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Direct and Regioselective Monofluorination of *N*-Protected Pyridone Derivatives using *N*-Fluorobenzenesulfonimide (NFSI)

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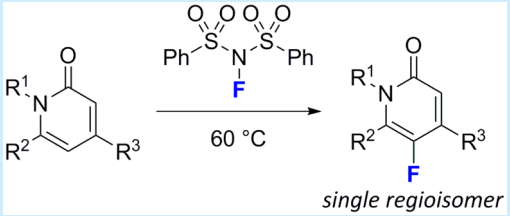
Supporting Information

ABSTRACT: The direct monofluorination of *N*-protected pyridone derivatives has been developed using a stable electrophilic fluorinating reagent, *N*-fluorobenzenesulfonimide (NFSI). Interestingly, the fluorine atom is regioselectively introduced at the position opposite the carbonyl group in the pyridone substrate during the reaction. This method is applicable to a wide range of substrates and allows the regioselective late-stage monofluorination of pyridone scaffolds.



The regioselective introduction of fluorine atoms to organic molecules has attracted much attention in the field of drug discovery because of the resulting improvement in biological activity and physicochemical properties (e.g., bioavailability, lipophilicity, and metabolic stability).[1] Electrophilic fluorination is a simple and convenient method to introduce fluorine atoms to organic compounds.[2] Although this reaction enables the fluorination of various heterocyclic compounds, few processes are applicable to the direct fluorination of pyridone derivatives.[3,4] Pyridone scaffolds are commonly found in pharmaceutical compounds and are rapidly gaining importance in the development of new drug candidates.[5] Therefore, the direct and regioselective introduction of a fluorine atom to such scaffolds will allow researchers not only to rapidly obtain structure−activity relationships but also to improve the physicochemical profiles in the drug discovery process.

In 1982, Kobayashi et al. demonstrated the first monofluorination reaction of pyridone derivatives using gaseous fluorine, which required specialized equipment to be safely handled.[3a] These days, a variety of electrophilic fluorinating reagents have been developed that are less toxic and easier to handle than the conventional fluorinating reagents.[6−9] Moreover, the comparison of the reactivity of such fluorinating reagents was investigated by Rozatian et al. (Figure 1a).[10] 1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane di(tetrafluoroborate) (Selectfluor)[6] has often been used in the fluorination of pyridone derivatives as a bench-stable electrophilic fluorinating reagent. However, this procedure still has limitations in regard to its substrate scope due to the difficulties in controlling its reactivity in the reaction. For example, the direct monofluorination of monocyclic pyridin-2(1*H*)-ones with Selectfluor results in a highly complex product mixture, which is difficult to separate.[4a]

Whereas the fluorination of cytisine derivatives bearing a bicyclic pyridone scaffold has also been reported, the reaction affords several fluorinated products with a large amount of recovered starting material (Figure 1b).[4b] Very recently, the regioselective monofluorination of 4-aryl- or methyl-substituted pyridin-2(1*H*)-ones using Selectfluor was reported by Zhou et al. (Figure 1c).[4d] This procedure can provide the corresponding 3-monoflorinated pyridone products with high regioselectivity. On the contrary, the highly regioselective monofluorination of monocyclic 2-pyridone derivatives at the five-position has not been reported to date to the best of our knowledge (Figure 1d). Herein we report the direct monofluorination of *N*-protected pyridones under mild conditions using a bench-stable and easily handled electrophilic fluorinating reagent, *N*-fluorobenzenesulfonimide (NFSI), focusing on the difference in the reactivity of the fluorinating reagents shown in Figure 1a. This method enables the regioselective introduction of a fluorine atom at the position opposite to the carbonyl group.

To investigate the optimized reaction conditions for the monofluorination of pyridone derivatives, a number of fluorinating reagents were initially investigated in the fluorination of *N*-methylisoquinolone (**1a**), which contains a bicyclic pyridone scaffold (Table 1). When the fluorination reaction of **1a** was performed in acetonitrile (MeCN) for 1 h using Selectfluor, a commonly used electrophilic fluorinating reagent, a complex mixture of products was obtained containing trace amounts of the desired 4-monofluoro-substituted product (**2a**) (entry 1). The reaction was also conducted at rt for 16 h, which resulted in **2a** being formed in 5% yield along with significant amounts of byproducts (entry 2). These results suggest that Selectfluor shows extremely high reactivity toward **1a** and that controlling its reactivity is difficult. The previous report shown in Figure 1a encouraged us to explore other less reactive electrophilic fluorinating reagents such as Synfluor, NFSI, and FP-T300 to suppress the overreaction observed when using Selectfluor.

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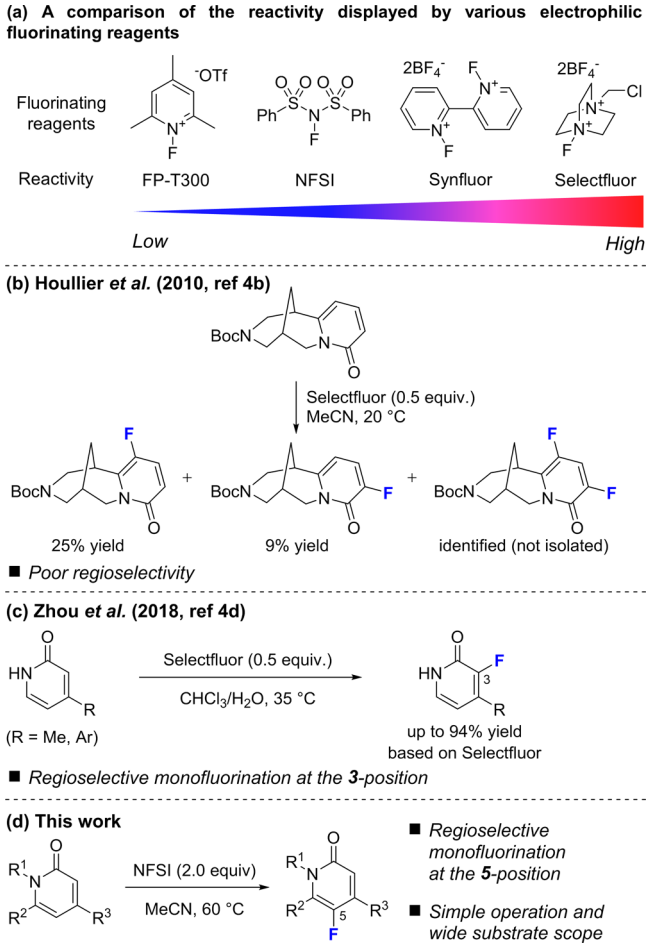
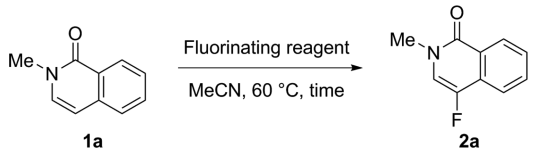


Figure 1. Direct monofluorination of pyridone scaffolds.

Table 1. Screening of the Fluorinating Reagents Used for the Monofluorination of 1a

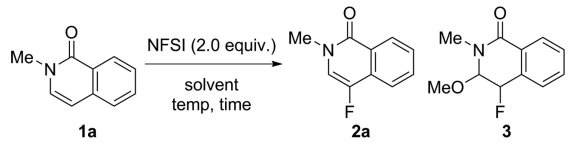


entry	fluorinating reagent (equiv)	time (h)	yield (%)[a]
1	Selectfluor (1.1)	1	–[b]
2[c]	Selectfluor (1.1)	16	5
3	Synfluor (1.1)	1	–[b]
4	NFSI (1.1)	1	33
5	NFSI (2.0)	1	50
6	FP-T300 (1.1)	12	NR
7	Fluolead (1.1)	12	NR[d]

[a]Isolated yield. [b]Complex mixture of products containing trace amounts of **2a**. [c]Reaction was performed at rt. [d]Toluene was used as the reaction solvent instead of MeCN.

Whereas the reaction of **1a** with Synfluor gave a complex mixture of products, NFSI was found to be the better fluorinating reagent in regard to the efficiency and regioselectivity of the reaction, providing the corresponding 4-monofluorinated product (**2a**) in 33% yield and as a single regioisomer (entry 3 vs 4). Furthermore, the use of 2.0 equiv of NFSI improved the yield of **2a** to 50% without the generation of any byproducts (entry 5). The reaction using FP-T300 did not proceed at all due to its lower reactivity compared with the other electrophilic fluorinating reagents studied (entry 6). When a common nucleophilic fluorinating reagent, 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead),[11] was used in the reaction, no reaction occurred, even after 12 h (entry 7). Consequently, screening of the reaction conditions was carried out (Table 2). The reaction of **1a** with

Table 2. Optimization of the Reaction Conditions Used for the Monofluorination of 1a with NFSI



entry	solvent	temp (°C)	time (h)	yield of **2a** (%)[a]
1	MeCN	60	1	50
2	DMF	60	1	45
3	DMA	60	1	27
4	MeOH	60	1	ND[b]
5	HFIP	60	1	48
6	EtOAc	60	1	35
7	DME	60	1	38
8	THF	60	1	31
9	toluene	60	1	39
10	DCE	60	1	34
11	MeCN	90	1	–[c]
12	MeCN	rt	16	trace
13	MeCN	60	2	51
14	MeCN	60	3	42
15	MeCN	60	16	–[c]

[a]Isolated yield. [b]LC–MS analysis of the reaction mixture revealed that compound **3** appeared to be obtained instead of **2a**. [c]Reaction afforded a complex mixture of products.

2.0 equiv of NFSI using an aprotic polar solvent such as *N*,*N*′-dimethylformamide (DMF) and *N*,*N*′-dimethylacetoamide (DMA) gave the 4-monofluorinated product (**2a**) in lower yield when compared with the reaction performed in MeCN (entries 2 and 3). When using an alcohol solvent such as methanol, LC–MS analysis of the reaction mixture revealed a peak corresponding to the methanol adduct (**3**) instead of the target product (**2a**) (entry 4).[4a] The use of 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP), which is a more acidic alcohol with weak nucleophilicity, provided **2a** in 48% yield, and the alcohol adduct obtained when using methanol as the solvent was not observed (entry 5).

Solvent screening was further conducted using EtOAc, 1,2-dimethoxyethane (DME), THF, toluene, and 1,2-dichloroethane (DCE) (entries 6–10). Although the yield of **2a** was not improved when using these solvents, it confirmed that various types of solvent are tolerated in the reaction. Subsequently, screening of the reaction temperature was conducted using MeCN as the reaction solvent. The reaction was performed at high temperature (90 °C) to improve the yield of **2a** (entry 11). However, the as-obtained monofluorinated product was decomposed during the reaction. Lowering the temperature to rt for 16 h afforded a trace amount of **2a** with recovered starting material obtained as the main product (entry 12). When the reaction time was prolonged to 2 h, **2a** was obtained in 51% yield without generating any byproducts (entry 13). However, the yield of **2a**

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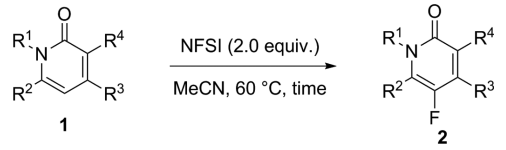
slightly decreased after the reaction was conducted for 3 h (entry 14). The longer reaction time resulted in a complex mixture of products, suggesting that product **2a** was decomposed during the reaction (entry 15).

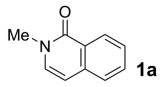
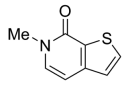
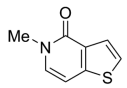
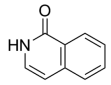
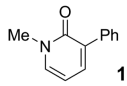
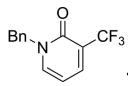
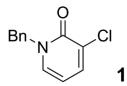
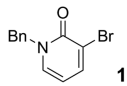
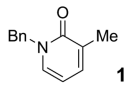
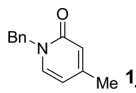
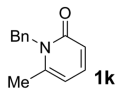
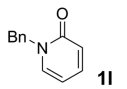
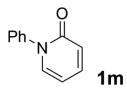
With the optimized reaction conditions in hand, the monofluorination of various pyridone derivatives **1** was investigated (Table 3). *N*-Methyl-substituted thieno[2,3-*c*]-pyridin-7(6*H*)-one **1b** and thieno[3,2-*c*]pyridin-4(5*H*)-one **1c** also underwent the monofluorination reaction with 2.0 equiv of NFSI in MeCN at 60 °C, providing their corresponding monofluorinated products (**2b** and **2c**) in 49 and 32% yield, respectively, and were formed as a single regioisomer (entries 2 and 3). The versatility of the reaction could be confirmed using *N*-methylated bicyclic pyridone compounds. Unfortunately, the reaction of isoquinolin-1(2*H*)-one **1d** in MeCN resulted in a highly complex mixture of products (entry 4). Because of the poor solubility of **1a** in MeCN, DMA was used in the reaction to improve its solubility (entry 5). Although **1a** completely dissolved in DMA, only a trace amount of the desired product was generated during the reaction. We then expanded this methodology to the monofluorination of monocyclic pyridones. The reaction of *N*-methylpyridone **1e** bearing a phenyl group at the three-position also proceeded to give the corresponding monofluorinated product **2e** in 37% yield and as a single regioisomer (entry 6). In the reaction of **1f** bearing an electron-withdrawing group ($-CF_3$), a higher reaction temperature and longer reaction time were required to provide **2f** in moderate yield (entry 7). The reaction of pyridones **1g** and **1h** bearing a 3-halo substituent also gave monofluorinated products **2g** and **2h** in 22 and 36% yield, respectively (entries 8 and 9). An electron-donating group, such as a methyl group at the three-position of the pyridone moiety, was also tolerated in the reaction, and the corresponding monofluorinated product **2i** was obtained in 43% yield (entry 10). Finally, this method was also applied to *N*-protected monocyclic pyridones **1j**–**m** without any substituents at the three-position. When 4-methylpyridone **1j** was reacted with NFSI for 5 h, 5-fluoropyridone **2j** was obtained in 42% yield with high regioselectivity (entry 11). Interestingly, the 3-fluorinated regioisomer of **1j** was not formed during the reaction. In entry 12, the reaction of 6-methyl-substituted pyridone **1k** also gave the monofluorinated product (**2k**) in 43% yield without generating the 3-monofluorinated product. Furthermore, nonsubstituted *N*-benzylpyridone (**1l**) underwent the reaction to provide the corresponding monofluorinated products **2l** in 46% yield as a single regioisomer (entry 13). Pirphenidone analogue **1m** without the 5-methyl group was also regioselectively monofluorinated at the five-position, providing **2m** in 42% yield (entry 14).

As shown in Figure 1b, the previously reported fluorination of *N*-protected pyridones using Selectfluor revealed that controlling the regioselectivity of the reaction was difficult.[4b] On the contrary, when using our method with NFSI, it was notable that no fluorine atom was introduced at any other position except that opposite the carbonyl group in the *N*-protected pyridone derivatives studied, even in the case of sterically hindered pyridones such as **1k**. A mechanistic insight into the excellent regioselectivity observed under our reaction conditions is currently under investigation in our laboratory and will be reported in due course.

In conclusion, we have developed the direct monofluorination of *N*-protected pyridone derivatives using NFSI under mild conditions. A wide substrate scope has been demonstrated in the reaction. In addition, the reaction is highly regioselective with monofluorination only occurring at the position opposite to the carbonyl group of the pyridone substrate. This method allows the regioselective late-stage

Table 3. Substrate Scope in the Monofluorination of Pyridones Using NFSI



Entry	Substrate	Time (h)	Yield (%)[a]
1	 **1a**	2	51
2	 **1b**	3	49
3	 **1c**	3	32
4	 **1d**	3	–[c]
5[b]		3	trace
6	 **1e**	5	37
7[d]	 **1f**	48	41
8	 **1g**	6	22
9	 **1h**	6	36
10	 **1i**	6	43
11	 **1j**	5	42
12	 **1k**	2	43
13	 **1l**	24	46
14	 **1m**	30	42

[a]Isolated yield. [b]DMA was used as the reaction solvent instead of MeCN. [c]Reaction afforded a complex mixture of products. [d]Reaction was performed at 120 °C in a sealed tube.

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introduction of a fluorine atom to pyridone scaffolds and is expected to contribute to further advances in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02482.

General information, synthetic procedures and characterization, and NMR spectra of all characterized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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