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Electrochemical Flash Fluorination and Radiofluorination

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Abstract

A new method for rapid late-stage fluorination using the cation pool technique is presented. Fluorination and no-carrier-added radiofluorination of methyl (phenylthio) acetate, methyl 2-(methylthio) acetate, and methyl 2-(ethylthio) acetate were performed. The carbocations formed through electrochemical oxidation were stabilized by using a divided electrochemical cell and 2,2,2-trifluoroethanol (TFE) as the solvent at -20°C . At the end of electrolysis, either stable-isotope [^{19}F]fluoride or no-carrier-added radioactive [^{18}F]fluoride was added to the reaction mixture to form the fluorinated or radiofluorinated product.

Keywords

cation pool; electrochemical organic synthesis; electrochemical oxidation; fluorination; radiofluorination

Fluorinated organic compounds have distinguishing physical, biological and chemical properties with a wide range of applications in fields such as agrochemicals, pharmaceuticals and materials science.^[1–3] Recently, there has been growing interest in the chemistry and properties of fluorinated organic compounds.^[3–5] Fluorine gas and anhydrous HF have been broadly used for fluorination of organic compounds.^[6–8] However, these chemicals are costly, highly reactive, corrosive, hazardous, and difficult to handle.

There is a consensus in the community that given the wide-ranging applications of fluorine in design of bioactive molecules and molecular imaging through positron emission tomography (PET), there is still a strong demand for further development of new synthetic methodologies to expand the chemist's toolbox for easier access to a broader scope of

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Conflict of Interest

The authors declare no conflict of interest.

fluorinated and radiochemical compounds.^[9] There have been significant recent developments in the area of nucleophilic fluorination, a more accessible form of fluorination, and their application to radiochemistry with [¹⁸F]fluoride, such as synthesis of aryl fluorides directly from the corresponding phenols,^[10] hypervalent iodine reagents used as fluorine sources in fluorocyclization reactions,^[11,12] radiofluorination of diaryliodonium salts and Cu-catalyzed mesityl-aryl-iodonium precursors,^[13] metal-catalyzed aryl fluoride bond formation,^[14] and recent reviews on these advances and their limitations.^[15]

Despite the development of modern fluorination techniques, many challenges still exist in terms of limited substrate scope, lack of functional group tolerance, difficulty in synthesizing the precursors and their stability, and the need for strict control of synthesis conditions. No one technique can address all the challenges for site specific fluorination. The electrochemical approach to fluorination of stabilized cations presents a unique method for direct and very rapid fluorination in one step under mild conditions. The method described here can target moieties such as thioethers not amenable to late-stage fluorination with existing methodologies, allowing their radiofluorination for PET tracer development.

Electrochemistry is gaining renewed prominence as a versatile tool in organic synthesis.^[16,17] Electrochemical fluorination of organic compounds can be a powerful alternative technique for direct fluorination. Electrochemical oxidation can create an electron-poor carbon, potentially without the need for chemical modification, preparing the organic molecules for nucleophilic fluorination.^[18,19] Fluorine atoms can be added to organic compounds in one step under mild conditions using electrochemistry, even for electron rich moieties such as aromatic and heteroaromatic rings, without the need to have leaving groups.^[20,21]

Traditionally, the oxidative formation of a carbocation intermediate in electroorganic synthesis has been performed in the presence of an excess of nucleophile due to the instability of the carbocations. The presence of reactive and low oxidation potential nucleophiles and products in the anodic chamber during electrolysis can limit reaction yields and scope. To overcome this problem Yoshida and co-workers developed the cation pool method, with which they could stabilize the carbocations formed during the electrochemical oxidation of carbamates by performing the electrochemical oxidation at low temperatures (−72 °C) followed by addition of nucleophiles such as allylsilanes post electrolysis.^[22] Subsequently, the same group reported thiofluorination of alkenes and alkynes using low-temperature anodic oxidation of ArSSAr in Bu₄NBF₄/CH₂Cl₂.^[23] In their process, the counter anion of the supporting electrolyte (BF₄[−]), which was present during the electrolysis was also the source of fluoride.

Here, for the first time, the electrochemical fluorination and radiofluorination of organic molecules using the cation pool technique is reported, where the fluoride is added post electrolysis. This approach enables the use of the cation pool method for the widely useful application of rapid and late-stage fluorination and radiochemistry. The cation pool method has tremendous potential especially for radiofluorination experiments. The excess concentration of reactive cations can provide an efficient reaction mechanism for late-stage fluorination under low fluoride concentrations encountered during radiofluorination.^[24]

Furthermore, radiochemical yield, which is reduced by decay of the radioisotope, can benefit from a rapid late-stage fluorination reaction. The cation pool can be prepared prior to cyclotron production of [^{18}F]fluoride isotope, thereby, providing a truly late-stage fluorination reaction, maximizing radiochemical yield by minimizing decay through a flash reaction of the previously prepared cations with [^{18}F]fluoride.

In this study, a divided electrochemical cell was used for electrolysis. The anodic and cathodic chambers were separated by a Nafion membrane. Methyl (phenylthio) acetate (12 mM) was used as substrate and 2,2,2-trifluoroethanol (TFE) as solvent with different supporting electrolytes in the anodic chamber. TFE, tetrabutylammonium perchlorate (TBAP) and triflic acid were used in the cathodic chamber. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) has also recently been reported as a solvent for electroorganic synthesis with a stabilizing effect on carbocation intermediates.^[29–32] However, yields were negligible due to instability of fluorinated products reported here in HFIP. Previous reports on electrochemical fluorination of Methyl (phenylthio) acetate guided our choice for the substrate.^[25,26] Traditional fluorination of sulfoxides have been based on fluoro-Pummerer rearrangement with DAST, electrophilic fluorination of thioethers and the combinations of chemical oxidants with nucleophilic fluorinating reagents.^[27] Previous electrochemical fluorination of thioethers were performed with excess amounts of HF salts or TBAF present in the cell during electrolysis, resulting in low fluoride conversion yield and preventing no-carrier-added fluorination.^[20,26,28]

Here, electrochemical oxidation was performed for 60 min at a constant potential of 1.6 V vs Ag wire quasi-reference electrode followed by addition of a fluoride nucleophile to the anodic chamber at the end of electrochemical oxidation. The mixture was stirred and allowed to react for 30 min while the temperature was rising to room temperature. With 168 mM of CsF, KF, Et₃N_x3HF and tetrabutylammonium fluoride (TBAF) used as fluoride (nucleophile) sources, respective yields of 4.5 %, 1.4 %, 4 % and 4.5 % of methyl 2-fluoro-2-(phenylthio) acetate were obtained. The yields were quantified using gas chromatography mass spectrometry (GC-MS). Scheme 1 shows the schematic of the reaction and representative GC-MS chromatograms can be found in the supporting information.

Electrolysis was repeated with TBAF at different temperatures of 21 °C, 0 °C, –20 °C and –40 °C and chemical yields of 2.2 %, 4 %, 6 % and 3 % were obtained respectively. The drop in the yield from –20 °C to –40 °C is due to the low oxidation current resulting in the slowing of precursor oxidation. 68 % of the precursor was consumed when oxidation was performed at –20 °C, while only 12 % of the precursor was consumed at –40 °C. –20 °C was chosen as the optimum temperature for further optimization. The effect of changes in supporting electrolyte on the chemical yield is shown in Table 1. It can be seen from Table 1 that TBAP alone results in negligible product formation, while addition of 14.2 mM of triflic acid increases the yield to 6 %. The highest yield of 12.5 % was obtained where only 142 mM of triflic acid was used without addition of salts as supporting electrolyte.

Further optimization was performed using only triflic acid as supporting electrolyte and the effect of triflic acid concentration on the yield was examined. Yields of 3.6 %, 12.5 % and

0 % was obtained when 71 mM, 142 mM and 284 mM of triflic acid were used, respectively. The effect of precursor concentration on the product yield is presented in Table 2. Precursor concentration changes from 0.5 mM to 24 mM resulted in only a moderate change in the yield.

Due to the diminishing [^{18}F]TBAF concentration during no-carrier-added radiochemistry experiments, the effect of lowering of TBAF concentration and ratio of TBAF to triflic acid concentration were also investigated and the results are shown in table 3. It was observed that by lowering the TBAF concentration the product yield decreased to 1.5 % when 21 mM of TBAF was used. It was further observed that the ratio of TBAF to triflic acid concentration plays a crucial role with optimum product yield obtained when this ratio is maintained at 1.18. This may be due to the instability of product at low pH where TBAF addition can act as a base to increase the pH of the solution.

Using the optimized parameters, radiofluorination of **1** was performed with the cation pool method with 142 mM of triflic acid and 24 mM of **1** in TFE in the anodic chamber. Radiochemical fluorination efficiencies (RCFEs) were calculated based on conversion of [^{18}F]fluoride to product **2**. Initially [^{18}F]fluoride in the form of [^{18}F]TBAF was added to the anodic chamber after 60 min of electrolysis, however no radio-fluorinated product was observed. Due to the diminishing TBAF concentrations in the radiochemistry experiment, addition of a non-nucleophilic base was necessary to increase the pH to 3, at which point the product was observed to be stable. To address this challenge, 5 mCi of [^{18}F]fluoride was mixed with 300 mM of 2,6-di-tert-butyl-4-methylpyridine and the mixture was added to the anodic chamber after electrolysis resulting in RCFE of 5.7 ± 1.0 % ($n=3$) and molar activity of 1.13 ± 0.2 Ci/ μM ($n=3$). Similar to cold experiments with [^{19}F]-TBAF, samples for characterization were taken 30 min after [^{18}F]fluoride addition. Notably, RCFE of 4.8 ± 0.6 % ($n=3$) was obtained after just 5 min post [^{18}F]fluoride addition. Successful radiofluorination of methyl 2-(methylthio) acetate and methyl 2-(ethylthio) acetate were performed using cation pool technique with same condition as above, the RCFE of 20.6 ± 2.0 % and 18.2 ± 1.5 % were obtained, respectively (Scheme 2).

In Summary, this report demonstrates a new tool for rapid late-stage fluorination and radiofluorination using the cation pool method. This is made possible through generation and pooling of stable cations under low temperature using TFE as solvent, and the subsequent fluorination reaction of carbocations with fluoride under non-oxidative conditions. Cation pool fluorination prevents further oxidation of the fluorinated product during the electrolysis and rapid late-stage radiofluorination can minimize the losses of [^{18}F]fluoride due to radioactive decay. More in-depth studies of scope and the use of microfluidic platforms are currently in progress to increase yields and introduce automation. Flash fluorination and radiofluorination based on the cation pool method can be used to produce PET radiotracers and fluorinated pharmaceuticals, potentially expanding the library of fluorinated bioactive molecules available for medicinal chemistry and molecular imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Schematic of the cation pool method for fluorination of methyl 2-(phenylthiol) acetate.

Scheme 2.
Schematic of the radiofluorination reactions.

Table 1.

Effect of supporting electrolyte on the chemical yield of 2. Electrolysis was carried out using 12 mM of 1 in TFE for 60 min at 1.6 V vs Ag wire at -20°C followed by addition of 168 mM of TBAF post electrolysis.

Electrolyte (TFE based)	Yield [%]
50 mM NBu_4ClO_4 (TBAP)	0
300 mM NBu_4ClO_4 (TBAP)	0
300 mM NBu_4ClO_4 + 14.2 mM triflic acid	6.0
300 mM NBu_4BF_4 + 14.2 mM triflic acid	1.3
300 mM p-toluenesulfonic acid + 14.2 mM triflic acid	2.0
142 mM triflic acid	12.5

Table 2.

Effect of precursor 1 concentration on the chemical yield of product 2. Electrolysis was carried out using precursor 1, and 142 mM of triflic acid in TFE for 60 min at 1.6 V vs Ag wire at -20°C . 168 mM TBAF was added at the of electrochemical oxidation.

Precursor concentration [mM]	Yield [%] ($n = 3$)
0.5	8.5 ± 0.9
1	9.6 ± 1.0
2	11.5 ± 1.2
4	10.6 ± 1.1
6	12.7 ± 1.4
12	11.2 ± 1.3
24	9.2 ± 1.0

Table 3.

Effect of TBAF concentration and TBAF concentration/triflic acid concentration ratio on the chemical yield of product 2. Electrolysis was carried out using 12 mM of 1 and triflic acid in TFE for 60 min at 1.6 V vs Ag wire at -20°C . The values marked with an asterisk in the second column reflect experiments where triflic acid concentration was kept constant at 142 mM.

TBAF concentration [mM]	TBAF concentration/triflic acid concentration	Yield [%]
21	1.18	1.6
	0.15*	0
42	1.18	3.8
	0.30*	0
84	1.18	4.0
	0.60*	0
168	1.18*	12.5
	0.60	0
	2.36	3.6