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Fluorination-Oxidation of 2-Hydroxymethylindole Using Selectfluor

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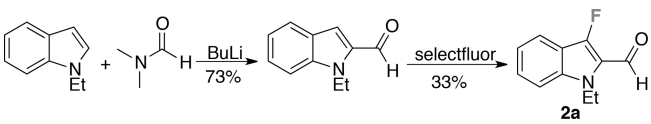
Abstract: An unexpected fluorination-oxidation of 2-hydroxymethylindole using selectfluor under mild condi-tions without a catalyst is described. This new chemistry allows for efficient and rapid synthesis of various 3-fluoroindole-2-aldehydes and novel quaternary 3-fluoro-3-hydroxymethyl-2-oxindoles with up to 86% isolated yield.

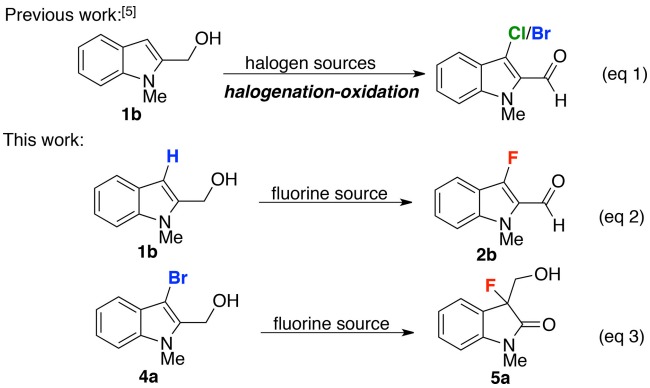
Keywords: Fluorination; Oxidation; 2-Hydroxymethylindole; Selectfluor

Indole scaffolds cover a large range of natural and bioactive molecules, which are important in both organic and medicinal chemistry.[1] The incorporation of a fluorine atom into the indole skeleton offers significant potential in medicinal applications. The fluorine substituent affects nearly all of the physical properties of a lead compound, including its absorption, distribution, metabolism and excretion.[2] Although the fluorination strategies in recent developments have been diverse, the incorporation of a fluorine atom into the C3 position of an indole moiety remains a challenging task.[3] For instance, 3-fluoroindole-2-aldehyde compound **2a** was obtained with less than a 24% overall yield because the final fluorination process returned only a 33% yield (Scheme 1).[4] Therefore, development of novel strategy to produce the 3-fluoro-indole compound is useful for both organic and medicinal chemistry.

We have previously reported a facile pathway to synthesize diverse 3-chloro/bromoindole-2-aldehyde compounds from 2-hydroxymethylindole via the halogenation-oxidation process (Scheme 2, eq 1).[5] We expected that fluorination-oxidation of 2-hydroxymethylindole might lead to the formation of the 3-fluoroindole-2-aldehyde compound **2b** in a similar fashion (Scheme 2, eq 2). A fluorine source, such as selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(t-etrafluoroborate), is a versatile mediator or catalyst in organic synthesis.[6-8] It serves as a strong oxidant for diverse "fluorine-free" functionalizations.[7] Selectfluor is widely used as a mediator in transformations of oxidizable functional groups. Selectfluor can oxidize a hydroxymethyl group to form an aldehyde group. As such, when combined with the fluorination and oxidation properties of selectfluor, the desired product 3-fluoroindole-2-aldehyde **2b** can be formed from the corresponding 2-



Scheme 1. Formation of **2a**.



Scheme 2. Reactions of Halogenation-Oxidation.

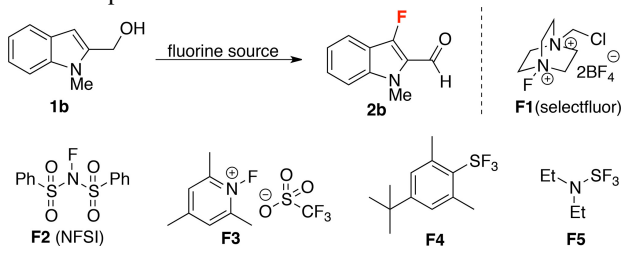
hydroxymethylindole **1b** in a one-pot reaction (Scheme 2, eq 2).

We also discovered that novel quaternary 3,3-disubstituted 2-oxindole **5a** was formed when 3-bromo-2-hydroxymethylindole **4a** was used in the presence of fluorine source (Scheme 2, eq 3). This process might occur due to the rearrangement properties of selectfluor.[6,9]

Herein, we report an unexpected fluorination-oxidation of 2-hydroxymethylindole to produce various 3-fluoroindole-2-aldehyde compounds and novel quaternary 3-fluoro-3-hydroxymethyl-2-oxin-dole compounds.

As demonstrated in Table 1, a yield of up to 70% of 3-fluoroindole-2-aldehyde **2b** was achieved in the presence of 2.5 equiv. of selectfluor and K_2CO_3 when acetonitrile was used as a solvent at room temperature (Table 1, entry 4). The absence of a base (Table 1, entry 2) returned a comparable yield. The yield significantly decreased when the temperature was decreased (Table 1, entry 3). Only 26% of the desired product was detected when 1.2 equiv. of selectfluor (Table 1, entry 1) were applied, suggesting that the mechanistic pathway consumed two equiv. of the fluorine source. Replacement of selectfluor with *N*-fluorobenzenesulfonimide (**F2**) (Table 1) produced **2b** with inferior yields (Table 1, entries 5–7). Alterations to other fluorine sources such as 1-fluoro-2, 4, 6-trimethylpyridinium triflate (**F3**) (Table 1, entry 8), 4-tert-butyl-2, 6-dimethyl-phenylsulfur (**F4**) (Table 1, entry 9) and diethylaminosulfur trifluoride (**F5**) (Table 1, entry 10) failed to produce the desired product. Changing K_2CO_3 to other bases, such as Na_2CO_3, $CsCO_3$, and Na_3PO_4 (Table 1, entries 11–13), could not produce **2b** with a superior yield. Acetonitrile appeared to be a suitable solvent for this reaction because other solvent systems, such as acetone, THF, and 1, 4-dioxane, had negative effects on this reaction (Table 1, entries 14–16). In addition, we obtained product **2b** in similar yields when performed control experiments under nitrogen and oxygen respectively, suggesting that oxygen might not involve in the oxidation process (Table 1, entries 17 and 18).

Table 1. Optimization of Substrate **1b**.

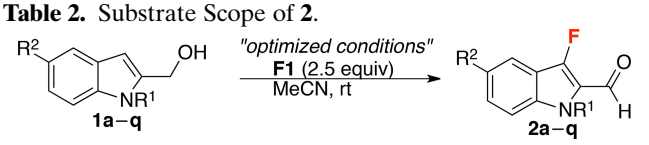


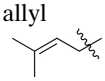
Entry[a]	Solvent	Base[b]	Fluorine source	Temp (°C)	Yield (%)[e]
1	MeCN	–	F1[c]	rt	26
2[f]	MeCN	–	F1[d]	rt	70
3	MeCN	–	F1[d]	0	44
4	MeCN	K_2CO_3	F1[d]	rt	70
5	MeCN	–	F2[d]	rt	12
6	MeCN	K_2CO_3	F2[d]	rt	54
7	Me_2CO	K_2CO_3	F2[d]	rt	49
8	MeCN	K_2CO_3	F3[d]	rt	<5
9	MeCN	K_2CO_3	F4[d]	rt	<5
10	MeCN	K_2CO_3	F5[d]	rt	<5
11	MeCN	Na_2CO_3	F1[d]	rt	63
12	MeCN	$CsCO_3$	F1[d]	rt	62
13	MeCN	Na_3PO_4	F1[d]	rt	66
14	Me_2CO	K_2CO_3	F1[d]	rt	50
15	THF	K_2CO_3	F1[d]	rt	47
16	Dioxane	K_2CO_3	F1[d]	rt	38
17[g]	MeCN	–	F1[d]	rt	69
18[h]	MeCN	–	F1[d]	rt	70

[a] Reactions were carried out at 0.2 mmol scale in 8 mL of solvent under air.
[b] Base used were 2.5 equiv.
[c] Fluorine source used were 1.2 equiv.
[d] Fluorine source used were 2.5 equiv.
[e] Isolated yield.
[f] Reaction conditions of using 2.5 equiv. of **F1**(selectfluor) in MeCN at room temperature under air was the "optimized conditions".
[g] Reaction was conducted under oxygen atmosphere.
[h] Reaction was conducted under nitrogen atmosphere.

With the optimized conditions chosen, we proceeded to study the effect of the substrate on this transformation. As illustrated in Table 2, substrate **1a** produced the desired product **2a** with up to a 72% yield in a one-pot procedure (Table 2, entry 3). Diverse *N*-substituents of indole were compatible with this reaction, including the ones with alkyne and alkene moieties (Table 2, entries 8–12). Other *N*-substituents, such as alkyl and aryl groups produced good yields (Table 2, entries 2, 4, 7 and 13). Additionally, the reactive indolic hydrogen had a slight effect on this reaction, increasing the yield up to 61% (Table 2, entry 1). Functional groups such as F and CN in the alkyl chain were well-suited to these reaction conditions and delivered good yields (Table 2, entries 5 and 6). Acceptable yields could be achieved when the Ar system of the indole ring was electron-deficient (Table 2, entries 14, 15 and 18). A high yield was successfully obtained when the Ar system was substituted with an alkyl group (Table 2, entry 16) as well. Unfortunately, we could not detect any of the desired product when the electron-donating system of the indole ring was applied (Table 2, entry 17). We suspected that the electron-rich Ar ring, for example, a 5-OMe–Ar system of **1q**, probably triggered the substitution reaction in the benzene ring rather than triggering the oxidation process in the alcoholic moiety.

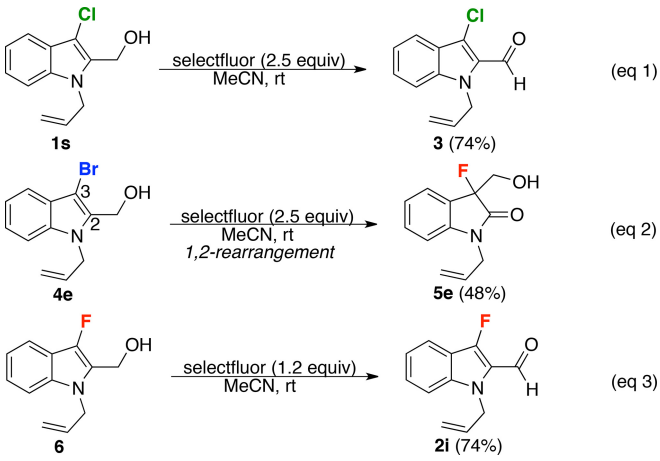
Table 2. Substrate Scope of **2**.



Entry[a)]	Substrate	R^1	R^2	Product	Yield (%)[b)]
1	**1c**	H	H	**2c**	61
2	**1b**	CH_3	H	**2b**	70
3	**1a**	CH_3CH_2	H	**2a**	72
4	**1d**	isopropyl	H	**2d**	83
5	**1e**	$F(CH_2)_2$	H	**2e**	82
6	**1f**	$NC(CH_2)_3$	H	**2f**	80
7	**1g**	Bn	H	**2g**	85
8	**1h**	propargyl	H	**2h**	73
9	**1i**	allyl	H	**2i**	82
10	**1j**		H	**2j**	64
11	**1k**		H	**2k**	65
12	**1l**		H	**2l**	82
13	**1m**	Ph	H	**2m**	79
14	**1n**	H	F	**2n**	66
15	**1o**	H	Br	**2o**	67
16	**1p**	H	Me	**2p**	76
17	**1q**	H	OMe	–	<5
18	**1r**	H	Cl	**2q**	71

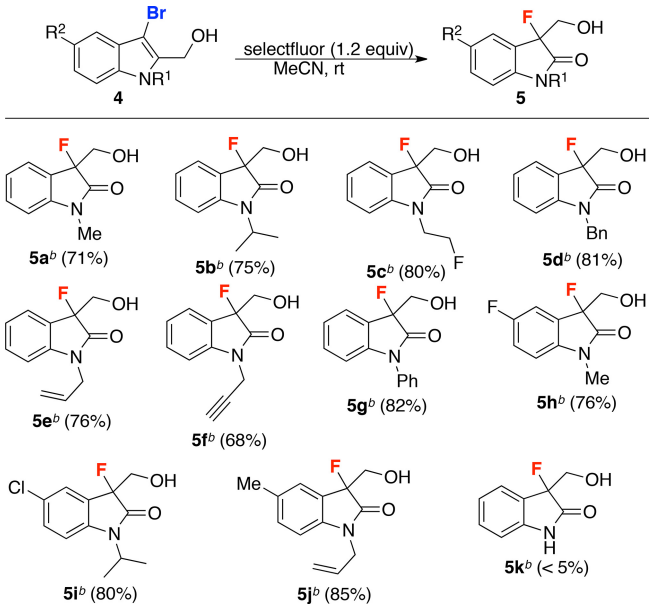
[a] All reactions were carried out at 0.2 mmol scale with 0.5 mmol of F1 in MeCN (8 mL) under air.
[b] Isolated yield.

We discovered that the substituent at the C3 position has a fundamental effect on the fluorination-oxidation process developed herein. As previously discussed, the fluorination-oxidation process proceeded smoothly to generate the 3-fluoroindole-2-aldehyde product **2** when a 3-hydrogen-2-hydroxy-methylindole substrate was used. However, 3-chloroindole-2-aldehyde **3** was formed under the optimized conditions if the C3 position processed a chloride group (Scheme 3, eq 1). Given this result, selectfluor only served as an oxidizing reagent.[7] Compared to a chloride group, a bromide group is a better leaving group. The incorporation of a bromide group into the C3 position may trigger a 1,2-rearrangement process. As shown in Scheme 3, 3-bromo-2-hydroxymethyl-indole substrate **4e**, which bears a bromide group in the C3 position, was replaced by a fluorine substituent in the presence of selectfluor. Subsequent 1,2-rearrangement followed by oxidation produced the desired 3-fluoro-3-hydroxymethyl-2-oxindole product **5e** with a moder-ate yield (Scheme 3, eq 2). We also found that 3-fluoro-2-hydroxymethyl-indole substrate **6** was oxidized to give aldehyde product **2i** under the identical conditions (selectfluor 1.2 equiv., Scheme 3, eq 3), implying that the fluorination-oxidation process might involve a stepwise mechanism.



Scheme 3. Reactions of 1 s, 4e and 6.

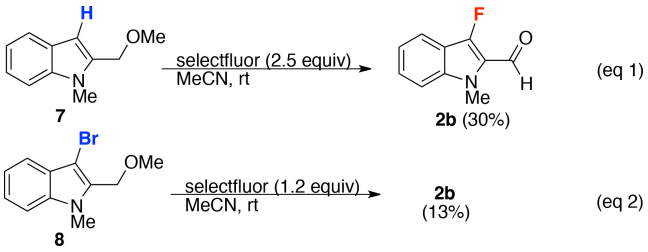
We found that the 1,2-rearrangement oxidation process proceeded well when 1.2 equiv. of selectfluor were applied and when acetonitrile was used as the solvent at room temperature.[10] Versatile *N*-substituents of indole, such as alkyl, aryl, allyl, and propargyl, were well-suited to this reaction and allowed for up to an 86% isolated yield to be obtained (**5j**) (Scheme 4). However, the presence of indolic hydrogen, such as in substrate **4k**, was an exception. We suspected that the reactive indolic hydrogen might cause side reactions,



Scheme 4. Substrate Scope of **5**.[a a)]All reactions were carried out at 0.2 mmol scale of **4** in MeCN (8 mL) with 1.2 equiv. of selectfluor under air. [b)] Isolated yield.

resulting in the negative formation of **5k** (Scheme 4). These novel quaternary 3-fluoro-3-hydroxymethyl-2-oxindole pr-oducts supplement the quaternary 3-hydroxymethyl-2-oxindole compounds. Previous methods for quaternary 3-hydroxymethyl-2-oxindole compounds were lengthy and required air-sensitive transition metals as catalysts.[11–16] Quaternary 3-hydroxy-methyl-2-oxindole compounds are useful intermedi-ates in total synthesis. This successful synthesis of quaternary 3-fluoro-3-hydroxymethyl-2-oxindole co-mpounds under mild conditions without a catalyst is beneficial to organic and medicinal applications.

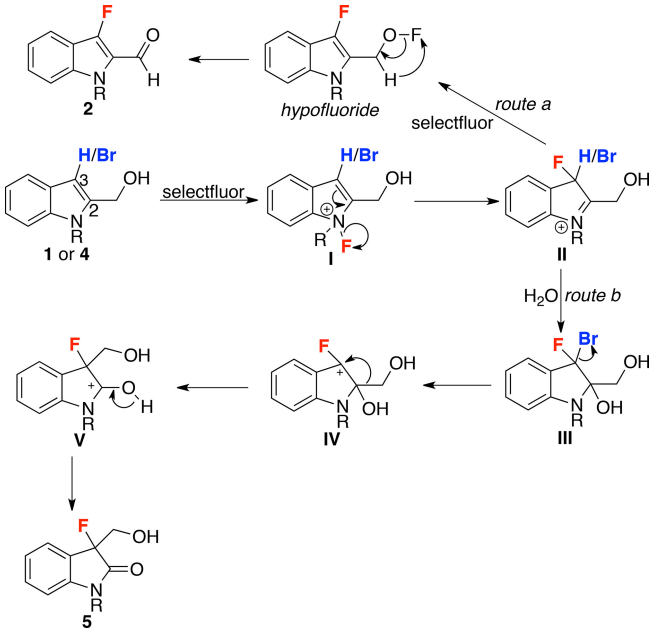
It is noteworthy to mention that the free alcohol group probably has certain important influence on the reactivity in the formation of 3-fluoro-2-aldehyde product **2** and 3-fluoro-3-hydroxymethyl-2-oxin-dole **5**. As illustrated in Scheme 5, alcohol protected substrate **7** returned product **2b** with a low yield under optimized conditions (Scheme 5, eq 1). The fluorination-oxidation reaction of 3-bromo-2-methoxymethyl-indole substrate **8** resulted in a complicated mixture (Scheme 5, eq 2). In this case, we could only isolate a small amount of 3-fluoroindole-2-aldehyde **2b** instead of the 3-fluoro-2-oxindole rearrangement product.



Scheme 5. Reactions of **7** and **8**.

For the formation of 3-fluoroindole-2-aldehyde compounds, a two-step mechanism may be required because we recovered a certain amount of the initial material and fluorinated 2-hydroxymethylindole when 1.2 equiv. of selectfluor were applied. We suggested that the nitrogen atom in substrates **1** and **4** could contribute to the fluorination to give an iminium ion intermediate **I** (Scheme 6). Subsequent fluorination of C3 position might offer a 3-fluoroindolenium ion intermedate **II** which served as a common intermediate for both route a and route b pathways.

For the formation of 3-fluoroindole-2-aldehyde compounds **2**, a two-step mechanism was probably involved when the C3 position contained a hydride group because the fluorination of the C3 position was likely to result in the formation of intermediate **II**. This step was supported by significant work demonstrating that 3-hydrogen-indoles react with selectfluor to introduce a C–F bond in the C3 position.[17]



Scheme 6. Proposed Mechanism.

Subsequent oxidation with extra equiv. of selectfluor might offer a hypofluoride[18] which may lead to the generation of 3-fluoroindole-2-aldehyde **2**.

In the case of 3-bromo-substrate **4**, the 3-fluoroindolenium ion **II** preferred to initiate the 1,2-rearrangement process with concomitant loss of bromide to form an intermediate **V** (Scheme 6, route b). In the course of this oxidative 1,2-rearrangement, a trace amount of water in the media might attack C2 position to offer an intermediate **III**. Because bromide is a good leaving group, then a carbocation **IV** could be produced. This carbocation intermediate could become a driving force for the adjacent hydroxymethyl group to migrate to C3 position. Subsequently, the resultant oxonium ion intermediate **V** furnished the oxidative rearrangement product **5**. This 1,2-rearrangement process was further supported by the rearrangement of indolyl acetates and carbonates,[19] as well as the recent discovery of 1,2-rearrangement oxidation of 2,3-disubstituted indole using selectfluor.[9]

In conclusion, a facile method to produce diverse 3-fluoroindole-2-aldehyde compounds from the corresponding 2-hydroxymethylindole has been established. The method also allows for the efficient and rapid synthesis of novel quaternary 3-fluoro-3-hydroxymethyl-2-oxindole compounds. Various 3-fluoroindoles or 3-fluorooxindoles are now prod-ucible with good yields under mild conditions without a catalyst, which is beneficial for synthetic and medicinal applications.

Experimental Section

General Procedure for Fluorination-oxidation.

To a solution of alcohol **1** (0.2 mmol, 1.0 equiv.) in MeCN (8 mL) was added selectfluor (177.1 mg, 0.50 mmol, 2.5 equiv.) in one portion under air. The resultant mixture was stirred at room temperature and monitored by TLC. After removing the solvent *in vacuo*. The residue was purified by flash column chromatography (Hexanes/EtOAc 9:1) to yield the corresponding 3-fluoro-indole-2-aldehyde compounds **2.**

General Procedure for fluorination, 1,2-Rearrangeme-nt Oxidation.

To a solution of alcohol 4 (0.2 mmol, 1.0 equiv.) in MeCN (8 mL) was added selectfluor (85 mg, 0.24 mmol, 1.2 equiv.) in one portion under air. The resultant mixture was stirred at room temperature and monitored by TLC. After removing the solvent *in vacuo*. The residue was purified by flash column chromatography (Hexanes/EtOAc 3:1) to yield the corresponding 3-fluoro-3-hydroxymethyl-2-oxindole compounds 5.

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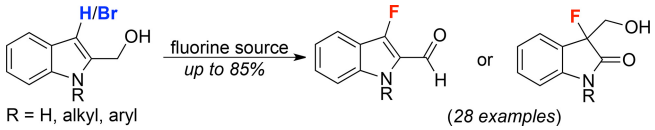
UPDATES

Fluorination-Oxidation of 2-Hydroxymethylindole Using Selectfluor



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