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Sulfur-assisted ring contraction of polyfluoroalkylthiopyran derivatives as a route to functionalized fluorine-containing thiophenes

Sergiy A. Siry, Vadim M. Timoshenko, Yuriy G. Schermolovich *

Institute of Organic Chemistry, National Academy of Science of Ukraine, Murmans'ka Str, 5, Kyiv 02094, Ukraine

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ABSTRACT

A synthetic route to functionalized α-(polyfluoroalkyl)thiophenes based on the reactions of ring contraction of polyfluoroalkyl substituted thiopyran derivatives has been explored. Potent 6-membered precursors for the preparation of thiophenes were obtained by the addition of bromine to the double bonds of 2-chloro-2-(trifluoromethyl)-3,6-dihydro-2*H*-tetrahydrothiopyran and 6-(polyfluoroalkyl)-2*H*-thiopyrans. The reactions of the resulted 4,5-dibromo-2-chloro-2-(trifluoromethyl)tetrahydrothiopyrans and *trans*-3,4-dibromo-6-(polyfluoroalkyl)-3,4-dihydro-2*H*-thiopyrans with sodium acetate in acetic acid produced 2-(acetoxymethyl)-5-(polyfluoroalkyl)thiophenes. Base-catalyzed methanolysis of the acetoxymethyl derivatives allowed preparing the corresponding 2-(hydroxymethyl)-5-(polyfluoroalkyl)thiophenes. The mechanism, which includes formation and nucleophilic cleavage of thiiranium cations, has been suggested for the transformation of dibromothiopyran derivatives to substituted thiophenes.

1. Introduction

Thiophene derivatives bearing poly- or perfluoroalkyl substituent at the position 2 or 5 attract considerable interest as materials with useful electric and optical characteristics [1,2] and biologically active compounds [3–5]. The synthetic routes to fluoroalkylated thiophenes were discussed in detail in recent reviews [6]. Based on the analysis of the available literature, it can be assumed, that most existing methods are suitable for the preparation of polyfluoroalkylthiophenes without reactive functionalities in the cycle. In contrast, a limited number of satisfactory methods for the synthesis of functionally substituted α-(polyfluoroalkyl)thiophenes is known. The most convenient procedures are based on the construction of the thiophene core from sulfur- and fluorine-containing building blocks [7–9]; other methods, although efficient, require expensive catalysts [5,10] or dangerous fluorinating reagents and special equipment [11].

We decided to investigate an alternative approach for the preparation of functionalized fluoroalkylthiophenes consisting in the reactions of the ring contraction of α-polyfluoroalkylated thiopyran derivatives, the chemistry of which is of our primary scientific interest [12,13]. It is known that non-fluorinated tetrahydrothiopyrans bearing potential leaving groups in the positions 3 or 5 of the cycle can be transformed to thiolanes [14,15], and 3-bromothiochromanes can produce 2,3-dihydrobenzothiopenes [16]. The formation of the rearranged products is explained by the transannular participation of the nucleophilic sulfur atoms and the formation of highly reactive bicyclic thiiranium cations, which give 5-membered heterocycles after the cleavage by the nucleophiles. If the initially formed thiolanes or thiolenes contain heterosubstituents, they can undergo subsequent elimination to yield thiophenes [15,17,18]. Recently, we observed the formation of α-trifluoromethylated thiolanes as a result of the sulfur-assisted rearrangement of 6-(trifluoromethyl)-2,3,4-triacetoxytetrahydrothiopyrans [19]. This prompted us to study similar reactions of other heterosubstitued polyfluoroalkylthiopyran derivatives in order to prepare 5-(polyfluoroalkyl)thiophenes with functional groups in the position 2 and free positions 3 and 4 of the cycle (Fig. 1).

In order to obtain potent precursors for the preparation of thiophenes, we studied the addition of bromine to the double bonds of 2-chloro-2-(trifluoromethyl)-3,6-dihydro-2*H*-thiopyran **1** and 6-(polyfluoroalkyl)-2*H*-thiopyrans **2a** and **2b**, as it seemed to be a convenient way for the introduction of potent leaving groups into the molecules of thiopyran derivatives without affecting sulfur atoms. Compounds **1** and **2a**,**b** were prepared according to

* Corresponding author.
E-mail address: sherm@ioch.kiev.ua (Y.G. Schermolovich).

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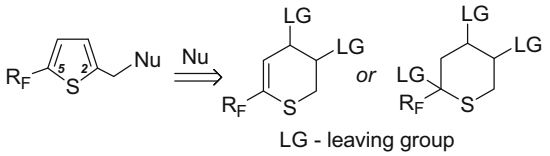


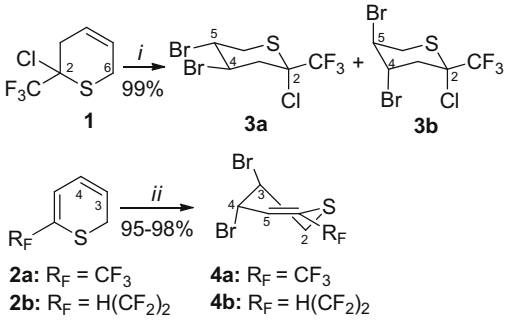
Fig. 1. An approach to thiophenes based on ring contraction reactions of polyfluoroalkylthiopyran derivatives.

the known thia-Diels–Alder methodology described in our earlier report [20].

2. Results and discussion

Only few examples of the addition of bromine to C4=C5 double bonds of 3,6-dihydro-2*H*-thiopyrans were described in the literature [21,22]. We have found, that 2-chloro-2-(trifluoromethyl)-3,6-dihydro-2*H*-thiopyran **1** reacts with bromine rather slowly. Treatment of compound **1** without solvent with small excess of bromine afforded quantitative yield of the mixture of two products, which were identified as diastereomeric 4,5-dibromo-2-chloro-2-(trifluoromethyl)tetrahydrothiopyrans **3a** and **3b** in ratio 2.5:1 based on the analysis of the NMR data. The values of the spin-spin coupling constants observed in the ^{1}H NMR spectrum are in accordance with the predominance of *chair* conformation for the molecules of both compounds in the solution ($CDCl_3$). The axial orientation of the protons H-4 and H-5 in the molecule of the major diastereomer is evident from the values of the corresponding vicinal coupling constants ($J_{H4,H5}$ = 6.7 Hz, $J_{H4,H3ax}$ = 11.0 Hz, $J_{H4,H3eq}$ = 6.7 Hz, $J_{H5,H6ax}$ = 10.4 Hz, $J_{H5,H6eq}$ = 3.8 Hz), therefore, the bromine atoms are equatorial. In contrast, the values of the constants observed in the signals of the minor product correspond to the equatorial orientation of the protons H-4 and H-5 ($J_{H4,H5}$ = 4.6 Hz, $J_{H4,H3ax} = J_{H4,H3eq}$ = 5.2 Hz, $J_{H5,H6ax} = J_{H5,H6eq}$ = 7.3 Hz), the bromine atoms being axial. Chemical shifts of the ^{19}F nuclei (−76.6 ppm for the major isomer and −78.1 ppm for the minor one) are more typical for the equatorially oriented trifluoromethyl groups [23]. Based on this, structure **3a** was assigned for the major diastereomer; structure **3b** was assigned for the minor one (Scheme 1).

To the best of our knowledge, the addition of bromine to non-fused 2*H*-thiopyrans has not been described to date. We have found that the reactions of thiopyrans **2a** and **2b** with bromine in chloroform immediately produce *trans*-3,4-dibromo-3,4-dihydro-2*H*-thiopyrans **4a** and **4b**, respectively (Scheme 1). Both these compounds were isolated in almost quantitative yields and appeared to be stable at ambient conditions. No product of 1,4-addition was detected. The addition of bromine to C5=C6 double bonds of thiopyrans **2a**,**b** or dibromides **4a**,**b** did not take place even when the excess of bromine was used. The latter can be explained by the electron-withdrawing properties of the fluorinated substituents, which inhibit the electrophilic attack of the C5=C6 bond with bromine.



Scheme 1. Reagents and conditions: (*i*) neat Br_2, 0 °C to rt; (*ii*) Br_2 in $CHCl_3$, 0–5 °C.

Stereochemistry of the dibromides **4a** and **4b** was established by the ^{1}H NMR measurements. The values of the vicinal coupling constants observed for the signal of the proton H-4 ($J_{H4,H5}$ = 5.7 Hz and 5.5 Hz for **4a** and **4b**, $J_{H4,H3}$ = 3.0 Hz and 4.6 Hz **4a** and **4b**, respectively) indicate its pseudo-equatorial orientation. Small coupling constants between the proton H-3 and the diastereotopic protons of the CH_2 group (4.7 Hz and 2.2 Hz for **4a**, 4.4 Hz and 2.3 Hz for **4b**) reveal its equatorial orientation. Thus, the molecules of both dibromides **4a** and **4b** adopt preferably *half-chair* conformation in the solution ($CDCl_3$) with the axial orientation of the bromine atoms in the positions 3 and pseudo-axial orientations of the ones in the positions 4 of the cycle. It is noteworthy, that dibromo derivatives **4a** and **4b** resemble structurally related *trans*-3,4-dibromothiochromanes in conformational behavior [24] and differ considerably from their dihydroxy, diacetoxy and 3-bromo-4-hydroxy counterparts, which adopt *half-chair* conformations with the equatorially oriented substituents in the positions 3 and 4 [25].

The presence of bromine atoms in β-positions to the sulfur atoms of the molecules of the compounds **3a**,**b** and **4a**,**b** is favorable for the formation of thiiranium species, which upon the cleavage of three-membered rings with nucleophiles and subsequent loss of hydrogen halide would afford the desired thiophenes. We studied the reactions of the dibromides **3a**,**b** and **4a**,**b** with sodium acetate in acetic acid, since such conditions have also been reported to facilitate analogous transformations of non-fluorinated polysubstituted tetrahydrothiopyrans [15]. We have found, that heating of the mixture of dibromotetrahydrothiopyrans **3a**,**b** with excess of sodium acetate in acetic acid produced expected acetoxymethylthiophene **5a**, which was isolated in 78% yield (Scheme 2). At the same conditions dibromodihydrothiopyrans **4a** and **4b** reacted affording the compounds **5a** and **5b**, which were isolated in 60% and 81% yields, respectively.

The transformation of dibromo derivatives **3a**,**b** and **4a**,**b** to thiophenes **5a**,**b** is apparently a multi-step process. We propose the reaction pathway depicted in Scheme 2. The initial step of the reaction is the formation of thiiranium intermediates **7** and **9** as a result of the transannular participation of sulfur atoms. Thiiranium cations **7** and **9** undergo nucleophilic cleavage of 3-membered rings with acetate anions giving thiolane **8** and thiolenes **10**, respectively, which then afford thiophenes **5a**,**b** after dehydrohalogenation at the reaction conditions. Probably, the last step is facilitated by the formation of thermodynamically favored heteroaromatic products that is why the intermediates **8** and **10** could not be detected in the mixtures. Tetrahydrothiopyran derivatives **3a**,**b** appeared to be more reactive than dibromodihydrothiopyrans **4a**,**b**. In particular, compounds **3a**,**b** could be completely converted into thiophene **5a** in 5 h, whereas, at the same conditions, the transformation of the dibromides **4a** and **4b** required 15 h and 8 h, respectively. The higher rate of the transformation of the compounds **3a**,**b** may be attributed to the higher ability of their sulfur atoms to transannular participation due to the absence of the conjugation with C=C double bond, what is possible in the molecules of the compounds **4a**,**b**.

Both acetates **5a** and **5b** were converted to the corresponding hydroxymethyl derivatives **6a** and **6b** in high yields by the base-catalyzed methanolysis (Scheme 2). Acetates **5a**,**b** and compound **6b** have not been described to date. Compound **6a** was earlier prepared by the reduction of 5-(trifluoromethyl)thiophene-2-carboxylic acid and mentioned in patents as a reagent for the introduction of (5-(trifluoromethyl)-2-thienyl)methyl moiety into the molecules of potent drugs [26].