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ACYLATION OF α-SCF_3 SUBSTITUTED ß-CARBONYL ACETIC ACID AND THIACETIC ACID DERIVATIVES WITH OXALYL CHLORIDE

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SUMMARY

α-CF_3S-substituted ß-ketoacidamides, nitriles, thioamides and their Schiff bases are synthesised and their reactions with oxalyl chloride are investigated. As a new phenomenon the elimination of the CF_3S group during cyclisation to substituted 2,3,5-trioxo-1,4-oxazepine (7), 4-pyrroline-2,3-dione (9) and oxalyl (10) is observed. Factors influencing this course of the reaction and mechanism of product formation are discussed.

INTRODUCTION

Earlier publications had described cyclisation of some ß-keto-acid and thioacid derivatives with oxalyl chloride led to the five membered polycarbonyl heterocycles such as pyrrolidine-2,4,5-triones [1], pyrrolidine-2-thioxo-4,5-diones [2], pyrroline- and furane-2,3-diones [3].

The intention of this work was to elucidate the influence of the CF_3S-group attached to ß-ketoacid amides, nitriles, thioamides and their derivatives as Schiff bases in analogous reactions. It was found, that the starting materials, ß-ketoacid derivatives, react as CH-acids with trifluoromethylsulfenylchloride, giving substituted compounds as had been already shown by Bayreuther and Haas [4]. By analogy with unsubstituted substances the same course of cyclisation and biological activities of the

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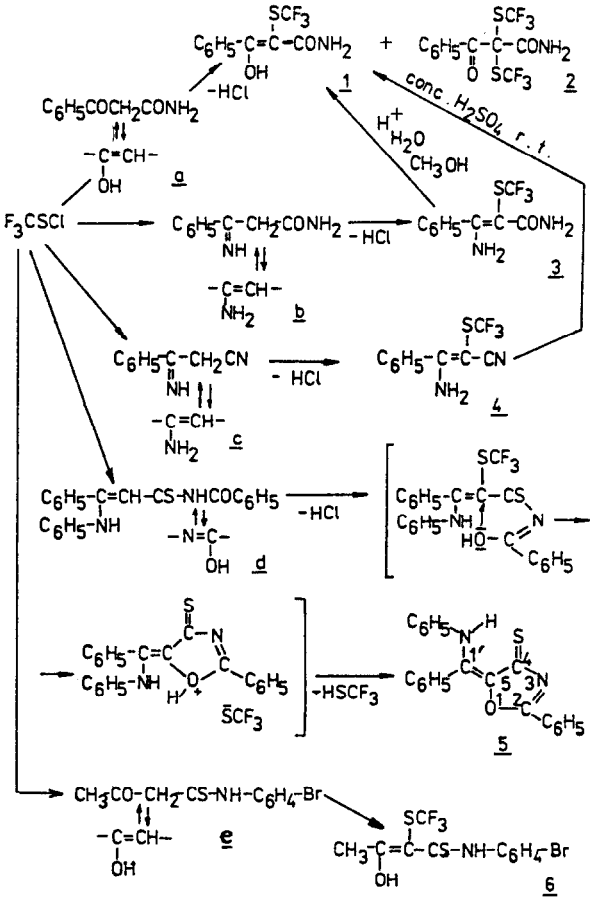
heterocycles formed were expected. The products of these transformations can be used as intermediates for the synthesis of new biologically active compounds.

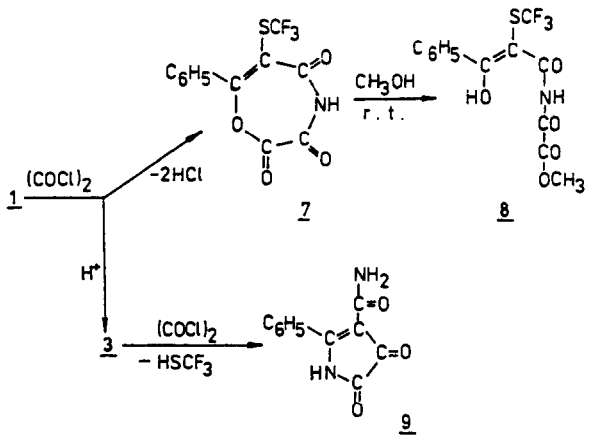
DISCUSSION

Trifluoromethylsulfenylation of benzoylacetamide (a) delivered α-trifluoromethylthio- (1) in 88 % yield and only 4 % of α,α-bis(trifluoromethylthio)-benzoylacetic acid amide (2).



Scheme 1

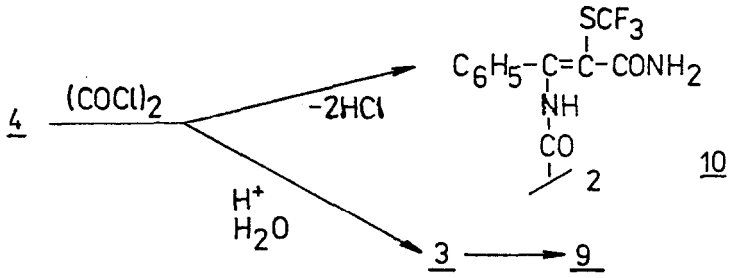
Cyclocondensation of 1 with oxalyl chloride provided a seven membered lactonolactame i.e. 7 phenyl-6-trifluoro-methyl-thio-Δ^6, 4H-2,3,5 trioxo-1,4-oxazepine (7) as shown below.



Scheme 2

The structure of 7 is suggested by its ^{1}H NMR spectrum, in which the OH resonance, characteristic for 1 is absent. The mass spectrum contains a peak at m/z = 263 (18 %) [M^+ - (2CO-2H)] as expected for 7. Methanolysis of 7 gave ester 8 with (CH_3) at 3.6 (s) ppm in ^{1}H NMR spectrum and m/z = 290 (5 %) (M^+ - $COOCH_3$) in the mass spectrum.

ß-Aminocinnamic amide b is substituted by trifluoromethylsulfenylchloride (see scheme 1) in the same α-position, as well. ß-Amino-trifluoromethylthiocinnamic acid amide (3) reacted with oxalyl chloride in a similar manner as the non trifluoromethylsulfenylated compound and yielded the already known substance 9 [3].



Scheme 3

The removal of the CF_3S-substituent occurred probably because of a stronger nucleophile attack on α-C. This procedure might be relevant for ring closure and ring formation. By reacting 1 with $(COCl)_2$ via scheme 3 9 is obtained in small amounts together with 7.

The ß-amino-cinnamic acid nitrile c is easily substituted in the α-position by a trifluoromethylthio group forming 4 in 90 % yield (scheme 1). Its cyclisation with oxalyl chloride (scheme 3) proceeds differently to that of the trifluoromethyl-sulfenylated compound giving 10. It is impure, containing traces of 9. The diagnostic spectroscopic data for 10 are: MS peaks m/z at 289 = $[M^+/2]$ (100 %); 104 = $[C_6H_5C{=}NH]$ (70 %) and 69 = $[CF_3]$ (12 %).

The reaction of the Schiff base of benzoylthioacetic acid N-benzoylamide d with trifluoromethyl-sulfenyl chloride, giving the nonsubstituted 5 seems very interesting. The following reaction mechanism is suggested: substitution at α-C, followed by intramolecular cyclization. This becomes possible by attack of the free electron pair at oxygen in a tautomeric amide group on electron defficient α-C. The electron-withdrawing CF_3S-group is eliminated with formation of oxazole derivative 5.

The structure of 5 was confirmed spectroscopically by its MS spectrum m/z 356 = $[M^+]$ (25 %), its IR spectrum with a strong

band for (C-O-C) at 1330 cm^{-1} in oxazole [5] and its ^{13}C-NMR spectrum [6] (see experimental part).
Compound 6 with a α-trifluoromethylthio-acetylthioacetic acid p-bromoanilide structure is obtained from e in an analogous way (scheme 1). It did not react with oxalyl chloride under conditions mentioned.
The structure of all compounds obtained were confirmed by elemental analysis, IR, ^1H NMR, ^{19}F NMR, MS and for 5 by ^{13}C NMR spectral data.

EXPERIMENTAL

IR spectra: Solids are recorded as Nujol suspensions on a Perkin Elmer 125 spectro-photometer. ^{19}F, ^1H and ^{13}C NMR spectra are measured with a Bruker HX 60/5 spectrometer in C_6F_6 solution, (internal standard C_6F_6; δ-values in ppm calculated for $CFCl_3$), and in $CDCl_3$ or acetone-d_6 solution with TMS as internal standard. Mass spectra are recorded with a LKB 2091.

General method for the preparation of CF_3S substituted ß-ketoacid derivatives: 1 to 6

Trifluoromethylsulfenyl chloride (0.02 mole or more) are slowly added (15 min) to a solution of 0.02 mole a, b, c, d or e in 40 ml of dry chloroform. The mixture was stirred under reflux at 0°C (condenser cooled with methanol to -35°C) for 30 min and then 20 h at room temperature. 40 ml of an 10 % aqueous $NaHCO_3$ solution is poured into reaction mixture and stirred for several hours. The chloroform layer was separated, washed three times with water, dried over Na_2SO_4 and the solvent evaporated to dryness in vacuo. Recrystallization provided pure 1, 2, 3, 4, 5 or 6.

Remarks:

a) The substance, which was separated from the mother liquor after crystallization of 1 is the by-product 2.

b) Product 1 was obtained in two other ways:
   1. in the thermal acidic hydrolysis of compound 3 (in CH_3OH, H_2O and some drops of HCl_{aq}), in quantitative yield;
   2. in the acidic hydrolysis of compound 4 (with conc. H_2SO_4 at room temperature), in 86 % yield.

c) The starting material d gave product 5, as oxazole derivative, without a CF_3S substituent. The intermediate was not isolated.

α-Trifluoromethylthio-benzoylacetic acid amide (1)

Yield 88 %, m.p. 112 - 113°C (from n-hexane), IR (cm^{-1}): 3485 (OH), 3290, 3220, 3150 (NH_2), 1650 (CONH), 1620 (C=C), 1180 - 1080 (C-F). ^1H NMR ($CDCl_3$): 6.2 - 6.8 (2H)NH_2, 7.2 - 7.7 (5H)arom., 13.6 (1H) OH. ^{19}F NMR (C_6F_6): 46.0, 46.98 (ketone-enol). MS m/z (%): 263 M^+ (28), 194 $[M^+-CF_3]^+$ (8), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (33), 69 $[CF_3]^+$ (3). Found: C, 45.7 %; H, 2.7 %; N, 5.4 %; S, 12.2 %. Calculated for $C_{10}H_8F_3NO_2S$ (263.2): C, 45.6 %; H, 3.1 %; N, 5.3 %; S, 12.2 %.

α,α-Bis(trifluoromethylthio)benzoylacetic acid amide (2)

Yield 4 %, m.p. 170 - 174°C, [from $CHCl_3$/n-hexane (1 : 1)]. IR (cm^{-1}): 3400 - 3200 (NH_2), 1690 (CO), 1660 (CONH), 1195 - 1030 (CF). ^1H NMR ($CDCl_3$): 6.3 - 6.6 (2H) NH_2, 7.2 - 7.6 (5H) arom. ^{19}F NMR (C_6F_6): 38.4. MS m/z (%): 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (45), 69 $[CF_3]^+$ (3). Found: C, 37.2 %; H, 2.1 %; N, 4.1; S, 17.6 %. Calculated for $C_{11}H_7F_6NO_2S_2$ (363.3) C, 36.7 %; H, 1.9 %; N, 3.9 %; S, 17.6 %.

ß-Amino-α-trifluoromethylthio-cinnamic acid amide (3)

Yield 90 %, m.p. 164 - 165°C, [from $CHCl_3$/n-hexane (1 : 1)]. IR (cm^{-1}): 3485, 3425, 3295, 3190 (NH_2, NH_2), 1650 (CONH), 1190 - 1030 (C-F). ^1H NMR ($CDCl_3$): 2.2 (2H) enamine, 6.3 - 6.8 (2H) $CONH_2$, 7.2 - 7.4 (5H) arom. ^{19}F NMR (C_6F_6): 48.0. MS m/z (%): 263 $[M^+ + 1]^+$ (10), 262 $[M^+]$ (78), 193 $[M^+ - CF_3]$ (38), 177 [176 + 1]$^+$ (12), 176 $[M^+ - CF_3, - NH_3]^+$ (100), 104 $[C_6H_5C{=}NH]^+$ (64), 77 $[C_6H_5]^+$ (32). Found: C, 45.9 %; H, 3.4 %; N, 10.8 %; S, 12.3 %. Calculated for $C_{10}H_9F_3N_2OS$ (262.3): C, 45.8 %; H, 3.4 %; N, 10.7 %; S, 12.2 %.

ß-Amino-α-trifluoromethylthio-cinnamic acid nitrile (4)

Yield 90 %, m.p. 68 - 69°C, [from $CHCl_3$/n-hexane (1 : 1]. IR (film, cm^{-1}): 3460, 3330, 3225 (NH_2), 2210 (C=N), 1620 (C=C), 1180 - 1070 (C-F). ^1H NMR (acetoned^6): 5.8 - 6.2 (2H) NH_2, 7.3 - 7.7 (5H) arom. ^{19}F NMR (C_6F_6): 45.5, 48.0 (imine - enamine). MS m/z (%): 229 $[M^+ - NH]^+$ (70), 167 $[M^+ - C_6H_5]^+$ (15), 166 $[M^+ - C_6H_5, - 1H]$ (100), 165 $[M^+ - C_6H_5, - 2H]^+$ (25), 104 $[C_6H_5{-}C{=}NH]^+$ (28), 77 $[C_6H_5]^+$ (35). Found: C, 48.8 %; H, 2.9 %; N, 11.0 %; S, 13.1 %. Calculated for $C_{10}H_7F_3N_2S$ (244.2): C, 49.2 %; H, 2.9 %; N, 11.3 %; S, 13.1 %.

2-Phenyl-4-thioxo-5-(1'-phenylaminobenzalo)-1,3-oxazole (5)

Yield 74 %, m.p. 166 - 167°C, [from $CHCl_3$/n-hexane (1 : 2)]. IR (cm^{-1}): 1330 (C-O-C). ^1H NMR ($CDCl_3$), 7.1 - 7.5 (15 H) arom., 8.3 - 8.5 (1H) NH. MS m/z (%): 356 M^+ (25), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (47). ^{13}C NMR ($CDCl_3$, TMS, δ in ppm): 150.3 (C-2), 175.8 (C-4), 139.1 (C-5), 134.4 (C-1'). Found: C, 73.7 %; H, 4.5 %; N, 8.3 %; S, 9.0 %. Calculated for $C_{22}H_{16}ON_2S$ (356.4): C, 74.1 %; H, 4.5 %; N, 7.9 %; S, 9.0 %.

p-Bromoanilide of α-trifluoromethylthio-acetothiaoacetic acid (6)

Yield 66 %, m.p. 156 - 157°C, [from $CHCl_3$/n-hexane (1 : 1)]. IR (cm^{-1}): 3100 (NH), 1175 - 1090 (C-F). ^1H NMR ($CDCl_3$): 2.48 (3H) CH_3, 7.3 - 7.5 (4H) arom., 7.9 (1H) NH. ^{19}F NMR (C_6F_6): 47.2. MS m/z (%): 372 M^+ (5), 371 $[M^+-1H]^+$ (42), 302 $[M^+ - CF_3, - 1H]^+$ (100), 259 $[M^+ - 1H, - CF_3, - CH_3CO]^+$ (29), 69 $[CF_6]^+$ (15), 43 $[CH_3CO]^+$ (65). Found: C, 35.6 %; H, 2.8 %; N, 4.2 %; S, 17.0 %. Calculated for $C_{11}H_9BrF_3NOS_2$ (372.2): C, 35.5 %; H, 2.4 %; N, 3.8 %; S, 17.1 %.

Cyclisation reactions of compounds 1, 3 and 4 with oxalyl chloride. General procedure for 7, 9 and 10

To a stirred solution of 0.01 mole of 1, 3 or 4 in 80 ml of dry benzene, 1 ml (about 0.01 mole) of oxalyl chloride is added at room temperature and refluxed during 12 h. From a cooled mixture compound 7, 9 or 10 was filtered off and recristallized. The mother liquor of 7 and 10 contained small amounts of 9.

α-Trifluoromethylthio-benzoylacetic acid N-methoxyoxalyl-amide (8)

0.005 mole of 7 was left in 50 ml methanol at room temperature for 12 h. The precipitate was recristallized from ether.

7-Phenyl-6-trifluoromethylthio-Δ^6-2,3,5-trioxo-1,4-oxazepine (7)

Yield 57 %, m.p. 142 - 143°C, [from $CHCl_3$/n-hexane (1 : 1)]. IR (cm^{-1}): 3180 (NH), 1830 (OC=O), 1790, 1715 (CO-NH), 1605 (C=C), 1170 - 1070 (C-F). ^1H NMR (acetone d_6) 7.5 - 7.8 (6H) arom., NH; ^{19}F-NMR (C_6F_6): 44.79. MS m/z (%): 263 $[M^+ - 2CO, + 2H]^+$ (18), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (38), 69 $[CF_3]^+$ (3). Found: C, 45.3 %; H, 2.1 %; N, 4.7 %; S, 10.1 %. Calculated for $C_{12}H_6F_3NO_4S$ (317.2): C, 45.4 %; H, 1.9 %; N, 4.4 %; S, 10.2 %.

α-Trifluoromethylthio-benzoylacetic acid N-methoxyoxalyl amide (8)

Yield 90 %, m.p. 158 - 161°C, (from ether). IR (cm^{-1}): 3500 - 3000 (OH), 1785, 1710, 1690, 1670 (CO), 1180 - 1050 (C-F). ^1H NMR ($CDCl_3$): 3.6 (3H) CH_3, 7.2 - 7.8 (5H) arom., 9.9 - 10.4 (1H) NH. ^{19}F NMR (C_6F_6): 43.55, 45.14 (ketone enol). MS m/z (%): 290 $[M^+ - COOCH_3]^+$ (5), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (50), 32 CH_3OH (52), 30 $[CH_2O]^+$ (60). Found: C, 45.2 %; H, 2.8 %; N, 4.3 %, S, 10.0 %. Calculated for $C_{13}H_{10}F_3NO_5S$ (349.2): C, 44.7 %; H, 2.9 %; N, 4.0 %; S, 9.3%.

5-Phenyl-4-carbamoyl-4-pyrroline-2,3-dione (9) [3]

Yield 86 %, m.p. 272°C, (from methanol).

Bis(ß-amino-α-trifluoromethylthio-benzoylacetic acid amide)N,N'-(enamino)-oxalyle (10)

Yield 74 %, m.p. 280°C, (sublimation). IR (cm^{-1}): 3280 - 3100 (NH), 1705, 1660 (CO), 1610 (C=C), 1175 - 1090 (C-F). ^1H NMR (aceton d_6): 7.2 - 7.9 (16H) arom. and NH. ^{19}F NMR (C_6F_6): 43.72. MS m/z (%): 290 $[M^+/2 + 1H]^+$ (5), 289 $[M^+/2]^+$ (17), 288 $[M^+/2 - 1H]^+$ (100), 220 $[M^+/2 - CF_3]^+$ (6), 104 $[C_6H_5C{=}NH]^+$ (70), 69 $[CF_3]^+$ (12). Found: C, 45.3 %; H, 2.4 %; N, 9.6 %; S, 11.1 %. Calculated for $C_{22}H_{16}F_6N_4O_4S_2$ (578.5): C, 45.7 %; H, 2.8 %; N, 9.7 %; S, 11.1 %.

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