ORGANIC LETTERS

2012
Vol. 14, No. 2
456–459

Mild Reaction Conditions for the Terminal Deuteration of Alkynes

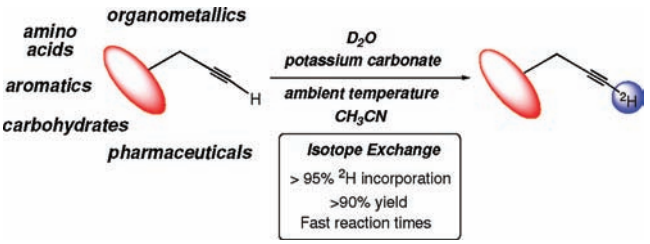
Sean P. Bew,* Glyn D. Hiatt-Gipson, Jenny. A. Lovell, and Christophe Poullain

School of Chemistry, University of East Anglia, Norwich Research Park, Norwich, U.K., NR4 7TJ

s.bew@uea.ac.uk

Received October 28, 2011

ABSTRACT



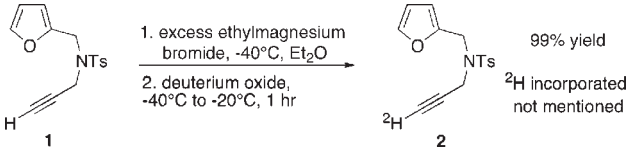
Routinely employed syntheses of terminally deuterated alkynes often utilize strong bases (i.e., LDA, *n*-BuLi, or Grignard reagents) or low (i.e., −78 °C) or elevated (i.e., 56 °C) reaction temperatures; furthermore many of these procedures afford average yields and in some cases less than optimum deuterium incorporation. Herein we report the application of alternative extremely mild reaction conditions that readily afford quantitative yields of terminally deuterated alkynes in a matter of minutes with exceptional isotope incorporation at ambient temperature.

The development of protocols that afford high value, deuterated molecules in high yields and, importantly, with excellent levels of deuterium incorporation is very important to academia and biotechnology, medicinal, analytical, pharmaceutical, and agrochemical industries.

^{2}H-alkynes are valuable, synthetically useful entities[1] capable of being used for the synthesis of additional deuterated molecules; e.g., ^{2}H-alkyne hydrogenation generates *cis*- or *trans*-^{2}H-alkenes[2] or ^{2}H-alkanes.[3] Alternatively aqueous gold salts[4] afford ^{2}H-ketones, and ^{2}H-alkyne cyclotrimerization affords ^{2}H-aromatics.[5]

Protocols for deuterated alkyne synthesis employ either elevated[6] or subambient reaction conditions;[7] extended, often hour-long reaction times;[8] or strong bases, i.e. *n*-BuLi,[9] Grignard reagents[10] (Scheme 1), or LDA;[11] or an expensive transition metal salt,[12] a consequence of which is the requirement that anhydrous reaction conditions and solvents be maintained at all times.

Scheme 1. Synthesis of Deuterated Alkyne **2** from **1**



(1) Diederich, F. *Acetylene Chemistry: Chemistry, Biology and Material Science*; Stang, P., Tykwinski, R. R., Eds.; Wiley-VCH: 2004. Denes, F.; Perez-Luna, A.; Chemia, F. *Chem. Rev.* **2010**, *110*, 2366. Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207. Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435. Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 478.

(2) Lindlar, H.; Dubuis, R. *Org. Synth., Coll. Vol. 5* **1973**, 880. Trost, B. M.; Ball, Z. T.; Joege, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922.

(3) Vanier, G. S. *Synlett* **2007**, 131. Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6556.

(4) Marion, N; Ramon, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448.

(5) Agenet, N.; Bruisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Organic Reactions* **2007**, *68*, 1−302.

(6) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474.

(7) Hislop, J.-A.; Hunt, M. B.; Fielder, S.; Rowan, D. D. *J. Agric. Food Chem.* **2004**, *52*, 7075.

(8) Sabot, C.; Kumar, K. A.; Antheaume, C.; Mioskowski, C. *J. Org. Chem.* **2007**, *72*, 5001.

(9) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823.

(10) Hashmi, A. S. K.; Rudolph, M.; Siehl, H.-U.; Tanaka, M.; Bats, J. W.; Frey, W. *Chem.—Eur. J.* **2008**, *14*, 3703.

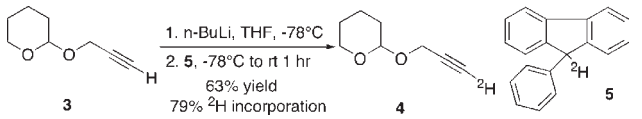
(11) Chen, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 15598.

(12) Lewandos, G. S.; Maki, J. W.; Ginnebaug, J. P. *Organometallics* **1982**, *1*, 1700.

10.1021/ol2029178
Published on Web 01/11/2012

Furthermore many afford subquantitative yields of product with reduced levels of deuterium incorporation or employ multistep procedures requiring presynthesized bespoke 'not off the shelf' reagents, i.e. **5** (Scheme 2),[13] or hazardous to handle alkali metals.[14]

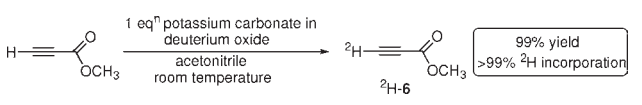
Scheme 2. Synthesis of Deuterated Alkyne **4** from **3** Using **5**



A mild, quick, and efficient protocol capable of generating terminal ^{2}H-**6** was required (Scheme 3). Our initial thoughts focused on reacting methyl propiolate with sodium deuteroxide/D_2O mixtures; however significant ester hydrolysis was observed. Using *less* basic reaction conditions, the weaker base potassium carbonate was probed; furthermore using a water ether biphasic reaction medium we envisaged may negate the ester hydrolysis problem, affording high yields of ^{2}H-**6**. After methyl propiolate was dissolved in ether, it was stirred with a 1 M aqueous (D_2O) potassium carbonate solution. ^{2}H-**6** was generated in an average yield with relatively poor (25%) ^{2}H-incorporation. Gratifyingly it seemed these less basic reaction conditions mediated significantly less ester hydrolysis but at the expense of lower deuterium incorporation. A solvent study using dichloromethane, toluene, 1,2-dichloroethane, *tert*-butylmethyl ether, ethyl acetate, hexane, toluene, and 1,1,1-trichloroethane and employing the same reaction conditions again generated ^{2}H-**6**, but the yields were unacceptable and purification of ^{2}H-**6** from methyl propiolate was tedious and time-consuming.

Aqueous potassium carbonate had negated the ester hydrolysis problem; however the efficiency of the reaction, i.e. conversion of methyl propiolate to ^{2}H-**6**, was poor. We considered that part of the problem lies in the biphasic nature of the reaction system. Mindful that switching to water miscible acetonitrile and aqueous potassium carbonate would result in extensive ester hydrolysis, we were delighted to observe the formation of ^{2}H-**6** in *both* quantitative yield and ^{2}H-incorporation (Scheme 3).

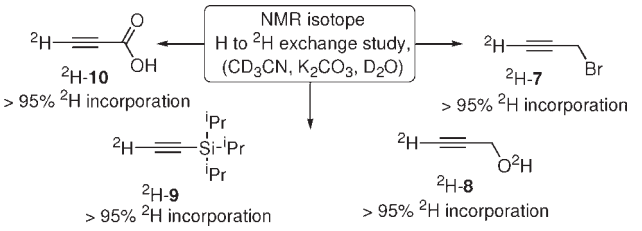
Scheme 3. Mild Synthesis of Deuterated Propiolate Ester ^{2}H-**6**



Probing the rate of the reaction, we dissolved methyl propiolate in CD_3CN and ran the ^{1}H NMR. To the same sample was added potassium carbonate (1 eq^n) in D_2O. Interestingly the deuteration of methyl propiolate was extremely fast, complete within minutes affording ^{2}H-**6** in >99% (Supporting Information (SI)).

Buoyed by this result we undertook a study using propargyl alcohol, propargyl bromide, monotri(*iso*propyl)-silylacetylene, and propiolic acid (Scheme 4). Using ^{1}H NMR as an efficient, sensitive 'real time investigative probe' we established terminal alkyne deuteration was, again, fast and complete within minutes.

Scheme 4. Deuteration of Alkynes Monitored *via* ^{1}H NMR



This limited substrate scope indicated our isotope exchange reaction tolerated a range of functionality that included the relatively base labile propargyl bromide, as well as propargyl alcohol, TIPS-acetylene (TMS-acetylene did not survive the reaction[15]), and electron-poor substrates such as propiolic acid. This simple protocol afforded ^{2}H-**7**–^{2}H-**10** via a straightforward process and with excellent levels of ^{2}H-incorporation (see SI).

Confident our protocol was robust, we subjected dodec-1-yne to terminal deuteration. ^{2}H-**11** was generated in both quantitative yield and ^{2}H-incorporation (judged by the disappearance of the terminal alkyne triplet at 1.93 ppm). Similarly ethynylbenzene as well as 1- and 2-ethynylnaphthalenes afforded ^{2}H-**12**, ^{2}H-**13**, and ^{2}H-**14** in quantitative yields. Gratifyingly performing a one-pot double deuteration on (*Z*)-hexa-3-en-1,5-diyne generated ^{2}H-**15** in a quantitative yield and with >95% ^{2}H-incorporation. Using ^{1}H NMR as our investigative tool no (*Z*)-^{2}H-**15** to (E)-^{2}H-**15** isomerization was observed.[16]

Using ethynylbenzene (**12**) we investigated, independently, water miscible dioxane and THF as possible alternatives to acetonitrile. Both afforded ^{2}H-**12** with >99% deuterium incorporation and essentially quantitative yields (K_2CO_3, rt, 1 h). To probe alternative inorganic or organic bases, the synthesis of ^{2}H-**12** was attempted using cesium carbonate, sodium carbonate, sodium hydrogen carbonate, triethylamine, and polystyrene bound *tris*amine (all 1 eq^n). All the inorganic bases afforded ^{2}H-**12** in excellent yield and deuterium incorporation, i.e. >99%. Triethylamine and immobilized *tris*amine afforded ^{2}H-**12** in good yields; however the ^{2}H-incorporation was slightly lower, i.e. 95%.

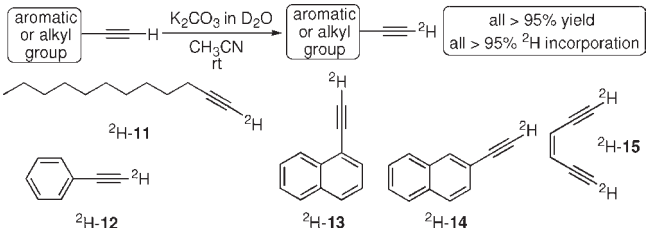
(13) Cintrat, J. C.; Pillion, F.; Rousseau, B. *Tetrahedron Lett.* **2001**, *42*, 5001.

(14) Sirokan, G.; Molnar, A.; Bartok, M. *J. Labelled Compds. Radiopharm.* **1989**, *27*, 439.

(15) Diederich, F.; Stang, P. J. *Metal Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Chichester, 1998.

(16) McMahon, R. J.; Halter, R. J.; Fimmen, R. L.; Wilson, R. J.; Peebles, S. A.; Kuczkowski, R. L.; Stanton, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 939–949.

Scheme 5. Synthesis of ^{2}H-Aliphatic and ^{2}H-Aromatic Species



Probing the generality of the deuteration process, a series of structurally diverse heterocyclic and heteroatom alkynes were investigated. 4-Ethynylpyridine (**16**), 1-(prop-2-ynyl)-1*H*-benzo[*d*]imidazole (**17**), ethynyl 2,2,3,3-tetramethylcyclopropanecarboxylate (**18**), 1-ethynyl-4-nitrobenzene (**19**), 4-(prop-2-ynyloxy)-1*H*-isochromen-1-one (**20**), 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran (**21**), 2-(prop-2-ynyl)isoindoline-1,3-dione (**22**), and 4-(prop-2-ynyl)-morpholine (**23**) reacted (standard reaction conditions employed in Scheme 5), within minutes, affording ^{2}H-**16**–^{2}H-**23** in quantitative yields and excellent levels of deuterium (Figure 1). Incorporating multiple deuterium atoms into terminal *bis*- or *tetra(*alkynes) in quantitative yield and ^{2}H-incorporation had significant appeal. Subjecting diprop-2-ynyl pyridine-2,6-dicarboxylate and diethyl 2,2-di(prop-2-ynyl)malonate to our standard D_2O/K_2CO_3 (2.5 eq^n) reaction conditions afforded ^{2}H-**24** and ^{2}H-**25** in quantitative yields and, importantly, 100% deuterium incorporation. To exploit this further, the incorporation of four deuteriums was attempted using a calix[4]arene appended with four lower-rim *O*-propargyl ethers. To our delight ^{2}H-**26** was afforded in a quantitative yield and with outstanding levels of deuterium incorporation.

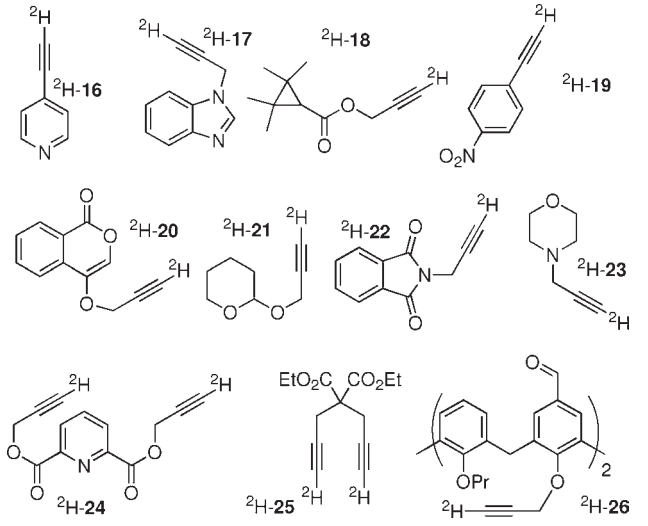
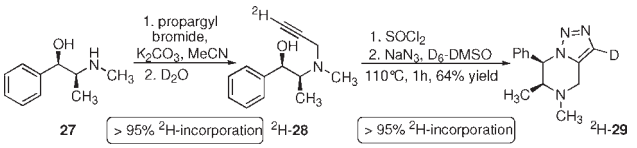


Figure 1. Examples of deuterated molecules ^{2}H-**16**–^{2}H-**26**.

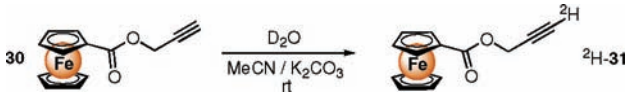
A terminally deuterated alkyne attached to an optically active molecule engenders it with synthetic 'appeal' especially if it can be used to synthesize optically active (deuterated) building blocks or drug-like molecules. Using an exceptionally mild, one-pot, two-step procedure, (1*R*,2*S*)-ephedrine (**27**) was *N*-propargylated using conditions reported[17] by Couty et al. (Scheme 6); we were delighted that, without workup, the introduction of deuterium oxide afforded ^{2}H-**28** with quantitative ^{2}H-incorporation. Treatment of ^{2}H-**28** with thionyl chloride and subsequently sodium azide (D_6-DMSO, 110 °C) afforded >95% incorporated ^{2}H-**29** in a 64% yield. No reduction in ^{2}H-incorporation was observed for this transformation (*cf.* >95% for ^{2}H-**28**). Worthy of note is that this exceeds the 80% ^{2}H-incorporation reported by Couty et al. for their low temperature (−78 °C) deprotonation (*n*-BuLi) electrophilic quench process using non-^{2}H **28**.

Scheme 6. Synthesis of Deuterated Triazole Piperazine ^{2}H-**29**



To further demonstrate the broad scope of this exceptionally mild deuteration protocol, its exploitation for the chemoselective deuteration of an organometallic complex was sought. Synthesis of ferrocene propargyl acetate **30** (48% yield) was straightforward.[18] Gratifyingly, dissolving **30** in acetonitrile, adding deuterium oxide and potassium carbonate, allowed the efficient synthesis of ^{2}H-**31** with >95% deuterium incorporation and in an excellent 98% yield (Scheme 7); no evidence of cyclopentadienyl ^{1}H–^{2}H exchange was detected.

Scheme 7. Synthesis of Isotopically Labelled Ferrocene ^{2}H-**31**



The synthesis of isotopically labeled α-amino acids and carbohydrates is critically important to (in)organic and biological mechanism elucidation, probing for kinetic isotope effects, and protein structure analysis. To validate the extremely mild nature of our protocol, the deuteration of variously N,C-protected-α-amino acids and O-protected carbohydrates was investigated. N-Boc-C-*tert*-butyl-*O*-

(17) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2004**, *45*, 3725.
(18) Bew, S. P.; Hiatt-Gipson, G. D. *J. Org. Chem.* **2010**, *75*, 3897.

propargyl-(*S*)-tyrosine, (*S*)-prop-2-ynyl-2-(tert-butoxycarbonylamino)pent-4-ynoate, N-Boc-C-propargyl-(*S*)-phenylalanine, and N-Boc-C-propargyl-(*S*)-4-fluorophenylglycine (unnatural α-amino acid) were transformed (standard conditions) into ^{2}H-**32**–^{2}H-**35** (Figure 2) with >99% ^{2}H-incorporation and excellent yields. The terminal deuteration (*S*)-N-Boc-C-propargyl methione, (*S*)-N-dansylproline propargyl ester, and N-Bn-**38** afforded ^{2}H-**36**–^{2}H-**38** in excellent yields and, again, levels of deuterium. Incorporating *O*-propargylated glucose, biotin, and lactose afforded the corresponding deuterated derivatives, ^{2}H-**39**–^{2}H-**41** respectively, in excellent yields and levels of deuterium incorporation.

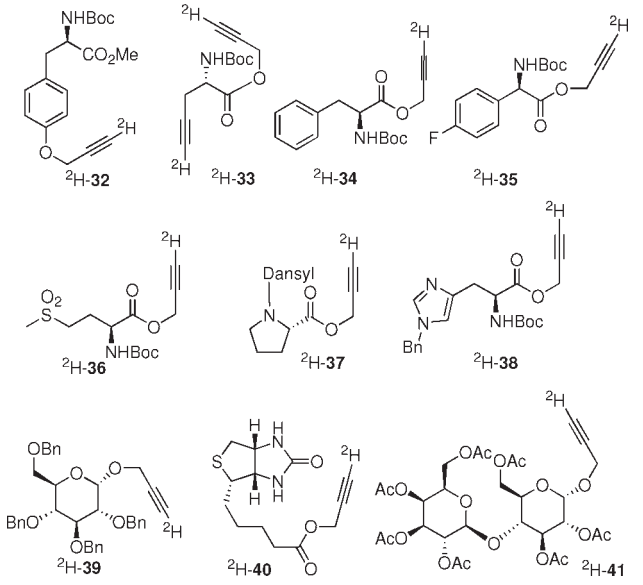
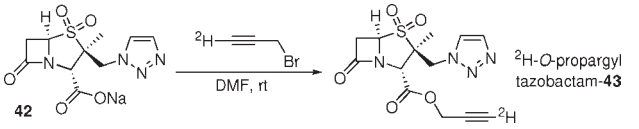


Figure 2. ^{2}H-alkyne derived α-amino acids and carbohydrates.

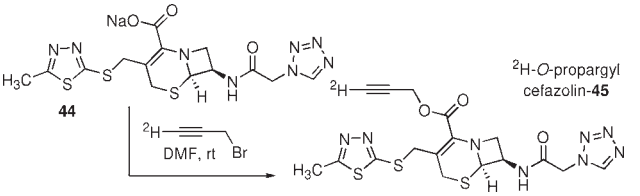
Isotopically labeled entities are crucial to the pharmaceutical, agrochemical, and biotechnology industries (ADME and PKME studies); therefore efficient routes to labeled drug compounds are very important. β-Lactam antibiotics are very sensitive to β-lactam ring opening under aqueous basic or acidic conditions. When *O*-propargyl tazobactam **42** was subjected to our standard slightly basic D_2O/K_2CO_3 ^{2}H-propargylating reaction conditions, none of the desired ^{2}H-**43** was isolated; instead as expected extensive decomposition was observed. While investigating (immobilized) base, solvent, and temperature conditions, we were unable to prevent ring-opening.

Scheme 8. Synthesis of ^{2}H-*O*-Propargyltazobactam ^{2}H-**43**



Negating this, 3-deutero propargyl bromide ^{2}H-**7** (see Scheme 4) reacted directly with the sodium salt of the β-lactam tazobactam **42** affording ^{2}H-**43** in excellent yield and >95% ^{2}H-incorporation (Scheme 8). Similarly reacting the sodium salt of **44** with **7** at ambient temperature in DMF afforded the desired ^{2}H-*O*-propargylcefazolin **45** in excellent yield and deuterium incorporation (Scheme 9).

Scheme 9. Synthesis of ^{2}H-*O*-Propargylcefazolin **45**



In summary, this is an exceptionally mild, synthetically versatile, extremely practical protocol that efficiently transforms terminal alkynes into their deuterated analogs; is straightforward; does not use low temperature, anhydrous solvent, or strong base; is cheap and environmentally friendly; and should prove useful to the organic, inorganic, medicinal and agrochemist alike.

Acknowledgment. The authors would like to acknowledge UEA, Chemistry Innovation and Librarion for financial support and the Mass Spectroscopy Service at the University of Wales for MS analysis.

Supporting Information Available. Data for compounds ^{2}H-**11**–^{2}H-**41**, ^{2}H-**43**, and ^{2}H-**45**. This material is available free of charge via the Internet at http://pubs.acs.org.