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Dehydroxylative trifluoromethylthiolation, trifluoromethylation, and difluoromethylation of alcohols

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CF_3S, CF_3 and HCF_2 groups have been identified as valuable functionalities for drug development. Despite significant accomplishments in the trifluoromethylthiolation, trifluoromethylation and difluoromethylation reactions, directly converting common functional groups into CF_3S, CF_3 or HCF_2 groups are still highly desirable. Described here is the dehydroxylative trifluoromethylthiolation, trifluoromethylation and difluoromethylation of alcohols promoted by a R_3P/ICH_2CH_2I system. All of these dehydroxylative reactions were achieved under mild conditions via the activation of the hydroxyl group by the R_3P/ICH_2CH_2I system. A wide substrate scope and good functional group tolerance were observed.

Due to its unique electronic properties such as strong electronegativity (4.0 in Pauling scale) and small atomic radius (r_v = 0.71 Å), fluorine has been considered as a magic element in medicinal chemistry, agrochemistry, and material science.[1] It is well known that the incorporation of a fluorine atom or a fluorinated group into an organic molecule can result in profound changes of the physicochemical properties. A survey in 2006 showed that approximately 20% of all drugs contain at least one fluorine atom (over 150 fluorinated drugs),[2] and the percentage have increased to 30% until now.[3] Many fluorinated groups, including CF_3S, CF_3 and HCF_2 have been recognized as valuable functionalities for drug development. A large number of pharmaceuticals containing one of these fluorinated groups have emerged, such as Cefazaflur, Efavirenz, Eflornithine and Deracoxib. Therefore, intensive research efforts have been devoted to the development of efficient methods for trifluoromethylthiolation,[4] trifluoromethylation,[4d, 5] and difluoromethylation[6] reactions. Despite many accomplishments in these transformations, general protocols for directly converting common functional groups into CF_3S, CF_3 or HCF_2 groups are still highly desirable.

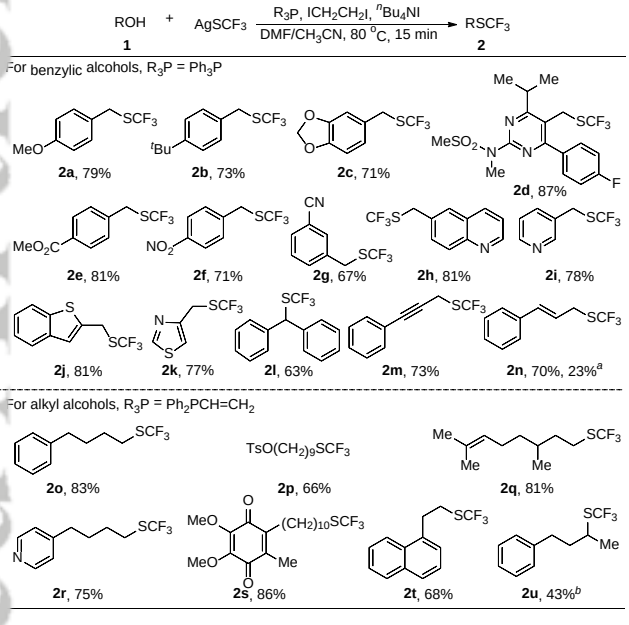
Hydroxyl moiety is a common functional group and alcohols are important structural motifs in various bioactive molecules, materials, and synthetic intermediates. Given the ubiquity of alcohols, direct dehydroxylative trifluoromethylthiolation, trifluoromethylation and difluoromethylation of alcohols are apparently attractive protocols for the installation of CF_3S, CF_3 and HCF_2 groups, respectively. However, due to the poor leaving ability of the hydroxyl group, these reactions are challenging and have been less developed. Rueping,[7] Qing,[8] and other groups[9] have reported the dehydroxylative trifluoromethylthiolation via the OH activation. These methods are quite effective, but they suffer from a limited substrate scope (limited to allylic and benzylic alcohols),[7] a long reaction time (10 h),[8] or a tedious process for the synthesis of the CF_3S-reagent.[9a, 9c] Trifluoromethylation usually requires a multi-step procedure involving the conversion of the OH group into a good leaving group.[10] Recently, Altman and co-workers disclosed that one-step trifluoromethylation could be enabled by the in situ activation of the hydroxyl group.[11] Direct dehydroxylative difluoromethylation of alcohols is an issue that remains to be addressed. In these dehydroxylative reactions, the activation of the OH group is a key step. However, a general reagent system for the OH activation to achieve all of the dehydroxylative trifluoromethylthiolation, trifluoromethylation, and difluoromethylation reactions has never been developed.

We have previously shown that the $R_3P/XCH_2CH_2X/I^-$ (X= Cl or Br) or R_3P/ICH_2CH_2I system could effectively activate the carbonyl or hydroxyl group for nucleophilic reactions.[12] In continuation of our research interests in fluoroalkylation[13] and fluoroalkylthiolation[14] conversions, we have now investigated the R_3P/ICH_2CH_2I-promoted dehydroxylative trifluoromethylthiolation, trifluoromethylation, and difluoromethylation of alcohols. R_3P/ICH_2CH_2I was found to be a general activation system for all of these reactions.

After screening the reaction conditions (See Supporting Information, Table S1), it was found that the trifluoromethylthiolation of benzylic alcohols with $AgSCF_3$ promoted by Ph_3P/ICH_2CH_2I proceeded rapidly (15 min). As shown in Table 1, a wide substrate scope was observed, and various functional groups could be tolerated, including ether, sulfonyl amide, ester, nitro, cyano, and heteroaryl groups. A moderate yield was obtained for the conversion of a secondary benzyl alcohol (**2l**). Besides benzylic alcohols, propargylic alcohols and primary allylic alcohols (**2m-2n**) also showed high reactivity. Interestingly, the conversion of secondary allylic alcohol

PhCH(OH)CH=CH_2 afforded the terminal substitution product, **2n** (PhCH=$CHCH_2SCF_3$), in 23% yield, and internal substitution product PhCH(SCF_3)CH=CH_2 was almost not detected, probably because of a resonance effect and a steric effect. In the case of alkyl alcohols, the use of Ph_3P led to a low yield, and the yield was increased significantly by using $Ph_2PCH=CH_2$ instead of Ph_3P (See Supporting Information, Table S2). Primary alkyl alcohols could be converted smoothly into the desired products (**2o-2t**), whereas secondary alcohols showed a lower reactivity and thus a higher reaction temperature was necessary (**2u**).

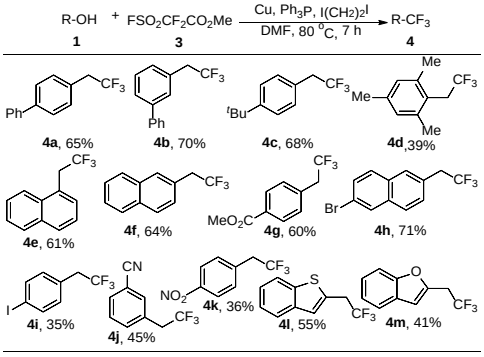
Table 1 Trifluoromethylthiolation of alcohols



Isolated yields. Reaction conditions for benzylic alcohols: alcohol **1** (0.5 mmol), CH_3CN-solvated $AgSCF_3$ (1 M, 1.5 mL), Ph_3P (1.4 equiv), ICH_2CH_2I (1.4 equiv), and $^nBu_4NI$ (1.5 equiv) in DMF (3 mL) at 80 °C for 15 min under a N_2 atmosphere; For alkyl alcohols: alcohol **1** (0.5 mmol), CH_3CN-solvated $AgSCF_3$ (1 M, 1 mL), $Ph_2PCH=CH_2$ (2.6 equiv), ICH_2CH_2I (1.2 equiv), and $^nBu_4NI$ (1.0 equiv) in DMF (3 mL) at 80 °C for 15 min under a N_2 atmosphere. [a]For the conversions of allylic alcohols PhCH=$CHCH_2OH$ and PhCH(OH)CH=CH_2, product **2n** was isolated in 70% and 23% yields, respectively; [b]In the case of product **2u**, 1.75 mL of $AgSCF_3$ solution and 3.0 mmol of $^nBu_4NI$ were used, and the reaction was performed at 100 °C.

Chen's reagent, $FSO_2CF_2CO_2Me$, was developed in 1989[15] and has become one of the most widely used trifluoromethylation reagents.[16] CuI is usually required to promote the trifluoromethylation with this reagent by forming a key intermediate, [$CuCF_3$]. Interestingly, a brief survey of the conditions for the Ph_3P/ICH_2CH_2I-initiated dehydroxylative trifluoromethylation revealed that Cu (zero valent copper) instead of CuI could also give a good yield (See Supporting Information, Table S3). After the optimal conditions were established, the substrate scope was investigated (Table 2). Good functional group tolerance was observed. Although aryl halides have proved to be reactive towards Cu-promoted trifluoromethylation,[15, 17] aryl bromides remained intact under these conditions (**4h**). In the case of aryl iodides, undesired trifluoromethylation of C-I bond was observed, and thus a low yield of the desired product was obtained (**4i**). Lower yields were obtained when the aromatic rings contained a strong electron-withdrawing group (**4k**). Although benzylic alcohols were found to be quite reactive, no expected product was detected for the conversions of alkyl alcohols.

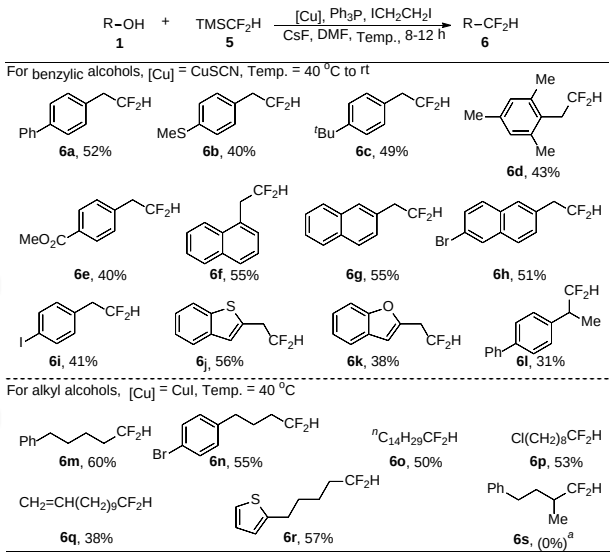
Table 2. Dehydroxylative trifluoromethylation of alcohols



Isolated yields. Reaction conditions: alcohol **1** (0.5 mmol), $FSO_2CF_2CO_2Me$ (5.0 equiv), Cu (1.0 equiv), Ph_3P (1.2 equiv), ICH_2CH_2I (1.2 equiv) in DMF (5 mL) at 80 °C for 7 h under a N_2 atmosphere.

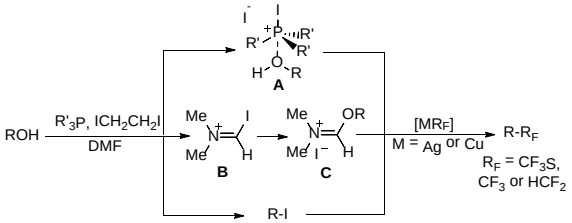
The successful trifluoromethylthiolation and trifluoromethylation prompted us to examine the difluoromethylation of alcohols (See Supporting Information, Tables S4-S5 for the optimization of the reaction conditions). Although the in situ preparation of [$CuCF_2H$] complex is necessary, the difluoromethylation process under the optimal reaction conditions could be extended to a variety of alcohols (Table 3). In contrast to trifluoromethylation, difluoromethylation could be applied well to alkyl alcohols. Secondary benzylic alcohols showed a low reactivity(**6l**). Secondary alkyl alcohols could not undergo difluoromethylation under these conditions (**6s**), and 54% of the substrate remained as determined by ^1H NMR spectroscopy.

Table 3. Dehydroxylative difluoromethylation of alcohols.



Isolated yields. Reaction conditions for benzylic alcohols: CuSCN (2.0 mmol), **5** (1.5 mmol), and CsF (2.5 mmol) in DMF (2 mL) at 40 °C for 1h. Into the mixture was added a solution of alcohol **1** (0.5 mmol), Ph_3P (1.2 equiv.), and ICH_2CH_2I (1.2 equiv) in DMF (3 mL). The resulting mixture was stirred at room temperature for 8-12 h under a N_2 atmosphere. For alkyl alcohols: CuI (1.0 mmol), CsF (2.5 mmol) and **5** (2.5 mmol) in DMF (2 mL) at 40 °C for 1h. Into the mixture was added the solution of alcohol **1** (0.5 mmol), Ph_3P (1.2 equiv.) and ICH_2CH_2I (1.2 equiv) in DMF (3 mL). The mixture was stirred at 40 °C for 8-12 h under a N_2 atmosphere. *a*The ^{19}F NMR analysis revealed that **6s** was not produced.

Based on the above results and combined with our previous reports,[12] we propose the plausible reaction mechanism, as shown in Scheme 1. We have previously shown that a strong halogen bonding between R'_3P and ICH_2CH_2I would drive the formation of iodophosphonium salt ($R'_3P^+I\ I^-$), which could activate the alcohols by coordination to form complex **A**. The iodophosphonium salt may also react with the solvent DMF to generate a Vilsmeier-Haack-type intermediate **B**, by which the alcohols could be activated via the formation of intermediate **C**.[12b, 12c] Further transformation of intermediate **A** or **C** with $AgSCF_3$ or $[CuR_F]$ (R_F = CF_3 or HCF_2) by a direct nucleophilic attack[12c] or an oxidative addition of $[CuR_F]$ (R_F = CF_3 or HCF_2) complexes followed by reductive elimination delivers the final products. Since the R'_3P/ICH_2CH_2I system could lead to iodination of alcohols,[12a] the path involving the generation of iodides (R-I) may not be ruled out.



Scheme 1 The proposed mechanism

In summary, we have described the dehydroxylative trifluoromethylthiolation, trifluoromethylation and difluoromethylation of alcohols promoted by the R_3P/ICH_2CH_2I system. This is the first general protocol for the installation of CF_3S, CF_3 and HCF_2 groups from easily available alcohols. Due to the ubiquity of alcohols, this dehydroxylation protocol may find applications in the synthesis of biologically active fluorine-containing molecules.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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