N-Bromosuccinimide and Lithium Bromide: An Efficient Combination for the Dibromination of Carbon–Carbon Unsaturated Bonds

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Received 25 November 2005

Abstract: Compounds possessing unsaturated bonds such as alkenes, alkynes, allenes, and methylenecyclopropanes (MCPs) can be dibrominated within minutes by NBS and lithium bromide in THF at room temperature in good to excellent yields under mild conditions.

Key words: NBS, lithium bromide, unsaturated compounds, dibromination reaction

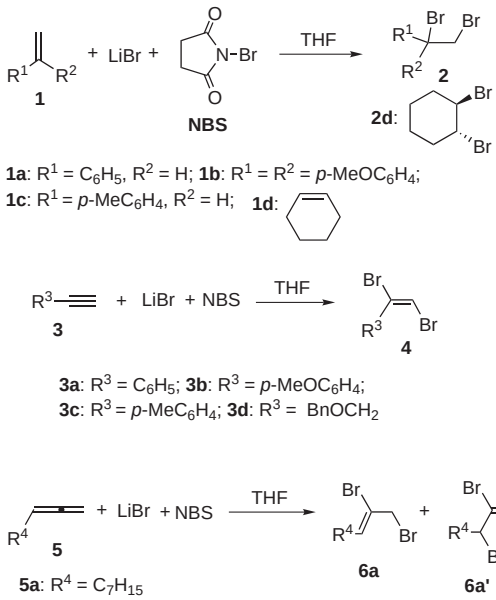
Dihalo derivatives are important compounds in organic synthesis as well as in analytical chemistry. The electrophilic addition of molecular bromine to unsaturated bonds via a bromonium ion[1] remains the method of choice for the generation of dibrominated compounds. In such a procedure, halogen addition is carried out in CCl_4, one of the common solvents used in bromination. However, CCl_4 is currently on the 'environmental blacklist'. In CCl_4 the electrophilic additions are slow and radical reactions may occur, resulting in a range of products. In addition, despite the widespread use of molecular bromine as an electrophilic reagent it is a toxic, difficult to handle, low-boiling lachrymatory liquid, which causes severe burns on contact with skin.[2] Moreover, since molecular bromine is a strong oxidizing agent, attempted bromination of complex organic substrates can be hampered by undesired competing oxidation processes.[3] These concerns over selectivity, handling, and toxicity issues associated with Br_2 have fuelled research into new strategies for the bromination of organic substrates. Though some convenient methods have been developed for the mono-bromination of organic substrates using an oxidant and metal bromide combination as an electrophilic Br^+ source instead of Br_2,[4] molecular Br_2 is still the preferred choice in the dibromination of organic substrates. There have been some other developments, such as ionic liquids being used as the solvent instead of CCl_4[5] and pentylpyridinium tribromide being used as the source of molecular Br_2.[6] Today's increased environmental awareness prompts chemists to search for clean and sustainable synthetic methodologies. In situ formation of reactive halogen compounds is one of the most promising approaches to overcome the safety and waste-handling problems. Initially, we assumed that if two independent sources of Br^+ and Br^- were used in the system for the dibromination reactions, perhaps molecular Br_2 could be avoided as a source of brominating agent and many more solvents could be used.

It should be noted that though NBS is usually used as a brominating agent via a radical procedure,[7] it is also a potential source of electrophilic Br^+.[8] On the other hand, many metal bromides can be chosen as a source of Br^-.

Herein, we will present our results on the dibromination of carbon–carbon unsaturated bonds such as alkenes, alkynes, allenes, and methylenecyclopropanes (MCPs) by NBS and LiBr in THF as the solvent.

The results of the dibromination of alkenes, alkynes, and allenes are summarized in Scheme 1 and Table 1. Initial examination using alkene **1a** as the substrate showed that two equivalents of NBS and LiBr are required; with one equivalent or 1.5 equivalents the reaction became messy and no desired product was obtained. An excess of NBS and LiBr (3.0 equiv and 5.0 equiv) had no effect on the reaction and the product was obtained in nearly the same yield. The reactions proceeded smoothly to give the desired dibrominated products within minutes in good to excellent yields (Scheme 1, Table 1).[9] For the styrene derivatives examined, the substituent on the phenyl ring had a dramatic effect on the reaction rate. For styrene **1a**, the reaction was somewhat sluggish and was complete after 30 minutes (Table 1, entry 1). For the styrenes, substituted with an electron-donating group, **1b** (*p*-MeO) and **1c** (*p*-Me), the reactions were complete within two minutes in good to high yields (Table 1, entries 2 and 3). For cyclohexene **1d** (aliphatic olefin), the reaction also proceeded smoothly to give the corresponding product **2d** in good yield (Table 1, entry 4). For substituted phenylacetylenes **3a**, **3b**, and **3c**, all these reactions were complete within two minutes to give the desired products in good yields (Table 1, entries 5–7). For the alkyl group substituted alkyne **3d**, the reaction was somewhat sluggish and the corresponding product **4d** was obtained in lower yield (Table 1, entry 8). It is noteworthy that only the dibromination of acetylene took place to give the 1,2-dibrominated product **4**; no further bromination of **4** was observed presumably due to its electron-deficiency. In addition, dibromination of allene **5a** was complete within two minutes to give the 1,2- and 2,3-dibrominated mixtures of **6a** and **6a′** in high yield (Table 1, entry 9).

SYNLETT 2006, No. 8, pp 1269–1271
Advanced online publication: 05.05.2006
DOI: 10.1055/s-2006-941558; Art ID: W31405ST



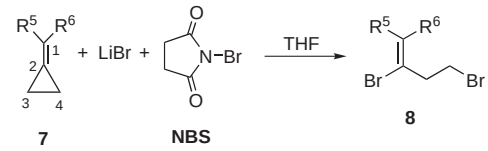
Scheme 1

Table 1 Dibromination of Alkenes, Alkynes, and Allenes

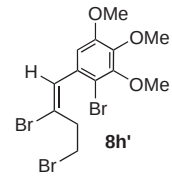
Entry[a]	Substrate	Time (min)	Product	Yield (%)[b]
1	**1a**	30	**2a**	56
2	**1b**	2	**2b**	94
3	**1c**	2	**2c**	71
4	**1d**	2	**2d**	61
5	**3a**	2	**4a**	82
6	**3b**	2	**4b**	66
7	**3c**	2	**4c**	82
8	**3d**	30	**4d**	26
9	**5a**	2	**6a**/**6a′**	94 (1:1)[c]

[a] All reactions were carried out with substrate (1 equiv), NBS (2 equiv), LiBr (2 equiv).
[b] Isolated yields.
[c] Ratio of **6a** and **6a′**.

The dibromination of MCPs **7**[10,11] was also carried out with NBS and LiBr. Initial examination of the dibromination of MCP **7a** showed that the addition sequence of the reactants significantly affected the results. 1,2- and 2,3-Dibrominated products were obtained as an inseparable mixture in a ratio of about 1:4 if the three components were added at the same time. The best result was obtained if NBS was added after sufficient mixing of MCP and LiBr in THF.[12] As shown in Scheme 2 and Table 2, the reactions proceeded smoothly to give the desired products in good to excellent yields for the majority of MCPs **7** examined. The terminal substituents on the MCPs have no effect on the reaction rate and for all MCPs examined the reaction was complete within two minutes. For MCPs **7a**, **7d**, and **7e** higher yields were obtained with a shorter reaction time in comparison with the dibromination reactions by molecular Br_2.[11] For the unsymmetrical diaryl-substituted MCPs such as **7c** and **7f**, the products were obtained as mixtures of *Z*- and *E*-isomers (Table 2, entries 3 and 6). For unsymmetrical MCPs such as **7h**, **7i**, and **7j** (substituents, one aryl group and one hydrogen atom), the corresponding products **8h**, **8i**, and **8j** were obtained with the *E*-isomer as the sole product (Table 2, entries 8–10). The structures of **8h**, **8i**, and **8j** were further determined by ^{1}H NMR NOESY spectroscopy. For the extremely electron-rich MCP **7h**, further electrophilic substituted product **8h′** was obtained in 49% yield, along with the normal dibrominated product **8h** (Table 2, entry 8).



7a: $R^5 = R^6 = C_6H_5$
7b: $R^5 = R^6 = 4\text{-}MeOC_6H_4$
7c: $R^5 = 4\text{-}MeOC_6H_4$, $R^6 = C_6H_5$
7d: $R^5 = R^6 = 4\text{-}MeC_6H_4$
7e: $R^5 = R^6 = 4\text{-}ClC_6H_4$
7f: $R^5 = 4\text{-}ClC_6H_4$, $R^6 = C_6H_5$
7g: $R^5 = R^6 = 4\text{-}FC_6H_4$
7h: R5 = H, R6 = 3, 4, 5-$MeOC_6H_2$
7i: R^5 = H, $R^6 = 4\text{-}MeOC_6H_4$
7j: R^5 = H, $R^6 = 4\text{-}MeC_6H_4$



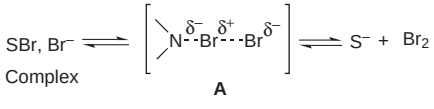
Scheme 2

Table 2 Dibromination of Methylenecyclopropanes (MCPs)

Entry[a]	Substrate **7**	Time (min)	Product	Yield (%)[b]
1	**7a**	2	**8a**	99
2	**7b**	2	**8b**	77[c]
3	**7c**	2	**8c**	85 (1:1)[d]
4	**7d**	2	**8d**	99
5	**7e**	2	**8e**	70
6	**7f**	2	**8f**	76[e]
7	**7g**	2	**8g**	92
8	**7h**	2	**8h**	26[f]
9	**7i**	2	**8i**	90
10	**7j**	2	**8j**	60

[a] Unless otherwise specified, all reactions were carried out with **7** (1 equiv), NBS (2 equiv), and LiBr (2 equiv).
[b] Isolated yields.
[c] NBS (1.2 equiv) and LiBr (1.2 equiv) were used.
[d] Ratio of the two isomers.
[e] Ratio of the two isomers was difficult to determine by ^{1}H NMR spectroscopy.
[f] Along with **8h′** as a by-product.

Ross and co-workers investigated the true nature of the brominating agent in a similar system, NBS and quaternary ammonium bromide, and its role in the dibromination of olefins.[13] They believed that molecular Br_2 was the real brominating agent for the dibromination of olefins in their system and an equilibrium between the complex and molecular Br_2 was postulated (Scheme 3).



Scheme 3

In the present dibromination reaction, we believe that a similar complex between NBS and LiBr might exist and the equilibrium described by Ross could also be involved.[13–15] We also confirmed that the dibromination reaction of **7a** under the optimized conditions was unaffected by the addition of the radical inhibitors such as 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (0.1 equiv), rendering unlikely the intervention of a radical pathway.[16]

In conclusion, we have found a convenient and efficient method for the dibromination of substrates bearing carbon–carbon unsaturated bonds such as alkenes, alkynes, allenes, and MCPs with NBS and LiBr. It is noteworthy that the present method has provided a new route for the dibromination reactions in the absence of molecular Br_2 and that THF was used as the solvent to alleviate the problem of toxic organic solvents in traditional reactions. Further studies are now under way to investigate the details of the related reactions.

Acknowledgment

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (203900502, 20025206, and 20272069).

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(9) Alkene **1a** (0.2 mmol), LiBr (0.4 mmol), NBS (0.4 mmol), and THF (2.0 mL) were added to a Schlenk tube successively under an ambient atmosphere. The mixture was stirred at r.t. for the appropriate time. Sat. aq $Na_2S_2O_3$ was added to quench the reaction, the organic layer was washed, then dried over anhyd Na_2SO_4. Flash column chromatography gave the pure product **2a** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ = 3.98–4.11 (m, 2 H), 5.14 (dd, 1 H, *J* = 5.4, 9.9 Hz), 7.34–7.42 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ = 34.99, 50.84, 127.62, 128.83, 129.15, 138.56. MS: *m*/*z* (%) = 262 (M^+, 1), 185 (86), 183 (90), 104 (100).
(10) For reviews, see: (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 598. (b) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (c) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.
(11) For the dibromination of MCPs in the presence of $TiBr_4$ and DEAD/DIAD, or by molecular Br_2, see: Shao, L.-X.; Zhao, L.-J.; Shi, M. *Eur. J. Org. Chem.* **2004**, 4894; and references cited therein.
(12) MCP **1a** (0.2 mmol), LiBr (0.4 mmol), and THF (2.0 mL) were placed in a Schlenk tube under an ambient atmosphere and the mixture was stirred for about 10 min at r.t. Then NBS (0.4 mmol) was added and the mixture was stirred at r.t. for the appropriate time. Sat. aq $Na_2S_2O_3$ was added to quench the reaction. The mixture was washed and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give product **8a** as a colorless liquid. IR (CH_2Cl_2): 3933, 3054, 2985, 1486, 1443, 1265, 896, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ = 3.07 (t, 2 H, *J* = 6.9 Hz), 3.62 (t, 2 H, *J* = 6.9 Hz), 7.20–7.32 (m, 10 H, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ = 31.04, 40.76, 123.20, 127.42, 127.57, 128.06, 128.51, 128.72, 128.83, 140.31, 142.68, 144.87. MS: *m*/*z* (%) = 368 (29), 366 (60), 364 (M^+, 34), 192 (100). HRMS: *m*/*z* calcd for $C_{16}H_{14}Br_2$: 363.9457; found: 363.9470.
(13) Finkelstein, M.; Hart, S. A.; Moore, W. M.; Ross, S. D.; Eberson, L. *J. Org. Chem.* **1986**, *51*, 3548; and references cited therein.
(14) We found that the reaction mixture quickly changed from colorless to deep orange as soon as NBS was added. After the reaction was complete, the reaction solution changed to pale yellow. When the reaction was quenched with a sat. solution of aq $Na_2S_2O_3$, the reaction mixture immediately changed from pale yellow to colorless. These phenomena suggest that molecular Br_2 is involved in the equilibrium.
(15) We were unsuccessful in obtaining a crystal structure, however, the white solid obtained from the reaction of NBS and LiBr in THF decomposed to pyrrolidine-2,5-dione, which was confirmed by X-ray diffraction.
(16) The yields in the presence of TEMPO and BHT were 99% and 96%, respectively.