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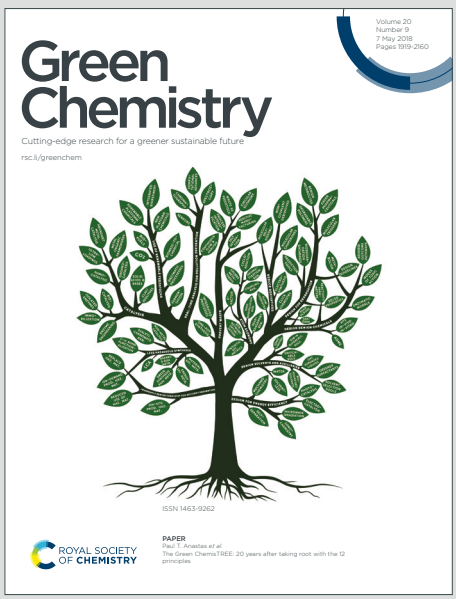

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A mild, general, metal-free method for site-specific deuteration induced by visible light using D_2O as source

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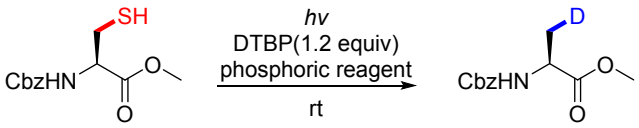
A radical deuteration procedure using D_2O as the source of deuterium atoms is strongly preferred in term of mildness, sustainability, and cost. Herein, we disclose a radical approach for site-specific, highly efficient and metal-free deuteration using D_2O under visible light condition. This desulfurization-deuteration strategy features mild conditions, broad substrate scope, highly efficient D-incorporation, excellent functional group compatibility, sustainable energy and is hardly affected by substrate steric factors.

Deuteration as a labeling technique has long been regarded as an important tool, [1-10] not only in mechanism investigations, but also in drug discovery and development. Deutetrabenazine, [11] the first deuterated drug approved by FDA in 2017, has significantly stimulated the development of synthetic methods for deuteration. [12-24] To date, reported labeling approaches mainly include dehalogenative deuteration, [12-15] deoxygenative deuteration, [16,17] and hydrogen/deuterium isotope exchange.[18-24] However, most methods developed rely on the use of transition metal or have limited substrate scope. As recently pointed out by Philippe Renaud[13], developing a radical procedure using D_2O as a source of deuterium atoms[25-31] represents by far the most appealing procedure in term of mildness (functional group tolerance), sustainability, and cost. Herein, we disclose a radical approach for site-specific, highly efficient and metal-free deuteration using D_2O based on the desulfurization-deuteration strategy under very mild conditions.

Our research was initially inspired by the work of Hoffmann and Walling[32-34]. We began our study by using cysteine **1a** as the model substrate and examined different conditions under visible light at room temperature. We found that the combination of DTBP (Di-*tert*-butyl peroxide) and PPh_3 worked smoothly in mixed solvent DCM/D_2O and gave the desired product in 91% yield with 95% D-incorporation (Table 1, entry 1). The deuteration ratio was further improved to 96% with Ph_2POEt (Table 1, entry 2). The reaction also worked well in EtOAc/D_2O with 94% yield and 95% D-incorporation (Table 1, entry 3). However, $P(OEt)_3$ didn't work probably due to the liability to hydrolysis (Table 1, entry 4). When the reactions were carried out in CD_3OD, the deuteration ratio was only 64% (Table 1, entry 5). With other deuterated solvents, such as D_6-DMSO and $CDCl_3$, the deuteration hardly took place (Table 1, entry 6 and 7). The control experiments suggested that desulfurization-deuteration didn't occur in the absence of phosphoric reagent, DTBP, or visible light (Table 1, entry 8-10).

Table 1. Optimization of reaction conditions for the deuteration[a].



1a **2a**

entry	phosphoric reagent	solvent	Yield (%)[b]	D-incorp. (%)[c]
1	2.0 eq PPh_3	DCM/D_2O	91	95
2	2.0 eq Ph_2POEt	DCM/D_2O	96	96
3	2.0 eq Ph_2POEt	EtOAc/D_2O	94	96
4	2.0 eq $P(OEt)_3$	DCM/D_2O	N.D.	—
5	2.0 eq Ph_2POEt	CD_3OD	93	64
6	2.0 eq Ph_2POEt	D_6-DMSO	95	N.D.
7	2.0 eq Ph_2POEt	$CDCl_3$	91	N.D.
8	—	DCM/D_2O	N.D.	—
9[d]	2.0 eq Ph_2POEt	DCM/D_2O	N.D.	—
10[e]	2.0 eq Ph_2POEt	DCM/D_2O	N.D.	—

[a]Standard conditions: **1a** (0.75 mmol), DTBP (0.90 mmol), phosphoric reagent (0.90 mmol), solvent (6 ml), 36 W household CFL bulb irradiation on two sides, 10 h. [b]Yield of the isolated product. [c]Deuterium incorporation was determined by ^1H NMR spectroscopy. [d]Without DTBP. [e]Without visible light. N.D. = not detected. DCM = dichloromethane. DTBP = di-*tert*-butyl peroxide.

The generality and robustness of this method was challenged with different substrates. Various functional groups could be

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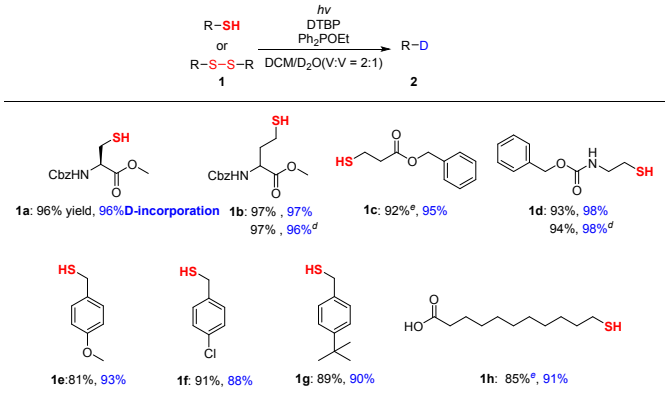
tolerated under this mild condition and all tested compounds gave excellent deuteration, such as carbamate (79% - 97% yield, 96% - 99% D-incorporation, Table 2, substrate **1a**, **1b**, **1d**, **1D**, **1E**), ester (79% - 97% yield, 94% - 99% D-incorporation, Table 2, substrate **1a**, **1b, 1c**, **1i**, **1j, 1n, 1s, 1w, 1x, 1y, 1B, 1D, 1E**), aromatic ring (73% - 91% yield, 88% - 95% D-incorporation, Table 2, substrate **1e, 1f, 1g, 1l**), benzyl group (92% - 93% yield, 95% - 98% D-incorporation, Table 2, substrate **1c, 1d**), ether (81% - 95% yield, 93% - 94% D-incorporation, Table 2, substrate **1e, 1k, 1F**), ketone (95% yield, 97% D-incorporation, Table 2, substrate **1z**), alkene (97% yield, 90% D-incorporation, Table 2, substrate **1u**), free hydroxy group (90% - 92% yield, 91% - 94% D-incorporation, Table 2, substrate **1q, 1v**), free acid group (85% - 97% yield, 91% - 96% D-incorporation, Table 2, substrate **1h, 1o, 1r, 1G**), free amino group (>95 yield, 98% - 99% D-incorporation, Table 2, substrate **1H, 1I**), sodium sulfonate (75% yield, 96% D-incorporation, Table 2, substrate **1p**), sugar moiety (96% yield, 96% D-incorporation, Table 2, substrate **1s**), etc. As for substrate **1r**, the desulfurization and subsequent ring-opening reaction occurred and the deuteration happened at the β position of the alkene (97% yield, 94% D-incorporation), thus suggesting a radical process. Secondary thiols worked well (90% - 97% yield, 94% - 99% D-incorporation, Table 2, substrate **1s - 1x**). The high efficiency of this radical protocol was hardly affected by steric factors. Even strongly hindered tertiary thiols worked smoothly at room temperature and afforded the corresponding products in excellent yields (89% - 95%) and excellent D-incorporation (89% - 97%) (Table 2, substrate **1y, 1z, 1A**). This mild and metal-free condition was especially useful for the deuteration of drugs. In this context we tested Captopril (**1m**), Mesna (**1p**), 3-Azetidinethiol (**1t**), and Thiocholesterol (**1u**), and all of these commercial drugs were highly efficiently deuterated (75% - 97% yield, 90% - 96% D-incorporation).

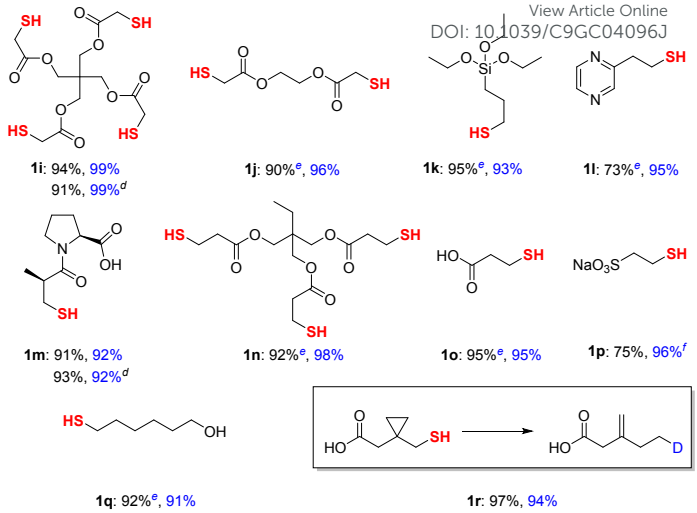
It should be noted that disulfides also worked well with good to excellent yields under this mild condition (81% - 92% yield, 94% - 99% D-incorporation, Table 2, substrate **1B - 1G),** and different functionalities could be tolerated.

Table 2. Substrates scope for desulfurization-deuteration reactions. [a, b, c]



1a: 96% yield, 96%**D-incorporation** **1b**: 97% , 97%, 97% , 96%[d] **1c**: 92%[e], 95% **1d**: 93%, 98%, 94%, 98%[d]

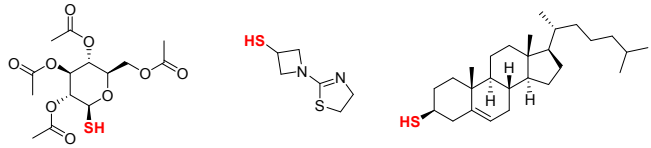
1e:81%, 93% **1f**: 91%, 88% **1g**: 89%, 90% **1h**: 85%[e], 91%



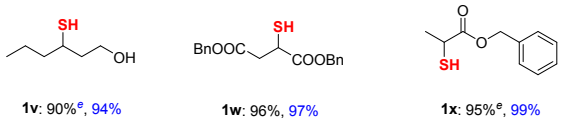
1i: 94%, 99%, 91%, 99%[d] **1j**: 90%[e], 96% **1k**: 95%[e], 93% **1l**: 73%[e], 95%

1m: 91%, 92%, 93%, 92%[d] **1n**: 92%[e], 98% **1o**: 95%[e], 95% **1p**: 75%, 96%[f]

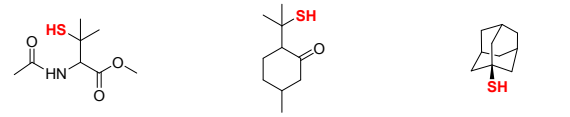
1q: 92%[e], 91% **1r**: 97%, 94%



1s: 96%, 96% **1t**: 94%, 94%, 93%, 94%[d] **1u**: 97%, 90%[g]

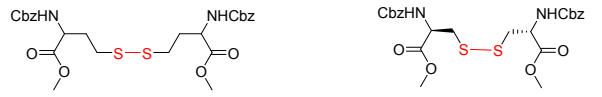


1v: 90%[e], 94% **1w**: 96%, 97%, 95%, 97%[d] **1x**: 95%[e], 99%

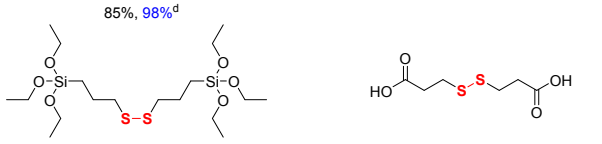


1y: 89%[e], 95% **1z**: 95%, 97% **1A**: 90%, 89%

1B: 81%[e], 95% **1C**: 84%, 99%



1D: 83%, 98%, 85%, 98%[d] **1E**: 79%, 99%



1F: 90%[e], 94% **1G**: 92%[e], 96%

Glu-Cys-Gly (**1H**) (>95% yield, 98%[g] D-incorporation)

Cys-Glu-Gly-Pro-Glu-Val-Asp-Val-Asn-Leu-Pro-Lys (**1I**)(>95% yield, 99%[g] D-incorporation)

Ala-Arg-Gly-Asn-Glu-Ser-Ser-Cys-Met-Asp-Thr-Pro-Thr-Glu-Gly-Cys (**1J**)(>95% yield, 97%[g] D-incorporation)

[a]Reaction conditions: For thiols: substrate (0.75 mmol), DTBP (0.90 mmol), Ph_2POEt (1.50 mmol), DCM/D_2O (2:1, v/v, 6 mL). For disulfides: substrate (0.375 mmol), DTBP (0.90 mmol), Ph_2POEt (1.50 mmol), DCM/D_2O (2:1, v/v, 6 mL). For peptides: cysteinyl peptide (1 mM), TPPTS (30 mM), DTBP (30 mM), TBM (30 mM), D_2O (2 mL). 36 W household CFL bulb irradiation on two sides, 25 °C, 6 h. [b]Yields refer to isolated yields. [c]D-incorporation was based on ^1H NMR. Reactions were carried out in EtOAc/D_2O (2:1, v/v, 6 mL). [e]Yields by ^1H NMR analysis. [f]Reaction was carried out in CD_3OD/D_2O

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(2:1, v/v, 6 mL). [g]D-incorporation was assessed by mass spectrometry. TBM = 2-methylpropane-2-thiol.

Furthermore, we tested a few substrates in EtOAc/D_2O. The reactions also worked well and excellent results were obtained (Table 2, **1b** (97%, 96%)**, 1d** (94%, 98%)**, 1i** (91%, 99%)**, 1m** (93%, 92%)**, 1t** (93%, 94%)**, 1w** (95%, 97%)**, 1D** (85%, 98%)). Thus, EtOAc/D_2O could also be the solvent of choice.

The rich functional group tolerances prompted us to try even challenging substrates. We tested this strategy on glutathione first (Table 2, substrate **1H**). When water-soluble phosphoric reagent such as TPPTS (Triphenylphosphine-3, 3', 3''-trisulfonic acid trisodium salt) was employed instead of Ph_2POEt, this radical deuteration strategy worked smoothly in D_2O and provided the desired product with excellent result (> 95% yield, 98% D-incorporation). When longer peptides such as **1I** and **1J** were used, the reactions also worked well and different functional groups in the peptides didn't affect the deuteration efficiency at all (> 95% yield, 97% - 99% D-incorporation, Table 2, substrate **1I**, **1J**).

We did the scale-up reaction for substrate **1d** to further demonstrate the feasibility of this protocol (Figure 1). The high efficiency was maintained and the product was isolated in 87% yield with 95% D-incorporation on 1.5 gram scale.

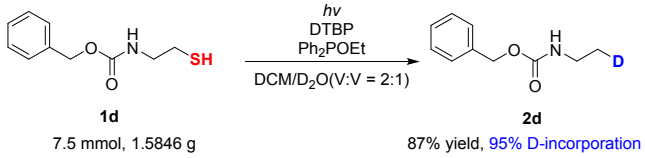

Fig 1. Scale-up reaction of **1d** on gram scale

To gain insight into the mechanism of this reaction, we performed radical-inhibition experiment by the addition of 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO) and EPR experiment using 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as an EPR spin trap to the model reaction (see the Supporting Information for details). Both experiments suggested the possibility of a radical process. Hence, we propose a plausible mechanism described in Figure 2.

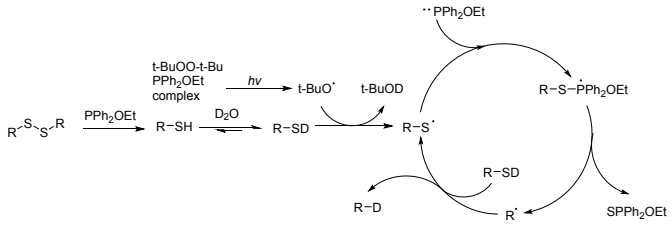

Fig 2. Plausible reaction mechanism of the desulfurization-deuteration reaction

Conclusions

We have developed a mild, general and metal-free desulfurization-deuteration method induced by visible light using D_2O as the source of deuterium atoms. This radical approach features green conditions, robustness, and excellent functionality compatibility. It worked smoothly with primary, secondary and tertiary thiols, thus providing a simple yet reliable and powerful approach for site-specific and highly efficient deuteration.

Conflicts of interest

There are no conflicts to declare.

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