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One-pot, two-step conversion of alkynes to α-amino (α,α-diamino) ketones with a DMF-activated *N*-bromoimide strategy†

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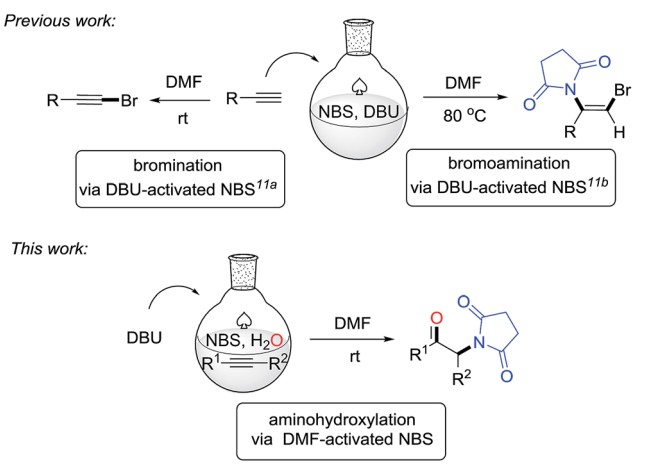
A simple, one-pot, two-step cascade reaction for the synthesis of α-amino ketones has been developed. Both terminal and internal alkynes react with DMF-activated *N*-bromosuccinimide (phthalimide) and water (as external *O*-nucleophile), followed by the introduction of DBU, giving imidated ketones efficiently (the N-sources arise from inherent *N*-haloimides). Monoamino ketones were the main products with NBS. Mono and/or diamino ketones are produced when NBP is utilized. A mechanism of sequential oxy-1,1-dibromogenation of alkynes, nucleophilic substitution and reductive debromination (or second nucleophilic substitution) is proposed.

α-Amino ketones constitute an important class of biologically active compounds. For example, they are key scaffolds existing widely in a variety of natural products and pharmaceuticals such as amfepramone, bupropion, *etc.*[1] α-Amino ketones have also been used as synthetic intermediates in organic transformations.[2] Traditional methods to synthesize α-amino ketones start from ketones, which incorporate nucleophilic amination,[3] electrophilic amination[4] and oxidative amination.[5] The methods to synthesize α-amino ketones directly starting from alkynes are relatively less documented.[6–8] In 2012, Miura *et al.* reported a rhodium(II)-catalyzed denitrogenative hydration reaction of *N*-sulfonyl-1,2,3-triazoles that opens a new synthetic route towards α-amino ketones from terminal alkynes.[7] In the same year, palladium-catalyzed synthesis of α-amino ketones from propargylic carbonates was reported by Cacchi and co-workers.[8] Thus, the development of novel synthetic methods to α-amino ketones directly from alkynes still remains a challenge, especially under metal-free conditions.[9]

In our research, we have developed *N*-haloimides to be a versatile aminating reagent (rather than traditional brominating reagent) applied in a variety of organic transformations.[10] Recently, we carried out the work of DBU-activated *N*-haloimides with alkyne substrates. 1-Haloalkynes could be readily prepared in good to excellent yields at room temperature.[11a] Upon heating to 80 °C, aminohalogenation of terminal alkynes were achieved in high efficiency with high regio- and stereoselectivities (Scheme 1, top).[11b] In this case, NBS was mixed with DBU firstly (with DBU to activate NBS[12]), followed by the addition of alkyne substrate. In further work, we found that another type of difunctionalization product, *i.e.*, α-amino ketones can be attained, simply by varying the feed sequence of the above-mentioned substrates (Scheme 1, bottom). That is, NBS and alkynes were dissolved in wet DMF in the first step (using DMF to activate NBS[13a]) and DBU was added in the second step.[14] The reaction may take place at room temperature and both internal and terminal alkynes are suitable substrates. The approach provides a simple and efficient conversion of unactivated alkynes into α-amino ketones under mild and metal-free conditions.



Scheme 1 Reactions of alkynes with NBS in our group.

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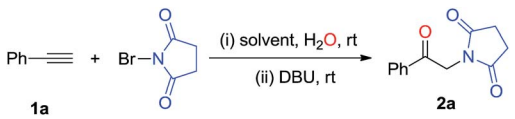
Table 1 Optimization of the reaction conditions[a]



	Step 1[b]			Step 2		
Entry	Solvent	H_2O (equiv.)	Time (h)	Base (equiv.)	Time (min)	Yield[c] (%)
1	DMF	1.5	1	DBU (1.1)	5	47
2	DMF	1.5	1	DBU (2.2)	5	89
3	DMF	0	1	DBU (1.1)	5	0
4	THF	1.5	1	DBU (2.2)	60	0
5	MeCN	1.5	6	DBU (2.2)	60	0
6	DCE	1.5	6	DBU (2.2)	60	0
7	DMSO	1.5	3	DBU (2.2)	5	25
8	DMA	1.5	3	DBU (2.2)	10	48
9	NMP	1.5	1	DBU (2.2)	5	49
10	DMF	1.5	1	DABCO (2.2)	60	Trace
11	DMF	1.5	1	NEt_3 (2.2)	60	Trace
12	DMF	1.5	1	TMG (2.2)	5	65
13	DMF	1.5	1	NaOH (2.2)	5	80
14	DMF	1.5	1	K_2CO_3 (2.2)	30	82

[a] Reactions were carried out with **1a** (1.0 mmol), NBS (2.2 equiv.), base (1.1 or 2.2 equiv.) in 2.0 mL solvent at room temperature. [b] α,α-Dibromo ketone was produced in the first step. [c] Isolated yield.

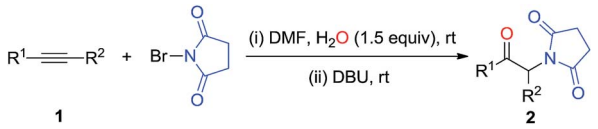
Table 1 shows the reaction conditions for the synthesis of 1-(2-oxo-2-phenylethyl)pyrrolidine-2,5-dione **2a** with phenylacetylene **1a** as model substrate. To our delight, with NBS (2.2 equiv.), H_2O (1.5 equiv.) and DBU (1.1 equiv.) in DMF at room temperature, the desired product **2a** was obtained in 47% yield (Table 1, entry 1). When 2.2 equiv. of DBU was used, the yield of product **2a** reached up to 89% (entry 2). The product **2a** was not obtained in the absence of water, indicating that H_2O plays a key role for the transformation (entry 3). The target product **2a** was not observed in other solvents such as THF, MeCN and DCE (entries 4–6). Nevertheless, solvents DMSO, DMA and NMP were beneficial in producing **2a**, although the yields are incomparable to that in DMF (entries 7–9).[13] Further attempt to improve the yield by using DABCO, NEt_3, TMG, instead of DBU as the base gave unsatisfactory results (entries 10–12). Inorganic bases like NaOH and K_2CO_3 were also able to achieve the transformation (entries 13 and 14).

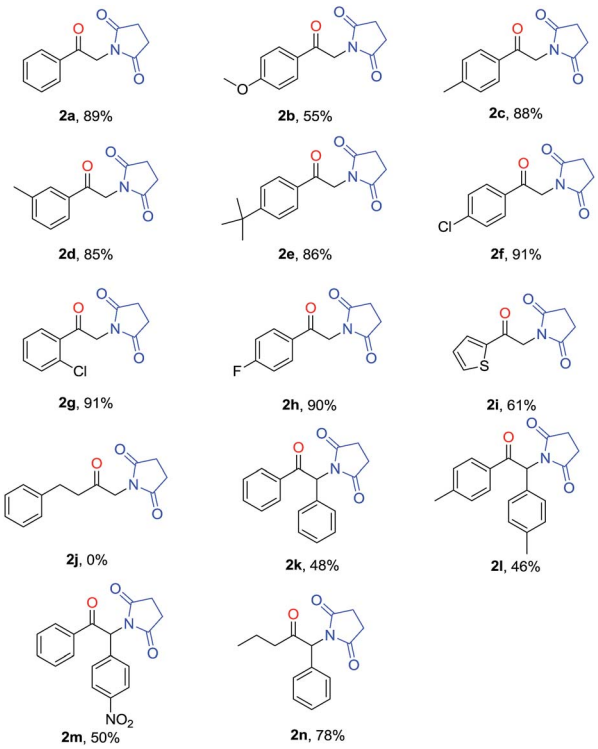
With the optimized conditions in hand, we turned to evaluate the generality of this protocol (Table 2). The reactions of terminal alkynes proceeded smoothly to afford the corresponding α-amino ketones (**2b–h**) in good to excellent yields (61–91%). In particular, the substituents on the alkyne substrates may be aryls bearing either electron-donating (*e.g.* methoxyl, methyl and *t*-butyl) substituents (**2b–e**) or electron-withdrawing groups, like chlorine and fluorine atoms (**2f–h**), and heteroaryls such as 2-thienyl (**2i**). Alkyl alkyne showed sluggishness, probably due to an increase in the electron density of the alkyne triple bond.[15] Encouraged by the results obtained with terminal alkynes, internal alkynes were subjected to the reaction sequence. Symmetrical alkynes such as diphenylacetylene and 1,2-di-*p*-tolylethyne afforded the desired α-amino ketones **2k** and **2l** in moderate yields. As for unsymmetrical diarylalkynes, *e.g.* 1-(4-methylphenyl)-2-phenylacetylene, a mixture of two types of α-amino ketones were produced due to regioselectivity. To our delight, unsymmetrical diarylalkynes like 1-(4-nitrophenyl)-2-phenylethyne and aryl alkyl alkynes like 1-phenyl-1-pentyne could give single α-amino ketones **2m** and **2n**, respectively. Probably due to the steric hindrance effect, the transformation for internal alkyne substrates into the corresponding α-amino ketones generally required prolonged reaction time.

In the following work, the reactions of alkynes with *N*-bromophthalimide (NBP) were conducted (Table 3). Similar to NBS, NBP was also a competent reagent. However, different from NBS, both α-amino ketones 3 and α,α-diamino ketones 4 were obtained in this case. For terminal alkynes such as 4-F-, 4-Cl-, 3-Me-phenylacetylene, 2-thienylacetylene and 4-phenyl-1-butyne, α,α-diamino ketones **4a–e** proved to be the main products (for the possible reason, see the following mechanism part). Symmetrical diarylalkynes such as diphenylacetylene could not afford the target products, while unsymmetrical diarylalkynes like 1-nitro-4-(phenylethynyl)benzene gave single monoaminated ketone **3g** in 51% yield. As an example of aryl alkyl alkyne, 1-phenyl-1-pentyne, gave the α-amino ketone **3h** in 73% yield, with only trace amount of α,α-diamino ketone **4h**.[16]

In the reaction of 3-hexyne (**2i**) and NBP, we found that aminated eone **5** and α,α-diamino ketone **6** were produced in 40% and 44% yield, respectively (Scheme 2). By prolonging the reaction time and increasing the amount of NBP and DBU to be

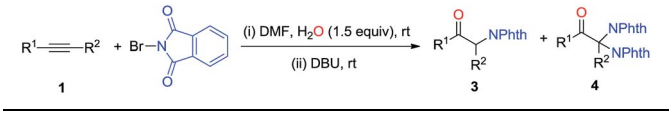
Table 2 Reactions of alkynes with NBS[a,b,c,d]

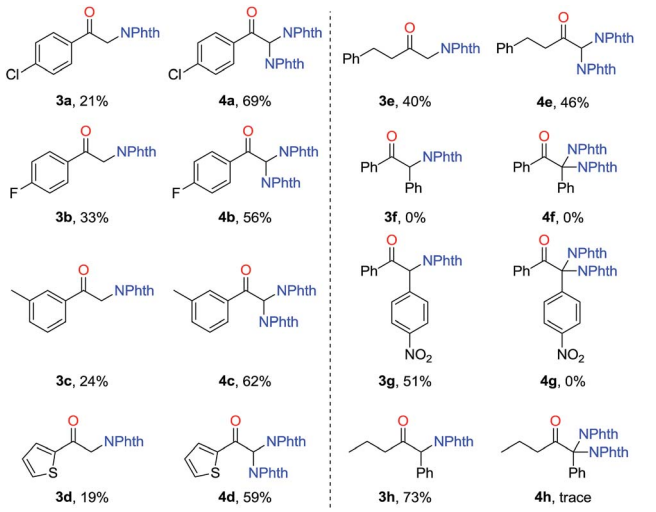




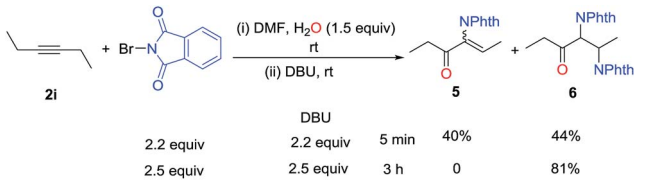
[a] Reactions were carried out with **1** (1.0 mmol), NBS (2.2 equiv.), H_2O (1.5 equiv.), DBU (2.2 equiv.) in DMF (2.0 mL) at room temperature. [b] Isolated yield. [c] α,α-Dibromo ketones can be observed in the first step. [d] Trace amount of α,α-diamino ketones were observed.

Table 3 Reactions of alkynes with NBP[a,b]

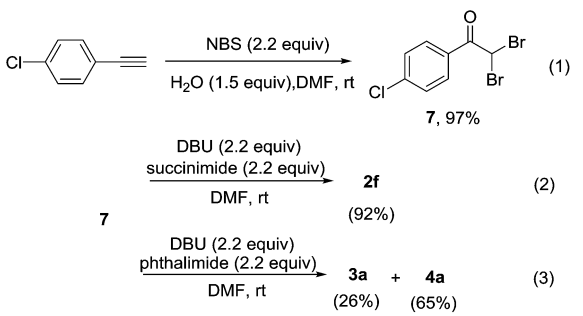




[a] Reactions were carried out with **1a** (1.0 mmol), NBP (2.2 equiv.), H_2O (1.5 equiv.), DBU (2.2 equiv.) in DMF (2.0 mL) at room temperature. [b] Isolated yield.



Scheme 2 Reaction of 3-hexyne with NBP.

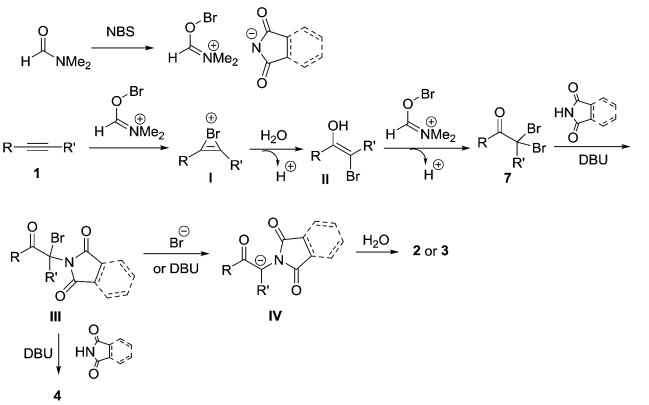


Scheme 3 Control experiment.

2.5 equivalent, product **6** could be obtained in 81% yield as the single product.[17]

To elucidate the mechanism, the following control experiments were conducted (Scheme 3). In the absence of DBU, 4-chlorophenylacetylene reacts with NBS and water in DMF, furnishing α,α-dibromo ketone **7** in 97% yield (eqn (1)).[18] When isolated **7** was treated with DBU (2.2 equiv.) in the presence of succinimide (2.2 equiv.) in DMF at room temperature, target product **2f** can be obtained in 92% yield (eqn (2)). The reaction of α,α-dibromo ketone **7** with phthalimide and DBU afforded **3a** and **4a** in 26% and 65% yields, respectively (eqn (3)).

On the basis of the results described above, a possible mechanism for the one-pot two-step reaction was proposed in Scheme 4. Firstly, DMF-activated NBS would react with alkynes to form bromonium intermediate **I**.[13] Then, water attack generates brominated enol **II**, which would further react with DMF-activated NBS. α,α-Dibromo ketone **7** is thus produced. Sequential nucleophilic substitution by succinimide or phthalimide nucleophile arising from NBS(P) and reductive debromination[19] leads to the formation of α-amino ketone **2** or **3**. Double nucleophilic substitution by phthalimide anion affords the corresponding α,α-diamino ketone **4**. We think that the difference in the formation of monoaminated and/or diaminated products are attributed to, on one hand, the different nucleophilicities of succinimide relative to phthalimide. On the



Scheme 4 Mechanistic proposal.

other hand, two types of C–Br bond cleavage involved in intermediate **III** (nucleophilic substitution to produce 4 and reductive debromination to give **IV**) are competitive, somewhat influenced by the electronic and steric effects within **III**.

In summary, we have developed a simple, highly efficient and metal-free difunctionalization of unactivated alkynes to synthesize medicinally important α-amino ketones and α,α-diamino ketones under mild reaction conditions. The reaction exhibits broad substrate scope, good functional group tolerance and easy handing. A tandem mechanism of oxy-1,1-dibromogenation of alkynes, nucleophilic substitution and reductive debromination (second nucleophilic substitution for the formation of **4**) was proposed. The result presented here further demonstrates that imido-moiety arises from inherent NBS(P) can be used *in situ* as N-sources in organic transformation.[10,11b]

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