

Trifluoropyruvamides from Isocyanides and Trifluoroacetic Anhydride

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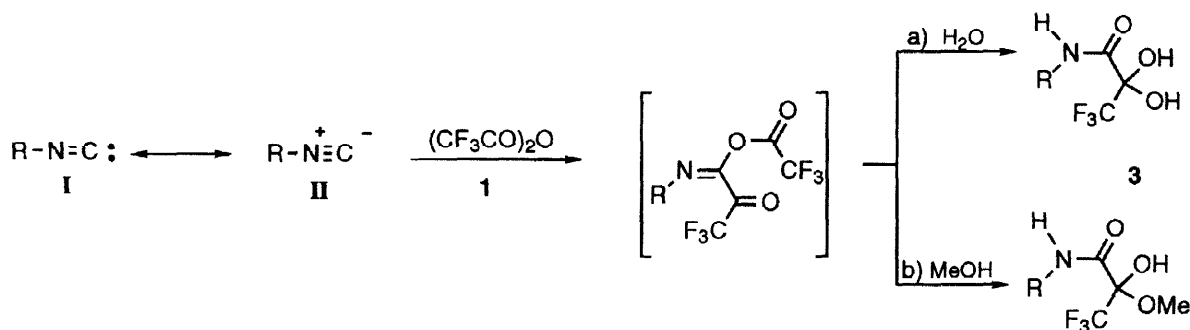
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Abstract: Addition of trifluoroacetic anhydride to isocyanides proceeds smoothly to give after treatment trifluoropyruvamide derivatives in high yield. © 1998 Elsevier Science Ltd. All rights reserved.

In the search for new biologically active compounds, investigations in the field of complex organofluorine structures have been fruitfully conducted in the last few decades. Trifluoromethyl ketones in particular have emerged as valuable intermediates and targets.¹ Their reversible inhibitory effect on various enzymatic systems is mainly associated with stabilisation by the trifluoromethyl group of tetrahedral adduct on the ketone.²

Following our first publication on the use of trifluoroacetic anhydride (1) as useful building block for the introduction of the trifluoromethyl group in organic compounds,³ we were interested by other reactions of anhydride (1) leading to new carbon-carbon bond formation and started a study on the interaction of (1) with isocyanides.

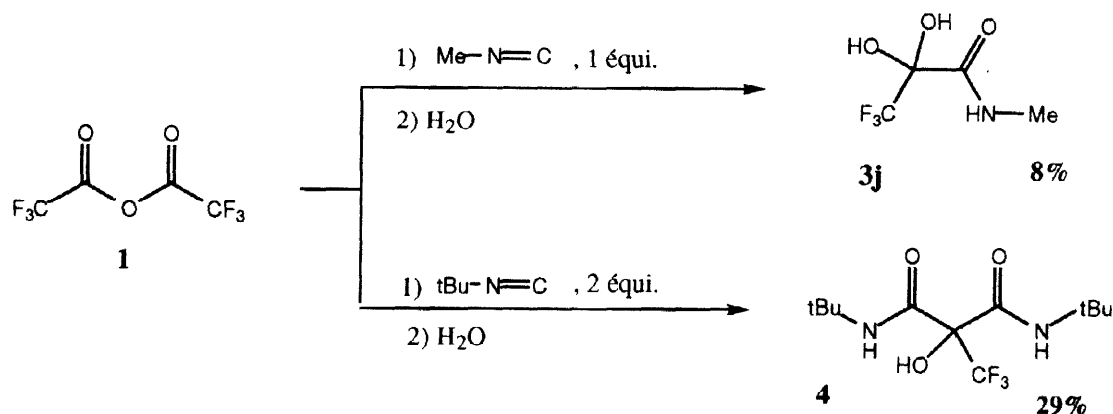
Isocyanides can be viewed as hybrids of two limiting forms: a carbene structure (I) and a charge separated form (II) (Scheme 1), the latter consistent with nucleophilic activity at the terminal carbon atom. Their reaction with various electrophiles is well documented,⁴ giving in the first place an imine α adduct which eventually evolves to an amide. In the Ugi-Passeroni reaction of isocyanides with ketones and aldehydes derivatives, this behaviour was fruitfully exploited for new formation of carbon-carbon σ bonds. In contrast, the interest of their reaction with acid derivatives to give α -keto acids seems to be underestimated.⁵ We anticipated that on exposure to the highly electrophilic anhydride (1), fluoro-pyruvamides (3) could be recovered after workup (Scheme 1).



Scheme 1

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At the time we started this study and reported our first communication,⁶ we were not aware that a previous study was made on the reaction of isocyanides with trifluoroacetic anhydride; the report of Krivinka and Honzl in 1972 describes the reaction of methyl isocyanide with (1) forming fluoropyruvamide (3j) in a 8% yield whereas *tert*-butylisocyanide was reported to give a (2:1) adduct with (1) instead of the expected trifluoropyruvamide (Cf (3b), (3b') in Table 1) (scheme 2).⁷



Scheme 2

The contrast between their result and our successful preparation of pyruvamides (3) was rather surprising; we thus now give a full report on our result, with a thorough examination of *tert*-butylisocyanide reaction and by-product formation.

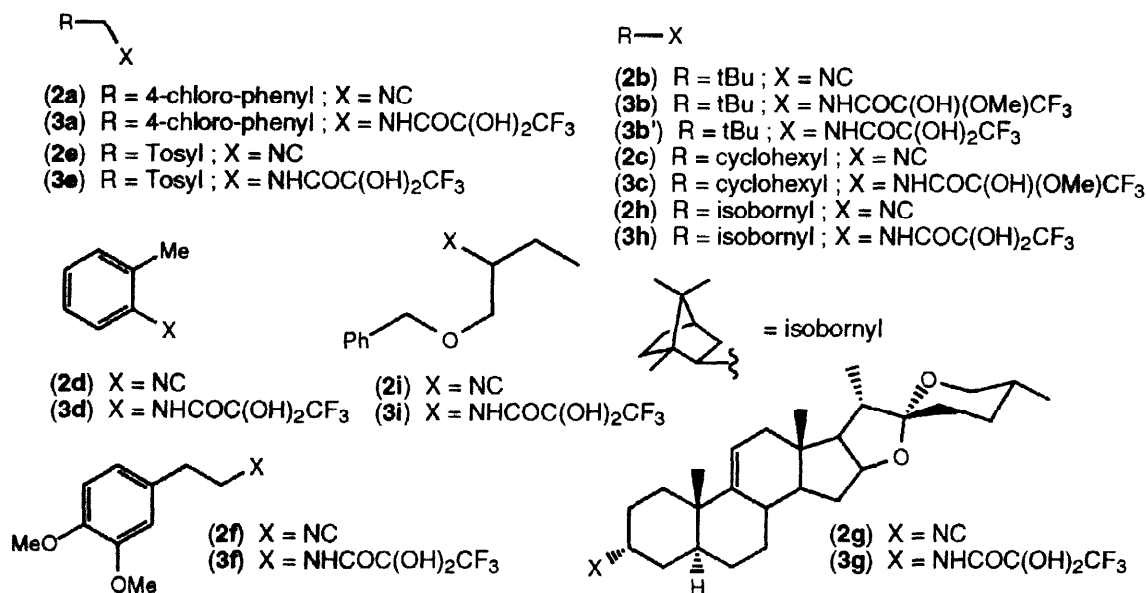
Upon addition of (1) to a cold solution ($-60\text{ }^{\circ}\text{C}$) of isocyanide (2a) in dry dichloromethane under nitrogen, the fluoroderivative (3a) was isolated in good yield after hydrolysis of the mixture. A number of other isocyanides behaved similarly, as shown by the results collected in Table 1. As observed for trifluoropyruvate esters,⁸ the hydrated form of the trifluoropyruvamides thus prepared is greatly stabilized by the presence of two electron withdrawing groups. The hydrates prepared in this reaction were all found to be highly crystalline and stable; in most cases, they crystallize from the reaction mixture after the addition of water and can be recovered by filtration. Except for pyruvamide (3e), all hydrates were highly soluble in hot toluene indicating a possible equilibrium between the ketone and its hydrate in this solvent. Several attempts to convert the hydrate into the free ketone didn't meet with success.

Water can be advantageously replaced by methanol for the preparation of hemiketal derivatives (Scheme 1-path b-). The fluorocompounds (3b) and (3c) were thus obtained in quantitative yield from the respective isocyanides. The fluorinated hemiketal formed is easily hydrolysed to the pyruvamide hydrate. Compound (3d) was thus obtained in 86% yield after methanolysis of the reaction mixture followed by chromatography on silica gel which effected the hydrolysis of the predicted hemiacetal. The best preparation of (3b') was obtained on methanolysis of the cold reaction mixture followed by evaporation of the solvent and treatment of the crude residue with hydrochloric acid in hot toluene. On cooling the pyruvamide crystallizes from the toluene solution giving (3b') in a 95% isolated yield.

Ethyl isocyanoacetate gives a complex mixture of products when treated with trifluoroacetic anhydride in cold dichloromethane. In contrast, sulfone (**2e**) was quite unreactive, giving the expected product (**3e**) only after several hours at room temperature.

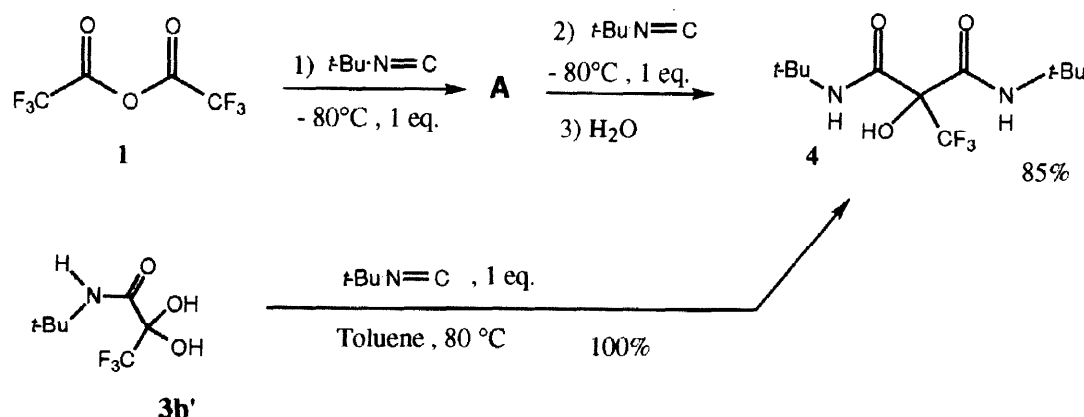
Table 1 : Reaction of $(\text{CF}_3\text{CO})_2\text{O}$ with isocyanides

Starting mat.	Reaction temp./°C	Reaction time/min	Treatment	Product (yield)
(2a)	- 60	120	H_2O	(3a) (63 %)
(2b)	- 80	60	MeOH	(3b) (quant.)
(2b)	- 80	60	$\text{MeOH}/\text{H}_2\text{O}, \text{HCl}$	(3b') (95%)
(2c)	- 70	180	MeOH	(3c) (quant.)
(2d)	- 10	15	MeOH	(3d) (86 %)
(2e)	-60 to r.t.	600	H_2O	(3e) (quant.)
(2f)	- 80	90	H_2O	(3f) (83 %)
(2g)	- 60	120	H_2O	(3g) (quant.)
(2h)	-60	120	H_2O	(3h) (66%)
(2i)	-50	240	H_2O	(3i) (74%)



On several occasions we observed a significant diminution in yields when scaling up the reaction or increasing the concentration of the reactants. In view of these difficulties and the results obtained by Krivinka and Honzl,⁷ we decided to reinvestigate more carefully the reaction of tert-butyliisocyanide with (1). Effecting the reaction at room temperature or raising the concentration in the medium ($c > 0.4 \text{ M}$) gives after hydrolysis significant formation of a by-product which was found identical to the (2:1) adduct (**4**) described by Krivinka. In both cases, inverse addition of isocyanide (**2b**) to trifluoroacetic anhydride solutions did not suppress the formation of (**4**). High yields of (**4**) were obtained when an additional equivalent of isocyanide was added after one hour to intermediate **A** (scheme 3). The same adduct was

obtained in quantitative yield through treatment of fluoropyruvamide (**3b'**) with *tert*-butylisocyanide in toluene.

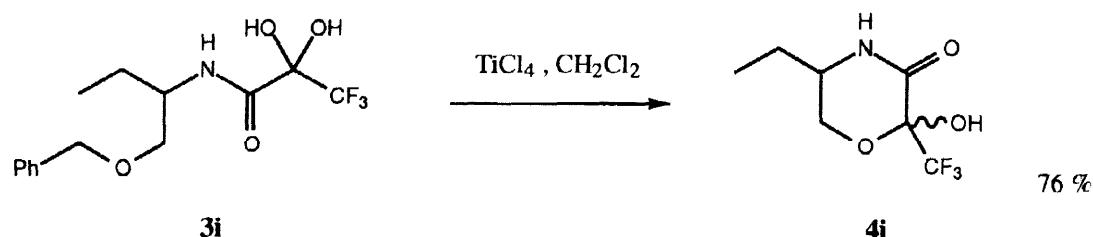


Scheme 3

Temperature and concentration must thus be carefully controlled in this reaction. Isocyanides are best added between -80°C and -60°C . The temperature can be slowly increased if no reaction is observed after half an hour. These conditions insure high yields in the preparation of fluoropyruvamides.

The compounds obtained under our conditions are related to ethyl trifluoropyruvate; this product has been extensively used for the synthesis of various fluorinated compounds.⁹ In comparison with esters, the related trifluoropyruvamides have been poorly studied, being mainly described with simple amines (diethylamine, ammonia);^{10,11} high electrophilicity of the carbonyl next to the trifluoromethyl group probably hamper the preparation of higher pyruvamides.¹²

This reaction can be successfully applied to heterocyclic synthesis as shown in scheme 4. When reacting (**3i**) with titanium tetrachloride, the benzyl group is lost and the new morpholine derivative (**4i**) is obtained as a single diastereoisomer in a 76 % isolated yield.



Scheme 4

In conclusion we have disclosed an efficient preparation of trifluoropyruvamides under smooth conditions, the hydrated form of these pyruvamides is stable and could efficiently replace pyruvic esters in many synthetic applications.¹³

EXPERIMENTAL SECTION

Experiments with trifluoroacetic anhydride were carried out under a nitrogen atmosphere in oven-dried glassware. Liquid nitrogen in acetone was used as a cryogenic and all temperatures are internal measures. THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Toluene was distilled and stored on sodium wires. NMR spectra have been recorded on a Bruker AC 200 in CDCl₃ unless otherwise stated. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard in NMR ¹H spectra. CDCl₃ has been used as reference in NMR ¹³C spectra.

Preparation of isocyanides. Isocyanides (**2b**),¹⁴ (**2d**)¹⁵ were prepared according reported procedures. (**2c**), (**2e**) were bought from Aldrich and (**2g**) was a gift from Dr. Zard.

4-Chlorobenzylisocyanide (2a): To a solution of sodium hydroxide (70 g, 1.7 mol) in water (90 ml) is added over 30 minutes under strong agitation a solution of 4-chlorobenzylamine (35 g, 0.25 mol), chloroform (30 g, 0.25 mol) and TEBA (0.6 g) in dichloromethane (130 ml). After 6 hours of vigorous agitation, water is added and the mixture is extracted with dichloromethane. After evaporation of the solvent and filtration over silica gel (CH₂Cl₂/petroleum ether, 50/50), the isocyanide (**2a**)¹⁶ is recovered (24 g, 0.16 mol, 64 %) as a vile smelling, yellow liquid.

2-(3,4-Dimethoxyphenyl)ethylisocyanide (2f): To a solution of sodium hydroxide (49 g, 1.2 mol) in water (60 ml) is added over 30 minutes under strong agitation a solution of homoveratrylamine (30 ml, 0.18 mol), chloroform (14 ml, 0.17 mol) and TEBA (0.4 g, 0.002 mol) in dichloromethane (130 ml). After one day of vigorous agitation, water is added and the mixture is extracted with dichloromethane. After evaporation of the solvent and filtration on silica gel (CH₂Cl₂), the isocyanide (**2f**) is recovered (20 g, 0.11 mol, 61 %) as an odorless oil which solidify on standing in cold. IR (KBr): 2937, 2835, 2147, 1592, 1513 cm⁻¹; NMR ¹H: 6.8 (m, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.6 (m, 2H), 2.9 (m, 2H); NMR ¹³C: 148.8, 148.0, 129.1, 120.6, 111.7, 111.2, 55.7, 43.1, 35.1.

Isocyano-1,7,7-trimethylbicyclo[2.2.1]heptane (2h): (1R,2R,4R)-2-amino-1,7,7-trimethyl-bicyclo[2.2.1]heptane (25.4 g; 0.17 mol) is dissolved in methylformate (170 ml) and allowed to stand 4 days under argon. After evaporation of the solvent, the crude formamide is recovered in quantitative yield. To a cold solution (-10°C) of the latter in dry dichloromethane (150 ml) under argon is added triethylamine (54.6 ml, 0.39 mol) followed by phosphorous oxychloride (16 ml; 0.16 mol) over 30 minutes. After stirring the resultant mixture at 0°C for one hour, a solution of sodium carbonate (80 g) in water (200 ml) is added while keeping the temperature under 10 °C. After one hour more water is added and the mixture is extracted with dichloromethane. Evaporation and flash chromatography over basic alumina (Eluant: dichloromethane) affords isocyanide (**2h**) (21.6 g, 0.13 mol, 76 %) as a brownish solid. M.p. = 105–107°C; IR: 2954, 2135 (N=C), 1457, 1392, 1054 cm⁻¹; NMR ¹H: 3.42 (m, 1H), 2.06 (m, 1H), 1.90–1.50 (m, 4H), 1.10–0.76 (m, 11H, with 1.07 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 0.87 (s, 3H, CH₃)); NMR ¹³C: 155.1 (NC), 60.1, 48.9, 47.7, 44.6, 38.5, 34.6, 26.8, 19.9, 19.7, 12.4.

1-Benzoyloxy-2-isocyanobutane (2i): To a suspension of phthalic anhydride (7.9 g; 53 mmol.) in anhydrous toluene (75 ml) under argon is added 2-aminobutan-1-ol (5 ml, 53 mmol.) and 4,4-dimethylaminopyridine (0.1 g). The mixture is heated under reflux with a Dean-Stark apparatus for 4 hours. After filtration on silica and evaporation of the solvent, the crude 2-(2-hydroxy-ethyl)-isoindole-1,3-dione (oil) is added to a solution of benzyl bromide (6.3 ml; 47 mmol) in dry THF (100 ml). Sodium hydride (60% dispersion) (2.46 g; 61 mmol.) is added and the mixture is agitated at room temperature over 24 hours.

After filtration on silica and evaporation of the solvent, the phthalimide (14.3 g of a mixture with mineral oil) is added to a solution of hydrazine hydrate (8 ml; 0.18 mmol) in ethanol (100 ml) then heated under reflux during one hour. The solid that separates is washed with hydrochloric acid (150 ml of a 6N solution then 150 ml of a 2N solution) and discard; ethanol is evaporated and the acid aqueous solution extracted twice with petroleum ether. The aqueous solution is made basic (pH 12) with a potassium

hydroxide solution (12 N). Extraction with ether affords 1-benzyloxy-2-aminobutane as a yellowish oil (6.2 g; 33 mmol).

A solution of 1-benzyloxy-2-aminobutane (6.2 g; 33 mmol) in methyl formate (100 ml) is left one week at room temperature under argon. Methyl formate is evaporated and replaced by dry dichloromethane (150 ml). This solution under argon is cooled to -10°C , triethylamine (10.6 ml, 76 mmol) is added followed by a slow addition of phosphorous oxychloride (2.95 ml; 32 mmol) while the temperature is kept at -10°C . After one hour agitation at 0°C , the mixture is hydrolysed with a sodium carbonate saturated solution (100 ml). Extraction, evaporation and chromatography on silica gel (CH_2Cl_2 /petroleum ether: 2/1) affords 1-benzyloxy-2-isocyanobutane (**2i**) (5.38 g; 28.5 mmol) as a colorless oil. IR (KBr): 2950, 2160, 1460, 1370, 1120, 745, 705 cm^{-1} ; NMR ^1H : 7.34 (m, 5H), 4.57 (s, 2H), 3.7–3.4 (m, 3H), 1.7 (m, 2H), 1.04 (t, 3H, $J = 7\text{ Hz}$); NMR ^{13}C : 156.5, 137.3, 128.4, 127.8, 127.6, 73.3, 71.0, 56.0, 24.8, 9.8.

General procedure for the preparation of trifluoropyruvamide from isocyanides (except for (**2g**)). To a solution of isocyanide (**2**) (7 mmol) in dry cold dichloromethane (20 ml, see temperature given in table 1) under argon is added trifluoroacetic anhydride (1.2 ml, 8.4 mmol). The cold mixture is then agitated under argon till completion.

N-(4-Chloro-benzyl)-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3a): After 2 hours water (2 ml) is added and the temperature is rapidly brought to 25°C . The pyruvamide (1.02 g, white crystals) is filtered from the reaction medium and the resulting mother liquor after extraction and evaporation of the solvent is purified via flash column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 70/30) affording additional pyruvamide (0.230 g). Overall yield 1.250 g (4.4 mmol, 63%). M.p. = $128\text{--}130^{\circ}\text{C}$ (from hot toluene); IR (KBr): 3365, 3308, 1673, 1553, 1494, 1283 cm^{-1} ; NMR ^1H (in DMSO): 8.84 (m, NH, 1H), 7.80 (s, OH, 2H), 7.37 (d, $J = 8.4\text{ Hz}$, 2H), 7.27 (d, $J = 8.4\text{ Hz}$, 2H), 4.28 (m, 2H); NMR ^{13}C (in DMSO): 166.6, 138.1, 131.3, 129.0, 128.1, 122.6 (q, JC-F = 290 Hz), 90.7 (q, JC-CF = 32 Hz), 41.7; Mass Spectrum: 283, 265, 140; Microanal. calculated for $\text{C}_{10}\text{H}_9\text{ClF}_3\text{NO}_3$: C, 42.35; H, 3.2; N, 4.94. Found: C, 42.41; H, 3.13; N, 4.66.

N-tert-Butyl-3,3,3-trifluoro-2-hydroxy-2-methoxy-propionamide (3b): After two hours methanol (5 ml) is added and the temperature is brought to 25°C . Evaporation of the solvent leaves the pyruvamide (**3b**) as a colorless oil formed in a quantitative yield. NMR ^1H : 6.25 (bs, X-H), 5.90 (bs, X-H), 3.33 (s, 3H), 1.40 (s, 9H); NMR ^{13}C : 164.1, 121.4 (q, JC-F = 287 Hz), 93.5 (q, JC-CF = 33 Hz), 52.7, 50.5, 28.2.

N-tert-Butyl-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3b'): To a solution of pyruvamide (**3b**) (1.6 g, 7 mmol) in toluene (25 ml) is added water (4 ml) and a 30% hydrochloric acid solution (0.1 ml). The mixture is refluxed over a day; evaporation of the solvent affords pyruvamide (**3b'**) as white crystals in a quantitative yield. M.p. = $105\text{--}108^{\circ}\text{C}$ (from hot toluene); IR (KBr): 3303, 2985, 1680, 1550, 1375 cm^{-1} . NMR ^1H (in DMSO): 7.7 (bs, 2H), 7.10 (s, 1H), 1.25 (s, 9H); NMR ^{13}C (in DMSO): 165.7, 122.6 (q, JC-F = 290 Hz), 90.7 (q, JC-CF = 31 Hz), 50.7, 28.2; Microanal. calculated for $\text{C}_7\text{H}_{12}\text{F}_3\text{NO}_3$: C, 39.07; H, 5.62; N, 6.51. Found: C, 39.36; H, 5.05; N, 6.54.

N-Cyclohexyl-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3c): After 3 hours methanol (5 ml) is added and the temperature raised to 25°C . Evaporation of the solvent leaves pyruvamide (**3c**), formed in a quantitative yield. White crystals from cold Et_2O : M.p. = $90\text{--}120^{\circ}\text{C}$ (sublimation); IR (KBr): 3320, 1682 cm^{-1} ; NMR ^1H : 6.40 (bs, 1H), 6.05 (bs, 1H), 3.8 (m, 1H), 3.33 (s, 3H), 2.0–1.0 (m, 10H); NMR ^{13}C : 164.2, 121.6 (q, JC-F = 290 Hz), 93.7 (q, JC-CF = 30 Hz), 50.6, 49.9, 32.6, 32.4, 25.3, 24.6; Microanal. calculated for $\text{C}_{10}\text{H}_{16}\text{F}_3\text{NO}_3$: C, 47.06; H, 6.32; N, 5.49. Found: C, 47.32; H, 6.31; N, 5.49.

N-o-Tolyl-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3d): After 15 minutes methanol (5 ml) is added and the temperature raised to 25°C . Evaporation of the solvent and chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 90/10) provides pyruvamide (**3d**) (1.5 g, 6 mmol, 86%) as a white solid. White crystals (from hot toluene): M.p. = $110\text{--}113^{\circ}\text{C}$; IR (KBr): 3308, 1695, 1544, 1422, 1253 cm^{-1} ; NMR ^1H (in DMSO): 9.50 (s, 1H), 8.00 (bs, OH), 7.2 (m, 4H), 2.15 (s, 3H); NMR ^{13}C (in DMSO): 165.2, 135.4,

132.4, 130.4, 126.2, 126.0, 122.6 (q, JC-F' = 290 Hz), 125.1, 91.1 (q, JC-CF = 31 Hz), 17.4; Microanal. calculated for $C_{10}H_{10}F_3NO_3$: C, 48.2; H, 4.04; N, 5.62. Found C, 48.3; H, 4.25; N, 5.57.

N-(Toluene-4-sulfonylmethyl)-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3e): After 1 hour at -60°C no reaction is observed. More trifluoroacetic anhydride (1.2 ml, 8.4 mmol) is added to the mixture and the temperature is slowly raised to 25°C . The mixture is then left under argon overnight. Water (5 ml) is added followed by a saturated sodium hydrogenocarbonate solution. Extraction of the mixture and evaporation of the solvent affords pyruvamide (3e) in a quantitative yield. White crystals (from acetone and toluene): M.p. = $124-130^\circ\text{C}$; IR (KBr): 3398, 3331, 1695, 1549 cm^{-1} ; NMR ^1H (in DMSO): 8.9 (m, 1H), 7.9 (s, 2H), 7.70 (d, $J = 8.1\text{ Hz}$, 2H), 7.42 (d, $J = 8.1\text{ Hz}$, 2H), 4.65 (m, 2H), 2.40 (s, 3H); NMR ^{13}C : 166.7, 144.6, 135.1, 129.7, 128.5, 122.3 (q, JC-F = 290 Hz), 90.6 (q, JC-CF = 31 Hz), 60.6, 21.2; Microanal. calculated for $C_{11}H_{12}F_3NSO_5$: C, 40.51; H, 3.7; N, 4.28. Found: C, 40.51; H, 3.71; N, 4.12.

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3f): After 90 minutes, water and acetone are added to the mixture (10 ml, 50/50) and the temperature is raised to 25°C . The pyruvamide (3f) (1.3 g, white crystals) is filtered from the reaction medium and the resulting mother liquor after extraction and evaporation of the solvent is purified via flash column chromatography (Silica gel, $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 70/30) affording additional pyruvamide (0.39 g). Overall yield 1.69 g (5.8 mmol, 83%); white crystals (from hot toluene): M.p. = $114-119^\circ\text{C}$ (sublimation); IR: 3392, 3330, 2955, 1673, 1550, 1519 cm^{-1} ; NMR ^1H (in DMSO): 8.2 (bs, 1H), 6.8 (m, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 3.3 (m, 2H), 2.65 (t, $J = 6\text{ Hz}$, 2H), 2.5 (bs, OH); NMR ^{13}C (in DMSO): 166.2, 148.5, 147.2, 131.6, 122.5 (q, JC-F = 289 Hz), 120.4, 112.4, 111.7, 90.5 (q, JC-CF = 30 Hz), 55.4, 55.2, 34.3; Microanal. calculated for $C_{13}H_{16}F_3NO_5$: C, 48.3; H, 4.99; N, 4.33. Found: C, 48.35; H, 4.76; N, 4.19.

N-[(25R-5 α -spirost-9(11)-en-3 α -yl]-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3g): To a solution of isocyanide (2g) (0.1 g, 0.24 mmol) in dry cold dichloromethane (5 ml, see temperature given in table 1) under argon is added trifluoroacetic anhydride (0.1 ml, 0.7 mmol). The cold mixture is left under argon for 2 h and treated rapidly with a saturated sodium hydrogenocarbonate solution (3 ml). Extraction of the mixture and evaporation of the solvent affords pyruvamide (3g) in a quantitative yield; white crystals: M.p. = $140-142^\circ\text{C}$; IR (KBr): 3432, 2955, 1688, 1537, 1180 cm^{-1} ; NMR ^1H : 6.77 (d, $J = 8\text{ Hz}$, NH), 5.23 (s, 1H), 4.35 (m, 1H), 4.10 (m, 1H), 3.55 (m, 2H), 0.87 (s, 3H), 0.72 (d, $J = 5.8\text{ Hz}$), 0.62 (s, 3H); NMR ^{13}C (22.4 MHz): 165.0, 146.6, 121.5 (q, JC-F = 290 Hz), 116.2, 100.3, 90.3 (q, JC-CF = 31 Hz), 80.8, 66.7, 61.1, 53.5, 46.0, 42.0, 41.6, 38.1, 38.6, 39.2, 35.4, 32.7, 32.6, 32.4, 31.2, 31.0, 30.1, 28.5, 27.9, 25.5, 16.9, 16.8, 15.7, 13.9; Microanal. calculated for $C_{30}H_{44}F_3NO_5$: C, 64.85; H, 7.98; N, 2.52. Found: C, 64.41; H, 8.02; N, 2.64.

N-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl)-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3h): After 2 hours, water (20 ml) is added followed by a saturated sodium hydrogenocarbonate solution. After extraction and evaporation of the solvent, the crude is purified by crystallization (CHCl_3 /petroleum ether) followed by evaporation of the mother liquor and chromatography on silica gel (Ether/petroleum ether: 10/90 \rightarrow 50/50) affording (3h) (1.36 g, 4.6 mmol) as white crystals. M.p.: $114-116^\circ\text{C}$; IR: 3433, 3331, 1682, 1540, 1286, 1210, 1178, 1157, 1091, 1079 cm^{-1} ; NMR ^1H : 6.6 (d, 1H, $J = 5\text{ Hz}$), 5.1 (bs, 2H), 3.8 (m, 1H), 2.0-1.5 (m, 5H), 1.4-1.1 (m, 2H), 1.05-0.75 (m, 9H), 0.92 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H); NMR ^{13}C : 165.4, 121.7 (q, $J = 288\text{ Hz}$), 90.5 (q, $J = 33\text{ Hz}$), 57.8, 48.9, 47.1, 44.7, 38.3, 35.7, 26.9, 20.1, 19.8, 11.3. $[\alpha]_D^{25} = -0.35$ (c 0.9, CHCl_3); Microanal. calculated for $C_{13}H_{20}F_3NO_3$: C, 52.88; H, 6.83; N, 4.74. Found: C, 52.62; H, 6.55; N, 4.68.

N-(2-Benzyloxy-ethyl)-3,3,3-trifluoro-2,2-dihydroxy-propionamide (3i): After 3 hours, water (20 ml) is added followed by a saturated sodium hydrogenocarbonate solution. After extraction and evaporation of the solvent, the crude is purified by crystallization (toluene) followed by evaporation of the mother liquor and chromatography on silica gel (Ether/petroleum ether: 10/90 \rightarrow 50/50) affording (3i) (1.67 g, 5.2 mmol, 74%) as white crystals. M.p. (from toluene): $97-98^\circ\text{C}$; IR (KBr): 3332, 1676, 1561, 1284, 1198, 1186, $1125, 1078\text{ cm}^{-1}$; NMR ^1H : 7.30 (m, 4H), 7.01 (m, 1H), 5.76 (bs, 2H), 4.51 (m, 2H, AB type system with δ : 4.56, 4.46, $J_{AB} = 12.0\text{ Hz}$), 3.99 (m, 1H), 3.47 (d, 2H, $J = 3.5\text{ Hz}$), 1.58 (m, 2H), 0.86 (t, 3H, $J =$

7 Hz); NMR ^{13}C : 166.1, 137.3, 128.4, 127.9, 121.6 (q, $J = 261$ Hz); 90.6 (q, $J = 33$ Hz), 73.1, 70.3, 51.9, 24.3, 10.1; Microanal. calculated for $\text{C}_{14}\text{H}_{18}\text{F}_3\text{NO}_4$: C, 52.34; H, 5.65; N, 4.36. Found: C, 52.11; H, 5.59; N, 4.21.

***N,N'*-Di(tert-butyl)-2-trifluoromethyltartronamide (4):**

A) To a solution of *tert*-butylisocyanide (**2**) (0.8 ml, 7 mmol) in dry dichloromethane (20 ml) at -80°C under argon is added trifluoroacetic anhydride (1 ml, 7 mmol). The cold mixture is then agitated under argon during 2 hours and *t*-butylisocyanide (0.8 ml, 7 mmol) is added again to the solution. The temperature is kept at -80°C during 2 hours and slowly raised to room temperature. After addition of water (5 ml), extraction and evaporation of the solvent, the crude is purified on a silica gel column (AcOEt/petroleum ether, 5/95) giving the diamide (**4**) (1.75 g, 5.9 mmol) as white crystals. M.p. (from hexane): $77-78^\circ\text{C}$; IR (KBr): 3360, 3315, 1720, 1685 cm^{-1} ; NMR ^1H : 7.4 (bs, 2H), 5.6 (bs, 1H), 1.37 (s, 18H); NMR ^{13}C : 162.9, 122.1 (q, $J = 283$ Hz), 75.5 (q, $J = 28$ Hz), 52.5, 28.4.

B) A solution of *t*-butylisocyanide (0.2 ml, 1.77 mmol) and pyruvamide (**3b'**) (0.380 g, 1.77 mmol) in dry toluene (5 ml) is heated at 80°C under argon during 3 hours. Evaporation of the solvent affords the diamide (**4**) in a quantitative yield.

5-Ethyl-2-hydroxy-2-trifluoromethyl-morpholin-3-one (4i): To a solution of *N*-(2-Benzyloxy-ethyl)-3,3,3-trifluoro-2,2-dihydroxy-propionamide (**3i**) (0.3 g; 0.9 mmol) in dry dichloromethane (10 ml) at room temperature is added titanium tetrachloride (0.2 ml, 1.8 mmol). The solution is left under agitation over two hours and water (10 ml) is added to the resulting suspension. Several extractions with ethyl acetate affords after evaporation and chromatography (silica gel, ethyl acetate/dichloromethane, 2/1) the morpholinone (**4i**) as a white powder (0.15 g, 0.71 mmol, 76%). M.p.: $156-157^\circ\text{C}$; IR (KBr): 3295, 1677, 1559, 1186, 1161 cm^{-1} ; NMR ^1H (DMSO, d_6): 7.79 (s, 1H), 7.72 (s, 1H), 4.7 (t, 1H, $J = 5.2$ Hz), 4.2-3.2 (m, 2H), 1.7-1.3 (m, 2H), 0.80 (t, 3H, $J = 7.6$ Hz); NMR ^{13}C (DMSO, d_6): 170, 126.5 (q, $J = 280$ Hz), 94.6 (q, $J = 31$ Hz), 66.5, 56.6, 27.5, 14.4; Mass spectrum: 116, 154, 182, 200, 213; Microanal. calculated for $\text{C}_7\text{H}_{10}\text{F}_3\text{NO}_3$: C, 39.44; H, 4.73; N, 6.57. Found: C, 39.32; H, 4.80; N, 6.22.

REFERENCES AND NOTES

- 1) Bégué J.P.; Bonnet-Delpon D., *Tetrahedron*, **1991**, 47, 3207-3258.
- 2) Musgrave W.K.R., *Quart. Rev.*, **1954**, 8, 331; and references given in 1)
- 3) Boivin J.; El Kaïm L.; Zard S.Z., *Tetrahedron Lett.*, **1992**, 33, 1285-1288.
- 4) Seagusa T.; Ito Y.: Simple α -addition. In *Isonitrile Chemistry*; Ugi I., Academic Press, New York, London, **1971**; pp.65-90.
- 5) Nef J. U., *Ann.*, **1892**, 270, 267.
Ugi I.; Fetzer U., *Chem. Ber.*, **1961**, 94, 1116.
- 6) El Kaïm L.; *Tetrahedron. Lett.*, **1994**, 35, 6669-6670.
- 7) Krivinka P.; Honzl J., *Coll. Czechoslov. Chem. Com.*, **1972**, 37, 4035-4041.
- 8) Tordeux M.; Francèse C.; Wakselman C., *J. Chem. Soc. Perkin I*, **1990**, 1951-1955.
- 9) Saloutin V.I.; Pashkevitch K.I.; Postovskii I.Ya., *Russian Chem. Reviews*, **1982**, 51, 736-745.
Fokin A.V., L'actualité chimique, **1987**, 163-167.
Golubev A.S.; Kolomiets A.F.; Fokin A.V., *Russian Chem. Reviews*, **1990**, 59, 89-102.
Golubev A.S.; Kolomiets A.F.; Fokin A.V., *Russian Chem. Reviews*, **1992**, 61, 779-797.
- 10) Saloutin V.I.; Pitserskikh I.A.; Pashkevitch K.I., *Izv. Akad. Nauk. SSSR, Ser Khim*, **1986**, (3), 625-634.
- 11) Selman S., US P. 3 475 456 (**1969**); *Chem Abs.*, **1970**, 72, 2167.
- 12) Soloshonok V.A.; Yagupol'skii Yu.L.; Kukhar V.P., *Zh. Org. Khim.*, **1988**, 24, 1638-1644.
- 13) El Kaïm L.; Guyoton S.; Meyer C., *Tetrahedron Lett.*, **1996**, 37, 375-378.
El Kaïm L.; Olivier C., *Synlett.*, **1997**, 797-798.
- 14) Gokel G. W.; Widera R.P.; Weber W.P. in *Organic Syntheses*; Noland W.E., Ed.; John Wiley & Sons, **1988**; Collect. Vol. VI, p.232-235.
- 15) Ugi I.; Meyr R. in *Organic Syntheses*; Baumgarten H.E., Ed.; John Wiley & Sons, **1973**; Collect. vol. V, p.1060-1063.
- 16) Ugi I.; Fetzer U.; Eholzer U.; Knufer H.; Offermann K., *Angew. Chem.*, **1965**, 77, 492-504.