## **RSC Advances**



View Article Online

View Journal | View Issue

### COMMUNICATION



Cite this: RSC Adv., 2015, 5, 92954

Received 15th September 2015 Accepted 22nd October 2015

DOI: 10.1039/c5ra18921g

www.rsc.org/advances

# Mild deuteration method of terminal alkynes in heavy water using reusable basic resin<sup>†</sup>

Tsuyoshi Yamada, Kwihwan Park, Yasunari Monguchi, Yoshinari Sawama\* and Hironao Sajiki\*

The mild and efficient deuteration of terminal alkynes (monosubstituted 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.<sup>1,2</sup> Among them, deuterated terminal alkynes were also utilized for mechanistic reaction studies3 and as useful building blocks to construct deuterium labeled materials (e.g., deuterated alkenes<sup>3a,b,h,4</sup> by hydrogenation, 1,2,3-triazole<sup>5</sup> by Huisgen cycloaddition with azido compounds, and aromatics3fg by Lewis acidcatalyzed intra or intermolecular annulation and aromatization, etc.). The deuterated terminal alkynes are traditionally prepared via an acetylide, generated by the stoichiometric use of organolithium,<sup>3a,b,c,g</sup> Grignard reagents<sup>3f</sup> or Na metal<sup>3h</sup> in a nonprotic solvent, and subsequent quench using deuterium sources, such as D<sub>2</sub>O and CD<sub>3</sub>OD, in association with the production of a large amount of metal sludge. Additionally, the deuteration using the silver salt/CD<sub>3</sub>CO<sub>2</sub>D combination<sup>6</sup> or triazabicyclodecene (TBD)7 and N-heterocyclic carbene8 in CDCl3 has also been reported. Bew et al. recently developed a mild deuteration method of terminal alkynes under basic reaction conditions in the presence of K2CO3 in a D2O/CH3CN mixedsolvent.5 We have also reported a deuteration method using Et<sub>3</sub>N as an organic base in a D<sub>2</sub>O/THF mixed-solvent at nearly the same time.4 However, the development of the deuteriumlabeled method using a reusable catalyst in D<sub>2</sub>O 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<sub>2</sub>O 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<sup>10</sup> and oxidations.<sup>11</sup> We first investigated the effect of the substituent connected to the polystyrene polymer backbone for the direct deuteration of 4ethynylanisole (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<sub>2</sub>O 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<sup>™</sup> A21 possessing a structure similar to WA30 (ref. 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<sub>1</sub>.

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  $1a \cdot d_1$  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

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; Fax: +81-58-230-8109; Tel: +81-58-230-8109

<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Details of the general procedure for deuteration, and NMR spectral data of the products. See DOI: 10.1039/c5ra18921g



L	WA30	99	93
2	AMBERLYST <sup>TM</sup> A21	93	86
3	CR11	98	93
1	CR20	34	96
5	HP20	0	100

<sup>*a*</sup> 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.

Table 2 Effect of resin usage



<sup>a</sup> Isolated yield.

Table 3 Reuse test

MeO <sup></sup>	H WA30 ()	152 mg/mmol) ) (0.25 M) rt, 8 h N	AeO la-d <sub>1</sub>
Try	D content (%)	Yield (%)	Recovery yield of WA30 (%)
1 <sup>st</sup>	99	95	97
2 <sup>nd</sup>	99	96	99
3 <sup>rd</sup>	99	97	>99
$4^{\text{th}}$	99	97	99
5 <sup>th</sup>	98	Quant.	99

times without any deactivation and technical loss to accomplish the excellent D contents and isolated yield of  $1a-d_1$  (Table 3).

The present reaction efficiencies were significantly affected by the physical state of the substrates (oil or solid, Table 3 vs. eqn (1) and Table 4). An oily substrate, such as **1a**, smoothly and efficiently underwent the deuteration in  $D_2O$  (Table 3). While 1ethynyl-4-phenylbenzene (**1b**) as a solid-state substrate was never deuterated in  $D_2O$  (eqn (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 ESI†). Furthermore, WA30 used in a  $D_2O$ /toluene mixed-solvent could also be repeatedly reused (see ESI†).



Various mono aryl- and alkyl-substituted alkynes could be efficiently deuterated to give the corresponding monodeuterium labeled alkynes (Table 4). 2-Methoxy (1c) and trifluoromethyl (1d) ethynylbenzene as oily substrates were smoothly deuterated with excellent deuterium efficiencies in  $D_2O$  (1c- $d_1$  and 1d- $d_1$ ) (Entries 1 and 2). The oily propargyl alcohol derivatives (1e-g) were also efficiently 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<sub>2</sub>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<sub>2</sub>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<sub>1</sub>, 1j-d<sub>1</sub>) and  $1k-d_1$  (Entries 8, 10 and 12). On the other hand, the deuteration of the solid-state N-(propargyloxy)-phthalimide (11) 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<sub>2</sub>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 ESI<sup>†</sup>).

#### Conclusions

We have developed a mild and efficient deuteration method of terminal alkynes by using a heterogeneous basic polystyrene

#### Table 4 Scope of substrates

R	≡-н	D <sub>2</sub> O (1	WA30 (152 mg/r mL) (and co-solv	nmol) /ent ; 0.2 mL)	► R-=-D		
(0.25	mmoi)		rt				
Entry	Pro	oduct	Co-solvent	Time (h)	D content (% [yield (%)]		
Oily su	bstrates						
		_ D					
1		<b>1c-d</b> 1 Me	—	8	96 [95]		
		D					
2	C C	<b>1d-d₁</b> F₃	—	8	99 [59]		
	0 II						
3	$\bigcirc$	0 1e-d <sub>1</sub>	 D	8	99 [quant.]		
4	$\bigcirc$	0 1f-d <sub>1</sub>	D —	8	99 [90]		
5	s.		_	8	95 [93]		
		ig-a <sub>1</sub>					
6 <sup><i>a</i></sup>	M9	_D 1h-d <sub>1</sub>	_	16	93 [65]		
Solid-state substrates							
7		, D	—	8	15 [91]		
8	H <sub>2</sub> N	1i-d <sub>1</sub>	Toluene	12	97 [97]		
9	-	, D	—	8	18 [94]		
10	Ĺ		Toluene <sup>b</sup>	12	94 [97]		
	0 <sub>2</sub> N	<b>1j</b> -α <sub>1</sub>					
11			_D —	8	19 [98]		
12	ĺ		Toluene	12	96 [quant.]		
	MeO	1k-1	d <sub>1</sub>				
$13_{14^a}$	0	———D	—	8	19 [86]		
14		°O 1I-d₁	Totuene	12	[جو] دد		
15	$\sim$	н он	_	8	0 [84]		
16 <sup><i>a</i></sup>	HO	→ <sup>H</sup> 1m-d <sub>1</sub>	AcOEt <sup>b</sup>	24	92 [94]		

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

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.

#### Notes and references

- Review: (a) J. Atzrodt, V. Derdau, T. Fey and J. Zimmermann, Angew. Chem., Int. Ed., 2007, 46, 7744–7765; (b) Y. Sawama, Y. Monguchi and H. Sajiki, Synlett, 2012, 23, 959–972; (c) J. M. Herbert, J. Labelled Compd. Radiopharm., 2010, 53, 658–661.
- 2 Our recent H/D exchange reactions using heterogeneous platinum metal on carbon; (a) Y. Sawama, Y. Yabe, H. Iwata, Y. Fujiwara, Y. Monguchi and H. Sajiki, *Chem.-Eur. J.*, 2012, 18, 16436–16442; (b) Y. Sawama, T. Yamada, Y. Yabe, K. Morita, K. Shibata, M. Shigetsura, Y. Monguchi and H. Sajiki, *Adv. Synth. Catal.*, 2013, 355, 1529–1534; (c) T. Yamada, Y. Sawama, K. Shibata, K. Morita, Y. Monguchi and H. Sajiki, *RSC Adv.*, 2015, 5, 13727–13732.
- 3 (a) J. M. Brown and G. C. Lloyd-Jones, J. Am. Chem. Soc., 1994, 116, 866–878; (b) J. E. Baldwin and R. C. Burrell, J. Org. Chem., 1999, 64, 3567–3571; (c) J.-C. Cintrat, F. Pillon and B. Rousseau, Tetrahedron Lett., 2001, 42, 5001–5003; (d) M.-Y. Chou, A. B. Mandal and M.-k. Leung, J. Org. Chem., 2002, 67, 1501–1505; (e) C. H. Oh, H. H. Jung, K. S. Kim and N. Kim, Angew. Chem., Int. Ed., 2003, 42, 805–808; (f) A. S. K. Hashmi, M. Rudolph, H.-U. Siehl, M. Tanaka, J. W. Bats and W. Frey, Chem.-Eur. J., 2008, 14, 3703–3708; (g) T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamure and E. Shirakawa, J. Am. Chem. Soc., 2008, 130, 15823–15835; (h) G. Zhang, L. Cui, Y. Wang and L. Zhang, J. Am. Chem. Soc., 2010, 132, 1474–1475.
- 4 Y. Yabe, Y. Sawama, Y. Monguchi and H. Sajiki, *Chem.–Eur. J.*, 2013, **19**, 484–488.
- 5 S. P. Bew, G. D. Hiatt-Gipson, J. A. Lovell and C. Poullain, *Org. Lett.*, 2012, **14**, 456–459.
- 6 G. S. Lewandos, J. W. Maki and J. P. Ginnebaugh, *Organometallics*, 1982, **1**, 1700–1705.
- 7 C. Sabot, K. A. Kumar, C. Antheaume and C. Mioskowski, *J. Org. Chem.*, 2007, **72**, 5001–5004.
- 8 F. Perez, Y. Ren, T. Boddaert, J. Rodriguez and Y. Coquerel, *J. Org. Chem.*, 2015, **80**, 1092–1097.
- 9 (a) Y. Kitamura, K. Taniguchi, T. Maegawa, Y. Monguchi, Y. Kitade and H. Sajiki, *Heterocycles*, 2009, 77, 521–532; (b)
  Y. Monguchi, K. Sakai, K. Endo, Y. Fujita, M. Niimura, M. Yoshimura, T. Mizusaki, Y. Sawama and H. Sajiki, *ChemCatChem*, 2012, 4, 546–558; (c) Y. Monguchi, K. Nozaki, T. Maejima, Y. Shimoda, Y. Sawama, Y. Kitamura, Y. Kitade and H. Sajiki, *Green Chem.*, 2013, 15, 490–495; (d) Y. Monguchi, Y. Sawama and H. Sajiki, *Heterocycles*, 2015, 91, 239–264; (e) Y. Monguchi, T. Ichikawa, M. Netsu, T. Hattori, T. Mizusaki, Y. Sawama and H. Sajiki, *Synlett*, 2015, 26, 2014–2018.

- 10 (a) Y. Monguchi, Y. Fujita, K. Endo, S. Takao, M. Yoshimura,
  Y. Takagi, T. Maegawa and H. Sajiki, *Chem.–Eur. J.*, 2009, 15, 834–837; (b) Y. Monguchi, T. Ichikawa, K. Nozaki, K. Kihara,
  Y. Yamada, Y. Miyake, Y. Sawama and H. Sajiki, *Tetrahedron*, 2015, 71, 6499–6505.
- 11 Y. Monguchi, F. Wakayama, H. Takada, Y. Sawama and H. Sajiki, *Synlett*, 2015, **26**, 700–704.
- 12 Although WA30 and AMBERLYST<sup>TM</sup> 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.