

Regioselective and high-yielding bromination of aromatic compounds using hexamethylenetetramine–bromine

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Abstract—A regioselective and highly efficient method for bromination of aromatic compounds in the presence of a stoichiometric amount of hexamethylenetetramine–bromine (HMTAB) as an efficient reagent in dichloromethane is reported. The selectivity depends on the temperature and nature of the substituent on the substrate. The reactivity of this reagent was increased by supporting it to silica gel for bromination of less activated compounds.

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1. Introduction

There are frequently advantages to be gained by bromine substitution in a biologically active molecule, it may be an enhanced activity or it may be a desirable shift in the antibacterial spectrum.^{1,2} Halogenated aromatic compounds belong to an important class of organic intermediates that are used as precursors of organometallic compounds applied for the manufacture of a number of natural and bio-active substances as well as pharmaceuticals.³ The classical direct bromination involves the use of potentially hazardous, difficult to handle and store elemental halogen,⁴ expensive transition-metal-based catalysts,⁵ alkali metal halides associated with NaIO₄⁶ or the combination of aqueous TBHP or H₂O₂ together with a hydrohalic acid,⁷ which can be decomposed during the reaction and work up to produce corrosive side products that create separation and disposal problems in the end. Thus, a range of new methods has been published recently whilst the development of new halogenation methods focused on environmentally acceptable techniques and materials with improved atom, have continued to receive wide attention.⁸

Very recently *N*-bromosuccinimide,^{9a} Br₂/SO₂Cl₂^{9b} and *N,N,N,N*-tetrabromobenzene-1,3-disulfonylamide^{9c} have

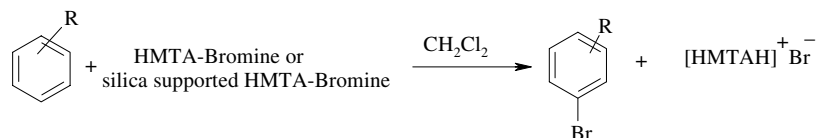
been used for regioselective bromination of aromatic compounds. In this letter, we wish to reveal a simple and efficient method for selective electrophilic bromination of aromatic rings using a hexamethylenetetramine–bromine complex. In this complex, hexamethylenetetramine forms a simple 1:2 charge-transfer complex with bromine (hexamethylenetetramine–2Br₂).¹⁰

We have recently reported the oxidation of alcohols,¹¹ deoxygenation¹² and oxidative deprotection of silyl ethers¹³ and THP ethers¹⁴ using the hexamethylenetetramine–bromine complex. The kinetics and mechanism of the oxidative ability of the hexamethylenetetramine–bromine complex has been well documented¹⁵ and the crystal structure of the 1:2 bromine complex has been determined.¹⁶ A selective procedure for α -bromination of alkanones using this reagent on basic alumina has also been reported.¹⁷

In fact, while we were trying to implement the oxidative cleavage of the phenylhydrazone of 4-methoxybenzaldehyde, using hexamethylenetetramine–bromine, we observed that instead of being cleaved, this compound was exclusively brominated and gave 3-bromo-4-methoxybenzaldehydephenylhydrazone in high yield. This finding prompted us to study the bromination of more reactive aromatic rings than benzaldehyde using hexamethylenetetramine–bromine. 4-Bromoaniline in CH₂Cl₂ was brominated immediately by this reagent at room temperature to afford 2,4-dibromoaniline. Aniline was brominated selectively at the 4-position at –15 °C showing that the selectivity depends on the temperature


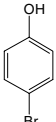

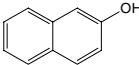
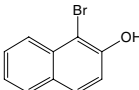
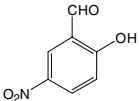
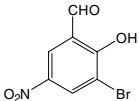
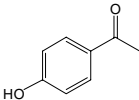
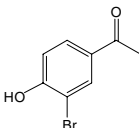
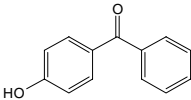
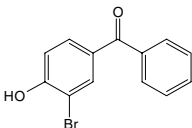
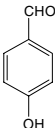
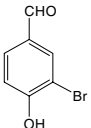
Keywords: Bromination; Hexamethylenetetramine–bromine; Silica gel supported.

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Table 1. Bromination of aromatic compounds using hexamethylenetetramine–bromine

Entry	Substrate	<i>T</i> (°C)	Time (min)	Product	Yield ^a (%)	Mp (°C)	Mp (°C) ^{lit.}
1		-15	45		85	62–64	56–62 ^{18a}
2		rt	Immediately		98	78–80	78–80 ^{18a}
3		rt	Immediately		96	71–74	70–72 ^{18a}
4		rt	Immediately		97	66–68	64–68 ^{18a}
5		rt	30		98	109–112	110–113 ^{18a}
6		rt	60		98	100–102	104.5 ^{18b}
7		rt	Immediately		93	134–136	133–138 ¹⁶
8		rt	Immediately		98	52–53	53–54 ^{18a}
9		rt	Immediately		98	Liq	Liq ^{18b}
10		rt	Immediately		98	46–48	48–51 ^{18a}

Table 1 (continued)

Entry	Substrate	T (°C)	Time (min)	Product	Yield ^a (%)	Mp (°C)	Mp (°C) ^{lit.}
11		-15	90		45	63–65	61–64 ^{18a}
					34	Liq	Liq ^{18a}
12		rt	Immediately		98	77–79	78–81 ^{18a}
13		rt	90		98	148–150	146–149 ¹⁶
14		-5	150		88	108–110	112 ^{18c}
15		-5	145		97	181–183	183.25 ^{18d}
16		-5	240		97	130–132	130–135 ^{18a}

^a Yields are based on GC analysis.

^b Boiling point.

and the nature of substituents on the aromatic ring. To establish the general applicability of this reagent, variously substituted aromatic rings were brominated selectively and efficiently.

However, benzaldehyde could not be brominated by this reagent. This result justifies the high yielding oxidative ability of this reagent.^{11–14} After formation of a formyl group, the reagent cannot brominate the ring to decrease the yield of oxidation products. The results are summarized in Table 1.

When acetanilide was brominated using this reagent, the reaction did not proceed to completion even after a prolonged reaction time. In view of the current focus on using supported reagents on various solid inorganic surfaces¹⁹ and due to the electrophilic substitution nature of the reaction we thought it is most suitable to support hexamethylenetetramine–bromine on a solid-support to make the bromine more electrophilic. Among solid supports such as basic alumina, zeolite and silica gel, the latter gave the best results in terms of reaction time and yield. Less activated aromatic rings were brominated efficiently and selectively by the silica gel-sup-

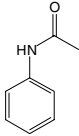
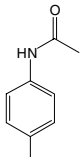

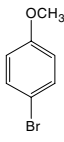
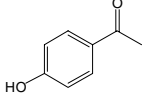
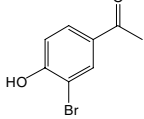
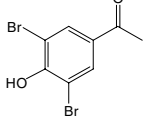
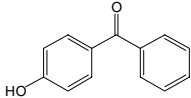
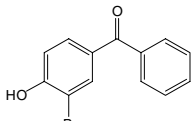
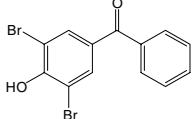
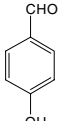
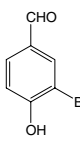
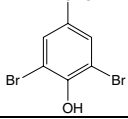
ported hexamethylenetetramine–bromine complex. The results and reaction conditions are summarized in Table 2.

Although the mechanism of this reaction is not completely clear, we suggest formation of the complex due to interaction of the π -electrons of aromatic compound with HMTAB. The formation of a similar complex has been postulated in the oxidation of alcohols,²⁰ aldehydes²¹ and sulfides²² with HMTAB involving non-bonded pairs of electrons on oxygen or sulfide atoms.

In fact, donation of electron density into the antibonding orbital of bromine weakens the Br–Br bond resulting in the generation of an electrophilic bromine. This phenomenon has also been observed in a complex of iodine with nitrogen compounds.²³

In conclusion, we have developed an efficient, selective and general method for the bromination of aromatic rings using the readily available hexamethylenetetramine–bromine complex. This yellow-orange, nonhygroscopic, homogenous solid is very stable at room temperature and is not affected by exposure to light,

Table 2. Bromination of aromatic compounds using silica-supported hexamethylenetetramine–bromine

Entry	Substrate	<i>T</i> (°C)	Time (min)	Product	Yield ^a (%)	Mp ^a (°C)	Mp (°C) ^{lit.}
1		rt	30		98	167–169	165–169 ^{18a}
2		rt	30		98	Liq	Liq ^{18a}
3		rt	5		56	108–110	112
					44	180–183	183–184 ^{18c}
4		rt	5		60	181–183	183.25
					40	148–150	153.5 ^{18d}
5		rt	5		70	130–132	130–135
					30	180–183	181–185 ^{18a}

^a Yields are based on GC analysis.

air or water and has no offensive odor of typical bromine or amines. The ease of work up, high yields and high level of selectivity are other salient features of this reagent.

2. Experimental

2.1. Preparation of the hexamethylenetetramine–bromine complex

A solution of bromine (20.0 g, 125 mmol) in CHCl_3 (100 mL) was added dropwise with stirring to a solution of hexamethylenetetramine (8.5 g, 60 mmol) in chloroform (100 mL). A yellow solid separated out as the bromine was taken up. The mixture was stirred for an additional 30 min, then the yellow solid was collected by vacuum filtration. Yield: 25.5 g (92%), mp = 170–

175 °C (dec.); $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 1460, 1360, 1325, 1045, 840 and 782 (found: C, 15.9; H, 2.7; N, 12.8. $\text{C}_6\text{H}_{12}\text{Br}_4\text{N}_4$ requires C, 15.87; H, 2.63; N, 12.68). The active bromine content of this complex is 1.5 mol Br_2 per mol of the complex, as determined by thiosulfate titrations.

2.2. Preparation of silica supported HMTAB

HMTAB was added to a suspension of silica gel (in a 1:1 weight ratio) in dichloromethane and stirred until a homogeneous mixture was obtained.

2.3. General procedure for the bromination of aromatic compounds using HMTAB

To a mixture of aromatic compound (1 mmol) in dichloromethane in a 25 cm³ round-bottomed flask was added, with stirring, HMTAB (0.5 mmol) or silica-supported

HMTAB (0.5 mmol). The reaction mixture was stirred until the yellow colour of the complex disappeared. The reaction was monitored by TLC. After completion of the reaction the mixture was filtered and the solid residue was washed with dichloromethane. The dichloromethane solution was washed successively with dilute (3%) aqueous sodium carbonate solution and water. The dried (MgSO₄) organic fraction was concentrated to afford the brominated compound in excellent yields.

References and notes

1. Felton, L. C.; McLaughlin, C. B. *J. Org. Chem.* **1947**, *12*, 298–302.
2. Zsolnai, T. *Biochem. Pharmacol.* **1960**, *5*, 1–19.
3. For example: *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley: Weinheim, 1998.
4. De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976; Chapter 5.
5. Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1989; p 315.
6. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501–4504.
7. Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 4085–4088.
8. For recent examples of chlorination and bromination protocols, see: (a) Smith, K.; Butters, M.; Paget, W. E.; Goubet, D.; Fromentin, E.; Nay, B. *Green Chem.* **1999**, *1*, 83; (b) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127; (c) Rotheberg, G.; Clark, J. H. *Org. Proc. Res. Dev.* **2000**, *4*, 270; (d) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247; (e) Narender, N.; Mohan, K. V. V. K.; Reddy, R. V.; Srinivasa, P.; Kulkarni, S. J.; Raghavan, K. V. *J. Mol. Catal. A* **2003**, *192*, 73.
9. (a) Bagheri, M.; Azizi, N.; Saidi, M. R. *Can. J. Chem.* **2005**, *83*, 143; (b) Gnaïm, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **2005**, *46*, 4456; (c) Ghorbani-Vaghei, R.; Jalili, H. *Synthesis* **2005**, *7*, 1099.
10. Garg, D.; Kothans, S. *J. Chem. Sci.* **2004**, *116*, 333.
11. Heravi, M. M.; Ajami, D.; Nooshabadi, M. A. *Iran J. Chem. Eng.* **1999**, *18*, 88.
12. Beheshtiha, Y. Sh.; Heravi, M. M.; Sarmad, N.; Hekmat-Shoar, R. *J. Chem. Res.* **2001**, 79.
13. Dehkordi, M. B.; Heravi, M. M.; Khosrofar, P.; Ziafati, A.; Ghassemzadeh, M. *Phosphorus, Sulfur, Silicon* **2004**, *179*, 2595.
14. Dehkordi, M. B.; Heravi, M. M.; Ziafati, A.; Khosrofar, P.; Ghassemzadeh, M. *Phosphorus, Sulfur, Silicon* **2004**, *179*, 1493.
15. (a) Garg, D.; Kathari, S. *J. Chem. Sci.* **2004**, *116*, 33; (b) Sharma, P. K. *Indian J. Chem. Soc.* **2004**, *81*, 291; (c) Kathari, S.; Sharma, P. K.; Banerji, K. K. *Indian J. Chem. Soc.* **2003**, *80*, 431.
16. Eia, G.; Hassel, O. *Acta Chem. Scand.* **1956**, *10*, 139.
17. Paul, S.; Varinder, G.; Gupta, R. *Synth. Commun.* **2003**, *33*, 1917.
18. (a) www.sigmaaldrich.com; (b) Wast, R. C. *CRC Handbook of Chemistry and Physics*, 69th ed.; 1988–1989; c-67; (c) Edkins, R. P.; Linnell, W. H. *Quart. J. Pharm. Pharmacol.* **1936**, *9*, 75–109; (d) Montagne, P. J. *Rec. Trav. Chim.* **1922**, *41*, 703–721; (e) Joshi, G. G.; Shah, N. M. *J. Indian Chem. Soc.* **1954**, *31*, 220–222.
19. (a) Heravi, M. M.; Ajami, D.; Aghapoor, K.; Ghassemzadeh, M. *Chem. Commun.* **1999**, 833; (b) Heravi, M. M.; Ajami, D.; Aghapoor, K.; Ghassemzadeh, M. *Synthesis* **1999**, 339; (c) Heravi, M. M.; Azemian, P. K.; Oskooie, H. A.; Ghassemzadeh, M. *J. Chem. Res.* **2005**, *2*, 105.
20. (a) Pareek, A.; Kothari, S.; Banerji, K. K. *Indian J. Chem.* **1996**, *35B*, 970; (b) Gangwani, H.; Sharma, P. K. *J. Chem. Res. (S)* **1999**, *1*, 854.
21. Pareek, A.; Varshney, S.; Banerji, K. K. *React. Kinet. Catal. Lett.* **1997**, *60*, 127.
22. Choudhary, K.; Suri, D.; Kothari, S.; Banerji, K. K. *J. Phys. Org. Chem.* **2000**, *13*, 283.
23. Bailey, R. S.; Drake, G. W.; Hanks, T. W.; Hook, L. L.; Pennington, T. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2773.