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Trifluoromethylsulfonyl pyridinium salt for trifluoromethythiolation of indoles☆

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ABSTRACT

The trifluoromethylsulfonyl pyridinium salt (TFSP) was used as a CF_3S source for the trifluoromethylthiolation of indole derivatives. It is proposed that TFSP is reduced in the presence of diethyl phosphite and NaCl. The protocol features a facile access to the CF_3S source, and high efficiency and transition-metal free conditions for trifluoromethylthiolation.

1. Introduction

Installing a trifluoromethylthiol (CF_3S) group into organic molecules may improve their metabolic stability and cell membrane permeability compared with parent compounds due to the electron-withdrawing effect and good lipophilic nature of the CF_3S group [1]. During the past several decades, many biological activity molecules containing a trifluoromethylthiol (CF_3S) group, such as Toltrazuril, Tiflorex, Cefazaflur, have been developed [2]. Therefore, the development of an efficient and practical method for the installation of the trifluoromethylthiol (CF_3S) group into desired scaffolds is an active research area because of its great potential in pharmaceutical chemistry and agrochemistry [3].

Indole is a key motif in a number of biological active molecules [4]. And the direct trifluoromethylthiolation of indole derivatives has been achieved with SCF_3-containing reagents through the cleavage of N-SCF_3 [5], O-SCF_3 [6] and I-SCF_3 [7] bonds under various conditions. Besides these straightforward trifluoromethylthiolation reagents, another strategy for the introduction of the SCF_3 group into indoles is the utilization of trifluoromethanesulfonyl (CF_3SO_2) units as SCF_3 sources under reducing conditions [8] (Scheme 1A). Although efficient, some of these methods may still have drawbacks. Some reagents suffer from high volatility, or the need of multi steps or the use of expensive fluorinated starting materials for their preparations. It will be of great practical value if the trifluoromethylthiolation of indoles is achieved with the use of reagents which can be synthesized from cheap industrial materials by convenient operations.

We have recently developed an efficient trifluoromethylation reagent, trifluoromethylsulfonyl pyridinium salt (TFSP), which can be readily prepared from the easily available bulk industrial feedstock, trifluoromethanesulfonic anhydride (Tf_2O). TFSP can generate a trifluoromethyl radical under photocatalysis with blue LED irradiation to enable the effective azido- or cyano-trifluoromethylation [9], hydro-trifluoromethylation of alkenes [10], and C–H trifluoromethylation of (hetero)arenes [11]. Based on our continued research interest in the chemistry of fluoroalkylthiolation [12], we envisioned that TFSP might be used as for the synthesis of SCF_3 molecules through deoxygenative reduction of TFSP (Scheme 1B). We then used indole as substrates to evaluate our working hypothesis.

2. Results and discussion

In our preliminary experiments, we first examined the reaction of indole with TFSP in various solvents. Most solvents were ineffective (Table 1, entries1-5). Fortunately, the trifluoromethylthiolation product was obtained in 60% yield in the presence of NaCl in DMF when diethyl phosphite was used as a reducing agent (Table 1, entry 6). Inspired by

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this result, we next optimized the reaction conditions by screening reaction temperatures, substrate equivalents, and reaction time. When elevating the temperature from 60°C to 80°C, the yield of **3a** increased to 79% (entry 8). To our delight, the same yield was obtained using the catalytic amount of NaCl (entry 9). In addition, decreasing the loading of the reducing agent from 4 to 3.5 equiv. has little effect on the yield (78%, entry 11). However, it was found that changing the amount of TFSP from 2 to 1.5 equiv. decreased the yield from 78% to 66% (entry 12). And prolonging the reaction time has little improvement on the reaction yield (79%, entry 13).

With the optimized conditions in hand (Table 1, entry 11), the substrate scope of the trifluoromethylthiolation reaction was investigated. As shown in Scheme 2, the reaction is compatible with various indole derivatives bearing electron-donating (alkyl, alkyloxy) (**3d, 3e, 3h, 3p**) or withdrawing substituents (halo, ester) (**3f, 3i, 3j, 3k, 3l, 3q, 3r, 3s, 3t**). 2-Phenyl-substituted indoles were converted into the expected products (**3c**, 59%), suggesting that the conversion is not very sensitive to steric effects. Bpin-(**3g, 3o)** and halo (Cl, Br, I)-substituted indoles could also undergo electrophilic trifluoromethylthiolation successfully with the functional groups remaining intact, which makes further functionalization possible via transition-metal-catalyzed reactions. Besides free (NH)- indoles, the desired product of *N*-methyl indole was obtained in moderate yield (**3b,**71%). 5-alkynylindole derivative reacted very well, providing the desired products in 54% yield (**3n**). 3-Substituted indole cannot be well converted under these conditions, and only a low yield was obtained (**3u**). In the case of electron-rich arenes such as 1,3,5-trimethoxybenzene, no desired product was detected. Our efforts also failed to convert *N*-phenyl-pyrrole and benzofuran.

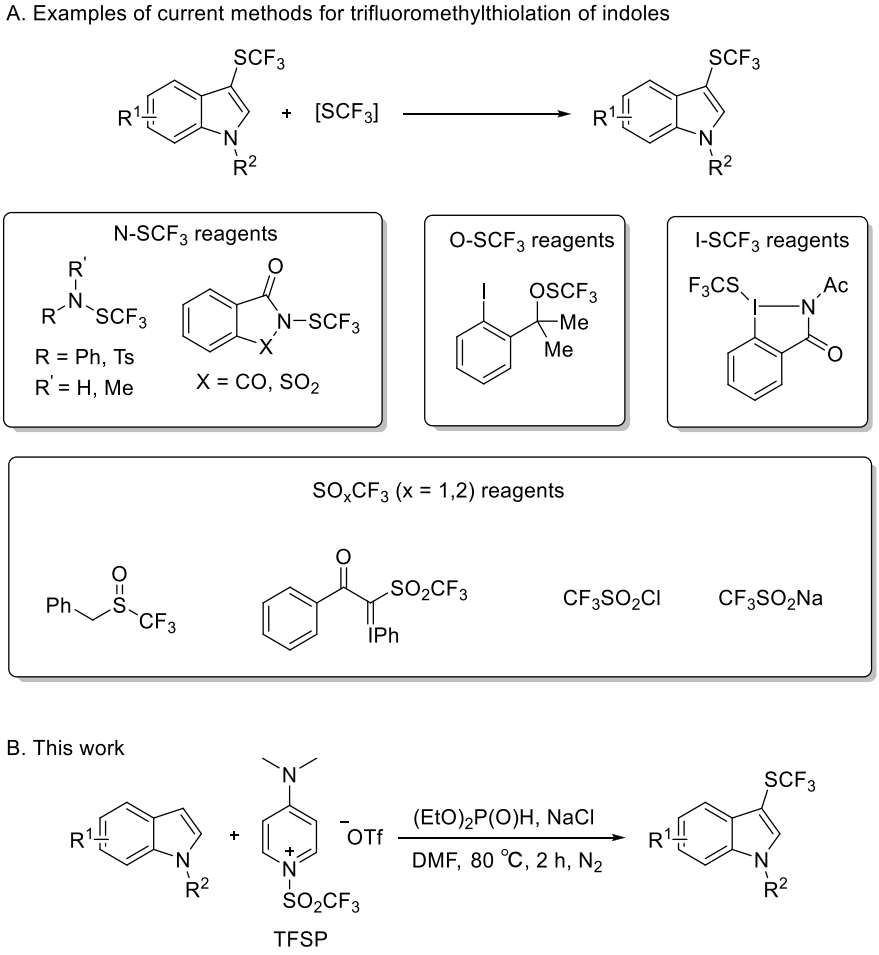
In order to gain insights into the reaction mechanism, we further carried out control experiments. It was found that the desired product was not formed without diethyl phosphite or NaCl, which indicated that both of them played an important role in the reaction (Table 2).

Based on previous literature [8c,d] and the above results, a plausible reaction mechanism was proposed as shown in Scheme 3. TFSP could react with diethyl phosphite to form intermediate **A** (path I). In addition, a chloride anion attacks TFSP to produce CF_3SO_2Cl, which could also be transformed into intermediate **A** (path II). Intermediate **A** is attacked by a chloride anion to form trifluoromethylsulfinyl chloride ($CF_3S(O)Cl$). $CF_3S(O)Cl$ could be reduced to CF_3SCl by diethyl phosphite. Finally, indole attacks CF_3SCl to produce the corresponding trifluoromethylthiolation product.

More evidence was collected to support the proposed paths involving CF_3SO_2Cl and CF_3SOCl. Since only 0.2 equiv of the chloride source (NaCl) was used, CF_3SO_2Cl or CF_3SOCl can hardly be detected in the reaction system. However, increasing the loading of NaCl can led to the conversion of TFSP into CF_3SO_2Cl (Scheme 4, Eq. (1)). The evidence for the generation of CF_3SOCl is the observation of a CF_3SO-containing byproduct for the trifluoromethylthiolation of 5-MeO-indole (Eq. (2)).

3. Conclusions

In summary, we have demonstrated that the trifluoromethylsulfonyl pyridinium salt (TFSP) is able to act as a CF_3S source for the trifluoromethylthiolation of indole derivatives. The reaction tolerates a series of functional groups and affords the products in moderate to



Scheme 1. Some previous related reports and this work.

excellent yields. The protocol features the use of a cheap CF_3S source, and transition-metal free conditions and high efficiency for trifluoromethylthiolation. Therefore, it may find potential utility in the synthesis of CF_3S-indole-containing biologically active molecules.

4. Experimental section

4.1. General remark

^1H, ^{13}C and ^{19}F NMR spectra were detected on a 400 MHz or 300 MHz NMR spectrometer. Data for ^1H NMR, ^{13}C NMR and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *q* = quartet, coupling constant (s) in Hz). Mass spectra were obtained on GC-MS (EI) or LC-MS (ESI). High resolution mass data were recorded on a high-resolution mass spectrometer in the EI or ESI mode. The mass analyzer types for HRMS-EI and HRMS-ESI are time-of-flight and Fourier transform mass spectrometer, respectively.

4.2. General Procedure for the trifluoromethylthiolation of indoles

Into a 10-mL Schlenk tube were added Indole **1a** (0.5 mmol, 1.0 equiv), **2** (TFSP) (404.3 mg, 1 mmol, 2.0 equiv) and NaCl (5.8 mg, 0.1 mmol, 0.2 equiv) under a N_2 atmosphere. Then $(EtO)_2P(O)H$ (225 μL, 1.75 mmol, 3.5 equiv.) and DMF (3 mL) was added. The resulting mixture was stirred at 80 °C for 2 h. After being cooled to room temperature, the crude reaction was diluted with DCM (20 mL). The solution was washed with water (20 mL) and brine (5 × 20 mL), and then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subject to flash column chromatography to give the final product **3a.**

4.3. Compound data of the trifluoromethylthiolation products

4.3.1. 3-((Trifluoromethyl)thio)-1H-indole (3a) [8h]

Yellow liquid (76.2 mg, 70%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H),7.91-7.82 (m, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.46-7.38 (m, 1H), 7.37-7.29 (m, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.51 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.97 (s), 132.80 (s), 129.45 (q, *J* = 309.9 Hz), 129.39 (s), 123.39 (s), 121.60 (s), 119.26 (s), 111.68 (s). 94.42 (q, *J* = 2.5 Hz), **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_6F_3NS$, 217.0; found, 217.0.

4.3.2. 1-Methyl-3-((trifluoromethyl)thio)-1H-indole (3b) [8h]

White solid (81.9 mg, 71%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.44-7.28 (m, 4H), 3.81 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.19 (s), 136.91 (s), 130.19 (s), 129.43 (q, *J* = 310.1 Hz), 122.90 (s), 121.25 (s), 119.43 (s), 109.97 (s), 92.93 (q, *J* = 2.5 Hz), 33.16 (s). **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{10}H_8F_3NS$, 231.0; found, 231.0.

4.3.3. 2-phenyl-3-((trifluoromethyl)thio)-1H-indole (3c) [8h]

Yellow solid (86.8 mg, 59%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.91-7.95 (m, 1H), 7.79 (m, 2H), 7.64-7.47 (m, 3H), 7.47-7.39 (m, 1H), 7.39-7.29 (m, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -43.35 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.34 (s), 135.27 (s), 131.41 (s), 130.59 (s), 129.75 (q, *J* = 311.4 Hz), 129.21 (s), 128.78 (s), 128.65 (s), 123.63 (s), 121.76 (s), 119.72 (s), 111.22 (s), 92.37 (q, *J* = 2.3 Hz);**LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{15}H_{10}F_3NS$, 293.0; found, 293.0.

4.3.4. 4-Methoxy-3-((trifluoromethyl)thio)-1H-indole (3d) [8h]

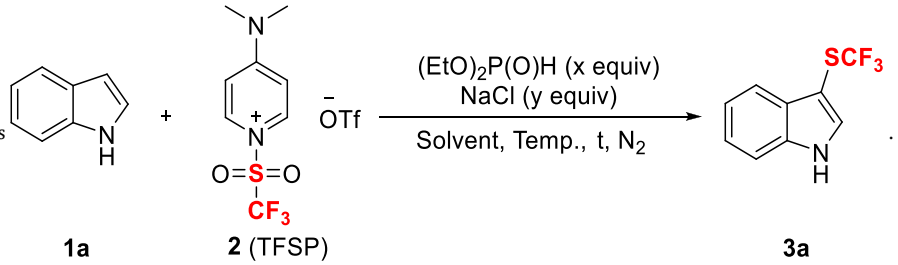
White solid (104.0 mg, 84%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 3.99 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.36 (s), 137.84 (s), 132.48 (s), 129.41 (q, *J* = 309.3 Hz), 124.24 (s), 118.44 (s), 104.92 (s), 102.07 (s), 94.10 (q, *J* = 2.5 Hz), 55.46 (s); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{10}H_8F_3NOS$, 247.0; found, 247.0.

4.3.5. 4-Methyl-3-((trifluoromethyl)thio)-1H-indole (3e) [8h]

Brown solid (73.2 mg, 63%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.29-7.15 (m, 2H), 7.03 (d, *J* = 6.8 Hz, 1H), 2.88 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.33 (s), 134.04 (s), 131.58 (s), 129.17 (q, *J* = 309.3 Hz), 126.67 (s), 123.36 (s), 109.72 (s), 94.91 (q, *J* = 2.4 Hz), 19.31 (s);**LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{10}H_8F_3NS$, 231.0; found,

Table 1

Optimization of the reaction parameters



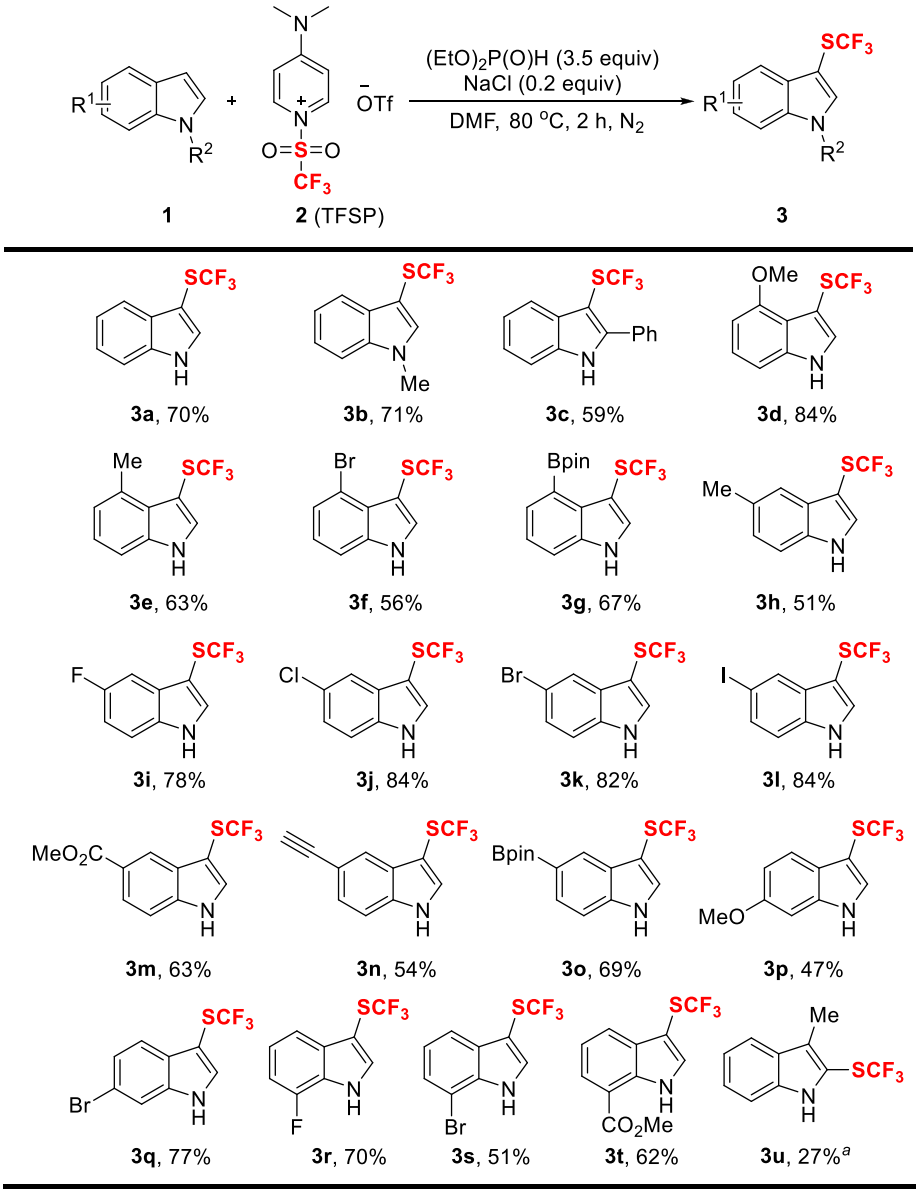
1a **2** (TFSP) **3a**

Entry	Ratio[a]	T/°C	Solvent	t/h	Yield (%)[b]
1	1:1.5:3:0.5	60	P-xylene	1	N.D.
2	1:1.5:3:0.5	60	DCE	1	N.D.
3	1:1.5:3:0.5	60	THF	1	N.D.
4	1:1.5:3:0.5	60	EtOAc	1	N.D.
5	1:1.5:3:0.5	60	MeCN	1	N.D.
6	1:1.5:3:0.5	60	DMF	1	60
7	1:2:4:2	60	DMF	2	73
8	1:2:4:2	80	DMF	2	79
9	1:2:4:0.2	80	DMF	2	79
10	1:2:3:0.2	80	DMF	2	73
11	1:2:3.5:0.2	80	DMF	2	78
12	1:1.5:3.5:0.2	80	DMF	2	66
13	1:2:3.5:0.2	80	DMF	4	79

Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2** (TFSP), $(EtO)_2P(O)H$ (x equiv), NaCl (y equiv), solvent (2 mL) under a N_2 atmosphere.

[a] Molar ratio of **1a: 2:** $(EtO)_2P(O)H$: NaCl

[b] Yields were determined by ^{19}F NMR spectroscopy with trifluoromethylbenzene as an internal standard.



Scheme 2. Scope of trifluoromethylthiolaton of indole derivatives.
Reaction conditions: **1** (0.5 mmol, 1 equiv), **2** (TFSP) (1 mmol, 2 equiv), $(EtO)_2P(O)H$ (1.75 mmol, 3 equiv), NaCl (0.1 mmol, 0.2 equiv), DMF (3 mL), under N_2, 80 °C, 2 h. Isolated yields are shown. [a]The yield of **3u** was determined by ^{19}F NMR spectroscopy.

231.0.

4.3.6. 4-Bromo-3-((trifluoromethyl)thio)-1H-indole (3f) [8j]

Yellow solid (83.2 mg, 56%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.57 (d, J = 2.7 Hz, 1H), 7.43 (dd, J = 8.0, 0.6 Hz, 1H), 7.36 (dd, J = 8.0, 0.6 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -45.40 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.07 (s), 135.32 (s), 128.98 (q, J = 309.5 Hz), 126.65 (s), 125.97 (s), 124.18 (s), 114.20 (s), 111.33 (s), 96.16 (q, J = 2.5 Hz); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5^{79}BrF_3NS$, 294.9; found, 294.9.

4.3.7. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3-((trifluoromethyl)thio)-1H-indole (3g) [8a]

White solid (115.5 mg, 67%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.35 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 1.46 (s, 12H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -45.01 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.64 (s), 133.92 (s), 131.62 (s), 129.54 (q, J = 309.6 Hz), 128.80 (s), 128.13 (s), 122.37 (s), 113.83 (s), 95.77 (q, J = 2.3 Hz), 84.28 (s), 24.91 (s); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{15}H_{17}BF_3NO_2S$, 343.1; found, 343.1.

4.3.8. 5-Methyl-3-((trifluoromethyl)thio)-1H-indole (3h) [8j]

Brown solid (58.7 mg, 51%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.64 (s, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 2.54 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.26 (s), 132.82 (s), 131.17 (s), 129.63 (s), 129.46 (q, J = 309.9 Hz), 125.04 (s), 118.78 (s), 111.34 (s), 94.73 (q, J = 2.4 Hz), 21.45 (s). **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{10}H_8F_3NS$, 231.0; found, 231.0.

4.3.9. 5-Fluoro-3-((trifluoromethyl)thio)-1H-indole (3i) [8h]

Yellow solid (91.7 mg, 78%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.34 (dd, J = 8.8, 4.1 Hz, 1H), 7.05 (td, J = 9.0, 2.0 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.60 (s, 3F), -121.65 ~ -121.71 (m, 1F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.04 (d, J = 237.5 Hz), 134.35 (s), 132.42 (s), 130.31 (d, J = 10.4 Hz),

Table 2
Control experiments-

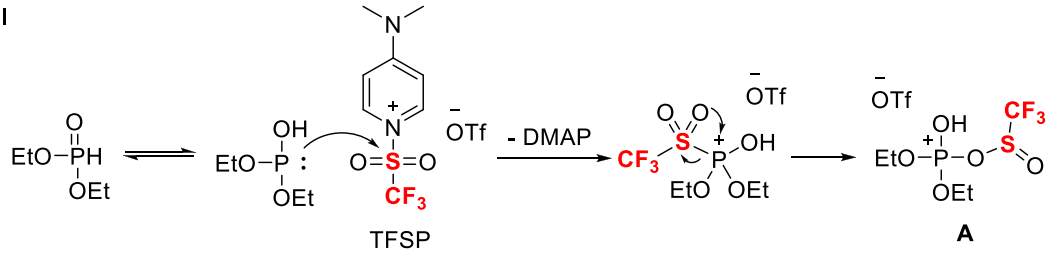
1a **2** (TFSP) **3a**

Entry	Conditions	Yield (%)[a]
1	Standard conditions	79
2	No diethyl phosphite	N.D.
3	No NaCl	N.D.

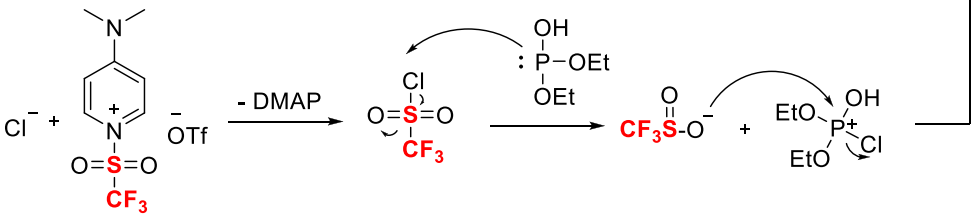
Reaction conditions: **1a** (0.5 mmol, 1 equiv.), **2** (TFSP) (1 mmol, 2 equiv.), $(EtO)_2P(O)H$ (1.75 mmol, 3 equiv.), NaCl (0.1 mmol, 0.2 equiv.), DMF (3 mL), under N_2, 80 °C, 2 h.
[a] Yields were determined by ^{19}F NMR spectroscopy with trifluoromethylbenzene as an internal standard.

The formation of Intermediate **A**:

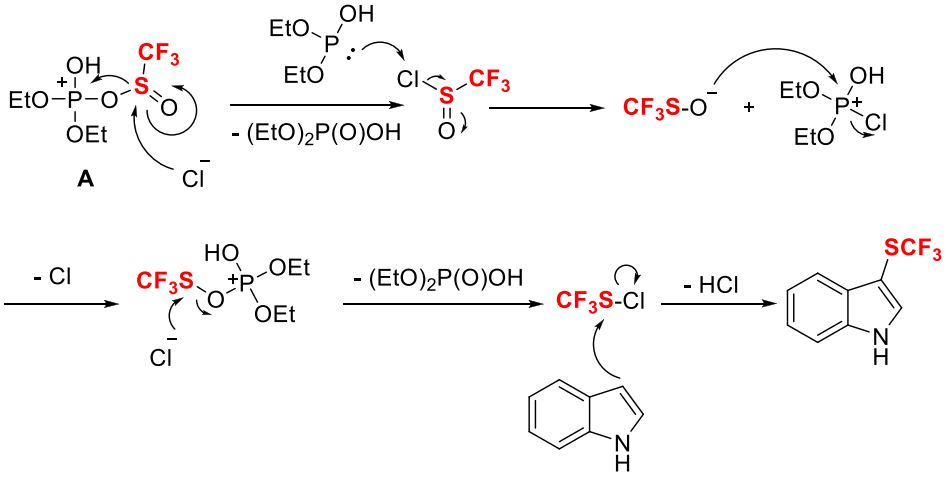
Path **I**



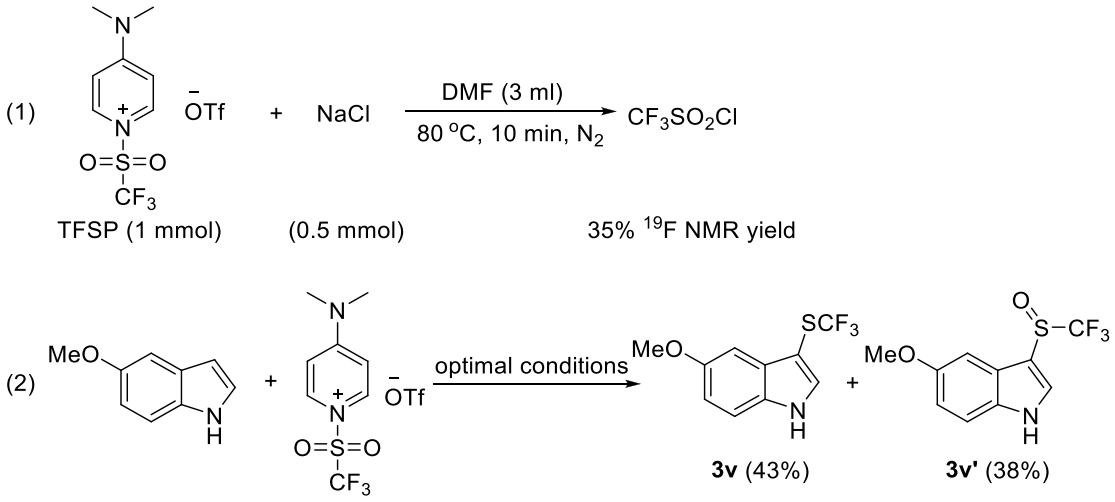
Path II



Further transformation of intermediate **A**:



Scheme 3. The plausible reaction mechanism.



Scheme 4. Experimental evidence.

129.34 (q, J = 310.0 Hz), 112.63 (d, J = 9.6 Hz), 112.06 (d, J = 26.6 Hz), 104.44 (d, J = 24.7 Hz), 95.65 (q, J = 2.3 Hz); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5F_4NS$, 235.0; found, 235.0.

4.3.10. 5-Chloro-3-((trifluoromethyl)thio)-1H-indole (3j) [8h]

Yellow liquid (105.6 mg, 84%);1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.75 (s, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.49 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.34 (s), 133.97 (s), 130.60 (s), 129.25 (q, J = 310.1 Hz), 127.62 (s), 123.90 (s), 118.83 (s), 112.79 (s), 95.36 (q, J = 2.5 Hz); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5^{35}ClF_3NS$, 251.0; found, 251.0.

4.3.11. 5-Bromo-3-((trifluoromethyl)thio)-1H-indole (3k) [8h]

Pale yellow solid (121.6 mg, 82%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.92 (s, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.34 (dd, J = 8.6, 2.0 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.60 (s), 133.81 (s), 131.10 (s), 129.22 (q, J = 310.91 Hz), 126.39 (s), 121.84 (s), 115.07 (s), 113.19 (s), 95.15 (q, J = 2.5 Hz);**LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5^{81}BrF_3NS$, 296.9; found, 296.9.

4.3.12. 5-Iodo-3-((trifluoromethyl)thio)-1H-indole (3l) [8d]

Pale yellow solid (144.1 mg, 84%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.14 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.14 (d, J = 8.5 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.04 (s), 133.39 (s), 131.79 (s), 131.68 (s), 129.17 (q, J = 310.1 Hz), 128.03 (s), 113.59 (s), 94.74 (q, J = 2.5 Hz), 85.39 (s); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5F_3INS$, 342.9; found, 342.9.

4.3.13. Methyl 3-((trifluoromethyl)thio)-1H-indole-5-carboxylate (3m) [8h]

White solid (87.0 mg, 63%);**^{1}H NMR** (400 MHz, Acetone-d_6) δ 11.39 (s, 1H), 8.45 (s, 1H), 7.97 (d, J = 2.6 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 3.90 (s, 4H). **^{19}F NMR** (376 MHz, Acetone-d_6) δ -45.72 (s, 3F). **^{13}C NMR** (101 MHz, Acetone-d_6) 166.97 (s), 139.37 (s), 136.30 (s), 129.62 (q, J = 309.0 Hz), 129.14 (s), 123.94 (s), 123.50 (s), 120.96 (s), 112.42 (s), 94.50 (q, J = 2.5 Hz), 51.31 (s). **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{11}H_8F_3NO_2S$, 275.0; found, 275.0.

4.3.14. 5-Ethynyl-3-((trifluoromethyl)thio)-1H-indole (3n)

Pale yellow solid (65.6 mg, 54%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.99 (s, 1H), 7.53 (s, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 3.09 (s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.44 (s, 3F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.83 (s), 133.77 (s), 129.25 (s), 129.25 (q, J = 310.0 Hz), 127.28 (s), 123.73 (s), 115.23 (s), 111.84 (s), 95.92 (q, J = 2.5 Hz) 84.49 (s), 75.80 (s); **HRMS (EI)** m/z: $[M]^+$ Calculated for $C_{11}H_6F_3NS$, 241.0173; found, 241.0164. **IR** (neat)/cm^{-1} 3361, 3303, 2104, 1613, 1505, 1468, 1455, 1416, 1299, 1239, 1147, 1110, 1008, 893, 805, 751, 664, 605, 629, 572, 552, 416.

4.3.15. 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3-((trifluoromethyl)thio)-1H-indole (3o) [8k]

White solid (118.0 mg, 69%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.35 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.35 (d, J = 8.2 Hz, 1H), 1.40 (s, 12H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.08 (s), 133.05 (s), 129.34 (q, J = 309.8 Hz), 129.30 (s), 129.04 (s), 126.76 (s), 111.22 (s), 95.91 (q, J = 2.4 Hz), 83.82 (s), 24.83 (s); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{15}H_{17}BF_3NO_2S$, 343.1; found, 343.1.

4.3.16. 6-Methoxy-3-((trifluoromethyl)thio)-1H-indole (3p) [8h]

White solid (58.2 mg, 47%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.43 (s, 1H), 6.94 (d, J = 8.9 Hz, 1H), 6.90 (s, 1H), 3.86 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.67 (s, 3F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.40 (s), 136.83 (s), 131.56 (s), 129.40 (q, J = 309.9 Hz), 123.62 (s), 120.02 (s), 111.66 (s), 95.59 (q, J = 2.3 Hz), 94.98 (s), 55.71 (s);**LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{10}H_8F_3NOS$, 247.0; found, 247.0.

4.3.17. 6-Bromo-3-((trifluoromethyl)thio)-1H-indole (3q) [8j]

Yellow liquid (108.7 mg, 73%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.49 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.71 (s), 133.26 (s), 129.27 (q, J = 310.0 Hz), 128.35 (s), 125.01 (s), 120.64 (s), 116.97 (s), 114.62 (s), 96.07 (q, J = 2.5 Hz); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5^{81}BrF_3NS$, 296.9; found, 296.9.

4.3.18. 7-Fluoro-3-((trifluoromethyl)thio)-1H-indole (3r) [8l]

Yellow solid (82.7 mg, 70%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 2.5 Hz, 1H), 7.21 (td, J = 7.9, 4.8 Hz, 1H), 7.03 (dd, J = 10.8, 8.1 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.47 (s, 3F), -135.12 (dd, J = 10.9, 4.7 Hz, 1F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.41 (d, J = 245.5 Hz), 133.28 (s), 132.82 (d, J = 4.3 Hz), 129.32 (q, J = 309.9 Hz), 124.54 (d, J = 14.0 Hz), 121.97 (d, J = 6.1 Hz), 115.08 (d, J = 3.6 Hz), 108.25 (d, J = 15.9 Hz), 96.62-96.73 (m); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5F_4NS$, 235.0; found, 235.0.

4.3.19. 7-Bromo-3-((trifluoromethyl)thio)-1H-indole (3s)

Pale yellow liquid (76.1 mg, 51%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71

(s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.44 (s, 3F);^{13}C NMR (101 MHz, $CDCl_3$) δ 134.75 (s), 133.20 (s), 130.60 (s), 129.26 (q, J = 309.9 Hz), 125.78 (s), 122.81 (s), 118.65 (s), 105.05 (s), 97.05 (q, J = 2.4 Hz); **HRMS (EI)** m/z: $[M]^+$ Calculated for $C_9H_5^{79}BrF_3NS$, 294.9278; found, 294.9266. **IR** (neat)/cm^{-1} 3462, 1563, 1489, 1426, 1400, 1335, 1309, 1281, 1211, 1196, 1110, 1045, 1020, 880, 882, 779, 753,737, 573, 510, 485.

4.3.20. Methyl 3-((trifluoromethyl)thio)-1H-indole-7-carboxylate (3t) [5e]

White solid (85.7 mg, 62%);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 7.1 Hz, 1H), 7.63 (d, J = 2.5 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 4.00 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.91 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.39 (s), 135.98 (s), 133.82 (s), 130.43 (s), 129.28 (q, J = 309.8 Hz), 125.53 (s), 124.91 (s), 120.89 (s), 113.36 (s), 95.70 (q, J = 2.4 Hz), 52.04 (s);**LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{11}H_8F_3NO_2S$, 275.0; found, 275.0.

4.3.21. 5-Methoxy-3-((trifluoromethyl)thio)-1H-indole (3v) [5f]

Brown solid (53.5 mg, 43%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.46 (d, J = 2.7 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 6.94 (dd, J = 8.8, 2.3 Hz, 1H), 3.90 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -44.66 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.52 (s), 133.26 (s), 130.89 (s), 130.26 (s), 129.46 (q, J = 310.0 Hz), 113.92 (s), 112.56 (s), 100.48 (s), 94.88 (q, J = 2.4 Hz), 55.78 (s); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{10}H_8F_3NOS$, 247.0; found, 247.0.

4.3.22. 5-Methoxy-3-[(trifluoromethyl)sulfinyl]-1H-indole (3v') [8o]

Yellow solid (50.2 mg, 38%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.66 (d, J = 2.9 Hz, 1H), 7.36 (s, 1H), 7.32 (d, J = 8.9 Hz, 1H), 6.94 (dd, J = 8.9, 2.0 Hz, 1H), 3.75 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -72.48 (s, 3F); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.97 (s), 131.75 (s), 131.40 (s), 125.65 (q, J = 334.3 Hz), 124.81 (s), 115.01 (s), 113.48 (s), 106.92 (q, J = 2.1 Hz), 101.41 (s), 55.60 (s); **LRMS (EI)** m/z: $[M]^+$ Calculated for $C_{10}H_8F_3NO_2S$, 263.0; found, 263.0.

Declaration of Competing Interest

No conflict of interest of the present work with others.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2022.110047.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

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