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Metal-free C–N cross-coupling of electrophilic compounds and *N*-haloimides†

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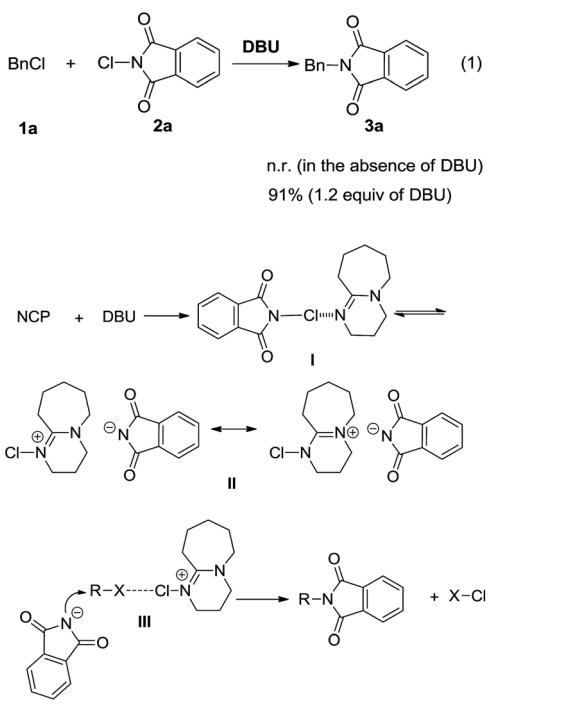
When DBU is added, the cross-coupling reaction between alkyl halides (halogen = Cl, Br and I) and *N*-haloimides (halogen = Cl, Br) occurs, resulting in the formation of aminated products. A halogen bond activated nucleophilic substitution mechanism was proposed. The methodology represents an elegant example of applying the halogen bond activation strategy in an organic transformation.

Amine is an important raw material and intermediate in medicines, pesticides, as well as liquid crystal materials. Phthalimides are versatile synthetic tools that are primarily employed in the preparation of amines *via* the Gabriel reaction.[1] The Gabriel reaction has proven to be a very effective means of forming *N*-alkylphthalimides. Starting from *N*-substituted phthalimides, for example, and using Nefkens' reagent, *N*-alkylphthalimides can also be prepared.[2] Adimurthy *et al.* found an L-proline catalyzed transamidation method of phthalimide with amines, to achieve new amines.[3] A. K. Yadav and L. D. S. Yadav used *N*-tosylhydrazone and phthalimides to prepare amines.[4] Additionally, transition metal-catalyzed C–N coupling has been developed as a powerful method.[5] Herein, we would like to report a new type of cross-coupling reaction[6] between alkyl halides[7] and *N*-haloimides, which provides an efficient and straightforward method for the synthesis of amines and functionalized amines.

In our recent research, we have developed *N*-haloimides to be a versatile amination reagent used in organic transformation.[8] In further work, we found that, with organobases like DBU as the activator,[9] benzyl chloride can react with *N*-chlorophthalimide (NCP, 1.2 equiv.), giving the corresponding imidation product in 91% yield. It was not surprising that no reaction can occur in the absence of DBU (eqn (1)). The possible mechanism for the imidation is depicted in Scheme 1.[10] The interaction between NCP and DBU gives halogen bond adduct **I**,[11] which delivers an ion pair intermediate **II** containing highly electrophilic chlorine cation and potentially nucleophilic phthalimide anion.[12] The nucleophilic substitution of alkyl halides by phthalimide anion affords the imidation product.[13] We think that the halogen bond between 1-chloro-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepinium (**III**) and alkyl halide may facilitate the nucleophilic substitution reaction.[9] The mutual activation induced by halogen bonding makes otherwise inert reaction to take place.[14]



Scheme 1 Proposed mechanism.

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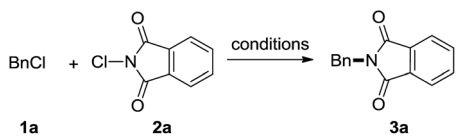
Our initial optimization of the model reaction commences from benzyl chloride (**1a**). The impact of various parameters on the efficiency of the reaction of **1a** with NCP (**2a**) is summarized in Table 1. In the presence of DBU (1.2 equiv.), the reaction mixture conducted in DCE at room temperature, afforded product **3a** in 31% isolated yield (entry 1). Other solvents screened include MeCN, DMF and DMSO (entries 2–4). DMSO proved to be the most efficient (85% yield) (entry 4).[15] The reaction mixture performed at 60 °C gave product **3a** in improved yield (91%) and shortened reaction time (5 min) (entry 5). Besides DBU, NaOH, *t*-BuONa, PPh_3, DBN, MTBD, and DABCO were selected as the activators. MTBD gave similar reactivity and DBN exhibits relatively lower efficiency (entries 6 and 7). However, NaOH, *t*-BuONa, PPh_3 and DABCO appear to be inert (entries 8–11). Catalytic amount of DBU, *e.g.*, 0.2 equiv., could not drive the reaction to completion (entry 12), which may support the presence of the halogen bonding interaction between 1-chloro-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepinium and alkyl halide, *i.e.*, adduct **III** in Scheme 1.[16]

With optimized reaction conditions in hand (Table 1, entry 5), we investigated this methodology by reacting various alkyl halides with NCP (Table 2).[17] The scope of this new coupling reaction is fairly broad. Alkyl chlorides examined includes benzyl chloride, *n*-butyl chloride, α-chlorocyclopentanone and α-chloro *N*,*N*-dimethyl acetamine. Benzyl chloride is highly efficient, while *n*-butyl chloride exhibits relatively lower efficiency. α-Chlorocyclopentanone and α-chloro *N*,*N*-dimethylacetamine gave satisfactory yields. Primary alkyl bromides containing various substituents like benzyl, allyl,[18] ethyl, homobenzyl, isobutyl are suitable substrates. A lot of functional groups are compatible with the reaction conditions, such as methoxy, dimethoxyacetal, carbonyl and ester. Secondary alkyl bromides like isopropyl bromide and diphenylmethyl bromide can also afford the corresponding aminated product, albeit in low yields. However, cyclic alkyl bromide, *i.e.*, cyclohexyl bromide, was inefficient. Alkyl iodide like methyl iodide worked very well. In one word, alkyl halides RX (X = Cl, Br and I) exhibit increased reactivity in the order of RCl, RBr and RI. The gram-scale synthesis of **3a** (1.51 g) was also achieved in 92% yield by DBU-mediated reaction of benzyl bromide and NCP.

Interestingly, we found that dihalides are also suitable for the cross-coupling reaction (Scheme 2). In the reaction of 1,2-dibromoethane with NCP (1.2 equiv.), two types of products could be prepared, depending the feed ratio of DBU employed.

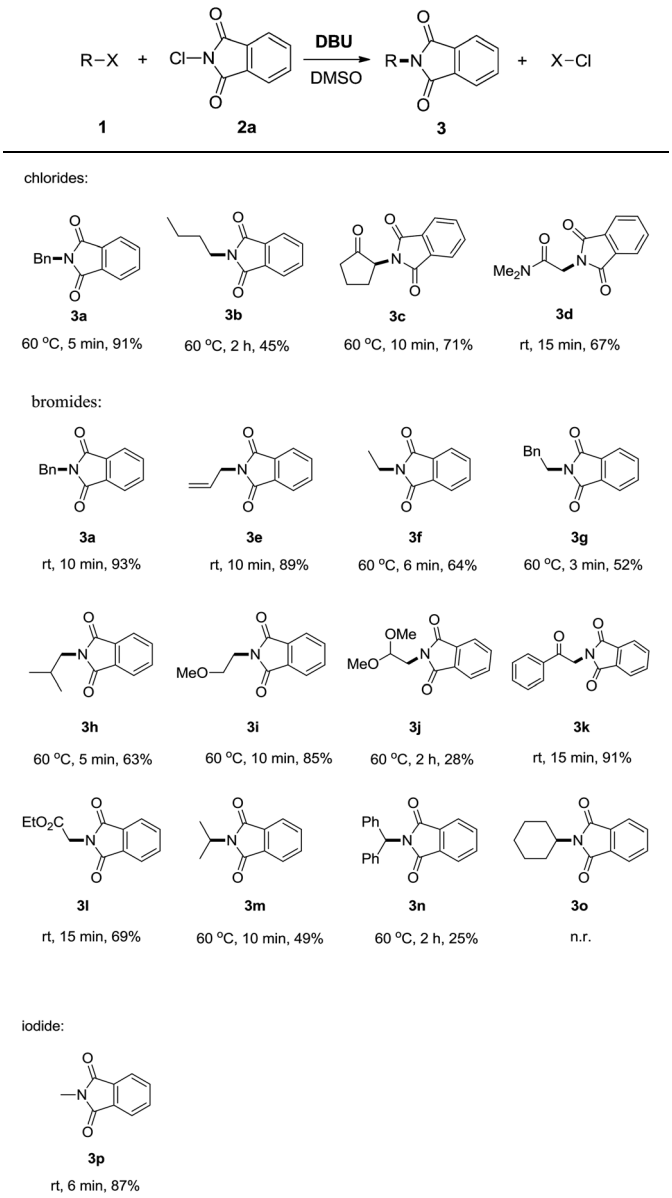
Table 1 Optimization of the reaction conditions[a]



Entry	Temp (°C)	Activator	Solvent[b]	Time (min)	Yield[c] (%)
1	rt	DBU	DCE	180	31
2	rt	DBU	MeCN	120	56
3	rt	DBU	DMF	120	57
4	rt	DBU	DMSO	30	85
5	60	DBU	DMSO	5	91
6	60	DBN	DMSO	180	61
7	60	MTBD	DMSO	6	88
8	60	NaOH	DMSO	180	n.r
9	60	*t*-BuONa	DMSO	180	n.r
10	60	Ph_3P	DMSO	180	n.r
11	60	DABCO	DMSO	180	n.r
12	60	DBU (0.2 equiv.)	DMSO	180	16

[a] Reactions were carried out with **1a** (1.0 mmol), **2a** (1.2 equiv.) and activator (1.2 equiv.) in solvent (2.0 mL). [b] Dry solvents were used in all cases to prevent the hydrolysis of benzyl chloride. [c] Isolated yield.

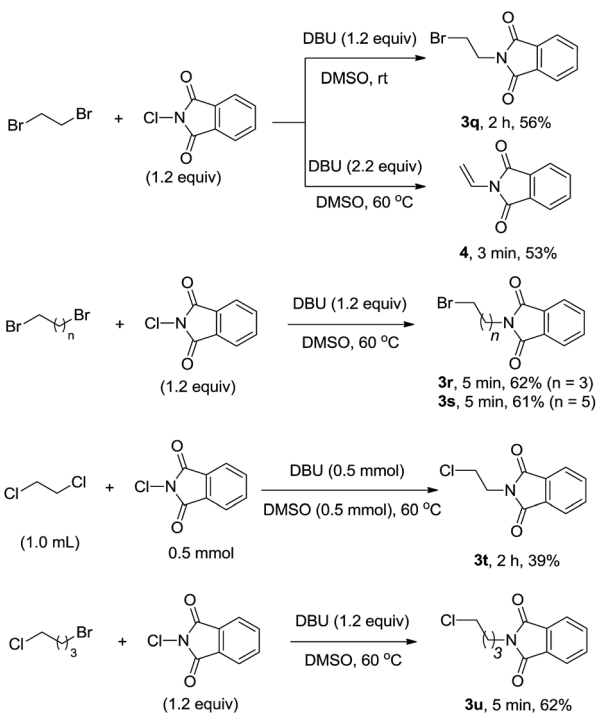
Table 2 Cross-coupling reaction of alkyl halides with NCP[a,b]



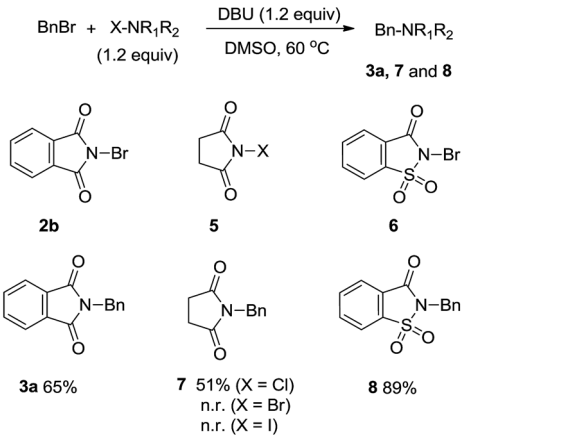
[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.2 equiv.) and DBU (1.2 equiv.) in DMSO (2.0 mL). [b] Isolated yields.

When 1.2 equiv. of DBU was used, the mixture afforded monobromo substituted amine **3q** in 56% yield. In the case of 2.2 equiv. of DBU, further elimination of HBr occurs, giving rise to enamine **4** in 53% yield. However, no elimination of HBr or HCl was observed for 1,4-dibromobutane, 1,6-dibromooctane and 1,2-dichloroethane substrates, even though excess amount of DBU was used. The corresponding imidation products **3r–t** with a pendant bromine or chlorine atom were attained in low to moderate yields, which may be potentially useful in further transformation.[19] Mixed dihalides were also subjected to the reaction sequence. For example, 1-bromo-4-chlorobutane gave chlorine atom-tolerant imidation product **3u** as the only product, due to the different reactivity between bromine and chlorine atoms.

We investigated the efficacy of *N*-haloimides by reacting them with benzyl bromide (Scheme 3). Different *N*-haloimide exhibits different reactivity. NBP is less efficient than NCP (65%). Similar trend was observed for *N*-halosuccinimides. NCS gave product **7** in 51% yield while NBS and NIS could not react. From Scheme 1 one can see there are two types of halogen bonding interaction, *N*-haoimide and DBU (adduct **I**), and the resulting chlorine cation in 1-chloro-2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepinium with alkyl halide RX (adduct **III**). For the latter, chlorine atom gives stronger halogen bonding ability than bromine atom, due to the larger electron negativity, thus leading to R–X bond cleavage easier (nucleophilic substitution is the rate-determining step). *N*-Bromosaccharin was a competent reagent, affording 2-benzylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide **8** in 89% yield. Other *N*-haloimides like 1,3-dibromo-5,5-dimethyl hydantoin and *N*-bromoacetamide proved to be inefficient. All the above reactions indicated relatively high efficiency and broad scope for both alkyl halides and *N*-haloimides.



Scheme 2 Cross-coupling reaction of dihalides with NCP.



Scheme 3 Cross-coupling reaction of benzyl bromide with *N*-haloimides.

In summary, we have developed a highly efficient and metal-free cross-coupling reaction of alkyl halides and *N*-haloimides. With this strategy, various alkyl- and functionalized alkylamines were synthesized. The scope of the reaction is broad in terms of both alkyl halides and *N*-haloimides. A halogen bond activated nucleophilic substitution mechanism was proposed. This work demonstrated the feasibility and potential of halogen bonding activation in organic transformation.

Acknowledgements

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16 That DBU binding to the halogen in any step will help us to understand why stoichiometric amount of DBU is required in the reaction.

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18 The C=C double bond is tolerant under such conditions. One possible reason is no reaction occurs on the C=C double bond due to the low concentration of the dihalogen. The other reason is halogenation takes place, followed by a rapid elimination. Thus, the net result is the C=C double bond is intact.

19 No second coupling (imidation) takes place.