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Article

Synthesis and Physicochemical Properties of 2-SF_5-(Aza)Indoles, a New Family of SF_5 Heterocycles

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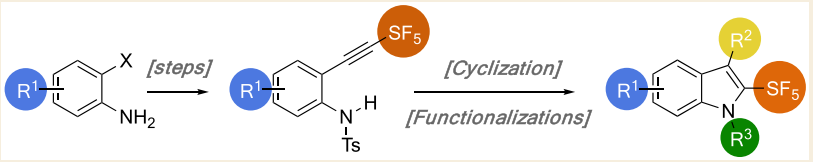

ABSTRACT: Structural diversity in heterocyclic chemistry is key to unlocking new properties and modes of action. In this regard, heterocycles embedding emerging fluorinated substituents hold great promise. Herein is described a strategy to access 2-SF_5-(aza)indoles for the first time. The sequence relies on the radical addition of SF_5Cl to the alkynyl π-system of 2-ethynyl anilines followed by a cyclization reaction. A telescoped sequence is proposed, making this strategy very appealing and reproducible on a gram scale. Downstream functionalizations are also demonstrated, allowing an easy diversification of N- and C3-positions. Ames test, pK_a, log *P*, and differential scanning calorimetry measurements of several fluorinated 2-Rf-indoles are also disclosed. These studies highlight the strategic advantages that a C2-pentafluorosulfanylated motif impart to a privileged scaffold such as an indole.

KEYWORDS: *structural diversity, fluorinated indoles, heterocyclic chemistry, pentafluorosulfanyl*

INTRODUCTION

The incorporation of a fluorinated motif in organic or inorganic molecules influences chemical and physical properties (metabolic stability, bioavailability, pK_a, etc), and this strategy is nowadays widely used in medicinal chemistry.[1] Among the so-called "emerging" fluorinated groups, the pentafluorosulfanyl group (SF_5)[2,3] is of growing interest in heterocyclic synthesis,[4−7] materials science,[8] and medicinal chemistry.[9] The SF_5 group has a volume of 55.4 Å^3, between the *t*-Bu (76.9 Å^3) and CF_3 (34.6 Å^3) groups, and its unique octahedral geometry allows a more selective interaction of SF_5-containing molecules with biological receptors.[10−12] The high lipophilicity of SF_5, expressed by the Hansch parameter (π = 1.23),[2,13] is greater than the ones of CF_3 (0.88) or OCF_3 (1.04) groups and may confer an enhanced cell membrane permeating ability. The high electronegativity of SF_5 expressed by the Hammett constant (σ_p = 0.68, σ_m = 0.61)[2,13] is also greater than that of CF_3 (σ_p = 0.53, σ_m = 0.43)[2,13] which, in turn, confers high metabolic stability. All of these properties make SF_5 an interesting alternative to the CF_3 group as a bioisostere, especially in drug development.[9,14−16]

However, synthetic routes to SF_5-containing compounds and their structural diversity remain highly challenging. Two general methods are reported for accessing SF_5-containing small molecules. The first method is an oxidative fluorination reaction of (hetero)aromatic disulfides, thiols, or, more recently, sulfenyl phthalimides which give access to ClF_4S- and then SF_5-(hetero)aromatic compounds after a final chloride−fluoride exchange step.[17−23] The second method is a direct introduction of the SF_5 group to an alkyne, an alkene, or an α-diazo carbonyl thanks to the use of SF_5Cl gas[24] under radical conditions to yield SF_5-containing compounds.[25−28] Although the use of commercially available gaseous SF_5Cl is atom economical and quite straightforward from a practical point of view, recent efforts toward its preparation from sulfur powder, potassium fluoride, and trichloroisocyanuric acid have been disclosed.[29,30] Recently, SF_6 was used as an alternative source of $SF_5^\bullet$ in photoredox catalysis, but this method up to now is limited to reactions with styrene derivatives.[31−33]

Indoles are privileged scaffolds in medicinal chemistry, and developing synthetic strategies to modulate their structures and physicochemical properties is of central importance.[34−36] In this regard, combining indoles and original fluorinated moieties such as the pentafluorosulfanyl group is of interest as it would pave the way to structural and physicochemical studies that could have an impact in medicinal chemistry. Only a handful of 5-[37−42] and 6-SF_5-indoles[43−45] are known and were obtained from commercially available SF_5-anilines or nitrophenyls (Scheme 1B). However, introducing the SF_5

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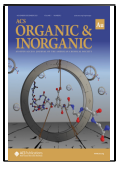

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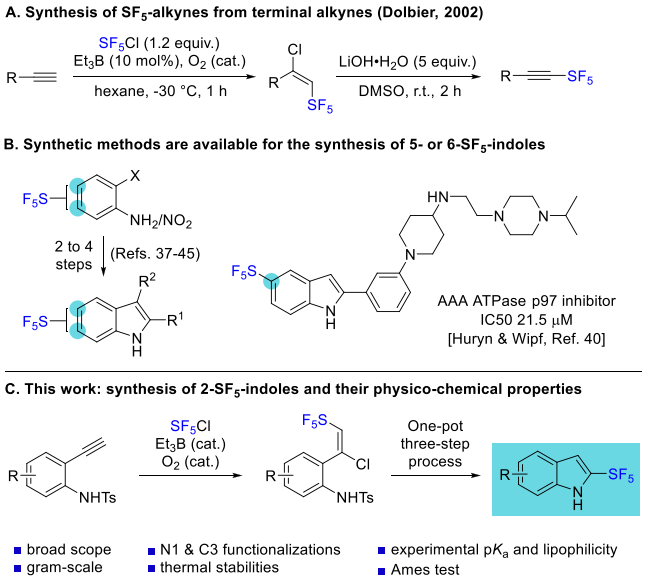
Scheme 1. State of the Art for the Introduction of the SF_5 Group on Alkyne (A) and on the C5- or C6-Position of Indoles (B) and Proposed Synthetic Strategy for the Preparation of C2-SF_5-Indole (C)



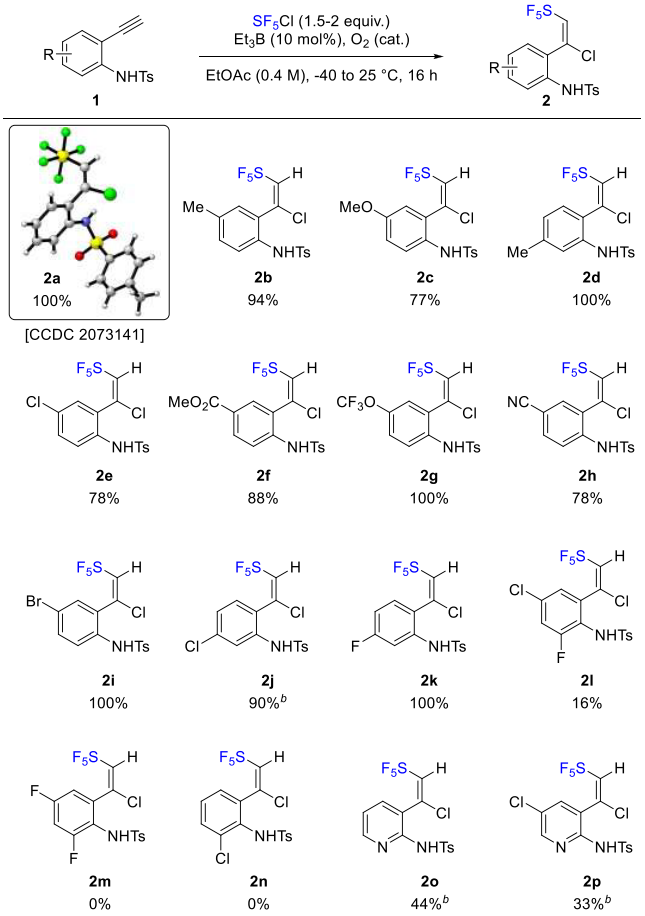
group on other positions of the indole nucleus, and more precisely on the C2-position, which is as close as possible to the nitrogen atom, is highly challenging and still not reported. Among the different strategies to access C2-SF_5-indoles, the intramolecular 5-*endo-dig* cyclization[46−49] of an *ortho*-alkynylaniline appears to be the most promising (Scheme 1C). Indeed, SF_5-substituted alkynes are easily prepared by the reaction between SF_5Cl and a terminal alkyne under radical conditions followed by basic elimination, as demonstrated by Dolbier (Scheme 1A).[25] In addition, Tsui reported that 2-CF_3-indoles could be synthesized via a domino trifluoromethylation/5-*endo-dig* cyclization of *ortho*-alkynylanilines.[49] Herein, we report that this strategic blueprint allows for a general synthesis of 2-SF_5-indoles from readily available starting materials. Their thermal stabilities, pK_a values, and lipophilicities were also studied and compared to more classical C2-fluorinated/fluoroalkylated indoles. Finally, evaluation of the mutagenic potential (Ames test) of a selection of 2-SF_5-indoles was performed.

RESULTS AND DISCUSSION

N-Tosyl-2-ethynylaniline **1a** was selected as a model compound for the screening of chloropentafluorosulfanylation conditions (Scheme 2).[50] Using catalytic amounts of triethylborane and oxygen,[51,52] the reaction proceeded smoothly in ethyl acetate or dichloromethane (0.4 M) at −40 to −20 °C, delivering **2a** in quantitative yield. Gratifyingly, a single regio- and stereoisomer was observed, with the structure of **2a** being unambiguously confirmed by X-ray diffraction (CCDC 2073141).[53] As reported by Paquin in 2019,[54] several classical organic solvents are compatible with SF_5Cl, and we found that ethyl acetate turned out to be the solvent of choice for the synthesis of **2a−p** in terms of conversions and, more importantly, purity. Indeed, in most cases, no further purification of **2** is needed.[55]

Electron-donating (4-Me **2b**, 4-OMe **2c**, and 5-Me **2d**) and electron-withdrawing (4-Cl **2e**, 4-CO_2Me **2f**, 4-OCF_3 **2g**, 4-CN **2h**, 4-Br **2i**, 5-Cl **2j**, and 5-F **2k**) substituents on the aromatic ring are well-tolerated and give high NMR yields (77−100%). Noteworthy, when the conversion is high, the crude product **2** is very clean and can be used for the next step without further purification. In a few cases, we noticed that with 6-F **2l**,**m** and 6-Cl **2n** aniline derivatives, very low conversion or no reaction was observed. Much to our delight, 2-aminopyridine derivatives are tolerated, and SF_5 adducts **2o**,**p** were obtained in 44 and 33% yields, respectively.

Scheme 2. Scope and Limitations for the Addition of SF_5Cl to 1[a]



[a]Yields determined by ^{19}F NMR and ^{1}H NMR using trifluorotoluene as internal standard. [b]Reaction performed in CH_2Cl_2 instead of EtOAc.

For the subsequent step, we first tested basic conditions described by Dolbier for the dehydrochlorination reaction (LiOH in DMSO).[25] After 16 h at room temperature, we were pleased to observe full conversion of **2a** to the expected SF_5-alkyne **3a**, along with *N*-Ts-2-SF_5-indole **4a** in a 50:50 ratio (as measured by ^{19}F NMR, Scheme 3). Extended reaction times, up to 84 h, afforded a 47:53 mixture of *N*-Ts-2-SF_5-indole **4a** and 2-SF_5-indole **5a** (arising from the deprotection of **4a** under basic conditions). Structures of **4a** (CCDC 2073143) and **5a** (CCDC 2073142) were unambiguously confirmed by X-ray diffraction.[56] After careful optimization, it was found that full conversion of **2a** into **5a** was obtained after 40 h at 40 °C. This one-pot three-step sequence (dehydrochlorination, 5-*endo-dig* cyclization, and deprotection of the tosyl moiety) is general and proceeds smoothly with all substrates **2a−p** independently of the substitution.

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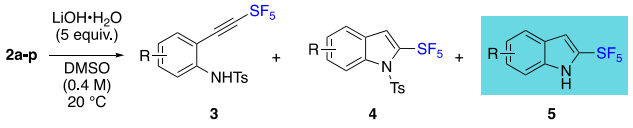
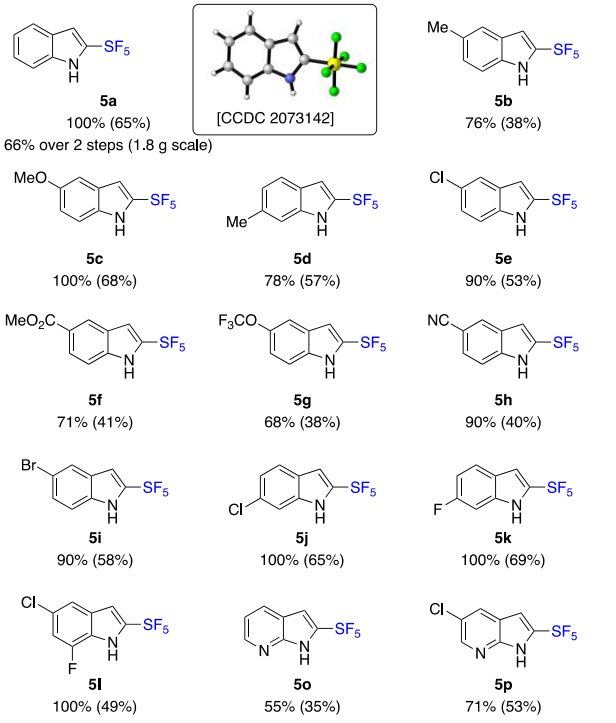
Scheme 3. Scope and Limitations for the Synthesis of 2-SF_5-Indoles 5[a]



- ^{19}F NMR ratios from **2a** (R = H)

after 16 h	50	:	50	:	0
after 84 h	0	:	47	:	53

- Optimized conditions for the scope : LiOH•H_2O (5 equiv.), DMSO (0.4 M), 40 °C, 40 h

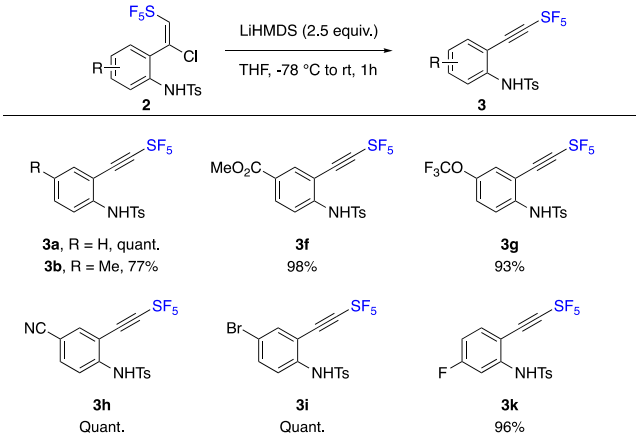


[a]NMR yields determined by ^{19}F NMR and ^{1}H NMR using trifluorotoluene as internal standard. Isolated yields in brackets after purification on SiO_2.

Good to excellent NMR yields ranging from 55% to quantitative are obtained. Noteworthy, functional groups such as ester **5f**, nitrile **5h**, halides **5e−5i,j**, or even the more exotic OCF_3 **5g** are well-tolerated. It should be noted that isolated yields of 2-SF_5-indoles **5** are 34 ± 16% lower (after chromatography on silica gel) than NMR yields. Unfortunately, all of the purification media that were screened, such as deactivated silica gel, demetalated silica gel,[57] C-18 reversed-phase silica, Florisil, or alumina did not improve yields further. However, 60−70% overall yields are still highly relevant considering that this is a formal three-step sequence. In addition, the reaction is easily scalable up to 1.8 g (4 mmol) in reproducible 66% isolated yield.

While the synthesis of N-unprotected 2-SF_5-indoles **5** is of interest, keeping the *N*-tosyl protecting group would also be an asset. After an extensive screening of base, it was found that lithium hexamethyldisilazane (LiHMDS) led to a smooth dehydrochlorination reaction at −78 °C for 1 h (Scheme 4). SF_5-Alkynes **3** were formed in 77−100% yield, with an excellent functional group tolerance. In addition, the reaction was very clean, and no purification was needed. Next, for the cyclization step, it was found that K_3PO_4 was able to convert

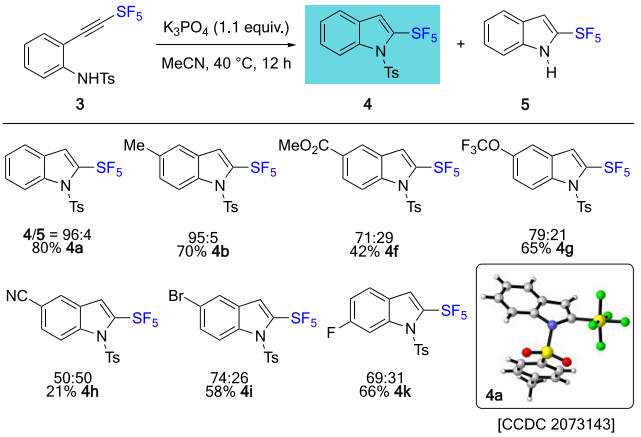
Scheme 4. Synthesis SF_5-Alkynes 3[a]



[a]Isolated yields after extraction; no purification needed.

SF_5-alkynes **3** into the desired *N*-Ts-2-SF_5-indoles **4** in acetonitrile at 40 °C for 12 h alongside the deprotected indole **5** (Scheme 5). As expected from an electronic point of view, electron-neutral or electron-donating substituents as in **3a,b** gave high selectivity for the corresponding *N*-Ts-2-SF_5-indoles **4a,b**.

Scheme 5. Synthesis of *N*-Ts-2-SF_5-Indoles 4[a]



[a]Isolated yields after purification on SiO_2. Ratio of **4**/**5** determined by ^{19}F NMR using trifluorotoluene as an internal standard.

In contrast, with electron-withdrawing substituents, a non-negligible amount of 2-SF_5-indoles **5f−i,k** (R = Br, F, OCF_3, CO_2Me, CN) was observed ranging from 30% with R = CO_2Me OCF_3, Br, F) to 50% with R = CN. Quite interestingly, isolated yields of *N*-Ts-2-SF_5-indoles **4** are much closer to NMR yields, which indicates that N-substituted 2-SF_5-indoles possess improved stability toward purification. This was further confirmed by the independent preparation of *N*-Bn-2-SF_5-indole **7** and *N*-Me-2-SF_5-indole **8** via the interception of the intermediate **6** by the corresponding electrophiles (Scheme 6A). Clean reactions and excellent yields for five steps were obtained, in line with the NMR yields (92% for **7** and 73% for **8**, a mean deviation of 7 ± 2% from the isolated yields).

C3-Functionalizations of 2-SF_5-indoles **5** were next investigated (Scheme 6B,C). We first focused on the innate C3-nucleophilicity of **5a** in halogenation reactions. Double

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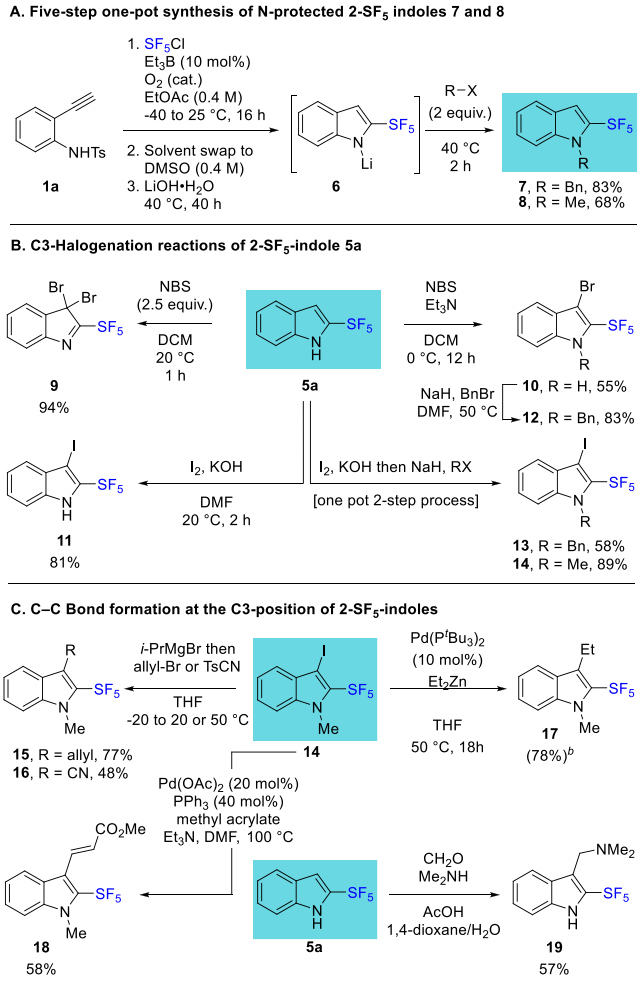
Scheme 6. Downstream Functionalizations of 2-SF_5-Indoles[a]



[a]NMR yield determined by ^{19}F NMR using trifluorotoluene as an internal standard. [b]Obtained as an inseparable mixture with indole **8**.

bromination reaction[58] with an excess of *N*-bromosuccinimide (NBS) is very efficient and yielded **9a** in 94% yield. Monobromination is also possible using a slight excess (1.1 equiv) of NBS in the presence of triethylamine.[59] The reaction proceeded quantitatively by NMR and **10** was isolated in 55% yield. Incorporation of a C3-iodine atom is also possible using molecular iodine in the presence of potassium hydroxide,[60] delivering **11** in 81% yield. The iodination step can then be combined in a one-pot process with N-benzylation (**13**, 58%) or N-methylation (**14**, 89%). Finally, C−C bond formations were investigated (Scheme 6C). Iodine−magnesium exchange of **14** followed by trapping with an electrophile such as allyl bromide or tosyl cyanide delivered **15** (77%) and **16** (48%), respectively.[61] Negishi cross-coupling with diethylzinc[62] proved to be efficient with the formation of **17** in 78% NMR yield (along with the reduced indole **8** as an inseparable mixture). Heck cross-coupling[63,64] with methyl acrylate is also productive, yielding **18** in 58% yield as a single *E*-stereoisomer. Finally, we evaluated the reactivity of the 2-SF_5-indole **5a** toward Eschenmoser salt for the synthesis of **19** (57%), the 2-SF_5 analogue of the naturally occurring indole alkaloid gramine.[65]

Having designed a synthetic strategy toward 2-SF_5-indoles and explored a selection of downstream functionalizations, we turned our attention to the investigation of their physicochemical properties and how they compare with differently C2-substituted indoles. Six indoles were selected: the 2-SF_5-indoles **5a** and **8** alongside four C2-substituted indoles, 2-H (**20**), 2-Me (**21**), 2-F (**22**), and 2-CF_3 (**23**).

We started with differential scanning calorimetry (DSC)[66−69] analysis to gain information about the thermal tolerance threshold of our process and the thermal stability of 2-SF_5-indoles (Figure 1A).[55] Both 2-SF_5-indole **5a** and **8** induce a strong release of energy (exothermic) when the threshold of thermal stability is reached, with enthalpies of −1180 kJ/kg with an onset above 165 °C for **5a** and −1324 kJ/kg starting above 310 °C for **8**.

This highly exothermic event is characteristic of a violent decomposition. However, this threshold appears at relatively high temperatures (>165 °C for **5a**, 310 °C for **8**) and therefore much higher than the maximum temperatures used for the synthesis of 2-SF_5-indoles (up to 40 °C) or their functionalization (up to 100 °C). This means that the

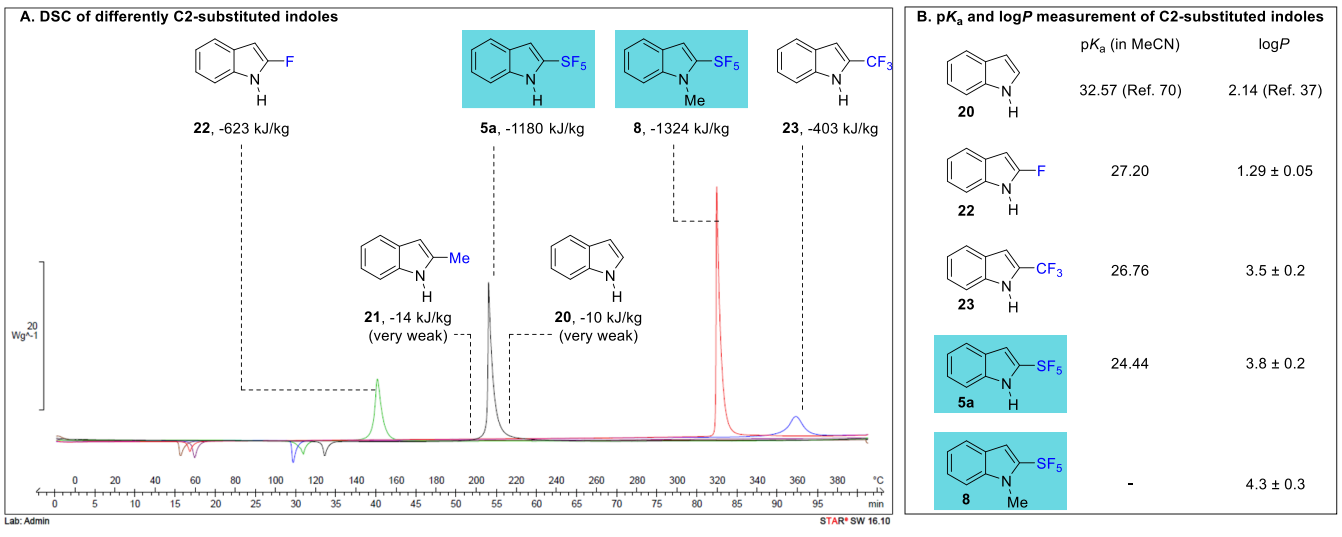


Figure 1. Differential scanning calorimetry (A) and pK_a and log *P* (B) of C2-substituted indoles.

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synthetic methods devised in Schemes 2−6 are safe with a fairly large safety margin gap (>120 °C) between the reaction processes and the decomposition onsets. As expected, the protection of 2-SF_5-indole **5a** by a methyl group (**8**) significantly increases its thermal stability. Among the fluorinated indole analogues, 2-CF_3 indole **23** is the most stable heterocycle with an exothermic degradation above 325 °C (−403 kJ/kg), whereas 2-F indole **22** degrades above 120 °C (−623 kJ/kg). It is important to note that, in comparison, the temperatures and degradation energies of 2-Me indole **21** (low exotherm above 165 °C, enthalpy of −14 kJ/kg) and indole **20** (low exotherm above 190 °C, enthalpy of −10 kJ/kg) are negligible.

Incorporation of a fluorine atom or a fluorinated group has a tremendous impact on physicochemical properties of molecules and nearby functional groups. In the specific case of the pentafluorosulfanyl moiety, physicochemical data are scarce[2−6] and experimental measurements of the acidity (pK_a)[70] and lipophilicity (log *P*)[71,72] imparted by the pentafluorosulfanyl moiety would be useful data for medicinal chemistry programs. We thus turned our attention to a subset of indoles substituted at C-2 by H (**20**), F (**22**), CF_3 (**23**), or SF_5 (**5a**/**8**), and the results are summarized in Figure 1B. Values of pK_a were measured in acetonitrile by spectrophotometric titration.[55] The pK_a of indole **20** (32.57)[70] decreases dramatically by 5.4 units upon fluorine and fluorine-containing substitution at C2, resulting in pK_a 27.20 for **22**. Swapping C2-F for a C2-CF_3 substituent only slightly impacted the pK_a by 0.44 units (pK_a of **23**: 26.76). On the other hand, a pronounced drop in pK_a was measured for **5a** possessing a C2-SF_5 motif; with a pK_a of 24.44, it stands 2.32 units lower than the pK_a of **23** and is comparable to the pK_a of 2-nitroindole (23.64).[70]

Fine modulation of lipophilicity is central to drug development,[73−75] and fluorine-containing substituents play an important role in this regard, whether in the aromatic[76] or aliphatic series.[77−79] As a consequence, assessing the impact of the pentafluorosulfanyl motif at the C2-position of indoles on log *P* was of interest. The lipophilicities of the five indole derivatives were obtained by combining experimental and computational data.[55] The average log *P* values are given in Figure 1B. Replacement of the C2-hydrogen atom of indole **20** by a fluorine atom (**22**) decreases the lipophilic character by 0.85 unit (from 2.14 to 1.29). Although lipophilicity classically increases upon H−F swap in the aromatic series, this drop in log *P* between **20** and **22** can be rationalized by the increased polarization of the N−H bond, leading to the increased hydrogen bond donating ability of **22** (favoring hydrophilicity) balanced by a small increase in hydrophobic surface area.[76,80] On the other hand, the latter parameter dramatically increases in the case of 2-CF_3-indole **23**, overcompensating the increased hydrogen bonding ability. An increase of log *P* to 3.5 ± 0.2 was measured for **23**. Replacing 2-CF_3 with 2-SF_5 substituent as in compound **5a** further increases log *P* by roughly 0.3 units, to 3.8 ± 0.2. Finally, N-methylation of **5a** logically led to an increased log *P* of 4.3 ± 0.3. Overall, these results allow the assessment of the impact of the pentafluorosulfanyl group compared to a fluorine atom or a trifluoromethyl group in the C2-position of indoles. A pronounced drop in pK_a and a simultaneous increase in log *P* are unambiguously demonstrated, thereby modulating physicochemical properties of this relevant heterocycle in a unique fashion.

Finally, as indole is a privileged scaffold in drug discovery, we thought that the mutagenic character of the newly synthesized compounds **5a** and **8** will be important to be determined and valuable information to be provided to the community. In silico assessment is typically done in the first place to estimate the mutagenic potential of a compound against databases. Indole is considered to be nonmutagenic, and therefore, there is no mutagenicity concern emerging from the indole moiety. However, uncovered fragment $-SF_5$ was detected in the used systems (Derek, Sarah Nexus, and Case Ultra).[55] Hence, due to incomplete coverage, it was recommended to perform further tests to evaluate potential mutagenic activity of the SF_5 moiety. We thus performed the Ames test which is a classical biological test to determine the mutagenic potential of a chemical compound.[55] Since cancers are often linked to damage to DNA, this rapid, reliable, and inexpensive test is used to estimate the carcinogenic and genetic activity at the nucleotide level, based on different histidine-requiring bacterial strains of *Salmonella typhimurium* carrying mutations in the genes in the absence and presence of a liver-metabolizing system.[81,82] Over the years, a large database has been accumulated with this assay, confirming its ability to detect genetically active compounds of most chemical classes with around 80−90% sensitivity and specificity. The 2-SF_5-indoles **5a** and **8** have been tested, and no mutagenic evidence was observed over the different bacterial strains tested, which means that they can potentially be used for further development in drug discovery.[55]

CONCLUSION

In conclusion, we developed an efficient synthesis of 2-SF_5-indoles and azaindoles from 2-ethynylaniline derivatives in a two-step telescoped procedure. This sequence consists of four formal synthetic steps: radical addition of SF_5Cl followed by dehydrochlorination, 5-*endo*-*dig* cyclization and deprotection of the tosyl fragment in basic conditions. We then decomposed the full sequence into a stepwise synthesis allowing to keep the N-protecting group on the 2-SF_5-indole. A selection of downstream functionalizations was demonstrated, including N-alkylation and benzylation, C3-halogenation, alkylation, allylation, cyanation, and alkenylation. Carcinogenic potential (Ames test) and relevant physicochemical properties (such as thermal stability (DSC), acidity (pK_a), and lipophilicity (log *P*) were measured in order to highlight the strategic advantages that a C2-pentafluorosulfanylated motif could impart on the indole nucleus.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00010.

Detailed procedures and characterization of all products; copies of ^1H, ^{13}C, and ^{19}F NMR (PDF)

Accession Codes

CCDC 2073141−2073143 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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