Selective oxidation of alcohol-$d_1$ to aldehyde-$d_1$ using MnO$_2$†

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The selective oxidation of alcohol-$d_1$ to prepare aldehyde-$d_1$ was newly developed by means of NaBD$_4$ reduction/activated MnO$_2$ oxidation. Various aldehyde-$d_1$ derivatives including aromatic and unsaturated aldehyde-$d_1$ can be prepared with a high deuterium incorporation ratio (up to 98% D). Halogens (chloride, bromide, and iodide), alkene, alkyne, ester, nitro, and cyano groups in the substrates are tolerated under the mild conditions.

1. Introduction

Deuterium (²H, d) is a stable, non-radioactive, and safe isotope of hydrogen (¹H). Since its discovery,¹ d has been widely utilized in organic chemistry, biochemistry, analytical chemistry, pharmaceutical science, and drug discovery.²,³ Because of the high demand for d-labelled molecules in the scientific research fields, many efforts have been devoted to developing a new method for the synthesis of d-labelled molecules.

Aldehyde-$d_1$ 2 has received significant attention as a synthetic target due to the facts that aldehyde 1 is a useful feedstock in organic synthesis. Various methods have been performed in the synthesis of alkyl and aryl aldehyde-$d_1$. For example, more than 40 syntheses (25 different reaction conditions) of benzaldehyde-$d_1$ (PhCDO) were conducted even since 2018 in the studies to develop new d-incorporation method or reaction mechanism using PhCDO.⁴⁻⁸

The previous synthetic approaches to access d-labelled molecules are classified into 5 types; (A) addition of D⁻ followed by oxidation, (B) carbonyl Umpolung approach, (C) radical reaction, (D) transition metal-catalysed reaction, and (E) others. Recently, mild, one-step, and catalytic syntheses of aldehyde-$d_1$ 2 have been achieved by deuteration of the Breslow intermediates,⁹ deuteration of acyl radicals,¹⁰ and transition metal-catalysed deuterium incorporation.¹¹ However, the previous synthetic methods including the modern direct syntheses often suffered from drawbacks such as over-deuteration, requirements of harsh conditions (high and low temperature, and strong base and acids), and the use of expensive catalysts. Moreover, the synthetic examples of substituted acrolein and propynal-$d_1$ are much less than those of alkyl and aryl aldehyde-$d_1$,¹²,¹³ though recently developed NHC-catalysed H–D exchange reactions allowed access to various substituted acrolein-$d_1$ derivatives.⁹ In this context, development of a new d-incorporation method which allows flexible synthesis of aromatic and unsaturated aldehyde-$d_1$ 2 remains to be a challenging synthetic task (Scheme 1).

Method A using D⁻ as a deuterium source has been recognized as a robust and conventional synthetic method to prepare aldehyde-$d_1$ 2 (Scheme 2). The synthesis is typically performed

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in two steps: (i) reduction of carboxylic acid derivatives using LiAlD4 to provide alcohol-d1, 3 and (ii) oxidation to aldehyde-d1 using activated MnO2 (eqn (1)).14 In this approach, the deuterium incorporation ratio (%D) of the commercially available D sources such as LiAlD4 (>98 atom) is reliably transferred into the product. On the other hand, the use of highly reactive LiAlD4 often limits the synthetic scope. Under the conditions, various functional groups such as nitro, nitrile, ester, and acid moieties, and alkene and alkyne with electron-withdrawing group (s) are not tolerated. To overcome the limitation, we emerged selective oxidation of alcohol-d1, 4 (Scheme 2 (eqn (2))). It is expected that various alcohol-d1, 4 can be prepared by the mild NaBD4 reduction. The next selective oxidation of D (H/D selectivity) is the key to this approach. Recently, oxidation of benzyl alcohol-d1 (PhCDHOD) with PCC or PDC was conducted to prepare PhCDO with ~85% D.3,15,16,17 On the other hand, further efforts to improve the selectivity (%D) in the selective oxidation have not been well-examined. Herein, we would like to report that NaBD4 reduction followed by activated MnO2 oxidation (NaBD4/MnO2 system). The simple and mild protocol allows expansion of the synthetic range of aldehyde-d1, 2 including not only aromatic aldehyde-d1 derivatives but also substituted acrolein-d1 and propynal-d1 derivatives with high %D (up to 98%).

2. Results and discussion

In a similar manner to the previous synthetic examples of NaBH4 reduction of aldehyde 1, the reduction with NaBD4 gave the corresponding alcohol-d1, 4 with excellent functional group compatibility and yields (Scheme 3). Chloride, bromide, iodide, methoxy, ethoxy, or methylene acetal, nitrite, ester, nitro, and alkene groups on the aromatic ring of 4c–4q were tolerated under the conditions. Substituted acrolein and propynal tr–1aa also underwent smooth NaBD4 reduction to provide 4r–4aa without loss of the alkene and alkyn moiety, and tetrahydropyanyl (THP), benzoyl (Bz), and tert-butyldimethylsilyl (TBS) protecting groups.

We next examined the key oxidation of alcohol-d1, 4 using 4-phenylbenzyl alcohol-d1 (4a) (Table 1). As a result, activated MnO2 was found to be superior to other general oxidation reagents [entry 1, Table 1]. Treatment of 4a with 23 eq. of MnO2 in CH2Cl2 gave aldehyde-d1, 2a with 92% D in 2 h. The use of pyridinium dichlorochromate (PDC) gave 2a in good selectivity (88% D).18 However, the isolate yield was moderate (entry 2). Dess–Martin periodinane oxidation, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) oxidation in the presence of PhI(OAc)2, and Parikh–Doering oxidation (sulfur trioxide–pyridine complex in dimethyl sulfoxide (DMSO)) resulted in lower selectivities (74, 76 and 66%D, entries 3–5).

Activated MnO2 oxidation was successfully expanded to the synthesis of various aldehyde-d1, 2a–2aa with high %D (85–96% D) (Scheme 4A–C). Chloride, bromide, iodide, methoxy, ethoxy, or methylene acetal, nitrite, ester, nitro, and alkene groups on the aromatic ring of 4c–4q are preserved under the mild oxidation conditions (Scheme 4A). Substituted acrolein 4r–4v and propynal 4w–4aa smoothly underwent MnO2 oxidation to provide 2r–2aa without loss of the alkene and alkyn moiety (Scheme 4B and C). The synthetic utility was further demonstrated by the synthesis of 2v with a bromo group at the α-position of cinnamaldehyde. In addition, Bz, THP, and TBS protecting groups of 4y, 4z, and 4aa were also maintained under the conditions. These propargyl alcohols 4y, 4z, and 4aa were smoothly converted to the corresponding propynal derivatives 2y, 2z, and 2aa with high %D, respectively.

In conjunction with our recent efforts toward elucidation of biosynthetic reaction mechanisms of terpene synthases using d-labelled prenols,15,16 we needed geranylgeraniol-d3 (6) as an enzyme substrate. Previously, the synthesis of 6 (ref. 17) and other acyclic prenol-d3 derivatives18 was performed in four steps from 5 via reduction of ester 7 with LiAlD4. However, commercially available LiAlD4 is almost out of stock in recent years. In addition, low temperature conditions (−20 °C) is required for the LiAlD4 reduction to avoid the undesired 1,4-reduction. We
expected that NaBD₄/MnO₂ system would be an alternative to the LiAlD₄ procedure to prepare 6, conveniently. According to the literature, geranylgeraniol (5) was converted to aldehyde 8 by MnO₂ oxidation (Scheme 5). Aldehyde 8 was subjected to NaBD₄/MnO₂ to deliver d-enriched aldehyde 9 which was subsequently reduced by NaBD₄ to provide geranylgeraniol-d₂ (6) in 70% yield over four steps with satisfactory deuterium incorporation ratio (94% D). Under the conditions, the undesired 1,4-addition reaction was not observed. Thus, an

| Entry | Conditions | Yield¹ (%) | %D² |
|-------|------------|------------|-----|
| 1     | MnO₂ (23 eq.), 1 h | 92 | 92 |
| 2     | PDC (1.2 eq.), MS4A, 2 h | 51 | 88 |
| 3     | Dess–Martin periodinane (1.5 eq.), 5 min | 84 | 74 |
| 4     | TEMPO (0.01 eq.), Bu₄NHSO₄ (0.05 eq.), NaOCl (1.2 eq.), 1 h | 96 | 76 |
| 5     | DMSO (10 eq.), SO₃–pyridine (4 eq.), iPr₂NEt (5 eq.), 1.5 h | 75 | 66 |

¹ 0.5 mmol scale. ² Isolated yield. ³ %D for 2a is calculated based on the integration ratios of aldehyde and aromatic proton. MnO₂ = activated manganese dioxide, PDC = pyridinium dichlorochromate, MS4A = molecular sieves 4A, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl, DMSO = dimethyl sulfoxide.

Scheme 4  MnO₂ oxidation of alcohol-d₁ 4. (A) synthetic examples of aromatic aldehyde-d₁ 2, (B) synthetic examples of substituted acrolein-d₁ 2, and (C) synthetic examples of substituted propynal-d₁ 2. ² 2 h, ⁶ 6 h, ¹² 12 h.
3. Conclusions

We have established a facile synthesis of aldehyde-\textit{d}_{4} derivatives by NaBD_{4}/MnO_{2} system. The new method is characterized by a high degree of functional group compatibility and a wide range of substrate scope including the synthesis of \textit{d}-containing unsaturated aldehydes. Aromatic aldehyde-\textit{d}_{4} derivatives such as \textit{2c} and \textit{2g} would be a useful synthetic intermediate for olefination,amination, hydride reduction, Suzuki cross coupling, and Sonogashira coupling reactions.\textsuperscript{15-18} Substituted acroleins and propynals can be used for Michael addition reaction, cycloaddition reaction, and transition metal catalysed transformations. In this context, NaBD_{4}/MnO_{2} system would offer vital opportunity to the synthesis of highly functionalized \textit{d}-labelled molecules \textit{via} facile preparation of aromatic and unsaturated aldehyde-\textit{d}_{4}. \textit{Deuterium}-labelled compounds are often needed for the investigation of the mechanisms or determination of the rate-limiting step. The present synthetic method supports the studies from the viewpoint of the facile preparation of aldehyde-\textit{d}_{4} and its derivatives. Further application and mechanism studies are ongoing in our laboratory.

Author contributions

Y. Yasuno and HO are contributed equally. Y. Yasuno, HO, and TS designed the synthetic route. TS wrote the manuscript. HO, Y. Yasuno, and AN prepared ESI.† HO, Y. Yasuno, AN, K. Kumadaki, K. Kitsuwa, KO, YT, and Y. Yamamoto performed syntheses of 2.

Conflicts of interest

There are no conflicts to declare.

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