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Visible-light-induced oxidative difunctionalization of styrenes: synthesis of α -trifluoromethylthio-substituted ketones[†]

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A novel and practical synthesis of α -trifluoromethylthio-¹⁰ substituted ketones has been accomplished using visible-lightinduced aerobic oxidation of styrenes. The protocol employs the combination of CF₃SO₂Na and CS₂ as a new source of SCF₃ radical in the presence of eosin Y as photoredox catalyst.

¹⁵ The introduction of SCF₃ group in organic scaffolds has recently attracted a great deal of attention due to its unique pharmaceutical and agrochemical properties.¹ The physicochemical effect of SCF₃ function is ascribed to its electronic properties, high stability and lipophilicity, which facilitates the transmembrane ²⁰ permeation and bioavailability of CF₃S-containing molecules.² Among such molecules, α -SCF₃-substituted ketones constitute a vital building block of various medicinal and natural product analogs such as Cafazaflur, Estrone and Cephalosporin (see ESI, page 2).³ Thus, the synthesis of α -SCF₃-substituted ketones is ²⁵ highly important, although considerably less explored. The existing synthetic approaches for trifluoromethylthiolation (Scheme 1) involve the reaction of either (i) electrophilic SCF₃

(benche 1) involve the relation of entite (i) electropine Set 3 with simple ketones/ β -ketoesters (Approach A),^{3a-d} or (ii) nucleophilic SCF₃ with phenacyl bromides, and α,β -unsaturated 30 carboxylic acids (Approach B).^{3e,f} However, the former approach involves the use of expensive, toxic, and moisture/air sensitive reagents as well as harsh conditions, while the later one makes use of a highly lachrymator starting material and metal catalysis.

Yet, the synthesis of α -SCF₃-substituted ketones via radical ³⁵ approach remains unexplored and challenging.

Alkenes are among the most readily accessible synthetic units, and free radical difunctionalization of such species has opened a new window for the creation of highly functionalized skeletons in a single click, with a lot of prospect for designing new synthetic

- ⁴⁰ strategies.^{4,5} Photoredox catalysis, pioneered by the work of MacMillan, Yoon and Stephenson, has now become a powerful tool in organic synthesis both for the target oriented synthesis and methodology development.⁶ It has the capability of dioxygen activation, thereby acting as a green oxidant as well as an ideal
- ⁴⁵ oxygen source for the functionalization of organic molecules.⁷ However, photocatalysts such as Ru(bpy)₃Cl₂ (bpy = 2,2'-bipyridine) or Ir(dtbbpy)₃Cl₂ (dtbbpy = 4,4'-di-*tert* butyl-2,2'-bipyridine) are typically transition-metal based inorganic complexes,⁸ and have the disadvantage of potential toxicity, high ⁵⁰ cost and problematic removal from the products wherever traces

of metals are undesirable. Eosin Y (EY) has been identified as an efficient alternative organophotoredox catalyst recently applied in organic synthesis.⁹

Langlois' reagent (CF₃SO₂Na) is newly used as stable surrogate 55 of CF₃ radical under photoredox conditions.¹⁰ We hypothesized that CF₃ radical generated in situ under photoredox catalysis from with CF₃SO₂Na might react CS_2 followed by dethiocarbonylation,¹¹ to form SCF₃ radical, which might also implicate the direct use of CS2 as a sulfur source in 60 trifluoromethylthiolation reaction, hitherto unknown in the literature. In view of the above and in continuation to our work on visible light driven aerobic oxidative difunctionalization of styrenes, ^{5a} and syntheses of fine chemicals, ¹² we report herein an efficient eosin Y catalysed synthesis of α -SCF₃-substituted 65 ketones from styrenes in the presence of CF₃SO₂Na and CS₂ under open air atmosphere at RT (Scheme 1).

In order to realise our idea, a model reaction using styrene (1a) was initially investigated by varying different parameters like photocatalyst, CF₃ source, sulfur source and solvent; and the ⁷⁰ findings are reported in Table 1. The reaction commenced using 1a (1.0 mmol), CF₃SO₂Na (1.5 equiv), CS₂ (2.0 equiv) and eosin Y (1 mol%) in CH₃CN under irradiation with green LED light [2.50 W, $\lambda = 535$ nm] in open air (Table 1, entry 1), which afforded the desired product 1-phenyl-2-⁷⁵ ((trifluoromethyl)thio)ethanone (2a) in 27% yield. An increase in the catalyst loading of eosin Y (2 mol%), however, enhanced the product yield (entry 2), but a further increase in the catalyst

loading (3 mol%) did not increase the yield again (entry 3). Then was screened the molar proportion of CF_3SO_2Na which revealed so 3 mol equiv as the best quantity for optimum product yield

(entries 4 & 5). The effect of other photocatalysts like eosin B, rose Bengal, rhodanine and fluorescein was also tested but none of them could surpass the efficacy of eosin Y (entries 6 to 9). The use of some other CF_3 source like CF_3COONa and $TMSCF_3$,

⁸⁵ when tried, also proved futile (entries 10 & 11). Carbon disulfide was required in excess (3 equiv) due to its volatile nature (entry 12), but a large excess (4 equiv) could not cause much difference (entry 13). Notably, the reaction did not proceed at all with other sulfur sources such as S₈ and Na₂S (entries 14 & 15). Out of ⁹⁰ different solvents tried, DMSO was found to be the best choice (entries 12, 16 & 17). Conclusively, entry 17 was identified as the best fit for the present protocol. In order to make the effect of visible light, eosin Y, air and CS₂ more explicit in the optimized

reaction (entry 17), a series of experiments were undertaken which evinced the presence of all four parameters essential to bring about the transformation, as there is no product formation at all in the absence of any of these (for details, see ESI page 2). ⁵ The reaction using white LED (7 W) led to somewhat low product yield. The reaction under O₂ atmosphere also provided a comparable yield to that of the entry 17 (Table 1).

Previous work:

Approach A: Angew. Chem., Int. Ed., 2013, 52, 12856; 3457; 12860

$$\begin{array}{c} O \\ Ar \\ (X = H, CODE1) \end{array} \xrightarrow{N-SCF_3 \text{ or } I/CL-SCF_3} Ar \\ \begin{array}{c} V \\ SCF_3-DAST \end{array} \xrightarrow{V} X \\ X \end{array}$$

Approach B: Org. Lett. 2014, 16, 3284; Chem. Asian J. 2016, 11, 2854

Ar-X
$$Cu(OTf)_2, TMSCF_3, S_8 \text{ or}$$

Fe(OAc)_2, AgSCF_3 Ar Ar

$$(X = COCH_{2}Br, HC = CHCOOH)$$

Present work:

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10 Scheme 1 Synthesis of α -trifluoromethylthiolated ketones.

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Table 1 Optimization of reaction conditions^a

		green LED γ Photo- $\lambda = 535 \text{ nm}$ catalyst		t	O SCF3		
Ph >		CF ₃ sour	ce, <mark>Sulfur</mark> source,S	olvent	Ph 2a		
Entry	Photoc	atalyst	CF ₃ source	Sulfur	Solvent	Yield	
	(mol%))	(equiv)	source		2a (%) ^b	
				(equiv))		
1	eosin Y	Z (1)	CF ₃ SO ₂ Na (1.5)	$CS_2(2)$	CH ₃ CN	27	
2	eosin Y	(2)	CF ₃ SO ₂ Na (1.5)	$CS_{2}(2)$	CH ₃ CN	34	
3	eosin Y	(3)	CF ₃ SO ₂ Na (1.5)	$CS_{2}(2)$	CH ₃ CN	34	
4	eosin Y	(2)	$CF_3SO_2Na(3)$	$CS_{2}(2)$	CH ₃ CN	63	
5	eosin Y	(2)	CF ₃ SO ₂ Na (4)	$CS_2(2$) CH ₃ CN	63	
6	eosin B	3 (2)	$CF_3SO_2Na(3)$	$CS_2(2)$	CH ₃ CN	37	
7	rose Be	engal (2)	$CF_3SO_2Na(3)$	$CS_{2}(2)$	CH ₃ CN	42	
8	rhodan	ine (2)	$CF_3SO_2Na(3)$	$CS_{2}(2)$	CH ₃ CN	28	
9	fluores	cein (2)	$CF_3SO_2Na(3)$	$CS_{2}(2)$	CH ₃ CN	34	
10	eosin Y	(2)	CF ₃ COONa (3)	$CS_{2}(2)$	CH ₃ CN	Zero	
11	eosin Y	(2)	$TMSCF_3(3)$	$CS_2(2)$	CH ₃ CN	Zero	
12	eosin Y	(2)	$CF_3SO_2Na(3)$	$CS_2(3)$	CH ₃ CN	68	
13	eosin Y	(2)	$CF_3SO_2Na(3)$	$CS_{2}(4)$	CH ₃ CN	69	
14	eosin Y	(2)	CF ₃ SO ₂ Na (3)	$S_8(3)$	CH ₃ CN	Zero	
15	eosin Y	(2)	$CF_3SO_2Na(3)$	Na_2S (3) CH ₃ CN	Zero	
16	eosin Y	(2)	$CF_3SO_2Na(3)$	$CS_2(3)$	DMF	70	
17	eosin Y	<i>l</i> (2)	CF ₃ SO ₂ Na (3)	$CS_2(3)$) DMSO	76	
^a Reac	tion cond	litions: 1	a (1.0 mmol), sol	vent (3 ml	L), Luxeon	Rebel high	
power	green LE	ED [2.50	W, $\lambda = 535 \text{ nm}$]	irradiation	in open air	at rt for 10	
h. ^b Iso	plated yie	ld.					

¹⁵ Markedly, the reaction was quenched with 2,2,6,6tetramethylpiperidyl-1-oxyl (TEMPO, 3.0 equiv) under the standard conditions, implying the involvement of radical intermediates. Further, the reaction was not quenched by DABCO (3.0 equiv), that shows the involvement of triplet oxygen in the ²⁰ reaction.^{13a}

Having identified the best reaction conditions, the generality

and scope of the present protocol was examined using diverse styrenes having substituent like Me, MeO, EtO, Cl, Br, F, NO₂, CN & MeCOO at different positions (*o/m/p*). The reaction ²⁵ invariably worked well in all the cases and afforded a range of products **2a-2q** in good to excellent yields (Table 3, entries 1-17). **Table 3** Substrate scope^{*a*}

	$\lambda = 53$	5 nm 2 mol%			
	Ar CF ₃ SC	D ₂ Na, C <mark>S₂,</mark> 10-12 h, rt	7 2 b		
Entry	Substrate (1)	Product (2)	Time (h)	Yield (%)	
1	Ph 1a	Ph SCF ₃	10	76/68 ^c /63 ^d	
2	4-MeC ₆ H ₄	4-MeC ₆ H ₄ 2b	10	85/73 ^c /65 ^d	
3	4-EtOC ₆ H ₄ 1c	4-EtOC ₆ H ₄ 2c	10	92	
4	4- <i>t</i> -BuC ₆ H ₄ 1d	4- <i>t</i> -BuC ₆ H ₄ 2d	10	80	
5	3-MeC ₆ H ₄	3-MeC ₆ H ₄ SCF ₃ 2e	10	83	
6	4-CIC ₆ H ₄ 1f	4-CIC ₆ H ₄ 2f	12	72/64 ^d	
7	4-BrC ₆ H ₄ 1g	4-BrC ₆ H ₄ 2g	12	73	
8	4-FC ₆ H ₄ 1h	4-FC ₆ H ₄ 2h	12	68	
9	3-CIC ₆ H ₄ 1i	3-CIC ₆ H ₄ 2i	11	70	
10	3-BrC ₆ H ₄	3-BrC ₆ H ₄ 2j	11	71	
11	2-CIC ₆ H ₄	2-CIC ₆ H ₄ SCF ₃	12	68/58 ^d	
12	4-NO ₂ C ₆ H ₄ 11	4-NO ₂ C ₆ H ₄ 2I	12	65	
13	4-CNC ₆ H ₄ 1m	4-CNC ₆ H ₄ 2m	12	63	
¹⁴ 4	-MeCOOC ₆ H ₄ 1n	4-MeCOOC ₆ H ₄ 2n	12	79	
15	C ₁₀ H ₇ 10	C ₁₀ H ₇ 20	12	84	
16	Ph Ph 1p	Ph SCF ₃ 2p Ph	11	82	
17 3	B-MeOC ₆ H ₄ 1q	3-MeOC ₆ H ₄ O ² q	10	68	
18	4-C ₅ H ₄ N 1r	4-C ₅ H ₄ N SCF ₃	12	Traces	
19	() 1s	2s	12	Traces	

^{*a*} Reaction conditions: **1** (1.0 mmol), CF₃SO₂Na (3.0 equiv), CS₂ (3.0 equiv), eosin Y (2 mol%) in DMSO (3 mL) using Luxeon Rebel high power green LED [2.50 W, $\lambda = 535$ nm] in open air at rt. ^{*b*} Isolated product yield (For general procedure and characterization of compounds, see ESI). ^{*c*} Yield using phenylacetylenes. ^{*d*} Yield using cinnamic acids.

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70

95

100

However, 4-vinylpyridine and cyclohexene did not afford the product (2r & 2s). It was observed that the presence of electrondonating group on the aromatic ring of styrene 1 facilitates the reaction and affords somewhat higher yield in comparison to ^s those bearing electron-withdrawing group (entries 2-5, 14 & 17

vs 6-13). On the basis of control experiments and existing literature, 5,13 a plausible mechanism is outlined in Scheme 2. The reaction begins with the single electron transfer (SET) involving CF₃SO₂Na and

¹⁰ excited EY* to afford CF₃ radical via desulfonylation.¹⁰ The photoredox cycle is completed by the aerobic oxidation of EY^{*}. The *in situ* formed CF₃ radical then reacts with CS₂ to generate the SCF₃ radical, which adds on to the olefin linkage of molecule 1 to produce the benzylic radical intermediate A. The
¹⁵ combination of A with aerobic oxygen (O₂) forms the peroxy radical intermediate B, which on further combination with another molecule of the intermediate A followed by homolysis of O–O bond gives rise to the intermediate C.^{13b} The intermediate C

- is eventually oxidized by superoxide anion radical to afford the ²⁰ final product **2**. The involvement of superoxide anion radical during the course of reaction was confirmed by the detection of the resulting H_2O_2 using KI/starch indicator.^{13c} The reaction pathway is also corroborated by the quantum yield of a representative reaction giving product **2a**.¹⁴
- ²⁵ In conclusion, a novel, metal-free, one-pot synthesis of α-trifluoromethylthio-substituted ketones has been accomplished under photoredox catalysis using readily accessible styrenes. The combination of CF₃SO₂Na and carbon disulfide has been disclosed for the first-time as an efficient SCF₃ radical source
 ³⁰ under photoredox catalysis. The present report has the advantage of utilizing eco-sustainable atmospheric oxygen and visible light in the presence of inexpensive eosin Y as photoredox catalyst at



Scheme 2 Plausible mechanism.

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