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TfNHNHBoc as a SCF_3 source for the sulfenylation of indoles

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An unprecedented use of trifluoromethanesulfonyl hydrazides as effective SCF_3 sources has been established in the sulfenylation of indoles. A range of substituted indoles participated in CuCl-catalyzed oxidative sulfenylation reaction with TfNHNHBoc in the presence of dimethyl sulfoxide to furnish structurally diverse 3-indolyl trifluoromethyl thioethers in moderate to good yields with very high regioselectivity.

In recent years, the use of arene- and alkanesulfonyl hydrazides as sulfenylating agents in the formation of C-S bonds have been recognized as a powerful approach for the preparation of various thioethers.[1,2] In general, sulfonyl hydrazides are readily accessible and stable solids, free of unpleasant odor, and compatible with water and air, and consequently, they are much more amenable to manipulation when compared to traditional sulfenylating agents such as thiols, disulfides, sulfenyl halides, and sulfonamides. To extend the scope of sulfonyl hydrazides in the sulfenylation reactions, we have successively established that TfNHNHBoc is able to serve as an effective SCF_3 source for the sulfenylation of indoles.

The SCF_3 group is present in some pharmaceuticals such as Tiflorex, Toltrazuril, and Cefazaflur.[3] Recently, much attention has been paid to the introduction of the SCF_3 group into target compounds using a variety of nucleophilic and electrophilic reagents.[4] In this regard, indolyl trifluoromethyl thioethers have been reported to be accessed through functionalization of indoles with SCF_3-containg reagents via cleavage of S-N[5] and S-O[6] bonds under various conditions.[7] Combination of CF_3SO_2Cl[8] or CF_3SO_2Na[9] with a reducing agent has also emerged as an important approach for the introduction of the SCF_3 group into indoles. Some drawbacks of these methods include requiring multiple steps and expensive fluorinated starting materials for the preparation of SCF_3-containg reagents, using highly corrosive liquids, and generating excessive phosphorus compounds as wastes. In this context, we investigated the possibility of using trifluoromethanesulfonyl hydrazides as SCF_3 sources to functionalize indoles.

We have recently reported a copper-catalyzed oxidative chlorotrifluoromethylation of arylalkenes with NaCl and trifluoromethanesulfonyl hydrazides.[10] On this basis, we envisioned that changing reaction conditions might deliver the SCF_3 moiety of trifluoromethanesulfonyl hydrazides to target compounds. Initially, we surveyed a few trifluoromethanesulfonyl hydrazides in the model reaction of indole (**1a**) in the presence of 10 mol% of CuCl and one equivalent of dimethyl sulfoxide in acetonitrile at 80 °C (Table 1, entries 1-6). The *N′*-substituent was found to affect significantly the ability of a trifluoromethanesulfonyl hydrazide to serve as a SCF_3 source and the best results were obtained from the reaction with TfNHNHBoc (**2a**), delivering thioether **3a** in 78% yield (determined by ^{19}F NMR spectroscopic analysis) with very high regioselectivity (Table 1, entry 1). Replacing CuCl with some other copper salts, dimethyl sulfoxide with some other oxidants, or acetonitrile with some other solvents led to much lower yields or even no desired product at all (Table 1, entries 7-22). Interestingly, both increasing and decreasing the amount of dimethyl sulfoxide led to much lower yields, and furthermore, the use of dimethyl sulfoxide as the solvent decreased the yield to 2% (Table 1, entries 23-25). Finally, elevating the temperature to 100 °C slightly decreased the yield to 72% (Table 1, entry 26).

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Electronic Supplementary Information (ESI) available: General information, experimental procedures, characterization data, and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra. For ESI, see DOI: 10.1039/x0xx00000x

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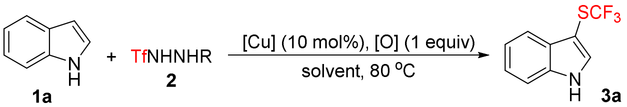
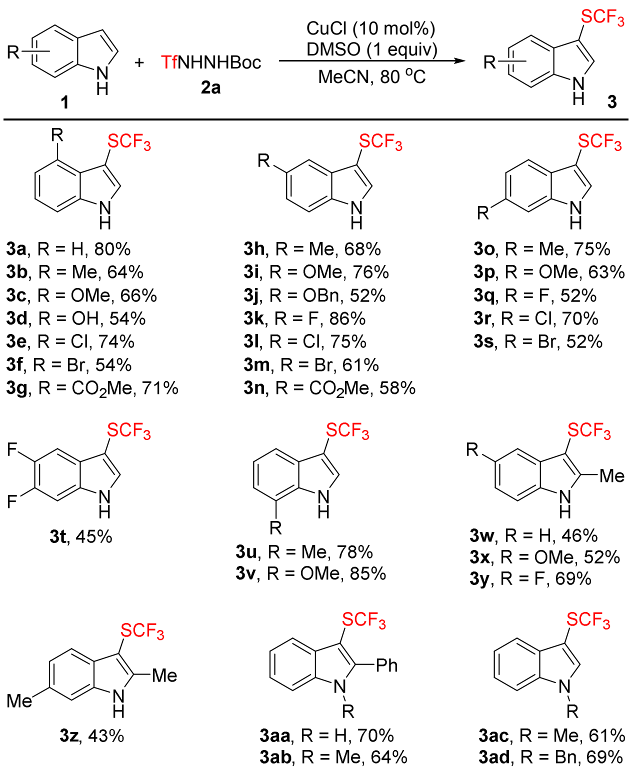
Table 1 Optimization of the reaction conditions[a]



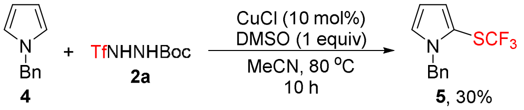
Entry	**2**, R	[Cu]	[O]	Solvent	Yield[b] (%)
1	**2a**, Boc	CuCl	DMSO	CH_3CN	78
2	**2b**, CO_2Et	CuCl	DMSO	CH_3CN	13
3	**2c**, Cbz	CuCl	DMSO	CH_3CN	trace
4	**2d**, COPh	CuCl	DMSO	CH_3CN	0
5	**2e**, Ts	CuCl	DMSO	CH_3CN	3
6	**2f**, Ph	CuCl	DMSO	CH_3CN	0
7	**2a**	CuBr	DMSO	CH_3CN	20
8	**2a**	CuI	DMSO	CH_3CN	21
9	**2a**	$Cu(MeCN)_4BF_4$	DMSO	CH_3CN	41
10	**2a**	$Cu(MeCN)_4PF_6$	DMSO	CH_3CN	0
11	**2a**	$CuCl_2{\cdot}2H_2O$	DMSO	CH_3CN	0
12	**2a**	$CuSO_4{\cdot}5H_2O$	DMSO	CH_3CN	0
13	**2a**	CuCl	H_2O_2	CH_3CN	0
14	**2a**	CuCl	TBHP	CH_3CN	0
15	**2a**	CuCl	$K_2S_2O_8$	CH_3CN	25
16	**2a**	CuCl	air	CH_3CN	48
17	**2a**	CuCl	O_2	CH_3CN	53
18	**2a**	CuCl	DMSO	Dioxane	2
19	**2a**	CuCl	DMSO	DMF	0
20	**2a**	CuCl	DMSO	EtOH	0
21	**2a**	CuCl	DMSO	DCE	8
22	**2a**	CuCl	DMSO	Toluene	0
23[c]	**2a**	CuCl	DMSO	CH_3CN	38
24[d]	**2a**	CuCl	DMSO	CH_3CN	32
25	**2a**	CuCl	DMSO	DMSO	2
26[e]	**2a**	CuCl	DMSO	CH_3CN	72

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.40 mmol), [Cu] (10 mol%), [O] (1.0 equiv), solvent (1.0 mL), 80 °C, 10 h. [b] Determined by ^{19}F NMR spectroscopic analysis using $PhCF_3$ as an internal standard. [c] 0.50 equiv of DMSO was used. [d] 2.0 equiv of DMSO was used. [e] The reaction was performed at 100 °C.

Under the optimized reaction conditions, a range of substituted indoles smoothly participated in the copper-catalyzed oxidative sulfenylation reaction with TfNHNHBoc (**2a**) to furnish structurally diverse 3-indolyl trifluoromethyl thioethers in moderate to good yields with very high regioselectivity (Scheme 1). It is noteworthy that the reaction tolerated a variety of functional groups such as alkoxy, hydroxyl, fluoro, chloro, bromo, and ester. When the C-3 position of the indole ring was occupied by a substituent (e.g. in 3-methyl-1*H*-indole), the C-2 sulfenylation product was not obtained. The sulfenylation reaction with TfNHNHBoc (**2a**) was further extended to pyrrole **4**, delivering 2-pyrrolyl trifluoromethyl thioether **5** in 30% yield but with very high regioselectivity (eqn (1)). Increasing the amount of CuCl to one equivalent improved the yield to 37%, and in contrast, elevating the temperature to 100 °C decreased the yield to 11%. Finally, the reaction was not applicable to less reactive aromatic compounds such as *N*,*N*-dimethylaniline and naphthalen-2-ol.



Scheme 1 Sulfenylation of indoles with TfNHNHBoc. [a] Reaction conditions: **1** (0.40 mmol), **2a** (0.80 mmol), CuCl (10 mol%), DMSO (1.0 equiv), acetonitrile (2.0 mL), 80 °C, 10 h. [b] Isolated yields were given.



(1)

To gain insights into the reaction mechanism, we performed the following reactions. Simply heating TfNHNHBoc (**2a**) in acetonitrile at 80 °C for 4 h gave CF_3SSCF_3, which was detected by ^{19}F NMR spectroscopic analysis (eqn (2)). Addition of one equivalent of CuCl to the above mixture led to the formation of $CuSCF_3$ (eqn (3)). Heating TfNHNHBoc (**2a**) in acetonitrile at 80 °C for 4 h followed by addition of indole (**1a**) and CuCl furnished thioether **3a** in 25% yield (determined by ^{19}F NMR spectroscopic analysis) (eqn (4)). The yield is much lower than that performed under the standard conditions as shown in Scheme 1 (80% yield) due to the low boiling point (34-35 °C) of CF_3SSCF_3 generated in the first step. A control experiment without CuCl only gave a trace amount of thioether **3a** (eqn (5)). Finally, replacing dimethyl sulfoxide with dibenzyl sulfoxide permitted us to isolate BnSBn in 41% yield, demonstrating the role of dimethyl sulfoxide as an oxidant in the above sulfenylation reaction (eqn (6)).

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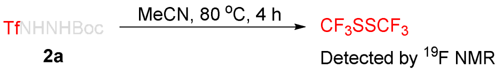
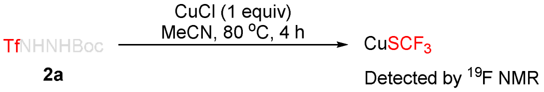


(2)



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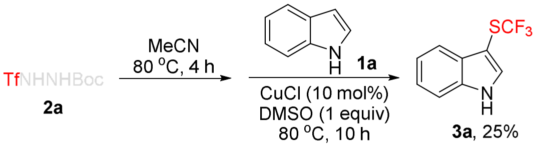
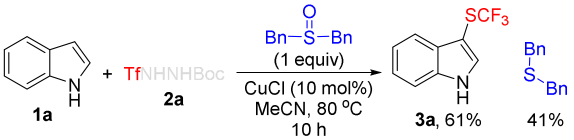


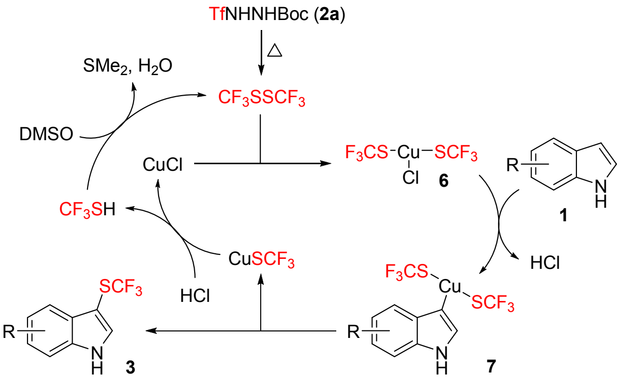
(4)

(5)



(6)

On the basis of the above experimental results and previous relevant studies, we propose the following reaction pathways for the copper-catalyzed oxidative sulfenylation of indoles with TfNHNHBoc (**2a**) (Scheme 2). At the early stage, TfNHNHBoc (**2a**) is subjected to redox decomposition to give CF_3SSCF_3.[1a,11] Then, oxidative addition of CF_3SSCF_3 to CuCl leads to the formation of copper(III) species **6**,[12] which is attacked by indole **1** to give copper(III) species **7**. Reductive elimination of copper(III) species **7** gives thioether **3** as well as $CuSCF_3$.[12] Anion exchange of $CuSCF_3$ with HCl releases CF_3SH and regenerates CuCl to continue the catalytic cycle. CF_3SH is oxidized by dimethyl sulfoxide to regenerate CF_3SSCF_3.[13]



Scheme 2 Proposed reaction pathways.

In summary, we have demonstrated an unprecedented application of trifluoromethanesulfonyl hydrazides as effective SCF_3 sources in the sulfenylation of indoles. A range of substituted indoles smoothly participated in CuCl-catalyzed oxidative sulfenylation reaction with TfNHNHBoc in the presence of dimethyl sulfoxide to furnish structurally diverse 3-indolyl trifluoromethyl thioethers in moderate to good yields with very high regioselectivity. All the starting materials and reagents are readily accessible and/or inexpensive. Preliminary mechanistic studies showed that at an early stage TfNHNHBoc decomposed to CF_3SSCF_3 and at a late stage CuCl catalyzed the oxidative sulfenylation of indoles with CF_3SSCF_3.

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Conflicts of interest

There are no conflicts to declare.

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