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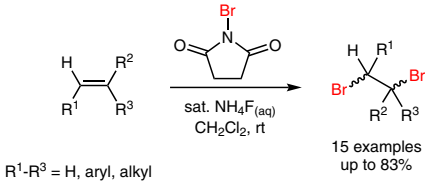
Mild and Efficient Vicinal Dibromination of Olefins Mediated by Aqueous Ammonium Fluoride

Wing Hin Ng
Tony K. M. Shing*
Ying-Yeung Yeung*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, P. R. of China
yyyeung@cuhk.edu.hk



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Abstract A mild and efficient vicinal dibromination of olefins has been developed by using saturated aqueous ammonium fluoride solution as the promoter. Inexpensive and commercially available *N*-bromosuccinimide (NBS) was used as the brominating reagent. The corresponding vicinal dibromoalkanes could be obtained in good to excellent yields.

Key words olefins, dibromination, halogen, *N*-bromosuccinimide, metal-free

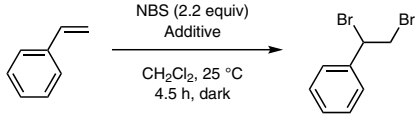
Vicinal dibromination of olefins is a classical and important organic transformation. For instance, vicinal dibromides can be converted into vinyl bromides[1] and vinyl azides[2] under basic conditions. Vinyl bromides are useful synthons in Grignard reactions[3] and cross-coupling reactions[4] while vinyl azides are important precursors for nitrogen heterocycle synthesis.[5] Furthermore, cyclopropanes[6] and alkynes[7] can be synthesized directly from vicinal dibromides. Vicinal dibrominated compounds are valuable intermediates that can be utilized in agrochemicals, pharmaceuticals, and other fine chemicals. In addition, numerous marine natural products are found to be heavily halogenated.[8] Therefore, (di)halogenation methods are required for synthesis and derivatization.[9]

From a mechanistic aspect, an equivalence of bromenium (Br^+) and bromide (Br^-) are needed in the addition reaction of olefin for vicinal dibromination. Based on this rationale, several approaches have been developed for olefinic vicinal dibromination. The first type of approach involved the use of molecular bromine or bromine carrier, where the reagents themselves are already comprised of Br^+ and Br^- in Br_2. Quaternary ammonium and pyridinium tribromide reagents such as Me_4NBr_3,[10] Bu_4NBr_3,[11] $PhMe_3NBr_3$,[12] and PyHBr[13] have been developed as bromine carriers for various dibromination reactions. The second approach involves the direct combination of electrophilic brominating reagent (Br^+) and bromide source (Br^-). *N*-Bromosuccinimide (NBS) and lithium bromide were employed together to allow dibromination of olefins and other C–C unsaturated bonds.[14] This approach has also been adapted by Burns for the challenging asymmetric dibromination of allylic alcohols, utilizing diethyl dibromomalonate and bromotitanium triisopropoxide pair with chiral TADDOL ligands.[15] The third approach referred to bromide oxidation, where Br^- is oxidized to Br^+ for the generation of Br_2 in situ. Oxidant–bromide pairs such as DMSO–HBr,[16] H_2O_2–HBr,[17] oxone–NaBr,[18] and cerium(IV) ammonium nitrate (CAN)–KBr,[19] for dibromination have been documented. The forth approach referred to bromenium reduction, in which Br^+ is reduced to Br^- to generate Br_2 in situ. Some novel organocatalytic protocols for dibromination of olefins that have emerged in recent years fall into this category. NBS and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) were utilized as Br sources using thiourea,[20] hypervalent iodine,[21] pyrrolidine,[22] and benzoic acid[23] as the organocatalysts, although the reductants in their systems remained unclear.

Herein, we report our discovery of a mild reductive dibromination of olefins by using the halogen source *N*-bromosuccinimide (NBS) with saturated aqueous ammonium fluoride solution ($NH_4F_{(aq)}$) as the promoter. NBS is commonly used as a mild source of electrophilic Br because it is inexpensive, commercially available, and easy to handle (free-flowing crystalline solid). It has been reported that ammonium chloride could act as an additive in the dibromination of alkenes using iodine(III) catalyst, but ammonium chloride alone could not drive the reaction. In contrast, here, we demonstrate that simply applying ammonium fluoride alone could promote the dibromination with appreciable efficiency.[21]

At the outset of our experimentation, styrene (**1a**) was used as the model substrate. When **1a** was reacted with NBS in dichloromethane at room temperature, no reaction was observed. To our surprise, in the presence of saturated ammonium fluoride solution, styrene reacted with NBS to afford dibromination product **1b** in 61% yield (Table 1, entry 1).

Table 1 Performance of Promoters[a]



1a **1b**

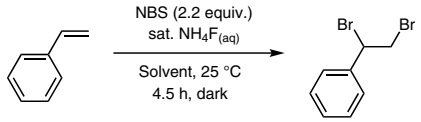
Entry	Additive	Time (h)	Yield (%)[c]
1	sat. $NH_4F_{(aq)}$	21	61
2	sat. $(NH_4)_2SO_{4(aq)}$	48	trace
3	sat. $NaF_{(aq)}$	48	trace
4	$NH_4F_{(s)}$[b]	48	22
5	H_2O	30	no reaction

[a] Reactions were carried out with styrene (**1a**; 0.2 mmol), NBS (0.44 mmol) and additive (0.03 mL) in dichloromethane (1 mL) at 25 °C in the dark for 4.5 h.
[b] Ammonium fluoride (0.1 equiv) was used.
[c] Isolated yield.

To study the effect of ammonium salt in the reaction, the performance of various saturated salt solutions were evaluated. Changing the ammonium fluoride solution to ammonium sulfate led to a sluggish reaction, suggesting that the fluoride anion played a crucial role in the dibromination (Table 1, entry 2). The ammonium cation was also found to be important since aqueous sodium fluoride solution did not promote the reaction (entry 3). A solid suspension of NH_4F in dichloromethane gave a sluggish reaction, which indicated the importance of having the ionized components (entry 4). A control experiment was conducted in which water alone as the additive was used; this did not promote the reaction (entry 5).

Having identified aqueous NH_4F as a suitable promoter, the reaction was further optimized by varying the solvent and the amount of aqueous NH_4F (Table 2). A survey on different solvents revealed that CH_2Cl_2 remained the optimum reaction medium (entries 1–9). Other polar solvents including THF, ethanol, and DMF led to poor yields of dibromination products. It could be rationalized that the nucleophilic solvents could capture the bromiranium intermediate formed between NBS and styrene, leading to the formation of side products (see the Supporting Information).[24] Further increasing the amount of saturated aqueous ammonium fluoride returned a higher yield (68%; entry 10). It should be noted that, based on the solubility of NH_4F in water (45.3 g/100 mL water, equivalently 12.2 M, at 25 °C),[25] approximately 10 equivalents of NH_4F were used in the reaction summarized in entry 10. Further doubling the amount of saturated aqueous ammonium fluoride only gave a slight increase in yield (entry 11). Therefore, the conditions shown in entry 10 were selected as the optimized conditions.

Table 2 Reaction Optimization[a]



1a **2a**

Entry	Solvent	Sat. $NH_4F_{(aq)}$ (mL)	Yield (%)[b]
1	CH_2Cl_2	0.03	59
2	$CHCl_3$	0.03	36
3	PhMe	0.03	20
4	THF	0.03	24
5	EtOAc	0.03	36
6	CH_3CN	0.03	23
7	EtOH	0.03	trace
8	DMF	0.03	trace
9	DMSO	0.03	trace
10	CH_2Cl_2	0.16	68
11	CH_2Cl_2	0.32	70

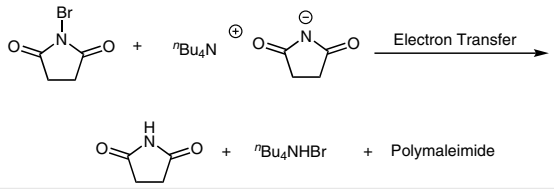
[a] Reactions were carried out with styrene (**1a**; 0.2 mmol), NBS (0.44 mmol), and saturated $NH_4F_{(aq)}$ at 25 °C in the dark for 4.5 h.
[b] Isolated yield.

With the optimized conditions in hand, we then expanded the substrate scope of the reaction; the results are shown in Table 3. Styrenes **1a–f** with both electron-donating and electron-withdrawing substituents were compatible with the conditions and gave the dibromide **2a–f** in good yields (entries 1–6). In addition, 1,2-disubstituted benzylic olefinic systems **1g–j** could also give the desired dibrominated products **2g–j** in appreciable conversions (entries 7–10). Dibromination of aliphatic terminal olefins **1k** and **1l** gave good yields of **2k** and **2l** (80 and 77%, respectively; entries 11 and 12). Use of the cyclic olefin cyclooctene **1n** resulted in an excellent yield of 83%, whereas the use of cyclohexene **1m** resulted in moderate conversion with NMR yield of 51% (entries 13 and 14).

During our experimentation, it was observed that there was an instant color change from colorless to orange when saturated aqueous NH_4F was added to a solution of NBS in CH_2Cl_2. Subsequent addition of styrene resulted in decolorization of the orange solution gradually. It was suspected that the formation of the orange color was due to the generation of molecular Br_2 in situ. However, in the reaction system, NBS was the only source of Br atom on the product and

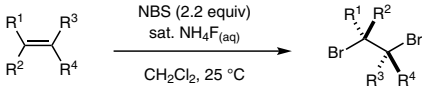
NBS can generally be a source of Br^+ or Br radical. This situation resembles those of the organocatalytic dibromination cases reported by Barbas III,[18] Gulder,[19] Córdova,[20] and Zhao[21] in which solely *N*-bromoimide reagents were sufficient to perform dibromination without an apparent source of bromide anion for the generation of molecular Br_2 in situ.

To generate the counter bromide anion, a stoichiometric reductant is required to convert Br^+ (from NBS) into Br^-. Ross reported that an electron-transfer reaction could take place in the complex of NBS and succinimide anion, resulting in succinimide, polymeric maleimide and bromide ion as products (Scheme 1).[26] After the electron-transfer reaction, two succinimidyl radicals were produced, which could further disproportionate to succinimide and maleimide. Maleimide was reported to further polymerize to give polymeric maleimide. This suggested that succinimide anion might be the possible reductant for the generation of Br^-.



Scheme 1 Electron-transfer reaction between NBS and succinimide anion

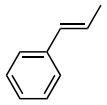
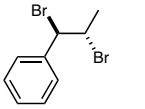
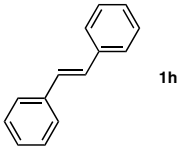
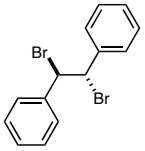
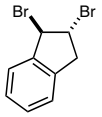
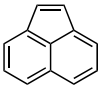
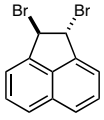
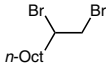
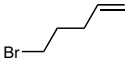
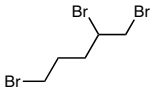
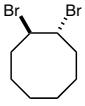
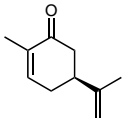
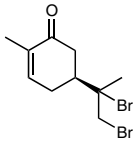
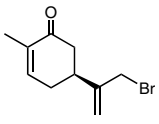
Table 3 Substrate Scope[a]



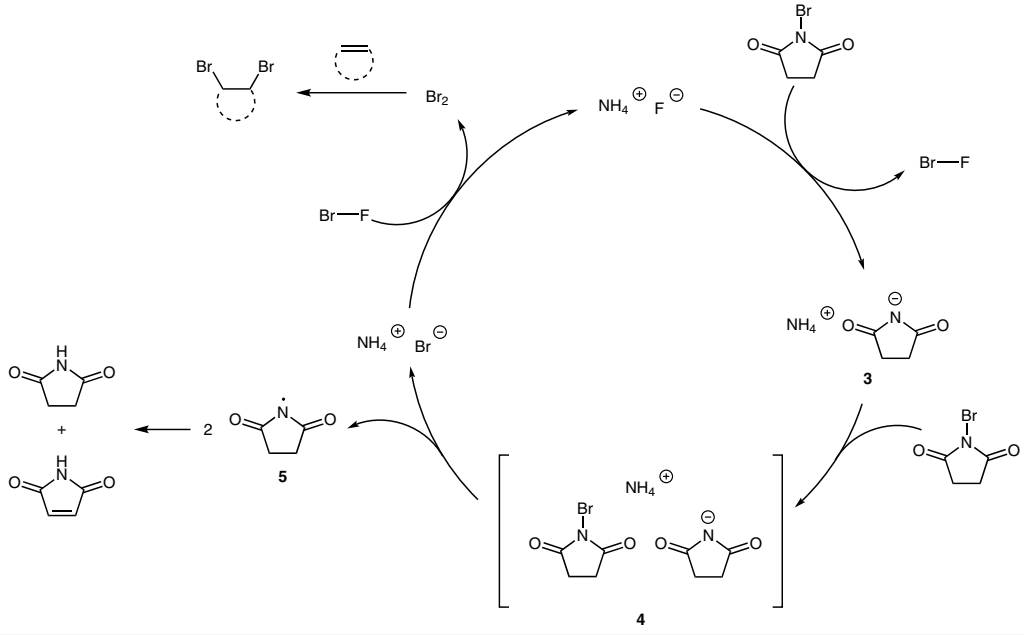
1 2

Entry	Substrate	Product	Time (h)	Yield (%)[b]	dr
1	**1a**	**2a**	4.5	68	–
2	**1b**	**2b**	1	58	–
3	**1c**	**2c**	2	58	–
4	**1d**	**2d**	4.5	73	–
5	**1e**	**2e**	22.5	71	–
6	**1f**	**2f**	1	62	–

Table 3 (continued)

Entry	Substrate	Product	Time (h)	Yield (%)[b]	dr
7	 **1g**	 **2g**	1	67	10:1
8	 **1h**	 **2h**	16	76	1:3
9	 **1i**	 **2i**	2	55 (78)[c]	2:1
10	 **1j**	 **2j**	4.5	31	*anti* only
11	 **1k**	 **2k**	2	80	–
12	 **1l**	 **2l**	2	77	–
13	 **1m**	 **2m**	3.5	36 (51)[c]	*anti* only
14	 **1n**	 **2n**	2	83	*anti* only
15	 **1o**	 **2o**	2.5	37	–
		 **2o'**		27	–

[a] Reactions were carried out with olefin **1** (0.2 mmol), NBS (0.44 mmol), and saturated $NH_4F_{(aq)}$ (0.16 mL) in dichloromethane (1 mL) at 25 °C in the dark.
[b] Isolated yield.
[c] Yield by ^1H NMR spectroscopic analysis using dimethyl terephthalate as internal standard.



Scheme 2 Plausible mechanism for generation of bromine from NBS

Based on these precedent studies, herein we propose a plausible mechanistic picture depicted in Scheme 2. Nucleophilic attack of F^- to NBS could produce BrF and ammonium succinimide **3**. Complex **4** could be formed by the reaction between NBS and **3**. Subsequent electron transfer from succinimide anion to NBS might proceed to give Br^- and two succinimidyl radicals **5**. The Br^- generated could react with BrF generated previously to give molecular bromine for olefinic dibromination. Alternatively, BrF itself could also be the electrophilic Br source. Two succinimidyl radicals produced after the electron-transfer reaction might disproportionate to give succinimide and maleimide, where maleimide could further polymerize to give polymeric maleimide.[26]

In summary, we have developed a mild dibromination of olefin.[27] Non-hazardous, easy-to-handle and commercially available NBS and ammonium fluoride was used in the reaction at room temperature, making this protocol practical for the dibromination of olefinic compounds. Further optimization of this protocol to other substrates and mechanistic studies are in progress.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588506.

References and Notes

(1) Piou, T.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 11292.
(2) Ramachary, D. B.; Reddy, G. S.; Peraka, S.; Gujral, J. *ChemCatChem* **2017**, *9*, 263.
(3) Garst, J. F.; Soriaga, M. P. *Coord. Chem. Rev.* **2004**, *248*, 623.
(4) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(5) Hu, B.; DiMagno, S. G. *Org. Biomol. Chem.* **2015**, *13*, 3844.
(6) Goudreau, N.; Brochu, C.; Cameron, D. R.; Duceppe, J.-S.; Faucher, A.-M.; Ferland, J.-M.; Grand-Maître, C.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S. *J. Org. Chem.* **2004**, *69*, 6185.
(7) Gröst, C.; Berg, T. *Org. Biomol. Chem.* **2015**, *13*, 3866.
(8) (a) Faulkner, D. J. *Nat. Prod. Rep.* **1988**, *5*, 613. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1992**, *9*, 323.
(9) (a) Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514. (b) Snyder, S. A.; Tang, Z. Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744. (c) Kanady, J. S.; Nguyen, J. D.; Ziller, J. W.; Vanderwal, C. D. *J. Org. Chem.* **2009**, *74*, 2175. (d) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573.
(10) Avramoff, M.; Weiss, J.; Schächter, O. *J. Org. Chem.* **1963**, *28*, 3256.
(11) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K. *Tetrahedron Lett.* **1998**, *39*, 8163.
(12) Tanaka, K.; Shiraishi, R.; Toda, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3069.
(13) Nakamatsu, S.; Toyota, S.; Jones, W.; Toda, F. *Chem. Commun.* **2005**, 3808.
(14) Shao, L.-X.; Shi, M. *Synlett* **2006**, 1269.

(15) Hu, D. X.; Shibuya, G. M.; Burns, N. Z. *J. Am. Chem. Soc.* **2013**, *135*, 12960.
(16) Karki, M.; Magolan, J. *J. Org. Chem.* **2015**, *80*, 3701.
(17) Ho, T. L.; Gupta, B.; Olah, G. A. *Synthesis* **1977**, 676.
(18) Kim, K. M.; Park, I. H. *Synthesis* **2004**, 2641.
(19) Nair, V.; Panicker, S. B.; Augustine, A.; George, T. G.; Thomas, S.; Vairamani, M. *Tetrahedron* **2001**, *57*, 7417.
(20) Hernández-Torres, G.; Tan, B.; Barbas, I. II C. F. *Org. Lett.* **2012**, *14*, 1858.
(21) Stodulski, M.; Goetzinger, A.; Kohlhepp, S. V.; Gulder, T. *Chem. Commun.* **2014**, 3435.
(22) Zhu, M.; Lin, S.; Zhao, G. L.; Sun, J.; Córdova, A. *Tetrahedron Lett.* **2010**, *51*, 2708.
(23) Xue, H.; Tan, H.; Wei, D.; Wei, Y.; Lin, S.; Liang, F.; Zhao, B. *RSC Adv.* **2013**, *3*, 5382.
(24) (a) Das, B.; Venkateswarlu, K.; Damodar, K.; Suneel, K. *J. Mol. Catal. A: Chem.* **2007**, *269*, 17. (b) Zhou, L.; Tan, C. K.; Zhou, J.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2010**, *132*, 10245. (c) Souza, A. V. A.; Mendonca, G. F.; Bernini, R. B.; Mattos, M. C. S. *J. Braz. Chem. Soc.* **2007**, *18*, 1575.
(25) Papcun, J. R. *Fluorine Compounds, Inorganic, Potassium*, In *Kirk–Othmer Encyclopedia of Chemical Technology*; John Wiley and Sons, Inc: Weinheim, **2000**.
(26) (a) Barry, J. E.; Finkelstein, M.; Moore, W. M.; Ross, S. D. *Tetrahedron Lett.* **1984**, *25*, 2847. (b) Eberson, L.; Barry, J. E.; Finkelstein, M.; Moore, W. M.; Ross, S. D. *Acta Chem. Scand., Ser. B* **1985**, *39*, 249. (c) Finkelstein, M.; Hart, S. A.; Moore, W. M.; Ross, S. D. *J. Org. Chem.* **1986**, *51*, 3548.
(27) **Typical Procedure for the Dibromination of Olefin 1a Using NBS and Aqueous Ammonium Fluoride:** To a solution of olefin (**1a**; 21 mg, 0.202 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added *N*-bromosuccinimide (78.3 mg, 0.44 mmol, 2.2 equiv) and saturated aqueous ammonium fluoride (0.16 mL) in the absence of light. The resulting mixture was stirred at room temperature and the reaction was monitored by TLC. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography to yield the dibromide **2a** (37.1 mg, 70%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 5 H), 5.16 (dd, *J* = 10.6, 5.5 Hz, 1 H), 4.09 (dd, *J* = 10.2, 5.5 Hz, 1 H), 4.03 (t, *J* = 10.4 Hz, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 138.66, 129.25, 128.93, 127.73, 50.98, 35.15; HRMS (EI): *m*/*z* [M]$^+$ calcd. for $C_8H_8Br_2$: 263.8967; found: 263.8972.