

# *N*-Bromosuccinimide/ 1,8-Diazabicyclo[5.4.1]undec-7-ene Combination: $\beta$ -Amination of Chalcones via a Tandem Bromoamination/ Debromination Sequence

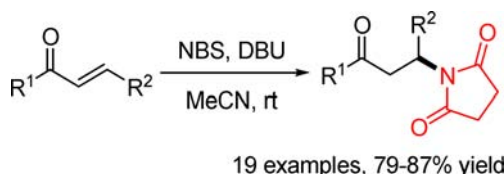
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## ABSTRACT



A one-pot cascade transformation of chalcones into  $\beta$ -imidoketones has been developed, in which NBS provides both electrophilic bromine and nucleophilic nitrogen sources, and DBU functions as a nucleophilic reagent to activate NBS to be a more electrophilic bromine species and to further remove the bromine of  $\alpha$ -bromoketones. The whole process involves tandem bromoamination and debromination, which represents a unique example of preparing  $\beta$ -aminoketones by the reaction of chalcones with the NBS/DBU combination.

$\beta$ -Aminoketones are highly valuable molecules regarding their vast applications as building blocks of drugs and biologically active compounds.<sup>1</sup> Conventional approaches for the synthesis of  $\beta$ -aminoketones include the Mannich reaction of methyl ketones with an amine and para-formaldehyde,<sup>2</sup> amination of  $\beta$ -haloalkyl ketones, and aza-Michael addition of an appropriate *N*-nucleophile to

an  $\alpha,\beta$ -unsaturated ketone.<sup>3</sup> To date, some new methods have been developed for the synthesis of  $\beta$ -aminoketones.<sup>4–7</sup> For example, the Gomtsyan group reported the addition of vinyl Grignard reagents to *N*-methoxyamides.<sup>4</sup> Tu and co-workers developed an aziridino alcohol rearrangement (semipinacol rearrangement) as an efficient approach toward  $\beta$ -aminoketones.<sup>5</sup> Additionally, the *N*-heterocyclic carbene mediated reaction of enals with aziridines<sup>6</sup> and the CuBr/TBHP catalyzed reaction of silyl enol ethers and *N,N*-dimethylaniline<sup>7</sup> have been recently presented. Although a variety of methods have been reported, further development of more efficient and atom-economical routes

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to  $\beta$ -aminoketones still remains a hot topic in modern organic synthesis.

In our research on halogen (e.g., halogenation, halonium, hypervalent halogen, and halogen bond) mediated organic reactions,<sup>8</sup> we recently reported a one-pot cascade reaction of methyl ketones with the NBS/DBU combination affording  $\alpha$ -aminoketones (Scheme 1a).<sup>8c</sup> In this reaction, NBS plays a dual role in providing both electrophilic bromine and nucleophilic nitrogen sources, and DBU functions as a base to deprotonate methyl ketones to be enolates and a nucleophilic promoter to activate NBS to be a more electrophilic bromine species. In our continued work, we became interested in exploring the reaction with chalcone substrates. As a result,  $\beta$ -aminoketones were achieved via a domino bromoamination/debromination sequence, which provides a convenient and economic route toward  $\beta$ -aminoketones (Scheme 1b). This represents a unique example of preparing  $\beta$ -aminoketones by the reaction of chalcones with the NBS/DBU combination.<sup>9</sup>

**Scheme 1.**  $\alpha$ - vs  $\beta$ -Aminoketones by a Combination of NBS and DBU



Initially, the model reaction of chalcone **1a** with NBS was examined under basic conditions (Table 1). No reaction occurred in CH<sub>2</sub>Cl<sub>2</sub> at rt, by the utilization of NaOH, NaOEt, NaH, *t*-BuOK, and DABCO as the base (entries 1–5). Gratifyingly, the reaction with DBN or DBU (1.2 equiv)<sup>10</sup> as the base in CH<sub>2</sub>Cl<sub>2</sub> gave 1-(3-oxo-1,3-diphenylpropyl)-pyrrolidine-2,5-dione (**2a**) in 75% and 78% yield, respectively (entries 6 and 7). When THF, toluene, and DMF were selected as the solvent, the yields decreased (entries 8, 9, and 11). Among all the solvents tested, MeCN was the most efficient, affording **2a** in 81% yield (entry 10). One can see that DBU and DBN worked well in the one-pot amination reaction while other bases were inefficient. The reason for this may be attributed to the activation of NBS by DBU or DBN to be a more electrophilic bromine species via halogen bond interaction.<sup>11,12</sup> Additionally, NIS and NCS showed similar reactivity to NBS.

Under the optimized conditions (Table 1, entry 10), a range of reactions were carried out with various chalcones

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(9) Generally, the reaction of  $\alpha,\beta$ -unsaturated enones with NBS gave haloaminated products under acidic conditions, most often with external amino sources. Examples with the imido moiety from NBS itself are rare. For such a recent example of vicinal haloamination of enecarbamates with NBS catalyzed by phosphate salt, see: Alix, A.; Lalli, C.; Retaillieu, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, 134, 10389.

(10) It was found that a catalytic amount (e.g., 0.2 equiv) of DBU was not enough to drive the reaction to completion.

**Table 1.** Optimization of the Reaction Conditions<sup>a</sup>

entry	base	solvent	<b>2a</b> yield (%) <sup>b</sup>
1	NaOH	CH <sub>2</sub> Cl <sub>2</sub>	n.r.
2	NaOEt	CH <sub>2</sub> Cl <sub>2</sub>	n.r.
3	NaH	CH <sub>2</sub> Cl <sub>2</sub>	n.r.
4	<i>t</i> -BuOK	CH <sub>2</sub> Cl <sub>2</sub>	n.r.
5	DABCO	CH <sub>2</sub> Cl <sub>2</sub>	n.r.
6	DBN	CH <sub>2</sub> Cl <sub>2</sub>	75
7	DBU	CH <sub>2</sub> Cl <sub>2</sub>	78
8	DBU	THF	67
9	DBU	toluene	51
10	<b>DBU</b>	<b>MeCN</b>	<b>81</b>
11	DBU	DMF	70

<sup>a</sup> Reactions were carried out with **1a** (1.0 mmol), NBS (1.2 equiv), and base (1.2 equiv) in solvent (2.0 mL) for 12 h. <sup>b</sup> Isolated yield.

**Table 2.** Tandem Reactions of Chalcones with NBS and DBU Combination<sup>a</sup>

entry	<b>1</b>	R <sup>1</sup>	R <sup>2</sup>	<b>2</b>	yield (%) <sup>b</sup>
1	<b>1a</b>	Ph	Ph	<b>2a</b>	81
2	<b>1b</b>	Ph	4-MeC <sub>6</sub> H <sub>4</sub>	<b>2b</b>	84
3	<b>1c</b>	Ph	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>2c</b>	83
4	<b>1d</b>	Ph	3,4-O <sub>2</sub> CH <sub>2</sub> Ph	<b>2d</b>	84
5	<b>1e</b>	Ph	2-ClC <sub>6</sub> H <sub>4</sub>	<b>2e</b>	79
6	<b>1f</b>	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	<b>2f</b>	82
7	<b>1g</b>	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	<b>2g</b>	81
8	<b>1h</b>	Ph	4-FC <sub>6</sub> H <sub>4</sub>	<b>2h</b>	83
9	<b>1i</b>	Ph	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>2i</b>	79
10	<b>1j</b>	Ph	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>2j</b>	80
11	<b>1k</b>	Ph	2-furyl	<b>2k</b>	80
12	<b>1l</b>	Ph	2-thienyl	<b>2l</b>	85
13	<b>1m</b>	Ph	<i>t</i> -Bu	<b>2m</b>	81
14	<b>1n</b>	4-BrC <sub>6</sub> H <sub>4</sub>	Ph	<b>2n</b>	87
15	<b>1o</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	<b>2o</b>	86
16	<b>1p</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	<b>2p</b>	82
17	<b>1q</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Ph	<b>2q</b>	81
18	<b>1r</b>	2-naphthyl	Ph	<b>2r</b>	85
19	<b>1s</b>	2-pyridyl	Ph	<b>2s</b>	84

<sup>a</sup> Reactions were carried out with **1** (1.0 mmol), NBS (1.2 equiv), and DBU (1.2 equiv) in MeCN (2.0 mL) for 12 h. <sup>b</sup> Isolated yield.

**1** and NBS (1.2 equiv) in the presence of DBU (1.2 equiv) in MeCN (Table 2). The reactions proceeded smoothly to afford the corresponding  $\beta$ -imidoketones **2a–s** in moderate to high yields (79–87%). The R<sup>2</sup> group of substrate

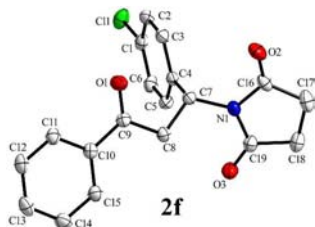
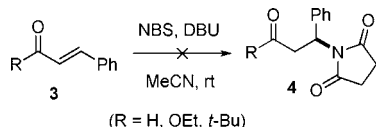


Figure 1. ORTEP drawing of **2f**.

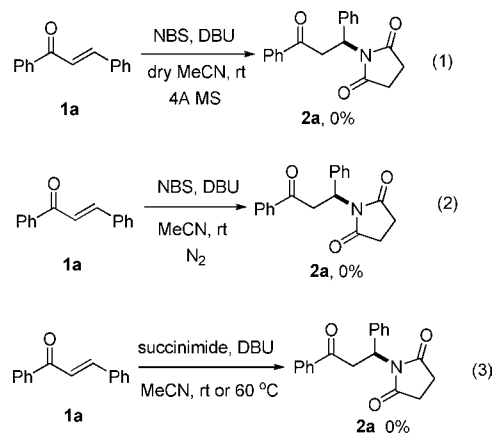
**1** may be either electron-rich (entries 1–4) or electron-deficient aryl (entries 5–10), heteroaryl (entries 11 and 12), and alkyl groups (entry 13). The  $R^1$  substituents were also broad, including electron-deficient aryl (entries 14 and 15), electron-rich aryl (entries 16 and 17), naphthyl (entry 18), and heteroaryl (entry 19). The structure of **2f** was confirmed by the single-crystal X-ray diffraction (Figure 1).<sup>13</sup> The scope of the reaction was further explored in regard to  $\alpha,\beta$ -unsaturated enone substrates (Scheme 2). Nevertheless, when cinnamaldehyde ( $R = H$ ), ethyl cinnamate ( $R = OEt$ ), and 4,4-dimethyl-1-phenylpent-1-en-3-one ( $R = t-Bu$ ) were subjected to otherwise identical conditions, no desired products were obtained.<sup>14</sup>

Scheme 2. Further Scope Exploration



To gain insight into the mechanism, several control experiments were performed (Scheme 3). In order to explore the influence of water in the reaction system, the reaction of chalcone **1a** and NBS/DBU was conducted in dry MeCN, along with the addition of 4 Å MS (eq 1). As a result, product **2a** was not observed with intact substrate **1a** retractable. It was thus concluded that a trace amount of water is crucial for the reaction to proceed. Furthermore, no reaction took place if the same reaction was performed in wet MeCN under a  $N_2$  atmosphere (eq 2). This

Scheme 3. Control Experiments



indicated that dioxygen in air might facilitate the reaction, although the reason was still unclear.<sup>15</sup> Comparatively, the mixture of chalcone **1a**, succinimide (1.2 equiv), and DBU (1.2 equiv) stirred in MeCN either at rt or at 60 °C did not give the  $\beta$ -imidated product **2a** (eq 3). The results indicated that such a transformation cannot be readily achieved via Michael addition, due to the weak nucleophilicity of the corresponding succinimide anion.<sup>3</sup>

On the basis of all the results described above, along with our previous work,<sup>8c</sup> a plausible mechanism for the  $\beta$ -imidation of chalcones was proposed, as depicted in Scheme 4.<sup>16</sup> First, NBS reacts with DBU to form a 1:1 adduct **I** via halogen bond interaction,<sup>11</sup> which further transforms into a more electrophilic species **II**.<sup>17</sup> Second, reaction between chalcones and activated bromide **II** furnishes DBU-stabilized bromonium ion **III**.<sup>18,19</sup> Nucleophilic attack of **III** by the succinimide anion **IV** leads to the formation of  $\beta$ -imino- $\alpha$ -brominated ketone **V**. Third,

(15) Indeed, in the experiment we found that all the reactions need to be carried out in the open air. Reactions in a sealed tube would lead to a prolonged reaction time with slightly lowered yields.

(16) The authors would like to thank the reviewers for the valuable suggestion for the proposed mechanism.

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(18) For Lewis base stabilized bromonium intermediates, refer to: (a) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, 107, 20655. (b) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, 51, 10938. (c) Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2012**, 134, 16492.

(19) For  $Br^+$  transfer via an equilibrium between chalcones **1**, electrophilic bromine species **II**, and the resulting bromonium intermediate **III**, see: (a) Brown, R. S. *Acc. Chem. Res.* **1997**, 30, 131. (b) Cui, X.-L.; Brown, R. S. *J. Org. Chem.* **2000**, 65, 5653.

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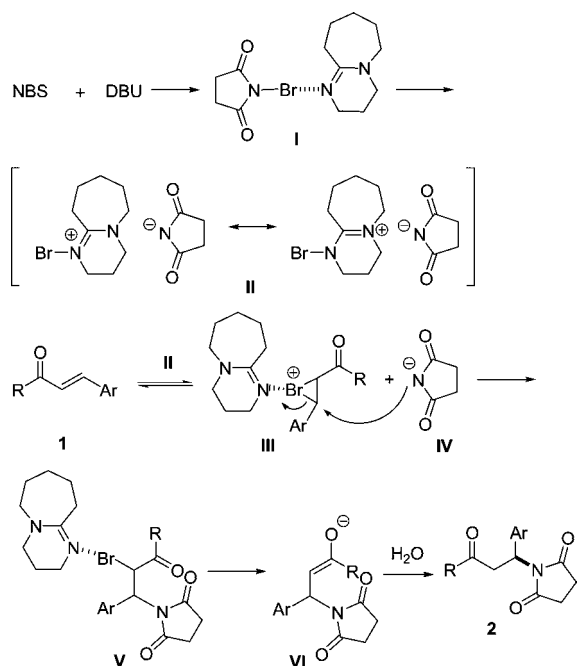
(11) For halogen bond complexes formed between imines and NIS, see: (a) Castellote, I.; Morón, M.; Burgos, C.; Alvarez-Builla, J.; Martín, A.; Gómez-Sal, P.; Vaquero, J. J. *Chem. Commun.* **2007**, 1281. DABCO and NBS, see: (b) Crowston, E. H.; Lobo, A. M.; Prabhakar, S.; Rzepa, H. S.; Williams, D. J. *Chem. Commun.* **1984**, 276. Hexamethylenetetramine and NIS, see: (c) Raatikainen, K.; Rissanen, K. *Chem. Sci.* **2012**, 3, 1235. Alkylated DABCO with  $Br_2$ , see: (d) Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, 134, 12928.

(12) A highly polar complex might be formed, as observed on the TLC plate, in the mixture of NBS and DBU in solution.

(13) CCDC 879831 (**2f**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). See the Supporting Information.

(14) The reaction of **1a** with *N*-bromophthalimide instead of NBS led to a complex mixture that was inseparable.

**Scheme 4.** Plausible Mechanism for the Formation of  $\beta$ -Aminoketones **2**



assisted by the synergistic effect from both the halogen bond interaction<sup>20</sup> between DBU and alkyl bromide and the electron-withdrawing property of the carbonyl group, a positive bromine is abstracted and enolate **VI** is thus generated.<sup>21,22</sup> Finally, imidated product **2** is formed via

(21) In this case, DBU can be regarded as an electron donor and ketone as an electron acceptor.

(22) Most probably, molecular oxygen plays a certain role in the transformation of **V** $\rightarrow$ **VI**.

protonation of **VI** by a trace amount of water. Obviously, it was the successive bromoamination/debromination by the NBS/DBU combination that led to the  $\beta$ -imidation of chalcones. DBU functions as a nucleophilic promotor to activate NBS (in the bromoamination step) and to further remove the bromine (in the subsequent debromination step).

In conclusion, a novel and efficient one-pot  $\beta$ -amination of chalcones has been developed by using an NBS and DBU combination, in which NBS functions as both electrophilic bromine and nitrogen sources and DBU as a nucleophilic promotor to activate NBS to be a more electrophilic bromine species and to remove the bromine of  $\alpha$ -bromoketone. The tandem bromoamination/debromination involved in the whole transformation makes the reaction more intriguing. The reaction features mild conditions, a relatively broad scope, and high efficiency. Further work on the reaction of the NBS/DBU combination with alkenes and alkynes is ongoing in our laboratory.

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**Supporting Information Available.** Experimental details and characterization for all new compounds and crystal structure data (CIF file). This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.