# RSC Advances

## COMMUNICATION

# *N*-Bromosuccinimide–carboxylic acid combination: mild and efficient access to dibromination of unsaturated carbonyl compounds†

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A mild, efficient and practical method for the preparation of dihalogenated products has been developed. Benzoic acid (0.2 equiv.) is capable of catalyzing the reactions of unsaturated carbonyl compounds with *N*-halosuccinimides (NXS, X = Br and Cl) to afford a series of dihalogenated products at room temperature.
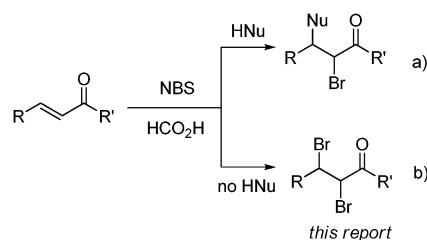
Dihalogenated organic compounds are important synthetic intermediates in the manufacture of pharmaceuticals, agrochemicals and other speciality chemicals.[1] The reactions of unsaturated carbon–carbon bonds with halogens are widely used for the preparation of dihalogenated products.[2] However, due to its toxic, corrosive and volatile nature, the use of elemental bromine is troublesome and environmentally hazardous, which heavily limits its applications. Therefore, it is necessary to develop new (di)bromination protocols.

Several more environmentally benign dihalogenation methods have been developed.[3–5] Solid organic pyridinium and quarternary ammonium tribromides such as Me$_4$NBr$_3$,[3a] Bu$_4$NBr$_3$,[3b,c] PhMe$_3$NBr$_3$,[3c] PyHBr$_3$,[3c,e] and 1,2-dipyridiniumditribromide-ethane (DPTBE)[3f] have been utilized as the source of Br$_2$ for dibromination.[3] It is worth noting that these brominating agents need to be prepared in advance from elemental bromine and/or bromides. Another fundamental method involves the utilization of bromide generated *in situ* from the oxidation of bromide ions.[4] The combinations of oxidants and bromides such as H$_2$O$_2$–HBr,[4a] *t*-BuOOH–HBr,[4b] oxone–HBr,[4c] NaNO$_2$–HBr[4d] oxone–NaBr,[4e,f] cerium(IV) ammonium nitrate (CAN)–KBr,[4g] have been employed in these bromination reactions, but require a two-phase (water and an organic solvent) system.

Comparatively, *N*-halosuccinimide (NXS), as a versatile reagent, can be used as a mild source of dihalogenation, in addition to monohalogenation.[5] For instance, Li and co-workers reported the synthesis of α,β-dihaloalkenes by the reaction of alkynes with NXS in the absence of any catalyst.[5a] Shi and Shao demonstrated that the combination of NBS and LiBr was an efficient protocol for the dibromination of unsaturated carbon–carbon bonds.[5b] A pyrrolidine-promoted dibromination of alkenes by a combination of NBS and succinimide is presented by Córdova and co-workers.[5c] More recently, Barbas III *et al.* communicated organocatalytic dibromination of a variety of functionalized alkenes using a stable, inexpensive halogen source, 1,3-dibromo-5,5-dimethylhydantoin, and a simple thiourea catalyst at room temperature.[5d] Nicolaou and co-workers developed an enantioselective allylic alcohol dichlorination with aryl iododichlorides as chlorine sources catalyzed by dimeric cinchona alkaloid derivatives.[5e]

In our research of halogen mediated (halonium, halogen bond, hypervalent halogen, halogenation) organic reactions,[6] we reported halonium-initiated electrophilic cascades leading to 3(2*H*)-furanones and dihydrofuropyridinones, using NBS as a halonium-producing reagent.[6a,b] It was known that, in the presence of an external nucleophile, the reaction of α,β-unsaturated enones with NBS under acidic conditions generates α,β-bifunctionalized ketones (Scheme 1a).[7] By contrast, we found in our continued work that, in the absence of an external nucleophile, the reaction afforded dibrominated products under otherwise identical conditions (Scheme 1b). Thus, a simple, mild and novel dibromination method has been developed, by the utilization of the combination of NBS and carboxylic acid as a

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**Scheme 1** Reactions of α,β-unsaturated enones in the presence or absence of an external nucleophile with NBS present.

**Table 1** Optimization of the reaction conditions[a]



| Entry | NBS (equiv.) | RCO$_2$H (equiv.) | Solvent | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 2.2 | HCO$_2$H (2.2) | DMF | 6 | — |
| 2 | 2.2 | HCO$_2$H (2.2) | DCM | 6 | 56 |
| 3 | 2.2 | HCO$_2$H (2.2) | MeCN | 5 | 75[c] |
| 4 | 2.2 | HCO$_2$H (2.2) | Toluene | 4 | 83 |
| 5 | 2.2 | HCO$_2$H (2.2) | THF | 4 | 85[c] |
| 6 | 2.2 | MeCO$_2$H (2.2) | THF | 5 | 86 |
| 7 | 2.2 | PhCO$_2$H (2.2) | THF | 7 | 91 |
| 8 | 2.2 | PhCO$_2$H (1.2) | THF | 7 | 91 |
| 9 | 2.2 | PhCO$_2$H (0.2) | THF | 9 | 91 |
| 10 | 1.1 | PhCO$_2$H (0.2) | THF | 8 | 48 |

[a] Reactions were carried out with 1a (1.0 mmol), NBS (1.2–2.2 equiv.), and a catalyst (0.2–2.2 equiv.) in solvent (2.0 mL). [b] Isolated yield. [c] Bromohydrin 3a was observed.
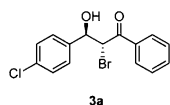


potential dihalogenation agent. The reaction may proceed efficiently at room temperature. Herein, we would like to report the experimental results and present the possible mechanism.

Initially, the model reaction of chalcone 1a with NBS was examined under acidic conditions (Table 1). No reaction occurred in the mixture of NBS (2.2 equiv.) and HCO$_2$H (2.2 equiv.) in DMF at room temperature (entry 1). To our delight, when the reaction was conducted in DCM, the dibrominated product 2a was obtained in 56% yield (entry 2). The structure of 2a was confirmed unambiguously by X-ray single crystal diffraction (Fig. 1).[8] The reaction in MeCN gave 2a in 75% yield, along with the separation of bromohydrin 3a in 21% yield (entry 3).[9] Solvents like toluene and THF afforded 2a in good yields (entries 4 and 5). The reaction with MeCO$_2$H (2.2 equiv.) as the catalyst exhibited a similar efficiency, giving 2a in 86% yield (entry 6). Considering the influence of water in the reaction system (entries 3 and 5), benzoic acid, as an easily available, cheap, safe and environmentally benign organic carboxylic acid, was finally examined. Gratifyingly, the reaction afforded the desired product 2a in 91% yield, no matter whether 2.2 or 1.2 equiv. of PhCO$_2$H was used (entries 7
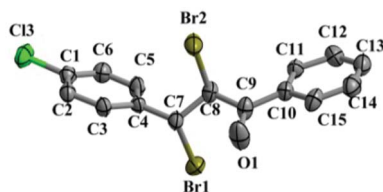


**Fig. 1** ORTEP drawing of 2a.

**Table 2** Dibromination of α,β-unsaturated carbonyl compounds by a NBS–PhCO$_2$H combination[a]



| Entry | R$^1$ | R$^2$ | Time (h) | 2 | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 4-ClC$_6$H$_4$ | Ph | 6 | 2a | 91 |
| 2 | 1a (5 g) | | 7 | 2a | 84[c] |
| 3 | Ph | Ph | 5 | 2b | 85 |
| 4 | 4-CH$_3$C$_6$H$_4$ | Ph | 5 | 2c | 87 |
| 5 | 4-MeOC$_6$H$_4$ | Ph | 9 | 2d | 81 |
| 6 | 4-OCH$_2$OC$_6$H$_4$ | Ph | 4 | 2e | 80 |
| 7 | 4-BrC$_6$H$_4$ | Ph | 7 | 2f | 89 |
| 8 | 4-FC$_6$H$_4$ | Ph | 7 | 2g | 94 |
| 9 | 3-NO$_2$C$_6$H$_4$ | Ph | 8 | 2h | 91 |
| 10 | 2-naphthyl | Ph | 4 | 2i | 92 |
| 11 | 2-thienyl | Ph | 4 | 3b | 89[d] |
| 12 | t-Bu | Ph | 12 | — | n.r. |
| 13 | Ph | Me | 8 | 2j | 92 |
| 14 | Ph | t-Bu | 6 | 3c | 89 |
| 15 | Ph | 4-ClC$_6$H$_4$ | 5 | 2k | 82 |
| 16 | Ph | 4-BrC$_6$H$_4$ | 5 | 2l | 83 |
| 17 | Ph | 4-CH$_3$C$_6$H$_4$ | 5 | 2m | 87 |
| 18 | Ph | OEt | 12 | 2n | 81 |
| 19 | Ph | CH=CHPh | 6 | 2o | 81 |
| 20 | 4-CH$_3$C$_6$H$_4$ | CH=CHPh | 5 | 2p | 86 |
| 21 | 4-MeOC$_6$H$_4$ | 4-MeOC$_6$H$_4$ | 12 | — | complex |

[a] Reactions were carried out with 1 (1.0 mmol), NBS (2.2 equiv.) and a catalyst (0.2 equiv.) in anhydrous THF (2.0 mL). [b] Isolated yield. [c] Isolated yield after crystallization from ethanol. [d] Bromohydrin 3b and 3c were obtained as the main product after column chromatography.
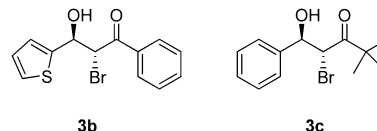


and 8). More importantly, a catalytic amount of benzoic acid was capable of driving the reaction to completion, furnishing 2a in comparable yields (entry 9). It was noteworthy that, even though 1.1 equiv. of NBS was used, the product 2a could still be obtained, but in merely 48% yield (Table 1, entry 10).

With the optimized conditions in hand, a range of reactions were carried out with various α,β-unsaturated carbonyl compounds 1 in the presence of NBS (2.2 equiv.) and PhCO$_2$H (0.2 equiv.) (Table 2). Substrates 1, containing both electron-poor and electron-rich R$^1$ groups, could react with NBS smoothly, giving the desired products 2a–i in good to excellent yields (entries 1–10). A wide range of functionalities such as nitro and halogen groups was tolerated under the reaction conditions. It is noteworthy that the gram-scale preparation of compound 2a was readily achieved in 84% yield simply by recrystallization in ethanol (entry 2). When a heteroaryl such as 2-thienyl-containing enone was introduced to this reaction, bromohydrin 3b, instead of dibromination product, was obtained as the main product after column chromatography (Table 2, entry 11).[10] For a t-butyl substituted enone substrate, no reaction took place, presumably due to the steric effect of the R$^1$
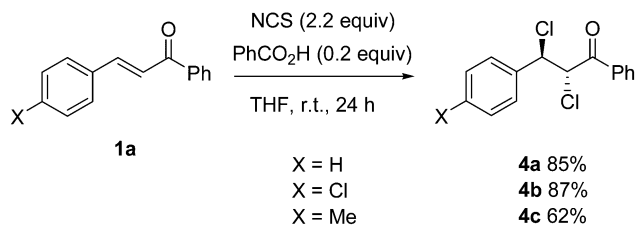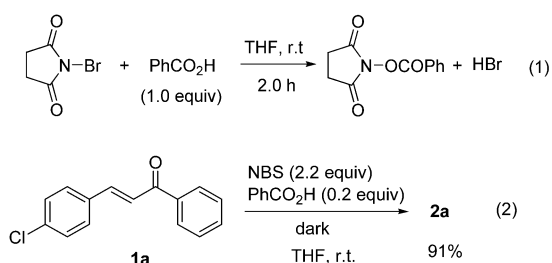
**Scheme 2** Dichlorination reactions.

group (entry 12). The $R^2$ substituent of α,β-unsaturated ketones may be either the alkyl or the aryl groups (entries 13–17). α,β-Unsaturated esters were proven to be compatible. For example, product **2m** was obtained in 81% yield, but with a prolonged reaction time (entry 18). Dienone substrates were also investigated. In the presence of 2.2 equiv. of NBS, chemoselective dibromination of one double bond in the substrates was observed and products **2o** and **2p** were achieved in good yields (entries 19 and 20). However, when both $R^1$ and $R^2$ are electron-donating MeO groups, the reaction gave a complex mixture (entry 21).
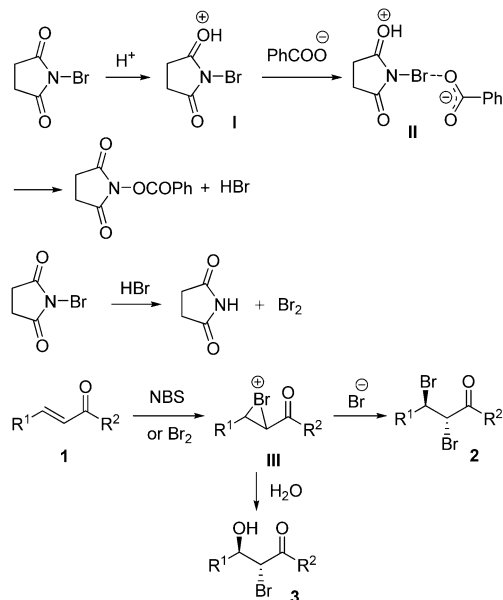
In addition to NBS, reactions with NCS and NIS were performed. As a result, the dichlorinated products **4a–c** were successfully prepared in 62–87% yields, while the reaction with NIS proved to be inefficient (Scheme 2).

In order to elucidate the possible mechanism for the carboxylic acid-catalyzed dihalogenation reaction, the control experiments were carried out (Scheme 3). When the mixture of NBS (1.0 mmol), benzoic acid (0.2 equiv.) and THF (2 mL) was stirred at room temperature (eqn (1)), the colorless solution turned dark red within 30 min. After 2 h, the NBS was consumed and succinimide was observed on the TLC plate. In another isolated experiment, the reaction mixture of **1a** (1.0 mmol), NBS (2.2 equiv.) and benzoic acid (0.2 equiv.) was conducted in the dark under otherwise identical conditions (eqn (2)). The corresponding product **2a** was obtained in comparable yield (Table 2, entry 1), which, to some extent, excludes a radical mechanism involved in the transformation.

Based on all the results described above and a recent report by Barbas III,[5d] a possible mechanism for the carboxylic acid catalyzed dibromination of α,β-unsaturated carbonyl compounds by NBS was proposed in Scheme 4. Firstly, a halogen bond[11] interaction between NBS and benzoic acid leads to the formation of complex **II** via the protonated NBS **I**.[12] Then, 2,5-dioxopyrroli-



**Scheme 4** Possible mechanism for the benzoic acid catalyzed dibromination by NBS.

din-1-yl benzoate and HBr are supposed to be generated via a formal polarity reversal of bromide. Thus, elemental bromine would be generated in situ by the reaction of HBr and excess NBS.[13] The unsaturated carbonyl compounds **1** would react with NBS or $Br_2$ to produce the bromonium ion intermediate **III**,[14] which is subsequently trapped by the bromide anion (derives from HBr for the former). The final dibromonated product **2** is thus attained. If intermediate **III** is captured by the water in the reaction system, by-product **3** would be generated.[15]

In conclusion, the combination of NBS and carboxylic acid has been, for the first time, used as a dibromination agent in the reaction with unsaturated compounds. The reaction features mild conditions and is readily scalable and environmentally benign. The halogen bond interaction between NBS and benzoic acid leads to the formation of HBr, and thus, elemental bromide was generated in situ by further reaction with NBS. Further work on the halogen mediated organic reactions is ongoing in our laboratory.

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**Scheme 3** Control experiments.

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8  CCDC 892370 (**2a**) 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.

9  The water in the reaction system has some influence on the reaction. In the following work, anhydrous THF was used as the solvent and benzoic acid was utilized as the catalyst.

10  Dibrominated product was produced in high yield, while it appears to be unstable and decomposes to bromohydrin **3** upon silica gel column purification.

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14  For a review on bromonium ion intermediate, see: R. S. Brown, *Acc. Chem. Res.*, 1997, **30**, 131–137.

15  A radical mechanism for the generation of elemental bromine can not be completely excluded
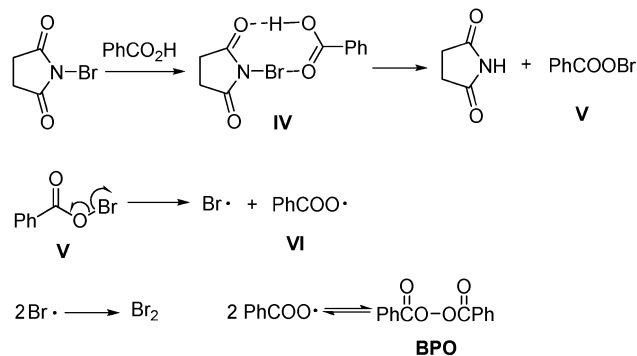
For the homolytic cleavage of the O–Br bond in intermediate V, please refer to the Hunsdiecker reaction. The introduction of a radical traping agent like TEMPO to the reaction system to verify the radical mechanism appears to be ineffective, because TEMPO may react with NBS substrate and finally consume NBS.