ORGANIC
LETTERS

2012
Vol. 14, No. 20
5334–5337

Visible Light Photocatalytic Synthesis of Benzothiophenes

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Received September 12, 2012

ABSTRACT

The photocatalytic reaction of *o*-methylthio-arenediazonium salts with alkynes yields substituted benzothiophenes regioselectively through a radical annulation process. Green light irradiation of eosin Y initiates the photoredox catalysis. The scope of the reaction was investigated by using various substituted diazonium salts and different alkynes.

The synthesis of benzothiophene derivatives has attracted much attention in recent years due to their wide application in biology,[1] pharmacy,[2] catalysis,[3] and material science.[4] Several active drugs on the market contain the benzothiophene core: Zileuton is a potent and selective inhibitor of 5-lipoxygenase,[5] while raloxifene[6] and arzoxifene[7] are selective estrogen receptor modulators and antitubulin agents (Figure 1).

Many elegant methods have been reported for the synthesis of substituted benzothiophenes.[8] Most of these methodologies rely on two approaches: (a) direct arylation of the benzothiophene moiety; (b) electrophilic cyclization and coupling cyclization reactions to construct the benzothiophene ring.[8a,9] Cyclization reactions are of more interest since they yield only the desired regioisomer. Typically, cyclization reactions are catalyzed by transition metals, such as palladium-catalyzed iodocyclizations,[10] copper-mediated halocyclizations,[11] and gold-promoted annulation reactions.[12] Recently, we have reported a

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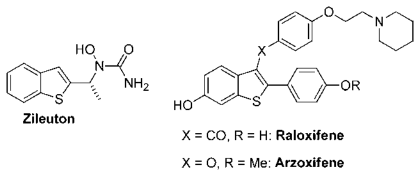
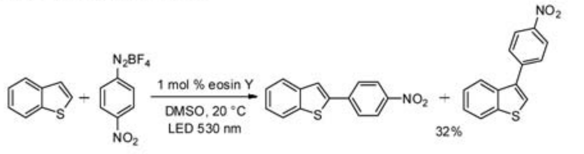


Figure 1. Benzothiophene moiety containing drug molecules.

methodology for the arylation of heteroarenes using aryl diazonium salts in visible light photocatalysis.[13] We used the reaction for the synthesis of 2-substituted benzothiophenes, but unfortunately mixtures of regioisomers were obtained in rather low yields (Scheme 1a).

Scheme 1. Photocatalytic Approaches to Benzothiophenes

(a) Photocatalytic direct arylation of benzothiophene yields a mixture of regioisomers

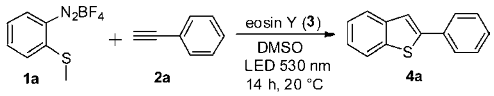


(b) Photocatalytic cyclization gives the benzothiophene ring as single isomer in good yield (this work)

To overcome such disadvantages in the direct arylation of benzothiophene, we decided to explore an annulation method to construct the benzothiophene ring. Giuseppe Zanardi et al. first reported the synthesis of benzothiophenes from the reaction of *o*-methylthio-arenediazonium salts with alkynes using transition metals as catalysts.[14] In 2000, Larry G. Huffman, Jr. et al. reported the synthesis of benzothiophenes from diazonium salts with stoichiometric amounts of $FeSO_4$ and $TiCl_3$.[15] Recently Carl H. Schiesser et al. prepared a potent AT_1 receptor antagonist through a cyclization process involving the addition of aryl radicals to alkynes, followed by intramolecular homolytic substitution at a sulfur or selenium heteroatom.[16]

All of these annulation reactions typically require stoichiometric amounts of transition metals and rather harsh reaction conditions. Visible light photocatalysis is emerging as a powerful tool for mild and selective organic transformations.[17] We report here the visible light mediated synthesis of privileged benzothiophenes through a radical annulation process catalyzed by eosin Y at ambient conditions.

Table 1. Optimizing Reaction Conditions



entry	conditions	yield[a]
1	**3** (1 mol %), **2a** (2 equiv), DMSO	58
2	**3** (1 mol %), **2a** (5 equiv), DMSO	64
3	**3** (1 mol %), **2a** (5 equiv), DMF	56
4	**3** (5 mol %), **2a** (2 equiv), DMSO	68
5	**3** (5 mol %), **2a** (5 equiv), DMSO	75
6	**3** (5 mol %), **2a** (10 equiv), DMSO	75
7	rose bengal (5 mol %), **2a** (5 equiv), DMSO	59
8	**3** (5 mol %), **2a** (5 equiv), DMSO, no light	15[b]
9	no catalyst, **2a** (5 equiv), DMSO	12[b]

[a] Isolated yields after purification by flash column chromatography using silica gel. [b] 36 h irradiation time.

Our initial studies focused on the reaction of the *o*-methylthio-benzenediazonium salt **1a** with phenyl acetylene using eosin Y (**3**) as a photoredox catalyst by irradiating at 530 nm. We examined the amount of catalyst loading (Table 1, entries 2 and 5) and different equivalents of alkyne (Table 1, entries 4, 5, and 6) on this photoreaction. To our delight, when 5 mol % of eosin Y and 5 equiv of alkyne were used in DMSO, the desired product was obtained in good yield (Table 1, entry 5). We also examined rose bengal as a photocatalyst,[22] giving the expected product in 59% yield (Table 1, entry 7). To prove the essential role of photocatalysis for the annulation reaction, experiments without green light irradiation or without dye

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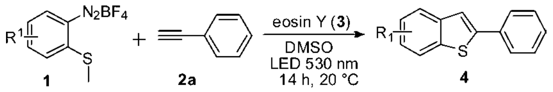
under irradiation were performed. As expected, we observed only a 15% and 12% product yield, respectively, after 36 h at 20 °C (Table 1, entries 8 and 9).

Table 2. Photocatalyzed Annulation of *o*-Methylthioarenediazonium Salts with Phenyl Acetylene[a]



entry	substrate	R^1	alkyne	product	yield[b]
1	**1a**	H	**2a**	**4a**	75
2	**1b**	4-Cl	**2a**	**4b**	70
3	**1c**	4-Me	**2a**	**4c**	72
4	**1d**	5-Cl	**2a**	**4d**	65
5	**1e**	4-OMe	**2a**	**4e**	63
6	**1f**	4-Br	**2a**	**4f**	72
7	**1g**	4-OEt	**2a**	**4g**	76
8	**1h**	4-F	**2a**	**4h**	62

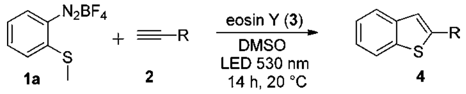
[a] The reaction was performed with **1** (0.25 mmol), phenyl acetylene (5 equiv), and eosin Y (0.05 equiv) in 1.0 mL of DMSO. [b] Isolated yields after purification by flash column chromatography using silica gel.

Having optimized reaction conditions in hand, we investigated the reaction scope for *o*-methylthio-arenediazonium salts with phenyl acetylene for the photoannulation reaction. All diazonium salts were prepared according to literature described procedures.[15] *O*-Methylthio-arenediazonium salts bearing electron-donating substituents (Table 2, entries 3, 5, and 7) reacted well in the photoreaction to afford the corresponding benzothiophenes in good yields. Diazonium salts bearing halogen substituents (Table 2, entries 2, 4, 6, and 8) gave the corresponding benzothiophenes with an intact carbon–halogen bond. Such molecules are difficult to synthesize using conventional methods and very useful for further synthetic elaborations.

Next we investigated the reaction scope of terminal alkynes in this photoreaction and the results are summarized in Table 3. Aromatic alkynes react smoothly and afford good yields (Table 3, entries 1–5). 3-Ethynylthiophene also reacted with **1a** to give the corresponding product in 62% yield (Table 3, entry 9). Molecules of this type find applications in the synthesis of optoelectronic materials. With ester, TMS, and *n*-butyl substituents on the alkynes, good to moderate yields (Table 3, entries 6, 7, 8, and 10) were obtained.

Thionaphthene-2,3-dialkyl esters are precursors for the synthesis of the corresponding cyclohydrazides of thionapthene, which are useful as indicators.[18] The synthesis of thionapthene-2,3-dialkyl esters is largely unexplored compared to other benzothiophene derivatives and only a few literature reports exist including a recent paper by P. G. Jones et al. describing an approach using palladium chemistry.[19] We synthesized thionapthene 2,3-dialkyl esters by simply reacting dialkyl but-2-ynedioate with *o*-methylthio-arenediazonium salts using eosin Y in visible light. The results are summarized in Table 4. Different diazonium salts were converted with dialkyl but-2-ynedioate affording thionapthene-2,3-dialkyl esters in good to moderate yield.

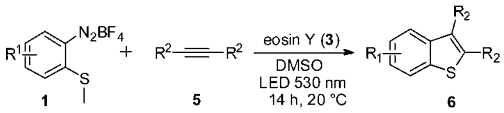
Table 3. Photocatalyzed Annulation of *o*-Methylthiobenzenediazonium Salt with Terminal Alkynes[a]



entry	substrate	alkyne	R	product	yield[b]
1	**1a**	**2a**	Ph	**4a**	75
2	**1a**	**2b**	4-NO_2-C_6H_4	**4i**	81
3	**1a**	**2c**	4-OMe-C_6H_4	**4j**	72
4	**1a**	**2d**	3-CF_3-C_6H_4	**4k**	62
5	**1a**	**2e**	4-F-C_6H_4	**4l**	64
6	**1a**	**2f**	CO_2Me	**4m**	60
7	**1a**	**2g**	TMS	**4n**	45
8	**1a**	**2h**	CO_2Et	**4o**	65
9	**1a**	**2i**	3-C_4H_3S	**4p**	62
10	**1a**	**2j**	*n*-butyl	**4q**	30

[a] The reaction was performed with **1a** (0.25 mmol), terminal alkyne (5 equiv), and eosin Y (0.05 equiv) in 1.0 mL of DMSO. [b] Isolated yields after purification by flash column chromatography using silica gel.

Table 4. Photocatalyzed Annulation of *o*-Methylthioarenediazonium Salts with Dialkyl But-2-ynedioates[a]



entry	substrate	R^1	alkyne	R^2	product	yield[b]
1	**1a**	H	**5a**	CO_2Me	**6a**	61
2	**1a**	H	**5b**	CO_2Et	**6b**	50
3	**1h**	4-F	**5a**	CO_2Me	**6c**	55
4	**1h**	4-F	**5b**	CO_2Et	**6d**	42
5	**1g**	4-OEt	**5a**	CO_2Me	**6e**	53
6	**1f**	4-Br	**5a**	CO_2Me	**6f**	55
7	**1f**	4-Br	**5b**	CO_2Et	**6g**	40
8	**1d**	5-Cl	**5a**	CO_2Me	**6h**	40
9	**1d**	5-Cl	**5b**	CO_2Et	**6i**	51

[a] The reaction was performed with **1** (0.25 mmol), internal alkyne (5 equiv), and eosin Y (0.05 equiv) in 1.0 mL of DMSO. [b] Isolated yields after purification by flash column chromatography using silica gel.

Finally, we employed our methodology to prepare the key intermediate **7** of the raloxifene synthesis providing a metal-free route.[15] We prepared **1e** from the corresponding amine and reacted it with **2c** using standard photocatalysis conditions to furnish **7** in 70% isolated yield (Scheme 2).

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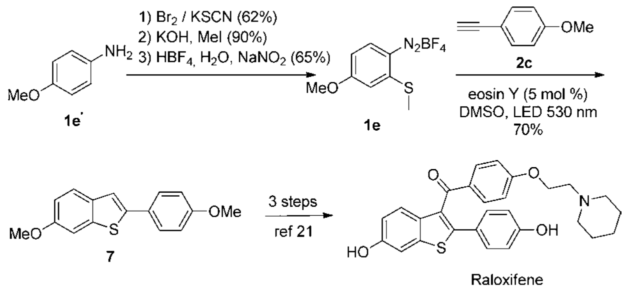
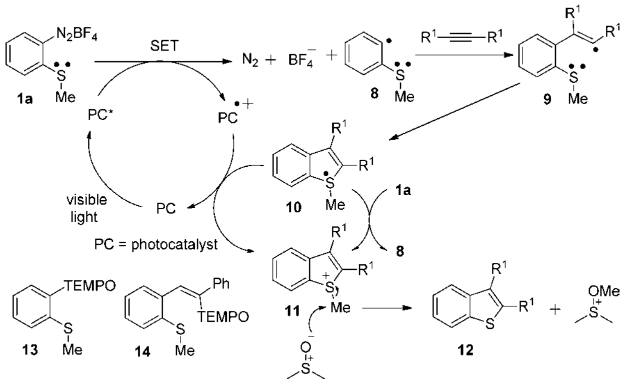
Scheme 2. Photocatalytic Synthesis of the Key Intermediate **7** of Raloxifene



To investigate the mechanism of the photoreaction, we performed radical trapping experiments. TEMPO adducts **13** and **14** (see the Supporting Information for full details) were identified by mass spectrometry supporting the radical pathway. In accordance to literature reports[13,14,20] and the radical trapping experiments we propose a tentative mechanism in Scheme 3. Initially aryl radical **8** is formed by SET from the excited state of the photocatalyst to diazonium salt **1a**. Addition of **8** to the alkyne yields the corresponding vinyl radical **9**, which then further cyclizes, to give sulphuranyl radical **10**. Radical **10** is oxidized to cation **11** that transfers a methyl group to nucleophiles present in the reaction mixture by an S_N2 process giving product **12**. Radical **10** is oxidized by either the cation radical of the photocatalyst to complete the electron transfer cycle or the diazonium salt in a chain transfer mechanism. Investigations to elucidate the reaction mechanism in more detail are ongoing.

Scheme 3. Proposed Reaction Mechanism



In conclusion, the first photocatalytic synthesis of benzothiophenes from diazonium salts has been accomplished. The method provides mild and efficient access to different types of benzothiophenes avoiding metal catalysts and high temperatures. Instead, only green light and a catalytic amount of organic dye as the catalyst are required. The substrate scope is large, and many products have the potential for further synthetic transformations as demonstrated by the synthesis of the key intermediate of the drug raloxifene. Experiments to investigate the mechanism of the reaction, to expand the scope of the reaction, and to apply it to the synthesis of other biologically active molecules are ongoing in our laboratory.

Acknowledgment. This work was supported by the GRK 1626 (Chemical Photocatalysis) of the German Science Foundation (DFG).

Supporting Information Available. Experimental procedures and spectral characterization of all compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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