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A practical and efficient method for late-stage deuteration of terminal alkynes with silver salt as catalyst

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ABSTRACT

A practical and efficient H/D exchange method for selective deuteration of terminal alkynes was disclosed. The reaction was simply performed with CF_3COOAg as catalyst at room temperature, affording products with high level of deuterium incorporation. The excellent site-selectivity and promising functional group tolerance of this protocol enabled deuteration of pharmaceuticals and nature product derivatives.

Introduction

The increasing applications of deuterium-labeled compounds in various scientific fields [1–4] have recently demanded for convenient, selective, and especially catalytic methods for their preparation [5–7]. As one of the most utilized synthons in organic reactions, terminal alkynes have been widely applied in organic synthesis [8]. Thus, deuterated terminal alkynes become a common reagent being applied in mechanistic study in chemical and biological processes [9], and served as a versatile building block enabling quick access to a good range of important deuterium-labeled molecular architectures [10]. Although much effort has been made for preparation of deuterated compounds, the synthesis of deuterated terminal alkynes is mainly relied on traditional method of a subsequent hydrogen abstraction and quenching process by strong bases [11]. However, use of stoichiometric amounts of alkali metals or organic/inorganic bases leading to poor functional group tolerance disadvantaged further application of these protocols in late-stage deuterium-labeling. Recently, a catalytic H/D exchange protocol of terminal alkynes has been disclosed, despite using expensive ruthenium complex as catalyst (Scheme 1) [12]. Thus, an efficient catalytic approach for selective deuterium-labeling of terminal alkynes under mild condition is highly demanded.

Our group is devoted to develop novel method for preparation of deuterated compounds [13]. Recently, we have successfully achieved selective deuteration of five-membered heterocycles via a silver salt catalyzed H/D exchange protocol under mild condition [14]. Due to the cheap cost and wide application in organic reactions, silver salt is considered to be a potential catalyst for preparation of many useful

deuterated organic compounds [15]. It has been well studied that activation of the C(sp)-H bond of terminal alkynes can be promoted by prior π coordination of silver salt to triple bond, which enabled cross-coupling of terminal alkynes with a series of molecules [16]. However, these transformations are always completed in the presence of excess amount of bases, which are believed to play an important role in the formation of key intermediate silver acetylide. In addition, a mechanism study of C(sp)-H bond activation showed that deuterated terminal alkynes can be produced with stoichiometric AgOTf and excess amount of CD_3COOD as deuterium source [17]. However, the silver salt mediated H/D exchange process with catalysis mode has rarely been explored. Herein, we disclose an efficient H/D exchange protocol with CF_3-COOAg as catalyst and heavy water as deuterium source at room temperature, which enabled preparation of a series of deuterated terminal alkynes, especially deuterated bioactive molecules with sensitive functional groups.

As shown in Table 1, our initial efforts focused on H/D exchange process of terminal alkyne **1a** with different silver salt as catalyst. Although silver chloride and silver bromide are totally ineffective (Table 1, entries 1–2), to our delight, deuterium-labeled terminal

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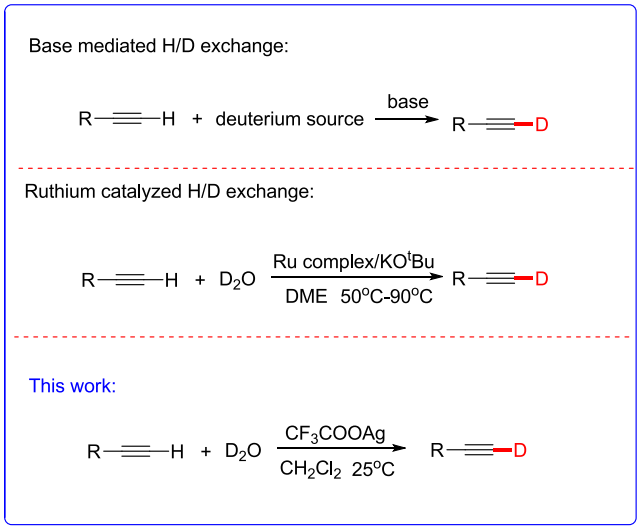
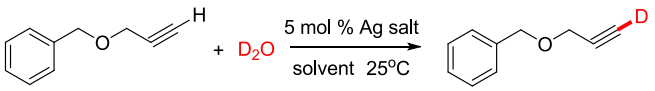


Scheme 1. Various Routes for deuterium incorporation of terminal alkyne.

Table 1
Condition optimal.



1a **2a**

Entry	Catalyst	Solvent	D incorporation
1	AgCl	DME (0.5 M)	2%
2	AgBr	DME (0.5 M)	3%
3	Ag_2O	DME (0.5 M)	32%
4	CF_3COOAg	DME (0.5 M)	92%
5	Ag_2CO_3	DME (0.5 M)	53%
6	AgOAc	DME (0.5 M)	78%
7	CF_3SO_3Ag	DME (0.5 M)	54%
8	CF_3COOAg	DME (1 M)	83%
9	CF_3COOAg	DME (0.7 M)	76%
10	CF_3COOAg	DME (0.3 M)	83%
11	CF_3COOAg	DME (0.5 M)	86%
12	CF_3COOAg	DME (0.5 M)	85%
13	CF_3COOAg	Toluene (0.5 M)	87%
14	CF_3COOAg	DMSO (0.5 M)	86%
15	CF_3COOAg	Dioxane (0.5 M)	84%
16	CF_3COOAg	THF (0.5 M)	76%
17	CF_3COOAg	DCM (0.5 M)	96%
18	CF_3COOAg	DMF (0.5 M)	87%
19	CF_3COOAg	CH_3CN (0.5 M)	82%

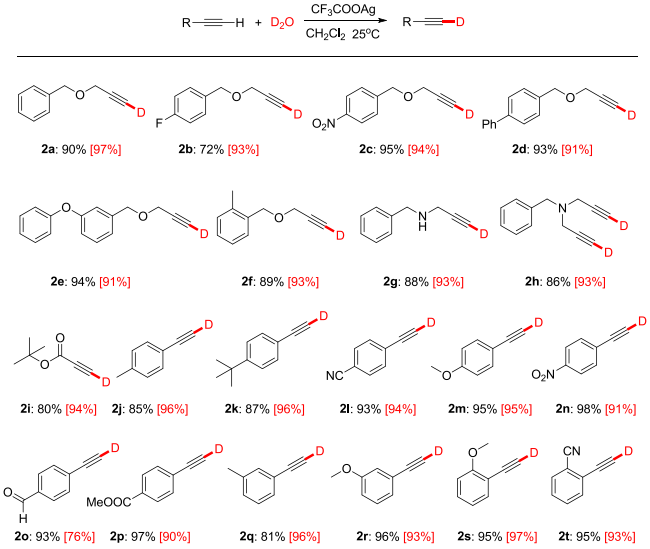
a.The reaction was conducted on 0.4 mmol of **1a**, 8 mmol of D_2O, 5 mol % of CF_3COOAg, in different solvents at 25 °C; level of deuterium incorporation was determined by GC-MS.b.at 40°C. c.at 60 °C.

alkynes were indeed obtained by using Ag_2O, Ag_2CO_3, CF_3COOAg, AgOAc and CF_3SO_3Ag as catalyst (Table 1, entries 3–7). Among them, CF_3COOAg was identified as the most effective catalyst, affording product with 92% deuterium incorporation. We found concentration played an important role in the H/D exchange process, as a higher level of deuterium incorporation was observed by performing reaction in 0.5 M solution (Table 1, entries 4, 8–10). The test of reaction in different temperature showed that elevated temperature has no positive effect on H/D exchange process (Table 1, entries 11–12). The choice of solvent is crucial, and high atom% deuterium incorporation was observed with CH_2Cl_2 as solvent (Table 1, entries 13–19). Therefore, the optimal condition was established with CF_3COOAg as catalyst in CH_2Cl_2 at 25 °C. Importantly, although homo-coupling byproduct was commonly observed in metal-catalyzed transformations involving terminal alkynes, we found deuterium-labeled terminal alkynes is the only product under the optimal reaction condition.

With the optimal reaction condition in hand, we set out to explore the generality of this method with respect to different terminal alkynes as shown in Table 2. The benzyl propargyl ethers with different substitutions were first examined (**2a**-**2f**). We found several functional groups, including fluoride, nitro, phenyl and methyl groups, were compatible with the standard condition, affording products **2a**-**2f** with 91% to 97% deuterium incorporation. In addition, benzyl propargyl amine (**2 g**) with free N—H bond was also found to be good substrate, affording 93% deuterium incorporation. The attempt for H/D exchange of two terminal alkynes in one molecule (**2 h**) was also realized, providing high level of deuterium incorporation at both terminal alkynes. Moreover, we found *tert*-butyl propiolate (**2i**) is a good substrate for this H/D exchange protocol, affording product with 94% deuterium incorporation. Aryl alkynes with different substitutions (**2j**-**2 t**) were then tested. Both electron-donating and electron-withdrawing groups on the *para*-, *meta*- and *ortho*-positions of aryl alkynes were compatible with standard condition. In all cases, the reaction showed excellent site selectivity with H/D exchange occurring at alkyne terminal C—H even in the presence of aldehyde or methoxyl groups [14]. The combination of simple operation process in the open air without exclusion of oxygen or water and facile isolation process through filtration, extraction and concentration without further purification by column chromatograph made this method very attractive for large-scale preparation. Finally, we were delighted to find this H/D exchange reaction was amenable to scale up using 1.1 g of **2m** without loss of efficiency.

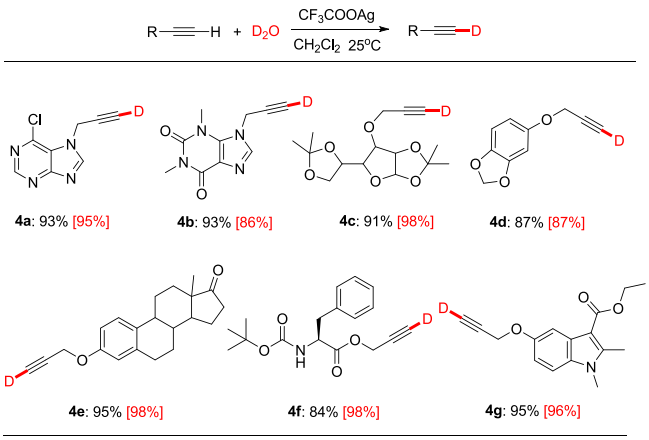
The excellent site-selectivity and promising functional group tolerance of this protocol promoted us to investigate its potential application in deuteration of pharmaceuticals and natural product derivatives. As shown in Table 3, the H/D exchange of nucleotide derivatives was successfully achieved in 95% and 86% deuterium

Table 2
Substrates scope.[a]



[a]The reaction was conducted on 1 mmol of **1**, 20 mmol of D_2O, 5 mol % of CF_3COOAg in 2 mL of CH_2Cl_2 at 25°C; Isolated yield; level of deuterium incorporation is determined by ^1H NMR

Table 3
Deuteration of pharmaceuticals and natural product derivatives.

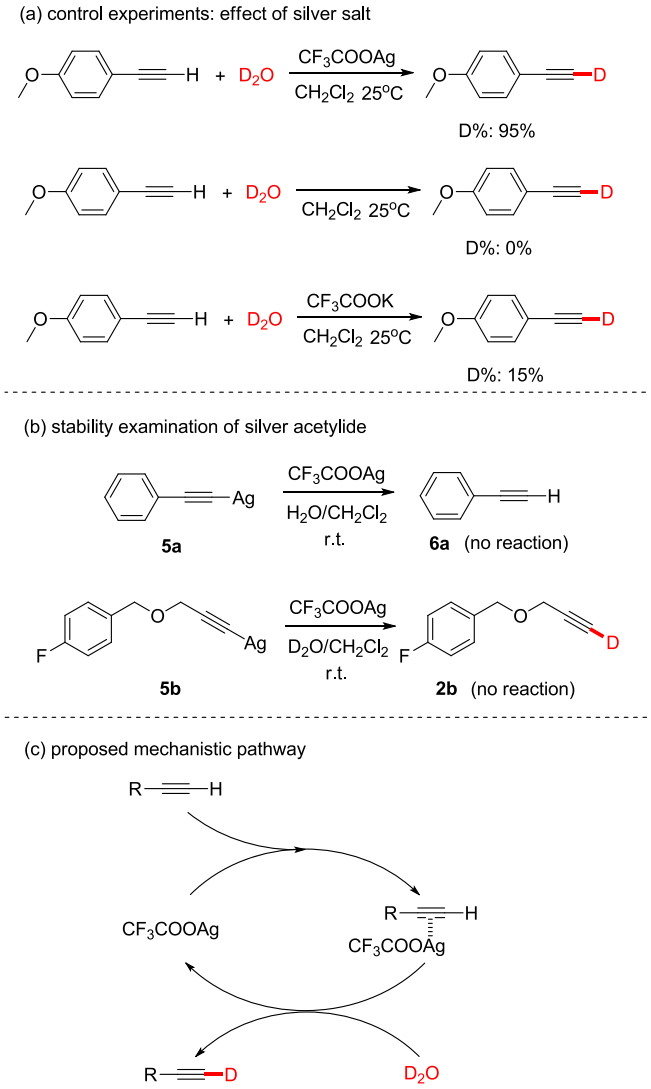


[a]The reaction was conducted on 1 mmol of **1**, 20 mmol of D_2O, 5 mol % of CF_3COOAg in 2 mL of CH_2Cl_2 at 25°C; Isolated yield; level of deuterium incorporation is determined by ^1H NMR

incorporation (**4a** and **4b**). Deuterated glucofuranose (**4c**), sesamol (**4d**), estrone (**4e**) and α-amino acid (**4f**) derivatives were synthesized from the corresponding terminal alkyne precursors in high level of deuterium incorporation. It is noteworthy that excellent site-selectivity of deuteration was observed in these cases, though these molecules contained sensitive chemical bonds such as N—H bond, as well as C—H bond neighboring to carbonyl or carboxylate groups. Moreover, the reaction using mecarbinate derivatives as substrate lead to 96% deuterium incorporation (**4g**).

With the attempt to get more insight into the reaction mechanism, a series of experiments have been performed. We first conducted the reaction without silver salt, and no deuterium incorporation was observed. Replacement of silver trifluoroacetate with potassium trifluoroacetate resulted in much lower level of deuterium incorporation (Scheme 2a). These results suggested that silver salt was essential for this H/D exchange process. It is well reported that silver acetylide served as intermediate in the silver catalyzed coupling reactions of terminal alkynes [16]. However, we noticed that silver acetylide derivatives were commonly prepared with water as solvent at room temperature [18], which made us doubt that H/D exchange reaction proceeded via silver acetylide. Indeed, no formation of compounds **6a** and **2b** were observed with silver acetylide **5a** and **5b** as substrates under the standard condition at room temperature (Scheme 2b), which suggested that silver acetylide may not be responsible for the H/D exchange process. According to these experiment results, we proposed a mechanistic pathway as follows (Scheme 2c): Terminal C—H bond was first activated by the coordination of silver salt with triple bond. Then, the step of H/D exchange between heavy water and terminal alkynes may occur, followed by the release of deuterated terminal alkynes and silver salt.

In summary, a practical approach for H/D exchange of terminal alkynes with CF_3COOAg as catalyst is disclosed. There are several advantages of this reaction. First of all, this reaction showed excellent functional group tolerance under mild condition, which enabled directly deuterium-labelling of bioactive molecules. Second, it is an operational-friendly process, avoiding the fussy operation including protection with N_2 and purification by column chromatograph. Third, the deuterated terminal alkynes were easily prepared with high level of deuterium incorporation. Thus, these advantages made this reaction an extremely practical and efficient method for preparation of deuterated terminal alkynes. Further



Scheme 2. Control Experiments and Proposed Mechanistic Pathway.

extension of this silver catalyzed H/D exchange reaction to other type of substrates is still ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152807.

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