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Visible-Light-Promoted Cross-Coupling Reactions of Aryldiazonium Salts with *S*-Methyl-d_3 Sulfonothioate or *Se*-Methyl-d_3 Selenium Sulfonate: Synthesis of Trideuteromethylated Sulfides, Sulfoxides, and Selenides

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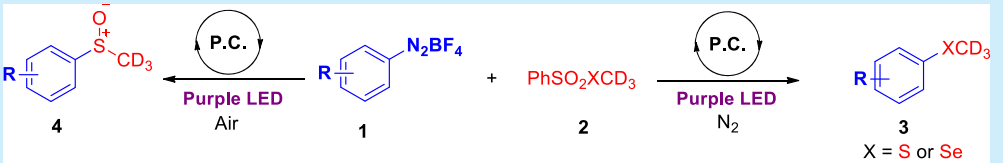

- *Deuterated methylthiolation/methylselenation reagents*
- *Selective Oxygenation with Ground-State Oxygen*
- *Metal-free, no oxidant, mild temperature*
- *Broad substrate scope*
- *D-incorporation up to 97%*

ABSTRACT: A novel visible-light-photocatalytic deuterated thiomethylation/methylselenation of aryldiazonium salts utilizing *S*/*Se*-methyl-d_3 sulfonothioate has been developed. The mild conditions and the various functional groups provide a green protocol for the efficient and rapid introduction of the *S*-CD_3 or *Se*-CD_3 group with useful levels of deuterium content (>91% D). Trideuteromethyl sulfoxides have also been successfully chemoselectively observed by simple atmospheric changes under photocatalytic conditions.

Deuterium is a stable nonradioactive isotope of hydrogen and is well-known to medicinal chemists for its wide application in drug discovery and development.[1] The important feature of deuterium is that the C−D bond length is shorter and the vibrational frequency is lower, so it is stronger than the C−H bond, which can directly affect the absorption, distribution, metabolism, and excretion of some drug molecules, thereby improving the efficacy, tolerance, and safety of those drugs.[2,3] Deuterium-labeled compounds are pivotal diagnostic tools in research determination of the products and mechanistic investigations of organic reactions.[4] Notably, deutetrabenazine was approved by the FDA for the treatment of dyskinesia associated with Huntington's disease as the first deuterated drug in 2017.[5] It also means that deuterated drugs have entered a new era with a promising future.

The methyl group is one of the most common functional groups in biologically active compounds, and methyl groups are usually introduced to improve the biological activity and physical properties of molecules.[6] Among them, aryl methyl sulfide and methyl sulfoxide are important building blocks in medicinal chemistry and widely exist in biological molecules,[7] agrochemicals,[8] and pharmaceuticals.[9] Examples include sulprofos,[10] an insecticide to worms, thiocolchicine,[11] a proliferative disease drug, thioridazine,[12] an antipsychotic drug, and sulmazole,[13] a cardiovascular drug. Therefore, it is meaningful and attractive to develop trideuteromethylated analogues of aryl methyl sulfide and methyl sulfoxide. However, there are limited reports on the synthesis of trideuteromethylated analogues of aryl methyl sulfide and methyl sulfoxide compounds.[14] We developed a new method for the preparation of *S*-methyl-d_3 sulfonothioate ($PhSO_2SCD_3$) and *Se*-methyl-d_3 selenium sulfonate ($PhSO_2SeCD_3$) as new deuterated methylthiolation/methylselenation reagents. On the basis of Wang's work,[14c] trimethylsulfoxonium iodide reacted efficiently with less toxic DMSO-d_6 to generate trideuteromethylsulfoxonium iodide, which further reacted with $PhSO_2SNa$ to afford $PhSO_2SCD_3$ with a deuteration rate of up to 97% (Figure 1). In addition,

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$PhSO_2SeCD_3$ was also synthesized with a deuteration rate of up to 91%, as shown in Figure 1.

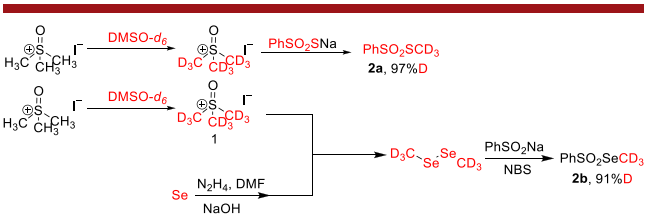


Figure 1. Preparation of $PhSO_2SCD_3$ and $PhSO_2SeCD_3$.

With the deuterated methylation reagents $PhSO_2SCD_3$ and $PhSO_2SeCD_3$ in hand, we envisioned that trideuteromethyl sulfides, sulfoxides, and selenides could be synthesized by the reaction of readily available aryldiazonium salts with these reagents via a radical pathway. Herein we report visible-light-promoted cross-coupling reactions of aryldiazonium salts with $PhSO_2SCD_3$ and $PhSO_2SeCD_3$ to afford trideuteromethyl sulfides, sulfoxides, and selenides (Figure 2).

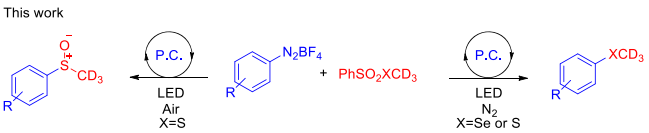


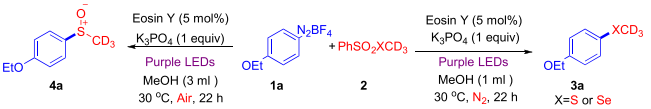
Figure 2. Visible-light photoredox construction of trideuteromethyl sulfides, sulfoxides, and selenides.

Initially, a model reaction of 4-ethoxyphenyldiazonium tetrafluoroborate (**1a**) with *S*-methyl-d_3 sulfonothioate **2a** in DMSO catalyzed by eosin Y under irradiation with 40 W purple LED light was investigated. To our delight, the desired deuterated product **3a** was isolated in 48% yield (Table 1, entry 1). Furthermore, a series of additives such as K_3PO_4, $NaHCO_3$, KOAc, and CsF were explored (Table 1, entries 2−5). Among the above examined additives, K_3PO_4 was the most efficient one. Next, we screened a range of solvents such as MeOH, MeCN, DMF, and DCM, and the yield of **3a** increased to 76% when the reaction was carried out in MeOH (Table 1, entries 6−9). We used white, blue, and orange LEDs, leading to the corresponding products in 52, 72, and 33% yield, respectively (Table 1, entries 10−12).

Notably, 1-ethoxy-4-((methyl-d_3)sulfinyl)benzene (**4a**) instead of **3a** was obtained in 51% isolated yield when the reaction was performed under an air atmosphere (Table 1, entry 13). We further carefully investigated the reaction concentration. It was found that 3 mL of MeOH was the ideal quantity for the reaction, and the yield of **4a** could be increased to 76% (Table 1, entry 14).

With the optimized reaction conditions in hand, a variety of diazonium salts **1** were explored, and the results are summarized in Scheme 1. Aryldiazonium salt derivatives bearing electron-donating groups reacted smoothly to afford the desired products (**3a**, **3d**, **3f**, **3g**, **3h**) in good yields with 97% D incorporation. Aryldiazonium salt derivatives with functional groups such as cyano (**1e**), phenyl (**1i**), ester (**1j**), amide (**1k**), ketone (**1m**, **1n**), nitro (**1p**), and *α,β*- unsaturated lactone (**1q**) were well-tolerated in this transformation to afford the desired products with 97% D incorporation. Moreover, the reactions of halogen (Cl, Br, I)-substituted aryldiazonium salts proceeded well, affording the desired

Table 1. Screening of Reaction Conditions[a]



			yield (D inc.)[b]	
entry	additive	solvent (mL)	3a	4a
1	−	DMSO (1)	48% (97%)	0
2	K_3PO_4	DMSO (1)	65% (97%)	0
3	$NaHCO_3$	DMSO (1)	54% (97%)	0
4	KOAc	DMSO (1)	57% (97%)	0
5	CsF	DMSO (1)	49% (97%)	0
6	K_3PO_4	DMF (1)	36% (97%)	0
7	K_3PO_4	MeCN (1)	37%(97%)	0
8	K_3PO_4	DCM (1)	42% (97%)	0
9	K_3PO_4	MeOH (1)	76% (97%)	0
10[d]	K_3PO_4	MeOH (1)	52% (97%)	0
11[e]	K_3PO_4	MeOH (1)	72% (97%)	0
12[f]	K_3PO_4	MeOH (1)	33% (97%)	0
13[c]	K_3PO_4	MeOH (1)	0	51% (97%)
14[c]	K_3PO_4	MeOH (3)	0	76% (97%)

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), PC (5 mol %), and additive (0.2 mmol) in the solvent at 30 °C for 22 h under N_2 with 40 W purple LED irradiation (λ = 395 nm). [b]Isolated yields. Deuterium incorporation levels were determined by ^{1}H NMR spectroscopy. [c]Under air. [d]40 W white LEDs. [e]40 W blue LEDs. [f]40 W orange LEDs.

products (**3b**, **3c**, **3o**) in excellent yields with 97% D incorporation while retaining the C−X bond intact, which can be useful for further modification. Notably, substrates with condensed aromatic rings, such as indane and fluorene, were compatible with the optimized reaction conditions as well, furnishing the corresponding products **3l** and **3r** with 97% D incorporation. Heteroaryldiazonium salts could also be adapted to the reaction under the optimized conditions to provide the desired products **3s−u,** respectively.

On the other hand, through only transforming the atmosphere to air, a wide range of diazonium salts bearing electron-withdrawing or electron-donating groups at the *para* position were transformed well into the corresponding sulfoxide products (**4a−j**) in yields ranging from 27% to 76% (Scheme 2). Moreover, disubstituted and trisubstituted aryldiazonium salts also reacted smoothly under the standard conditions to give the desired products **4k**, **4l**, and **4n** in 48, 34, and 52% yield, respectively.

Furthermore, *Se*-methyl-d_3 sulfonoselenoate ($PhSO_2SeCD_3$) could be successfully coupled with various of diazonium salts. The (methyl-d_3)(phenyl)selanes (**5a−c**) were successfully observed in moderate to good yields (Scheme 3).

To further reveal the practicability of the visible-light-promoted cross-coupling protocol, late-stage modifications of drug candidates were further conducted. Sulfonamides are an important class of drugs[15] that have a variety of pharmacological effects, including antibacterial, antitumor, anticarbonic anhydrase, and diuretic.[16] *p*-Sulfide sulfonamide also shows important biological activity.[17] We explored the late-stage deuterothiomethylation of sulfonamide pharmaceuticals. Sulfamethazine and sulfamethoxazole were converted to trideuteromethyl sulfides or trideuteromethyl sulfoxides (**6a**, **6b**, **7a**) in good yields with 97% D incorporation from the corresponding diazonium salt substrates (Scheme 4).

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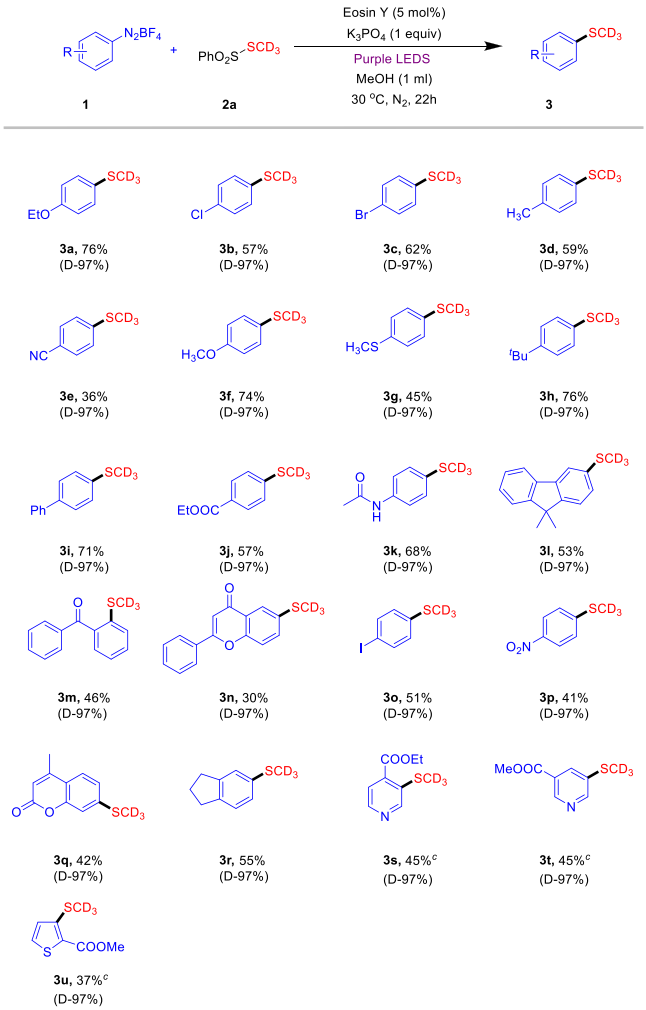
Scheme 1. Substrate Scope of Trideuteromethyl Sulfides[a,b]

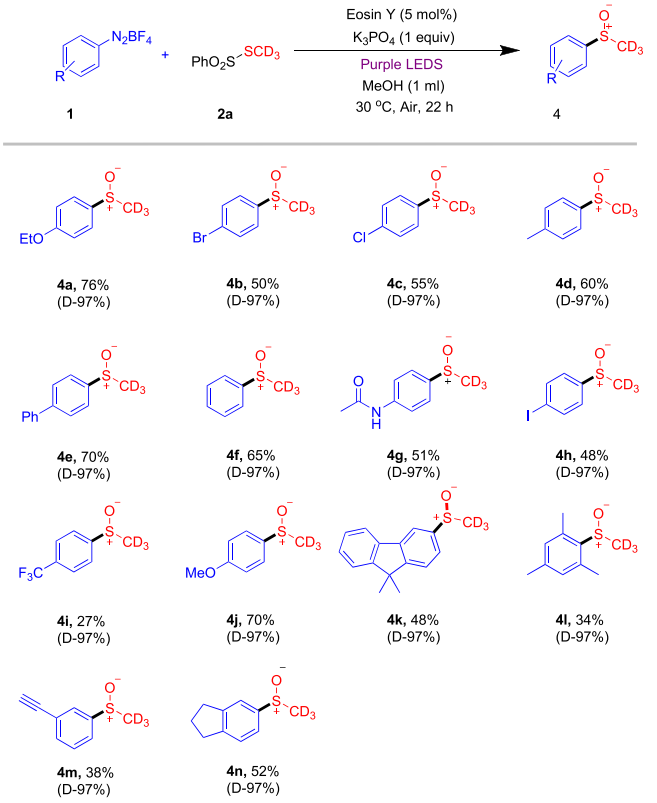


[a]Standard conditions: **1** (0.2 mmol), **2a** (0.3 mmol), PC (5 mol %), and K_3PO_4 (0.2 mmol) in MeOH at 30 °C for 22 h under N_2 with 40 W purple LED irradiation (λ = 395 nm). [b]Isolated yields are shown. Deuterium incorporation levels were determined by ^1H NMR spectroscopy. [c]1 mL of DMSO was used.

To further reveal the practicability of this protocol, a gram-scale reaction of **1h** (4 mmol) with **2a** (6 mmol) in the presence of 2 mol % eosin Y and K_3PO_4 was investigated (Scheme 5a). The desired product **3h** was obtained in 74% yield with 97% D incorporation. To investigate the possible mechanism of the reaction, several control experiments were conducted (Scheme 5b,c). When 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) was added to the reaction system under the standard reaction conditions, the reaction was completely suppressed. Furthermore, the LC−ESI-MS analysis of the reaction mixture indicated the formation of the TEMPO−PhOEt adduct, which confirmed that a radical pathway might be involved.

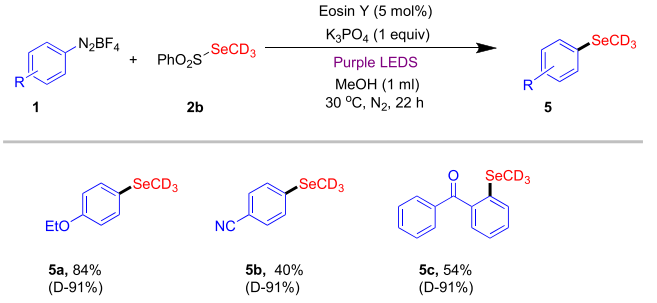
On the basis of the above results and literature reports,[18] a plausible reaction mechanism is proposed in Scheme 6. EY* is generated from EY under visible-light irradiation and subsequently assists with the reaction of aromatic diazonium salt **1** through a single electron transfer (SET) process to generate aryl radical **8**. Subsequently, aryl radical **8** reacts with $PhSO_2SCD_3$ to afford trideuteromethyl sulfide **3** and sulfone radical **9**. Then sulfone radical **9** undergoes SET with the

Scheme 2. Substrate Scope of Trideuteromethylated Sulfoxides[a,b]



[a]Standard conditions: **1** (0.2 mmol), **2a** (0.3 mmol), PC (5 mol %), and K_3PO_4 (0.2 mmol) in MeOH at 30 °C for 22 h under air with 40 W purple LED irradiation (λ = 395 nm). [b]Isolated yields are shown. Deuterium incorporation levels were determined by ^1H NMR spectroscopy.

Scheme 3. Substrate Scope of Trideuteromethyl Selenides[a,b]



[a]Standard conditions: **1** (0.2 mmol), **2b** (0.3 mmol), PC (5 mol %), and K_3PO_4 (0.2 mmol) in MeOH at 30 °C for 22 h under N_2 with 40 W purple LED irradiation (λ = 395 nm). [b]Isolated yields are shown. Deuterium incorporation levels were determined by ^1H NMR spectroscopy.

radical cation of the photocatalyst to furnish a sulfonyl cation and regenerate the photocatalyst (EY). On the other hand, the energy transfer between $^3O_2$ and EY* generates $^1O_2$, which can oxidize the trideuteromethyl sulfide to the corresponding trideuteromethyl sulfoxide **4**.

In summary, we prepared two novel and bench-stable deuterated reagents: $PhSO_2SCD_3$ and $PhSO_2SeCD_3$. These two deuterated methylthiolation/methylselenation reagents

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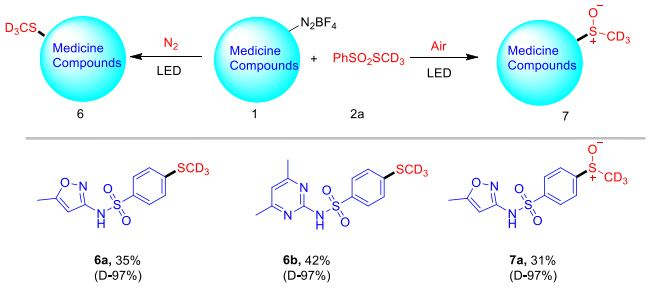
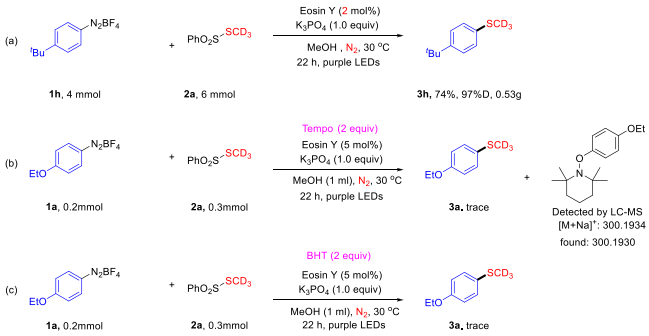
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Late-Stage Modification of Pharmaceuticals[a,b]

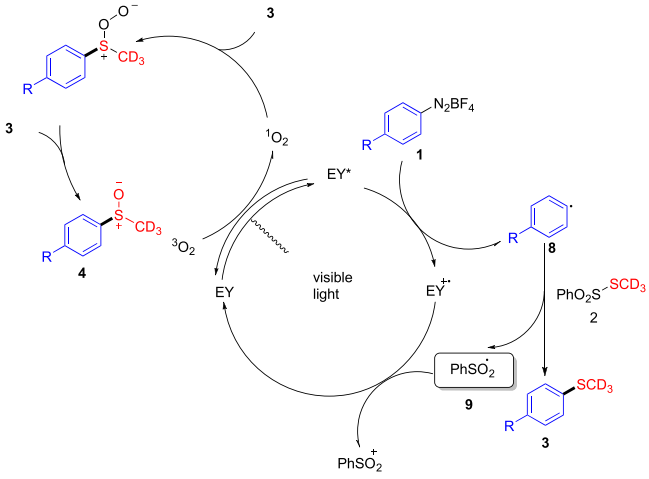


[a]Standard conditions: **1** (0.2 mmol), **2a** (0.3 mmol), PC (5 mol %), and K_3PO_4 (0.2 mmol) in MeOH at 30 °C for 22 h under air or N_2 with 40 W purple LED irradiation (λ = 395 nm). [b]Isolated yields are shown. Deuterium incorporation levels were determined by ^1H NMR spectroscopy.

Scheme 5. Gram-Scale Reactions and Control Experiments



Scheme 6. Proposed Mechanism



were successfully applied to reactions with diazonium salts under visible-light catalysis for the construction of trideuteromethyl sulfides, sulfoxides, and selenides. The reactions were carried out under mild conditions, and various functional groups were compatible. The application of this method in late modification of bioactive molecules further proves the superiority of this method. Thus, this strategy provides an alternative and attractive method for the synthesis of trideuteromethyl sulfides, sulfoxides, and selenides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03562.

Detailed experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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