Fluorination

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Fluorodecarboxylation for the Synthesis of Trifluoromethyl Aryl Ethers

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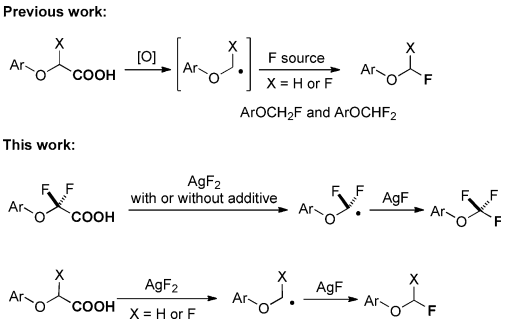
Abstract: *The synthesis of mono-, di-, and trifluoromethyl aryl ethers by fluorodecarboxylation of the corresponding carboxylic acids is reported. AgF_2 induces decarboxylation of aryloxydifluoroacetic acids, and AgF, either generated in situ or added separately, serves as a source of fluorine to generate the fluorodecarboxylation products. The addition of 2,6-difluoropyridine increased the reactivity of AgF_2, thereby increasing the range of functional groups and electronic properties of the aryl groups that are tolerated. The reaction conditions used for the formation of trifluoromethyl aryl ethers also served to form difluoromethyl and monofluoromethyl aryl ethers.*

Fluoromethyl aryl ethers are increasingly being investigated for agrochemical, pharmaceutical, and materials science.[1] Indeed, the introduction of a fluorine atom in a molecule allows one to tune the structure and electronic properties of the molecule as a means to modulate both pharmacokinetic and pharmacodynamic properties.[2] For example, the trifluoromethoxy group in a trifluoromethoxy aryl ether is oriented perpendicular to the aryl ring instead of being oriented closer to the plane of the aryl ring as in a methyl aryl ether. This difference in conformation results from the small degree of conjugation of the lone pair of electrons on the oxygen atom with the aryl ring because of the electron-withdrawing power of the CF_3 group and hyperconjugation of the electron pair with the C–F σ* orbitals.[3] Although many agrochemicals and pharmaceuticals containing trifluoromethyl aryl ethers have already been approved or are being developed, convenient methods to form these structures would greatly increase the applications of this class of molecule.[4]

Synthetic methods to form fluoromethyl aryl ethers are less developed than the methods to prepare other fluoroalkyl compounds.[1] Although several routes to mono- and difluoromethyl ethers are documented,[5,6] methods to form trifluoromethyl aryl ethers are less developed.[4–6] The traditional synthesis of trifluoromethyl ethers is typically achieved by nucleophilic substitution of the corresponding trichloromethyl ethers with fluoride, deoxyfluorination of fluoroformates, and fluorodesulfurization reactions of sulfonate esters, all of which require harsh reaction conditions.[7] Several new strategies have been developed recently, but none of the resulting procedures are broadly applicable. The limitations include either unstable reagents which require handling at low temperature, substrates that must contain a directing group, formation of mixtures of isomeric products, complex experimental conditions, or excess quantities of multiple reagents. Thus, the development of new strategies for the formation of aryl fluoromethyl ethers would be valuable for a range of synthetic applications.[8,9]

In principle, fluorodecarboxylation could provide a general method to access aryl trifluoromethyl ethers, as well as the analogous monofluoro- and difluoromethyl ethers (Scheme 1) from reactants which are readily accessible by a simple substitutions with phenols.[10] However, determining the appropriate reagents to induce the decarboxylation of α-fluoro carboxylic acids, as well as an appropriate source of F• to quench the fluoroalkyl radical, is challenging. The first fluorodecarboxylation reaction was reported with an alkyl carboxylic acid in 1969 by Grakauskas and co-workers with F_2 as both the oxidant and the source of fluorine.[11] Later, Patrick and co-workers improved the scope of the reaction by conducting reactions with the more easily handled XeF_2.[12] Recently, the groups of Sammis, Li, Gouverneur, Groves, MacMillan, and Ye all have reported decarboxylative fluorinations of alkyl, aryl, or aryloxy carboxylic acids by Hunsdiecker-type fluorinations and photoredox fluorinations.[13–16] However, the decarboxylative fluorination to generate trifluoromethyl ethers has not been reported.[17]



Scheme 1. Fluorodecarboxylation for the synthesis of fluoromethyl aryl ethers.

Decarboxylation reactions are strongly dependent on the electronic properties of the substrates because the process occurs by oxidation of the carboxylate. Thus, decarboxylation of α-fluoro- and α,α-difluorocarboxylates, particularly those containing accompanying aryloxy groups to form difluoromethyl and trifluoromethyl ethers, are distinct from decarboxylation reactions of simple alkyl groups. Indeed, the

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synthesis of only difluoromethyl aryl ethers starting from α-fluoro acids has been disclosed, and just one report of this transformation has been published.[14a] On the basis of our previous fluorination with the relatively inexpensive and readily available AgF_2,[18] we envisioned that oxidative fluorination to form aryl trifluoromethyl ethers could be conducted with AgF_2 as a reagent (Scheme 1).[19]

We report a facile decarboxylative fluorination reaction for the synthesis of trifluoromethyl ethers. The reactions occur with either AgF_2 or a combination of AgF_2 and AgF under mild reaction conditions with a broad range of aryl groups. The reactivity of AgF_2 was tuned by an electron-poor pyridine additive, thus enabling the synthesis of products with a broad substrate scope. We also found that the addition of AgF increased the yields, presumably, by serving as a source of ·F during the early stages of the reaction.

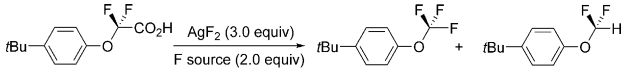
To identify reaction conditions for the decarboxylative fluorination to form aryl trifluoromethyl ethers, we conducted a series of reactions with the α-phenoxy-α,α-difluoro acetic acid **1a** (see Table 1) We initially investigated the decarboxylation of **1a** by methods reported by the groups of Li,[15a] Sammis and Paquin,[14b] MacMillan,[14c] and Groves[16] but these methods gave less than 5% of the trifluoromethyl ether (see the Supporting Information). Based on the ability of AgF_2 to act as a source of fluorine and oxidant,[18,19] we conducted reactions of **1a** with AgF_2 in acetonitrile under various reaction conditions (Table 1). An excess of AgF_2 was used because of the background decomposition from interaction with the solvent.[18] In the absence of any additional source of fluorine, the reaction gave the trifluoromethoxyarene **2a** in 49% yield, along with the difluoromethyl ether **3a** in 2% yield (entry 1). This result showed that either AgF_2 or AgF, or both, could function as the source of the fluorine atom to quench a putative alkyl radical. However, large amounts of **1a** decomposed during this reaction. We hypothesized that this decomposition results from rapid oxidative decarboxylation to generate high concentrations of the alkyl radical and that this high concentration leads to intermolecular processes that compete with C–F bond formation. Copper difluoride, NFSI, and Selectfluor were investigated as alternative sources of ·F (entries 2–4), but reactions conducted with AgF_2 and these reagents generated low yields (<5 to 12%) of **2a**. However, reactions conducted with added AgF occurred in a significantly increased yield of 71% (entry 5). The AgF added or present in the commercial samples of AgF_2 could serve as a base to generate the carboxylate anion from the carboxylic acid or a source of fluorine to quench the alkyl radical, or both.

Studies of additional reaction parameters further increased the yield. Reactions at slightly lower or higher temperatures (0 °C and 40 °C) gave lower yields than those at room temperature (Table 1, entries 6 and 7). Reactions in propionitrile as the solvent occurred in lower yields than those in acetonitrile and with a significant increase in the formation of the byproduct **3a** (entry 8). Reactions in pivalonitrile gave no trifluoromethyl ether product (entry 9), even though this solvent might suppress the formation of byproducts because of a lack of weak C–H bonds α to the cyano group. Ultimately, we found that the addition of pyridines to coordinate the AgF_2 (initially to reduce its oxidizing potential)[8i,18] led to higher yields of **2a**. A series of reactions with added pyridines (entries 10–14) showed that the reaction conducted with 2,6-difluoropyridine as an additive occurred in 95% yield (entry 14).

In addition to adding AgF to increase the availability of F·, we controlled the concentration of radical intermediates by adding **1a** slowly with a syringe pump (Table 1, entry 15). Under these reaction conditions, the concentration of AgF generated in situ should be sufficient to quench the alkyl radical. Indeed, the reaction conducted in this fashion with AgF_2 alone generated **1a** in 96% yield, as determined by ^{19}F NMR spectroscopy, and gave 91% yield of the isolated product (entry 15). The reaction of **1a** under these conditions on a 1 mmol scale occurred in a comparable yield of 86% (isolated). Therefore, both sets of reaction conditions were used to evaluate the substrate scope. Although we conducted most reactions in a glovebox, we also conducted the reaction of **1a** using standard Schlenk techniques, which gave 60% yield of **2a**. For detailed procedures, see the Supporting Information.

The substrate scope of this decarboxylative reaction with a series of substrates containing distinct substitution patterns and a range of functional groups is shown in Table 2. These reactions were generally conducted with the combination of AgF_2, AgF, and 2,6-difluoropyridine. The acid was generally added manually, without a syringe pump, but when the yields from reactions conducted by this procedure were low, a syringe pump was used to add the acid to AgF_2 without

Table 1: Evaluation of the effects of reaction parameters.[a]

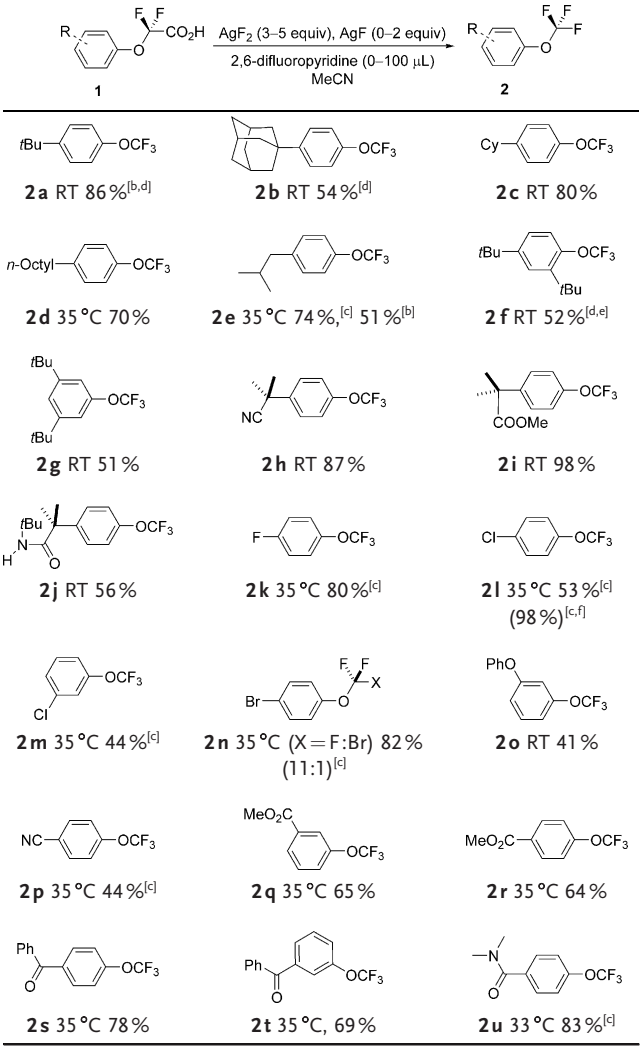


1a **2a** **3a**

Entry	Additives	Solvent	Yield of **2a** [%][b]	Yield of **3a** [%][b]
1	–	MeCN	49	2
2	CuF_2	MeCN	12	<5
3	NSFI	MeCN	<5	<5
4	Selectfluor	MeCN	12	3
5	AgF	MeCN	71	5
6[c]	AgF	MeCN	44	12
7[d]	AgF	MeCN	49	8
8	AgF	EtCN	<5	18
9	AgF	*t*BuCN	n.r.	n.r.
10[e]	AgF, **A1** (50 μL)	MeCN	58	5
11[e]	AgF, **A2** (50 μL)	MeCN	73	2
12[e]	AgF, **A3** (50 μL)	MeCN	13	<1
13[e]	AgF, **A4** (50 μL)	MeCN	83	<1
14[e]	AgF, **A4** (100 μL)	MeCN	95	<1
15[e,f]	**A4** (100 μL)	MeCN	96 (91)[g] (86)[h]	<1

[a] **1a** (0.1 mmol) in 1 mL MeCN was added to a mixture containing AgF_2 (3.0 equiv), F source (2.0 equiv), and additive in 1 mL MeCN at RT. The reaction was stirred for an additional 1 h. [b] Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard. [c] 0 °C. [d] 40 °C. [e] Used 5.0 equiv of AgF_2. [f] **1a** in MeCN was added by syringe pump over 1 h. [g] Yield of isolated product. [h] Yield of isolated product from reaction run on 1 mmol scale. **A1** = 2,6-dimethoxypyridine, **A2** = 2-fluoro-6-methylpyridine, **A3** = 2-(trifluoromethyl)pyridine, **A4** = 2,6-difluoropyridine.

Table 2: Substrate scope.



[a] **1** (0.3 mmol), AgF_2 (5.0 equiv), AgF (2.0 equiv), and 2,6-difluoropyridine (100 μL). Yield is that of isolated product. Please see the Supporting Information for details. [b] Yield of isolated product using 1 mmol substrate [c] Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard; 0.1 mmol substrate. [d] Syringe pump used, no AgF. [e] No **A4** additive. [f] Yield based on reacted substrate.

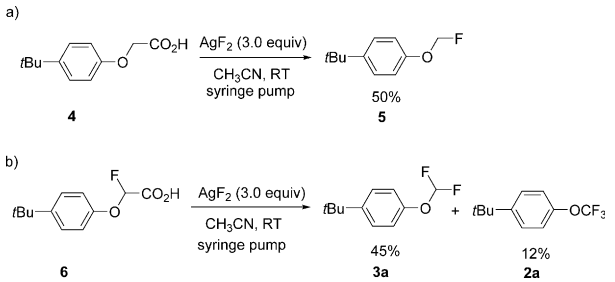
added AgF (**1b** and **1f**). For reaction of the most electron-rich **1f**, 2,6-difluoropyridine was omitted. The reactions of the carboxylic acids **2a**–**g** showed that subtle differences in the type and position of alkyl substituents had a measurable influence on the decarboxylative fluorination, although the process occurred in acceptable to good yields in each case. For example, the reactions of carboxylic acids containing tertiary (**1a** and **1b**) and secondary alkyl (**1c**) substituents in the *para* position proceeded smoothly at room temperature to afford **2a**, **2b**, and **2c** in 86, 54, and 80% yield, respectively. However, the reactions of substrates containing a primary alkyl group (**1d** and **1e**) were slower and required a slightly elevated temperature of 35°C to proceed within times comparable to those of **2a**–**c**, but they did form **2d** and **2e** in high 70 and 74% (51% isolated) yields, respectively. Reaction of the more-electron-rich acid containing *tert*-butyl groups in the 2- and 4-positions (**1f**) required reaction conditions in which a syringe pump was used to add the carboxylic acid slowly, and under these conditions, **2f** was isolated in 52% yield in the absence of 2,6-difluoropyridine. Finally, the carboxylic acid **1g**, containing *tert*-butyl groups at the two *meta* positions, also gave the trifluoromethyl ether product **2g** in a moderate 51% yield.

The functional-group compatibility is shown by reactions of the acids **2h**–**u** (Table 2). In general, the decarboxylative fluorination occurred in the presence of a wide range of electrophilic functional groups. The reaction of **1h** containing a cyanoalkyl group and **1i** containing a carbomethoxyalkyl group gave the corresponding trifluoromethyl ethers **2h** and **2i** in excellent yields of 87 and 98%, respectively, without any effect of the pendant functionality on the decarboxylative fluorination process. Likewise, the decarboxylative fluorination in the presence of the secondary amide in **1j** gave the trifluoromethyl ether **2j** in 56% yield. Aryl halides **1k**–**n** also underwent decarboxylative fluorination without interference of this functionality and gave the products **2k**–**n** in 44–82% yield. Reaction of the electronically related phenoxy-substituted acid **2o** gave the product in a modest 41% yield.

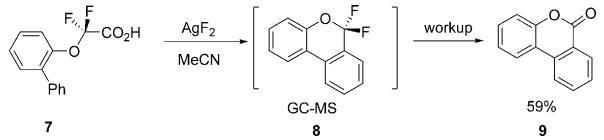
Even substrates containing substituents that are more electron-withdrawing reacted in high yield (**1p**–**u**; Table 2). For example, reactions of aryloxy difluoroacetates containing a cyano group (**1p**) in the *para* position gave the product in 44% yield, while those containing a carbomethoxy group in the *para* or *meta* position, a carbamoyl group in the *para*-position and a phenacyl group in the *para* position gave the difluoromethyl ether product in 64–78% yields. It is possible that the conjugated π system involving these groups would stabilize the radical intermediate, thus reducing the barrier for the oxidative decarboxylation step. However, for more-electron-rich substrates, such as one containing a *para*-methoxy group, a side-reaction predominated, thus giving the desired product in much lower yield.

The reaction conditions we developed for the formation of trifluoromethyl ethers were also suitable for the formation of aryl difluoromethyl ethers and monofluoromethyl ethers. Under the conditions used for reaction of the more-electron-rich difluoroacetate to form **2f** in Table 2, the monofluoromethyl ether **5** was obtained from the aryloxy carboxylic acid **4** in 50% yield upon isolation (Scheme 2a). Likewise, reaction of the α-fluoro aryloxy carboxylic acid **6** gave **3a** in 45% yield.[20]

To assess the potential intermediacy of alkyl radicals in this reaction, we synthesized the carboxylic acid **7**, which



Scheme 2. Fluorodecarboxylation for the synthesis of mono- and difluoromethyl ethers.



Scheme 3. Probe for an alkyl radical intermediate.

contains an *ortho*-phenyl substituent and would be expected to trap an alkyl radical to form a cyclized product (Scheme 3). The reaction of **7** under the conditions of Table 1 gave lactone **9** as the major product. Analysis of the crude reaction mixture by EI-HRMS prior to workup showed that the difluoroether intermediate **8** formed from the decarboxylative fluorination. This difluoroether was hydrolyzed to the ester upon aqueous workup under acidic or basic conditions. This result is consistent with fluorination by intermolecular reaction of an alkyl radical with AgF.

In conclusion, we have shown that AgF_2 induces fluorodecarboxylation of phenoxy-substituted difluoroacetates to form trifluoromethyl aryl ethers, as well as decarboxylation from a phenoxy-substituted monofluoroacetate and a non-fluorinated acetate to form di- and monofluoromethyl ethers, respectively. These reactions occur by exploiting the high oxidation potential of AgF_2 and weak coordination of 2,6-difluoropyridine to increase the solubility of AgF_2. These reaction conditions lead to decarboxylative fluorination to form a wide array of aryl trifluoromethyl ethers containing a range of functional groups. This process, along with our previous publications[18] on fluorinations with AgF_2, show that this long-known compound has unrealized synthetic potential. Further investigations toward fluorinations with AgF_2 are ongoing in our laboratories.

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[20] This reaction also gave **2a** in 12% yield. Subjecting **3a** to the reaction conditions did not form **2a**. It is possible that **6** was partially transformed into **1a**, which could generate the trifluoromethyl ether.

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