Direct Conversion of Indoles to 3,3-Difluoro-2-oxindoles *via* Electrophilic Fluorination
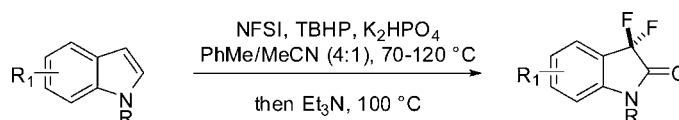
Yee Hwee Lim,* Qunxiang Ong, Hung A. Duong,* Tuan Minh Nguyen, and Charles W. Johannes

Organic Chemistry, Institute of Chemical and Engineering Sciences (ICES), Agency for Science, Technology and Research (A*STAR), 11 Biopolis Way, The Helios Block, #03-08, Singapore 138667

lim_yee_hwee@ices.a-star.edu.sg; duong_hung@ices.a-star.edu.sg

ABSTRACT

3,3-Difluoro-2-oxindoles can be obtained directly from indoles in moderate yields *via* electrophilic fluorination using *N*-fluorobenzenesulfonimide as a mild fluorinating reagent. The presence of *tert*-butyl hydroperoxide during the reaction, together with additional heating after quenching the reaction with triethylamine, is beneficial to the formation of the desired product.

The introduction of fluorine(s) into organic molecules typically changes their physiochemical properties significantly due to the strong electronegativity and the relatively small size of the fluorine atom. Fluorine and fluoroalkyls are known to increase the metabolic stability, lipophilicity, bioavailability, membrane permeability, and binding affinity of bioactive molecules.[1] It is estimated that 30–40% of agrochemicals and 20% of pharmaceuticals contain fluorine.[1a,b] The radioisotope [18]F ($t_{1/2}$ = 109.7 min) is used in Positron Emission Tomography (PET) to provide real time visualization and quantitative measurements of metabolic, biochemical, and physiological function *in vivo*.[2] Moreover, perfluorinated compounds have found a wide range of applications in materials.[3]

Significant advances have been made by various research groups in the area of nucleophilic, electrophilic, and radical fluorination, difluoromethylation, and trifluoromethylation over the past few decades.[1c,4] A number of novel fluorination methods have been reported

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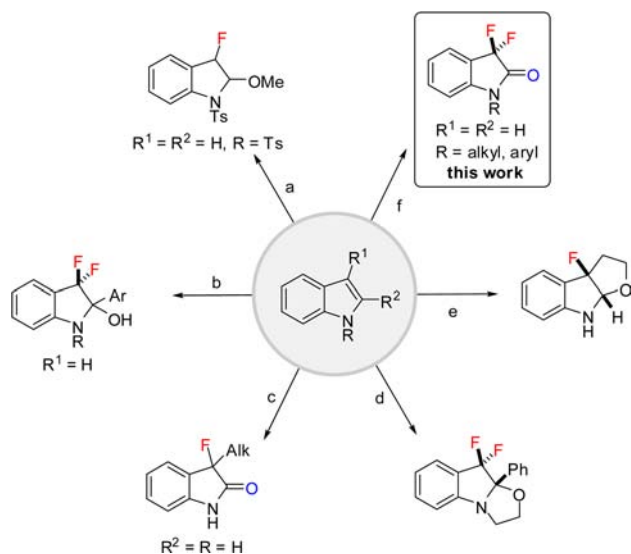
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recently.[5,6] Yet, these areas remain of immense interest to the synthetic community.

Isatin and derivatives have been shown to display antimicrobial, anticancer, antiviral, and anti-inflammatory activities.[7] The replacement of the keto carbonyl in isatins with the isosteric[8] *gem*-difluoro moiety leads to 3,3-difluoro-2-oxindole, a useful analogue for biological studies.[9,10] This class of compounds is often synthesized by nucleophilic fluorination of isatins using thermally unstable diethylaminosulfur trifluoride (DAST)[9f] or, more recently, bis(methoxyethyl)aminosulfur trifluoride (Deoxofluor)[9d] and 4-*tert*-butyl-2,6-dimethylphenyl-sulfur trifluoride (Fluolead).[9b] Alternatively, copper-mediated intramolecular cyclization of iododifluoroace-tamides affords 3,3-difluoro-2-oxindoles in moderate yields.[11] Yet, to the best of our knowledge, there has been no report on the direct conversion of broadly available indoles to 3,3-difluoro-2-oxindoles. This is rather remarkable considering the rich chemistry that indoles display.

Scheme 1. Electrophillic Fluorination of Indoles

Electrophilic fluorination of indoles can lead to diverse fluorinated structures, depending on the substitution pattern of the precursors. Fluorination of *N*-tosylindole in the presence of either cesium fluoroxysulfate or Selectfluor in an acetonitrile/methanol mixture (1:1) affords 3-fluoro-2-methoxyindoline (Scheme 1a).[12] Recently, indoles possessing substituents at either C2 or C3 were shown to undergo electrophilic fluorination with Selectflour to produce 3,3-difluoroindolin-2-ols (Scheme 1b)[13] or 3-fluorooxindoles (Scheme 1c),[14] respectively. Indoles with pendant hetero-nucleophiles tethered at either C3 or N can give rise to interesting heterocyclic structures under fluorocycliza-tion conditions (Scheme 1d and 1e).[14,15] Herein, we report a one-step synthesis of 3,3-difluoro-2-oxindoles from *N*-alkylindoles (where R_1, R_2 = H) *via* electrophilic fluorination (Scheme 1f).

The initial investigation focused on the fluorination of *N*-methylindole (**1a**) with various electrophilic fluorinating reagents such as Selectfluor and *N*-fluorobenzenesulfoni-mide (NFSI). Under conditions similar to those previously employed for electrophilic fluorination of indoles,[12-15] only trace amounts of the desired product could be observed by ^{19}F NMR.[16] Pleasantly, treating **1a** with 3 equiv of NFSI in a solvent mixture of toluene/acetonitrile (4:1) at 70 °C for 1 h gave difluorooxindole **2a** in 18% yield as determined by ^{19}F NMR (Table 1, entry 1). The addition of *tert*-butyl hydroperoxide (TBHP) to the reaction mixture proved highly beneficial as the yield of **2a** improved to 32% (entry 2). Significant amounts of two other fluorinated species were observed in the crude mixture by ^{19}F NMR. We speculated that they could be the hemiaminal intermediates[17] (*vide infra*) that were not fully converted to the desired difluorooxindole. Running the reaction at a higher temperature (100 °C, 60 min) or for a longer reaction time (70 °C, 120 min) only gave **2a** in 21% and 36% yields, respectively (entries 3 and 4). A yield of 46% could be obtained, however, if the reaction was first run at 70 °C until the complete consumption of **1a**, followed by addition of excess triethylamine (Et₃N) and further heating at 100 °C for 1 h (entry 5). A clean conversion of the hemiaminal intermediates to the desired product was observed by ^{19}F NMR in this case. Upon screening a range of additives,[16] we found that addition of K₂HPO₄ led to an additional enhancement in yield to 55% (entry 6). While running the fluorination at ambient temperature for 16 h resulted in a much lower yield (13%) of the product (entry 7), a yield of 62% could be obtained at 90 °C after 20 min (entry 8). Finally, the optimized conditions involve 1.5 equiv of TBHP, 5 equiv of K₂HPO₄, and 3 equiv of

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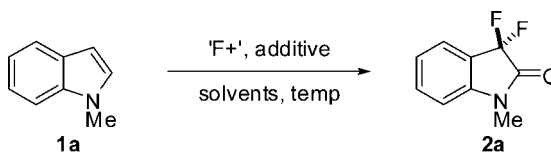
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(16) For more details, see Supporting Information.

(17) One of the hemiaminal intermediates identified as **V** (Scheme 2) was isolated as a mixture with oxindole **IX** for the case of **1a**.

NFSI (entries 9–12). It should be noted that the presence of TBHP at the beginning of the reaction was important. Indeed, when TBHP and Et$_3$N were added after **1a** had been fully consumed, further heating at 100 °C for 1 h only resulted in a 23% yield of **2a** (entry 13). No formation of **2a** was observed when Selectfluor was used instead of NFSI (entry 14).

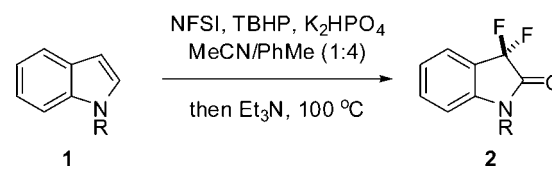**Table 1.** Screening Results for Electrophilic Fluorination of *N*-Methylindole[a]

entry	TBHP (equiv)	K$_2$HPO$_4$ (equiv)	temp (°C)	t (min)[b]	% yield[c]
1	–	–	70	60	18
2	3	–	70	60	32
3	3	–	100	60	21
4	3	–	70	120	36
5[d]	3	–	70	60	46
6[d]	3	5	70	60	55
7[d]	3	5	25	960	13
8[d]	3	5	90	20	62
9[d,e]	3	5	90	20	55
10[d,f]	3	5	90	20	55
11[d]	3	3	90	20	51
12[d]	1.5	5	90	20	63
13[d,g]	1.5	5	90	20	23
14[d,h]	1.5	5	90	20	0

[a] Conditions: Indole (1 equiv), NFSI (3 equiv), PhMe/MeCN (4:1, 0.05 M). [b] Reaction was monitored by tlc until all starting material was consumed. [c] Determined by ^{19}F NMR with 2-fluoronitrobenzene as an internal standard. [d] After the reaction, Et$_3$N (18 equiv) was added, and the reaction was heated further at 100 °C for 1 h. [e] 4 equiv of NFSI was used. [f] 2 equiv of NFSI was used. [g] TBHP was added at the end of the reaction instead, together with Et$_3$N. [h] Selecfluor was used instead of NFSI.

Under the optimized conditions, *N*-methyl-3,3-difluoro-2-oxindole (**2a**) was isolated in 50% yield (Table 2, entry 1). Other *N*-substituted indoles were also tested. The bulkier ^{i}Pr group resulted in a lower yield (32%) compared to other straight chain alkyl groups (entries 2–5). A slightly higher yield was obtained with the benzyl protecting group (60%, entry 6). Substituted benzyl groups with varied electronic and steric requirements on the benzene ring did not influence the reaction to any significant extent, with the exception of requiring longer reaction times for completion (entries 7–9). The reactions of *N*-aryl indoles (**1j** and **1k**) proceeded rather slowly under the standard conditions. Running the reactions at 120 °C for a prolonged reaction time in the absence of K$_2$HPO$_4$ could help to obtain **2j** and **2k** in 40% and 48% yields, respectively (entries 10 and 11). Of note, free indoles or indoles possessing electron-withdrawing *N*-protecting groups, such as Boc, Ts, and Ac, only resulted in trace amounts of the desired products under all the conditions tested.

Table 2. Fluorination of Different *N*-Substituted Indoles[a]

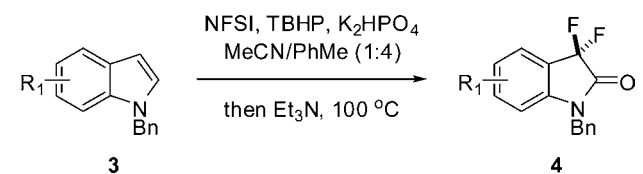| entry	indole	R	temp (°C)	t (min)[b]	% yield[c]
1	**1a**	Me	90	20	50
2	**1b**	CH$_2$CH$_2$OBn	90	20	46
3	**1c**	^{i}Pr	90	20	32
4	**1d**	Bu	90	20	47
5	**1e**	*s*-Bu	90	20	43
6	**1f**	Bn	90	20	60
7	**1g**	4-^{t}BuC$_6$H$_4$CH$_2$	90	45	56
8	**1h**	2-O$_2$NC$_6$H$_4$CH$_2$	90	70	57
9	**1i**	5-MeO-2-Br-C$_6$H$_4$CH$_2$	90	30	64
10[d]	**1j**	C$_6$H$_5$	120	180	40
11[d]	**1k**	4-MeOC$_6$H$_4$	120	120	48

[a] Conditions: Indole (1 equiv), NFSI (3 equiv), K$_2$HPO$_4$ (5 equiv), PhMe/MeCN (4:1, 0.05 M) at the specified temperature and time; then Et$_3$N (18 equiv), 100 °C for 1 h. [b] Reaction was monitored by tlc until all starting material was consumed. [c] Isolated yields. [d] K$_2$HPO$_4$ was not used.

A variety of *N*-benzylindoles can be converted to the corresponding 3,3-difluoro-2-oxindoles employing our method (Table 3). A higher temperature (120 °C) was necessary to achieve good conversions for substrates possessing an electron-withdrawing substituent (entries 1–5, 9, 10, and 12). Functional groups amenable to further manipulations, such as bromide (entries 1, 10, and 12), nitro (entry 3), ketone (entry 4), and nitrile (entry 9), are all compatible with our conditions to give the corresponding difluorooxindoles in moderate yields (45–60%). It is noteworthy that carbonyl containing indole **3d** can also be difluorinated, demonstrating the complementarity of our method to the existing nucleophilic conditions (entry 4).[9b,d,f] For *N*-benzyl 5-nitroindole (**3c**), the reaction proceeded with a reasonable conversion only when K$_2$HPO$_4$ was eliminated from the reaction to give **4c** in 50% yield (entry 3). For indoles with electron-donating groups, yields of 42–54% were achieved at slightly lower temperatures (70–90 °C) (entries 6–8).

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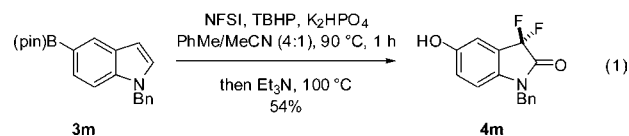
The hydroxyl functional group is not tolerated under the fluorination conditions. However, indole **3m** can be directly transformed to the oxindole **4m** in 54% yield (eq 1), where the boronic ester effectively serves as a masked hydroxyl group for further manipulations.

Several mechanistic scenarios can be envisioned for the electrophilic fluorination of indoles leading to

Table 3. Scope of *N*-Benzyl Indoles[a]

entry	indole	product	temp (°C)	t (min)[b]	% yield[c]
1[d]	3a	4a	120	60	60
2	3b	4b	120	30	57
3[e]	3c	4c	120	300	50
4	3d	4d	120	180	45
5	3e	4e	120	120	46
6	3f	4f	90	20	54
7	3g	4g	70	60	42
8	3h	4h	70	60	42
9	3i	4i	120	120	55
10[f]	3j	4j	120	40	50
11	3k	4k	90	20	58 (64)[g]
12	3l	4l	120	60	46

[a] Conditions:: Indole (1 equiv), NFSI (3 equiv), K_2HPO_4 (5 equiv), PhMe/MeCN (4:1, 0.05 M) at the specified temperature and time; then TEA (18 equiv), 100 °C for 1 h. [b] Reaction was monitored by tlc until all starting material was consumed. [c] Isolated yields. [d] Reaction mixture was heated for 1.5 h at 100 °C after addition of Et_3N instead. [e] K_2HPO_4 was not used. [f] 1 equiv K_2HPO_4 was used. [g] Benzene was used instead of toluene.

3,3-difluoro-2-oxindoles (Scheme 2). Electrophilic fluorination at C3 of indole **I** followed by rearomatization leads to the monofluorinated indole **III** (*path a*). A second fluorination step then leads to iminium **IV** which can be captured by water in the medium to give hemiaminal **V**.[17]

Scheme 2. Proposed Pathways for Electrophilic Fluorination of Indoles Leading to 3,3-Difluoro-2-oxindoles
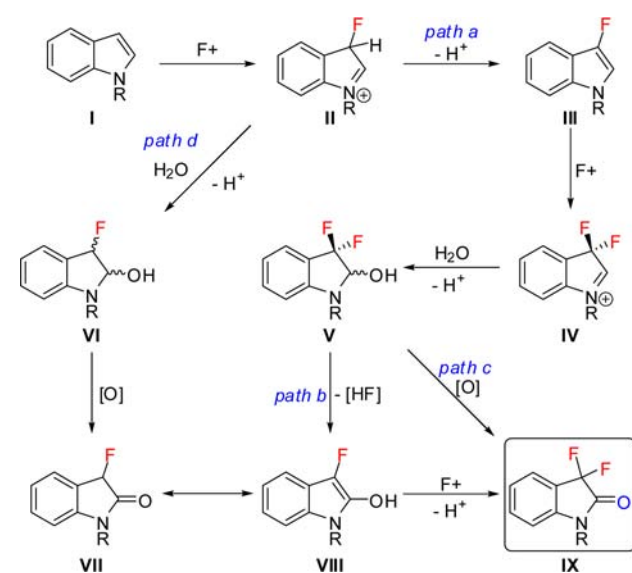
Elimination of HF followed by another fluorination step and tautomerization can lead to the oxindole **IX** (*path b*). Direct oxidation of the hemiaminal **V** could also directly produce the desired product (*path c*). Alternatively, **VIII** can be formed via *path d*, involving trapping of **II** with water followed by oxidation and fluorination. While the exact role of TBHP remains unclear at this stage, it is possible that TBHP could promote the oxidative steps in *path a* and/or *path d* over other unproductive events.

In conclusion, we have developed a convenient method for the synthesis of 3,3-difluoro-2-oxindoles directly from indoles under electrophilic conditions. A wide range of indoles incoporating different substituents and functional groups can be fluorinated in reasonable yields. Studies into extending this method for the synthesis of other fluorinated classes of compounds are ongoing and will be reported in due course.

Supporting Information Available. Full experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.