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Thiophilic nucleophilic trifluoromethylation of α-substituted dithioesters. Access to *S*-trifluoromethyl ketene dithioacetals and their reactivity with electrophilic species

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ABSTRACT

The nucleophilic trifluoromethylation of dithioesters bearing a nucleofugal group in α-position, using CF_3TMS under fluoride activation, afforded unprecedented *S*-CF_3 ketene dithioacetals via a domino process thiophilic trifluoromethylation–β-elimination. The best results were obtained with non-enolisable α-carbamoyloxydithioesters. The higher homologues *S*-C_2F_5 ketene dithioacetals were prepared by a similar way. These new dithioacetals react with methylating reagents quantitatively and chemoselectively at sulfur to give stable dimethylsulfonium type salts. They react more classically with triflic acid, protonation taking place at the β-carbon to give a dithiolium salt, characterized in solution but non-isolable.

Research topic

Fluorine Chemistry at the university of Reims

The group from Reims became involved in fluorine chemistry around 1985. Our interest was focused on methodologies in organofluorine chemistry, sometimes turned towards specific applications in the framework of cooperation with industrial companies (building blocks (BB) of pharmaceutical interest, surfactants). The main research topics have been:

- *Fluorine associated with other heteroelements*
  - (i) F & Si. Taking advantage of the high reciprocal affinity of these two elements to develop new multistep one pot transformations, in particular from reaction of acylsilanes and organometallic reagents (R_FLi, R_FMgI, R_FSiMe_3). Key BBs in this field: perfluoroenoxysilanes, which are both nucleophilic and electrophilic. Applications: *gem*-difluoro terpenes, difluoro-*C*-glycosides, *vic*-F,R_F–heterocycles, difluoromethyl derivatives.
  - (ii) F & S. Taking advantage of the versatility of sulfur (various oxidation states, low polarizability...). Key BBs in this field: perfluoroketene dithioacetals and perfluorodithiocarboxylic acid derivatives. Main applications: synthesis of a wide variety of trifluoromethylated heterocycles via γ-keto-α-R_F–thiolesters, α-R_F–succinic derivatives...
- *Perfluoroalkylation*
  Radical and nucleophilic *F*-alkylation using R_FI and R_FTMS were used for well defined applications: synthesis of highly fluorinated compounds, of *C*-trifluoromethylated sugars or more generally of multifunctionalized fluorinated derivatives.
- *Quaternary CF_3-containing BBs*
  - (i) Synthesis of enantiopure trifluoromethylated BBs from tartaric acid based substrates.
  - (ii) Development of new CF_3-cyclopentane difunctionalized BBs.

1. Introduction

Due to the high polarizability of sulfur, sulfur containing organic compounds exhibit a versatile chemistry. Thus both carbophilic and thiophilic addition can be observed on thiocarbo-

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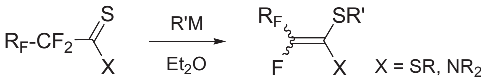


Scheme 1. *S*-alkylation of perfluorodithioacid derivatives.

nyl compounds as well as on dithiocarboxylic derivatives [1]. The strong withdrawing character of fluorine allows perfluorothiocarboxylic derivatives to react selectively with organometallics at sulfur, with subsequent fluoride β-elimination. We have thus developed a closely related chemistry of perfluoroketene dithioacetals and perfluorodithioesters or, more generally, perfluorothiocarboxylic derivatives (Scheme 1) [2]. These studies were focused on the addition of non-fluorinated reagents on fluorinated substrates [3]. More recently we reported that nucleophilic trifluoromethylation of perfluorodithioesters occurs also at sulfur as the first step of a domino process where the corresponding *S*-CF_3 perfluoroketene dithioacetal is the first intermediate [4].

To complete these studies we have investigated the behavior of non-fluorinated substrates bearing in α-position a nucleofugal group under nucleophilic trifluoromethylation conditions with the expectation that a similar sequence *S*-addition–β-elimination would give an unprecedented *S*-CF_3 ketene dithioacetal (Scheme 2). The properties of such a new intermediate of course would deserve to be explored. We report herein the results of this study.

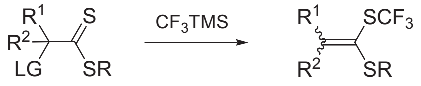
2. Results and discussion

2.1. Preconditions

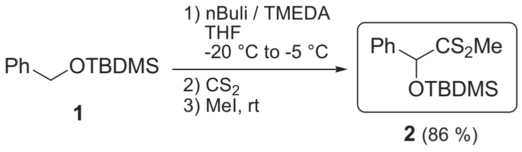
Regarding the model substrates for this study, we have chosen α-phenyl dithioacetic esters type derivatives, considering that a phenyl substituent would stabilize the postulated ketene dithioacetal and possible further intermediates for reactivity study. Trifluoromethyl(trimethyl)silane (TFMTMS), already assessed as a thiophilic reagent on perfluorodithioesters [4] and widely used in this laboratory, was systematically used for nucleophilic trifluoromethylation experiments. Extension to pentafluoroethyl(trimethyl)silane (PFETMS) was also considered. The leaving group should have the property to favor the chain transfer in a reaction performed under nucleophilic initiation.

2.2. Synthesis of substrates

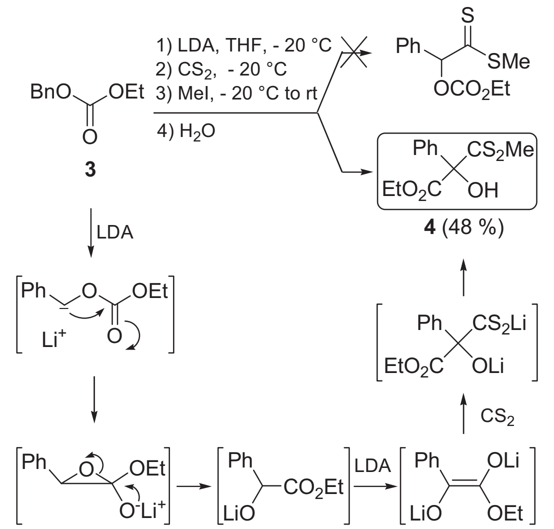
In a first approach, α-*t*-butyl(dimethyl)silyl (TBDMS) dithioester **2** was prepared from silyl ether **1**, with a good yield of 86% (Scheme 3).[3] Ethoxycarbonyloxyl group was a second possible leaving group, since the corresponding ethoxide resulting from its decarboxylation would constitute an excellent transfer reagent to activate TFMTMS. The corresponding carbonate **3** was submitted to a similar reaction sequence, giving the unexpected rearranged dithioester **4**, the structure of which was confirmed by X-Ray diffraction analysis [6] (Scheme 4 and Fig. 1).



Scheme 2. Purpose: *S*-trifluoromethylation of α-substituted dithioesters.



Scheme 3. Synthesis of α-*t*-butyl(dimethyl)silyloxy dithioester **2**.



Scheme 4. Synthesis of dithioester **4** via a rearrangement of a lithiated carbonate.

Compound **4** is the result of a Chan type rearrangement [7] occurring at the intermediate carbanion stage, followed by a second deprotonation prior to reaction with carbon disulfide (Scheme 4). Such a rearrangement, discovered with acyloxyacetates, was reported later from carbonate derivatives [8]. This transformation required two equivalents of LDA, which is consistent with such a mechanism. The selectivity in the final methylation at sulfur is coherent in terms of HSAB correlation.

To avoid this rearrangement, we decided to synthesize a carbamate derivative (Scheme 5). Starting from benzylcarbamate **5**, the desired carbamate **6** was obtained in a poor yield using LDA as a base. Changing LDA for *sec*-butyl lithium/TMEDA [9] afforded, from a complex reaction mixture, the dithioketene **7**, indicating that the deprotonation and further transformation of **6** is the limiting factor of this synthesis. To circumvent this side reaction, we turned to α-alkyl substituted compounds. 1-Phenylethyl and 1-phenylpropyl dimethylcarbamates **8a**,**b** were easily prepared. They were deprotonated according to conditions previously described [10] and converted in high yields into the desired dithioesters **9a**,**b** (Scheme 6). The latter were obtained in high purity after the simple filtration of their dichloromethane solution through a pad of silicagel and solvent removal.

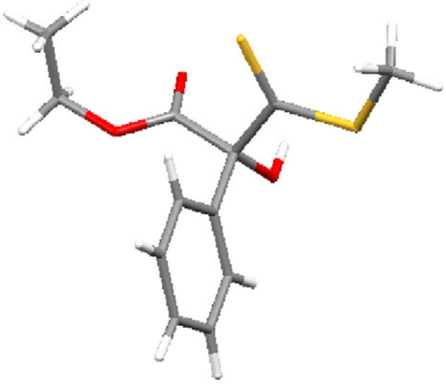


Fig. 1. Structure of **4** from X-ray analysis.