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Organic Synthesis

Decarboxylative Fluorination of 2-Pyridylacetates

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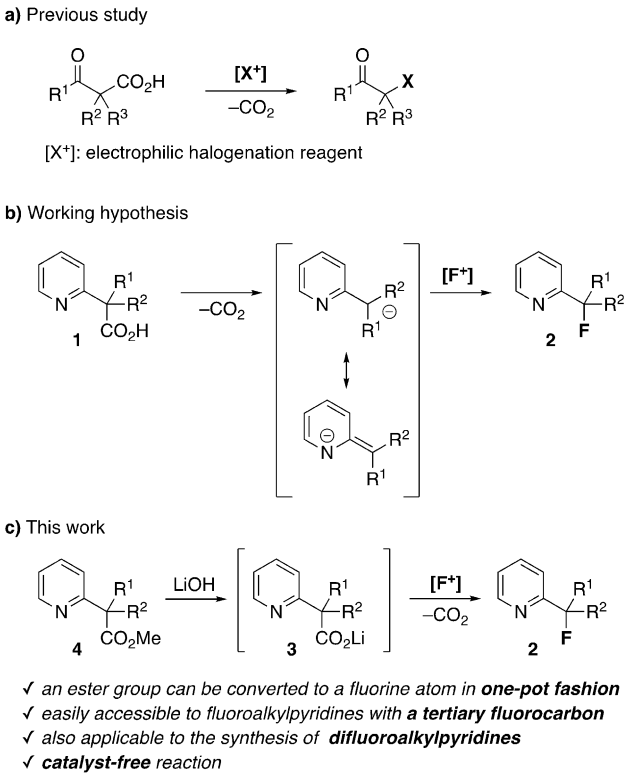
Abstract: Syntheses of substituted pyridines and fluorinated compounds, which are often pharmaceutical targets, are important objectives in organic chemistry. Herein, we found that decarboxylative fluorination of lithium 2-pyridylacetates occur under catalyst-free conditions. The phenomenon can be applied to one-pot transformation of substituted methyl 2-pyridylacetate to 2-(fluoroalkyl)pyridine by decarboxylative fluorination of the intermediate lithium 2-pyridylacetate. This method was also applied to the syntheses of 2-(difluoroalkyl)pyridines.

The pyridine backbone is an important substructure found in numerous medicinally relevant molecules.[1] Therefore, the development of efficient methods for preparing substituted pyridines is an important requirement in medicinal chemistry. Hence, functionalizations of a carbon adjacent to the pyridine ring have been studied intensively in recent years.[2,3] Since the introduction of one or more fluorine atom into biologically active compounds often improves their pharmacokinetics and/or biological activities, the regio- and stereoselective fluorinations of organic molecules are also important synthetic operations in drug discovery.[4] Therefore, development of methods for fluorination on pyridylic carbon atoms have recently attracted much attention. As noteworthy examples, Britton's and Humbeck's research groups achieved monofluorination of heterobenzylic C–H bonds in the absence of transition-metal catalysts.[3] Meanwhile, decarboxylative halogenation of aliphatic carboxylic acids is a useful method for the synthesis of various alkyl halides because carboxylic acid is a fundamental and easily available functional group.[5] Recently, excellent methods for catalytic decarboxylative fluorination of aliphatic carboxylic acids have been reported with a silver catalyst[6a] or Ru- or Ir-based photoredox catalysts.[6b,c] However, these methods require the use of expensive transition-metal catalysts. On the other hand, β-oxocarboxylic acids are known to easily undergo decarboxylation without any transition-metal catalyst.[7] Using this property, several decarboxylative functionalizations, including fluorination reactions (Scheme 1 a),[8] have been intensively studied.[9] Very recently, our research group also reported the highly enantioselective decarboxylative chlorination of tertiary β-ketocarboxylic acids using a chiral primary amine catalyst and decarboxylative fluorination under catalyst-free conditions.[8d,10] This easy release of carbon dioxide from β-oxocarboxylic acids can be attributed to resonance stabilization of the resulting enolate. Considering this background, we envisaged 2-pyridylacetic acids **1** would produce a picolyl anion by decarboxylation under mild conditions in a manner similar to β-oxocarboxylic acids; the resulting carbanion is stabilized by a resonance effect in which the negative charge is delocalized on a nitrogen atom, and should react with an electrophilic fluorinating reagent to afford the corresponding 2-(fluoroalkyl)-pyridine **2** (Scheme 1 b). Indeed, some old research in the literature reported that 2-pyridylacetic acids undergo thermal decarboxylation to produce protonated products.[7e,11] However, to our surprise, there are very few published studies on its application to functionalization reactions,[12] except for examples with transition-metal catalysts.[2a,13] Based on the above-mentioned hypothesis (Scheme 1 b), we herein found that decar-



Scheme 1. Reaction design: the decarboxylative fluorination of 2-pyridylacetic acids.

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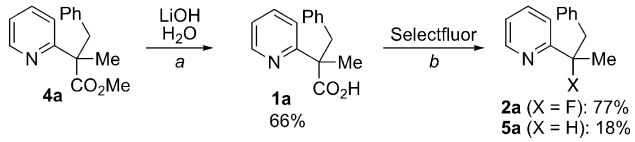
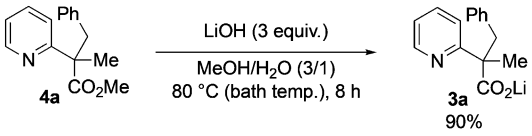
boxylative fluorination of lithium 2-pyridylacetates **3** yields 2-(fluoroalkyl)pyridines **2**. Furthermore, methyl esters **4** of 2-pyridylacetic acids can be converted to **2** in a one-pot manner by the decarboxylative fluorination of lithium salts **3** (Scheme 1 c). This method enables us to convert a methyl ester group into a fluoride group in a one-pot manner without using expensive transition-metal catalysts. Various starting compounds, methyl 2-pyridylacetates **4** with two alkyl substituents (R^1 and R^2), can be prepared by simple S_N2 alkylation of nonsubstituted 2-pyridylacetate; which is also an advantage of the method.

We began by synthesizing the substituted 2-pyridylacetic acid **1a** by alkaline hydrolysis of the corresponding methyl ester **4a** and subsequent neutralization (Scheme 2). Although **1a** was fluorinated to yield **2a**, involving decarboxylation by treatment with Selectfluor, even in the absence of a base,[14] **1a** was difficult to handle because it slowly decomposed spontaneously, even at room temperature, to generate the protonated product **5a** (Scheme 2). During the above-mentioned investigation, we noticed that the lithium salt of **1a** is more stable toward decarboxylative protonation than **1a** itself.[15]



Scheme 2. Synthesis and decarboxylative fluorination of **1a**. a) LiOH (5 equiv), MeOH/H_2O (3:1), 80 °C (bath temp.), 8 h, followed by neutralization with HCl; b) Selectfluor (3 equiv), DMF, rt, 12 h.

Hence, we examined the reactivity of the lithium salt **3a** towards decarboxylative fluorination. Lithium salt **3a** was obtained in 90% yield by filtration of the precipitate following alkaline hydrolysis of **4a** (Scheme 3). Treatment of **3a** with Selectfluor in DMF successfully afforded the desired fluoride **2a** in 90% yield without generation of the protonated product **5a** (Table 1, entry 1). When *N*-fluorobenzenesulfonimide (NFSI) was used as the fluorinating reagent, a slightly lower yield of **4a** was obtained (entry 2). Interestingly, decarboxylation did not occur at room temperature in the absence of any electrophilic fluorinating reagent (entry 3), whereas it occurred by heating to 100 °C (entry 4). These results indicate that the fluorinating reagent accelerated the decarboxylation of **3a** in some way. Solvent screening revealed DMF as the optimum solvent (entries 1, 5–8).



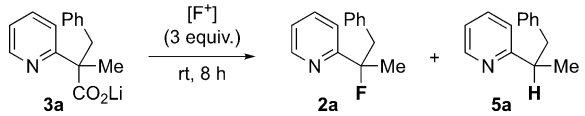
Scheme 3. Synthesis of lithium carboxylate **3a**.

We also envisaged that hydrolysis of methyl ester **4** and subsequent decarboxylative fluorination could be performed in a one-pot fashion. To that end, **4a** was treated with lithium hydroxide in MeOH/H_2O. Following hydrolysis, the solvent was evaporated under reduced pressure. DMF and Selectfluor were then added and the mixture was stirred at room temperature. The reaction successfully afforded the desired product **2a** in 85% yield over two steps (Table 2). Thus, we examined the substrate scope of the sequential hydrolyses and decarboxylative fluorinations of methyl 2-pyridylacetates **4**. As summarized in Table 2, several methyl 2-pyridylacetates **4** were converted to the corresponding fluorides **2** in good yields using the one-pot procedure. The reaction tolerated several functional groups such as alkenes, nitro groups, cyano groups, and alkyl ethers. The reaction with quinoline and isoquinoline derivatives also yielded the corresponding fluorides **2m** and **2n**, respectively.

Encouraged by the successful decarboxylative fluorinations of α,α-disubstituted 2-pyridylacetates, we examined the reactions of α-monosubstituted 2-pyridylacetates; **4o** was reacted using a procedure similar to that shown in Table 2. The difluorinated product **6o** was obtained in 64% yield, along with the monofluorinated product **2o** in 22% yield (Table 3). The reaction is supposed to proceed by base-mediated α-fluorination of lithium 2-pyridylacetate and subsequent decarboxylative fluorination. The reactions of several α-monosubstituted 2-pyridylacetates **4p–t** afforded the corresponding 2-(difluoroalkyl)pyridines **6p–t** in one-pot processes, whereas the use of **4u–w** afforded the monofluorinated products **2u–w** in good yields.

Since electrophilic fluorinating reagents accelerate the decarboxylation of **3a**, as indicated by the results shown in Table 1, entries 1–3, we proposed the reaction mechanism shown in Scheme 4. An electrophilic fluorine atom on Selectfluor approaches the nitrogen atom on a pyridine ring to promote decarboxylation by forming *N*-fluoro-1,2-dihydropyridine intermediate **I**, which would immediately isomerize to afford 2-(fluoroalkyl)pyridines **2**. Easy decarboxylation from 2-pyridylacetates **4** can be explained by the resonance stabilization of

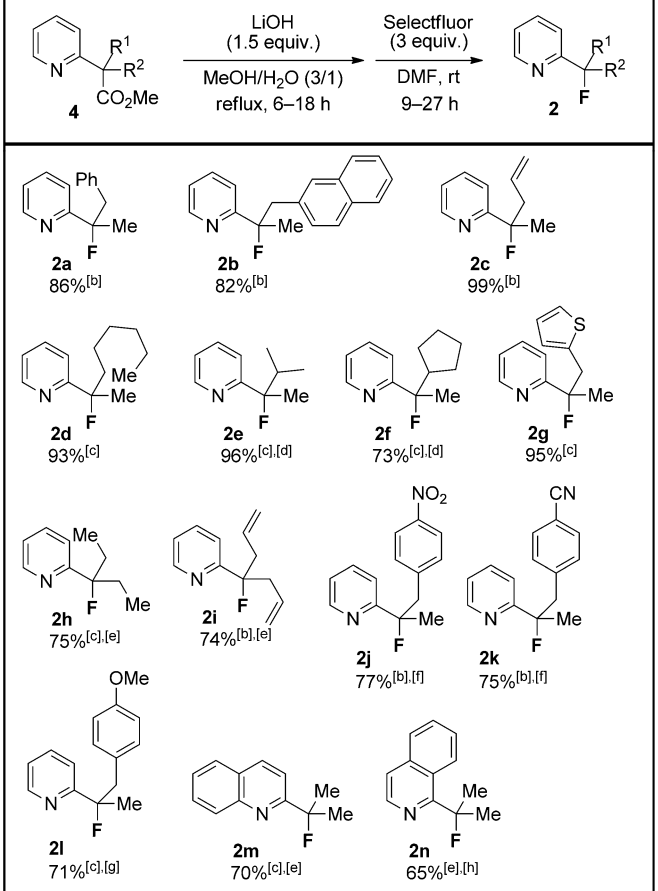
Table 1. Optimization of the reaction conditions.[a]



Entry	[F$^+$]	Solvent	Yield of **2a** [%][b]	Yield of **5a** [%][b]
1	Selectfluor	DMF	90	0
2	NFSI	DMF	71	6
3[c]	–	DMF	0	0
4[c,d]	–	DMF	0	68
5	Selectfluor	toluene	0	18
6	Selectfluor	MeCN	16	65
7	Selectfluor	THF	17	0
8	Selectfluor	MeOH	30	55

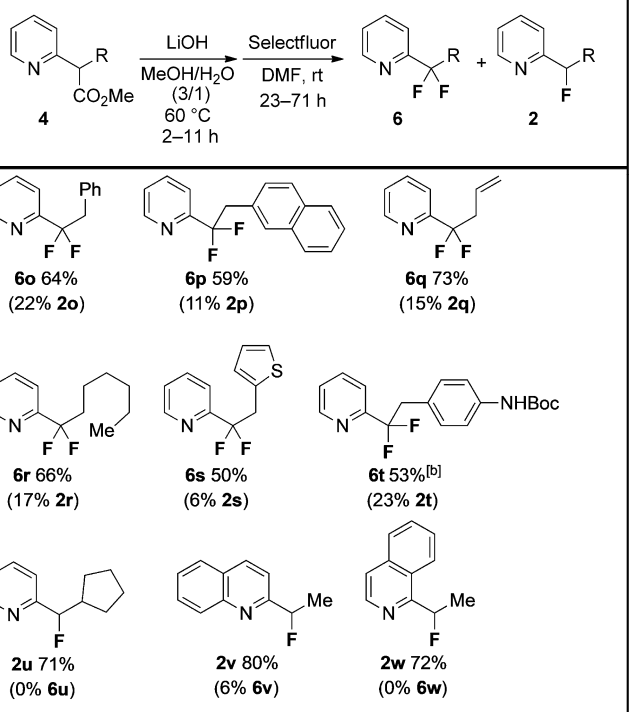
[a] Reactions were carried out with **3a** and 3 equiv of fluorinating reagent at room temperature for 8 h, unless otherwise noted. [b] Determined after silica gel column purification. [c] No fluorinating reagent was employed. [d] Reaction was carried out at 100 °C.

Table 2. Substrate scope.[a]

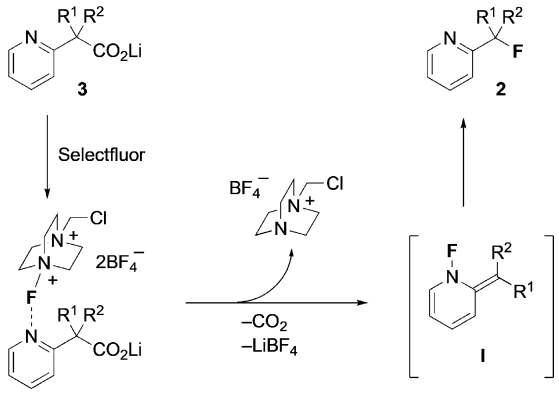


[a] Hydrolysis of **4** was carried out with 1.5 equiv of LiOH in MeOH/H_2O (3/1) under reflux conditions (bath temp. 110 °C), and 3.0 equiv of Selectfluor was used in the fluorination, unless otherwise noted. Yield was determined after silica-gel column purification. [b] Hydrolysis of **4** was carried out at 80 °C (bath temp.). [c] Hydrolysis of **4** was carried out for 23–32 h. [d] LiOH (5 equiv) and Selectfluor (7 equiv) were used. [e] LiOH (3 equiv) and Selectfluor (5 equiv) were used. [f] Fluorination was carried out for 96 h (**2j**) or 40 h (**2k**). [g] Hydrolysis of **4** was carried out at 80 °C (bath temp.), and 3.6 equiv of Selectfluor was used in the fluorination. [h] Hydrolysis of **4** was carried out for 90 h.

Table 3. Reaction of α-monosubstituted 2-pyridylacetates.[a]



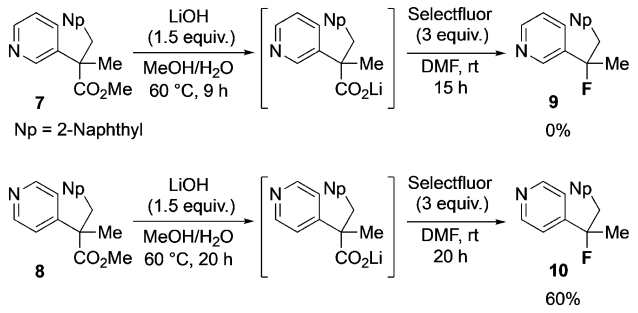
[a] Hydrolysis of **4** was carried out with 1.5 equiv of LiOH in MeOH/H_2O (3/1) at 60 °C, and 5 equiv of Selectfluor was used in the fluorination. Yield was determined after silica gel column purification. [b] Hydrolysis of **4** was carried out with 2.0 equiv of LiOH at 80 °C (bath temp.) for 45 h.



Scheme 4. Proposed reaction pathway.

the resulting carbanion by the delocalization of the negative charge on a nitrogen atom (Scheme 1 b). To support this hypothesis, we examined the reaction with 3- and 4-pyridylacetates as the substrates (Scheme 5). The 3-pyridylacetate **7** did not afford the fluorinated product at all under the same reaction conditions, despite complete hydrolysis of the methyl ester, whereas the 4-pyridylacetate **8** afforded the corresponding fluorinated product **10** in 60% yield. These results imply a correlation between the reactivity of pyridylacetates towards decarboxylation and stability of the resulting carbanion; the negative charge in a carbanion generated by decarboxylation of 3-pyridylacetates can not be delocalized on a nitrogen atom in contrast to the cases with 2- and 4-pyridylacetates.

In conclusion, we found that the decarboxylative fluorination of lithium 2-pyridylacetates, prepared by the alkaline hydrolyses of the corresponding methyl esters, proceeds smoothly to produce 2-(fluoroalkyl)pyridines in good yields. Alkaline hydrolysis and subsequent decarboxylative fluorination can be performed in a one-pot manner; as a result, the one-pot transformation of an ester group to a fluorine atom was achieved. The method is also applicable to the synthesis of 2-(difluoroalkyl)-pyridines. The resulting fluorides would be useful for the preparation of medicinally relevant molecules that are important pharmaceutical targets. We are currently investigating the application of the method to other functionalizations, including C–C bond-forming reactions.



Scheme 5. Reaction of 3- and 4-pyridylacetates.

Experimental Section

General procedure for decarboxylative fluorination of 2-pyridylacetates 4 (Table 2)

Lithium hydroxide was added to a solution of methyl 2-pyridylacetate **4** in MeOH/H_2O (3:1, 0.2 M), and the mixture was stirred until the reaction completed. After all solvents were evaporated under reduced pressure, Selectfluor and DMF were added to the mixture, and the mixture was stirred until the reaction completed. The reaction mixture was directly subjected to flash column chromatography to give the corresponding fluorinated product **2**. Detailed experimental procedures, characterization data, and traces of NMR spectra are available in the Supporting Information

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Conflict of interest

The authors declare no conflict of interest.

Keywords: decarboxylation · difluoromethyl group · fluorination · methyl ester · pyridine

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Substituted pyridines: Decarboxylative fluorination of lithium 2-pyridylacetates occur under catalyst-free conditions. The phenomenon was applied to one-pot transformation of a substituted methyl 2-pyridylacetate into a 2-(fluoroalkyl)pyridine. The method was also applied to the syntheses of 2-(difluoroalkyl)pyridines (see scheme).

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