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 β-lactam triflones as a trifluoromethanesulfonfonyl (SO₂CF₃) building block under catalyst-free thermal conditions, is rediscovered as an effective electrophilic trifluoromethylthiolation reagent under copper catalysis. A broad set of enamines, indoles, β-κeto esters, pyrroles, and anilines were nicely transformed into corresponding trifluoromethylthio (SCF₃) 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 (SCF₃) group more than ever before because of its high potential value as a structural unit of agrochemicals and pharmaceuticals, although SCF₃ compounds have been known for three quarters of a century.[1,2] The highest lipophilicity of the SCF₃ 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 (CF₃) group in drug candidates by SCF₃ is an attractive strategy for fine-tuning a candidate’s properties, due to their similar electron-withdrawing properties [αCF₃: 0.44 (CF₃); 0.40 (SCF₃)], albeit different lipophilicities [α: 0.88 (CF₃); 1.44 (SCF₃)].[3] Thus, the development of effective methods for the synthesis of SCF₃ compounds is of great importance in medicinal chemistry.[4] SCF₃ compounds are prepared by a halogen-fluorine exchange reaction, trifluoromethylation of thiols or their derivatives, and direct trifluoromethylthiolation.[2,4] The direct introduction of a SCF₃ group into target compounds by trifluoromethylthiolation reagents is certainly the most straightforward method possible. However, reagents initially used for this purpose such as Hg(SCF₃)₂, HSCF₃, C(═S)CF₃, or CF₃SCF₃ are toxic and/or gaseous in character, which make them difficult to handle.[5] In this context, shelf-stable electrophilic trifluoromethylthiolation reagents have been drawing attention (Figure 1).[3,4]

Since the initial report of N-trifluoromethylthiophosphoramid derivative by Munavalli,[6a] several shelf-stable reagents have been reported, including trifluoromethanesulfenamide reagents (Billard, 2008),[6b] a trifluoromethylthio-ether reagent (Shen, 2013),[6d] and trifluoromethylthio saccharine (Shen, 2014).[6c] In 2013, we disclosed trifluoromethanesulfonyl hypervalent iodonium ylide 1 as a novel, shelf-stable reagent for the electrophilic trifluoromethylthiolation of enamines, indoles, and β-κeto esters,[6d] and the utility of 1 was greatly expanded to the functionalization of pyrroles,[7a] allylsilanes and silyl enol ethers,[7b] boronic acids, and allylic alcohols (Figure 1).[7b] Even though 1 is a trifluoromethanesulfonfonyl (SO₂CF₃) compound, it effectively releases electrophilic SCF₃ 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)[8a,b] as a shelf-stable reagent for electrophilic trifluoromethylthiolation reactions.

Diazotriflone 2 was originally developed as an effective SO₂CF₃ building block for the synthesis of triflones.[8] Under thermal conditions, 2 reacts with imines to provide multiple substituted β-lactam triflones in essentially quantitative yields.
via successive carbene-generation, Wolf rearrangement (ketene), and Staudinger [2+2] cycloaddition (Scheme 1a).[8b]

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/oxathirene-2-oxide/sulfoxide/thioperoxoate rearrangement (Scheme 1b).[7b,8b]

Herein, we disclose that 2 is effective for the electrophilic trifluoromethylthiolation of a variety of nucleophiles including enamines, indoles, β-keto esters, pyrroles, and anilines under copper catalysis to provide corresponding SCF3-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-SCF3 compounds in acceptable yields. This is a unique example of the two-sided utility of the fluorinated compound 2 as a fluoro-functionalized reagent (SCF3-reagent) and a fluorinated building block (SO2CF3-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.[7a] 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 SCF3-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 furnish 4e–g in 52–74% yield. Enamino ketone 3h was converted into the corresponding SCF3-product 4h in 46% yield.

Other nucleophilic substrates, such as indoles, β-keto ester, pyrrole, and anilines, were next investigated for trifluoromethylthiolation by 2 (Scheme 4). Indole substrates 3i and 3j were transformed into corresponding SCF3-products in the presence of 20 mol% dimethylaniline as an additive to provide 4i and 4j in 61% and 55% yield, respectively. β-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 SCF3.[7a]

We further examined the trifluoromethylthiolation of aromatic compounds under a cross-coupling type of trifluoromethylthiolation reaction. First, 4-iodo-toluene 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
Cu, solvent (2.5 mL), 50 °C for 12 h, then 4-iodotoluene (3.0, 0.2 mmol), and 120 °C for another 12 h. The mixture was diluted with Et2O (30 mL), washed once with H2O (20 mL) and brine (20 mL), and the organic phase was dried by dry Na2SO4. Solvent was removed in vacuo, and the sample purified by column chromatography to afford SCF$_3$-products 4a–n.

**Typical procedure for copper-catalyzed trifluoromethylthiolation of aryl iodides**

To aryl iodides 3o–t (0.2 mmol) in DMF solution (2.5 mL) in a sealed tube, diazo-triflone 2 (0.4 mmol) and CuCl (or CuF$_2$) (0.04 mmol) were added under N$_2$ atmosphere, the tube was sealed, and the mixture was heated at 50 °C for 12 h. The mixture was then heated at 120 °C for 2 h. The temperature was increased to 120 °C at 12 h.
Et₂O (30 mL) and washed once with H₂O (20 mL) and brine (20 mL), and the organic phase was dried by dry Na₂SO₄. Solvent was removed in vacuo, and the sample purified by column chromatography (or preparative thin-layer plates) to afford SCF₃-products 4a–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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