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Aqueous Base Promoted *O*-Difluoromethylation of Carboxylic Acids with $TMSCF_2Br$: Bench-Top Access to Difluoromethyl Esters

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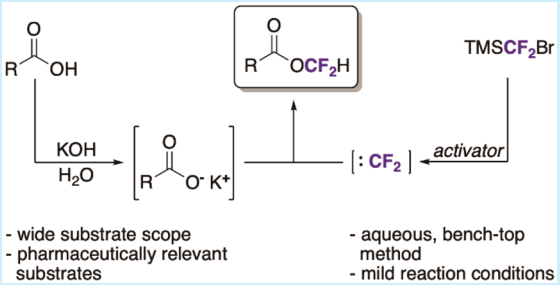
Supporting Information

ABSTRACT: A method for the *O*-difluoromethylation of carboxylic acids using commercially available $TMSCF_2Br$ is disclosed. The devised benchtop reaction system is air-stable and offers mild reaction conditions while using readily available reagents and solvents. The method is applicable to both aliphatic and aromatic carboxylic acids while demonstrating compatibility with a range of commonly encountered functional groups. The difluoromethyl esters of FDA approved drugs and pharmaceutically relevant molecules are also presented, demonstrating the potential for late-stage functionalization.



Among the plethora of fluorinated groups pursued for their ability to modify the physical and chemical properties of molecules,[1−3] the difluoromethyl group stands out as a potentially invaluable unit in the preparation of bioisosteres of medicinally relevant compounds, owing to its similarity to −OH.[4,5] This potential application to drug discovery has spurred the development of novel methods for its installation, including *gem*-difluorination[6−8] and direct difluoromethylation[9−12] reactions. An alternative approach comes in the form of difluorocarbene. Generated from silicon-based reagents, this intermediate has received much recent interest, having been applied to C,[13−15] N,[16] B,[17] O,[18] S,[19] Se,[20] and P[21] centers. Considering the abundance of carboxylic acids in nature and in pharmacologically relevant molecules, it is interesting that such an approach has rarely been applied (Figure 1) for the generation of difluoromethyl esters, which could prove to be valuable compounds. One reported approach uses fluorosulfonyldifluoroacetic acid at room temperature with metal carboxylates to form the corresponding difluoromethyl esters in moderate to good yields, but this also generates SO_2 as an undesirable byproduct.[22] Another report describes a difluoromethylation using $Ph_3P^+-CF_2-COO^-$, wherein triphenylphosphine and carbon dioxide are byproducts.[23] Benzoic acid with trimethyl(trifluoromethyl)stannane has been shown to yield difluoromethyl benzoate.[24]

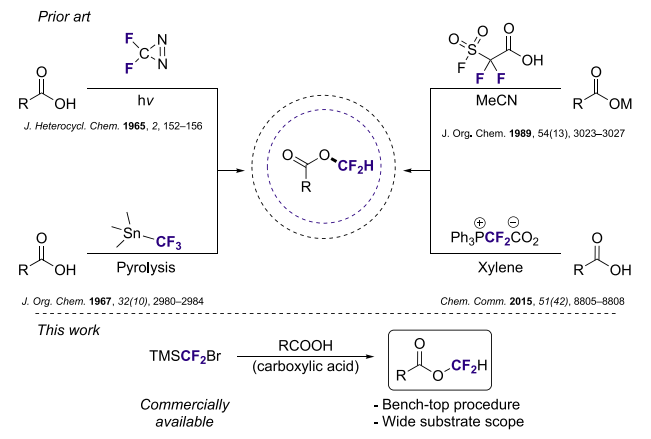


Figure 1. Prior art on the direct difluoromethylation of carboxylic acids.

Owing to the inherent toxicity of SO_2, PPh_3, and tin compounds, an alternative difluoromethylation approach is desirable. CF_2N_2 can produce $-CF_2-$ esters from the corresponding carboxylic acids, but the hazards associated with the synthesis and use of this gaseous and explosive reagent render this approach less accessible.[25]

Silicon reagents, by virtue of their mild activation conditions[26−29] and nontoxic byproducts, provide one such alternative. Among the various reagents used to release difluorocarbene, $TMSCF_2Br$, first prepared by our group,[30a] stands out owing to its availability, effectiveness, and compatibility with aqueous reaction systems.[30b] Using $TMSCF_2Br$ to perform a difluoromethylation of carboxylic acids would be a facile, accessible, and safe method to synthesize difluoromethyl esters. Based on our previous experience with difluorocarbene chemistry,[20,21] we envisioned a reaction system wherein the carbene generated from $TMSCF_2Br$ would react with a carboxylate anion, yielding a difluoromethyl ester upon protonation (Scheme 1). Benzoic

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acid **1a** was chosen as a model for optimization studies (Table 1).

Scheme 1. Mechanistic Hypothesis

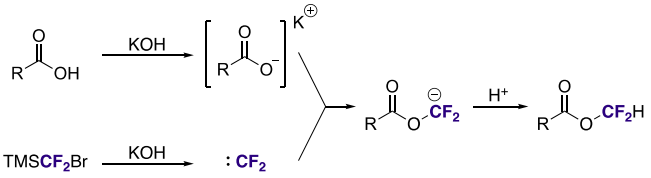


Table 1. Optimization Experiments on 2a

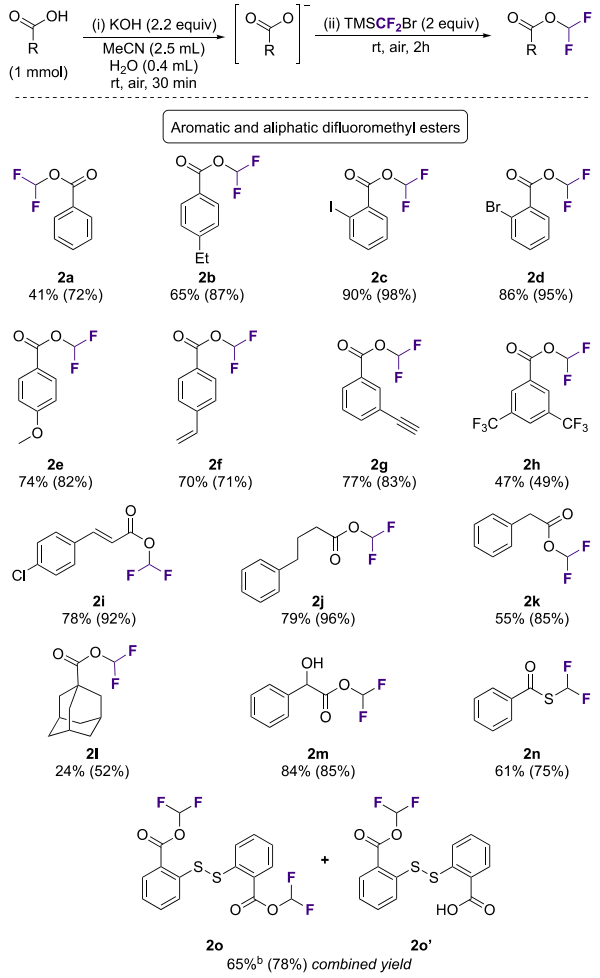
trial[a]	base (equiv)	solvent[b]	$TMSCF_2Br$ (equiv)	**2a** (%)[c]
1	NaO*t*Bu (1.1)	triglyme	2	44
2	KO*t*Bu (1.1)	triglyme	2	39
3	KO*t*Bu (1.1)	CH_3CN	2	58
4	K_2CO_3 (1.1)	CH_3CN	2	27
5	KOH (1.1)	CH_3CN	2	48
6	KOH (2.2)	DMF	2	10
7	KOH (2.2)	CH_3CN	2	72
8[d]	KOH (2.2)	CH_3CN	2	72
9[d]	KOH (2.2)	CH_3CN	3	69
10[d]	KOH (2.2)	CH_3CN	4	66

[a]Reactions performed with 0.25 mmol of **1a**. [b]0.4 M concentration of **1a** in solvent. [c]Yield determined by ^{19}F NMR using fluorobenzene as internal standard. [d]100 μL of H_2O added.

Sodium *tert*-butoxide (trial 1) and potassium *tert*-butoxide (trial 2) proved mildly effective in facilitating this transformation in triglyme. Performing the reaction in acetonitrile increased the amount of difluoromethyl benzoate (**2a**) observed (trial 3). Of the bases screened, KOH worked the best, with 72% of **2a** detected by ^{19}F NMR (trial 5). DMF was found to be ineffective in promoting the chemistry, with a severely diminished yield of **2a** (trial 6). It was found that higher loadings of KOH resulted in higher yields, with the maximum being 72% of **2a** observed when 2.2 equiv of KOH was used (trial 7). To remove the potential for variability in the system by virtue of water absorbed by the hygroscopic KOH, 100 μL of water was added to the system, and the yield remained unchanged (trial 8). With the optimal base and solvent system determined, efforts were made to determine the optimal amount of $TMSCF_2Br$ required in this system. Higher loadings of $TMSCF_2Br$ (trials 9 and 10) did not afford increased yields. The optimum conditions were then applied to a series of carboxylic acids (Scheme 2).

The model substrate **1a** afforded **2a** in 72% yield by ^{19}F NMR and was isolated in 41% yield. The reduced isolated yield may be attributed to the volatility of the product. Similarly, **2b** was isolated in 65% yield (87% by NMR). Haloarenes are tolerant to the reaction conditions, as is demonstrated by **2c** and **2d**, which were isolated in high yields. Compound **2e**, bearing the electron-donating 4-OMe substituent, was obtained in good yield. Despite the facile nature of difluorocarbene cyclopropanation reactions with alkenes, substrate **1f**, containing a 4-vinyl group, gave none of the difluorocyclopropane product, instead providing only the desired difluoromethyl ester **2f**.[30,31] Similarly, the terminal alkyne unit on **2g** was left untouched; no difluorocyclopropene was observed. This exquisite selectivity could be advantageous in the *O*-difluoromethylation of complex carboxylic acids. An

Scheme 2. Substrate Scope[a]



[a]Reactions performed at 1 mmol scale for isolated yields. Yields in parentheses determined by ^{19}F NMR at 0.25 mmol reaction scale. [b]Four equiv of $TMSCF_2Br$.

electron deficient ester, **2h**, with two trifluoromethyl groups, was obtained in moderate yield. Among the aryl carboxylic acids (**1a**–**1h**), it appears that the yield is directly related to the electron density on the aryl ring: electron-donating groups enhance the yield, while electron-withdrawing groups diminish the yield. Under the optimized conditions, 4-chlorocinnamic acid saw high conversion to **2i**.

Aliphatic carboxylic acids were also tested under the optimized conditions. Difluoromethyl 4-phenylbutanoate **2j** was formed with excellent conversion. The phenyl acetic acid derivative **2k** was obtained in a slightly lower yield than the phenyl butyric acid derivative **2j**, possibly due to the stronger withdrawing effect of the phenyl group in **2k** by virtue of proximity to the carboxylic acid group. 1-Adamantyl carboxylic **1l** acid was derivatized in moderate yields despite the strong electron-donating effect of the adamantyl group. Strong steric repulsion may be responsible for this diminished yield. Aliphatic alcohols, despite their propensity to react with CF_2 carbene,[18] were found to be tolerant to the conditions: **2m** was furnished from mandelic acid in 84% yield with none of the difluoromethyl ether observed. Thiocarboxylic acid ester **2n** was prepared in 75% conversion with the carbene showing a preference for the S atom over the O atom (inferred from ^{19}F NMR and IR data, see the Supporting Information). Finally,

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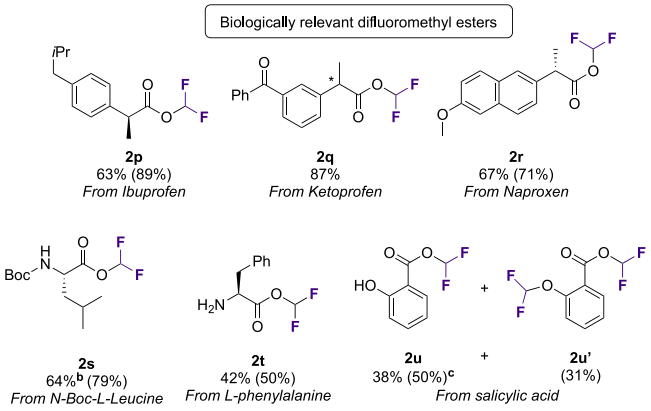
disulfide containing **1o** produced a 1:1 mixture of **2o** and **2o′**, with <4% formation of the *gem*-difluoromethyl dithioacetal (the product of CF_2 insertion into the S−S bond).[20]

As stated previously, carboxyl groups can be found in a number of FDA approved drugs and in biologically relevant molecules. To test the applicability of this method on complex molecules, acids **1p**−**1u** were subjected to the reaction conditions (Scheme 3).

Scheme 3. *O*-Difluoromethylation of Biologically Relevant Carboxylic Acids[a]



[a]Reactions were performed at 1 mmol scale using standard reaction conditions. [b]Conducted at 0.5 mmol scale. [c]Three equivalents of $TMSCF_2Br$.

Ibuprofen (**1p**) furnished **2p** in high conversion. Ketoprofen (**1q**) was transformed to the corresponding difluoromethyl ester (**2q**) in excellent yield. Notably, the ketone functionality in **1q** was left untouched; i.e., neither the bromodifluoromethyl carbinol from nucleophilic bromodifluoromethylation[32] nor the difluoroalkane resulting from deoxo-*gem*-difluorination at the carbonyl group[33,34] were observed. Naproxen **1r** furnished **2r** in good yield. Ester **2s** was prepared from Boc-protected leucine in good yield with retention of the Boc group despite the ability of difluorocarbene to replace the *tert*-butyl group, generating an *O*-difluoromethyl carbamate.[35] Furthermore, the unprotected amino acid phenylalanine (**1t**) furnished **2t** in moderate yield with no evidence of the N−CF_2H product, demonstrating applicability to even unprotected primary amines. Under the optimized conditions, salicylic acid (**1u**) formed a mixture of products by virtue of competing *O*-difluoromethylation at the carboxylic acid and alcohol functionalities. Increasing the loading of $TMSCF_2Br$ to 3 equiv resulted in an easily separable 5:3 (**2u**:**2u′**) mixture of the mono- and disubstituted products with an 81% overall conversion of **1u**.

Reports on difluoromethyl esters are scarce. This work presents a method to access these potentially valuable compounds under accessible benchtop conditions using commercially available reagents without the need for drying or any special pretreatment of the reactants. The procedure is compatible with a variety of commonly encountered functional groups, which supports its potential applicability in late-stage functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03604.

Procedures, characterization, and images of spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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