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Selective Transformation of α,α-Dibromomethyl Ketones into α-Monosulfenylated Ketones

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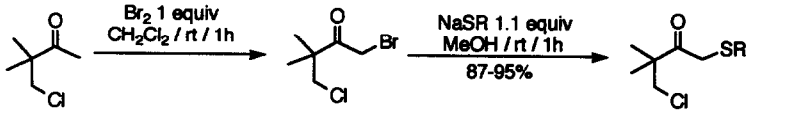
ABSTRACT

When α,α-dibromomethyl ketones are treated with sodium thiolates only the α-monosulfenylated ketones are formed. Evidence is put forward that the reaction mechanism proceeds by an initial nucleophilic substitution of one bromo atom and reduction by single electron transfer (SET) - hydrogen atom abstraction of the second bromo atom.

RESULTS AND DISCUSSION

During an investigation on the synthesis of non-proteinogenic α-amino acids, functionalized α-sulfenylated ketones **3** were required as intermediates. These trifunctional compounds **3** were made accessible by bromination of the corresponding β-chloro ketone **1** and subsequent nucleophilic substitution of the introduced bromo atom with the appropriate sodium thiolates (Scheme 1).[1,2] For practical reasons only the

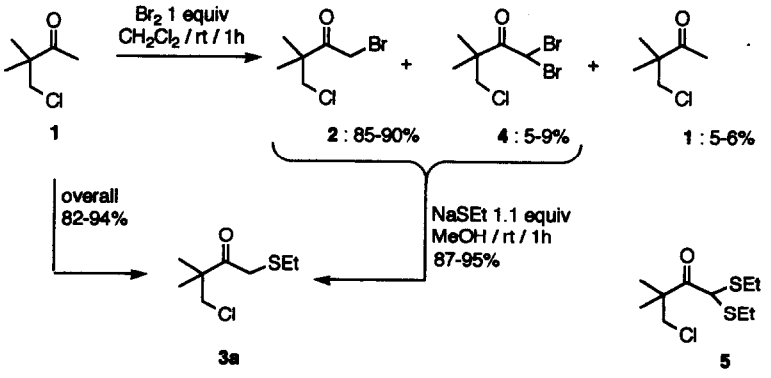


1 **2** **3a** : R = Et **3b** : R = C_6H_5

Scheme 1

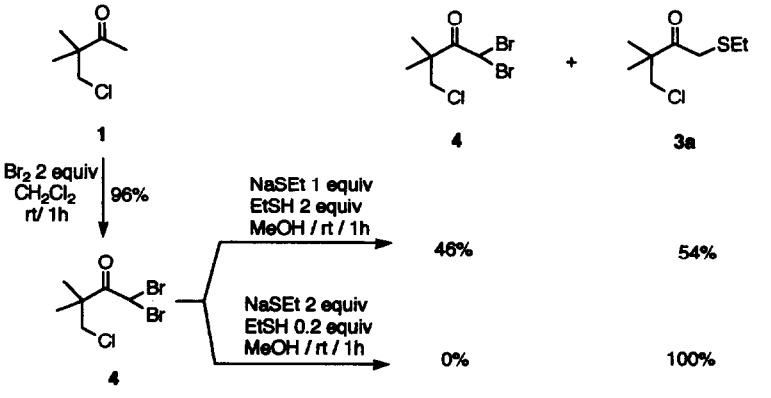
ethylthio derivative **3a** was used in these experiments. During this sequence, a somewhat peculiar reaction was observed. As expected, a completely selective α-monobromination of an acetyl moiety as present in the β-chloro ketone **1** is difficult to achieve.[3] This lack of selectivity leads to the presence of little amounts (5-9%) of α',α'-dibromo ketone **4** next to starting material (5-6%), non-reacted or obtained by disproportionation of the resulting α'-monobromo ketone **2** (Scheme 2). These side-reactions cannot be circumvented by slowly adding the substrate and reagent to the solvent in a simultaneous and equable way. Therefore, the reaction mixture was used as such in the following step. Out of the resulting reaction mixture the α'-ethylthio ketone **3a** was isolated as the major product next to diethyldisulfide and,

as expected, the non-substituted β-chloro ketone 1 (5-6%). The latter two compounds were removed from 3a under reduced pressure (0.1 mmHg, 35 °C) without appreciable loss of the target compound 3a. However, not a trace of the disubstituted ketone 5 could be observed, neither via ^{1}H-NMR, nor via GC-MS coupling. Preparative gas chromatography is not possible since the ketone 3a cannot withstand these conditions. In addition, the yield of the thiomethyl ketone 3a (82-94% overall) was higher than theoretically possible taking into account the relative proportion of the α'-monobromo ketone 2 in the starting reaction mixture (85-90% after bromination of the β-chloroketone 1). To look into this mechanistic pic-



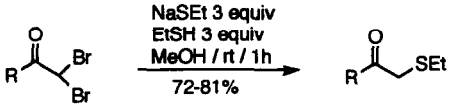
Scheme 2

ture, the α',α'-dibromo ketone 4, prepared from bromination of ketone 1 with two equivalents of bromine, itself was treated with sodium ethylthiolate under different reaction conditions (Scheme 3). The outcome of these experiments showed that the α',α'-dibromo ketone 4 also yields the monosubstituted α'-(ethylthio)ketone 3a in which the number of equivalents of sodium ethylthiolate seems to be the determining factor. When using only one equivalent of sodium ethylthiolate and an



Scheme 3

excess of ethanethiol (2 equiv.), only half of the α',α'-dibromomethyl ketone **4** is converted while the other half remains unreacted. Instead, using two equivalents of sodium ethylthiolate and only a slight excess of ethanethiol (0.2 equiv.) a complete conversion is achieved. This type of reaction is more general. Applying similar reaction conditions on other structurally different dibromomethyl ketones

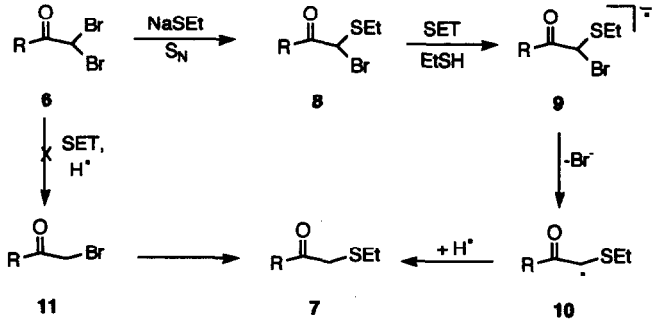


6a : R = C_6H_5
6b : R = p-ClC_6H_4
6c : R = t-Bu
6d : R = Et_2CCH_2Cl
6e : R = Me_2CCH_2OMs

7a-e

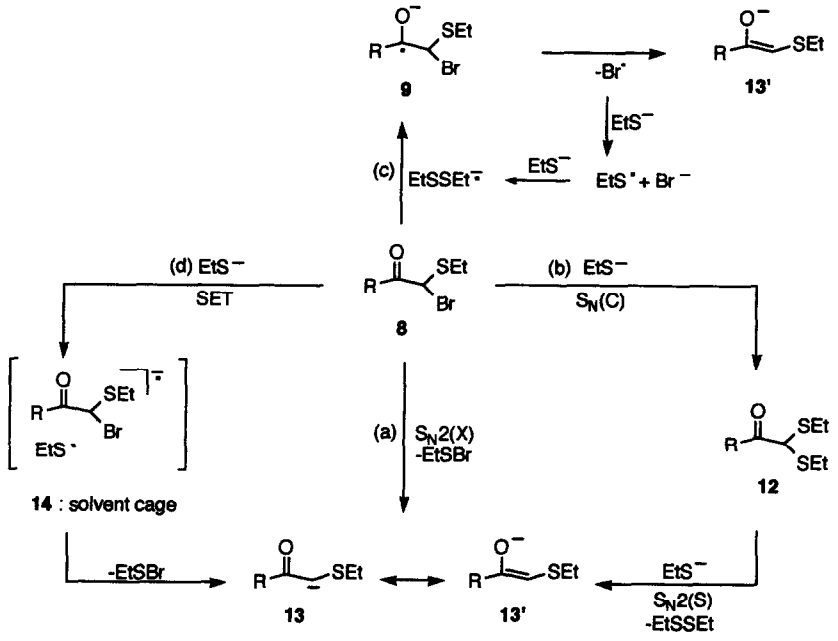
Scheme 4

also gave only the corresponding α-monosulfenylated products **7** (Scheme 4). The formation of α-monosulfenylated ketones from dibromomethyl ketones is noteworthy for its ease of execution, mild reaction conditions and satisfying yields. This given was used to obtain a selective monosulfenylation of the β-chloro ketone **1** on a preparative scale without loss of starting material. Although removal of the diethyldisulfide formed during the reaction can easily be accomplished by simple evaporation under reduced pressure, purification was also performed by flash chromatography on silica gel. Elution with pentane completely removes the diethyldisulfide after which the thiomethyl ketone **7** or **3a** is collected in one fraction using dichloromethane as solvent. Because of the large difference in retention times of both compounds (Table), this procedure is also useful on a preparative scale. It should be noted that the title transformation was reported with thiophenyl in benzene to afford (phenylthio)methyl ketones.[4,5] Under these apolar conditions, the mechanism was interpreted to involve carbanionic species by means of nucleophilic attack on halogen[4] [$S_N2(X)$] or increased polarization of the carbonyl group causing the removal of halogen as a halonium ion[5].



Scheme 5

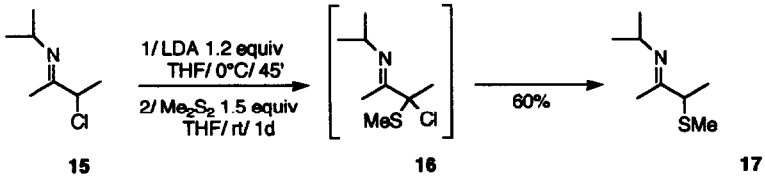
In the course of the ongoing program it was not the intention to unravel fully the mechanistic details. However, based on some experimental results, literature data and commonly accepted considerations, it is felt appropriate to put forward a possible mechanistic explanation (Scheme 5), slightly different from that proposed by Bowman for the thiolate reduction of 2-substituted 2-nitropropanes (Scheme 5).[6,7] Primarily, a nucleophilic substitution of one bromo atom by sodium thiolate results in the formation of the α-bromo-α-ethylthio ketone 8. The intermediate is then reduced by a single electron transfer (SET) in which the second equivalent of sodium thiolate functions as single electron donor.



Scheme 6

The radical anion 9 (ketyl radical anion) expels the second bromo atom as bromide to leave a captodatively stabilized radical 10. Finally, the radical 10 takes up a hydrogen atom from the surroundings. Both the substitution and reduction step proceed very rapidly. Even at 0°C precipitation of sodium bromide is almost instantaneous when, performing the experiment at small scale, the substrate is added in one portion to the solution of the thiolate. Still then, the first step is rate determining since otherwise a clear cut halfway conversion using only one equivalent of sodium thiolate would not be possible. The mechanism for the thiolate promoted reduction still remains somewhat speculative and can only stand for the reaction conditions as used here. There have been different reports describing the difficulty distinguishing between a X-philic [$S_N2(X)$, i.e. nucleophilic attack on the halogen] and a single electron transfer (SET) mechanism in thiol- or thiolate-promoted reductions of this type (Scheme 5 and Scheme 6; pathway a).[6-10] Reduction seems to be favored over substitution by the use of polar

protic solvents, more basic (nucleophilic) thiolates and readily abstracted leaving groups. All these features are met under the given reaction conditions. Furthermore, with a variety of compounds, thiolates have been shown to react differently depending on the conditions used. 2-Halomethyl-5-nitrofuranes yield 5-nitro-2-furfurylmethyl sulfides via a normal $S_N2(C)$ process and/or 2-methyl-5-nitrofurans by a $S_N2(X)$ mechanism, although for both reactions a non chain radical mechanism by SET could not be excluded.[8] Various 2-substituted 2-nitropropanes exhibit a competition between a radical radical-anion chain mechanism ($S_{RN}1$) which gives the corresponding α-nitro sulfides and a $S_N2(X)$ reaction resulting in reduction of the substrates. A possible alternative redox mechanism by SET has been suggested here also.[6,7] On the other hand, α-bromo isobutyrophenones are apt to undergo reduction depending on reaction conditions while α-chloro isobutyro-phenones do not show this tendency.[10] Analogously, different aliphatic and aromatic α-chloro- and α-bromo ketones react normally with thiols via $S_N2(C)$, whereas the corresponding iodomethyl ketones exclusively afford methyl ketones.[10] In the last two cases no direct evidence to support or differentiate between mechanistic pathways could be given. More closely related, α-chloro-α-sulfonyl sulfides, with sodium thiophenolate, give nucleophilic attack on both the halogen [$S_N2(X)$, 43%] and the halogen bearing carbon [normal $S_N(C)$, 22%].[12] In this case only reduction of the intermediate α-chloro-β-keto sulfide occurs. Arguments for the mechanism as shown above are the following. First of all, thiolates are known as excellent single electron donors and the more strongly basic, the greater the likelihood they will react by SET rather than by a S_N2 pattern.[6] Then, lack of inhibition in the presence of m-dinitrobenzene (m-DNB, an electron acceptor) at the level of 0.1 equivalents but not at equimolar amounts is indicative of a non chain radical mechanism with the intermediacy of radical anions.[13-14] Even when lack of inhibition should occur at equimolar amounts, radical intermediates cannot be excluded as such.[8] In cases where an X-philic mechanism was postulated to be operative nucleophilic attack of thiolate on the intermediate sulfenyl chloride would account for disulfide formation.[8,12] In this way, a second equivalent of thiolate is required for the reduction. Indeed, in these cases two or more equivalents of thiolate were necessary or anyway used. On the contrary, the use of only one equivalent of thiolate is a necessary but also a satisfying condition for the reduction of the intermediate α-chloro-β-keto sulfide. This fact is nicely illustrated in a related experiment. α-Sulfenylation of the 1-azaenolate of α-chloro ketimine 15 using dimethyldisulfide generates exactly one equivalent of thiolate which is enough to reduce the intermediate α-chloro-α-(methylthio)ketimine 16 (Scheme 7).

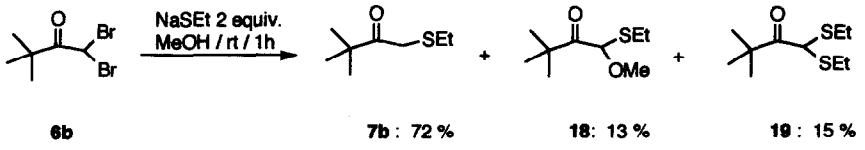


15 16 17

Scheme 7

For the same reasons, other alternative pathways can be rejected (Scheme 6). These include S_N2 on sulfur of an intermediate thioacetal 12 (pathway b),[15-17] a chain oxidative dimerisation (pathway c)[18,19] and

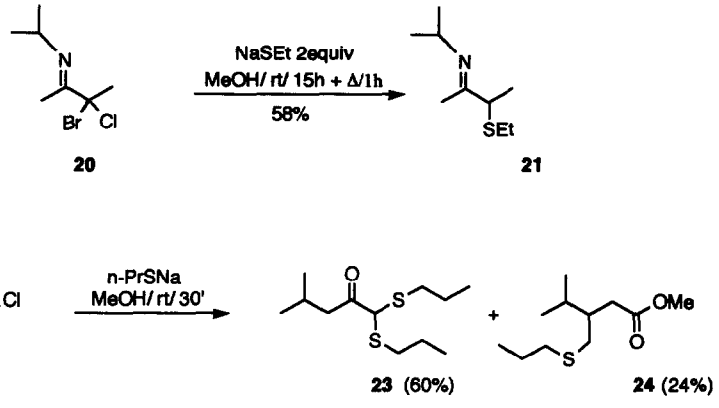
a solvent cage reaction (pathway d)[6,7]. The last mechanism was proposed as an alternative for a $S_N2(X)$ reaction in the reduction of 2-substituted 2-nitropropanes because the latter was not in agreement with experimental details. Though also being a non chain mechanism proceeding by SET as proposed here, it is based on a strong protic solvation of the nitro group in the intermediate radical anion leading to a sulfenyl halide. Treatment of the α,α-dibromo ketone **6b** with exactly two equivalents of sodium ethylthiolate and no free ethanethiol results in competition and formation of side-products like **18** and **19**, the latter pointing in the direction of the α-bromo-α-ethylthio ketone **8** as intermediate (Scheme 8). This is



6b **7b** : 72 % **18**: 13 % **19** : 15 %

Scheme 8

important, because reduction prior to substitution would also be possible (Scheme 5). In similar way, the α-bromo-α-chloro ketimine **20** almost exclusively yields the monosulfenylated imine **21**, broadening the scope of the reaction (Scheme 9). On the contrary, dichloromethylketones like **22** generate the disubstituted product **23**, next to a small amount of Favorskii-type rearrangement product **24** (Scheme 9). This behavior reflects the importance of an α-bromo substituent in these reduction reactions with thiolates.



20 **21**

22 **23** (60%) **24** (24%)

Scheme 9

EXPERIMENTAL

Infrared spectra were recorded on a Perkin Elmer 1310 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured on Jeol PMX60SI (60 MHz), Jeol JNM EX270 (270 MHz), Varian T-60 and Varian T-80 spectrometers. Mass spectra were obtained on a Varian MAT 112 mass spectrometer (70

eV) using GC-MS coupling with a Varian 2700 gas chromatograph (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). Gas chromatographic analyses were performed with Varian 1400 (RSL 150, 20m glass capillary column, i.d. 0.53 mm, H_2 carrier gas) and Varian 920 (glass column, 1.5 m, 5-10% SE-30, Chromosorb W 60-80, H_2 carrier gas) gas chromatographs. Flash chromatography was performed using Merck Kieselgel 60 (40-63 μm). Solvent systems were determined via initial tlc analysis (Merck Kieselgel 60 F_{254}, precoated). Melting points were measured on a Reichert Jung (Kofler type) hotbench. The β-chloro ketone 1 was synthesized according to a previously described procedure[20] although in a slightly modified way[1]. 1,1-Dibromoacetophenone[21] **6a** and 1,1-dibromo-3,3-dimethyl-2-butanone[22] **6c** were prepared according to known literature procedures.

1,1-Dibromo-4-chloro-3,3-dimethyl-2-butanone (4).

In a well ventilated hood bromine (12.8 g, 0.08 mol), dissolved in some dichloromethane (10 ml), is added dropwise to a solution of β-chloro ketone 1 (5.36 g, 0.04 mol) in the same solvent (40 ml). After complete addition, the reaction mixture is stirred for one additional hour, washed with 1N $NaHCO_3$ (until neutral or slightly alkaline), followed by 0.5 N $NaHSO_3$ (until colourless). The organic phase is dried, filtered and evaporated to afford the α',α'-dibromo ketone 4 as a pale yellow crystalline solid. Yield 11.24 g (96%). The product recrystallized easily and quantitatively in pentane at -20°C, mp. 38°C. ^{1}H-NMR δ ($CDCl_3$, 270 MHz) [ppm] : 1.46 (6H, s, Me_2); 3.64 (2H, s, CH_2); 6.36 (1H, s, CH). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) [ppm] : 23.52 (Me_2); 37.92 (CH); 49.02 ($Me_2\underline{C}$); 198.76 (C=O). IR (KBr) $\nu_{C=O}$ = 1722 cm^{-1}. MS (70eV) m/z (rel. intens.) : no M$^+$; 199/201/203(1); 171/173/175(2); 119/121 (5); 91/93 (100); 65(4); 63(11); 56(10); 55(87); 53(5); 41(17). Anal. Calcd for $C_6H_9Br_2ClO$: C, 24.65; H, 3.10. Found : C, 24.76; H, 3.17.

1,1-Dibromo-4-chloroacetophenone (6b).

1,1-Dibromo-4-chloroacetophenone **(6b)** was prepared analogous to 1,1-dibromoacetophenone **(6a)**; mp = 91.5°C (recrystallized from pentane). ^{1}H-NMR δ ($CDCl_3$, 270 MHz) 6.65 (1H, s, $CHBr_2$); 7.48 and 8.05 (2xd, AA'BB', J = 9.58 Hz, C_6H_4). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) 39.33 ($CHBr_2$); 129.23 and 131.14 (Co and C_m); 129.02 and 141.00 (Cp and Cq); 184.85 (C=O). IR (KBr, cm^{-1}) $\nu_{c=o}$ = 1650-1690. MS (70eV) m/z (rel. intens.) : 310/312/314/316 (M$^+$, 2); 203/205/207(5); 139/141(100); 124(5); 111/113(26); 89(15); 76(5); 75(21); 74 (6); 63(6); 62(4); 51(5); 50(12); 40(26). Anal. Calcd for $C_8H_5Br_2ClO$: C, 30.76; H, 1.61. Found : C, 30.86; H, 1.63.

1,1-Dibromo-4-chloro-3-ethyl-2-pentanone (6d).

1,1-Dibromo-4-chloro-3-ethyl-2-pentanone **(6d)** was prepared analogous to 1,1-dibromo-4-chloro-3,3-dimethyl-2-butanone (4). ^{1}H-NMR δ ($CDCl_3$, 270 MHz) 0.89 [6H, dxd, J = 7.25 and 7.59 Hz, $(CH_2\underline{C}H_3)_2$]; 1.78 and 1.88 [4H, ABxq, J_{AB} = 14.68 Hz, J_{vic} = 7.25 and 7.59 Hz, $(\underline{C}H_2CH_3)_2$]; 3.72 (2H, s, CH_2Cl); 6.38 (1H, s, $CHBr_2$). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) 8.43 [$(CH_2\underline{C}H_3)_2$]; 26.06 [$(\underline{C}H_2CH_3)_2$]; 37.29 ($CHBr_2$); 44.85 ($Et_2\underline{C}$); 57.27 (CH_2Cl); 199.15 (C=O). IR (NaCl, cm^{-1}) $\nu_{c=o}$ = 1720. MS (70eV) m/z (rel. intens.) no M$^+$; 171/173/175(2); 147/149(38); 119/121(75); 84(9); 83(100); 79(4); 77(10); 69(6); 67(3); 65(3); 63(3); 57 (16); 56(6); 55(88); 53(9); 44(10); 43(38); 41(38). Anal. Calcd for $C_8H_{13}Br_2ClO$:

C, 29.99; H, 4.09. Found : C, 29.90; H, 4.02.

1,1-Dibromo-4-mesyloxy-3,3-dimethyl-2-butanone (6e).

1,1-Dibromo-4-mesyloxy-3,3-dimethyl-2-butanone (6e) was prepared analogous to 1,1-dibromo-4-chloro-3,3-dimethyl-2-butanone (4). Mp = 74°C (recrystallized from pentane). ^{1}H-NMR δ ($CDCl_3$, 270 MHz) 1.43 (6H, s, Me_2); 3.06 (3H, s, SO_2Me); 4.23 (2H, s, CH_2O); 6.37 (1H, s, $CHBr_2$). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) 22.03 (Me_2); 37.16 and 37.38 ($CHBr_2$ and SO_2Me); 47.33 (Me_2C); 74.27 (CH_2O); 198.69 (C=O). IR (KBr, cm^{-1}) $\nu_{C=O}$ = 1721. MS (70eV) m/z (rel. intens.) no M^+; 199/201/203(1); 179(22); 153(2); 152(3); 151(38); 150(3); 149(3); 148(3); 129(2); 123(5); 121(4); 97(3); 91(5); 83(3); 79(17); 73(17); 57(4); 56(41); 55(100); 43(8); 42(7); 41(20); 40(4). Anal. Calcd for $C_7H_{12}Br_2O_3S$: C, 25.02; H, 3.60. Found : C, 25.18; H, 3.63.

1-(Ethylthio)acetophenone (7a) ; Typical Procedure.

To an ice cooled solution of 2N sodium methoxide in methanol (37.5 ml, 75 mmoles) is added ethanethiol (9.3 g, 150 mmoles). After stirring for five minutes α,α-dibromoacetophenone **6a** (6.95 g, 25 mmoles) is added in portions at such a rate as to ensure a smooth reaction (exothermic reaction). Within a few minutes a white precipitate is formed. After the addition is completed the icebath is removed and the reaction mixture is stirred for one additional hour. The mixture is then poured into water (300 ml) and extracted with dichloromethane (3 x 50 ml). The combined extracts are washed with a saturated sodium chloride solution (150 ml), dried ($MgSO_4$) and filtered. After evaporation of the solvent the residual oil is subjected to flash chromatography (R_f CH_2Cl_2=0.60; EtSSEt R_f pentane=0.55, R_f CH_2Cl_2=0.89). Yield 3.42 g (76%).

1-(Ethylthio)acetophenone (7a).

^{1}H-NMR δ ($CDCl_3$, 270 MHz) [ppm] : 1.23 (3H, ~t, J=7.26 and 7.59Hz, $CH_2\underline{CH_3}$); 2.57 (2H, ~q, J=7.26 and 7.59Hz, $\underline{CH_2}CH_3$); 3.78 (2H, s, $\underline{CH_2}S$); 7.4-7.5 (2H, m, H_m); 7.5-7.6 (1H, m, H_p); 7.9-8.0 (2H, m, H_o). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) [ppm] : 14.13 ($SCH_2\underline{C}H_3$), 26.22 ($S\underline{C}H_2CH_3$); 36.68 ($CO\underline{C}H_2$); 128.59 and 128.71 (Co + Cm); 133.23 (Cp); 135.18 (Cq); 194.41 (C=O). IR (NaCl) : $\nu_{C=O}$ = 1675 cm^{-1}. MS (70 eV) m/z (rel. intens.) : 180 (M^+, 10); 121(6); 120(41); 106(9); 105(100); 91(4); 78(7); 77(60); 76(2); 75(9); 65(4); 51(17); 50(4); 47(11); 45(4); 41(3); 40(7).

4-Chloro-1-(ethylthio)acetophenone (7b).

R_f CH_2Cl_2=0.64. ^{1}H-NMR δ ($CDCl_3$, 270 MHz) 1.24 (3H, t, J = 7.26 Hz, $SCH_2\underline{CH_3}$); 2.56 (2H, q, J = 7.26 Hz, $S\underline{CH_2}CH_3$); 3.76 (2H, S, CH_2S); 7.41 and 7.91 (2x2H, AA'BB', J = 8.58 Hz, C_6H_4). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) 14.12 ($SCH_2\underline{C}H_3$); 26.25 ($S\underline{C}H_2CH_3$); 36.62 (CH_2S); 128.91 and 130.22 (Co and Cm); 133.51 and 139.60 (Cp and Cq); 193.15 (C=O). IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1675. MS (70 eV) m/z (rel. intens.) 214/216 (M^+, 14); 154/156(59); 139/141(100); 125/127(5); 111/113(41); 89(5); 77(4); 76(8); 75(49); 63(3); 59(3); 51(5); 50(8); 47(20); 45(8); 41(5). Anal. Calcd for $C_{10}H_{11}ClOS$: C, 55.94; H, 5.16. Found : C, 55.82; H, 5.12.

1-(Ethylthio)-3,3-dimethyl-2-butanone (7c).

R_f CH_2Cl_2=0.73. Full spectroscopic data of compound 7b are provided here because they do not match completely with those reported earlier.[23] ^{1}H-NMR δ ($CDCl_3$, 270 MHz) [ppm] : 1.21 (9H, s, Me_3); 1.25 (3H, t, J=7.26Hz, $CH_2\underline{CH_3}$); 2.57 (2H, q, J=7.26Hz, $\underline{CH_2}CH_3$); 3.45 (2H, s, CH_2). ^{13}C-NMR δ ($CDCl_3$, 67.8 Mhz) [ppm]: 14.20 ($SCH_2\underline{CH_3}$); 26.06 ($S\underline{CH_2}CH_3$); 26.85 (Me_3); 35.81 ($CO\underline{CH_2}$); 44.04 ($Me_3\underline{C}$); 210.06 (C=O). IR (NaCl) : $\nu_{C=O}$ = 1705 cm^{-1}. MS (70 eV) m/z (rel. intens.) : 160 (M^+, 8); 138(5); 85(19); 82(19); 76(8); 75(17); 61(4); 57(100); 55(4); 48(5); 47(12); 43(4); 41(37); 40(10). Anal. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06. Found : C, 60.03; H, 10.09.

4-Chloro-3-ethyl-1-(ethylthio)-2-pentanone (7d).

R_f CH_2Cl_2=0.67. ^{1}H-NMR δ ($CDCl_3$, 270 MHz) 0.81 [6H, dxd, J=7.25 and 7.59 Hz, $(CH_2\underline{CH_3})_2$]; 1.25 (3H, t, J = 7.26 Hz, $SCH_2\underline{CH_3}$); 1.73 and 1.80 [4H, ABxq, J_{AB} = 14.51 Hz, J_{vic} = 7.25 and 7.59 Hz, $\underline{CH_2}CH_3)_2$]; 2.60 (2H, q, J = 7.26 Hz, $S\underline{CH_2}CH_3$), 3.47 and 3.72 (2x2H, 2xs, CH_2S and CH_2Cl). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) 8.27 [$(CH_2\underline{CH_3})_2$]; 14.16 ($SCH_2\underline{CH_3}$); 25.84 [$(\underline{CH_2}CH_3)_2$]; 26.31 ($S\underline{CH_2}CH_3$); 36.89 (CH_2S); 45.70 ($Et_2\underline{C}$); 56.48 (CH_2Cl); 207.62 (C=O). IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1696. MS (70 eV) m/z (rel. intens.) 222/224 (M^+, 15); 187(2); 186(2); 147/149(14); 119/121(51); 84(16); 83(100); 77(9); 75(49); 69(16); 57(10); 56(8); 55(59); 53(4); 47(16) ; 43(24); 41(24). Anal. Calcd for $C_{10}H_{19}ClOS$: C, 53.91; H, 8.60. Found : C, 53.79; H, 8.55.

1-(Ethylthio)-4-mesyloxy-3,3-dimethyl-2-butanone (7e).

R_f CH_2Cl_2=0.56. ^{1}H-NMR δ ($CDCl_3$, 270 MHz) 1.25 (3H, t, J = 7.59 Hz, $SCH_2\underline{CH_3}$); 1.31 (6H, s, Me_2); 2.55 (2H, q, J = 7.59 Hz, $S\underline{CH_2}CH_3$); 3.05 (3H, s, SO_2Me); 3.49 (2H, s, CH_2S); 4.23 (2H, s, CH_2O). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) 14.12 ($SCH_2\underline{CH_3}$); 21.96 (Me_2); 25.93 ($S\underline{CH_2}CH_3$); 36.68 and 36.93 (CHS_2 and SO_2Me); 47.47 ($Me_2\underline{C}$); 74.95 (CH_2O), 206.75 (C=O). IR (NaCl, cm^{-1}) $\nu_{C=O}$ = 1768. MS (70 eV) m/z (rel. intens.) no M^+, 220(25); 174(19); 159(22); 145(41); 127(75); 125(15); 124(39); 123(21); 101(16); 89(19); 88(17); 85 (25); 75(61); 70(18); 69(30); 68(10); 67(10); 61(22); 60(20); 59(21); 57(20); 56(28); 55(100); 47(32); 45 (21); 43(43); 41(57). Anal. Calcd for $C_9H_{18}O_4S_2$: C, 42.50; H, 7.13. Found : C, 42.58; H, 7.18.

4-Chloro-1-(ethylthio)-3,3-dimethyl-2-butanone (3a).

R_f CH_2Cl_2=0.76. ^{1}H-NMR δ ($CDCl_3$, 270 MHz) [ppm] : 1.25 (3H, t, J=7.59Hz, $CH_2\underline{CH_3}$); 1.33 (6H, s, $\underline{Me_2}$); 2.56 (2H, q, J=7.59Hz, $\underline{CH_2}CH_3$); 3.46 (2H, s, $\underline{CH_2}SEt$); 3.64 (2H, s, $\underline{CH_2}Cl$). ^{13}C-NMR δ ($CDCl_3$, 67.8 MHz) [ppm] : 14.09 ($SCH_2\underline{CH_3}$); 23.34 (Me_2); 25.95 ($S\underline{CH_2}CH_3$); 36.77 ($CO\underline{CH_2}$); 48.97 ($Me_2\underline{C}$); 52.06 ($\underline{CH_2}Cl$); 206.81 (C=O). IR (NaCl) : $\nu_{C=O}$ = 1705 cm^{-1}. MS (70 eV) m/z (rel. intens.) : 194/6 (M^+, 32); 159(14); 138/40(6); 134/6(9); 119/21(17); 110/12(10); 91/3(68); 85(100); 56(12); 55(32); 49(7); 47(24); 44(11); 41(14). Anal. Calcd for $C_8H_{15}ClOS$: C, 49.35; H, 7.76. Found : C, 49.38; H, 7.82.

N-(3-Methylthio-2-butylidene)isopropylamine (15).

To an ice cooled solution of LDA (5,5 mmoles) in THF (10 ml) under N_2-atmosphere is added dropwise

N-(3-chloro-2-butylidene)isopropylamine 15 (0,74 g, 5 mmoles in 10 ml THF). After stirring for 45 minutes dimethyldisulfide (0,56 g, 6 mmoles in 5 ml THF) is added dropwise and the reaction mixture is stirred for 24 hours at room temperature. The reaction mixture is poured into water (40 ml) and extracted with ether (3x30 ml). The combined organic extracts are dried (K_2CO_3), filtered and evaporated. Gas chromatographic analysis showed the α-(methylthio)ketimine 17 to be the major component (60%) next to dimethyldisulfide.

N-(3-Methylthio-2-butylidene)isopropylamine (15).
^{1}H-NMR : δ ($CDCl_3$, 60 MHz) [ppm] : 1,12 (6H, d, J=6Hz, CHMe$_2$); 1,34 (3H, d, J=7Hz, MeCH); 1,90 (3H, s, MeC=N); 1,98 (3H, s, MeS); 3,40 (1H, q, J=7Hz, CHSMe); 3,68 (1H, septet, J=6Hz, NCH). ^{13}C-NMR δ ($CDCl_3$, 20 MHz) [ppm] : 9,34 and 10,88 (each, q, MeCS and MeC=N); 14,67 (q, MeS); 21,24 and 20,87 (each q, CHMe$_2$); 48,01 and 48,25 (each d, CHN and CHS); 162,91 (s, C=N). IR (NaCl) : $\nu_{C=N}$ = 1644 cm^{-1}. Anal. Calcd for $C_8H_{17}NS$: C, 60.34; H, 10.77; N, 8.80. Found : C, 60.40; H, 10.74; N, 8.84.

Reaction of α,α-dibromopinacolone with an equimolar amount of sodium ethylthiolate.
To an ice cooled solution of 2N sodium methoxide in methanol (2 ml, 4 mmoles) is added ethanethiol (0,25 g, 4 mmoles). After stirring for five minutes α,α-dibromopinacolone 6b (0,52 g, 2 mmoles) is added. The icebath is removed and the reaction mixture is stirred for one additional hour. The mixture is then poured into water (20 ml) and extracted with dichloromethane (3x10 ml). The combined extracts are washed with a saturated sodium chloride solution (20 ml), dried ($MgSO_4$) and filtered. After evaporation of the solvent the residual oil is subjected to preparative gas chromatography. The chromatogram shows four peaks which are collected and identified as being diethyldisulfide, 1-(ethylthio)-3,3-dimethyl-2-butanone 7b (72%), 1-(ethylthio)-1-methoxy-3,3-dimethyl-2-butanone 15 (13%) and 1,1-di(ethylthio)-3,3-dimethyl-2-butanone 16 (15%) in the order mentioned.

1-(Ethylthio)-1-methoxy-3,3-dimethyl-2-butanone (18).
^{1}H-NMR δ (CCl_4, 60 MHz) [ppm] : 1.22 (9H, s, Me$_3$); 1.24 (3H, t, J=7.5Hz, CH_2CH_3); 2.53 (2H, q, J=7.75Hz, CH_2CH_3); 3.43 (3H, s, OMe); 5.09 (1H, s, CH). IR (NaCl) : $\nu_{C=O}$ = 1705 cm^{-1}. MS (70 eV) m/z (rel. intens.) : 190 (M$^+$, 0.2); 130(1); 105(100); 85(1); 77(28); 76(1); 73(2); 72(1); 71(1); 69(2); 61(2); 59(1); 57(16); 56(1); 55(2); 53(2); 49(1); 47(3); 46(2); 45(19); 44(4); 43(2); 42(1); 41(14); 40(17). Anal. Calcd for $C_9H_{18}O_2S$: C, 56.81; H, 9.54. Found : C, 56.85; H, 9.50.

1,1-Di(ethylthio)-3,3-dimethyl-2-butanone (19).
^{1}H-NMR δ (CCl_4, 60 MHz) [ppm] : 1.26 (9H, s, t-Bu); 1.26 (3H, t, J=7.5Hz, CH_2CH_3); 2.4-2.9 (2H, m, CH_2CH_3); 4.80 (1H, s, CH). IR (NaCl) : $\nu_{C=O}$ = 1690 cm^{-1}. MS (70 eV) m/z (rel. intens.) : 220 (M$^+$, 2); 135(100); 107(17); 102(4); 79(2); 78(2); 75(2); 74(2); 69(3); 63(4); 61(4); 60(2); 59(2); 58(3); 57(28); 56(2); 55(3); 47(4); 46(3); 45(14); 44(5); 43(3); 42(2); 41(17). Anal. Calcd for $C_{10}H_{20}OS_2$: C, 54.52; H, 9.16. Found : C, 54.57; H, 9.19.

N-(3-Ethylthio-2-butylidene)isopropylamine (21).

N-(3-Ethylthio-2-butylidene)isopropylamine **21** was prepared according to the typical procedure described above. The combined organic extracts were dried on K_2CO_3. Gas chromatographic analysis showed the imine to constitute 58% of the reaction mixture next to a few minor compounds.

N-(3-Ethylthio-2-butylidene)isopropylamine (21).

^{1}H-NMR δ ($CDCl_3$, 60 MHz) [ppm] : 1.11 (6H, d, J=6.5 Hz, CH$\underline{Me_2}$); 1.21 (3H, t, J=6.5 Hz, $SCH_2\underline{CH_3}$); 1.26 (3H, d, J=7 Hz, $\underline{CH_3}CH$); 1.89 (3H, s, N=C$\underline{CH_3}$); 2.39 (2H, q, J=7 Hz, $S\underline{CH_2}CH_3$); 3.56 (2H, m, N$\underline{CH}$+S$\underline{CH}$). IR (NaCl) : $\nu_{C=N}$ = 1648 cm^{-1}. ^{13}C-NMR δ ($CDCl_3$, 20 MHz) [ppm] : 166.45 (C=N); 50.60 and 49.78 (N $\underline{C}$H+S $\underline{C}$H); 24.93, 23.78, 23.41, 17.79, 14.30 and 11.78 (not designated). Anal. Calcd for $C_9H_{19}NS$: C, 62.38; H, 11.06; N, 8.09. Found : C, 62.33; H, 11.02; N, 8.04.

4-Methyl-1,1-di(propylthio)-2-butanone (23).

4-Methyl-1,1-di(propylthio)-2-butanone **23** was prepared according to the typical procedure described above. Gas chromatographic analysis showed three peaks which were collected and identified as dipropyldisulfide (8%), methyl 4-methyl-3-(propylthio)pentanoate **24** (24%) and 4-methyl-1,1-di(propylthio)-2-butanone **23** (60%) in the order mentioned.

4-Methyl-1,1-di(propylthio)-2-butanone (23).

^{1}H-NMR δ (CCl_4, 60 MHz) [ppm] : 0.96 (6H, d, J=6Hz, $\underline{Me_2}$CH); 1.01 (6H, ~t, 2xMe); 1.3-2.1 (5H, m, 2xCH_2+C$\underline{H}Me_2$); 2.4-2.8 (6H, m, 2xSCH_2+CH_2C=O); 4.38 (1H, s, SCHS). IR (NaCl) : $\nu_{C=O}$ = 1712 cm^{-1}. MS (70 eV) m/z (rel. intens.) : 248 (m^+; 3); 205(2); 163(100); 131(3); 121(22); 89(8); 85(3); 79(12); 57(8); 43(29); 41(22). Anal. Calcd for $C_{12}H_{24}OS_2$: C, 58.03; H, 9.75. Found : C, 57.98; H, 9.71.

Methyl 4-methyl-3-(propylthio)pentanoate (24).

^{1}H-NMR δ ($CDCl_3$, 60 MHz) [ppm] : 0.95 and 1.02 (each 3H, each d, J=6.5 Hz, CH$\underline{Me_2}$); ~1 covered (3H, CH_3); 1.3-2.1 (3H, m, $\underline{CH_2}CH_3$+$Me_2\underline{C}H$); 2.4-2.7 (4H, m, SCH_2+CH_2C=O); 3.0 (1H, dxdxd, J=2.6 and 12 Hz, SCH); 3.73 (3H, s, OMe). ^{13}C-NMR δ ($CDCl_3$, 20 MHz) [ppm] : 172.72 (C=O); 51.65 (S CH), 49.25 (SCH_2); 38.77; 34.72; 32.46 and 23.21 (not designated); 19.73 and 18.82 (Me_2) ; 13.50 ($CH_2\underline{C}H_3$). IR (NaCl) : $\nu_{C=O}$ = 1740 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O_2S$: C, 60.51; H, 10.16. Found : C, 60.44; H, 10.19.

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