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 thiphosgene 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 described2,3 (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-benzylxoyazetidine (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 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. The hindered rotation about the C–N bond in N,N-disubstituted thioamides is well documented. 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 $^1$H-NMR spectrum. 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 $^1$H- as well as the $^{13}$C-NMR spectrum. 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 $^1$H-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 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.

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 CH₂Cl₂ 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 Cl₂C=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 (13C). In the 13C-NMR spectrum, the signal of the C=S group appears at 189.4 ppm, and two signals for the two CH₂ 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 13C-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 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 Cl₂C=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).
**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. Phenyl chlorodithioformate (5a), benzyl chlorodithioformate (5b), and propyl chlorodithioformate (5c) were synthesized from the corresponding sulfane and thiophosgene in CHCl$_3$/aq. NaOH (5a) or in CS$_2$ (5b, 5c).

2,2-Dimethyl-3-(4-fluorophenyl)-1-azabicyclo[1.1.0]butane (1e). Yield: 3.20 g (65%). Colorless, thick oil distilled in a Kugelrohr at 80°C/0.2 Torr. IR (KBr): 1522, 1223, 833, 607. $^1$H-NMR (CDCl$_3$): 1.14, 1.18 (2 s, 2 Me), 2.49, 2.62 (AB, J = 1.6 Hz, CH$_2$N), 6.90–7.46 (m, 4 arom. H). $^{13}$C-NMR (CDCl$_3$): 12.8, 22.8 (2 Me), 41.3 (Me$_2$C), 54.2 (CH$_2$N), 68.4 (C$_q$), 115.3 (d, $^2$J$_{C,F}$ = 21.7 Hz, 2 arom. CH), 130.2 (d, 113.4 (d, 2 arom. CH), 142.6 (d, 2 arom. CH).
$^3J_{C,F} = 8.3$ 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$_q$F).

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$_2$Cl$_2$ 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$_2$Cl$_2$ 3:2 as the eluent. Analytically pure samples were obtained by crystallization from MeOH/CH$_2$Cl$_2$, Et$_2$O 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$_2$Cl$_2$ was treated with a mixture of 101 mg (1 mmol) of Et$_3$N and 2 mmol of the corresponding thiol in 1 mL of CH$_2$Cl$_2$ at rt. The mixture was stirred for 24 h, the solution was diluted with 7 mL of CH$_2$Cl$_2$ 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$_2$Cl$_2$ (reaction with thiophenol) or after preparative layer chromatography using plates precoated with silica and hexane/CH$_2$Cl$_2$ 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$_2$Cl$_2$). 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$_2$N), 7.38–7.52 (m, 10 arom. H).

$^{13}$C-NMR (CDCl$_3$): 60.9 (C$_q$), 69.4, 70.3 (2 CH$_2$N), 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 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$_2$O). IR (KBr): 1479s, 1440s, 1171s, 979s, 725m, 695s, 614m.

$^1$H-NMR (CDCl$_3$): 4.56 (s, CH$_2$S), 4.76, 4.82 (AB, $J = 11.1$ Hz, CH$_2$N), 4.88, 4.97 (AB, $J = 12.1$ Hz, CH$_2$N), 7.25–7.42 (m, 10 arom. H).

$^{13}$C-NMR (CDCl$_3$): 40.7 (CH$_2$S), 61.1 (C$_q$), 68.8, 70.2 (2 CH$_2$N), 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 C$_{17}$H$_{16}$NCIS$_2$: 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): 1485vs, 1448s, 1436s, 1422m, 1172vs, 977s, 718m, 693s, 619m, 524m.
1H-NMR (CDCl₃): 1.02 (t, J = 7.4 Hz, MeCH₂), 1.67–1.79 (m, MeCH₂CH₂), 3.26 (t, J = 7.5 Hz, CH₂S), 4.76–4.97 (m, 2 CH₂N), 7.33–7.43 (m, 10 arom. H). 13C-NMR (CDCl₃): 13.3 (MeCH₂), 22.4 (MeCH₂CH₂S), 38.0 (MeCH₂CH₂S), 61.1 (Cδ), 68.8, 70.0 (2 CH₂N), 125.6, 128.7, 128.9 (5 arom. CH), 140.7 (arom. Cδ), 196.2 (C=S). CI-MS: 288 (40), 287 (16, [M+1]+), 286 (100, M⁺), 252 (28). Anal. Calcd for C₁₃H₁₆NClS₂: 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 CH₂Cl₂ in an ice-water bath was stirred magnetically and 115 mg (1 mmol) of thiophosgene in 1 mL of CH₂Cl₂ 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): 1513m, 1500m, 1460m, 1447m, 1173m, 990m. 1H-NMR (CDCl₃): 4.78–4.98 (m, 2 CH₂N), 7.35–7.47 (m, 5 arom. H). 13C-NMR (CDCl₃): 58.4 (Cδ), 70.0, 71.3 (2 CH₂N), 125.6, 129.1, 129.1 (5 arom. CH), 140.0 (arom. Cδ), 172.6 (C=S). CI-MS: 250 (11), 248 (69), 247 (12, [M+1]+), 246 (100, M⁺), 212 (25), 210 (45, [M–Cl]+). Anal. Calcd for C₁₀H₈NClS: 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): 1488br, 1443m, 1128m, 738m, 697m, 645m, 586m. 1H-NMR (CDCl₃): major rotamer: 1.26, 1.99 (2s, 2 Me), 4.53, 5.06 (AB, J = 12.8 Hz, 2 CH₂N), 7.21–7.57 (m, 5 arom. H); minor rotamer: 1.35, 2.05 (2s, 2 Me), 4.65, 5.20 (AB, J = 12.8, 2 CH₂N), 7.21–7.57 (m, 5 arom. H). 13C-NMR (CDCl₃): major rotamer: 23.5, 25.6 (2 Me), 66.1 (2 CH₂N), 72.1 (Me₂C), 84.3 (Cδ), 129.6, 131.6 (5 arom. CH), 140.8 (arom. Cδ), 173.1 (C=S); minor rotamer: 22.5, 25.2 (2 Me), 68.0 (2 CH₂N), 71.9 (Me₂C), 83.0 (Cδ), 129.5, 131.7 (5 arom. CH), 140.4 (arom. Cδ), 174.8 (C=S). CI-MS: 278 (14), 277 (13), 276 (68), 275 (21, [M+1]+), 274 (100, M⁺), 240 (25), 238 (60, [M–Cl]+), 196 (18). Anal. Calcd for C₁₂H₁₃NClS₂: 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 (7e).** Yield: 278 mg (95%). Yellowish, thick oil. IR (KBr): 1490br, 1443s, 1236s, 1156m, 1123m, 842m, 829m, 818m, 754m, 591m, 569m. 1H-NMR (CDCl₃): major rotamer: 1.25, 1.98 (2s, 2 Me), 4.53, 5.02 (AB, J = 12.8 Hz, CH₂N), 6.96–7.48 (m, 5 arom. H); minor rotamer: 1.34, 2.04 (2s, 2 Me), 4.66, 5.16 (AB, J = 12.8 Hz, CH₂N), 6.96–7.48 (m, 5 arom. H). 13C-NMR (CDCl₃): major rotamer: 23.5, 25.6 (2 Me), 66.3 (2 CH₂N), 71.3 (Me₂C), 84.3 (Cδ), 118.3 (d, J_C,F = 22.6 Hz, 2 arom. CH), 131.7 (d, J_C,F = 8.8 Hz, 2 arom. CH), 136.9 (d,
4J_{CF} = 3.6\text{ Hz}, \text{arom. C}_q), 166.2 (d, 1J_{CF} = 253.2\text{ Hz}, \text{arom. C}_q\text{F}), 174.8 (C=S); \text{minor rotamer:} 22.5, 25.3 (2\text{ Me}), 68.2 (2\text{ CH}_2\text{N}), 71.5 (\text{Me}_2\text{C}), 83.0 (C_q), 118.3 (d, 2J_{CF} = 22.6\text{ Hz}, 2\text{ arom. CH}), 131.6 (d, 3J_{CF} = 8.8\text{ Hz}, 2\text{ arom. CH}), 136.9 (d, 4J_{CF} = 3.6\text{ Hz}, \text{arom. C}_q), 166.2 (d, 1J_{CF} = 253.2\text{ Hz}, \text{arom. C}_q\text{F}), 173.2 (C=S). \text{Cl-Ms:} 294 (68), 292 (100, M^+), 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): 2934m, 1495s, 1464s, 1446s, 1380s, 1348m, 1319m, 1281m, 1252s, 1222m, 701m. 1H-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). 13C-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). Cl-Ms: 297 (3), 295 (7, M^+), 261 (17), 260 (18), 259 (100, [M–Cl]^+). Anal. Caled for C_{16}H_{15}N_{2}Cl: C, 56.65; H, 5.77; N, 9.44; S, 10.80. Found: C, 57.06; 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): 1474s, 1443s, 1431s, 1348s, 1308s, 1278s, 1231s, 1114s. 1H-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). 13C-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). Cl-Ms: 299 (38), 298 (17, [M+1]^+), 297 (100, M^+), 263 (55), 261 (40, [M–Cl]^+), 217 (15). Anal. Caled for C_{14}H_{17}N_{2}OCl: 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): 1537s, 1497m, 1452s, 1419m, 1348m, 696s. 1H-NMR (CDCl_3): 4.58–4.62 (m, 2 CH_2N), 7.10–7.57 (m, 10 arom. H). 13C-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). Cl-Ms: 305 (38), 304 (21, [M+1]^+), 303 (100, M^+), 269 (10), 267 (13), 266 (10). Anal. Caled for C_{16}H_{15}N_{2}Cl: 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, 1492s, 1448m, 1432m, 1279s, 1268m, 1234vs, 1147m, 696m. \(^1^H\)-NMR (CDCl\(_3\)): 4.00 (s, MeO), 4.60–4.85 (m, 2 CH\(_2\)N), 7.25–7.50 (m, 5 arom. H). \(^1^C\)-NMR (CDCl\(_3\)): 58.0 (MeO), 61.0 (C\(_q\)), 67.3, 68.7 (2 CH\(_2\)N), 126.0, 129.1, 129.3 (5 arom. CH), 141.5 (arom. C\(_q\)), 189.4 (C=S). Cl-MS: 244 (37), 243 (16, [M+1]^+), 242 (100, M^+). 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): 1489vs, 1456m, 1440s, 1265s, 1252s, 1221m, 1139s, 738s, 693s. \(^1^H\)-NMR (CDCl\(_3\)): major rotamer: 1.08, 1.83 (2s, 2 Me), 4.04 (s, MeO), 4.43, 4.98 (AB, J = 12.0 Hz, CH\(_2\)N), 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 CH\(_2\)N), 7.29–7.31 (m, 5 arom. H). \(^1^C\)-NMR (CDCl\(_3\)): major rotamer: 24.5, 25.1 (2 Me), 57.4 (MeO), 61.9 (2 CH\(_2\)N), 71.3 (Me\(_2\)C), 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\(_2\)N), 71.3 (Me\(_2\)C), 77.4 (C\(_q\)), 127.2, 128.9 (5 arom. CH), 139.3 (arom. C\(_q\)), 189.7 (C=S). Cl-MS: 272 (36), 271 (17, [M+1]^+), 270 (100, M^+), 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): 1496s, 1266m, 1253m, 1234m. \(^1^H\)-NMR (CDCl\(_3\)): major rotamer: 1.08, 1.81 (2s, 2 Me), 4.03 (s, MeO), 4.43, 4.93 (AB, J = 12.0 Hz, 2 CH\(_2\)N), 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 CH\(_2\)N), 6.93–7.47 (m, 5 arom. H). \(^1^C\)-NMR (CDCl\(_3\)): major rotamer: 24.7, 24.9 (2 Me), 57.4 (MeO), 61.8 (2 CH\(_2\)N), 70.4 (Me\(_2\)C), 77.2 (C\(_q\)), 115.6 (d, \(^3^J_{CF} = 21.7\) Hz, 2 arom. CH), 128.8 (d, \(^3^J_{CF} = 8.2\) Hz, 2 arom. CH), 134.9 (d, \(^4^J_{CF} = 3.4\) Hz, arom. C\(_q\)), 162.4 (d, \(^1^J_{CF} = 249.0\) Hz, arom. C\(_q\)F), 189.1 (C=S); minor rotamer: 22.7, 23.7 (2 Me), 56.2 (MeO), 61.8 (2 CH\(_2\)N), 71.9 (Me\(_2\)C), 78.3 (C\(_q\)), 115.6 (d, \(^3^J_{CF} = 21.7\) Hz, 2 arom. CH), 128.8 (d, \(^3^J_{CF} = 8.2\) Hz, 2 arom. CH), 134.9 (d, \(^4^J_{CF} = 3.4\) Hz, arom. C\(_q\)), 162.4 (d, \(^1^J_{CF} = 249.0\) Hz, arom. C\(_q\)F), 189.1 (C=S). Cl-MS: 290 (38), 289 (15, [M+1]^+), 288 (100, M^+), 254 (10), 252 (9, [M-Cl]^+). Anal. Calcd for C\(_{13}\)H\(_{15}\)NOClSF: 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).\textsuperscript{28} All measurements were performed on a *Nonius KappaCCD* area-detector diffractometer\textsuperscript{29} using graphite-monochromated Mo$K_\alpha$ radiation ($\lambda$ 0.71073 Å) and with an *Oxford Cryosystems Cryostream 700* cooler. The data collection and

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystallized from</td>
<td>MeOH/CH$_2$Cl$_2$</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C$<em>{16}$H$</em>{14}$O$_2$S$_4$</td>
</tr>
<tr>
<td>Formula weight [g mol$^{-1}$]</td>
<td>319.87</td>
</tr>
<tr>
<td>Crystal color, habit</td>
<td>colorless, prism</td>
</tr>
<tr>
<td>Crystal dimensions [mm]</td>
<td>0.12 × 0.30 × 0.32</td>
</tr>
<tr>
<td>Temperature [K]</td>
<td>273(1)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$P2_1/c$</td>
</tr>
<tr>
<td>$Z$</td>
<td>4</td>
</tr>
<tr>
<td>Reflections for cell determination</td>
<td>20580</td>
</tr>
<tr>
<td>2$\theta$ range for cell determination [$^\circ$]</td>
<td>4 – 55</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td></td>
</tr>
<tr>
<td>$a$ [Å]</td>
<td>9.2577(2)</td>
</tr>
<tr>
<td>$b$ [Å]</td>
<td>18.3804(4)</td>
</tr>
<tr>
<td>$c$ [Å]</td>
<td>8.9874(2)</td>
</tr>
<tr>
<td>$\beta$ [$^\circ$]</td>
<td>94.382(1)</td>
</tr>
<tr>
<td>$V$ [Å$^3$]</td>
<td>1524.83(6)</td>
</tr>
<tr>
<td>$D_X$ [g cm$^{-3}$]</td>
<td>1.393</td>
</tr>
<tr>
<td>$\mu$(Mo$K_\alpha$) [mm$^{-1}$]</td>
<td>0.512</td>
</tr>
<tr>
<td>Scan type</td>
<td>$\phi$ and $\omega$</td>
</tr>
<tr>
<td>2$\theta$(max) [$^\circ$]</td>
<td>55</td>
</tr>
<tr>
<td>Transmission factors (min; max)</td>
<td>0.836; 0.942</td>
</tr>
<tr>
<td>Total reflections measured</td>
<td>32689</td>
</tr>
<tr>
<td>Symmetry independent reflections</td>
<td>3489</td>
</tr>
<tr>
<td>Reflections with $I &gt; 2\sigma(I)$</td>
<td>2776</td>
</tr>
<tr>
<td>Reflections used in refinement</td>
<td>3488</td>
</tr>
<tr>
<td>Parameters refined</td>
<td>181</td>
</tr>
<tr>
<td>Final $R(F) [I &gt; 2\sigma(I)$ reflections]</td>
<td>0.0395</td>
</tr>
<tr>
<td>$wR(F^2)$ (all data)</td>
<td>0.1046</td>
</tr>
<tr>
<td>Weights: $w = [\sigma^2(F_o^2) + (0.0493P)^2 + 0.7442P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$</td>
<td></td>
</tr>
<tr>
<td>Goodness of fit</td>
<td>1.048</td>
</tr>
<tr>
<td>Final $\Delta_{\text{max}}/\sigma$</td>
<td>0.001</td>
</tr>
<tr>
<td>$\Delta\rho$ (max; min) [e Å$^{-3}$]</td>
<td>0.28; -0.51</td>
</tr>
</tbody>
</table>

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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. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method was applied. The structure was solved by direct methods using SIR92, 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 1.2\(U_{eq}\) 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. 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.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Part of the planned Ph. D. thesis of M. W., University of Lodz.
4. Some polycyclic compounds containing 1-azabicyclo[1.1.0]butane fragments were described by Prinzbach and coworkers. On the other hand, 2-chloro substituted derivatives were postulated as reactive intermediates responsible for the in situ formation of unstable azacyclobutadiene.5b
18. In the analogous 3-chloro-1-(methoxycarbonyl)-3-phenylazetidine, the two CH$_2$ groups absorb as a broad singlet at 4.63 (1H) and as a singlet at 65.8 ppm (13C), respectively.\(^7\)
28. CCDC-611938 contains the supplementary crystallographic data for compound (6a). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.


b) D. C. Creagh and W. J. McAuley, ibid. Table 4.2.6.8, p. 219. c) D. C. Creagh and J. H. Hubbell, ibid. Table 4.2.4.3, p. 200.

