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Communication

# A facile transformation of alkynes into α-amino ketones by an *N*-bromosuccinimide-mediated one-pot strategy

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ABSTRACT

A facile transformation of alkynes into α-amino ketones by an *N*-bromosuccinimide-mediated one-pot cascade strategy is described. A variety of α-amino ketones are obtained in moderate to good yields under mild conditions. To overcome the multi-step synthesis, *N*-bromosuccinimide is involved in multiple tasks, playing a key role in the reaction course.



α-Amino ketones are a class of highly valuable molecules that widely exist in natural products and pharmaceuticals [1]. In particular, they have gained much attention due to their roles as key intermediates in the syntheses of biologically active compounds [2]. Various approaches have been developed to construct this class of molecules [3]. All these conventional methods involve the α-bromination of ketones [4] or bromohydroxylation of olefins followed by oxidation [5]. Such processes have been frequently carried out with lachrymatic phenacyl halides [4], toxic bromine [6] and precious metals [7], which hinder their widespread applications due to the chemical toxicity and tedious handling requirements. Recently, halogen-activated organic reactions have provided an attractive approach to this transformation under metal-free conditions, especially the halonium-initiated one-pot cascade [8]. For example, Sudalai reported the direct transformation of alkenes and enol ethers into α-imido carbonyl compounds with the combination of *N*-bromosuccinimide (NBS) and dimethyl sulfoxide (DMSO) [9]. The Kshirsagar group demonstrated an NBS-promoted one-pot strategy [10]. Liang and co-workers developed the method of simultaneous intramolecular C=O and *C—N* bond formation of α-amino ketones *via* halogen activation [11]. However, there have been few reports of the simple and efficient conversion of alkynes into α-amino ketones under metal-free conditions [12]. Addressing the regioselectivity and expanding the substrate scope still remain challenges. Therefore, the development of a novel efficient approach for the rapid chemoselective construction of α-amino ketones directly from various alkynes is highly desired. In this context, we wish to report a facile transformation consisting of *N*-bromosuccinimide-mediated one-pot cascade under metal-free conditions (Scheme 1).

Phenyl acetylene **1a** was selected as the test substrate. The model reaction of phenyl acetylene **1a** with NIS (2.0 equiv.) in $H_2O$ at 80 °C for 1 h, followed by the addition of DBU (3.0 equiv.) and acetone (1 mL) and stirring at room temperature for 2 h, was initially examined. 1-(2-*Oxo*-2-phenylethyl)pyrrolidine-2,5-dione (**2a**) was obtained only in 18% yield (Table 1, entry 1). The use of NCS instead of NIS did not provided the desired product **2a**, whereas with NBS, the yield of **2a** reached 71% (Table 1, entries 2, 3), indicating that NBS played a key role in the reaction course. The effects of various bases were investigated and we found that other bases, besides DBU, were found to be less effective or even inefficient (Table 1, entries 3–9). Lower yields were obtained when the reaction was performed with THF, MeCN, DCM, DMSO, or DMF as the solvent (Table 1, entries 10–14). To further improve the yield, the reaction conditions, such as the dosage of DBU, reaction temperature and time were also optimized. When the reaction temperature was reduced to 60 °C, the yield significantly decreased (53%, Table 1, entry 15). Increasing the reaction temperature did not change the yield (70%, Table 1, entry 16). However, considering energy consumption, 80 °C was selected as the optimal reaction temperature. Additionally, a lower conversion was obtained upon lowering the amount of DBU to 2.0 equiv. (63%, Table 1, entry 17). A similar yield was achieved in the presence of 3.0 equiv. of DBU

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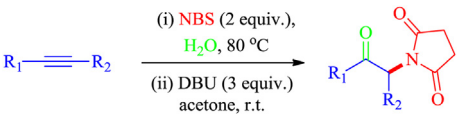
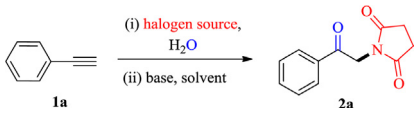



**Scheme 1.** One-pot conversion of alkynes to $\alpha$-amino ketones.

**Table 1**
Optimization of the reaction conditions.[a]




| Entry | Halogen source | Base | Solvent | Yield(%)[b] |
|---|---|---|---|---|
| 1 | NIS | DBU | Acetone | 18 |
| 2 | NCS | DBU | Acetone | 0 |
| 3 | NBS | DBU | Acetone | 71 |
| 4 | NBS | $Et_3N$ | Acetone | 21 |
| 5 | NBS | DABCO | Acetone | 12 |
| 6 | NBS | $NaHCO_3$ | Acetone | 15 |
| 7 | NBS | $K_2CO_3$ | Acetone | 11 |
| 8 | NBS | *t*-BuOK | Acetone | 26 |
| 9 | NBS | NaOH | Acetone | 38 |
| 10 | NBS | DBU | DMF | 45 |
| 11 | NBS | DBU | DCM | 29 |
| 12 | NBS | DBU | MeCN | 31 |
| 13 | NBS | DBU | DMSO | 0 |
| 14 | NBS | DBU | THF | 12 |
| 15[c] | NBS | DBU | Acetone | 53 |
| 16[d] | NBS | DBU | Acetone | 70 |
| 17[e] | NBS | DBU | Acetone | 63 |
| 18[f] | NBS | DBU | Acetone | 71 |
| 19[g] | NBS | DBU | Acetone | 70 |

[a] Reactions conditions: **1a** (1.0 mmol), halogen source (2.0 equiv.) in 1 mL of $H_2O$, 80 °C, 1 h then solvent (1 mL), base (3.0 equiv.), r.t., 2 h.
[b] Isolated yield.
[c] 70 °C.
[d] 90 °C.
[e] With 2.0 equiv. of DBU.
[f] With 3.0 equiv. of DBU.
[g] Reaction performed at 80 °C for 2 h, then at r.t. for 4 h.

(71%, Table 1, entry 18). A prolonged reaction time had no effect on the yield (70%, Table 1, entry 19). Studies showed that a combination of NBS (2 equiv.) and DBU (3 equiv.) worked well for the transformation.

To evaluate the generality of this protocol, the one-pot cascade reaction was extended to various substituted alkynes under the optimized conditions, providing the corresponding $\alpha$-amino ketones in 50%–77% yields (Fig. 1). Terminal alkynes containing electron-rich aryl (Fig. 1, **2b**, **2c**, **2f**) and electron-deficient aryl (Fig. 1, **2d**, **2e**, **2g**, **2h**) moieties were found to be excellent substrates for the transformation, providing the desired products (Fig. 1, **2a–h**). In addition, the scope of the reaction was further explored for 2-naphthyl, 2-pyridyl and 2-thienyl substrates, affording the corresponding products in moderate yields of 65%, 53% and 58%, respectively (Fig. 1, **2j**, **2k** and **2l**). For alkyl alkynes, the transformation also proceeded smoothly, leading to the corresponding products **2i**, **2m** and **2o** in 50%, 63% and 62% yields, respectively. Nevertheless, substrate **1n** was ineffective under these conditions. Notably, a variety of internal alkynes were successfully converted into the target products in moderate yields (Fig. 1, **2p**, **2q** and **2y**).

This highly efficient synthesis of functionalized $\alpha$-amides ketones permits access to various important $\alpha$-amino ketones. Treating **2a** with dilute sodium hydroxide by hydrolyzing the

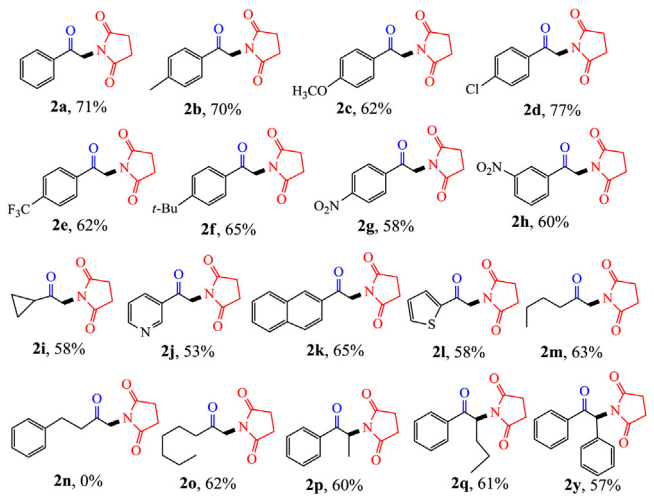
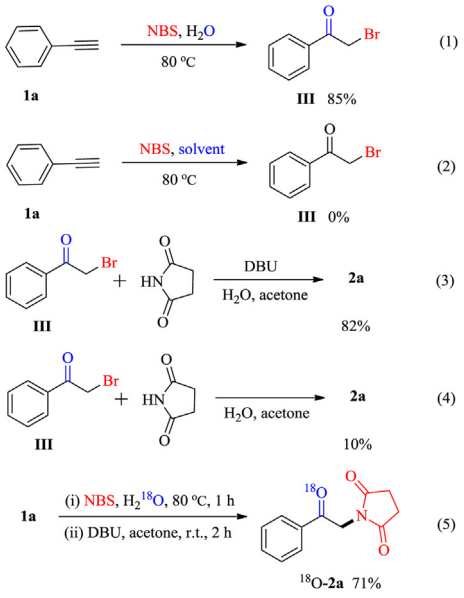



**Fig. 1.** Scope and limitation for the synthesis of $\alpha$-imido ketones. Isolated yield.

succinimide gave 2-amino-1-phenylethanone in 89% yield (Supporting information).

To gain insight into the reaction mechanism, control experiments were performed (Scheme 2). To explore the role of NBS in the reaction system, alkyne **1a** was treated with NBS in the absence of DBU in $H_2O$, and phenacyl bromide III was obtained in 85% yield (Scheme 2, Eq. (1)). Furthermore, the same reaction was conducted without water, and no corresponding product III was observed (Scheme 2, Eq. (2)). This indicated that water was crucial in this step. Phenacyl bromide and succinimide in the presence of DBU in acetone at r.t. for 2 h gave the corresponding product **2a** in 82% yield (Scheme 2, Eq. (3)), confirming that the reaction proceeded *via* an intermediate phenacyl bromide. The absence of DBU in the same reaction did not alter the formation of product **2a** (Scheme 2, Eq. (4)), demonstrating that DBU promotes the nucleophilic reaction in the reaction system. When alkyne **1a** was subjected to the standard conditions in the presence of $H_2{}^{18}O$, $^{18}O$-**2a** was detected (Scheme 2, Eq. (5)), which further indicated that the oxygen atom of benzoyl group originated from water.

Based on our experimental results described above and previously reported studies, a plausible mechanism for the




**Scheme 2.** Control experiments.

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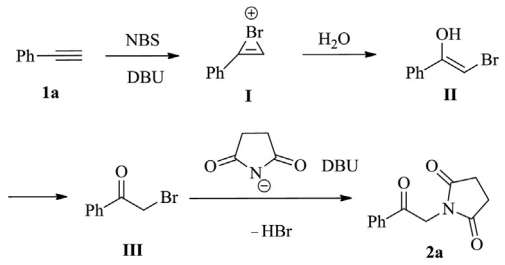


**Scheme 3.** Plausible reaction mechanism.

α-imidation of ketones is proposed in Scheme 3. Initially, the reaction of alkyne **1a** with NBS led to the formation of the bromonium ion intermediate (**I**), which is further regioselectively attacked by water to generate brominated enol (**II**). Subsequently, α-bromoketone (**III**) is formed *via* a rearrangement reaction. Upon nucleophilic substitution by the succinimide anion, α-bromoketone (**III**) transforms into the corresponding α-imido ketone **2a**.

To summarize, a facile efficient transformation of commercially available alkynes into α-amino ketones by an *N*-bromosuccinimide-mediated one-pot cascade strategy was developed. A variety of α-amino ketones were obtained in moderate to good yields under mild conditions. The reaction was simple and amenable to a number of functional groups, which makes the current process a practical method to prepare α-amino ketones from alkynes. To overcome the multi-step synthesis, NBS was involved in multiple tasks, playing a key role in the reaction course. Further efforts will be devoted to exploring various nucleophiles and expanding the applications of this synthesis strategy.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cclet.2018.03.031.

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