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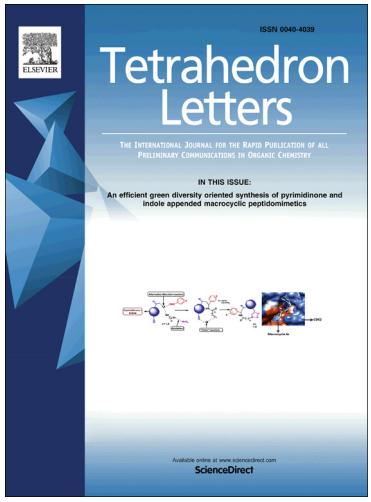

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ABSTRACT

Eosin Y/$K_2S_2O_8$ catalyzed C2-alkylation reactions of benzothiazoles with *N,N*-dimethylamides under visible light have been developed. The reactions completed smoothly in the presence of Eosin Y as the photocatalyst and $K_2S_2O_8$ as the oxidant under solvent-free conditions in open air. This green and simple method provides an alternative route for the synthesis of C2-alkylation of benzothiazoles and tolerates a number of functional groups to afford moderate to excellent yields.

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Introduction

C2-substituted benzothiazole derivatives have attracted great synthetic interests[1] due to their broad biological properties.[2] Amongst them, the structure of a benzothiazole attaching to an amide is also a building block of bioactive compounds, such as herbicide,[3] antivirulence drugs,[4] androgen receptor antagonists,[5] dipeptidyl Peptidase IV Inhibitors[6] **(Fig. 1)**. Great efforts have been devoted to preparing C2-substituted benzothiazole derivatives.[7] From the perspective of synthetic simplicity and atom economy, the construction of C2-substituted benzothiazole frameworks has focused on direct oxidative coupling reactions with aromatic aldehydes,[8] benzylamines,[9] phenylglycine derivatives,[10] diaryliodonium salts,[11] dicumylperoxides, methylarenes and cycloalkanes,[12] as well as amides.[13,14] Although advances have been achieved, still there are some disadvantages, such as requirements of transition-metal catalysts, strong bases, poisonous addictives, or high temperature.[15]

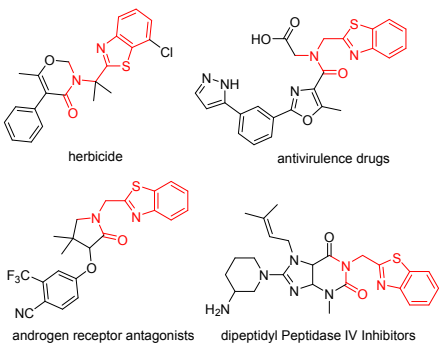
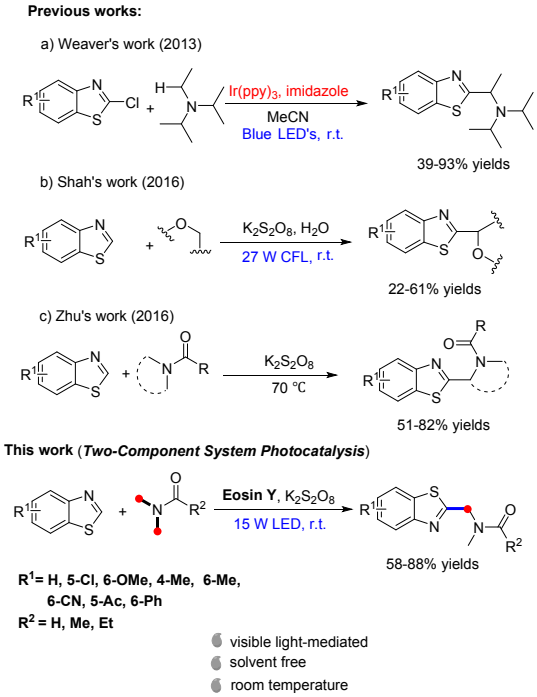


Fig. 1. Pharmaceuticals containing the structure of C2-amidoalkylation of benzothiazole



Scheme 1. Methods for the preparation of C2-alkylation of benzothiazoles

Over the years, the visible light-promoted reactions[16] have emerged as powerful tools in organic synthesis[17] owing to abundant solar energy, convenient reaction devices and novel reaction mechanisms.[18] Amongst them, there is likewise a growing trend of introducing photocatalysis into alkylation reactions of benzothiazoles in recent years. In 2013, Weaver and

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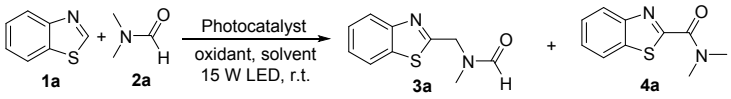
co-workers developed a visible light-induced and tris-*fac*-Ir(ppy)$_3$ catalyzed C2-alkylation of 2-chlorobenzothiazole derivatives with tertiary aliphatic amines at room temperature **(Scheme 1a)**.[19] However, the high cost, complex handling procedures, potential toxicity and limited availability of Ru/Ir complexes in the future are disadvantages of these transition metal-based methods,[20] as stated earlier. In 2016, Shah et al. developed the visible light-induced C2-alkylation of benzothiazoles with ethers employing potassium persulfate as the catalyst at room temperature **(Scheme 1b)**.[21] Herein, we report an efficient two-component photocatalytic system comprising of Eosin Y/$K_2S_2O_8$ for C2-alkylation reactions of benzothiazoles with *N,N*-dimethylamides under visible light. It's notable that, compared to the previous work of Zhu group **(Scheme 1c)**,[14] our protocol works with the advantages of milder conditions and higher yields in some cases.

Results and discussion

Table 1. Optimization of Reaction Conditions [a]



entry	catalyst (mol %)	oxidant (eq.)	solvent	yield(3a:4a, %) [b]
1	Eosin B (1.0)	--	H_2O	trace
2	Eosin Y (1.0)	--	H_2O	19:4
3	Rhodamine B (1.0)	--	H_2O	10:0
4	Rose Bengal (1.0)	--	H_2O	15:3
5	Eosin Y (1.0)	$K_2S_2O_8$ (3)	H_2O	45:20
6	Eosin Y (1.0)	$Na_2S_2O_8$ (3)	H_2O	22:3
7	Eosin Y (1.0)	$(NH_4)_2S_2O_8$ (3)	H_2O	12:3
8	--	$K_2S_2O_8$ (3)	H_2O	20:6
9[c]	Eosin Y (1.0)	$K_2S_2O_8$ (3)	H_2O	44:16
10[c]	Eosin Y (1.0)	$K_2S_2O_8$ (3)	C_2H_5OH	26:4
11[c]	Eosin Y (1.0)	$K_2S_2O_8$ (3)	CH_3CN	25:5
12[c]	Eosin Y (1.0)	$K_2S_2O_8$ (3)	$CHCl_3$	28:6
13[c]	**Eosin Y (1.0)**	**$K_2S_2O_8$ (3)**	**DMF**	**68:12**
14[c]	4CzIPN		DMF	n.d.
15[c]	9-mesityl-10-methylacridinium perchlorate		DMF	n.d.
16[c,d]	Eosin Y (1.0)	$K_2S_2O_8$ (3)	DMF	65:10
17[c]	Eosin Y (0.5)	$K_2S_2O_8$ (3)	DMF	58:8
18[c]	Eosin Y (1.5)	$K_2S_2O_8$ (3)	DMF	65:10
19[c]	Eosin Y (2.0)	$K_2S_2O_8$ (3)	DMF	62:10
20[c]	Eosin Y (3.0)	$K_2S_2O_8$ (3)	DMF	55:12
21[c]	Eosin Y (5.0)	$K_2S_2O_8$ (3)	DMF	54:9
22[c]	Eosin Y (1.0)	$K_2S_2O_8$ (2)	DMF	63:10
23[c]	Eosin Y (1.0)	$K_2S_2O_8$ (4)	DMF	67:10
24[c]	Eosin Y (1.0)	$K_2S_2O_8$ (5)	DMF	65:10
25[c]	Eosin Y (1.0)	--	DMF	24:5
26[c]	--	$K_2S_2O_8$ (3)	DMF	29:9
27[e]	Eosin Y (1.0)	$K_2S_2O_8$ (3)	DMF	31:2
28[f]	Eosin Y (1.0)	$K_2S_2O_8$ (3)	DMF	28:7

[a]Reaction condition: **1a** (0.5 mmol), **2a** (3.0 equiv, 1.5 mmol), oxidant (3.0 equiv), photocatalyst (0.005 mmol, 1.0 mol%), solvent (5 mL), open to the air, at room temperature, 15 W Blue LED (λ= 450 nm), 48 h. [b]Isolated yield. [c]For 24 h. [d]anhydrous DMF. [e]Degassed with N_2. [f]in the dark.

In our initial studies, the reaction of benzothiazole (**1a**, 0.5 mmol) with an excess amount of *N,N*-dimethylformamide (**2a**, 1.5 **mmol)** was chosen as a model to optimize the reaction conditions. The results showed that Eosin Y was an effective photocatalyst for this transformation, which afforded the target alkylation product of benzothiazole **(3a)** in 19% yield and the acylation product of benzothiazole **(4a)** in 4% yield with irradiation by a 15 W blue light-emitting diode (LED) at room temperature under air atmosphere after 48 hours **(Table 1, entries 1-4)**. Inspired by previously reported C2-alkylation reactions of benzothiazoles utilizing persulfates as

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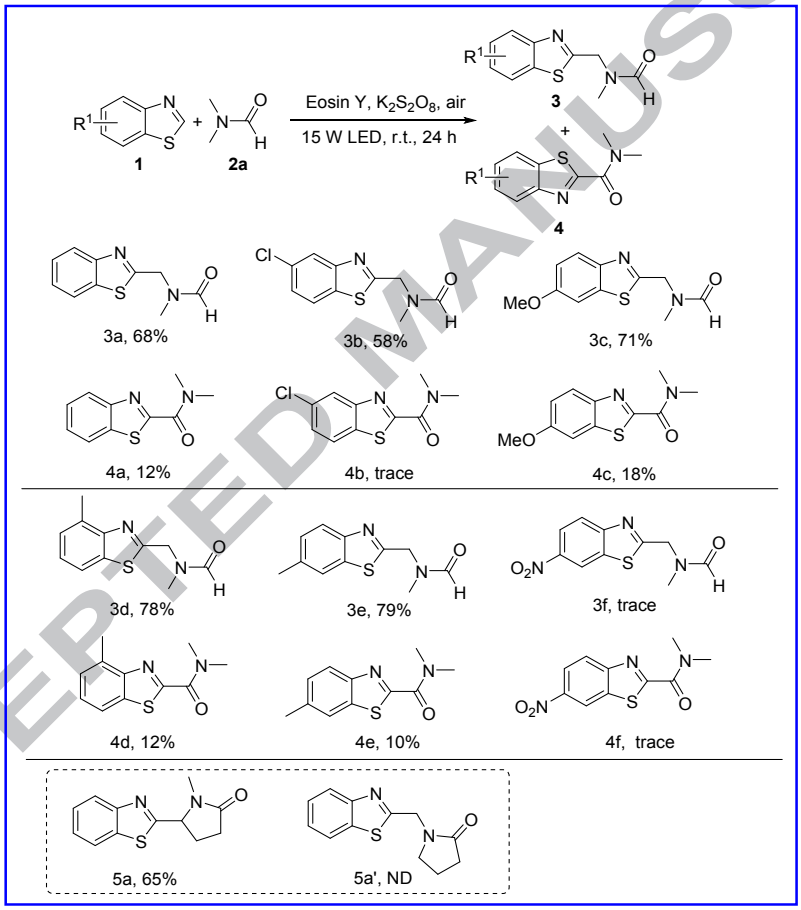
oxidant,[21,22] three kinds of common persulfates ($Na_2S_2O_8$, $(NH_4)_2S_2O_8$, $K_2S_2O_8$) were tried in the reactions, respectively. Delightfully, we found that the reaction proceeded smoothly in the presence of persulfates, and $K_2S_2O_8$ resulted in better conversion which afforded **3a** in 45% yield **(Table 1, entries 5-7)**. To ensure the significance of the catalyst, a control experiment was carried out without the photocatalyst, and a lower yield (20%) of the product was observed as expected **(Table 1, entry 8)**. Encouraged by this promising result, we tried to shorten the reaction time to 24 h, the yield of **3a** did almost not changed **(Table 1, entry 9)**. Next, we surveyed a range of solvents, the results indicated that C_2H_5OH, CH_3CN and $CHCl_3$ were inferior to DMF **(Table 1, entries 10−13)**. The better yield in DMF was highly probably given by the reaction equilibrium driven by a lot excess of amides. And it was reported that Eosin Y was subjected to tautomeric/protolytic equilibria and EYH_2 was an effective photoredox catalyst only if the base was added.[23] Accordingly, we thought that the basicity of DMF might also led to the increase of the yield. Furthermore, other photocatalysts, 4CzIPN and 9-mesityl-10-methylacridinium perchlorate, which can also act as strong oxidants at excited state, failed to deliver the desired product **(Table 1, entry 14-15).** It was also noted that aqueous DMF **(Table 1, entry 13)** used in the reaction gave a superior product yield compared with that of anhydrous DMF **(Table 1, entry 16)**. With respect to the amount of catalyst and oxidant used in the reaction, 1.0 mol% of Eosin Y was found to be optimal, the model reaction was not completed with less or more than 1.0 mol% of Eosin Y **(Table 1, entries 13, 17-21)**, and no increased yield of **3a** was observed with less or more than 3 equiv of $K_2S_2O_8$ **(Table 1, entries 13, 22-24)**. Control experiments without oxidant, photocatalyst, oxygen or light resulted in lower yields of the target product, which showed that all components were necessary for the optimized protocol **(Table 1, entries 25−28)**. Therefore, optimal reaction conditions involved Eosin Y **(1.0 mol %)** and $K_2S_2O_8$ **(3 eq.)** in solvent free condition at room temperature under air atmosphere for 24 h.

Table 2. substrate scope of benzothiazoles[a,b]



[a]Reaction conditions: benzothiazoles (**1**, 0.5 mmol), *N,N*-dimethylformamide (**2a**, 5 mL), $K_2S_2O_8$ (3.0 equiv, 1.5 mmol), Eosin Y (1.0 mol%), open to the air, 15 W Blue LED (λ= 450 nm) at room temperature for 24 h. [b]Isolated yield.

With the conditions in hand, the scope of substituted benzothiazoles was investigated first in reactions with *N,N*-dimethylformamide **(Table 2)**. Generally, corresponding alkylated products **(3)** were smoothly produced in moderate to good yields **(58−79%)** with acylated benzothiazoles **(4)** in low yields **(10−18%).** The results demonstrated that benzothiazole derivatives with 5-chloro **(3b)**, 6-methoxyl **(3c)**, 4-methyl **(3d)** and 6-methyl **(3e)** substituents on the aromatic ring were well tolerated. Next, we investigated the regioselectivity of the protocol. The reaction of benzothiazole with *N*-methylpyrrolidin-2-one (NMP) only gave **5a** in 65% without **5a'**, which indicated that the secondary amino carbon was preferred to construct the C-C bond.

To further investigate the substrate scope of this protocol, we evaluated various kinds of amides **(2)** in the reactions with substituted benzothiazoles **(Table 3)**. Much to our delight, *N,N*-dimethylacetamide (DMA) and *N,N*-dimethylpropanamide (DMP) also tolerated the reaction conditions furnishing the desired products in moderate to excellent yields. The reactions of benzothiazole with DMA and DMP gave **3g** and **3s** in 86% and 66% yields, respectively. Benzothiazoles with a 5-chloro **(3i)**, 6-methoxyl **(3j, 3t)**, 4-methyl **(3k, 3u)**, 6-methyl **(3l, 3v)** and 6-phenyl **(3r)** substituent on the aromatic ring gave corresponding alkylation products **3** in moderate to good yields **(45%-88%)**. However, the reactions of 6-cyano **(3m)** and 5-acetyl **(3n)** benzothiazoles with DMA only gave products in

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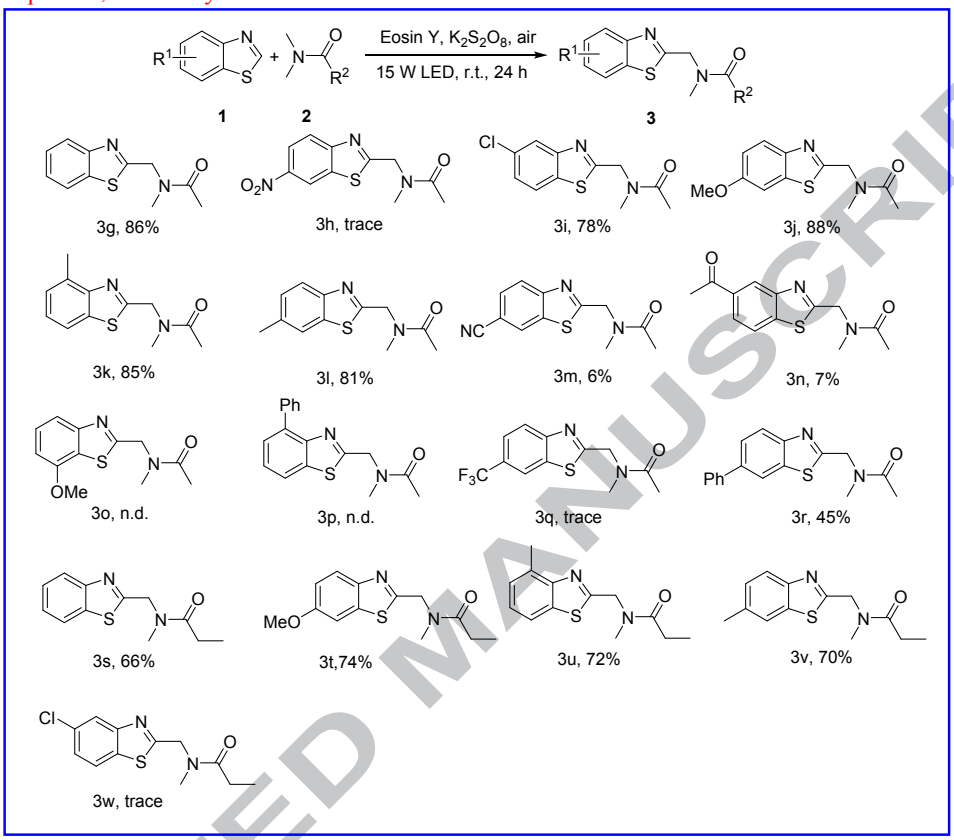
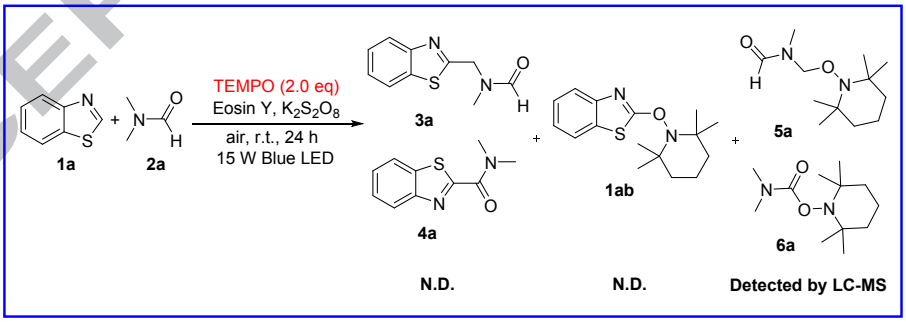
6% and 7% yields, respectively. Benzothiazoles with 6-nitro **(3h)**, 6-trifluoromethyl **(3q)** and 5-chloro **(3w)** only gave trace amount of the alkylation product **(3).** Interestingly, benzothiazoles with 7-methoxyl **(3o)** and 4-phenyl **(3p)** did not react with DMA, whereas 6-methoxyl **(3j)** and 6-phenyl **(3r)** benzothiazole gave product in 88% and 45%, respectively. The results showed that the reactions seemed to be sensitive to the steric hindrance at 4- and 7-position of benzothiazoles. It is obvious that the isolated yields of the corresponding products were decreased along with the increasement of chain length in the amides **(3g, 3i, 3j, 3k, 3l compared to 3s, 3w, 3t, 3u, 3v, respectively)**. The electronic characteristics of the substituents **(R^1)** of benzothiazoles were found to have an effect on the reactivity, where benzothiazoles with electron-withdrawing groups generally gave lower yields.

Table 3. substrate scope of *N,N*-dimethylamides[a,b]



[a]Reaction conditions: benzothiazoles (**1**, 0.5 mmol), amides (**2**, 5 mL), $K_2S_2O_8$ (3.0 equiv, 1.5 mmol), Eosin Y (1.0 mol%), open to the air, 15 W Blue LED (λ= 450 nm) at room temperature for 24 h. [b]Isolated yield.



Scheme 2. Control Experiment

For studying the possible mechanism of the transformation, a radical trapping agent TEMPO (2,2,6,6-tetramethyl-1-piperidinyl-oxy) was added under the optimal reaction conditions. Alkylated benzothiazole **(3a)**, acylated benzothiazole **(4a)** and adduct of benzothiazole **(1ab)** were not detected from the reaction mixture, and only adducts of DMF radicals with TEMPO **(5a** or **6a)** were observed by LC-MS **(Scheme 2)**, which indicated that the transformation might occur through a radical pathway and benzothiazole radical was not formed in the system.

According to the results of the control experiments, both Eosin YH_2 and $K_2S_2O_8$ had certain catalytic effects when they acted alone, and the catalytic effect was greatly improved when they worked together. Therefore, we speculated that the reaction may occur through multiple routes **(Scheme 3)**. Initially, the excited-state EYH_2^* was generated from EYH_2 by irradiation of visible light. $^1EYH_2^*$ was known to undergo fast ISC, which attributed to very brief **(~0.5-2.7** ns**)** singlet $^1EYH_2^*$ life times,[24] and thus, the triplet state $^3EYH_2^*$ (98.8 μs) was typically considered to be the most relevant excited state in reactions.[24,25] A hydrogen atom transferred (HAT) between $^3EYH_2^*$ and DMF **(2a)** to produce $EYH_3^\bullet$ and DMF radicals **(2ab** and **2ac).**[26] Photoredox cycle was closed by deprotonation of $EYH_3^\bullet$ under the assistance of molecular oxygen O_2 [27] and sulfate anion radical $SO_4^{\bullet-}$ generated through homolytic cleavage of a peroxydisulfate dianion $S_2O_8^{2-}$. On the other hand, sulfate radical anion $SO4^{\bullet-}$ could react with the DMF **(2a)** through a hydrogen abstraction process to form DMF radicals **(2ab** and **2ac)** and HSO_4^-.[28] The resulting DMF radicals **(2ab** and **2ac)** would attack the 2-

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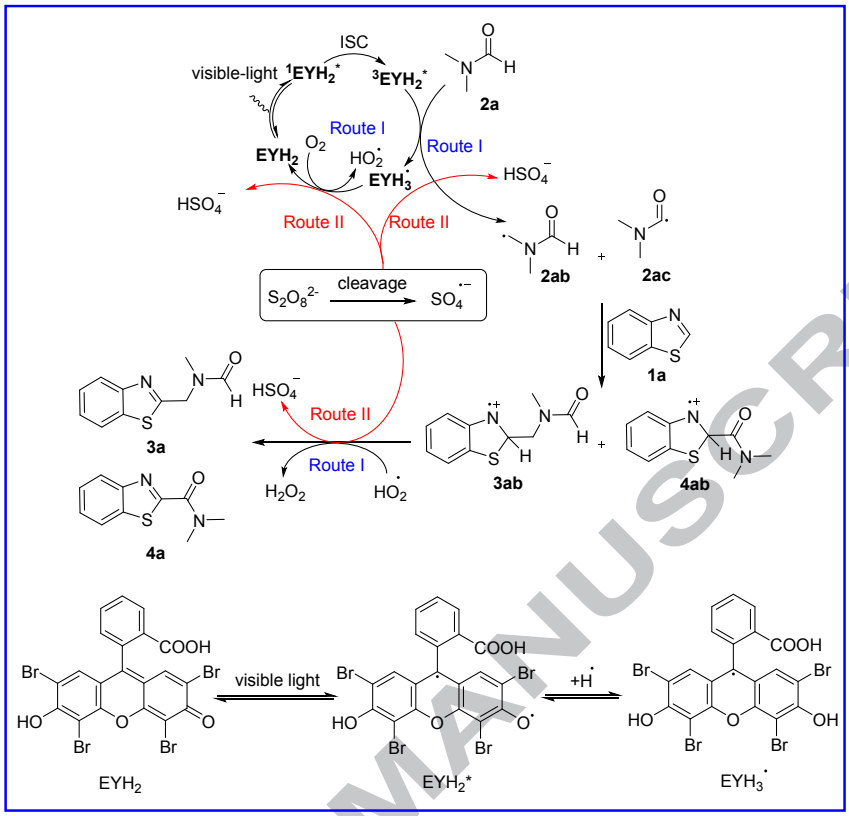
position of benzothiazole **(1a)** to form radical cation intermediates (**3ab or 4ab**),[29] which were deprotonated by the formed $HO_2^{\bullet}$[30] or $SO4^{\bullet-}$ to give the products (**3a** and **4a**). In addition, the structures of EYH_2 in neutral, excited-state and radical forms are listed below.[26]



Scheme 3. Plausible Mechanism

Conclusion

In conclusion, we have developed a two-component photocatalytic system for C2-alkylation reactions of benzothiazoles with *N,N*-dimethylamides under solvent-free conditions mediated by visible light. Eosin Y, a cheap and readily available xanthene dye, was applied as the photocatalyst and $K_2S_2O_8$, an inexpensive and readily available inorganic salt, acted as the oxidant. This reaction is mild enough to tolerate various functional groups furnishing a series of coupling reactions in moderate to excellent yields. Current efforts in our laboratory are directed toward applying two-component system to other alkylation reactions of heterocyclic compounds.

Acknowledgments

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Graphical Abstract

ACCEPTED MANUSCRIPT

Alkylation Reactions of Benzothiazoles with *N,N*-dimethylamides catalyzed by the Two-Component System under Visible Light

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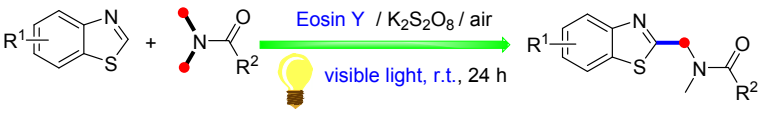

R^1= H, 5-Cl, 6-OMe, 4-Me, 6-Me, 6-CN, 5-Ac, 6-Ph
R^2= H, Me, Et

up to 88% yield

- visible light-mediated
- solvent free
- mild condition

Highlights

- C2-amidoalkylation of benzothiazoles induced by visible light was developed.
- Eosin Y/$K_2S_2O_8$ acted as efficient two-component photocatalytic system.
- This green protocol features mild conditions, broad substrates and high yields.

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