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One-Pot Cascade Leading to Direct α-Imidation of Ketones by a Combination of *N*-Bromosuccinimide and 1,8-Diazabicyclo[5.4.1]undec-7-ene

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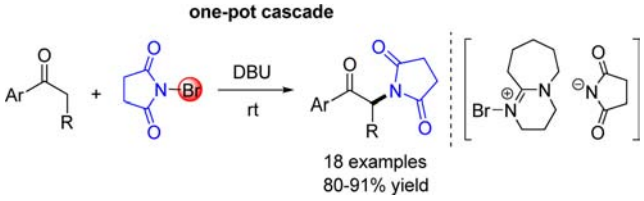
ABSTRACT



A one-pot cascade transformation of ketones into α-imidoketones has been developed, in which *N*-bromosuccinimide (NBS) provides both electrophilic bromine and nucleophilic nitrogen sources, and diazabicyclo[5.4.1]undec-7-ene (DBU) functions as a base and a nucleophilic promoter for the activation of NBS. α-Bromination is supposed as the key step in the process, which takes place between more electrophilic bromide active species and enolates.

N-Bromosuccinimide (NBS) is a versatile reagent for synthetic organic chemistry.[1] Traditionally, NBS can be considered as a convenient source of either cationic bromine used in electrophilic addition reactions[2] or a bromine radical used in radical substitution reactions.[3] In general, relatively inert succinimide would be generated as a byproduct in the reaction. From the atom economic point of view, direct installment of the succinimido moiety of NBS into the target molecules, as well as further transformation thereby, is highly desirable. Herein, we would like to present a unique mode, in which both the bromine cation and succinimide anion of NBS were involved in a one-pot conversion of ketones into α-imidoketones.

Recently, halogen activated organic reactions (e.g., halonium,[2] hypervalent halogen,[4a−g] and halogen bonding[4h−m]) have attracted increasing interest, and in our research on halonium-initiated cascades,[5] an intramolecular

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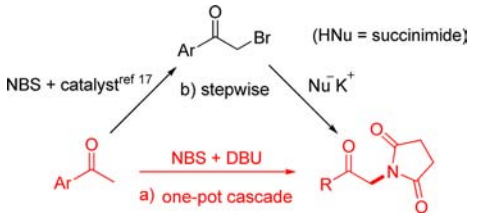
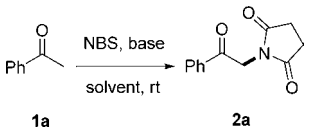
Scheme 1. One-Pot Cascade Leading to α-Imidation of Ketones by a Combination of NBS and DBU



C−O bond formation between carbonyl methyl and the amide oxygen atom was developed.[5a] In our continued work, we devoted our effort to the intermolecular carbon−carbon and carbon−heteroatom bond construction of ketones with appropriate nucleophiles via halogen activation. In this context, we disclosed the one-pot cascade reaction of ketones with NBS leading to direct imidation,[6] in which NBS plays a dual role to provide both electrophilic bromine and nucleophilic nitrogen sources (Scheme 1a).[7] Generally, the procedure requires multiple steps, as exemplified in the Gabriel synthesis (Scheme 1b).[8] *To the best of our knowledge, this represents one of the rare examples of employing two components of NBS in a one-pot cascade transformation.*[9]

Table 1. Optimization of the Reaction Conditions[a]

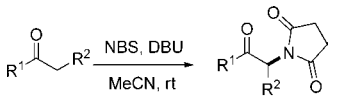


1a 2a

entry	base	solvent	**2a** yield (%)[b]
1[c]	NaOH	DMF	n.r.
2	NaOEt	DMF	n.r
3[c]	NaH	DMF	n.r
4[c]	*t*-BuOK	DMF	n.r
5	DABCO	DMF	n.r.
6	DBU	DMF	52
7	DBU	THF	59
8	DBU	toluene	49
9	DBU	CH_2Cl_2	81
10	**DBU**	**MeCN**	**87**

[a] 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. [b] Isolated yield. [c] To the mixture of **1a** (1.0 mmol) and base (0.9 equiv), NBS (1.2 equiv) was added after 30 min; no **2a** was observed.

Table 2. Cascade Reactions of Ketones with NBS and DBU[a]



1 2

entry	**1**	R^1	R^2	**2**	yield (%)[b]
1	**1a**	Ph	H	**2a**	87
2	**1b**	2-MeC_6H_4	H	**2b**	91
3	**1c**	4-MeC_6H_4	H	**2c**	90
4	**1d**	4-$CH_3OC_6H_4$	H	**2d**	84
5	**1e**	4-BrC_6H_4	H	**2e**	81
6	**1f**	4-ClC_6H_4	H	**2f**	82
7	**1g**	3-$NO_2C_6H_4$	H	**2g**	83
8	**1h**	4-$NO_2C_6H_4$	H	**2h**	80
9	**1i**	2-naphthyl	H	**2i**	85
10	**1j**	2-furyl	H	**2j**	86
11	**1k**	2-thienyl	H	**2k**	83
12	**1l**	2-pyridyl	H	**2l**	81
13	**1m**	PhCH=CH	H	**2m**	77
14	**1n**	Ph	Me	**2n**	88
15	**1o**	Ph	Et	**2o**	86
16	**1p**	Ph	Ph	**2p**	85

[a] 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. [b] Isolated yield.

Initially, the model reaction of acetophenone (**1a**) with NBS was examined under basic conditions (Table 1). No reactions occurred in DMF at rt, by the utilization of NaOH, NaOEt, NaH, *t*-BuOK, and DABCO as the base (entries 1−5). Gratifyingly, the reaction with DBU as the base gave 1-(2-oxo-2-phenylethyl)pyrrolidine-2,5-dione (**2a**) in 52% yield (entry 6).[10] Switching the solvents from DMF to THF and toluene did not change the yields significantly (entries 7 and 8). The yield was improved to 81% when performed in CH_2Cl_2 under otherwise identical conditions (entry 9). Among all the solvents tested, MeCN was the most efficient, affording **2a** in 87% yield (entry 10). One can see that DBU worked well in the one-pot imidation reaction while other bases were inefficient. The reason for this may be attributed to the specific interaction between DBU and NBS.[11]

With the optimized conditions in hand, the scope and generality of the one-pot cascade reaction were investigated. Thus, the reactions of various ketones with NBS were conducted (Table 2). It was found that methyl aryl ketones containing both electron-donating groups (2-MeC_6H_4, 4-MeC_6H_4, 4-$CH_3OC_6H_4$) and electron-withdrawing groups (4-Br, 4-Cl, 3-NO_2, 4-NO_2) on the aryl rings could be smoothly transformed into the desired products **2b**−**h**

(6) For two examples of imidation of arenes with imides using iodine(III) as an oxidant, see: (a) Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382. (b) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960.

(7) For excellent work on double duty of alkynyl halides, cyanogen bromide, and bromoperfluoroarenes, see: (a) Trofimov, A.; Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 13538. (b) Li, Z.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2808. (c) Li, Z.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 1225. For excellent work on using *N*-(benzylthio)succinimides as both a nucleophilic and an electrophilic reactant, see: (d) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468.

(8) For one example of stepwise synthesis of α-imidoketones, see: Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626.

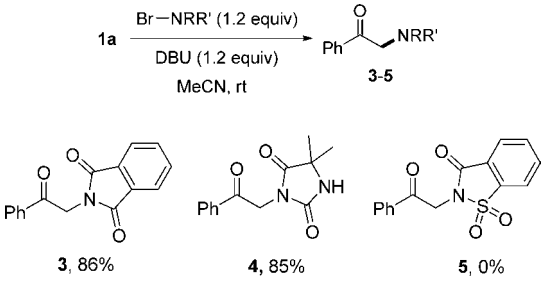
(9) A most recent publication was found.Alix, A.; Lalli, C.; Retaileau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389.

(10) The reaction was also examined under acidic conditions (HCO_2H, $PhCO_2H$, CuBr, etc.) but proved to be unsuccessful.

(11) A mixture of NBS and DBU may form a highly polar complex, as observed on TLC plate.

(80–91%, entries 2–8). In addition, 2-naphthyl methyl ketone (**1i**) also provided the corresponding product **2i** in 85% yield (entry 9). Encouraged by the results obtained with aryl ketones, we turned our attention to the heteroaryl ketones. The heterocycles, including furan (**1j**), thiophene (**1k**), and pyridine (**1l**), were converted into the target products **2j**–**l** in 81–86% yields (entries 10–12). 4-Phenylbut-3-en-2-one (**1m**) was also a suitable substrate, affording **2m** in 77% yield (entry 13). Propiophenone (**1n**) and butyrophenone (**1o**) gave the corresponding products **2n** and **2o** in 88% and 86% yields, respectively (entries 14 and 15). α-Phenyl acetophenone (**1p**) was also efficient, affording 1-(2-oxo-1,2-diphenylethyl)pyrrolidine-2,5-dione (**2p**) in high yield. Nevertheless, when isobutyrophenone and α-tetralone were used as substrates, no reactions took place, which was probably due to the steric effect of the alkyl substituents.[12]

Scheme 2. Reactions of Acetophenone **1a** with *N*-Bromoimides



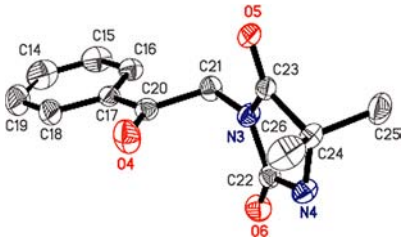
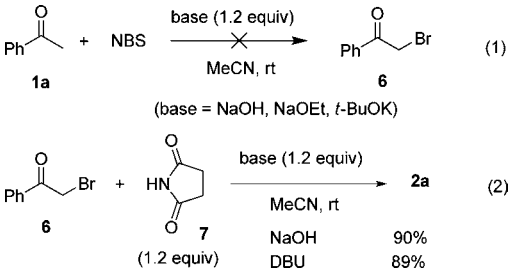


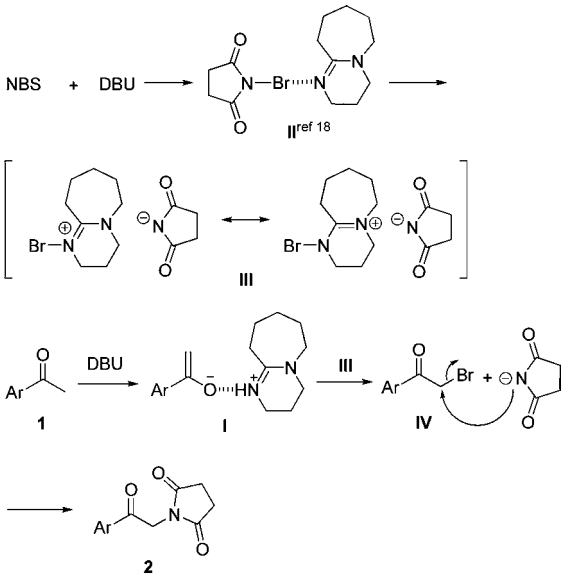
Figure 1. ORTEP drawing of **4**.

Next, we investigated the efficacy of other *N*-haloimides (Scheme 2).[13] Similar to NBS, *N*-bromophthalimide (NBP) was also a competent reagent, affording the desired isoindole-1,3-diones **3** in high yield. For the reaction of **1a** with 1,3-dibromo-5,5-dimethylhydantoin, due to the reactivity of the bromine attached to the imine N-atom being higher than that on the amide N-atom, the corresponding α-imidated ketone **4** was produced in high yield.[14] The structure of **4** was confirmed by single-crystal X-ray diffraction (Figure 1).[15] However, when *N*-bromosaccharin was subjected to the reaction conditions, no imidated product was observed. Both pyrrolidine-2,5-dione and isoindole-1,3-dione derivatives have been used extensively in synthetic chemistry, with a wide range of applications, particularly in biological and pharmaceutical chemistry.[16]

Scheme 3. Control Experiments



Scheme 4. Possible Mechanism for the Formation of α-Imidated Ketones **2**–**4**



To gain insight into the mechanism, several control experiments were performed (Scheme 3). No corresponding α-bromoacetophenone (**6**) was observed in the reactions of **1a** and NBS with various bases like NaOH, NaOEt, and *t*-BuOK, with substrate **1a** recovered quantitatively (eq 1). The reactions of **6** and succinimide **7** (1.2 equiv) at rt for 12 h gave product **2a**, with either NaOH or DBU (1.2 equiv) as the base (eq 2). The results indicated

(12) Reactions of fully aliphatic ketones like acetone and butanone with NBS gave a complex mixture. Additionally, ethyl acetate was selected as an ester substrate and subjected to otherwise identical conditions but proved to be inefficient.

(13) NIS showed similar reactivity to NBS, but NCS was inefficient.

(14) The bromine atom on the amide nitrogen is deactivated during the transformation.

(15) CCDC 873495 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information.

that (i) α-bromoketone is involved in the mechanism as the key step and (ii) DBU plays an important role in this step (α-bromination of ketones).[17]

On the basis of all the results described above and work by Vanquero et al.,[18a] a possible mechanism for the α-imidation of ketones was proposed (Scheme 4). First, enolate **I** is produced in the presence of DBU (1.0 equiv at the most). At the same time, NBS reacts with DBU to form a 1:1 adduct **II** via halogen bond interaction,[18,4h−4m] which further transforms into a more electrophilic species **III**.[19] Second, reaction between enolate **I** and activated bromide **III** furnishes α-bromoketone **IV**. Finally, imidated product **2** is formed via nucleophilic substitution of **IV** by the succinimide anion. The function of DBU is to deprotonate ketones (as base) and to activate NBS (as nucleophilic promoter).[20] Such an efficient one-pot cascade transformation involves sequential N−Br cleavage, C−Br formation, C−Br cleavage, and C−N formation. With this protocol, we achieved the in situ cross-coupling between two (pro)nucleophiles.[21]

In conclusion, a novel and efficient one-pot α-imidation of ketones has been developed by using an NBS and DBU combination, in which NBS functions as both halogen and nitrogen sources and DBU as both a base and a nucleophilic promoter to activate NBS. The activation of NBS by DBU to be a more electrophilic bromide active species was supposed to be the driving force for the one-pot cascade imidation reaction. The reaction features mild conditions, broad scope, and high efficiency. Work on further expanding the substrate scope with an NBS and DBU combination 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.

(16) Some isoindole-1,3-dione derivatives display pharmacological activities as anticonvulsants, anti-inflammatories, analgesics, and herbicidal and insecticidal agents. See: (a) harma, U.; Kumar, S. P.; Kumar, N.; Singh, B. *Mini-Rev. Med. Chem.* **2010**, *10*, 678. (b) Meng, X.-B.; Han, D.; Zhang, S.-N.; Guo, W.; Cui, J. R.; Li, Z.-J. *Carbohydr. Res.* **2007**, *342*, 1169. (c) Abdel-Hafez, A. A. *Arch. Pharm. Res.* **2004**, *27*, 495. (d) Lima, L. M.; Castro, P.; Machado, A. L.; Fraga, C. A. M.; Lugnier, C.; Gonc, V. L.; Barreiro, E. *J. Bioorg. Med. Chem.* **2002**, *10*, 3067. (e) Collin, X.; Robert, J.; Wielgosz, G.; Baut, G. L.; Bobin-Dubigeon, C.; Grimaud, N.; Petit, J. *Eur. J. Med. Chem.* **2001**, *36*, 639. (f) Groutas, W. C.; Chong, L. S.; Venkataraman, R.; Kuang, R.; Epp, J. B.; Houser-Archield, N.; Huang, H.; Hoidal, J. R. *Arch. Biochem. Biophys.* **1996**, *332*, 335. (g) Antune, R.; Buttista, H.; Strivastuva, R. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3071.

(17) α-Bromination of ketones is an important transformation in synthetic chemistry. For α-bromination of ketones with NBS catalyzed by AIBN or BPO, see: (a) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003**, *32*, 932. (b) Cope, A. C.; Burrows, E. P.; Derieg, M. E.; Moon, S.; Wirth, W.-D. *J. Am. Chem. Soc.* **1965**, *87*, 5452. (c) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1946**, *29*, 573. For catalysis by NH_4OAc, see: (d) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashia, K.; Horaguchi, T. *Chem. Commun.* **2004**, *40*, 470. For catalysis by $Mn(ClO_4)_2$, see: (e) Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429.

(18) For halogen bond complexes formed between imines and NIS, see: (a) Castellote, I.; Morón, M.; Burgos, C.; Alvarez-Builla, J.; Martin, A.; Gómez-Sal, P.; Vaquero, J. J. *Chem. Commun.* **2007**, 1281. For DABCO and NBS, see: (b) Crowston, E. H.; Lobo, A. M.; Prabhakar, S.; Rzepa, H. S.; Williams, D. J. *Chem. Commun.* **1984**, 276. For hexamethylenetetramine and NIS, see: (c) Raatikainen, K.; Rissanen, K. *Chem. Sci.* **2012**, *3*, 1235.

(19) For examples of NBS activation by a Lewis base: For NBS/Ph_3P, see ref 2b. For $Et_2SBr\cdot SbCl_5Br$, see: (a) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899. (b) Snyder, S. A.; Treitler, D. L.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303. For NBS/DABCO, see: (c) Ghasemnejad-Bosra, H.; Haghdadi, M.; Khanmohammade, O.; Gholipour, A. M.; Asghari, G. *J. Chin. Chem. Soc.* **2008**, *55*, 464. For the bromocollidinium ion, see: (d) Cui, X.-L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653.

(20) Under acidic conditions, both ketones and NBS may be activated by an acid catalyst and an α-brominated product can be achieved. Under basic conditions, transformation of ketones into enolates without the activation of NBS is probably not sufficient for α-bromination to occur. DBU can activate both ketones (into enolates) and NBS (into a more electrophilic active species like **III**). In this case α-bromination of ketones took place.

(21) For a recent review on bond formation between two nucleophiles, see:Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.

The authors declare no competing financial interest.