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Synthesis of Quaternary 3,3-Disubstituted 2-Oxindoles from 2-Substituted Indole Using Selectfluor

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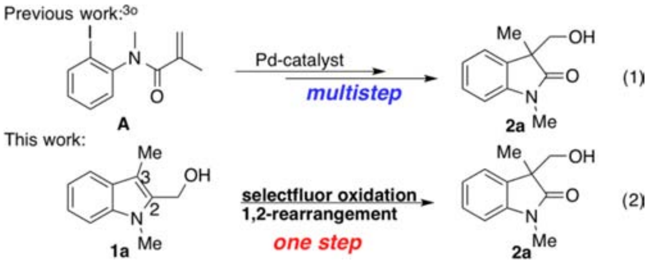
Supporting Information

ABSTRACT: A facile method to construct quaternary 3,3-disubstituted 2-oxindole from 2-substituted indole without a catalyst in mild conditions is developed. A mechanistic study suggests that an iminium-intermediate-triggered 1,2-rearrangement is involved, and a trace amount of water is required for subsequent oxidation.

Oxindoles, especially 3,3-disubstituted 2-oxindoles, are very important compounds in organic synthesis due to their wide applications in natural, bioactive, and pharmaceutically useful products.[1,2] A number of methods are developed to achieve this scaffold with transition-metal-catalyzed[3] and organocatalytic[4] strategies as the main processes. Other procedures, including photochemical,[5] Ullmann-type,[6] and radical-promoted cyclizations of saturated 2-haloanilide compounds,[7] have been reported. Although a transition-metal-catalyzed cyclization strategy is useful to generate diverse 3,3-disubstituted 2-oxindoles and is important to construct chiral ones,[3n,q] the high cost and air-sensitive nature of transition metals make other methods worth developing.

For instance, previous establishments of quaternary 3-hydroxymethyl-2-oxindole compounds were lengthy and required high cost and harsh conditions.[3−8] As illustrated in Scheme 1, an expensive and air-sensitive Pd catalyst was used when starting with 2-iodoanilide **A**, with subsequent multistep reactions resulting in the expected 3-hydroxymethyl-2-oxindole **2a** (Scheme 1, eq 1).[3o] Thus, it is evident that there remains a further need to develop alternative synthetic approaches to produce quaternary 3-hydroxymethyl-2-oxindole compounds.

Scheme 1. Formation of 2a



Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) as a versatile mediator or catalyst in organic synthesis is well-documented.[9] It serves as a strong oxidant for diverse "fluorine-free" functionalizations.[10] Selectfluor is widely used as a mediator in transformations of oxidizable functional groups. It is possible for selectfluor to oxidize indole to produce 2-oxindole. It also serves as a mediator for stereoselective rearrangement processes.[9] As such, combined with the oxidation and rearrangement properties of selectfluor, desired product 3-hydroxymethyl-2-oxindole **2a** might be formed from the corresponding 2-hydroxymethylindole **1a** in a one-pot reaction (Scheme 1, eq 2) through a 1,2-rearrangement process.

Herein, we report a facile method to synthesize diverse quaternary 3,3-disubstituted 2-oxindole compounds from the corresponding 2-substituted indole using selectfluor without a catalyst in mild conditions.

We evaluated several fluorine sources for the in situ 1,2-rearrangement oxidation process, and the results are shown in Table 1. Selectfluor (**F1**) (Table 1, entry 1) was the best mediator to convert 2-hydroxymethylindole **1a** into the desired quaternary 3-hydroxymethyl-2-oxindole **2a**. Up to 76% isolated yield of **2a** could be achieved using 1.2 equiv of selectfluor when acetonitrile was used as solvent at room temperature (Table 1, entry 1). If we increased the amount of selectfluor, the yield decreased (Table 1, entry 2) considerably, suggesting that **2a** could be decomposed by selectfluor. Comparable yield could be obtained when the temperature was decreased to 0 °C (Table 1, entry 3), albeit with a longer reaction time. Addition of a base such as K_2CO_3 failed to increase the yield (Table 1, entry 4). Replacement of selectfluor with *N*-fluorobenzenesulfonimide (**F2**) (Table 1) failed to return the desired product with acceptable yield (Table 1, entries 5−7). Only very low yield of **2a** was obtained when 1-fluoro-2,4,6-trimethylpyridinium triflate (**F3**) (Table 1, entries 8 and 9, <5%) was applied. Alteration to other fluorine sources such as 4-*tert*-butyl-2,6-dimethylphenylsulfur (**F4**) (Table 1, entry 10, <5%) and diethylaminosulfur trifluoride (**F5**) (Table 1, entry 11, <5%) could not produce the desired product. We also tried to optimize the reaction conditions with different solvent systems, such as acetone,

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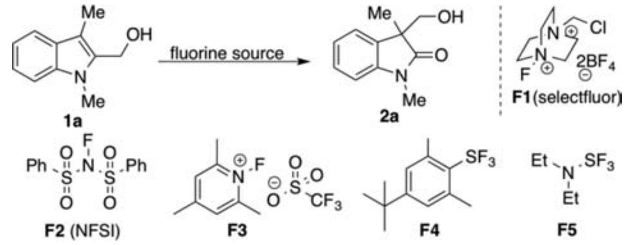
Table 1. Optimization of Substrate 1a



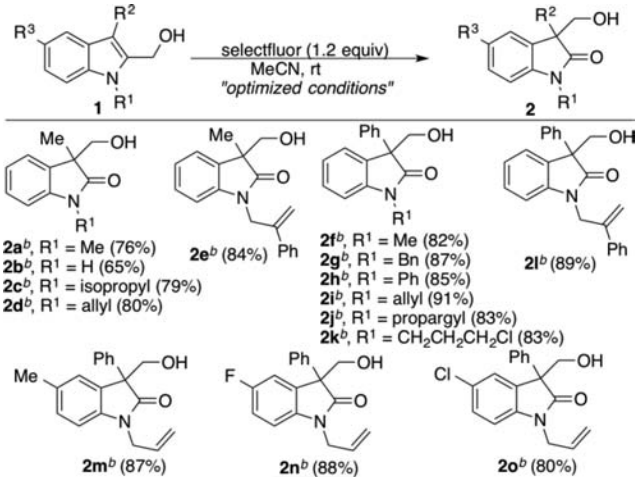
entry[a]	solvent	base[b]	fluorine source	temp (°C)	yield (%)[c]
1	MeCN		**F1** (1.2 equiv)	rt	76
2	MeCN		**F1** (2.5 equiv)	rt	65
3	MeCN		**F1** (1.2 equiv)	0	75
4	MeCN	K_2CO_3	**F1** (1.2 equiv)	rt	72
5	MeCN		**F2** (1.2 equiv)	rt	<5
6	MeCN	K_2CO_3	**F2** (2.5 equiv)	rt	<10
7	Me_2CO	K_2CO_3	**F2** (2.5 equiv)	rt	<10
8	MeCN	K_2CO_3	**F3** (1.2 equiv)	rt	35
9	MeCN		**F3** (1.2 equiv)	rt	36
10	MeCN	K_2CO_3	**F4** (1.2 equiv)	rt	<5
11	MeCN	K_2CO_3	**F5** (1.2 equiv)	rt	<5
12	Me_2CO		**F1** (1.2 equiv)	rt	69
13	THF		**F1** (1.2 equiv)	rt	57
14	dioxane		**F1** (1.2 equiv)	rt	70

[a] All reactions were carried out at 0.2 mmol scale in solvent (8 mL). [b] 2.5 equiv. [c] Isolated yield.

THF, and 1,4-dioxane. However, these solvent systems failed to deliver higher yield (Table 1, entries 12−14).

With the optimized conditions in hand, we proceeded with the substrate scope of the reaction, and the results are demonstrated in Scheme 2. High yields could be achieved when an alkyl (i.e., Me) or an aryl (i.e., Ph) group was attached to the C3 position. A number of amine protecting groups were compatible with the 1,2-rearrangement oxidation process. For instance, protecting groups containing alkyl, aryl, allyl, propargyl, and chloride tolerated the reaction conditions. Up to 91% isolated yield could be obtained (**2i**) (Scheme 2) when an allyl protecting group was used. An exception was the NH situation, where amine was not protected and only 65% isolated yield was obtained (**2b**) (Scheme 2). We suspected that the indolic hydrogen probably triggered other side reactions, leading to lower yield. Bulky and electron-poor substituents of the indolic Ar ring had a positive effect on this reaction and delivered excellent yields (**2m**−**2o**) (Scheme 2). However, we failed to detect any desired product when an electron-rich substituent, such as a methoxyl group, was introduced into the indolic Ar ring (data not shown). The structure of these 1,2-rearrangement oxidation compounds was determined by X-ray analysis of **2e**.[11]

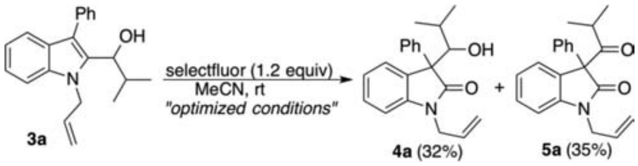
Scheme 2. Substrate Scope of 2[a]



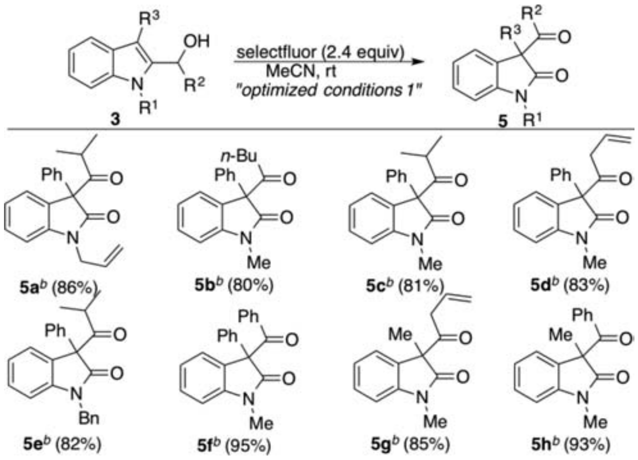
[a] All reactions were carried out at 0.2 mmol scale of **1** in MeCN (8 mL) with 1.2 equiv of selectfluor. [b] Isolated yield.

Subsequent study focused on constructing the quaternary 3-hydroxymethyl-2-oxindole compounds with secondary alcohol. Although the current method has a minimal effect on constructing the desired secondary alcohol product **4a** (Scheme 3), we observed that ketone compound **5a** existed in a certain amount when 1.2 equiv of selectfluor was used. We assumed that the secondary alcohol moiety was highly sensitive to the oxidizing reagent (i.e., selectfluor) and eventually formed the carbonyl group instead. Indeed, **4a** could be quantitatively transformed into **5a** in the presence of 1.2 equiv of selectfluor in MeCN. As such, we took advantage of selectfluor as the strong oxidant and synthesized diverse 3,3-disubstituted 2-oxindole compounds with carbonyl groups, and the results are illustrated in Scheme 4.

Scheme 3. Formation of 4a and 5a



Scheme 4. Substrate Scope of 3[a]



[a] All reactions were carried out at 0.2 mmol scale of **3** in MeCN (8 mL) with 2.4 equiv of selectfluor. [b] Isolated yield.

We discovered that up to 86% isolated yield of quaternary 3-ketone-2-oxindole compound **5a** could be obtained when 2.4 equiv of selectfluor was applied. A number of modifications could be made to the secondary alcohol indole substrate **3**, resulting in various quaternary 3-ketone-2-oxindole compounds **5**. As shown in Scheme 4, up to 95% isolated yield could be achieved when a phenyl ring was attached to the secondary alcohol (**5f**). Other

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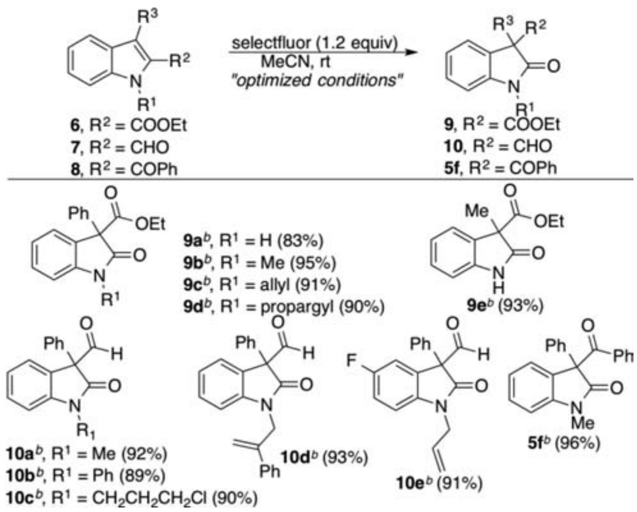
substituents were well-suited for these reaction conditions and returned excellent yields.

The current 1,2-rearrangement oxidation process also works for ester, aldehyde, and ketone functional groups. As shown in Scheme 5, various quaternary 3-ester/aldehyde/ketone-2-oxindole **9**, **10**, and **5** could be synthesized with 1.2 equiv of selectfluor when MeCN was used as solvent. Indolic hydrogen, halogen, aryl, alkene, and alkyne moieties were well-tolerated in this transformation and delivered up to 95% (**10b**) (Scheme 5) isolated yield. Up to 96% isolated yield could be achieved when R^2 was substituted by a ketone group (**5f**) (Scheme 5). 3-Ester/aldehyde-2-oxindole supplemented the 3-hydroxymethyl/ketone-2-oxindole by simply using the corresponding 2-ester/aldehyde indole starting material.

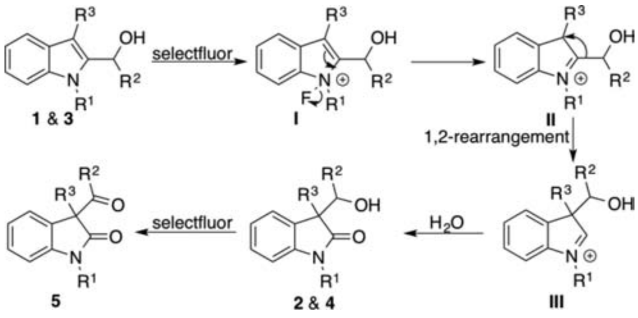
Scheme 5. Substrate Scope of the Directing Group[a]



[a] All reactions were carried out at 0.2 mmol scale of **8**, **9**, or **10** in MeCN (8 mL) with 1.2 equiv of selectfluor. [b] Isolated yield.

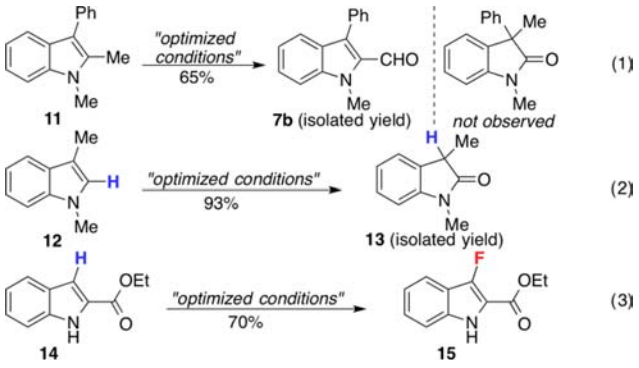
For a mechanistic study, we believed that the nitrogen atom in substrates **1** and **3** could contribute to the fluorination to give an iminium ion intermediate **I** (Scheme 6). The cation intermediate **II** initiated the 1,2-rearrangement process and formed intermediate **III**. This 1,2-rearrangement process was further supported by rearrangement of indolyl acetates and carbonates.[12] Subsequent oxidation with a trace amount of water in the media furnished the quaternary 3,3-disubstituted 2-oxindole product **2** or **4**. Further oxidation of secondary alcohol **4** with an extra equivalent of selectfluor furnished the final quaternary 3-ketone-2-oxindole products **5**.

Scheme 6. Proposed Mechanism



Note that the alkyl group might not be suitable to direct the 1,2-rearrangement process, as the 2-methylindole substrate **11** failed to form the desired 3,3-disubstituted 2-oxindole compound. As illustrated in Scheme 7, the strong oxidative effect of selectfluor preferred to turn the methyl group into an aldehyde group and generated 2-aldehyde indole **7b** in 65% isolated yield instead (Scheme 7, eq 1). We also discovered that hydride could direct selectfluor to perform the 1,2-hydride shift. As indicated in Scheme 7, hydride at the C2 position migrated to the C3 position, leading to the formation of the desired tertiary 3-substituted 2-oxindole product **13** (Scheme 7, eq 2). Because hydride, hydroxymethyl, ester, aldehyde, and ketone were able to create hydrogen bonds, we assumed that a hydrogen bonding effect was necessary to coordinate selectfluor and direct the rearrangement process. However, we failed to detect the 1,2-hydride shift oxidation process if hydride was placed at the C3 position. Instead, fluorination of the C3 position resulted in formation of 3-fluoroindole compound **15** (Scheme 7, eq 3).

Scheme 7. Reaction of Substrates 11, 12, and 14



In summary, a facile method to construct diverse quaternary 3,3-disubstituted 2-oxindole without catalyst in mild conditions is developed. The current chemistry can be extended to synthesize a tertiary 3-substituted 2-oxindole compound if hydride is placed at the C2 position of an indole skeleton. Various functional groups, such as hydroxymethyl, ketone, aldehyde, and ester groups, can be easily incorporated into a quaternary carbon center. A mechanistic study implies that an iminium-intermediate-triggered 1,2-rearrangement is involved, and a trace amount of water is required for subsequent oxidation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01367.

Experimental details and characterization data (PDF)

X-ray crystal structure of compound **2e** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) X-ray data of **2e** (CCDC 1476348) are contained in supplementary information. These data can also be obtained free of charge from the Cambridge crystallographic data center via www.ccdc.cam.ac.uk/data_request/cif.

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