# Ring-Opening Fluorination of Isoxazoles

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**ABSTRACT:** A ring-opening fluorination of isoxazoles has been developed. By treating isoxazoles with an electrophilic fluorinating agent (Selectfluor®), fluorination followed by deprotonation leads to tertiary fluorinated carbonyl compounds. The present method features mild reaction conditions, good functional group tolerance, and simple experimental procedure. Diverse transformations of the resulting α-fluorocyanoketones were also demonstrated, furnishing a variety of fluorinated compounds.

The incorporation of fluorine atoms into molecules is one of the most important topics in pharmaceutical, agrochemical, and material sciences because fluorine-containing compounds exhibit unique chemical and physical properties.[1] Indeed, the demand for fluorinated compounds is growing in medicinal chemistry due to their higher liposolubility and metabolic stability, which renders them suitable for use in pharmaceuticals.[2] Consequently, numerous fluorination reactions have been investigated.[3] In particular, ring-opening fluorination, where a fluorine atom is introduced into a cyclic compound with concomitant ring cleavage, has attracted attention in recent years. This method is useful for efficiently constructing complex fluorine-containing compounds while rearranging the organic framework of the starting material. So far, ring-opening fluorination has been reported mainly by using three- or four-membered rings with large ring distortions such as oxiranes, aziridines, and cyclopropanols (Figure 1A).[4] Despite the usefulness of this method, reactions using ring sizes larger than five remains limited. Recently, the Lectka, Leonori, Lim, and Ma groups independently reported ring-opening fluorinations involving a C–C bond cleavage of five to eight-membered carbocycles.[5] The Sarpong group also disclosed a deconstructive fluorination of cyclic amines using a Ag(I)/Selectfluor® combination.[6] As for heteroatom–heteroatom bond cleavages, the Yao group reported a ring-opening fluorination of cyclohexene-fused isoxazoline *N*-oxides *via* N–O and C–C bond cleavage.[7] Although several ring-opening fluorinations have been developed, all of these compounds are limited to carbocycles or heterocycles, and application to aromatic compounds has been extremely rare.

Our group previously reported the first example of a ring-opening fluorination of heteroaromatic compounds (bicyclic azaarenes) such as pyrazolo[1,5-*a*]pyridines (Figure 1B).[8] In this reaction, electrophilic fluorination of the C3 position proceeded to give a cationic intermediate. Subsequent deprotonation at the C2 position followed by N–N bond cleavage of the pyrazole moiety occurred to afford fluorocarbons with a C($sp^3$)–F bond. Although this reaction could be regarded as a simple electrophilic aromatic fluorination using heteroaromatic compounds as nucleophiles, the resulting product is a tertiary fluorinated compound rather than an aromatic fluoride, which is a novel type of fluorination. We envisioned that this chemistry can be extended to isoxazoles as another monocyclic heteroaromatic compound with a heteroatom–heteroatom (N–O) bond similar to pyrazolo[1,5-*a*]pyridines.

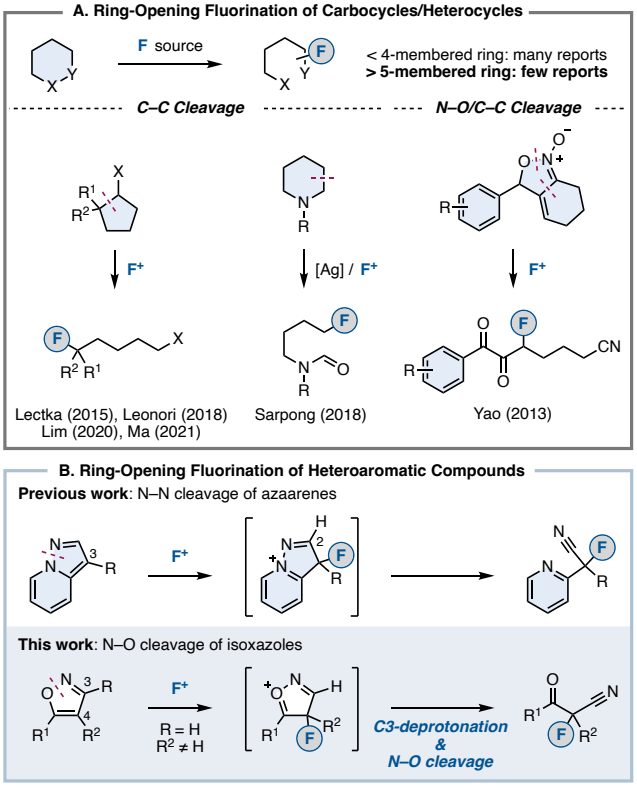


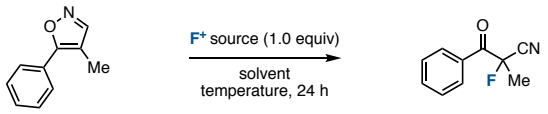

**Figure 1.** (A) Ring-opening fluorination of carbocycles/heterocycles. (B) Ring-opening fluorination of heteroaromatic compounds.

Isoxazole is frequently accessible from commercial sources and is an important framework in medicinal chemistry because it is a bioisostere of various heteroles and 1,3-dicarbonyl compounds.[9] As for fluorination of isoxazoles, electrophilic aromatic fluorination at the C4 position was reported by Sato, Sanford, and co-workers in 2016, where a C3-substituted isoxazole was treated with an electrophilic fluorinating agent to furnish the corresponding C4-fluorinated products.[10] However, there have been no examples of fluorination of isoxazoles without substituents at the C3 position. Additionally, although two examples of the synthesis of the resulting α-fluorocyanoketones have been reported, the substrate scope was

limited.[11] Therefore, we conceived that a variety of α-fluorocarbonyl compounds could be synthesized through a ring-opening fluorination of C3-unsubstituted isoxazoles as a starting material. Herein, we report a ring-opening fluorination of isoxazoles *via* N–O bond cleavage.

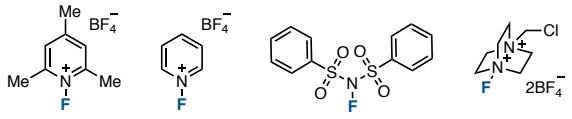
We first investigated various fluorinating agents using 4-methyl-5-phenylisoxazole (**1A**) as the model substrate in MeCN at 80 °C for 24 h (Table 1). With *N*-fluoropyridinium salts (**F1** and **F2**) and NFSI, no reaction proceeded and **1A** was recovered (Table 1, entries 1–3). The use of another N–F based fluorinating agent, Selectfluor®, produced the desired ring-opening fluorinated product **2A** in 93% yield (Table 1, entry 4).[12] The yield decreased as the reaction temperature was lowered (Table 1, entries 5 and 6), and the reaction did not proceed at all at room temperature. Since **1A** was not recovered, it is presumed that fluorination proceeds to generate the cationic intermediate even at 50 °C, but the subsequent deprotonation requires higher temperatures. When other polar solvents such as DMF and MeOH were used, the yield was diminished (Table 1, entries 7 and 8).

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




**1A** **2A**

| entry | F+ source | Temp/°C | solvent | **2A** (%) | **1A** (%) |
|---|---|---|---|---|---|
| 1 | F1 | 80 | MeCN | 0 | 100 |
| 2 | F2 | 80 | MeCN | 0 | 99 |
| 3 | NFSI | 80 | MeCN | 0 | 100 |
| 4 | Selectfluor® | 80 | MeCN | 93 | 0 |
| 5 | Selectfluor® | 70 | MeCN | 72 | 0 |
| 6 | Selectfluor® | 60 | MeCN | 44 | 0 |
| 7 | Selectfluor® | 80 | DMF | 8 | 60 |
| 8 | Selectfluor® | 80 | MeOH | 20 | 15 |




**F1** **F2** **NFSI** **Selectfluor®**

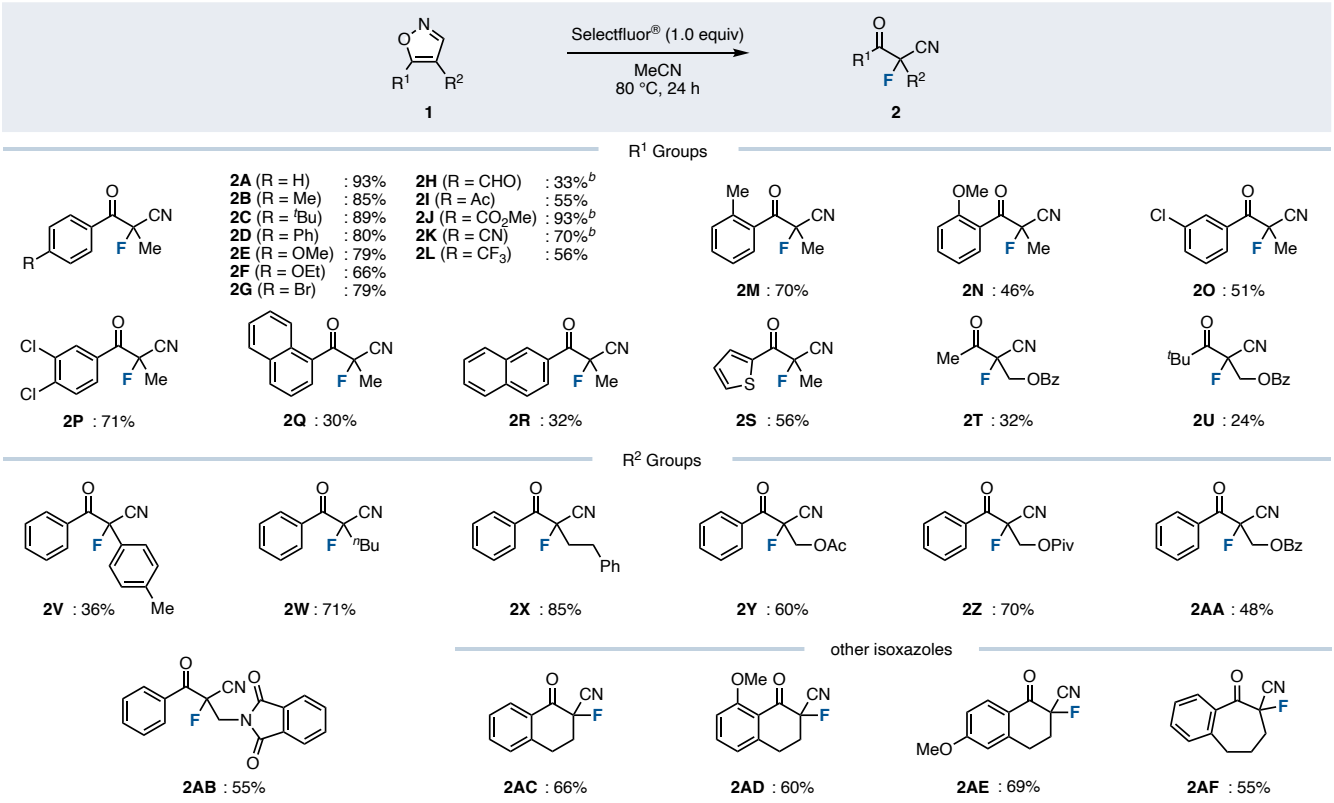
[a] Conditions; **1A** (0.20 mmol), F+ source (1.0 equiv), solvent (1.0 mL), 60–80 °C, 24 h. NFSI = *N*-Fluorobenzenesulfonimide, Selectfluor® = 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

With the optimized conditions in hand, the substrate scope of this fluorination was investigated (Scheme 1). Firstly, 4-methylisoxazoles **1** with various substituents at the C5 position were tested. Phenyl (**1A**), *p*-tolyl (**1B**), *tert*-butylphenyl (**1C**), and biphenyl (**1D**) as the C5-substituent afforded the corresponding products **2A**–**2D** in good yields. Even in the presence of an aryl group with an electron-donating substituent (**1E** and **1F**), the ring-opening products were obtained in moderate yields (**2E** and **2F**) without electrophilic fluorination on the aromatic ring. This reaction exhibited good functional group tolerance, as bromo (**1G**), formyl (**1H**), acetyl (**1I**), methoxycarbonyl (**1J**), cyano (**1K**), and trifluoromethyl (**1L**) were compatible (**2G**–**2L**). Although some substrates such as **1H**, **1J**, and **1K** showed lower reactivities, addition of $NaClO_4$ (1.0 equiv) was effective to improve the yields. The role of this additive is uncertain at this stage, but we speculate that the anion exchange of the intermediates might affect the ease of deprotonation at the C3 position.[13] The fluorination using isoxazoles with *ortho*- and *meta*-substituted aryl groups (**1M**–**1P**) proceeded to generate the corresponding products **2M**–**2P** in moderate to good yields. Compounds with naphthyl (**1Q** and **1R**) and thienyl (**1S**) moieties at the C5 position were converted to products **2Q**–**2S** in low to moderate yields because several side reactions including fluorination of the aromatic ring occurred. When the aryl group at the C5 position was changed to an alkyl group such as methyl (**1T**) and *tert*-butyl (**1U**), the reaction proceeded but in low yields (**2T** and **2U**). This result might be explained by the stability of the cationic intermediate on the electrophilic aromatic fluorination. In the case of aryl groups at the C5 position, this intermediate is stabilized by the formation of a benzoyl cation (benzoyl oxonium ion) species, but there is no such contribution in the case of the alkyl group.

The generality of 5-phenylisoxazoles with substituents at the C4 position was also examined. Using an aryl group instead of a methyl at the C4 position, **1V** was found to be less reactive to give the product **2V** in a low yield. This result also involves the stability of the cationic intermediate, suggesting that an aryl group at the C4 position, which is more electron-withdrawing than an alkyl group, is less likely to proceed with the reaction. Isoxazoles bearing alkyl groups (**1W** and **1X**) were smoothly fluorinated to give the products **2W** and **2X** in good yields. Substrates with carboxylate groups (**1Y**–**1AA**) and phthalimide (**1AB**) were transformed into the fluorinated products **2Y**–**2AB** in moderate to good yields. Isoxazoles fused with 6- and 7-membered rings (**1AC**–**1AF**) were also applicable to this reaction to afford the corresponding products **2AC**–**2AF** in moderate yields. Of note, various isoxazoles can be readily prepared from the corresponding arylketones in a one-pot process. However, if there is an electron-donating group on the aryl group at the C5 position, their yields would be diminished.

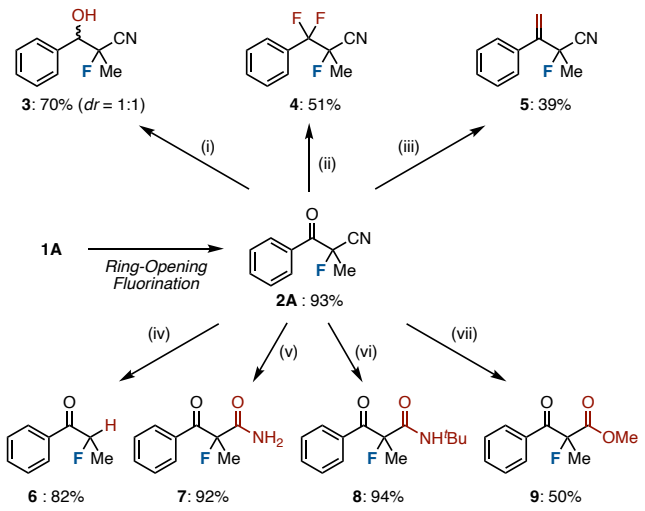
Next, several derivatizations of the α-fluorocyanoketone **2A** was demonstrated (Scheme 2). Reduction of ketone **2A** by $NaBH_4$ gave alcohol **3** in 70% yield as a mixture of diastereomers (1:1 ratio). Upon treatment with DAST, deoxofluorination of **2A** occurred to afford difluoromethylene compound **4** in 51% yield.[14] **2A** also led to styrene **5** by Wittig reaction. Furthermore, the transformations of the cyano group of the product were attempted. Removal of the cyano group proceeded under acidic conditions to afford α-fluoroketone **6**. **2A** was successfully converted to amides **7** and **8** by Pd-catalyzed hydration of the cyano group, and Ritter reaction, respectively.[15] α-Fluoro-β-ketoester **9** was synthesized by methanolysis of **2A** as well.

**Scheme 1. Substrate scope**[a]




[a] Conditions; **1** (0.12–1.0 mmol), Selectfluor® (1.0 equiv), MeCN (0.20 M), 80 °C, 24 h. [b] $NaClO_4$ (1.0 equiv) was added.

**Scheme 2. Derivatization of products.**

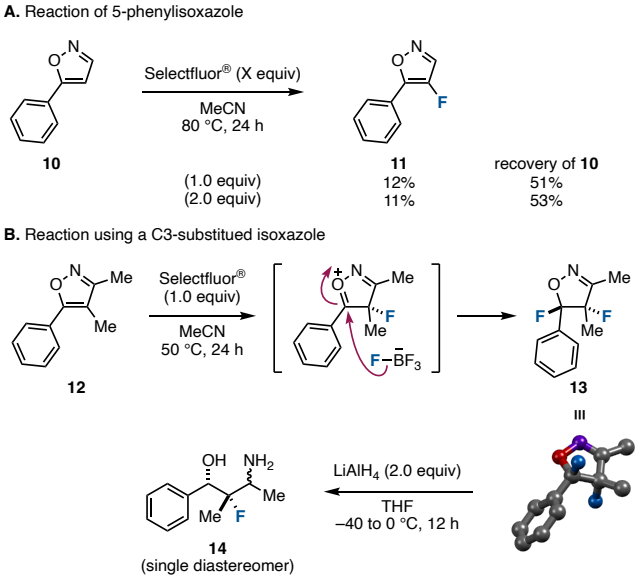



Conditions: (i) $NaBH_4$ (2.0 equiv), MeOH, 0 °C to RT, 12 h; (ii) DAST (30 equiv), $CH_2Cl_2$, 0 °C to RT, 1 h; (iii) $Ph_3PCH_3Br$ (1.1 equiv), *n*-BuLi (1.1 equiv), THF, 0 °C to RT, 1 h; (iv) HCl (5.0 equiv), MeOH, 70 °C, 6 h; (v) $Pd(OAc)_2$ (4.0 mol %), acetaldoxime (10 equiv), 1,4-dioxane, 100 °C, 1 h; (vi) tBuOAc (6.0 equiv), conc. $H_2SO_4$ (1.0 equiv), 40 °C, 2 h; (vii) TMSCl (5.0 equiv), MeOH, 50 °C, 6 h.

Next, this ring-opening fluorination was applied to 5-phenylisoxazole **10** as substrate without substituents at the C3 and C4 positions (Scheme 3A). In this case, only electrophilic aromatic fluorination at the C4 position occurred to give 4-fluoro-5-phenylisoxazole **11** in 12% yield, which was not affected by increasing the amount of Selectfluor®.[16] From this result, the present ring-opening fluorination requires C4-substituted isoxazoles. Finally, we were then interested in applying C3-substituted isoxazoles to the reaction (Scheme 3B). Upon treatment of isoxazole **12** with Selectfluor®, an unusual difluorinated compound **13** was obtained in 57% yield as a single isomer. The relative stereochemistry of **13** was assigned by X-ray crystallographic analysis, confirming the *anti* configuration of the fluorine atoms. The postulated reaction mechanism involves an electrophilic aromatic fluorination of isoxazole, followed by nucleophilic attack with the fluorine anion in $BF_4$.[10] The difluoro compound **13** can be converted to fluorinated β-amino alcohol **14** by reduction with $LiAlH_4$.

In summary, we have developed a ring-opening fluorination of isoxazoles. Electrophilic fluorination of isoxazoles followed by deprotonation leads to tertiary fluorinated compounds *via* N–O bond cleavage. With mild conditions and simple experimental procedure of the present reaction, various isoxazoles with diverse functionalities were found to be efficiently and readily converted to fluorine-containing compounds. Further studies to expand the generality of this ring-opening functionalization utilizing other aromatic compounds as well as electrophilic participants are ongoing in our laboratory.

**Scheme 3. (A) Reaction of 5-phenylisoxazole (B) Reaction using a C3-subsituted isoxazole**




## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectroscopic data for compounds including $^{1}H$, $^{13}C$, $^{19}F$ NMR spectra (PDF)

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### Notes

No competing financial interests have been declared.

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(14) Although we attempted to isolate the derivatized product **4**, it was found to be easily decomposed during purification process.

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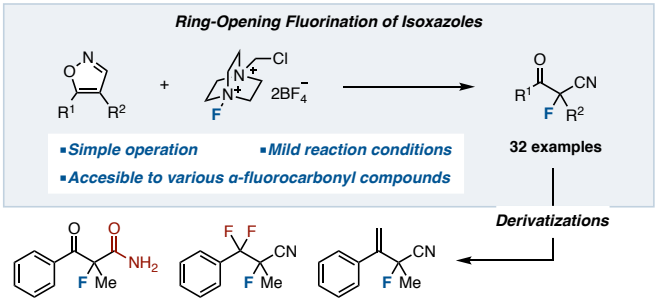
(16) In ref. 8, we previously reported that ring-opening difluorination occurred with the use of C3-unsubstituted pyrazolo[1,5-*a*]pyridine. However, as for 5-phenylisoxazole, such a reaction was not observed. The reason might be that the second electrophilic fluorination did not proceed due to the low nucleophilicity of **11**.


Ring-Opening Fluorination of Isoxazoles
2BF4
32 examples
Simple operation
Mild reaction conditions
Accesible to various α-fluorocarbonyl compounds
Derivatizations