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

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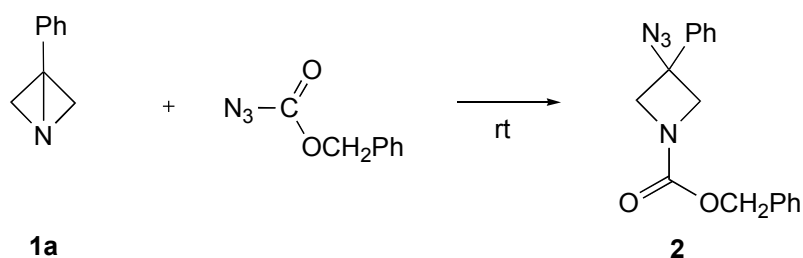
Abstract – The reaction of 3-phenyl-1-azabicyclo[1.1.0]butane (**1a**) with chlorodithio-formates (**5**) at room temperature yielded 3-chloro-3-phenylazetidine-1-carbodithioates (**6**). The same products were obtained in a two-step procedure by treatment of **1a** with thiophosgene to give azetidine-1-carbothioyl 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, ClCO₂R, N₃CO₂R, TsCl, TsN₃, HF, etc) across the weakest C-N bond to give azetidine derivatives. As an example, the addition of benzyl

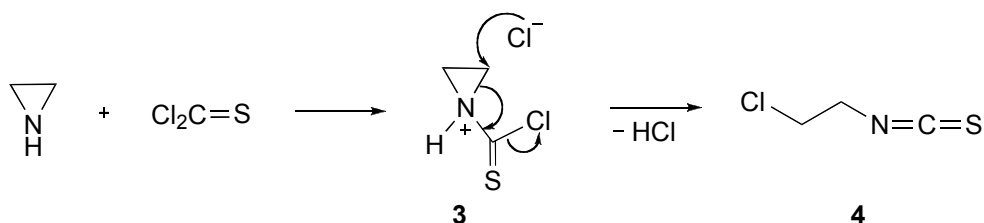
azidoformate with 3-phenyl-1-azabicyclo[1.1.0]butane (**1a**) leading to 1-benzyloxyazetidine (**2**) is shown in *Scheme 1*.⁷

Scheme 1



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

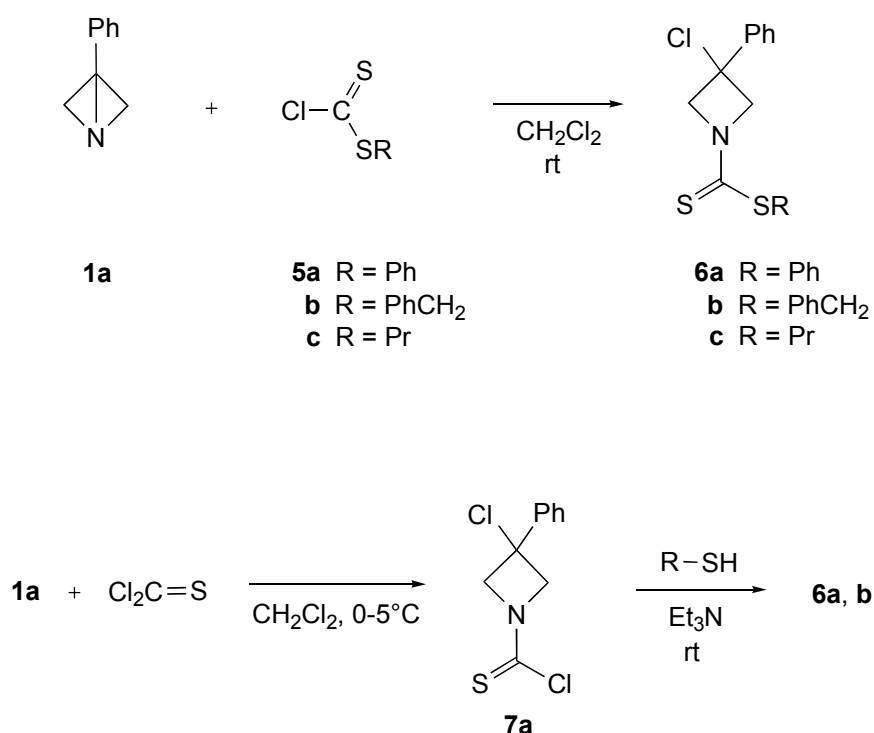


RESULTS AND DISCUSSION

The reaction of **1a** with phenyl chlorodithioformate (**5a**) was carried out at room temperature in CH₂Cl₂. 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 ¹H-NMR spectrum, the

signals of the two CH₂ groups appear as a complex multiplet (4.87–5.00 ppm); the corresponding ¹³C 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 ¹³C-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



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 CH₂ groups appear as a multiplet at 4.78–5.28 ppm. The ¹³C-NMR spectrum shows a characteristic absorption for C=S at 172.6 ppm (*N,N*-dimethylthiocarbamoyl chloride: 187.3 ppm^{21b} or 173.1 ppm²³) as well as two triplets for CH₂ 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 Et₃N. 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 ¹H-NMR spectrum revealed the presence of unconsumed **7a**.

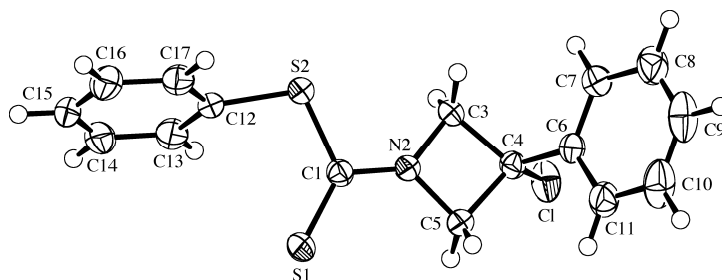
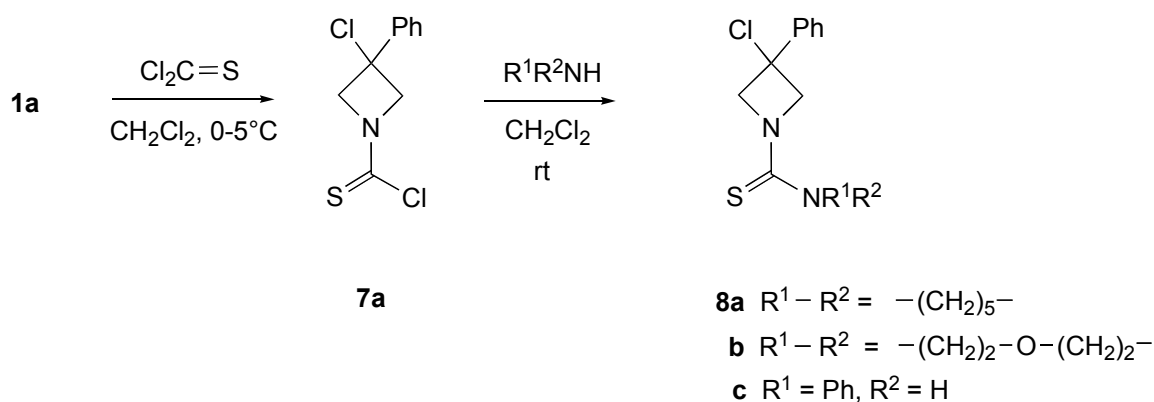


Figure 1. ORTEP plot²² of the molecular structure of **6a** (50% probability ellipsoids; arbitrary numbering of atoms).

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 ¹³C-NMR spectra of thioureas (**8**) showed only one CH₂-absorption for the azetidine ring.

Scheme 4

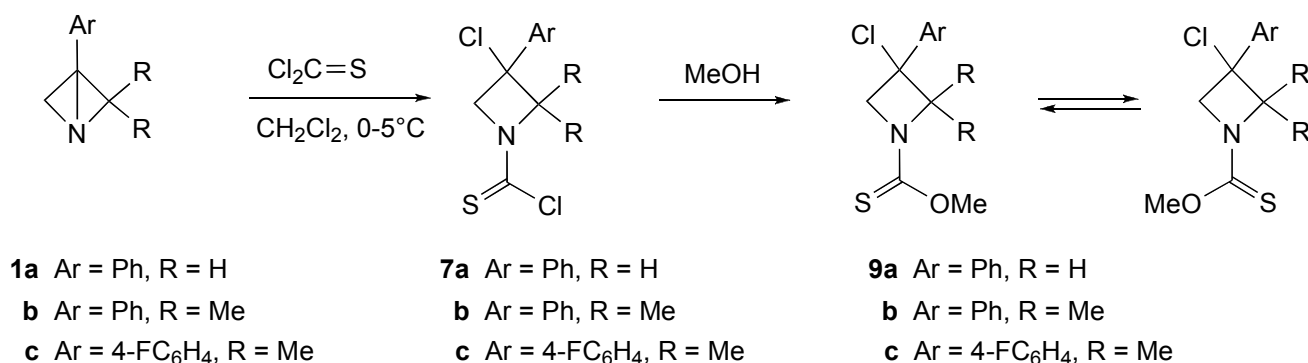


Furthermore, the α- and β-C atoms of the piperidine and morpholine residues showed one signal for two CH₂ groups in each case. This phenomenon indicates that the rotation barrier for the CN bonds in the thiourea derivatives (**8**) is significantly lower than in the dithiocarbamates (**6**). This observation 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 $0-5^\circ\text{C}$ 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.

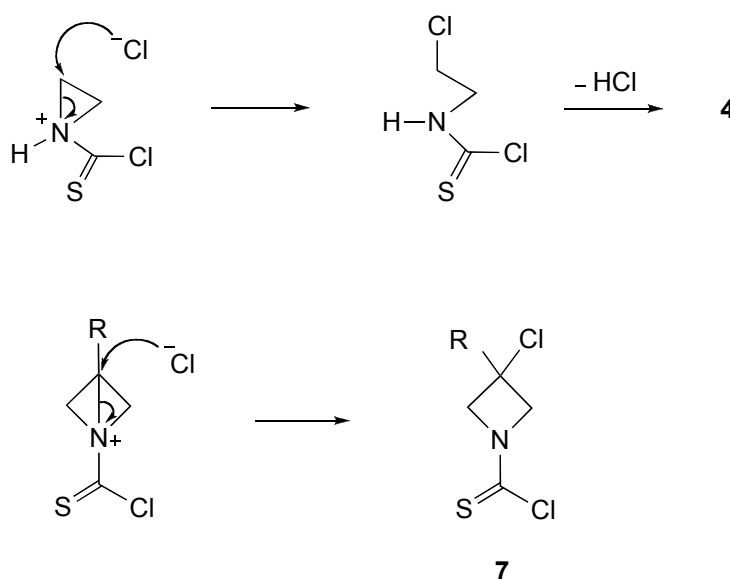
In extension of the reactions of **7a** with thiols and amines, MeOH was used as an *O*-nucleophile. The crude **7a**, prepared in a typical manner (1:1 ratio of **1a** and $\text{Cl}_2\text{C}=\text{S}$), was dissolved in MeOH, and the solution was left at room temperature over night. A crystalline product was isolated and identified as thiocarbamate (**9a**) (Scheme 5). The MeO group of this product absorbs at 4.00 (^1H) and 58.0 ppm (^{13}C). In the ^{13}C -NMR spectrum, the signal of the $\text{C}=\text{S}$ 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 $\text{C}=\text{S}$ 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 ^1H -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



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 $\text{Cl}_2\text{C}=\text{S}$ 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. ^1H - 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 $\text{CHCl}_3/\text{aq. NaOH}$ (**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 $80^\circ\text{C}/0.2$ Torr. IR (KBr): 1522s, 1223s, 833s, 607m, 553s. ^1H -NMR (CDCl_3): 1.14, 1.18 (2s, 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, $^2J_{\text{C,F}} = 21.7$ Hz, 2 arom. CH), 130.2 (d,

$^3J_{\text{C,F}} = 8.3$ Hz, 2 arom. CH), 130.6 (*d*, $^4J_{\text{C,F}} = 2.9$ Hz, arom. C_q), 162.5 (*d*, $^1J_{\text{C,F}} = 246.4$ 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 CH₂Cl₂ 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/CH₂Cl₂ 3:2 as the eluent. Analytically pure samples were obtained by crystallization from MeOH/CH₂Cl₂, Et₂O 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 CH₂Cl₂ was treated with a mixture of 101 mg (1 mmol) of Et₃N and 2 mmol of the corresponding thiol in 1 mL of CH₂Cl₂ at rt. The mixture was stirred for 24 h, the solution was diluted with 7 mL of CH₂Cl₂ 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 MgSO₄. Analytically pure samples were obtained after crystallization from a mixture of MeOH and CH₂Cl₂ (reaction with thiophenol) or after preparative layer chromatography using plates precoated with silica and hexane/CH₂Cl₂ 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/CH₂Cl₂). IR (KBr): 1467s, 1438s, 1176s, 982m, 748m, 699m. $^1\text{H-NMR}$ (CDCl₃): 4.87–5.00 (*m*, 2 CH₂N), 7.38–7.52 (*m*, 10 arom. H). $^{13}\text{C-NMR}$ (CDCl₃): 60.9 (C_q), 69.4, 70.3 (2 CH₂N), 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^+). Anal. Calcd for C₁₆H₁₄NCIS₂: 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 (Et₂O). IR (KBr): 1479s, 1440s, 1171s, 979s, 725m, 695s, 614m. $^1\text{H-NMR}$ (CDCl₃): 4.56 (*s*, CH₂S), 4.76, 4.82 (*AB*, $J = 11.1$ Hz, CH₂N), 4.88, 4.97 (*AB*, $J = 12.1$ Hz, CH₂N), 7.25–7.42 (*m*, 10 arom. H). $^{13}\text{C-NMR}$ (CDCl₃): 40.7 (CH₂S), 61.1 (C_q), 68.8, 70.2 (2 CH₂N), 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^+), 300 (26), 178 (23). Anal. Calcd for C₁₇H₁₆NCIS₂: 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): 1485vs, 1448s, 1436s, 1422m, 1172vs, 977s, 718m, 693s, 619m, 524m.

^1H -NMR (CDCl_3): 1.02 (*t*, $J = 7.4$ Hz, MeCH_2), 1.67–1.79 (*m*, MeCH_2CH_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 (MeCH_2), 22.4 ($\text{MeCH}_2\text{CH}_2\text{S}$), 38.0 ($\text{MeCH}_2\text{CH}_2\text{S}$), 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 ($\text{C}=\text{S}$). CI-MS: 288 (40), 287 (16, $[M+1]^+$), 286 (100, M^+), 252 (28). Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{NClS}_2$: 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*. ^1H -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 ($\text{C}=\text{S}$). CI-MS: 250 (11), 248 (69), 247 (12, $[M+1]^+$), 246 (100, M^+), 212 (25), 210 (45, $[M-\text{Cl}]^+$). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NCl}_2\text{S}$: 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*. ^1H -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 ($\text{C}=\text{S}$); 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 ($\text{C}=\text{S}$). CI-MS: 278 (14), 277 (13), 276 (68), 275 (21, $[M+1]^+$), 274 (100, M^+), 240 (25), 238 (60, $[M-\text{Cl}]^+$), 196 (18). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NCl}_2\text{S}$: 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*. ^1H -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*, $^2J_{\text{C,F}} = 22.6$ Hz, 2 arom. CH), 131.7 (*d*, $^3J_{\text{C,F}} = 8.8$ Hz, 2 arom. CH), 136.9 (*d*,

$^4J_{\text{C,F}} = 3.6$ Hz, arom. C_q), 166.2 (*d*, $^1J_{\text{C,F}} = 253.2$ Hz, arom. C_qF), 174.8 (C=S); minor rotamer: 22.5, 25.3 (2 Me), 68.2 (2 CH₂N), 71.5 (Me₂C), 83.0 (C_q), 118.3 (*d*, $^2J_{\text{C,F}} = 22.6$ Hz, 2 arom. CH), 131.6 (*d*, $^3J_{\text{C,F}} = 8.8$ Hz, 2 arom. CH), 136.9 (*d*, $^4J_{\text{C,F}} = 3.6$ Hz, arom. C_q), 166.2 (*d*, $^1J_{\text{C,F}} = 253.2$ Hz, arom. C_qF), 173.2 (C=S). CI-MS: 294 (68), 292 (100, M^+), 258 (26), 256 (67, $[M-\text{Cl}]^+$).

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 CH₂Cl₂ was treated with 2 mmol of the corresponding amine in 1 mL of CH₂Cl₂ and the mixture was stirred magnetically at rt. After 4 h, the solution was diluted with 7 mL of CH₂Cl₂ and shaken with water. The organic phase was dried over MgSO₄ 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*. $^1\text{H-NMR}$ (CDCl₃): 1.63–1.65 (*m*, 3 CH₂), 3.46–3.70 (*m*, 2 CH₂N), 4.74, 4.85 (*AB*, $J = 9.7$ Hz, CH₂N), 4.74, 4.86 (*AB*, $J = 10.1$ Hz, CH₂N), 7.30–7.44 (*m*, 5 arom. H). $^{13}\text{C-NMR}$ (CDCl₃): 24.2 (CH₂), 25.7 (2 CH₂), 50.8 (2 CH₂N), 61.4 (C_q), 70.3 (2 CH₂N), 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^+), 261 (17), 260 (18), 259 (100, $[M-\text{Cl}]^+$). Anal. Calcd for C₁₅H₁₉N₂ClS: 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*. $^1\text{H-NMR}$ (CDCl₃): 4.01–4.08 (*m*, 2 NCH₂CH₂O), 5.06, 5.18 (*AB*, $J = 9.8$ Hz, CH₂N), 5.07, 5.18 (*AB*, $J = 10.2$ Hz, CH₂N), 7.61–7.72 (*m*, 5 arom. H). $^{13}\text{C-NMR}$ (CDCl₃): 49.8 (2 CH₂N), 61.4 (C_q), 66.3 (2 CH₂O), 70.3 (2 CH₂N), 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^+), 263 (55), 261 (40, $[M-\text{Cl}]^+$), 217 (15). Anal. Calcd for C₁₄H₁₇N₂OCIS: 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/CH₂Cl₂). IR (KBr): 1537*s*, 1497*m*, 1452*s*, 1419*m*, 1348*m*, 696*s*. $^1\text{H-NMR}$ (CDCl₃): 4.58–4.62 (*m*, 2 CH₂N), 7.10–7.57 (*m*, 10 arom. H). $^{13}\text{C-NMR}$ (CDCl₃): 60.9 (C_q), 69.0 (2 CH₂N), 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^+), 269 (10), 267 (13), 266 (10). Anal. Calcd for C₁₆H₁₅N₂ClS: 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. ¹H-NMR (CDCl₃): 4.00 (s, MeO), 4.60–4.85 (m, 2 CH₂N), 7.25–7.50 (m, 5 arom. H). ¹³C-NMR (CDCl₃): 58.0 (MeO), 61.0 (C_q), 67.3, 68.7 (2 CH₂N), 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⁺). Anal. Calcd for C₁₁H₁₂NOCIS: 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. ¹H-NMR (CDCl₃): major rotamer: 1.08, 1.83 (2s, 2 Me), 4.04 (s, MeO), 4.43, 4.98 (AB, J = 12.0 Hz, CH₂N), 7.29–7.31 (m, 5 arom. H); minor rotamer: 1.32, 2.03 (2s, 2 Me), 3.97 (s, MeO), 4.43, 4.98 (AB, J = 12.0 Hz, 2 CH₂N), 7.29–7.31 (m, 5 arom. H). ¹³C-NMR (CDCl₃): major rotamer: 24.5, 25.1 (2 Me), 57.4 (MeO), 61.9 (2 CH₂N), 71.3 (Me₂C), 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 CH₂N), 71.3 (Me₂C), 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⁺), 131 (13). Anal. Calcd for C₁₃H₁₆NOCIS: 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. ¹H-NMR (CDCl₃): major rotamer: 1.08, 1.81 (2s, 2 Me), 4.03 (s, MeO), 4.43, 4.93 (AB, J = 12.0 Hz, 2 CH₂N), 6.93–7.47 (m, 5 arom. H); minor rotamer: 1.30, 2.03 (2s, 2 Me), 3.97 (s, MeO), 4.43, 4.93 (AB, J = 12.0 Hz, 2 CH₂N), 6.93–7.47 (m, 5 arom. H). ¹³C-NMR (CDCl₃): major rotamer: 24.7, 24.9 (2 Me), 57.4 (MeO), 61.8 (2 CH₂N), 70.4 (Me₂C), 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 CH₂N), 71.9 (Me₂C), 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⁺), 254 (10), 252 (9, [M-Cl]⁺). Anal. Calcd for C₁₃H₁₅NOCIFS: 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 diffractometer²⁹ using graphite-monochromated $\text{MoK}\alpha$ radiation (λ 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	$\text{C}_{16}\text{H}_{14}\text{O}_2\text{S}_4$
Formula weight [g mol^{-1}]	319.87
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	$0.12 \times 0.30 \times 0.32$
Temperature [K]	273(1)
Crystal system	monoclinic
Space group	$P2_1/c$
Z	4
Reflections for cell determination	20580
2θ range for cell determination [$^\circ$]	4–55
Unit cell parameters	
a [Å]	9.2577(2)
b [Å]	18.3804(4)
c [Å]	8.9874(2)
β [$^\circ$]	94.382(1)
V [Å ³]	1524.83(6)
D_x [g cm^{-3}]	1.393
$\mu(\text{MoK}\alpha)$ [mm^{-1}]	0.512
Scan type	ϕ and ω
$2\theta(\text{max})$ [$^\circ$]	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 $\Delta_{\text{max}}/\sigma$	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 method³¹ 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 $\sum w(F_o^2 - F_c^2)^2$. 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 ; 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

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