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Selective Fluorination of 4-Substituted 2-Aminopyridines and Pyridin-2(1*H*)-ones in Aqueous Solution

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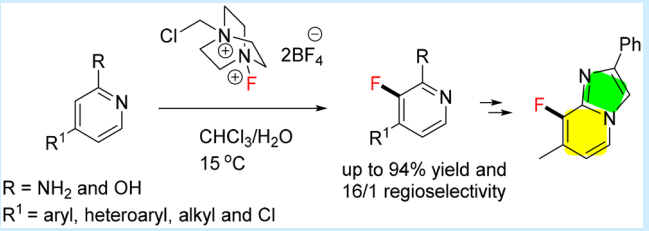
Supporting Information

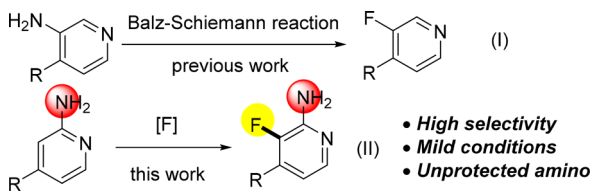
ABSTRACT: Fluorination of 2-aminopyridines and pyridin-2(1*H*)-ones in the presence of Selectfluor, water, and chloroform under mild conditions has been realized. This method gives fluorinated pyridines in good to high yields with high regioselectivities. The electron-deficient pyridine system is activated by an amino or hydroxyl group at C2. The regioselectivity of the fluorination reaction is strongly dependent upon the substituent pattern in the 2-aminopyridine or pyridin-2(1*H*)-one. The transformation of the 3-fluoro-substituted pyridine derivative into fluorinated zolimidine was achieved as well.



Pyridines are widely found in the scaffold of naturally occurring compounds and popular drugs, such as nicotine, pyridoxine, esomeprazole, and lansoprazole.[1] Incorporating a fluorine atom into organic compounds often leads to a significant change in chemical, physical, and biological properties.[2] Accordingly, new methods for introducing a fluorine atom into pyridine have been drawing great attention in the past decade. In particular, the fluorine substituent pattern on the pyridine ring has an extreme impact on the chemical, physical, and biological activities.[3] In fact, selective fluorination of pyridines is a challenging task. Recently, fluorination at C2 of the pyridine with silver(II) fluoride (AgF_2) by means of C−H bond activation fluorination was developed.[4] Some bioactive compounds such as gemifloxacin and trovafloxacin mesylate show excellent biological activities and contain a 3-fluoropyridine moiety.[5] Fluorinated pyridine derivatives are usually synthesized by alternative strategies, including the Balz−Schiemann reaction and nucleophilic aromatic substitution of chloro- or nitropyridines with anhydrous fluoride (eq I in Scheme 1).[6]

The Balz−Schiemann reaction involves strongly acidic and oxidizing conditions to produce a diazonium salt. This key intermediate is then heated in anhydrous HF or tetrafluoroborate salt to induce fluorination.

Scheme 1. Syntheses of Fluorinated Pyridines from Aminopyridines



3-Fluoro-2-aminopyridine derivatives are useful synthetic intermediates.[5] The known methods for the synthesis of 3-fluoro-2-aminopyridines require the use of strong fluorinating reagents, which are often unselective and difficult to handle, or the utilization of less reactive reagents that attack only the most activated arenes, which reduces the substrate scope. For example, direct fluorination at C3 with F_2 occurs to give 3-fluoro-substituted pyridine derivatives in low yield with poor regioselectivity.[7] In connection with our previous work,[8] we speculated that the pyridine could be activated by a 2-amino group and that selective fluorination could occur (eq II in Scheme 1). In this paper, we describe the fluorination of 2-aminopyridines and 2-hydroxypyridines with high regioselectivities.

We began with the reaction of 4-phenyl-2-aminopyridine (**1a**) with Selectfluor (**2a**)[9] or AgF_2 (**2b**)[4] in the presence of silver or palladium species that are effective catalysts for direct fluorination of pyridines,[4] pyrimidines,[8] and arenes,[10] but no fluorinated pyridines were observed (Table 1, entries 1−3). To our delight, in the absence of a metal catalyst, trace amounts of fluorinated pyridine were detected with CH_3CN as the solvent (entry 4). The formation of 3-fluoro-4-phenyl-2-aminopyridine (**3a**) (10%) and 5-fluoro-4-phenyl-2-aminopridine (**3a′**) (trace) was observed when the reaction was conducted in dichloromethane (DCM) at room temperature (entry 5). Interestingly, the regioselective fluorination at C3 of the 2-aminopyridine is not in agreement with the results of the well-known electrophilic halogenation of 2-aminopyridines, which generally occurs at C5.[11] For instance, chlorination of 4-cyano-2-aminopyridine at C5 is favored.[12] Selectfluor (**2a**) worked as not only an oxidizing agent but also a fluorine source in this

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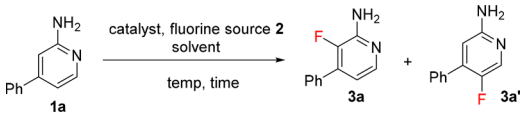
Table 1. Optimization of the Reaction Conditions[a]



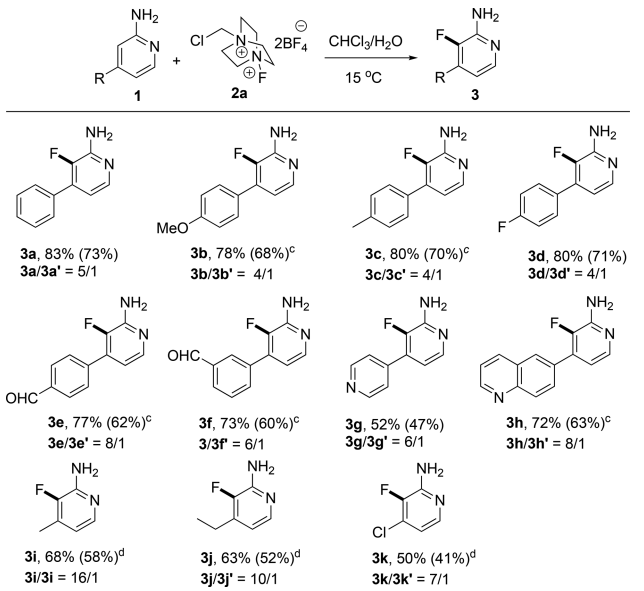
entry	catalyst (20 mol %)	fluorine source **2**	solvent	yield (%)[b] **3a**	yield (%)[b] **3a′**
1	Ag_2CO_3	Selectfluor	CH_3CN	–	–
2	AgF_2	AgF_2	CH_3CN	–	–
3	$[Pd(MeCN)_4](BF_4)_2$	Selectfluor	CH_3CN	–	–
4	–	Selectfluor	CH_3CN	trace	–
5	–	Selectfluor	DCM	10	trace
6	–	Selectfluor	THF	trace	–
7	–	Selectfluor	toluene	trace	–
8	–	Selectfluor	DCM/H_2O[c]	36	10
9	–	Selectfluor	$CHCl_3$/H_2O[c]	44	9
10	–	Selectfluor	DCE/H_2O[c]	38	9
11[d]	–	Selectfluor	$CHCl_3$/H_2O[c]	76	18
12[d,e]	–	Selectfluor	$CHCl_3$/H_2O[c]	62	23
13[d,f]	–	Selectfluor	$CHCl_3$/H_2O[c]	83 (73)	15 (9)
14[d,g]	–	Selectfluor	$CHCl_3$/H_2O[c]	24	5
15[d]	–	NFSI	$CHCl_3$/H_2O[c]	–	–

[a]Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol), and solvent (2 mL) at room temperature. [b]Determined by ^{19}F NMR analysis using 1-fluoronaphthalene as an internal standard (isolated yields are given in parentheses). [c]Organic solvent/H_2O = 1/1. [d]**1a** (0.20 mmol) and **2** (0.10 mmol). [e]35 °C, 6 h. [f]15 °C, 24 h. [g]5 °C, 72 h.

case.[9b,c] Examination of solvents such as CH_3CN, DCM, toluene, and THF revealed that DCM led to a better yield than others (entries 4–7). More significantly, the two-component solvent containing water in a 1/1 ratio with the organic solvent was beneficial for this fluorination, as the solubility of **2a** was improved. Further investigation of halogenated solvents showed that $CHCl_3$/H_2O is suitable for this fluorination (entries 8–10). The **1a**/**2a** ratio has a large effect on the results: for **1a**/**2a** = 1/2, a trace amount of 3,5-difluoro-4-phenyl-2-aminopyridine (**3a″**) and lower yield of **3a** and **3a′** were obtained. To avoid the formation of the byproduct, an excess of **1a** was employed in further investigations (entry 11). The reactions at temperatures ranging from 5 to 35 °C were tested, and the one at 15 °C gave the best result (entries 12–14). When 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (0.4 mmol) was added to the reaction mixture under the conditions of entry 13, neither **3a** nor **3a′** was observed. These results suggest that this fluorination reaction may pass through a radical process.[13] Next, the bench-stable fluorinating reagent *N*-fluorobenzenesulfonimide (NFSI) (**2c**) was examined and proved to be ineffective for this reaction (entry 15).

Having established the optimized reaction conditions, we next examined the scope of various 2-aminopyridines. **1a** and substrates **1b** and **1c** with an electron-donating group (*p*-MeO and *p*-Me, respectively) on the phenyl ring gave the corresponding products **3a**–**3c** in good to high yields with 4/1 to 5/1 regioselectivity (Scheme 2). A single crystal of **3a** was obtained, and X-ray diffraction revealed that the fluorination occurred at C3 of the pyridine. The 4-aryl-substituted substrates **1d**–**f** with an electron-withdrawing group (*p*-F, *p*-CHO, and *m*-CHO, respectively) on the phenyl ring produced the fluorinated products **3d**–**f** in good yields with 4/1 to 8/1 regioselectivity (Scheme 2). The substrates **1g** and **1h** with a heteroaryl group (pyridinyl and quinolinyl, respectively) gave rise to **3g** and **3h**[14] in fair to good yields with 6/1 to 8/1 regioselectivity; no other fluorinated

Scheme 2. Scope of 2-Aminopyridine Substrates 1[a,b]



[a]Reaction conditions: 2-aminopyridine **1** (0.20 mmol), **2a** (0.10 mmol), and 1/1 $CHCl_3$/H_2O (2 mL) at 15 °C for 24 h. [b]Yields were determined by ^{19}F NMR analysis using 1-fluoronaphthalene as an internal standard (isolated yields are given in parentheses). [c]Room temperature, 24 h. [d]**1i**–**k** (0.40 mmol) and **2a** (0.10 mmol) in 1/1 $CHCl_3$/H_2O (0.5 mL).

heterocyclic compounds were observed in these cases. Furthermore, the substrates **1i**–**k** with an aliphatic substituent (Me or Et) or Cl at C4 of the pyridine afforded the corresponding fluorinated products **3i**–**k** in good yields with a high level of regioselectivity (Scheme 2). Notably, no other fluorinated 2-aminopyridines were observed in each case. It is noteworthy that the fluorination of ethylpyridine derivatives

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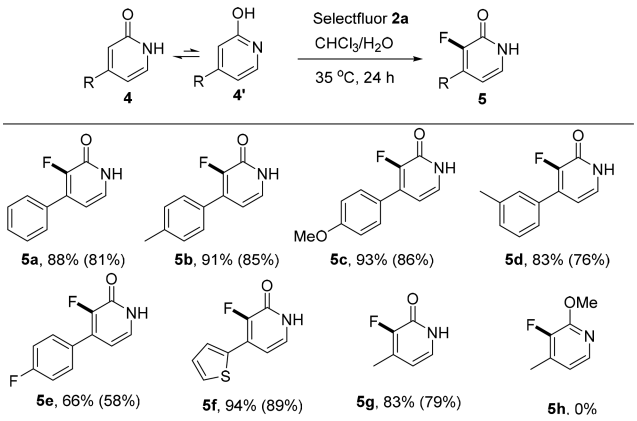
with Selectfluor (**2a**) occurred at the benzyl carbon rather than at the pyridine ring through radical fluorination.[15] The formation of a benzyl carbon radical is key for this fluorination.

We extended this method to the other pyridine derivatives such as amides **4**, the isomers of 2-hydroxypyridines **4′** (Scheme 3). It is noteworthy that popular drugs[16] such as

Scheme 3. Scope of 2-Hydroxypyridine Substrates 4[a,b]

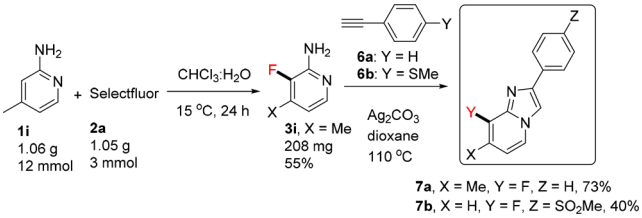


[a]Reaction conditions: **4** (0.2 mmol), **2a** (0.1 mmol), and $CHCl_3$/H_2O (2 mL) at 35 °C for 24 h. [b]Yields were determined by ^{19}F NMR analysis using 1-fluoronaphthalene as an internal standard (isolated yields are given in parentheses).

pyridoxine (vitamin B_6)[16a] and omeprazole (Prilosec)[16b] contain a hydroxypyridine moiety, which is of great importance in regard to medicinal chemistry. Thus, a range of amide substrates **4** was examined under the optimal conditions at a considerably higher reaction temperature than that of 2-aminopyridines. The experimental results illustrate that (1) the fluorination occurred only at C3 on the pyridine ring, and no other fluorinated 2-hydroxypyridines were observed; (2) the fluorinated 4-aryl-substituted amides **5**, the isomers of 4-substituted 3-fluoro-2-hydroxypyridines **5′**, were obtained in good to high yields, except for **4e**, which contains an electron-withdrawing substituent on the 4-phenyl ring; (3) heteroaryl-substituted amides such as 4-(thiophen-2-yl)pyridin-2(1*H*)-one (**4f**) and aliphatic-substituted amides such as 4-methylpyridin-2(1*H*)-one (**4g**) work very well; (4) no fluorination occurred when a hydroxyl group on the pyridine ring was replaced with a methoxy group. This outcome indicated that the hydroxyl group is required for this fluorination (Scheme 3). X-ray diffraction of **5b** illustrated that the fluorination occurred at C3.

Scheme 4 demonstrates the large-scale synthesis of the fluorinated pyridine **3i**. The reaction of 4-methyl-2-aminopyridine (**1i**) (1.30 g, 12 mmol) with **2a** (1.06 g, 3 mmol) in a

Scheme 4. Large-Scale Synthesis of 3i and Its Application for the Synthesis of 7

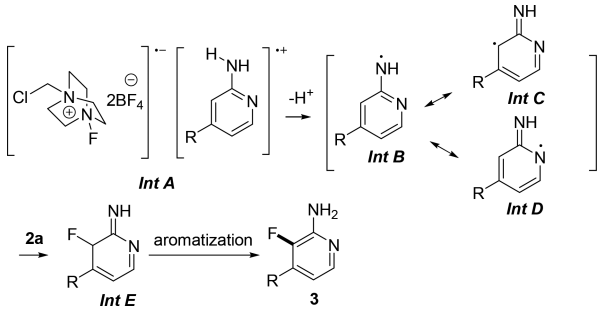


1/1 mixture of chloroform (7.5 mL) and water (7.5 mL) as the solvent was conducted at 15 °C. After the completion of this fluorination, **3i** (208 mg, 55% yield, **3i**/**3i′** = 25/1) was obtained (Scheme 4).

To demonstrate the potential utilization of **3i** for the synthesis of bioactive imidazo[1,2-*a*]pyridine compounds,[17] a [3 + 2] annulation reaction[18] of **3i** with ethynylbenzene (**6a**) in the presence of Ag_2CO_3 at 110 °C selectively provided 8-fluoro-7-methyl-3-phenylimidazo[1,2-*a*]pyridine (**7a**) in 73% yield. Fluorinated zolimidine[17] (**7b**) was obtained as well in 40% yield over the two steps (Scheme 4).

On the basis of our observations and those of others,[15] a plausible mechanism is proposed in Scheme 5. Treatment of 4-

Scheme 5. Plausible Mechanism for This Fluorination



substituted 2-aminopyridine **1** with **2a** in CH_3Cl/H_2O at 15 °C initially gives ***Int A***, which forms radical ***Int B***, releasing a proton through single electron transfer.[15] ***Int B*** then isomerizes to form resonance isomers ***Int C*** and ***Int D***.[13] Consequently, the reaction of radical ***Int C*** with **2a** followed by aromatization of ***Int E*** affords 3-fluoro-2-aminopyridine **3** (Scheme 5).

In conclusion, we have developed a selective fluorination of pyridines with Selectfluor in aqueous solution under mild conditions. This method allows the use of 2-aminopyridines and 2-hydroxypyridines as substrates, tolerates various functional groups, and affords fluorinated pyridines in good to high yields with high regioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02003.

Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments, and copies of ^1H, ^{19}F, and ^{13}C NMR spectra for all new compounds reported in the text (PDF)

Accession Codes

CCDC 1842092−1842093 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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