ARTICLE INFO
Received 18 May 2023
Accepted 15 June 2023
Available online June 2023

SYNTHESIS OF FLUORINE-CONTAINING 2-METHOXYPROPANOIC AND BENZOIC ACIDS THIOESTERS

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Abstract: The reactions of 2,3,3,3-tetrafluoro-2-methoxypropanoic and 2- and 4-fluorobenzoic acid chlorides with various thiols in inert solvents have been studied. It has been shown that the best yields of target thiol esters are achieved in the presence of triethylamine as a base (using an excess of thiol).

Keywords: thiols, *N*-(2-mercaptoethyl)acetamide, 2,3,3,3-tetrafluoro-2-methoxypropanoyl chloride, 2-fluoro- and 4-fluorobenzoyl chloride, *S*-cyclohexyl- and *S*-(2-acetamidoethyl)-2,3,3,3-tetrafluoro-2-methoxypropanethioates, 2- and 4-fluoro-substituted *S*-alkyl- and *S*-(2-acetamidoethyl)-benzothioates.

In previous studies, we developed a method for preparation of fluorine-containing 2-methoxypropanamides [1] and fluorine-substituted benzamides [2]. The aim of this study was the synthesis of other derivatives of fluorine-containing carboxylic acids, i. e. thiol esters. Organic sulfur derivatives, especially thiol ethers, play an important role in various biological processes and are also in great demand for obtaining biologically active and medical compounds [3]. Some *S*-containing derivatives of 2-methylpropanoic acid are used to treat hypertension, for example, the captopril (Capoten) drug [4].

For synthesis of target compounds, 2-methoxytetrafluoropropanoic acid, as well as 2- and 4-fluorobenzoic acids, were chosen as fluorine-containing acids. The preparation of thiol esters of these acids was carried out using cyclohexylmercaptan ($C_6H_{11}SH$), *N*-acetylcysteamine (NAC), and *n*-amylmercaptan. Of all the thiol esters, NAC derivatives of carboxylic acids are of the greatest interest, since they are effective precursors in the synthesis of analogues of unnatural polyketides. Polyketides are known to be widely used as antibiotics, anti-cancer agents, cholesterol-lowering

drugs, and so on. [5, 6]. Little is known about preparation of thiol esters of fluorobenzoic acid. Thus, the synthesis of *S*-cyclohexyl-4-fluorobenzothioate in low yield (18%) by reaction of 4-fluorobenzoyl chloride with $C_6H_{11}SH$ in the presence of 1,4-diazabicyclo[2.2.0]octane was described [7].

Later, this thioether was obtained in 62% yield by the reaction of 4-fluorobenzaldehyde with $C_6H_{11}SH$ in the presence of diisopropyl azodicarboxylate and Cs_2CO_3 in DMF [8]. At the same time, there is no information in literature about the synthesis of thioesters of fluorine-containing 2-methoxypropanoic acids.

Non-fluorinated analogs of NAC thioethers, i. e. *S*-(2-acetylaminoethyl)-2-hydroxy- or 2-methoxyalkanthioates, were previously obtained by reacting the corresponding acids with NAC in the presence of carbodiimides. These thioethers were used to obtain the antitumor agents (analogues of cryptophycin) [9-11]. In recent years, many studies have been devoted to synthesis of NAC-thioester of benzoic acid. Thus, its preparation by reaction of PhCOCl and NAC in the presence of Et_3N [12, 13] or i-Pr_2NEt (DIPEA) [14] has been described. A variety of reagents were used to synthesize the thioester from benzoic acid and NAC: $Ph_2P(O)N_3$ azide and Et_3N [15], dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide [16], pentafluoropyridine and DIPEA [17], 4-dimethylaminopyridine (DMAP), and DCC [18], 1-ethyl-3(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI), Et_3N and 1-hydroxybenzotriazole [19, 20], as well as DMAP and EDCI [5]. Based on NAC-benzothioate, analogues of simvastatin (a hypolipidemic agent) [12], antibiotics (antimycin [15], myxopyronine [18], pactamycin [20]), and polyketides [5, 14, 16, 19] were obtained.

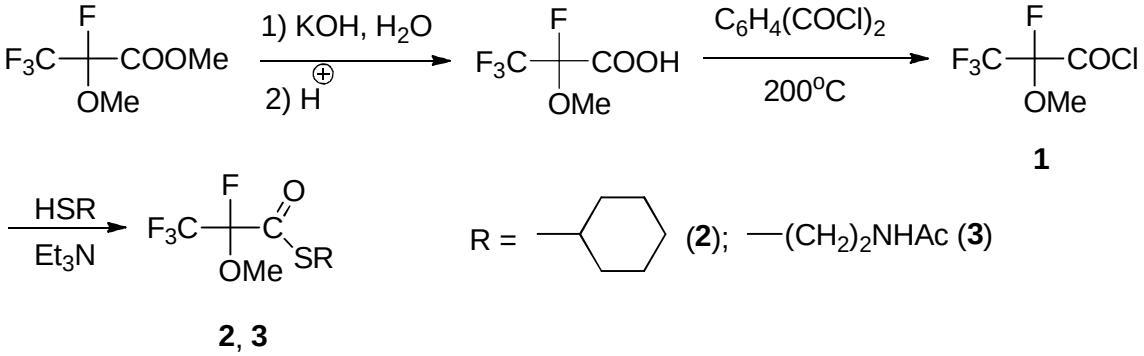
Several methods have been proposed for preparation of another thioether, i. e. *S*-cyclohexylbenzothioate. Its synthesis from benzoyl chloride and $C_6H_{11}SH$ in the presence of catalysts $(CF_3)_2CHOH$ [21] or ZnO [22] has been described. Thioesterification of benzoic acid with this mercaptan was carried out in the presence of CF_3COOH [23], anhydride $(MeSO_2)_2O$ [24], or the mixture of 4,4'-azopyridine – Ph_3P composition [25]. The oxidative thioesterification of benzaldehyde with thiol occurred in the presence of phenazine, an organic base, and NHC catalyst [26, 27] or under the action of dibromoisocyanuric acid [28]. Cross-coupling of benzaldehyde with cyclohexyl disulfide in the presence of di-tert-butyl peroxide gives the thioether in a lower yield (44%) [29]. In the reaction of iodobenzene thiocarbonylation in the presence of hexacarbonyls $M(CO)_6$ (M = Cr, Mo) and catalytic amounts of nickel halide, the yield of thioether with thiol is also 2 times higher [30] than when using disulfide and zinc [31].

S-Pentylbenzothioate was previously obtained by acylation of *n*-pentanethiol with benzoyl chloride (in the presence of ZnO) [22] or benzoyl bromide at the silica gel surface [32]. Good yields

of this thioester are also obtained by condensation of benzoic acid with thiol under the action of 4,4'-azopyridine and Ph_3P [25] or the system of reagents Ph_2PCl/I_2 and imidazole [33]. The synthesis of thioether by the reaction of benzaldehyde with thiol using the oxidizing agent (phenazine) and catalytic amounts of a base (DBU) and poly(3,4-dimethyl-5-vinylthiazol-3-inium) iodide has been described [26].

Thiocarbonylation of iodobenzene with thiol to form the thioether proceeds smoothly under the action of chromium hexacarbonyl in the presence of catalyst ($NiCl_2$) [30]. It should be noted that the methods described above for preparation of thiol esters are most often multicomponent reactions; therefore, in all cases, column chromatography was required to isolate the products, which complicates the process.

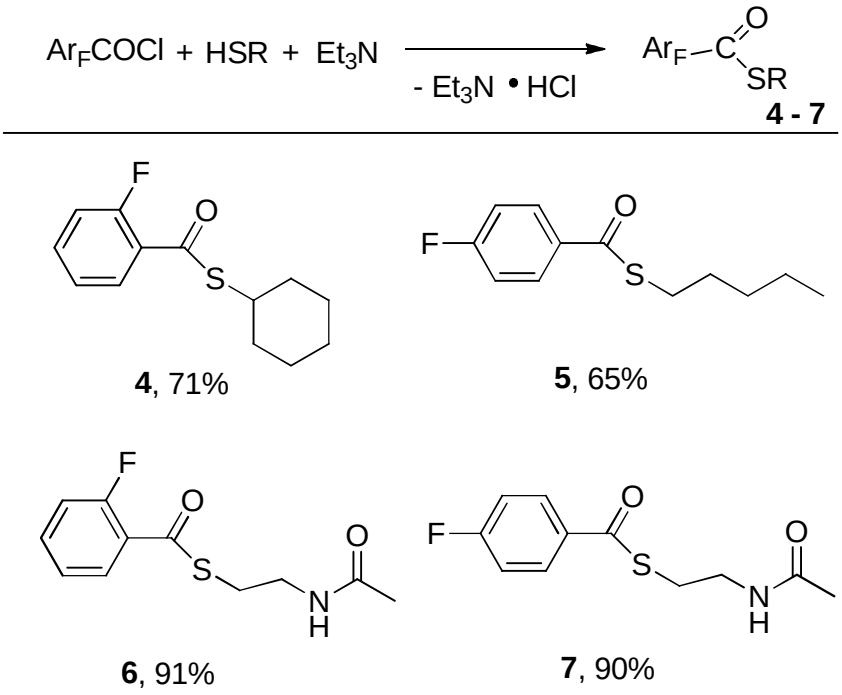
Numerous examples of increased activity of fluorine-containing drugs compared to hydrogenated analogs are known [34, 35], so the synthesis of new fluorine-substituted acylthioethers is an urgent task. To obtain thiol esters of fluorinated 2-methoxypropanoic acid, 2,3,3,3-tetrafluoro-2-methoxypropanoyl chloride **1**, obtained by saponification of a readily available methyl ester and subsequent reaction of acid with phthaloyl dichloride, was chosen as a starting compound [1]. The reactions of acid chloride **1** with thiols ($C_6H_{11}SH$ or NAC) in the presence of triethylamine in inert solvent gave the corresponding thioethers (**2, 3**) in 59% and 60% yields (after purification by vacuum distillation) (see Scheme 1).



Scheme 1. *Synthesis of thiol esters of 2-methoxytetrafluoropropanoic acid* ***2, 3****.*

It should be noted that if the synthesis of thioester **3** requires an equimolar amount of NAC, then in the case of easily oxidized $C_6H_{11}SH$, its excess of 1.7 equiv.

We obtained thiol esters of fluorinated benzoic acids in good yields similarly to reaction of fluorosubstituted benzoyl chlorides with thiols ($C_6H_{11}SH$, *n*-amylmercaptan, and NAC) in benzene (see Scheme 2). The reactions were carried out in the presence of triethylamine; if pyridine was used instead of Et_3N, then the yields and purity of target products decreased.



Scheme 2*. Synthesis of thiol esters of fluoro-substituted benzoic acids* ***4-7****.*

In this case, the best yields of target benzothioates **4-7** are achieved at molar ratio ArFCOCl/HSR equal to 1/1.4-1.7 for R = cyclohexyl or *n*-pentyl, while in the case of R = -$(CH_2)_2$NHAc this ratio was 1/1.2.

Synthesized *S*-alkyl esters **2-5** are light yellow or colorless oils, easily purified by vacuum distillation; NAC-benzothioates **6** and **7** are crystalline solids whose composition and structure were proven by elemental analysis and ^{1}H and ^{19}F NMR spectroscopy. In ^{19}F NMR spectra of alkanethioates **2** and **3**, the signal from CF group appears in the region of -133.35÷-134.66 ppm, while the signal from CF_3group appears at -79.38÷-80.73 ppm. In ^{19}F NMR spectra of 2-fluorobenzothioates **4** and **6**, the fluorine signal is observed in the range -110.33÷-111.26 ppm, and for 4-fluoro-substituted compounds **5** and **7**, a singlet at -106.24÷-106 is characteristic, 90 ppm.

Thus, in this study, based on reaction of thiolation of acyl chlorides with mercaptans in the presence of Et_3N, various thiol esters of F-containing carboxylic acids were obtained in good yields (59-91%). The syntheses developed by us are preparative, can be easily scaled up and do not require the use of chromatographic purification methods. This makes the obtained new compounds available in quantities sufficient for synthesis of biologically active substances. It is known that thioethers are actively used to obtain peptides and pharmaceuticals [3, 8 ,31, 36].

Experimental part

NMR spectra were recorded via Bruker Avance-200, Bruker Avance-300 and Bruker Avance-400 spectrometers at operating frequencies of 200 MHz, 300 MHz and 400 MHz, using internal standard $SiMe_4$ for ^1H NMR, and 188 MHz, 282 MHz and 376 MHz for ^{19}F NMR ($CFCl_3$), respectively. Elemental analysis was performed at Laboratory of Microanalysis of INEUM RAS. The reaction progress was monitored by TLC method using Merck plates (silica gel 60 F_{254}, 0.25 mm). The R_F values of obtained compounds were determined in the systems acetone - CCl_4 = 1:3; 3:1 or petroleum ether - ethyl acetate = 3:1. The starting 2,3,3,3-tetrafluoro-2-methoxy-propanoyl chloride **1** was obtained from corresponding acid and phthaloyl dichloride [1]. 2-Fluoro and 4-fluorobenzoyl chlorides are commercially available reagents. All solvents used were purified according to standard procedures.

S-Cyclohexyl-2,3,3,3-tetrafluoro-2-methoxypropanthioate (2).

To a solution of 2.0 g (10.0 mmol) of acid chloride 1 in 25 ml of hexane was added a solution of Et_3N (1.14 g, 11.0 mmol) and $C_6H_{11}SH$ (1.94 g, 16.7 mmol) in hexane (20 ml) in portions, until a positive reaction to SH-group appears. The next day, the precipitated hydrochloride was filtered off, the mother liquor was evaporated in vacuo, the residue was distilled. 1.69 g of compound **2** (with yield 60%) was obtained as a light-yellow oil with b.p. 96-98°C at 10 mm Hg, n_D = 1.4340 (20°C), R_F = 0.73 (in the system petroleum ether - ethyl acetate = 3:1).

^{1}H NMR spectrum (400 MHz, $CDCl_3$, *d*, ppm): 1.24-1.37 (m, 1H, CH_2); 1.43-1.55 (m, 4H, 2 CH_2); 1.63-1.66 (m, 1H, CH_2); 1.74-1.78 (m, 2H, CH_2); 1.97-2.00 (m, 2H, CH_2); 3.60 (s, 3H, OCH_3); 3.64-3.69 (m, 1H, CH).

^{19}F NMR spectrum (376 MHz, $CDCl_3$, *d*, ppm): -80.73 (s, 3F, CF_3); -134.66 (s, 1F, CF).

Founded (%): C, 43.63; H, 4.91; S, 11.42. $C_{10}H_{14}F_4O_2S$. **Calculated** (%): C, 43.80; H, 5.11; S, 11.68.

S-(2-Acetamidoethyl)-2,3,3,3-tetrafluoro-2-methoxypropanthioate (3).

Synthesis was carried out similarly to preparation **2**, but using equimolar amounts of reagents **1**, Et_3N, and NAC in benzene medium. Product **3** was obtained (with yield 59%) as a light-yellow oil with b. p. 150-152°C at 0.2 mm Hg.

^{1}H NMR spectrum (200 MHz, $CDCl_3$, *d*, ppm): 2.00 (s, 3H, CH_3); 3.12-3.27 (m, 2H, CH_2S); 3.38-3.55 (m, 2H, CH_2N); 3.60 (s, 3H, OCH_3); 6.13 (br.s, 1H, NH).

^{19}F NMR spectrum (188 MHz, $CDCl_3$, *d*, ppm): -79.38 (s, 3F, CF_3); -133.35 (s, 1F, CF).

Founded (%): C, 34.86; H, 4.12; N, 5.29. $C_8H_{11}F_4NO_3S$. **Calculated** (%): C, 34.66; H, 3.97; N, 5.05.

S-Cyclohexyl-2-fluorobenzothioate (4).

To a solution of 0,95 g (6.0 mmol) of 2-fluorobenzoyl chloride in 10 ml of benzol was added a solution of Et_3N (0.61 g, 6.0 mmol) and $C_6H_{11}SH$ (1.18 g, 10.0 mmol) in benzol Et_3N (0.61 g, 6.0 mmol) and $C_6H_{11}SH$ (1.18 g, 10.0 mmol) in benzene (13 ml) was added in portions, until a positive reaction to the SH-group appears. The next day, the precipitated hydrochloride was filtered off, the mother liquor was washed twice with cold water and dried over $MgSO_4$. After removal of MgSO4, the filtrate was evaporated in vacuo and the residue was distilled. 1.01 g of product **4** (with yield 71%) was obtained as a colorless oil with b. p. 96-98°C at 0.05 mm Hg, n_D = 1.5592 (16°C), R_F = 0.68 (in the system petroleum ether - ethyl acetate = 3:1).

^{1}H NMR spectrum (300 MHz, $CDCl_3$, *d*, ppm): 1.27-1.37 (m, 1H, CH_2); 1.42-1.55 (m, 4H, $2CH_2$); 1.59-1.66 (m, 1H, CH_2); 1.73-1.79 (m, 2H, CH_2); 2.03-2.07 (m, 2H, CH_2); 3.72-3.79 (m, 1H, CH); 7.11-7.24 (m, 2H, Ar); 7.46-7.54 (m, 1H, Ar); 7.81-7.87 (m, 1H, Ar).

^{19}F NMR spectrum (282 MHz, $CDCl_3$, *d*, ppm): -111.26 (s, 1F, F-Ar).

Founded (%): C, 65.34; H, 6.15; S, 13.32. $C_{13}H_{15}FOS$. **Calculated** (%): C, 65.55; H, 6.30; S, 13.45.

S-Pentyl-4-fluorobenzothioate (5).

The synthesis was carried out similarly to preparation of **4** from 0.95 g (6.0 mmol) 4-fluorobenzoyl chloride, 0.61 g (6.0 mmol) Et_3N and 0.87 g (8.4 mmol) *n*-amylmercaptan. 0.88 g of product **5** (with yield 65%) was obtained as a colorless oil with b. p. 55-57°C at 0.03 mm Hg, n_D = 1.5334 (16°C).

^{1}H NMR spectrum (200 MHz, $CDCl_3$, *d*, ppm, *J*/Hz): 0.86 (t, 3H, CH_3, *J* = 7.7); 1.21-1.67 (m, 6H, 3 CH_2); 2.99 (t, 2H, SCH_2, *J* = 7.7); 7.15 (t, 2H, Ar, *J* = 9.2); 7.85-8.05 (m, 2H, Ar).

^{19}F NMR spectrum (282 MHz, $CDCl_3$, *d*, ppm): -106.24 (s, 1F, F-Ar).

Founded (%): C, 63.58; H, 6.47; S, 13.98. $C_{12}H_{15}FOS$. **Calculated** (%): C, 63.72; H, 6.64; S, 14.16.

S-(2-Acetamidoethyl)-2-fluorobenzothioate (6).

The synthesis was carried out similarly to the preparation of **4** from 1.42 g (9.0 mmol) 2-fluorobenzoyl chloride, 1.0 g (9.9 mmol) Et_3N and 1.33 g (11.2 mmol) NAC in benzene (25 ml),

but without distillation. 1.97 g of product **6** (with yield 91%) was obtained as a white crystalline solid, with m. p. 71-73°C, R_F = 0.68 (solution in benzene, in the system acetone - CCl_4 = 3:1).

^{1}H NMR spectrum (200 MHz, C_6D_6, *d*, ppm): 1.57 (s, 3H, CH_3); 2.82-3.00 (m, 2H, CH_2S); 3.14-3.37 (m, 2H, CH_2N); 5.69 (s, 1H, NH); 6.43-6.59 (m, 2H, Ar); 6.63-6.78 (m, 1H, Ar); 7.55-7.73 (m, 1H, Ar).

^{19}F NMR spectrum (282 MHz, C_6D_6, *d*, ppm): -110.33 (s, 1F, F-Ar).

Founded (%): C, 54.94; H, 4.86; N, 5.68. $C_{11}H_{12}FNO_2S$. **Calculated** (%): C, 54.77; H, 4.98; S, 5.81.

S-(2-Acetamidoethyl)-4-fluorobenzothioate (7).

The synthesis was carried out similarly to preparation of **6** from 1.31 g (8.3 mmol) 4-fluorobenzoyl chloride, 0.84 g (8.3 mmol) Et_3N and 1.21 g (10.1 mmol) NAC in benzene (35 ml). 1.8 g of product **7** (with yield 90%) was obtained as a white crystalline solid, with m. p. 98-100°C, R_F = 0.20 (solution in benzene, in the system acetone - CCl_4 = 1:3).

^{1}H NMR spectrum (300 MHz, CD_3OD, *d*, ppm, *J*/Hz): 1.95 (s, 3H, CH_3); 3.22 (t, 2H, CH_2S, *J* = 6.6); 3.44 (t, 2H, CH_2N, *J* = 6.6); 4.93 (s, 1H, NH); 7.26 (t, 2H, Ar, *J* = 8.7); 8.03-8.07 (m, 2H, Ar).

^{19}F NMR spectrum (282 MHz, CD_3OD, *d*, ppm): -106.90 (s, 1F, F-Ar).

Founded (%): C, 54.98; H, 4.83; N, 5.62. $C_{11}H_{12}FNO_2S$. **Calculated** (%): C, 54.77; H, 4.98; S, 5.81.

Acknowledgment

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (Contract/agreement No. 075-03-2023-642) and was performed employing the equipment of Center for molecular composition studies of INEOS RAS.

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