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Articles

Deuterated-alkylation reagents based on sulfonium salts as cation and radical sources

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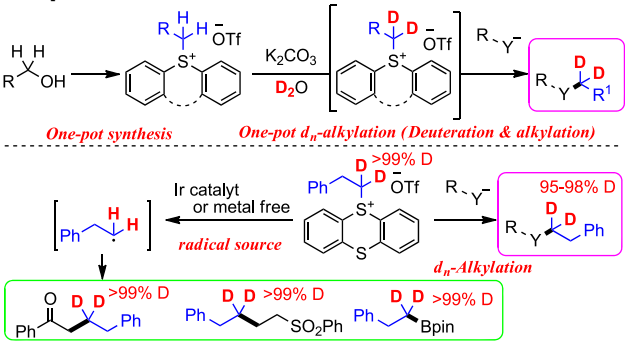
Abstract

The replacement of C–H bonds with more stable C–D bonds at the α-position of heteroatoms, which is the typical metabolic site for cytochrome P450, is important in drug discovery. Recently, we have developed d_n (deuterated)-alkylated sulfonium salts (**1a**-d_n), which were easily prepared by deuteration (H/D exchange reaction) with D_2O of the corresponding alkyl diphenylsulfonium salts (**1a**), as electrophilic d_n-alkylating reagents (cation sources). Herein, we newly report an improved preparation method of **1a** and one-pot synthesis of d_n-alkylated compounds via the deuteration of **1a** with D_2O and the subsequent nucleophilic substitution under basic conditions. Additionally, d_n-alkyl thianthrenium salts (**1b**-d_n) were also found to work as d_n-alkylating reagents (cation sources). Furthermore, **1b**-d_n served as radical sources under photo-induced reaction conditions with Ir photocatalyst, Hantzsch ester, or triphenylamine to obtain various regioselectively deuterium-incorporated alkyl compounds. These d_n-alkylating reagents will contribute to advance the drug discovery.

Keywords: alkylation, deuteration, sulfonium salts.

Graphical Abstract



1. Introduction

Compounds bearing deuterium (D), a nonradioactive and stable isotope of hydrogen (H), have broad applications such as tags to elucidate reaction mechanism in organic chemistry and kinetics using Raman imaging, neutron scattering, mass spectrometry imaging, magnetic resonance spectroscopy, tracers to reveal the metabolic pathways in medicinal chemistry, functional enhancement of pharmaceutical drugs and organic light-emitting diodes, and so on.[1] The deuterium kinetic isotope effect,[2] attributed from the higher dissociation energy of the carbon–deuterium (C–D) bond compared with that of carbon–hydrogen (C–H) bond, has attracted

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considerable attention in recent drug discovery studies.[1a,1b,3] Most pharmaceutical drugs undergo cytochrome P450 (CYP)-mediated oxidative metabolism, and the replacement of C–H bonds with the more stable C–D bonds at their metabolic sites of drugs, especially at the α-position to heteroatoms, can improve their pharmacokinetics and/or toxicity profile. Since deutetrabenazine, the first deuterium-incorporated drug, was approved by FDA in 2017, numerous deuterated drug candidates have entered stages of clinical trials (Fig. 1).[1b,3a,4]

Commercially available d_3-methyl sources (e.g. CD_3I, CD_3OD, and CD_3NH_2·HCl) are frequently utilized for the syntheses of deuterated compounds, including the approved heavy drugs, deutetrabenazine and deucravacitinib (Fig. 1).[5,6] Although d_n-alkylated reagents, such as 1-d_2-ethylamine ($CH_3CD_2NH_2$) and 1-d_2-phenethylamine ($PhCH_2CD_2NH_2$), which were prepared by the reductive deuteration of corresponding nitrile substrates using $LiAlD_4$, $NaBD_4$, and so on, were also used for synthesizing d_n-alkylated compound.[7] However, these reductants as D^- sources are impractical owing to their high cost and/or moisture sensitivity. Recently, we developed d_n-alkylated sulfonium salts (**1a**-d_n) as electrophilic d_n-alkylating reagents (Fig.2a).[8] **1a**-d_n was easily prepared by deuteration (H/D exchange reaction) of the corresponding alkyl diphenylsulfonium salt (**1a**) with D_2O as an inexpensive deuterium source under basic conditions using K_2CO_3 via sulfonium ylide **1a′**. **1a**-d_n is proven to be a powerful tool to introduce d_n-alkyl group into various drug skeletons (**2**) to produce compounds (**3**), bearing deuterium atoms at the α-position to heteroatoms on the drug skeletons. Herein, we report an improved preparation method of **1** (Fig. 2b-1, the details are described later) and a one-pot method to provide the deuterated products (**3**) via the deuteration for **1a** to **1a**-d_n and the subsequent nucleophilic substitution of **2** toward **1a**-d_n (Fig. 2b-2). In additionally, the diversification of alkyl sulfonium salts (**1**) was investigated. Consequently, d_n-alkyl thianthrenium salts (**1b**-d_n; >99% D) were effective as electrophilic d_n-alkylating reagents (cation sources) under basic conditions to give the desired products (**3**), bearing deuterium atoms at the α-position to heteroatoms (Fig. 2b-3). Furthermore, **1b**-d_n served as radical sources under photo-induced reaction conditions in the presence of Ir catalyst, Hanztsch ester, or Ph_3N to give the corresponding products, on which the deuterium atoms were regioselectively introduced (Fig. 2b-4). Ni-catalyzed d_n-alkylation has been very recently reported using **1b**-d_n with 97% D,[9] prepared from the corresponding hydrogen form with K_2CO_3 in D_2O/CH_3CN similar to our previous literature[8] (Fig. 2c). **1b**-d_n was adapted to the radical reaction under the photo-induced reaction conditions or thermal conditions; however, there are no examples of the use of **1b**-d_n as a cation source and radical source without transition metal catalysts. Because some transition metals are scarce and expansive, the development of transition metal-free d_n-alkylation method is important from the view point of sustainability and industrial synthesis.

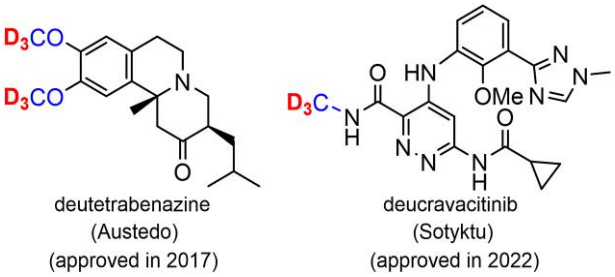


Fig. 1. Deuterated drugs.

2. Results and discussion

Alkyl sulfonium salts **1** were directly prepared from the corresponding alkyl iodides in the presence of silver reagents (Fig. 3a-I).[8,10] Alternatively, various analogs of **1** could be constructed from the corresponding highly accessible alcohols in a stepwise manner via the activation of a hydroxy group (trifluoromethylsulfonylation in the presence of trifluoromethanesulfonic anhydride [Tf_2O] and pyridine (Fig. 3a-II)[8,9,11–13] or formylation using HCO_2Et with $Bi(OTf)_3$ (Fig. 3a-III)).[13] First, an improved one-pot method for preparing alkyl sulfonium salt (**1aa**) from phenethyl alcohol **4a** as the model substrate was investigated (Fig. 3b-1). After the construction of triflate intermediate **A** using Tf_2O and 2,6-lutidine, the addition of diphenyl sulfide (**DS**) did not give the desired alkyl sulfonium salt (**1aa**), and *N*-phenethyl lutidinium salt (**5**) was detected. Probably, the nucleophilic attacks of 2,6-lutidine or **DS** on **A** were competed

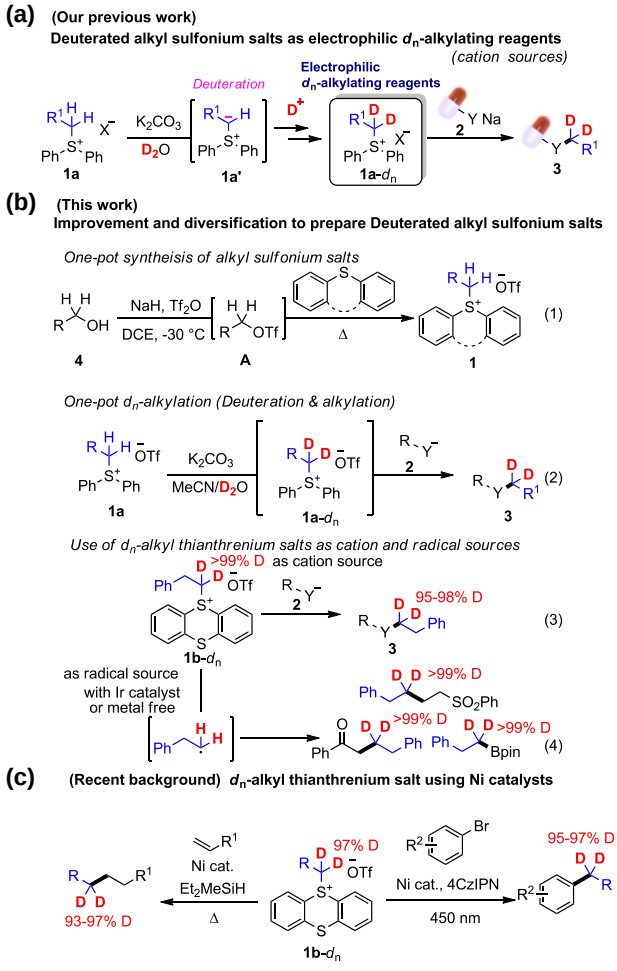


Fig. 2. d_n-Alkylating reagents. DCE, 1,2-dichloroethane; 4CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene.

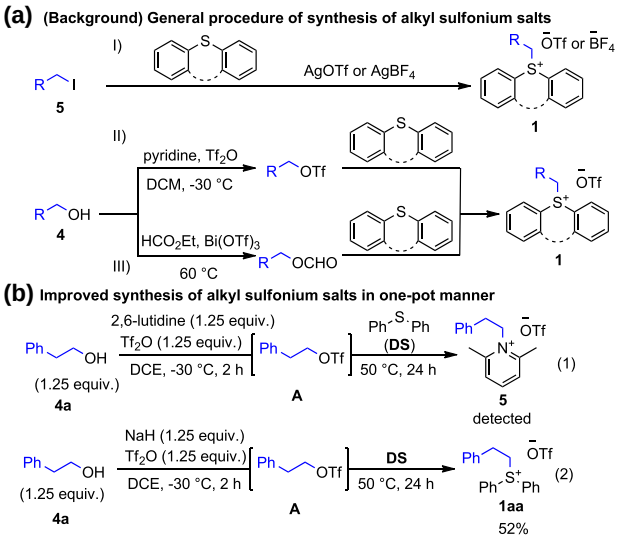


Fig. 3. One-pot synthesis of alkyl sulfonium salts from alcohol. DCE, 1,2-dichloroethane; Tf_2O, trifluoromethanesulfonic anhydride.

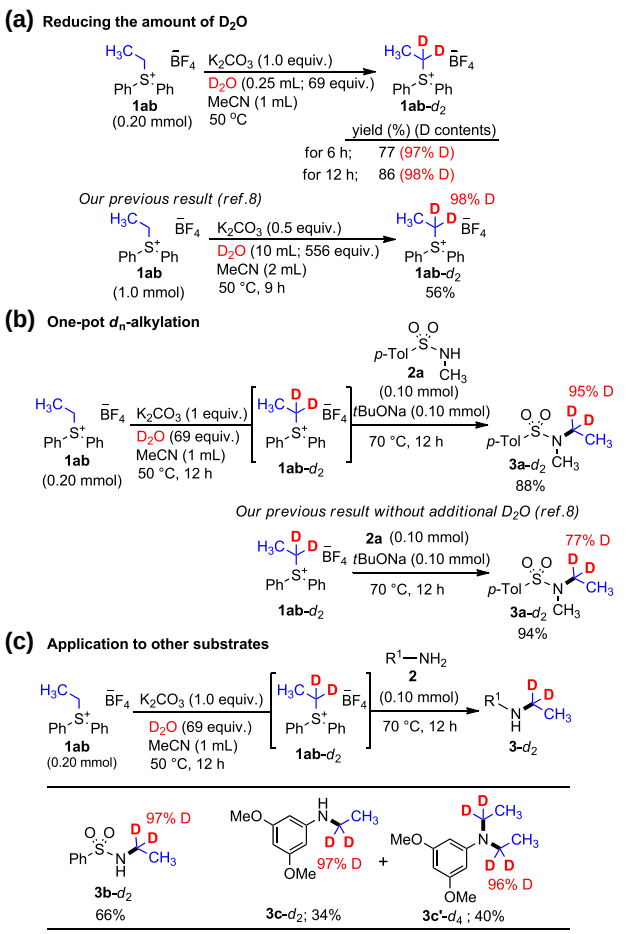


Fig. 4. One-pot d_n-alkylation (deuteration and alkylation). *p*-Tol, *para*-tolyl.

to give the undesired product. When NaH was used instead of 2,6-lutidine, the phenethyl sulfonium salt (**1aa**) was produced in 52% yield (Fig. 3b-2).

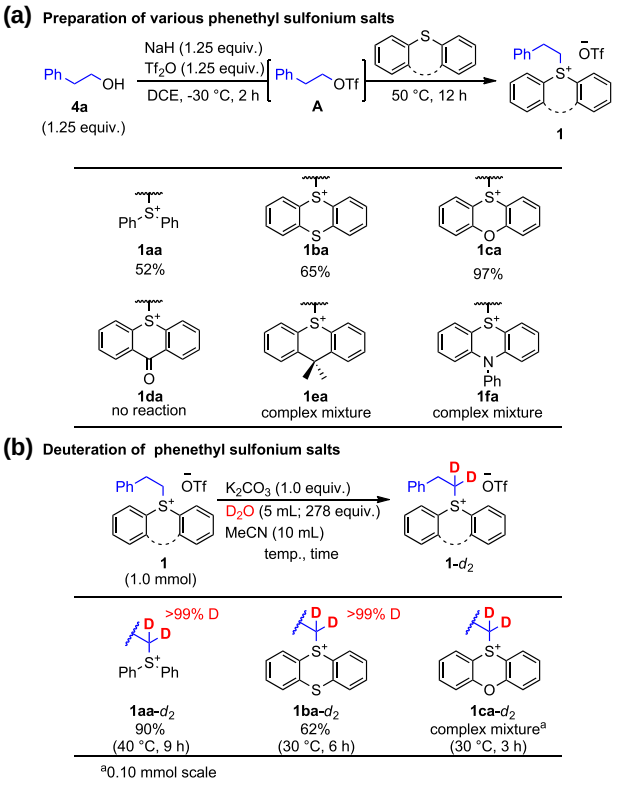
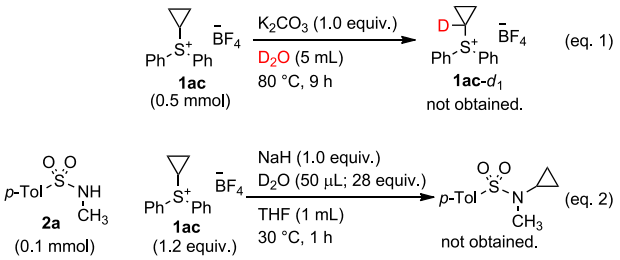


Fig. 5. The diversification of phenethyl sulfonium salts.

Next, the deuteration step was improved by using ethyl diphenylsulfonium salt (**1ab**) as the model substrate (Fig. 4). In a previous study,[8] excess D_2O (556 equiv.) for **1ab** was used in CH_3CN with K_2CO_3 to give the deuterated product (**1ab**-d_2) in 56% yield and 98% D (Fig. 4a-bottom), and the use of D_2O was not optimized. The reduction in the amount of D_2O to 69 equiv. provided sufficient D content (97% D at 6 h, 98% D at 12 h; Fig. 4a-upper). Next, the one-pot method involving the deuteration of **1ab** to **1ab**-d_2 and subsequent nucleophilic substitution using *N*-methyl-*p*-toluenesulfonamide (**2a**) in the presence of *t*BuONa was investigated (Fig. 4b). Consequently, the desired product (**3a**-d_2), bearing two deuterium atoms at the α-position of the nitrogen atom with high D contents (95% D), was obtained. In our previous stepwise method,[8] the latter nucleophilic substitution step without additional D_2O caused the loss of D contents to give **3a**-d_2 with 77% D. The present one-pot method is useful from the viewpoints of simplicity, ease of handling, and low cost when smaller amounts of D_2O are used. Mono-d_2-ethylation of phenylsulfonamide was also accomplished in a one-pot manner, and the d_2-ethylation of 3,5-dimethoxyaniline provided a mono-d_2-ethylated product (**3c**-d_2; 34% yield) and a di-d_2-ethylated product (**3c′**-d_4; 40% yield) with 97% D and 96% D (Fig. 4c). Although this one-pot operation could provide sufficient and high D contents, further improvement to achieve the perfect D contents will be required for drug discovery to demand the high purity of D contents. Further improvements are ongoing in our laboratory.

The deuteration of the cyclopropyl diphenylsulfonium salt (**1ac**), as a secondary alkyl sulfonium salt, using K_2CO_3 in D_2O gave no desired product, unfortunately (eq. 1). Furthermore, the alkylation of **2a** with **1ac** (hydrogen form) did not proceed at all due to the steric hindrance (eq. 2).



The diversification of the skeleton of the sulfonium salts (**1**) and the deuteration of **1** were investigated (Fig. 5). One-pot phenethylation using **4a** was accomplished using diphenyl sulfide as well as thianthrene (**TT**) and phenoxathiine to give the corresponding phenethylated sulfonium salts (**1aa**, **1ba**, and **1ca**; Fig. 5a). However, the addition of thioxanthone did not result in phenethylation due to the less nucleophilicity of the sulfur atom on thioxanthone bearing the electron-withdrawing carbonyl group. Furthermore, the reactions using 9,9-dimethylthioxanthen or 10-phenyl-10*H*-phenothiazine gave a complex mixture. Deuteration of **1aa** and **1ba** in the presence of K_2CO_3 and D_2O (278 equiv.) in MeCN provided the desired deuterated products (**1aa**-d_2 and **1ba**-d_2) with excellent D contents (>99% D) (Fig. 5b). However, the deuteration of **1ca** resulted in a complex mixture, due to generation of *O*-alkyl phenoxathiinium salt, and **1ca**-d_2 was not obtained.

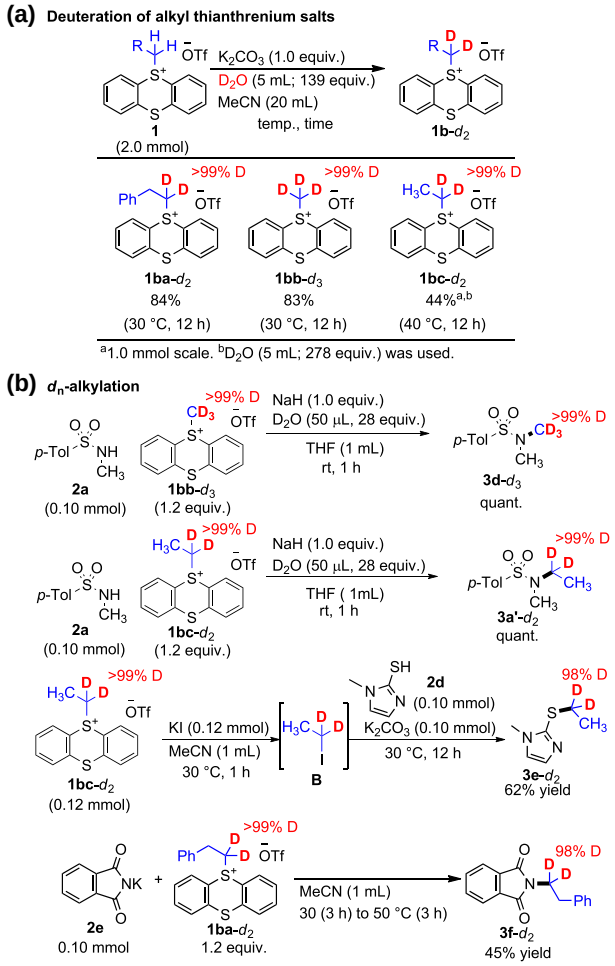


Fig. 6. Substrate scopes of deuteration using d_n-alkylated thianthrenium salts.

Deuteration of phenethyl thianthrenium salts efficiently proceeded even when the amount of D_2O decreased from 278 equiv. to 139 equiv. (**1ba**-d_2; Fig. 5b vs. Fig. 6a). d_3-Methyl and d_2-ethyl thianthrenium salts (**1bb**-d_3 and **1bc**-d_2) were obtained using D_2O (139 equiv. or 278 equiv.) from the corresponding thianthrenium salts with >99% D (Fig. 6a; methyl and ethyl thianthrenium salts were prepared from commercially available MeOTf (Fig. 3a-II method) or EtOH/NaH/Tf_2O (Fig. 3b-2 method), respectively). d_n-Alkyl thianthrenium salts (**1ba**-d_2, **1bb**-d_3, and **1bc**-d_2) were also used as electrophilic d_n-alkylating reagents (Fig. 6b). In our previous study,[8] we revealed that the absence of D_2O in the d_n-alkylation step caused a loss of D contents in the products (see Fig. 4b), and the preliminary transformation of d_n-alkylated sulfonium salts using KI to the corresponding iodides could suppress the loss of D contents. d_3-Methylation of **2a** using **1bb**-d_3 and d_2-ethylation of **2a** using **1bc**-d_2 proceeded efficiently in the presence of additional D_2O (28 equiv.) to obtain the desired deuterated products (**3d**-d_3 and **3a′**-d_2) with >99% D. Furthermore, the in situ formation of d_2-ethyl iodide (**B**) from **1bc**-d_2 and KI and subsequent nucleophilic substitution of thiamazole (**2d**) to **B** in the presence of K_2CO_3 gave **3e**-d_2 with 98% D. d_2-Phenethylation of potassium phthalimide (**2e**) using **1ba**-d_2 was also accomplished to give **3f**-d_2 with 98% D. In this reaction, additional D_2O was not required, because substrate **4c** has no acidic protons to cause the loss of D contents.

Finally, the proposed radical pathway for d_2-phenethylation using **1ba**-d_2 was tested, because alkyl or aryl thianthrenium salts were well-known to be adapted in the photo-induced reactions (Fig. 7).[12–15] **1ba**-d_2 reacted with vinyl sulfone (**6a**) in the presence of Ir catalyst and Hantzsch ester (HE) under 456 nm LED irradiation, and

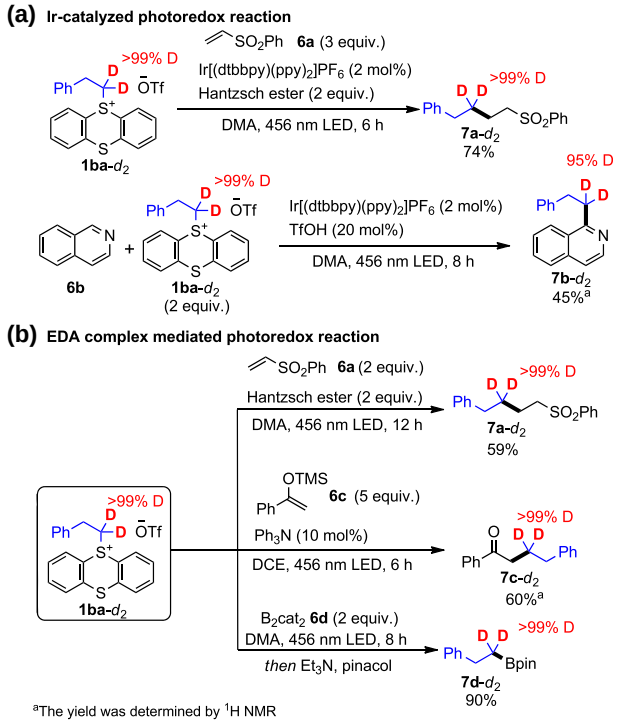


Fig. 7. Applications for photo-induced reactions using 1-d_2-phenethyl thianthrenium salts. EDA complex, electron–donor–acceptor complex; dtbbpy, 4,4′-di-*tert*-butyl-2,2′-bipyridine; ppy, 2,2′-bipyridyl; TfOH, trifluoromethanesulfonic acid; cat, catechol.

Giese reaction product (**7a**-d_2) was obtained in 74% yield without any loss of D contents (>99% D) (Fig. 7a).[13] Isoquinoline (**6b**) underwent Minisci reaction using **1ba**-d_2 to give d_2-phenethyl compound (**7b**-d_2) with 95% D.[13] Metal-free d_2-phenethylation was also adapted using **1ba**-d_2 (Fig. 7b). The electron–donor–acceptor (EDA) complex was formed from **1ba**-d_2 and HE,[14] and reacted with **6a** to provide **7a**-d_2 with >99% D. **1ba**-d_2 was also converted to the EDA complex with Ph_3N to give β-deuterated ketone (**7c**-d_2) in 60% yield (UV–vis analysis is described in the supporting information (Supplementary Fig. S1)).[15] Furthermore, boronic ester (**7d**-d_2) with >99% D was obtained via the EDA complex of **1ba**-d_2 and **6d**.[13]

3. Conclusion

We established an improved preparation method for alkyl sulfonium salts (**1**) from accessible alcohols (**4**), and a simple one-pot method to provide d_n-alkyl compounds from **1a** via deuteration with D_2O as an inexpensive deuterium source and subsequent nucleophilic substitution. By screening the effect of sulfonium salt skeletons, alkyl diphenyl sulfonium salts (**1a**) and alkyl thiantrenium salts (**1b**) were found to be suitable d_n-alkylating reagents. Furthermore, we succeeded in using alkyl thiantrenium salts (**1b**) as radical sources for photo-induced reactions. Notably, the regioselective introduction of deuterium atoms with excellent D contents was accomplished in every reaction. We believe that the present discovery of deuterium science will contribute to the advancement of various scientific fields, such as medicine, biology, chemistry, and so on.

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Supplementary data

Supplementary material is available at *Bulletin of the Chemical Society of Japan* online.

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Conflict of interest statement. None declared.

Data availability

Experimental procedures and spectroscopic data are available in Supporting Information.

References

1a. Recent selected reviews about the utilizations of deuterium-incorporated compounds, see: R. Ogasahara, K. Ban, M. Mae, S. Akai, Y. Sawama, *ChemMedChem* **2024**, *19*, e202400201. https://doi.org/10.1002/cmdc.202400201
1b. R. M. C. Di Martino, B. D. Maxwell, T. Pirali, *Nat. Rev. Drug Discov.* **2023**, *22*, 562. https://doi.org/10.1038/s41573-023-00703-8
1c. E. S. Roig, H. M. De Feyter, T. W. Nixon, L. Ruhm, A. V. Nikulin, K. Scheffler, N. I. Avdievich, A. Henning, R. A. de Graaf, *Magn. Reason. Med* **2023**, *89*, 29. https://doi.org/10.1002/mrm.29439
1d. K. Dodo, K. Fujita, M. Sodeoka, *J. Am. Chem. Soc.* **2022**, *144*, 19651. https://doi.org/10.1021/jacs.2c05359
1e. S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge, M. Beller, *Chem. Rev.* **2022**, *122*, 6634. https://doi.org/10.1021/acs.chemrev.1c00795
1f. E. Takeo, E. Fukusaki, S. Shimma, *Anal. Chem.* **2020**, *92*, 12379. https://doi.org/10.1021/acs.analchem.0c02106
1g. J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758. https://doi.org/10.1002/anie.201704146
2. S. Scheiner, M. Čuma, *J. Am. Chem. Soc.* **1996**, *118*, 1511. https://doi.org/10.1021/ja9530376
3a. Reviews about KIE, see: R. D. Jansen-Van Vuuren, L. Jedlovčnik, J. Košmrlj, T. E. Massey, V. Derdau, *ACS Omega* **2022**, *7*, 41840. https://doi.org/10.1021/acsomega.2c04160
3b. R. P. Bell, *Chem. Soc. Rev.* **1974**, *3*, 513. https://doi.org/10.1039/cs9740300513
3c. K. B. Wiberg, *Chem. Rev.* **1955**, *55*, 713. https://doi.org/10.1021/cr50004a004
4. A. Mullard, *Nat. Rev. Drug Discov.* **2022**, *21*, 623. https://doi.org/10.1038/d41573-022-00139-6
5. S. M. Paek, *Molecules* **2020**, *25*, 1175. https://doi.org/10.3390/molecules25051175
6. D. S. Treitler, M. C. Soumeillant, E. M. Simmons, D. Lin, B. Inankur, A. J. Rogers, M. Dummeldinger, S. Kolotuchin, C. Chan, J. Li, A. Freitag, F. Lora Gonzalez, M. J. Smith, C. Sfouggatakis, J. Wang, T. Benkovics, J. Deerberg, J. H. Simpson, K. Chen, S. Tymonko, *Org. Process Res. Dev.* **2022**, *26*, 1202. https://doi.org/10.1021/acs.oprd.1c00468
7a. H. Sun, D. W. Piotrowski, S. T. M. Orr, J. S. Warmus, A. C. Wolford, S. B. Coffey, K. Futatsugi, Y. Zhang, A. D. N. Vaz, *PLoS One* **2018**, *13*, e0206279. https://doi.org/10.1371/journal.pone.0206279
7b. G. Xia, R. Benmohamed, R. I. Morimoto, D. R. Kirsch, R. B. Silverman, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5098. https://doi.org/10.1016/j.bmcl.2014.08.066
8. K. Ban, K. Imai, S. Oyama, J. Tokunaga, Y. Ikeda, H. Uchiyama, K. Kadota, Y. Tozuka, S. Akai, Y. Sawama, *Angew. Chem. Int. Ed.* **2023**, *62*, e202311058. https://doi.org/10.1002/anie.202311058
9a. M. Jiao, J. Zhang, M. Wang, H. Lu, Z. Shi, *Nat. Commun.* **2024**, *15*, 5067. https://doi.org/10.1038/s41467-024-48590-w
9b. J. Zhang, M. Jiao, Z. Lu, H. Lu, M. Wang, Z. Shi, *Angew. Chem. Int. Ed.* **2024**, *63*, e202409862. https://doi.org/10.1002/anie.202409862
10. B. Altundas, C. V. S. Kumar, F. Fleming, *ACS Omega* **2020**, *5*, 13384. https://doi.org/10.1021/acsomega.0c01586
11. L.-Z. Qin, M.-Y. Wu, X. Yuan, H. Sun, X. Duan, J.-K. Qiu, K. Guo, *Cell Rep. Phys. Sci.* **2024**, *5*, 101843. https://doi.org/10.1016/j.xcrp.2024.101843
12. F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223. https://doi.org/10.1038/s41586-019-0982-0
13. C. Chen, Z.-J. Wang, H. Lu, Y. Zhao, Z. Shi, *Nat. Commun.* **2021**, *12*, 4526. https://doi.org/10.1038/s41467-021-24716-2
14. X. Li, W. Si, Z. Liu, H. Qian, T. Wang, S. Leng, J. Sun, Y. Jiao, X. Zhang, *Org. Lett.* **2022**, *24*, 4070. https://doi.org/10.1021/acs.orglett.2c01525
15. A. Dewanji, L. Dalsen, J. A. Rossi-Ashton, E. Gasson, G. E. M. Crisenza D, J. Procter, *Nat. Chem.* **2023**, *15*, 43. https://doi.org/10.1038/s41557-022-01092-y