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Efficient synthesis of 5′-fluoroalkoxythiazoles via α-bromo-α-fluoroalkoxyacetophenones Hantzsch type cyclization with thioureas or thioamides

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ABSTRACT

Novel α-fluoroalkoxyacetophenones were synthesized by addition of the readily available 2,2-dimethoxy-2-phenylethanol to fluoroolefins. α-Bromination yielded α-bromo-α-fluoroalkoxyacetophenones, which on treatment with thioureas or thioamides gave thiazoles with fluoroalkoxy groups at the 5′-position by the Hantzsch-type cyclization. This provides a versatile methodology for the construction of heterocycles from aliphatic fluoroalkoxy containing building blocks.

1. Introduction

Polyfluoroalkoxy groups hold a considerable promise for the fine-tuning of technical and biological properties of organic molecules. While aromatic, as well as benzene fused heterocyclic, α-fluorinated ethers since the first publication [1] in 1955 were extensively studied and widely used as pharmaceuticals and crop protection agents [2], heterocyclic compounds with such a group directly attached to a heterocyclic ring are rare. As for five membered heterocycles, in 1977 3-trifluoromethoxybenzofuran and indole derivatives were synthesized by the action of the trifluoromethylhypofluorite [3]. This methodology is limited because of high toxicity and extreme reactivity of the trifluoromethylhypofluorite. Some pyrazole and indazole derivatives were obtained by direct polyfluoroalkylation of their hydroxy derivatives with difluorocarbene or fluoroolefins or dihaloperfluoroalkanes [4]. This approach cannot be applied for wide range of heterocycles due to the dominance of the keto-form over the hydroxy one in their structures [5]. The direct O-perfluoroalkylation in contrast to standard well known O-alkylations is still a real challenge [2a–b].

Therefore, the synthesis of the heterocyclic rings from aliphatic per- and polyfluoroalkoxy containing precursors is an attractive offer.

2. Results and discussion

Bromoacetophenones are convenient and widely used building blocks for various types of heterocyclization and for the Hantzsch's thiazole synthesis in particular [6]. Thus, in the current paper we present a novel convenient synthesis of the thiazole ring with fluoroalkoxy groups at the 5′-position based on the cyclization of α-bromo-α-fluoroalkoxyacetophenones with thioureas or thioamides.

In the course of our study we divided the required precursors into two groups – acetophenones **3a–b** with polyfluoroalkoxy substituents and perfluoroalkoxyacetophenones **3c–e**.

We found out that compounds **3a–b** can be conveniently prepared by addition of 2,2-dimethoxy-2-phenyl-ethanol (**1**) to fluoroolefins at atmospheric pressure in the presence of catalytic amounts of its potassium derivative with further deprotection of the carbonyl function (Scheme 1). Both stages of this synthesis are characterized by high yields and easy handling. Alcohol **1** is readily available from acetophenone [7].

It should be noted, that attempts of 2-oxophenylethanol addition to fluoroolefins failed.

The nucleohpilic substitution of the halogen atom or a triflic group with perfluoroalcoholate anions is a suitable method for the aliphatic ethers preparation [8]. α-Perfluoroalkoxyacetophenones **3c–e** were prepared by substitution of bromine atom in α-bromoacetophenones with cesium perfluoroalcoholates (Scheme 2). Trifluoromethanesulfonic acid trifluoromethyl ester and CsF were used as CF_3O^- source. Pentafluoroethyl- and heptafluoro-*iso*-propylalcoholates were prepared by addition of

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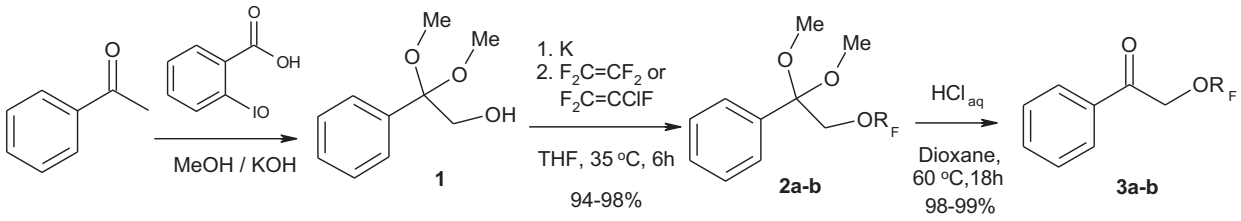
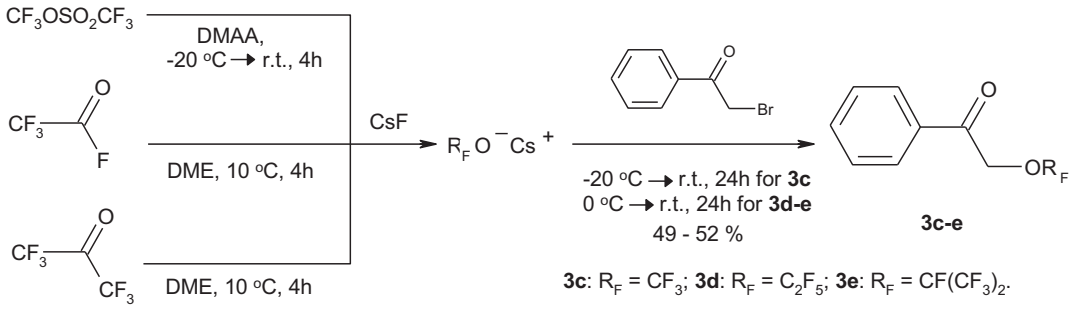


2a, **3a**: $R_F = CF_2CHF_2$; **2b**, **3b**: $R_F = CF_2CHClF$

Scheme 1. Synthesis of acetophenones with polyfluoroalkoxy substituents.



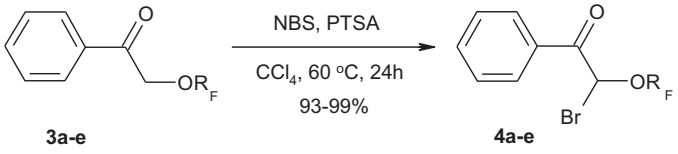
3c: $R_F = CF_3$; **3d**: $R_F = C_2F_5$; **3e**: $R_F = CF(CF_3)_2$.

Scheme 2. Synthesis of acetophenones with perfluoroalkoxy substituents.

CsF to trifluoroacetyl fluoride and hexafluoroacetone, respectively. Cesium perfluoroalcoholates were not isolated and utilized immediately as obtained.

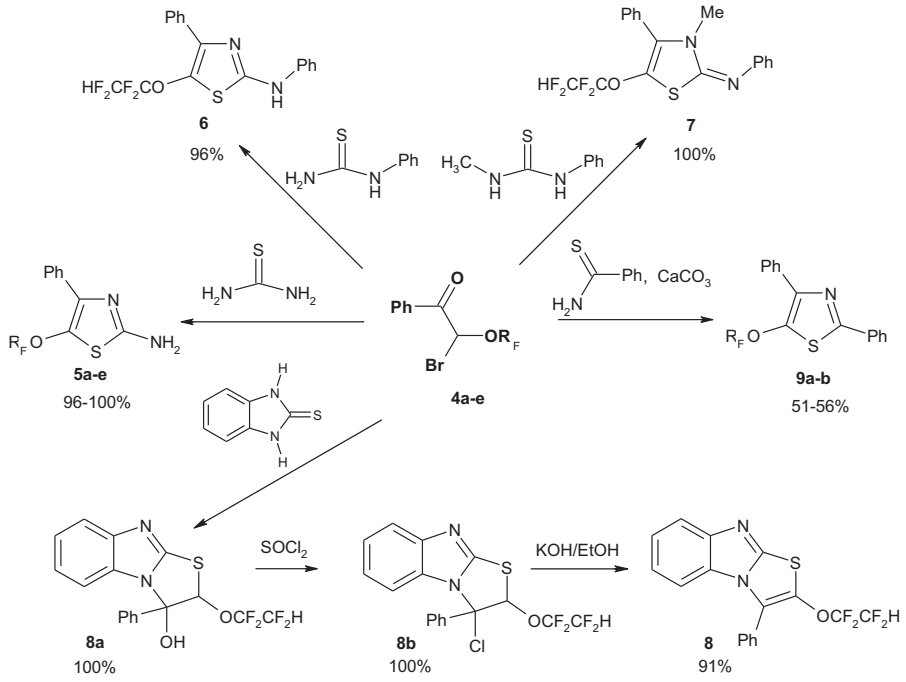
Further bromination of acetophenones **3a–e** with NBS in the presence of toluene-4-sulfonic acid (PTSA) resulted in α-bromo-α-fluoroalkoxyacetophenones **4a–e** with high yields (Scheme 3).

We found out that α-bromo-α-fluoroalkoxyacetophenones **4a–e** readily react with thiourea and *N*-monosubstituted thioureas in aqueous dioxane at room temperature giving the desired 2-aminothiazoles **5a–e** and **6** with almost quantitative yields (Scheme 4). Reaction of α-bromo-α-perfluoro-*iso*-propyloxyacetophenone **4e** with thiourea requires longer reaction time,



3a, **4a**: $R_F = CF_2CHF_2$; **3b**, **4b**: $R_F = CF_2CHClF$;
3c, **4c**: $R_F = CF_3$; **3d**, **4d**: $R_F = C_2F_5$; **3e**, **4e**: $R_F = CF(CF_3)_2$.

Scheme 3. Bromination of acetophenones.



4a, **5a**, **9a**: $R_F = CF_2CHF_2$; **4b**, **5b**, **9b**: $R_F = CF_2CHClF$; **4c**, **5c**: $R_F = CF_3$; **4d**, **5d**: $R_F = C_2F_5$; **4e**, **5e**: $R_F = CF(CF_3)_2$.

Scheme 4. Hantzsch-type thiazole synthesis.