A convenient synthesis of 3,3,3-trifluoroalanine derivatives*

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A one-pot synthesis of *N*-substituted 3,3,3-trifluoroalanine esters from alkyl trifluoropyruvates and carboxamides or substituted ureas was developed.

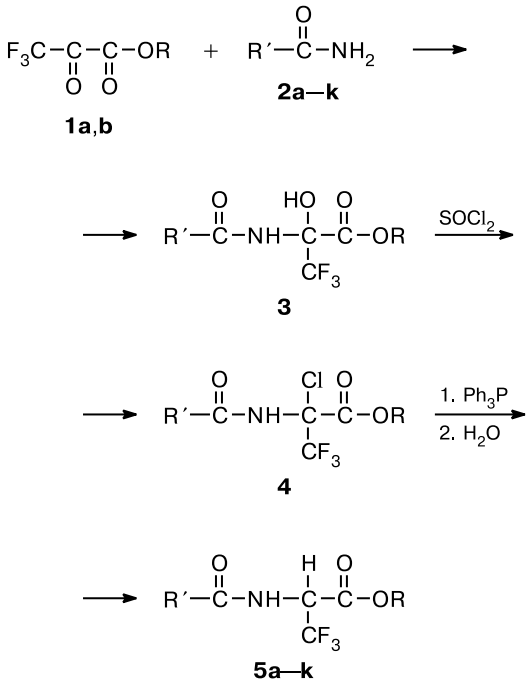
Key words: *N*-acyl-3,3,3-trifluoroalanine esters, reduction.

Fluorine-containing amino acids and their derivatives known to date have been obtained by syntheses: no such amino acids occur in nature. Biological activity of these compounds was studied. It was shown that 3,3,3-trifluoroalanine examined to the greatest extent possesses bactericidal activity owing to the inhibition of alanine racemase and γ-cystathionase of bacterial cells.[1] The known methods for the synthesis of 3,3,3-trifluoroalanine and its derivatives are based on the reduction of hexafluoroacetone or trifluoropyruvate *N*-acylimines by tin dichloride, sodium borohydride, cyclohexadiene, or trimethyl phosphite[2—5]; in several cases, the syntheses involve labor-consuming intermediate stages. It is also of note that the starting *N*-acylamines are not easily accessible compounds.

We developed a convenient one-pot method for the synthesis of 3,3,3-trifluoroalanine derivatives, namely, various *N*-substituted trifluoroalanine esters from alkyl trifluoropyruvates **1** and urethane, carboxamides, and *N*-substituted ureas **2a—k**. The procedure does not require sophisticated equipment and consists in successive one-pot treatment of amides **2** with equimolar amounts of ethyl or methyl trifluoropyruvate **1a**,**b**, $SOCl_2$, Ph_3P, and H_2O. In the case of urethane (**2a**), we isolated and identified intermediate products of these reactions, *viz.*, adduct **3** (R = R′ = Et) and the corresponding chlorinated derivative **4** (Scheme 1).

N-Substituted 3,3,3-trifluoroalanine esters **5a**—**k** are solid substances, whose compositions and structures were established by elemental analysis, ^1H and ^{19}F NMR spectroscopy, and chemical transformations. Heating of ester **5a** with PCl_5 affords isocyanate **6** in 60% yield. The latter reacts with aniline to yield urea **5k** (Scheme 2). It is noteworthy that isocyanate **6** has previously been obtained by the Leuckart reaction from ester **1a** and formamide in a rather low yield (36%).[6]

Scheme 1

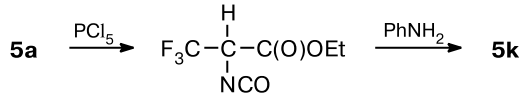


R = Et (**1a**, **3**—**5a**,**e**—**k**), Me (**1b**, **5b**—**d**); R′ = OEt (**3**, **4**)

2, **5**	**a**	**b**	**c**	**d**	**e**	**f**
R′	OEt	3-MeC_6H_4	4-$MeOC_6H_4$	4-FC_6H_4	Me	Et

2, **5**	**g**	**h**	**i**	**j**	**k**
R′	CH_2Cl	Ph	MeNH	AcNH	PhNH

Scheme 2



* Dedicated to the memory of A. F. Kolomiets.

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Thus, the method proposed provides wide possibilities for syntheses of various *N*-substituted 3,3,3-trifluoroalanine derivatives.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DPX-200 spectrometer. Melting points were determined in a glass capillary.

Ethyl 2-ethoxycarbonylamino-3,3,3-trifluoro-2-hydroxypropionate (3). Urethane (**2a**) (8.9 g, 0.1 mmol) was mixed with ester **1a** (17.0 g, 0.1 mol). After the end of the exothermic reaction, the resulting mixture was recrystallized from hexane to give adduct **3** (23.5 g, 91%), m.p. 41—43 °C. Found (%): C, 37.15; H, 4.77; N, 5.25. $C_8H_{12}F_3NO_5$. Calculated (%): C, 37.07; H, 4.67; N, 5.40. ^1H NMR ($CDCl_3$), δ: 1.20 (t, 3 H, $\underline{Me}CH_2OCN$, J = 7 Hz); 1.26 (t, 3 H, $\underline{Me}CH_2OCC$, J = 7 Hz); 4.10 (q, 2 H, CH_2OCN, J = 7 Hz); 4.30 (q, 2 H, CH_2OCC, J = 7 Hz); 5.60 (br.s, 1 H, OH); 6.20 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 2.99 (s).

Ethyl 2-chloro-2-ethoxycarbonylamino-3,3,3-trifluoropropionate (4). Compound **3** (25.9 g, 0.1 mol) was mixed with $SOCl_2$ (11.9 g, 0.1 mol). The reaction mixture was heated at 60 °C until a constant weight was established (~2 h) and fractionated to obtain compound **4** (33.2 g, 84%), b.p. 110—112 °C (3 Torr). Found (%): C, 34.55; H, 4.09; N, 5.11. $C_8H_{11}ClF_3NO_4$. Calculated (%): C, 34.61; H, 3.99; N, 5.05. ^1H NMR ($CDCl_3$), δ: 1.20 (t, 3 H, $\underline{Me}CH_2OCN$, J = 7 Hz); 1.26 (t, 3 H, $\underline{Me}CH_2OCC$, J = 7 Hz); 4.10 (q, 2 H, CH_2OCN, J = 7 Hz); 4.30 (q, 2 H, CH_2OCC, J = 7 Hz); 6.38 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 1.43 (s).

Ethyl 2-ethoxycarbonylamino-3,3,3-trifluoropropionate (5a).
A. Triphenylphosphine (13.1 g, 0.05 mol) was added with stirring to a solution of compound **4** (13.9 g, 0.05 mol) in diethyl ether (100 mL). After 10 min, H_2O (50 mL) was added. The mixture was stirred for 20 min, the ethereal layer was separated and dried with $MgSO_4$. The solvent was evaporated, and the residue was fractionated to obtain compound **5a** (9.8 g, 81%), b.p. 88 °C (3 Torr).

B. Urethane (**2a**) (8.9 g, 0.1 mol) was mixed with ester **1a** (17.0 g, 0.1 mol). After the exothermic reaction completed, $SOCl_2$ (11.9 g, 0.1 mol) was added, and the reaction mixture was heated at 60 °C until a constant weight was established (~2 h). Then diethyl ether (200 mL) and Ph_3P (26.2 g, 0.1 mol) were added, and after 10 min H_2O (100 mL) was added. The mixture was stirred for 20 min, the ethereal layer was separated and dried with $MgSO_4$. The solvent was evaporated, and the residue was fractionated to obtain compound **5a** (16.4 g, 68%), b.p. 88 °C (3 Torr).

Table 1. Yields, melting points, and elemental analysis data for compounds **5a—k**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula
5a	68	48—50	39.79 39.53	5.08 4.98	5.63 5.76	$C_8H_{12}F_3NO_4$
5b	57	88—89	52.25 52.37	4.67 4.39	5.23 5.09	$C_{12}H_{12}F_3NO_3$
5c	69	100—102	49.40 49.49	4.33 4.15	4.83 4.81	$C_{12}H_{12}F_3NO_4$
5d	73	107—109	47.14 47.32	3.34 3.25	5.05 5.02	$C_{11}H_9F_4NO_3$
5e	70	80—81	39.60 39.44	4.53 4.73	6.62 6.57	$C_7H_{10}F_3NO_3$
5f	82	93—94	42.58 42.30	5.22 5.32	6.03 6.17	$C_8H_{12}F_3NO_3$
5g	64	76—78	33.89 33.96	3.90 3.66	5.59 5.66	$C_7H_9ClF_3NO_3$
5h	78	109—110	52.59 52.37	4.52 4.39	5.36 5.09	$C_{12}H_{12}F_3NO_3$
5i	71	130—131	36.59 36.85	4.52 4.86	12.12 12.28	$C_7H_{11}F_3N_2O_3$
5j	85	79—80	37.39 37.51	4.47 4.33	10.84 10.94	$C_8H_{11}F_3N_2O_4$
5k	79	140—142	49.44 49.66	4.34 4.51	9.54 9.65	$C_8H_{11}F_3N_2O_4$

Methyl 2-(3-toluylamino)- (5b), methyl 2-(4-anisoylamino)- (5c), methyl 2-(4-fluorobenzoylamino)- (5d), ethyl 2-acetamido- (5e), ethyl 2-propionamido- (5f), ethyl 2-chloroacetamido- (5g), ethyl 2-benzamido- (5h), ethyl 2-(3-methylureido)- (5i), ethyl 2-(3-acetylureido)- (5j), and ethyl 2-(3-phenylureido)-3,3,3-trifluoropropionate (5k) were synthesized similarly (procedure ***B***). The yields, melting points, and spectroscopic characteristics for compounds **5a—k** are presented in Tables 1 and 2.

Ethyl 2-isocyanato-3,3,3-trifluoropropionate (6). Propionate **5a** (24.3 g, 0.1 mol) was mixed with PCl_5 (21.0 g, 0.1 mol). The reaction mixture was heated to 100 °C and stored for 30 min at this temperature, and $POCl_3$ was distilled off. The residue was

Table 2. ^1H and ^{19}F spectra of compounds **5a—k***

Compound	NMR, δ (J/Hz) ^1H	^{19}F (d, 3 F)
5a	1.30 (t, 3 H, $\underline{Me}CH_2OCN$); 4.32 (q, 2 H, CH_2OCC); 5.36 (dq, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 9); 6.76 (d, 1 H, NH, $J_{H,H}$ = 8); 6.95—7.60 (m, 5 H, Ph)	5.39 ($J_{H,F}$ = 9)
5b	2.40 (s, 3 H, MeAr); 3.80 (s, 3 H, MeO); 5.52 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 7.30, 7.80 (both m, 2 H each, H arom.); 9.20 (d, 1 H, NH, $J_{H,H}$ = 8)	7.18 ($J_{H,F}$ = 8.0)
5c	3.80, 3.86 (both s, 3 H each, MeO); 5.50 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 6.90, 7.90 (both d, 2 H each, H arom.); 9.05 (d, 1 H, NH, $J_{H,H}$ = 8)	7.20 ($J_{H,F}$ = 8.8)

(*to be continued*)

Table 2 (*continued*)

Compound	NMR, δ (*J*/Hz)	
	^{1}H	^{19}F (d, 3 F)
5d	3.85 (s, 3 H, MeO); 5.50 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 7.05—7.25, 7.95—8.10 (both m, 2 H each, H arom.); 9.30 (d, 1 H, NH, $J_{H,H}$ = 8)	7.20 ($J_{H,F}$ = 8.2); −30.03**
5e	1.30 (t, 3 H, MeCH$_2$); 1.97 (s, 3 H, MeC(O)); 3.86 (q, 2 H, CH$_2$O); 5.52 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 8.95 (d, 1 H, NH, $J_{H,H}$ = 8)	7.14 ($J_{H,F}$ = 8.4)
5f	1.08 (t, 3 H, MeCH$_2$C); 1.30 (t, 3 H, MeCH$_2$O); 2.23 (q, 2 H, CH$_2$C(O)); 4.25 (q, 2 H, CH$_2$O); 5.25 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 8.87 (d, 1 H, NH, $J_{H,H}$ = 8)	7.10 ($J_{H,F}$ = 8.2)
5g	1.30 (t, 3 H, MeCH$_2$O, J = 7); 4.13 (s, 2 H, CH$_2$Cl); 4.25 (q, 2 H, CH$_2$O, J = 7); 5.28 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 9.25 (d, 1 H, NH, $J_{H,H}$ = 8)	7.16 ($J_{H,F}$ = 8.2)
5h	1.30 (t, 3 H, MeCH$_2$O, J = 7); 4.30 (q, 2 H, CH$_2$O, J = 7); 5.52 (dq, 1 H, CH, $J_{H,H}$ = 7, $J_{H,F}$ = 8); 7.40—7.60 (m, 3 H, H arom.); 7.95 (m, 2 H, H arom.); 9.35 (d, 1 H, NH, $J_{H,H}$ = 7)	7.08 ($J_{H,F}$ = 8.1)
5i	1.30 (t, 3 H, MeCH$_2$O, J = 7); 2.62 (s, 3 H, MeN); 4.25 (q, 2 H, CH$_2$O, J = 7); 4.25 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 6.03 (s, 1 H, NH); 6.90 (d, 1 H, NHCH, $J_{H,H}$ = 8)	7.18 ($J_{H,F}$ = 8.0)
5j	1.30 (t, 3 H, MeCH$_2$O, J = 7); 2.09 (s, 2 H, MeC(O)); 4.30 (q, 2 H, CH$_2$O, J = 7); 5.23 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 9.21 (d, 1 H, NH, $J_{H,H}$ = 8); 10.72 (s, 1 H, NH)	7.24 ($J_{H,F}$ = 8.3)
5k	1.35 (t, 3 H, Me, J = 7); 4.30 (q, 2 H, CH$_2$O, J = 7); 5.30 (quint, 1 H, CH, $J_{H,H}$ = 8, $J_{H,F}$ = 8); 6.30 (d, 1 H, NH, $J_{H,H}$ = 8); 7.08 (t, 1 H, *p*-H arom., J = 6); 7.34 (t, 2 H, *m*-H arom., J = 6); 7.56 (d, 2 H, *o*-H arom., J = 6); 7.70 (s, 1 H, NH)	5.46 ($J_{H,F}$ = 8.2)

* The ^{1}H and ^{19}F NMR spectra of compounds **5b—j** were recorded in DMSO-d$_6$, and those for **5a**,**k** were recorded in acetone-d$_6$.
** (m, 1 F).

fractionated to yield isocyanate **6** (11.2 g, 57%), b.p. 148—150 °C (*cf.* Ref. 6: 56 °C (20 Torr)). ^{1}H NMR (acetone-d$_6$), δ: 1.26 (t, 3 H, MeCH$_2$OCC, J = 7 Hz); 4.30 (q, 2 H, CH$_2$OCC, J = 7 Hz); 5.10 (dq, 1 H, CH, $J_{H,H}$ = 8 Hz, $J_{H,F}$ = 9 Hz). ^{19}F NMR (acetone-d$_6$), δ: 2.45 (d, $J_{H,F}$ = 9 Hz).

Ethyl 2-(3-phenylureido)-3,3,3-trifluoropropionate (5k) (independent synthesis). Isocyanate **6** (1.97 g, 0.01 mol) was added to a solution of aniline (0.93 g, 0.01 mol) in hexane (20 mL). The reaction mixture was stirred for 30 min, and the precipitate that formed was filtered off to obtain compound **5k** (2.6 g, 89.6%), m.p. 141—143 °C.

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