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Alkyne aminohalogenation enabled by DBU-activated *N*-haloimides: direct synthesis of halogenated enamines†

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Activated by DBU, *N*-haloimides can be used as both halogen and nitrogen sources to achieve the difunctionalization of terminal alkynes, giving rise to useful halogenated enamines with high efficiency and high regio- and stereoselectivities. The cascade reaction features simple manipulation, mild conditions, a broad substrate scope, readily available reagents, and atom-economy.

Halogenated enamines are versatile building blocks in organic synthesis and medicinal chemistry, as well as valuable intermediates in the construction of biologically active natural products. A few synthetic methods have been developed to date.[1,2] For example, Headley and Li and co-workers communicated palladium-catalyzed aminochlorination by the reaction of arylalkynes with *N*,*N*-dichlorobenzenesulfonamide.[1e] In 2012, Urabe and co-workers described nucleophilic addition of sulfonamides to bromoacetyls to give (*Z*)-2-(sulfonylamino)-1-bromoalkenes.[1f,g] Most recently, Jiang *et al.* developed palladium-catalyzed dehydrogenative aminohalogenation of alkenes.[1h] Although considerable progress has been made, the difunctionalization of carbon–carbon multiple bonds with halogen and amine groups remains an intriguing challenge in modern organic chemistry. Therefore, new and efficient synthetic protocols are still required.

N-Bromosuccinimide (NBS)[3] can be generally employed as a convenient source of either cationic bromine or bromine radicals (Fig. 1, modes I and II).[4,5] In these cases, succinimide would be liberated as a by-product. Obviously, atom economic utilization of both bromine cations and succinimide anions of NBS is highly desirable, but this type of reactivity mode (mode III) is quite less-documented.[6] In our research on halogen-mediated organic transformation,[7] we found that NBS or NBP (*N*-bromophthalimide) activated by DBU *via* halogen bond interaction[8] brings about significantly enhanced electrophilic reactivity for bromine and nucleophilicity for an imido-nitrogen atom. Using the NBS(P)–DBU combination strategy, direct installation of nitrogen functionality has been achieved in the α-amination of alkyl aryl ketones,[7a] β-amination of α,β-unsaturated enones,[7b] and allylic amination of specific alkenes.[7c] In the continued study, we envisioned that the type of dual activation may provide unique opportunity for assembling both Br and N moieties (double duty of NBS(P))[9] into the target molecules, which implies the possibility of NBS(P) to be an electrophile and a nucleophile in the one-pot cascade reaction. Along this line, we conducted DBU-mediated reaction of alkynes and *N*-haloimide, with the aim to achieve aminohalogenation (Scheme 1). Herein, we wish to communicate a novel, atom-economic and efficient approach towards halogenated enamines.

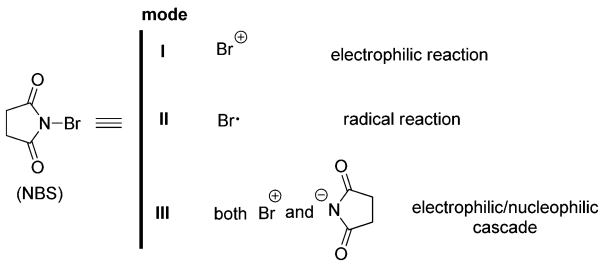
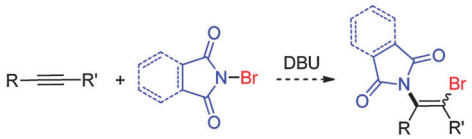


Fig. 1 Reactivity modes of NBS.

Initially, the reaction of phenylacetylene (**1a**) with NBP was chosen as the model reaction (Table 1). As expected, in the presence of 1.1 equivalent of DBU in MeCN at 80 °C, the aminobromonated



Scheme 1 Synthetic exploration of difunctionalization of alkynes *via* dual activation of NBS(P) by DBU.

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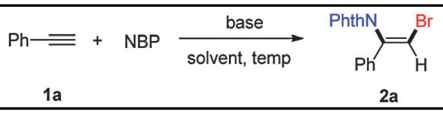
† Electronic supplementary information (ESI) available: Experimental details and characterization of all new compounds and crystal structure data. CCDC 970879 (**2a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc49572h

Table 1 Optimization of the reaction conditions[a]



1a 2a

Entry	Base (equiv.)	Solvent	T (°C)	Time (h)	Yield[b] (%)
1	**DBU (1.1)**	**MeCN**	**80**	**12**	**91**
2	DBU (1.1)	DMF	80	12	62
3	DBU (1.1)	Toluene	80	12	39
4	DBU (1.1)	DCM	Reflux	12	35
5	DBU (1.1)	THF	Reflux	12	16
6	DBU (1.1)	DCE	80	12	NR
7	DBU (1.1)	DMSO	80	12	NR
8	DBN (1.1)	MeCN	80	12	62
9	DABCO (1.1)	MeCN	80	12	0
10	DBU (0.2)	MeCN	80	18	32

[a] Reactions were carried out with **1a** (1.0 mmol), NBP (1.1 equiv.) and base (1.1 equiv.) in 4.0 mL solvent. [b] Isolated yield. NBP = *N*-bromophthalimide; DBU = 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine; DBN = 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine; DABCO = 1,4-diazabicyclo[2.2.2]octane.

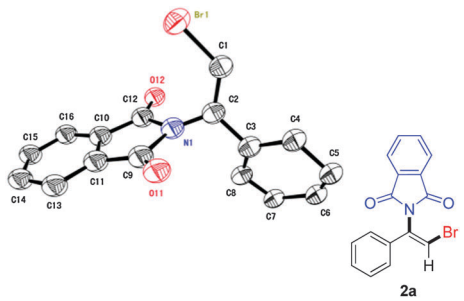
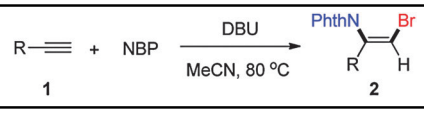


Fig. 2 The single-crystal structure of **2a**.

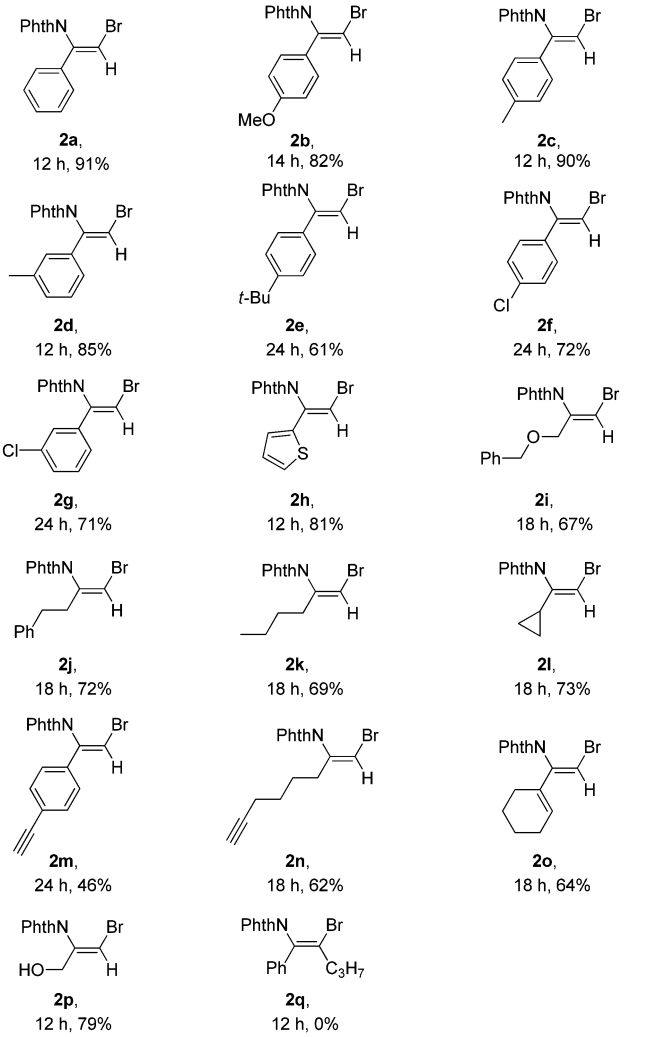
product, (*Z*)-2-(2-bromo-1-phenylvinyl)isoindoline-1,3-dione (**2a**) was obtained in 91% yield (entry 1). The structure of **2a** and its regio- and stereochemistry were confirmed by single-crystal X-ray diffraction (Fig. 2).† Then, other solvents were screened. DMF, toluene, DCM and THF gave decreased yields (entries 2–5) and no reaction was observed in DCE and DMSO (entries 6 and 7) under otherwise identical conditions. Besides DBU, DBN could afford the product as well, albeit in lower yield (62%, entry 8). However, DABCO proved to be completely inefficient (entry 9). A catalytic amount of DBU, *e.g.* 0.2 equiv., was also tried, but it was not enough to drive the reaction to completion (entry 10).

Under the optimized conditions (Table 1, entry 1), a range of reactions were carried out with various alkynes **1** and NBP (1.1 equiv.) in the presence of DBU (1.1 equiv.) in MeCN at 80 °C (Table 2). The reactions of terminal alkynes proceeded smoothly to afford the corresponding bromoenamines **2a–p** in good to excellent yields (46–91%). The substituents on the alkyne substrates may be aryls including either electron-donating substituents (**2a–e**) or electron-withdrawing groups (**2f** and **2g**), heteroaryls such as 2-thienyl (**2h**), alkyl groups (**2i–k**) and cyclopropyl (**2l**). Diynes afforded monobromoenamine products with one terminal acetylene functional group intact (**2m** and **2n**). In the conjugated enyne substrate, the ethylenic bond is more reactive than the C–C double bond, giving product **2o** in 64% yield. The hydroxyl

Table 2 Scope of alkynes[a,b]

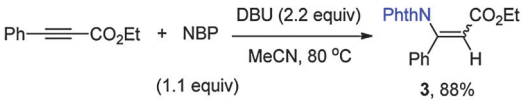


1 2

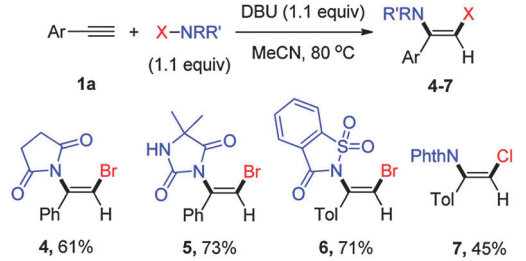


[a] Reactions were carried out with **1a** (1.0 mmol), NBP (1.1 equiv.) and DBU (1.1 equiv.) in MeCN (4.0 mL) at 80 °C. [b] Isolated yield.

group on the alkyne substrate can be tolerable, product **2p** was obtained in 79% yield. In the subsequent work, we moved to explore the reaction with internal alkynes as substrates. The reaction of 1-phenylpentyne and diphenylacetylene with NBP (1.1 equiv.) and DBU (1.1 equiv.) did not occur in MeCN at 80 °C for 12 h. When internal alkynes containing electron-poor groups like ethyl 3-phenylpropiolate were used, the reactions with NBP (1.1 equiv.) and DBU (2.2 equiv.) afforded the amination product, *i.e.*, ethyl 3-(1,3-dioxoisoindolin-2-yl)-3-phenylacrylate (**3**) in high yield (Scheme 2).[10] From the above results one can see that, on one hand, the protocol provides an efficient and highly regio- and stereoselective synthesis of (*Z*)-bromonated enamines from various terminal alkynes.[1b,c] On the other hand, the NBS(P)–DBU combination indeed may be used as a potential haloamination or amination agent.[7a–c]



Scheme 2 Reaction of electron-withdrawing alkyne with NBP–DBU combination.

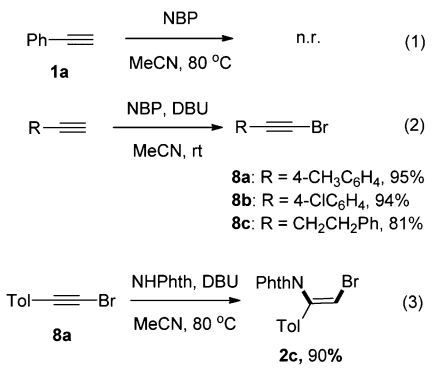


Scheme 3 Reactions of arylacetylenes with *N*-haloimides.

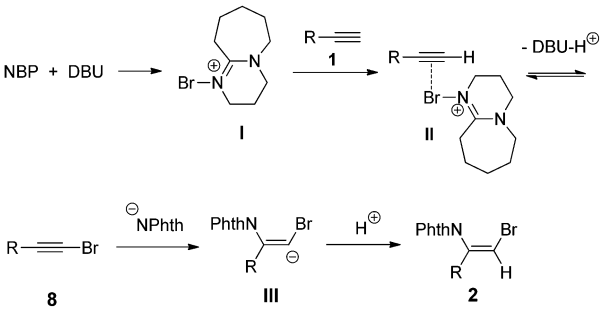
To explore the scope of the halogen and nitrogen components, the reactions of alkynes with other *N*-haloimides were conducted (Scheme 3). In addition to NBP, *N*-bromogenic reagents including NBS, 1,3-dibromo-5,5-dimethylhydantoin and *N*-bromosaccharin were suitable for the reaction, and various imido-moieties were successfully incorporated, affording products **4–6** in 61–73% yields. When NCP was used, chloroenamine **7** was achieved in 45% yield.[11] Halogenated enamine products **2–7** can be utilized as useful synthetic building blocks for further transformation.[12]

To elucidate the reaction mechanism, several control experiments were performed (Scheme 4). In the absence of DBU, the reaction did not take place at all, indicating that DBU plays a vital role in the reaction (eqn (1)). In the reactions of selected alkynes **1** with NBP and DBU performed at room temperature, alkynyl bromides **8a–c** were successfully isolated in good to excellent yields (eqn (2)).[13] The alkynyl bromides may further react with phthalimide in the presence of DBU at 80 °C, giving bromoenamines exclusively (eqn (3)). On the basis of all the results described above, a possible mechanism for the haloenamidation of alkynes is proposed in Scheme 5. The process involves the initial formation of alkynyl halides, subsequent nucleophilic addition,[14–16] and final protonation.[17]

In conclusion, a simple, novel and efficient one-pot aminohalogenation of terminal alkynes has been developed by using



Scheme 4 Control experiments.



Scheme 5 Mechanistic proposal.

N-haloimides as both halogen and nitrogen sources, *via* the DBU dual activation strategy. This aminohalogenation process provided a new idea for the regio- and stereoselective synthesis of *cis*-halogenated enamines. The mechanism for the formation of alkynyl halides, subsequent nucleophilic addition and final protonation was proposed. Starting from electron-poor internal alkynes, enamines may be efficiently achieved. The reaction features mild conditions, a relatively broad substrate scope, readily available reagents, high efficiency and atom-economy. Further work on the exploration of the DBU–*N*-haloimide system in organic synthesis is ongoing.

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Notes and references

1 (*a*) U. Wille, O. Krüger, A. Kirsch and U. Lüning, *Eur. J. Org. Chem.*, 1999, 3185; (*b*) G. Li, H.-X. Wei, S. Kim and M. Neighbors, *Org. Lett.*, 1999, **1**, 395; (*c*) D. Chen, L. Guo, J. Liu, S. Kirtane, J. F. Cannon and G. Li, *Org. Lett.*, 2005, **7**, 921; (*d*) G. Li, S. R. S. Saibabu Kotti and C. Timmons, *Eur. J. Org. Chem.*, 2007, 2745; (*e*) S. Karur, S. Kotti, X. Xu, J. F. Cannon, A. Headley and G. Li, *J. Am. Chem. Soc.*, 2003, **125**, 13340; (*f*) M. Yamagishi, K. Nishigai, T. Hata and H. Urabe, *Org. Lett.*, 2011, **13**, 4873; (*g*) M. Yamagishi, K. Nishigai, A. Ishii, T. Hata and H. Urabe, *Angew. Chem., Int. Ed.*, 2012, **51**, 6471; (*h*) X. Ji, H. Huang, W. Wu and H. Jiang, *J. Am. Chem. Soc.*, 2013, **135**, 5286.

2 For transition metal catalyzed intramolecular alkyne aminohalogenation, see: (*a*) J. Qian, Y. Liu, J. Zhu, B. Jiang and Z. Xu, *Org. Lett.*, 2011, **13**, 4220; (*b*) T. Xu and G. Liu, *Org. Lett.*, 2012, **14**, 5416; (*c*) C. Jonasson, A. Horvath and J.-E. Backvall, *J. Am. Chem. Soc.*, 2000, **122**, 9600.

3 (*a*) A. Wohl, *Ber.*, 1919, **52**, 51; (*b*) K. Ziegler, A. Spath, E. Schf, W. Schumann and E. Winkelmann, *Ann.*, 1942, **551**, 80; (*c*) C. Djerassi, *Chem. Rev.*, 1948, **43**, 271; (*d*) R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, 1963, **85**, 3142; (*e*) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937.

4 Selected references: (*a*) M. Sasaki and A. K. Yudin, *J. Am. Chem. Soc.*, 2003, **125**, 14242; (*b*) A. Sakakura, A. Ukai and K. Ishihara, *Nature*, 2007, **445**, 900; (*c*) L. Zhou, C. K. Tan, J. Zhou and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2010, **132**, 10245; (*d*) L. Zhou, C. K. Tan, X. Jiang, F. Chen and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2010, **132**, 15474; (*e*) Y. Cai, X. Liu, Y. Hui, J. Jiang, W. Wang, W. Chen, L. Lin and X. Feng, *Angew. Chem., Int. Ed.*, 2010, **49**, 6160; (*f*) R. S. Brown, *Acc. Chem. Res.*, 1997, **30**, 131.

5 (*a*) L. Horner and E. H. Winkelmann, *Angew. Chem.*, 1959, **71**, 349; (*b*) C. Walling, A. L. Rieger and D. D. Tanner, *J. Am. Chem. Soc.*, 1963, **85**, 3129; (*c*) G. A. Russell and K. M. Desmond, *J. Am. Chem. Soc.*, 1963, **85**, 3139; (*d*) M. Y. Niu, Z. G. Yin, H. Fu and Y. Y. Jiang, *J. Org. Chem.*, 2008, **73**, 3961.

6 (*a*) A. Alix, C. Lalli, P. Retailleau and G. Masson, *J. Am. Chem. Soc.*, 2012, **134**, 10389; (*b*) L. Song, S. Luo and J.-P. Cheng, *Org. Lett.*, 2013, **15**, 5702; (*c*) W. Li, Z. Chen, J. Zhou, J. Hu and W. Xia, *Chin. J. Chem.*, 2012, **30**, 830.

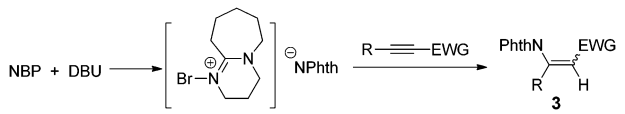
7 With NBS–DBU combination: (*a*) Y. Wei, S. Lin and F. Liang, *Org. Lett.*, 2012, **14**, 4202; (*b*) Y. Wei, S. Lin, F. Liang and J. Zhang, *Org. Lett.*, 2013, **15**, 852; (*c*) Y. Wei, F. Liang and X. Zhang, *Org. Lett.*, 2013, **15**, 5186. With NBS–carboxylic acid combination: (*d*) Y. Wei, S. Lin, J. Zhang, Z. Niu,

Q. Fu and F. Liang, *Chem. Commun.*, 2011, **47**, 12394; (*e*) Y. Wei, S. Lin, H. Xue, F. Liang and B. Zhao, *Org. Lett.*, 2012, **14**, 712; (*f*) H. Xue, H. Tan, D. Wei, Y. Wei, S. Lin, F. Liang and B. Zhao, *RSC Adv.*, 2013, **3**, 5382.

8 For a recent review of NBS activation by Lewis base, see: (*a*) S. E. Denmark, W. E. Kuester and M. T. Burk, *Angew. Chem., Int. Ed.*, 2012, **51**, 10938; selected papers: (*b*) Ref. 4*b*; (*c*) S. A. Snyder and D. S. Treitler, *Angew. Chem., Int. Ed.*, 2009, **48**, 7899; (*d*) X.-L. Cui and R. S. Brown, *J. Org. Chem.*, 2000, **65**, 5653; (*e*) S. A. Snyder, D. L. Treitler and A. P. Brucks, *J. Am. Chem. Soc.*, 2010, **132**, 14303; (*f*) H. Ghasemnejad-Bosra, M. Haghdadi, O. Khanmohammade, A. M. Gholipour and G. Asghari, *J. Chin. Chem. Soc.*, 2008, **55**, 464; (*g*) W. Zhang, H. Xu, H. Xu and W. Tang, *J. Am. Chem. Soc.*, 2009, **131**, 3832.

9 For excellent work on double duty of alkynyl (cyanogen) halides and bromoperfluoroarenes, see: (*a*) A. Trofimov, N. Chernyak and V. Gevorgyan, *J. Am. Chem. Soc.*, 2008, **130**, 13538; (*b*) Z. Li and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2011, **50**, 2808; (*c*) Z. Li and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2012, **51**, 1225.

10 Product **3** was supposed to be formed through the Michael addition of an imido-moiety, which was liberated in situ from the NBP–DBU combination, to the α,β-unsaturated alkynones.



11 Unfortunately, NCS and NIS proved to be inefficient at the moment.

12 (*a*) X. Chen, D. Chen, Z. Lu, L. Kong and G. Zhu, *J. Org. Chem.*, 2011, **76**, 6338; (*b*) H. J. Kim, J. Kim, S. H. Cho and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 16382; (*c*) Ref. 1*h*.

13 Haloalkynes are versatile synthons for synthetic organic chemistry. For the preparation of 1-haloalkynes, see: (*a*) D. Naskar and S. Roy, *J. Org. Chem.*, 1999, **64**, 6896; (*b*) X. Nie and G. Wang, *J. Org. Chem.*, 2006, **71**, 4734; (*c*) A. Leyva-Pérez, P. Rubio-Marqués, S. S. Al-Deyab, S. I. Al-Resayes and A. Corma, *ACS Catal.*, 2011, **1**, 601; (*d*) Z. Mu, L. Shu, H. Fuchs, M. Mayor and L. Chi, *J. Am. Chem. Soc.*, 2008, **130**, 10840; (*e*) D. Sud, T. J. Wigglesworth and N. R. Branda, *Angew. Chem., Int. Ed.*, 2007, **46**, 8017; (*f*) A. Fujii and S. I. Miller, *J. Am. Chem. Soc.*, 1971, **93**, 3694; (*g*) G. R. Ziegler, C. A. Welch, C. E. Orzech, S. Kikkawa and S. I. Miller, *J. Am. Chem. Soc.*, 1963, **85**, 1648; (*h*) K. Okuhara, *J. Org. Chem.*, 1976, **41**, 1487. The protocol developed here may also provide an alternative mild and efficient access to 1-haloalkynes.

14 Selected papers on the nucleophilic addition to haloacetylenes: (*a*) Ref. 1*f*; (*b*) M. Yamagishi, J. Okazaki, K. Nishigai, T. Hata and H. Urabe, *Org. Lett.*, 2012, **14**, 34; (*c*) Z. Chen, H. Jiang, Y. Li and C. Qi, *Chem. Commun.*, 2010, **46**, 8049.

15 Nucleophilic addition appears to be the rate-determining step.

16 The same stereochemistry was observed as that reported by Ureba *et al.* (ref. 1*f* and *g*). We suppose that the weak interaction between alkynyl bromide, DBU, and phthalimide exists, which may be the reason for the stereochemistry outcome and why a catalytic amount of DBU cannot drive the reaction to completion.

17 The proton may arise from either terminal alkyne hydrogen or water in the reaction system.