Asian Journal of Chemistry; Vol. 28, No. 10 (2016), 2159-2163

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19893

Trifluoromethylation of Disubstituted Morpholines by Metal-Free Visible Light Photoredox Catalysis

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Received: 6 February 2016; *Accepted*: 28 April 2016; *Published online*: 30 June 2016; AJC-17959

A mild and efficient one-pot visible light-induced method has been developed for the trifluoromethylation of disubstituted morpholines. This method includes synthesis of substituted 4-tosyl-5-[(trifluoromethyl)thio]morpholine **4(a-l)** from tosylaziridine **1(a-l)** and oxiran-2-thiol (**2**) in presence of eosin Y as an organophotoredox catalyst at room temperature under aerobic condition.

Keywords: Eosin Y, Visible-light, Organophotoredox, Arylisothiocyanate, Aerobic condition, Morpholine.

INTRODUCTION

Organic compounds with CF_3 groups are very important in the production of agrochemicals and pharmaceuticals [1]. Fluorine is the most abundant halogen in the earth's crust [2] and is widely used during lead optimization in drug discovery [3,4]. In medicinal chemistry, for example, valuable physiological properties are often conferred on "drug-like" molecules *via* the incorporation of CF_3 groups that enhance binding selectivity, elevate lipophilicity and/or improve metabolic stability [5,6]. Hence, it has been of great synthetic interest to develop an efficient method for incorporation of CF_3 into organic structures [7,8]. The plant growth regulators have earned fluorine a unique place in the toolbox of the agrochemical chemist, given that it represents about the 35 to 40 % of the active ingredients in crop protection products [9]. Furthermore, fluorinated functional materials are emerging as important chemical tools to achieve improved performance and higher stability under a variety of conditions [10].

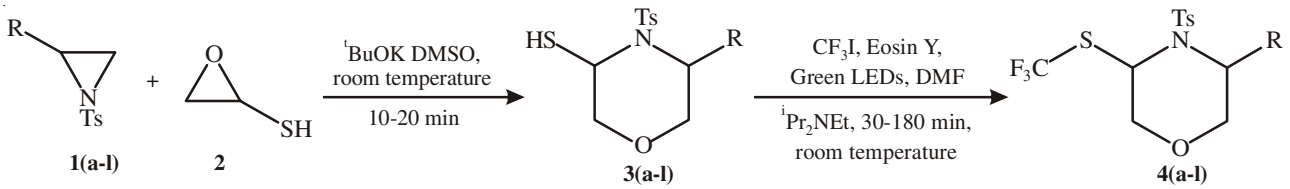
The design and synthesis of chiral heterocycles has received a lot of attention in synthetic organic chemistry due to their diverse applications as drug candidates [11], materials [12] and for catalysis [13]. Among them, morpholine structural units are generally used in pharmaceutical industry. World Drug Index cites 100 drugs containing a morpholine core. Morpholine containing structural units exhibit a wide range of biological activites [14], including antidepressant [15] antioxidant [16], serotonin agonist, NK-1 and NK-2 receptor antagonist and antifungal [17] and GABAB receptor antagonist [18,19]. Further drugs containing morpholine moiety have exhibited remarkable biological properties, *viz*. phendimetrazine as CNS stimulant, moricizine as antiarrhythmic, timolol as antihypertensive, gefitinib as anticancer and linezolid exhibit antimicrobial activity [20,21].

Sunlight is a unique and renewable natural source [22]. The development of methods to efficiently harness the solar radiation energy has emerged as one of the central scientific challenges of the twenty first century [23,24]. Therefore, some pioneering researchers have dedicated to converting solar energy into chemical energy for chemical transformations [25,26]. Recently, a surge of interest from the synthetic community has brought photoredox manifolds to the forefront of catalysis. In this sequence visible light photoredox catalysis has recently received much attention in organic synthesis owing to ready availability, sustainability, non-toxicity and ease of handling of visible light [27-32].

Encouraged by organocatalytic visible-light-mediated transformations and in continuation of our work on development of novel environmentally benign synthesis [33-36] herein we report a simple, efficient and green protocol for the two step photoredox-catalyzed α-trifluoromethylation of morpholine using eosin Y and CF_3I as a novel and highly efficient combination system for as depicted in **Scheme-I**.

EXPERIMENTAL

All chemicals used were reagent grade and were used as received. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX (400 MHz and 75 MHz) FT spectrometer in DMSO using TMS as an internal reference (chemical



Entry	R	Product	Time (min)	Yield (%)
1	4-Cl.C_6H_4	**4a**	120	82
2	3-Cl.C_6H_4	**4b**	120	85
3	2-Cl.C_6H_4	**4c**	90	87
4	4-OCH_3.C_6H_4	**4d**	30	96
5	C_6H_5	**4e**	60	90
6	4-Br.C_6H_4	**4f**	120	85
7	3-Br.C_6H_4	**4g**	120	86
8	4-O_2N.C_6H_4	**4h**	180	78
9	3-O_2N.C_6H_4	**4i**	180	84
10	4-CH_3.C_6H_4	**4j**	30	94
11	2,4-CH_3.C_6H_3	**4k**	30	96
12	2,4-OCH_3.C_6H_3	**4l**	30	97

Scheme-I

shift in δ, ppm). Mass spectra were recorded on JEOL SX-303 (FAB) mass spectrophotometer at 70 ev. Elemental analyses were carried out using a Coleman automatic C, H, N analyzer.

Synthesis of 5-substituted 4-tosylmorpholine-3-thiol 3(a-l): To a stirred solution of tosylaziridine (**1**) (500 mg, 2.09 mmol) and oxiran-2-thiol (**2**) (0.14 mL, 2.09 mmol) in anhydrous DMSO (10 mL) was added tBuOK (281 mg, 2.51 mmol) and then the mixture was stirred for 10-20 min at room temperature. After completion of reaction, the reaction mixture was diluted with water and aqueous layer was extracted with ethyl acetate (2 × 50 mL). Removal of solvent under vacuum and column chromatography of the crude product on silica gel with ethyl acetate-hexane (2.5:7.5) as eluent to furnish **3(a-l)** as a colourless oil.

General synthesis of substituted 4-tosyl-5-[(trifluoromethyl)thio]morpholine 4(a-l): In an oven-dried Schlenk tube, to the solution of substituted 4-tosylmorpholine-3-thiol (0.2 mmol), CF_3I (1.6 equiv) in $^iPr_2NEt$ (2 equiv.) and DMF (3 mL), was added with eosin Y (2 mol %). Then, the tube was degassed and filled with nitrogen for three times. The resulting reaction mixture was stirred at room temperature by irradiation with green LEDs (2.4 W, 120 lm) for 30-180 min. When the reaction was finished, saturated $NaHCO_3$ solution (5 mL) was added into the reaction mixture and extracted with ethyl acetate for four times. The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting product was purified by silica gel column chromatography using a gradient mixture of hexane/ethyl acetate as eluent to afford an analytically pure sample of **4(a-l)**.

3-(4-Chlorophenyl)-4-tosyl-5-[(trifluoromethyl)thio]-morpholine (4a): *m/z*: 451.03; m.w.: 451.91; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.40-7.74 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 59.3, 73.5, 77.1, 128.2, 128.3, 128.6, 129.3, 132.6, 134.2, 136.4, 136.7, 137.6; Anal. calcd. for $C_{18}H_{17}NO_3S_2ClF_3$: C, 47.84: H, 3.79: N, 3.10. Found: C, 47.82: H, 3.75; N, 3.08.

3-(3-Chlorophenyl)-4-tosyl-5-[(trifluoromethyl)thio]-morpholine (4b): *m/z*: 451.03; m.w.: 451.91; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.17-7.74 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 58.8, 73.5, 77.1, 126.0, 127.1, 127.7, 128.3, 129.3, 129.9, 134.1, 134.2, 136.7, 137.6, 139.7; Anal. calcd. for $C_{18}H_{17}NO_3S_2ClF_3$: C, 47.84: H, 3.79: N, 3.10. Found: C, 47.82: H, 3.75; N, 3.08.

3-(2-Chlorophenyl)-4-tosyl-5-[(trifluoromethyl)thio]-morpholine (4c): *m/z*: 451.03; m.w.: 451.91; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.21-7.74 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 54.2, 73.0, 77.1, 126.6, 128.3, 128.4, 128.6, 129.3, 133.2, 134.2, 136.7, 137.6, 138.3; Anal. calcd. for $C_{18}H_{17}NO_3S_2ClF_3$: C, 47.84: H, 3.79: N, 3.10. Found: C, 47.82: H, 3.75; N, 3.08.

3-(4-Methoxyphenyl)-4-tosyl-5-[(trifluoromethyl)-thio]morpholine (4d): *m/z*: 447.08; m.w.: 447.49; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 3.83 (s, 3H, -OCH_3), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 6.94-7.74 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 55.8, 59.3, 73.5, 77.1, 114.1, 127.6, 128.3, 129.3, 130.6, 134.2, 136.7, 137.6, 158.9; Anal. calcd. for $C_{19}H_{20}NO_4S_2F_3$: C, 51.00: H, 4.50: N, 3.13. Found: C, 50.97: H, 4.48; N, 3.10.

3-Phenyl-4-tosyl-5-[(trifluoromethyl)thio]morpholine (4e): *m/z*: 417.07; m.w.: 417.47; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-),

4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.27-7.74 (d, 9H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 59.3, 73.5, 77.1, 127.0, 127.9, 128.3, 128.5, 129.3, 134.2, 136.7, 137.6, 138.3; Anal. calcd. for $C_{18}H_{18}NO_3S_2F_3$: C, 51.79: H, 4.35: N, 3.36. Found: C, 51.77: H, 4.32; N, 3.33.

3-(4-Bromophenyl)-4-tosyl-5-[(trifluoromethyl)thio]-morpholine (4f): *m/z*: 494.98; m.w.: 496.36; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.18-7.92 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 59.3, 73.5, 77.1, 121.4, 128.2, 128.3, 128.6, 129.3, 131.4, 134.2, 136.7, 137.3, 137.6; Anal. calcd. for $C_{18}H_{17}NO_3S_2BrF_3$: C, 43.56: H, 3.45: N, 2.82. Found: C, 43.54: H, 3.43; N, 2.80.

3-(3-Bromophenyl)-4-tosyl-5-[(trifluoromethyl)thio]-morpholine (4g): *m/z*: 494.98; m.w.: 496.36; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.23-7.74 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 58.6, 73.5, 77.1, 122.9, 126.9, 127.1, 128.3, 129.3, 129.9, 132.7, 134.2, 136.7, 137.6, 140.5; Anal. calcd. for $C_{18}H_{17}NO_3S_2BrF_3$: C, 43.56: H, 3.45: N, 2.82. Found: C, 43.54: H, 3.43; N, 2.80.

3-(4-Nitrophenyl)-4-tosyl-5-[(trifluoromethyl)thio]-morpholine (4h): *m/z*: 462.05; m.w.: 462.46; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.40-8.21 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 59.3, 73.5, 77.1, 123.7, 124.4, 128.3, 129.3, 134.2, 136.7, 137.6, 144.4, 146.2; Anal. calcd. for $C_{18}H_{17}N_2O_5S_2F_3$: C, 46.75: H, 3.71: N, 6.06. Found: C, 46.73: H, 3.70; N, 6.03.

3-(3-Nitrophenyl)-4-tosyl-5-[(trifluoromethyl)thio]-morpholine (4i): *m/z*: 462.05; m.w.: 462.46; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.40-8.18 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 58.3, 73.5, 77.1, 121.5, 122.2, 128.3, 129.3, 134.0, 134.2, 136.7, 137.6, 139.2, 147.7; Anal. calcd. for $C_{18}H_{17}N_2O_5S_2F_3$: C, 46.75: H, 3.71: N, 6.06. Found: C, 46.73: H, 3.70; N, 6.03.

3-(*p*-Tolyl)-4-tosyl-5-[(trifluoromethyl)thio]morpholine (4j): *m/z*: 431.08; m.w.: 431.49; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 6H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 7.17-7.74 (d, 8H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 59.3, 73.5, 77.1, 126.3, 128.3, 128.8, 129.3, 134.2, 135.3, 136.7, 137.6; Anal. calcd. for $C_{19}H_{20}NO_3S_2F_3$: C, 52.89: H, 4.67: N, 3.25. Found: C, 52.87: H, 4.64; N, 3.23.

3-(2,4-Dimethylphenyl)-4-tosyl-5-[(trifluoromethyl)-thio]morpholine (4k): *m/z*: 445.10; m.w.: 445.52; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 9H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 6.99-7.74 (d, 7H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.4, 21.3, 21.6, 45.1, 56.8, 73.8, 77.1, 125.8, 127.7, 128.3, 129.3, 130.7, 133.6, 134.2, 135.6, 136.7, 137.6; Anal. calcd. for $C_{20}H_{22}NO_3S_2F_3$: C, 53.92: H, 4.98: N, 3.14. Found: C, 53.90: H, 4.96; N, 3.11.

3-(2,4-Dimethoxyphenyl)-4-tosyl-5-[(trifluoromethyl)-thio]morpholine (4l): *m/z*: 477.09; m.w.: 477.52; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 3H, -CH_3), 3.84 (dd, 1H, -O-CH_2'-), 3.88 (dd, 1H, -O-CH_2-), 3.90 (d, 1H, -S-CH_2-), 3.83 (s, 6H, -OCH_3), 4.09 (d, 1H, -O-CH_2'-), 4.13 (d, 1H, -O-CH_2-), 4.20 (d, 1H, -N-CH_2-), 6.50-7.74 (d, 7H, ArH), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.3, 45.1, 53.4, 55.8, 56.1, 73.8, 77.1, 100.2, 109.5, 116.4, 128.3, 129.3, 134.2, 136.7, 137.6, 158.5, 159.9; Anal. calcd. for $C_{20}H_{22}NO_5S_2F_3$: C, 50.30: H, 4.64: N, 2.93. Found: C, 50.27: H, 4.66; N, 2.91.

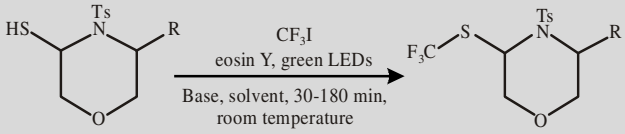
RESULTS AND DISCUSSION

The proposed trifuoromethylation strategy was first evaluated with substituted 4-tosylmorpholine-3-thiol, eosin Y and a green LEDs (2.4 W, 120 lm) with CF_3I was used as a CF_3 source. The use of an organic base effectively suppressed by-product formation. Optimal conditions were obtained when 2 equivalents of ^{i}Pr_2NEt (DIEA) was introduced to the reaction, resulting in the selective trifluoromethylation of substituted 4-tosylmorpholine-3-thiol within specified time.

With the optimized conditions in hand, we set out to explore the scope of this photocatalytic transformation. Broad arrays of electron-withdrawing and electron-donating functional groups were optimized to trifuoromethylation protocol (**Scheme-I**).

Next, the reaction conditions were optimized with respect to solvents and the catalyst used in the reaction. In all the tested solvents (DMF, DMSO, MeOH and EtOH) the yield of **4(a-l)** was > 55 % (Table-1), which indicates that the reaction is not very sensitive to reaction media. DMF was the best solvent in terms of the reaction time and yield (Table-1, entry 1), hence it was used throughout the synthesis. When the amount of the catalyst was decreased from 2 to 1 mol %, the yield of **4(a-l)** considerably reduced (Table-1, entry 3), but the use of 3 mol % of the catalyst did not affect the yield (Table-1, entry 1).

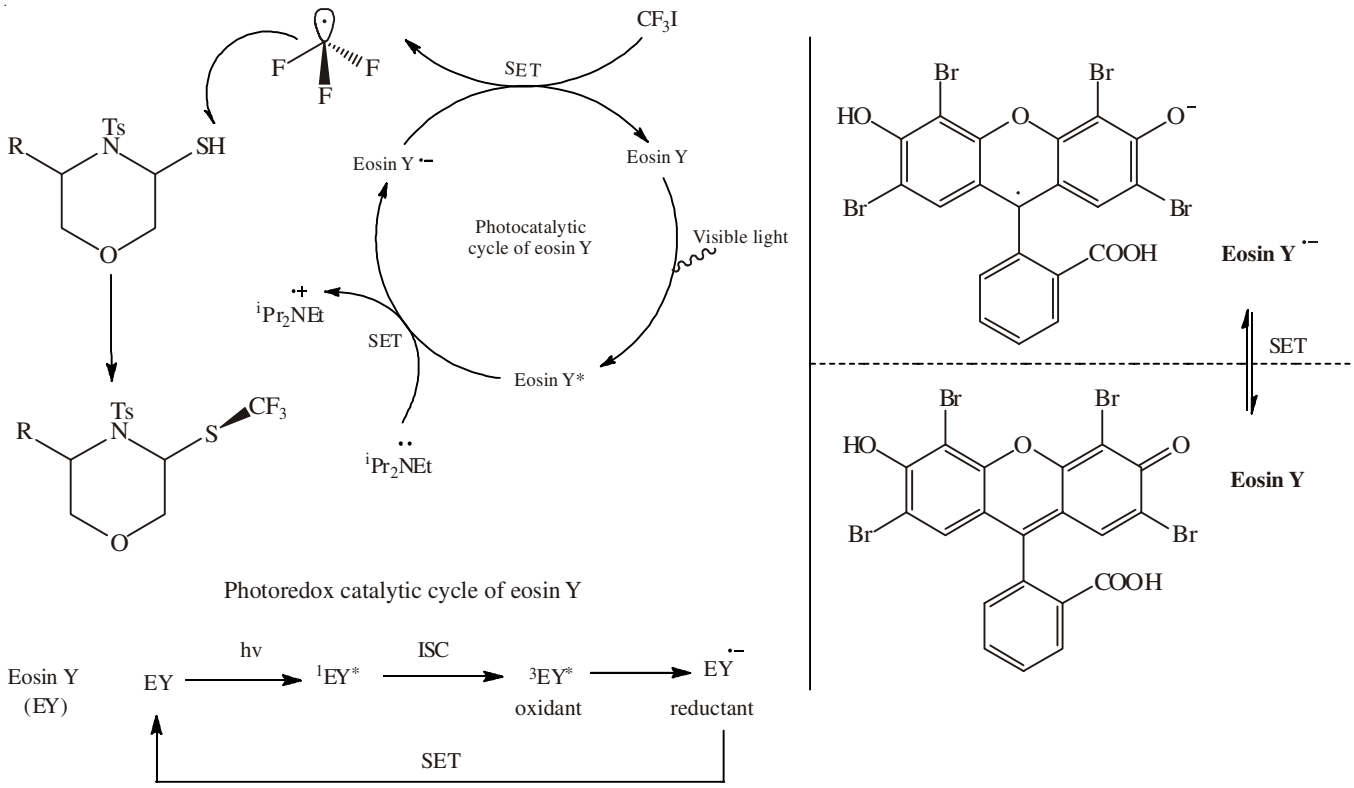
TABLE-1
OPTIMIZATION OF REACTION CONDITIONS[a]



3(a-l) 4(a-l)

Entry	Eosin Y (mol %)	Base	Solvent	Time (min)	Yield (%)[b]
1	3	^{i}Pr_2NEt	DMF	30	97
2	2	^{i}Pr_2NEt	DMF	30	97
3	1	^{i}Pr_2NEt	DMF	30	42
4	2	^{i}Pr_2NEt	MeOH	180	72
5	2	^{i}Pr_2NEt	EtOH	180	62
6	2	DBU	DMF	180	52
7	2	DABCO	DMF	180	55
8	2	^{i}Pr_2NEt	DMSO	30	82
9	2	Et_3N	DMF	180	65

[a]Reaction conditions: substituted 4-tosylmorpholine-3-thiol (0.2 mmol), eosin Y (2.0 mol %), Base (2.0 equiv.), DMF (3.0 mL), green LEDs 2.4 W, 120 lm at room temperature. [b]Isolated yield of the product (**4a-l**).



Scheme-II: Proposed mechanism for the photocatalytic trifluoromethylation of substituted 4-tosylmorpholine-3-thiol

This clearly shows that the reaction is very mild and applicable to aryl and alkyl, tolerates considerable functional group variations like, MeO, Br, Me, Cl and NO_2 in the substrate **1(a-l)**, which results the desired product **4(a-l)** in good to excellent yields (72-97 %). On the basis of the above observations and the literature precedents, a plausible mechanism involving photocatalytic trifluoromethylation of substituted 4-tosylmorpholine-3-thiol is depicted in **Scheme-II**.

On absorption of visible light, the organophotoredox catalyst eosin Y (EY) is excited to its singlet state ^{1}EY* which through inter system crossing (ISC) comes to its more stable triplet state ^{3}EY* and undergoes a single electron transfer (SET). Reductive quenching of the exited state of eosin Y occurs *via* a nitrogen base. Next, oxidizing the eosin Y species to its ground state generates an electrophilic CF_3 radical [37,38]. This CF_3 radical can subsequently react with the substituted 4-tosylmorpholine-3-thiol substrate to yield the desired product.

Conclusion

In conclusion, we have developed a mild and fast photocatalytic approach to the direct trifluoromethylation of substituted 4-tosylmorpholine-3-thiol. The method was shown to have a broad substrate scope allowing for the preparation of substituted aryl and alkyl tosylmorpholine-3-thiol compounds in good-to-excellent yields. Due to the operational simplicity of this protocol, we anticipate that our photocatalytic method for the tri-fluoromethylation of substituted 4-tosylmorpholine-3-thiol will find broad application in academia and industry. The present methodology also offers many advantages of green chemistry such as high atom economy, reduced reaction time, one-pot consolidated procedure and high efficiency.

ACKNOWLEDGEMENTS

The authors thank SAIF, CDRI, Lucknow, India and IISc, Banglaore, India for providing microanalyses and spectra.

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