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An Efficient Difluorohydroxylation of Indoles Using Selectfluor as a Fluorinating Reagent

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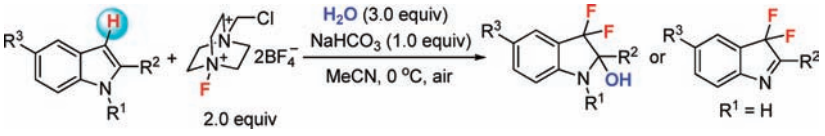
ABSTRACT



An efficient difluorohydroxylation of substituted indoles leading to 3,3-difluoroindolin-2-ols with good yields by using Selectfluor as the electrophilic fluorinating reagent has been developed. In this methodology, the indole rings were difluorinated highly regioselectively at the C3 carbon site. This protocol is practically convenient, easily handled under mild conditions, and provides an efficient way to produce the unique difluorinated indolin-2-ol structure. When alcohols were used as the nucleophiles instead of H_2O, the corresponding products were obtained in moderate yields. Based on the experimental observations, a plausible mechanism is proposed.

The indole unit is an ubiquitous skeleton of pharmaceuticals and bioactive natural products.[1] The modification of the indole structure has attracted great interest from organic chemists.[2] On the other hand, fluorinated compounds[3] often possess unique biological and physiochemical properties[4] and play an important role in pharmaceuticals,[5,6] agrochemicals,[7] and materials.[8] The strong electronegativity of fluorine and relatively small steric size of the fluorine atom uniquely affects the properties of organic molecules.[3] For example, introducing fluorine atoms into pharmaceutical molecules can make them more bioavailable and metabolically stable and can increase the strength of a compound's interactions with a target protein.[3−5]

We have recently been interested in the design and modification of indoles.[9] Our literature search revealed that although several methods for the synthesis of monofluorinated

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indole derivatives have been reported,[10] only a few methods are available for access to difluorinated indole derivatives.[11−13] In 1977, Hesse and co-workers reported the 2,3-difluoroindolines from indole derivatives in moderate yields by using the toxic gas CF_3OF in Freon at −78 °C.[11a] Recently, Fuchigami and co-workers[11b] reported the difluorination of indole derivatives by using an electrolysis technique with $Et_4NF−4HF$ as the fluorine sources, providing 2, 3-difluoroindolines in moderate yields. Middleton's group[11c] reported one case of 3,3-difluorooxindole from *isatin* by using the *nucleophilic fluorinating reagent* DAST (Figure 1), which was thermally unstable (it would fume in air and reacted explosively on contact with water).[11d] Shreeve's group[11e] developed an analogue, bis(methoxyethyl)aminosulfur trifluoride (Deoxofluor) (Figure 1), with enhanced thermal stability, to achieve higher yields of 3,3-difluorooxindoles from *isatins* by using an excess (3.0 equiv) of fluorinating reagent. Very recently, Umemoto et al.[11f] developed a new fluorinating agent, 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead) (Figure 1), which had high thermal stability and unusual resistance to aqueous hydrolysis which could also produce the 3,3-difluorooxindoles from electrophilic *isatins*.

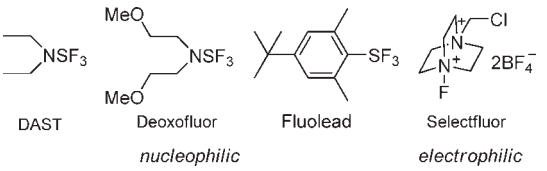

Figure 1. Fluorinating reagents.

Herein, we describe an efficient difluorohydroxylation of readily available indoles to afford 3,3-difluoroindolin-2-ols using an electrophilic fluorinating reagent. The significance of the present method is twofold: (1) The electrophilic fluorinating reagent Selectfluor[14] (Figure 1), which is safe, nontoxic, and easy to handle, was used as the fluorinating reagent. (2) By using electrophilic fluorinating reagent, the readily available indoles, which are natively nucleophliles, could be directly fluorinated and a novel difluorohydroxylated indoline structure was produced.

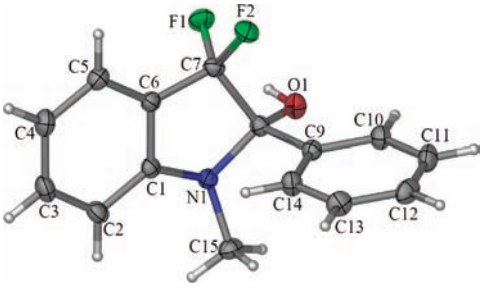

Figure 2. X-ray structure of **2a**.

First, the reaction of 1-methyl-2-phenylindole (**1a**) was investigated using the commercially available Selectfluor as the electrophilic fluorinating reagent, which was widely used for the fluorination of organic molecules.[14] Interestingly, 3,3-difluoro-1-methyl-2-phenylindolin-2-ol (**2a**) was accidentally obtained instead of the anticipated C3 monofluorinated indole. The structure of **2a** was further confirmed by single-crystal X-ray analysis (Figure 2).

Subsequently, various parameters were screened to improve the reaction efficiency (Table 1). The results indicate that the choice of solvent, the amount of H_2O, and the temperature were important for optimizing the yield of **2a**. The reaction yield increased to 57% when MeCN was used as the solvent (entry 2, Table 1). Considering that the hydroxyl group in **2a** was originated from H_2O in air (entries 1−2), 1.0 equiv of H_2O was added to the reaction system, which improved the yield a little (entry 3). **2a** was obtained in 81% yield when the reaction was carried out at a lower temperature (0 °C, entry 6). The best result was obtained (85% yield) when the reaction was performed under air at 0 °C with

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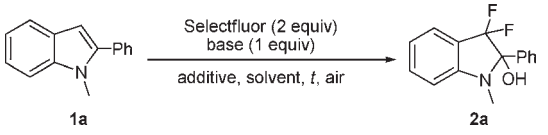
3.0 equiv of H_2O in MeCN (entry 8). It is possible that water might help to dissolve $NaHCO_3$ and Selectfluor to react with organic compounds dissolved in MeCN more efficiently. In some reported cases, the employment of an excess of Selectfluor was required to realize optimal results.[10d,q] In this present methodology, 2.0 equiv (as the reaction needed) of Selectfluor were enough to obtain the desired products in high yields. The other solvent was not as good as MeCN (entries 11–13). The

Table 1. Reaction of 1-Methyl-2-phenylindole (**1a**) with Selectfluor[a]



1a 2a

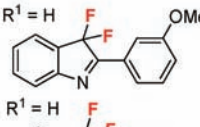
entry	base	additive	solvent	t (°C)	yield (%)[b]
1	$NaHCO_3$	–	DCE	90	31
2	$NaHCO_3$	–	MeCN	25	57
3	$NaHCO_3$	H_2O (1 equiv)	MeCN	25	59
4	$NaHCO_3$	H_2O (5 equiv)	MeCN	25	56
5	$NaHCO_3$	–	MeCN	0	74[e]
6	$NaHCO_3$	H_2O (1 equiv)	MeCN	0	81
7	$NaHCO_3$	H_2O (2 equiv)	MeCN	0	79
8	**$NaHCO_3$**	**H_2O (3 equiv)**	**MeCN**	**0**	**85**[e]
9	-	H_2O (3 equiv)	MeCN	0	67
10[c]	$NaHCO_3$	H_2O (3 equiv)	MeCN	0	56
11	$NaHCO_3$	H_2O (3 equiv)	Et_2O	0	trace
12	$NaHCO_3$	H_2O (3 equiv)	CH_3NO_2	0	78
13[d]	$NaHCO_3$	H_2O (3 equiv)	acetone	0	75
14	Na_2CO_3	H_2O (3 equiv)	MeCN	0	82
15	$KHCO_3$	H_2O (3 equiv)	MeCN	0	73
16	K_2CO_3	H_2O (3 equiv)	MeCN	0	76
17	DABCO	H_2O (3 equiv)	MeCN	0	63
18	$NaHCO_3$	H_2O (3 equiv)	MeCN	−20	81

[a] Reaction conditions: **1a** (0.2 mmol), Selectfluor (2.0 equiv), base (1.0 equiv), additive, and solvent (1 mL) for 0.5 h under air atmosphere. [b] Isolated yields. [c] NFSI was used instead of Selectfluor. [d] The reaction time was 4.5 h. [e] This experiment has been carried out for three trials.

reation yield dropped to 67% in the absence of a base (entry 9). Other bases such as $KHCO_3$, K_2CO_3, and DABCO gave low efficiencies (entries 14–17). A lower yield of **2a** was obtained when another electrophilic fluorinating reagent (NFSI) was used instead of Selectfluor (entry 10). This transformation occurred well even at −20 °C (81%, entry 18, Table 1).

Under these optimized reaction conditions, the difluorohydroxylation of different substituted indoles were investigated (Table 2). Indoles with *N*-protecting groups such as Me, Et, and Bn were well tolerated to give the desired products **2** with excellent yields, respectively (entries 1–3, Table 2). A variety of substituents were well-tolerated at the indoles, including a halo-group (**2d**, **2e**, **2l**), an aryl group (**2a**–**2i**), a heteroaryl group (**2j**, **2k**), and an ester group (**2l**). The substitution of the phenyl ring with an *o*-methoxyl group even led to a higher yield than that with a *p*-methoxyl

Table 2. Difluorohydroxylation of **1** with Selectfluor[a]

entry	product		t (h)	yield (%)[b]
1		**2a**: R = Me	0.5	84
2		**2b**: R = Et	0.5	80
3		**2c**: R = Bn	1.0	86
4		**2d**	1.0	70
5		**2e**: R = 4-F	1.0	82
6		**2f**: R = 4-Me	0.5	87
7		**2g**: R = 4-OMe	0.5	69
8		**2h**: R = 3-OMe	0.5	85
9		**2i**: R = 2-OMe	0.5	82
10		**2j**	1.0	36
11		**2k**	0.5	81
12		**2l**	6.0	18
13		**3a**	0.5	73
14		**3b**	0.5	71
15		**3c**	0.5	74

[a] Reaction conditions: **1** (0.2 mmol), Selectfluor (2.0 equiv), $NaHCO_3$ (1.0 equiv), H_2O (3.0 equiv), and MeCN (1 mL) at 0 °C under air atmosphere. [b] Isolated yields.

group, showing the steric hindrance did not affect the efficiency of the reaction (cf. entries 7 and 9, Table 2). As expected the difluorinated indolenines instead of the hydroxyl substituted indoline were obtained when the unprotected indole derivatives were used as the substrates (**3a**–**3c**). With a different substituted aryl group, the difluorination products were isolated in good yields (**3a**–**3c**).

The intermolecular reaction with different nucleophiles such as PhCOOH, $Ph(CH_2)_2COOH$, *p*-toluidine, $BnNH_2$, and CH_3CONH_2 have been investigated. However, the desired corresponding products were not obtained. Interestingly, alcohols are well tolerated in this transformation as shown in Figure 3. Furthermore, the intramolecular reaction using 2-(2-phenyl-*1*H-indol-1-yl)ethanol as the substrate was also investigated. The desired difluorinated

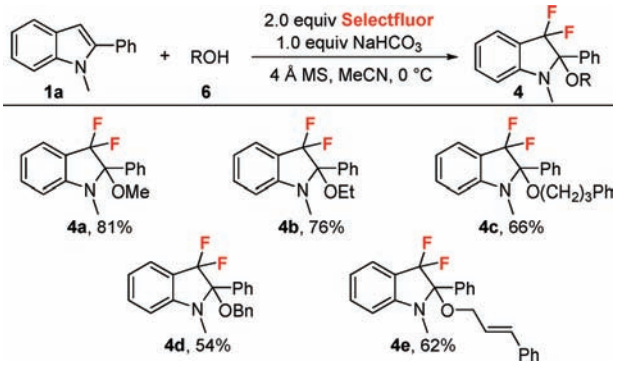
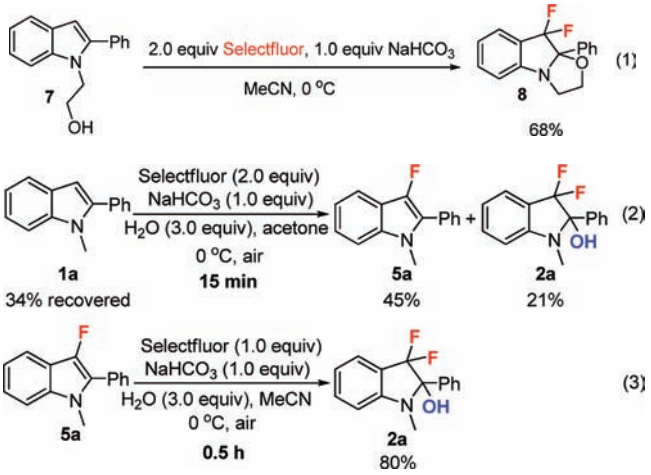


Figure 3. Difluorination of **1a** using alcohols as nucleophiles.

tricyclic tetrahydrooxazolo[3,2-*a*]indole was obtained in 68% isolated yield (eq 1).[15]



During the process of optimizing the conditions, when the reaction of **1a** was stopped at 15 min in acetone as the solvent, the desired difluorinated product **2a** (21%) and monofluorinated product **5a** (45%) were obtained with 34% of **1a** recovered (eq 2). Furthermore, **5a** was then resubjected to the standard reaction conditions (only using 1.0 equiv of Selectfluor), which produced **2a** in 80% yield (eq 3). These results indicate that the monofluorinated product serves as an intermediate in the transformation.

On the basis of the above results and information from the literature,[10d,14b] the mechanism of this transformation is proposed (Scheme 1). Initially, reaction of **1** with Selectfluor yields the unstable 3-fluoroindoline cation **A** or its resonance 3-fluoroindolenine cation **B**, and then the proton is extracted by the base ($NaHCO_3$ or DABCO from Selectfluor[16]) quickly to give the 3-fluoroindole **5**. Alternatively, the unstable 3-fluoroindoline cation **A** or its resonance 3-fluoroindolenine cation **B** can also be attacked by H_2O to furnish the

(15) During the revision of this manuscript, a similar intramolecular result has been reported; see: Lozano, O.; Blessley, G.; del Campo, T. M.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman R.; Gouverneur, V. *Angew. Chem., Int. Ed.* DOI: 10.1002/anie.201103151.

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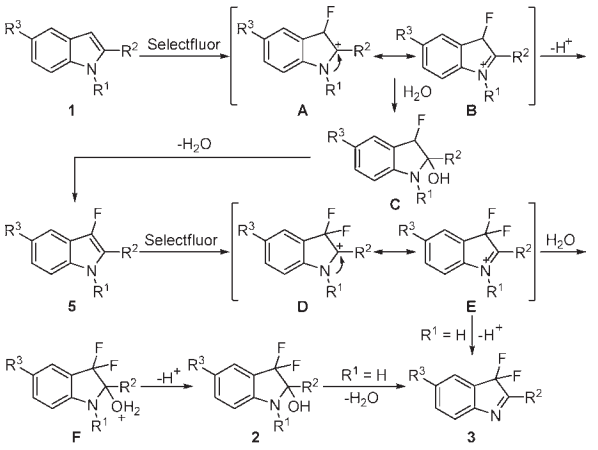
Scheme 1. Proposed Mechanism for the Transformation



3-fluoroindolin-2-ol **C**. Dehydration of **C** gives the 3-fluoroindole **5**, which then undergoes the same process to produce the unstable 3,3-difluoroindoline cation **D** or 3,3-difluoroindolenine cation **E**. Finally, the carbon cation of **D** or **E** is attacked by H_2O to produce 3,3-difluoroindolin-2-ol **2**. When the substitutional group R^2 is an aryl group, which can stabilize the carbon cation, the substrates would generally achieve good yields as shown in Table 2. In contrast, when the R^2 was changed to an ester group, the carbon cation was not stable enough and the yield dropped (**2l**, Table 2). We also tried the methyl group; although we could obtain the desired product, it was not stable enough at room temperature and decomposed quickly. In the cases of unprotected indole derivatives (R^1 = H) as the substrates, the direct deprotonation of intermediate **D** or **E**, or dehydration of **2** leads to the formation of **3**. When alcohols are used as nucleophiles instead of H_2O, the reactions proceed through a similar mechanism.

In summary, we have developed an efficient method for the synthesis of 3,3-difluoroindolin-2-ol. In this method, the indole ring was difluorinated highly regioselectively at the C3 carbon site with equivalent (not excess) Selectfluor. Additionally, mild conditions and practical convenience would make it a valuable synthetic tool in organic chemistry. When alcohols were used as the nucleophiles instead of H_2O, the corresponding products were obtained in moderate yields. The study of the bioactivity of these novel compounds is ongoing in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.