Journal of Fluorine Chemistry, *36* (1987) 29–40

Received: July 23, 1986; accepted: January 4, 1987

THE REACTION OF β-DICARBONYL COMPOUNDS WITH TRIFLUOROMETHYLSULPHENYL CHLORIDE.*
PART I. CF_3S-SUBSTITUTED ESTERS, ANILIDES OF β-KETO ACIDS, AND THEIR SCHIFF BASES: SYNTHESIS AND STABILITY.

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SUMMARY

The reactions of the β-keto acid derivatives with trifluoromethylsulphenyl chloride were carried out to give the α-SCF_3 substituted esters, anilides, and their Schiff bases of acetyl- and benzoylacetic acids. Ethyl esters of α-(trifluoromethylthio)acetoacetic and α-(trifluoromethylthio)benzoylacetic acids heated in dimethylsulphoxide/water solution give trifluoromethylthioacetone and ω-(trifluoromethylthio)acetophenone respectively, whereas with potassium hydroxide solution they form trifluoromethylthioacetic acid in a good yield.

INTRODUCTION

α-Sulphenylation of various enolates, in view of searching new ways in organic synthesis, has been extensively studied recently [1 - 4]. One of the standard methods of RS-group introduction into organic molecules is the reaction of sulphenyl chlorides with the active methylene and methine compounds [5]. Sulphenyl chlorides containing fluorine were

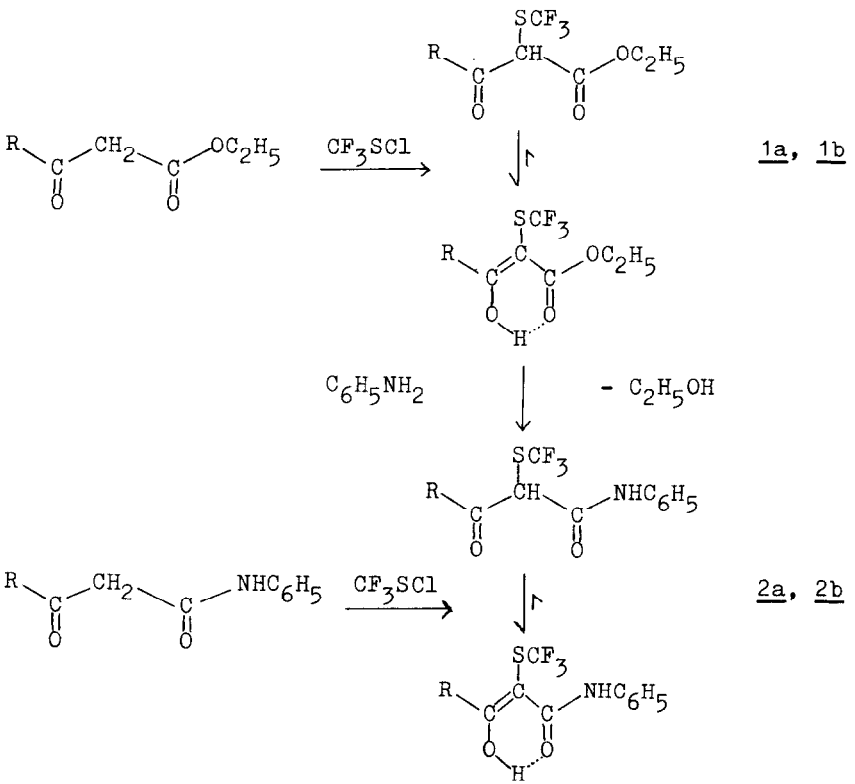
*Paper presented at the XIth International Symposium on Fluorine Chemistry, Berlin (G. D. R.) August 5 - 9, 1985, J. Fluorine Chem. 29 (1985) 162.

0022-1139/87/$3.50

used in the reactions with ketones, diketones, acetoacetic [6] and malonic [7] esters, and β- and γ-keto esters, derivatives of cyclohexenone [8] only, so it was interesting to extend the range of β-keto acid derivatives reacting with CF_3SCl, as well as to pay some more attention to the reactivity of the products obtained.

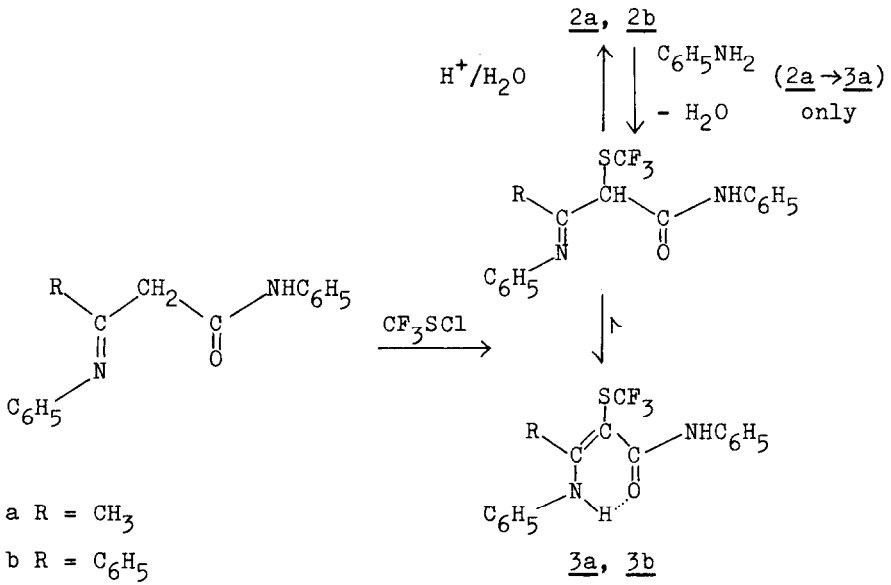
RESULTS AND DISCUSSION

In the present paper the reaction of benzoylacetic ethyl ester as well as acetoacetic and benzoylacetic acid anilides and their Schiff bases with trifluoromethylsulphenyl chloride was studied as shown below:



a R = CH_3

b R = C_6H_5



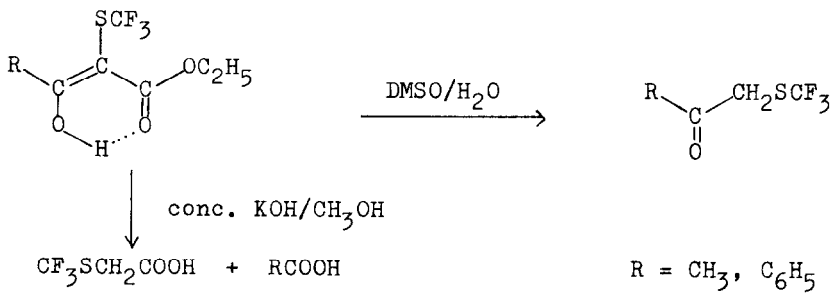
The direct introduction of a CF_3S- substituent into the active methylene group of the compounds studied, by means of CF_3SCl, goes smoothly producing always, in a good yield, monosubstituted products 1, 2, and 3. It does not depend on the molecular ratio of the reagents. The excess of CF_3SCl used, leads exclusively to the products 1, 2, and 3. What is more, all the attempts to force these products to react again with CF_3SCl failed. Such selectivity is not typical for analogous reactions with alkyl sulphenyl chlorides [5]. On the contrary, special synthetic methods had to be developed to keep sulphenylation under control [9]. It could be explained by the electronegativity of the CF_3S- substituent (2.7 [10]) that causes a shift of the tautomeric equilibrium of the compounds investigated into the direction of enolic or enamine form, sometimes up to 100% (see ^1H NMR data). E. g., ^1H NMR spectrum of benzoylacetic acid anilide taken in $CDCl_3$ at room temperature shows the presence of about 23% enolic form, whereas its α-trifluoromethylthio analogue is present in enolic form exclusively.

Compounds of type 1 could be easily converted into 2 by the reaction with aniline in boiling xylene with pyridine as a catalyst, according to the general method [11]. Substance 2a produces with aniline its Schiff base 3a, analogously to [12],

but at higher temperature (boiling xylene) and with aniline hydrochloride as a catalyst, whereas anilide 2b does not react with aniline even under these temperature conditions. Schiff bases 3a and 3b hydrolyze easily in acidic medium providing 2a and 2b respectively.

The structure of compounds investigated was fully confirmed by means of elemental analysis, IR, MS, ^{1}H and ^{19}F NMR spectra.

It was also interesting to investigate how $-SCF_3$ substituted β-keto esters behave in alkaline media in comparison to their unsubstituted analogues. When boiled with 5% aqueous solution of sodium hydroxide, α-(trifluoromethylthio)acetoacetic ester 1a and α-(trifluoromethylthio)benzoylacetic ester 1b give trifluoromethylthioacetone [6] and ω-(trifluoromethylthio)acetophenone [13] respectively but as mixtures with the starting materials. Much better results could be achieved by Krapcho's method [14]. On boiling with $DMSO/H_2O$ these esters produce appropriate pure CF_3S- substituted ketones.



Under the influence of concentrated methanolic potassium hydroxide solution 1a and 1b give, besides corresponding acetic and benzoic acids, trifluoromethylthioacetic acid [15], a substance of significant importance especially in the synthesis of cephalosporin antibacterials [16]. During the alkaline splitting of β-keto esters, ketones are formed as well as acids and this usually eliminates the practical usage of the method [17]. But during the alkaline splitting of $-SCF_3$ substituted β-keto esters no ketone formation is observed and

trifluoromethylthioacetic acid is obtained in a good yield. Thus, in comparison with relatively complicated methods of its synthesis described in the literature [18 - 21], this new one could be also taken into consideration.

It is worth mentioning that in none of the reactions carried out in the present work, CF_3S- group splitting is observed. According to my observation not only the substituent itself is strongly bonded, but also the stability of the CF_3S-substituted compounds increases in comparison with the unsubstituted ones.

EXPERIMENTAL

Melting and boiling points are not corrected. ^1H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on Perkin-Elmer R-12 spectrometer. ^{19}F NMR spectra were taken in $CDCl_3$ with C_6F_6 as internal standard on Bruker HX 60/5. Positive values of chemical shift are given upfield from $CFCl_3$. IR spectra were measured in KBr pellets on Zeiss UR 10 apparatus. Mass spectra were recorded at 70 eV on LKB 2091 spectrometer for compounds 1b, 2a, 2b, and 3b and on Varian MAT CH-7 spectrometer for compound 3a; m/z, relative abundance in % and supposed assignment are given.

The reaction of β-dicarbonyl compounds with trifluoromethylsulphenyl chloride - general procedure

The solution of the reacting substance was placed in a three-necked flask equipped with a stirrer, a reflux condenser filled with methanol cooled down to -50°C by cryostate and connected with a trap cooled down to -80°C protected by calcium chloride tube, and with a gas inlet attached to a glass tube fitted with PTFE valve and containing CF_3SCl liquidized under pressure. The flask was cooled down to -30°C and gaseous CF_3SCl in 20% excess to the proper molar ratio was slowly condensed into the stirred solution. The reaction mixture was stirred overnight at room temperature, then neutralized with water solution of sodium carbonate, washed thoroughly with water, dried over magnesium sulphate and after removal of solvent the products were separated.

Ethyl α-(trifluoromethylthio)benzoylacetate 1b

Ethyl benzoylacetate (34.0 g, 0.177 mole) was treated with trifluoromethylsulphenyl chloride (27.5 g, 0.2 mole) in a manner described above but without solvent. After the reaction was completed, the reaction mixture was diluted with n-pentane, some benzoic acid was filtered off, the filtrate was neutralized, washed with water and dried. Then the solvent was removed and the crude product was fractionated under reduced pressure through a Fischer's distillation column. Colourless liquid (30.7 g, 59% yield). B.p. 136.5°C/5 mm Hg. Analysis calc. for $C_{12}H_{11}F_3O_3S$ (292.266): 49.3% C, 3.8% H, 11.0% S; found: 49.3% C, 3.9% H, 10.8% S.
^{1}H NMR δ [ppm]: 1.2, t, J = 11 Hz (ketone CH_3); 1.35, t, J = 11 Hz (enol CH_3); 4.25, q, J = 11 Hz (ketone CH_2O); 4.4, q, J = 11 Hz (enol CH_2O); 5.65, s ($COCH(SCF_3)CO$); 7.4 - 8.2, m (aromatic); 14.55, s (OH); 38% of ketone, 62% of enol form;
^{19}F NMR δ [ppm]: 47.41, m (enol SCF_3); 41.75, m (ketone SCF_3);
IR ν [cm^{-1}]: 3070 w (CH arom.), 2990 m (CH alif.), 2700 b (OH), 1730 s (C=O ester), 1680 s (C=O ketone), 1270 s (C-O), 1115 - 1170 s (C-F);
MS: 292, 5.7, M^+; 277, 1.6, $(M - CH_3)^+$; 106, 6.8, $C_6H_5COH^+$; 105, 100.0, $C_6H_5CO^+$; 93, 9.4, $C_6H_5O^+$; 77, 14.0, $C_6H_5^+$; 45, 4.0, $C_2H_5O^+$; 43, 3.9, CH_3CO^+.

α-(Trifluoromethylthio)acetoacetanilide 2a

a) Acetoacetanilide (50.0 g, 0.282 mole) in 300 ccm of dry chloroform was treated with trifluoromethylsulphenyl chloride (46.0 g, 0.337 mole). After the reaction the solution was filtered off from small amount of aniline hydrochloride and worked up as above. The solid product obtained (58.7 g, 75% yield) was crystallized from methanol.

b) Ethyl α-(trifluoromethylthio)acetoacetate (25.2 g, 0.11 mole) was dissolved in 150 ccm of xylene and the solution was put into a flask equipped with a distillation head having

a dropping funnel instead of a thermometer. Aniline (10.2 g, 0.11 mole) diluted by 50 ccm of xylene with 0.5 ccm pyridine was added dropwise to the boiling ester solution at the same spead at what a mixture of ethanol, pyridine and xylene distilled. Then the solution was thickened to 30 ccm, cooled down and the precipitate of the product 2a (26.6 g, 87% yield) was filtered off and crystallized from methanol. Colourless needles. M. p. 57 -59°C. Analysis calc. for $C_{11}H_{10}F_3NO_2S$ (277.256): 47.7% C, 3.6% H, 5.1% N, 11.6% S; found: 47.7% C, 3.8% H, 5.2% N, 11.4% S.

^{1}H NMR δ [ppm]: 2.35, s, 3H (CH_3); 7.0 - 7.6, m, 5H (aromatic); 8.35, broad s, 1H (NH); 16.15, s, 1H (OH); 100% of enol form;

^{19}F NMR δ[ppm]: 46.45, m (SCF_3);

IR ν[cm^{-1}]: 3380 m (NH), 3600 -3100 b (OH), 1685 vw (C=O), 1540 b (NHCO), 1130 and 1150 s (CF);

MS: 277, 13.0, M^+; 208, 2.6, $(M - CF_3)^+$; 165, 2.5, $(M - CF_3, - COCH_3)^+$; 124, 3.0, $C_3H_2F_2SO^+$; 120, 2.4, $C_6H_5NHCO^+$; 93, 100.0, $C_6H_5NH_2^+$; 88, 10.1, CH_3COCHS^+; 77, 11.6, $C_6H_5^+$; 69, 5.3, CF_3^+; 66, 7.0, $C_4H_2O^+$; 65, 10.4, $C_5H_5^+$; 51, 7.0, $C_4H_3^+$; 45, 6.3, CHS^+; 43, 37.9, CH_3CO^+; 39, 8.2, $C_3H_3^+$.

α-(Trifluoromethylthio)benzoylacetanilide 2b

c) Benzoylacetanilide (40.0 g, 0.167 mole) in 300 ccm of dry chloroform was treated with trifluoromethylsulphenyl chloride (32.6 g, 0.239 mole). After the reaction the small amount of aniline hydrochloride was filtered off and the solution was worked up as usual. The solid product obtained (41.0 g, 72% yield) was crystallized from methanol.

d) Ethyl α-(trifluoromethylthio)benzoylacetate (15.0 g, 0.051 mole) was treated with aniline (5.0 g, 0.052 mole) in the same manner as in b). After the reaction the product 2b (16.0 g, 92% yield) was filtered off and crystallized from methanol. Colourless plates. M. p. 112 - 114°C. Analysis calc. for $C_{16}H_{12}F_3NO_2S$ (339.322): 56.6% C, 3.6% H, 4.1% N, 9.5% S; found: 56.7% C, 3.6% H, 4.3% N, 9.3% S.

^{1}H NMR δ [ppm]: 7.2 - 7.7, m, 10H (aromatic); 8.7, broad s, 1H (NH); 16.6, s, 1H (OH); 100% of enol form;
^{19}F NMR δ [ppm]: 46.26, m (SCF_3);
IR ν [cm^{-1}]: 3370 s (NH), 1620 m (C=O), 1530 b (NHCO), 1125 and 1140 s (CF);
MS: 339, 17.3, M^+; 247, 4.3, $(M - C_6H_5NH)^+$; 220, 2.8, $(M - C_6H_5NCO)^+$; 151, 5.9, $C_6H_5C(OH)CHS^+$; 121, 4.9, $C_6H_5NHCOH^+$; 105, 57.3, $C_6H_5CO^+$; 93, 100.0, $C_6H_5NH_2^+$; 77, 47.7, $C_6H_5^+$; 69, 3.8, CF_3^+; 65, 10.5, $C_5H_5^+$; 51, 16.8, $C_4H_3^+$; 45, 7.1, CHS^+.

α-(Trifluoromethylthio)-β-(phenylamino)crotonanilide 3a

e) β-(Phenylamino)crotonanilide - crude oily product was used - (5.8 g, 0.021 mole) in 150 ccm of dry chloroform was treated with trifluoromethylsulphenyl chloride (9.2 g, 0.067 mole). After the reaction the small amount of aniline hydrochloride was filtered off and the filtrate was worked up as usual. The oily product obtained was crystallized from methanol or petroleum benzin (5.0 g, 62% yield).

f) A mixture of α-(trifluoromethylthio)acetoacetanilide (14.0 g, 0.050 mole), aniline (5.0 g, 0.051 mole), 100 ccm xylene, and 1 drop of hydrochloric acid was refluxed under Dean-Stark water separator for 3 hours. The traces of aniline hydrochloride were filtered off, the solution was thickened and after cooling the product 3a was filtered off (14.2 g, 80% yield) and crystallized from methanol. Colourless plates. M. p. 96 - 98°C. Analysis calc. for $C_{17}H_{15}F_3N_2OS$ (352.364): 57.9% C, 4.3% H, 8.0% N; found: 58.0% C, 4.2% H, 7.7% N.
^{1}H NMR δ [ppm]: 2.38, s, 3H (CH_3), 7.03 - 7.65, m, 10H (aromatic), 8.68, broad s, 1H (NH amide); 13.08, broad s, 1H (NH enamine); 100% of enamine form;
^{19}F NMR δ [ppm]: 46.95, m (SCF_3);
IR ν [cm^{-1}]: 3390 s (NH), 1605 s (C=C), 1560 s, 1520 b (NHCO), 1120 - 1130 s and 1150 s (CF);
MS: 352, 54.0, M^+; 283, 5.0, $(M - CF_3)^+$; 260, 74.0, $(M - C_6H_5-NH)^+$; 251, 5.0, $(M - SCF_3)^+$; 240, 82.0, $(M - C_6H_5NH_2, - F)^+$; 221, 7.0, $(M - C_6H_5NH_2, - 2F)^+$; 191, 10.0, $CH_3C(NHC_6H_5)C(S)CO^+$; 162, 17.0, $CH_3C(NC_6H_5)CS^+$; 131, 51.0, $CH_3C(NC_6H_5)CH^+$; 130, 44.0, $CH_3C(NC_6H_5)C^+$; 118, 91.0, $CH_3CNC_6H_5^+$; 93, 100.0, $C_6H_5NH_2^+$; 77, 62.0, $C_6H_5^+$.

α-(Trifluoromethylthio)-β-(phenylamino)cinnamanilide 3b

β-(Phenylamino)cinnamanilide (19.6 g, 0.062 mole) in 150 ccm of dry chloroform was treated with trifluoromethylsulphenyl chloride (10.0 g, 0.073 mole). After the reaction the small amount of aniline hydrochloride was filtered off and the solution was worked up as usual. The oily product obtained was crystallized from methanol (17.6 g, 83% yield). Colourless prisms. M. p. 108.5 - 110.5°C. Analysis calc. for $C_{22}H_{17}F_3N_2OS$ (414.430): 63.8% C, 4.1% H, 6.8% N, 7.7% S; found 63.8% C, 4.2% H, 6.8% N, 7.7% S.
^{1}H NMR δ [ppm]: 6.6 - 7.6, m, 15H (aromatic); 8.8, broad s, 1H (NH amide); 13.1, broad s, 1H (NH enamine); 100% of enamine form;
^{19}F NMR δ [ppm]: 46.95, m (SCF_3);
IR ν [cm^{-1}]: 3320 m (NH), 1605 s (C=C), 1575 s, 1560 s, 1520 b (NHCO), 1110 s and 1140 - 1150 s (CF);
MS: 414, 44.5, M^+; 322, 100.0, $(M - C_6H_5NH)^+$, 321, 19.0, $(M - C_6H_5NH_2)^+$; 313, 5.4, $(M - SCF_3, - H)^+$; 303, 9.6, $(M - C_6H_5NH, - F)^+$; 302, 46.3, $(M - C_6H_5NH_2, - F)^+$; 252, 12.3, $C_6H_5C(NC_6H_5)CSCO^+$; 225, 2.7, $C_6H_5C(NHC_6H_5)CS^+$; 193, 19.6, $C_6H_5C(NHC_6H_5)C^+$; 180, 24.1, $C_6H_5CNC_6H_5^+$; 105, 4.3, $C_6H_5CNH_2^+$; 93, 19.1, $C_6H_5NH_2^+$; 77, 1.8, $C_6H_5^+$.

Acid hydrolysis of α-(trifluoromethylthio)-β-(phenylamino)-crotonanilide 3a

A mixture of 1 g (0.003 mole) of Schiff base 3a, 15 ccm of conc. hydrochloric acid, and 50 ccm of water was refluxed for 30 minutes, then poured onto ice and the precipitate of compound 2a (0.65 g, 82% yield) was filtered off.

Acid hydrolysis of α-(trifluoromethylthio)-β-(phenylamino)-cinnamanilide 3b

A mixture of 1 g (0.002 mole) of Schiff base 3b, 15 ccm of conc. hydrochloric acid and 50 ccm of ethanol was refluxed for 30 minutes, then poured onto ice and the precipitate of compound 2b (0.8 g, 98% yield) was filtered off.

Decomposition of α-(trifluoromethylthio)- substituted β-keto esters by heating in dimethylsulphoxide diluted with water

A mixture of 25 ccm DMSO, 1 ccm water and 7 g (0.03 mole) of ethyl α-(trifluoromethylthio)acetoacetate or 8.8 g (0.03 mole) of ethyl α-(trifluoromethylthio)benzoylacetate 1b, respectively, was refluxed for 4 hours. After cooling the dark solution was poured into cold water, brown oil was extracted with n-pentane, dried with calcium chloride and after evaporation of solvent, distilled. In the first case 2.1 g, 44% yield of α-(trifluoromethylthio)acetone (its b. p. and IR spectrum were consistent with the literature data [6]) and in the second 4.35 g, 66% yield of ω-(trifluoromethylthio)acetophenone (its b. p. and n_D^{20} were consistent with the literature data [13]) were obtained.

Decomposition of ethyl α-(trifluoromethylthio)acetoacetate under the influence of concentrated potassium hydroxide solution

Ethyl α-(trifluoromethylthio)acetoacetate (9.15 g, 0.04 mole) was mixed with a solution of 2.2 g (0.04 mole) of potassium hydroxide in 20 ccm of methanol and left at room temperature overnight. Then the solution was poured into the mixture of concentrated sulphuric acid (3 ccm) and ice (150 g), and the yellow oil was extracted with ether. The combined extracts were dried with magnesium sulphate and the residue after removal of solvent was fractionated under reduced pressure through a Fischer's distillation column. α-(Trifluoromethylthio)acetic acid (5.7 g, 89% yield) was obtained and identified by comparison of its b. p. , n_D^{20} and IR spectrum with the literature data [15, 18].

Decomposition of ethyl α-(trifluoromethylthio)benzoylacetate 1b under the influence of concentrated potassium hydroxide solution

Ethyl α-(trifluoromethylthio)benzoylacetate (6.7 g, 0.023 mole) was mixed with a solution of 1.7 g (0.03 mole) of potas-

sium hydroxide in 14 ccm of methanol and left overnight. Then the solidified mixture was treated with a mixture of conc. sulphuric acid (3 ccm) and ice (150 g). The precipitated benzoic acid (1.5 g) was filtered off, washed with water and the filtrate was extracted with ether. The combined extracts were dried with magnesium sulphate and the residue after removal of solvent was fractionated under reduced pressure through a Fischer's distillation column. α-(Trifluoromethylthio)acetic acid (2.2 g, 60% yield) was obtained. From the residue after distillation 0.7 g of benzoic acid was separated.

ACKNOWLEDGMENTS

The author gratefully acknowledges Prof. Dr. mult. A. Haas from Ruhr University Bochum (F. R. G.) where this work was carried out for his support and helpful discussion, and the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship.

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