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Abstract: Indoles substituted by electron-depleted thio groups at positions 1 and 3 react as C2=C3 dipolarophiles with an electron-rich azomethine ylide dipole under flow conditions. The dearomatizing (3+2) cycloadditions readily occur to afford the corresponding fluorinated 3D-pyrrolidinoindolines bearing a tetrasusbtituted carbon centre at the ring junction.

Key words: Organofluorine chemistry, Dearomatization, (3+2)-Cycloaddition, Electron-poor arenes, Hetero-aromatics

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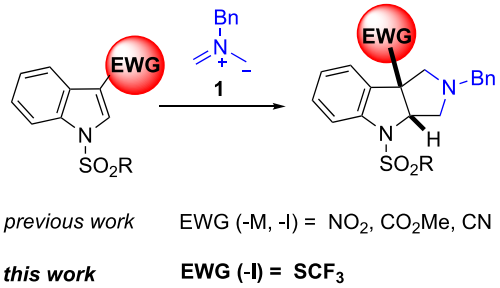
Dearomatization reactions have become an important topic in organic synthesis due to their ability to generate high value 3D-structures from planar raw substrates.[1-4] In this context, indole dearomatization strategies are meaningful due to the prominence of the indoline scaffold among biologically relevant compounds. Taking advantage of the well-recognized C3-nucleophilicity of the electron-rich indole heterocycle, different elegant alkaloid syntheses have been developed.[5-9] Complementarily, 3-nitroindoles have recently emerged as interesting electrophilic partners benefiting from the high electron-withdrawing character of the nitro group.[10] As a matter of fact, we just demonstrated that the electrophilicity of *N*-protected 3-nitroindoles is surprisingly in the range of nitrostyrenes.[10b] Different (3+2) dearomatization processes have been developed in this context, involving the C2=C3 indolic moiety as an

electron-poor dipolarophile. In these cycloadditions, replacing the nitro substituent in position 3 by another electron-withdrawing group appears rather difficult, and the examples reporting the reactivity of differently substituted indoles are scarce. Actually, the only examples described so far involved indoles bearing mesomeric attracting substituents such as a cyano or a methoxycarbonyl.[11,12] To the best of our knowledge, no purely inductive (–I) group has been reported to be so electron-withdrawing to create an *umpolung* effect on the C2=C3 double bond of indoles. In this context, we wondered if the now popular trifluoromethylthio group, displaying a purely inductive attractive effect without the favourable assistance of a mesomeric attractive effect, could be sufficiently electron-withdrawing to enable the (3+2) cycloaddition with an electron-rich dipole such as the non-stabilized azomethine ylide **1** (Scheme 1). In addition to the methodologic challenge that this dearomatizing process represents, generating an indoline bearing a trifluoromethylthio group at a tetrasusbtituted ring junction position would be interesting from a biopharmaceutical viewpoint considering the contribution of the SCF_3 motif to greatly enhance the lipophilicity of molecules. Indeed, the exceptional lipophilicity of SCF_3, which is determined by the Hansch hydrophobic parameter (π = 1.44), is greater than those of NO_2 (-0.28), CN (-0.57), and CO_2Me (-0.01).[13] Saturation that accompanies the dearomatization of indoles together with the presence of the hydrophobic SCF_3 group could better fit the criteria of lipophilicity in drug design.[14] This fluoromethylthio group enriches our range of C3 motifs and complements our library of new bicyclic pyrrolidinoindoline scaffolds as three-dimensional drug candidates. This fluoromethylthio group enriches our range of C3 motifs and complements our library of new scaffolds as three-dimensional drug candidates.



Scheme 1: Dearomatizing 1,3-dipolar cycloaddition between electron-poor indoles and azomethine ylide **1.**

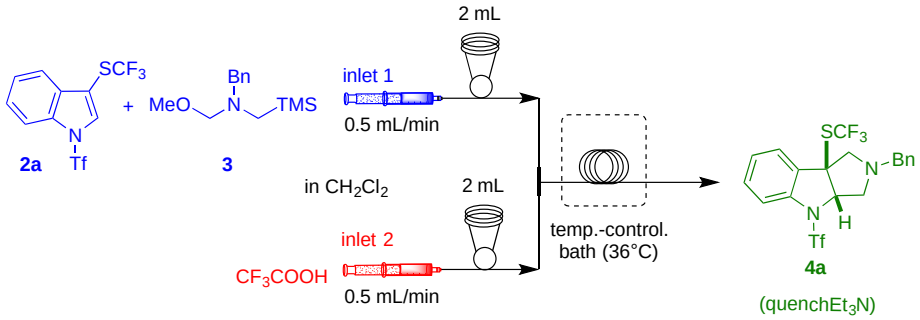
The use of miniaturised reactors operating in continuous flow has been shown to be invaluable tools to generate and trap unstable transient species reach at short reaction times

but unreachable under classical batch conditions.[15-17] Moreover, such devices offer the possibility to handle and treat significant amounts of unfriendly reagents without exposing the operator.[18-22] Due to superior mass transfer and fine residence time control obtained in flow microreactors, competitive undesired reactions can sometimes be avoided.[23-25] In this context, we have recently shown that the 1,3-dipolar cycloaddition involving 1-trifluoromethylsulfonyl-3-cyanoindoles and azomethine ylide **1** can be performed under flow conditions within only 1 min. Inspired by this work, we were interested to study the reactivity of indoles **2** in these dearomatizing cycloadditions. Access to the 3-trifluoromethylthioindoles was achieved by regioselective trifluoromethylthiolation of the corresponding indoles under the recently reported reductive conditions involving trifluoromethanesulfonyl chloride as source of electrophilic SCF_3 and a phosphine as reducing agent.[26] *N*-trifluoromethylsulfonylation, which had proven most adequate for the intended cycloadditions in our previous works,[11] was performed under classical conditions, in the presence of trifluoromethylsulfonyl anhydride (See Supporting Information).

Interaction of indole **2a** with hemiaminal **3**, used as dipole precursor in acidic medium, was envisaged in flow conditions (Table 1). The set-up was composed of two inlets, inlet 1 containing a mixture of hemiaminal **3** and indole **2a** and inlet 2 containing TFA, in order to avoid the accumulation of the unstable dipole, generated in acidic conditions, and thus the formation of undesired self-condensed oligomers. In the presence of a three-fold excess of hemiaminal **3**, we were pleased to observe the formation of the desired *cis* indoline **4a**. Even if the transformation proved incomplete in 2 min., this showed the feasibility of the dearomatizating cycloaddition starting from a trifluoromethylthio substituted substrate (entry 1). The reaction conditions were then optimized. The influence of residence time t^R was investigated by tuning the flow rates of reagents (entries 2-3). Decreasing the flow rate allowed to increase the conversion (entry 2), but was not sufficient to complete the reaction (entry 3), probably because of the competitive dipole self-condensation that can take place when the flow slows down. In contrast, increasing the amount of dipole precursor to six equivalents with a total flow rate Q_T = 1 mL/min (0.5 mL/min/inlet) allowed to reach a full conversion of the substrate within 20 min residence time t^R (entry 4) and the desired (3+2) cycloadduct **4a** was isolated in a quantitative yield (entry 4). A comparative experiment showed that similar results could also be obtained under batch conditions within the same timeframe. However, scaling up these reactions under classical batch conditions is often problematic with the increase of the quantity of trifluoroacetic acid accumulated in the

medium, exothermicity/thermalisation issues and competitive side reactions (dimerization and oligomerization of the 1,3-dipole).

Table 1. Optimization of the reaction conditions



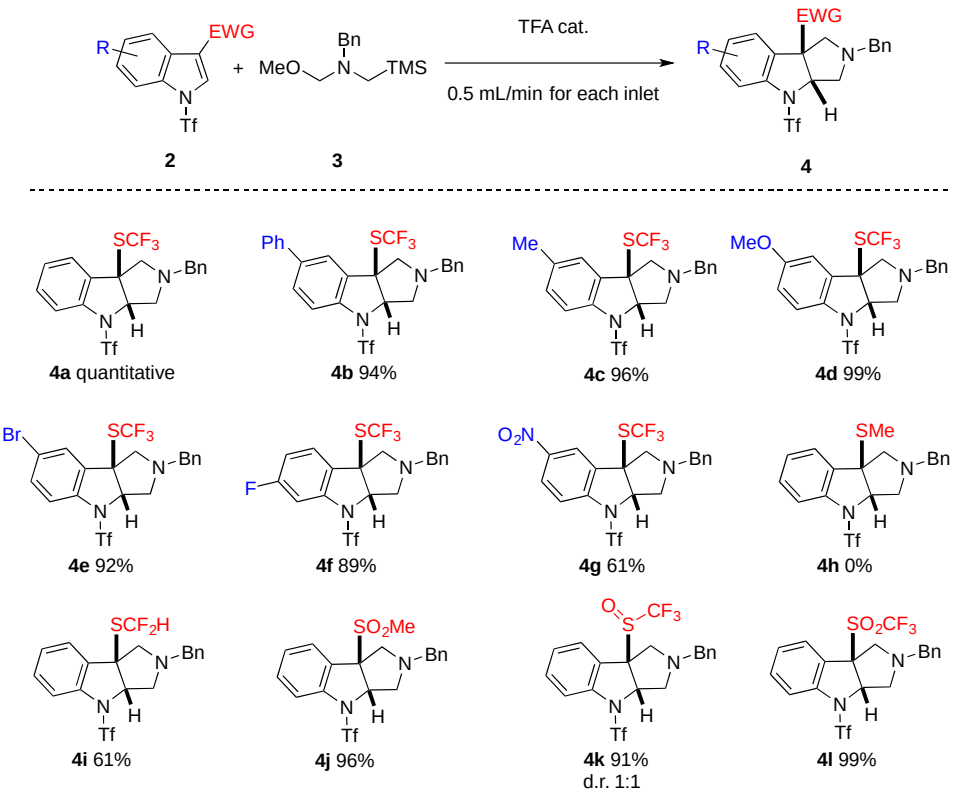
Entry	Total flow rate (mL/min)	t^R (min)	**3** (equiv)	Conv. (%)[a]
1	20	1	3	46
2	4	5	3	61
3	2	10	3	90
4	**1**	**20**	**6**	**100**

[a] conversion of the indole **2a** into **4a** determined by ^{1}H NMR on the crude reaction mixture

Having these conditions in hand, we set out to explore the scope of this transformation (scheme 2). Different 3-trifluoromethylthio- indoles **2** were reacted with hemiaminal **3** to afford differently substituted indolines **4** in good to excellent yields. Thus, indole **2b** bearing a phenyl group at position 5 readily afforded the tricyclic cycloadduct **4b** in 94% yield. Similarly, indoles **2c** and **2d** bearing an electron-releasing group at position 5, respectively a methyl and a methoxy substituent, gave the corresponding cycloadducts **4c-d** in 96-99% yields. The influence of a halogen substituent, either 5-bromo or 6-fluoro, having contradictory inductive and mesomeric effects, proved negligible, furnishing **4e** and **4f** in excellent yields (89-92%). Noteworthy, despite its various functionalities, the bromo substituted cycloadduct **4e** reacted nicely under classical Suzuki coupling conditions to furnish **4b** in 99% yield, showing its synthetic potential in cross-coupling reactions (See Supporting Information). The presence of a strongly electron-withdrawing nitro group at position 5 slightly diminished the isolated yield to 61% for **4g**. The requirement for an electron-withdrawing group on the indole substrate in position 3 was confirmed by

performing the same reaction with 3-thiomethylated indole **2h**, which remained inert under these conditions.

We next modified the sulfur group at the key position 3 of the indole substrate. Attention was paid to the difluoromethylthio SCF_2H group not only for its high lipophilicity, yet lower than the one of SCF_3, but principally for its H-bonding ability, which makes it a valuable group for the design of bioactive molecules.[27,28] We were pleased to observe a 71% conversion with the less electron-withdrawing difluoromethylthio group in indole **2i**.[29] The corresponding indoline **4i** was isolated in 61% yield. Expectedly, the more depleted 3-methylsulfonyl-, -trifluoromethylsulfinyl-, and -trifluoromethylsulfonyl indoles **2j**, **2k** and **2l**, respectively, furnished the dearomatized indolines **4j-l** in excellent yields (91-99%). In the case of the chiral at sulfur racemic sulfinylindole **2k**, a 1:1 diastereomeric ratio was observed in cycloadduct **4k**.

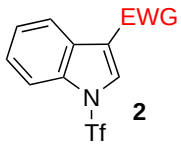


Scheme 2: Scope of the reaction under the optimized flow conditions.

In these polar cycloadditions, the efficiency of the process is linked to the electrophilicity of the starting heteroaromatic indole, anticipated to be strongly influenced by the electron-withdrawing substituent placed at position 3.[30] Computationally, global electrophilicity, as defined by Parr *et al.*,[31] is an easily accessible parameter of conceptual

DFT which can be useful to understand the reactivity of molecules in their ground states. The global electrophilicity parameter, ω was thus evaluated for *N*-trifluoromethylsulfonyl indoles differently substituted at position 3 (Table 2). The computed ω values showed that 3-nitroindole should be the most electrophilic (Table 2, entry 1), while 3-trifluoromethylsulfonyl- (entry 7), 3-cyano- (entry 2), 3-trifluoromethylsulfinyl- (entry 5) and 3-Ms-indoles (entry 6) should come next. 3-Trifluoromethylthioindole proved a little less electrophilic (entry 3) followed by 3-difluoromethylthioindole (entry 4). Expectedly, the 3-thiomethylindole was the least electrophilic of the series (entry 8). These values are in full adequation with the experimental results,[12,13] and illustrate the usefulness of this parameter for further evaluation of the reactivity of electrophilic indoles in dearomatizing polar cycloadditions.

Table 2. Field (*F*) and resonance (*R*) parameters for EWG groups.[30] LUMO energy and global electrophilicity parameter ω[32] for different indoles **2**.



2

Entry	EWG	F^a	R^a	E_{LUMO} (eV)[b]	ω (eV)[b]
1	NO_2	0.65	0.13	–1.80	1.95
2	CN	0.51	0.15	–0.82	1.36
3	SCF_3	0.36	0.14	–0.60	1.25
4	SCF_2H	0.32	0.05	–0.50	1.19
5	$SOCF_3$	0.58	0.11	–0.79	1.36
6	SO_2CH_3	0.53	0.19	–0.68	1.31
7	SO_2CF_3	0.74	0.22	–1.03	1.50
8	SCH_3	0.23	–0.23	–0.38	1.11

[a]. Hammett and modified Swain–Lupton constants for the EWG group.[30]

[b]. Energy of the LUMO and global electrophilicity parameter ω (in eV) for optimized indole derivatives **2** (See SI for details)

In short, we have described the flow synthesis of a novel class of highly functionalized tricyclic indolines bearing valuable fluoromethylthio groups such as SCF_3, SCF_2H, $S(O)CF_3$ or SO_2CF_3 on a tetravalent carbon atom at the ring junction. This path goes through the dearomatizing cycloaddition of *N*-triflyl-3-fluoromethylthioindoles. In the presence of an

electron-rich azomethine ylide 1,3-dipole, these heteroarenes behave for the first time as electron-poor dipolarophiles. These results demonstrate that the presence of an attracting group, placed at position 3 of the starting indole, even only inductively attracting, is sufficient to promote the dearomatizing (3+2) cycloadditions. These results pave the way to fast dearomatizing processes for the simple access to a large family of structurally sophisticated 3D molecules as interesting drug candidates.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest

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