The Preparation of Stable α-Chlorosulfenyl Chlorides from Sterically Crowded Tetramethylcyclobutanethiones and Chlorine

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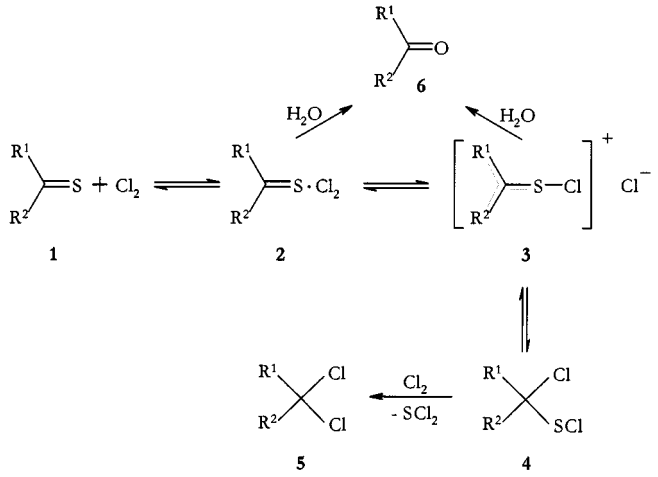
The sterically crowded 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**7**) and its dithio analogue **9** were found to react readily with gaseous chlorine to afford 1:1 and 1:2 adducts, respectively. The stable, crystalline products were identified as the α-chlorosulfenyl chlorides **8** and **12** which yielded corresponding disulfides after treatment with equimolar amounts of thioacetic acid.

Recently, the number of reports dealing with various aspects of thioketone chemistry increased remarkably and conversions such as cycloadditions, reductions, and oxidations involving C=S double bonds have been in the focus of attention of many research groups[1]. However, reports of reactions with halogens (fluorine, chlorine, bromine) which would be expected to result in formation of synthetically useful α-halosulfenyl halides have been very scarce.



Scheme 1. Possible interactions between thiocarbonyl compounds and chlorine

According to the present knowledge, the interaction of a thiocarbonyl compound **1** with chlorine takes place in a number of discrete steps (cf. Scheme 1), which might or might not lead to the corresponding α-chlorosulfenyl chloride **4**. Depending on the donor-acceptor properties of R^1 and R^2 (and, probably, so far largely unexplored steric effects of R^1 and R^2) the reversible interaction between **1** and chlorine can stop at the CT complex stage **2**, at the stage of the salt **3**, or go all the way to the α-chlorosulfenyl chloride **4**.[2] In some cases overchlorination of **4**, resulting in the formation of the corresponding *gem*-dichloro compound **5** (observed with thiobenzophenone[3], dithiocarboxylates[4], and trithiocarbonates[5]) could not be avoided. Traces of water can hydrolyse adducts **2** and/or **3** to the corresponding carbonyl compounds **6**.[6][7] The course of chlorine addition to the C=S double bond in **1** is expected to involve intermediates of type **2** and/or **3** and can be followed in solution by means of IR or ^{13}C NMR, even in cases where only labile adducts are formed such as during the attempted reaction of Cl_2 with 4,4-dichloro-1,3-dithietane-2-thione[8].

There have been described some specifically substituted thiocarbonyl compounds **1**, other than thioketones, which react smoothly with chlorine to give stable adducts of type **4**, i.e. thiophosgene[29], halothioformates[7–11], halodithioformates[5,9–18], trithiocarbonates and their derivatives.[5,12,19–24]

Alkyl and aryl groups R^1 and/or R^2 (typically present in common thioketones) are expected to stabilize the intermediates **2** and/or **3**, and thus counteract the formation of the final adduct **4**. However, one has to take into account that the same effects which counteract the formation of stable **4** may favour the hydrolysis of **2** and/or **3** as well as the overchlorination of **4**.

There are only very few and partially confusing reports about attempted reactions of chlorine with thioketones. Thiobenzophenone ($R^1 = R^2 = C_6H_5$ in general formula **1**) has been reported to form, under mild conditions, a labile, non-covalent adduct with chlorine in one instance[25] while other authors described an exothermic chlorination leading directly to dichlorodiphenylmethane[3]. Loose chlorine adducts corresponding to **2** and/or **3** (without formation of adducts **4**) have been described for thiocamphor[6] and the electron-rich 4,4′-dimethoxythiobenzophenone[6]. A report mentioning the formation of the labile 3-chloro-2,2,4,4-tetramethyl-3-pentanesulfenyl chloride from di(*tert*-butyl) thioketone ($R^1 = R^2 = t$Bu in **1**) is lacking in experimental detail.[26] Finally, the smooth formation of a stable covalent adduct of type **4** was described for hexafluorothioacetone ($R^1 = R^2 = CF_3$ in **1**).[27]

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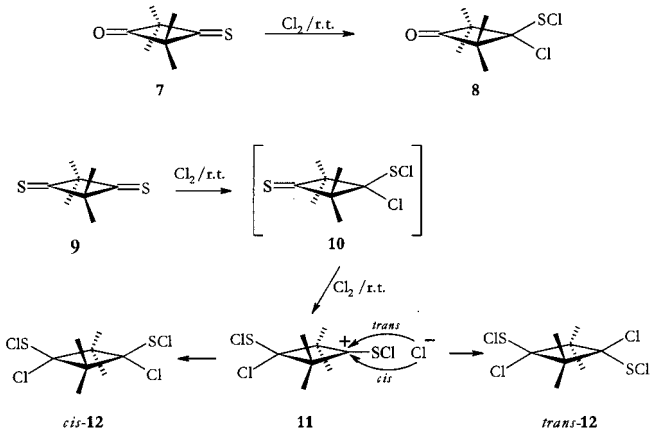
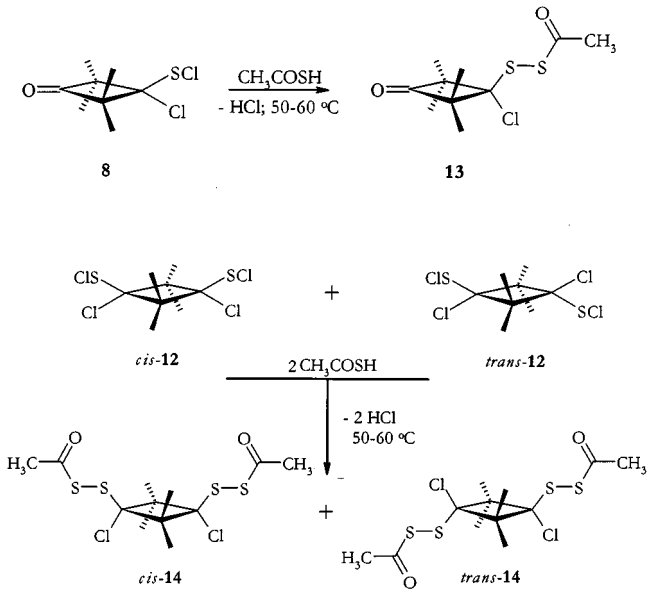


Scheme 2 The chlorination of cyclobutanethiones



Scheme 3 Derivtion of 1-chloro-1-cyclobutanesulfenyl chlorides with thioacetic acids

The sterically crowded 2,2,4,4-tetramethylcyclobutanedione[28] can be converted to a mixture of monothione **7** and dithione **9** after heating in pyridine solution with a slight excess of phosphorus pentasulfide and separation of both thioketones can be achieved by means of column chromatography.[29] Unlike other thioketones, the non-enolizable **7** and **9** are stable, non-odorous compounds and can be stored for a long time at ambient temperature. Due to these superior properties they have found numerous applications as model representatives of the C=S bond containing compounds.[30]

In our hands, the monothione **7** could be chlorinated in CCl_4 solution at ambient temperature and the result of this experiment is shown in Scheme 2. The reaction mixture rapidly changed its colour from dark red to yellow and the crude product was subsequently dried in vacuo to remove traces of solvent and the starting material. The residue formed a yellow, viscous oil (crude yield 97%) which was identified as 1:1 adduct **8**. This product, stable to storage at ambient temperature was sufficiently pure for full characterization as well as for synthetic purposes.

When the dithione **9** was subjected to the same treatment with gaseous chlorine, the initially red reaction mixture turned yellowish and evaporation of the solvent in vacuo afforded a pale yellow oil which slowly crystallized and finally changed into a solid. ^{1}H-NMR examination of this crystalline material showed the presence of two isomeric 1:2 adducts, *cis*-**12** and *trans*-**12,** in the ratio 42:58. Both isomers showed characteristic differences in the ^{1}H-NMR spectra; whereas *cis*-**12** showed two signals of methyl groups (each 2 CH_3) at δ = 1.62 and 1.64, the spectrum of *trans*-**12** contained only one singlet for all equivalent 4 CH_3 at δ = 1.63. All attempts to separate the mixture either by fractional crystallization or by means of chromatographic procedures were in vain.

As far as we could ascertain the only 1-chlorocyclobutanesulfenyl chloride known prior to our present work was 1,2-dichloro-2,3,3,4,4-pentafluorocyclobutanesulfenyl chloride which was obtained by Russian authors using a completely different, quite tedious methodology.[31] Our simple procedure based on application of easily available thioketones and yielding **8** and **12** as practically pure compounds for further applications, opens a new route for the preparation of isolable, reactive building blocks of type **4**.

Both **8** and **12** are expected to undergo easy substitution with nucleophilic reagents. In order to show one of their possible applications in the syntheses of sulfur-containing, organic products we carried out their derivatization with thioacetic acid (Scheme 3) and obtained **13** and *cis*-**14**/*trans*-**14** (the latter two isomers being separable by analytical HPLC), respectively. Acetyl α-chloroalkyl disulfides such as **13** and **14** can be explored as convenient precursors of thiosulfines and/or dithiiranes.[32]

In summary, our results described in a preliminary form in this paper show that the ring strain (i.e. Baeyer and/or Pitzer strain) in crowded cyclobutanethiones is the driving force for the smooth addition of chlorine and, by the same token, protects the corresponding α-chlorosulfenyl chlorides from loss of chlorine as well as from the undesired overchlorination.

The scope and limitation of this simple procedure for the synthesis of α-chlorosulfenyl chloride using other sterically hindered cycloaliphatic ketones is under study in our laboratories and will be published elsewhere.

Experimental Section

^{1}H-NMR spectra were recorded at 300 MHz in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference. ^{13}C-NMR spectra were recorded at 75 MHz with the solvent peak ($CDCl_3$, δ = 77.0) as a reference.

1-Chloro-2,2,4,4-tetramethyl-3-oxocyclobutanesulfenyl Chloride (8): 2,2,4,4-Tetramethyl-3-thioxocyclobutanone[29] (**7**, 0.34 g, 2.1 mmol) was dissolved in 40 mL of CCl_4 and stirred magnetically at ambient temperature. Gaseous chlorine was passed through the solution until TLC showed that the reaction was complete (10 min). During this time the reaction mixture changed its colour from dark red to

yellow. The reaction solution was then purged with N_2 to remove remaining chlorine and concentrated in vacuo to yield 471 mg (97%) of pure **8** as a yellow oil. − IR (NaCl): $\tilde{\nu}$ = 2975, 2934, 1782, 1465, 1383, 1026, 839 cm^{-1}. − ^1H NMR: δ = 1.47 (s, CH_3), 1.51 (s, CH_3). − ^{13}C NMR: δ = 20.46 (CH_3), 23.89 (CH_3), 69.76 [$C(CH_3)_2$], 87.29 (CClS), 214.63 (CO). − MS (EI); *m/z* (%): 191 (44) [M^+ − Cl], 156 (26) [M^+ − 2 Cl], 131 (47) [M^+ − Cl, − CO, − S], 121 (20) [$(CH_3)_2CCClS$], 86 (34) [$SCC(CH_3)_2$], 70 (100) [$OCC(CH_3)_2$]. − MS (CI, ammonia); *m/z* (%): 227 (34) [MH^+]. − $C_8H_{12}Cl_2OS$ (227.1): calcd. C, 42.30, H, 5.32; found C, 41.81, H, 5.30.

***cis*-1,3-Dichloro-2,2,4,4-tetramethyl-1,3-cyclobutanedisulfenyl Dichloride (*cis*-12) and *trans*-1,3-Dichloro-2,2,4,4-tetramethyl-1,3-cyclobutanedisulfenyl Dichloride (*trans*-12):** 2,2,4,4-Tetramethylcyclobutane-1,3-dithione[29] (**9**, 2.27 g, 13.1 mmol) was dissolved in 60 mL of CCl_4, stirred at ambient temperature and treated with chlorine as above (15 min). During this time the reaction mixture changed its colour from clear red to yellow. Work-up as above yielded a yellow oil which crystallized overnight to give 4.09 g (99%) of a pure, yellow crystalline mixture of *cis*-**12**/*trans*-**12**, m.p. 57.5−83.6°C. − IR (KBr): $\tilde{\nu}$ = 2978, 1465, 1382, 1370, 1189, 1164, 930, 845 cm^{-1}. − EI MS; *m/z* (%): 312 (3) [M^+], 275 (14) [M^+ − Cl], 245 (4) [M^+ − Cl, − S], 207 (11), 175 (35) [M^+ − 3 Cl, − S], 156 (100)[$(CH_3)_2CCClSCl$], 121 (46) [$(CH_3)_2CCClS$], 86 (33)[$(CH_3)_2CCS$], 77 (29). − $C_8H_{12}Cl_4S_2$ (314.1): calcd. C, 30.59, H, 3.85; found C, 30.97, H, 3.83. − *cis*-**12**: ^1H NMR: δ = 1.62 (s, CH_3) 1.64 (s, CH_3). − ^{13}C NMR: δ = 22.23 (CH_3), 28.71 (CH_3), 59.28 [$C(CH_3)_2$], 90.42 (CClS). − *trans*-**12**: ^1H NMR: δ = 1.63 (s, CH_3). − ^{13}C NMR: δ = 25.49 (CH_3), 58.71 [$C(CH_3)_2$], 90.64 (CClS)

Acetyl 1-Chloro-2,2,4,4-tetramethyl-3-oxocyclobutyl Disulfide (13): Compound **8** (0.60 g, 2.62 mmol) and thioacetic acid (0.2 mL, 2.81 mmol) were dissolved in 25 mL of CCl_4 and heated at 50−60°C until TLC showed that the reaction was complete (30 min). The pale yellow reaction mixture was concentrated in vacuo to afford 772 mg of an oily residue. The crude product was column-chromatographed (SiO_2, eluent hexane/diethyl ether, 5:1) to yield 486 mg of a colourless oil which was column-rechromatographed (SiO_2, eluent hexane/ether, 7:1) to give 399 mg (57%) of pure **13** as a colourless oil. − IR (NaCl): $\tilde{\nu}$ = 2974, 2934, 1790, 1745, 1706, 1464, 1382, 1366, 1245, 1108, 1026, 941, 886, 832 cm^{-1}. − ^1H NMR: δ = 1.41 (s, CH_3), 1.51 (s, CH_3), 2.52 (s, acetyl CH_3). − ^{13}C NMR: δ = 22.43 (CH_3), 23.56 (CH_3), 28.67 (acetyl CH_3), 69.31 [$C(CH_3)_2$], 86.87 (CClS), 192.92 (COS), 215.49 (CO). − MS (EI); *m/z* (%): 196 (100) [M^+ − $OCC(CH_3)_2$], 188 (25) [M^+ − CH_3COCl], 154 (43) [$(CH_3)_2CCClSSH$], 131 (31) [M^+ − CH_3COSS, − CO], 95 (24), 70 (30) [$OCC(CH_3)_2$]. − MS (CI, ammonia); *m/z* (%): 267 (33) [M^+]. − $C_{10}H_{15}ClO_2S_2$ (266.8): calcd. C, 45.02, H, 5.67; found C, 44.75, H, 5.62.

***cis*-1,3-Bis(acetyldithio)-1,3-dichloro-2,2,4,4-tetramethylcyclobutane (*cis*-14) and *trans*-1,3-Bis(acetyldithio)-1,3-dichloro-2,2,4,4-tetramethylcyclobutane (*trans*-14):** The inseparable mixture of *cis*-**12** and *trans*-**12** (619 mg, 1.97 mmol) and thioacetic acid (0.84 mL, 11.8 mmol) were dissolved in 20 mL of CCl_4 and heated at 50−60°C until TLC showed that the reaction was complete (2 h). The yellowish reaction mixture was concentrated in vacuo to leave 918 mg of crude product which was column-chromatographed (SiO_2, eluent hexane/ether, 4:1) to yield 666 mg of a colourless oil. After trituration with hexane/ether (6:1) it changed to a colourless crystalline material with m.p. 61.3−68.6°C (387 mg, 50%) which was identified as a mixture of *cis*-**14** and *trans*-**14**. − IR (KBr): $\tilde{\nu}$ = 2985, 2939, 1741, 1471, 1450, 1382, 1351, 1194, 1109, 943, 858, 825 cm^{-1}. − MS (CI, ammonia); *m/z* (%): 410 (13) [MNH_4^+], 357 (2) [M^+ − Cl], 279 (88), 247 (18), 207 (100), 175 (17). − $C_{12}H_{18}Cl_2O_2S_4$ (393.4): calcd. C, 36.64, H, 4.61; found C, 36.52, H, 4.63. − *cis*-**14**: ^1H NMR: δ = 1.51 (s, CH_3), 1.68 (s, CH_3), 2.48 (s, acetyl CH_3). − ^{13}C NMR: δ = 25.73 (CH_3), 27.92 (CH_3), 28.60 (acetyl CH_3), 58.45 [$C(CH_3)_2$], 90.57 (CClS), 193.50 (COS). − *trans*-**14**: ^1H NMR: δ = 1.59 (CH_3, s), 2.48 (acetyl CH_3, s). − ^{13}C NMR: δ = 26.84 (CH_3), 28.60 (acetyl CH_3), 58.54 [$C(CH_3)_2$], 90.36 (CClS), 193.59 (COS). − The isomers *cis*-**14** and *trans*-**14** were separated only by means of analytical HPLC. Conditions: Stationary phase, Nucleosil 100−7 7.0 μm; column, 250 × 4.6 mm; mobile phase, 1 mL min^{-1}, hexane/$CHCl_3$/EtOAc, 20:1:0.1; UV detector, 254 nm. R_t = 19.62 min and 20.24 min, respectively.

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