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A general route for constructing difluoromethyl ethers

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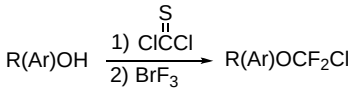
ABSTRACT

Chlorodifluoromethyl ethers are easily obtained from the corresponding alcohols. These ethers, when treated with tributyltin hydride, produce difluoromethyl ethers in high yields.

Following the success of the trifluoromethyl group in either enhancing or creating desirable biological features in numerous organic molecules, the difluoromethyl group is also rapidly gaining wide popularity. This is due mainly to the fact that for most purposes it is as stable as the trifluoromethyl moiety and yet is less bulky and is able to form hydrogen bonds. Indeed, the CHF_2 group can be found in a large number of families of organic compounds such as prostaglandins,[1] sugars,[2] steroids,[3] and many more.[4]

Similarities between trifluoromethyl and difluoromethyl ethers are emerging rapidly. While the importance of the former is well established, the utility of the latter is increasing. This group can be found in anticancer drugs,[5] antidiabetic and neuroprotective compounds,[6] antihypertensives,[7] in modern anesthetics,[8] and in many more fields. Several methods for the synthesis of the OCF_3 group are available,[9] but the lack of a wide-ranging method for the construction of the $OCHF_2$ group is conspicuous, and to date an individual synthesis has had to be devised for each compound possessing this moiety.[10] We report here a general route for transforming alcohols into difluoromethoxy compounds in good yields using bromine trifluoride. The opportunity for such a process presented itself when we developed recently an efficient and rapid method for converting the hydroxyl moiety to a chlorodifluoromethyl ether by reaction with thiophosgene followed by bromine trifluoride (Scheme 1).[11]

Unfortunately, many chemists still feel somewhat uneasy about BrF_3 and although known for almost a century, it remains a rarity in organic chemistry,[12] as was the situation with F_2 some years ago. The general notion is that this reagent is dangerous and so reactive that selectivity could not be achieved. We have, however, started to show that maybe the situation is not that hopeless for both F_2[13] and BrF_3.[14] Thus, by using bromine trifluoride we have been able to transform carbonyls to a CF_2 moiety,[15] substitute halogens in alkyl halides with a CHF_2 group,[16] and achieve difficult aromatic brominations.[17]



Scheme 1. Conversion of alcohols into difluorochloromethyl ethers.[11]

Since the C–Cl bond in dichlorofluoromethyl ethers is stronger than that in common alkyl halides, we found that Raney Ni, hydrogen, or diisobutylaluminum hydride (DIBAL-H) were not effective in substituting the chlorine atom with hydrogen, and only the starting material was recovered. On the other hand, applying $LiAlH_4$ or Na/MeOH resulted in complicated mixtures in which the difluoromethyl ether was present as a minor component only. We reckoned that since the difluoromethyl radical—$RCF_2^{\cdot}$—is a relatively stable and easily formed species, a reaction of a radical nature could be of help.[18]

Of all the hydrogen radical sources, tributyltin hydride is one of the best. Thus, refluxing chlorodifluoromethyl octyl ether (**1a**) with Bu_3SnH and 1,1′-azobis(cyclohexane-carbonitrile) (ABCN) in dry THF for 2 h resulted in an 85% yield of difluoromethyl octyl ether (**2a**) (Scheme 2).[19] Similar results were obtained for branched, cyclic, and acyclic chlorodifluoromethyl ethers. Chlorodifluoromethyl-3,7-dimethyloctyl ether (**1b**) and chlorodifluoro-methyl-3-cyclohexylpropyl ether (**1c**) were converted to the corresponding difluoromethyl-3,7-dimethyloctyl ether (**2b**) and difluoromethyl-3-cyclohexylpropyl ether (**2c**) in 90% and 85% yields, respectively.

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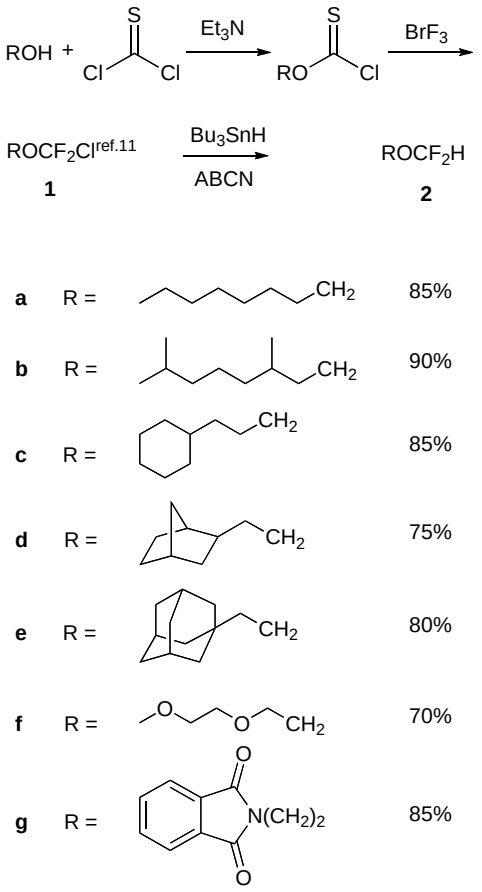
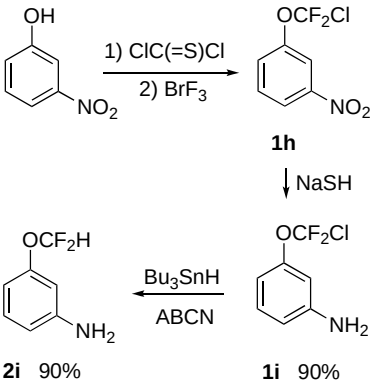


Scheme 2. Preparation of difluoromethyl ethers.

Bi- and tricyclic compounds such as the norbornyl (**1d**) and adamantylethyl (**1e**) derivatives also behaved similarly, and the desired difluoromethyl-1-norbornylethyl ether (**2d**) and difluoromethyl-1-adamantylethyl ether (**2e**) were obtained in 75% and 80% yields, respectively. The ether function is also tolerated in this reaction as demonstrated by the ethylene glycol derivative, chlorodifluoromethyl-(2-methoxyethoxy)ethyl ether (**1f**), which was converted into difluoromethyl-(2-methoxyethoxy)ethyl ether (**2f**) in 70% yield. Amines can also serve as substrates although they have to be protected prior to the reactions described in Scheme 1. This situation was demonstrated by amino ethanol which was transformed into chlorodifluoromethyl-*N*-phthalimidoethyl ether (**1g**), which was reduced easily with Bu_3SnH in refluxing toluene to difluoromethyl-*N*-phthalimidylethyl ether (**2g**) in high yield.

Since aromatics which are susceptible to electrophilic attack are usually brominated by BrF_3,[17] it is easy to use deactivated ring compounds such as 3-nitrophenol which was transformed to 3-chlorodifluoromethoxynitrobenzene (**1h**). The nitro group, however, inhibits the radical chain reaction induced by tributyltin hydride, but this difficulty can be circumvented by first reducing **1h** to the corresponding 3-chlorodifluoromethoxyaniline (**1i**), which posed no problem for the key step with Bu_3SnH to form 3-difluoromethoxyaniline (**2i**) in 90% yield (Scheme 3). Such aniline derivatives could serve as substrates for numerous further transformations.

In conclusions, the method outlined above is an inviting way to produce the still quite rare difluoromethoxy group that is becoming important for biologically related, as well as for other fields of chemistry.



Scheme 3. Aromatic difluoromethyl ethers.

Acknowledgment

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Typical procedure for the synthesis of difluoromethyl ethers (**2**): 2.7 Mmol of chlorodifluoromethyl ether (**1a**) was dissolved in 20 mL of anhydrous THF followed by the addition of 350 mg of 1,1′-azobis(cyclohexane-carbonitrile) (1.5 mmol), and 2.2 mL of tributyltin hydride (8.1 mmol). The solution was refluxed for 2 h. For the preparation of **2g** and **2i**, toluene was used as the solvent and the reflux continued for 6 h. After evaporation of the solvent, the product was purified by flash chromatography, which also removed all traces of any tin derivatives. All yields are for isolated compounds, and their analytical purity was established by elemental microanalysis, which was satisfactory for all the difluoromethyl ethers. Below are characteristic analytical data for the compounds discussed in this work.

Entry	^{1}H NMR (CHF_2)[a]	^{13}C NMR (CHF_2)[b]	^{19}F NMR (CHF_2)[c]	MS[d]
2a	6.24 (1H, t, *J* = 75 Hz)	116.1 (t, *J* = 258 Hz)	−84.5 (d, *J* = 75 Hz)	180
2b	6.21 (1H, t, *J* = 75 Hz)	116.0 (t, *J* = 258 Hz)	−84.4 (d, *J* = 75 Hz)	208
2c	6.17 (1H, t, *J* = 75 Hz)	116.1 (t, *J* = 251 Hz)	−84.3 (d, *J* = 75 Hz)	192
2d	6.22 (1H, t, *J* = 75 Hz)	116.2 (t, *J* = 257 Hz)	−84.2 (d, *J* = 75 Hz)	190
2e	6.17 (1H, t, *J* = 75 Hz)	116.1 (t, *J* = 257 Hz)	−84.4 (d, *J* = 75 Hz)	230
2f	6.27 (1H, t, *J* = 75 Hz)	116.0 (t, *J* = 257 Hz)	−84.6 (d, *J* = 75 Hz)	170
2g	6.18 (1H, t, *J* = 75 Hz)	115.7 (t, *J* = 258 Hz)	−85.3 (d, *J* = 75 Hz)	264[e]

[a] 200 MHz or 400 MHz, $CDCl_3$.
[b] 50.2 MHz or 100.5 MHz, $CDCl_3$ (Me_4Si as internal standard).
[c] 188.1 MHz, $CDCl_3$ ($CFCl_3$ as internal standard).
[d] See Ref. 19.
[e] ESI-QqTOF-$(M+Na)^+$