Synthesis of trifluoromethylated α-hydroxy acids and their derivatives based on alkyl trifluoropyruvates

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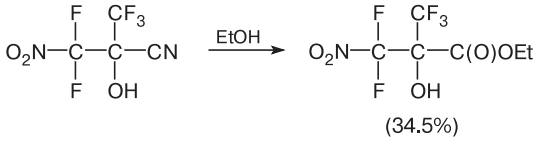
The reactions of trifluoropyruvates with nitromethane and arylmagnesium bromides leading to trifluoromethyl-containing α-hydroxy acid esters were studied and various derivatives of the acids were obtained.

Key words: ethyl trifluoropyruvate, methyl trifluoropyruvate, alkylation, arylation, fluorine-containing α-hydroxy- and α-methoxycarboxylic acids and their derivatives, α-hydroxy acid nitro derivatives.

The increased interest to α-trifluoromethyl-α-hydroxycarboxylic acid derivatives in recent years is associated with their unique pharmaceutical and agrochemical properties. Thus, more than 2,800 bioactive compounds containing this structural unit are described in drug synthesis studies, with some of which being the subject of 330 patents.[1] Earlier, we reported the use of α-alkynyl-α-hydroxy-α-trifluoromethyl acids, obtained upon treatment of ethynyl- or allenylmagnesium bromides with methyl trifluoropyruvate, for the synthesis of fluorine-containing peptide conjugates.[2] The present work is devoted to the development of preparative methods for the synthesis of CF_3-substituted hydroxy acids and their derivatives containing α-positioned nitroalkyl or aryl substituents. Although such compounds are of interest for the modification of bioactive substances, information on their synthesis in the literature is scarce. Thus, there are described reactions of methyl trifluoropyruvate with conjugated nitroalkenes and nitrodienes in the presence of 40—100 mol.% of 4-dimethylaminopyridine,[3,4] with some of the obtained α-hydroxyalkylation products showing anticancer activity in low concentrations.[4] However, this method gives only α-hydroxy-α-trifluoromethyl-β-nitroalkenoic acid esters. It was reported about the synthesis of ethyl α-hydroxy-β-nitroperfluoroisobutanoate by hydrolysis of the corresponding cyanohydrin in the presence of ethanol[5] (Scheme 1), but the product yield was low.

Scheme 1



Reagents and conditions: H_2SO_4, 100 °C, 5 h.

There are known several methods for the preparation of CF_3-containing α-hydroxyalkanoic acids with an α-aryl group. An unusual approach was suggested for obtaining optically active esters of such acids consisting in the reaction of 2-aryl-1-trifluoromethylethane-1,2-diones with 8-phenyl-L-menthol in the presence of zinc triflate and bis-oxazoline ligand.[1] A similar system of catalysts based on copper triflate and chiral methylenebis(4,5-diphenyloxazoline) ligands was used in the synthesis of ethyl α-(*p*-alkoxyphenyl)- or α-(*p*-aryloxyphenyl)-α-hydroxy-α-trifluoromethylacetates by the Friedel—Crafts reaction of aryl ethers ArOR (R = Alk, Ph) with ethyl trifluoropyruvate (ETFP).[6] The reaction of ETFP with aryl ethers ArOAlk (Alk = Me, Et) containing *meta* NH_2 or NHMe groups proceeded without catalyst under microwave irradiation at 150 °C at *p*-position to the amino group; some of these reaction products showed activity against the HIV virus.[7] Phenol and its *ortho*-substituted analogs undergo hydroxyalkylation with trifluoropyruvates in the presence of Bu^tNH_2 or Et_3N exclusively at *p*-position[8] (Scheme 2).

However, phenol ethers did not undergo this reaction,[8] though later it was accomplished using another catalysts.[6] In the case of phenols with electron-donating RO groups (R = Me, Bn, TBS) at *meta*- rather than at *ortho*-position, the reaction with ETFP was catalyzed by quinine derivatives to obtain products of *para*-hydroxyalkylation with respect to the RO rather than to the HO group.[9] There is a report on the synthesis of some CF_3-substituted α-hydroxy acid esters upon treatment of arylmagnesium halides with ETFP, however, this method is not preparative since it was carried out in microscale amounts using column chromatography for the isolation of products.[10]

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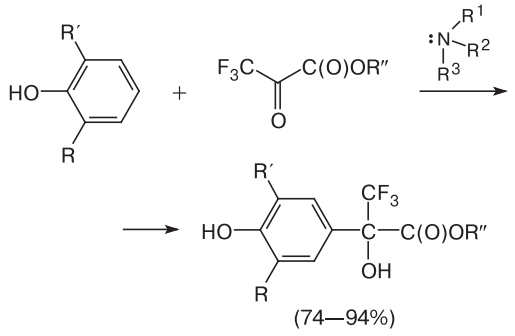
Scheme 2

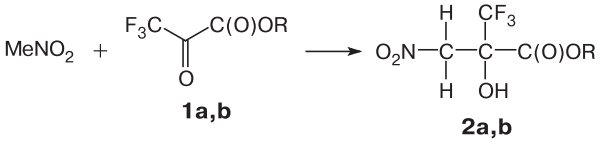


R = R′ = H, Me, Bu^t, OMe, Hal; R′′ = Me, Et
R^1 = R^2 = R^3 = Et; R^1 = R^2 = H, R^3 = Bu^t

Results and Discussion

In the present work, we describe preparative methods for the synthesis of CF_3-containing α-hydroxy acid derivatives using universal building blocks, available alkyl trifluoropyruvates (**1**). Thus, the reaction of the latter with nitromethane gave rise to new compounds, α-CF_3-containing α-hydroxy-β-nitropropanoic esters (**2a**,**b**) (Scheme 3).

Scheme 3



R = Me (**a**), Et (**b**)

Conditions: Et_3N (5 mol.%).

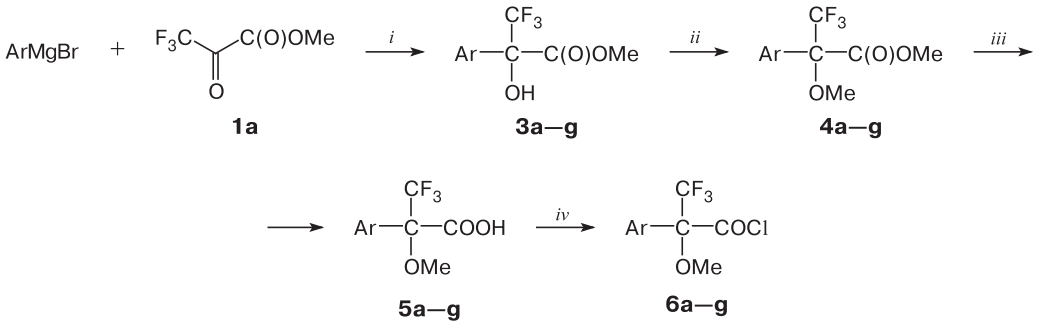
Compounds **2a**,**b** were not formed in the absence of the catalyst, however, in the presence of 5 mol.% of triethylamine a vigorous reaction took place already at 20 °C. The highest yields (90—93%) of the target products **2a**,**b** were achieved when pyruvates were added to a pre-prepared mixture of $MeNO_2$ and Et_3N. When the reagents are mixed in the reverse order, the yields of products **2a**,**b** decrease, probably due to a side cyclodimerization reaction of the starting pyruvates in the presence of Et_3N. It is known that pyruvate **1** treated with K_2CO_3 or metallic sodium undergoes conversion to a cyclodimer, 2-methoxycarbonyl-4-methoxy-2,4-bis(trifluoromethyl)-1,3-dioxolan-5-one.[11]

The nitromethylation reaction of alkyl pyruvates (see Scheme 3) can become useful for the synthesis of poorly available fluorine-containing α-hydroxy-β-aminocarboxylic acids.

In the IR spectra of compounds **2**, the ν(CO) frequency is considerably increased (to 1780 cm^{-1}) due to the influence of two electron-withdrawing substituents (CF_3 and CH_2NO_2), which agrees with the known data.[12] Attempted synthesis of ethyl α-trifluoromethyl-β-nitroacrylate upon treatment of hydroxy ester **2b** with excess of P_2O_5 at 200 °C failed, apparently, because of the dehydration product instability. Hydroxy ester **2b** is stable towards acetic anhydride (on catalysis with CF_3SO_3H). At the same time, in the presence of triethylamine it vigorously reacts with Ac_2O, resulting in the destruction of the molecule with the loss of the fluorine atom instead of expected acetylation.

Though, fluoroaryl-containing drugs possess higher activity as compared to hydrogenated analogs,[13] only limited number of methods for the synthesis of α-arylalkanoic acids fluorinated in the side chain are described. This prompted us to develop a general approach to the synthesis of α-CF_3-α-hydroxy esters containing an α-positioned aryl group, which can be used for large scale amounts. It consists in the reaction of an ether solution of arylmagnesium bromides with methyl trifluoropyruvate (**1a**) in THF at low temperatures (Scheme 4). We obtained various α-CF_3-α-hydroxy esters **3a**—**d**,**f**—**g** in good yields (60—75%, Table 1), except for 2,4-dichlorophenyl-substituted compound **3e**, whose low yield (34%) is explained

Scheme 4



3—6: Ar = 3-ClC_6H_4 (**a**), 2-ClC_6H_4 (**b**), 3,4-$Me_2C_6H_3$ (**c**), 3,5-$Cl_2C_6H_3$ (**d**), 2,4-$Cl_2C_6H_3$ (**e**), 4-$CF_3C_6H_4$ (**f**), 4-$PhOC_6H_4$ (**g**)

Reagents and conditions: *i*. THF—ether, −76 °C; *ii*. MeI/NaH, DMF, 50—60 °C or $(MeO)_2SO_2$/KOH, dioxane, 45—55 °C; *iii*. KOH, MeOH—H_2O, reflux 1.2—9.5 h; *iv*. $SOCl_2$, 3—15 mol.% of Py, reflux 4.5—15 h or 15 mol.% of imidazole, reflux 14—15 h.

Table 1. Physicochemical characteristics of synthesized α-CF_3-α-hydroxy esters **3a—g**

Compound	Yield (%)	B.p./°C (*p*/Torr)	n_D (*T*/ °C)	R_F[a]
3a	73	84—87 (1)	1.4860 (22)	0.52[b]
3b	60	90—95 (1)	1.4939 (20)	0.20[b]
3c	75	100—105 (2)	1.4730 (22)	0.48[b]
3d	62	117—118[c]	—	0.65[b] 0.41[d]
3e	34	117—120[e] (3)	—[e]	0.27[d] 0.51[f]
3f	65	84—87 (3)	—	0.21[d]
3g	62	156—160 (2)	1.5240 (21)	0.40[b]

[a] A crimson spot under UV light.
[b] $CHCl_3$.
[c] M.p./°C (CCl_4—light petroleum ether).
[d] The system CCl_4—$CHCl_3$ (1 : 1).
[e] Crystallizes upon storage, m.p. 38—42 °C.
[f] The system dioxane—toluene (1 : 10).

by the low reactivity of the starting aryl bromide in the Grignard reaction even in the presence of catalysts (iodine and dibromoethane). The target products **3a—g** were isolated by distillation *in vacuo* or crystallization. Their yields and physicochemical properties are given in Table 1.

New α-CF_3-α-hydroxy esters **3a—g** are convenient starting compounds in the synthesis of different α-CF_3-α-aryl-substituted acid derivatives. Thus, hydroxy esters **3a—g** were successfully methylated with iodomethane in the presence of sodium hydride (or with dimethyl sulfate—potassium hydroxide pair) upon moderate heating. After distillation, α-CF_3-α-methoxy esters **4a—g** were isolated in pure form in high yields (82—96%) (see Scheme 4 and Table 2). α-Methoxy acid methyl esters **4a—g** were saponified using a 1.5-fold excess of KOH in refluxing aqueous methanol; in the case of 3,5-dichlorophenyl- and 4-phenoxyphenyl-substituted compounds **4d**,**g**, more prolonged heating for 5—9.5 h was required. After recrystallization (or reprecipitation) arylacetic acids with α methoxy and CF_3 groups, namely compounds **5a—g**, were obtained in 77—96% yields (see Scheme 4 and Table 3).

It was of special interest to obtain α-CF_3-α-methoxy acyl chlorides, which can be used for modification of bioactive amines to improve their lipophilicity. Acyl chlorides **6a—g** were synthesized by the solvent-free reaction of the corresponding α-CF_3-α-methoxy-α-arylacetic acids **5a—g** with an excess of thionyl chloride catalyzed with pyridine or imidazole. Arylacetic acids containing a chlorine atom at position 2 (compounds **5b**,**e**) were the least active in this reaction, their conversion was increased using larger amounts of $SOCl_2$ and the catalyst and more prolonged heating (~15 h). Though most acyl chlorides are low-melting-point solid compounds **6a—e**, all the

Table 2. Physicochemical characteristics of synthesized α-CF_3-α-methoxy esters **4a—g**

Starting hydroxy ester	Method of synthesis	Product	Yield (%)	B.p./°C (*p*/Torr)	n_D (*T*/ °C)	R_F[a]
3a	*A*	**4a**	87	114—116 (3—4)	1.4780 (20)	0.39[b]
3b	*A*	**4b**	89	97—100 (1)	1.4863 (18.5)	0.59[c]
3c	*A*	**4c**	93	104—107 (1.5)	1.4694 (23.5)	0.35[b] 0.56[c]
3d	*Б*	**4d**	93	106—110 (2)	—[d]	0.61[b] 0.79[c]
3e	*Б*	**4e**	89	122—127 (2—3)	—	0.67[e]
3f	*Б*	**4f**	82	76—78 (3)	—	0.37[b]
3g	*A*	**4g**	96	—[f]	—	0.65[c] 0.77[g]

[a] A crimson spot under UV light.
[b] The system CCl_4—$CHCl_3$ (1 : 1).
[c] $CHCl_3$.
[d] Crystallizes upon storage, m.p. 45—46 °C.
[e] The system dioxane—toluene (1 : 10).
[f] A dense oil, pure according TLC and ^1H NMR spectrum.
[g] The system AcOEt—light petroleum ether (1 : 1).

Table 3. Physicochemical characteristics of synthesized α-CF_3-α-methoxy acids **5a—g**

Starting hydroxy ester	τ/h[a]	Product	Yield (%)	M.p. /°C	R_F[b]
4a	0.7—1.2	**5a**	89	65—66	0.24[c]; 0.55[d]
4b	1.7	**5b**	80	62—64[e]	0.11[c]; 0.35[d]
4c	2.0	**5c**	94	—[f]	0.43[d]; 0.20[g]
4d	5.0	**5d**	77	139—141	0.60[d]
4e	1.5	**5e**	96	102—104	0.60[d]
4f	1.3	**5f**	91	73—75	0.57[d]
4g	9.5	**5g**	93	—[h]	0.10[c]; 0.42[d]

[a] Conditions: the ratio of reagents: methoxy ester **4** : KOH = = 1 : 1.5; the time of reflux (τ) was determined using TLC.
[b] A crimson spot under UV light.
[c] The system Me_2CO—CCl_4 (1 : 10).
[d] The system AcOEt—light petroleum ether (1 : 1).
[e] From CCl_4.
[f] A dense oil.
[g] The system Me_2CO—CCl_4 (1 : 5).
[h] A dense oil. The product was purified upon treatment with 40% NaOH with subsequent acidification with concentrated HCl and extraction with CCl_4.

products **6a—g** can be easily purified by distillation *in vacuo* to isolate them in good yields (76—94%) (see Scheme 4 and Table 4).

In conclusion, in the present work we showed that highly reactive methyl and ethyl trifluoropyruvates are convenient starting agents in the synthesis of trifluoromethyl-substituted α-hydroxy acids containing α-positioned aryl or nitromethyl groups. Various α-CF_3-α-methoxy-α-arylacetic acids and their derivatives (methyl esters and acyl chlorides) were obtained based on the C-alkylation reaction of arylmagnesium bromides by methyl trifluoropyruvate. All the preparative syntheses developed by us can be easily scaled and do not require chromatographic purification of the products, which make new compounds available in amounts sufficient for the use in organic synthesis.

The recent review on polyfluoroalkyl-containing compounds points out that they are of interest as biologically active compounds.[14]

Experimental

NMR spectra were recorded on Bruker Avance-300 and Bruker Avance-400 spectrometer (300 and 400 MHz for ^1H NMR (an internal standard $SiMe_4$) and 282 and 376 MHz for ^{19}F NMR (an internal standard $CFCl_3$), respectively). IR spectra were obtained on a UR-20 spectrometer for neat samples. Elemental analysis was carried out in the Elemental analysis laboratory of the A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences. TLC monitoring of reaction progress was carried out on Merck plates (silica gel 60 F254, 0.25 mm). All the solvents used were purified according to the standard procedures. Characteristics of synthesized compounds **3—6** are given in Tables 1—4.

Synthesis of alkyl 2-hydroxy-3-nitro-2-trifluoromethylpropionoates (2a,b). Methyl or ethyl trifluoropyruvate (0.115 mol) was added to a solution of triethylamine (0.58 g, 0.0057 mol) in nitromethane (12.4 mL, 14 g, 0.23 mol) with stirring and cooling by ice-cold water. The reaction mixture was maintained at ~20 °C on 24 h, then distilled.

Table 4. Physicochemical characteristics of synthesized α-CF_3-α-methoxy acyl chlorides **6a—g**

Starting acid	Conditions[a]		τ/h	Product	Yield (%)	B.p./°C (*p*/Torr)	M.p./°C (n_D (*T*/°C))	R_F[b]
	5 : $SOCl_2$	Catalyst (mol.%)						
5a	1 : 3	Py (3)	5	**6a**	90	75—80 (1)	34—37	0.71[c]
5b	1 : 4	Imidazole (14.7)	14	**6b**	77	84—86 (1)	54—58	0.72[c]
5c	1 : 3	Py (4.3)	5	**6c**	88	86—91 (2)	70—72	0.75[c]
5d	1 : 3	Py (3)	4.5	**6d**	94	95—99 (3)	50—51	0.70[d]
5e	1 : 4.8	Py (15)	6.5	**6e**	76	94—97 (2)	40—43	0.74[d]
5f	1 : 3.1	Py (3.3)	4.5	**6f**	82	63—67 (3)	(1.4336 (21))	0.82[d]
5g	1 : 3	Py (3)	7.5	**6g**	90	139—141 (1)	(1.5290 (20))	0.72[c]

[a] The time of reflux (τ) was determined using TLC.
[b] A crimson spot under UV light.
[c] The system Me_2CO—CCl_4 (1 : 10).
[d] The system Me_2CO—CCl_4 (1 : 12).

Methyl 2-hydroxy-3-nitro-2-trifluoromethylpropionoate (2a). The yield was 90%, a colorless oil, b.p. 91—92 °C (15 Torr), n_D^{22} 1.3928. ^{1}H NMR (300 MHz, acetone-d_6), δ: 3.90 (s, 3 H, OCH_3); 4.86 (d, 1 H, CH_2, J_{AB} = 14.0 Hz); 5.28 (d, 1 H, CH_2, J_{AB} = 14.0 Hz); 6.18 (br.s, 1 H, OH). ^{19}F NMR (282 MHz, acetone-d_6), δ: −81.14 (s, 3 F, CF_3). Found (%): C, 27.42; H, 2.93; N, 6.21. $C_5H_6F_3NO_5$. Calculated (%): C, 27.65; H, 2.76; N, 6.45.

Ethyl 2-hydroxy-3-nitro-2-trifluoromethylpropionoate (2b). The yield was 93%, a colorless oil, b.p. 60—62 °C (3 Torr), n_D^{20} 1.3950. IR, ν/cm^{-1}: 1110, 1180 (C—F); 1390, 1590 (NO_2); 1780 (C=O); 3520 (OH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.36 (t, 3 H, CH_3, J = 7.5 Hz); 4.40—4.51 (m, 2 H, OCH_2 + 1 H, OH); 4.82 (d, 1 H, CH_2, J_{AB} = 13.5 Hz); 5.08 (d, 1 H, CH_2, J_{AB} = 13.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −76.84 (s, 3 F, CF_3). Found (%): C, 31.36; H, 3.76; F, 24.64. $C_6H_8F_3NO_5$. Calculated (%): C, 31.17; H, 3.46; F, 24.67.

Reaction of methyl trifluoropyruvate (1a) with Grignard reagent

Step 1. Preparation of arylmagnesium bromides. A solution of aryl bromide (0.3 mol) (see Table 1) in diethyl ether (~215 mL) was added to a mixture of Mg turnings (7.29 g, 0.3 mol), diethyl ether (~17 mL), and a catalyst (several iodine crystals) under argon with stirring at such a rate that the ether was boiling, then the mixture was refluxed for 1—1.5 h. Since 1-bromo-2,4-dichlorobenzene (the starting compound for the synthesis of α-hydroxy ester **3e**) did not react with magnesium under these conditions, the Grignard reaction for it was carried out in the presence of a large amount of iodine and dibromoethane (4 mL) upon reflux for 2.5 h.

Step 2. Reaction of arylmagnesium bromides with pyruvate 1a (general procedure). A solution of arylmagnesium bromide obtained in step 1 was slowly added to a solution of **1a** (46.8 g, 0.3 mol) in THF (240 mL) at –73÷–78 °C under argon with stirring. After 1 h (–72÷–78 °C), the cooling bath was removed, the reaction mixture was allowed to warm-up to ~20 °C and poured into a glass with a solution of concentrated HCl (42 mL) in water (~1.6 L). The product was extracted with CCl_4 (or benzene) then with a ~1 : 1 mixture of $CHCl_3$ and CH_2Cl_2 (3×150 mL). The organic phases were dried with $MgSO_4$, the solvent was evaporated, the residue was distilled. Compounds **3a—c**,**e—g** were obtained as colorless or light yellow oils. 3,5-Dichloro derivative **3d** was isolated as white crystals after crystallization from a mixture of CCl_4—light petroleum ether (~2 : 1). The yields and the constants of obtained compounds **3a—g** and the data of their TLC analysis are given in Table 1.

Methyl 2-(3-chlorophenyl)-3,3,3-trifluoro-2-hydroxypropionate (3a). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.02 (s, 3 H, OCH_3); 4.39 (s, 1 H, OH); 7.36—7.44 (m, 2 H, Ar); 7.71 (d, 1 H, Ar, J = 7.6 Hz); 7.82 (s, 1 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −73.18 (s, 3 F, CF_3). Found (%): C, 44.87; H, 2.84. $C_{10}H_8ClF_3O_3$. Calculated (%): C, 44.69; H, 2.98.

Methyl 2-(2-chlorophenyl)-3,3,3-trifluoro-2-hydroxypropionate (3b). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.90 (s, 3 H, OCH_3); 4.48 (br.s, 1 H, OH); 7.28—7.50 (m, 4 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −72.84 (s, 3 F, CF_3). Found (%): C, 44.94; H, 2.80. $C_{10}H_8ClF_3O_3$. Calculated (%): C, 44.69; H, 2.98.

Methyl 3,3,3-trifluoro-2-(3,4-dimethylphenyl)-2-hydroxypropionate (3c). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.18 (s, 6 H, 2 CH_3), 3.96 (s, 3 H, OCH_3); 4.22 (s, 1 H, OH); 7.35—7.51 (m, 3 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −72.12 (s, 3 F, CF_3). Found (%): C, 54.80; H, 5.09. $C_{12}H_{13}F_3O_3$. Calculated (%): C, 54.96; H, 4.96.

Methyl 2-(3,5-dichlorophenyl)-3,3,3-trifluoro-2-hydroxypropionate (3d). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.02 (s, 3 H, OCH_3); 4.42 (br.s, 1 H, OH); 7.43 (s, 1 H, Ar); 7.70 (s, 2 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −67.80 (s, 3 F, CF_3). Found (%): C, 39.84; H, 2.46. $C_{10}H_7Cl_2F_3O_3$. Calculated (%): C, 39.60; H, 2.31.

Methyl 2-(2,4-dichlorophenyl)-3,3,3-trifluoro-2-hydroxypropionate (3e). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.90 (s, 3 H, OCH_3); 4.60 (s, 1 H, OH); 7.31—7.34 (m, 1 H, Ar); 7.46 (d, 1 H, Ar, J = 2.3 Hz); 7.61—7.65 (m, 1 H, Ar). ^{19}F NMR (376 MHz, $CDCl_3$), δ: −72.26 (s, 3 F, CF_3). Found (%): C, 39.47; H, 2.19. $C_{10}H_7Cl_2F_3O_3$. Calculated (%): C, 39.60; H, 2.31.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(4-trifluoromethylphenyl)-propionate (3f). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.02 (s, 3 H, OCH_3); 4.45 (s, 1 H, OH); 7.70 (d, 2 H, Ar, J = 8.3 Hz); 7.97 (d, 2 H, Ar, J = 8.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −68.42 (s, 3 F, CF_3); −62.56 (s, 3 F, CF_3). Found (%): C, 43.81; H, 2.45. $C_{11}H_8F_6O_3$. Calculated (%): C, 43.71; H, 2.65.

Methyl 3,3,3-trifluoro-2-hydroxy-2-(4-phenoxyphenyl)propionate (3g). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.00 (s, 3 H, OCH_3); 4.28 (s, 1 H, OH); 6.97—7.20 (m, 5 H, Ph); 7.32—7.43 (m, 2 H, Ar); 7.75 (d, 2 H, Ar, J = 7.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −72.87 (s, 3 F, CF_3). Found (%): C, 59.01; H, 4.05. $C_{16}H_{13}F_3O_4$. Calculated (%): C, 58.90; H, 3.99.

Methylation of methyl 2-aryl-3,3,3-trifluoro-2-hydroxypropionates 3a—g. Method *A*. Synthesis of methoxy esters 4a—c,g. Equimolar amounts of sodium hydride (preliminarily washed off the mineral oil on a filter with light petroleum) and iodomethane were added in small portions to a solution of hydroxy ester **3a—c**,**g** (0.307 mol) in DMF (280 mL) with stirring and cooling by ice-cold water. The mixture was heated for ~1.5 h at 50—60 °C. If TLC showed the presence of the starting compound **3a—c**,**g**, excesses of NaH and MeI were added to the reaction mixture, with the total amount of 60% NaH and methyl iodide could have reached 22.1 g (0.553 mol) and 78.5 g (0.553 mol), respectively. Once a complete conversion of the starting compound was reached, the reaction mixture was filtered, the precipitate was rinsed with toluene. The solvents (DMF and toluene) were removed from the filtrate *in vacuo*, the residue was combined with the precipitate, and this was treated with water, then thrice extracted with chloroform. The organic layers were combined and dried with $MgSO_4$. After evaporation of the solvent and distillation *in vacuo*, compounds **4a—c** were obtained as colorless or light yellow oils; product **4g** as a dense dark yellow oil was used without distillation.

Method *B*. Synthesis of methoxy esters 4d—f. Dimethyl sulfate (28.47 g, 0.226 mol) was added to a mixture of hydroxy ester **3d—f** (0.178 mol), dioxane (145 mL), and ground KOH (13.95 g, 0.249 mol) with efficient stirring, keeping temperature within 45—55 °C, then the mixture was stirred for ~1 h at 20 °C. In the synthesis of compounds **4d**,**f**, additional amounts of KOH and $(MeO)_2SO_2$ (to 2.5 mol per 1 mol of compound **3**) were required to complete the reaction. The mixture was dissolved in water, then thrice extracted with CCl_4. The organic phases were combined, dried with Na_2SO_4, and filtered. After removal of the solvent on a rotary evaporator and distillation, compounds **4d—f** were obtained as colorless or light yellow oils.

TLC monitoring of reaction mixtures in the methylation by method *A* or *B* was carried out in the 1 : 1 CCl_4—$CHCl_3$ system.

The yields, the constants, and the TLC analysis data of obtained methoxy esters **4a—g** are given in Table 2.

Methyl 3,3,3-trifluoro-2-(3-chlorophenyl)-2-methoxypropionate (4a). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.58 (s, 3 H, OCH_3); 3.92 (s, 3 H, OCH_3); 7.29—7.46 (m, 3 H, Ar); 7.56 (s, 1 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –71.72 (s, 3 F, CF_3). Found (%): C, 46.90; H, 3.32. $C_{11}H_{10}ClF_3O_3$. Calculated (%): C, 46.72; H, 3.54.

Methyl 2-(2-chlorophenyl)-3,3,3-trifluoro-2-methoxypropionate (4b). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.45 (s, 3 H, OCH_3); 3.77 (s, 3 H, OCH_3); 7.22—7.54 (m, 4 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –69.76 (s, 3 F, CF_3). Found (%): C, 46.88; H, 3.35. $C_{11}H_{10}ClF_3O_3$. Calculated (%): C, 46.72; H, 3.54.

Methyl 2-(3,4-dimethylphenyl)-3,3,3-trifluoro-2-methoxypropionate (4c). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.30 (s, 6 H, 2 CH_3); 3.55 (s, 3 H, OCH_3); 3.90 (s, 3 H, OCH_3); 7.14—7.29 (m, 3 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –71.51 (s, 3 F, CF_3). Found (%): C, 56.62; H, 5.64. $C_{13}H_{15}F_3O_3$. Calculated (%): C, 56.52; H, 5.43.

Methyl 2-(3,5-dichlorophenyl)-3,3,3-trifluoro-2-methoxypropionate (4d). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.62 (s, 3 H, OCH_3); 3.95 (s, 3 H, OCH_3); 7.38—7.50 (m, 3 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –66.31 (s, 3 F, CF_3). Found (%): C, 41.87; H, 2.86. $C_{11}H_9Cl_2F_3O_3$. Calculated (%): C, 41.64; H, 2.84.

Methyl 2-(2,4-dichlorophenyl)-3,3,3-trifluoro-2-methoxypropionate (4e). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.54 (s, 3 H, OCH_3); 3.93 (s, 3 H, OCH_3); 7.41 (dd, 1 H, Ar, J = 8.7 Hz, J = 2.1 Hz); 7.49 (d, 1 H, Ar, J = 2.3 Hz); 7.76 (d, 1 H, Ar, J = 8.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$), δ: –69.93 (s, 3 F, CF_3). Found (%): C, 41.79; H, 2.62. $C_{11}H_9Cl_2F_3O_3$. Calculated (%): C, 41.64; H, 2.84.

Methyl 3,3,3-trifluoro-2-methoxy-2-(4-trifluoromethylphenyl) propionate (4f). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.46 (s, 3 H, OCH_3); 3.80 (s, 3 H, OCH_3); 7.55—7.75 (m, 4 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –66.75 (s, 3 F, CF_3); –61.95 (s, 3 F, CF_3). Found (%): C, 45.79; H, 3.27. $C_{12}H_{10}F_6O_3$. Calculated (%): C, 45.57; H, 3.16.

Methyl 3,3,3-trifluoro-2-methoxy-2-(4-phenoxyphenyl)propionate (4g). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.62 (s, 3 H, OCH_3); 3.97 (s, 3 H, OCH_3); 7.04—7.12 (m, 4 H, Ar); 7.19—7.24 (m, 1 H, Ar); 7.39—7.43 (m, 2 H, Ar); 7.53 (d, 2 H, Ar, J = 8.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$), δ: –70.89 (s, 3 F, CF_3). Found (%): C, 59.72; H, 4.19. $C_{17}H_{15}F_3O_4$. Calculated (%): C, 60.00; H, 4.41.

Synthesis of 2-aryl-3,3,3-trifluoro-2-methoxypropionic acids 5a—g. Ground KOH (22.4 g, 0.4 mol) and water (8 mL) were added to a solution of methoxy ester **4a—g** (0.27 mol) in methanol (190 mL), then the mixture was refluxed with stirring until the reaction reached completion. The time of heating (monitored by TLC) is indicated in Table 3. The reaction mixture was concentrated dry *in vacuo*, water (270—350 mL) was added to the residue. The opaque alkaline solution was washed with diethyl ether and light petroleum ether, then treated with concentrated hydrochloric acid (to pH ~1), and extracted with $CHCl_3$ (or CH_2Cl_2). The combined organic layers were washed with brine and dried with $MgSO_4$. After removal of the solvent, the residue was purified by crystallization or reprecipitation, then dried *in vacuo* over P_2O_5. The yields, the constants, and the TLC analysis data of obtained compounds 5**a—g** are given in Table 3.

2-(3-Chlorophenyl)-3,3,3-trifluoro-2-methoxypropionic acid (5a). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.65 (s, 3 H, OCH_3); 7.35—7.52 (m, 3 H, Ar); 7.65 (s, 1 H, Ar); 10.08 (s, 1 H, COOH). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –69.54 (s, 3 F, CF_3). Found (%): C, 44.75; H, 3.14. $C_{10}H_8ClF_3O_3$. Calculated (%): C, 44.69; H, 2.98.

2-(2-Chlorophenyl)-3,3,3-trifluoro-2-methoxypropionic acid (5b). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.47 (s, 3 H, OCH_3); 5.55 (br.s, 1 H, COOH); 7.41—7.56 (m, 3 H, Ar); 7.73—7.79 (m, 1 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –70.43 (s, 3 F, CF_3). Found (%): C, 44.80; H, 3.22. $C_{10}H_8ClF_3O_3$. Calculated (%): C, 44.69; H, 2.98.

2-(3,4-Dimethylphenyl)-3,3,3-trifluoro-2-methoxypropionic acid (5c). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.33 (s, 6 H, 2 CH_3); 3.55 (s, 3 H, OCH_3); 7.18—7.35 (m, 3 H, Ar); 9.40 (br.s, 1 H, COOH). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –70.85 (s, 3 F, CF_3). Found (%): C, 55.19; H, 5.14. $C_{12}H_{13}F_3O_3$. Calculated (%): C, 54.96; H, 4.96.

2-(3,5-Dichlorophenyl)-3,3,3-trifluoro-2-methoxypropionic acid (5d). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.65 (s, 3 H, OCH_3); 7.44 (s, 1 H, Ar); 7.56 (s, 2 H, Ar); 8.85 (br.s, 1 H, COOH). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –65.82 (s, 3 F, CF_3). Found (%): C, 39.35; H, 2.13. $C_{10}H_7Cl_2F_3O_3$. Calculated (%): C, 39.60; H, 2.31.

2-(2,4-Dichlorophenyl)-3,3,3-trifluoro-2-methoxypropionic acid (5e). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.45 (s, 3 H, OCH_3); 7.41 (d, 1 H, Ar, J = 8.0 Hz); 7.52 (s, 1 H, Ar); 7.66 (d, 1 H, Ar, J = 8.0 Hz); 8.16 (br.s, 1 H, COOH). ^{19}F NMR (376 MHz, $CDCl_3$), δ: –70.60 (s, 3 F, CF_3). Found (%): C, 39.79; H, 2.15. $C_{10}H_7Cl_2F_3O_3$. Calculated (%): C, 39.60; H, 2.31.

3,3,3-Trifluoro-2-methoxy-2-(4-trifluoromethylphenyl)propionic acid (5f). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.52 (s, 3 H, OCH_3); 7.64 (d, 2 H, Ar, J = 7.7 Hz); 7.88 (d, 2 H, Ar, J = 7.7 Hz); 9.13 (br.s, 1 H, COOH). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –68.09 (s, 3 F, CF_3); –61.29 (s, 3 F, CF_3). Found (%): C, 44.00; H, 2.70. $C_{11}H_8F_6O_3$. Calculated (%): C, 43.71; H, 2.65.

3,3,3-Trifluoro-2-methoxy-2-(4-phenoxyphenyl)propionic acid (5g). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.59 (s, 3 H, OCH_3); 6.92—7.24 (m, 5 H, Ph); 7.31—7.47 (m, 2 H, Ar); 7.53 (d, 2 H, Ar, J = 9.8 Hz); 9.45 (br.s, 1 H, COOH). ^{19}F NMR (376 MHz, $CDCl_3$), δ: –71.35 (s, 3 F, CF_3). Found (%): C, 59.05; H, 4.26. $C_{16}H_{13}F_3O_4$. Calculated (%): C, 58.90; H, 3.99.

Synthesis of 2-aryl-3,3,3-trifluoro-2-methoxypropionyl chlorides 6a—g. A mixture of acid **5a—g** (0.13 mol), an excess of thionyl chloride, and a catalyst (pyridine or imidazole) was refluxed with stirring until the reaction reached completion (monitored by TLC). The excess of $SOCl_2$ was removed *in vacuo*, the residue was diluted with a mixture of CCl_4 and light petroleum (1 : 1, 80 mL). The solid admixtures were removed by filtration, the filtrate was concentrated and distilled. The amounts of $SOCl_2$ and catalyst used, the time of heating, as well as the yields, the constants, and the TLC analysis data of obtained compounds 6**a—g** are given in Table 4. Chlorides **5a—e** are low-melting-point white solid compounds, **5f** is a colorless oil, **5g** is a pale yellow oil.

2-(3-Chlorophenyl)-3,3,3-trifluoro-2-methoxypropionyl chloride (6a). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.79 (s, 3 H, OCH_3); 7.32—7.49 (m, 3 H, Ar); 7.60 (s, 1 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –70.11 (s, 3 F, CF_3). Found (%): C, 42.09; H, 2.63. $C_{10}H_7Cl_2F_3O_2$. Calculated (%): C, 41.81; H, 2.44.

2-(2-Chlorophenyl)-3,3,3-trifluoro-2-methoxypropionyl chloride (6b). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.63 (s, 3 H, OCH_3); 7.37—7.48 (m, 3 H, Ar); 7.79—7.86 (m, 1 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –69.50 (s, 3 F, CF_3). Found (%): C, 41.99; H, 2.65. $C_{10}H_7Cl_2F_3O_2$. Calculated (%): C, 41.81; H, 2.44.

2-(3,4-Dimethylphenyl)-3,3,3-trifluoro-2-methoxypropionyl chloride (6c). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.35 (s, 3 H, CH_3); 2.37 (s, 3 H, CH_3); 3.81 (s, 3 H, OCH_3); 7.23—7.39 (m, 3 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –69.74 (s, 3 F, CF_3). Found (%): C, 51.56; H, 4.46. $C_{12}H_{12}ClF_3O_2$. Calculated (%): C, 51.34; H, 4.28.

2-(3,5-Dichlorophenyl)-3,3,3-trifluoro-2-methoxypropionyl chloride (6d). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.76 (s, 3 H, OCH_3); 7.40—7.53 (m, 3 H, Ar). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –66.18 (s, 3 F, CF_3). Found (%): C, 37.49; H, 2.00. $C_{10}H_6Cl_3F_3O_2$. Calculated (%): C, 37.33; H, 1.87.

2-(2,4-Dichlorophenyl)-3,3,3-trifluoro-2-methoxypropionyl chloride (6e). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.66 (s, 3 H, OCH_3); 7.38 (d, 1 H, Ar, J = 8.9 Hz); 7.46 (s, 1 H, Ar); 7.79 (d, 1 H, Ar, J = 8.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –69.15 (s, 3 F, CF_3). Found (%): C, 37.57; H, 2.02. $C_{10}H_6Cl_3F_3O_2$. Calculated (%): C, 37.33; H, 1.87.

3,3,3-Trifluoro-2-methoxy-2-(4-trifluoromethylphenyl)propionyl chloride (6f). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.64 (s, 3 H, OCH_3); 7.50 (d, 2 H, Ar, J = 7.5 Hz); 7.62 (d, 2 H, Ar, J = 7.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –65.61 (s, 3 F, CF_3); –60.18 (s, 3 F, CF_3). Found (%): C, 41.36; H, 2.27. $C_{11}H_7ClF_6O_2$. Calculated (%): C, 41.19; H, 2.18.

3,3,3-Trifluoro-2-methoxy-2-(4-phenoxyphenyl)propionyl chloride (6g). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.78 (s, 3 H, OCH_3); 7.02—7.27 (m, 5 H, Ph); 7.35—7.47 (m, 2 H, Ar); 7.53 (d, 2 H, Ar, J = 9.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$), δ: –70.07 (s, 3 F, CF_3). Found (%): C, 55.94; H, 3.63. $C_{16}H_{12}ClF_3O_3$. Calculated (%): C, 55.73; H, 3.48.

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