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Article

Visible-Light-Driven C−S Bond Formation Based on Electron Donor−Acceptor Excitation and Hydrogen Atom Transfer Combined System

Tatsuhiro Uchikura, Yurina Hara, Kazushi Tsubono, and Takahiko Akiyama*

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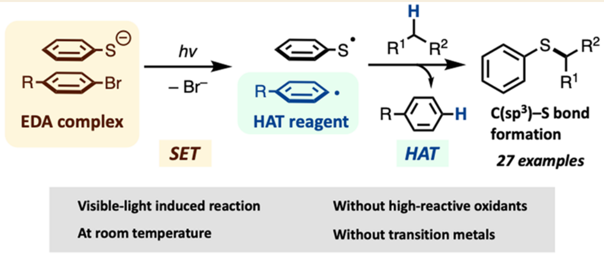
ABSTRACT: Developed herein is a visible-light-driven synthesis of sulfides by an electron donor−acceptor/single electron transfer and hydrogen atom transfer combined system without transition metals and strong oxidants. This reaction proceeds through the excitation of an electron donor−acceptor complex between a thiolate and an aryl halide, followed by the hydrogen atom transfer from an alkane to the generated aryl radical.



KEYWORDS: *bond formation, donor−acceptor excitation, hydrogen atom transfer*

INTRODUCTION

Organosulfur compounds are widely used in pharmaceuticals and functional materials.[1,2] In this regard, C−S bond formation is a very important process in organic synthesis.[3,4] In particular, C(sp^3)−S bond formation has attracted much attention because many C(sp^3)−S bonds exist in biologically active compounds (Figure 1).[5−10] The C(sp^3)−S bond is generally formed by the S_N2 reaction of thiolate with haloalkane. The direct C−H sulfenylation of alkanes via radical processes utilizing thiyl radicals is an atom-economical reaction.[11] A drawback of the formation of the thiyl radical is that strong oxidants or transition metals are required for the generation of the radical species (Figure 2a),[12−15] and mild conditions for C−S bond formation reactions are desired.

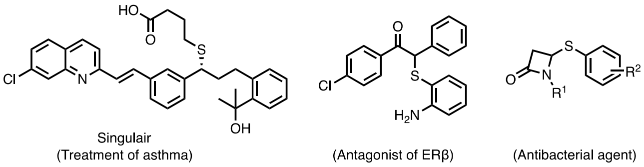


Figure 1. Pharmaceuticals bearing a C(sp^3)−S bond.

In the past decade, photocatalytic radical coupling reactions have been reported for the generation of radical species under mild conditions.[16−19] For example, Fu et al. reported a photoinduced radical C−S bond formation reaction using a photocatalyst.[20−24] More recently, an electron donor−acceptor (EDA) complex was developed for use in the visible-light-driven photoreaction instead of photocatalysts because EDA complexes often absorb visible light.[25−39] Miyake et al. reported a visible-light-driven C(sp^2)−S bond formation reaction via the EDA complexes of aryl thiols and aryl halides (Figure 2b),[35]

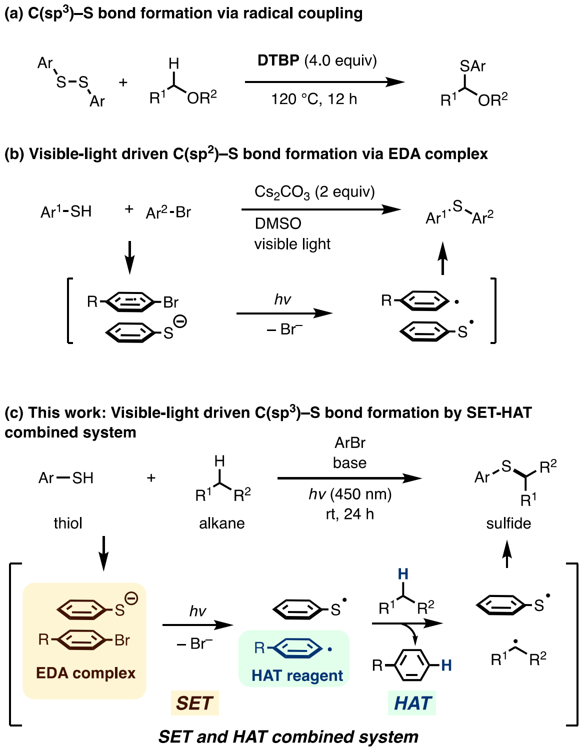


Figure 2. C−S bond-forming reactions mediated by thiyl radicals.

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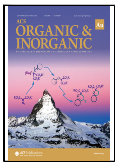
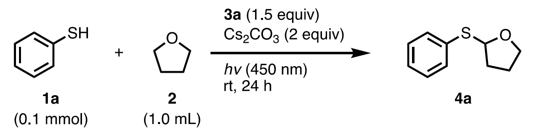


Table 1. Standard Reaction Conditions and Control Experiments[a]



entry	deviation from the standard conditions	yield[b]
1	none	71%[c]
2	without **3a**	<5%
3	without irradiation	0%
4	without Cs_2CO_3	0%
5	in air	0%
6	4-bromobenzonitrile (**3b**) instead of **3a**	33%[c]
7	K_2CO_3 instead of Cs_2CO_3	0%

[a]Performed with **1a** (0.1 mmol), **2** (1.0 mL), **3a** (0.15 mmol), and Cs_2CO_3 (0.2 mmol). [b]Determined by ^1H NMR measurement. [c]Isolated yield.

wherein reactive radical species are generated by single electron transfer (SET) from the EDA complexes. On the other hand, the reactive radical species can abstract a $C(sp^3)$−H hydrogen atom (hydrogen atom transfer: HAT[40−45]) to give alkyl radical species. By utilizing these phenomena, novel photoreactions via EDA-SET and HAT combination are achieved.[46−48]

We wish to report herein transition-metal- and strong-oxidant-free visible-light-driven radical coupling reactions of thiols and alkanes to form C−S bonds based on the SET and HAT combination system (Figure 2c). Mechanistic studies revealed that the aryl radical species generated from the EDA excited state abstracted the hydrogen atom from alkanes to generate alkyl radicals.

■ RESULTS AND DISCUSSION

At the outset, we examined the reaction of benzenethiol (**1a**) and THF in the presence of *p*-bromoacetophenone (**3a**) and cesium carbonate under blue LED irradiation. The desired C−S bond formation product **4a** was obtained in 71% yield (Table 1, entry 1). Control experiments indicated that light irradiation and the addition of base and **3a** were necessary for this reaction (entries 2−4). **4a** was not obtained in air, and disulfide **5** was generated (entry 5). Therefore, the degassed condition was necessary for this reaction. Use of 4-bromobenzonitrile (**3b**) instead of **3a** decreased the yield of **4a** probably because the generation of an aryl radical was unfavorable due to the stability of the anion radical species and the instability of the radical (entry 6).[49−51] Potassium carbonate was not suitable due to its low solubility (entry 7).[52]

Under the optimized conditions, the generality of thiols was investigated (Figure 3). A range of *para*-substituted aryl thiols bearing *tert*-butyl, methoxy, hydroxy, chloro, and bromo moieties participated in the reaction successfully to give corresponding C−S coupling products (**4a**−**4f**) in good to moderate yields. The *meta*- and *ortho*-methoxythiophenols also gave corresponding products (**4g** and **4h**) efficiently. 4-Aminothiophenol did not give **4i** probably because of the lack of acidity for generating thiolate.

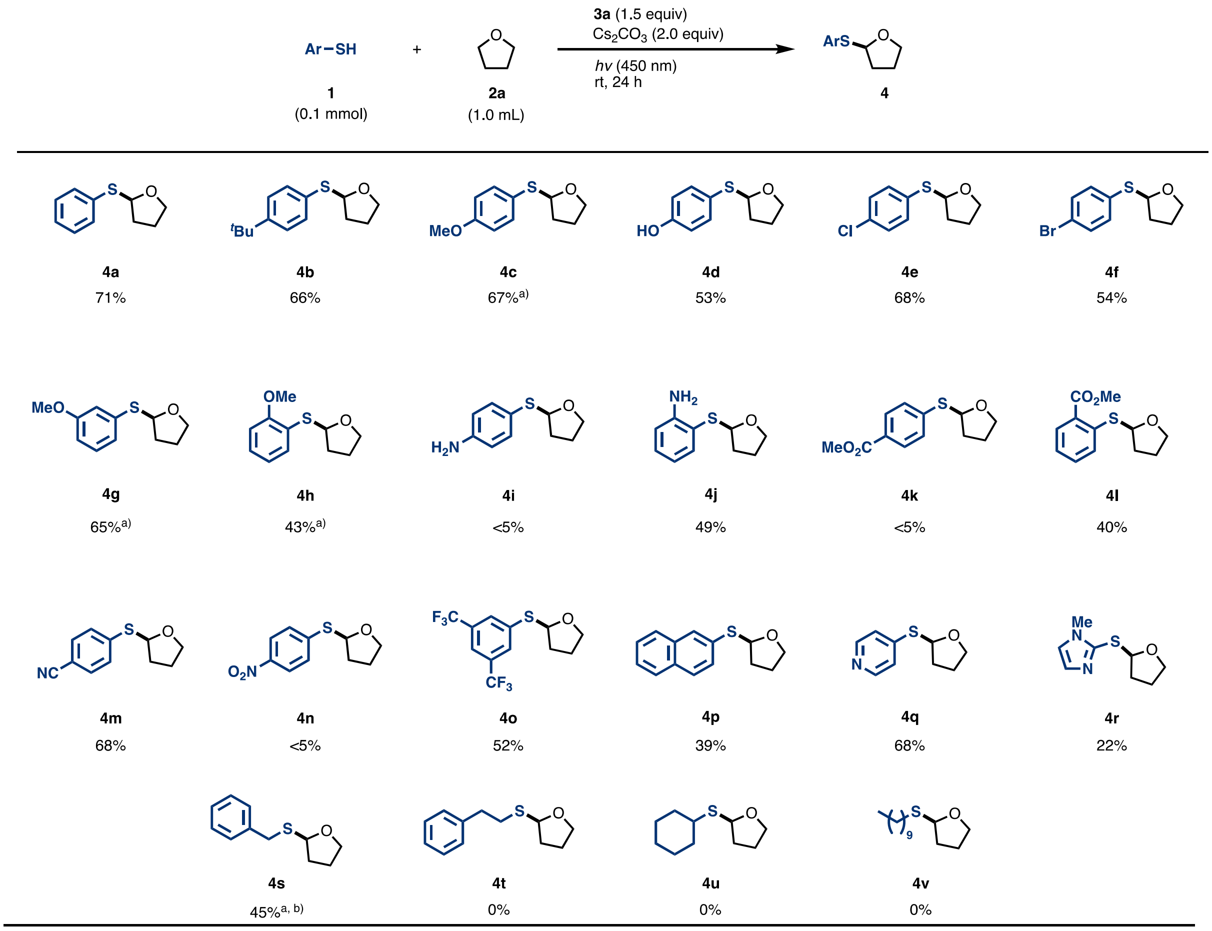
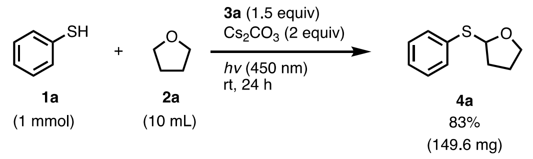


Figure 3. Generality of thiols. [a]*p*-Bromobenzophenone (**3c**) was used as aryl halide instead of *p*-bromoacetophenone (**3a**). [b]After the irradiation, $NaBH_4$ (1.0 equiv) and MeOH (1 mL) were added to the reaction mixture to reduce residual ketone.

Scheme 1. 1 mmol Scale Reaction



In contrast, 2-aminothiophenol gave **4j** in a moderate yield due to the stabilization of the thiolate anion by the *ortho*-amino group. In the case of methoxycarbonyl-substituted thiophenol, although *para*-substituted thiophenol did not furnish **4k**, *ortho*-substituted thiophenol gave **4l** in a moderate yield because the thiyl radical generated by the excitation of the EDA complex was stabilized by three-electron−two-center S−O bond formation with the carbonyl group at the *ortho* position.[53−56] Interestingly, *p*-cyanobenzenethiol (**1m**) and 3,5-bis(trifluoromethyl)benzenethiol (**1o**) bearing electron-withdrawing groups, which are unfavorable compounds for EDA complex formation, were also suitable substrates. In contrast, *p*-nitrobenzenethiol (**1n**), which has a yellow color, was not suitable due to self-absorption of visible light to inhibit EDA absorption or its low electron density to donate the electron to **3a**. Furthermore, 2-naphthalenethiol (**1p**) and heteroarenethiols (**1q** and **1r**) afforded C−S coupling products in moderate yields. Interestingly, whereas phenylmethanethiol gave **4s** in 45% yield, phenylethanethiol did not proceed to give **4t** presumably because the aromatic moiety and sulfur anion are far apart. Alkanethiols without a phenyl group, such as cyclohexanethiol and decanethiol, did not give the coupling products (**4u**, **4v**). The reaction of thiophenol with tetrahydrofuran proceeded smoothly on a 1 mmol scale to give the **4a** in 83% yield (Scheme 1).

We investigated the generality of alkanes using 20 equiv of alkanes in ethyl acetate[57] (Figure 4). Ethers, such as 1,4-dioxane, tetrahydropyran, 2,2-dimethyl-1,3-dioxolane, and *o*-xylylene oxide, gave corresponding thioacetals (**4a**, **6b**−**6e**) in modest to good yields. However, isochroman and cyclopentyl methyl ether gave products (**6f** and **6g**) in low yields due to steric hindrance, and acyclic primary ether was not suitable due to the low stability of the radical. Tetrahydrothiophene gave corresponding dithioacetal **6h** in 51% yield. Cyclic amides, such as dimethyl imidazolidinone and *N*-methyl pyrrolidone, were also suitable substrates, furnishing products (**6i** and **6j**) in moderate yields. Furthermore, cycloalkanes, such as cyclopentane, cyclohexane, and cycloheptane, were also applicable, generating desired sulfides (**6k**−**6m**) in modest yields.

Several experiments were carried out to acquire mechanistic insight. First, the UV−vis spectra were measured in acetonitrile (Figure 5).[58] The formation of the EDA complex was confirmed by the absorption in the 420−550 nm region in a mixture of sodium benzenethiolate (**1a-Na**) and **3a**. This absorption was not observed in individual substrates (**1a** and **3a**) or in a mixture of benzenethiol **1a** and **3a**. Thus, the generation of thiophenolate from **1a** and base was necessary for the formation of the EDA complex.[59]

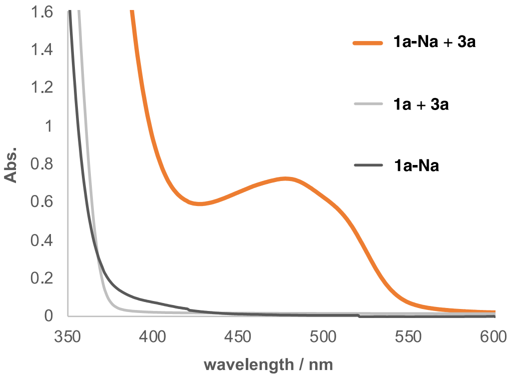


Figure 5. UV−vis spectra of the EDA complex in CH$_3$CN. Orange line: mixture of sodium benzenethiolate (**1a-Na**) and **3a**. Light gray line: mixture of **1a** and **3a**. Dark gray line: **1a-Na**.

Furthermore, the different reactivity of phenylmethanethiol and other alkanethiols (Figure 3) supports that $\pi-\pi$ interaction between thiolate and aryl halide would be the driving force for formation of the EDA complex.

Next, radical inhibitors were added to the reaction mixture under the standard conditions (Scheme 2A). Because the addition of radical scavengers, such as 9,10-dihydroanthracene and TEMPO, inhibited the reaction, the radical process is plausible. Use of THF-d_8 gave 4′-deuterated acetophenone **7** as the side product (Scheme 2B). This means that the hydrogen atom of alkanes was abstracted by an aryl radical generated from aryl halide via EDA-SET. Furthermore, when a 1:1 mixture of THF and THF-d_8 was used, the k_H/k_D value was estimated to be

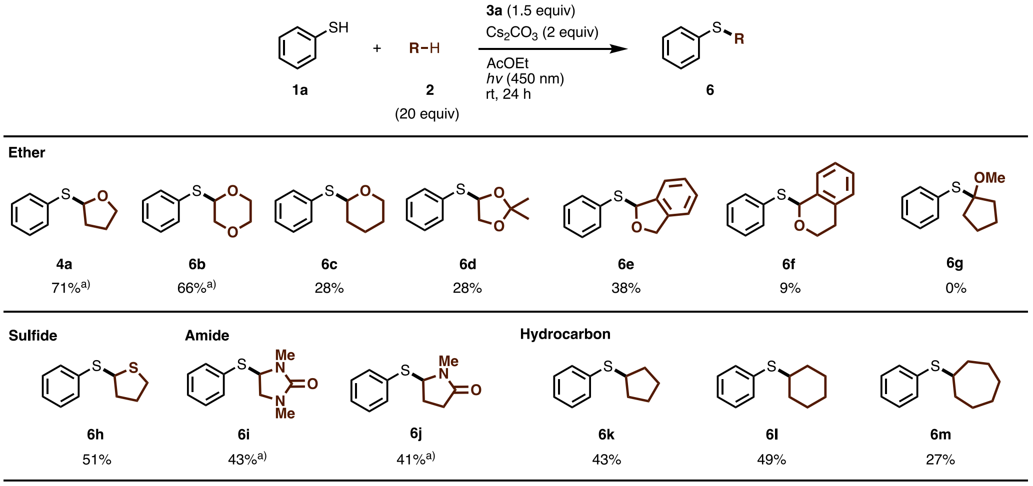
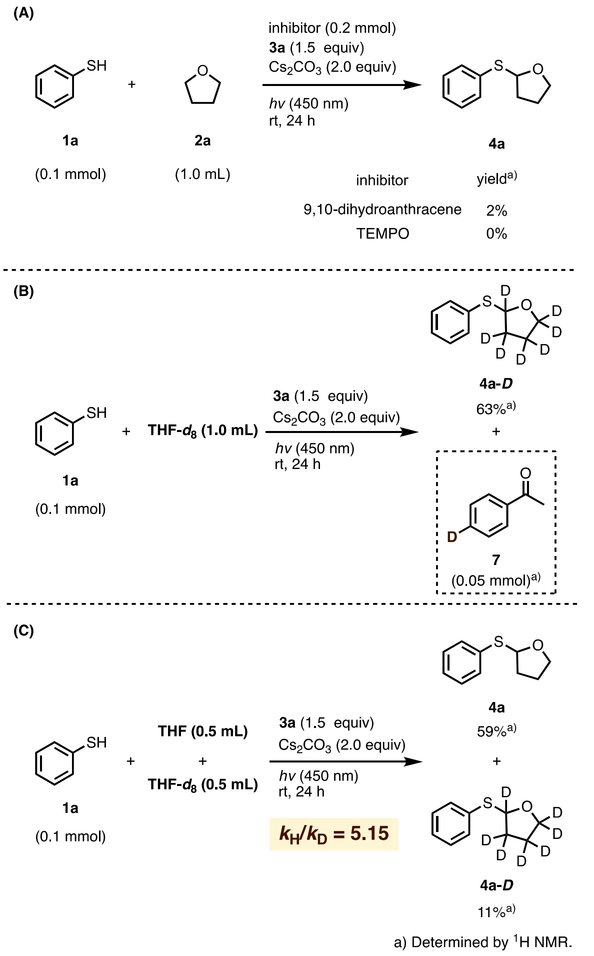


Figure 4. Generality of alkanes. ^{a}Using 1.0 mL of hydrocarbons without AcOEt.

Scheme 2. Mechanistic Studies



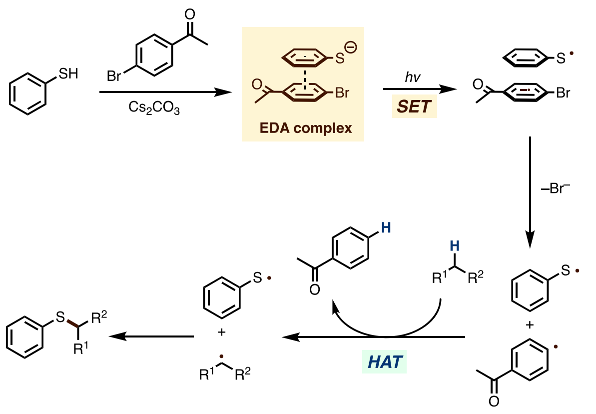


Figure 6. Proposed mechanism.

5.15 (Scheme 2C). Thus, C−H abstraction is expected to be the rate-determining step in this reaction.

Based on these results, we propose the mechanism shown in Figure 6. First, an EDA complex of thiolate and 4′-bromoacetophenone is formed driven by $\pi-\pi$ interaction (**3a**). This is followed by photoexcitation to generate a thiyl radical and an anion radical of aryl halide. Then, bromide is eliminated from the anion radical of aryl halide to generate aryl radical species, which in turn abstracts a hydrogen atom from an alkane[10] to produce alkyl radical. Finally, a C−S bond is formed between the thiyl radical and the alkyl radical.

■ CONCLUSION

In summary, a visible-light-driven C(sp^3)−S bond formation reaction via the EDA excited state was developed. This reaction proceeds via the SET and HAT combination system. Mechanistic studies indicate that an aryl radical generated by EDA excitation abstracts a hydrogen atom from alkane, and the generated alkyl radical couples with the thiyl radical. To the best of our knowledge, this reaction is the first example of the EDA-SET and HAT combined photoreaction system that is expected to have several applications to other reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00007.

Experimental details including further optimization studies, and analytical and spectroscopic data for new compounds; copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Takahiko Akiyama − *Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo 171-8588, Japan;* orcid.org/0000-0003-4709-4107; Email: takahiko.akiyama@gakushuin.ac.jp

Authors

Tatsuhiro Uchikura − *Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo 171-8588, Japan;* orcid.org/0000-0002-0327-3675
Yurina Hara − *Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo 171-8588, Japan*
Kazushi Tsubono − *Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo 171-8588, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsorginorgau.1c00007

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Notes

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(49) According to the screening of aryl halide, *p*-bromoacetophenone and 4′′-bromobenzophenone gave the best results (Table S1; see Supporting Information).

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(57) Ethyl acetate was the most suitable solvent for the SET−HAT combined reactions. Use of more polar solvents such as DMF or acetonitrile led to the formation of C(sp^2)−S coupling product (Miyake's reaction; see ref 35) as a major product (Table S3; see Supporting Information).

(58) In THF, the EDA absorption band was not observed due to the insolubility of cesium carbonate. The reaction probably proceeded by the small amount of dissolving thiolate. In acetonitrile, the desired coupling product was obtained in a low yield (Table S3; see Supporting Information).

(59) The EDA complex was supported to be 1:1 complex by a Job plot by the method of continuous variation (Figure S2; see Supporting Information).