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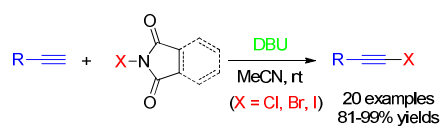
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Graphical Abstract:



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Facile and efficient synthesis of 1-haloalkynes via DBU-mediated reaction of terminal alkynes and *N*-haloimides under mild conditions

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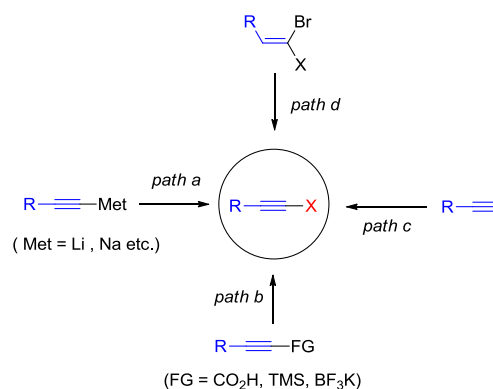
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Mengru Li,^a Yueju Li,^a Baozhong Zhao,^a Fushun Liang^{*a} and Long-Yi Jin^{*b}

Directly from terminal alkynes and with *N*-halosuccinimides (halo = Br and I) or *N*-chlorophthalimide as the halogen sources, DBU as the activator, 1-haloalkynes were prepared in good to excellent yields at room temperature. Bis(bromoalkyne) and bis(iodoalkyne) were also synthesized in excellent yields with the NBS(NIS)/DBU combination. The reaction features inexpensive and readily available reagents, mild conditions, simple execution, extremely short reaction time, broad halogen scope, high efficiency and metal-free. Compared to literature reported methods, our synthetic strategy provided a greener approach towards 1-haloalkynes.

Haloalkynes are both versatile intermediates in organic synthesis¹ and important building blocks in material and polymer sciences.² Classical approaches for the synthesis of 1-haloalkynes up to now include halogenation of metal acetylides (path a, Scheme 1),³ halogenations of propiolic acid/trialkylsilyl acetylenes/alkynyltrifluoroborates (path b, Scheme 1),⁴ oxidative halogenation of terminal alkynes (path c, Scheme 1),⁵ and dehydrohalogenation of 1,1-dihaloalkenes (path d, Scheme 1).⁶ Among all the methods described above, path c, i.e., the preparation of 1-haloalkynes directly from terminal alkyne substrates are highly desirable. In this regard, the utilization of AuPtBu₃/NBS,^{5a} AgF/NBS,^{5b} AgNO₃/NBS,^{5c-d} *n*-BuLi/X₂,^{5e-g} *n*-BuLi/NCS or NBS,^{5h-l} DBU/CCl₃Br,^{5j} PPh₃/CBr₄,^{5k} and KOH/CBr₄^{5l} have been reported. However, some of these methods may suffer from hazardous reagents, harsh reaction conditions, or generation of wastes that bring about environmental problems. Although considerable progress has been made, the development of new and efficient and environmentally benign protocols is still required.

Scheme 1. Approaches toward 1-haloalkynes



In our research on halogen-mediated organic transformations,⁷ we discovered that NBS (*N*-bromosuccinimide) or NBP (*N*-bromophthalimide) activated by DBU via a halogen bond interaction can be used as an efficient aminating reagent^{7a-c} or bromoamination reagent.^{7d} Herein, we would like to communicate that DBU-activated NXS (X = Br or I) or NCP can be used as a straightforward and efficient brominating reagent in the conversion of terminal alkynes into 1-haloalkynes under very mild conditions (Scheme 2).

Scheme 2. This work

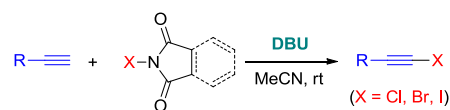
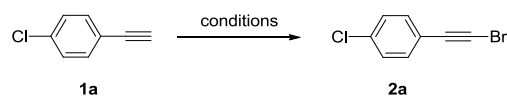


Table 1. Optimization of the reaction conditions^a



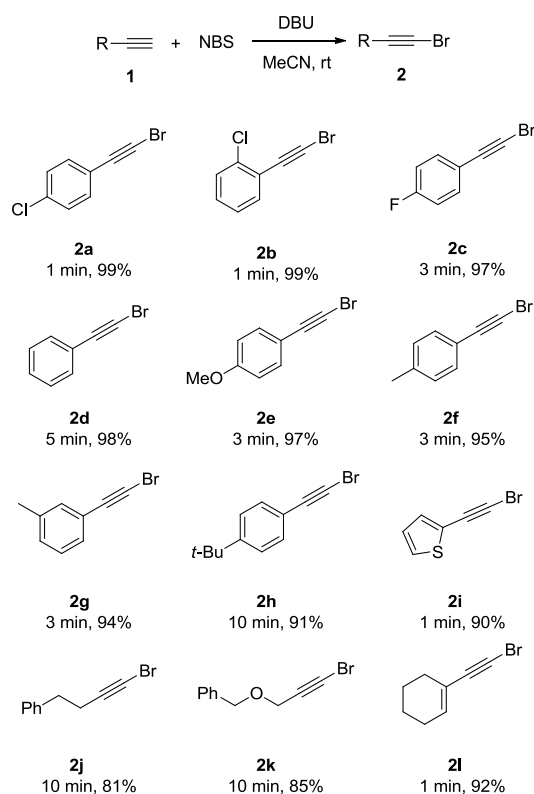
entry	NBS(P)	activator (equiv)	solvent	time (min)	yield ^b (%)
1	NBS	DBU (1.1)	MeCN	1	99
2	NBS	DBU (1.1)	DCM	5	98
3	NBS	DBU (1.1)	DMF	5	94
4	NBS	DBU (1.1)	toluene	10	60
5	NBS	DBU (1.1)	THF	10	51
6	NBS	DBN (1.1)	MeCN	15	95
7	NBS	DABCO (1.1)	MeCN	30	trace
8	NBS	NEt ₃ (1.1)	MeCN	30	20
9	NBP	DBU (1.1)	MeCN	25	96
10	NBS	DBU (0.2)	MeCN	240	93 ^c
11	NBS	—	MeCN	30	n.r.

^a Reactions were carried out with **1a** (1.0 mmol), NBS(P) (1.1 equiv) and the activator in 2.0 mL solvent at rt. ^b Isolated yield. ^c Performed at 0 °C.

Our initial experiment was carried out with 1-chloro-4-ethynylbenzene (**1a**), NBS (1.1 equiv), and DBU (1.1 equiv) in MeCN (2.0 mL) at room temperature (Table 1). The reaction proceeded rapidly and after 1 min (monitored by TLC), 1-(bromoethynyl)-4-chlorobenzene (**2a**) was produced in 99% isolated yield (Table 1, entry 1). Other solvents tested include DCM, DMF, toluene and THF (Table 1, entry 2-5). DCM and DMF gave similar to or slightly lower yield, but the yield of **2a** in toluene and THF was much lower than that in MeCN. Similar to DBU, DBN can also be used to produce **2a** in 95% yield (Table 1, entry 6). Other bases like NEt₃ and DABCO proved to be less efficient (Table 1, entries 7 and 8). Upon replacing NBS by NBP, the reaction proceeded well, furnishing product **2a** in a comparable yield (Table 1, entry 9). Catalytic amount of DBU (0.2 equiv) was also tried and product **2a** could be obtained in 93% yield, with prolonged reaction time (240 min) (Table 1, entry 10). By contrast, in the absence of DBU, the reaction could not occur at all, with starting material **1a** quantitatively recoverable (Table 1, entry 11).

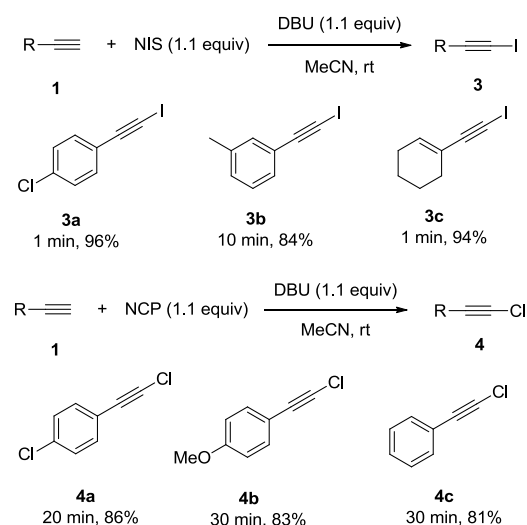
With the optimized conditions in hand (Table 1, entry 1), we explored the scope of terminal alkynes in the bromination reaction (Table 2). A variety of 1-bromoalkynes were prepared in good to excellent yields. The substituents on the alkyne substrates may be aryls including either electron-withdrawing groups (**2a-c**) or electron-donating substituents (**2e-h**), heteroaryls such as 2-thienyl (**2i**), and alkyl groups (**2j-k**). For conjugated enyne substrate, the ethynylic bond is more reactive than the C=C double bond, giving rise to product **2l** in 92% yield.

Table 2. Synthesis of 1-bromoalkynes: scope of terminal alkynes^{a,b}



^a Reactions were carried out with **1a** (1.0 mmol), NBS (1.1 equiv), DBU (1.1 equiv) in 2.0 mL MeCN at rt. ^b Isolated yield.

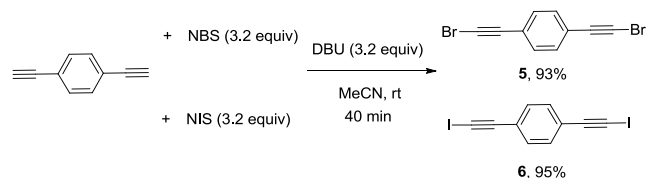
Scheme 3. Synthesis of 1-iodo(chloro)alkynes



Next, we wish to synthesize 1-haloalkynes containing other halogen atoms like chlorine and iodine. Thus, the reactions of alkynes with *N*-halosuccinimides were conducted (Scheme 3). Reactions of terminal alkynes with *N*-iodosuccinimide (NIS)

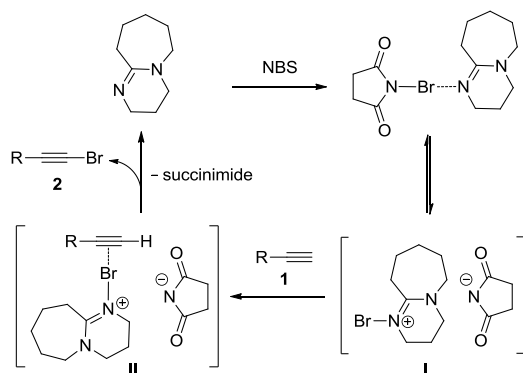
proceeded smoothly, giving the desired products **3a-c** in high to excellent yields. However, treatment of **1a** with *N*-chlorosuccinimide (NCS) under otherwise identical conditions gave no reaction. When *N*-chlorophthalimide (NCP) was employed, the reactions could proceed efficiently, and corresponding 1-chloroalkynes **4a-c** were isolated in 81-86% yields. We can not elucidate the different reactivity exhibited by NCS and NCP in the explored chlorination reactions at the current stage.

Scheme 4. Synthesis of bis(haloalkyne)s



Considering that bis(haloalkyne)s are quite important building block, we tried to synthesize such type of compounds using the strategy developed herein. To our delight, under the conditions of NBS or NIS (3.2 equiv)/DBU (3.2 equiv), 1,4-bis(bromoethynyl)benzene (**5**) and 1,4-bis(iodoethynyl)benzene (**6**) were successfully prepared in excellent yields of 93% and 95% yields, respectively (Scheme 4).

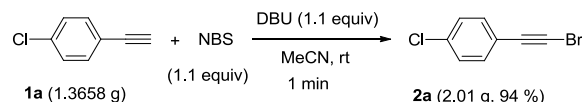
Scheme 5. Possible mechanism



On the basis of the results described above, along with previous study by others^{5a,b} and us^{7a-d}, a possible mechanism for the halogenation of the terminal alkynes was proposed in Scheme 5. Initially, a highly electrophilic bromine species **I** is supposed to generate from the 1:1 NBS/DBU halogen bond adduct.⁸ Then, the bromine species **I** reacts with alkyne **1** to form a π -coordinated complex **II**. Finally, alkynyl halides would be produced via deprotonation of terminal alkynes by DBU, along with succinimide or phthalimide side-product.⁹

To demonstrate the practicality of this halogenation reaction of alkynes, we carried out the reaction on a gram scale (Scheme 6). Reaction of 1.3658 g (10 mmol) of 1-chloro-4-ethynylbenzene (**1a**) with NBS (1.1 equiv)/DBU (1.1 equiv) in acetonitrile at room temperature gave **2a** (2.01 g) in 94% isolated yield.

Scheme 6. Multigram scale preparation of 1-bromophenylacetylene (**2a**)



Conclusions

In summary, a simple, novel and efficient halogenation of terminal alkynes has been developed by using DBU-activated *N*-halosuccinimide(phthalimide) as the halogen sources. The reaction mechanism involves the activation of *N*-halosuccinimide(phthalimide) by DBU to be a highly electrophilic bromine, and subsequent deprotonative halogenation of terminal alkynes. The reaction has distinct advantages of inexpensive and readily available reagents, mild conditions, simple execution, short reaction time, broad halogen scope, high efficiency and metal-free. Compared to literature reported methods, our synthetic strategy provided a greener approach towards 1-haloalkynes. Further work on halogen-mediated organic reactions is ongoing in our laboratory.

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Notes and references

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