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Metal-Free sp^3 C-SCF$_3$ Coupling Reactions between Cycloketone Oxime Esters and *S*-trifluoromethyl 4-Methylbenzenesulfonothioate

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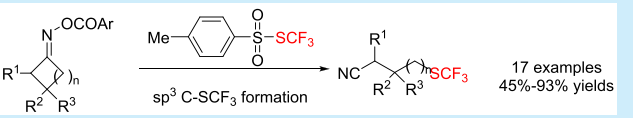
ABSTRACT: A novel sp^3 C-SCF$_3$ coupling reaction between cycloketone oxime esters and *S*-trifluoromethyl 4-methylbenzenesulfonothioate was achieved. Ethanol was found to facilitate this transformation by trapping the sulfonyl cation. The metal-free and photocatalyst-free reaction conditions, as well as the broad substrate scope, make this a green protocol for the synthesis of SCF$_3$-substituted nitriles.

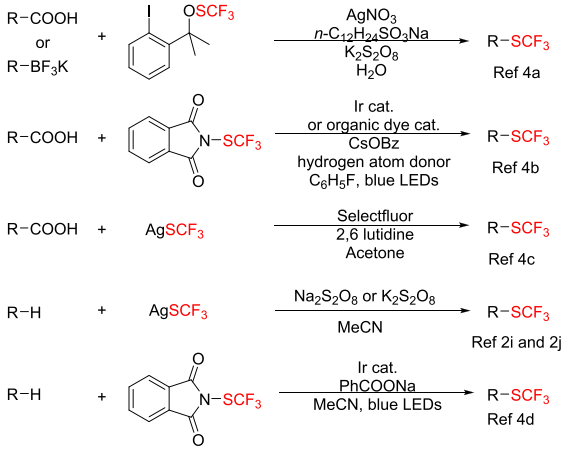


Over the past decade, the trifluoromethylthio group (SCF$_3$) has attracted much attention from organic and medicinal chemists, because it is one of the most privileged fragments that can improve the lipophilicity and cell membrane permeability of druglike molecules.[1] To this end, direct trifluoromethylthiolation has seen great progress,[2] in addition to the indirect incorporation of SCF$_3$ into organic molecules via trifluoromethylation of thiols.[3] The majority of the direct trifluoromethylthiolation methods involve the construction of a C−S bond between the sp^2 carbon and the SCF$_3$ group. The existing protocols for sp^3 C-SCF$_3$ bond formation are efficient but require either expensive trifluoromethylthiolation reagents or complex catalytic systems (see Scheme 1).[2i,j,4] Hence, constructing sp^3 C-SCF$_3$ bonds using inexpensive and readily accessible reagents with simple catalytic systems is highly desirable.

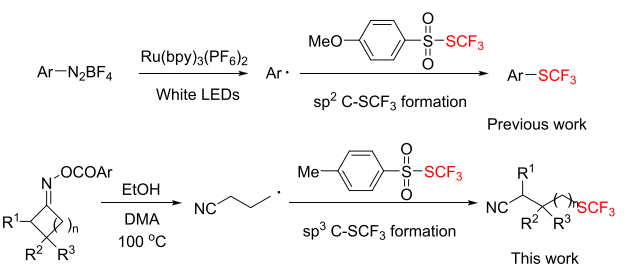
Cyclobutanone oximes esters are useful and versatile intermediates in organic synthesis, because they can be transformed to functionalized nitriles via iminyl radicals by transition-metal catalysis,[5] visible-light photocatalysis,[6] and acid catalysis.[7] Moreover, fragmentation of cyclobutanone oxime esters can be realized by microwave irradiation[8] and $B_2(OH)_4$/dimethylacetamide activation.[9] In 2018, we reported a photocatalyzed sp^2 C-SCF$_3$ bond formation reaction between aryldiazonium salts and *S*-trifluoromethyl-4-methoxybenzenesulfonothioate.[10] As part of our ongoing program to develop efficient methods for C-SCF$_3$ bond construction,[11] we envisioned that fragmentation of cyclobutanone oxime could generate a cyanoalkyl radical, which may be trapped by *S*-trifluoromethyl-4-methylbenzenesulfonothioate (TsSCF$_3$) to form SCF$_3$-substituted nitriles. Herein we demonstrate a novel ethanol-promoted sp^3 C-SCF$_3$ coupling reaction between cycloketone oxime esters and *S*-trifluoromethyl 4-methylbenzenesulfonothioate under metal-free conditions (see Scheme 2).

We attempted the sp^3 C-SCF$_3$ coupling reactions between cyclobutanone *O*-(4-(trifluoromethyl)benzoyl) oxime **1a** with

Scheme 1. Selective Methods for sp^3 C-SCF$_3$ Bonds Formation Reaction via Radical Intermediate



Scheme 2. Direct Trifluoromethylthiolation by *S*-trifluoromethyl Arylsulfonothioate via Radical Process



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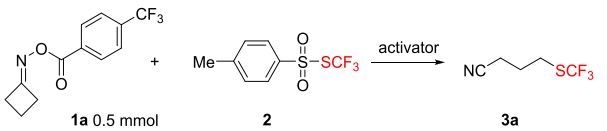
S-(trifluoromethyl)-4-methylbenzenesulfonothioate in *N*,*N*-dimethylformamide (DMF) at 100 °C. To our delight, the desired trifluoromethylthiolation product was obtained in 48% yield. To improve the yield, we screened other solvents such as acetonitrile (MeCN), dimethyl sulfoxide (DMSO), 1,4-dioxane, and *N*,*N*-dimethylacetamide (DMA), among which DMA gave the best yield. According to the literature, the addition of ferrous sulfate (0.1 equiv) as an activator improved the yield to 60%. Surprisingly, when ferrous sulfate heptahydrate was used as the activator, the yield increased to 73%. We envisioned that water may play an important role in the activation of **1a**. Indeed, the addition of 0.7 equiv water as the activator in the present reaction enhanced the yield from 52% to 58% (see Table 1, entries 8 vs 5). Moreover, the

Table 1. Reaction Optimization[a]



1a 0.5 mmol **2** **3a**

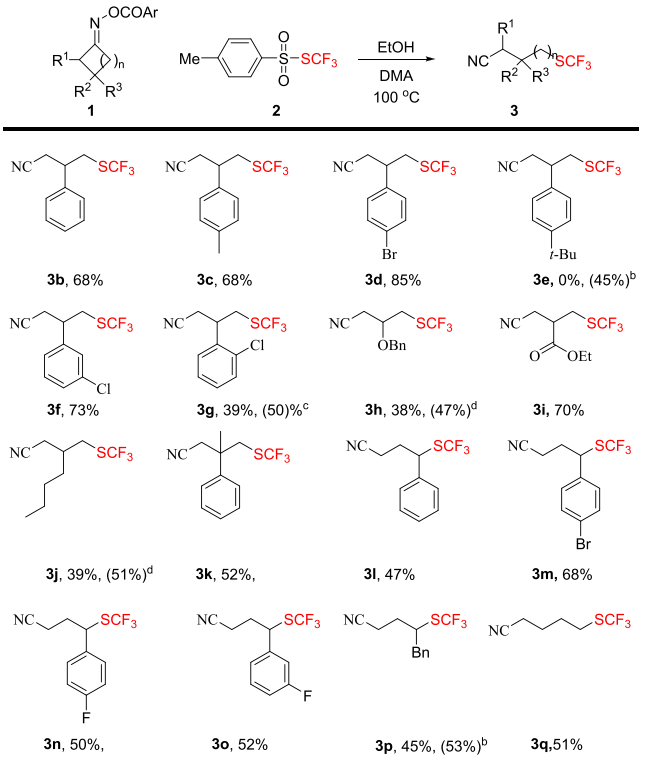
entry	**2** (equiv)	activator (equiv)	solvent (mL)	temperature, *T* (°C)	yield (%)
1	1.5	–	DMF (6 mL)	100	48
2	1.5	–	MeCN (6 mL)	100	trace
3	1.5	–	DMSO (6 mL)	100	trace
4	1.5	–	1,4-dioxane (6 mL)	100	trace
5	1.5	–	DMA (6 mL)	100	52
6	1.5	$FeSO_4$ (0.1)	DMA (6 mL)	100	60
7	1.5	$FeSO_4{\cdot}7H_2O$ (0.1)	DMA (6 mL)	100	73
8	1.5	H_2O (0.7)	DMA (6 mL)	100	58
9	1.5	H_2O (1.0)	DMA (6 mL)	100	62
10	1.5	H_2O (1.2)	DMA (6 mL)	100	65
11	1.5	H_2O (1.5)	DMA (6 mL)	100	75
12	1.5	H_2O (1.8)	DMA (6 mL)	100	63
13	1.5	H_2O (1.5)	DMA (5 mL)	100	69
14	1.5	H_2O (1.5)	DMA (7 mL)	100	72
15	1.8	H_2O (1.5)	DMA (6 mL)	100	80
16	2.0	H_2O (1.5)	DMA (6 mL)	100	80
17	1.8	H_2O (1.5)	DMA (6 mL)	90	70
18	1.8	H_2O (1.5)	DMA (6 mL)	110	68
19	1.8	EtOH (1.5)	DMA (6 mL)	100	93
20	1.8	MeOH (1.5)	DMA (6 mL)	100	85
21	1.8	*i*-PrOH (1.5)	DMA (6 mL)	100	67
22	1.8	TsOH (1.5)	DMA (6 mL)	100	53

[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75−1.0 mmol), activator (0−0.9 mmol), solvent (5−7 mL) at 90−110 °C for 12 h.

loading of water was investigated; 1.5 equiv of water gave the best yield. The reaction concentration, the loading of **2**, and reaction temperature then were examined; the results indicated that increasing or decreasing the reaction concentration diminished the yield. When the loading of **2** was increased to 1.8 equiv, the yield improved to 80%, but a further increase in the loading to 2.0 equiv had no notable effect on the yield. When the reaction temperature was decreased to 90 °C or increased to 110 °C, the yield decreased. Finally, other activators with different pK_a values, including ethanol, methanol, isopropanol, and *p*-toluenesulfonic acid (TsOH), were examined, and 93% yield was obtained when using ethanol. Thus, the optimized reaction conditions were as established follows: **1a** (0.5 mmol), **2** (0.9 mmol), EtOH (0.75 mmol) in DMA (6 mL), at 100 °C.

With the optimized reaction conditions in hand, we next examined the generality of this reaction by employing a series of cyclobutanone oxime esters (**1b−1p**) as substrates; the results are summarized in Scheme 3. 3-Phenyl cyclobutanone

Scheme 3. Substrate Scope for Trifluoromethylthiolation of Cyclobutanone Oxime Esters[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.9 mmol), EtOH (0.75 mmol) in DMA (6 mL), at 100 °C for 5−12 h, Ar = 4-(trifluoromethyl)phenyl. [b]**2** (1.0 mmol) was used, Ar = perfluorophenyl. [c]**2** (1.0 mmol) was used. [d]Ar = 3,5-bis(trifluoromethyl)-phenyl.

oxime ester **1b** furnished the desired product **3b** in 68% yield. Other 3-aryl cyclobutanone oxime esters with *para*, *meta*, or *ortho* substitution on the phenyl ring (**1c−1g**) were well-tolerated under the present reaction conditions and gave the desired product (**3c−3g**) in moderate to good yields. In addition, 3-benzyloxy-, 3-ethoxycarbonyl-, 3-butyl-, and 3-methyl-3-phenyl-substituted cyclobutanone oxime esters were compatible with this transformation and furnished the desired products (**3h−3k**). Moreover, 2-aryl- and 2-benzyl-substituted cyclobutanone oxime esters (**1l−1p**) gave the desired products (**3l−3p**) in moderate to good yields. Notably, in some cases, an increase in the loading of **2** to 2.0 equiv or the use of more electron-withdrawing cyclobutanone oxime esters such as *O*-perfluorobenzoyl oxime ester or *O*-(3,5-bis(trifluoromethyl)-benzoyl) oxime ester improved the yield. To further expand the substrate scope of this transformation, cyclopentanone *O*-(4-(trifluoromethyl)benzoyl) oxime (**1q**) was employed as the substrate. To our delight, the desired product (**3q**) was obtained in 51% yield.

Based on related mechanisms in the literature,[8,9] we presumed that the alkyl radical might be the key intermediate

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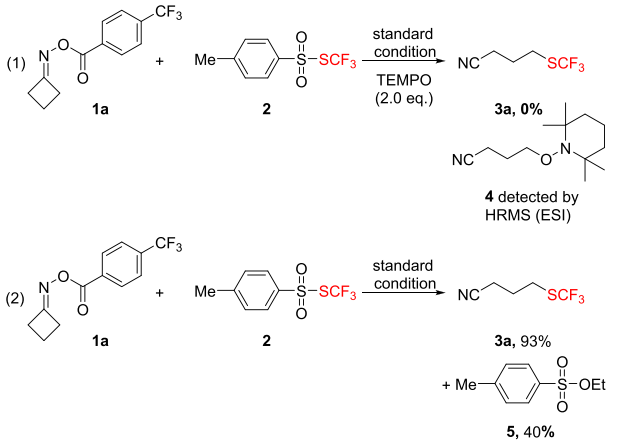
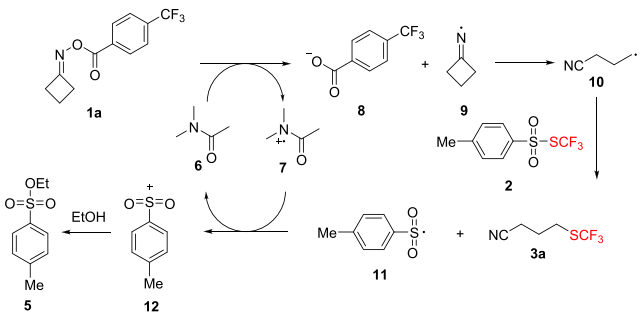
in this transformation. To prove this hypothesis, we performed an additional experiment using 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 2 equiv) as the radical trapping reagent under the standard reaction conditions. The results showed that no desired product was obtained and a TEMPO-alkane adduct **4** were detected by electron spin ionization−high-resolution mass spectroscopy (ESI-HRMS). Notably, ethyl 4-methylbenzenesulfonate **5** was obtained as a byproduct under the standard reaction condition in 40% yield (see Scheme 4).

Scheme 4. Elucidation of Reaction Mechanism



Based on the aforementioned results and related literature, a plausible mechanism for the trifluoromethylthiolation is proposed (Scheme 5). Initially, a single-electron transfer

Scheme 5. Plausible Mechanism of Ethanol-Mediated Trifluoromethylthiolation of Cyclobutanone Oxime Esters

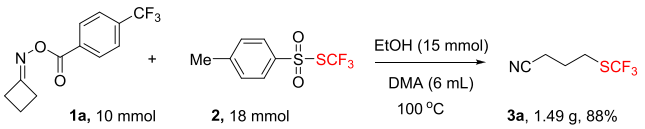


(SET) between cyclobutanone oximes esters **1a** and DMAC **6** led to the generation of **7**, 4-(trifluoromethyl)benzoate **8**, and iminyl radical **9**, which undergoes a ring-opening process to generate cyanoalkyl radical **10**. Intermediate **10** then reacts with *S*-trifluoromethyl-4-methoxybenzenesulfonothioate **2** to afford the product **3a** and sulfone radical **11**, which is converted to sulfonyl cation **12** by SET with **7**. Finally, **12** is trapped by ethanol to produce **5**.

Finally, the practical application of this transformation was investigated by performing the trifluoromethylthiolation of cyclobutanone oxime esters on a 10 mmol scale (see Scheme 6). The desired product **3a** was obtained in 88% yield.

In summary, we report for the first time the synthesis of SCF_3-substituted allyl nitriles by a metal-free sp^3 C-SCF_3 coupling reaction between cycloketone oxime esters and *S*-trifluoromethyl-4-methylbenzenesulfonothioate. Mechanistic

Scheme 6. Scaleup of Trifluoromethylthiolation



investigations by radical trapping experiments confirmed the intermediacy of free radicals in this reaction. Notably, ethanol was found to facilitate this transformation by trapping the sulfonyl cation. Synthesis of other sulfur-substituted allyl nitriles from cycloketone oxime esters by this strategy is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04343.

Experimental procedures and characterization data for all the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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