A Facile and Convenient Synthetic Method for *N*-β-Trifluoroacetylvinyl Amino Acid Esters, α-Aminoacetophenones and Aminoacetonitriles as Potentially Useful Precursors of Fluorine-Containing Pyrroles

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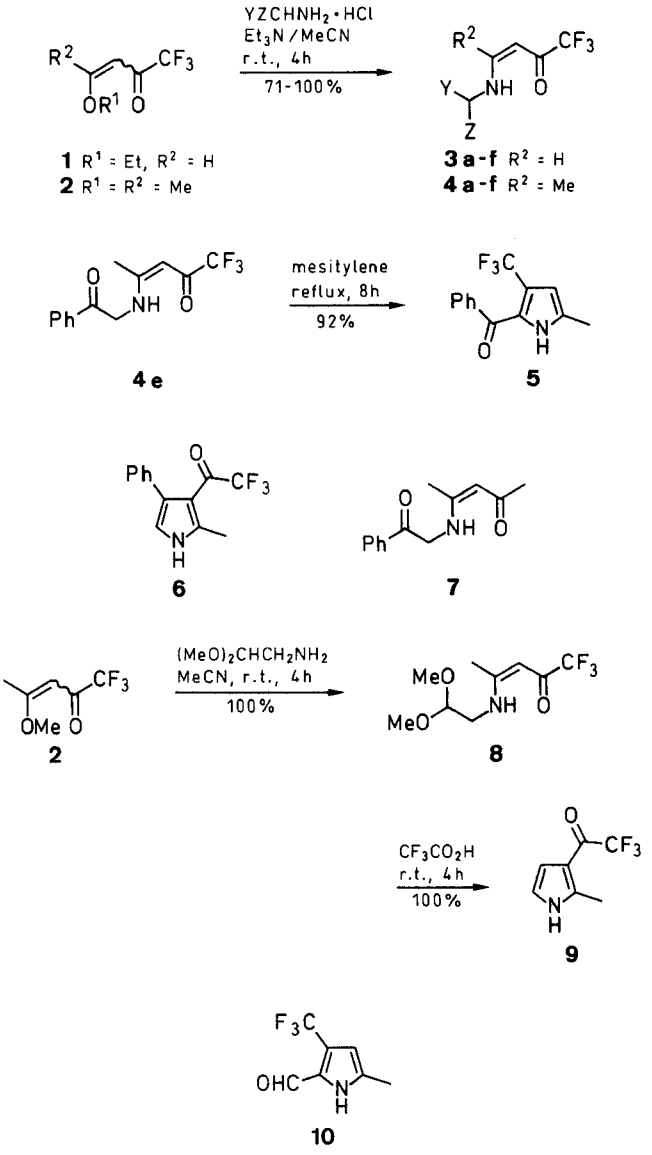
N-(4,4,4-Trifluoro-3-oxo-1-butenyl) amino acid esters, α-aminoacetophenones and aminoacetonitriles **3** and **4** are easily obtained in excellent yields by O–N exchange reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1** and **2** with some amino acid esters, α-aminoacetophenone and aminoacetonitrile. Cyclodehydration of some resultant products into fluorine-containing pyrroles is also described.

In the course of our extensive investigations on the nucleophilic substitutions at olefinic carbon atoms,[1-4] it was found that 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1** and **2** readily undergo O–N exchange reactions with various amines to give the corresponding (4,4,4-trifluoro-3-oxo-1-butenyl)amines in high yield.[2] As an extension of this work we have studied the synthesis of the title compounds **3** and **4** by nucleophilic substitution of **1** and **2** with various amino acid esters, α-aminoacetophenone and aminoacetonitrile. In recent years much attention has been paid to the development of new methods for the synthesis of fluorine-containing heterocycles because of their importance in medicinal and agricultural scientific fields.[5-7] Utility of pyrrole synthesis for nonfluorinated *N*-β-acylvinyl amino acids, α-aminoacetophenones and aminoacetonitriles is now recognized and several synthetic methods have been described in the literature.[8-12] Possibly, these new compounds **3** and **4** can serve as useful precursors of pyrroles and 4,5-dihydropyrroles bearing a trifluoromethyl group, which may be expected to show interesting biological activities.

Nucleophilic O–N exchange reaction of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**), which can be easily prepared[13] by trifluoroacetylation of ethyl vinyl ether, with hydrochlorides of amino acid esters occurred readily at room temperature. In the presence of triethylamine in acetonitrile for 4 hours, the reaction afforded *N*-(4,4,4-trifluoro-3-oxo-1-butenyl) amino acid esters **3a–d** in 71–95% yield. Very recently, Gerus and co-workers reported about the use of the β-trifluoroacetylvinyl group as a *N*-protective group of amino acids,[14] as an application of our O–N exchange reaction.[2] The hydrochlorides of α-aminoacetophenone and aminoacetonitrile also reacted cleanly to yield the corresponding *N*-(4,4,4-trifluoro-3-oxo-1-butenyl) compounds **3e** and **3f** in 100% and 88% yield, respectively. This type of substitution was successfully extended to 1,1,1-trifluoro-4-methoxy-3-penten-2-one (**2**), synthesized from 2,2-dimethoxypropane and trifluoroacetic anhydride,[15] to give the expected O–N exchanged products **4a–f** in 72–100% yield.

The stereochemistry of products **3** and **4** was confirmed by ^{1}H NMR spectra. The small magnitude of the coupling constant (7 Hz) for the olefinic protons and/or the much deshielded peak (δ = 9.40–12.13) of amino protons by hydrogen bonding between NH and C=O show the cis and *Z* configurations.



3,4	Y	Z	3,4	Y	Z
a	CO_2Et	H	d	CO_2Et	Ph
b	CO_2Et	Me	e	COPh	H
c	CO_2Me	CH_2CH_2SMe	f	CN	H

The compound **4e** derived from α-aminoacetophenone could be converted into pyrrole **5** in 92% yield by heating at reflux temperature for 8 hours in mesitylene. The ^{13}C NMR spectrum obtained for **5** showed two diagnostic signals, which enabled discrimination between 2-acylpyr-

Table. Compounds **3–5**, **8**, **9** Prepared

Product	Yield[a] (%)	mp (°C) (solvent) or bp (°C)/mbar[b]	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS)[e] δ, J (Hz)
3a	71	105–106 (hexane/$CHCl_3$)	$C_8H_{10}F_3NO_3$ (225.2)	3210, 1748, 1662, 1608	1.28 (t, 3H, J = 7, CH_3), 3.97–4.37 (m, 4H, CH_2CH_3, NCH_2), 5.36 (d, 1H, J = 7, =CHCO), 6.96 (dd, 1H, J = 7, 14, NCH=), 9.40–10.44 (br, 1H, NH)
3b	88	120/5	$C_9H_{12}F_3NO_3$ (239.2)	3255, 1746, 1650, 1590[f]	1.28 (t, 3H, J = 7, CH_2CH_3), 1.55 (d, 3H, J = 7, $CHCH_3$), 3.76–4.41 (m, 3H, CH_2CH_3, CHN), 5.42 (d, 1H, J = 7, =CHCO), 7.20 (dd, 1H, J = 7, 14, NCH=), 9.81–10.80 (br, 1H, NH)
3c	94	155/4	$C_{10}H_{14}F_3NO_3S$ (285.3)	3279, 1771, 1672, 1609[f]	2.06–2.27 (m, 5H, SCH_3, SCH_2CH_2), 2.43–2.67 (m, 2H, SCH_2CH_2), 3.72 (s, 3H, OCH_3), 4.04–4.40 (m, 1H, CHN), 5.34 (d, 1H, J = 7, =CHCO), 7.05 (dd, 1H, J = 7, 13, NCH=), 9.70–10.39 (br, 1H, NH)
3d	95	140/6	$C_{14}H_{14}F_3NO_3$ (301.3)	3300, 1771, 1680, 1611[f]	1.18 (t, 3H, J = 7, CH_3), 4.16 (q, 2H, J = 7, CH_2), 5.09 (d, 1H, J = 6, CHN), 5.36 (d, 1H, J = 7, =CHCO), 7.00 (dd, 1H, J = 7, 13, NCH=), 7.27 (s, $5H_{arom}$), 10.47–11.20 (br, 1H, NH)
3e	100	138–139 (hexane/benzene)	$C_{12}H_{10}F_3NO_2$ (257.2)	3300, 1708, 1671, 1609	4.88 (d, 2H, J = 6, CH_2), 5.41 (d, 1H, J = 7, =CHCO), 7.05–8.12 (m, 6H, $5H_{arom}$, NCH=), 9.95–10.72 (br, 1H, NH)[g]
3f	88	84–85 (hexane/benzene)	$C_6H_5F_3N_2O$ (178.1)	3263, 2270, 1663, 1618	4.22 (d, 2H, J = 6, CH_2), 5.49 (d, 1H, J = 7, =CHCO), 7.02 (dd, 1H, J = 7, 13, NCH=), 9.66–10.69 (br, 1H, NH)
4a	72	126–127 (hexane/$CHCl_3$)	$C_9H_{12}F_3NO_3$ (239.2)	3180, 1740, 1617, 1589	1.30 (t, 3H, J = 7, CH_2CH_3), 2.05 (s, 3H, CH_3), 3.77–4.46 (m, 4H, $NCH_2CO_2CH_2CH_3$), 5.35 (s, 1H, =CH), 10.63–11.63 (br, 1H, NH)
4b	98	130/4	$C_{10}H_{14}F_3NO_3$ (253.2)	3210, 1744, 1620, 1588[f]	1.27 (t, 3H, J = 7, CH_2CH_3), 1.51 (d, 3H, J = 7, $CHCH_3$), 2.05 (s, 3H, CH_3C=), 3.96–4.53 (m, 3H, $CHCH_3$, CH_2CH_3), 5.20 (s, 1H, =CH), 10.90–11.44 (br, 1H, NH)[h]
4c	93	160/6	$C_{11}H_{16}F_3NO_3S$ (299.3)	3210, 1750, 1622, 1591[f]	2.06–2.37 (m, 8H, SCH_3, CH_3C=, SCH_2CH_2), 2.43–2.70 (m, 2H, SCH_2CH_2), 3.72 (s, 3H, OCH_3), 4.31–4.67 (m, 1H, CHN), 5.30 (s, 1H, =CH), 10.90–11.47 (br, 1H, NH)
4d	99	200/4	$C_{15}H_{16}F_3NO_3$ (315.3)	3170, 1766, 1643, 1594[f]	1.20 (t, 3H, J = 7, CH_2CH_3), 1.95 (s, 3H, CH_3C=), 4.19 (q, 2H, J = 7, CH_2CH_3), 5.27 (d, 1H, J = 7, CHN), 5.38 (s, 1H, =CH), 7.35 (s, $5H_{arom}$), 11.62–12.13 (br, 1H, NH)
4e	100	165–166 (hexane/$CHCl_3$)	$C_{13}H_{12}F_3NO_2$ (271.2)	3225, 1704, 1629, 1601	2.09 (s, 3H, CH_3), 4.78 (d, 2H, J = 5, CH_2), 5.37 (s, 1H, =CH), 7.28–8.07 (m, $5H_{arom}$), 11.22–11.81 (br, 1H, NH)
4f	89	88–89 (hexane/benzene)	$C_7H_7F_3N_2O$ (192.1)	3195, 2250, 1620, 1595	2.21 (s, 3H, CH_3), 4.23 (d, 2H, J = 7, CH_2), 5.45 (s, 1H, =CH), 10.50–11.41 (br, 1H, NH)
5	92	101–102 (pentane)	$C_{13}H_{10}F_3NO$ (253.2)	3306, 1617	2.25 (s, 3H, CH_3), 6.19 (d, 1H, J = 2, H-4), 7.13–7.65 (m, $5H_{arom}$), 9.89–10.62 (br, 1H, NH)
8	100	55/5	$C_9H_{14}F_3NO_3$ (241.2)	3210, 1622, 1590[f]	2.07 (s, 3H, CH_3C=), 3.38–3.52 (m, 8H, OCH_3, NCH_2), 4.42 (t, 1H, J = 5, NCH_2CH), 5.25 (s, 1H, =CH), 10.73–11.38 (br, 1H, NH)
9	100	108–109 (hexane/$CHCl_3$)	$C_7H_6F_3NO$ (177.1)	3330, 1650	2.58 (s, 3H, CH_3), 6.56–6.64 (m, 2H, H-4, -5), 8.35–10.28 (br, 1H, NH)

[a] Yield of isolated products.
[b] Oven temperature of Kugelrohr distillation.
[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.14, N ±0.27, F ±0.30; exception: **3a**, F +0.48: **4e**, C −0.41: **8**, C −0.43; **3c, d, 4a–d**, F not analyzed.
[d] Recorded on a Hitachi Model EPI-G3 grating spectrophotometer.
[e] Measured using a JEOL PMX-60SI spectrometer.
[f] Measured as film.
[g] In $CD_3CN/CDCl_3$.
[h] In CCl_4.

role **5** and its possible 3-acyl isomer **6**. The carbonyl carbon of the benzoyl group was observed at δ = 186.7 (s) and the pyrrole-ring carbon (C-3) bearing the trifluoromethyl group appeared at δ = 120.5 (q, J_{CF} = 36.6 Hz). It seems of much interest to note that the present cyclization proceeds regiospecifically to give exclusively 2-acylpyrrole **5** without any formation of the regioisomer **6**, in striking contrast to the reported case of nonfluorinated compound **7** (at reflux temperature for 4 hours in mesitylene), which gave a mixture of **5** (CH_3 in place of CF_3) and **6** (CH_3 in place of CF_3) (ratio, 44:56).[10] According to this two-step process, a combination of O–N exchange and cyclodehydration, 2-methyl-3-trifluoroacetylpyrrole (**9**) was also synthesized regioselectively and quantitatively without any formation of its 2-formyl isomer **10** via intermediate **8** from β-acylvinyl ether **2** and aminoacetaldehyde dimethyl acetal.

In summary, the present method provides a facile and convenient access to *N*-(4,4,4-trifluoro-3-oxo-1-butenyl) amino acid esters, α-aminoacetophenones and aminoacetonitriles **3** and **4**, which are potentially useful precursors of fluorine-containing pyrroles and 4,5-dihydropyrroles.

***N*-(4,4,4-Trifluoro-3-oxo-1-butenyl) Amino Acid Esters, α-Aminoacetophenones and Aminoacetonitriles 3 and 4; General Procedure:**
To a suspension of **1**[13] or **2**[15] (10 mmol) and hydrochlorides of amino acid ester, α-aminoacetophenone or aminoacetonitrile (10 mmol) in MeCN (40 mL) was added Et_3N (10 mmol), and the

mixture was stirred at r.t. for 4 h. Most of the solvent was evaporated and CH_2Cl_2 (200 mL) was then added. The whole mixture was washed with 1 N HCl (200 mL) and H_2O (200 mL), and the organic layer was separated and dried (Na_2SO_4). After removal of the solvent pure product **3** or **4** was obtained (Table).

2-Benzoyl-5-methyl-3-trifluoromethylpyrrole (5):
A solution of **4e** (2.712 g, 10 mmol) in mesitylene (40 mL) was refluxed for 8 h with stirring. The solvent was removed in vacuo to afford **5**; yield: 2.329 g (92%).

^{13}C NMR ($CDCl_3$/TMS): δ = 12.6 (q), 109.8 (q, J_{CF} = 4.9 Hz), 120.5 (q, J_{CF} = 36.6 Hz), 123.0 (q, J_{CF} = 267.3 Hz), 127.2 (s), 128.2 (d), 128.9 (d), 132.4 (d), 134.7 (s), 138.8 (s), 186.7 (s).

4-(2,2-Dimethoxyethylamino)-1,1,1-trifluoro-3-penten-2-one (8):
To a solution of **2** (1.681 g, 10 mmol) in MeCN (40 mL) was added aminoacetaldehyde dimethyl acetal (1104 mg, 10.5 mmol). The mixture was stirred at r.t. for 4 h and the solvent was removed in vacuo to give practically pure product **8**; yield: 2.410 g (100%).

2-Methyl-3-trifluoroacetylpyrrole (9):
A solution of **8** (965 mg, 4 mmol) in CF_3CO_2H (4 mL) was stirred at r.t. for 4 h and evaporated in vacuo to afford **9**; yield: 705 mg (100%).

^{13}C NMR ($CDCl_3$/TMS): δ = 176.6 (q, J_{CF} = 34.3 Hz),142.2 (s), 117.7 (d), 117.4 (q, J_{CF} = 290.5 Hz), 113.6 (s), 111.0 (d), 14.2 (q).

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