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A Series of Deoxyfluorination Reagents Featuring OCF_2 Functional Groups

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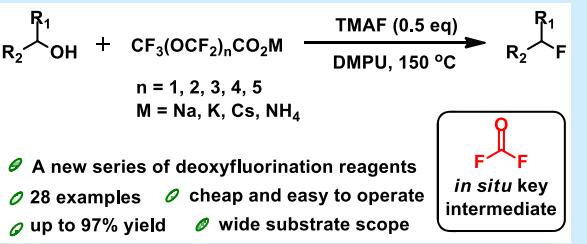
ABSTRACT: Research on perfluoroalkyl ether carboxylic acids (PFECAs) as alternatives for perfluoroalkyl substances continues with the goal of protecting the environment. However, very little is known about the utilization of decomposition products of PFECAs. We report herein a new series of deoxyfluorination reagents featuring OCF_2 functional groups derived from certain PFECAs. Alkyl fluorides were generated from various alcohols in ≤97% yield by these novel reagents. The mechanistic experiment verified *in situ* generation of carbonic difluoride (COF_2).



Because of the unique properties of per- and polyfluoroalkyl substances (PFASs) (e.g., hydrophobicity, lipophobicity, and thermal stability), they have been extensively used in a wide range of applications, such as the production of fluoropolymers, surface repellent coatings, metal plating, and firefighting foam.[1] The very strong C−F bond makes PFAS substances unable to easily degrade naturally, which in turn leads to global PFAS persistent pollution [e.g., perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS)].[2] Perfluoroalkyl ether carboxylic acids (PFECAs), upon insertion of oxygen atoms into perfluoroalkyl chains, have been developed as "environmentally friendly" alternatives to full-carbon-chain predecessor PFASs. However, toxicological studies have revealed an even higher bioaccumulation potential and toxicity of some PFECAs compared to those of PFOA, and PFECAs have been recognized as a new class of contaminants of emerging concern.[3] A few studies have investigated the destruction of these PFASs and PFECAs, including thermal and nonthermal destruction, advanced oxidation or reduction processes, sorption using activated carbon, and other treatment processes.[4] However, few studies have focused on the utilization of decomposition products of PFECAs.

PFECAs are basic starting materials for designing a variety of fluorinated surfactants and functional materials.[5] PFECAs featuring OCF_2 functional groups [structure of $CF_3(OCF_2)_nCOOH$] are generated mainly as byproducts in the manufacture of hexafluoropropene oxide (HFO) by oxidation of hexafluoropropene (HFP) with oxygen. The amounts of several key PFECA precursors with a general structure of $CF_3(OCF_2)_nCOF$ would reach 30−100 tons in the production of 1000 tons of HFO normally, depending on different oxidation conditions.[6] CF_3OCF_2COOH, $CF_3(OCF_2)_2COOH$ (PFO2HxA), and their salts are prominent among the derivatives of $CF_3(OCF_2)_nCOF$. The reclaiming of these PFECAs featuring OCF_2 functional groups will reduce the amount of fluorinated byproducts that are disposed and create new economic value.

Palmer reported the trifluoromethylation of aryl iodide using the trifluoromethyl anion (CF_3^-) liberated from thermal destruction of PFO2HxA salts in 1995.[7] Since then, there has been no progress in the utilization of decomposition products of PFECAs. We supposed that PFO2HxA salts might release carbonic difluoride (COF_2) when it generated trifluoromethyl anion (CF_3^-) through thermal degradation. As the most promising semiconductor equipment cleaning and etching material, COF_2 is an important fluorinated material.[8] However, its application in synthetic chemistry remains largely unexplored because special safety precautions must be taken during storage and transfer of COF_2 [e.g., high toxicity and low boiling point (−84 °C)]. We envisioned that we might utilize COF_2 generated *in situ* from the thermal degradation of PFO2HxA salts for organic transformations.

Alkyl fluorides are common components in the field of medicinal chemistry and drug design because of the unique properties of fluorine.[9] The high electronegativity of fluorine atoms can regulate the lipophilicity, binding affinity, and metabolic stability of pharmaceutical candidates. Therefore, various synthetic methods have been used for the synthesis of alkyl fluorides, such as nucleophilic, electrophilic, and radical fluorination.[10] Among them, deoxyfluorination has been considered as one of most effective methods for the introduction of fluorine atoms into organic molecules due to

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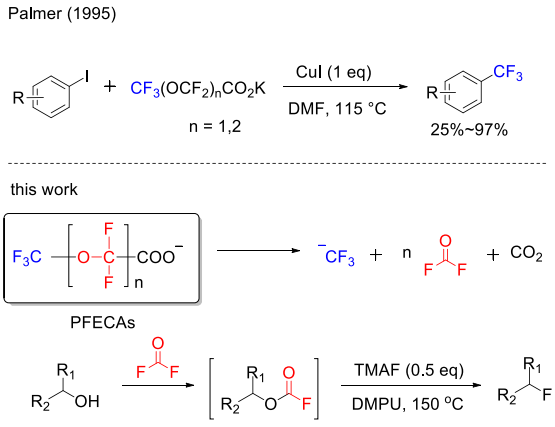
the abundance of both natural and synthetic alcohols.[11] As a consequence, several deoxyfluorination reagents have been developed in recent years, ensuring the efficient synthesis of alkyl fluorides from alcohols, such as DAST,[11a] Deoxo-Fluor,[11b] XtalFluor,[11c] Fluolead,[11d] Ishikawa's reagent,[11e] PhenoFluor,[11f] AlkylFluor,[11g] PBSF,[11h] PyFluor,[11i] CpFluors,[11j] and *N*-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor).[11k] However, most of these deoxyfluorination reagents have some limitations, such as complicated synthesis steps, high cost, or low stability, and there are also certain risks in large-scale industrial use for some of the deoxyfluorination reagents mentioned above. To overcome the high cost and poor stability of existing deoxyfluorination reagents, more efforts are needed in this field.

Herein, we report a new series of deoxyfluorination reagents [$CF_3(OCF_2)_nCO_2M$], which can generate COF_2 *in situ*. Olofson and co-workers reported that alcohols reacted with COF_2, which was produced *in situ* via triphosgene and KF, to produce alkyl fluoroformates. Most of the neat fluoroformates were distilled in pure form and subsequently cleaved to the alkyl fluorides by being heated at 120−125 °C using hexabutylguanidinium fluoride (HBGF) as the catalyst.[12] However, the fluoroformate needs to be purified before further fluorination reaction to obtain alkyl fluorides. We assume that the concise conversion of alkyl alcohols to alkyl fluorides can be achieved through a one-pot process via COF_2 generated *in situ* from the thermal degradation of $CF_3(OCF_2)_nCO_2M$ (Scheme 1). The conversion of alcohol to alkyl fluoride is

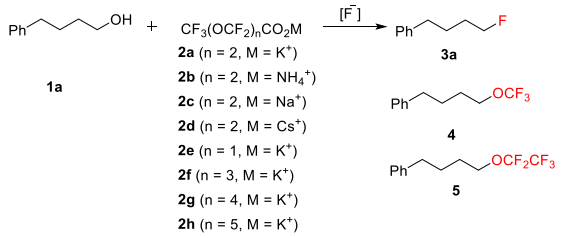
Scheme 1. Direct Deoxyfluorination by PFECAs Featuring OCF_2 Functional Groups



simple and efficient through the one-pot method via the fluoroformate intermediate. More importantly, the synthesis of alkyl fluorides was realized by using $CF_3(OCF_2)_nCO_2M$ compounds, which are generated mainly as byproducts in the manufacture of hexafluoropropene oxide (HFO).

Following this design, 4-phenyl-1-butanol (**1a**) was chosen as the model substrate to optimize the reaction conditions (see the Supporting Information). At 100 °C in *N*,*N*-dimethyltrimethyleneurea (DMPU) under a nitrogen atmosphere for 24 h, we obtained (4-fluorobutyl)benzene (**3a**), [4-(trifluoromethoxy)butyl]benzene (**4**), and [4-(perfluoroethoxy)butyl]benzene (**5**) in yields of 12%, 48%, and 3%, respectively (Table 1, entry 1). We investigated the temperature effect and found that the yield gradually increased as the temperature increased, reaching 70% at 150 °C (Table 1, entries 2−5). To our delight, we further screened various types

Table 1. Screening of the Reaction Conditions[a]



entry	ratio[b]	2	[F⁻]	*T* (°C)	yield of **3a** (%)[c]	yield of **4** (%)[c]	yield of **5** (%)[c]
1	1:1.5:0	**2a**	–	100	12	48	3
2	1:1.5:0	**2a**	–	120	32	25	4
3	1:1.5:0	**2a**	–	140	56	20	4
4	1:1.5:0	**2a**	–	150	70	9	1
5	1:1.5:0	**2a**	–	160	69	8	1
6[d]	1:1.5:1	**2a**	CsF	150	75	14	0
7[d]	1:1.5:1	**2a**	KF	150	45	32	4
8[d]	1:1.5:1	**2a**	KHF_2	150	43	31	5
9[d]	1:1.5:1	**2a**	TMAF	150	97	0	0
10[d]	1:1.5:0.5	**2a**	TMAF	150	95	0	0
11[d]	1:1.5:0.5	**2a**	TMAF	130	91	0	0
12[d]	1:1.5:0.5	**2b**	TMAF	150	46	5	1
13[d]	1:1.5:0.5	**2c**	TMAF	150	71	7	0
14[d]	1:1.5:0.5	**2d**	TMAF	150	88	4	1
15[d]	1:3:0.5	**2e**	TMAF	150	66	17	3
16[d]	1:1:0.5	**2f**	TMAF	150	81	3	0
17[d]	1:0.75:0.5	**2g**	TMAF	150	65	5	1
18[d]	1:0.6:0.5	**2h**	TMAF	150	60	3	2

[a]Reaction conditions: 4-phenylbutan-1-ol (**1a**, 0.2 mmol), $CF_3(OCF_2)_nCO_2M$ (as indicated), fluorides (as indicated), at the indicated reaction temperatures in DMPU solvent (2 mL) under a nitrogen atmosphere for 24 h. [b]**1a**:$CF_3(OCF_2)_nCO_2M$:[F^-] ratio. [c]The yields were determined by ^{19}F NMR analysis of crude reaction mixtures using benzotrifluoride as the internal standard. [d]Reaction time of 5 h.

of added fluoride salts and found that the addition of fluoride salt could increase the yield of the reaction and the use of tetramethylammonium fluoride (TMAF) was able to increase the yield to 95% (Table 1, entries 6−9). When the amount of fluoride salt was reduced to 0.5 equiv or the reaction temperature was reduced to 130 °C, the target product was obtained in a yield of >90% (Table 1, entries 10 and 11). Furthermore, we explored the effect of the cation species of the fluorination reagent on the reaction. We found that regardless of whether we used ammonium salt ($CF_3OCF_2OCF_2CO_2NH_4$), sodium salt ($CF_3OCF_2OCF_2CO_2Na$), or cesium salt ($CF_3OCF_2OCF_2CO_2Cs$), good yields were obtained (Table 1, entries 12−14). Finally, we examined the reactivity of other reagents. We found that the use of $CF_3OCF_2CO_2K$, $CF_3OCF_2OCF_2OCF_2CO_2K$, $CF_3OCF_2OCF_2OCF_2OCF_2CO_2K$, and $CF_3OCF_2OCF_2OCF_2OCF_2OCF_2CO_2K$ gave yields of 66%, 81%, 65%, and 60%, respectively (Table 1, entries 15−18, respectively).

We further focused on increasing the yield of deoxytrifluoromethoxylation product **4**. Unfortunately, **4** was obtained in an optimum yield of 58% with the generation of 3% of **3a**, 9% of **5**, 3% of **6**, and 12% of **7** (Scheme 2). These byproducts (**3a** and **5**−**7**) were similar in polarity to the trifluoromethoxylated product (**4**), and we failed to obtain pure **4** because of the difficulty of separation.

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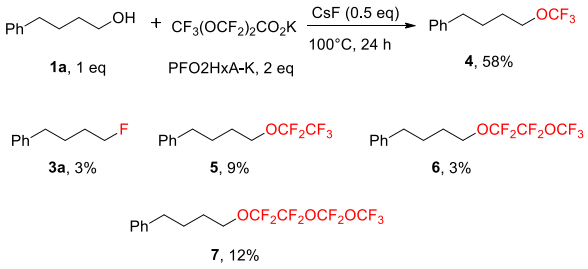
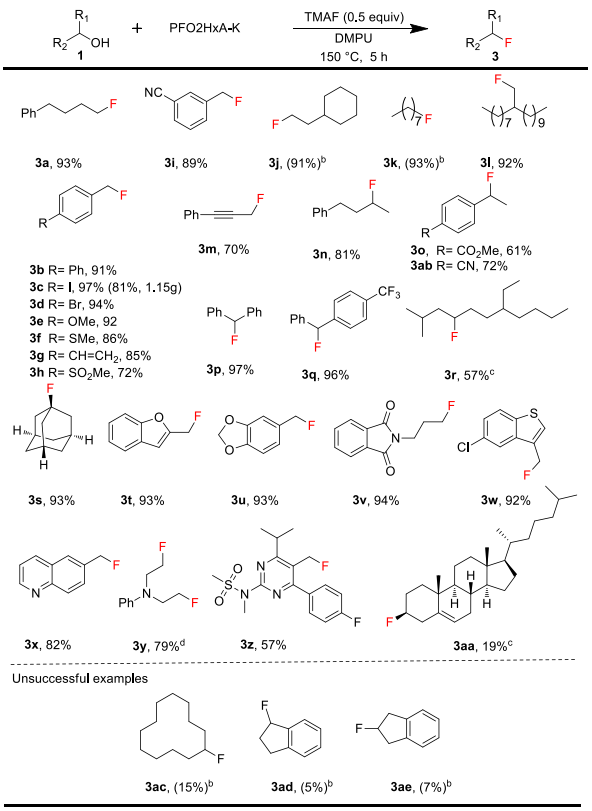
Scheme 2. An Optimum Example of Deoxytrifluoromethoxylation Reaction via PFO2HxA-K



Having established optimized reaction conditions (Table 1, entry 10), we then explored the scope of the deoxyfluorination of alcohols (Scheme 3). We have found that the reaction could

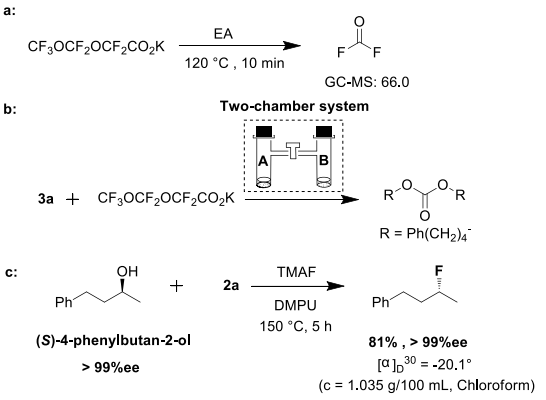
Scheme 3. Substrate Scope for Deoxyfluorination of Alcohols[a]



[a]Reaction conditions: alkyl alcohol (0.3 mmol), PFO2HXA-K (0.45 mol), TMAF (0.15 mol), at 150 °C in DMPU (3 mL) under a nitrogen atmosphere for 5 h. [b]The yields were determined by ^{19}F NMR analysis of crude reaction mixtures using benzotrifluoride as the internal standard. [c]Reaction conditions: alkyl alcohol (0.3 mmol), PFO2HXA-K (0.45 mol), TMAF (0.3 mol), at 150 °C in DMPU (3 mL) under a nitrogen atmosphere for 5 h. [d]Reaction conditions: alkyl alcohol (0.3 mmol), PFO2HXA-K (0.9 mol), TMAF (0.3 mol), at 150 °C in DMPU (3 mL) under a nitrogen atmosphere for 5 h.

produce the target product in moderate to excellent yields for diverse alcohols. First, we investigated primary alcohols. The yields were in the range of 70−97%. We found the reactions were tolerant of a series of functional groups, including cyano, ester, carbonyl, methoxy, methylthio, sulfone, iodine, bromo, olefin, and alkyne, under the reaction conditions (**3a**−**3m**). Moreover, the deoxyfluorination reaction of 4-iodobenzyl alcohol (**3c**) on a gram scale was carried out to study the possible scalability of the reactions. It was found that the reaction proceeded smoothly and yielded the desired product (1.15 g) in 81% yield. Second, we investigated some secondary alcohol substrates and found that the target products (**3n**−**3r** and **3ab**) were obtained in moderate to good yields (57−97%). Third, for tertiary alcohols, we found that 1-fluoroadamantane was obtained in a yield of 93% from 1-adamantanol. However, for general tertiary alcohols, the reaction gave rise to the target products in only low yields (see the Supporting Information). This may be due to the S_N2 mechanism of the reaction (see Scheme 4c). This may also be the reason for the low yield of

Scheme 4. Control Experiments and Mechanistic Studies



cyclic secondary alcohols (**3ac**−**3ae**). Considering the applications of heterocycles in drug molecules, we explored alcohols bearing heterocycles. We found that the target product could be obtained in moderate to excellent yields (79−94%) in most heterocyclic substrates (**3t**−**3x**). Also, we examined the substrate containing two hydroxyl groups, which also gave the difluoro target product (**3y**) in 79% yield. Finally, we selected rosuvastatin sodium drug molecular intermediates (**3z**) and steroid alcohols (**3aa**) as reaction substrates and obtained the target products in 57% and 19% yields, respectively. Note that products **3aa** were obtained with retention of the configuration because the reaction may include special carbocation intermediates involving the participation of homoallylic olefin so that the inversion did not occur.[11j,13]

To gain more insight into the reaction mechanism, several control experiments were conducted (Scheme 4). First, we investigated the generation of COF_2 from the decomposition of PFO2HxA-K. COF_2 could be produced by simply heating PFO2HxA-K in ethyl acetate (EA), as confirmed by using gas chromatography−mass spectrometry. Through the two-chamber reaction, COF_2 entered the B chamber from the A chamber through the pipeline, thereby yielding bis(4-phenylbutyl) carbonate (70%) by the reaction of one molecule of COF_2 with two molecules of the alcohol. Both experiments demonstrated the production of COF_2. With regard to whether the substitution reaction undergoes S_N1 or S_N2 reaction, we selected (*S*)-4-phenyl-2-butanol as the reaction substrate and carried out the reaction under the optimal reaction conditions; (*R*)-(3-fluorobutyl)benzene (>99% ee) was obtained in an isolated yield of 81%, and the configuration was completely reversed, indicating that the reaction was more likely to undergo the S_N2 reaction process.[11i]

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In conclusion, we have described deoxyfluorination of alcohols with a new series of deoxyfluorination reagents $[CF_3(OCF_2)_nCO_2M]$, which can generate COF_2 *in situ*. This method enables the transformation of various primary and secondary alcohols into the corresponding fluorides and tolerates a wide range of functional groups. The mechanistic experiment verifies the production of carbonic difluoride (COF_2), and the reaction may undergo the S_N2 process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03238.

Experimental procedures, data for experimental design, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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