Studies on Thiazolidine-4,5-dithiones. Synthesis of 5-Hydrazonothiazolidine-4-thiones and 5-Unsubstituted Thiazolidine-4-thiones

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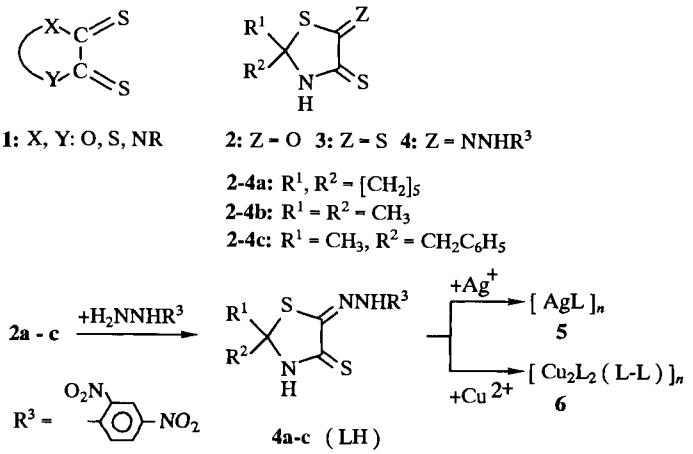
In attempts to generate dithiones **3**, 4-thioxothiazolidin-5-ones **2a–c** were converted into hydrazones **4a–c**, which, however, could not be thiolyzed. Also thionation of **2a, b** did not provide **3**, but resulted in reduction to thiazolidine-4-thiones **7a, b**.

The chemistry of cyclic thiooxalic acid derivatives with a 1,2-dithione moiety raises interesting synthetic and theoretical questions, but also the potential of these compounds as ligands in coordination chemistry is noteworthy. However, attempts to prepare cyclic tetrathiooxalates **1** (X = Y = S) did not meet with success[1]. An unstable cyclic dithiooxalic acid ester **1** (X = Y = O) was described only recently[2]. In contrast, cyclic dithiooxamides **1** with X = Y = NR (R not hydrogen) are readily accessible[3–6]. However, 1,2-dithiones **1** [X = NH, Y = $N(CH_3)NH$] could be prepared by cyclization of dithiooxalic 1-methylhydrazide amide with ketones[7]. 4-Thioxothiazolidin-5-ones **2**, which are easily available from sodium cyanodithioformate and aliphatic ketones in the presence of secondary amines[8], should be suitable starting materials for the synthesis of five-membered cyclic 1,2-dithiones **3**. The results of attempts to effect O/S exchange in compounds **2** in order to obtain 1,2-dithiones **3** are reported herein. Two different ways were probed, i.e. thiolysis of hydrazones **4** and sulfurization of **2** with tetraphosphorus decasulfide or other thionating agents.

Scheme 1



5-(2,4-Dinitrophenylhydrazono)thiazolidine-4-thiones 4

Synthesis of thiones by thiolysis of the corresponding imines or hydrazones is a well-established method. Attempts to transform **2** into 5-imines were not successful as both ammonolysis and aminolysis led to ring cleavage[9]. Similarly, reaction of **2** with hydrazine or more basic, substituted hydrazines gave mixtures of acyclic products. However, treatment of **2** with ethanolic 2,4-dinitrophenylhydrazine in the presence of an equimolar amount of sulfuric acid provided 5-(2,4-dinitrophenylhydrazono)thiazolidine-4-thiones **4** in moderate yields as sparingly soluble orange-colored crystals.

The IR spectra of **4a–c** confirm hydrazine incorporation. Thus, compared with **2a–c**[8], the typical C=O stretching frequencies around 1700 cm^{-1} are absent, and the nearly unchanged thioamide frequencies around 1585 and 975 cm^{-1} give evidence that the C(S)–NH unit of **2** was not involved in the reaction. A new absorption at 1620 cm^{-1} is assigned to the exocyclic C=N bond in **4**. The poor solubility of **4** prevented measurement of NMR spectra in solution.

With bases, compounds **4** form thiolate anions which give coordination compounds with mono- or divalent heavy-metal cations. Thus, silver(I) salts and **4a** (LH) afford a yellow precipitate with the empirical formula Ag(I)L (**5a**). With copper(II) ions, hydrazones **4a–c** undergo a redox reaction yielding copper(I) complexes **6a–c** with the empirical formula $Cu_2L_2 \cdot (L-L)$. Here, the thiol LH apparently acts as reducing agent forming the disulfide L–L, which is coordinated as an additional ligand and can also be detected in the mass spectra of **6**. The same copper(I) complexes are available from copper(I) chloride and the ligand LH (molar

ratio 1:2) in acetonitrile with access of air (dioxygen as oxidizing agent). Similar silver(I) and copper(I) coordination compounds have been synthesized with thiolate ligands derived from thiazolidines **2**[10].

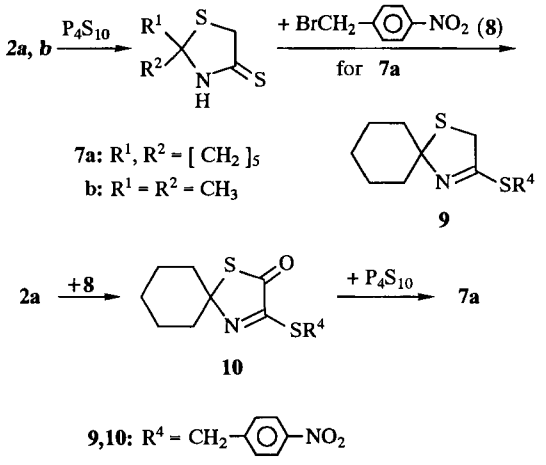
Attempts to recrystallize the slightly soluble copper(I) complexes **6** from DMF or DMSO led to partial exchange of solvent molecules for the disulfide ligand. Heating the poorly soluble silver(I) complex **5** in the same solvents gave silver and disulfide L–L as result of a redox reaction. The IR spectra of complexes **5** and **6** differ only slightly from those of **4**. Thus, absorptions of the ring thioamide NH around 1570 cm^{-1} of compounds **4** are absent in the coordination compounds indicating that thiolate anions were formed. The IR spectra do not allow reliable conclusions regarding additional coordinative bonds between metal and donor atoms of the ligands. The presence of higher molecular clusters in **5** and **6** is suggested by the mass spectra of **5** (FAB in sulfolane) showing not only the expected fragments of ligands L and disulfides L–L in addition to the copper-containing units CuL and CuL_2, but also numerous fragments with *m/z* up to 2000.

Attempts to thiolyze hydrazono compounds **4** to 1,2-dithiones **3** were unsuccessful. At different temperatures (0–100°C) and in various solvents only tarry mixtures were formed containing 2,4-dinitrophenylhydrazine and the corresponding thiazolidine **2** besides some unidentified products.

2,2-Disubstituted Thiazolidine-4-thiones 7

In attempts to obtain 1,2-dithiones **3** from thiazolidines **2** by the action of thionating agents, compounds **2** were heated with P_4S_{10} in toluene leading only to tarry decomposition products independent of reaction time and temperature. Probably, oxygen/sulfur exchange takes place, but products **3** are unstable under the reaction conditions. Reactions of **2** with Lawesson reagent[11a] or 2,4-bis(methylthio)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Davy reagent)[11b] led to complex mixtures of reaction products which further deteriorated on attempted isolation by column chromatography on alumina. But differences in solubility allowed us to isolate and identify small amounts (<10%) of the starting material **2** and the unexpected 5-unsubstituted thiazolidine-4-thiones **7**, which obviously are formed by reduction of C-5 in **2** or in a 5-thione intermediate **3**.

Scheme 2



Thionation of carbonyl groups with mixtures of P_4S_{10}/$NaHCO_3$ is reported as a mild method leading to pure reaction products in good yields[12]. But on treatment of thiazolidines **2** with this reagent, not 1,2-dithiones **3**, but, besides small amounts of some unidentified compounds and sulfur, again 2,2-disubstituted thiazolidine-4-thiones **7** are the main products. A 1:6 molar ratio gives the best yields of **7**.

Compounds **7** show IR absorption around 3115 and 1535 cm^{-1} indicative of a secondary thioamide unit. Structure **7** resulting from reduction of **2** at C-5 and not at C-4 is also supported by benzylation of **7a** to afford the *S*-benzyl derivative **9**. Here, the presence of a thioimidate moiety is confirmed by an IR absorption at 1619 cm^{-1} ($\nu_{C=N}$). Also a singlet for the methylene group and the NH proton around δ = 4.1 and 10.1 in the ^{1}H-NMR spectra of **7** are in accord with reduction at the 5-position. The shifts of the ring carbons of **7** are comparable with the corresponding data of compounds **2** (e.g. **2a**: C-2 δ = 76.3 and C-4 183.5)[13], whereas for **9** a low-field shift of C-2 and a high-field shift of C-4 are observed (Table 1). Similar shifts are found for the *S*-benzylated derivative **9** of **2a** (C-2 δ = 93.2 and C-4 166.2)[13].

Table 1. ^{13}C-NMR spectra ($CDCl_3$, δ values) of **7a**, **b** and **9**

	C-2	C-4	C-5	CH_2 (cyclohexyl) C-2′, -6′, -3′, -5′, -4′		
7a	79.88	198.74	44.15	40.33	24.01	24.35
7b[a]	78.29	198.81	45.37			
9[b,c]	94.65	162.95	42.83	41.45	24.46	25.03

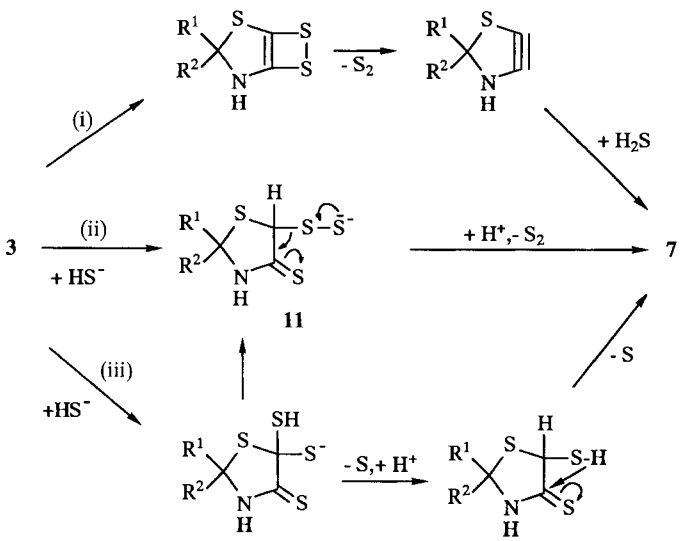
[a] CH_3: δ = 31.55. – [b] Aryl: δ = 145.71 (C-1″), 123.58 (C-3″, -5″), 129.92 (C-2″, -6″), 147.15 (C-4″). – [c] CH_2 (benzyl): δ = 35.53.

Related reductions of a thiocarbonyl to a methylene unit in 1,2-dithione chemistry are formation of 2-ethoxythioacetic acid in the reaction of *O,O*-diethyl dithiooxalate with hydrogen sulfide in the presence of tertiary amines[14] and formation of 1,3-diphenyl-4-thiohydantoin in the thiolysis of 4-imino-5-thioxoimidazolidin-2-one. Here, a 1,2-dithione is discussed as an intermediate[15]. Obviously, in these reactions hydrogen sulfide acts as the reducing agent. By analogy, it is assumed that the formation of **7** is the result of a two-step reaction involving thionation of **2** in the 5-position and reduction of the resulting 1,2-dithione **3** by hydrogen sulfide.

Formation of hydrogen sulfide in solutions containing mixtures of P_4S_{10} and $NaHCO_3$ is in accord with the known reactions of thiophosphoric acid intermediates. Yields of **7** should depend on the hydrogen sulfide concentration. Indeed, passing hydrogen sulfide through the reaction mixtures increases yields of **7** up to 60%.

Three different mechanisms can be considered to explain the reduction of 1,2-dithiones by hydrogen sulfide (Scheme 3):

Scheme 3



i. Electrocyclic ring closure of the 1,2-dithione **3** gives a dithiete. An alkyne intermediate is then formed by S_2 elimination, and addition of hydrogen sulfide leads to the $CH_2-C(S)$ unit[15].

ii. The first step involves thiophilic[16] attack of hydrogen sulfide on the thiocarbonyl group on C-5 leading to **11**. Then a Grob fragmentation[17] would provide a pathway to elimination of sulfur (S_2). Protonation and tautomerization of the enethiol to the thione conclude the sequence.

iii. Nucleophilic addition of hydrogen sulfide to the reactive thiocarbonyl group on C-5 may be considered[14]. However, reduction on C-5 might then involve reorganization to the intermediate **11** of mechanism ii, possibly via a dithiirane intermediate or by loss of sulfur, one atom at a time, perhaps via thiirane intermediates.

Further insights into the course of the reaction from **2** to **7** could be obtained by attempts to thionate the *S*-benzyl derivative **10** with $P_4S_{10}/NaHCO_3$ in the presence of hydrogen sulfide. Here, again reduction of a carbonyl group is observed giving **7a** in good yields. Formation of this product could only be reconciled with the hetaryne mechanism i, if thiolysis of the thioimidate unit to **3** occurred as the first step. Similarly, an attempt to trap the putative hetaryne intermediate derived from 4-imino-1,3-diphenyl-5-thioxoimidazolidin-2-one[15] by addition of cyclopentadiene failed. This makes intermediate **11** the most probable precursor of **7**. Starting from **10**, thiazolidine **7** appears to be formed after reduction on C-5 by thiolysis of the thioimidate unit.

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Experimental

Melting points: Boetius-Heiztischmikroskop (VEB Carl Zeiß Jena). — Elemental analyses: Microanalytical Laboratory of Fachbereich Chemie, Universität Rostock. — IR: VEB Carl Zeiß Jena UR-20 and Nicolet 205 FT-IR. — ^1H NMR: Tesla BS 487 C (80 MHz), TMS as internal standard. — ^{13}C NMR: Bruker WM 250, TMS as internal standard. — MS: LKB 9000 (70 eV) and AMD 402 Intectra GmbH.

4-Thioxothiazolidin-5-ones (**2a–c**)[8a] *and 4'-(4-Nitrobenzylthio)-spiro[cyclohexane-1,2'(5'H)-thiazol]-5'-one* (**10**)[18] were prepared according to known methods.

5-(2,4-Dinitrophenylhydrazono)thiazolidine-4-thiones (**4a–c**). — *General Procedure:* A solution of **2** (6 mmol), 2,4-dinitrophenylhydrazine (1.19 g, 6 mmol), and concd. sulfuric acid (0.59 g, 6 mmol) in 30 ml of ethanol was refluxed for 1–1.5 h. The resulting red solution was allowed to stand overnight at 6°C. The orange-red crystals of **4** were collected, washed with ethanol/petroleum ether and recrystallized from DMF/water.

5'-(2,4-Dinitrophenylhydrazono)spiro[cyclohexane-1,2'-thiazolidine]-4'-thione (**4a**): Yield 0.80 g (35%), m.p. 228–230°C (dec.). — IR (KBr): $\tilde{\nu}$ = 3264, 3100, 3089 (NH), 1616 (C=N), 1572 (thioamide), 1516, 1336 cm^{-1} (NO_2). — MS (70 eV), *m/z*: 381 [M^+]. — $C_{14}H_{15}N_5O_4S_2$ (381.4): calcd. C 44.08, H 3.96, N 18.36, S 16.81; found C 44.38, H 4.25, N 18.03, S 16.24.

5-(2,4-Dinitrophenylhydrazono)-2,2-dimethylthiazolidine-4-thione (**4b**): Yield 0.61 g (30%), m.p. 227–229°C (dec.). — IR (KBr): $\tilde{\nu}$ = 3263, 3113, 3091, 1610, 1568, 1516, 1335 cm^{-1}. — MS (70 eV), *m/z*: 341 [M^+]. — $C_{11}H_{11}N_5O_4S_2$ (341.3): calcd. C 38.70, H 3.25, N 20.52, S 18.79; found C 39.01, H 3.15, N 20.11, S 18.51.

2-Benzyl-5-(2,4-dinitrophenylhydrazono)-2-methylthiazolidine-4-thione (**4c**): Yield 0.88 g (35%), m.p. 224–226°C (dec.). — IR (KBr): $\tilde{\nu}$ = 3234, 3165, 3090, 1616, 1561, 1516, 1335 cm^{-1}. — MS (70 eV), *m/z*: 417 [M^+]. — $C_{17}H_{15}N_5O_4S_2$ (417.5): calcd. C 48.91, H 3.62, N 16.78, S 15.36; found C 48.50, H 3.55, N 17.68, S 15.20.

Silver(I) Complex **5** *of* **4a**: A suspension of **4a** (0.38 g, 1.0 mmol) in 10 ml of acetone was treated with $AgNO_3$ (0.17 g, 1 mmol) in 5 ml of acetonitrile. The reaction mixture was stirred for 3 h at room temp. The bright yellow precipitate was collected, washed with acetonitrile/petroleum ether and dried. Yield 0.43 g (89%), m.p. >300°C (dec.). — IR (KBr): $\tilde{\nu}$ = 3247, 3090, 1616, 1519, 1335 cm^{-1}. The product could not be recrystallized and so gave no satisfactory elementary analysis.

Copper(I) Complexes **6** *of 5-(2,4-Dinitrophenylhydrazono)thiazolidine-4-thiones* **4**. — *General Procedure:* A mixture of $CuSO_4 \cdot 5H_2O$ (0.25 g, 1 mmol) in water (10 ml) and **4** (2 mmol) in DMF (30 ml) was shaken for 2 h at room temp. After precipitation by addition of water (25 ml), the orange-colored product was collected, washed with water and ethanol, and dried. The complexes were obtained in 92–95% yield. Above 280°C they begin to decompose without melting. For physical and analytical data see Table 2.

Table 2. Physical and analytical data of copper(I) complexes **6** with the empirical formula $Cu_2L_2(L-L)$

	LH	IR (KBr) [cm^{-1}]		Analysis calcd. found C	H	N
6a[a]	**4a**	3267,3103,, 1615,1517, 1338	$C_{56}H_{56}Cu_2N_{20}O_{16}S_8$ (1648.8)	40.80 41.40	3.42 3.40	16.99 16.37
6b	**4b**	3247,3089, 1616,1518, 1338	$C_{44}H_{40}Cu_2N_{20}O_{16}S_8$ (1488.5)	35.50 35.60	2.71 3.20	18.82 18.64
6c	**4c**	3266,3106, 1617,1516, 1338	$C_{68}H_{56}Cu_2N_{20}O_{16}S_8$ (1792.9)	45.55 46.00	3.15 4.00	15.63 15.68

[a] MS (FAB, Cs gun, LSIMS), *m/z* (%): 380 (85) [L], 444 (8) [CuL], 760 (85) [L_2], 824 (5) [CuL_2].

Thiazolidine-4-thiones **7**. — *General Procedure:* In a three-necked flask $NaHCO_3$ (7.5 g, 90 mmol) was added with stirring in small amounts to a suspension of finely powdered P_4S_{10} (6.9 g, 15 mmol) in a solution of 10 mmol of **2** (**2a**: 2.01 g, **2b**: 1.61 g) in diglyme (20 ml). When the generation of CO_2 had subsided, a stream of hydrogen sulfide was passed through the solution, which was heated in an oil bath at 110–130°C for 8 h. When TLC (toluene/acetone, 5:1) confirmed the disappearance of **4**, the mixture was allowed to stand overnight. Dilution with finely crushed ice gave pale yellow crystals of **7** which were collected, washed with water, air-dried, and recrystallized from MeOH. Extraction of the precipitate with ether led to slightly higher yields.

Spiro[cyclohexane-1,2'-thiazolidine]-4'-thione (**7a**): Yield 1.1 g (59%), m.p. 116–120°C. — IR (KBr): $\tilde{\nu}$ = 3122 (NH), 1538, 1149, 905, 743 cm^{-1} (thioamide). — ^1H NMR ($CDCl_3$) = 1.25–2.13 (m, 10H), 4.04 (s, 2H), 9.43–10.25 (s, br., 1H). — MS (70 eV), *m/z* (%): 187 (25) [M^+]. — $C_8H_{13}NS_2$ (187.3): calcd. C 51.29, H 7.00, N 7.48, S 34.23; found C 51.10, H 6.91, N 7.58, S 34.20.

2,2-Dimethylthiazolidine-4-thione (**7b**): Yield 0.66 g (45%), m.p. 103–106°C. — IR (KBr): $\tilde{\nu}$ = 3110 (NH), 1540, 1170, 905, 750 cm^{-1} (thioamide). — ^1H NMR ($CDCl_3$): δ = 1.66 (s, 6H), 4.14 (s, 2H), 9.88–10.4 (s br., 1H). — $C_5H_9NS_2$ (147.3): calcd. C 40.78, H 6.16, N 9.51, S 43.55; found C 40.50, H 6.20, N 9.30, S 43.10.

4'-(4-Nitrobenzylthio)spiro[cyclohexane-1,2'(5'H)-thiazole] (**9**): A solution of **7a** (1.0 g, 5.0 mmol), NaOH (0.20 g, 5.0 mmol), and *p*-nitrobenzyl bromide (1.08 g, 5.0 mmol) in 20 ml of methanol was stirred at room temp. for 3 h. The yellow crystalline product which separated during this time was collected, washed with petroleum ether and recrystallized from methanol. Yield 1.55 g (95%), m.p. 68–69°C. — IR (KBr): $\tilde{\nu}$ = 1619 (C=N), 1426, 1137, 893 cm^{-1}. — ^1H NMR ($CDCl_3$): δ = 1.25–2.13 (m, 10H), 3.8 (s, 2H), 4.29 (s, 2H), 7.0–8.16 (m, 4H). — MS (70 eV), *m/z* (%): 322 (40) [M^+]. — $C_{15}H_{18}N_2O_2S_2$ (322.4): calcd. C 55.87, H 5.63, N 8.69, S 19.89; found C 55.50, H 5.60, N 8.63, S 19.52.

Thionation of **10** *to* **7a**: Following the general procedure for the preparation of **7**, the reaction of $NaHCO_3$ (7.5 g, 90 mmol) and P_4S_{10} (6.9 g, 15 mmol) with **10** (3.36 g, 10 mmol) in diglyme (20 ml) gave 1.46 g of **7a** (78%).

[1] K. Hartke, Th. Kissel, J. Quante, R. Matusch, *Chem. Ber.* **1980**, *113*, 1898–1906.
[2] K. Hartke, T. Lindenblatt, *Synthesis* **1990**, 281–284.
[3] R. Isaksson, T. Liljefors, J. Sandström, *J. Chem. Res. (S)* **1981**, 43; *(M)* 664–682.
[4] H. Bock, P. Hänel, H.-F. Herrmann, H. tom Dieck, *Z. Naturforsch., Teil B*, **1988**, *43*, 1240–1246.
[5] H. W. Roesky, H. Hofmann, W. Clegg, M. Noltemeyer, G. M. Sheldrick, *Inorg.Chem.* **1982**, *21*, 3798–3800.
[6] D. C. Morrison, A. Furst, *J. Org. Chem.* **1956**, *21*, 470–471.
[7] H. U. Kibbel, D. Dannenberger, W. Kalies, *Z. Chem.* **1989**, *29*, 336.
[8] [8a] J. Teller, H. U. Kibbel, Dtsch. Wirtsch.-Pat. (DDR) 209826, **1984**; *Chem. Abstr.* **1985**, *102*, P 45936. — [8b] Dtsch. Wirtsch.-Pat. (DDR) 209827, **1984**; *Chem. Abstr.* **1985**, *102*, P 78869.
[9] J. Teller, H. U. Kibbel, Dtsch. Wirtsch.-Pat. (DDR) 144767, **1980**; *Chem. Abstr.* **1981**, *95*, P 24303.
[10] H. Blödorn, Diplomarbeit, Universität Rostock, **1987**.
[11] [11a] M. P. Cava, M. I. Levinson, *Tetrahedron* **1985**, *41*, 5061–5087. — [11b] H. Davy, *J. Chem. Soc., Chem. Commun.* **1982**, 457–458.
[12] J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard, *Synthesis* **1973**, 149–151.
[13] J. Teller, R. Radeglia, H. U. Kibbel, *Z. Chem.* **1983**, *23*, 60–61.
[14] K. Hartke, H. Hoppe, *Chem. Ber.* **1974**, *107*, 3121–3129.
[15] R. Ketcham, E. Schaumann, *J. Org. Chem.* **1980**, *45*, 3748–3750.
[16] H. Viola, H. Hartenhauer, R. Mayer, *Z. Chem.* **1988**, *28*, 269–277; W. Thiel, R. Mayer, *Sulfur Rep.* **1988**, *8*, 1–58.
[17] C. A. Grob, P. W. Schiess, *Angew. Chem.* **1967**, *79*, 1–14; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 1–15.
[18] J. Teller, H. U. Kibbel, Inv., Dtsch. Wirtsch.-Pat. (DDR) 209823, **1984**; *Chem. Abstr.* **1985**, *102*, 78868.

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