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Metal-free oxidative trifluoromethylation of indoles with CF_3SO_2Na on the C2 position†

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An efficient method of synthesizing 2-trifluoromethylindoles from indoles with easy-to-handle, cheap and low-toxic CF_3SO_2Na under metal-free conditions is described, which selectively introduces trifluoromethyl to indoles on the C2 position. The desired product can be obtained in 0.7 g yield. A radical intermediate may be involved in this transformation.

Introduction

Indole compounds are widely found in nature and most of them are bioactive and diffusely used in medicine, as food additives and in other fields.[1] For example, indometacin is one of the strongest prostaglandins and synthetic inhibitors (Fig. 1a).[2] As a special functional group, trifluoromethyl is often applied to materials, pesticides and pharmaceuticals,[3] which can enhance the polarity, stability and lipophilicity.[4] For instance, Prozac is mainly used for the treatment of mental illness and fludelone can effectively inhibit cancer cells (Fig. 1b and c).[5] Given the importance of indoles and trifluoromethyl groups, combining the two into a single entity would be very interesting. In this context, it is of profound significance to study new and potentially physiologically active indoles containing trifluoromethyl from the perspective of synthetic methodology and application prospects.

The classical methods for the synthesis of trifluoromethyl compounds usually use Umemoto,[6] Ruppert–Prakash,[7] Langlois[8] and Togni[9] reagents or other reagents.[10,12] For the past few decades, exploring effective ways to obtain 2-trifluoromethylindoles from indoles has gained increasing attention. Rey-Rodriguez *et al.*[11] demonstrated the iron(II) catalyzed trifluoromethylation of indole under mild reaction conditions (Fig. 2a). Unfortunately, it showed low regioselectivity. Furthermore, Choi *et al.*[12] described the platinum(II) complexes catalyzed trifluoromethylation of indole on the C2 position in the presence of CF_3I and visible light; however, CF_3I is difficult to preserve and toxic (Fig. 2b). In the recent years, CF_3SO_2Na has gradually become an environmentally friendly and cheap source of trifluoromethyl in the field of organic synthesis.[13] Shi[14] offered an efficient copper-catalyzed oxidation method for the trifluoromethylation of C3 position-blocked indoles (Fig. 2c). CF_3SO_2Na has been widely used as a CF_3 source in organic synthesis; however, the metal-free and highly regioselective synthesis of 2-trifluoromethylindoles has rarely been reported. The disadvantages of expensive reagents, poor regioselectivity or difficult-to-handle reagents are often encountered. As part of our ongoing interest in the synthesis of indoles derivatives,[15] we reported herein a *tert*-butyl hydroperoxide (TBHP)-promoted metal-free and highly regio-selective trifluoromethylation of indole on the C2 position using easy-to-handle and low-toxic CF_3SO_2Na as the trifluoromethyl source.

Initially, indole (**1a**) and CF_3SO_2Na were selected as model substrates for the optimization of the reaction conditions (Table 1). When **1a**, 1 equiv. of CF_3SO_2Na, 2 equiv. of TBHP and 2 mL CH_3CN were added to a sealed Pyrex test tube under room temperature, **2a** was obtained in the yield of 15% (entry 1). Subsequently, higher temperature (80 °C and 140 °C) gave the desired product **2a** in higher yields (36% and 45%, respectively) (entries 2–3). Next, we switched the ratio of raw materials. It was found that the amount of CF_3SO_2Na would greatly affect the yield of **2a**, which showed that a small loading of CF_3SO_2Na resulted in less desired product and a higher loading of CF_3SO_2Na would result in byproduct **3a** (entries 5–6). A higher yield of **2a** was obtained in the presence of 3 equiv. of TBHP (entries 3–5). A reaction time of 18 hours was found to be enough for this transformation, which gave the desired product **2a** in 66% yield (entry 5). Shortening the reaction time to 16 hours or prolonging the reaction time to 20 hours (even 24 hours) afforded **2a** in the yield of 53% and 65% (66%), respectively

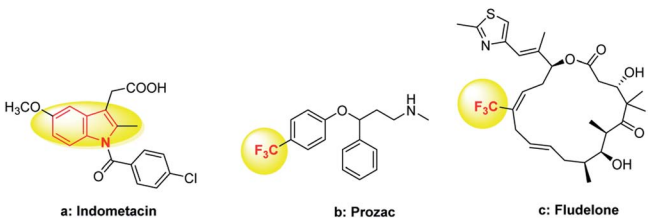

Fig. 1 Indoles and trifluorides with biological activities.

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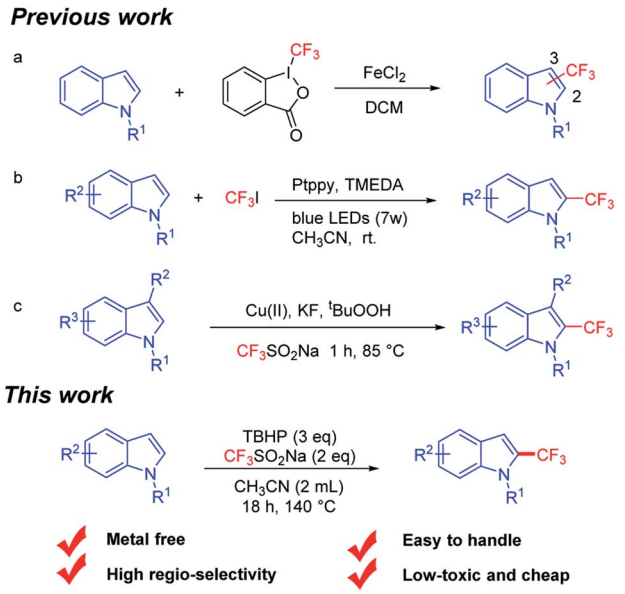


Fig. 2 Preparation of trifluoromethylindoles from indoles.

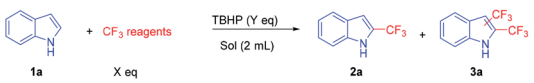
(entries 5–9). When toluene, DMF and H_2O were used as solvents, **2a** was obtained in the yield of 49%, 41% and 30%, respectively (entries 10–11), while no targeting product **2a** was obtained with DMSO or 1,4-dioxane as solvents. Besides, we also investigated other trifluoromethylation reagents such as $TMSCF_3$ (trifluoromethyltrimethylsilane), using which only trace **2a** was observed. In brief, CF_3SO_2Na (2.0 equiv.), TBHP (3.0 equiv.), CH_3CN (2 mL), 140 °C and 18 h are the optimized reaction conditions, as shown in entry 5. The two-dimensional NMR (H–H COSEY) plot also supported that trifluoromethylation was on the C2 position of indoles (ESI 5†).

With the optimized reaction conditions in hand, we investigated the substrate scopes with respect to different substituents on indole scaffolds shown in Table 2. To our delight, most of the transformations went smoothly and provided the corresponding products in moderate to good yields. When the hydrogen of NH was replaced by methyl, trifluoromethylation took place and gave **2b** in the yield of 56%. It should be noted that when the position of the methyl group on the scaffold of indole was changed from C3 to C7, the corresponding products were obtained with the yield of 73% to 57% (**2c**, **2d**, **2g**, **2m**, **2t**). Indoles with the methyl group substituted at C4 or C6 position successfully converted into corresponding products with the yields of 76% (**2d**) and 75% (**2m**), respectively, showing a higher activity. Importantly, this approach was compatible with halogen groups such as bromine (**2k**) and iodine (**2l**), which presented corresponding products with the yield of 54% and 59%, respectively. Except for the fluorine-containing substituents, it was found that the yield of electron-donating groups was slightly higher than that of the electron-withdrawing groups (**2h**, **2n**, **2r**). For example, 7-azaindole was successfully converted into its corresponding trifluoromethylation product **2s** with the yield of 64%.

Subsequently, we studied other indole derivatives under optimized conditions (Fig. 3), such as 2-methylindole (**1u**), indoline (**1v**) and indazole (**1w**). The desired product was not obtained, which may indicate that trifluoromethylation occurred on the C2 position and indoline could not be compatible in the present system.

Investigations established that a large-scale amplification experiment of **1b** (5 mmol) under optimized conditions at 80 °C

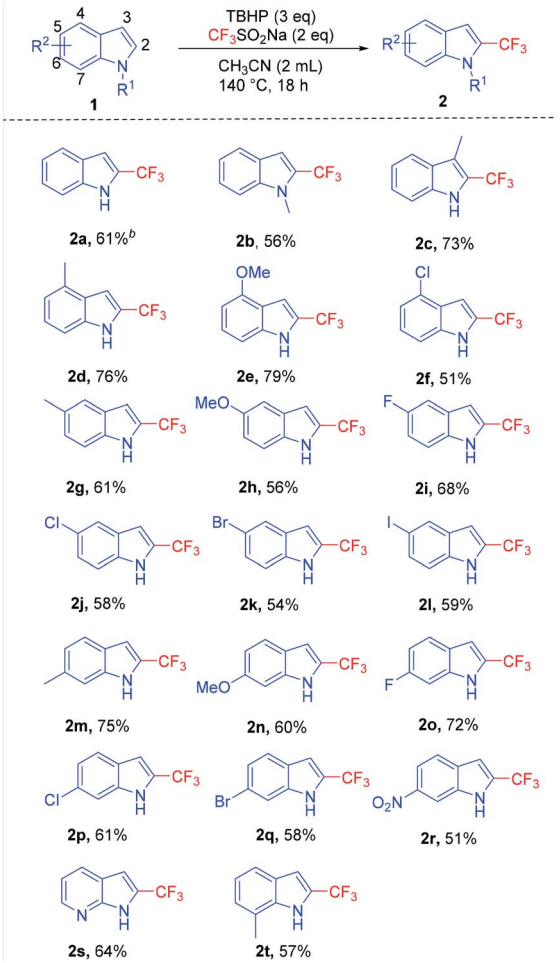
Table 1 Screening of the reaction conditions[a]



Entry	CF_3 reagent(X eq.)	Y eq.	Sol (2 mL)	Temp/°C	Time/h	Yield[b] **2a**/(**3a**) %
1	CF_3SO_2Na(2 eq.)	1	CH_3CN	25	18	15
2	CF_3SO_2Na(2 eq.)	1	CH_3CN	80	18	36
3	CF_3SO_2Na(2 eq.)	1	CH_3CN	140	18	45
4	CF3SO2Na(2 eq.)	2	CH_3CN	140	18	50
5	CF_3SO_2Na(2 eq.)	3	CH_3CN	140	18	66
6	CF_3SO_2Na(3 eq.)	3	CH_3CN	140	18	56(16)
7	CF_3SO_2Na(2 eq.)	3	CH_3CN	140	16	53
8	CF_3SO_2Na(2 eq.)	3	CH_3CN	140	20	65
9	CF_3SO_2Na(2 eq.)	3	CH_3CN	140	24	66
10	CF_3SO_2Na(2 eq.)	3	Toluene	140	18	49
11	CF_3SO_2Na(2 eq.)	3	DMF	140	18	41
12	CF_3SO_2Na(2 eq.)	3	H_2O	140	18	30
13	CF_3SO_2Na(2 eq.)	3	DMSO	140	18	nr
14	CF_3SO_2Na(2 eq.)	3	1,4-Dioxane	140	18	nr
15	$TMSCF_3$(2 eq.)	3	CH_3CN	140	18	Trace

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.3 mmol) and solvent CH_3CN (2 mL), 140 °C, stirred for 18 h in air. [b] Isolated yields.

Table 2 Trifluoromethylation of indoles[a,b]



[a] The reaction was carried with **1** (0.3 mmol), CF_3SO_2Na (2.0 equiv.) and TBHP (3.0 equiv.) were used in CH_3CN (2 mL) at 140 °C in air for 18 h. [b] Isolated yields.

smoothly gave **2b**. We were pleased to observe that 0.507 g of the corresponding product was isolated with the yield being 51% (Fig. 4).

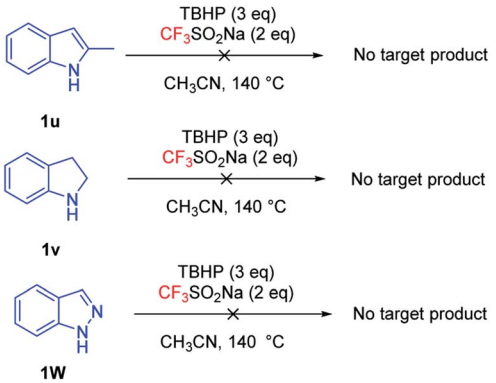


Fig. 3 Trifluoromethylation of other indole derivatives.

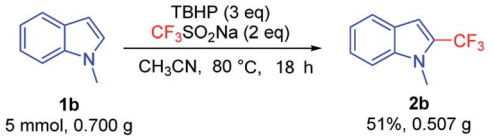


Fig. 4 Gram-scale experiment.

In order to get insights into the reaction mechanism, a series of control experiments were conducted. When 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (4 equiv.), butylatedhydroxytoluene (BHT) (4 equiv.) or 1,4-benzoquinone (4 equiv.) was respectively added under the standard reaction conditions (Table 1, entry 6), almost no desired products were detected (Fig. 5). In addition, a radical intermediate (molecular weight: 288) was detected by GC-MS when a radical scavenger (BHT) was used. Based on these results, we proposed herein a plausible reaction pathway (Fig. 6).[8a,14] At first, a free radical, $^tBuO^{\bullet}$ (**II**) generated from TBHP (**I**) by heating reacts with a trifluorosulfinate anion to provide the free radical $CF_3SO_2^{\bullet}$(**III**). Subsequently, a free radical $CF_3^{\bullet}$ was formed by releasing SO_2 from the radical $CF_3SO_2^{\bullet}$ (**III**). The intermediate (**V**) was generated from the radical $CF_3^{\bullet}$ with substrate **1**. TBHP accepted one electron from the intermediate (**V**) to give the intermediate cation (**VI**) and release OH^-. Finally, the product **2** was obtained by releasing a proton from the intermediate cation (**VI**).

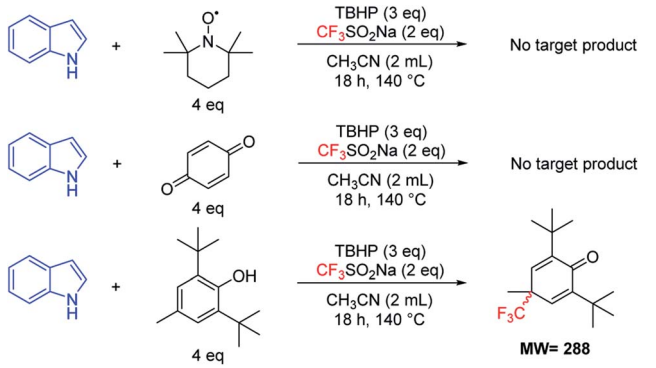


Fig. 5 Control experiments.

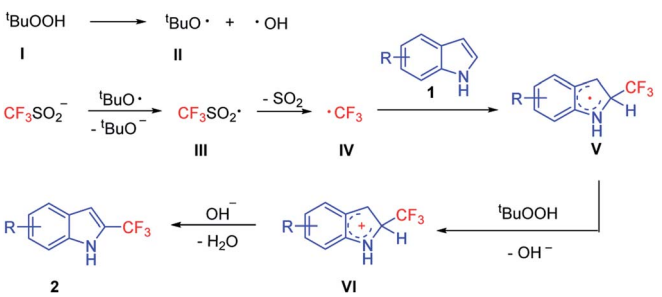


Fig. 6 Proposed mechanism for trifluoromethylation of indoles.

Conclusions

In summary, we have developed an original method of synthesizing 2-trifluoromethylindoles from indoles with easy-to-handle, cheap and low-toxic CF_3SO_2Na under metal-free conditions, which selectively proceeded on the C2 position of indoles. High functional group tolerance and moderate to good yield were presented in this transformation. The control experiments provided evidences that the reaction may undergo a free radical pathway. Further applications of 2-trifluoromethylindoles are currently being carried out in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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