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2-Polyfluoroalkyl thiopyrylium salts: synthesis and reactions with nucleophiles

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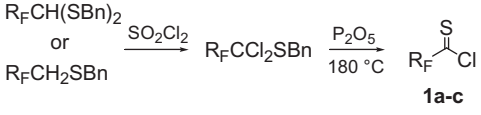
ABSTRACT

2-Polyfluoroalkylthiopyrylium salts have been synthesized by oxidative aromatization of 2-polyfluoroalkyl-2*H*-thiopyrans with triphenylmethane tetrafluoroborate. Nucleophilic addition of methanol, sodium azide, or urea to 2-trifluoromethylthiopyrylium tetrafluoroborate in a basic medium proceeds at the α-position to give the corresponding 2-substituted 6-trifluoromethyl-2*H*-thiopyrans whereas imidazoles, fluorine-containing 1,2,3-triazole, potassium thiolacetate, and sodium nitromethane afford mixtures of 2*H*- and 4*H*-thiopyrans. *cis*-Dihydroxylation of 6-trifluoromethyl-2-methoxy-2*H*-thiopyran affords the fluorine-containing thiohexenopyranoside derivative **8**.

Thiopyrylium salts are known as six-membered heteroaromatic compounds with a variety of applications because of their remarkable photophysical and photochemical properties.[1] Substances with the thiopyrylium core have been investigated for the preparation of diverse photosensitive materials for both technical and medical purposes.[2] Being a highly reactive species, thiopyrylium salts have found use as scaffolds in the synthesis of sulfur-containing heterocyclic compounds. The chemistry of thiopyrylium cations is relatively well studied and a number of substituted derivatives,[3] as well as an unsubstituted one,[4] have been described. However, no fluoroalkyl-containing thiopyrylium salt is known to date. It has been well documented that the incorporation of fluorine into a heterocycle may substantially modify the physicochemical and biological properties of the compound.[5] As a part of our ongoing interest in fluorine-containing sulfur heterocycles[6] we report herein the synthesis of the first polyfluoroalkyl thiopyrylium salt and its reactivity toward nucleophiles.

One method employed for the synthesis of thiopyrylium salts involves the aromatization of 2*H*-thiopyrans. Polyfluoroalkyl-containing thiopyrans are easily obtained by thia-Diels–Alder reactions of thiocarbonyl compounds.[7] Trifluoromethyl-2*H*-thiopyran was reported by Middleton[8] who observed its formation during the slow elimination of HF from the cycloadduct of trifluorothioacetyl fluoride and buta-1,3-diene. It has also been reported that cycloaddition of tetrafluorothiopropionyl chloride with 2,3-dimethylbuta-1,3-diene proceeds with spontaneous loss of hydrogen chloride to afford 6-tetrafluoroethyl-3,4-dimethyl-2*H*-thiopyran.[9] Taking into account that polyfluorothioalkanoyl chlorides **1** can be easily obtained from the corresponding 1,1-dichloropolyfluoroalkyl benzylsulfides on a multigram scale (Scheme 1),[9,10] we have used these thiocarbonyl dienophiles for preparing fluoroalkyl 2*H*-thiopyrans, the starting compounds for syntheses of thiopyrylium salts.

The cycloaddition of thiocarbonyl chlorides **1a–c** to buta-1,3-diene proceeded rapidly: bubbling buta-1,3-diene through a violet solution of compound **1** in an inert solvent at 0 °C caused decoloration indicating the end of the reaction. The stability of the cycloadducts formed depended on the length of the fluoroalkyl chain. Trifluorothioacetyl chloride (**1a**) afforded a relatively stable adduct **2** (92% yield) which was isolated and characterized. Chlorides with longer fluoroalkyl chains (**1b**, $R_F = HCF_2CF_2$) and (**1c**, $R_F = H(CF_2)_4$), gave directly, after evaporation of the mixture, 2*H*-thiopyrans **3b** and **3c** which were isolated after distillation in 55% and 80% yields, respectively (Scheme 2). Dehydrochlorination of **2** to thiopyran **3a** was achieved by heating a solution in DMF at 100 °C for 2 h. 6-Polyfluoroalkyl-2*H*-thiopyrans **3** are distillable liquids, compounds **3a** and **3c** are stable enough for storage in a freezer; compound **3b** decomposed in one day.



1a-c

$R_F = CF_3$ (**a**), HCF_2CF_2 (**b**), $H(CF_2)_4$ (**c**); Bn = CH_2Ph

Scheme 1. Synthesis of polyfluorothioalkanoyl chlorides **1**.[9,10]

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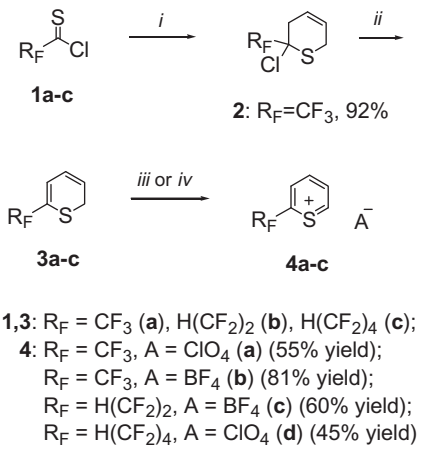


Scheme 2. Reagents and conditions: (i) buta-1,3-diene, Et_2O, 0 °C; (ii) for $R_F = CF_3$, DMF, 100 °C; (iii) $SO_2Cl_2/CHCl_3$, −50 °C, then $HClO_4$, −50 °C; (iv) Ph_3CBF_4, CH_3CN, 0 °C.

Two synthetic approaches to thiopyrylium salts by aromatization of 2*H*-thiopyrans **3** were investigated. Initially the known protocol[11] consisting of oxidation of 2*H*-thiopyrans with sulfuryl chloride followed by treatment of the intermediate formed with perchloric acid was studied. Thiopyrylium perchlorates **4a** and **4d** were obtained by this procedure as fairly insoluble crystals with melting points of 130 °C and 205 °C, respectively, but perchlorates are potentially explosive at elevated temperatures and must be handled with precautions. Therefore, we decided to prepare less dangerous and more soluble salts with the tetrafluoroborate counterion. Reactions of thiopyrans **3a,b** with trityl tetrafluoroborate in CH_3CN at 0 °C afforded salts **4b,c** in good yields[12] (Scheme 2).

Tetrafluoroborates **4b,c** are stable crystalline compounds and are moderately soluble in CH_3CN and 1,2-dimethoxyethane (DME). They are hydrolytically unstable and decompose in wet solvents in contrast to unsubstituted thiopyrylium salts, which show a remarkable stability with respect to H_2O.[4] This indicated the high reactivity of the 2-polyfluoroalkyl substituted thiopyrylium nucleus, hence the electrophilic properties of the trifluoromethyl derivative **4b** were investigated.

It is known that thiopyrylium salts can be attacked by nucleophiles at the two reactive α- and γ-positions.[1,13] To explore the synthetic utility of fluorine-containing salts **4**, a series of *O*-, *N*-, *S*-, and *C*-nucleophiles were tested in reactions with the trifluoromethyl derivative **4b**. The reactions were carried out in DME or CH_3CN at ambient temperature under basic conditions to neutralize the HBF_4 formed. The reactions were usually complete within 1–2 h (monitoring by ^{19}F NMR), the reaction mixtures were then diluted with $CHCl_3$ to precipitate insoluble material and, after evaporation, the residues were analyzed by NMR spectroscopy. The results are summarized in Table 1 (details of experimental procedures and NMR spectra of compounds obtained are presented as Supplementary data). The position of nucleophile addition can be unambiguously established by NMR in so much as 2*H*- or 4*H*-substituted thiopyrans display different chemical shifts, multiplicities, and coupling constants (see Supplementary data). 4*H*-Products have characteristic signals due to H-5 (a doublet of doublets at 5.7–6.0 ppm with $J_{5,4}$ = 3.7–5.6 Hz and $J_{5,6}$ = 9.3–10.3 Hz) and H-6 (a doublet at 6.3–6.6 ppm with corresponding $J_{5,6}$ values), whereas for 2*H*-products the most recognizable features are downfield signals due to H-5 (a doublet of quartets at 6.8–7.0 ppm with $J_{5,4}$ = 3.7–5.6 Hz and $^4J_{HF}$ = 1.0–1.5 Hz).

Alcohols gave only 2-substituted products, no significant 4*H*-isomers being observed in the crude reaction mixture from the reactions of salt **4b** with an excess of methanol or isopropanol in the presence of K_2CO_3. Compounds **5a** and **5b** were isolated in 61% and 90% yields, respectively, after work-up of the reaction mixtures with purities >95%. Treatment of **4b** with primary or secondary amines (ethylamine, toluidine, benzylamine, morpholine) immediately led to the appearance of a deep-violet color and resulted in complex mixtures. The color of the reaction mixture may be the result of the formation of deeply-colored dienylammonium salts as one of the products, as reported for similar reactions of an unsubstituted thiopyrylium salt.[14] However, with heterocycles, such as imidazole and benzimidazole, salt **4b** reacted smoothly to produce mixtures of the isomeric 2*H*- and 4*H*-thiopyrans **5c,6c** and **5d,6d**, respectively, with predominant formation of the 2*H*-isomers.

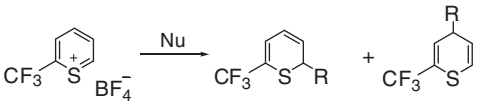
Another azaheterocycle, which was found to add to salt **4b**, was 4-(ω-H-hexafluoropropyl)-5-tosyl-1,2,3-triazole, the potassium salt of which[15] gave a mixture of isomers with little preference for the 4*H*-isomer **6e** over the 2*H*-isomer **5e**. Only a 2*H*-adduct was obtained in the reaction of **4b** with urea. The isolated yield of **5f** was only 33% because of losses during crystallization, although in the reaction mixture it was the sole product. The reaction of **4b** with sodium azide afforded exclusively the 2-azido-2*H*-thiopyran **5g** in a 90% yield. The regioselectivity of the addition of an *S*-nucleophile such as potassium thiolacetate was insignificant, the ratio of **5h**:**6h** being 3:1.

Among the *C*-nucleophiles used, the reaction of **4b** with sodium nitromethane gave a mixture of isomers **5i** and **6i** in a ratio of 1:2 in an 88% combined yield. When potassium cyanide was applied, a complex mixture was formed; NMR and GC–MS analyses allowed the assignment of the products as compounds **7a–c** in the ratio of 0.8:0.2:1 (Scheme 3). Attempts to separate this mixture by chromatography on SiO_2 led to the isolation of a 2:1 mixture of 6-(trifluoromethyl)-2*H*-thiopyran-2-carbonitrile (**7a**) and 2-(trifluoromethyl)-2*H*-thiopyran-6-carbonitrile (**7b**) in a 10% overall yield. The ^1H NMR spectrum of isomer **7a** displayed a similar pattern to that found for the other 2*H*-adducts **5**. The formation of isomer **7b** can be explained as a result of a 1,5-proton shift in **7a**. The structure of **7b** was established by the presence, in its ^1H and ^{19}F NMR spectra, of the characteristic signal of the CF_3–CH moiety (a quintet at 4.1 ppm with $^3J_{HF} = {}^2J_{HH}$ = 7.7 Hz in its ^1H NMR and a doublet at −76 ppm with $^3J_{FH}$ = 7.7 Hz in its ^{19}F NMR spectra).

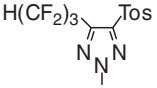
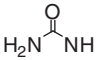
Next, we examined the potential of adduct **5a** as a precursor for thioglycoside synthesis. Selective *cis*-dihydroxylation of **5a** was achieved with the $K_3[Fe(CN)_6]$–K_2CO_3 system in water-*tert*-butanol using OsO_4 (10 mM solution in 0.05 M sulfuric acid) as catalyst.[16] After work-up of the reaction mixture and chromatography, the thiohexenopyranoside derivative **8** was isolated as a single diastereomer in a 10% yield (Scheme 4), although in the crude reaction mixture compound **8** was the main product as indicated by NMR and GC–MS analyses, so the low yield of **8** can be explained by difficulties in isolation.

The values of the coupling constants in the ^1H NMR spectrum of **8**[17] ($J_{2,3}$ = 4.8 Hz, $J_{3,4}$ = 4.1 Hz) did not reveal unambiguously its stereochemistry, but the relationship between the OMe and the two *cis*-hydroxy groups in **8** can be deduced as follows. The OMe group in the starting material **5a** preferably adopts the pseudoaxial position, although it is known that the anomeric effect for sulfur compounds is lower than for the corresponding oxygen analogs.[18] This suggestion agrees well with our DFT calculations (RI-BP86/TZVPP) for **5a** which indicate that the anomeric product with the pseudoaxial position of the OMe group is, by ca. 4.5 kcal/mol, lower in energy than the structure with pseudoequatorial OMe group (see Supplementary data). It is possible to assume that *cis*-dihydroxylation occurs from the less hindered face, opposite to the OMe group, providing the product with a *trans*-orientation of the OMe and OH groups. DFT calculations show only an insignificant energy

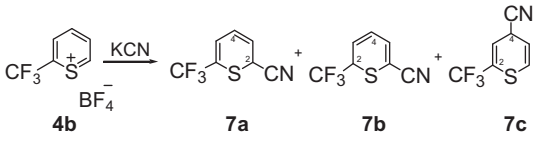
Table 1
Reactions of salt **4b** with various nucleophiles



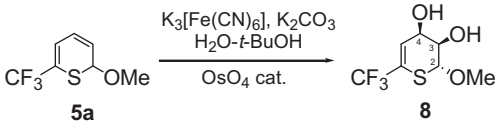
4b **5** **6**

R	MeO	*i*-PrO					N_3		CH_2NO_2
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
Nu, Reaction conditions[a]	Excess CH_3OH, K_2CO_3, 1 h	Excess *i*-PrOH, K_2CO_3, 1 h	Imidazole, 2 equiv, DME, 0.5 h	Benzimidazole, 2 equiv, DME, 0.5 h	1 equiv, DME, 0.5 h	Urea, 4 equiv, CH_3CN, 0.5 h	NaN_3, 2 equiv, DME, 0.5 h	CH_3COSK, 1.5 equiv, DME, 2 h	$NaCH_2NO_2$, 2.2 equiv, DME, 8 h
Ratio of **5**:**6**[b]	1:0	1:0	5:1	3:1	1:1.5	1:0	1:0	3:1	1:2
Yield[c]	61	90	98	95	70	33	90	65	88

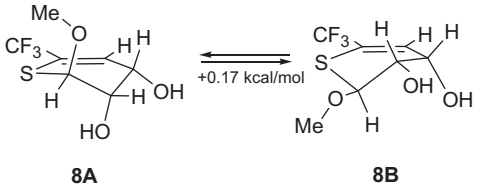
[a] All reactions were carried out at room temperature.
[b] Molar ratio determined by NMR analyses.
[c] Isolated yield of isomers.



Scheme 3. Reaction of thiopyrylium salt **4b** with potassium cyanide.



Scheme 4. Dihydroxylation of 2*H*-thiopyran **5a**.



Scheme 5. Conformational equilibrium of **8**.

difference (ca. 0.2 kcal/mol) between the two conformers **8A** and **8B**, so neither prevails and, in NMR spectra at ambient temperature, signals of the equilibrium mixture of the conformers (Scheme 5) are observed.

In summary, we have reported the synthesis of the first 2-polyfluoroalkyl substituted thiopyrylium salts and have demonstrated their use as fluoroalkyl-containing thiopyranoside and nucleoside precursors.

Acknowledgments

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Supplementary data

Supplementary data (details of experimental procedures and NMR spectra of compounds obtained are presented) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.131.

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12. *Preparation of* **4b**: 6-Trifluoromethyl-2*H*-thiopyran (**3a**) (1.67 g, 10 mmol) was added to a suspension of trityl tetrafluoroborate (3.4 g, 10.3 mmol) in dry CH_3CN (10 ml) at 0 °C with stirring. The solution was stirred at rt for 30 min, Et_2O (30 ml) was added, and the precipitate of thiopyrylium salt was filtered off, washed with Et_2O and dried. Yield 2.05 g (81%), mp (decomp.) 150–160 °C, fine colorless crystals which turned pink on standing. ^{19}F NMR (CD_3CN, 188 MHz): δ −59.84 (3F, s, CF_3), −149.26 (4F, s, BF_4). ^1H NMR (CD_3CN, 400 MHz): δ 9.09 (1H, t, J = 8.3 Hz, H-5), 9.21 (1H, d, J = 8.3 Hz, H-3), 9.30 (1H, t, J = 8.3 Hz, H-4), 10.40 (1H, d, J = 8.3 Hz, H-2). ^{13}C NMR (CD_3CN, 100 MHz): δ 121.35 (q, J = 277 Hz, CF_3), 137.93 (q, J = 3 Hz, C-3), 140.58 (s, C-5), 153.58 (s, C-4), 156.41 (q, J = 38 Hz, C-2), 160.82 (s, C-6).
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17. *NMR data for compound* **8**. ^{19}F NMR ($CDCl_3$, 188 MHz): δ −67.21 (m, CF_3). ^1H NMR ($CDCl_3$, 400 MHz): δ 3.52 (3H, s, CH_3), 4.10 (1H, dd, J = 4.8 Hz, 4.1 Hz, H-3), 4.41 (1H, dm, J = 4.1 Hz, H-4), 4.94 (1H, d, J = 4.8 Hz, H-2), 6.36 (1H, dq, J = 3.6 Hz, $^4J_{HF}$ = 1.2 Hz, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 57.55 (s, CH_3), 64.82 (s, CH–OH), 66.16 (s, CH–OH), 87.14 (s, C-2), 121.61 (q, J = 274 Hz, CF_3), 123.59 (q, J = 33.3 Hz, C-6), 127.48 (q, J = 5.0 Hz, C-5).
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