3,3,3-Trifluoro-2-isocyanopropionates, new versatile building blocks for the introduction of trifluoromethyl groups into organic molecules [1]*

Klaus Burger**, Christian Schierlinger and Kerstin Mütze
Organisch-Chemisches Institut der Technischen Universität München, Lichtenbergstrasse 4, D-85747 Garching (Germany)

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Abstract

α-Trifluoromethyl-substituted α-amino acid esters **1** give *N*-formyl α-trifluoromethyl α-amino acid esters **2** on reaction with formic acid/acetic anhydride. 3,3,3-Trifluoro-2-isocyanopropionates **3** are obtained from **2** upon treatment with diphosgene/triethylamine.

Introduction

Trifluoromethylated compounds have become increasingly important for a large number of industrial applications such as pharmaceuticals, agrochemicals, dyes, polymers, etc. [2]. Hence the selective introduction of trifluoromethyl groups into organic molecules is of continuing interest. Two fundamentally different strategies have been developed by which trifluoromethyl groups can be introduced: (1) direct substitution in a late stage of the synthetic sequence [3, 4]; (2) use of trifluoromethyl-substituted building blocks derived from readily available starting materials [5, 6].

Although several trifluoromethylation reagents are available [3, 4], control of selectivity is often difficult to achieve. Consequently, the building block concept still attracts a lot of attention and sometimes offers elegant solutions for synthetic problems. In this context, the development of new trifluoromethyl-containing building blocks is of synthetic interest. The versatility of a trifluoromethyl-containing building block can be increased significantly by the type and the number of additional functional groups present.

In this paper we report on the synthesis of 3,3,3-trifluoro-2-isocyanopropionates. This new versatile type of trifluoromethyl-containing building block exhibits high synthetic potential because of the presence of both an isocyano and an ester group.

*In memoriam, Prof. Dr I.L. Knunyants.
**To whom all correspondence should be addressed.

Experimental

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AM 360 spectrometer at 360, 90 and 339 MHz or with a Bruker AC 250 spectrometer at 250, 62.5 and 235 MHz. As reference standard TMS was used for ^{1}H and ^{13}C NMR spectra (internal) and trifluoroacetic acid for ^{19}F NMR spectra (external). Infrared (IR) spectra were recorded using Perkin-Elmer 157 G or 257 spectrophotometers. Mass spectra were recorded with electron ionization (EI, 70 eV) on a Varian MAT CH5 instrument and with chemical ionization (CI) on a Varian MAT M 112S instrument. Melting points (not corrected) were determined using a Tottoli apparatus (Büchi SMP-20). Elemental microanalyses were carried out with a Heraeus CHN-Elemental Analyzer.

N-*Formyl-2-trifluoromethyl α-amino acid esters* **2**
General procedure

A solution of 2-trifluoromethyl α-amino acid ester **1** (5 mmol) [7], formic acid (20 ml) and acetic anhydride (5 ml) was stirred overnight at room temperature. The reaction mixture was evaporated to dryness *in vacuo* and the crude product **2** purified by chromatography on silica gel (eluent: hexane/AcOEt, 1:1).

Methyl *N*-formyl-2-trifluoromethyl-alaninate (**2a**): Colourless solid, m.p. 45–47 °C (0.83 g, 83%), 5:2 mixture of *s-cis/s-trans* conformers. Analysis: Calc. for $C_6H_8F_3NO_3$ (199.12): C, 36.19; H, 4.05; N, 7.03%. Found: C, 36.14; H, 4.01; N, 7.26%. IR (film) ν (cm^{-1}): 3400–3300; 1760; 1695–1680. MS (ET) *m/z*: 199 $(M)^+$; 171 $(M-CO)^+$; 140 $(M-CO_2CH_3)^+$; 112 $(140-CO)^+$.

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s-cis Conformer: ^{1}H NMR ($CDCl_3$) δ: 1.82 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 6.82 (s, 1H, NH); 8.17 (s, 1H, NCHO) ppm. ^{13}C NMR ($CDCl_3$) δ: 18.35 (q, CH_3, ^4J=1.7 Hz); 53.45 (OCH_3); 61.13 (q, CCF_3, ^2J=29.3 Hz); 124.14 (q, CF_3, ^1J=285.1 Hz); 161.24 (NCH=O); 167.27 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 1.47 (s, CF_3) ppm.

s-trans Conformer: ^{1}H NMR ($CDCl_3$) δ: 1.82 (s, 3H, CH_3); 3.92 (s, 3H, OCH_3); 6.82 (d, 1H, NH, ^3J=11.6 Hz); 8.31 (d, 1H, NCHO, ^3J=11.6 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 18.25 (CH_3); 54.43 (OCH_3); 62.15 (q, CCF_3, ^2J=29.7 Hz); 123.63 (q, CF_3, ^1J=285.4 Hz); 163.45 (NCH=O); 167.08 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 0.36 (s, CF_3) ppm.

Methyl *N*-formyl-2-trifluoromethyl-leucinate (**2b**): Colourless oil (1.14 g, 95%), 4:3 mixture of *s-cis/s-trans* conformers. Analysis: Calc. for $C_9H_{14}F_3NO_3$ (241.22): C, 44.81; H, 5.85; N, 5.81%. Found: C, 44.96; H, 5.93; N, 5.85%. IR (film) ν (cm^{-1}): 3400–3200; 1755; 1695. MS (EI) *m/z*: 241 $(M)^+$; 198 $(M-HNCO)^+$; 185 $(M-C_4H_8)^+$; 182 $(M-CO_2CH_3)^+$; 166 $(M-CH_3OH)^+$.

s-cis Conformer: ^{1}H NMR ($CDCl_3$) δ: 0.76 (d, 3H, CH_3, ^3J=6.7 Hz); 0.96 (d, 3H, CH_3, ^3J=6.7 Hz); 1.67–1.76 (m, 1H, CH); 2.00 (dd, 1H, CH_2, ^2J=14.2 Hz, ^3J=9.0 Hz); 2.93 (dd, 1H, CH_2, ^2J=14.2 Hz, ^3J=4.3 Hz); 3.89 (s, 3H, OCH_3); 6.97 (s, 1H, NH); 8.26 (s, 1H, NCHO) ppm. ^{13}C NMR ($CDCl_3$) δ: 21.62, 23.61, 24.08 (2×CH_3, CH); 36.45 (CH_2); 53.98 (OCH_3); 64.93 (q, CCF_3, ^2J=28.5 Hz); 123.99 (q, CF_3, ^1J=288.4 Hz); 159.97 (NCH=O); 168.29 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.4 (s, CF_3) ppm.

s-trans Conformer: ^{1}H NMR ($CDCl_3$) δ: 0.83 (d, 3H, CH_3, ^3J=6.6 Hz); 0.99 (d, 3H, CH_3, ^3J=6.6 Hz); 1.67–1.76 (m, 1H, CH); 2.08 (dd, 1H, CH_2, ^2J=15.0 Hz, ^3J=4.7 Hz); 2.29 (dd, 1H, CH_2, ^2J=15.0 Hz, ^3J=8.9 Hz); 3.91 (s, 3H, OCH_3); 6.90 (d, 1H, NH, ^3J=11.9 Hz); 8.28 (dq, 1H, NCHO, ^3J=11.9 Hz, ^5J=1.5 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 21.40, 23.58, 23.89 (2×CH_3, CH); 38.24 (CH_2); 54.21 (OCH_3); 65.96 (q, CCF_3, ^2J=28.9 Hz); 123.54 (q, CF_3, ^1J=286.9 Hz); 162.72 (NCH=O); 166.93 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 1.3 (d, CF_3, ^5J=1.5 Hz) ppm.

Methyl *N*-formyl-2-trifluoromethyl-phenylalaninate (**2c**): Colourless oil (1.17 g, 85%), 3:1 mixture of *s-cis/s-trans* conformers. Analysis: Calc. for $C_{12}H_{12}F_3NO_3$ (275.23): C, 52.37; H, 4.39; N, 5.09%. Found: C, 51.81; H, 4.49; N, 4.96%. IR (film) ν (cm^{-1}): 3340–3260; 1755; 1690; 1505. MS (EI) *m/z*: 275 $(M)^+$; 230 $(M-HCONH_2)^+$; 91 $(C_7H_7)^+$.

s-cis Conformer: ^{1}H NMR ($CDCl_3$) δ: 3.44 (d, 1H, CH_2, ^2J=13.9 Hz); 4.19 (d, 1H, CH_2, ^2J=13.9 Hz); 3.87 (s, 3H, OCH_3); 6.65 (s, 1H, NH); 7.13–7.18 (m, 2H, arom.); 7.22–7.32 (m, 3H, arom.); 8.17 (s, 1H, NCHO) ppm. ^{13}C NMR ($CDCl_3$) δ: 34.01 (CH_2); 54.02 (OCH_3); 67.20 (q, CCF_3, ^2J=28.9 Hz); 123.82 (q, CF_3, ^1J=288.4 Hz); 127.80, 128.59, 130.07, 133.05 (C, arom.); 160.70 (NCH=O); 166.68 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 6.4 (s, CF_3) ppm.

s-trans Conformer: ^{1}H NMR ($CDCl_3$) δ: 3.30 (d, 1H, CH_2, ^2J=14.6 Hz); 3.68 (d, 1H, CH_2, ^2J=14.6 Hz); 3.86 (s, 3H, OCH_3); 6.56 (d, 1H, NH, ^3J=11.9 Hz); 7.05–7.10 (m, 2H, arom.); 7.22–7.32 (m, 3H, arom.); 8.39 (d, 1H, NCHO, ^3J=11.9 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 37.19 (CH_2); 54.25 (OCH_3); 66.30 (q, CCF_3, ^2J=28.2 Hz); 123.49 (q, CF_3, ^1J=286.9 Hz); 128.37, 129.12, 129.86, 131.46 (C, arom.); 163.28 (NCH=O); 165.82 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 4.0 (s, CF_3) ppm.

Methyl *N*-formyl-2-phenyl-3,3,3-trifluoroalaninate (**2d**): Colourless solid, m.p. 114 °C (1.20 g, 92%), 5:4 mixture of *s-cis/s-trans* conformers. Analysis: Calc. for $C_{11}H_{10}F_3NO_3$ (261.21): C, 50.58; H, 3.86; N, 5.36%. Found: C, 50.55; H, 3.90; N, 5.47%. IR (KBr) ν (cm^{-1}): 3300; 1760; 1750; 1705; 1675. MS (EI) *m/z*: 261 $(M)^+$; 233 $(M-CO)^+$; 217 $(M-CH_2NO)^+$; 202 $(M-CO_2CH_3)^+$; 174 $(202-CO)^+$.

s-cis Conformer: ^{1}H NMR ($CDCl_3$) δ: 3.80 (s, 3H, OCH_3); 7.40–7.45 (m, 6H, arom. and NH); 8.22 (s, 1H, NCHO) ppm. ^{13}C NMR ($CDCl_3$) δ: 53.64 (OCH_3); 66.49 (q, CCF_3, ^2J=29.0 Hz); 123.58 (q, CF_3, ^1J=287.5 Hz); 126.60, 128.95, 129.64, 131.57 (C, arom.); 160.37 (NCH=O); 166.56 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 6.3 (s, CF_3) ppm.

s-trans Conformer: ^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H, OCH_3); 7.22 (d, 1H, NH, ^3J=11.4 Hz); 7.40–7.45 (m, 5H, arom.); 7.87 (d, 1H, NCHO, ^3J=11.4 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 54.72 (OCH_3); 68.32 (q, CCF_3, ^2J=29.1 Hz); 123.25 (q, CF_3, ^1J=286.7 Hz); 127.19, 129.59, 130.06, 132.03 (C, arom.); 164.22, (NCH=O); 166.23 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 7.0 (s, CF_3) ppm.

Methyl 3,3,3-trifluoro-2-isocyanopropionates (3)

General procedure

Diphosgene (1.98 g, 10 mmol) in dichloromethane (10 ml) was added dropwise to an ice-cold stirred solution of an *N*-formyl α-amino acid ester **2** (10 mmol) and triethylamine (2.02 g, 20 mmol) in dichloromethane (40 ml). After 20 min, the mixture was allowed to warm up to room temperature. Stirring was continued at room temperature for 6 h. When ^{19}F NMR analysis of the reaction mixture indicated the complete transformation of **2** into the isocyanide **3**, the organic layer was washed three times with saturated $NaHCO_3$ solution and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the product was distilled in a Kugelrohr oven.

Methyl 2-methyl-3,3,3-trifluoro-2-isocyanopropionate (**3a**): Colourless liquid, b.p. 40 °C/0.8 mmHg (1.27 g, 70%). Analysis: Calc. for $C_6H_6F_3NO_2$ (181.11): C, 39.79;

H, 3.34; N, 7.73%. Found: C, 38.90; H, 3.55; N, 7.68%. IR (film) ν (cm^{-1}): 2150; 1760. GC–MS (50 °C) *m/z*: 182 $(M+1)^+$; 166 $(M-CH_3)^+$; 122 $(M-CO_2CH_3)^+$; 59 $(CO_2CH_3)^+$. ^1H NMR ($CDCl_3$) δ: 1.88 (s, 3H, CH_3); 3.94 (s, 3H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 20.79 (CH_3); 54.85 (OCH_3); 69.83 (q, CCF_3, $^2J=28.3$ Hz); 121.63 (q, CF_3, $^1J=285.1$ Hz); 163.01 (N=C); 165.63 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 0.47 (s, CF_3) ppm.

Methyl 2-isobutyl-3,3,3-trifluoro-2-isocyanopropionate (**3b**): Colourless liquid, b.p. 60 °C/0.3 mmHg (1.34 g, 60%). Analysis: Calc. for $C_9H_{12}F_3NO_2$ (223.18): C, 48.43; H, 5.42; N, 6.28%. Found: C, 48.20; H, 5.33; N, 6.08%. IR (film) ν (cm^{-1}): 2150; 1760. MS (EI) *m/z*: 222 $(M-1)^+$; 208 $(M-CH_3)^+$; 180 $(M-C_3H_7)^+$; 164 $(M-CO_2CH_3)^+$; 59 $(CO_2CH_3)^+$. ^1H NMR ($CDCl_3$) δ: 0.90 (d, 3H, CH_3, $^3J=6.6$ Hz); 1.07 (d, 3H, CH_3, $^3J=6.6$ Hz); 1.89–2.17 (m, 3H, $CHCH_2$); 3.92 (s, 3H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 21.55, 23.38, 24.59 ($2\times CH_3$, CH); 40.04 (CH_2); 54.66 (OCH_3); 69.07 (q, CCF_3, $^2J=31.0$ Hz); 121.77 (q, CF_3, $^1J=286.1$ Hz); 163.22 (N=C); 166.83 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 1.36 (s, CF_3) ppm.

Methyl 2-benzyl-3,3,3-trifluoro-2-isocyanopropionate (**3c**): Colourless liquid, b.p. 100 °C/0.02 mmHg (1.64 g, 64%). Analysis: Calc. for $C_{12}H_{10}F_3NO_2$ (257.10): C, 56.01; H, 3.92; N, 5.45%. Found: C, 55.10; H, 3.98; N, 5.30%. IR (film) ν (cm^{-1}): 2125; 1755. MS (CI) *m/z*: 258 $(M+1)^+$; 231 $(M-CN)^+$; 198 $(M-CO_2CH_3)^+$; 91 $(C_7H_7)^+$. ^1H NMR ($CDCl_3$) δ: 3.21 (d, 1H, CH_2, $^2J=13.6$ Hz); 3.55 (d, 1H, CH_2 $^2J=13.6$ Hz); 3.77 (s, 3H, OCH_3); 7.23–7.26 (m, 2H, arom.); 7.32–7.36 (m, 3H, arom.) ppm. ^{13}C NMR ($CDCl_3$) δ: 38.59 (CH_2); 54.38 (OCH_3); 70.44 (q, CCF_3, $^2J=29.2$ Hz); 121.38 (q, CF_3, $^1J=286.3$ Hz); 128.62, 128.79, 130.18, 130.63 (C, arom.); 161.95 (N=C); 167.95 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 2.6 (s, CF_3) ppm.

Methyl 2-phenyl-3,3,3-trifluoro-2-isocyanopropionate (**3d**): Colourless liquid, b.p. 105 °C/0.2 mmHg (2.14 g, 88%). Analysis: Calc. for $C_{11}H_8F_3NO_2$ (243.19): C, 54.33; H, 3.32; N, 5.76%. Found: C, 54.78; H, 3.43; N, 5.71%. IR (film) ν (cm^{-1}): 2140; 1760. MS (EI) *m/z*: 244 $(M+1)^+$; 243 $(M)^+$; 217 $(M-CN)^+$; 184 $(M-CO_2CH_3)^+$; 77 $(C_6H_5)^+$; 59 $(CO_2CH_3)^+$. ^1H NMR ($CDCl_3$) δ: 3.90 (s, 3H, OCH_3); 7.46–7.51 (m, 3H, arom.); 7.64–7.67 (m, 2H, arom.) ppm. ^{13}C NMR ($CDCl_3$) δ: 54.81 (OCH_3); 71.32 (q, CCF_3, $^2J=31.5$ Hz); 121.23 (q, CF_3, $^1J=286.6$ Hz); 126.49, 127.40, 129.34, 130.96 (C, arom.); 162.19 (N=C); 167.58 (CO_2CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.13 (s, CF_3) ppm.

Results and discussion

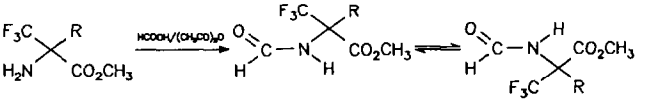
α-Trifluoromethyl-substituted α-amino acid esters **1** can be prepared from the corresponding *N*-benzyloxycarbonyl (*Z*-) and *N*-t-butyloxycarbonyl (BOC-) protected amino acid derivatives, respectively [7]. Transformation of compounds **1** *N*-formyl 2-trifluoromethyl α-amino acid esters **2** is achieved by refluxing with conc. formic acid [8] or on treatment with a mixture of formic acid/acetic anhydride at room temperature [9]. We have found that the latter method gives higher yields of compounds **2**.

The trifluoromethyl-substituted *N*-formyl α-amino acid esters **2** exist as a mixture of *s-cis*/*s-trans* conformers in solution at room temperature. The ratio of both stereoisomers depends on the steric bulk of the side chain R of the α-amino acid.

The ^1H NMR spectrum of the major isomer in the case of compound **2b** [$R=CH_2CH(CH_3)_2$] exhibits singlets corresponding to the NH and NCH=O protons at δ 6.97 (br.) and 8.26 ppm, whereas the NH proton of the minor isomer resonates at δ 6.90 ppm. This signal is split into a doublet [$^3J(HH)=11.9$ Hz] [10, 11]. The proton of the formyl group gives rise to a doublet of quartets [$^3J(HH)=11.9$ Hz, $^5J(FH)=1.5$ Hz] at 8.28 ppm. Based on these data, we ascribe the major isomer the structure of the *s-cis* and the minor isomer the structure of the *s-trans* conformer.

When compounds **2** are treated with diphosgene (trichloromethyl chloroformate) in the presence of triethylamine [12], the corresponding methyl 3,3,3-trifluoro-2-isocyanopropionates are formed in good yields.

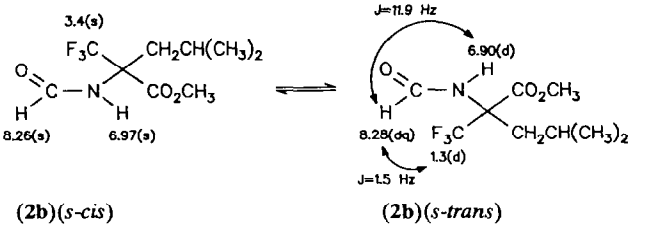
Compounds **3** are colourless, distillable, easy to handle liquids. The isocyano group shows a characteristic IR absorption in the 2125–2250 cm^{-1} region of the spectrum and in the ^{13}C NMR spectra exhibits a resonance absorption at δ 162–163 ppm.



(**1**)(**a–d**) *s-cis* (**2**)(**a–d**) *s-trans*

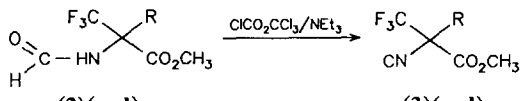
	R
a	CH_3
b	$CH_2CH(CH_3)_2$
c	$CH_2C_6H_5$
d	C_6H_5

Scheme 1.



(**2b**)(*s-cis*) major isomer (**2b**)(*s-trans*) minor isomer

Scheme 2.



(2)(a–d) (3)(a–d)

R

a	CH_3
b	$CH_2CH(CH_3)_2$
c	$CH_2C_6H_5$
d	C_6H_5

Scheme 3.

Isocyanides form a class of synthetically valuable compounds [13]. We intend to report in subsequent publications on the reaction potential of the new building block **3**, e.g. for the Passerini [14] and Ugi reactions [15].

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