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Synthesis of 2,3-Dihydrothiazolo[3,2-*a*]pyrimidin-5-ones by a *Michael*-type Tandem Reaction

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Summary. Although various thiazoles are known in literature for their biological and pharmacological properties only a few multi-step synthesis pathways for the preparation of thiazolo[3,2-*a*]pyrimidinones have been reported, which are tedious and time-consuming. An alternative synthesis pathway is described, which allows the preparation of 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-ones in a one-step process based on a *Michael*-type tandem reaction. By heating of 2-thiobarbituric acid with ethyl 4-bromocrotonate in ethanol at 60°C for 2 h, a 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one was obtained in 73% yield, whereas carrying out the reaction at room temperature results in the formation of an unstable unsaturated ester. The structures of both, the α,β-unsaturated ester as well as the 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one were confirmed by NMR spectroscopy. Additionally, the structure of the 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one was investigated by single-crystal X-ray analysis. The described approach offers a significant improvement over previously reported synthesis pathways because it allows the simple preparation of 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-ones with good yields in a one-step reaction.

Keywords. Cyclization; 2,3-Dihydrothiazolo[3,2-*a*]pyrimidin-5-ones; *Michael*-type tandem reaction.

Introduction

Thiazolo[3,2-*a*]pyrimidines have been described in literature as immunomodulators [1], anticancer agents [2], analgesics [3, 4], psychotropes [2, 5], and as

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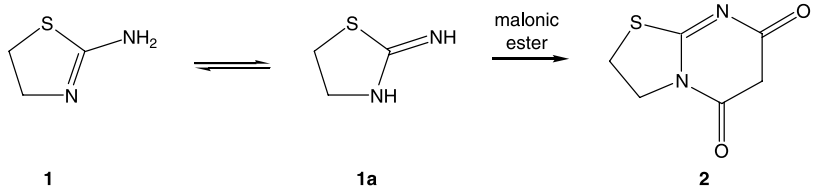
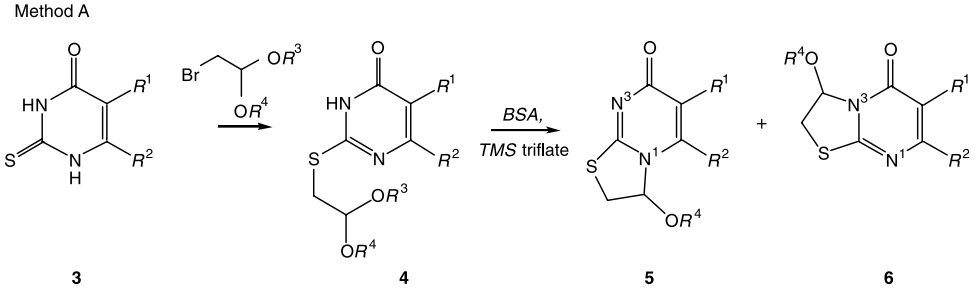


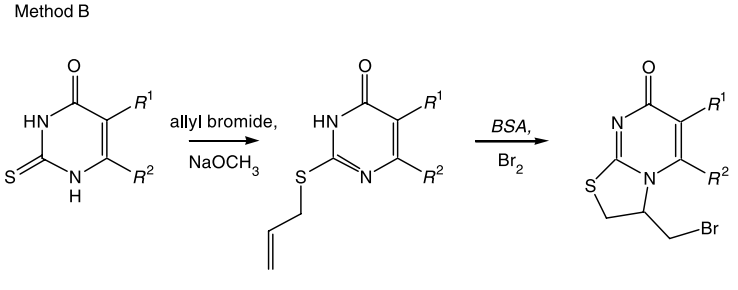
1 **1a** **2**

Scheme 1

anti-inflammatory and positive inotropic agents [6]. Moreover, *Danel et al*. have proven that the thiazolo[3,2-*a*]pyrimidin-7-ones **5** and **8**, which have been recently synthesized show antiviral activity against HIV-1 in MT-4 cells [7]. Nevertheless, only few synthesis pathways for the preparation of thiazolo[3,2-*a*]pyrimidinones have been reported. *Masters et al.* and *Glennon et al.* have described the synthesis of thiazolo[3,2-*a*]pyrimidindione (**2**) based on the condensation of 2-aminothiazoline (**1**) with malonic ester (Scheme 1) [8, 9]. In addition, two methods have been described by *Danel et al.* for the preparation of thiazolo[3,2-*a*]pyrimidin-5-ones and thiazolo[3,2-*a*]pyrimidin-7-ones. Method A (Scheme 2) begins with an S-alkylation of the starting pyrimidines **3** with the appropriate 2-bromoacetaldehyde acetal followed by protection of the 4-oxo group of the S-alkylated pyrimidines **4** with *N,O*-bis(trimethylsilyl)acetamide (*BSA*). The subsequent intramolecular cyclization can be achieved by modification of the method of *Niedballa* and *Vorbrüggen* using trimethylsilyl trifluoromethanesulfonate (*TMS* triflate) as catalyst [10]. Afterwards splitting-off of the protecting group was performed in acid medium. Because of the more nucleophilic character of N^1 compared to N^3, thia-



3 **4** **5** **6**



3 **7** **8**

Scheme 2

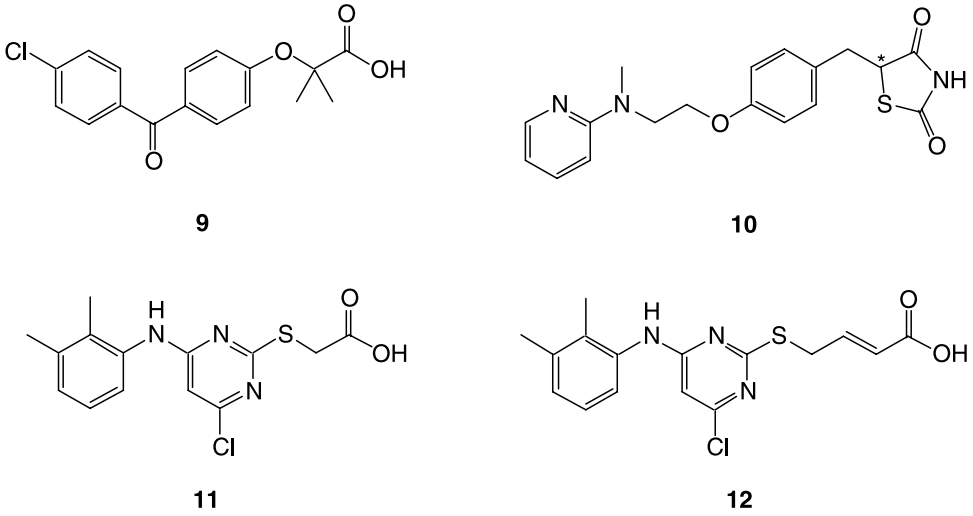
zolo[3,2-*a*]pyrimidin-7-ones **5** (N^1 regioisomers) were isolated as the main products in 10–50% yield whereas thiazolo[3,2-*a*]pyrimidin-5-ones **6** (N^3 regioisomers) were only isolated in minor yields (4–9%). Method B (Scheme 2) is based on the S-alkylation of the starting pyrimidines **3** with allyl bromide in the presence of anhydrous methanol and sodium methoxide. The treatment of 2-allylthiouracils **7** with bromine in methylene chloride after silylation with *BSA* leads to an intramolecular cyclization resulting in the formation of thiazolo[3,2-*a*]pyrimidin-7-ones **8**. Splitting-off of the protecting group was performed as mentioned in method A.

However, the synthesis pathways mentioned above are time-consuming multistep processes with rather moderate yields. In the search for new PPAR agonists we came across a simple pathway to prepare 2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-ones by a *Michael*-type tandem reaction in a one-step process.

Results and Discussion

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear hormone receptor family [11]. Drugs that bind to and modulate the transcriptional activity of one or more of the PPAR subtypes show great promise for treating various metabolic diseases as they control the transcription of genes involved in glucose metabolism, lipid metabolism, and inflammation [12, 13]. PPAR receptors have thus emerged as attractive therapeutic targets prompting the development of synthetic PPAR agonists. While saturated and unsaturated fatty acids belong to the class of endogenous PPAR modulators, the fibrates (*e.g.* fenofibric acid (**9**)) and thiazolidindiones (*e.g.* rosiglitazone (**10**)) represent synthetic fatty acid analogs, which are clinically used as hypolipidemic agents and insulin sensitizers (Scheme 3).

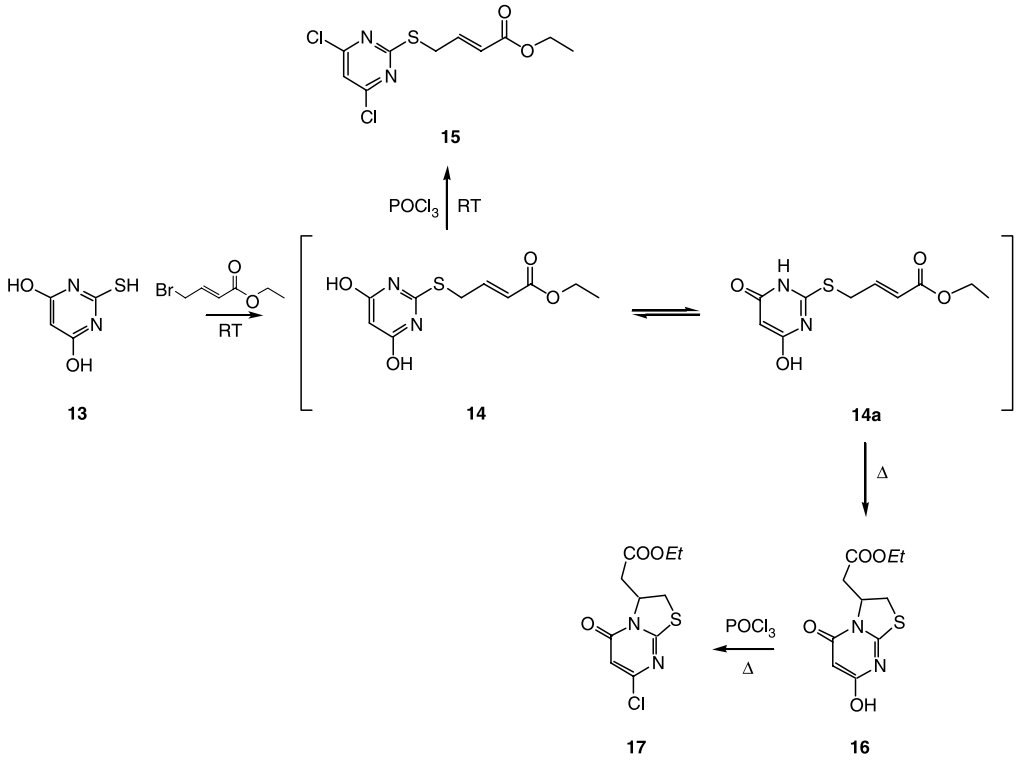
Like the fibrates pirinixic acid (**11**) has proven to be a potent PPARα agonist [14–16] of which no unsaturated derivative is known to date. In the search for new



9 **10**

11 **12**

Scheme 3



Scheme 4

PPAR agonists it was our aim to synthesize the α,β-unsaturated derivative **12** of the pirinixic acid molecule. The application of the well-known synthesis pathway to synthesize pirinixic acid [17] leads after reaction of thiobarbituric acid (**13**) with ethyl 4-bromocrotonate in ethanol at 25°C after 20 h to the expected unsaturated ester derivative (**14**). After chromatography on silica gel, the product **14** can be isolated with a yield of 66% (Scheme 4). Performing the reaction at 60°C results in the formation of the stable thiazolopyrimidin-5-one **16** with a yield of 73%. This course of reaction is not new. It has been described before by *Campbell et al.* for the synthesis of *GABA* receptor agonists, where starting from ethyl 4-bromocrotonate and thiourea an intramolecular cyclization also led directly to the formation of the structurally related 2-amino-2-thiazolines [18].

The mechanism to rationalize the formation of the thiazolopyrimidin-5-one **16** is outlined in Scheme 4. The first step consists in the deprotonation of the SH-group of **13** resulting in a thiolate anion. The unsaturated ester **14** is then formed by a second-order nucleophilic substitution reaction. Then **14** undergoes an N-nucleophilic cyclization step in a *Michael*-type reaction leading to the formation of the thiazolopyrimidin-5-one **16**. Similar reaction sequences have also been reported in connection with the heterocyclization of propenylthioquinazolinones [19], alkenylthiopyrimidin-6-ones [20], and allylthiopyrimidin-4-ones [21]. The unstable ester **14** as well as the stable 7-hydroxythiazolo[3,2-*a*]pyrimidin-5-one **16** can be chlorinated with phosphorus oxychloride resulting in **15** and **17**.

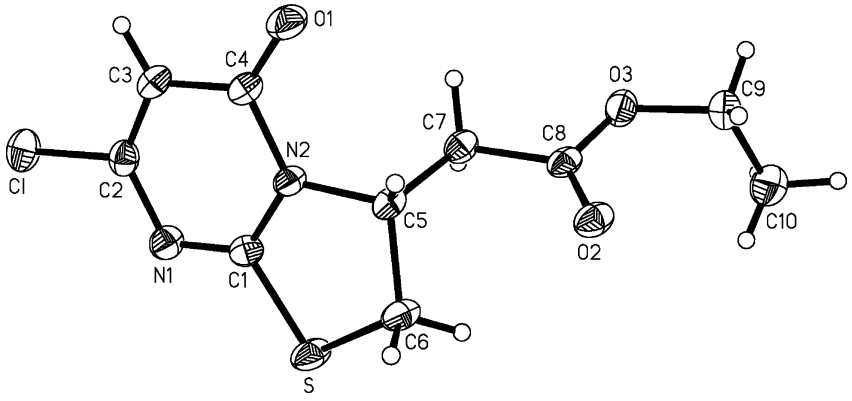


Fig. 1. ORTEP plot of the crystal structure of (7-chloro-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*] pyrimidin-3-yl)acetic acid ethylester (**17**)

The structure of the thiazolopyrimidin-5-one **17** was confirmed by NMR and X-ray crystal structure analysis. The assignment of the ^{13}C NMR signals was carried out on the basis of DEPT and two-dimensional HMBC experiments. In contrast to the ^{13}C NMR spectra of the unsaturated carbonyl compound **14** the DEPT spectra of the thiazolopyrimidin-5-one **16** shows three CH_2 signals and two signals for CH groups.

The X-ray crystal structure analysis of **17** revealed that the pyrimidin-5-one group is essentially planar (mean deviation from plane: 0.006 Å). The thiazolidine ring has an envelope conformation: C6 deviates 0.31 Å from the best plane through S, C1, N2, and C5. The C5–C7 bond has a pseudoaxial orientation with respect to the five-membered ring. The dimensions of the thiazolo[3,2-*a*]pyrimidin-5-one group are very similar to those observed in other crystal structures containing this group [22–24]. The crystal packing shows two intermolecular C–H···O contacts with H···O distances of 2.44(2) and 2.54(2) Å [25]. Figure 1 shows the ORTEP-plot of thiazolo[3,2-*a*]pyrimidin-5-one **17**.

Since compounds of similar structures are known to exhibit anti-inflammatory properties, the thiazolo[3,2-*a*]pyrimidin-5-ones **16** and **17** have been tested for their anti-inflammatory activity as possible 5-lipoxygenase (5-LO) inhibitors. Based on the background, that mammalian 5-LO catalyzes the conversion of arachidonic acid to leukotrienes, which are potent inflammatory mediators [26], 5-LO inhibition is directly associated with anti-inflammatory properties. However, our biological investigations revealed, that neither 7-hydroxythiazolo[3,2-*a*]pyrimidin-5-one **16** nor 7-chlorothiazolo[3,2-*a*]pyrimidin-5-one **17** inhibit the 5-LO in intact polymorphonuclear leucocytes (PMNL) [27].

In conclusion, thiazolo[3,2-*a*]pyrimidin-5-ones were successfully synthesized from ethyl 4-bromocrotonate and 2-thiobarbituric acid in ethanol at 60°C based on a *Michael*-type tandem reaction. This efficient and generally applicable approach offers a significant improvement over previously reported synthetic pathways, because it allows the preparation of thiazolo[3,2-*a*]pyrimidin-5-ones with high yields in a one-step reaction.

Experimental

Melting points were determined on a *Büchi-Tottoli* melting point apparatus. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or *DMSO*-d_6 solutions on a Bruker ARX 300 (^{1}H NMR) and AC 200 E (^{13}C NMR) spectrometer. Proton chemical shifts are relative to *TMS* as internal standard. Mass spectra were obtained on a Fisons Instruments VG Platform 2 spectrometer. Column chromatography was carried out on Merck silica gel 60. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates, and the compounds were visualized by UV illumination (254 nm). Elemental analysis (C, H, N) was performed by the Microanalytical Laboratory of the Institute of Organic Chemistry, University of Frankfurt, using a Foss Heraeus CHN–O–rapid elemental analyzer. The results were in good agreement (±0.3%) with the calculated values.

4-(4,6-Dihydroxypyrimidin-2-ylsulfanyl)but-2-enoic acid ethylester (**14**, $C_{10}H_{12}N_2O_4S$)
A solution of 0.4 g NaOH (10 mmol) in 10 cm^3 H_2O was added to a suspension of 1.44 g 2-thiobarbituric acid (10 mmol) in 10 cm^3 *Et*OH followed by the dropwise addition of 2.15 g ethyl 4-bromocrotonate (11.14 mmol). Then the reaction mixture was stirred for 19 h at room temperature. The suspension was filtered and the filtrate cooled in a refrigerator over night. Refiltering the obtained precipitate, washing with diethyl ether, and drying under vacuum yielded 1.7 g (66%) **14**. Mp 165°C; ^{1}H NMR (300.13 MHz, *DMSO*-d_6): $\delta = 1.32$ (t, $J = 7.1$ Hz, CH_2CH_3), 4.03 (d, $J = 7.2$ Hz, S–CH_2), 4.21 (q, $J = 7.1$ Hz, CH_2CH_3), 5.33 (s, Pyr-5-H), 6.25 (d, J (trans) = 15.5 Hz, Butene-2-H), 6.99 (dt, J (trans) = 15.5 Hz, $J = 7.2$ Hz, Butene-3-H), 11.82 (s (br), OH) ppm; ^{13}C NMR (50.32 MHz, *DMSO*-d_6): $\delta = 13.94$ (CH_3), 29.90 (S–CH_2), 59.91 (O–CH_2), 85.47 (Pyr-5-C), 123.07 (Butene-2-C), 143.17 (Butene-3-C), 162.44 (Pyr-2-C), 165.25 (CO), 167.55 (Pyr-4,6-C) ppm; MS (ESI–): $m/z = 254.8$ (M − 1).

4-(4,6-Dichloropyrimidin-2-ylsulfanyl)but-2-enoic acid ethylester (**15**, $C_{10}H_{10}Cl_2N_2O_2S$)
N,N-Diethylaniline (0.81 g, 5.46 mmol) was added dropwise to a solution of 1.4 g **14** (5.46 mmol) in 14.97 g $POCl_3$ (98.28 mmol). After stirring the reaction mixture for 25 h at room temperature the excessive $POCl_3$ was distilled off at the rotary evaporator under reduced pressure and the oily residue was poured upon 100 g crushed ice. The aqueous solution was extracted with *AcOEt* (3 × 30 cm^3), the combined organic layers were washed with diluted HCl (3 × 30 cm^3), saturated $NaHCO_3$ solution (3 × 30 cm^3), and finally with 50 cm^3 H_2O. The organic layer was then dried (Na_2SO_4) and evaporated under reduced pressure. Purifying the resulting oil by chromatography gave 0.8 g (50%) **15**. ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.4$ Hz, CH_2CH_3), 3.86 (dd, S–CH_2), 4.11 (q, $J = 7.4$ Hz, CH_2CH_3), 6.05 (d, J (trans) = 15.5 Hz, Butene-2-H), 6.91 (dt, J (trans) = 15.5 Hz, $J = 7.2$ Hz, Butene-3-H), 7.01 (s, Pyr-5-H) ppm; ^{13}C NMR (50.32 MHz, $CDCl_3$): $\delta = 14.12$ (CH_3), 31.96 (S–CH_2), 60.43 (O–CH_2), 116.38 (Pyr-5-C), 124.50 (Butene-2-C), 141.19 (Butene-3-C), 161.56 (Pyr-2-C), 165.77 (CO), 172.29 (Pyr-4,6-C) ppm.

(7-Hydroxy-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-3-yl)-acetic acid ethylester
(**16**, $C_{10}H_{12}N_2O_4S$)
A solution of 2.25 g NaOH (56.25 mmol) in 56 cm^3 H_2O was added to a suspension of 7.5 g 2-thiobarbituric acid (52.05 mmol) in 56 cm^3 *Et*OH. Ethyl 4-bromocrotonate (11.76 g, 60.9 mmol) was added dropwise and the reaction mixture was heated under stirring for 2 h at 60°C. Afterwards, the mixture was cooled in a refrigerator over night, the crystalline precipitate was filtered off, washed with H_2O and diethyl ether, and dried under vacuum to give 9.8 g (73%) pure **16**. Mp 163°C; ^{1}H NMR (300.13 MHz, *DMSO*-d_6): $\delta = 1.30$ (t, $J = 7.1$ Hz, CH_2CH_3), 2.84 (dd, CH_2CO), 2.99 (dd, CH_2CO), 3.41 (dd, S–CH_2), 3.98 (dd, 1H, S–CH_2), 4.19 (q, $J = 7.1$ Hz, CH_2CH_3), 5.24 (s, Pyr-6-H), 5.20–5.26 (m, N–CH), 11.67 (s, br, OH) ppm; ^{13}C NMR (50.32 MHz, *DMSO*-d_6): $\delta = 3.75$ (CH_3), 31.07 (S–CH_2), 34.63 (CH_2CO), 56.53 (N–CH), 60.40 (O–CH_2), 85.06 (6-C), 161.07 (5-C), 164.69 (8a-C), 169.20 (7-C), 169.58 (CO) ppm; MS (ESI+): $m/z = 257.13$ (M + 1).

(7-Chloro-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-3-yl)-acetic acid ethylester (**17**, $C_{10}H_{11}ClN_2O_3S$)

N,N-Diethylaniline (2.91 g, 19.51 mmol) was added dropwise to a solution of 5 g **16** (19.51 mmol) in 59.4 g $POCl_3$ (390 mmol). After refluxing for 6 h at 110°C the excessive $POCl_3$ was distilled off and the oily residue was poured upon 300 g crushed ice. The aqueous solution was extracted with *Ac*O*Et* ($3 \times 50\,cm^3$), the combined organic layers were washed with diluted HCl ($3 \times 40\,cm^3$), saturated $NaHCO_3$ solution ($3 \times 40\,cm^3$), and finally with $50\,cm^3$ H_2O). The organic layer was then dried (Na_2SO_4) and evaporated under reduced pressure. Recrystallization of the resulting red solid from $250\,cm^3$ *n*-hexane gave 2.14 g (40%) pure yellow crystals **17**. Mp 86°C; ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.2$ Hz, CH_2CH_3), 2.91 (m, CH_2CO), 3.32 (dd, S–CH_2), 3.79 (dd, S–CH_2), 4.16 (q, $J = 7.2$ Hz, CH_2CH_3), 5.28–5.35 (m, N–CH), 6.19 (s, 6-H) ppm; ^{13}C NMR (50.32 MHz, $CDCl_3$): $\delta = 14.05$ (CH_3), 31.73 (S–CH_2), 34.14 (CH_2CO), 57.32 (N–CH), 61.42 (O–CH_2), 108.39 (6-C), 158.59 (5-C), 159.22 (8a-C), 165.31 (7-C), 169.59 (CO) ppm; MS (ESI+): $m/z = 274.7$ ($M(^{35}Cl)+1$), 276.9 ($M(^{37}Cl)+1$).

*X-Ray Structure Determination of **17***

Crystal data: $C_{10}H_{11}ClN_2O_3S$, triclinic, space group *P*-1, $a = 5.1912(5)$ Å, $b = 10.4877(10)$ Å, $c = 11.1042(10)$ Å, $\alpha = 87.591(10)°$, $\beta = 77.845(10)°$, $\gamma = 84.121(10)°$, $V = 587.76(10)$ Å^3, $Z = 2$, μ(Mo-K_α) = 0.5 mm^{-1}, $T = -114$°C. A single crystal (yellow blade with dimensions $0.07 \times 0.40 \times 1.2\,mm^3$) of **17** was measured on a SIEMENS SMART CCD diffractometer, repeatedly measured reflections remained stable. An empirical absorption correction with program SADABS (Sheldrick, 2000) gave a correction factor between 0.822 and 1.000, equivalent reflections were averaged. $R(I)$internal = 0.038. The structure was determined by direct methods using program SHELXS. The H atoms were taken from a different synthesis and were refined with individual isotropic thermal parameters. The non-H atoms were refined with anisotropic thermal parameters. The structure was refined on F^2 values using program SHELXL-97. The final difference density was between −0.27 and +0.63 e/Å [25].

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[25] CCDC 264399 (**17**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk)
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