ChemComm

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COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 10602

Received 28th August 2013,
Accepted 24th September 2013

DOI: 10.1039/c3cc46564k

www.rsc.org/chemcomm

Cascade fluorofunctionalisation of 2,3-unsubstituted indoles by means of electrophilic fluorination†

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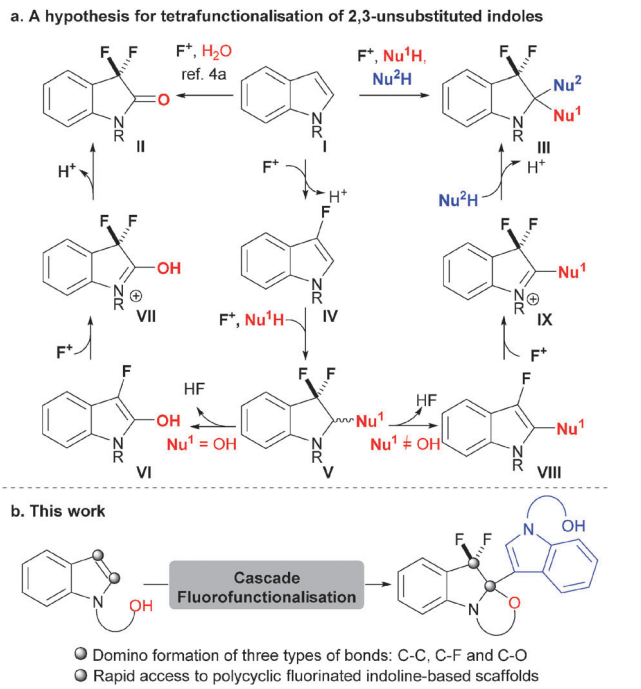
Cascade fluorofunctionalisation of 2,3-unsubstituted indoles featuring the formation of C–C, C–F and C–O bonds *via* electrophilic fluorination using *N*-fluorobenzenesulfonimide is described. The use of an *O*-nucleophile tethered to the nitrogen of indoles enables the synthesis of polycyclic fluorinated indoline derivatives from simple precursors in 40–63% yields.

The long-standing interests in fluorochemicals that are present in a wide range of applications in our daily lives,[1] for example, pharmaceuticals, agrochemicals and materials, give impetus to the development of new methods to efficiently install fluorine(s) or fluorine-containing functional groups in organic molecules.[2,3] In this context, electrophilic fluorination of indoles and indoline-2-ones or oxindoles has attracted the attention of a number of groups over the years,[4] since indole and indoline are amongst privileged structural motifs found in various drugs and natural products,[5a] as well as in materials.[5b,c] Electrophilic fluorocyclisation, a powerful method to synthesise fluorinated hetero- and carbocycles from alkenes,[6] can offer a convenient access to fluorinated indolines from indoles as demonstrated by several groups.[7] The common feature of this process is the concomitant formation of two types of bonds (*i.e.* C–F and C–O, or C–F and C–N). To the best of our knowledge, however, formation of three different types of bonds in a cascade fashion through fluorocyclisation reactions has not been documented to date. As one could envision, such a process can offer new opportunities to assemble highly complex structures in an efficient manner. We herein demonstrate the feasibility of a domino C–C/C–F/C–O bond forming sequence to rapidly access polycyclic difluorinated indoline derivatives.

We recently reported the conversion of indoles into 3,3-difluoro-2-oxindole **II** using *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating agent (Scheme 1a).[4a] A possible key intermediate of this process was proposed to be a hemiaminal (Scheme 1, **V**, Nu^1 = OH), which subsequently undergoes HF elimination and electrophilic fluorination to give oxindole **II**. We envisioned that if **V** could, however, be generated with a nucleophile ($Nu^1 \neq OH$), interception of the incipient iminium **IX** with a second nucleophile (Nu^2) may lead to a highly functionalized fluorinated indoline **III** (Scheme 1a). Moreover, complex polycyclic fluorinated scaffolds could potentially be generated if a fluorocyclisation step is incorporated into the process by employing a nucleophile, for example a hydroxyl group, tethered to the nitrogen of indole (Scheme 1b). Overall, this strategy entails a vicinal tetrafunctionalisation of indoles that installs four new bonds, featuring C–C, C–F and C–O bonds.



Scheme 1 Electrophilic fluorofunctionalisation of indoles.

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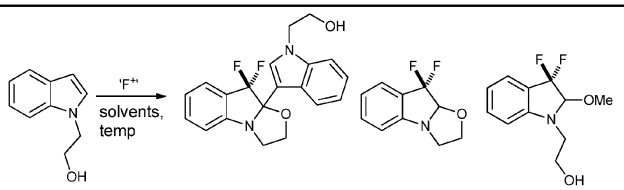
† Electronic supplementary information (ESI) available: Full experimental procedures, compound characterisation and copies of NMR spectra. See DOI: 10.1039/c3cc46564k

To test our hypothesis, we subjected indole **1a** possessing a hydroxyl group as the pendant nucleophile to electrophilic fluorination conditions, using NFSI in a 1 : 1 mixture of MeCN–MeOH at 25 °C (Table 1, entry 1). To our delight, compound **2a** was isolated in 35% yield (38% as determined by ^{19}F NMR) as the major product, demonstrating the viability of a cascade fluorofunctionalisation. The minor product **4a** was also observed by ^{19}F NMR in 8% yield. Screening of reaction temperatures and concentrations showed that the reaction was optimal at 0.05 M of **1a** and at −20 °C (entries 1–6). We next studied the influence of solvents on the reaction (entries 7–13). The use of a co-solvent system of MeOH with either MeCN, CH_2Cl_2 or PhMe was critical to the formation of **2a**.[8] Interestingly, oxazolidine **3a** was selectively obtained in 40% yield when the reaction was performed in a mixture of PhMe–MeCN (4 : 1) at 100 °C (entry 13). A basic additive such as $NaHCO_3$ or K_2HPO_4 was found to inhibit the reaction (entry 14), while the addition of an acid such as CF_3COOH or CH_3COOH led to a reduction in yield of **2a** to 40% (entry 15). Varying the amount of NFSI (entries 16 and 17) or switching to another fluorinating reagent such as Selectfluor (entry 18) was detrimental to the reaction outcome.

A range of indoles could undergo the cascade fluorofunctionalisation under our optimised conditions (Table 2). Notably, the three

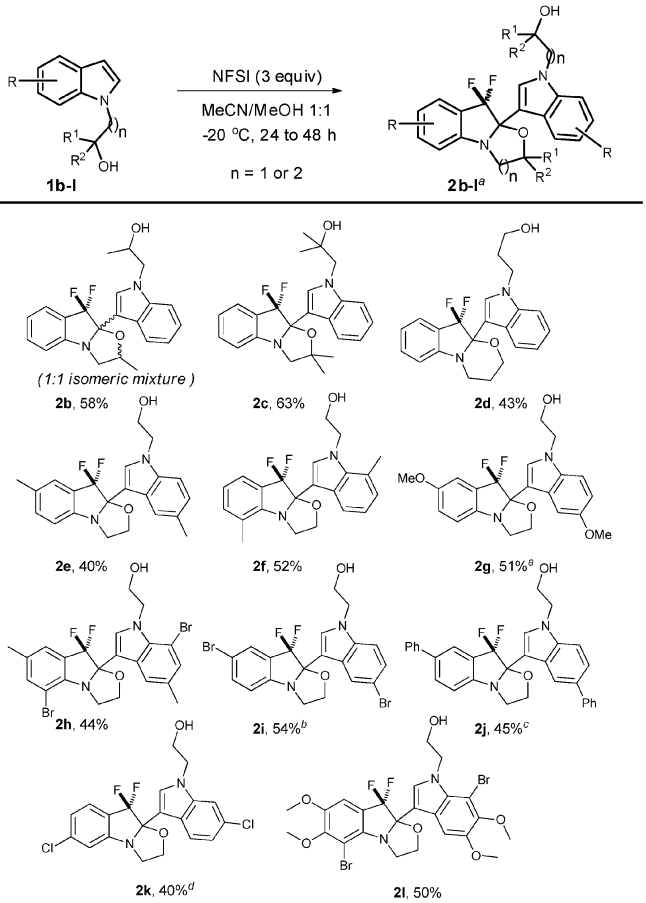
Table 1 Optimisation of the cascade fluorofunctionalisation



Entry[a]	Solvents (ratio)	T (°C)	Yield[b] (%) 2a	3a	4a
1	MeCN–MeOH (1 : 1)	25	38 (35)[c]	Trace	8
2[d]	MeCN–MeOH (1 : 1)	70	9	4	8
3	MeCN–MeOH (1 : 1)	−20	60 (54)	0	3
4	MeCN–MeOH (1 : 1)	−40	6	0	Trace
5[e]	MeCN–MeOH (1 : 1)	−20	26	0	Trace
6[f]	MeCN–MeOH (1 : 1)	−20	16	0	Trace
7	MeCN	−20	43	0	0
8	MeOH	−20	18	0	3
9	CH_2Cl_2	−20	28	Trace	—
10	PhMe	−20	42	Trace	—
11	CH_2Cl_2–MeOH (1 : 1)	−20	60	0	0
12	PhMe–MeOH (1 : 1)	−20	65	0	0
13[d,g]	PhMe–MeCN (4 : 1)	100	Trace	42 (40)	0
14[h]	MeCN–MeOH (1 : 1)	−20	0	0	0
15[i]	MeCN–MeOH (1 : 1)	−20	40	0	0
16[j]	MeCN–MeOH (1 : 1)	−20	40	Trace	Trace
17[k]	MeCN–MeOH (1 : 1)	−20	26	Trace	Trace
18[l]	MeCN–MeOH (1 : 1)	−20	0	0	0

[a] Conditions: indole (1 equiv.), *N*-fluorobenzenesulfonimide (NFSI, 3 equiv.), solvent (0.05 M), 20 h. [b] Yield determined by ^{19}F NMR using 1,3-bis(trifluoromethyl)benzene as the internal standard. [c] Isolated yield. [d] Reaction was completed in 1 h. [e] Reaction was performed at 0.01 M concentration. [f] Reaction was performed at 0.25 M concentration. [g] Difluorooxindole was also formed with an estimated yield of 16%. [h] $NaHCO_3$ (2 equiv.) or K_2HPO_4 (equiv.) was used as an additive. [i] CH_3COOH (2 equiv.) or CF_3COOH (2 equiv.) was used as an additive. [j] 5 equiv. of NFSI was used. [k] 2 equiv. of NFSI was used. [l] Selectfluor was used instead of NFSI.

Table 2 Substrate scope of the cascade fluorofunctionalisation

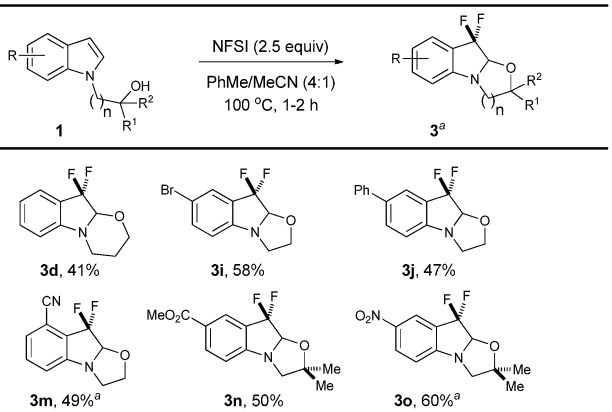


[a] Reaction was performed in a 1 : 1 mixture of MeCN–EtOH at −40 °C for 40 h. [b] Reaction was performed at −20 °C for 48 h. [c] Reaction was performed at −20 °C for 70 h. [d] Reaction was performed at −20 °C for 96 h.

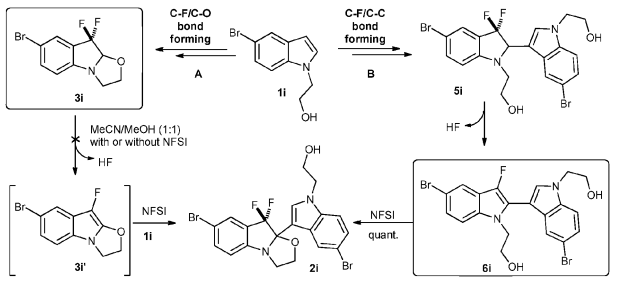
best solvent systems from our optimization were tested for each substrate (entries 3, 11 and 12) and MeCN–MeOH (1 : 1) was found to give better yields of the desired products in most cases. Indoles incorporating a pendant secondary or tertiary hydroxyl group underwent the reaction to give products **2b** and **2c** in 58% and 63% yields, respectively. Formation of tetrahydro-1,3-oxazine **2d**, however, was less favored as it was only obtained in 43% yield. Indoles possessing electron-donating, halogen or phenyl substituents on the benzenoid ring could be converted to the desired products in 40–52% yields (**2e–2l**). Notably, rapid polymerisation was observed with 4-methoxyindole **1g** under the standard conditions. Performing the reaction in EtOH instead of MeOH at −40 °C allowed for the isolation of **2g** in 51% yield. Indoles with diminished nucleophilicity such as **1i**, **1j** and **1k** required longer reaction times to convert. In accord with this trend, highly deactivated indoles possessing strongly electron-withdrawing groups such as nitrile (**1m**), ester (**1n**) or nitro (**1o**) failed to give the desired products. Interestingly, di- or tri-substituted indoles **1h** and **1l** afforded **2h** and **2l** in 44% and 50% yields, respectively.

We further examined the scope of difluorocyclisation (Table 1, entry 13) at high temperatures to prepare a range of oxazolidines and tetrahydro-1,3-oxazines **3** (Table 3). Indoles possessing a

Table 3 Difluorocyclisation of indoles **1** at high temperatures



[a] Reaction was performed at 100 °C for 18 h.



Scheme 2 Possible mechanism of the cascade fluorofunctionalisation of indoles **1**.

strong electron-withdrawing group such as nitrile (**1m**), ester (**1n**) or nitro (**1o**) afforded oxazolidines **3m–o** in 49–60% yield. Tetrahydro-1,3-oxazine **3d** was also obtained in 41% yield.[9]

To probe whether **3** is an intermediate *en route* to **2** (Scheme 2, pathway **A**), we subjected **3i** to the cascade fluorofunctionalisation conditions (NFSI, MeCN–MeOH 1 : 1). However, no conversion of **3i** was observed, suggesting that **3i** did not undergo the HF elimination process to afford **3i′**. Interestingly, we were able to isolate bisindole **6i** in *ca.* 4% yield in the reaction of **1i** with 1.7 equiv. of NFSI under the cascade fluorofunctionalisation conditions. Importantly, **6i** was fully converted to **2i** upon treatment with NFSI. Overall, these observations favour a mechanism whereby the C–C bond formation precedes the *O*-cyclisation step (Scheme 2, pathway **B**) *via* an intermediate such as difluorinated indoline **5i**.[10] The failure of electron-deficient indoles such as **1m–o** to give **2** could be explained by their inability to intercept an iminium intermediate. At high temperatures, indoles **1** could rapidly undergo fluorination with NFSI,[4a] rendering them unavailable towards the C–C bond forming process (pathway **B**). Thus, difluorocyclisation products were obtained under these conditions (pathway **A**).

In conclusion, we have developed a new cascade tetrafunctionalisation of 2,3-unsubstituted indoles *via* electrophilic fluorocyclisation. A range of polycyclic fluorinated indolines can be prepared in 40–63% yields by this process that simultaneously generates four new bonds, featuring C–C, C–F and C–O bonds. In cases of indoles bearing electron-withdrawing substituents on the benzenoid ring, the fluorocyclisation can produce oxazolidines and tetrahydro-1,3-oxazines **3** in 40–60% yields. Extension of the current strategy to incorporate other nucleophiles, and studies on the photochromic properties of these fluoroindoline derivatives as potential molecular switches[5b,c] are now underway in our laboratory.

Financial support for this work was provided by ICES, A*STAR, Singapore. We thank Ms Doris Tan (ICES) for high resolution mass spectrometric (HRMS) assistance, and the Experimental Therapeutic Center (ETC, A*STAR) for generous use of their NMR facilities for ^{19}F NMR analysis. We also thank Dr Paul Huleatt and Dr Brendan Burkett (ICES) for their support.

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8 Ethanol and i-propanol were also tried in this reaction and showed that the reaction rate was dramatically decreased.

9 Oxindoles were also formed under these reaction conditions in 15–20% yields as determined by ^{19}F NMR. See ESI† for the example **7i**.

10 An alternative pathway leading to **6i** from **1i** *via* an intermediate other than **5i** is also possible. See ESI† for more details.

