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Metal Free Synthesis of Organosulfur Compounds Employing Eosin Y as Photoredox Catalyst

Fayaz Mangi *, Fouzia Abdul Sattar [a], Can Zhong Lu [b]

[a] Department of Chemistry, FABS, BUITEMS, Quetta, Pakistan

[b] State key laboratory of structural chemistry, FJIRSM, CAS, Beijing, PR China

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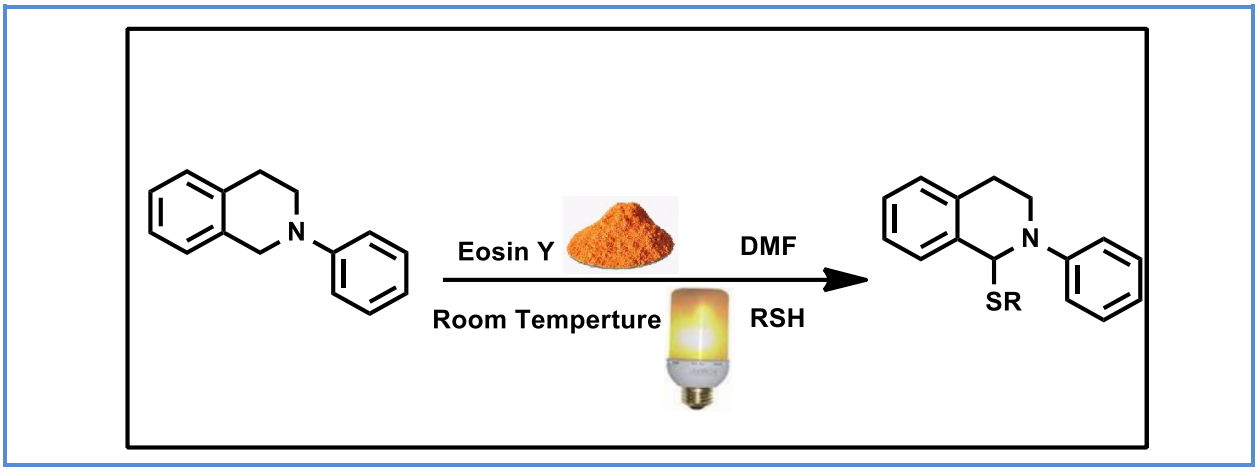
ABSTRACT

The organosulfur compounds are an important class of compounds with extensive pharmaceutical and synthetic concern as well as a prominent role in the living system. The development of effective methods for the introduction of sulfur atom into the carbon framework remains an eternal challenge, as most of the accounted process needs tenacious conditions. Owing to its economical and eco-friendly nature, eosin Y has emerged as a promising alternate to the transition metal catalyst in numerous organic transformations comprising C-H functionalization.

The current work aims at a direct, efficient and single step synthetic route for the construction of thioethers, through oxidative coupling of the reaction partners facilitated by eosin Y as an organo photoredox catalyst. The use of inexpensive and non-toxic dye, convenient reaction conditions, simple work-up procedure, and good to excellent yields are the advantages of this approach.

*Corresponding author: Department of Chemistry, FABS, BUITEMS, Quetta, Pakistan. *E-mail:* fayazmangi@yahoo.com

Graphical Abstract



Introduction

Recently, organic thioethers have developed an increasing interest as synthetic intermediates in organic and medicinal chemistry, with broad applications in pharmaceuticals, medicinal, and heterocyclic synthesis and been used as building blocks for the preparation of numerous biologically active compounds [1]. From synthetic perspective, the development of sustainable and efficient process for such compounds remains a crucial challenge and much attention has been focused in the recent years to realize this issue [2].

The classical methods existing for C-S bond formation in thioethers usually involve the condensation of activated halides with thiols [3]. These methods are usually inefficient, require strong basic condition and elevated reaction temperature with poor substrate scope; additionally the catalytic activity is also effected by the poisoning under these conditions [4]. To overrule such obstructions, there is an urgent need for the development of a convenient and efficient method for the construction of C-S bond. For such transformation the designed reactions can be made more eco-friendly if we can avoid the use of transition metals due to potential toxicity associated with them [5]. In this distinct aspect, numerous researchers have recently focused their attention to accomplish metal free coupling reactions [6-8]. The current endeavors for the sustainable development of metal free processes employing visible light has evoked considerable interest in organic synthesis [9-12], especially the pioneering work of König latest decade witnessed an unprecedented blossom in the realm of organo photocatalyzed transformations [13]. In various synthetic transformations involving the effective development of C–C and C–heteroatom bonds,

organic dyes have found much potential and have inspired the several researchers for employing this powerful method in organic synthesis [14]. With the massive numbers of organo photoredox systems eosin Y, a tetra-bromo substituted dye of the xanthene class presents a promising metal free low cost alternative to organometallic complexes owing to its unusual spectroscopic and photochemical properties [15].

Among these advances Lin and coworkers revealed an example of eosin Y mediated elimination of hydrogen from the thiol group to generate the thiyl radical under the visible light [16]. Encouraged by aforementioned effort prompted us to explore an innovative and benign protocol for the facile synthesis of thioethers facilitated by non-toxic and inexpensive organic dye eosin Y at room temperature in open atmosphere.

Experimental

Instrumentation

The ^{1}H NMR experiments were recorded on Varian INOVA operating at 400 MHz in $CDCl_3$ solution. Spectra were correlated to residual solvent peaks. Coupling constants (J) are noted in Hz and chemical shifts are reported in ppm. Finnigan DECAX -3000 LCQ deca XP ion trap mass spectrometer was used for EI-MS. The melting points calculated were imprecise. *N*-phenyl and *N*-paramethoxy phenyl tetrahydroisoquinoline were prepared by the reported method [1].

Materials and methods

All chemicals were received from Wako, Japan and Merck, Germany, and were used without further purification, unless otherwise specified. All the experiments were performed at room temperature. The Petroleum ether used was of the boing range 60–80 °C. The chromatographic adsorbent used was silica gel. The Organic extracts were dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure.

General procedure for photocatalyzed coupling reaction

In a 10 mL round bottom flask *N*-phenyl tetrahydroisoquinolines **1** (0.25 mmol) and eosin Y (2 mol%) were dissolved in DMF. Thio nucleophile (1.5 equiv.) was slowly added and the obtained mixture was irradiated from the base of the flask employing 5 W bulb. After the completion of reaction (as examined by TLC) the reaction mixture was shifted to a separating funnel, treated with diethyl ether and water. The aqueous extract was treated three times with diethyl ether. The anhydrous sodium sulfate was used for drying all organic extracts. The silica gel column

chromatography was employed for the purification of the product eluted with petroleum ether/ethylacetate.

2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-thiocarbonitrile **(3a)**: colorless crystalline solid; isolated yield (89%); Mp: 102-103 °C; IR (KBr,cm^{-1}): 2954 (CH), 2161 (SCN), 1531(C=C), 1203 (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.37 (m, 6H), 6.99-7.09 (m, 3H), 5.50 (s, 1H), 3.74-3.76 (m, 1H), 3.44-3.51 (m, 1H), 3.15-3.12 (m, 1H), 2.99-2.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 134.6, 129.6, 129.5, 128.7, 127.0, 126.8, 121.8, 117.7, 117.6, 53.1, 44.2, 28.5; MS(m/z): 266(M+),100%), 208 ([M-SCN]$^{+}$, 21%).

2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-methylsulfide **(3b)**: colorless crystalline solid; isolated yield (89%); Mp: 99-101 °C; IR (KBr,cm^{-1}): 2963 (CH), 1539 (C=C), 1199 (CN), 1025 (S-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.33 (m, 6H), 6.98-7.07 (m, 3H), 5.76 (s, 1H), 2.19 (s, 1H), 3.49-3.58 (m, 1H), 3.13 -3.22 (m, 1H), 2.54-2.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 140.6, 137.6, 129.4, 128.8, 127.7, 126.8, 125.6, 118.0, 113.1, 64.1, 44.4, 29.7, 11.2; MS(m/z): 255 (M+),100%), 241 ([M-CH_3]$^{+}$, 19%).

2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-phenylsulfide **(3c)**: Light brown solid; isolated yield (92%); Mp: 93-96 °C; IR (KBr,cm^{-1}): 2960 (CH), 1537 (C=C), 1201 (CN), 1029 (S-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.18 (m, 3H), 6.96-7.08 (m, 6H), 6.59-6.60 (m, 5H), 5.80 (s, 1H), 3.55-3.59 (m, 1H), 3.19-3.25 (m, 1H), 2.68-2.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 140.4, 139.6, 135.5, 129.4, 128.7, 127.8, 126.6, 125.8, 118.0, 113.1, 67.1, 51.4, 29.7; MS(m/z): 317 (M+), 100%), 209 ([M-PhS]$^{+}$, 13%).

2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-thiobenzimidazole **(3d)**: Light yellowish brown solid; isolated yield (79%); Mp.: 107-109 °C; IR (KBr,cm^{-1}): 3360 (NH), 1533 (C=C), 1204 (CN), 1031 (S-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.26 (m, 4H), 7.08-7.01 (m, 4H), 7.00-6.96 (m, 2H), 6.61-6.57 (m, 3H), 5.61 (s, 1H), 3.45-3. 36 (m, 1H), 3.28-3.23 (m, 1H), 2.59-2.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 144.6, 139.9, 139.4, 137.7, 137.5, 129.3, 129.3, 127.5, 126.8, 125.8, 122.8, 119.5, 113.6, 61.1, 47.4, 28.5; MS (m/z): 357 (M+), 100%), 356 ([M-H]$^{+}$, 11%).

2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-thioglycolate **(3e)**: colorless crystalline solid; isolated yield (89%); Mp: 98-103 °C; IR (KBr,cm^{-1}): 2961 (CH), 1534 (C=C), 1203 (CN), 1031 (S-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.08 (m, 4H), 6. 69-6.60 (m, 3H), 7.09-7.08 (m, 2H), 5.61 (s, 1H), 3.22 (s, 3H), 3.42-3.37 (m, 1H), 3.27-3.21 (m, 1H), 2.63-2.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3,

144.6, 140.5, 136.6, 129.5, 128.7, 127.0, 126.9, 125.3, 118.7, 114.6, 60.1, 47.4, 33.6, 28.7, MS (m/z): 299 (M+), 100%), 298 ([M-H]$^+$, 08 %).

Result and discussion

The initial investigation commenced with a model reaction was carried out on *N*-phenyl tetrahydroisoquinoline **1** a prominent structural motif in natural products and a substrate that is known to undergo oxidative C-H functionalization by Ru (III) [17], Cu (I) [18] and eosin Y [19]. By choosing the condition that is closely related to those reported by König [4] with ammonium thiocyanate we used 2 mol% eosin Y as a photoredox catalyst at room temperature in air atmosphere.

The reaction was performed in CH_3CN under irradiation with a 40 W fluorescence bulb. The desired product **3a** was delivered in 71% isolated yield after 18 h (Table 1, entry 1). Concomitantly, a minor back ground reaction furnishing the amide **4** was also observed that is in usual practice when the aerobic conditions are applied [5, 6].

Following the limited formation of unwanted oxidized product, optimization studies were conducted by screening solvents, catalyst loading, and light source employing **1** as the model substrate. Regarding the efficiency of all the applied solvents (Table .1 entries 1-11), the desired product was obtained in every case; however, apolar THF and polar protic (MeOH) suffered from poor yield and extended reaction time. Of all solvents, the tested DMF proved to be the best choice as in earlier studies [**7**]. Subsequently, the catalytic ratio was examined by increasing the catalytic loading to 5 mol % but this activity did not result any apparent yield enhancement. (Table 1 entry 9). During the optimization studies it was revealed that the effectiveness of irradiation power or light source has major impact on the course of reaction, and the reactions can be tuned by varying the light source [8].

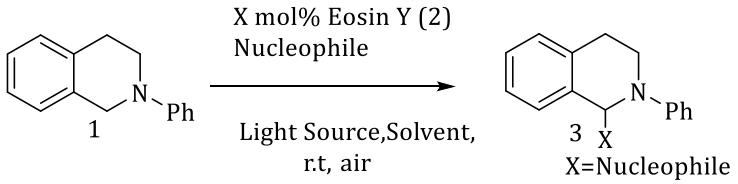
In case of the xanthene based dyes utilization of low power light source provided the desire transformation more efficiently as they operate within the spectral region of their absorption [9], alternately, the reaction proved to be susceptible regarding the catalyst or light source and elimination of either did not allow the desire transformation. (Table 1 entries 10, 11).

Based on these optimization results 2 mol % eosin Y in DMF under 5W fluorescent bulb at room temperature in open atmosphere were the best reaction condition in term of reaction time and yield. (Table 1 entry 6), and the side reaction was successfully suppressed and negligible amount of **4** was observed under the existing conditions.

Under the optimal condition, various thionucleophiles were investigated in order to determine the generality and scope of the oxidative coupling reaction. In all cases the reactions proceed smoothly and provided to the desired product in good to excellent yield (Table 2 entries 1-4).

In General, the nature of the nucleophile does not count much and the desired product was obtained in all cases, however thiophenoxide appear to react faster than its metho counterpart due to the existence of conjugated skeleton which facilitate the nucleophilicity and apparently non SN2 fashion of the reaction [10] (Table 2 entries 1, 2). Presumably higher equivalent ratios for 2-mercapto benzimidazole were employed to deliver the substantial outcome owing to minimal nucleophilicity of the resulting anion [11]; and even the product **3d** also resulted in quantative ratio but did not produce the desired yield (Table 2 entry 3), however thioglycolic acid (mercapto acetic acid) reacted readily at optimized conditions and deliver the product **3e** in 89% isolated yield (Table 2 entry 4). The acidity constant for ambident anion of thioglycolate is comparable to either side [12] and sincethe sulfur is better nucleophile then oxygen therefore the product was delivered readily with optimal yield (Table 2 entry 4).

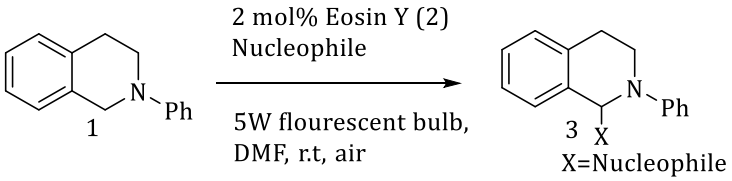
Table 1. Photocatalytic oxidative coupling and control reactions of 1

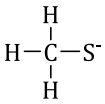
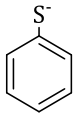
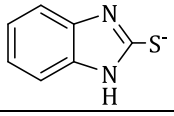
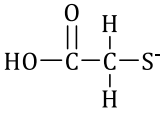


Entry	Solvent	Light Source	Time/h	EosinY (mol %)	Yield[b] (%)
1	DMF	Fluorescence bulb (40W)	12	2	77
2	MeCN	Fluorescence bulb (40W)	12	2	71
3	DMSO	Fluorescence bulb (40W)	12	2	64
4	THF	Fluorescence bulb (40W)	18	2	39
5	DCM	Fluorescence bulb (40W)	12	2	51
6	MeOH	Fluorescence bulb (40W)	16	2	43
7	DMF	Fluorescence bulb (07W)	10	2	81
8	DMF	Fluorescence bulb (05W)	10	2	87
9	DMF	Fluorescence bulb (05W)	10	5	89
10	DMF	-	22	2	0
11	DMF	Fluorescence bulb (05W)	22	-	0

[a]Reaction Conditions: The reaction was run with 1 (1.0 mmol), ammonium thiocyanate (4 equiv), EosinY (0.02-0.03 equiv) solvent (0.1M) Fluorescence bulb 40, 07 or 05 W irradiation under an air atmosphere at r.t.
[b]Isolated yield after purification on silica gel.

Table 2. Nucleophilic scope of photocatalytic oxidative coupling[a]



Entry	Nucleophile	Product	Time	Yield[b] (%)
1		**3b**	**10**	**89**
2		**3c**	**09**	**92**
3[c]		**3d**	**14**	**79**
4		**3e**	**10**	**89**

[a]Reaction Conditions: The reaction was run with 1 (1.0 mmol), thionucleophile (4 equiv), EosinY (0.02 equiv) solvent (0.1M) Fluorescence bulb 5 W irradiation under an air atmosphere at r.t
[b]Isolated yield after purification on silica gel
[c] 6 equiv. of the nucleophile

Conclusions

In conclusion, a general and efficient visible light mediated process for the formation of thioethers has been designed by employing the eosin Y. The reaction proceeded efficiently at milder conditions and provided the pertinent products nearly in quantitative yield. Due to the low toxicity, low cost and simple experimental conditions, the eosin Y is going to be indispensable in organic synthesis. Further studies are ongoing for the extension of eosin Y for the development of novel C-H activation reactions for the effective development of C-S bond under sustainable conditions.

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