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Trifluoromethoxylation

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Direct Dehydroxytrifluoromethoxylation of Alcohols**

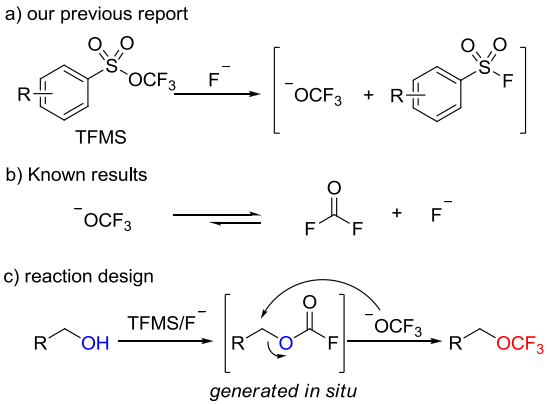
*Xiaohuan Jiang, Zhijie Deng and Pingping Tang**

Dedicated to Professor Biao Yu on the occasion of his 50th birthday

Abstract: *The first example of a direct dehydroxytrifluoromethoxylation of alcohols has been developed. This method generated an alkyl fluoroformate in situ from alcohols and followed nucleophilic trifluoromethoxylation with trifluoromethyl arylsulfonate (TFMS) as the trifluoromethoxylation reagent. This reaction is operationally simple, scalable and proceeds under mild reaction conditions, and provides access to a wide range of trifluoromethyl ethers from alcohols. In addition, this method is suitable for the late-stage trifluoromethoxylation of complex small molecules.*

Fluorinated compounds have become significant in agrochemical, pharmaceutical, and materials science.[1] Due to its strong electron-withdrawing effect and high lipophilicity, trifluoromethoxy (OCF_3) group has received much attention in the recent years.[2] However, methods for the synthesis of trifluoromethyl ethers are limited due to the reversible decomposition of trifluoromethoxide anion and limited trifluoromethoxylation reagents.[3] Thus, the development of efficient methods for the synthesis of OCF_3-containing compounds is of great importance.[4] Herein, we have successfully used the reversible decomposition property of trifluoromethoxide anion, which generated *in situ* from trifluoromethyl arylsulfonate (TFMS) to develop the first example of a direct dehydroxytrifluoromethoxylation of alcohols under the mild reaction conditions (Scheme 1).

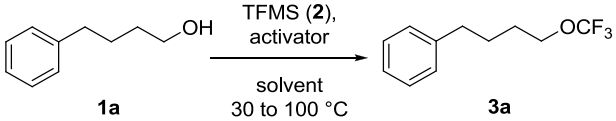
The conventional methods for the synthesis of alkyl trifluoromethyl ethers from alcohol through electrophilic trifluoromethylation suffer from harsh reaction conditions, poor substrates scope.[5-8] For example, Umemoto reported a direct electrophilic trifluoromethylation of alcohols with *O*-(trifluoromethyl)-dibenzofuranium reagents,[6] however, this Umemoto's reagent is highly active which need to be generated *in situ* from diazonium salts at -100 to -90 °C. Togni reported a zinc-mediated formation of trifluoromethyl ethers from alcohols with Togni's reagents.[7] Toste reported a direct electrophilic trifluoromethylation of alcohols with trifluoromethyl iodonium salts.[8] The disadvantage of these methods was the use of excess alcohols, and tertiary alcohols proved ineffectual. Recently, Qing reported a silver-mediated oxidative trifluoromethylation of alcohols to generate the alkyl trifluorometyl ethers with the Ruppert-Prakash reagent ($TMSCF_3$).[9] Various primary, secondary, and tertiary alcohols proceeded efficiently. However, this reaction required stoichiometric silver salts. Despite the development of these methods, the direct dehydroxytrifluoromethoxylation of alcohols was not reported to date. Therefore, the development of a general and practical method for direct dehydroxytrifluoromethoxylation of alcohols is highly desirable.



Scheme 1. Direct dehydroxytrifluoromethoxylation of alcohols.

Recently, trifluoromethyl arylsulfonate (TFMS) as a new trifluoromethoxylation reagent was found by our group, which was used to generate trifluoromethoxide anion ($^-OCF_3$) *in situ* in the presence of fluoride ions (Scheme 1a).[10] Although the reversible decomposition of trifluoromethoxide anion to form fluorophosgene and fluoride (Scheme 1b),[11] we wondered if it was possible to use this unique property to develop new reactions. Inspired by the Sheppard's work that alcohols react with fluorophosgene to form the corresponding fluoroformate,[12] we reasoned that a direct dehydroxytrifluoromethoxylation of alcohols could be achieved with trifluoromethyl arylsulfonate (TFMS) as the trifluoromethoxylation reagent, through alkyl fluoroformate generated *in situ* from alcohols and followed nucleophilic trifluoromethoxylation to prepare the alkyl trifluoromethyl ethers (Scheme 1c).

Table 1. Optimization of the reaction conditions.[a]



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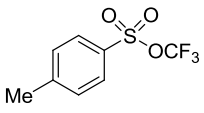
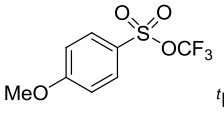
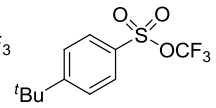
Entry	TFMS	Activator	Solvent	Yield(%)[b]
1	**2a**	none	NMP	0
2	**2a**	NaF	NMP	0
3	**2a**	KF	NMP	3
4	**2a**	CsF	NMP	50
5	**2a**	AgF	NMP	2
6	**2b**	CsF	NMP	16
7	**2c**	CsF	NMP	46
8	**2d**	CsF	NMP	45
9	**2e**	CsF	NMP	13
10	**2f**	CsF	NMP	10
11[c]	**2a**	CsF, TBABr	NMP	7
12[c]	**2a**	CsF, TMABr	NMP	78
13[c]	**2a**	CsF, TMACl	NMP	50
14[c]	**2a**	CsF, TMABr	DMA	86
15[c]	**2a**	CsF, TMABr	DMA/NMP	87
16[c]	**2a**	**CsF, TMABr**	**DMA/HMPA**	**88**



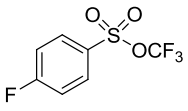
2a



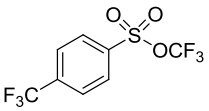
2b



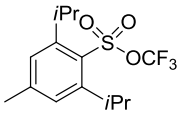
2c



2d



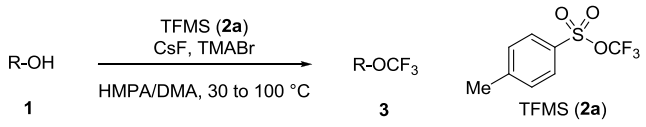
2e



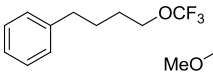
2f

[a] 3.0 equiv of TFMS and 2.5 equiv of fluorine salts were used. [b] Yields were determined by ^{19}F NMR with benzotrifluoride as a standard. [c] 0.5 equiv of quaternary ammonium salts was used.

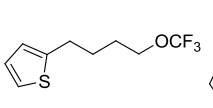
Initially, 4-phenyl-1-butanol (**1a**) was chose as the model substrate to optimize the reaction conditions. Various fluorine sources were evaluated in the presence of TFMS (**2a**) (Table 1, entries 1-5). Less than 5% desired product **3a** was found when NaF, KF or AgF was used. To our delight, 50% yield of the desired product **3a** was observed in the presence of CsF (Table 1, entry 4). Different trifluoromethyl arylsulfonates (TFMS, **2**) were evaluated, which revealed that substituents on the aromatic rings influenced the reaction yields, and trifluoromethyl 4-methylbenzenesulfonate (**2a**) gave the highest yield (Table 1, entries 5-10). To improve the solubility of CsF and increase the stability of trifluoromethoxide anion ($^{-}OCF_3$), different quaternary ammonium salts were investigated (Table 1, entries 11-13). The yield of **3a** was further improved to 78% by adding 0.5 equiv of tetramethylammonium bromide (TMABr). Further optimization of the reaction conditions to improve the reaction yields were achieved when different solvents were used (Table 1, entries 14-16). After thorough optimization of the reaction conditions (see more details in the Supporting Information), reactions with 2.5 equiv of CsF, 3.0 equiv of TFMS (**2a**), 0.5 equiv of TMABr in 9:1 (v:v) DMA/HMPA under N_2 atmosphere at 30 °C to 100 °C were found to give the high yields of the desired product.



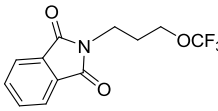
1 **3**



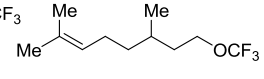
3a, 83% (80%[b]) **3b**, 83% (80%[b]) **3c**, 83%



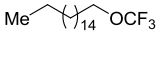
3d, 71%



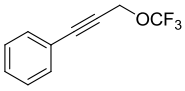
3e, 73%



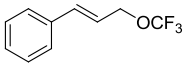
3f, 54%



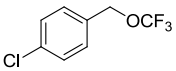
3g, 75%



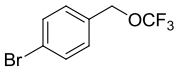
3h, 69%[c]



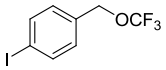
3i, 71%[d]



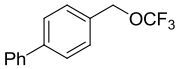
3j, 57%[e,f]



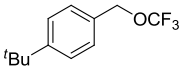
3k, 61%[e,f]



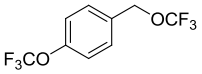
3l, 79%[e,f]



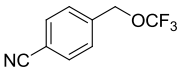
3m, 87%[e,f]



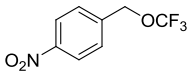
3n, 83%[e,f]



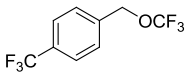
3o, 63%[e,f]



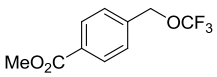
3p, 71%[e,f]



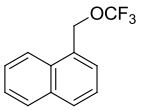
3q, 72%[e,f]



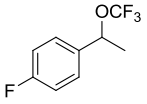
3r, 57%[e,f]



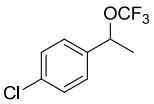
3s, 78%[e,f] (74%[b])



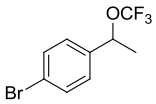
3t, 80%[e,f]



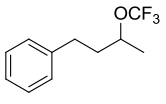
3u, 43%[e,g,i]



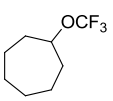
3v, 63%[e,g]



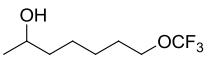
3w, 75%[e,g] (69%[b])



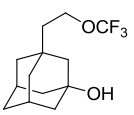
3x, 66%[g] (62%[b])



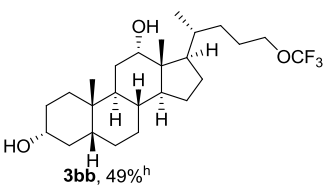
3y, 54%[g,i]



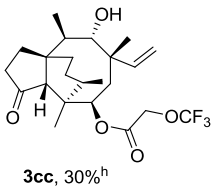
3z, 40%[h]



3aa, 68%[h]



3bb, 49%[h]



3cc, 30%[h]

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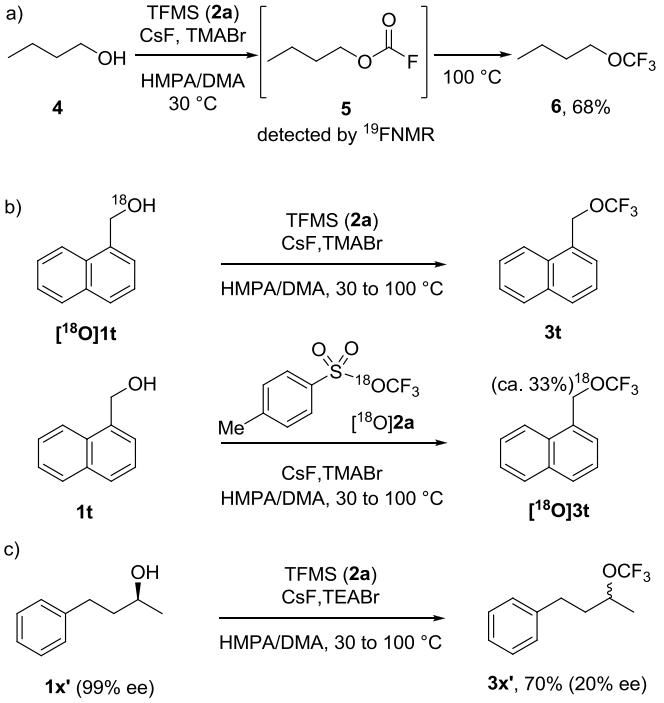
Scheme 2. Substrate scope for dehydroxytrifluoromethoxylation of alcohols. [a] Condition: alcohols (1.0 equiv), CsF (2.5 equiv), TFMS (**2a**) (3.0 equiv), TMABr (0.5 equiv), DMA/HMPA (v/v 9:1), N_2 atmosphere, 30 to 100 °C. Yields of isolated products are given unless otherwise noted. [b] DMA was used as the solvent. [c] 60 °C was used. [d] 40 °C was used. [e] 70 °C was used. [f] TMABr (0.3 equiv) was used. [g] CsF (3.5 equiv), TFMS (**2a**) (3.5 equiv), TEABr (1.0 equiv) were used. [h] CsF (5.0 equiv), TFMS (**2a**) (5.0 equiv) were used. [i] Yield was determined by ^{19}F NMR with benzotrifluoride as a standard. TMABr = tetramethylammonium bromide, TEABr = tetraethylammonium bromide.

Having established optimized reaction conditions, we then explored the scope of trifluoromethoxylation with structurally diverse alcohols. As displayed in Scheme 2, a wide range of primary and secondary alcohols including alkyl (**1a** to **1g, 1x**), propargyl (**1h**), allyl (**1i**), and benzyl alcohols (**1j** to **1w**), were successfully converted into the desired trifluoromethoxylation products with yields ranging from 43% to 87% (**3a** to **3x**). Substrates bearing electron-donating and electron-withdrawing substituents on aryl rings proceeded well. A good range of functional groups including ester, ether, ketone, nitrile, nitro, amide, chloride, bromide, and iodide were well tolerated under the mild reaction conditions. Moreover, the trifluoromethoxylation of cyclohepatanol (**1y**) proceeded smoothly to give the desired product **3y** in 54% yield. However, less than 5% yield of desired trifluoromethoxylation products were observed with cyclohexanol, and fluoroformate intermediate was found. For the substrate **1z** including primary and secondary hydroxyl groups, 43% yield of **3z** was isolated with dehydroxytrifluoromethoxylation of primary alcohol, along with 31% yield of trifluoromethoxylation of both hydroxyl groups. It is worth mentioning that highly chemoselective dehydroxytrifluoromethoxylation of primary alcohol in the presence of tertiary aclohols was observed. For example, the primary alcohol in substrate **1aa** was selective converted to trifluoromethoxy group while the tertiary alcohol remained intact. The yield of fluorination byproducts was less than 5% in all cases. These results encouraged the application of this method to more complex small molecules, which gave the corresponding trifluoromethoxylation products (**3bb**, **3cc)** in moderate yields. For example, pleuromutilin (**1cc**), which is an antibacterial drug,[13] were selectively converted the primary hydroxyl group to the trifluoromethoxylation product (**3cc**) in 30% isolated yield. Futhermore, due to the toxicity of HMPA, we also evaluated the reaction using DMA as the solvent, and slightly lower isolated yields were observed with selected substrates (**1a**, **1b**, **1s**, **1w** and **1x**). In addition, we prepared compound **3m** in gram scale under the standard reaction conditions in 80% isolated yield, which demonstrates the scalability and practicality of this method. The limitation of this method was that no desired products were observed with tertiary alcohols, and the major byproducts were an alkene; Substrates with free carboxylic acids and amines proved ineffectual under the standard conditions.

To gain more insight into the reaction mechanism, we performed some preliminary studies (Scheme 3). Monitoring of the reaction by ^{19}F NMR spectroscopy indicated that butyl fluoroformate **5** was generated from butanol *in situ* at 30 °C for 3 h, and 68% yield of desired product **6** was formed when temperature was increase to 100 °C (Scheme 3a). The NMR spectrum of isolated butyl fluoroformate **5** was in accord with the reported data.[14] These observations provides solid evidence that alkyl fluoroformate was generated *in situ* from alcohols in the reactions. In addition, no ^{18}O incorporation in the product **3t** was observed when **[^{18}O]1t** was used as the substrates. In the presence of [^{18}O]**2a**, the corresponding product [^{18}O]**3t** was generated with 33% ^{18}O incorporation. We reasoned that the equilibration of oxygen isotope occurred in the trifluoromethyl arylsulfonate (TFMS) during the reaction (see more details in the Supporting Information). Together, these results indicated that O atom of OCF_3 group in the product came from trifluoromethoxylation reagent (TFMS) (Scheme 3b). Furthermore, the substrate **1x'** with 99% ee was used and the product **3x'** with 20% ee was found (Scheme 3c), which suggested that the S_N1-type nucleophilic trifluoromethoxylation of alcohols might be involved in the reaction.



Scheme 3. Mechanism studies.

In conclusion, we have developed the first example of direct dehydroxytrifluoromethoxylation of alcohols with trifluoromethyl arylsulfonate (TFMS) as the trifluoromethoxylation reagent under mild reaction conditions. This method enables the transformation of various primary and secondary alcohols to the corresponding trifluoromethoxylation products and tolerates a wide range of functional groups. Additionally, preliminary mechanistic studies indicated that the reaction might proceed through an alkyl fluoroformate intermediate and followed S_N1-type nucleophilic trifluoromethoxylation. Owing to the efficient and practical of this reaction, we anticipate that this method will find a broad application to prepare alkyl trifluoromethyl ethers in the pharmaceutical and agrochemical fields.

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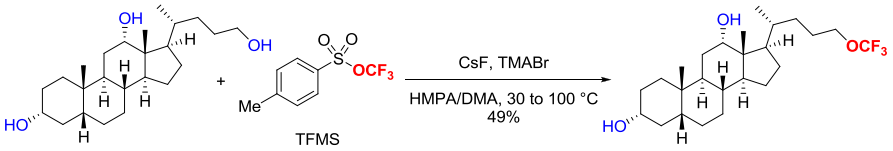
Trifluoromethoxylation

Xiaohuan Jiang, Zhijie Deng and Pingping Tang* _____ **Page – Page**

Direct Dehydroxytrifluoromethoxylation of Alcohols



A direct dehydroxytrifluoromethoxylation of alcohols with trifluoromethyl arylsulfonate (TFMS) as the trifluoromethoxylation reagent has been reported for the first time. The reaction is operationally simple and amenable to gram-scale synthesis. Preliminary mechanistic studies suggest that the reaction may proceed through an alkyl fluoroformate intermediate and followed nucleophilic trifluoromethoxylation.

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