Journal of Fluorine Chemistry 185 (2016) 31–35

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Methyl fluoroalkanoate as methyl-transferring reagent. Unexpected participation of $B_{Al}2$ (S_N2) mechanism in the reaction of methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate with amines

Bohumil Dolenský[a,*], Jaroslav Kvíčala[b], Oldřich Paleta[b]

[a] Department of Analytical Chemistry, University of Chemistry and Technology, Technická 5, Prague 6, Prague 166 28, Czech Republic
[b] Department of Organic Chemistry, University of Chemistry and Technology, Technická 5, Prague 6, Prague 166 28, Czech Republic

ARTICLE INFO

Article history:
Received 6 January 2016
Received in revised form 25 February 2016
Accepted 27 February 2016
Available online 2 March 2016

Keywords:
Methyl tetrafluoropropanoate
Methyl transfer
Amine methylation
$B_{Al}2$ mechanism
S_N2 mechanism

ABSTRACT

In the reaction of methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate with arylamines or arylmethylamines, an unexpected methyl transfer from the ester to the amine by the $B_{Al}2$ (S_N2) mechanism was observed leading to the corresponding *N*-methylamines under specific conditions. The reaction was accompanied by the formation of amides via $B_{Ac}2$ mechanism. The unexpected methyl transfer is highly dependent on the structure of the starting amine and is supported by the absence of solvent and high temperature.

1. Introduction

The transfer of methyl group from ester to amine is a well established reaction. It proceeds as the S_N2 reaction at the methyl group and is characteristic for methyl alkyl- or aryl-sulfonates, the presence of excellent sulfonate or sulfate leaving group being the key factor [1]. In contrast, this type of mechanism is quite rare for methyl alkanoates, where nucleophiles usually react at the carbonyl carbon to substitute the methoxy group by tetrahedral $B_{Ac}2$ mechanism [2]. The reaction analogous to sulfonate chemistry (assigned as $B_{Al}2$) is limited to derivatives of highly acidic acids: the methyl transfer from ester to amine was observed for methyl salicylate [3],*o*-nitrobenzoate [4] and dimethyl oxalate or fumarate [4]. The methyl transfer was also accomplished with dimethyl carbonate [5]. Heating of 2-amino-2′-hydroxy-3′-(methoxycarbonyl)binaphthol gave intermolecular methyl transfer in solid state [6]. As other examples of a B_{Al} mechanism, ring-opening of lactones [7], *N*-allylation under nickel catalysis [8], formation of *N*-methyl-pyridiniumcarboxylic acid from methyl pyridinecarboxylates [9], or ring-closure during gas-phase pyrolysis [10] can be considered.

In this article, we report unexpected methyl transfer from methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate (TFMP, **1**) to amines by the $B_{Al}2$ mechanism, depending both on the nature of the amine and the reaction conditions. In general, the alternative $B_{Al}1$ mechanism is not accounted as it requires an unlikely formation of methyl cation in solution.

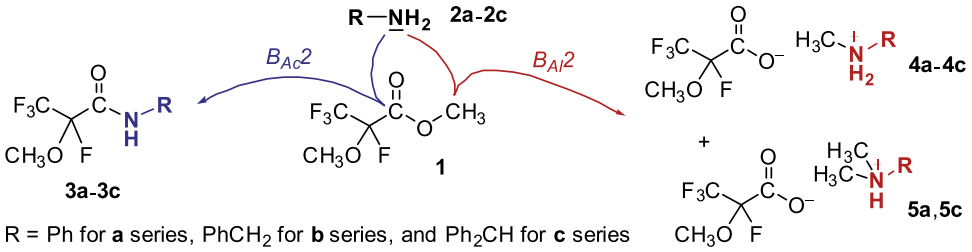
2. Results and discussion

During our study of chemistry of TFMP, we found that the reaction of the TFMP with amines **2a**–**2c** leads to the corresponding amides **3** (Scheme 1), however, under specific conditions the TFMP can act as a methylation agent. The transferring of one or two methyl groups to the nitrogen atom thus yielded unexpected products, namely *N*-methyl- and *N*,*N*-dimethylalkylammonium fluoroalkanoates **4** and **5** (Scheme 1).

In the first set of qualitative experiments, we studied the role of substrate, solvent and reaction temperature. The ratio of products in the crude reaction mixtures was determined by ^{19}F NMR spectroscopy (the signal of CF group of amides **3** can be observed at −136 ppm, for the salts **4** and **5** it can be found at −132 ppm), while

* Corresponding author.
E-mail address: dolenskb@vscht.cz (B. Dolenský).

http://dx.doi.org/10.1016/j.jfluchem.2016.02.012
0022-1139/



Scheme 1. Reaction of TFMP (**1**) with amines **2a–2c**.

Table 1
Screening of amidation/methyl transfer in the reaction of TFMP (**1**) with amines **2**.

Entry	Amine	Temp. (°C)	Time (h)	Solvent	Conversion of **1** (%)	**3**:(**4**+**5**) ratio	**2**:**6**:**7**[a] ratio
1	**2a**	Reflux	24	THF	0	No reaction	No reaction
2	**2a**	100	72	None	100	15:85	59:31:10
3	**2b**	rt	48	Heptane	95	98:2	n.d.
4	**2b**	rt	16	Methanol	100	>99:1	n.d.
5	**2b**	rt	336	THF	100	89:11	n.d.
6	**2b**	Reflux	26	THF	100	69:31	n.d.
7	**2b**	Reflux	72	1,4-Dioxane	73	56:44	n.d.
8	**2c**	Reflux	10	THF	<1	No reaction	No reaction
9	**2c**	115	24	None	81	36:64	85:7:8

[a] **6** and **7** are the corresponding *N*-methyl and *N*,*N*-dimethyl derivatives of amine **2**, resp.

the degree of methylation of the amines **2** was obtained by GC–MS analysis of the amine mixture formed after alkalization of the crude reaction mixture with sodium hydroxide. The results are listed in Table 1.

Thus, aniline (**2a**) as the least nucleophilic amine did not react with TFMP in refluxing THF (Table 1, entry 1). Similarly, the reactivity of benzhydrylamine (**2c**) was negligible under these conditions probably due to steric hindrance of the amino group (Table 1, entry 8). The reactivity dramatically changed when the solvent was omitted and the reaction temperature was raised. Thus, the reaction of aniline (**2a**) with 8-fold excess of TFMP at 100 °C for 9 h gave after alkalization a mixture of starting aniline (**2a**), *N*-methylaniline (**6a**) and *N*,*N*-dimethylaniline (**7a**) in a 59:31:10 ratio. Small amount of amide **3a** in the crude reaction product was also detected (Table 1, entry 2). Analogous reaction of TFMP with equivalent of benzhydrylamine (**2c**) at 115 °C gave after alkalization a mixture of starting amine **2c**, *N*-methylbenzhydrylamine (**6c**) and *N*,*N*-dimethylbenzhydrylamine (**7c**) in a 85:7:8 ratio (Table 1, entry 9). About one third of starting TFMP was converted to the corresponding amide **3c**.

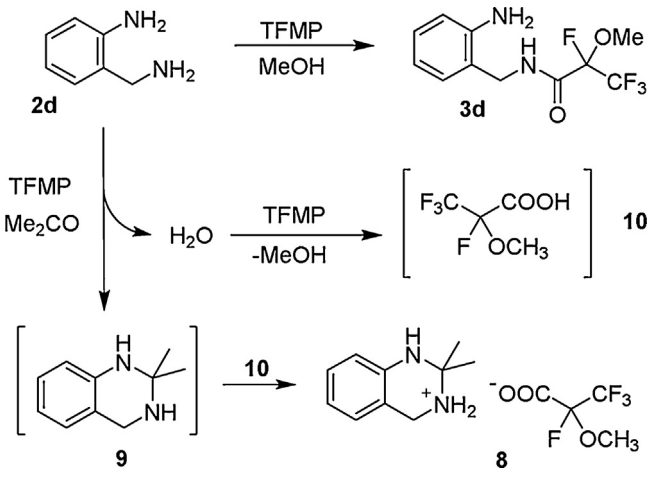
Benzylamine (**2b**) as a highly nucleophilic amine proved to be most sensitive to the reaction conditions and hence its reactivity was studied in detail. The amide **3b** was formed almost exclusively at room temperature, even when non-polar heptane or polar methanol as the solvent was used (Table 1, entries 3 and 4). However, the same reaction in THF afforded a mixture of amide **3b** and *N*-benzylammonium salt **4b** in a 89:11 ratio (Table 1, entry 5). Raising the temperature to reflux increased the content of salt **4b** to a 69:31 ratio (Table 1, entry 6) and further enhancement of the temperature to 100 °C (refluxing 1,4-dioxane as the solvent) led to the ratio of 45:55 (Table 1, entry 7). This identifies the reaction temperature as the key factor in the competition between amidation by the $B_{Ac}2$ mechanism (the alternative $B_{Ac}1$ mechanism is unlikely) and the methyl transfer by the $B_{Al}2$ mechanism.

In the preparative experiments (Table 2), conditions of entry 2 (110 °C, no solvent) using the excess of aniline to minimize double methylation were employed for the synthesis of *N*-methylanilinium salt **4a**, which was isolated in a 55% yield, along with 5% of amide **3a**. Analogously, conditions of entry 9 (115 °C, no solvent) allowed the isolation of the corresponding salt **4c** in a 64% yield and of the corresponding benzhydrylamide **3c** in a 23% yield. Unfortunately, neither crystallization nor column chromatography gave the salt **4c** of good purity. Similarly, the conditions of entry 4 (MeOH as solvent, r.t.) were employed for the synthesis of *N*-benzylamide **3b**, which was isolated in an excellent 92% yield, while the conditions of entry 7 (refluxing 1,4-dioxane) allowed the isolation of the corresponding salt **4b** in a 29% yield and *N*-benzylamide **3b** in 37% yield.

Finally, the diamine containing both arylamino and arylmethylamino group, 2-(aminomethyl) aniline (**2d**), was employed in the reaction with TFMP. In analogy to the reaction of benzylamine

Table 2
Preparation of amides **3** and salts **4** by the reaction of TFMP (**1**) with amines **2**.

Entry	Amine	Temp. (°C)	Time (h)	Solvent	yield of **3** (%)	yield of **4** (%)
1	**2a**	110	24	None	5	55
2	**2b**	rt	16	Methanol	92	Traces
3	**2b**	Reflux	72	1,4-Dioxane	37	29
4	**2c**	115	24	None	23	64



Scheme 2. Reactions of 2-(aminomethyl) aniline with TFMP (**1**).

(Table 1, entries 3 and 4), *N*-benzylamide **3d** was formed exclusively in heptane or methanol in 94% yield with only traces of the methyl transfer detected by ^{19}F NMR spectroscopy (Scheme 2). Interestingly, the reaction of the amine **2d** with TFMP in acetone as the solvent did give neither the expected *N*-benzylamide **3d** nor the salt **4** or **5** but tetrahydroquinazolinium salt **8** in a 65% preparative yield. We explain the formation of the salt **8** as a result of primary reaction of diamine **2d** with acetone to give tetrahydroquinazoline **9**, accompanied by the release of one molecule of water. TFMP is subsequently hydrolyzed to 2,3,3,3-tetrafluoro-2-methoxypropanoic acid (**10**), which in turn forms the final salt **8** with the compound **9** (Scheme 2).

3. Conclusion

During the study of aminolysis of methyl 2,3,3,3-tetrafluoro-2-methoxypropanoate (TFMP, **1**) with aromatic and aliphatic amines by common $B_{Ac}2$ mechanism giving amides **3**, we disclosed that aromatic or hindered aliphatic amines underwent an unexpected methylation to *N*-methyl and *N*,*N*-dimethylamines salts **4** and **5**, caused by a rare $B_{Al}2$ mechanism. This side-reaction proceeds preferably at higher temperatures in solvents of medium polarity or without solvent. We believe the products of $B_{Al}2$ mechanism are often overlooked due to their low content or improper isolation, which targets the expected neutral amide not an ionic salt. We hope that our observation will increase the attention on the B_{Al} mechanisms and its products in the field of electron-deficient carboxylates, particularly the fluorinated ones.

4. Experimental

4.1. General description of methods and materials

Temperature data were uncorrected. NMR spectra were recorded with a Varian Gemini 300 HC Spectrometer, ^1H NMR spectra at 300 MHz and ^{13}C NMR spectra at 75 MHz using residual signals of deuterated solvent as the internal standards and ^{19}F NMR spectra at 282 MHz using CCl_3F as the internal standard. Chemical shifts are given in parts per million, coupling constants in hertz. Mass spectra (ESI, APCI) were measured with a LCQ Fleet (Finnigan) instrument and GC-MW spectra (EI) with Hewlett-Packard MSD 5971A instrument. Infrared spectra in KBr pellets were scanned on a NICOLET 740 USA apparatus.

All reactions were performed in a dry argon atmosphere in an oven-dried flasks. All reagents were purchased from Sigma–Aldrich and used without additional purifications with the exception of aniline. The solvents were purified and dried according to standard procedures.

4.2. Liberation of the acid *10* and the amines *2a–2c*, *6a–6c*, *7a*, *7c* and *11* from the salts *4a–4c*, *5a*, *5c* and *8*

About 50 mg of a salt was diluted in 1 mL of water, and 1 mL of conc. HCl was added. After 30 min of stirring, the mixture was extracted by 2 × 2 mL of diethyl ether. The organic part was dried over $MgSO_4$ and analysed by GC–MS. In all cases, only propionic acid **10** was detected. The aqueous part was neutralized with solid K_2CO_3 and basified to pH 10 with conc. aqueous KOH. The mixture was extracted with 2 × 2 mL of diethyl ether, combined organic fractions were dried over $MgSO_4$ and analysed by GC–MS to identify the base parts of the salts (the spectral characteristics were in accord with database values).

Aniline (**2a**): MS (EI$^+$): 93 (100) [M$^+$], 66 (44), 65 (26), 39 (18).

N-methylaniline (**6a**): MS (EI$^+$): 107 (75) [M$^+$], 106 (100), 77 (24), 65 (8), 51 (14), 39 (8).

N,*N*-dimethylaniline (**7a**): MS (EI$^+$): 121 (67) [M$^+$], 120 (100), 104 (16), 91 (4), 77 (25), 51 (16), 42 (10).

Benzylamine (**2b**): MS (EI$^+$): 108 (2) [M + H$^+$], 107 (65) [M$^+$], 106 (100), 91 (15), 79 (44), 78 (17), 77 (31), 65 (7), 63 (7), 51 (24), 50 (14).

N-methylbenzylamine (**6b**): MS (EI$^+$): 122 (5) [M + H$^+$], 121 (59) [M$^+$], 120 (100), 106 (9), 104 (5), 92 (12), 91 (64), 79 (6), 78 (9), 77 (15), 65 (24), 63 (10), 51 (17), 44 (100), 42 (59).

Benzhydrylamine (**2c**): MS (EI$^+$): 183 (5) [M$^+$], 182 (35), 181 (6), 152 (3), 106 (8), 105 (100), 77 (66), 63 (2), 51 (28), 50 (9).

N-methylbenzhydrylamine (**6c**): MS (EI$^+$): 197 (5) [M$^+$], 196 (3), 182 (1), 167 (12), 165 (12), 152 (6), 139 (1), 121 (9), 120 (100), 119 (10), 106 (4), 105 (3), 104 (13), 91 (3), 77 (13), 63 (3), 51 (7), 42 (27).

N,*N*-dimethylbenzhydrylamine (**7c**): MS (EI$^+$): 212 (2) [M + H$^+$], 211 (12) [M$^+$], 210 (1), 168 (9), 167 (64), 166 (10), 165 (28), 152 (16), 135 (10), 134 (100), 118 (6), 106 (1), 91 (8), 77 (8), 65 (4), 63 (4), 51 (6), 42 (11).

2,2-Dimethyl-1,2,3,4-tetrahydroquinazoline (**11**): MS (EI$^+$): 162 (16) [M$^+$], 147 (77), 130 (4), 118 (3), 106 (100), 104 (100), 91 (3), 79 (7), 78 (11), 77 (20), 65 (4), 51 (9), 42 (12).

*4.3. Screening reactions of TFMP (**1**) with amines **2***

a) TFMP (**1**, 0.44 g, 2.3 mmol), aniline (**2a**, 0.22 g, 2.3 mmol) and THF (6 mL) were heated to reflux (66 °C) for 24 h. No reaction was observed by ^{19}F NMR spectroscopy.
b) TFMP (**1**, 2.02 g, 10.6 mmol) and aniline (**2a**, 0.39 g, 4.2 mmol) were heated without solvent to 100 °C for 3 days. Crude reaction mixture was diluted with aq. solution of NaOH (10%, 20 mL) and stirred at r.t. for 30 min. The mixture was extracted with chloroform (2 × 2 mL) and combined organic fractions were dried over $MgSO_4$. By GC–MS analysis, 59:31:10 ratio of aniline (**2a**), *N*-methylaniline (**6a**) and *N*,*N*-dimethylaniline (**7a**) was found.
c) TFMP (**1**, 0.51 g, 2.7 mmol), benzylamine (**2b**, 0.28 g, 2.6 mmol) and heptane (10 mL) were stirred at r.t. for 2 days. According to analysis by ^{19}F NMR spectroscopy, *N*-benzyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**) and *N*-methylbenzylammonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4b**) were formed in a 98:2 ratio at 95% conversion of TFMP.
d) TFMP (**1**, 0.44 g, 2.3 mmol), benzylamine (**2b**, 1.14 g, 10.7 mmol) and methanol (10 mL) were stirred at r.t. for 16 h. According to analysis by ^{19}F NMR spectroscopy, *N*-benzyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**) was formed quantitatively with only traces of *N*-methylbenzylammonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4b**) present.
e) TFMP (**1**, 0.43 g, 2.2 mmol), benzylamine (**2b**, 0.27 g, 2.5 mmol) and THF (6 mL) were stirred at r.t. for 14 days. According to analysis by ^{19}F NMR spectroscopy, *N*-benzyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**) and *N*-methylbenzylammonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4b**) were formed in a 89:11 ratio at 100% conversion of TFMP.
f) TFMP (**1**, 0.60 g, 3.2 mmol), benzylamine (**2b**, 1.24 g, 11.5 mmol) and THF (8 mL) were heated to reflux (66 °C) for 26 h. According to analysis by ^{19}F NMR spectroscopy, *N*-benzyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**) and *N*-methylbenzylammonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4b**) were formed in a 69:31 ratio at 100% conversion of TFMP.
g) TFMP (**1**, 3.50 g, 18.4 mmol), benzylamine (**2b**, 1.96 g, 18.3 mmol) and 1,4-dioxane (50 mL) were heated to reflux (101 °C) for 3 days. According to analysis by ^{19}F NMR spectroscopy, *N*-benzyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**) and *N*-methylbenzylammonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4b**) were formed in a 56:44 ratio at 73% conversion of TFMP.
h) TFMP (**1**, 0.40 g, 2.1 mmol), benzhydrylamine (**2c**, 0.39 g, 2.1 mmol) and THF (5 mL) were heated to reflux (66 °C) for 10 h. According to analysis by ^{19}F NMR spectroscopy, only traces of *N*-(diphenylmethyl)-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3c**) were detected in the reaction mixture.
i) TFMP (**1**, 0.50 g, 2.7 mmol) and benzhydrylamine (**2c**, 0.47 g, 2.6 mmol) were heated without solvent to 115 °C for 24 h. According to analysis by ^{19}F NMR spectroscopy, *N*-(diphenylmethyl)-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**) and *N*-methylbenzhydrylammonium 2,3,3,3-tetrafluoro-2-methoxypropionate (**4c**) were formed in a 36:64 ratio at 81% conversion of TFMP.

*4.4. Preparative reactions of TFMP (**1**) with amines **2***

a) *N*-phenyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3a**) and anilinium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4a**). TFMP (**1**, 0.90 g, 4.7 mmol) **1** and aniline (**2a**, 3.14 g, 33.7 mmol) were heated to 110 °C for 9 h. The reaction mixture was diluted with chloroform (10 mL) and precipitated white solid was filtered off to give anilinium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4a**, 0.70 g, 55%, white crystals). The filtrate was mixed with of aq. solution of NaOH (10%, 10 mL) and extracted with chloroform. The organic layer was dried over $MgSO_4$, evaporated to dryness and the residue was purified by column chromatography (30 g of silica, eluent petroleum ether/CH_2Cl_2 1:1) to give *N*-phenyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3a**, 64 mg, 5%, white crystals). *N*-phenyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3a**): ^{1}H NMR ($CDCl_3$): 8.18 (1H, bs), 7.60 (2H, d, J_{HH} = 7.7 Hz), 7.39 (2H, t, J_{HH} = 7.7 Hz), 7.22 (1H, t, J_{HH} = 7.4 Hz), 3.67 (3H, s) ppm. ^{13}C NMR ($CDCl_3$): 158.20 (d, J_{CF} = 30.3 Hz), 135.72, 129.26 (2C), 125.98, 120.24 (2C), 119.21 (qd, J_{CF} = 286.9 Hz, J_{CF} = 36.1 Hz), 105.68 (dq, J_{CF} = 246.2 Hz, J_{CF} = 35.5 Hz), 53.84 ppm. ^{19}F NMR ($CDCl_3$): −81.5 (3F, d, J_{FF} = 3.4 Hz), -135.6 (1F, m) ppm. IR (KBr): 3321 w, 1689 s, 1601 w, 1538 w cm^{-1}. T. subl. ~75 °C at 132 Pa. For $C_{10}H_9F_4NO_2$ (251.18): calcd. C 47.82, H 3.61, N 5.58; found C 47.65, H 3.73, N 5.55. Anilinium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4a**): ^{1}H NMR (DMSO-d_6): 7.34 (3H, bs), 7.23 (2H, t, J_{HH} = 7.1 Hz), 6.98–6.88 (3H, m, temp.), 3.51 (3H, s, temp.) ppm. ^{13}C NMR (DMSO-d_6): 161.75 (d, J_{CF} = 33.7 Hz), 141.27, 129.18 (2C), 121.15, 119.81 (qd, J_{CF} = 285.6 Hz, J_{CF} = 35.7 Hz), 118.00 (2C), ~104.8 (dm, J_{CF} = ~243 Hz), 53.46 ppm. ^{19}F NMR (DMSO-d_6): −76.2 (3F, d, J_{FF} = 3.0 Hz), −126.3 (1F, m) ppm. ^{19}F NMR ($CDCl_3$): −81.4 (3F, d, J_{FF} = 3.0 Hz), −132.8 (1F, m). IR (KBr): 3416 w, 3000–2500 w, 1665–1550 s, 1500 s, 1410 m, 1325 m, 1194 s, 1159 s, 1068 s, 1159 s, 827 s, 751 s, 718 m, 691 m cm^{-1}. T. subl. 80 °C at 264 Pa. M.p. 123-127 °C. For $C_{10}H_{11}F_4NO_3$ (269.20): calcd. C 44.62, H 4.12, N 5.20; found C 44.83, H 4.23, N 5.09.
b) *N*-benzyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**). TFMP (**1**, 0.44 g, 2.3 mmol), benzylamine (**2b**, 1.14 g, 10.7 mmol) and methanol (10 mL) were stirred at r.t. for 16 h. Reaction mixture was diluted with 10 mL of CH_2Cl_2, extracted with aq. HCl (1:1) and water. The organic part was dried over $MgSO_4$, filtered and evaporated to dryness. Purification by column chromatography (15 g of silica, eluent petroleum ether/CH_2Cl_2 1:1) gave *N*-benzyl-2,3,3,3-tetrafluoro-2-methoxypropanamide (**3b**, 0.56 g, 92% yield, oil, which solidified after several weeks). ^{1}H NMR ($CDCl_3$): 7.44 (1H, bs, temp.), 7.33–7.22 (5H, m), 4.47 (2H, d, J_{HH} = 6.0 Hz), 3.50 (3H, d, J_{HF} = 1.2 Hz) ppm. ^{13}C NMR ($CDCl_3$): 160.46 (d, J_{CF} = 31.4 Hz), 136.76, 128.65 (2C), 127.70, 127.47 (2C), 119.21 (qd, J_{CF} = 286.5 Hz, J_{CF} = 35.2 Hz), 105.64 (dq, J_{CF} = 245.6 Hz, J_{CF} = 35.1 Hz), 53.32, 43.54 ppm. ^{19}F NMR ($CDCl_3$): -81.7 (3F, d, J_{FF} = 3.7 Hz), −136.6 (1F, bs) ppm. MS (EI$^+$): 265 (22) [M$^+$], 245 (2), 230 (2), 202 (2), 190 (2), 164 (2), 131 (9), 104 (6), 97 (5), 91 (100), 77 (8), 69 (10), 65 (16), 51 (8). M.p. 39–40.5 °C. B.p. 110-115 °C/396 Pa. IR (KBr): 3333 w, 1684 s, 1607 w, 1537 w cm^{-1}. For $C_{11}H_{11}F_4NO_2$ (265.21): calcd. C 49.82, H 4.18, N 5.28; found C 50.38, H 4.22, N 5.32.
c) *N*-methylbenzylammonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4b**). TFMP (**1**, 3.50 g, 18.4 mmol), benzylamine (**2b**, 1.96 g, 18.3 mmol) and 1,4-dioxane (50 mL) were heated to reflux (101 °C) for 3 days. The reaction mixture was evaporated to dryness and anchored on 10 g of silica. Elution with CH_2Cl_2 gave 1.72 g (37% yield) of crude amide **3b**. The next elution with methanol gave 1.53 g (29% yield) of crude salt **4b**, whose purification by crystallization was unsuccessful. *N*-benzylamonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (**4b** impure): ^{1}H NMR (DMSO-d_6): 8.71 (2.5H, bs), 7.36–7.28 (2H, m), 7.23–7.17 (3H, m), 3.87 (2H, s), 3.35 (3H, s) ppm. ^{19}F NMR ($CDCl_3$/DMSO-d_6 4:1): −81.4 (3F, d, J_{FF} = 3.7 Hz), −131.9 (1F, m, J_{FF} = 3.7 Hz). IR (KBr): 3432 w, 3020–2000 w, 1660 s, 1496 m, 1459 m, 1383 m, 1325 m, 1200 s, 1175 s, 1155 s, 1061 s, 1042 s, 808 m, 762 m, 746 m, 706 m cm^{-1}.
d) *N*-(diphenylmethyl)-2,3,3,3-tetrafluor-2-methoxypropanamide (3c) and *N*-(benzhydryl)-ammonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (4c): TFMP (**1**, 0.50 g, 2.7 mmol) **1** and

benzhydrylamine (**2c**, 0.47 g, 2.6 mmol) were heated to 115 °C for 24 h. The reaction mixture was evaporated to dryness, anchored on silica (2 g), and separated by chromatography (5 g of silica, eluent ethyl acetate) to give 0.20 g (23% yield) of crude amide **3c**, which was purified by vacuum distillation. The next elution by methanol gave 0.60 g (64% yield) of crude salt **4c**, whose purification by crystallization or chromatography was unsuccessful. *N*-(diphenyl-methyl)-2,3,3,3-tetrafluor-2-methoxypropanamide (**3c**): ^{1}H NMR ($CDCl_3$): 7.39–7.27 (6H, m), 7.26–7.18 (4H, m), 7.09 (1H, bs), 6.31 (1H, d, J_{HH} = 8.2 Hz), 3.56 (3H, s) ppm. ^{19}F NMR ($CDCl_3$): −81.6 (3F, d, J_{FF} = 3.0 Hz), −136.3 (1F, m) ppm. ^{13}C NMR ($CDCl_3$): 159.52 (d, J_{CF} = 31.5 Hz), 140.09, 139.85, 128.91 (2C), 128.86 (2C), 128.01, 127.96, 127.28 (2C), 127.18 (2C), 119.22 (qd, J_{CF} = 286.5 Hz, J_{CF} = 35.2 Hz), 105.78 (dq, J_{CF} = 245.2 Hz, J_{CF} = 35.2 Hz), 57.43, 53.66 ppm. IR (KBr): 3317 w, 1686 s, 1604 w, 1525 w cm^{-1}. B.p. ∼150 °C/132 Pa. For $C_{17}H_{15}F_4NO_2$ (341.31): calcd. C 59.83, H 4.43, N 4.10, F 22.27; found C 59.72, H 4.52, N 4.03, F 22.61. MS (EI$^+$): 341 (25) [M$^+$], 306 (12), 290 (1), 278 (1), 264 (1), 240 (1), 216 (4), 210 (11), 180 (5), 168 (15), 167 (100), 166 (16), 165 (43), 152 (19), 131 (22), 115 (4), 105 (7), 104 (18), 97 (7), 83 (6), 77 (21), 69 (13), 63 (4), 51 (12), 42 (6). *N*-(benzhydryl) amonium 2,3,3,3-tetrafluoro-2-methoxypropanoate (4c impure): ^{1}H NMR (DMSO-d_6): 7.83 (4H, d, J_{HH} = 7.2 Hz), 7.72 (0.7H, d, J_{HH} = 7.0 Hz), 7.45–7.32 (7H, m), 5.54 (0.1H, s), 5.34 (0.9H, s), 3.56 (3.4H, d, J = 1.3 Hz), 2.81 (6.1H, s), 2.68 (0.5H, s) ppm. ^{19}F NMR ($CDCl_3$): −81.6 (3F, d, J_{FF} = 3.8 Hz), −131.8 (1F, m) ppm. ^{13}C NMR (DMSO-d_6): 165.01 (d, J_{CF} = 31.3 Hz), 138.92, 138.48 (impurity), 130.81, 130.54 (impurity), 130.28, 130.16 (impurity), 129.64, 129.44 (impurity), 122.42 (qd, J_{CF} = 284.5, J_{CF} = 36.1 Hz), 107.44 (dq, J_{CF} = 244.4 Hz, J_{CF} = 33.3 Hz), 77.66, 68.38 (impurity), 54.40 (impurity), 43.73, 32.80 (impurity). For $C_{17}H_{17}F_4NO_3$ (359.32): calcd. C 56.83, H 4.77, N 3.90, F 21.15; found C 58.39, H 5.48, N 3.49, F 19.98.

e) *N*-(2-aminobenzyl)-2,3,3,3-tetrafluor-2-methoxypropanamide (3d): TFMP (**1**, 2.01 g, 10.5 mmol), 2-(aminomethyl) aniline (**2d**, 1.30 g, 10.6 mmol) and heptane (40 mL) were stirred at r.t. for 24 days. The reaction mixture was evaporated to dryness, and the residue was separated by column chromatography (20 g of silica, eluent $CHCl_3$/Et_2O 3:1) to give 2.77 g (94% yield) of oily amide **3d**, which was purified by crystallization from petroleum ether to yield white crystals. ^{1}H NMR ($CDCl_3$): 7.14 (1H, td, J_{HH} = 7.7 Hz, J_{HH} = 1.6 Hz), 7.08 (1H, dd, J_{HH} = 7.7 Hz, J_{HH} = 1.6 Hz), 6.98 (1H, bs), 6.72 (1H, td, J_{HH} = 7.7 Hz, J_{HH} = 1.1 Hz), 6.68 (1H, dd, J_{HH} = 7.7 Hz, J_{HH} = 1.1 Hz), 4.55 (1H, dd, J_{HH} = 14.8 Hz, J_{HH} = 6.6 Hz), 4.40 (1H, dd, J_{HH} = 14.8 Hz, J_{HH} = 5.5 Hz), 3.95 (2H, br s), 3.56 (3H, s) ppm. ^{13}C NMR ($CDCl_3$): 160.8 (d, J_{CF} = 31.5 Hz), 145, 130.24, 129.26, 120.21, 119.06 (qd, J_{CF} = 286.3 Hz, J_{CF} = 34.9 Hz), 117.96, 115.83, 105.53 (dq, J_{CF} = 245.7 Hz, J_{CF} = 35.5 Hz), 53.31 (d, J_{CF} = 2.3 Hz), 40.57 ppm. IR (KBr): 3483 w, 3377 w, 3328 w, 1672 s, 1610 w, 1542 w cm^{-1}. M.p. 69.5–71.5 °C. For $C_{11}H_{12}F_4N_2O_2$ (280.22): calcd. C 47.15, H 4.32, N 10.00; found C 47.00, H 4.49, N 9.82.

f) 2,2-Dimethyl-1,2,3,4-tetrahydroquinazolinium 2,3,3,3-tetrafluoro-2-methoxypropanoate (8). TFMP (**1**, 1.37 g, 11.2 mmol), 2-(aminomethyl) aniline (**2d**, 2.69 g, 14.1 mmol) and acetone (10 mL) were stirred at r.t. for 45 days. The reaction mixture was evaporated to dryness to obtain 3.32 g of the mixture of crystals and oil. The crystals were washed with CH_2Cl_2 to give 2.36 g (65% yield) of white crystals of salt **8**, which was purified by recrystallization from ethanol. ^{1}H NMR (DMSO-d_6): 10.01 (2H, bs), 6.76 (1H, bs), 6.73–6.66 (2H, m), 4.25 (2H, s), 3.40 (3H, s), 1.49 (6H, s) ppm. ^{13}C NMR (DMSO-d_6): 161.73 (d, J_{CF} = 30.3 Hz), 140.4, 128.16, 126.94, 120.6 (qd, J_{CF} = 285.1 Hz, J_{CF} = 37.2 Hz), 117.69, 115.27, 112.87, 105.59 (dq, J_{CF} = 245.3 Hz, J_{CF} = 32.6 Hz), 66.17, 52.93 (d, J_{CF} = 1.1 Hz), 24.52 (2C) ppm. ^{19}F NMR (DMSO-d_6): −79.6 (3F, d, J_{FF} = 3.9 Hz), −126.9 (1F, qq, J_{FF} = 3.9 Hz, J_{HF} = 1.7 Hz). For $C_{14}H_{18}N_2O_3F_4$ (338.31): calcd.. C 49.71, H 5.36, N 8.28; found C 49.50, H 5.28, N 8.25.

Acknowledgement

We thank the Ministry of Education, Youth and Sports (Research Project No. 6046137301) for financial support.

References

[1] (a) D.D. Reynolds, W.O. Kenyon, J. Am. Chem. Soc. 72 (1950) 1597–1598;
(b) R.C. Elderfield, A.E. Hydorn, E. Schenker, K.K. Wyckoff, J. Org. Chem. 24 (1959) 1296–1301;
(c) A.M. Echavarren, N. Tamayo, O. de Frutos, A. Garcia, Tetrahedron 53 (1997) 16835–16846;
d) M. Lehr, J. Med. Chem. 40 (1997) 3381–3392.
[2] (a) K.C. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca, NY, 1953 p. 765;
(b) J. March, Advanced Organic Chemistry, 4th ed., J. Wiley & Sons, New York, 1992 p. 380.
[3] T. Kametani, K. Kigasawa, H. Hiiragi, H. Sugahara, T. Hayasaka, T. Iwata, H. Ishimaru, Tetrahedron Lett. 23 (1965) 1817–1822.
[4] T. Kametani, T. Hayasaka, K. Kigasawa, J. Pharm. Soc. Jpn. 87 (1967) 1298–1303.
[5] (a) P. Tundo, S. Bressanello, A. Loris, G. Sathicq, Pure Appl. Chem. 77 (2005) 1719–1725;
(b) M. Selva, P. Tundo, T. Foccardi, J. Org. Chem. 70 (2005) 2476–2485;
(c) M. Selva, P. Tundo, Tetrahedron Lett. 44 (2003) 8139–8142.
[6] M. Smrčina, Š. Vyskočil, V. Hanuš, M. Polášek, V. Langer, B.G.M. Chew, D.B. Zax, H. Verrier, K. Harper, T.A. Claxton, P. Kočovský, J. Am. Chem. Soc. 118 (1996) 487–488.
[7] (a) H.E. Zaugg, H.J. Glenn, R.J. Michaels, R.U. Schock, L.R. Swet, J. Am. Chem. Soc. 79 (1957) 3912–3915;
(b) E.S. Ratemi, J.C. Vederas, Tetrahedron Lett. 35 (1994) 7605–7608.
[8] H. Bricout, J.-F. Carpentier, A. Mortreux, Tetrahedron 54 (1998) 1073–1084.
[9] H.H. Fox, J. Org. Chem. 17 (1952) 547–554.
[10] N.A. Al-Awadi, M.H. Elnagdi, K. Kaul, G. Chuchani, J. Phys. Org. Chem. 13 (2000) 675–678.