Synthesis of substituted thiophenes based on fluorine-containing β-functionalized vinyl sulfides

A. N. Kovregin, A. Yu. Sizov, and A. F. Ermolov*

Military University of Radiational, Chemical and Biological Defense,
13 Brigadirskii per., 107005 Moscow, Russian Federation.
Fax: +7 (095) 267 5107

Derivatives of fluorine-containing 3-(methoxycarbonylmethylthio)acrylic acids readily undergo base-catalyzed cyclization to form 3-hydroxy- and 3-aminothiophenes.

Key words: fluorine-containing vinyl sulfides, cyclization, 3-hydroxythiophenes, 3-aminothiophenes.

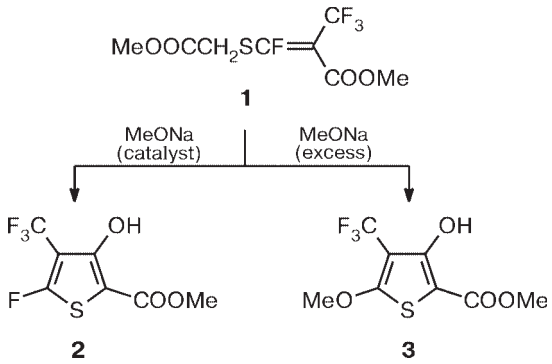
Fluorine-containing functionalized vinyl sulfides are promising reagents in cyclization reactions due to the presence of several reaction centers. The present study is devoted to intramolecular cyclization of alkyl vinyl sulfides containing the cyano and carbomethoxy groups in the β position of the polyfluoroalkenyl fragment. The procedure for the preparation of the latter compounds has been reported previously.[1] The reactions under consideration are generally performed in the presence of bases. Their conditions and reaction products depend substantially on the CH-acidic properties of the α-methylene group of the alkyl fragment.[2]

Results and Discussion

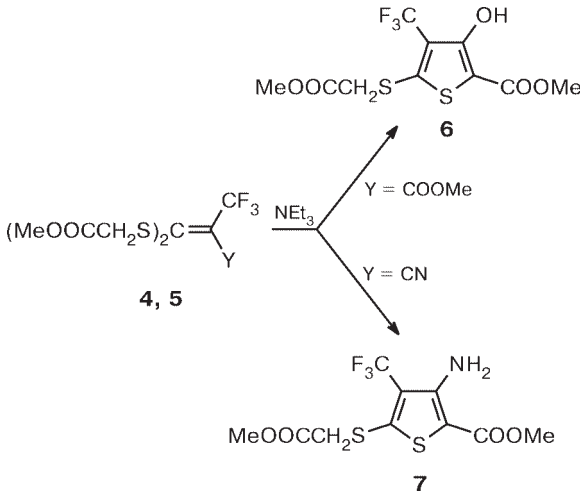
We found that 1,3,3,3-tetrafluoro-2-(methoxycarbonyl)propenyl methoxycarbonylmethyl sulfide (**1**) containing the activated α-methylene group underwent intramolecular cyclocondensation in the presence of sodium methoxide as a catalyst to form 5-fluoro-3-hydroxythiophene (**2**) (Scheme 1). In this reaction, the vinyl F atom remained intact. This atom was replaced already in the cyclic structure with the use of an excess of sodium methoxide to give 3-hydroxy-5-methoxythiophene (**3**). Apparently, the first step of the reaction involves the generation of the carbanion at the α-methylene group.

Derivatives of 3,3-bis(methoxycarbonylmethylthio)acrylic acids **4** and **5** were readily involved in analogous reactions to produce 3-hydroxythiophene **6** and 3-aminothiophene **7**, respectively (Scheme 2). The reactions with the use of triethylamine, which acts as a more efficient catalyst, gave products in nearly quantitative yields.

Scheme 1



Scheme 2



Y = COOMe (**4**), CN (**5**)

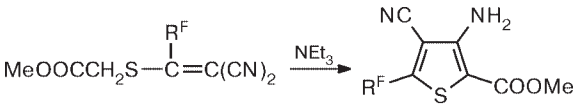
Under the same conditions (catalysis by triethylamine), 1,1-dicyano-2-methoxycarbonylmethylthio-2-(polyfluoroalkyl)ethylenes **8** and **9** underwent cyclization to yield thiophenes **10** and **11**, respectively (Scheme 3).

The starting vinyl sulfides **8** and **9** were prepared by the reactions of 2-chloro-1,1-dicyano-2-trifluoromethyl- and 2-chloro-1,1-dicyano-2-(pentafluoro-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 945—947, June, 2002.

1066-5285/02/5106-1028 $27.00

Scheme 3

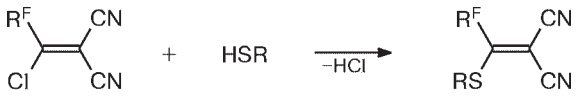


8, 9 **10, 11**

$R^F = CF_3$ (**8, 10**), C_2F_5 (**9, 11**)

ethyl)ethylenes with methyl thioglycolate (Scheme 4). Toluenethiol reacted analogously to give benzyl sulfide **12**.

Scheme 4



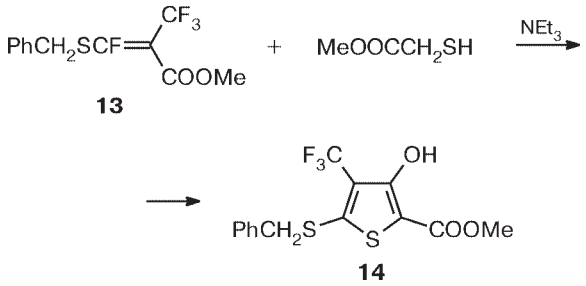
8, 9, 12

R = CH_2COOMe, $R^F = CF_3$ (**8**), C_2F_5 (**9**);
R = CH_2Ph, $R^F = CF_3$ (**12**)

The reactions were carried out upon heating of an equimolar mixture of the reagents to 60—70 °C. The course of the reactions was followed from evolution of hydrogen chloride. Attempts to lower the temperature with the use of acceptors of hydrogen chloride (for example, triethylamine) led to resinification of the reaction mixture as a result of which low-boiling thiols, such as MeSH and Bu^tSH, could not be involved in the reactions.

In some cases, heterocyclization can proceed in one step simultaneously with the insertion of the methoxycarbonylmethylthio group. As an example, we refer to the reaction of methyl 3-benzylthio-3-fluoro-2-(trifluoromethyl)acrylate (**13**) with methyl thioglycolate in the presence of triethylamine giving rise to thiophene **14** (Scheme 5).

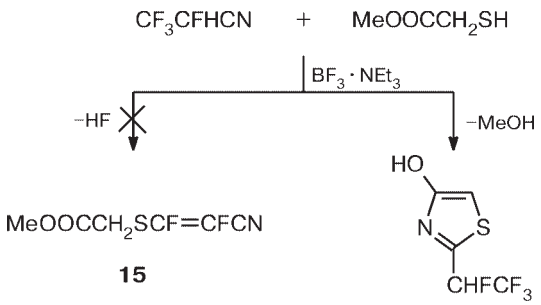
Scheme 5



13 **14**

An unexpected result was obtained in attempting to prepare 2,3-difluoro-3-(methoxycarbonyl)acrylonitrile (**15**), which is of interest as the starting compound for the synthesis of thiophenes. It appeared that the reaction of 2-hydrotetrafluoropropionitrile with methyl thioglycolate in the presence of the $BF_3 \cdot NEt_3$ complex led to the addition of thiol at the nitrile group accompanied by intramolecular cyclization even upon moderate heating (40—50 °C). As a result, 4-hydroxy-2-(1-hydrotetrafluoroethyl)thiazole (**16**) was isolated in 35% yield (Scheme 6).

Scheme 6



15 **16**

Evidently, the reaction follows this pathway because of the rather low CH-acidity of 2-hydrotetrafluoropropionitrile, which hinders its dehydrofluorination. Consequently, the function of the $BF_3 \cdot NEt_3$ complex is to activate thiol through the formation of the thiolate anion. In this case, the possibility of cyclization *via* the methoxycarbonyl group followed by "aromatization" of the ring is the major driving force for the irreversible addition of methyl thioglycolate at the nitrile group. Examples of analogous transformations were reported in the literature.[3]

Attempts to subject benzyl analogs of sulfides **1**, **4**, **5**, **8**, and **9** to cyclization failed due, apparently, to the low CH-acidity of the methylene group of the benzyl fragment.

To summarize, methoxycarbonylmethyl polyfluoroalkenyl sulfides are convenient precursors of substituted 3-hydroxy- and 3-aminothiophenes, which are of interest as synthons for the synthesis of new biologically active compounds.

Experimental

The ^{19}F NMR spectra were recorded on a Bruker AC-200F spectrometer (188.31 MHz). The ^1H NMR spectra were measured on a Bruker AC-300SF instrument (300.13 MHz). The chemical shifts (δ) are given relative to CF_3COOH (^{19}F, external standard) and Me_4Si (^1H, internal standard) for solutions in DMSO-d_6. The mass spectra (EI) of the reaction products were obtained on an HP-5890 gas chromatograph equipped with an HP-5972 mass-selective detector; the energy of ionizing electrons was 70 eV. The course of the reactions and the purities of the resulting compounds were monitored by TLC on Merck 60F-254 plates in an acetone—CCl_4 system.

The starting vinyl sulfides **1**, **4**, **5**, and **13** were synthesized according to a procedure reported previously.[1] 2-Chloro-1,1-dicyano-2-(polyfluoroalkyl)ethylenes were prepared according to a known method.[4]

5-Fluoro-3-hydroxy-2-methoxycarbonyl-4-(trifluoromethyl)thiophene (2). A solution of sulfide **1** (2.75 g, 10 mmol) in MeOH (10 mL) was added with stirring to a solution of MeONa in MeOH, which was prepared from Na (0.02 g, 1 mmol) and MeOH (10 mL). The reaction mixture was kept at 20 °C for 2 h and then poured into water. The precipitate that formed was filtered off, dried in air, and recrystallized from a 3 : 1 hexane—ethyl acetate mixture. Thiophene **2** was obtained in a yield of 0.9 g (37%), m.p. 35—37 °C, R_f = 0.55 (1 : 9). Found (%): C, 34.54; H, 1.60. $C_7H_4F_4O_3S$. Calculated (%): C, 34.43; H, 1.64. ^{1}H NMR: 3.88 (s, 3 H, OMe); 10.68 (br.s, 1 H, OH). ^{19}F NMR: −36.0 (q, 1 F, $J_{F,F}$ = 16 Hz); 17.9 (d, 3 F, CF_3, $J_{F,F}$ = 16 Hz). MS, *m/z*: 244 $[M]^+$.

3-Hydroxy-5-methoxy-2-methoxycarbonyl-4-(trifluoromethyl)thiophene (3). A solution of sulfide **1** (2.75 g, 10 mmol) in MeOH (10 mL) was added with stirring to a solution of MeONa in MeOH, which was prepared from Na (1.15 g, 50 mmol) and MeOH (10 mL). The reaction mixture was kept at 20 °C for 15 h and then poured into a 10% HCl solution. The precipitate that formed was filtered off and dried in air. Thiophene **3** was obtained in a yield of 1.4 g (55%), m.p. 180—182 °C, R_f = 0.70 (1 : 9). Found (%): C, 37.59; H, 2.77. $C_8H_7F_3O_4S$. Calculated (%): C, 37.50; H, 2.73. ^{1}H NMR: 3.83 and 4.07 (both s, 3 H each, 2 OMe); 10.40 (br.s, 1 H, OH). ^{19}F NMR: 18.2 (s, CF_3).

3-Hydroxy-2-methoxycarbonyl-5-methoxycarbonylmethylthio-4-(trifluoromethyl)thiophene (6). Triethylamine (1.0 g, 10 mmol) was added with stirring to a solution of sulfide **4** (3.6 g, 10 mmol) in ether (25 mL). The reaction mixture was kept at 20 °C for 15 h and then the solvent was removed *in vacuo*. A 10% HCl solution (50 mL) was added to the residue and the precipitate that formed was filtered off. Thiophene **6** was obtained in a yield of 2.9 g (88%), m.p. 182—184 °C, R_f = 0.25 (1 : 9). Found (%): C, 36.47; H, 2.70. $C_{10}H_9F_3O_5S_2$. Calculated (%): C, 36.36; H, 2.73. ^{1}H NMR: 3.87 (s, 5 H, OMe + CH_2); 3.99 (s, 3 H, OMe); 10.31 (br.s, 1 H, OH). ^{19}F NMR: 19.7 (s, CF_3).

3-Amino-2-methoxycarbonyl-5-methoxycarbonylmethylthio-4-(trifluoromethyl)thiophene (7). Triethylamine (0.2 g, 2 mmol) was added with stirring and cooling with cold water to a solution of sulfide **5** (3.3 g, 10 mmol) in MeOH (10 mL). The reaction mixture was kept at 20 °C for 20 min and the precipitate that formed was filtered off. Thiophene **7** was obtained in a yield of 3.1 g (94%), m.p. 92—94 °C, R_f = 0.60 (1 : 9). Found (%): C, 36.59; H, 3.03. $C_{10}H_{10}F_3NO_4S_2$. Calculated (%): C, 36.47; H, 3.04. ^{1}H NMR: 3.74 and 3.79 (both s, 3 H each, 2 OMe); 3.94 (s, 2 H, CH_2); 6.36 (br.s, 2 H, NH_2). ^{19}F NMR: 16.5 (s, CF_3). MS, *m/z*: 329 $[M]^+$.

3-Amino-4-cyano-2-methoxycarbonyl-5-(trifluoromethyl)thiophene (10) and **3-amino-4-cyano-2-methoxycarbonyl-5-(pentafluoroethyl)thiophene (11)** were prepared analogously. Compound **10**, the yield was 95%, m.p. 175—177 °C, R_f = 0.56 (1 : 9). Found (%): C, 38.48; H, 1.96. $C_8H_5F_3N_2O_2S$. Calculated (%): C, 38.40; H, 2.00. ^{1}H NMR: 3.83 (s, 3 H, OMe); 7.05 (br.s, 2 H, NH_2). ^{19}F NMR: 14.8 (s, CF_3).

Compound **11**, the yield was 92%, m.p. 171—173 °C, R_f = 0.50 (1 : 9). Found (%): C, 36.22; H, 1.76. $C_9H_5F_5N_2O_2S$. Calculated (%): C, 36.00; H, 1.67. ^{1}H NMR: 3.86 (s, 3 H, OMe); 7.00 (br.s, 2 H, NH_2). ^{19}F NMR: −5.0 (s, 3 F, CF_3); −29.2 (s, 2 F, CF_2).

Reactions of 2-chloro-1,1-dicyano-2-(polyfluoroalkyl)ethylenes with thiols (general procedure). A mixture of the corresponding chloroethylene (0.02 mol) and thiol (0.02 mol) was kept at 60—70 °C until evolution of hydrogen chloride ceased (3—4 h). Then fractionation or crystallization by trituration in hexane was carried out.

1,1-Dicyano-2-methoxycarbonylmethylthio-2-(trifluoromethyl)ethylene (8), the yield was 80%, b.p. 104—106 °C (3 Torr). Found (%): C, 38.45; H, 1.97. $C_8H_5F_3N_2O_2S$. Calculated (%): C, 38.40; H, 2.00. ^{1}H NMR: 3.81 (s, 3 H, OMe); 4.08 (s, 2 H, CH_2). ^{19}F NMR: 14.6 (s, CF_3). MS, *m/z*: 268 $[M]^+$.

1,1-Dicyano-2-methoxycarbonylmethylthio-2-(pentafluoroethyl)ethylene (9), the yield was 72%, m.p. 39—41 °C. Found (%): C, 36.18; H, 1.65. $C_9H_5F_5N_2O_2S$. Calculated (%): C, 36.00; H, 1.67. ^{1}H NMR: 3.85 (s, 3 H, OMe); 3.98 (s, 2 H, CH_2).

2-Benzylthio-1,1-dicyano-2-(trifluoromethyl)ethylene (12), the yield was 90%, m.p. 59—61 °C. Found (%): C, 53.77; H, 2.58. $C_{12}H_7F_3N_2S$. Calculated (%): C, 53.73; H, 2.61. ^{1}H NMR: 4.58 (s, 2 H, CH_2); 7.41 (m, 5 H, Ph). ^{19}F NMR: 14.3 (s, CF_3).

5-Benzylthio-3-hydroxy-2-methoxycarbonyl-4-(trifluoromethyl)thiophene (14). Triethylamine (1.2 g, 12 mmol) was added with stirring to a solution of sulfide **13** (2.95 g, 10 mmol) and methyl thioglycolate (1.05 g, 10 mmol) in ether (15 mL). The reaction mixture was kept at ~20 °C for 24 h. The solvent was removed *in vacuo* and the residue was crystallized by trituration in water. The crystals were filtered off and dried in air. Thiophene **14** was obtained in a yield of 2.4 g (69%), m.p. 141—143 °C, R_f = 0.51 (9 : 1). Found (%): C, 48.44; H, 3.21. $C_{14}H_{11}F_3O_3S_2$. Calculated (%): C, 48.28; H, 3.16. ^{1}H NMR: 3.85 (s, 3 H, OMe); 4.32 (s, 2 H, CH_2); 7.40 (m, 5 H, Ph); 10.15 (br.s, 1 H, OH). ^{19}F NMR: 19.0 (s, CF_3).

4-Hydroxy-2-(1-hydrotetrafluoroethyl)thiazole (16). A mixture of 2-hydrotetrafluoropropionitrile (2.5 g, 20 mmol), methyl thioglycolate (2.1 g, 20 mmol), and the $BF_3 \cdot NEt_3$ complex (6.8 g, 40 mmol) was kept in a sealed glass tube at 40—50 °C for 2 h. Then the tube was cooled and opened. The reaction mixture was washed with water and a 5% HCl solution, extracted with ether, and dried with Na_2SO_4. The solvent was removed *in vacuo* and the residue was recrystallized from hexane. Compound **16** was obtained in a yield of 1.4 g (35%), m.p. 45—47 °C. Found (%): C, 29.94; H, 1.47. $C_5H_3F_4NOS$. Calculated (%): C, 29.85; H, 1.49. ^{1}H NMR: 6.49 (s, 1 H, CH); 6.67 (dq, 1 H, CFH, $J_{H,F}$ = 48 and 8 Hz); 10.88 (br.s, 1 H, OH). MS, *m/z*: 201 $[M]^+$.

References

1. A. N. Kovregin, A. Yu. Sizov, and A. F. Ermolov, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 1000 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1044].
2. *Thiophene and its Derivatives*, Ed. S. Gronowits, J. Wiley, New York, Part 1, 1985, 840 pp.
3. *Comprehensive Organic Chemistry*, Eds. D. Barton and W. D. Ollis, Pergamon Press, Oxford—New York, 1979.
4. V. I. Krokhtyak, A. Ya. Il´chenko, and L. M. Yagupol´skii, *Zh. Org. Khim.*, 1981, **17**, 268 [*J. Org. Chem. USSR*, 1981, **17** (Engl. Transl.)].

Received January 29, 2002;
in revised form March 5, 2002