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Synthesis of fluorine-containing 1,3-thiazine derivatives from primary polyfluoroalkanethioamides

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ABSTRACT

New fluorine-containing 1,3-thiazine derivatives were obtained by the reactions of primary polyfluoroalkanethioamides with methyl vinyl ketone and ethyl acrylate in the presence of boron trifluoride etherate. The outcome of the reactions depends on the type of α,β-unsaturated carbonyl compound and the polyfluoroalkyl chain length. Hydrolysis of the obtained 1,3-thiazines leads to the formation of thioester derivatives.

1. Introduction

One of the most intensively developing directions in the chemistry of biologically active heterocycles is the synthesis of their fluorinated derivatives [1]. One of the most widely used methods of their preparation consists of the application of simple and reactive acyclic fluorinated compounds (building-blocks) [2]. Previously we have shown that amides of polyfluoroalkanethiocarboxylic acids can serve as such building-blocks. The use of these compounds allowed obtaining polyfluoroalkyl-substituted 1,2,4-thiadiazoles, 1,3-thiazolidineones, imidazolines, pyrimidines, 1,3-diazepines and thiopyranes [3].

In the present work we studied the possibility of using primary amides of polyfluoroalkanethiocarboxylic acids **1** for the synthesis of fluorine-containing 1,3-thiazine derivatives. It was reported previously that non-fluorinated thioamides react with α,β-unsaturated aldehydes, ketones, esters and keto esters under neutral, basic (Et_3N, $NaHCO_3$) and acidic conditions (dry HCl, boron trifluoride etherate) to give the corresponding 1,3-thiazines bearing hydroxyl group at the 4 position [4–13]. Some of the prepared 1,3-thiazines are promising compounds in the search for new antitubercular [10] and skin-depigmenting [11] agents.

2. Results and discussion

We found that polyfluoroalkanethioamides **1a,b** bearing heptafluoropropyl and tetrafluoroethyl groups reacted with methyl vinyl ketone and boron trifluoride etherate in dichloromethane at room temperature. After the work-up with a saturated $NaHCO_3$ aqueous solution, new 5,6-dihydro-4H-1,3-thiazin-4-ols **2a,b** were obtained (Scheme 1).

In the case of the reaction of trifluorothioacetamide **1c** with methyl vinyl ketone and boron trifluoride etherate, the corresponding heterocycle **2c** was not isolated. Probably, compound **2c** is not stable and instead of it, thioester **3c** was obtained after the treatment of the reaction mixture with a saturated $NaHCO_3$ aqueous solution (Scheme 1).

1,3-Thiazine derivatives **2a,b** are more stable in aqueous alkaline medium that allows to isolate them, and are easily hydrolyzed under acidic conditions (HCl conc.) to give the corresponding thioesters **3a,b** (Scheme 1).

The structure of 5,6-dihydro-4H-1,3-thiazin-4-ol **2a** was confirmed by single crystal X-ray diffraction (Fig. 1). In the asymmetric unit two independent molecules are arranged in chains along *ob* directions of O–H...O hydrogen bonds with the following parameters: O(1A)–H(1A) 0.68(3) Å, O(1A)...O(1B) 2.766(2) Å, O(1A)–H(1A)...O(1B) 176(3)°; O(1B)–H(1B) 0.66(3) Å, O(1A)...O(1B) 2.753(2) Å, O(1B) –H(1B)...O(1A) 168(3)°. Both molecules exhibit identical twist conformation for the central six-membered cycles.

NMR (^1H, ^{13}C, ^{19}F), IR and MS data are in good agreement with the structures of the compounds **2a,b** and **3a–c**. In the ^{13}CNMR

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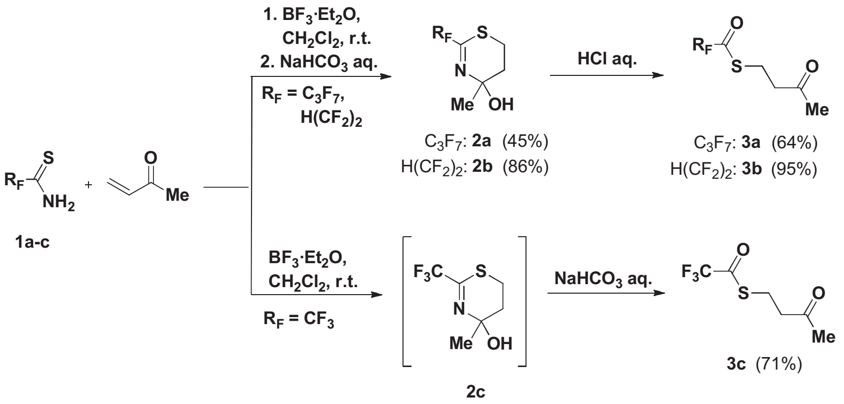

Scheme 1. Reactions of polyfluoroalkanethioamides **1a–c** with methyl vinyl ketone.

spectra of **3a–c**, the signals in the ranges of 205.4–205.7 ppm and 185.1–189.9 ppm were attributed to the carbonyl groups of ketone and thioester functions, respectively.

In contrast to methyl vinyl ketone, ethyl acrylate reacted with thioamides **1a–c** in the presence of boron trifluoride etherate more slowly (15 days at room temperature). After the treatment of the reaction mixture with a saturated $NaHCO_3$ aqueous solution, new fluorine-containing 1,3-thiazinan-4-ones **6a–c** were isolated by column chromatography (Scheme 2).

The formation of 1,3-thiazinan-4-ones probably proceeds *via* elimination–addition of ethanol involving intermediates **4, 5.**

Compounds **6a–c** are relatively stable in aqueous alkaline medium and are easily hydrolyzed under acidic conditions. Treatment of **6a–c** with HCl (conc.) at room temperature results in the formation of thioester derivatives **7a–c** (Scheme 3). The possible reaction scheme includes elimination of ethanol from **6a** to **c** catalyzed by HCl with its subsequent addition to **5** giving intermediate **4**. Hydrolysis of the latter leads to acyclic imine **8** which is converted into **7a–c** under acidic conditions. Compounds **7a–c** are also formed upon heating 1,3-thiazinane-4-ones **6a–c** with boron trifluoride etherate in toluene followed by the treatment of the reaction mixture with water.

The structure of 1,3-thiazinan-4-one **6c** was confirmed by single crystal X-ray diffraction (Fig. 2). It was found that in the asymmetric unit, two independent molecules are arranged in the dimer by pair of N–H...O hydrogen bonds with the following parameters: N(1A)–H(1A) 0.74(3) Å, N(1A)...O(2B) 2.881(3) Å, N(1A)–H(1A)–O(2B) 170(3)°; N(1B)–H(1B) 0.73(3) Å, N(1B)...O(2A) 2.888(3) Å, N(1B)–H(1B)–O(2A) 172(3)°. The molecules exhibit different conformations for the central six-membered cycles. In the molecule labeled by a letter A, six-membered cycle has twist conformation; in the molecule B, the conformation looks like a half-boat.

NMR (^{1}H, ^{13}C, ^{19}F), IR and MS data of the compounds **7a–c** and **6a–c** are in good agreement with the proposed structures. In the ^{13}CNMR spectra of **7a–c**, the signals in the ranges of 171.0–171.1 ppm and 184.8–189.6 ppm were attributed to the carbonyl groups of ester and thioester functions, respectively.

Noteworthy that only two examples of fluorine-containing 1,3-thiazinane-4-ones are described in the literature (Fig. 3). These

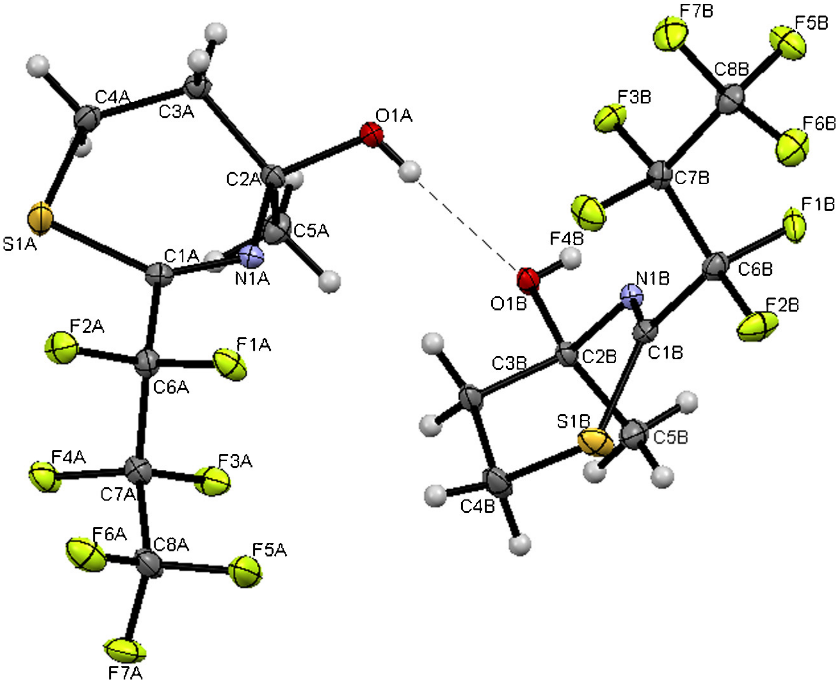

Fig. 1. A perspective view and labeling scheme for the molecules of **2a**. Selected bond lengths (Å) and angles (°): S(1A)–C(1A) 1.754(2), N(1A)–C(1A) 1.265(3), S(1B)–C(1B) 1.752(2), N(1B)–C(1B) 1.265(3), N(1A)C(1A)S(1A) 131.3(2), N(1B)C(1B)S(1B) 130.9(2).