Tetrahedron 66 (2010) 3579–3582

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

From carboxylic acids to the trifluoromethyl group using BrF_3

Or Cohen[a], Eyal Mishani[b], Shlomo Rozen[a,*]

[a] *School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel*
[b] *Radiochemistry, Hadassah Hospital, Hebrew University, 91120 Jerusalem, Israel*

ARTICLE INFO

Article history:
Received 13 November 2009
Received in revised form 22 February 2010
Accepted 15 March 2010
Available online 20 March 2010

ABSTRACT

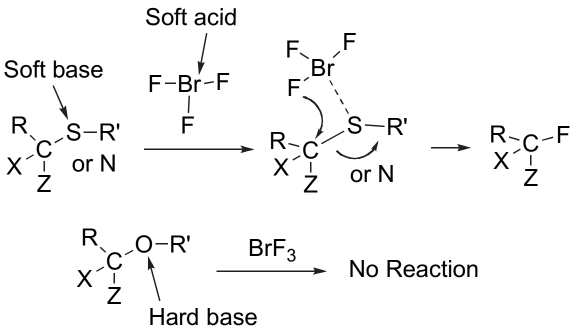
Organic trifluoromethyl derivatives were made from aromatic and aliphatic carboxylic acids by transforming them first into the corresponding dithioesters followed by reaction with bromine trifluoride under mild conditions (0 °C, 2 min).

1. Introduction

Compounds with the trifluoromethyl group enjoy high lipophilicity and increased stability compared to those with the methyl moiety and since, for many applications, the added steric distortion is not prohibitive, it is not surprising that this moiety can be found in various fields of organic chemistry especially in pharmaceuticals, anesthetics, agrochemicals, and polymers. Because of the intensive interest and high demand quite a few methods for the incorporation of the whole CF_3 group into organic molecules have been developed, such as using the popular Prakash–Rupert's reagent (CF_3SiMe_3),[1] fluoroform,[2] trifluoromethyl halides,[3] and electrophilic trifluoromethylations[4] to mention just a few. Sulfur tetrafluoride has also been used for constructing this desirable moiety.[5]

Bromine trifluoride is a commercial reagent, but because of its exothermic reactions with oxygen-containing solvents (see Experimental section) it has been rarely utilized by organic chemists.[6] Nevertheless, in the last years we have shown that when handled properly, it could be used under mild conditions for fast and selective reactions. We found that it can brominate aromatic rings, including very deactivated ones,[7] transfer carbonyls to the CF_2 group,[8] alcohols to trifluoromethyl or difluoromethyl ethers,[9,10] or under a different set of conditions to the corresponding acyl fluorides,[11] help in transforming RX to $RCHF_2$ derivatives,[12] and much more.[13]

The majority of the regiospecific reactions involving bromine trifluoride use the fact that the reagent's bromine atom is a soft acid, which can complex itself most effectively with soft bases, such as nitrogen or sulfur atoms, but not with hard ones, such as oxygen.[14] The complexation positions the nucleophilic fluorides near the potential reaction center resulting in an overall substitution of the nitrogen or sulfur atom(s) with fluorine (Scheme 1). Such complexation also reduces the chances of indiscriminate radical brominations and fluorinations for which this reagent was so infamous.[15]



Scheme 1. The complexation of BrF_3 with soft heteroatoms.

We describe in this work a new general method for transforming the aromatic and aliphatic carboxylic acid moiety into the important CF_3 group. This is accomplished by changing the hard basic oxygen with the soft sulfur atoms providing the much needed 'anchor' for the reagent enabling a selective reaction between the resulting dithioesters derivatives and BrF_3 for the eventual formation of the CF_3 products. Earlier results for fluorodesulforization processes with other [BrF] reagents (combination of two reactants, such as NBS and various forms of HF) were accomplished only with aromatic substrates.[16]

2. Results and discussion

Aromatic carboxylic acids **1** were converted to their acyl chlorides using oxalyl chloride, followed by a reaction with ethanethiol

---

* Corresponding author. Fax: 972 3 6409293; e-mail address: rozens@post.tau.ac.il.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.045

to form the appropriate thioesters **2**.[17] These thiocarbonyl containing derivatives were reacted with Lawesson reagent producing the corresponding dithioesters **3**, which were ready for the reaction with BrF_3. Thus, the dithioester of 4-cyanobenzoic acid **3a** was treated with 3 mole-equiv of bromine trifluoride for 2 min at 0 °C to give 4-(trifluoromethyl)benzonitrile (**4a**)[18] in 75% yield.[19] While BrF_3 is capable of transforming the nitriles themselves to CF_3 moieties,[20] the resulting **4a** suggests that the reaction with the dithioester group is more readily executed, since the soft–soft interaction between bromine and sulfur is better than bromine and nitrogen, so the cyano moiety was not affected (Table 1).

Table 1

Preparation of the trifluoromethyl moiety from benzoic acid derivatives

$$\underset{\mathbf{1}}{ArCOOH} \xrightarrow[2.\ EtSH]{1.\ (COCl)_2} \underset{\mathbf{2}}{ArCOSEt} \xrightarrow[reagent]{Lawesson} \underset{\mathbf{3}}{ArCSSEt} \xrightarrow{BrF_3} \underset{\mathbf{4}}{ArCF_3}$$

a	Ar=4-CNC_6H_4	95%	90%	75%
b	Ar=4-ClC_6H_4	95%	90%	70%
c	Ar=2-ClC_6H_4	95%	90%	70%
d	Ar=3-BrC_6H_4	95%	90%	75%
e	Ar=4-BrC_6H_4	95%	90%	75%
f	Ar=4-$CF_3C_6H_4$	95%	90%	65%
g	Ar=4-$HOOCC_6H_4$			
g′	Ar=4-$EtSSCC_6H_4$	95%	80%	30%

It is worth mentioning that BrF_3 also possesses the ability to exchange fluorine with other halogens.[21] As with the previous case, however, the halogen atom in the dithioesters of 4-chlorobenzoic acid (**1b**), 2-chlorobenzoic acid (**1c**), 3-bromobenzoic acid (**1d**), and 4-bromobenzoic acid (**1e**), remained intact during the reaction with bromine trifluoride, and the products **4b**–**e**[18] were obtained in 70–75% yields.

In general the best results in the aromatic field were obtained with compounds having a deactivated ring—a feature, which guards against aromatic electrophilic bromination. The deactivated 4-(trifluoromethyl)benzoic acid (**1f**), satisfies this requirement and eventually forms 1,4-bis(trifluoromethyl)benzene (**4f**)[18] in 65% yield. Alternatively this compound could be generated also from the terephtalic acid (**1g**), by converting it to its tetrathio diester **3g′** followed by a reaction with 6 mole-equiv of BrF_3 to form the expected **4f**. This result shows that the reaction is applicable also for cases where more than a single carboxylic acid group is present.

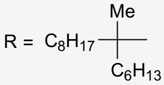
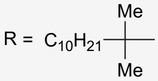
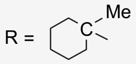
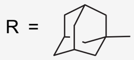
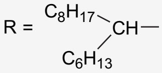
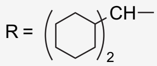
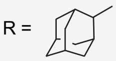
The reaction is not limited to aromatic carboxylic acids. Many aliphatic ones can serve as substrates as well. The dithioesters **8a** and **8b**, made from 2-hexyl-2-methyldecanoic acid (**7a**) and 2,2-dimethyldodecanoic acid (**7b**), were reacted with BrF_3 under the same mild conditions outlined above resulting in the previously unknown 7-methyl-7-(trifluoromethyl)pentadecane (**9a**) and 1,1,1-trifluoro-2,2-dimethyldodecane (**9b**) in 80 and 70% yield, respectively (Table 2). Cyclic carboxylic acids also work fine as can be demonstrated by 1-methyl-1-cyclohexanecarboxylic acid (**7c**), which was converted via its dithioester derivative (**8c**) to 1-methyl-1-trifluoromethylcyclohexane (**9c**)[22] in 80% yield.

In certain cases BrF_3 can be engaged in electrophilic fluorinations especially in the presence of tertiary hydrogen atoms.[23] Yet, when 1-adamantane carboxylic acid (**8d**) was reacted 1-(trifluoromethyl)adamantane (**9d**)[24] was formed without much electrophilic substitution of the tertiary hydrogens. This may point out to the substantial difference in the reactivity between centers that provide a strong anchor for the reagent (in our case sulfur atoms) and ones with much weaker complexation power.[25] The fast reaction completed under the mild conditions also ensures the integrity of the adamantane skeleton, which under harsh conditions, or strong oxidants, can undergo various rearrangements.[26]

Table 2

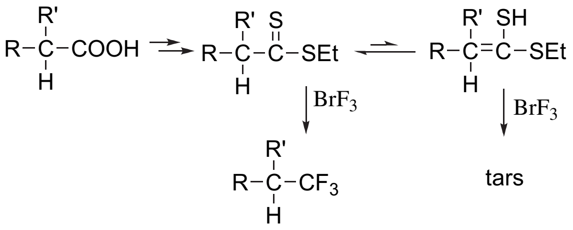
Preparation of the trifluoromethyl moiety from aliphatic carboxylic acids

$$\underset{\mathbf{7}}{RCOOH} \longrightarrow \longrightarrow \underset{\mathbf{8}}{RCSSEt} \xrightarrow{BrF_3} \underset{\mathbf{9}}{RCF_3}$$

a	 $R = C_8H_{17}-C(Me)(C_6H_{13})-$	70%	80
b	 $R = C_{10}H_{21}-C(Me)(Me)-$	90%	70%
c		90%	80%
d		95%	65%
e	 $R = (C_8H_{17})(C_6H_{13})CH-$	85%	45%
f		80%	40%
g		80%	35%
h	R=$C_{11}H_{23}$–	90%	Traces

With secondary carboxylic acids the yields of transforming the COOH group to the CF_3 one are usually lower. This is evident from several results among them the cases of 7-pentadecanoic acid (**7e**), 2,2-dicyclohexylethanoic acid (**7f**), and 2-adamantanecarboxylic acid (**7g**), which were converted via their dithioesters **8e**–**g**, to the previously unknown, 7-triflurométhylpentadecane (**9e**), 1,1-dicyclohexyl-2,2,2-trifluoroethane (**9f**), and 2-(trifluoromethyl)adamantane (**9g**)[27] all in about 40% yield. This trend is even more profound with primary acids, where dodecanoic acid **7h** can serve as a typical example. The reaction of its dithioester **8h**[28] with BrF_3 resulted in a mixture containing only traces of the 1,1,1-trifluoroundecane (**9h**).

We believe the reason for the different behavior of tertiary (and aromatic), secondary and primary acids, is rooted in the fact that the secondary, and even more so primary, dithioesters are prompt to some degree toward tautomerism, which shifts the equilibrium slightly more toward the enthiol structure. Obviously such process cannot take place in the tertiary or aromatic derivatives. As we have shown in the past, bromine trifluoride reacts very fast with any type of double bond,[29] which in this case leads mainly to nonspecific reactions (Scheme 2).



Scheme 2. The reaction with secondary and primary acid.

In conclusion, this work offers a new route for the formation of the important trifluoromethyl group derived from carboxylic acid derivatives using a simple sequence of reactions with the eventual use of BrF_3 as the source of the fluorine atoms. We hope that along with the new synthetic pathway, this work will contribute to reduce the recoil of many chemists from the thought of using