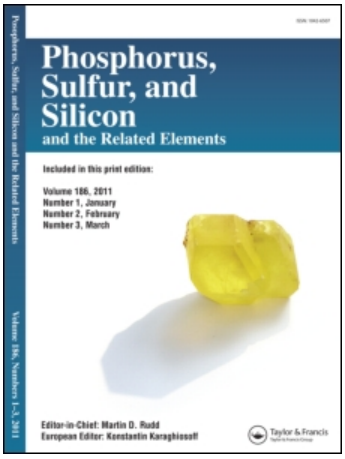

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SYNTHESIS OF ACYLAMIDO KETENE DITHIOACETALS AND 5-OXO-4,5-DIHYDROBENZO[F]-1,4-THIAZEPINE-DERIVATIVES BY DITHIOCARBOXYLATION OF α-AZA-C-NUCLEOPHILES

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SYNTHESIS OF ACYLAMIDO KETENE DITHIOACETALS AND 5-OXO-4,5-DIHYDROBENZO[F]-1,4-THIAZEPINE-DERIVATIVES BY DITHIOCARBOXYLATION OF α-AZA-C-NUCLEOPHILES

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N-acceptor methyl substituted 2,2,N-trimethyl-propionamides (**1** acc-group = *p*-$MeOC_6H_4CO$-, **2** acc-group = COOMe) afford in the procedure of dithiocarboxylation 3,3-[bis(alkylthio)]-prop-2-ene-1-ones **4a–c** and methyl 3,3-[bis(alkylthio)]-acrylates **5a–c**, respectively. 2-Chloro- or 2,4-dichloro-N-cyanomethyl-N-methyl-benzamide **3a,b** form in the reaction with carbon disulfide at lower temperature 3,3-bis(methylthio)-acrylonitriles **7a,b** whereas 2-alkylthio-4-methyl-5-oxo-4,5-dihydrobenzo[f]-1,4-thiazepine-3-carbonitriles **8a–c** are obtained at higher temperatures.

Keywords: Carbon disulfide; 2,2,N-trimethyl-propionamides; 2-chloro-N-cyanomethyl-N-methyl-benzamide; 2-alkylthio-4-methyl-5-oxo-4,5-dihydrobenzo[f]-1,4-thiazepine-3-carbonitriles; methyl 3,3-[bis(methylthio)]-acrylates; 3,3-[bis(methylthio)]-prop-2-ene-1-ones

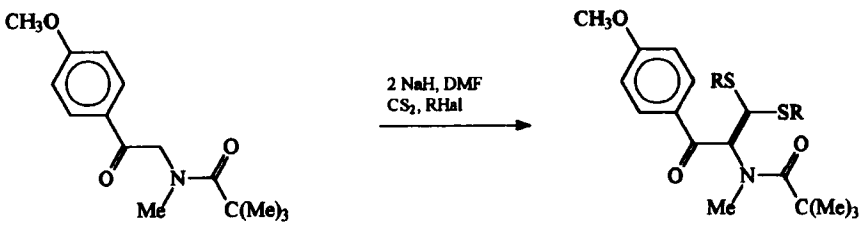
INTRODUCTION

We have been interested in reactions of α-heteroatom substituted C-nucleophiles and the treatment of such species with sulfur containing heterocumulenes. The nitrogen atom as heteroatom was of special interest to us[1,2] in order to compare its behaviour with similar carbanionic species containing sulfur or oxygen, which have been studied extensively in the chemical literature but the title compounds have not been previously reported. Therefore, herein we describe facile syntheses for these classes of compounds. On the other hand we also

describe first results of a new simple approach to the benzo[f][1,4]thiazepine skeleton. These compounds are known to have various pharmacological properties (e.g. neurological agents,[3] antiarrhythmics,[4] antihyperlipidemics[5,6,7]).

Results and Discussion

As potential α-heteroatom substituted C-nucleophiles we have prepared for the first time the amides **1–3**. These compounds are mixtures of E/Z-isomers based on results of NMR investigations. Amide **1** gives on treatment with two equivalents of sodium hydride and carbon disulfide in dry DMF the ene dithiolate which can be alkylated to **4a–c**. This behaviour is in agreement with general findings in this field.[8–11]



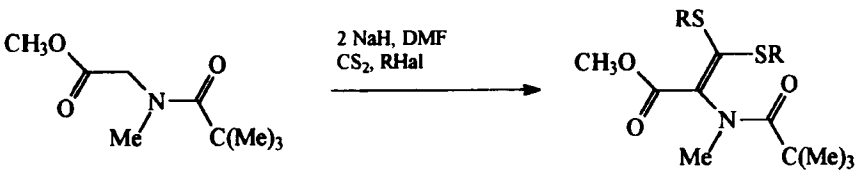
1 **4a-c**

4	R	R
a	CH_3	CH_3
b	CH_2CH_2	
c	$CH_2CH_2CH_2$	

SCHEME I

The assigned structures of products **4a–c** are supported by spectral and analytical data. The structure of **4a** was identified as follows: The MS gave peaks at *m/z* 320 (M-SCH_3, 100%) and 135 ($MeOC_6H_4CO$, 85%) and the ^1H NMR spectral properties were characteristic for a *p*-methoxybenzoyl- and the *tert.* amido group. Nearly all proton containing groups appeared as a double signal due to the E/Z isomerism in the amide structure (see experim. part).

Additionally, we found that amide **2** could be transformed by the above mentioned one-pot procedure to the desired ketene dithioacetals **5** as shown in scheme II. Compounds **5** exist as a mixture of isomers (E/Z) as identified by ^1H NMR, mass spectral and elemental analyses of **5** were consistent with the expected structures.



2 **5**

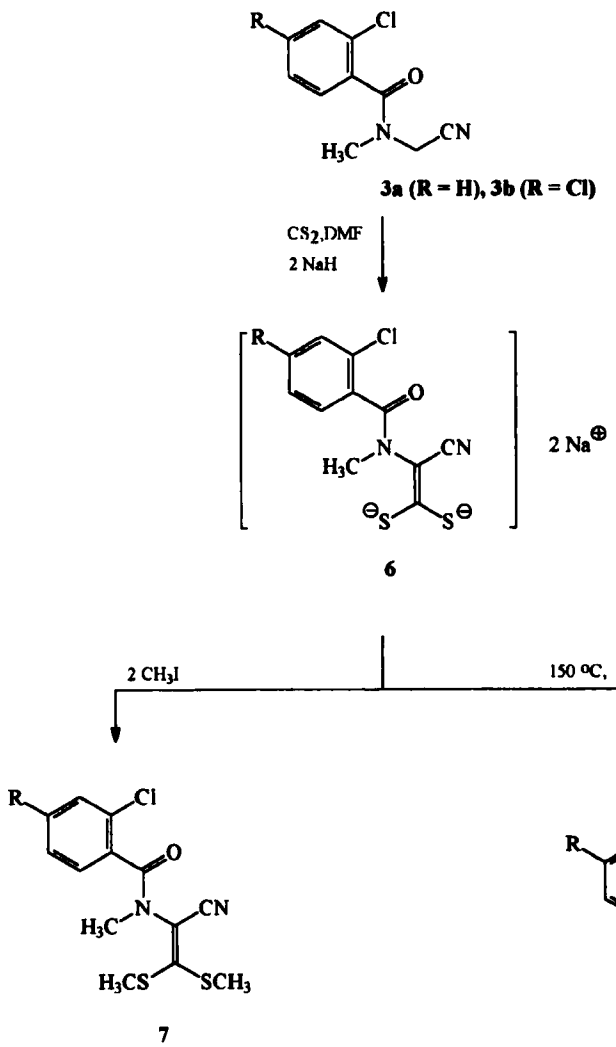
5	R	R
a	CH_3	CH_3
b	CH_2CH_2	
c	$CH_2CH_2CH_2$	

SCHEME II

There are several reports on the conversion to heterocycles of 2-haloacetophenones,[12] *o*-halobenzoylacetonitriles,[13] benzyl cyanides possessing an *o*-halogen atom[14] and aryl sulphones with *o*-halogen substituents[15] by reaction with carbon disulfide and intramolecular heterocyclisation. Nothing is known about the synthesis of the seven-membered heterocyclic ring system by such a procedure.[16,17] In fact, such reactions usually require prolonged reaction times at elevated temperatures.[8] By heating of 2-(2,2-diethoxyethylthio)-benzamid in toluene with p-toluenesulfonic acid the 8*H*-5-thia-8-aza-benzocyclohepten-9-one was formed.[18] The 2,3,4-trimethyl-5-oxo-4,5-dihydro-1,4-benzothiazepine and similar products have also been described in literature.[19,20]

Since benzyl cyanides possessing an ortho-halogen atom have been shown to react with carbon disulfide in the presence of base to afford benzo[b]thiophenes, we wished to study the corresponding reactions in the similarly designed series of benzamide derivatives.

Substituted 2-chloro-N-cyanomethyl-N-methyl-benzamides **3a,b** give on treatment with 2 equivalents of a suitable base, carbon disulfide, and an alkylating agent at temperatures up to 100 °C the expected substituted ketene dithioacetals **7a,b**. If the temperature was chosen around 150 °C and for a period of 6 h before the alkylation step of the intermediate ene dithiolate it is possible to obtain in poor yields after column chromatography and recrystallization the 2-alkylthio-4-methyl-5-oxo-4,5-dihydrobenzo[f]-1,4-thiazepine-3-carbonitriles **8a–c** as colourless needles. The analytical and spectroscopic data for thiazepines **8** are consistent with the proposed structures. When the ortho-halogenated benzamide derivatives were reacted with carbon disulfide in the presence of sodium



7	R
a	H
b	Cl

8	R^1	R
a	CH_3	H
b	C_2H_5	H
c	CH_3	Cl

SCHEME III

hydride in dimethyl formamide, followed by quenching with iodomethane or an other haloalkane, the thiazepines were obtained in moderate yields. The arene part is not electron deficient enough to obtain higher yields.[21–24] Indeed, the reaction is believed to proceed via the intermediacy of a ketene dithioacetal dianion where one of the thiolate anions displaces the chloro atom to produce the bicyclic product and the other is alkylated with the iodomethane or -alkane. Probably higher yields will be found with 2-fluoro-benzamide derivatives because the fluor atom is a better leaving group in aromatic nucleophilic substitutions. A comparable case was described in literature where 5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine was prepared by intramolecular nucleophilic displacement on 1-(2-fluorobenzyl)-2-mercaptomethylpyrrole.[25] There has been more interest in 1,4-thiazepines, as both rearrangement products and possible biogenetic precursors for penicillins and because of the pharmacological value of the benzo- and dibenzo-[1,4]thiazepines as antidepressants and coronary vasodilators.

In conclusion, we have demonstrated that dithiocarboxylation of methylene active acylamido compounds is synthetically useful. Furthermore, the reaction of carbon disulfide with the anions of 2-chloro-N-cyanomethyl-N-methyl-benzamides represents a new favourable route to benzo[f]-1,4-thiazepine derivatives (cf. reviews[27,28]). The simplicity of the experimental procedure and the ready access to the precursors render this procedure particularly attractive. However, studies are foreseen to try to improve or optimize the yields. Work on this topic is in progress to better define its scope and limitations.

EXPERIMENTAL PART

All dithiocarboxylation reactions were carried out under argon atmosphere. Melting points were determined on a Kofler hot stage microscope and are uncorrected. Infrared spectra were measured with a IR-spectrophotometer "Specord" Carl Zeiss Jena or FTIR-spectrometer 1000 of PERKIN-ELMER. ^{1}H and ^{13}C nmr spectra were recorded on either a BRUKER WP 200 or AC 80 or a VARIAN Gemini 200 or Unity 500 spectrometer in $CDCl_3$. Mass spectra were measured on a AMD 402 of the AMD Intectra GmbH. Reactions were monitored by TLC using Merck DC Alufolien Kieselgel 60 F_{254} plates and were visualized under UV irradiation. Column chromatography was performed with Kieselgel 60 (Merck; practical size 0.063-0.2 mm).

N-(p-Methoxyphenacyl)-N,2,2-trimethyl-propanamide 1

p-Methoxy-ω-methylaminoacetophenone hydrochloride (21.6 g, 0.1 mole) prepared by reaction of anisole and methylaminoacetonitrile-HCl[26] was dissolved in water (60 ml). Trimethylacetyl chloride (12 g, 0.1 mole) in toluene (60 ml) was added. Under cooling and vigorous stirring a sodium hydroxide solution was added until the reaction mixture was alkaline. After one hour stirring the layers were separated. The organic layer was washed three times with water, dried with anhydrous sodium sulfate and concentrated to give 22 g (yield: 84%) of a colourless solid.

m.p.: 80–82°C

$C_{15}H_{21}NO_3$ (263.34)

IR (Nujol): $\tilde{\nu}$ = 1685, 1605, 1595 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.33 (s, 9H, $C(CH_3)_3$), 3.21 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 4.71 (s, 2H, NCH_2), 6.93 (d, 2H, Aromat), 7.93 (d, 2H, Aromat) ppm.

^{13}C-NMR ($CDCl_3$): δ = 193.1 (C=O), 177.9(C=O, amide), 163.7(C-O, arom.), 130.1 (arom.), 128.5 (arom.), 113.8 (arom.), 56.1 (CH_2), 55.4 (OCH_3), 38.6 (N-CH_3), 38.2 ($\underline{C}(CH_3)_3$), 28.1 ($C\underline{C}H_3)_3$) ppm.

MS (m/z, %): 263 (M^+, 9), 248 (3), 206 (3), 178 (6), 163 (6), 150 (64), 135 (100), 128 (37), 121 (6), 107 (8), 92 (5), 85 (69), 77 (12), 57 (87).

Methyl (N-methyl-N-trimethylacetylamino)-acetate 2

Prepared from methyl sarcosinate hydrochloride and pivaloyl chloride (trimethylacetyl chloride) according to the above mentioned procedure as a colourless liquid.

Yield: 86%

IR (neat): $\tilde{\nu}$ = 1751, 1633, 1480, 1402, 1364, 1208, 1098, 1026, 935, 759 cm^{-1}

^{1}H-NMR ($CDCl_3$): δ = 1.25 (s, 9H, $C(CH_3)_3$), 3.09 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3), 4.00 (s, 2H, NCH_2) ppm.

^{13}C-NMR ($CDCl_3$): δ = 177.3(C=O, amide), 169.3(C=O, ester), 51.2(CH_2), 51.1 (OCH_3), 37.9 (N-CH_3), 37.4 ($\underline{C}(CH_3)_3$), 27.3 ($C\underline{C}H_3)_3$) ppm.

2-Chloro-N-cyanomethyl-N-methyl-benzamide 3a

Methylaminoacetonitrile-HCl (5.3 g, 0.05 mole) was dissolved in water (40 ml). 2-Chloro-benzoyl chloride (8.75 g, 0.05 mole) in toluene (40 ml) was added. Under cooling and vigorous stirring a sodium hydroxide solution was added

until the reaction mixture was alkaline. After one hour stirring the layers were separated. The organic layer was washed three times with water, dried with anhydrous sodium sulfate and concentrated to give 11 g of a dark oil which was distilled in vacuum to obtain a colourless viscous oil, R_f = 0.38 (ethyl acetate/ petrol ether 1:1).

Yield: 7.19 g (69%)

b.p.: 220°C (14 mbar)

$C_{10}H_9ClN_2O$ (208.65)

IR (neat): $\tilde{\nu}$ = 2985, 2249, 1725, 1653, 1594 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.97 (s) and 3.23 (s, 3H, CH_3), 4.05 (s) and 4.53 (s, 2H, NCH_2), 7.28–7.44 (m, 4H, Arom.) ppm.

^{13}C-NMR ($CDCl_3$): δ = 168.5 (C=O), 134.2, 131.2, 130.9, 130.4, 130.0, 129.8, 128.0, 127.8, 127.7, 127.4, (arom.), 114.6 (CN), 39.3, 35.9 (CH_2), 34.6, 32.8 (CH_3) ppm.

2,4-Dichloro-N-cyanomethyl-N-methyl-benzamide 3b

Methylaminoacetonitrile-HCl (5.3 g, 0.05 mole) was dissolved in water (40 ml). 2,4-Dichlorobenzoyl chloride (10.47 g, 0.05 mole) in toluene (40 ml) was added. Under cooling and vigorous stirring a sodium hydroxide solution was added until the reaction mixture was alkaline. After one hour stirring the precipitated product was separated by filtration to give 10.88 g (yield: 90%) of a colorless solid.

m.p.: 118–119.5°C

$C_{10}H_8Cl_2N_2O$ (243.09)

IR (KBr): $\tilde{\nu}$ = 3083, 3063, 2984, 2937, 1634, 1589, 1554, 1519, 1496, 1469, 1451, 1413, 1401, 1373, 1350, 1299, 1220, 1185, 1145, 1103, 1091, 1047, 989, 953, 923, 899, 826, 807, 759, 727, 697 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.98 (s) and 3.23 (s, 3H, CH_3), 4.04 (s) and 4.51 (s, 2H, NCH_2), 7.24 (d, H, ^{3}J = 8.25 Hz, Arom. H-6), 7.34 (dd, H, ^{3}J = 8.25 Hz, ^{4}J = 1.8 Hz, Arom. H-5), 7.44 (d; H, ^{4}J = 1.8 Hz, Arom., H-3) ppm.

3,3-[Bis(methylthio)]-1-(p-methoxyphenyl)-2-(methyl-pivaloyl-amino)-prop-2-ene-1-one 4a

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of N-(p-methoxyphenacyl)-N,2,2-trimethyl-propanamide **1** (1.32g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (20 ml) at −10°C. After the addition, the mixture was warmed up to room temperature and stirred for 2 h.

After which time it was cooled to −10°C. Methyl iodide (1.53g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water. The crude product (1.38 g) was obtained by filtration. Recrystallization from ethanol gave the pure sample (1.08 g, yield: 59%) as a pale yellow solid.

m.p.: 90-94

$C_{18}H_{25}NO_3S_2$ calc. C 58.82 H 6.86 N 3.81 S 17.45
(367.53) found C 58.62 H 6.89 N 3.72 S 17.55

IR (Nujol): $\tilde{\nu}$ = 1626 (C=O), 1600 (C=O), 1525, 1500, 1377, 1346, 1254, 1185, 1096, 1025, 854, 762 cm^{-1}.

^{1}H-NMR (80 MHz, $CDCl_3$): δ = 1.28 (s, 9H, $C(CH_3)_3$), 2.06 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 3.46 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 6.89 (d, 2H, Aromat), 7.99 (d, 2H, Aromat) ppm.

MS (m/z, %): 320 (M-SCH_3, 100), 297 (9), 282 (8), 241 (5), 192 (14), 177 (12), 149 (15), 135 (85), 125 (29), 111 (47), 97 (38), 85 (18), 71 (20), 57 (30).

N,2,2-Trimethyl-N-[2-(p-methoxyphenyl)-1-(1′,3′-dithiolane-2-ylidene)-2-oxo-ethyl]-propanamide 4b

To a solution of N-(p-methoxyphenacyl)-N,2,2-trimethyl propanamide **1** (1.32g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (20 ml) at −10°C was added sodium hydride (0.5g 80% in paraffin oil, 10 mmol). After the addition, the mixture was warmed up to room temperature and stirred for 2 h after which time it was cooled to −10°C. 1,3-Dibromo ethane (0.94 g, 0.5 ml, 5 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water and extracted twice with ethyl acetate. The combined organic layers were washed with water and were dried over anhydrous sodium sulfate. The residue (1.82 g) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 1.1 g (yield: 60%) of an amorphous yellow solid.

m.p.: 120-124°C

$C_{18}H_{25}NO_3S_2$ calc. C 59.15 H 6.34 N 3.83 S 17.54
(365.62) found C 58.99 H 6.22 N 3.77 S 17.51

IR (Nujol): $\tilde{\nu}$ = 1623 (C=O), 1600 (C=O), 1380, 1346, 1254, 1183, 1095, 1025, 856, 764 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.98 (s) and 1.20 (s, 9H, $C(CH_3)_3$), 2.99 (s) and 3.12 (s, 3H, NCH_3), 3.34–3.44 (m, 4H, 2*SCH_2), 3.75 (s, 3H, OCH_3), 6.81 (d, 2H, Aromat), 7.51 and 7.70 (2d, 2H, Aromat) ppm. From the intensity of the double signals a ratio E:Z of 3:1 is deduced.

^{13}C-NMR ($CDCl_3$): δ = 185.2 (C=O), 178.6(C=O, amide), 168.8(C-O, arom.), 162.3 (C=C), 130.9 (arom.), 129.8 (arom.), 129.6 (arom.), 128.7 (arom.), 113.6 (arom.), 113.1 (C=C), 55.2 (OCH_3), 40.8 (SCH_2), 40.3 (SCH_2), 38.5 (N-CH_3), 35.5 ($\underline{C}(CH_3)_3$), 28.9 ($C(\underline{C}H_3)_3$), 27.5 ppm.

MS (m/z, %): 365 (M^+, 22), 280 (24), 239 (58), 135 (100), 98 (32), 57 (26).

N,2,2-Trimethyl-N-[2-(p-methoxyphenyl)-1-(1′,3′-dithiane-2-ylidene)-2-oxo-ethyl]-propanamide 4c

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of N-(p-methoxyphenacyl)-N,2,2-trimethyl-propanamide **1** (1.32g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (20 ml) at −10°C. After the addition was completed, the mixture was warmed up to room temperature and stirred for 2 h after which time it was cooled to −10°C. 1,3-Dibromo propane (1.01 g, 0.5 ml, 5 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water and extracted twice with ethyl acetate. The combined organic layers were washed with water and were dried over anhydrous sodium sulfate. The residue (1.88 g) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 1.01 g (yield: 53%) of an amorphous yellow solid.

m.p.: 178–182°C.

$C_{19}H_{25}NO_3S_2$ (379.54).

IR (Nujol): $\tilde{\nu}$ = 1626 (C=O), 1600 (C=O), 1525, 1500, 1377, 1346, 1254, 1185, 1096, 1025, 854, 762 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.18 and 1.29 (s, 9H, $C(CH_3)_3$), 2.15 (quint, 2H, CH_2), 2.83 (t, 2H, SCH_2), 2.95 (t, 2H, SCH_2), 3.10 and 3.17 (s, 3H, NCH_3), 3.79 and 3.82 (s, 3H, OCH_3), 4.68 (s), 6.83 and 6.89 (2d, 2H, Aromat), 7.71 and 7.89 (2d, 2H, Aromat) ppm.

Methyl 3,3-[bis(methylthio)]-2-[(N-methyl-N-pivaloyl)-amino]-acrylate 5a

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of N-(methoxycarbonylmethyl)-N,2,2-trimethyl-propionamide **2** (0.94 g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMSO (30 ml) at 10°C. After the addition was completed, the mixture was warmed up to room temperature and stirred for 2 h after which time it was cooled to 10°C. Methyl iodide (1.5 g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water and extracted twice with

ether. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue (0.93 g, in DC only one product) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60, eluent ethyl acetate/*n*-hexane 1 : 1) to afford 0.28 g (yield: 63%) of a yellow oil as a pure sample.

$C_{12}H_{21}NO_3S_2$ calc. C 49.46 H 7.26 N 4.81 S 22.00
(291.43) found C 49.67 H 7.06 N 4.68 S 21.71

IR (neat): $\tilde{\nu}$ = 2928, 1711, 1642, 1481, 1433, 1399, 340, 1289, 1229, 1203, 1093, 1050, 1023, 926, 790, 761 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.18 (s, 8.2 H, $C(CH_3)_3$) and 1.32 (s, 0.8 H, $C(CH_3)_3$), 2.29 (s, 0.27 H, SCH_3), 2.33 (s, 0.27 H, SCH_3), and 2.40 (s, 2.73 H, SCH_3), 2.44 (s, 2.73 H, SCH_3), 3.08 (s, 2.73 H, NCH_3) and 3.19 (s, 0.27 H, NCH_3), 3.74 (s, 2.73 H, OCH_3), and 3.77 (s, 0.27 H, OCH_3) ppm.

^{13}C-NMR ($CDCl_3$): δ = 177.9 (C=O, amide), 163.5 (C=O, ester), 160.9 (C=C), 132.2 (C=C), 51.5 (OCH_3), 51.5 (N-CH_3), 37.7 ($\underline{C}(CH_3)_3$), 27.7 ($C(\underline{C}H_3)_3$), 18.2 (SCH_3), 16.8 (SCH_3) ppm.

MS (m/z, %): 244 (M^+-SCH_3, 100), 229 (5), 214 (7), 206 (11), 186 (13), 174 (5), 165 (11), 160 (6), 146 (4), 107 (10), 91 (9), 57 (19).

Methyl 2-(1,3-dithiolan-2-ylidene)-(N-methyl-N-trimethylacetylamino)-acetate 5b

Sodium hydride (0.7g 80% in paraffin oil, 20 mmol) was added to a solution of N-(methoxycarbonylmethyl)-N,2,2-trimethyl-propionamide **2** (1.87 g, 10 mmol) and carbon disulfide (0.76g, 0.6 ml 10 mmol) in dry DMF (30 ml) at −10°C. After the addition was completed, the mixture was warmed up to room temperature and stirred for 2 h after which time it was cooled to −10°C. 1,2-Dibromoethane (1.87 g, 0.88 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water and extracted twice with ether. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue (2.20 g, in DC three products) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60, eluent ethyl acetate/*n*-hexane 1 : 1) to afford 0.98 g (yield: 34%) of a yellow oil as a pure sample.

$C_{12}H_{19}NO_3S_2$ calc. C 49.80 H 6.62 N 4.84 S 22.16
(289.42) found C 49.87 H 6.73 N 4.68 S 22.36

IR (neat): $\tilde{\nu}$ = 2957, 2929, 1748, 1689, 1670, 1634, 1521, 1480, 1433, 1419, 1362, 1348, 1299, 1282, 1239, 1206, 1152, 1100, 1068, 1025, 999, 947, 883, 831, 785, 765, 735, 674, 503, 454 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.12 (s, 4.5 H, $C(CH_3)_3$) and 1.27 (s, 4.5 H, $C(CH_3)_3$), 3.35 (m, 1 H, SCH_2), 3.35 (m, 1 H, SCH_2), and 3.65 (m, 1 H, SCH_2), 3.72 (m, 1 H, SCH_2), 2.97 (br s, 1.5 H, NCH_3) and 3.17 (br s, 1.5 H, NCH_3), 3.93 (br s, 2.73 H, OCH_3), and 4.03 (br s, 0.27 H, OCH_3) ppm.

MS (m/z, %): 289 (M^+, 16), 244 (29), 218 (13), 204 (80), 196 (7), 172 (20), 163 (19), 144 (28), 135 (16), 128 (21), 98 (100), 85 (29), 72 (16), 57 (77).

Methyl 2-(1,3-dithian-2-ylidene)-(N-methyl-N-trimethylacetylamino)-acetate 5c

Sodium hydride (0.7g 80% in paraffin oil, 20 mmol) was added to a solution of N-(methoxycarbonylmethyl)-N,2,2-trimethyl-propionamide **2** (1.87 g, 10 mmol) and carbon disulfide (0.76g, 0.6 ml 10 mmol) in dry DMF (30 ml) at −10°C. After the addition was completed, the mixture was warmed up to room temperature and stirred for 2 h after which time it was cooled to −10°C. 1,3-Dibromopropane (2.02 g, 1.02 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water and extracted twice with ether. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue (2.45 g, in DC three products) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 1.33 g (yield: 34%) of a yellow oil as a pure sample.

$C_{13}H_{21}NO_3S_2$ calc. C 51.46 H 6.98 N 4.62 S 21.13
(303.45) found C 51.35 H 6.86 N 4.33 S 20.97

IR (neat): $\tilde{\nu}$ = 2928, 2855, 1748, 1714, 1647, 1431, 1407, 1364, 1294, 1242, 1190, 1150, 1099, 939, 913, 872, 761 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.12 (s, 4.5 H, $C(CH_3)_3$) and 1.27 (s, 4.5 H, $C(CH_3)_3$), 3.35 (m, 1 H, SCH_2), 3.35 (m, 1 H, SCH_2), and 3.65 (m, 1 H, SCH_2), 3.72 (m, 1 H, SCH_2), 2.97 (br s, 1.5 H, NCH_3) and 3.17 (br s, 1.5 H, NCH_3), 3.93 (br s, 2.73 H, OCH_3), and 4.03 (br s, 0.27 H, OCH_3) ppm.

MS (m/z, %): 303 (M^+, 16), 295 (9), 253 (9), 238 (9), 218 (69), 210 (21), 187 (17), 177 (20), 150 (100), 128 (38), 106 (57), 98 (32), 85 (30), 57 (92).

3,3-Bis(methylthio)-2-[N-(2-chloro-benzoyl)-N-methyl-amino]-acrylonitrile 7a

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2-chloro-N-cyanomethyl-N-methyl-benzamide **3** (1.04g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (30 ml) at −10°C. After the

addition, the mixture was warmed up to room temperature and stirred for 2 h. After which time it was cooled to −10°C. Methyl iodide (1.53g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water. The crude product (1.26 g) was obtained by filtration. Recrystallization from methanol/water gave the pure sample (0.98 g, yield: 63%) as a pale yellow solid.

m.p.: 73-77°C

$C_{13}H_{13}ClN_2OS_2$ calc. C 49.91 H 4.19 N 8.95 S 20.50
(312.84) found C 49.72 H 4.20 N 8.75 S 20.36

IR (KBr): $\tilde{\nu}$ = 2927, 2202 (CN), 1666 (CO), 1592, 1526, 1477, 1433, 1421, 1355, 1293, 1160, 1109, 1061, 1030, 926, 891, 783, 767, 749, 714, 648 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.13 (s, 2.5 H, SCH_3), 2,36 (s, 2.5 H, SCH_3), 2.49 (s, 0.5 H, SCH_3), 2.56 (s, 0.5 H, SCH_3), 3.00 (s, 0.5 H, NCH_3), 3.25 (s, 2.5 H, NCH_3), 7.21–7.46 (m, 3H, Aromat) ppm.

^{13}C-NMR ($CDCl_3$): δ = 167.8 (CO), 161.3, 134.9, 131.5, 131.0, 130.8, 130.0, 129.8, 127.9, 127.7, 127.2, 125.9, 115.0, 112.1, 36.3, 33.7 (NCH_3), 18.7, 18.5, 16.8 (SCH_3) ppm.

MS (m/z, %): 265 (M-SCH_3, 100, M-SCH_3 + 2 = 267 (38%)), 173 (4), 139 (78), 125 (4), 111 (20), 91 (8), 75 (8).

3,3-Bis(methylthio)-2-[N-(2,4-dichloro-benzoyl)-N-methyl-amino]-acrylonitrile 7b

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2,4-dichloro-N-cyanomethyl-N-methyl-benzamide **3** (1.22g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (30 ml) at −10°C. After the addition, the mixture was warmed up to room temperature and stirred for 2 h. After which time it was cooled to −10°C. Methyl iodide (1.53g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water. The crude product (1.29 g) was obtained by filtration. Recrystallization from ethanol gave the pure sample (1.1 g, yield: 63%) as a colourless solid.

m.p.: 74-75°C

$C_{13}H_{12}Cl_2N_2OS_2$ calc. C 44.96 H 3.48 N 8.07 S 18.47
(347.29) found C 44.99 H 3.48 N 8.02 S 17.73

IR (KBr): $\tilde{\nu}$ = 3059, 3025, 2971, 2927, 2202 (CN), 1664 (CO), 1587, 1553, 1515, 1447, 1463, 1445, 1414, 1374, 1355, 1318, 1291, 1256, 1187, 1140, 1113, 1104, 1063, 1028, 985, 954, 931, 905, 833, 806, 756, 695, 660, 587, 545 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.21 (s, 2.5 H, SCH_3), 2,38 (s, 2.5 H, SCH_3), 2.48 (s, 0.5 H, SCH_3), 2.55 (s, 0.5 H, SCH_3), 2.99 (s, 0.5 H, NCH_3), 3.24 (s, 2.5 H, NCH_3), 7.19–7.44 (m, 3H, Aromat) ppm.

^{13}C-NMR ($CDCl_3$): δ = 166.7 (CO), 161.6, 136.2, 133.0, 132.3, 131.3, 129.7, 129.6, 128.6, 128.2, 127.5, 126.3, 114.8, 114.5, 111.2, 36.2, 33.6 (NCH_3), 18.4, 18.3, 16.6 (SCH_3) ppm.

MS (m/z, %): 299 (M-SCH_3, 97), 301 (M-SCH_3 + 2, 69), 173 ($C_7H_3Cl_2O$, 100), 158 (5), 145 (22), 125 (6), 109 (17), 91 (16).

4-Methyl-2-methylthio-5-oxo-4,5-dihydrobenzo[f]-1,4-thiazepine-3-carbonitrile 8a

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2-chloro-N-cyanomethyl-N-methyl-benzamide **3a** (1.04g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (20 ml) at −10°C. After the addition, the mixture was warmed up to room temperature and stirred for 6 h at 150°C. After which time it was cooled to −10°C. Iodomethane (1.53g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water. The organic material was extracted several times with ethyl acetate. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue (1.47 g) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 0.16 g (yield: 12%, R_f = 0.50) of an oil. Recrystallization from ethanol gave the pure sample (0.06g, yield: 5%) as colourless needles.

m.p.: 111-111.5°C

$C_{12}H_{10}N_2OS_2$	calc.	C 54.94 H 3.84 N 10.68 S 24.44
(262.35)	found	C 54.76 H 3.85 N 10.68 S 24.57

IR (KBr): $\tilde{\nu}$ = 2989, 2920, 2212 (CN), 1712, 1643, 1589, 1565, 1551, 1469, 1439, 1417, 1361, 1297, 1288, 1252, 1164, 1129, 1112, 1065, 1042, 1027, 975, 957, 924, 893, 870, 789, 777, 747, 720, 691, 655 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.59 (s, 3H, SCH_3), 3.36 (s, 3H, NCH_3), 7.35–7.49 (m, 3H, Aromat), 7.79–7.83 (dd, 1H, Aromat H-6) ppm.

MS (m/z, %): 262 (M^+, 47), 215 (89), 195 (74), 187 (21), 151 (49), 134 (16), 108 (23), 91 (52), 76 (34), 67 (100).

2-Ethylthio-4-methyl-5-oxo-4,5-dihydrobenzo[f]-1,4-thiazepine-3-carbonitrile 8b

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2-chloro-N-cyanomethyl-N-methyl-benzamide **3a** (1.04g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (20 ml) at −10°C. After the

addition, the mixture was warmed up to room temperature and stirred for 6 h at 150°C. After this time it was cooled to −10°C. Ethyl iodide (1.56 g, 0.81 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water. The organic material was extracted several times with ethyl acetate. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue (1.59 g) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60, eluent ethyl acetate/*n*-hexane 1:1) to afford 0.36 g (R_f = 0.54) of an oil. Recrystallization from ethanol gave the pure sample (0.11 g, yield: 8%) as colourless needles.

m.p.: 114-115°C (ethanol)

$C_{13}H_{12}N_2OS_2$	calc.	C 56.50 H 4.38 N 10.14 S 23.20
(276.38)	found	C 56.56 H 4.43 N 10.14 S 23.06

IR (KBr): $\tilde{\nu}$ = 3091, 3028, 2973, 2926, 2207, 1856, 1639, 1588, 1563, 1437, 1415, 1361, 1295, 1259, 1173, 1111, 1067, 1058, 1043, 1027, 971, 926, 895, 791, 779, 751, 721, 692, 659, 647, 577 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.18 (t, 3H, CH_3), 2.90–3.10 (br s, H, SCH_2), 3.10–3.30 (br s, H, SCH_2), 3.36 (s, 3H, NCH_3), 7.32–7.50 (m, 3H, Aromat), 7.79–7.83 (dd, 1H, Aromat H-6) ppm.

^{13}C-NMR ($CDCl_3$): δ = 168.2 (C=O), 153.7 (C-2), 137.2 (C-9a), 132.6 (C-5a), 131.7 (C-8), 131.5 (C-9), 131.4 (C-6), 129.9 (C-7), 115.6 (CN), 113.7 (C-3), 35.8 (N-CH_3), 29.6 (S-CH_2), 15.3 (CH_3) ppm.

MS (m/z, %): 276 (M^+, 100), 247 (5), 215 (88), 209 (38), 203 (18), 187 (29), 181 (31), 162 (5), 137 (13), 108 (15), 67 (42), 59 (38).

8-Chloro-4-methyl-2-methylthio-5-oxo-4,5-dihydrobenzo[f]-1,4-thiazepine-3-carbonitrile 8c

Sodium hydride (0.5g 80% in paraffin oil, 10 mmol) was added to a solution of 2,4-dichloro-N-cyanomethyl-N-methyl-benzamide **3b** (1.22 g, 5 mmol) and carbon disulfide (0.38g, 0.3 ml 5 mmol) in dry DMF (20 ml) at −10°C. After the addition, the mixture was warmed up to room temperature and stirred for 6 h at 150°C. After this time it was cooled to −10°C. Iodomethane (1.53g, 0.66 ml, 10 mmol) was added and the resulting mixture was stirred for 1 h at RT. Then the solution was poured onto ice water. The organic material was extracted several times with ethyl acetate. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue (1.88 g) obtained after evaporation was purified by column chromatography on silica gel (MERCK 60,

eluent ethyl acetate/*n*-hexane 1:1) to afford 0.73 g of an oil. Recrystallization from ethanol gave the pure sample (0.46 g, yield: 31%) as colourless needles. m.p.: 179-180°C (ethanol)

$C_{12}H_9ClN_2OS_2$ (296.80) calc. C 48.56 H 3.06 N 9.44 S 21.61
found C 48.55 H 3.00 N 9.44 S 21.69

IR (KBr): $\tilde{\nu}$ = 3071, 3057, 2922, 2209, 1931, 1651, 1580, 1545, 1469, 1427, 1383, 1355, 1321, 1294, 1251, 1170, 1121, 1103, 1067, 1034, 966, 927, 894, 845, 812, 761, 753, 696, 671, 648, 593, 549 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.60 (s, 3H, SCH_3), 3.34 (s, 3H, NCH_3), 7.76 (d, H, ^3J = 8Hz, Aromat H-6), 7.43 (dd, H, ^3J = 8Hz, ^4J = 2 Hz, Aromat H-7), 7.38 (d, H, ^4J = 2 Hz, Aromat H-9) ppm.

^{13}C-NMR ($CDCl_3$): δ = 167.1 (C=O), 162.0 (C-2), 138.2 (C-9a), 137.7 (C-8), 135.5 (C-5a), 133.7 (C-6), 131.0 (C-9), 130.2 (C-7), 114.6 (CN), 113.4 (C-3), 35.7 (N-CH_3), 18.2 (SCH_3) ppm.

MS (m/z, %): 296 (M^+, 95), 249 (68), 229 (100), 222 (18), 185 (33), 142 (8), 110 (13), 91 (32), 67 (45).

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References

[1] W. Dölling, K. Frost, F. Heinemann and H. Hartung, *Z. Naturforsch. B*, **48b**, 493, (1993).
[2] W. Dölling, *Phosphorus, Sulfur, and Silicon*, **86**, 129, (1994).
[3] J. R. Housley, J. E. Jeffery, K. J. Nichol and B. J. Sargent, (Boots Co PLC), *WO 9411360*, *Chem. Abstr.* **121**, 134167, (1994).
[4] T. Oosawa, H. Murooka and A. Miwa, (Kirin Brewery), *JP Patent 05271208* (1993); *Chem. Abstr.* **120**, 245182, (1994).
[5] S. Kakehi and S. Ito, (Kissei Pharmaceutical, Japan), *Jpn. Kokai Tokkyo Koho 06025257 A2* (1994); *Chem. Abstr.* **121**, 134166, (1994).
[6] L. E. Brieaddy, (Wellcome Foundation Ltd., UK), *WO 9605188* (1996); *Chem. Abstr.* **125**, 114724, (1996).
[7] L. E. Brieaddy, (Wellcome Foundation Ltd.), *WO 9316055* (1993); *Chem. Abstr.* **120**, 164244, (1994).
[8] H. Junjappa, H. Ila and C. V. Asokan, *Tetrahedron*, **46**, 5423, (1990).
[9] H. Junjappa and H. Ila, *Phosphorous, Sulfur, and Silicon*, **95&96**, 35, (1994).
[10] M. Kolb, *Synthesis*, 171, (1990).
[11] A. D. Dunn and W. -D. Rudorf, *Carbon Disulfide in Organic Chemistry* (Ellis Horwood Limited Publishers, Chichester, 1989).
[12] W. -D. Rudorf, A. Schierhorn and M. Augustin, *Tetrahedron*, **35**, 551, (1979).
[13] W. -D. Rudorf, *Tetrahedron*, **34**, 725, (1978).
[14] W. -D. Rudorf, A. Schierhorn and M. Augustin, *J. Prakt. Chem.*, **321**, 1021, (1979).
[15] W. -D. Rudorf and D. Janietz *Synthesis*, 854, (1984).

[16] K. -H.Wünsch and A. Ehlers, *Z. Chem.*, **10**, 361, (1970).
[17] J. T. Sharp, *Seven-membered Rings with Two or More Heteroatoms*, in *Comprehensive Heterocyclic Chemistry*, Vol. 7, A. R. Katritzky and C. W.Rees, eds, (Pergamon Press, Oxford New York Toronto Sydney Paris Frankfurt, 1984) pp. 631–636.
[18] H. Shimizu, N. Ueda, T. Kataoka and M. Hori, *Chem. Pharm. Bull.*, **32**, 2571, (1984).
[19] H. Hofmann and H. Fischer, *Chem. Ber.*, **121**, 2147, (1988).
[20] R. B. Morin and D. O. Spry, *J. Chem. Soc. D*, 335, (1970).
[21] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273, (1951).
[22] J. Miller, *Aromatic Nucleophilic Substitution* (Elsevier, Amsterdam, 1968).
[23] N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith and P. A. Wade, *J. Org. Chem.*, **41**, 1560, (1976).
[24] C. Paradisi, *Arene Substitution via Nucleophilic Addition to Electron Deficient Arenes*, in *Comprehensive Organic Chemistry*, Vol. 4, B. M. Trost, I. Fleming and M. F. Semmelhack, eds, (Pergamon Press, Oxford New York Seoul Tokyo, 1991), pp. 423–450.
[25] A. Garofalo, V. Nacci, F. Corelli and G. Campiani, *Heterocycles*, **31**, 1291, (1949).
[26] M. Asscher, *Rec. trav. Chim. Pays-Bas*, **68**, 960, (1949).