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Direct α-C-H amination of β-dicarbonyl compounds using DBU-activated *N*-haloimides as nitrogen sources†

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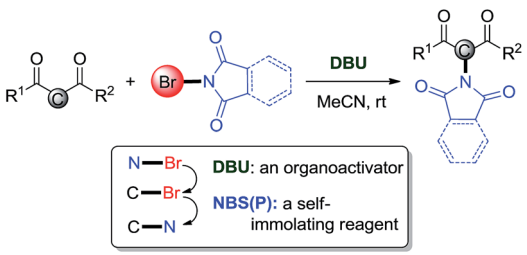
By DBU activation, *N*-haloimides may act as a self-immolating reagent, to convert β-dicarbonyl compounds into α-imidated products in high efficiency. The DBU/*N*-haloimide protocol provides a novel, mild, and complimentary access to α-imidated β-dicarbonyl compounds, without the necessity of external nitrogen sources.

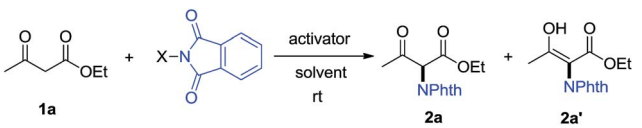
α-Amido β-dicarbonyl compounds are versatile organic intermediates in the synthesis of various heterocyclic compounds,[1] peptide mimetics,[2] α-amino acids and their derivatives,[3] and β-hydroxyl α-amino esters.[4] Classical methods for the synthesis of α-amido β-dicarbonyl compounds include the strong base-mediated acylation of the ketimine derivatives of α-amino esters[2] and N–C acyl migration of the *N*-*tert*-butoxycarbonyl-*N*-acylglycine ester;[5] the reduction of α-hydroxyimino[6] and phenylazo[7] β-dicarbonyl compounds; the hydrolysis of oxazole-4-carboxylate derivatives;[8] and N–H insertion of metal carbenes.[9] However, these methods are limited by the utilization of a strong base, substrate availability, and multistep procedures. Direct α-amination of the readily available β-dicarbonyl compounds is more convenient and highly desirable for the synthesis of α-amido β-dicarbonyl compounds. Most common methods involve electrophilic amination of β-dicarbonyl compounds to azodicarboxylates[10] and the *N*-selective nitroso aldol reaction.[11] Despite the significant advances made in the area, new and efficient methods, especially direct α-amination methods, are still required.

Recently, hypervalent iodine(III)-mediated α-amination of β-dicarbonyl compounds have been developed.[12] Zhang and co-workers reported a mild and efficient method for the direct and fast α-amination of β-dicarbonyl compounds using PhIO as the oxidant and $TsNH_2$ as the aminating reagent catalyzed by



Scheme 1 α-C-H imidation of β-dicarbonyl compounds by using DBU-activated *N*-haloimides.

Table 1 Optimization of the reaction conditions[a]



Entry	*N*-Haloimide	Activator	Solvent[b]	Time (min)	Yield[c] (%)
1	NBP	—	MeCN	20	45[d]
2	NBP	PPh_3	MeCN	180	n.d.
3	NBP	DMAP	MeCN	240	n.d.
4	NBP	DABCO	MeCN	60	Trace
5	NBP	DBU	MeCN	20	89
6	NBP	DBN	MeCN	30	85
7	NBP	MTBD	MeCN	7	90
8	NBP	DBU	DCE	20	85
9	NBP	DBU	THF	20	79
10	NBP	DBU	DMF	20	64
11	NBP	DBU	Toluene	240	60
12	NCP	DBU	MeCN	360	30

[a] Reactions were carried out with **1a** (1.0 mmol), NBP (1.5 equiv.), and activator (1.8 equiv.) in solvent (2.0 mL) at room temperature. [b] Solvent was used directly as received. [c] Isolated yield. [d] α-Bromonated product and α,α-dibromonated product were obtained in respective 45% and 42% yields. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

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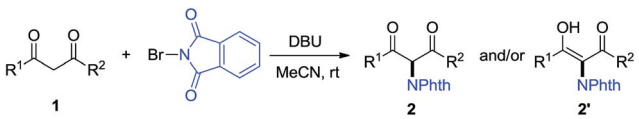
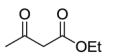
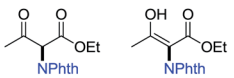
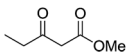
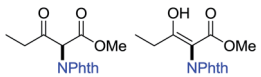
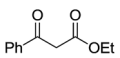
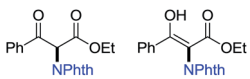
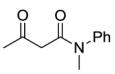
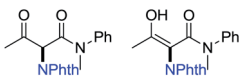
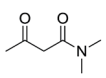
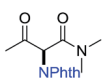
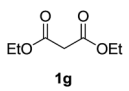
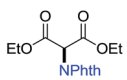
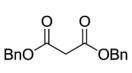
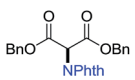
perchlorate zinc hexahydrate.[12a] Chan *et al.* described a copper(II) triflate catalyzed amination of 1,3-dicarbonyl compounds with PhI=NTs.[12b] In our research on halogen-mediated organic transformations,[13] we disclosed that DBU-activated NBS (*N*-bromosuccinimide) or NBP (*N*-bromophthalimide) *via* a halogen bond interaction can be utilized as an efficient halogenation reagent,[13a] amination reagent[13b–d] and haloamination reagent.[13e] Herein, we would like to communicate the direct α-C-H imidation of β-dicarbonyl compounds by using DBU-activated *N*-haloimides as both electrophilic and nuceophilic reagents (Scheme 1). The *N*-haloimide/DBU combination provides a convenient and economic protocol toward α-C-H imidation of β-dicarbonyl compounds. The distinct feature of the reaction is without the necessity of external nitrogen sources.

Initially, the model reaction of ethyl acetoacetate (**1a**) with NBP was examined under a variety of conditions (Table 1). In the absence of any activator, the reaction of **1a** and NBP (1.5 equiv.) in MeCN at room temperature gave α-bromonated and α,α-dibromonated products in respective 45% and 42% yields (entry 1). By the utilization of PPh_3 or DMAP as the activator, no imidated product was observed (entries 2–3). DABCO afforded only trace amount of the target molecule. However, once DBU was introduced, the reaction proceeded rapidly, and 2-(1,3-dioxoisoindolin-2-yl)-3-oxobutanoate (**2a**) and ethyl 2-(1,3-dioxoisoindolin-2-yl)-3-hydroxybut-2-enoate (**2a′**) were obtained in 89% yield within 20 min (entry 4). Amidine activator DBN and

Table 2 α-Imidation of β-dicarbonyl compounds[a]

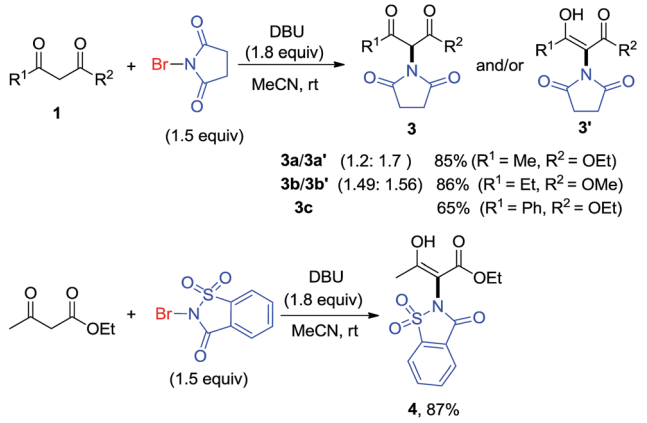


Entry	Substrate	Product	Time (min)	Yield[b] (%)
1	 **1a**	 **2a** **2a'** (1: 4.3)	20	89
2	 **1b**	 **2b** **2b'** (1: 3)	25	88
3	 **1c**	 **2c** **2c'** (1.3: 1)	180	83
4	 **1d**	 **2d** **2d'** (1: 1.7)	25	91
5	 **1e**	 **2e**	25	83
6	 **1f**	 **2f**	20	84
7	 **1g**	 **2g**	30	90
8[c]	 **1h**	 **2h**	30	92

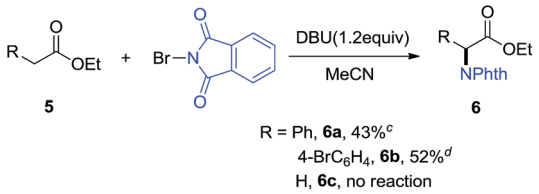
[a] Reactions were carried out with **1** (1.0 mmol), NBP (1.5 equiv.), and DBU (1.8 equiv.) in MeCN (2.0 mL) at rt. [b] Isolated yield. [c] Reactions were conducted with NBP (1.05 equiv.), and DBU (1.05 equiv.).

guanidine activator MTBD worked well (entries 5 and 6).[14] Solvent screening indicated that DCE, THF, DMF and toluene led to decreased yields (entries 8–11). The reactivity of NCP was evaluated and the reaction became sluggish, along with a fairly low yield (entry 12).

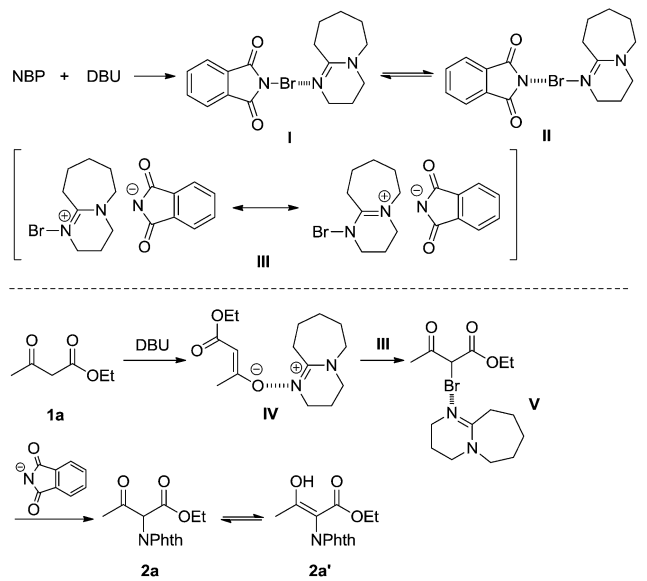
With optimized reaction conditions in hand (Table 1, entry 5), we investigated this methodology with a range of β-dicarbonyl compounds (Table 2). β-Keto esters **1a–c** afforded the corresponding α-imidation products **2a**/**2a**′–**2c**(**2c**′) in high yields (entries 1–3). Two β-ketoamides, *N*-methyl-3-oxo-*N*-phenylbutanamide and *N*,*N*-dimethyl-3-oxobutanamide were also examined. α-Imidation products **2d**/**2d**′ and **2e** (in complete keto form) were obtained in 91% and 85% yield, respectively (entries 4 and 5). Reaction with β-diketone **1f** proceeded smoothly, furnishing α-imidated product **2f** (in complete enol form) in 84% yield (entry 6). For malonic esters **1g** and **1h**, the corresponding α-imidated products **2g** and **2h** were obtained in excellent yields (entries 7 and 8).[15]



Scheme 2 Reactions of β-keto esters with *N*-bromoimides.



Scheme 3 α-Imidation of esters.[a,b] [a]Reactions were carried out with **1** (1.0 mmol), NBP (1.2 equiv.), and DBU (1.2 equiv.) in MeCN (2.0 mL). [b]Isolated yield. [c]At rt for 5 h. [d]At 80 °C for 2 h.



Scheme 4 Proposed mechanism for the α-imidation.

Next, we investigated the efficacy of other *N*-haloimides as potential self-immolating nitrogen sources[16] (Scheme 2). Similar to NBP, NBS was also a competent reagent, affording products **3a**/**3a**′, **3b**/**3b**′ and **3c** in 65–85% yields.[17] When *N*-bromosaccharin was subjected to the reaction sequence, the corresponding α-imidated compound **4** was produced in 87% yield (in complete enol form). All the above reactions indicate the high efficiency and broad scope for both β-dicarbonyl compounds and *N*-haloimides.

Other than β-dicarbonyl compounds, α-substituted ethyl acetates were also examined (Scheme 3). As a result, the α-imidation of esters was achieved and products **6a** (R = phenyl) and **6b** (R = 4-bromophenyl) were obtained in 43% and 52% yields, respectively. However, no reaction occurred in the case of using ethyl acetate as the substrate.

On the basis of all the results described above, along with our previous work,[13a–e] a possible mechanism for the α-imidation of β-dicarbonyl compounds was proposed in Scheme 4. On one hand, NBP reacts with DBU to form a 1 : 1 adducts **I** and **II** *via* halogen bond interaction, which may further transform into tight ion pair intermediate **III** with enhanced electrophilic and nucleophilic ability.[18] On the other hand, enolate **IV** is produced in the presence of DBU. The reaction between enolate **IV** and activated bromide intermediate **III** furnishes α-bromo β-dicarbonyl **V**.[19] Finally, imidated product **2a** and **2a**′ is formed *via* nucleophilic substitution of **V** by the phthalimide anion.[20] The function of DBU is to deprotonate β-dicarbonyl compounds (as base) and to activate NBP (as a nucleophilic promoter).

Conclusions

In summary, we have developed a highly efficient, atom-economic, environmentally friendly and metal-free methodology for direct α-imidation of 1,3-dicarbonyl compounds with *N*-haloimide (activated by DBU) as potential direct amination reagent at ambient temperature. The scope of the reaction is broad in terms of both the *N*-haloimides and the β-dicarbonyl compounds. Thus, without the necessity of external nitrogen sources, a variety of important imidation products were prepared rapidly in moderate to excellent yields. The self-immolating property of *N*-haloimides induced by halogen bonding activation appears to be attractive. Further research on the utilization of *N*-haloimide/DBU protocol in organic transformations is ongoing in our laboratory.

Acknowledgements

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14 MTBD is a more efficient activator than DBU, in regards to the reaction time and product yield. Nevertheless, DBU was used as the activator in the following work.

15 Cyclic β-dicarbonyl substrates like 5,5-dimethylcyclohexane-1,3-dione did not give desired product under otherwise identical conditions.

16 For a recent nice example of using *N*-succinimidyl perester as a self-immolating imidation reagent, see: (*a*) K. Foo, E. Sella, I. Thomé, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5279; For Shabat's self-immolative polymer, see: (*b*) A. Sagi, R. Weinstain, N. Karton and D. Shabat, *J. Am. Chem. Soc.*, 2008, **130**, 5434.

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