22.24.

**Reaction of azabicyclobutanes (1) with thiophosgene. General procedure.** A solution of 1 mmol of the corresponding azabicyclobutane (**1**) in 1 mL of $CH_2Cl_2$ in an ice-water bath was stirred magnetically and 115 mg (1 mmol) of thiophosgene in 1 mL of $CH_2Cl_2$ was added. The stirring was continued for 5 min. After evaporation of the solvent, the crude **7** was analyzed without purification.

*3-Chloro-3-phenylazetidine-1-carbothioyl chloride* (**7a**). Yield: 241 mg (98%). Yellowish, thick oil. IR (neat): 1513*m*, 1500*m*, 1460*m*, 1447*m*, 1173*m*, 990*m*. $^1$H-NMR ($CDCl_3$): 4.78–4.98 (*m*, 2 $CH_2N$), 7.35–7.47 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.4 ($C_q$), 70.0, 71.3 (2 $CH_2N$), 125.6, 129.1, 129.1 (5 arom. CH), 140.0 ( arom. $C_q$), 172.6 (C=S). CI-MS: 250 (11), 248 (69), 247 (12, $[M+1]^+$), 246 (100, $M^{+\cdot}$), 212 (25), 210 (45, $[M–Cl]^+$). Anal. Calcd for $C_{10}H_9NCl_2S$: C, 48.79; H, 3.69; N, 5.69. Found: C, 48.52; H, 3.71; N, 5.64.

*3-Chloro-2,2-dimethyl-3-phenylazetidine-1-carbothioyl chloride* (**7b**). Yield: 266 mg (97%). Yellowish, thick oil. IR (neat): 1488*br*, 1443*m*, 1128*m*, 738*m*, 697*m*, 645*m*, 586*m*.$^1$H-NMR ($CDCl_3$): major rotamer: 1.26, 1.99 (2*s*, 2 Me), 4.53, 5.06 (*AB*, *J* = 12.8 Hz, 2 $CH_2N$), 7.21–7.57 (*m*, 5 arom. H); minor rotamer: 1.35, 2.05 (2*s*, 2 Me), 4.65, 5.20 (*AB*, *J* = 12.8, 2 $CH_2N$), 7.21–7.57 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): major rotamer: 23.5, 25.6 (2 Me), 66.1 (2 $CH_2N$), 72.1 ($Me_2C$), 84.3 ($C_q$), 129.6, 131.6 (5 arom. CH), 140.8 (arom. $C_q$), 173.1 (C=S); minor rotamer: 22.5, 25.2 (2 Me), 68.0 (2 $CH_2N$), 71.9 ($Me_2C$), 83.0 ($C_q$), 129.5, 131.7 (5 arom. CH), 140.4 (arom. $C_q$), 174.8 (C=S). CI-MS: 278 (14), 277 (13), 276 (68), 275 (21, $[M+1]^+$), 274 (100, $M^{+\cdot}$), 240 (25), 238 (60, $[M–Cl]^+$), 196 (18). Anal. Calcd for $C_{12}H_{13}NCl_2S$: C, 52.56; H, 4.78; N, 5.11; S, 11.69. Found: C, 52.37; H, 4.97; N, 4.98; S, 11.63.

*3-Chloro-2,2-dimethyl-3-(4-fluorophenyl)azetidine-1-carbothioyl chloride* (**7c**). Yield: 278 mg (95%). Yellowish, thick oil. IR (KBr): 1490*br*, 1443*s*, 1236*s*, 1156*m*, 1123*m*, 842*m*, 829*m*, 818*m*, 754*m*, 591*m*, 569*m*. $^1$H-NMR ($CDCl_3$): major rotamer: 1.25, 1.98 (2*s*, 2 Me), 4.53, 5.02 (*AB*, *J* = 12.8 Hz, $CH_2N$), 6.96–7.48 (*m*, 5 arom. H); minor rotamer: 1.34, 2.04 (2*s*, 2 Me), 4.66, 5.16 (*AB*, *J* = 12.8 Hz, $CH_2N$), 6.96–7.48 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): major rotamer: 23.5, 25.6 (2 Me), 66.3 (2 $CH_2N$), 71.3 ($Me_2C$), 84.3 ($C_q$), 118.3 (*d*, $^2J_{C,F}$ = 22.6 Hz, 2 arom. CH), 131.7 (*d*, $^3J_{C,F}$ = 8.8 Hz, 2 arom. CH), 136.9 (*d*,

$^4J_{C,F}$ = 3.6 Hz, arom. $C_q$), 166.2 (*d*, $^1J_{C,F}$ = 253.2 Hz, arom. $C_qF$), 174.8 (C=S); minor rotamer: 22.5, 25.3 (2 Me), 68.2 (2 $CH_2N$), 71.5 ($Me_2C$), 83.0 ($C_q$), 118.3 (*d*, $^2J_{C,F}$ = 22.6 Hz, 2 arom. CH), 131.6 (*d*, $^3J_{C,F}$ = 8.8 Hz, 2 arom. CH), 136.9 (*d*, $^4J_{C,F}$ = 3.6 Hz, arom. $C_q$), 166.2 (*d*, $^1J_{C,F}$ = 253.2 Hz, arom. $C_qF$), 173.2 (C=S). CI-MS: 294 (68), 292 (100, $M^{+\cdot}$), 258 (26), 256 (67, $[M–Cl]^+$).

**Reaction of 7a with piperidine, morpholine, and aniline. General procedure**. To a solution of 1 mmol of the crude **7a** dissolved in 2 mL of $CH_2Cl_2$ was treated with 2 mmol of the corresponding amine in 1 mL of $CH_2Cl_2$ and the mixture was stirred magnetically at rt. After 4 h, the solution was diluted with 7 mL of $CH_2Cl_2$ and shaken with water. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The oily residue was purified by crystallization.

*(3-Chloro-3-phenylazetidin-1-yl)(piperidin-1-yl)methanethione* (**8a**). Yield: 90 mg (31%). Colorless crystals; mp 75–78°C (MeOH). IR (KBr): 2934*m*, 1495*s*, 1464*s*, 1446*s*, 1380*s*, 1348*m*, 1319*m*, 1281*m*, 1252*s*, 1222*m*, 701*m*. $^1$H-NMR ($CDCl_3$): 1.63–1.65 (*m*, 3 $CH_2$), 3.46–3.70 (*m*, 2 $CH_2N$), 4.74, 4.85 (*AB*, *J* = 9.7 Hz, $CH_2N$), 4.74, 4.86 (*AB*, *J* = 10.1 Hz, $CH_2N$), 7.30–7.44 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): 24.2 ($CH_2$), 25.7 (2 $CH_2$), 50.8 (2 $CH_2N$), 61.4 ($C_q$), 70.3 (2 $CH_2N$), 125.5, 128.4, 128.8 (5 arom. CH), 141.4 (arom. $C_q$), 188.4 (C=S). CI-MS: 297 (3), 295 (7, $M^{+\cdot}$), 261 (17), 260 (18), 259 (100, $[M$-Cl$]^+$). Anal. Calcd for $C_{15}H_{19}N_2ClS$: C, 61.10; H, 6.50; N, 9.50; S, 10.88. Found: C, 61.04; H, 6.31; N, 9.43; S, 10.73.

*(3-Chloro-3-phenylazetidin-1-yl)(morpholin-4-yl)methanethione* (**8b**). Yield: 70 mg (24%). Colorless crystals, mp 128–130°C (MeOH). IR (KBr): 1474*s*, 1443*s*, 1431*s*, 1348*s*, 1308*s*, 1278*s*, 1231*s*, 1114*s*. $^1$H-NMR ($CDCl_3$): 4.01–4.08 (*m*, 2 $NCH_2CH_2O$), 5.06, 5.18 (*AB*, *J* = 9.8 Hz, $CH_2N$), 5.07, 5.18 (*AB*, *J* = 10.2 Hz, $CH_2N$), 7.61–7.72 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): 49.8 (2 $CH_2N$), 61.4 ($C_q$), 66.3 (2 $CH_2O$), 70.3 (2 $CH_2N$), 125.5, 128.5, 128.8 (5 arom. CH), 141.2 (arom. $C_q$), 188.9 (C=S). CI-MS: 299 (38), 298 (17, $[M$+1$]^+$), 297 (100, $M^{+\cdot}$), 263 (55), 261 (40, $[M$-Cl$]^+$), 217 (15). Anal. Calcd for $C_{14}H_{17}N_2OClS$: C, 56.65; H, 5.77; N, 9.44; S, 10.80. Found: C, 57.06; H, 6.02; N, 9.25; S, 10.18.

*3-Chloro-3-phenylazetidine-1-carbothioic acid* N-*phenylamide* (**8c**). Yield: 68 mg (22%). Yellowish crystals; mp 154–158°C (hexane/$CH_2Cl_2$). IR (KBr): 1537*s*, 1497*m*, 1452*s*, 1419*m*, 1348*m*, 696*s*. $^1$H-NMR ($CDCl_3$): 4.58–4.62 (*m*, 2 $CH_2N$), 7.10–7.57 (*m*, 10 arom. H). $^{13}$C-NMR ($CDCl_3$): 60.9 ($C_q$), 69.0 (2 $CH_2N$), 125.2, 125.9, 126.7, 129.0, 129.3 129.5 (10 arom. CH), 138.3 (arom. $C_q$), 141.4 (arom. CN), 181.7 (C=S). CI-MS: 305 (38), 304 (21, $[M$+1$]^+$), 303 (100, $M^{+\cdot}$), 269 (10), 267 (13), 266 (10). Anal. Calcd for $C_{16}H_{15}N_2ClS$: C, 63.46; H, 4.99; N, 9.25; S, 10.59. Found: C, 62.57; H, 5.04; N, 9.05; S, 9.89.

**Reaction of 7 with methanol. General procedure**. 1 Mmol of crude **7** was crystallized from MeOH leading to the substitution product (**9**).

*3-Chloro-3-phenylazetidine-1-carbothioic acid* O-*methyl ester* (**9a**). Yield: 175 mg (71%). Colorless crystals; mp 94–96°C. IR (KBr): 1528*vs*, 1492*s*, 1448*m*, 1432*m*, 1279*s*, 1268*m*, 1234*vs*, 1147*m*, 696*m*. $^1$H-NMR ($CDCl_3$): 4.00 (*s*, MeO), 4.60–4.85 (*m*, 2 $CH_2N$), 7.25–7.50 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): 58.0 (MeO), 61.0 ($C_q$), 67.3, 68.7 (2 $CH_2N$), 126.0, 129.1, 129.3 (5 arom. CH), 141.5 (arom. $C_q$), 189.4 (C=S). CI-MS: 244 (37), 243 (16, $[M+1]^+$), 242 (100, $M^{+\cdot}$). Anal. Calcd for $C_{11}H_{12}NOClS$: C, 54.65; H, 5.00; Cl, 14.67; S, 13.27. Found: C, 52.93; H, 4.89; Cl, 14.22; S, 13.00.

*3-Chloro-2,2-dimethyl-3-phenylazetidine-1-carbothioic acid* O-*methyl ester* (**9b**). Yield: 162 mg (59%). Yellowish crystals; mp 106–109°C. IR (KBr): 1489*vs*, 1456*m*, 1440*s*, 1265*s*, 1252*s*, 1221*m*, 1139*s*, 738*s*, 693*s*. $^1$H-NMR ($CDCl_3$): major rotamer: 1.08, 1.83 (2*s*, 2 Me), 4.04 (*s*, MeO), 4.43, 4.98 (*AB*, *J* = 12.0 Hz, $CH_2N$), 7.29–7.31 (*m*, 5 arom. H); minor rotamer: 1.32, 2.03 (2*s*, 2 Me), 3.97 (*s*, MeO), 4.43, 4.98 (*AB*, *J* = 12.0 Hz, 2 $CH_2N$), 7.29–7.31 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): major rotamer: 24.5, 25.1 (2 Me), 57.4 (MeO), 61.9 (2 $CH_2N$), 71.3 ($Me_2C$), 77.4 ($C_q$), 127.2, 128.9 (5 arom. CH), 139.3 (arom. $C_q$), 189.7 (C=S); minor rotamer: 22.7, 23.8 (2 Me), 56.3 (MeO), 61.9 (2 $CH_2N$), 71.3 ($Me_2C$), 77.4 ($C_q$), 127.2, 128.9 (5 arom. CH), 139.3 (arom. $C_q$), 189.7 (C=S). CI-MS: 272 (36), 271 (17, $[M+1]^+$), 270 (100, $M^{+\cdot}$), 131 (13). Anal. Calcd for $C_{13}H_{16}NOClS$: C, 57.88; H, 5.98; N, 5.19; S, 11.89. Found: C, 57.67; H, 5.96; N, 5.08; S, 11.91.

*3-Chloro-2,2-dimethyl-3-(4-fluorophenyl)azetidine-1-carbothioic acid* O-*methyl ester* (**9c**). Yield: 165 mg (57%). Yellowish crystals; mp 116–118°C. IR (KBr): 1496*s*, 1266*m*, 1253*m*, 1234*m*. $^1$H-NMR ($CDCl_3$): major rotamer: 1.08, 1.81 (2*s*, 2 Me), 4.03 (*s*, MeO), 4.43, 4.93 (*AB*, *J* = 12.0 Hz, 2 $CH_2N$), 6.93–7.47 (*m*, 5 arom. H); minor rotamer: 1.30, 2.03 (2*s*, 2 Me), 3.97 (*s*, MeO), 4.43, 4.93 (*AB*, *J* = 12.0 Hz, 2 $CH_2N$), 6.93–7.47 (*m*, 5 arom. H). $^{13}$C-NMR ($CDCl_3$): major rotamer: 24.7, 24.9 (2 Me), 57.4 (MeO), 61.8 (2 $CH_2N$), 70.4 ($Me_2C$), 77.2 ($C_q$), 115.6 (*d*, $^2J_{C,F}$ = 21.7 Hz, 2 arom. CH), 128.8 (*d*, $^3J_{C,F}$ = 8.2 Hz, 2 arom. CH), 134.9 (*d*, $^4J_{C,F}$ = 3.4 Hz, arom. $C_q$), 162.4 (*d*, $^1J_{C,F}$ = 249.0 Hz, arom. $C_qF$), 189.1 (C=S); minor rotamer: 22.7, 23.7 (2 Me), 56.2 (MeO), 61.8 (2 $CH_2N$), 71.9 ($Me_2C$), 78.3 ($C_q$), 115.6 (*d*, $^2J_{C,F}$ = 21.7 Hz, 2 arom. CH), 128.8 (*d*, $^3J_{C,F}$ = 8.2 Hz, 2 arom. CH), 134.9 (*d*, $^4J_{C,F}$ = 3.4 Hz, arom. $C_q$), 162.4 (*d*, $^1J_{C,F}$ = 249.0 Hz, arom. $C_qF$), 189.1 (C=S). CI-MS: 290 (38), 289 (15, $[M+1]^+$), 288 (100, $M^{+\cdot}$), 254 (10), 252 (9, $[M-Cl]^+$). Anal. Calcd for $C_{13}H_{15}NOClFS$: C, 54.26; H, 5.98; N, 4.87; S, 11.14. Found: C, 54.48; H, 5.88; N, 4.98; S, 11.11.

**X-Ray Crystal-Structure Determination of 6a** (see *Table 1* and *Figure 1*).[28] All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer[29] using graphite-monochromated Mo$K_a$ radiation ($\lambda$ 0.71073 Å) and with an *Oxford Cryosystems Cryostream 700* cooler. The data collection and

Table 1. *Crystallographic Data of Compound* (**6a**)

| | | |
|---|---|---|
| Crystallized from | | $MeOH/CH_2Cl_2$ |
| Empirical formula | | $C_{16}H_{14}O_2S_4$ |
| Formula weight [g mol$^{-1}$] | | 319.87 |
| Crystal color, habit | | colorless, prism |
| Crystal dimensions [mm] | | 0.12 × 0.30 × 0.32 |
| Temperature [K] | | 273(1) |
| Crystal system | | monoclinic |
| Space group | | $P2_1/c$ |
| $Z$ | | 4 |
| Reflections for cell determination | | 20580 |
| $2\theta$ range for cell determination [°] | | 4 – 55 |
| Unit cell parameters | $a$ [Å] | 9.2577(2) |
| | $b$ [Å] | 18.3804(4) |
| | $c$ [Å] | 8.9874(2) |
| | $\beta$ [°] | 94.382(1) |
| | $V$ [Å$^3$] | 1524.83(6) |
| $D_x$ [g cm$^{-3}$] | | 1.393 |
| $\mu$(Mo$K_\alpha$) [mm$^{-1}$] | | 0.512 |
| Scan type | | $\phi$ and $\omega$ |
| $2\theta$(max) [°] | | 55 |
| Transmission factors (min; max) | | 0.836; 0.942 |
| Total reflections measured | | 32689 |
| Symmetry independent reflections | | 3489 |
| Reflections with $I > 2\sigma(I)$ | | 2776 |
| Reflections used in refinement | | 3488 |
| Parameters refined | | 181 |
| Final $R(F)$ [$I > 2\sigma(I)$ reflections] | | 0.0395 |
| $wR(F^2)$ (all data) | | 0.1046 |
| Weights: $w = [\sigma^2(F_o^2) + (0.0493P)^2 + 0.7442P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$ | | |
| Goodness of fit | | 1.048 |
| Final $\Delta_{max}/\sigma$ | | 0.001 |
| $\Delta\rho$ (max; min) [e Å$^{-3}$] | | 0.28; -0.51 |

refinement parameters are given in *Table 1*, and a view of the molecule is shown in *Figure 1*. Data reduction for was performed with *HKL Denzo* and *Scalepack*.[30] The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method[31] was applied. The structure was solved by direct methods using SIR92,[32] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom. The refinement of the structure was carried out on $F^2$ using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. One reflection, whose intensity was considered to be an extreme outlier, was omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from ref.[33a], and the scattering factors for H-atoms were taken from ref.[34] Anomalous dispersion effects were included in $F_c$;[35] the values for $f'$ and $f''$ were those of ref.[33b] The values of the mass attenuation coefficients are those of ref.[33c] All calculations were performed using the SHELXL97 program.[36]

**ACKNOWLEDGEMENT**

G. M., M. W. and K. U. thank the *Polish State Committee for Scientific Research* for financial support (Grant KBN No. 4 T09A 046 25); H. H. acknowledges financial support by *F. Hoffmann-La Roche AG*, Basel. We thank PD Dr. A. Linden, University of Zürich, for the crystal-structure determination.

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