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Journal Name

COMMUNICATION

Mild Deuteration Method of Terminal Alkynes in Heavy Water using Reusable Basic Resin

Tsuyoshi Yamada, Kwihwan Park, Yasunari Monguchi, Yoshinari Sawama* and Hironao Sajiki*
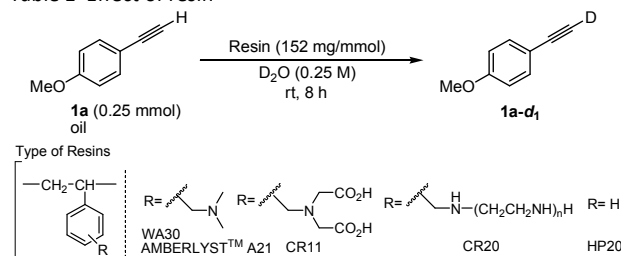
The mild and efficient deuteration of terminal alkynes (mono-substituted alkynes) proceeded in the presence of a basic anion exchange resin, WA30, which is a polystyrene polymer bearing a tertiary amine residue on the aromatic nuclei, in heavy water (D_2O) at room temperature. WA30 could be easily removed by a simple filtration and repeatedly reused.

The utility of deuterium-labeled compounds is widely recognized in various scientific fields, such as human metabolic, reaction mechanistic, analytic and material studies.[1,2] Among them, deuterated terminal alkynes were also utilized for mechanistic reaction studies[3] and as useful building blocks to construct deuterium labeled materials (*e.g.*, deuterated alkenes[3a,3b,3h,4] by hydrogenation, 1,2,3-triazole[5] by Huisgen cycloaddition with azido compounds, and aromatics[3f,3g] by Lewis acid-catalyzed intra or intermolecular annulation and aromatization, etc.). The deuterated terminal alkynes are traditionally prepared via an acetylide, generated by the stoichiometric use of organolithium[3a,3b,3c,3g], Grignard reagents[3f] or Na metal[3h] in a non–protic solvent, and subsequent quench using deuterium sources, such as D_2O and CD_3OD, in association with the production of a large amount of metal sludge. Additionally, the deuteration using the silver salt/CD_3CO_2D combination[6] or triazabicyclodecene (TBD)[7] and *N*-heterocyclic carbene[8] in $CDCl_3$ has also been reported. Bew et al. recently developed a mild deuteration method of terminal alkynes under basic reaction conditions in the presence of K_2CO_3 in a D_2O/CH_3CN mixed-solvent.[5] We have also reported a deuteration method using Et_3N as an organic base in a D_2O/THF mixed-solvent at nearly the same time.[4] However, the development of the deuterium-labeled method using a reusable catalyst in D_2O as a neutral and cheapest deuterium source without an organic co-solvent is still challenging from the viewpoint of green sustainable chemistry. We now demonstrate a clean and mild deuteration method of terminal alkynes using a reusable solid organic base in

D_2O at room temperature.

Various polystyrene polymer resins bearing an amine residue within the basic skeleton are readily available, and we have previously utilized basic and neutral resins (WA30, CR11, CR20 and HP20 shown in Table 1) as supports of a heterogeneous transition metal-catalyst for coupling reactions,[9] chemoselective reductions[10] and oxidations.[11] We first investigated the effect of the substituent connected to the polystyrene polymer backbone for the direct deuteration of 4-ethynylanisole (**1a**) as a terminal alkyne (Table 1). The deuteration of **1a** (0.25 mmol: oil) using 115 weight% (wt%) of the polystyrene WA30 resin bearing the tertiary amine residue purchased from the Mitsubishi Chemical Corporation in D_2O smoothly proceeded to give the desired deuterated terminal alkyne (**1a-d_1**) with an excellent deuterium content (99% D) and yield (93%) for 8 h (Entry 1). While AMBERLYST[TM] A21 possessing a structure similar to WA30[12] and CR11 bearing the iminodiacetic acid residue as a kind of tertiary amine were also effective (Entries 2 and 3), CR20 possessing secondary and primary amine moieties within the molecule was inefficient as a deuteration catalyst (Entry 4). Meanwhile, the use of the polystyrene resin without amine moieties (HP20) never facilitated the desired deuteration of **1a** (Entry 5). WA30 possessing a physically durable structure was chosen as the optimal basic solid catalyst to achieve the high deuterium content of **1a-d_1**.

Laboratory of Organic Chemistry, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan, E-mail: sawama@gifu-pu.ac.jp; sajiki@gifu-pu.ac.jp; Phone/Fax: +81-58-230-8109
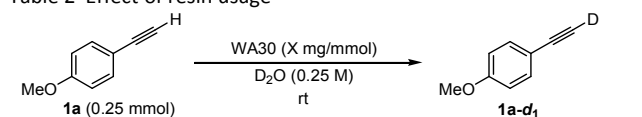† Electronic Supplementary Information (ESI) available: Details of the general procedure for deuteration, and NMR spectral data of the products. See DOI: 10.1039/x0xx00000x

Table 1 Effect of resin[a]

Entry	Resin	D contents (%)	Yield (%)[a]
1	WA30	99	93
2	AMBERLYST[TM] A21	93	86
3	CR11	98	93

| 4 | CR20 | 34 | 96 |
| 5 | HP20 | 0 | 100 |

[a] WA30, CR11, CR20 and HP20 were commercially available from Mitsubishi Chemical Corporation. AMBERLYST™ A21 was commercially available from the ORGANO Corporation. All resins were washed with water and methanol, then dried in vacuo before using them.

We next examined the efficiency based on the WA30 usage (Table 2). The deuterium contents of **1a** increased in tandem with the WA30 usage (Entries 1, 3 and 5). The efficient deuterium incorporation of **1a** to **1a-d_1** was never achieved using 10 or 50 wt% WA30 (Entries 2 and 4). Although 115 wt% of WA30 versus **1a** was required to obtain the quantitative deuterium efficiency for the shorter reaction time (Entries 4 *vs.* 5), it is remarkable that WA30 could be reused at least 5 times without any deactivation and technical loss to accomplish the excellent D contents and isolated yield of **1a-d_1** (Table 3).
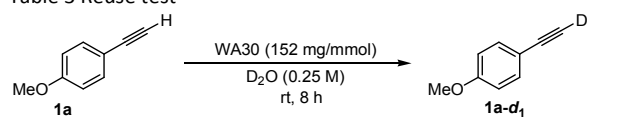
Table 2 Effect of resin usage

Entry	X	Time (h)	D content (%)
1	13.2 (10 wt%)	8	23
2	13.2 (10 wt%)	24	45
3	66.1 (50 wt%)	8	75
4	66.1 (50 wt%)	12	94
5	152 (115 wt%)	8	99 (93[a])

[a] Isolated yield.

Table 3 Reuse test

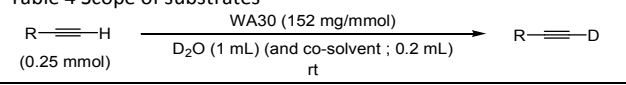| Try	D content (%)	Yield (%)	Recovery yield of WA30 (%)
1st	99	95	97
2nd	99	96	99
3rd	99	97	>99
4th	99	97	99
5th	98	Quant.	99

The present reaction efficiencies were significantly affected by the physical state of the substrates (oil or solid, Table 3 *vs.* eq. 1 and Table 4). An oily substrate, such as **1a**, smoothly and efficiently underwent the deuteration in D$_2$O (Table 3). While 1-ethynyl-4-phenylbenzene (**1b**) as a solid-state substrate was never deuterated in D$_2$O (eq. 1), the addition of a small amount of toluene as a co-solvent to dissolve the substrate dramatically improved the deuterium content to give the quantitatively deuterated **1b-d_1** (The effect of other organic solvents are described in the Supporting Information). Furthermore, WA30 used in a D$_2$O/toluene mixed-

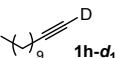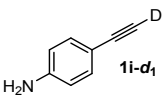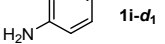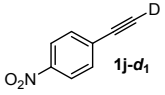solvent could also be repeatedly reused (see Supporting Information).

solvent D$_2$O (1 mL)   ; No deuteration (8 h)
D$_2$O/Toluene (1/0.2 mL) ; 99% D, 99% yield (12 h)
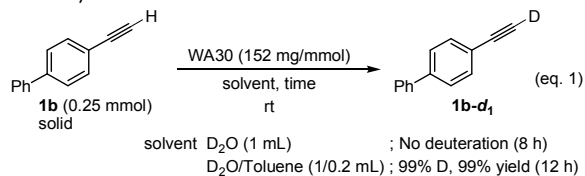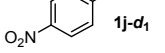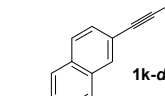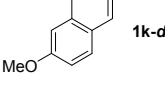
Various mono aryl- and alkyl-substituted alkynes could be efficiently deuterated to give the corresponding mono-deuterium labeled alkynes (Table 4). 2-Methoxy (**1c**) and trifluoromethyl (**1d**) ethynylbenzene as oily substrates were smoothly deuterated with excellent deuterium efficiencies in D$_2$O (**1c-d_1** and **1d-d_1**) (Entries 1 and 2). The oily propargyl alcohol derivatives (**1e-g**) were also efficie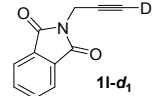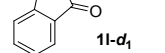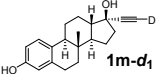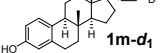ntly deuterated in quantitative deuterium contents (**1e-d_1**, **1f-d_1**, **1g-d_1**) accompanied without hydrolysis of the ester (**1e**) or decomposition of the benzyl ether (**1f**) and sulfide moiety (**1g**) under the present reaction conditions (Entries 3-5). Dodecyne (**1h**) as an oily aliphatic terminal alkyne was effectively deuterated in D$_2$O by heating at 50 °C (Entry 6). Although the 4-amino (**1i**) and nitro (**1j**) ethynylbenzenes and a naphthalene derivative (**1k**) as solid-state substrates were inefficiently deuterated in D$_2$O (Entries 7, 9 and 11), the addition of toluene as a co-solvent facilitated the deuteration of **1i**, **1j** and **1k** to give the corresponding deuterium-labeled alkynes, respectively (**1i-d_1**, **1j-d_1** and **1k-d_1**) (Entries 8, 10 and 12). On the other hand, the deuteration of the solid-state *N*-(propargyloxy)-phthalimide (**1l**) resulted in the low deuterium incorporation regardless of the addition of toluene as a co-solvent (**1l-d_1**) for some unaccountable reason (Entries 13 and 14). Ethynylestradiol (**1m**), which is crucial medicinal compound as the solid-state substrate, never underwent the deuteration in D$_2$O. The addition of AcOEt as a co-solvent facilitated the deuteration of **1m** (Entries 15 *vs.* 16), while the addition of toluene was ineffective. (See Supporting Information)

Table 4 Scope of substrates

Entry	Product	Co-solvent	Time (h)	D content (%) [Yield (%)]
Oily substrates				
1	**1c-d_1**	−	8	96 [95]
2	**1d-d_1**	−	8	99 [59]
3	**1e-d_1**	−	8	99 [quant.]
4	**1f-d_1**	−	8	99 [90]
5	**1g-d_1**	−	8	95 [93]

COMMUNICATION

6[a]	**1h-d₁**	–	16	93 [65]

Solid-state substrates

7	**1i-d₁**	–	8	15 [91]
8		Toluene	12	97 [97]
9	**1j-d₁**	–	8	18 [94]
10		Toluene[b]	12	94 [97]
11	**1k-d₁**	–	8	19 [98]
12		Toluene	12	96 [quant.]
13	**1l-d₁**	–	8	19 [86]
14[a]		Toluene	12	35 [89]
15	**1m-d₁**	–	8	0 [84]
16[a]		AcOEt[b]	24	92 [94]

[a] At 50 °C. [b] 0.5 mL of the co-solvent was added.

Conclusions

We have developed a mild and efficient deuteration method of terminal alkynes by using a heterogeneous basic polystyrene resin (WA30) in D_2O under mild conditions. It is noteworthy that oily substrates smoothly underwent the direct deuteration in D_2O, while the deuteration of solid substrates could be facilitated by the addition of a small quantity of a co-solvent, such as toluene and AcOEt. A wide variety of functional groups (*e.g.*, nitro, propargyl ester, sulfide, benzyl ether, etc.) could be tolerant under the present mild reaction conditions. WA30 could be repeatedly used without any loss of catalyst activity. The present clean deuteration method of terminal alkynes is expected to be utilized in not only laboratories, but also industrial fields as an economic and eco-friendly reaction.

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12 Although WA30 and AMBERLYST™ A21 both partially possess *tert*-amino functionalities on the polystyrene backbone, the apparent density and total ion-exchange capacity should be different. Nevertheless, both catalysts possess similar high catalyst activities.