

# 2-Diazo-1-phenyl-2-((trifluoromethyl)sulfonyl)ethan-1-one: Another Utility for Electrophilic Trifluoromethylthiolation Reactions

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2-Diazo-1-phenyl-2-((trifluoromethyl)sulfonyl)ethan-1-one (diazo-triflone) (**2**) is not only a building block but also a reagent. In this study, diazo-triflone, which was originally used for the synthesis of  $\beta$ -lactam triflones as a trifluoromethanesulfonyl ( $\text{SO}_2\text{CF}_3$ ) building block under catalyst-free thermal conditions, is rediscovered as an effective electrophilic trifluoromethylthiolation reagent under copper catalysis. A broad set of enamines, indoles,  $\beta$ -keto esters, pyrroles, and anilines were nicely transformed into corresponding trifluoromethylthio ( $\text{SCF}_3$ ) compounds in good to high yields by diazo-triflone under copper catalysis via an electrophilic-type reaction. A coupling-type trifluoromethylthiolation reaction of aryl iodides was also realized by diazo-triflone in acceptable yields.

Considerable attention in the past decade has been devoted to the trifluoromethylthio ( $\text{SCF}_3$ ) group more than ever before because of its high potential value as a structural unit of agrochemicals and pharmaceuticals, although  $\text{SCF}_3$  compounds have been known for three quarters of a century.<sup>[1,2]</sup> The highest lipophilicity of the  $\text{SCF}_3$  group allows molecules to dramatically improve their cell membrane permeability without altering their original structures/components too much when it is introduced into a suitable position in parent molecules.

Replacement of the trifluoromethyl ( $\text{CF}_3$ ) group in drug candidates by  $\text{SCF}_3$  is an attractive strategy for fine-tuning a candidate's properties, due to their similar electron-withdrawing properties [ $\sigma_m$ : 0.44 ( $\text{CF}_3$ ); 0.40 ( $\text{SCF}_3$ )], albeit different lipophilicities [ $\pi$ : 0.88 ( $\text{CF}_3$ ); 1.44 ( $\text{SCF}_3$ )].<sup>[3]</sup> Thus, the development of effective methods for the synthesis of  $\text{SCF}_3$  compounds is of great importance in medicinal chemistry.<sup>[2]</sup>  $\text{SCF}_3$  compounds are prepared by a halogen-fluorine exchange reaction, trifluor-

omethylation of thiols or their derivatives, and direct trifluoromethylthiolation.<sup>[2i,4]</sup> The direct introduction of a  $\text{SCF}_3$  group into target compounds by trifluoromethylthiolation reagents is certainly the most straightforward method possible. However, reagents initially used for this purpose such as  $\text{Hg}(\text{SCF}_3)_2$ ,  $\text{HSCF}_3$ ,  $\text{ClSCF}_3$ , or  $\text{CF}_3\text{SSCF}_3$  are toxic and/or gaseous in character, which make them difficult to handle.<sup>[5]</sup> In this context, shelf-stable electrophilic trifluoromethylthiolation reagents have been drawing attention (Figure 1).<sup>[2,6]</sup>

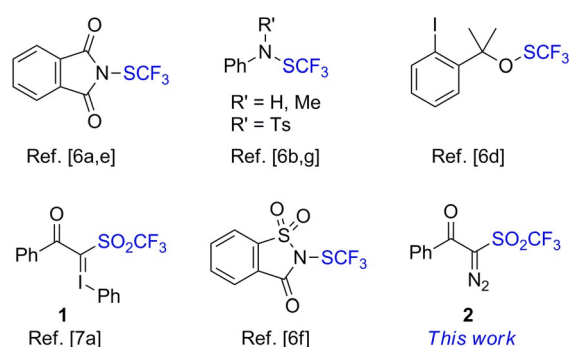


Figure 1. Shelf-stable reagents for electrophilic trifluoromethylthiolation.

Since the initial report of *N*-trifluoromethylthiophthalimide by Munavalli,<sup>[6a]</sup> several shelf-stable reagents have been reported, including trifluoromethanesulfenamide reagents (Billard, 2008),<sup>[6b]</sup> a trifluoromethylthio-ether reagent (Shen, 2013),<sup>[6d]</sup> and trifluoromethylthio saccharine (Shen, 2014).<sup>[6f]</sup> In 2013, we disclosed trifluoromethanesulfonyl hypervalent iodonium ylide **1** as a novel, shelf-stable reagent for the electrophilic trifluoromethylthiolation of enamines, indoles, and  $\beta$ -keto ester,<sup>[7a]</sup> and the utility of **1** was greatly expanded to the functionalization of pyrroles,<sup>[7b]</sup> allylsilanes and silyl enol ethers,<sup>[7c]</sup> arylamines,<sup>[7d]</sup> boronic acids, and allylic alcohols (Figure 1).<sup>[7e]</sup> Even though **1** is a trifluoromethanesulfonyl ( $\text{SO}_2\text{CF}_3$ ) compound, it effectively releases electrophilic  $\text{SCF}_3$  species via carbene generation. As part of an ongoing research program committed to trifluoromethylthiolation reactions, we were interested in the potential utility of 2-diazo-1-phenyl-2-((trifluoromethyl)sulfonyl)ethan-1-one (**2**)<sup>[8a,b]</sup> as a shelf-stable reagent for electrophilic trifluoromethylthiolation reactions.

Diazo-triflone **2** was originally developed as an effective  $\text{SO}_2\text{CF}_3$  building block for the synthesis of triflones.<sup>[8]</sup> Under thermal conditions, **2** reacts with imines to provide multiple substituted  $\beta$ -lactam triflones in essentially quantitative yields

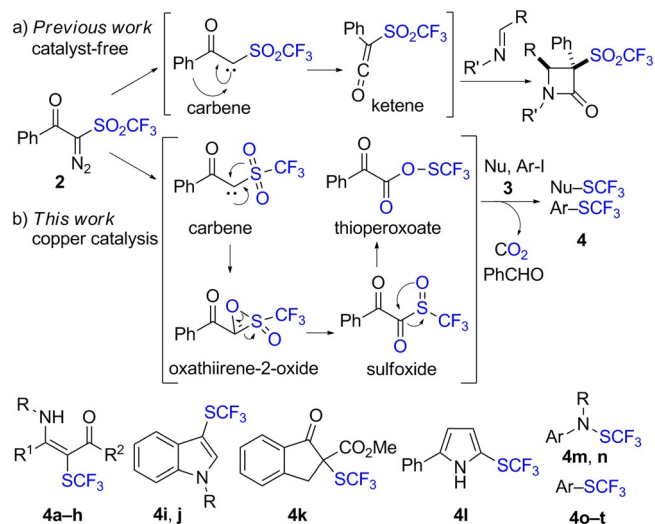
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via successive carbene-generation, Wolf rearrangement (ketene), and Staudinger [2+2] cycloaddition (Scheme 1a).<sup>[8b]</sup> The similarity of carbene generation from **2** and that from **1** led us to investigate a new utility of **2** for electrophilic trifluoromethylthiolation, via successive carbene-generation/oxathiirene-2-oxide/sulfoxide/thioperoxoate rearrangement (Scheme 1b).<sup>[7b,8b]</sup>

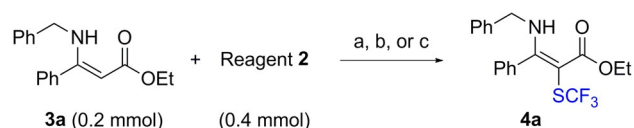


**Scheme 1.** Double-sided utility of **2** as an  $\text{SO}_2\text{CF}_3$  building block and a reagent for electrophilic trifluoromethylthiolation reaction ( $\text{SCF}_3$ -reaction).

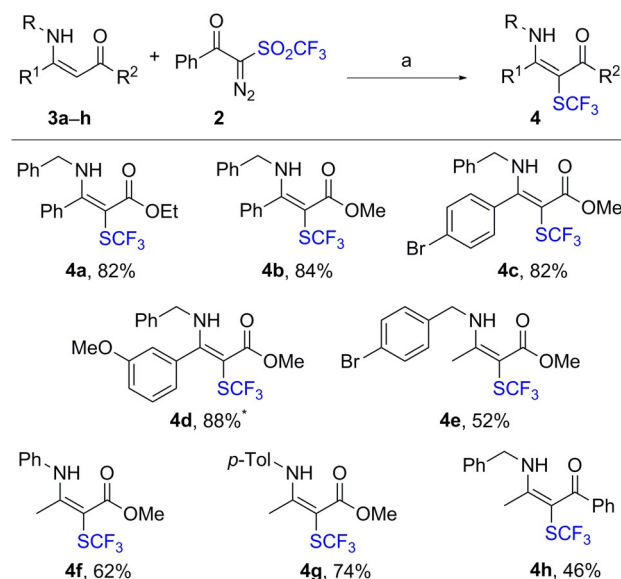
Herein, we disclose that **2** is effective for the electrophilic trifluoromethylthiolation of a variety of nucleophiles including enamines, indoles,  $\beta$ -keto esters, pyrroles, and anilines under copper catalysis to provide corresponding  $\text{SCF}_3$ -products in good to high yields. Trifluoromethylthiolation via a coupling-type reaction of aryl iodides was also realized by **2** under copper catalysis, providing aryl- $\text{SCF}_3$  compounds in acceptable yields. This is a unique example of the two-sided utility of the fluorinated compound **2** as a fluoro-functionalized reagent ( $\text{SCF}_3$  reagent) and a fluorinated building block ( $\text{SO}_2\text{CF}_3$  building block).

We first examined the reaction of enamine **3a** with **2** under standard conditions described in a previous report for the trifluoromethylthiolation of **3a** by **1**.<sup>[7a]</sup> However, trifluoromethylthiolated product **4a** was detected in 41% at room temperature for 48 h. The yield of **4a** was improved to 82% at 50 °C for 12 h, and decreased slightly to 79% at 100 °C for 12 h (Scheme 2).

Under the optimized reaction conditions, enamine substrates **3a–h** were smoothly trifluoromethylthiolated by **2** to provide corresponding  $\text{SCF}_3$  products **4a–h** in moderate to good yields (Scheme 3). Enamino esters **3a–d** were nicely trifluoromethylthiolated by **2** with over 80% yield almost independent of the size of esters and the substitution of the terminal aryl group. Enamino esters **3e–g** having an enolizable proton were also tolerated under the reaction conditions to



**Scheme 2.** Copper-catalyzed trifluoromethylthiolation of enamine **3a** with **2** (yield was detected by  $^{19}\text{F}$  NMR). *Reagents and conditions:* all conditions with  $\text{CuCl}$  (0.04 mmol), 1,4-dioxane (1.5 mL); a) rt, 48 h, 41%; b) 50 °C, 12 h, 82%; c) 100 °C, 12 h, 79%.

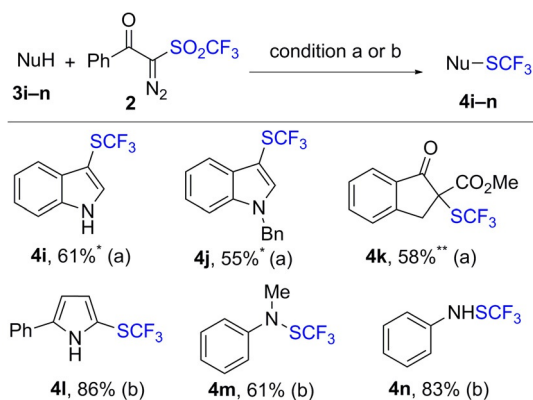


**Scheme 3.** Copper-catalyzed trifluoromethylthiolation of enamines **3a–h** with **2**. *Reagents and conditions:* a) enamine **3** (0.2 mmol), reagent **2** (0.4 mmol),  $\text{CuCl}$  (0.04 mmol, 20 mol%), 1,4-dioxane (1.5 mL), 50 °C, 12 h, isolated yields shown (%). \* Reagent **2** (0.3 mmol), 24 h.

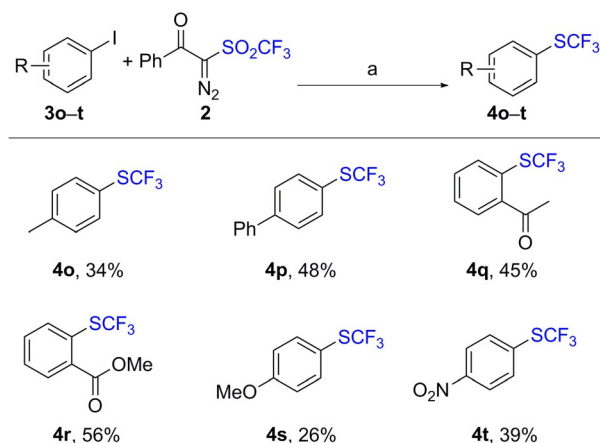
furnish **4e–g** in 52–74% yield. Enamino ketone **3h** was converted into the corresponding  $\text{SCF}_3$ -product **4h** in 46% yield.

Other nucleophilic substrates, such as indoles,  $\beta$ -keto ester, pyrrole, and anilines, were next investigated for trifluoromethylthiolation by **2** (Scheme 4). Indole substrates **3i** and **3j** were transformed into corresponding  $\text{SCF}_3$  products in the presence of 20 mol% dimethylaniline as an additive to provide **4i** and **4j** in 61% and 55% yield, respectively.  $\beta$ -Keto ester **3k** reacted with **2** in the presence of 20 mol% 2,4,6-collidine affording **4k** in 58% yield. Trifluoromethylthiolation of pyrrole **3l** and anilines **3m–n** with **2** was also achieved to give **4l–n** in good yields (61–86%). Dimethylaniline and 2,4,6-collidine presumably act as bases for deprotonation of substrates and/or activate a thioperoxoate intermediate (Scheme 1) to generate quaternary ammonium salts with  $\text{SCF}_3$ .<sup>[7a]</sup>

We further examined the trifluoromethylthiolation of aromatic compounds under a cross-coupling type of trifluoromethylthiolation reaction. First, 4-iodotoluene **3o** was selected as the model substrate for trifluoromethylthiolation by **2** (Table 1). A catalytic amount of copper salt afforded the reaction in low yields of 18–32% (entries 1–4), and dimethylformamide (DMF) showed better results than *N*-methyl-2-pyrrolidone (NMP) as



**Scheme 4.** Copper-catalyzed trifluoromethylthiolation of indoles,  $\beta$ -keto ester, pyrrole, and anilines with **2**. *Reagents and conditions:* a) indoles or  $\beta$ -keto ester **3** (0.2 mmol), **2** (0.4 mmol), CuCl (0.04 mmol), 1,4-dioxane (1.5 mL), 50 °C, 12 h; b) pyrrole or aniline **3** (0.2 mmol), **2** (0.4 mmol), CuF<sub>2</sub> (0.04 mmol), NMP (1.5 mL), 50 °C, 24 h, isolated yields shown (%). \*PhNMe<sub>2</sub> (0.04 mmol) was added. \*\*2,4,6-Collidine (0.04 mmol) was added.



**Scheme 5.** Copper-mediated trifluoromethylthiolation of aryl iodides **3 o–t** with **2**. *Reagents and conditions:* a) aryl iodide **3** (0.2 mmol), **2** (0.5 mmol), Cu (1.0 mmol, 5.0 equiv), DMF (2.5 mL), 50 °C for 12 h then 120 °C for 12 h, isolated yields shown (%).

**Table 1.** Optimization of reaction conditions of 4-iodotoluene **3 o** with reagent **2**.<sup>[a]</sup>

Entry	Molar ratio [3 o:2]	Catalyst	Cu [equiv]	Solvent	Yield <sup>[b]</sup> [%]
1	1:1.5	CuF <sub>2</sub>	2.5	DMF	18
2 <sup>[c]</sup>	1:2.5	CuF <sub>2</sub>	2.5	DMF	23
3	1:2.5	CuOAc	2.5	DMF	32
4	1:2.5	CuOAc	2.5	NMP	25
5	1:2.5	—	2.5	DMF	35
6	1:2.5	—	5.0	DMF	56
7	1:5	—	5.0	DMF	19
8	1:2.5	—	10.0	DMF	32
9 <sup>[d]</sup>	1:2.5	—	5.0	DMF	10
10 <sup>[e]</sup>	1:2.5	—	5.0	DMF	5
11	1:2.5	Pd(Ph <sub>3</sub> P) <sub>2</sub> Cl <sub>2</sub>	5.0	Toluene	0
12 <sup>[f]</sup>	1:2.5	—	5.0	DMF	trace

[a] Reaction conditions: 4-iodotoluene (**3 o**, 0.2 mmol), reagent **2**, catalyst, Cu, solvent (2.5 mL), 50 °C for 12 h then 120 °C for another 12 h. [b] Yields were determined by <sup>19</sup>F NMR spectroscopy with trifluoromethyl benzene as the internal standard. [c] **2**, Cu, DMF (2.5 mL), 50 °C for 12 h, then 4-iodotoluene (**3 o**, 0.2 mmol), and 120 °C for another 12 h. [d] Bipyridine (1.0 equiv) was added. [e] KF (1.0 equiv) was added. [f] The reaction was heated directly at 120 °C for 12 h.

a solvent (entries 3 and 4). Further optimization of the molar ratio of **3 o** with reagent **2** and copper led to suitable conditions, **3 o**/**2**: 1:2.5 and 5.0 equivalents of Cu in DMF, providing **4 o** in 56% (entries 5–10). A palladium catalyst in toluene was not effective (entry 11). A two-step heating protocol i.e., 50 °C for 12 h, followed by 120 °C for 12 h, was preferred, as greater yield was obtained than single heating at 120 °C for 12 h (entry 12).

With standard reaction conditions in hand, substrate scope was next investigated using aryl iodides **3 o–t** bearing elec-

tron-donating or electron-withdrawing groups. Although yields were not attractive, the desired Ar–SCF<sub>3</sub> products **4 o–t** were obtained in 34–56% isolated yields (Scheme 5).

In summary, diazo-triflone **2** was found to be effective for electrophilic trifluoromethylthiolation of a variety of substrates including enamino esters, enamino ketones, indoles,  $\beta$ -keto esters, pyrroles, and anilines under copper catalysis in good to high yields. The copper-mediated coupling-type trifluoromethylthiolation of aryl iodides was also made possible by **2** in acceptable yields. Since diazo-triflone **2** was originally examined as a fluorinated building block for the synthesis of  $\beta$ -lactam triflones, the present result reveals a unique double-sided property of **2**, as an SO<sub>2</sub>CF<sub>3</sub>-containing building block and as an electrophilic SCF<sub>3</sub>-transfer reagent. Further investigation of **2** is underway in our laboratory.

## Experimental Section

### Typical procedure for copper-catalyzed trifluoromethylthiolation of enamines, indoles, pyrroles, and anilines

To nucleophiles **3 a–n** (0.2 mmol) in 1,4-dioxane (or NMP) solution (1.5 mL), diazo-triflone **2** (0.4 mmol) and CuCl (or CuF<sub>2</sub>) (0.04 mmol) were added under N<sub>2</sub> atmosphere in the presence or absence of additives described in Schemes 3 and 4. The mixture was then heated at 50 °C for 12 or 24 h. The mixture was diluted with Et<sub>2</sub>O (30 mL), washed once with H<sub>2</sub>O (20 mL) and brine (20 mL), and the organic phase was dried by dry Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed in vacuo, and the sample purified by column chromatography to afford SCF<sub>3</sub>-products **4 a–n**.

### Typical procedure for copper-mediated trifluoromethylthiolation of aryl iodides

To aryl iodides **3 o–t** (0.2 mmol) in DMF solution (2.5 mL) in a sealed tube, diazo-triflone **2** (0.5 mmol) and Cu (1.0 mmol) were added under N<sub>2</sub> atmosphere, the tube was sealed, and the mixture was heated at 50 °C for 12 h. The temperature was increased to 120 °C and heated for another 12 h. The mixture was diluted by

Et<sub>2</sub>O (30 mL) and washed once with H<sub>2</sub>O (20 mL) and brine (20 mL), and the organic phase was dried by dry Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed in vacuo, and the sample purified by column chromatography (or preparative thin-layer plates) to afford SCF<sub>3</sub>-products **4o-t**.

Complete synthetic protocols together with characterization data, including spectra for all compounds described herein, are provided in the Supporting Information.

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**Keywords:** carbines · fluorine · sulfur · triflones · trifluoromethylthiolation

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