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Transition-metal- and phosphorus-free electrophilic trifluoromethylthiolation of indoles with sodium trifluoromethanesulfinates in ionic liquids

Fei Wang, Guo-Ping Lu, Yamei Lin *

School of Food Science and Pharmaceutical Engineering, Nanjing Normal University, Nanjing 210023, PR China

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An acid-promoted protocol has been developed to achieve the transition-metal- and phosphorus-free electrophilic trifluoromethylthiolation of indoles using sodium trifluoromethanesulfinates in an imidazolium-based ionic liquid ([Hmim]Br). [Hmim]Br not only acts as a recyclable solvent, but also as the reductant in this transformation. The advantages of this chemistry include simple operation, use of a recyclable solvent, avoidance of transition-metal and phosphorus, and gram-scale synthesis.

Introduction

Trifluoromethyl sulfides (CF_3SR) are widespread in various pharmaceuticals, agrochemicals, and functional materials due to their electron-withdrawing effects and extremely high lipophilicity ($\pi = 1.44$) [1]. Thus, various strategies have been reported for the trifluoromethylthiolation of organic compounds, especially aromatic derivatives [2]. Among them, the direct trifluoromethylthiolation using SO_2CF_3-based reagents has become one of the most efficient methods, since most SO_2CF_3-based reagents are stable and easy-to-handle [3]. In 2015, our group first reported the application of CF_3SO_2Na for direct introduction of the $-SCF_3$ group into indoles [4a]. Since then, increased attention has been paid to the direct trifluoromethylthiolation of organic compounds using SO_2CF_3-based reagents [3,4]. However, these approaches typically require stoichiometric amounts of toxic phosphorous reagents (Scheme 1a) [4,5]. Tf_2O was employed to initiate the disproportionation of CF_3SO_2Na, generating the "CF_3S^+" species *in situ* for the direct trifluoromethylthiolation in the absence of phosphorous reagents (Scheme 1b) [6]. Based on this work, a new SO_2CF_3-based reagent, TfNHNHBoc, was developed for direct trifluoromethylthiolation, which can form trifluoromethylthiolation species *via* a self-redox process (Scheme 1c) [7]. Nevertheless, TfNHNHBoc requires pre-preparation, and the use of a copper catalyst is necessary. Therefore, further exploration of reaction conditions for direct trifluoromethylthiolation using SO_2CF_3-based reagents is still of great importance.

On the other hand, imidazolium-based ionic liquids (ILs) exhibit several notable properties, such as hydrogen bonding [8], self-assembly [9] and significant solvation potential [10], which may help promote transformations when used as solvents or catalysts [11]. Although imidazolium-based ILs may cause potential environmental issues [12], they represent greener alternatives to organic solvents due to their negligible vapour pressure, non-flammability and recyclability [13].

Recently, our group has developed a novel acid-induced protocol for the chemoselective arylthiolation of electron-rich arenes using sodium arylsulfinates, in which imidazolium-based ILs play a dual role (solvent and reducer) [14]. Along this line, we reasoned that CF_3SO_2Na could be used as an analog of sodium arylsulfinate in ILs to achieve the transition-metal- and phosphorus-free electrophilic trifluoromethylthiolation of indole derivatives.

Results and discussion

Initially, we examined the model reaction of indole **1a** and CF_3SO_2Na **2** under various conditions (Table 1). As expected, the desired product **3a** was obtained in [Hmim]Br under acidic conditions (Entry 2), and no reaction took place without the acid (Entry 1). After screening different acids, HCl emerged as the best option (Entries 2–8). Other organic solvents were also used (Entries 9–16),

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* Corresponding author.
E-mail address: linyamei1992@126.com (Y. Lin).

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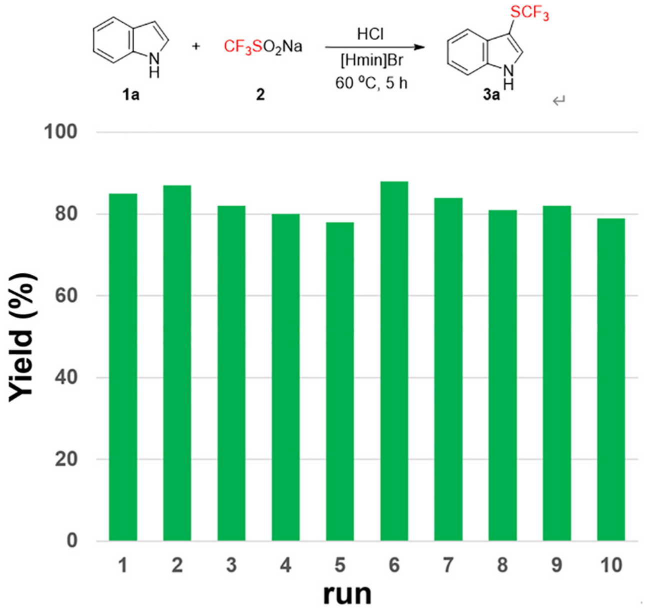


Scheme 1. Selected methods for the trifluoromethylthiolation of indoles or arenes.

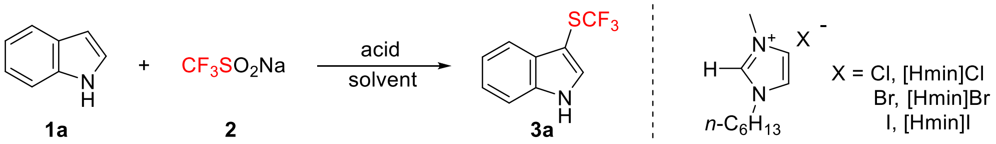
but the results were unsatisfactory, which verified the necessity of [Hmim]Br. Different anions of the IL had an obvious influence on the reaction. No product was afforded in case of [Hmim]Cl due to the poor reducing capacity of Cl^- (Entry 17). A much lower yield was observed in [Hmim]I (Entry 18). Although I^- has stronger reducing capacity than Br^-, the *in situ* generated "CF_3SI" may be too reactive to form the desired products [15].

With the optimized reaction conditions in hand, a series of indole derivatives were examined to establish the scope and generality of this protocol (Table 2). The trifluoromethylthiolation reaction selectively occurred at 3-position of indole derivatives containing methyl (**3b-f**), methoxy (**3g**), halogen (**3i-l**), nitro (**3m**) and benzyloxy (**3h**) groups. It can be observed that electron-donating and electron-withdrawing substituents did not significantly affect the trifluoromethylthiolation of indoles (**3b-m**). It was also found that the position of the substituents did not significantly affect the yields (**3c-f**), except in the case of **3b**, which is due to the increased steric hindrance. Furthermore, *N*-substituted indoles with alkyl groups gave moderate yields (**3n** and **3o**).

Other substrates such as 2-naphthol and acetophenone were also employed (Scheme 2). Only the brominated product was observed in the case of 2-naphthol (eq. 1), while both brominated and trifluoromethylthiolated products were obtained using acetophenone (eq. 2). These results were evidence for the generation of bromine during the reaction [14]. The yield did not decrease when two equivalents of the radical inhibitor TEMPO was added to the reaction (eq. 3), suggesting that the transformation does not involve a radical process [16].

According to these experiments and previous reports [4,14], a tentative mechanism was proposed (Scheme 3). Firstly, trifluorosulfinic acid derived from **2** under acidic conditions is further reduced by the acid and bromide anion to give **11** (path A) [4a,14]. Intermediate **11** can undergo electrophilic substitution with indoles to form 3-trifluoromethylthioindoles as the major pathway. Enhancement of the [Hmim]Br cation may be attributed to the formation of hydrogen bonds between the C-2 hydrogen and X (Br, OSO_2CF_3), and the charge-charge interaction of the quaternary nitrogen atom and X, resulting in electrophilic activation of the S-X bond [11,17]. Moreover, arylsulfinic acid can also afford electrophilic sulfur intermediate **13** through dehydrative

Table 1
Optimization of the reaction conditions.[a]

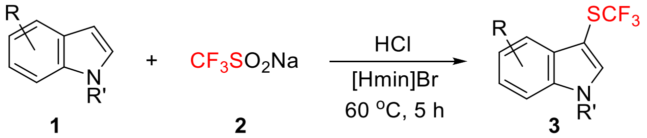


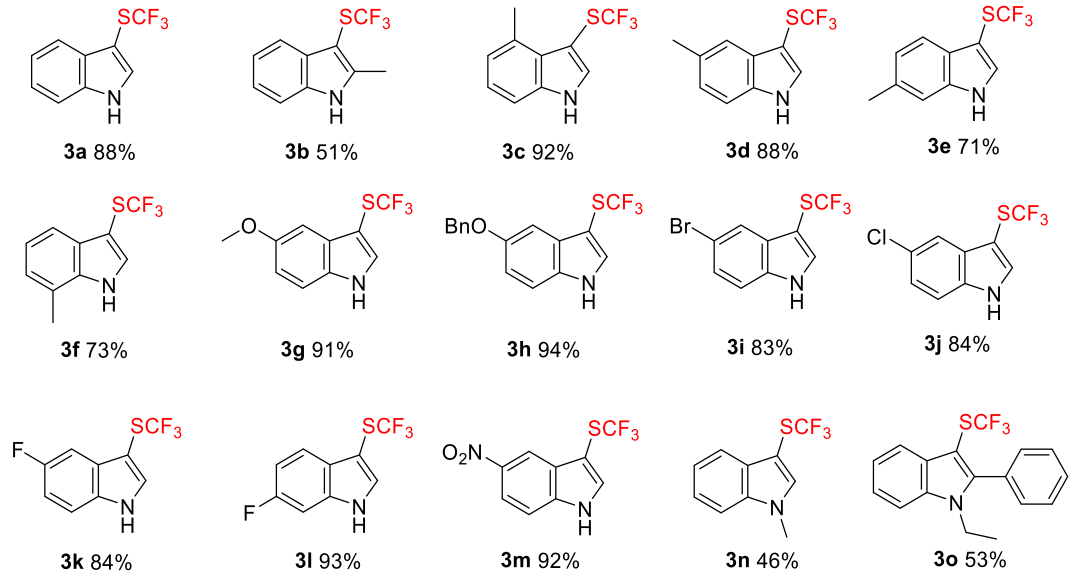
Entry	Acid	Solvent	Temp	Time	Yield **3a** (%)[b]
1	–	[Hmim]Br	60 °C	5 h	0
2	**HCl**	**[Hmim]Br**	**60 °C**	**5 h**	**93 (88)**[c]
3	HCOOH	[Hmim]Br	60 °C	5 h	0
4	$TsOH·H_2O$	[Hmim]Br	60 °C	5 h	76
5	HOAc	[Hmim]Br	60 °C	5 h	0
6	$H_2C_2O_4·2H_2O$	[Hmim]Br	60 °C	5 h	88
7	H_2SO_4	[Hmim]Br	60 °C	5 h	85
8	CH_3SO_3H	[Hmim]Br	60 °C	5 h	69
9	HCl	Toluene	60 °C	5 h	41
10	HCl	THF	60 °C	5 h	0
11	HCl	DMSO	60 °C	5 h	46
12	HCl	DMF	60 °C	5 h	0
14	HCl	Dioxane	60 °C	5 h	0
15	HCl	DCE	60 °C	5 h	3
16	HCl	EtOH	60 °C	5 h	0
17	HCl	[Hmim]Cl	60 °C	5 h	0
18	HCl	[Hmim]I	60 °C	5 h	35

[a] Reagents and conditions: **1a** (0.25 mmol), **2** (0.30 mmol), solvent (0.5 mL), acid (2 equiv.).
[b] Yields were determined by GC analysis using anisole as the internal standard.
[c] Isolated yield.

Table 2

Trifluoromethylthiolation of indoles in [Hmim]Br. Reagents and conditions: **1** (0.25 mmol), **2** (0.30 mmol), [Hmim]Br (0.5 mL), HCl (2 equiv.), 60 °C, 5 h. Isolated yields.

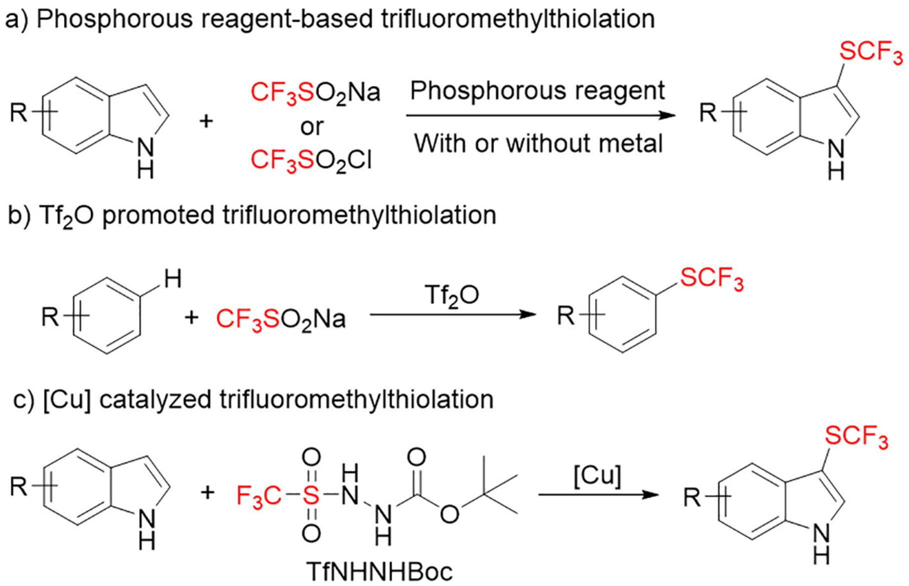




3a 88% **3b** 51% **3c** 92% **3d** 88% **3e** 71%

3f 73% **3g** 91% **3h** 94% **3i** 83% **3j** 84%

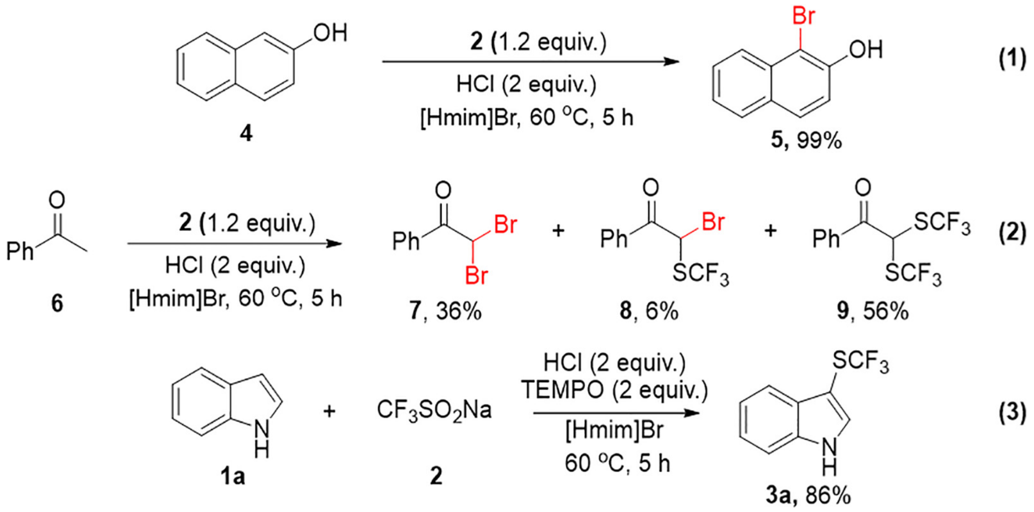
3k 84% **3l** 93% **3m** 92% **3n** 46% **3o** 53%



Scheme 2. Control experiments for the mechanistic study.

condensation and tautomerism (path B) [18], which can also react with indoles to form the desired product as the minor pathway. This result may explain why the reaction still occurs in the absence of Br⁻ with poor yields (Table 1, entries 9 and 11).

Finally, in order to examine the scalability of this protocol, the reaction of indole **1a** and CF_3SO_2Na **2** was conducted on a 10 mmol scale, affording the desired product **3a** in 85% yield. Meanwhile, investigations were also conducted to test the recyclability of [Hmim]Br. After reaction completion, an in-flask extraction using minimum amounts of MTBE was conducted to obtain the desired product. The ionic liquid recovered by extraction (after separation of the MTBE phase, the residual is the ionic liquid) was reused in



Scheme 3. Tentative pathway for the trifluoromethylthiolation of indoles in [Hmim]Br.

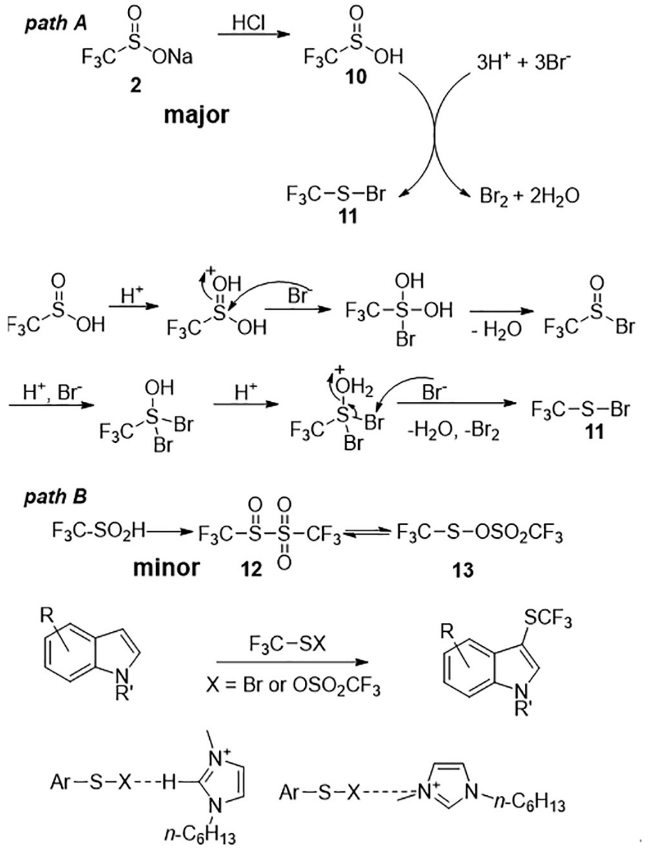


Fig. 1. Recycling studies. Reagents and conditions: **1a** (10 mmol), **2** (12 mmol), HCl (20 mmol), [Hmim]Br (10 mL), 60 °C, 5 h. Isolated yields. An additional distillation step was required for the dehydration of [Hmim]Br after being used five times.

the next round of reactions (additional details are shown in the ESI). It was found that [Hmim]Br could be used 10 times without a significant effect on the yields (Fig. 1). However, an additional distillation step was required for the dehydration of [Hmim]Br after being used five times.

Conclusion

In summary, we have developed a transition metal- and phosphorus-free methodology for the chemoselective trifluoromethylthiolation of indole derivatives using CF_3SO_2Na in [Hmim]Br. [Hmim]Br acts as reducing agent under acidic conditions to reduce CF_3SO_2Na to the "CF_3S^{+}" species. The advantages of this chemistry are simple operation, gram-scale synthesis and recyclable solvents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153015.

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