Remote Site-Selective Radical C(sp$^3$)–H Monodeuteration of Amides using D$_2$O

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Abstract: Site-selective incorporation of deuterium into biologically active compounds is of high interest in pharmaceutical industry. We present a mild and environmentally benign metal-free method for the remote selective radical C–H monodeuteration of aliphatic C–H bonds in various amides with inexpensive heavy water (D$_2$O) as the deuterium source. The method uses the easily installed N-allylsulfonyl moiety as an N-radical precursor that generates the remote C-radical via site-selective 1,5- or 1,6-hydrogen atom transfer (HAT). Methyl thioglycolate, that readily exchanges its proton with D$_2$O, serves as the radical deuteration reagent and as a chain-carrier. The highly site-selective monodeuteration has been applied to different types of unactivated sp$^3$–C–H bonds and also to the deuteration of C–H bonds next to heteroatoms. The potential utility of this method is further demonstrated by the site-selective incorporation of deuterium into natural product derivatives and drugs.

Introduction

Deuteration is valuable for organic synthesis,[1] mechanistic investigations[2] and spectrometric/scopic analysis.[3] Considering drug discovery, the biological profile of a given compound can be altered after deuteration, and deuterated analogues of drugs or drug candidates provide a diagnostic tool, addressing the metabolic profile of a drug both in vivo and in vitro.[4] The precise introduction of an isotopic label in a metabolically stable position is essential for the application of deuterium-labelled compounds in vivo, which is of great advantage to anchor the deuterium selectively at a chemically and enzymatically unreactive site to limit degradation during metabolism of the pharmaceutical drug. Because proximal deuterium can be swiftly trimmed by phase I metabolism, for example, oxidation and hydrolysis, a distally labelling position to activate heteroatoms in the molecule is potentially enhancing the metabolic stability of the deuterated compound in vivo.[5] In 2017, the FDA approved the first deuterated drug, deutetrabenazine, a fact that should further motivate organic chemists to develop novel deuteration methods for the efficient synthesis of deuterated drugs and their key building blocks.[6] In these cases, deuteration is preferentially requested at C–H sites that are readily oxidized during metabolism.

In general, selective deuterium-labelling of a pharmaceutical compound requires tedious multistep procedures.[7] Direct hydrogen isotope exchange (HIE) in a given compound at various C–H bonds is challenging but would be highly valuable for late-stage introduction of deuterium.[8] Along these lines, transition metal-catalyzed HIE reactions have been developed for deuteration of aromatic C(sp$^2$)–H bonds.[9] Although, aliphatic C(sp$^3$)-H moieties are highly abundant in organic compounds, the direct selective HIE of aliphatic C–H bonds has not been well investigated. Therefore, a general and practical HIE reaction of C(sp$^3$)–H bonds enabling high D-incorporation ideally site-selectively at activated as well as at unactivated positions is highly desirable for the pharmaceutical industry.[10]

Aliphatic amines and carboxylic acids can be found in many pharmaceutical drugs, in natural products and as bulk chemicals. The selective incorporation of deuterium at a distal unactivated C(sp$^3$)-H site in a complex amine or acid is very challenging, since such compounds generally contain multiple C–H sites where many of them are more activated than their inert aliphatic C–H positions. Deuterated analogues of these amines and acids could serve as important building blocks to construct value-added deuterium-labelled molecules.[11] Furthermore, mono-deuteration is indeed a rarely applied concept in life sciences and the effect of -CHD– groups on oxidative metabolism enzymes is unknown at present. The development of a site-selective mono-deuteration for aliphatic amines and carboxylic acids would provide a valuable tool, targeting the study of metabolic pathways of endogenous substrates and xenobiotics as well as the optimization of pharmacokinetic and pharmacodynamic parameters of drugs.[12]

Applying a directing group strategy, transition metal catalyzed HIE reaction of aliphatic C–H bonds is a common way to access α- and β-deuterated amines and alcohol derivatives.[13] The MacMillan group recently reported an elegant photoredox-catalyzed deuteration at α-amino C(sp$^3$)–H bonds.[13a] However, site-selective mono-deuteration at distal unactivated sites remains challenging using existing methodology.[10,13] The Hoffmann-Löfler-Freytag (HLF) re-
action and variants thereof reliably allow for remote site-selective generation of C-radicals at unactivated sites via 1,5 hydrogen atom transfer (HAT).[14,15] On that basis, our group has recently achieved remote C-H functionalization of unactivated C-H bonds in amides with various sulfones by using the readily installed N-allylsulfonyl moiety as the N-radical precursor.[16,17] Encouraged by these results, we decided to use such N-allylsulfonylamides as substrates in combination with a thiol in the presence of D₂O for remote site-selective radical C-H deuteration.[13a,18] Our reaction design with the underlying suggested mechanism for the remote radical (sp³)⁻H deuteration of N-allylsulfonylamides 1 is depicted in Scheme 1a.

![Scheme 1](image)

A thiol R-SH will quickly exchange its proton by D with D₂O (excess) to give the D-labelled thiol R-SD. Initiation of the radical chain leads to a thyl radical. Such S-centered radicals reversibly add[19] to the terminal double bond of the allylsulfonyl moiety in amide 1 to give the adduct radical A. This secondary radical A then undergoes β-fragmentation to give the allylsulfide 2 along with the amidosulfonyl radical B. After releasing SO₂, the thus generated N-radical C engages in a 1,5-HAT to afford the nucleophilic C-radical D, which is readily reduced by R-SD to afford the deuterated amide 3 and the chain carrying thyl radical. Notably, due to polar effects,[19b] the direct reduction of the electrophilic amidyl radical by the “electrophilic” D-donor R-SD should be slow. Moreover, unwanted addition of the chain carrying thyl radical to the allylsulphide byproduct 2 is a degenerate process that does not lead to any chain termination.[20] By using this strategy, we expected to access three different types of deuterium-labelled compounds, including β-D-primary amines, γ-D-aliphatic acids and α-D-secondary amines from the corresponding readily prepared precursors 1, 4 and 5 (Scheme 1b).

**Results and Discussion**

We started our investigations by using the sulfonamide 1a as the model substrate (Scheme 2). Optimization revealed that reaction is best conducted with methyl thioglycolate 2 as the R-SD precursor (1.1 equiv) and α,α’-azobisobutyronitrile (AIBN) as the radical initiator in CHCl₃/D₂O (v/v 2:1) at elevated temperature to afford the remote deuterated amide 3a with excellent yield (90%) and high level of D-incorporation (95%, as determined by mass spectrometry analysis). Other thiols, such as thiophenol, 2-propanethiol, 1-decanethiol, thiobenzoic acid and triisopropylsilane thiol led to lower yields and lower D-incorporation under the same conditions.

![Scheme 2](image)
conditions (for details on reaction optimization, see the Supporting Information). Replacing CHCl$_3$ by the more expensive CDCl$_3$ did not further improve the D-content.

With the optimized conditions in hand, the substrate scope was investigated. The starting allylsulfonamides 1 were readily prepared from the corresponding amines (see Supporting Information). Different N-protecting groups (PG) were tested first and we found that replacing the benzoyl group by other typical PGs led to lower D-incorporation or yield (see 3a–3f). Methine C–H deuteration worked efficiently for various systems including cyclic congeners to give the products 3g–3m in good to excellent yields (80–92\%) and high level of deuterium incorporation (81–97\%). For all these cases, regioselectivity for deuteration was complete. When the reaction was performed on larger scale, a slight decrease of the yield and D-incorporation was noted (3i). Notably, the deuteration occurred fully site-selectively also for substrates that contain more than one tertiary C–H bond (1g, 1h), documenting the advantage of the intramolecular HAT-strategy.

Along with tertiary C(sp$^3$)–H bonds, the more challenging deuteration of secondary C(sp$^3$)–H bonds was achieved by using this novel method (3n–3y). As expected, yields for deuteration and D-content of the less activated secondary C–H bonds were slightly lower, as compared to the methine deuteration. All these products were isolated with excellent regioselectivity and compounds 3q–3t were formed as mixture of the two diastereoisomers. Due to signal overlap in the NMR, unambiguous determination of the selectivity was not possible. Moreover, the selective monodeuteration of benzylic positions was achieved (3u–3y, 66–77\% yield; 84–94\% D-inc). Substituents, such as Cl, Br, CF$_3$, OMe, in different positions of the aryl group are well tolerated, albeit the 2-chloro substituted congener led to a slightly decreased yield but with comparable D-incorporation (3x, 66\% yield, 91\% D-inc), demonstrating that steric factors play a role. As expected, the Thorpe–Ingold effect improves D-incorporation efficiency (3v–3y).

We next tested deuteration of primary C(sp$^3$)–H bonds, where the intramolecular 1,5-HAT is thermodynamically less favored. Not surprisingly, remote radical deuteration of the non-activated terminal methyl group in 1z occurred in lower yield and lower D-incorporation (3z, 52\% yield; 42\% D-inc). However, sulfonamides 1aa–1ac bearing an activating heteroatom at the γ-position, such as oxygen, sulfur or nitrogen, could be successfully deuterated at the methyl group to afford the deuterated products 3aa–3ac in 67–83\% yields with high levels of deuterium incorporation (86–93\%).

Motivated by the broad scope of our method, we then tested its applicability to the site-selective deuteration of drug derivatives and biologically more relevant compounds starting with primary amines and carboxylic acids (Scheme 3). Introduction of a deuterium atom at the δ-position into amines derived from gemfibrozil (3ad) and menthol (3ae) was achieved in 75–89\% yield with high D-incorporation (89–96\%). For the gemfibrozil-derived substrate 1ad bearing...
a phenoxy substituent, the D-regioisomer formed via a 1.6-HAT was obtained as minor product (regioselectivity = 4:1). A (+)-tocopherol derivative that is conjugated with an 9-amino-nonyl chain via the phenolic O-atom was site-selectively deuterated with a good level of D-incorporation (see 3af). Various amino acid esters derived from natural amino acids could be deuterium-labelled at their side chains via this strategy. Hence, sulfonamides prepared from 2-aminocaproic acid, L-norleucine, pregabalin, L-2-aminoacidic acid, L-lysin and ethionine were converted with excellent yield and high D-incorporation to the corresponding D-derivatives 3ag–3al. For the lysine-derivative 3ak, a small amount of the regiosomeric product derived from a 1.6-HAT was observed. Deuteration occurred (if applicable) non-diastereoselectively for these amino acid esters. An androstanolone-derived steroid could be labelled to give the product in 82 % yield and 93 % D-incorporation as a mixture of the two regiosomers 3am and 3am'. Notably, the benzoyl protecting group could be removed to give D-labelled free amines (see Scheme 1 in Scheme 2 and 3ad in Scheme 3).

We next investigated whether the remote site-selective deuteration also works on acid derivatives. To this end, the amides 4a and 4b were readily prepared by reacting the corresponding acid chlorides with N-methyl allylsulfonamide (see Supporting Information). Pleasively, y-C(sp2)-H HIE reaction could be performed under the above optimized conditions on the steroid derivative 4a carrying multiple stereogenic centers and tertiary C–H bonds to deliver the monodeuterated product 6a as single regioisomer in 48 % yield with high level of deuterium incorporation (91 %, \(dr = 1.5:1\)). An amide derived from gemfibrozil also furnished deuterated products 6b in good yields and high D-incorporation (95 %) as a mixture of two regiosomers (1.2:1).

To further demonstrate the utility of the remote deuteration, we further expanded our method to the site-selective α-deuteration of secondary amines via an auxiliary aided remote HIE strategy. An easily removable β-alanine-based auxiliary was designed for accessing the desired site-selectively deuterated compounds via 1.6-HAT to N-radicals, which are generated from readily prepared N-allylsulfonamides 5 (Scheme 4). Under slightly modified reaction conditions, the targeted deuterium-labelled compounds 7 were obtained in excellent yields and high level of D-incorporation. Hence, pyrrolidine, piperidine, morpholine, thiomorpholine, piperezine, azocane and diethylamine, could be efficiently D-labelled at their α-position via this strategy (7a–7g). In these cases, D-incorporation level was high (>90%). However, deuteration of the 1-phenylpiperazine-derived substrate 5e gave the D-labelled product 7e with moderate 50 % D-incorporation (74 % yield). Further, the L-proline methyl ester 5h and the L-prolyl-L-proline dipeptide ester 5i provided the corresponding α-D-labelled derivatives 7h–7i in 74–93 % yields with 89–94 % deuterium incorporation. Due to signal overlap in the NMR, unambiguous determination of the diastereoselectivity was not possible. Importantly, we also demonstrated that the β-alanine-based auxiliary can be readily removed as documented by the hydrolysis of the D-labelled amide 7f under acidic conditions to give after renewed N-protection the Boc-protected α-D-azocane 8 in 92 % overall yield without compromising D-content (92 %).

Next, we sought to explore the practicality of the site-selective α-deuteration of secondary amines by choosing commercially available drugs (Scheme 5). We found that for biologically active compounds containing the piperazine and piperidine scaffold, such as Piperezine (its citrate salt as anesthetic), Litoxetine (antidepressant) and Paroxetine (antidepressant), the remote site-selective α-deuteration occurred in excellent yields and high level of deuterium incorporation (9–11, 11', 68–97 % yield; 85–91 % D-inc). Determination of the selectivity of the D-labelled Paroxetine derivative was not possible due to signal overlap in the NMR. The novel deuteration protocol was also applicable to acyclic secondary N-methylamine containing drugs, such as Protriptyline (antidepressant) and Fluoxetine (antidepressant). In both cases, HIE occurred efficiently with complete regioselectivity at the N-methyl position in high yield with an excellent degree of deuteration (12–13, 74–97 % yield; 91–92 % D-inc).

We tested whether our optimized reaction conditions are compatible with biomolecules to document the robustness of this transformation.22 Deuteration of 1a (0.2 mmol) to 3a was conducted in the presence of an array of biomolecules, including natural amino acids, nucleic acids, and proteins. We found that upon addition of an unprotected biomolecule (1 equiv), such as L-cysteine, L-lysine, L-serine, L-methionine, guanosine, uridine, naringine, a DNA single strand
The authors declare no conflict of interest.

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