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# The first general method for α-trifluoromethylation of carboxylic acids using $BrF_3$†

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***Received (in Cambridge, UK) 2nd December 2003, Accepted 16th January 2004***
***First published as an Advance Article on the web 3rd February 2004***

**2-Carbomethoxy-1,1-bis(methylsulfide)-1-alkenes, easily made from carboxylic acids, $CS_2$ and MeI, were treated with $BrF_3$ producing eventually the desired α-trifluoromethyl carboxylate derivatives – $RCH(CF_3)COOR'$ – in good yields.**

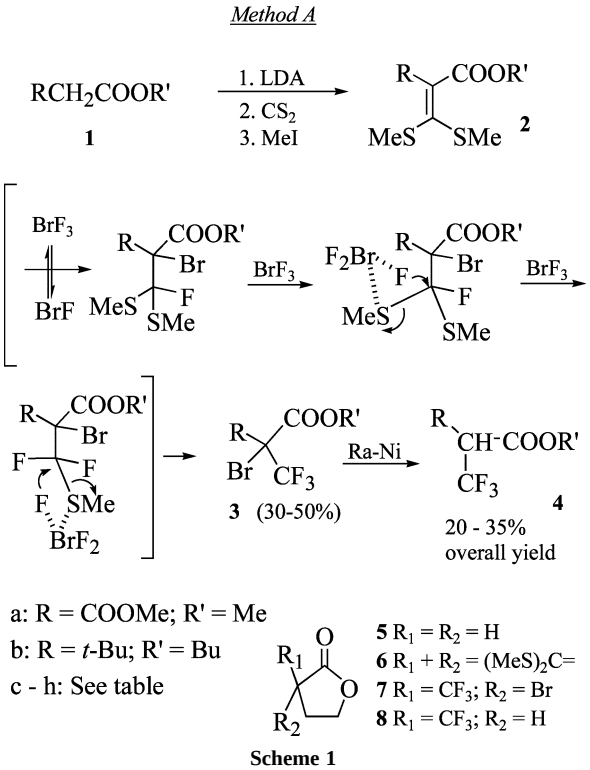
The α-position to the carboxylate moiety is unique when organic acids associated with biological activity are the issue. The importance of the $CF_3$ group has been outlined in numerous cases[1] and recently, Olah, Prakash and others have achieved remarkable results using $Me_3SiCF_3$ as a tool for introducing the trifluoromethyl group into electrophilic centers [*e.g.* $R_2CO \rightarrow R_2C(CF_3)OH$].[2]

Still, only a few, highly specific α-trifluoromethyl carboxylates have been described so far. Recent examples include constructing α-alkoxy-α-trifluoromethyl acids[3] and a procedure for electrophilic trifluoromethylation of the strongly nucleophilic carbon of β-ketocarboxylates.[4] Attempting α-alkylation of β,β,β- trifluoropropionates was proven impractical since a facile defluorination takes place even at −78 °C: ($CF_3CH_2COOR + B^- \rightarrow CF_2{=}CHCOOR$).[5] Clearly, a general method for introducing this important group into the α-position of a *given* carboxylic acid is needed. We describe here a method, based on the use of $BrF_3$, which closes this gap.

Bromine trifluoride has been rarely used in organic chemistry when not heavily halogenated molecules are in question. It plays a pivotal role in the synthesis of some modern anaesthetics such as sevoflurane[6] and recently in constructing the $CF_2$[7] and $CF_3$[8] groups. In most of these procedures the soft acidic bromine atom of the $BrF_3$ complexifies itself with soft basic nitrogen or sulfur atoms, placing the naked nucleophilic fluorides in the immediate vicinity of the electrophilic carbon α to the heteroatom. The formation of the CF bonds is thus facilitated and the reaction is usually completed within a few seconds. This greatly helps to keep undesirable radical side reactions to a minimum.

One of the best methods to place a sulfur atom near the α-position of an ester group of type **1** is to react its corresponding enolate with $CS_2$ followed by MeI.[9] In order to substitute both sulfur atoms of the resulting 2-carbomethoxy-1,1-bis(methylsulfide)-1-alkene **2c**–**h**, five molar equivalents of $BrF_3$ (*method A* – Scheme 1) had to be used to form 2-bromo-2-trifluoromethyl carboxylates **3c**–**h**. The bromine atom could then be removed by Raney nickel and the desired α-trifluoromethyl esters **4c**–**h** were obtained. The presence of the bromine atom suggests that the first step of the reaction is a nucleophilic attack of the olefinic center on the bromine atom in either $BrF_3$ or BrF, which is always present in the reagent (a known equilibrium since $BrF_3$ always contains some bromine). A second, and if supplied also a third molecule, of $BrF_3$ attacks the sulfur atoms resulting in CF bond formation with the nearby electrophilic carbon.[8a] Although the presence of an aromatic ring is usually prohibitive since it is easily brominated by the reagent[10] the reaction is not restricted only to straight chain acids. Butyrolactone **5** was converted to the corresponding bis(methylsulfide) derivative **6**[11] and reacted with $BrF_3$. Since the reaction is fast and is performed at 0 °C, the lactone ring was not affected and 2-bromo-2-trifluoromethylbutyrolactone **7** was obtained. Treatment with Raney nickel produced the desired 2-trifluoromethylbutyrolactone **8**.[12] Similarly, dimethyl malonate **1a** afforded the known dimethyl 2-trifluoromethylmalonate **4a**.[13] Strong steric hindrance to the carbon α to the carboxylate moiety as in butyl neopentanoate **1b** is responsible for low yields of the corresponding 1,1-bis(methyl sulfide) **2b** (20%), but the reactions with $BrF_3$ and Raney nickel proceed as expected resulting in butyl 2-trifluoromethyl-α-*t*-butyl acetate **4b**. The main disadvantage of this route, however, is the use of a large excess of $BrF_3$, which prompts radical reactions responsible in most cases for the low overall yield of 20–35%.

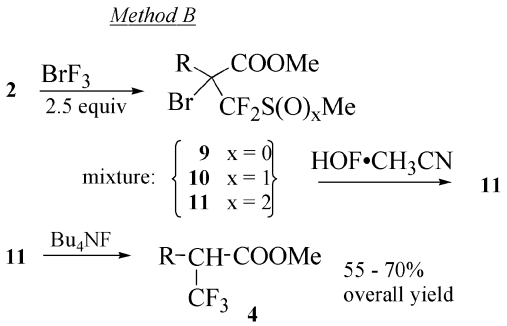
The reaction was considerably improved and the yields were more than doubled when a somewhat different route (*method B* – Scheme 2) was developed. When only 2.5 molar equivalents of $BrF_3$ were reacted for less than a minute with the disulfides **2**, mixtures of more than 85% of methyl 2-bromo-2-[difluoro(methylsulfide)methyl]alkanoates **9**, the respective sulfoxides **10**, and traces of the sulfones **11** were obtained. These mixtures were not resolved but treated 'as is' with $HOF{\cdot}CH_3CN$ at room temperature, transferring within a few minutes[14] all sulfur-containing compounds to the corresponding **11** which contain the good leaving sulfone group. These were reacted with $Bu_4NF$,[15] eliminating both bromine and sulfone groups to give the target α-trifluoromethylalkanoates **4** in overall yields of up to 70% based on the starting esters. It should be mentioned here that this method is also very suitable for introducing the important isotope $^{18}F$ into the $CF_3$ group for positron emitting tomography (PET) purposes.




**Scheme 1**

† Electronic supplementary information (ESI) available: complete experimental details and instructions of how to work and handle $BrF_3$ and $HOF{\cdot}CH_3CN$. $^1H$ NMR, $^{13}C$ NMR, $^{19}F$ NMR, IR and microanalysis data for all compounds. See http://www.rsc.org/suppdata/cc/b3/b315705a/

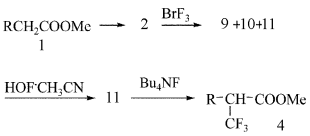
DOI: 10.1039/b315705a




**Scheme 2**

The scope of this reaction was investigated and is summarized in Table 1. The straight chain methyl heptanoate **1c**, methyl undecanoate **1d** and methyl tetradecanoate **1e** were α-trifluoromethylated to produce **4c**,[16] **4d**[17] and **4e**, respectively, in 65 – 70% overall yield. Both cyclic derivatives **1f** and **1g** reacted rapidly to form the unknown methyl 3-cyclopentyl-2-trifluoromethylpropanoate **4f** and methyl 4-cyclohexyl-2-trifluoromethylbutanoate **4g**. Bromine trifluoride is known to substitute chlorine atoms as demonstrated by the synthesis of the anaesthetic sevoflurane, but again the complexation and the fast reaction with the sulfur atoms in the reaction of **2h** leave the chlorine intact and methyl 5-chloro-2-trifluoromethylpentanoate **4h** was eventually obtained. It is known that unprotected alcohols are quickly oxidized by $BrF_3$ to acyl fluorides,[18] but when protected, either as ethers or pivaloyl esters (*e.g.* **1i** or **1j**), the reaction proceeds as expected and ethyl 4-ethoxy-2-trifluoromethylbutanoate **4i** and ethyl 6-pivalooxy-2-trifluoromethylhexanoate **4j** were formed. The reason for choosing a pivaloyl ester as a protecting group is its tolerance toward strong bases, which are required for the activation of the α-position in the **1** → **2** transformation. This is also the reason why ketones must first be protected as ketals (*e.g.* **1k** → **1l**), but after the formation of **2l** this protecting group could be removed. The ketone **2k** was thus reacted with $BrF_3$ with no complications to produce methyl 7-oxo-2-trifluoromethyloctanoate **4k**.

**Table 1** Percentage yields for investigation of the reaction *method B*




| Compound | R[a] | Overall yield of **4**[b] (%) |
|---|---|---|
| **c** | $CH_3(CH_2)_4$ | 65[16] |
| **d** | $CH_3(CH_2)_8$ | 70[17] |
| **e** | $CH_3(CH_2)_{11}$ | 65 |
| **f** |  | 65 |
| **g** |  | 65 |
| **h** | $Cl(CH_2)_3$ | 60 |
| **i**[c] | $EtO(CH_2)_2$ | 55 |
| **j**[c] | *t*-$BuCOO(CH_2)_4$ | 60 |
| **k** | $CH_3CO(CH_2)_4$ | 50 |
| **l** |  | |

[a] For spectral characterization of some representative compound **9**s, **10**s, and all **11**s see the ESI. [b] All α-trifluoromethyl esters of type **4** are oils. They are fully characterized by IR, $^1H$, $^{13}C$, $^{19}F$ NMR, HRMS and microanalysis. [c] These compounds are ethyl esters.

We thank the USA-Israel Binational Science Foundation (BSF), Jerusalem, Israel for financial support.

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