Tetrahedron Letters 58 (2017) 2757–2760

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A selective and cost-effective method for the reductive deuteration of activated alkenes

Hengzhao Li, Bin Zhang, Yanhong Dong, Ting Liu, Yuntong Zhang, Haiyu Nie, Ruoyan Yang, Xiaodong Ma, Yun Ling, Jie An *

College of Science, China Agricultural University, No.2 Yuanmingyuan West Road, Beijing 100193, China

ARTICLE INFO

Article history:
Received 23 April 2017
Revised 29 May 2017
Accepted 31 May 2017
Available online 1 June 2017

Keywords:
Reductive deuteration
Activated alkene
Deuterium-labeled compound
Single electron transfer reaction

ABSTRACT

A new single electron transfer reaction for the reductive deuteration of activated alkenes has been developed for the selective synthesis of α,β-dideuterio compounds. A cheap, stable and commercially-available sodium dispersion with high specific surface area is employed as the electron donor to replace the traditionally used sodium/liquid ammonium system. Deuterium source is provided by EtOD-d_1. Excellent yields and deuterium incorporations were obtained across a broad range of activated alkenes with good functional group tolerance. This method provided a cheap, efficient and operationally-simple method for the synthesis of deuterium labeled compounds.

Deuterium labelled compounds have been broadly employed as metabolic or pharmacokinetic probes,[1] analytical standards in mass spectrometry[2] and powerful tools for mechanistic investigations of organic reactions.[3] While deuterated compounds have been extensively studied in non-clinical settings, recent advances have further focused attention on deuterium substituted medicines, which is reflected by the emergence of new companies working in this field, and the recent entry of several deuterated drugs into clinical trials.[4] Because of the primary kinetic isotope effect, the carbon–deuterium bonds are more stable to chemical or enzymatic cleavage relative to the carbon–hydrogen bonds. Deuterium labelling is therefore expected to improve the half-life and toxicity profiles of medicines[5] and some other bioactive compounds, such as agrochemicals.[6] However, the application of deuterium labelled bioactive compounds is restricted by the limitation of synthetic methodologies and, more importantly, the cost of the deuterated compounds.

Post synthesis H/D-exchange[7] and reductive deuteration[8] mediated by alkali metal deuterides (e.g. $NaBD_4$ and $LiAlD_4$) are the most frequently used methods to introduce deuterium into a compound, which, however, either suffer from low selectivity and harsh reaction conditions (A, Fig. 1), or require expensive reagents. Recently, single electron transfer (SET) reaction became an emerging strategy in reductive deuterations (B, Fig. 1).[9] Previously, our group has reported a SET reaction for the selective synthesis of α,α-dideuterio alcohols.[10]

In order to develop a cost-effective method for the selective synthesis of α,β-dideuterio compounds, herein we report the first reductive deuteration reaction of alkenes mediated by sodium and EtOD-d_1 (D, Fig. 1)

Activated alkenes can be reduced by alkali metals, low-valent transition metal compounds, metal hydrides and organohydride. Electrochemical processes and catalytic hydrogenations are also used for this purpose.[11] Among them, alkali metal/liquid ammonium mediated reaction requires only cheap reagents, and always lead to relatively higher atom economy (C, Fig. 1). However, the use of liquid ammonium has restricted the application of this method. Given that Na/NH_3 is a strong reducing agent, the formation of over-reduced by-products was detected in some cases. Alternatively, in the heterogeneous reaction without liquid ammonium, electron is transferred from the metal surface to the substrate and the radical anion intermediates must diffuse to metal surface before the second electron transfer can occur. Due to the slow rate of the second electron transfer, significant amount of the dimerized by-product formed *via* **5** was always observed[11a] (C, Fig. 1).

The rate of heterogeneous reaction increases with the increasing of surface area of the solid phase. Given that various bench-stable sodium dispersions with very high special surface area have become commercially available, we proposed that a highly efficient deuteration reduction of alkenes can be achieved by using sodium dispersions/ROD-d_1 system in a suitable organic solvent

---

* Corresponding author.
E-mail address: jie_an@cau.edu.cn (J. An).

http://dx.doi.org/10.1016/j.tetlet.2017.05.092

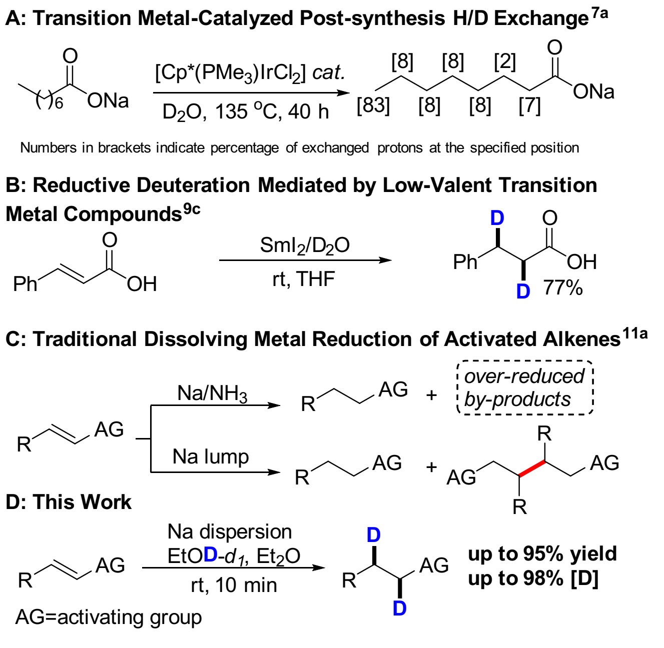


Fig. 1. A) Transition metal-catalyzed H/D exchange. B) Reductive deuteration mediated by low-valent transition metal compounds. C) Traditional dissolving metal reduction of activated alkenes. D) This work: reductive deuteration of activated alkenes mediated by sodium dispersion.

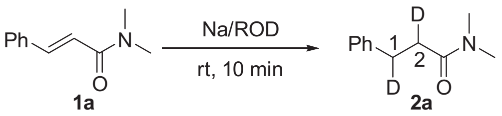
(D, Fig. 1). As this method requires only cheap reagents and is operationally-simple, it compares favorably with other reductive deuteration reactions mediated by metal deuterides,[12] SmI_2/D_2O[9c], and catalytic deuteration reactions.[13]

In this study, sodium dispersion in oil (particle size 5–10 μm, 40 wt%) was employed as the electron-donor as it is a bench-stable and commercially-available reagent which is easy to handle in an open atmosphere.[14] To our delight, the initial trial with sodium dispersions in oil (2.0 equiv) and EtOD-d_1 (2.0 equiv) lead to the formation of **2a** in a promising 58% yield and high deuterium incorporations at both C1 and C2 positions (Table 1, entry 1). The reduction of amide group was not observed. Higher yields were achieved by using more sodium dispersions (Table 1, entries 3 and 4). Increasing the amount of deuterium donor equivalents resulted in a greater degree of D incorporation up to 98% (Table 1, entries 5 and 6). However, excess EtOD-d_1 accelerated the side reaction with sodium and, therefore, led to a lower yield of **2a**. This reaction was significantly influenced by the nature of solvent. The best result was obtained with Et_2O. Different deuterium donors were also screened (Table 1, entries 9–11). The use of *i*-PrOD-d_1 led to a similar result as EtOD-d_1. The reactions with D_2O and CD_3-OD afforded lower yields of **2a**, which may due to the fast side reaction between the deuterium donors and sodium. Given the higher cost of *i*-PrOD-d_1, EtOD-d_1 was considered as a better deuterium donor. As we expected, using sodium lump instead of sodium dispersions led to a significantly lower yield of **2a** (Table 1, entry 12) and the formation of the dimerized by-product was detected.

With the optimal conditions identified (Table 1, entry 4), the scope of this reductive deuteration reaction was examined (Table 2). A broad range of activated alkenes can be successfully employed as substrates for this reductive deuteration reaction to furnish the corresponding dideuterated compounds in good yields and deuterium incorporations[15], including derivatives of cinnamic acid, α,β-unsaturated amides and conjugated alkenes. It is noteworthy that amides, carboxylate acids **2l**, un-activated alkenes **2f**, phenyl ethers **2j** and aromatic rings are stable under the reaction conditions. And a variety of halogens are also compatible, providing synthetic handles for further elaboration (**2g**, **2h** and **2k**). However, chlorine substitution on the *para*-position of the phenyl ring (**2i**) was reduced under the conditions, which was possible formed *via* intermediate **2i'**, albeit the corresponding fluoride **2k** is much more stable. Interestingly, chlorine substitution on the ortho position of the phenyl ring was stable under the tested conditions (**2g**). Furthermore, preliminary results also demonstrated that the reductive deuterations of 1,4-diene and activated alkyne can also be achieved using this method (Table 3), which suggest the potential application of this electron transfer protocol for the selective introduction of deuterium into unsaturated compounds.

A possible mechanism for this transformation is presented in Scheme 1. The dimerized product, formed *via* **5,** was not detected in any of the reactions mediated by sodium dispersions. However, using sodium lump instead of sodium dispersion led to the formation of **5** as the by-product (Table 1, entry 13), which indicated that the specific surface area of sodium metal was crucial to this reaction and the second electron transfer **3** → **4** was possibly the rate determine step of this reaction. A primary kinetic isotope effect

Table 1
Optimization of the Reductive Deuteration Mediated by Na/ROD-d_1.[a]



Entry	Na (eq.)	ROD-d_1 (eq.)	Solvent	Yield [b]	C1 [D][b]	C2 [D][b]
1	2.0	2.0	Et_2O	58%	80%	79%
2	2.0	3.0	Et_2O	56%	86%	93%
3	2.5	3.0	Et_2O	73%	90%	92%
4	*3.0*	*3.0*	*Et_2O*	*87%*	*89%*	*90%*
5	3.0	6.0	Et_2O	51%	91%	96%
6	3.0	9.0	Et_2O	39%	>98%	>98%
7	3.0	3.0	hexane	complicated mixtures		
8	3.0	3.0	THF	31%	75%	76%
9	3.0	CD_3OD 3.0	Et_2O	66%	80%	80%
10	3.0	*i*PrOD-d_1 3.0	Et_2O	91%	87%	90%
11	3.0	D_2O 3.0	Et_2O	38%	81%	80%
12[c]	3.0	3.0	Et_2O	28%	91%	94%

[a] Conditions: **1a** (0.50 mmol, 1.0 equiv), Na dispersions in oil (40 wt%, particle size 5–10 μm), solvent (2.5 mL), rt, 10 min, ROD-d_1 was first added followed by Na dispersion.

[b] Determined by ^1H NMR.

[c] Sodium lump was used instead of sodium dispersions.