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Journal of Fluorine Chemistry 115 (2002) 67–74

JOURNAL OF FLUORINE CHEMISTRY

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Methyl 3,3,3-trifluoropyruvate: an improved procedure starting from hexafluoropropene-1,2-oxide; identification of byproducts☆

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Received 12 September 2001; accepted 10 January 2002

Abstract

Optimized laboratory-scale preparation of methyl 3,3,3-trifluoropyruvate (**3**, MTFP) has been developed starting from industrial hexafluoropropene-1,2-oxide (**1**, HFPO) via methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate (**2**, MTPr), which was transformed to **3** using sulfuric acid with isolated yields up to 81%. Byproducts formed in the transformation of **2** to **3**, viz. methyl trifluoroacetate (**4**, MTAc), methyl 3,3,3-trifluoropyruvate hydrate (**5**), methyl hemiacetal of trifluoropyruvate (**6**), a dimer of methyl 3,3,3-trifluoropyruvate hydrate (**7**, DimMTP), and methyl fluorosulfate (**8**, Sulf) were identified and their amounts determined under various experimental conditions. Potential reaction pathways leading to the formation of the byproducts are discussed. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Hexafluoropropene-1,2-oxide; Methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate; Methyl 3,3,3-trifluoropyruvate preparation; Methyl 3,3,3-trifluoropyruvate hemiacetal

1. Introduction

Methyl 3,3,3-trifluoropyruvate (**3**, MTFP) and other esters of 3,3,3-trifluoropyruvic acid have become broadly applied building blocks in organic chemistry [1–4]. The esters have been prepared as follows: from hexafluoropropene-1,2-oxide (HFPO) via alkyl 2-alkoxy-2,3,3,3-tetrafluoropropanoates using sulfuric acid [5–8] or strong Lewis acids [9–11]; by esterification of the hydrate of 3,3,3-trifluoropyruvic acid with alcohols [12,13] or the reaction with diazomethane [5,12]; by ethanolysis of perfluoro-(3-methyl-3*H*-azirine) [13]; ethyl 3,3,3-trifluoropyruvate from diethyl oxalate using trifluoromethylzinc bromide [14–16].

For laboratory use, the synthesis of **3** from HFPO (**1**) via methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate (**2**, MTPr) (Scheme 1) has seemed to us the most convenient from a practical point of view. However, in our preparations of **3** for syntheses of heterocyclic compounds [17–20], we have obtained lower yields than reported [5,7,8]. We met no problems in reproducing the reaction of HFPO (**1**) with methanol to afford intermediate **2** [5,21], which was obtained in high yield. However, in the transformation of **2** to pyruvate **3** using sulfuric acid (96% or fuming) according to the literature [5–8], we obtained low yields of **3** and mixtures of products. No byproducts have previously been reported in the literature. The original isolated yield of **3** reported in [5] was relatively high (83%), but in a more recent paper [8] the reported yield was only 63%; moreover, the product **3** was characterized by two signals both in ^{1}H and ^{19}F NMR spectra without any mention about the possible second product present in **3**. The problems with insufficient purity of **3** and the necessity to purify it additionally or modify the original procedure [5] comes out from previous reports [6,7]. Therefore, we directed our research to an optimization of the procedure and identification of byproducts to obtain pyruvate **3** of high purity in high reproducible yields.

2. Results and discussion

2.1. Optimized preparation of methyl 3,3,3-trifluoropyruvate (3) and byproducts

The starting HFPO (**1**) can be prepared by epoxidation of hexafluoropropene on a laboratory scale using hydrogen peroxide in alkaline media. We applied conditions and experience recently used in the epoxidation of perfluoroallyl chloride [22]. The best, but still low, yields of 36% were obtained under phase-transfer catalysis with a suitable catalyst (Section 4).

☆ Presented at the 13th European Symposium on Fluorine Chemistry, Bordeaux, France, 15–20 July 2001 (Poster 1-P50).

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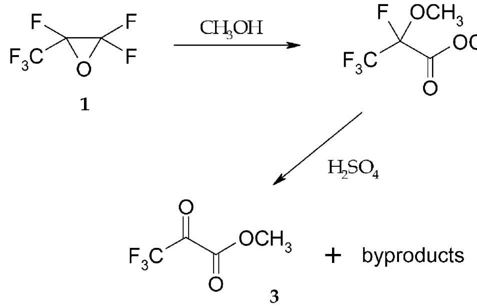
PII: S0022-1139(02)00007-6



Scheme 1. Synthetic steps in the preparation of MTFP (**3**).

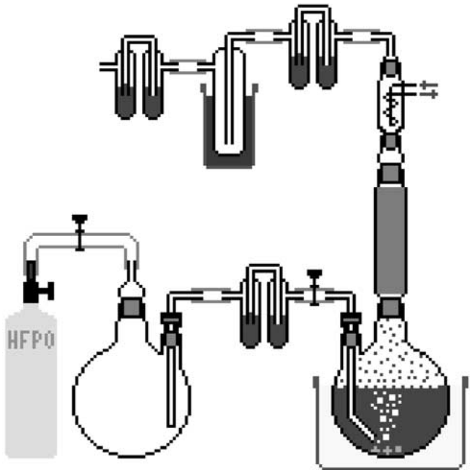
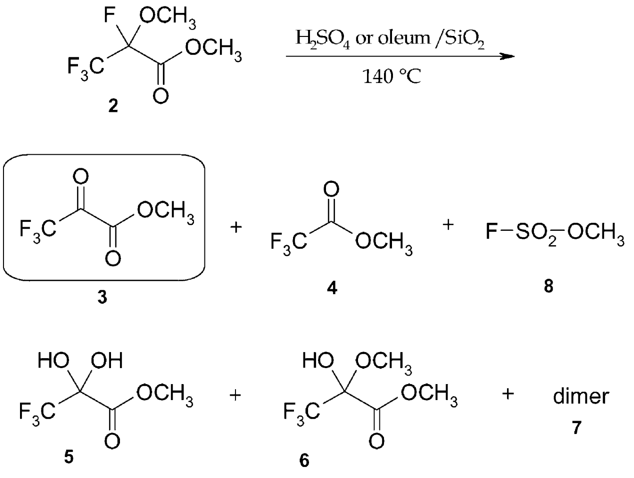


Fig. 1. Apparatus for the preparation of MTPr (**2**).

The preparation of MTPr (**2**) by the reaction of HFPO (**1**) with methanol (Scheme 1) was first carried out under pressure [2] in glass ampoules at room temperature, but led repeatedly to explosions [8]. Therefore, we used a non-high pressure arrangement according to [21,23]. The apparatus (Fig. 1) enabled complete recovery of unreacted HFPO (**1**) and its return to the reaction. However, our highest isolated yield of **2** (82%) lagged behind the value of 95% previously reported [21].



Scheme 2. Overview of byproducts **3**–**7** formed in the preparation of pyruvate **3** from methoxypropanoate **2**.

In the preparation of the pyruvate **3** by the reaction of the precursor **2** with 96% sulfuric acid (Scheme 2) according to [5], we obtained a product (58% to pure **3**) that contained pyruvate **3** (70% relative) and methyl trifluoroacetate (**4**, MTAc, 30% relative). Depending on the concentration of sulfuric acid, hydrate of methyl 3,3,3-trifluoropyruvate (**5**, HydMTP) and a dimer of methyl 3,3,3-trifluoropyruvate hydrate (**7**, DimMTP) were identified in the reaction mixture as byproducts (Scheme 2). The results of the optimization of the procedure are summarized in Table 1. The best isolated yield of MTFP (**3**), 95%, was obtained with concentrated H_2SO_4 in ca. 1:1 molar ratio to propionate **2** (MTPr). Concentrated phosphoric acid caused no reaction.

In the preparation of pyruvate **3** from the precursor **2** by the reaction with oleum according to [5], where no details on oleum amount and concentration were given, we obtained variable yields of product **3** depending on the relative amount of oleum and its concentration. The results are summarized in Table 2. The conversions of **2** were complete in all the runs carried out and reaction mixtures contained methyl fluorosulfate (**8**, Sulf) (Table 2). The highest yield of **3** (75%) was obtained when a low ratio of oleum to **2** was

Table 1
Optimization of yields of MTFP (**3**) in the reaction of MTPr (**2**) with sulfuric or phosphoric acid

H_2SO_4 or H_3PO_4 (%)	Ratio H_2SO_4:**2** (mol/mol)[a]	Yields of products (%)			Recovered **2** (%)
		3 (MTFP)	**4** (MTAc)	**5** (HydMTP)	
96	5.0	46	24	0	0
90	3.9	46	14	0	12
85	3.8	32	2	23	11
96	4.1	58	14	0	0
96	2.4	63	12	0	0
96	0.9	78	0	0	0
85[b]	4.6[b]	0	0	95	0

[a] Calculated to 100% acid.

Table 2
Yields of MTFP (**3**) in the reaction of MTPr (**2**) with oleum

Oleum (%)[a]	H_2SO_4:**2** ratio[b]	Yield of products (%)			
		3 (MTFP)	**4** (MTAc)	**5** (HydMTP)	**8** (Sulf)
60	1.6	5	34	0	38
60	0.3	75	11	0	6
23	3.6	9	29	0	21

[a] Concentration of SO_3 in 100% H_2SO_4.

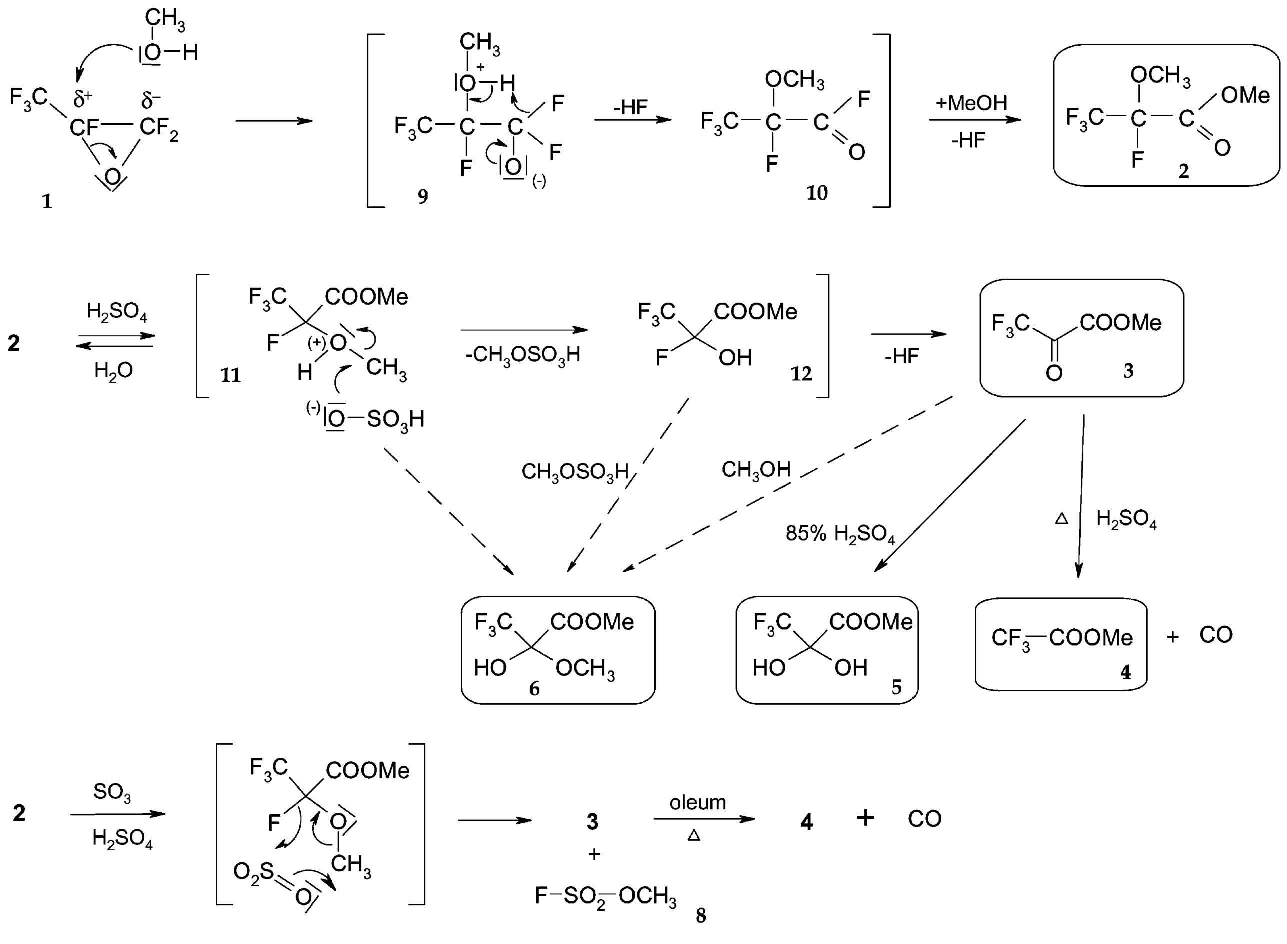
[b] Oleum calculated to 100% H_2SO_4.

used, but the product **3** was contaminated with ca. 13% of MTAc (**4**).

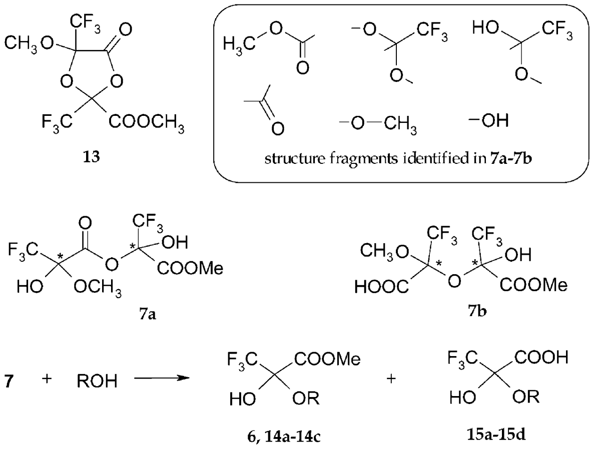
2.2. Formation of byproducts

Mechanisms of the transformations of methoxypropanoate **2** to pyruvate **3** and the formation of byproducts **4–8** have not been previously formulated. The formation of methoxypropanoate **2** from HFPO (**1**) can be understood as nucleophilic attack on HFPO by methanol at the more electrophilic carbon to form intermediate **8** that stabilizes itself by loosing hydrogen fluoride with the formation of acid fluoride **9**, which rapidly reacts with methanol to afford stable methoxypropanoate **2**. In the reaction of **2** with sulfuric acid under heating, the first step is probably protonation of the methoxy group at C-2 (**11**) and then nucleophilic cleavage of the ether bond as a general reaction (Scheme 3) leading to unstable 2-hydroxypropanoate **12**. This intermediate possessing a geminal C–F bond immediately eliminates hydrogen fluoride to afford the end trifluoropyruvate **3**. (Protonated methoxypropanoate **11** was probably detected by ^{19}F NMR in the reaction of **2** with concentrated sulfuric acid at room temperature: signals–80.5 (d, 3F) and –132.4 (bs, 1F)—see Section 4; **11** was converted back to the starting **2** by the addition of water to the mixture.) The product **3** undergoes subsequent decarbonylation, a general reaction of α-keto esters in concentrated sulfuric acid, to form trifluoroacetate **4**. The yields of **4** increase with a higher relative amount of sulfuric acid in the reaction mixture (Table 1). Lower concentration of sulfuric acid causes the formation of the hydrate of trifluoropyruvate (**5**). In the distillation residue, the methyl hemiacetal of trifluoropyruvate **6** was detected (Schemes 3 and 4). Possible reaction paths for its formation are depicted in Scheme 3.

The reaction of **2** with oleum afforded a different spectrum of products in comparison with the reaction in sulfuric acid (Table 2, Scheme 3). The amount of trifluoroacetate **4**



Scheme 3. Supposed pathways of the formation of products **2** and **3** and byproducts **4–6** and **8**.



6, **15a**, R = CH_3
14a, **15b**, R = C_2H_5
14b, **15c**, R = C_3H_7
14c, **15d**, R = C_4H_9

Scheme 4. Structural elucidation of dimers **7a** and **7b**.

was generally higher and no hydrate **5** was detected in the reaction mixtures. In contrast, Sulf (**8**) was formed in all the runs. It is probably formed by the reaction of **2** with sulfur trioxide (Scheme 3), as methyl ethers are cleaved by sulfur trioxide to afford fluorosulfate **8** [24].

2.3. Dimer of methyl 3,3,3-trifluoropyruvate hydrate (7)

The residue after distilling off the product **3** contained, as checked by GC–MS, traces of MTFP (**3**) and MTAc (**4**), some amount of hemiacetal **6** and other compound 7 (Scheme 4) consisting of two (isomeric) compounds A and B, which are separated by GC. The mass spectra of the isomers A and B are very similar one to another, usual for diastereoisomers thus indicating two stereogenic centers in the molecule. Repeated fraction distillation of the mixture of A and B enabled enrichment of some fractions for one of the diastereoisomers up to a 2:1 ratio and thus to assign ^1H, ^{19}F and ^{13}C NMR and GC–MS spectra to individual isomers. However, the spectral analyses and chemical reactions (vide infra) were not sufficient to confirm the structure of **7**. Two structures for the dimer **7**, viz **7a** or **7b** (Scheme 4) could be elucidated on the basis of the spectral data and chemical reactions (vide infra).

We tried to get some support for the structure of **7** in the literature. A dimer of MTFP, compound **13** (Scheme 4), has been reported in the literature [25] together with its preparation from MTFP (**3**) and refluxing methanol in the presence of potassium carbonate in a 70% yield. However, the published NMR data for **13** [25] were different to those for **7a** or **7b**. We tried to prepare standard **13** according to the published procedure, but instead of the published dimer **13** we obtained only some amount of hemiacetal **6** (Schemes 3 and 4) or fluoroform, which was probably formed in a haloform-like reaction.

Dimer 7 is slowly formed without other byproducts by mixing MTFP (**3**) with concentrated sulfuric acid at room temperature. In a preparative run, the reaction was performed at 100 °C over 24 h, when the conversion of **3** was complete, but the mixture also contained some byproducts. However, the results were not reproducible and the product **7** could be obtained only in 90% purity.

Dimer **7** is thermally unstable and slowly decomposes to MTFP (**3**) and reacts with O-nucleophiles (water, alcohols) to afford pairs of compounds (**14** and **15**, Scheme 4) in the ratio 1:1 even in cases, when one of the diastereoisomers A or B predominates (2:1) in the starting dimer **7**. Products of the nucleophilic reactions, viz. hydrate and hemiacetals **14** were identified by spectroscopic comparison with reference compounds **5** and **6**, **14a**–**14c** (Scheme 4). Compounds **15** are most probably the corresponding derivatives of 3,3,3-trifluoropyruvic acid as can be deduced from the following observations: NMR spectra of **15a**–**15d** are very similar to those of the corresponding compounds **6** and **14a**–**14c**; compounds **15a**–**15d** are completely decomposed in the heated inlet of a MS apparatus; compounds **15** are completely extracted by D_2O from the solution of a mixture of **14** and **15** in $CDCl_3$ as checked by ^1H, ^{19}F and ^{13}C NMR.

3. Conclusions

An optimized procedure for the laboratory preparation of MTFP (**3**, yields above 90%, purity 95%) by the reaction of MTPr (**2**) with concentrated sulfuric acid has been developed. The reaction of **2** with oleum afforded less pure **3** in lower yields. Byproducts such as MTAc (**4**), methyl 3,3,3-trifluoropyruvate hydrate (**5**), methyl hemiacetal of trifluoropyruvate (**6**), DimMTP (**7**), and Sulf (**8**) were identified.

4. Experimental

4.1. General comments

Temperature data were not corrected. GC analyses were performed on a Micromat HRGC 412 (GCa, Nordion Analytical; 25 m glass capillary column, SE-30) and Chrom 5 (GCb, Laboratorní pøístroje, Prague; FID, 380 cm × 0.3 cm packed column, silicone elastomer E-301 on Chromaton N-AW-DMCS (Lachema, Brno), nitrogen) instruments. NMR spectra were recorded on Varian Gemini 300 HC (^1H at 300 MHz, ^{13}C at 75.46 MHz) and Bruker WP 80 SY (^{19}F at 75.4 MHz) instruments: TMS and $CFCl_3$ as the internal standards, chemical shifts (ppm) (s: singlet, d: doublet, t: triplet, q: quadruplet, kv: quintet, sex: sextet, m: multiplet, bs: broad singlet), coupling constants *J* (Hz), solvent $CDCl_3$ and DMSO-d_6. MS spectra were scanned on a Hewlett-Packard MSD 5971A instrument (1989, EI 70 eV). Infrared spectra were scanned on a NICOLET 740 USA apparatus.

Chemicals used were as follows. Standard compounds, hydrate **5** and hemiacetals **6** and **14a**–**14c** were prepared according to the literature [26–28]. Hexafluoropropene-1,2-oxide (**1**) (Aldrich), silica gel (60–100 μm, Merck), diethyl ether (distilled over Na), dichloromethane (distilled, bp 42 °C). Methanol (distilled over Na, stored over molecular sieve).

*4.2. Preparation of methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate (**2**) by methanolysis of 1,1,2,3,3,3-hexafluoropropene-1,2-oxide (**1**)*

4.2.1. Apparatus

Pressure cylinder with hexafluoropropene-1,2-oxide (HFPO), safety flask (2 l), double-sided hydraulic seal with methanol, two-necked reaction flask (2.5 l), packed column (ceramic Berle saddles, 80 cm), reflux condenser, double-sided bubbler with methanol, a trap (cooled with dry ice–ethanol mixture), double-sided bubbler with methanol, silicon oil heated bath (Fig. 1).

4.2.2. Procedure

The reaction flask was charged with methanol (1400 ml, 1107 g, 34.5 mol) and boiling stones and heated to reflux. HFPO was then introduced into refluxing methanol at such a rate that almost all was consumed; in 12 h, 260 g (1.6 mol) of HFPO was bubbled into the reaction flask. Then, the cooled trap containing unreacted HFPO was replaced with a new one, the cylinder was replaced with the trap containing HFPO and the trapped HFPO was now bubbled into the reaction flask. The safety trap was then flushed with nitrogen through the reaction flask. The reaction mixture and methanol from all bubblers were combined and mixed with water (5.6 l), the organic layer was separated and water layer was extracted three times with dichloromethane (300 ml). The extracts and the organic layer were combined and dried over $MgSO_4$. Dichloromethane was distilled off and the residue was fractionally distilled on a packed column (see Section 4.2.1) with a heated jacket and take-off head. The main fraction was taken in the range of 125–126 °C, yield 100 g (33%), purity >99% (checked by GC). Lower and higher boiling fractions (177 g) were combined (purity ca. 66%) and also combined with analogous fractions from the second experiment and then again fractionally distilled. The overall yield of methoxypropanoate **2** was 217 g (73%), bp 126 °C.

^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.38 (bs, 3H, OCH_3), 3.84 (s, 3H, $COOCH_3$) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ 81.9 (d, 3F, CF_3, $^3J_{FF} = 3.3$ Hz), -135.3 (qq, 1F, $CF(OCH_3)$, $^3J_{FF} = 3.3$ Hz and $^4J_{FH} = 1.6$ Hz, d, q, $^3J_{FF} = 3.3$ Hz) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 53.15 (s, $COOCH_3$, $CFOCH_3$), 103.98 (dq, CF, $^1J_{CF} = 244.8$ Hz, $^2J_{CF} = 36.3$ Hz), 118.73 (dq, CF_3, $^1J_{CF} = 286.3$ Hz, $^2J_{CF} = 34.2$ Hz), 161.4 (d, $COOCH_3$, $^2J_{CF} = 37.8$ Hz) ppm.

MS ($M_r = 190$), *m/z* (% relative intensity): EI: 191/0.08 ($M^+ + 1$), 171/3, 160/22, 143/20, 140/4, 131/100, 128/7, 121/8, 112/15, 109/10, 100/13, 97/48, 93/34, 81/19, 78/11, 77/8, 69/98, 59/95, 50/6, 47/13, 45/14, 43/13, 33/5, 31/16.

*4.3. Methyl 3,3,3-trifluoropyruvate (**3**)*

*4.3.1. Preparation of **3***

A round-bottomed flask (100 ml) equipped with a take-off head combined with a drying tube ($CaCl_2$) was charged with methoxypropanoate **2** (20.7 g, 109 mmol), SiO_2 (1.5 g, 25 mmol) and concentrated sulfuric acid (95%, 26 ml). The mixture was heated to 140 °C to reflux on an oil bath while stirring (magnetic spinbar). A distillate was taken in the range 60–83 °C (9.87 g) that contained the product **3** and acetate **4** in a molar ratio 70:30 (calculated from ^{1}H and ^{19}F NMR spectra). Calculated yields: product **3**, 7.3 g (43%); acetate **4**, 2.57 g (18.4%). Preparation was carried out according to [2].

*4.3.1.1. MeTFP (**3**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 4.01 (s, 3H, $COOCH_3$) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ -76.3 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 55.41 (s, $COOCH_3$), 116.71 (q, CF, $^1J_{CF} = 289.6$ Hz), 155.36 (s, $COOCH_3$), 175.17 (q, C=O, $^2J_{CF} = 39.1$ Hz) ppm.

MS ($M_r = 156$), *m/z* (% relative intensity): EI: 156/0.02 (M^+), 126/0.09, 112/0.09, 109/0.02, 99/4, 97/4, 81/2, 78/2, 69/100, 59/66, 50/12, 44/3, 31/7.

*4.3.1.2. MTAc (**4**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.98 (s, 3H, $COOCH_3$) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ -75.6 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 55.47 (s, $COOCH_3$), 116.2 (q, CF, $^1J_{CF} = 284.7$ Hz), 159.64 (q, C=O, $^2J_{CF} = 42.3$ Hz) ppm [29].

4.3.2. Optimization of the preparation

4.3.2.1. Apparatus. Round-bottomed flask (10 ml) equipped with a short-path Hickmann still combined with a drying tube ($CaCl_2$), magnetic spinbar, oil bath heating.

4.3.2.2. Typical procedure with sulfuric acid. The flask was charged with starting components (propanoate **2** (1.99 g, 10.5 mmol), sulfuric acid (90%, 4.50 g, equivalent of 41.3 mmol 100% H_2SO_4) and silica gel (0.2 g, 3.26 mmol)), immersed completely in an oil bath at room temperature and the bath was slowly heated to 140 °C over 1 h while stirring the mixture. The temperature was maintained for 30 min and the distillate collected was analysed by ^{1}H and ^{19}F NMR. The distillate (1.16 g) contained pyruvate **3** (MTFP), trifluoroacetate **4** (MTAc) and hydrate of MTFP **5** (HydMTP) in a molar ratio 63.5:20:16.5. Calculated yields: MTFP (**3**) 0.75 g (46%), MTAc (**4**) 0.19 g (14%) and HydTFP (**5**) 0.22 g (12%).

4.3.2.3. Typical procedure with fuming sulfuric acid (oleum). Propanoate **2** (1.95 g, 10.3 mmol), oleum 60% (2 ml, i.e. 1.6 g (16.3 mmol) of 100% H_2SO_4 and 2.4 g (30 mmol) of free SO_3) and silica gel (0.2 g, 3.36 mmol) were reacted as shown earlier. The distillate (2.25 g) consisted of a mixture of products among which were identified MTFP (**3**) (4.6 mol%), MTAc (**4**) (34 mol%) and and fluorosulfate **8** (Sulf, 38 mol%). Calculated yield of **3** was ca. 6%.

Sulf (**7**): ^{19}F NMR (75.4 MHz, $CDCl_3$): δ +31.5 (s, CF_3) ppm; [30]: +31.4 ppm; [31]: +31.3 ppm.

4.3.2.4. Typical procedure with phosphoric acid. Propanoate **2** (1.08 g, 5.67 mmol), 85% H_3PO_4 (3 g, 26 mmol 100% H_3PO_4) and silica gel (0.11 g, 2.03 mmol) were reacted as shown earlier. The distillate consisted only of the recovered starting **2** (1.03 g).

*4.3.3. Methyl[1,2,2,2-tetrafluoro-2-(methoxy-carbonyl)-ethyl]oxonium hydrogensulfate (protonated methyl 3,3,3-trifluoropyruvate) (**11**)*

Methoxypropanoate **2** was mixed with 96% H_2SO_4 and stirred in a dry atmosphere for 1.5 h. ^{19}F NMR analysis showed signals that could be assigned to oxonium salt **11**. The addition of a small amount of water changed the ^{19}F NMR to that of the starting **2**.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −80.5 (d, CF_3, $^2J_{FF}$ = 3.7 Hz), −132.4 (bs, CF) ppm.

*4.3.4. Optimized procedure for the laboratory preparation of MTFP (**3**)*

4.3.4.1. Apparatus[1]. Silicon oil heated bath, magnetic stirrer;[2] reaction flask fitted with fraction-distillation head (with efficient reflux condenser), trap and drying tube ($CaCl_2$).

4.3.4.2. Procedure. Reaction flask (100 ml)[3] was charged with methoxypropanoate **2** (MTPr) (29.96 g, 157.6 mmol), 96% H_2SO_4 (15.11 g) and silica gel (2.99 g, 49.8 mmol). The flask was immersed (level-to-level)[4] into the mixed oil bath that was heated[5] to 125 °C and refluxed for 30 min. Then, the pyruvate was slowly collected over ca. 30–60 min while maintaining the reflux and after that the flask was wholly immersed in the bath and the rest of the pyruvate was distilled. MTFP (**3**) was obtained in a yield of 23.2 g (94.5%) and purity of 95% (checked by ^{1}H and ^{19}F NMR); the impurities were: MTPr (**2**) and methyl hemiacetal **6** (Scheme 4). The MTFP obtained was stored in the dark in fused glass ampoules.[6]

*4.4. Reactions of MTFP (**3**) with O-nucleophiles*

*4.4.1. Hydrate of MTFP: methyl 3,3,3-trifluoro-2,2-dihydroxypropanoate (**5**)*

A solution of MTFP **3** in $CDCl_3$ in a NMR measuring tube was mixed with a saturated ethereal solution of water and the ^{19}F NMR spectrum of hydrate **5** was immediately taken. After evaporation of volatile components (rotary evaporator, then oil pump), white crystalline **5** was obtained.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −83.7 (s) ppm.

^{13}C NMR (75.46 MHz, DMSO-d_6): δ 52.39, 90.3 (q, $^3J_{CF}$ = 32.1), 121.7 (q, $^2J_{CF}$ = 288.6), 166.6.

MS (M_r = 174), *m/z* (% relative intensity): EI: 157 (0.5, $M^+ - 17$); 146/1, 129/1, 126/1, 115 (78, $M^+ - 59$); 97/5, 95/61, 81/4, 78/11, 69/100, 67/8, 60/45, 59/91, 51/77, 50/18, 45/79, 33/23, 32/29, 31/50.

*4.4.2. Hemiacetals of MTFP (**6, 14a–14c**)*

A flask (10 ml) was charged with MTFP (**3**) (483 mg, 3.1 mmol) in diethyl ether (5 ml) and methanol (5 g, 156 mmol) was added dropwise while stirring (magnetic spinbar). Volatile components were then removed (rotary evaporator) to afford liquid hemiacetal **6**, yield 553 mg (95%), purity 96% (check by ^{1}H and ^{19}F NMR). In an analogous way, liquid hemiacetals **14a–14c** were prepared in yields of 87–96%.

*4.4.2.1. Methyl 3,3,3-trifluoro-2-hydroxy-2-methoxy-propanoate (**6**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.39 (s, 3H, OCH_3), 3.96 (s, 3H, $COOCH_3$), 4.91 (bs, ^{1}H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.5 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 51.14 (OCH_3), 54.43 ($COOCH_3$), 93.47 (q, $^2J_{CF}$ = 33.8 Hz), 120.87 (q, $^1J_{CF}$ = 287.4 Hz), 167.49 ($COOCH_3$) ppm.

MS (M_r = 188), *m/z* (% relative intensity): EI: 189/0.05 ($M^+ + 1$), 171/0.6, 157/0.5 ($M^+ - 31$), 143/1, 129/100 ($M^+ - 59$), 121/3, 119/4, 109/44, 97/4, 95/4, 93/4, 81/16, 78/6, 69/62, 67/8, 65/13, 59/71, 51/13, 50/8, 47/8, 45/23, 31 (20).

*4.4.2.2. Methyl 2-ethoxy-3,3,3-trifluoro-2-hydroxypropanoate (**14a**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 1.23 (t, 3H, CH_3, $^3J_{HH}$ = 7.1 Hz), 3.44 (dq, 1H, CH_2, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 7.1 Hz), 3.76 (dq, 1H, CH_2, $^2J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 7.1 Hz), 3.94 (s, 3H, $COOCH_3$), 4.47 (bs, 1H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.7 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.79 (CH_2), 54.57 ($COOCH_3$), 60.11 (CH_3), 93.65 (q, $^2J_{CF}$ = 34.3 Hz), 120.82 (q, $^1J_{CF}$ = 286.8 Hz), 167.90 ($COOCH_3$) ppm.

MS (M_r = 202), *m/z* (% relative intensity): EI: 157/4 ($M^+ - 45$), 143/34 ($M^+ - 59$), 129/2, 126/1, 115/100, 109/5, 97/3, 95/14, 81/2, 78/3, 69/37, 67/5, 60/9, 59/45, 57/3, 51/7, 50/5, 45/29, 43/4, 33/11, 32/3, 31/21.

*4.4.2.3. Methyl 3,3,3-trifluoro-2-hydroxy-2-propoxy-propanoate (**14b**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 0.91

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[1] The whole apparatus is dried before reaction in an oven at ca. 140 °C and cooled at room temperature under a stream of dry nitrogen.

[2] Intensive stirring is recommended to decrease foam formation in the reaction flask.

[3] Owing to intensive foaming at the beginning of the reaction, it is recommended to use a bigger flask.

[4] To reduce intensive foaming, it is convenient to immerse the flask so that liquids in the flask and the bath are at the same level and do not immerse the flask deeper.

[5] The reaction usually starts at 110–125 °C in the bath.

[6] Ampoules were dried in a flame and cooled in a dessicator over P_2O_5.

(t, 3H, CH_3, $^3J_{HH} = 7.4$ Hz), 1.62 (sex, 2H, $^3J_{HH} = 7.1$ Hz), 3.31 (td, 1H, CH_2, $^2J_{HH} = 8.8$ Hz, $^3J_{HH} = 6.6$ Hz), 3.65 (td, 1H, CH_2, $^2J_{HH} = 8.8$ Hz, $^3J_{HH} = 6.6$ Hz), 3.95 (s, 3H, $COOCH_3$), 4.58 (bs, 1H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.7 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 9.93 (CH_2), 25.30 (CH_2), 54.43 (CH_3), 65.83 ($COOCH_3$), 93.72 (q, $^2J_{CF} = 33.8$ Hz), 120.89 (q, $^1J_{CF} = 287.5$ Hz), 167.82 ($COOCH_3$) ppm.

MS ($M_r = 216$), m/z (% relative intensity): EI: 157/9 ($M^+ - 59$), 129/2, 115/1, 109/3, 105/3, 97/2, 95/1, 87/1, 81/1, 78/2, 69/17, 67/3, 60/2, 59/20, 51/2, 50/2, 45/5, 43/100, 41/25, 33/4, 32/1, 31/15.

*4.4.2.4. Methyl 2-butoxy-3,3,3-trifluoro-2-hydroxypropanoate (**14c**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 0.90 (t, 3H, CH_3, $^3J_{HH} = 7.2$ Hz), 1.37 (sex, 2H, CH_2, $^3J_{HH} = 7.1$ Hz), 1.59 (kv, 2H, CH_2, $^3J_{HH} = 6.6$ Hz), 3.36 (td, 1H, CH_2, $^2J_{HH} = 8.8$ Hz, $^3J_{HH} = 6.6$ Hz), 3.70 (td, 1H, CH_2, $^2J_{HH} = 8.8$ Hz, $^3J_{HH} = 6.6$ Hz), 3.68 (s, 3H, $COOCH_3$), 4.42 (bs, 1H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.8 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 13.54 (CH_2), 18.92 (CH_2), 31.29 (CH_2), 54.62 ($COOCH_3$), 64.12 (CH_3), 93.69 (q, $^2J_{CF} = 33.8$ Hz), 120.83 (q, $^1J_{CF} = 287.5$ Hz), 168.02 ($COOCH_3$) ppm.

MS ($M_r = 230$), m/z (% relative intensity): EI: 171/2 ($M^+ - 59$), 157/4 ($M^+ - 73$), 129/1, 115/1, 109/3, 105/4, 97/2, 95/1, 88/2, 81/1, 78/2, 69/20, 67/3, 60/1, 59/19, 57/100, 51/2, 50/3, 45/5, 43/6, 41/46, 39/7, 33/3, 31/10.

*4.5. Dimer of methyl 3,3,3-trifluoropyruvate hydrate (**7**) and its reactions with alkanols*

*4.5.1. Attempts to prepare dimer **13** as a reference compound*

(A) A round-bottomed flask (10 ml) equipped with a reflux condenser connected to a drying tube ($CaCl_2$) was charged with MTFP (**3**) (0.54 g, 3.5 mmol), K_2CO_3 (0.48 g, 3.5 mmol) and dichloromethane (2.6 ml) and the mixture was refluxed on a oil bath for 24 h while stirring (magnetic spinbar). After the reaction, the mixture contained only hemiacetal **6** as the product (analysis by ^{19}F NMR) [25].

(B) In the apparatus as earlier, hemiacetal **6** (0.57 g, 3.01 mmol) and K_2CO_3 (0.2 g, 1.47 mmol) were heated to 90 °C for 1 h while stirring. A sample of the mixture contained **6** and a small amount of a volatile compound as the only product, whose ^{19}F NMR signal corresponded to that of fluoroform. After additional 1 h heating of the mixture the ^{19}F NMR analysis showed no presence of any fluorinated compound in the mixture.

4.5.1.1. Fluoroform. ^{19}F NMR (75.4 MHz, $CDCl_3$): δ −78.5 (d, CHF_3, $^2J_{HF} = 78.9$ Hz) ppm; [32]: −78.3 (d, $^2J_{HF} = 79.1$ Hz) ppm.

*4.5.2. Preparation of the dimer **7***

Round-bottom flask (25 ml) equipped with a reflux condenser connected with a drying tube ($CaCl_2$) was charged with MTFP (**3**) (3.75 g, 24 mmol) and 96% H_2SO_4 (1.71 g, 16.7 mmol 100% H_2SO_4) and the mixture was heated at 100 °C on an oil bath for 24 h while stirring (magnetic spinbar). After cooling to room temperature, the mixture was extracted with CFC-113 (5 ml × 10 ml, check by GCb) and the combined extracts were dried ($MgSO_4$). The solvent was then removed from the filtrate on rotary evaporator (44 °C/39.6 kPa) and the residue was distilled to afford dimer **7**, yield 0.95 g (23%), purity 90% (GC) identified as a mixture of diastereoisomers A and B.

^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.97 (s, 3H), 3.98 (s, 3H), 4.07 (s, 6H), 5.01 (bs, 2H) ppm.

IR (KBr): ν 3700–2400, 1752, 1630, 1248, 1197, 1095, 991, 706 cm^{-1}.

4.5.3. Diastereoisomer A

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.9 (s, CF_3), −82.6 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 56.52, 93–99 (2q), 119.91 (q, $^1J_{CF} = 286.9$ Hz), 120.02 (q, $^1J_{CF} = 286.9$ Hz), 160.59, 160.84 ppm.

MS ($M_r = 330$), m/z (% relative intensity): EI: 282/0.5, 225/7, 197/7, 171/4, 157/1, 143/9, 129/1, 109/10, 97/11, 81/17, 69/100, 65/5, 59/56, 50/4, 45/2, 43/3, 31/3.

4.5.4. Diastereoisomer B

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.2 (q, CF_3, $J_{HF} = 2.9$ Hz), −82.3 (q, CF_3, $J_{HF} = 2.9$ Hz) ppm.

C^{13}C NMR (75.46 MHz, $CDCl_3$): δ 55.51, 56.52, 93–99 (2q), 119.33 (q, $^1J_{CF} = 285.2$ Hz), 119.73 (q, $^1J_{CF} = 286.9$ Hz), 160.90, 165.26 ppm.

MS ($M_r = 330$), m/z (% relative intensity): EI: 312/0.01, 282/1, 225/5, 197/7, 171/8, 143/8, 109/10, 97/10, 81/11, 69/100, 65/5, 59/70, 50/4, 45/2, 43/5, 31/2.

*4.5.5. Decomposition of dimer **7** by the reaction with alcohols*

Dimer **7** (0.4 g) was dissolved in dry Et_2O (8 ml) and the solution divided in four portions of 2 ml each. Alcohols (methanol, ethanol, propanol and butanol) were added to each portion and after standing for 24 h at room temperature the solutions were analyzed (GC–MS, ^{19}F NMR). Product mixtures were obtained by evaporation of volatile components and analyzed by ^{1}H and ^{13}C NMR. In all the reactions, 1:1 mixtures of products **6**, **14a–14c** and **15a–d** were obtained. GC–MS analysis of the products failed owing to decomposition of free acids in heated inlet.

For the spectra of compounds **6**, **14a–14c** see Section 4.3.2.

*4.5.5.1. 3,3,3-Trifluoro-2-hydroxy-2-methoxypropanoic acid (**15a**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.45 (m, 3H, OCH_3), 6.53 (bs, 2H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.9 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 51.19 (OCH_3), 93.43 (q, $^2J_{CF} = 33.8$ Hz), 120.97 (q, $^1J_{CF} = 287.4$ Hz), 168.23 (COOH) ppm.

*4.5.5.2. 2-Ethoxy-3,3,3-trifluoro-2-hydroxypropanoic acid (**15b**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 1.24 (t, 3H, CH_3, $^3J_{HH} = 7.1$ Hz), 3.40–3.60 (m, 1H, CH_2), 3.70–3.87 (m, 1H, CH_2), 7.01 (bs, 2H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −82 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.78 (CH_2), 60.36 (CH_3), 93.68 (q, $^2J_{CF} = 33.8$ Hz), 120.83 (q, $^1J_{CF} = 282.3$ Hz), 169.10 (COOH) ppm.

*4.5.5.3. 3,3,3-Trifluoro-2-hydroxy-2-propoxypropanoic acid (**15c**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 0.92 (t, 3H, CH_3, $^3J_{HH} = 7.2$ Hz), 1.6 (sex, 2H, $^3J_{HH} = 6.6$ Hz, $^3J_{HH} = 7.2$ Hz), 3.64 (t, 2H, CH_2, $^3J_{HH} = 6.6$ Hz), 5.55 (bs, 2H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −81.8 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 10.16 (CH_2), 22.59 (CH_2), 64.76 (CH_3), 93.56 (q, $^2J_{CF} = 33.8$ Hz), 121.06 (q, $^1J_{CF} = 282.3$ Hz), 168.53 (COOH) ppm.

*4.5.5.4. 2-Butoxy-3,3,3-trifluoro-2-hydroxypropanoic acid (**15d**).* ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 0.92 (t, 3H, CH_3, $^3J_{HH} = 7.4$ Hz), 1.32–1.46 (m, 2H, CH_2), 1.55–1.67 (m, 2H, CH_2), 3.49 (td, 1H, CH_2, $^2J_{HH} = 8.8$ Hz, $^3J_{HH} = 6.1$ Hz), 3.76 (td, 1H, CH_2, $^2J_{HH} = 8.8$ Hz, $^3J_{HH} = 6.1$ Hz), 6.89 (bs, 2H) ppm.

^{19}F NMR (75.4 MHz, $CDCl_3$): δ −82 (s, CF_3) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 13.59 (CH_2), 18.91 (CH_2), 31.24 (CH_2), 64.38 (CH_3), 93.63 (q, $^2J_{CF} = 33.8$ Hz), 120.78 (q, $^1J_{CF} = 282.3$ Hz), 169.44 (COOH) ppm.

Acknowledgements

The research was supported by the Ministry of Education (grant No. MSM 223100001) and the grant agency of the Czech Republic (project No. 203/02/0306).

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