*Tetrahedron* Vol 44, No 17, pp 5355 to 5360, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00
Pergamon Press plc

# SYNTHESIS OF 2-(PHENYLTRIFLUOROACETYLAMINO)-3-(TRIMETHYLSILOXY) ALKANOIC ACID AND N-PHENYL-N-TRIFLUOROACETYLDEHYDROAMINO ACID ESTERS

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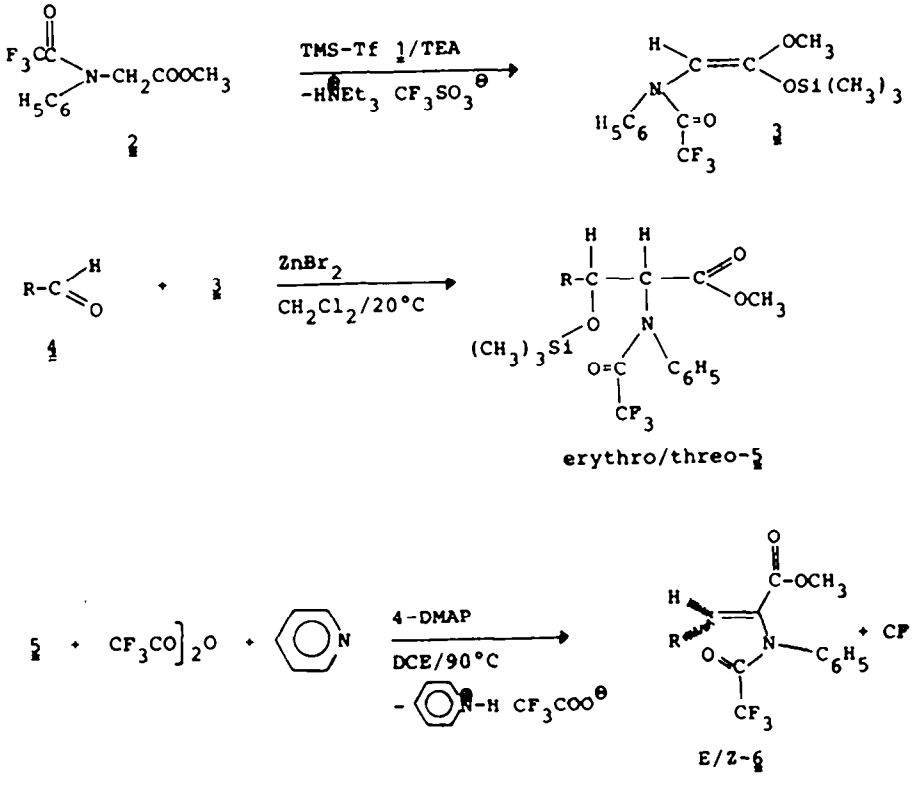
*(Received in USA 25 January 1988)*

**Abstract**: Reaction of aromatic aldehydes **4** with the ketene acetal **3** in presence of zinc bromide affords methyl 2-(phenyltrifluoroacetylamino)-3-trimethylsiloxy-alkanoates **5**. Elimination of trimethylsilanole from **5** by means of trifluoroacetic acid anhydride yields (E,Z) methyl 2-(phenyltrifluoroacetyl-amino)-2-alkenoates **6**.




| **4**, **5**, **6** | R | | R |
|---|---|---|---|
| **a** | $C_6H_5$ | **e** | 3,4,5-$(CH_3O)_2$ |
| **b** | 4-$CH_3C_6H_4$ | **f** | 2-furyl |
| **c** | 4-$CH_3OC_6H_4O$ | **g** | 2-thienyl |
| **d** | 3,4-$(CH_3O)_2C_6H_3$ | | |

Previously we reported the synthesis of 1,2-dialkoxy-1-(trimethylsiloxy)-1-alkenes by silylation of α-alkoxy carboxylic acid esters with trimethylsilyltriflate (1)/triethylamine[2]. In the same manner we succeeded in preparing N-protected α-amino ketene acetals starting from esters of N-trifluoroacetylglycine[2-4] and N-trifluoroacetyl sarcosine[5]. In reaction of these ketene acetals especially with aromatic carbaldehydes we obtained diastereomeric mixtures of α-amino-β-trimethylsiloxy-alkanoates[3-5]. β-elimination of trimethylsilanole by means of methane sulfonic acid anhydride or trifluoroacetic acid anhydride yielded mainly (Z)-α,β-dehydroamino acid esters[4,5]. We now describe the synthesis of the 2-N-phenylamino ketene acetal 3 by reaction of N-phenyl-N-trifluoroacetylglycine methylester (2) with trimethylsilyltriflate (1)/triethylamine under modified silylation conditions (exp. part). In an aldol type reaction catalysed by zinc bromide 3 adds to (hetero)aromatic aldehydes 4 resulting in formation of methyl 2-(phenyltrifluoroacetylamino)-3-trimethylsiloxyalkanoates 5 as erythro/threo mixtures (table 1). Stereoselective synthesis of 2-alkylamino-3-hydroxy alkanoic acids were realized by aldol type reactions with N-alkylglycines[6,7] or by hydroxyalkylation of isothiocyanato acetic acid derivatives[8]. Enantioselective preparation of 2-amino-3-hydroxy carboxylic acids could be performed from 2,5-dioxopiperazines by Schöllkopf et al.[9,10] or from 1,3-oxazolidinones by Seebach et al[11,12].
N-substituted dehydroamino acids are increasingly found as building blocks in peptides[13,14]. We therefore extended the synthesis of dehydroamino acid esters on the N-phenylesters 5 in a modified form. By β-elimination of "trimethylsilanole" with trifluoroacetic anhydride/pyridine in presence of catalytic amounts of 4-dimethylamino pyridine we obtained the N-phenyl alkenoic acid esters 6 in good yields till now as mixtures of the E/Z isomers (table 2). Examination of the reaction path of the aldol addition and the β-elimination are in progress.

**Acknowledgement**

We gratefully acknowledge the Deutsche Forschungsgemeinschaft for financial support.

**Experimental Data**

N-phenylglycine and trimethylsilyltriflate (1) as well as the aldehydes 4 are commercial products (Fluka AG, Buchs S.G., Switzerland). $^1$H-NMR spectra were recorded on Bruker CXP 300 in $CDCl_3$/TMS.

1-Methoxy-2-(N-phenyl-trifluoroacetylamino)-1-(trimethylsiloxy)ethen (3)

Methyl-2-(N-phenyl-trifluoroacetylamino)ethanoat (2) (26.19 g, 0.1 mol) is dissolved in a mixture of absolute triethylamine (200 ml) and 1,2-dichloroethane (50 ml). Trimethylsilyltriflate (1) (33.33 g, 0.15 mol) is gradually added at 0-5°C. Stirring is continued for 60 hours at room temperature, the organic phase is removed and the solvents are distilled off in vacuo. Pentane (100 ml) is added, stirred for 30 min and the pentan solution removed from a small amount of triethylammonium triflate. Pentane is distilled off in vacuo and the crude product purified by distillation; yield 27 g (81 %), b.p. 110-112°C/ 0.01 torr.

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{18}F_3NO_3Si$ | Calc. | C 50.43 | H 5.44 | N 4.20 |
| (333.4) | Found | 50.46 | 5.56 | 4.46 |

$^1$H-NMR ($CDCl_3$): δ = 0.10,0.30 (s,s,9H,$Si(CH_3)_3$), 3.51,3.64 (s,s,3H,$OCH_3$), 5.07 (s,1$H_{vinyl}$), 7.45 (s,5$H_{arom.}$).

Methyl-2-(phenyltrifluoroacetylamino)-3-(trimethylsiloxy)alkanoates 5; General Procedure:

The carbaldehyde 4 (15 mmol) and zinc bromide (0.17 g, 0.75 mmol) are dissolved in absolute dichloromethane (40 ml) and the ketene acetale 3 is slowly added with stirring at 0-5°C. Thereafter stirring is continued for some hours at room temperature (table 1). The solvent is evaporated, the oily residue dissolved in absolute pentane (80 ml), filtered from zinc bromide by suction the solution again evaporated and the raw products distilled. Raw procucts which cannot be purified by distillation are taken up in absolute ether (100 ml) and treated with charcoal for 24 h. The mixture is filtered and the ether evaporated in vacuo (table 1).

(E,Z)-Methyl-2-(phenyl-trifluoroacetylamino)-2-alkenoates 6; General Procedure:

The compound 5 (20 mmol) and 4-dimethylamino pyridine (0.49 g, 4 mmol) are placed in absolute dichloroethane (50 ml). Trifluoro acetic acid anhydride (5.04 g, 24 mmol) is slowly added at 0-5°C and the solution warmed up to 40°C with stirring for one hour. After cooling to room temperature absolute pyridine (3.5 g, 44 mmol) is gradually added and the mixture refluxed with stirring for 6 h (table 2). The reaction mixture is given to ether (150 ml) washed with water and the organic layer dried with calcium chloride. The solution is evaporated in vacuo and the residue recrystallized from chloroform/pentane 1:100.

Table 1a. Methyl 2-(phenyltrifluoroacetylamino)-3-(trimethylsiloxy)alkanoates 5 prepared

| Product No. | Reaction-time [h] | Yield [%] [erythro/threo]-distribution[a)] | b.p. [°C]/torr | Molecular Formula |
|---|---|---|---|---|
| 5a | 12 | 75 [56:44] | 115/0.001 | $C_{12}H_{24}F_3NO_4Si$ (439.5) |
| 5b | 12 | 74 [56:44] | 120/0.001 | $C_{22}H_{26}F_3NO_4Si$ (453.5) |
| 5c | 4 | 85 [55:45] | b | $C_{22}H_{26}F_3NO_5Si$ (469.5) |
| 5d | 4 | 89 [60:40] | b | $C_{23}H_{28}F_3NO_6Si$ (499.6) |
| 5e | 4 | 81 [63:37] | b | $C_{24}H_{30}F_3NO_6Si$ (529.6) |
| 5f | 2 | 80 [64:36] | b | $C_{19}H_{22}F_3NO_5Si$ (429.5) |
| 5g | 4 | 85 [55:45] | b | $C_{19}H_{22}F_3NO_4SSi$ (445.5) |

a) Determined by 1H-NMR spectroscopy; b) could not be distilled, see general procedure

Table 1b. Spectroscopic and analytical data of compounds 5

| Product No. | $^1$H-NMR spectra ($CDCl_3$, δ ppm) | | C | H | N | S |
|---|---|---|---|---|---|---|
| 5a | -0.08,0.00 (2s,9H,$Si(CH_3)_3$), 3.58,3.87 (2s,3H,$OCH_3$), 4.16,4.66 (d,d,J=8Hz,J=9.5Hz,1H,NCH), 5.37,5.67 (d,d,J=9.5Hz, J=8Hz,1H,OCH), 7.18-7.55 (m,10$H_{arom}$) | Calc. | 57.39 | 5.50 | 3.18 | |
| | | Found | 57.57 | 5.56 | 3.24 | |
| 5b | -0.07,0.00 (2s,9H,$Si(CH_3)_3$), 2.33,2.42 (2s,3H,$CH_3$), 3.60,3.87 (2s,3H,$OCH_3$), 4.21,4.66 (d,d,J=8Hz,J=9Hz,1H,NCH), 5.33 5.62 (d,J=9Hz,J=8Hz,1H,OCH), 7.05-7.63 (m,9$H_{arom}$) | Calc. | 58.26 | 5.77 | 3.08 | |
| | | Found | 58.16 | 5.79 | 3.18 | |
| 5c | -0.07,0.00 (2s,9H,$Si(CH_3)_3$), 3.60,3.80 3.87 (3s,6H,$OCH_3$), 4.25,4.67 (d,d,J=8Hz, J=9Hz,1H,NCH), 5.31,5.61 (d,d,J=9Hz,J=8Hz, 1H,OCH), 6.76-7.62 (m,9$H_{arom}$) | Calc. | 56.27 | 5.58 | 2.98 | |
| | | Found | 56.37 | 5.50 | 3.07 | |
| 5d | -0.06,0.00 (2s,9H,$Si(CH_3)_3$), 3.60,3.76 3.85,3.87,3.92 (5s,9H,$OCH_3$), 4.18,4.76 (d,d,J=8Hz,J=9Hz,1H,NCH), 5.26,5.60 (d, d,J=9Hz,J=8Hz,1H,OCH), 6.80-7.00 (m,3$H_{arom}$), 7.12-7.61 (m,5$H_{arom}$) | Calc. | 55.30 | 5.65 | 2.80 | |
| | | Found | 55.08 | 5.63 | 2.84 | |
| 5e | 0.00,0.01 (2s,9H,$Si(CH_3)_3$), 3.66,3.77 3.85,3.91,3.93 (5s,12H,$OCH_3$), 4.10,4.77 (d,d,J=8Hz,J=9Hz,1H,NCH), 5.27,5.63 (d, d,J=9Hz,J=8Hz,1H,OCH), 5.56,6.65 (2s, 2$H_{arom}$), 7.13-7.63 (m,5$H_{arom}$) | Calc. | 54.43 | 5.71 | 2.64 | |
| | | Found | 54.57 | 5.63 | 2.82 | |
| 5f | 0.00,0.02 (2s,9H,$Si(CH_3)_3$), 3.55,3.88 (2s,3H,$OCH_3$), 4.63,4.77 (d,d,J=9Hz, J=10Hz,1H,NCH), 5.48,5.72 (d,d,J=10Hz, J=9Hz,1H,OCH), 6.35 (s,2$H_{furane}$), 7.26-7.70 (m,6$H_{arom+furane}$) | | a) | | | |
| 5g | 0.00,0.06 (2s,9H,$Si(CH_3)_3$), 3.65,3.85 (2s,3H,$OCH_3$), 4.22,4.63 (d,d,J=8Hz,J=8Hz,NCH), 5.75,5.97 (d,d,J=8Hz,J=8Hz, OCH), 6.83-7.65 (m,8$H_{arom+thiophene}$) | Calc. | 51.22 | 4.97 | 3.14 | 7.19 |
| | | Found | 50.98 | 4.89 | 3.28 | 7.33 |

a) 5f could not be purified because of its instability.

Table 2a. Methyl 2-(phenyltrifluoroacetylamino)-2-alkenoates 6 prepared

| Product No. | Yield [%] | E:Z-Distribution[a)] | m.p. [°C] | Molecular Formula |
|---|---|---|---|---|
| 6a | 71 | 53:47 | 81- 82 | $C_{18}H_{14}F_3NO_4$ (349.3) |
| 6b | 71 | 61:39 | 109-110 | $C_{19}H_{16}F_3NO_3$ (363.3) |
| 6c | 75 | 69:31 | 89- 90 | $C_{19}H_{16}F_3NO_4$ (379.3) |
| 6d | 78 | 61:39 | 83- 84 | $C_{20}H_{18}F_3NO_6$ (409.4) |
| 6e | 73 | 55:45 | 90- 91 | $C_{21}H_{20}F_3NO_6$ (439.4) |
| 6f | 60 | 61:39 | 105-107 | $C_{16}H_{12}F_3NO_4$ (339.3) |
| 6g | 70 | 61:39 | 90- 91 | $C_{16}H_{12}F_3NO_3S$ (355.3) |

Table 2b. Spectroscopic and Analytical Data of Compound 6

| Product No. | $^1$H-NMR-Spectra ($CDCl_3$, δ ppm) | | C | H | N | S |
|---|---|---|---|---|---|---|
| 6a | 3.80,3.88 (s,s,3H,$OCH_3$), 7.05-7.65 (m, $10H_{arom}$), 7.83,7.98 (s,s,$1H_{vinyl}$) | Calc. | 61.89 | 4.04 | 4.01 | |
| | | Found | 62.02 | 4.23 | 3.91 | |
| 6b | 2.36,2.39 (s,s,3H,$CH_3$), 3.78,3.86 (s,s, 3H,$OCH_3$), 7.14-7.56 (m,$9H_{arom}$), 7.79, 7.96 (s,s,$1H_{vinyl}$) | Calc. | 62.81 | 4.43 | 3.85 | |
| | | Found | 62.77 | 4.45 | 3.83 | |
| 6c | 3.77,3.82,3.85 (s,s,s,6H,$OCH_3$), 6.90,6.92 6.96 (s,s,s,$2H_{arom}$), 7.20-7.48 (m,$5H_{arom}$), 7.60,7.63 (s,s,$2H_{arom}$), 7.75,7.94 (s,s, $1H_{vinyl}$) | Calc. | 60.16 | 4.25 | 3.69 | |
| | | Found | 60.03 | 4.31 | 3.70 | |
| 6d | 3.72,3.78,3.84,3.87,3.91,3.94 (6s,9H, $OCH_3$), 6.67-7.45 (m,$8H_{arom}$), 7.77,7.94 (s,s,$1H_{vinyl}$) | Calc. | 58.68 | 4.43 | 3.42 | |
| | | Found | 58.94 | 4.49 | 3.41 | |
| 6e | 3.75,3.79,3.82,3.86,3.90,3.92 (6s,12H, $OCH_3$), 6.74,6.90 (s,s,$2H_{arom}$), 7.19-7.45 (m,$5H_{arom}$), 7.76,7.91 (s,s,$1H_{vinyl}$) | Calc. | 57.40 | 4.58 | 3.18 | |
| | | Found | 57.58 | 4.65 | 3.17 | |
| 6f | 3.78 (s,3H,$OCH_3$), 6.54-6.57 (m,$1H_{arom}$), 6.84,6.89 (d,d,J=3.4Hz,$1H_{furane}$), 7.24-7.46 (m,$5H_{arom}$), 7.58-7.60 (m,$1H_{furane}$), 7.58,7.77 (s,s,$1H_{vinyl}$) | Calc. | 56.64 | 3.56 | 4.12 | |
| | | Found | 56.47 | 3.69 | 4.00 | |
| 6g | 3.78 (s,3H,$OCH_3$), 7.10-7.59 (m, $8H_{arom+thiophene}$), 8.00,8.22 (s,s, $1H_{vinyl}$) | Calc. | 54.08 | 3.40 | 3.94 | 9.02 |
| | | Found | 53.88 | 3.45 | 3.99 | 9.16 |

a) Determined by $^1$H-NMR-spectroscopy

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