Tetrameric DABCO™-Bromine: an Efficient and Versatile Reagent for Bromination of Various Organic Compounds

Majid M. Heravi,[a*] Fatemeh Derikvand[a] and Mitra Ghassemzadeh[b]

[a]Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran.
[b]Chemistry & Chemical Engineering Research Center of Iran, Tehran, Iran.

ABSTRACT

Tetrameric DABCO™-bromine is a powerful brominating agent but shows reasonable selectivity with certain substrates. The selective bromination for activated aromatic compounds and alkenes is reported. Synthesis of α-bromo ketones and nitriles has also been achieved by using this reagent and the results are also reported. All products reported were obtained in good to excellent yields.

KEYWORDS

Tetrameric DABCO™-Bromine, TDB, solid supports, bromination, α-bromination, 1,2-dibromo compounds, bromohydrin.

1. Introduction

Bromoaromatics are widely used as intermediates in the manufacture of pharmaceuticals, agrochemicals and other speciality chemical products.

α-Bromo carbonyls and nitriles are important synthetic intermediates. Some of them are used for the synthesis of a variety of biologically active heterocyclic compounds.[1–3]

The bromination of alkenes is an important organic transformation. It is noteworthy to mention that protection and deprotection of double bonds *via* bromination-debromination strategy is finding increasing application in organic synthesis.[4] A number of protocols are available to achieve the bromination of alkenes.[5–9]

The bromination of aromatic compounds by electrophilic substitution has been extensively investigated in the past. Despite the many bromination methods, that are available,[10,11] controlled bromination of activated aromatic compounds such as aniline derivatives remains a problem. Problems associated with the generation of mixtures of ortho, para products and poly-bromination products are limiting the synthetic application of many of these procedures.

α-Bromo carbonyl and nitriles have been synthesized by the reaction of bromine with appropriate carbonyl or nitrile substrates in suitable solvents such as water, chloroform, carbon tetrachloride, acetic acid or N,N-dimethyl formamide.[12] Several other reagents have also been used for this purpose, but most of them are quite expensive.[13]

In spite of the variety of reagents available for bromination of various organic compounds, the lack of selectivity and undesirable side-reactions continue to be problematic.

In this context a search for mild, selective and easy to handle reagents for the selective bromination of organic compounds remains attractive.

2. Results and Discussion

We recently reported the synthesis and characterization of tetrameric DABCO™-bromine (TDB) and its application in the oxidation of alcohols and oximes to the corresponding carbonyl compounds.[14,15] TDB is an easy to handle, storable reagent and could be readily prepared by adding a solution of bromine in dichloromethane to a solution of DABCO™ in the same solvent.

We wish to report further utilization of TDB for the bromination of aromatic compounds, α-bromination of carbonyls and nitriles and bromination of alkenes by varying the reaction conditions.

Supported reagents such as TDB have great potential as environmentally friendly alternatives to the more useful traditional catalysts. Supported reagents usually have large surface areas and are often layered or porous. Over the past few years, we have reported on the application of several supports in organic reactions.[16] TDB is a very useful source of bromine as this polymeric compound, combined with silica, can modify its reactivity and do selective bromination of aromatics. Although bromine itself is a powerful bromination agent, it lacks selectivity.

As shown in Scheme 1, silica-supported TDB was used to prepare brominated aromatic substrates in high yields and good regioselectivities. Silica-supported TDB could be prepared by mixing TDB with equal weight amount of silica gel.

In the absence of silica gel, aromatic compounds with moderate activity showed longer reaction times. For example, acetanilide gave 85% of bromo derivative after 10 h. The reaction times and yields of products varied significantly when the reaction was carried out in the presence or absence of silica-supported TDB (see Table 1).

Our studies show that it is necessary to control the molar ratio of the reactant and temperature. Aniline was brominated immediately at room temperature to afford 2,4-dibromoaniline, but it was brominated selectively at the 4-position at –15°C showing that the selectivity depends on the temperature and the nature of substituent on the aromatic ring.

The best chemoselectivity was obtained when the molar ratio of the aromatic compound:reagent was exactly 6:1. The reagent should be added slowly and in several steps to a solution of the aromatic compound. After completion of the reaction the colour of the reagent changed from yellow to white and the reagent transformed to easily removable products during the reaction (see Scheme 1).

* To whom correspondence should be addressed. E-mail: mmh1331@yahoo.com; fax: +98 21 88047861

Scheme 1
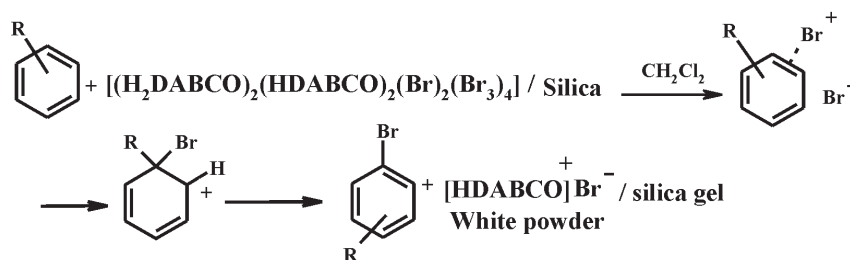
A number of different activated aromatic substrates were subjected to bromination reaction to test the generality of this method. The results are summarized in Table 1.

The obtained results for electrophilic bromination of aromatics prompted us to investigate the reactivity of carbonyls and nitriles for α-bromination using TDB. When acetophenone was reacted with TDB in chloroform, only 20% of phenacyl bromide was obtained after 8 h. Bromination of carbonyl compounds requires the substrates to be enolized and therefore some kind of acidic (or basic) environment is required to catalyse the reaction. Owing to the acidic or basic nature of solid supports we considered it most suitable to catalyse the reaction using a suitable support for TDB. Among solid supports such as silica gel, basic and acidic alumina, the latter gave the best results in the terms of reaction time and yield. It should be noted that TDB is only 'diluted' with the solid support and no covalent bond has formed, because it could be easily separated by washing with DMSO.

The efficiency of the reagent can be influenced by the nature of the solvent. Therefore, we have carried out a study on a variety of solvents and among the tested solvents, i.e. acetic acid, water, acetonitrile and chloroform, the last one was applied as solvent of choice.(Table 2).

The bromination of carbonyls and nitriles could be summarized in two steps: at the first step, the substrate is enolized, and then the produced intermediate transformed into the bromo compound. The suggested mechanism for the bromination of

alkanones is presented in Scheme 2.

In the case of 2-butanone only 3-bromo-2-butanone was obtained after 4 h. From this result we can conclude that the more stable enolate has been produced during the reaction condition. The results are shown in Table 2.

It should be noted that because of the production of some dibromo products in these reactions the reagent should not be used in excess amounts.

The work-up procedure is very simple, [DABCOH]$^+$Br$^-$ and acidic alumina could be separated by a simple filtration. The organic solution is washed with an aqueous solution of NaHCO$_3$ (10%) and water and dried over MgSO$_4$. Evaporation of the solvent gave the products in high yields.

We also studied the bromination of alkenes with TDB to produce the corresponding 1,2-dibromo derivatives in chloroform. (Scheme 3).

As shown in Table 3 a variety of alkenes were easily brominated with this reagent. Electron-rich alkenes such as methyl cyclohexene reacted faster than electron-poor alkenes such as dimethyl fumarate. The reaction of propargyl bromide, as an alkyn example, proceeds slower than the reaction of alkenes (entry 7, Table 3). As expected when water was used as solvent, bromohydrines were obtained as major products (Scheme 3, entries 8,9 Table 3).

All of the obtained products have anti configuration; it may be due to the creation of bromonium ions as intermediate in these reactions.

Table 1 Bromination of aromatic compounds using silica-supported TDB.

Entry	Substrate	Product	Temperature /°C	Time /min	Yield /% [a]	m.p. /°C	
						Found	Lit.
1	Aniline	4-Bromo aniline	–15	40	85	62–64	56–62 [17a]
2	2,6-Dimethyl aniline	4-Bromo-2,6-dimethyl aniline	r.t	2	98	46–48	48–51 [17a]
3	2-Nitro aniline	4-Bromo-2-nitro aniline	r.t	20	98	110–113	110–113 [17a]
4	4-Nitro aniline	2-Bromo-4-nitro aniline	r.t	40	98	102–104	104.5 [17b]
5	N,N-dimethyl aniline	4-Bromo- N,N-dimethyl aniline	r.t	2	98	52–53	52–54 [17a]
6	4-N,N-dimethyl amino Benzaldehyde	3-Bromo-4-N,N-dimethyl amino benzaldehyde	r.t	2	97	52–54	53–54 [17a]
7	4-Bromo aniline	2,4-Dibromo aniline	r.t	5	95	78–80	78–80 [17a]
8	Acetanilide	4-Bromo acetanilide	r.t	75	98	165–168	165–169 [17a]
9	2-Amino pyridine	5-Bromo-2-amino pyridine	r.t	2	92	135–136	133–138 [17a]
10	2-Naphtol	1-Bromo-2-naphtol	r.t	2	97	77–79	78–81 [17a]
11	Phenol	2-Bromo phenol	–15	60	15	63–65	61–64 [17a]
		4-Bromo phenol			70	61–63	61–64 [17a]
12	2-Hydroxy-5-nitro-benzaldehyde	3-Bromo-2-hydroxy-5-nitro-benzaldehyde	r.t	2	98	148–150	146–149 [17a]
13	4-Hydroxy benzaldehyde	3-Bromo-4-hydroxy benzaldehyde	–5	180	90	130–132	130–135 [17a]
14	4'-Hydroxy acetophenone	3'-Bromo-4'-hydroxy acetophenone	–5	150	92	108–110	112 [17c]
15	4 -Hydroxy benzophenone	3-Bromo-4 -hydroxy benzophenone	–5	120	90	181–183	183.25 [17d]
16	Anisole	4-Bromo anisole	r.t	45	98	222 [a]	223 [17a]

[a] Yields were obtained using GC analysis from crude products.

Table 2 Synthesis of α-brominated carbonyls and nitriles using acidic alumina-supported TDB in chloroform.

Entry	Substrate	Product	Time /h	Yield /% [a]
1	Acetophenone	Phenacyl bromide	5.5	85
2	4'-Methyl acetophenone	2-Bromo-4'-methyl acetophenone	7	75
3	3'-Nitro-acetophenone	2-Bromo-3'-nitro acetophenone	5	84
4	4'-Nitro-acetophenone	2-Bromo-4'-nitro acetophenone	5	86
5	Malononitrile	Bromo-malononitrile	0.15	92
6	Ethyl cyanoacetate	Bromo-ethyl cyanoacetate	1	90
7	Cyclohexanone	2-Bromo- cyclohexanone	5	70
8	2-Butanone	3-Bromo-2-butanone	4	75

[a]Yields were obtained using GC analysis from crude products.
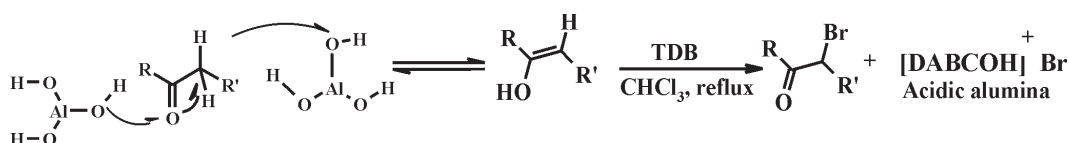
Scheme 2

In conclusion, TDB is an inexpensive brominating agent which promises to be efficient and versatile for bromination of a wide variety of compounds. TDB is a non-hygroscopic solid and is very stable at room temperature, and is not affected by ordinary exposure to light, air or water; ease of work-up and stability of the reagent make it a safe source of active bromine. The reagent is transformed during the reaction to the easily removable products and presents a convenient alternative to other N-halogen amines.

3. Experimental

Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^{1}HNMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. All products were characterized by spectral and physical data. TDB was prepared according to our reported method.[14]

3.1. Preparation of Silica-/Acidic Alumina-supported TDB
Silica-supported TDB could be prepared by crushing a mixture
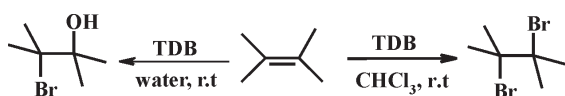
Scheme 3

of TDB (1 mmol, 1.57 g) and equal weight amount of silica gel to form an intimate mixture.

Acidic alumina-supported TDB was prepared by crushing of a mixture of TDB (1 mmol, 1.57 g) and acidic alumina (3.14 g) to form an intimate mixture.

3.2. Bromination of Aromatic Compounds: Typical Procedure
Silica-supported tetrameric DABCO-bromine (0.52 g, 0.16 mmol) was added slowly to a solution of 2-naphtol (0.14 g, 1 mmol) in dichloromethane (5 mL) by stirring at room temperature for 2 min. Upon the completion of reaction (monitored by TLC), the reaction mixture was filtered. The filter cake was also washed with another portion of dichloromethane (3 mL). The filtrates were combined together and the resulting organic phase was washed with a solution of HCl (5%, 10 mL), $NaHCO_3$ (10%, 10 mL) and H_2O (10 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. Evaporation of the solvent gave the desired product almost in quantitative yield (Table 1, entry 10).

3.3. α-Bromination of Carbonyls and Nitriles: Typical Procedures
A mixture of acetophenone (1 mmol), alumina-supported TDB (0.25 mmol, 1.17 g) and chloroform (5 mL) was refluxed for 5 h. Upon completion of the reaction (monitored by TLC) the reaction mixture was filtered, the cake was washed with chloroform (3 mL). The combined chloroform solutions were

Table 3 Bromination of alkenes using TDB in chloroform and water.

Entry	Substrate	Product	Solvent	Time /min	Yield /% [a]
1	methyl cyclohexene	1,2-Dibromo-1-methyl cyclohexane	$CHCl_3$	30	95
2	Cyclohexene	1,2-dibromo cyclohexane	$CHCl_3$	35	95
3	1-hexene	1,2-dibromo hexane	$CHCl_3$	35	94
4	1-dodecene	1,2-dibromo dodecane	$CHCl_3$	55	97
5	diethyl fumarate	diethyl-2,3-dibromo-butane-1,4-dicarboxylate	$CHCl_3$	350	76
6	dimethyl fumarate	dimethyl-2,3-dibromo-butane-1,4-dicarboxylate	$CHCl_3$	400	80
7	propargyl bromide	1,2,3-tribromo propene	$CHCl_3$	120	75
8	cyclohexene	2-bromo cyclohexanol	H_2O	3	70
9	1-hexene	1-bromo-2-hexanol	H_2O	5	72

[a] Yields were obtained using GC analysis from crude products.

RESEARCH ARTICLE

M.M. Heravi, F. Derikvand and M. Ghassemzadeh,
S. Afr. J. Chem., 2006, **59**, 125–128,
<http://journals.sabinet.co.za/sajchem/>.

128

washed with a solution of NaHCO$_3$ (5%, 10 mL) and water (10 mL), and dried over MgSO$_4$. Evaporation of the solvent gave the product in 85%, m.p. 49–51 (lit. 48–51[17a]), (Table 2, Entry 1). Further purification was obtained by column chromatography.

3.4. Bromination of Alkenes in Chloroform: General Procedure

TDB (0.26 g, 0.16 mmol) was added to a stirred solution of alkene (1 mmol) in chloroform (5 mL). Upon completion of the reaction (monitored by TLC) the reaction mixture was filtered, the cake was washed with chloroform (3 mL). The combined chloroform solutions were washed with a solution of NaHCO$_3$ (5%, 10 mL) and water (10 mL), and dried over MgSO$_4$. Evaporation of the solvent gave the product in good yield. Further purification was obtained by column chromatography.

3.5. Bromination of Alkenes in Water: General Procedure

TDB (0.26 g, 0.16 mmol) was added to a stirred solution of alkene (1 mmol) in water (5 mL). Upon completion of the reaction (monitored by TLC) chloroform (5 mL) and a solution of NaHCO$_3$ (5%, 10 mL) were added to the mixture, the organic layer was separated, washed with water and dried over MgSO$_4$. Evaporation of the solvent gave the corresponding bromohydrine in good yield. Further purification was obtained by column chromatography.

References and Notes

1 B.S. Holla, R. Gonsalves, B.K. Sarojini and S. Shenoy, *Indian J. Chem.*, 2001, **40B**, 475–478.

2 R. Martinez, *J. Het. Chem.*, 1999, **36**, 687–690.

3 A.P. Misra, K. Raj and A.P. Bhaduri, *Synth. Commun.*, 1999, **29**, 3227–3236.

4 B.C. Raun, S.K. Guchhait and A. Sarkar, *J. Chem. Soc. Chem. Commun.*, 1998, 2113–2114 and references cited therein.

5 V. Nair, S.B. Panicker, A. Augustine, T.G. George, S. Thomas and M. Vairamani, *Tetrahedron,* 2001, **57**, 7417–7422.

6 R. Rodebaugh and B. Fraser-Reid, *Tetrahedron,* 1996, **52**, 7663–7678.

7 J. Berthelot, Y. Benammar and C. Lange, *Tetrahedron Lett.,* 1991, **33**, 4135–4136.

8 M. Hassanein, A. Akelah, A. Selim and H. Elhamshary, *European Polymer Journal,* 1989, **25**(10), 1083–1085.

9 B.G. Hazra, M.D. Chordia, B.B. Bahule, V.S. Pore and S. Basu, *J. Chem. Soc., Perkin, Trans. 1,* 1994, 1667–1669 and references cited therein.

10 D.P. Das and K.M. Parida, *Applied Catalysis A: General,* 2006, **305**, 32–38.

11 T. Raju, K. Kulangiappar, M. Anbu Kulandainathan, U. Uma, R. Malini and A. Muthukumaran, *Tetrahedron Lett.,* 2006, **47**, 4581–4584.

12 (a) P.A. Levene, *Org. Synth.,* 1943, **II**, 88; (b) C. Rappe, *Org. Synth.,* 1973, **53**, 123–127; (c) W.D. Langley, *Org. Synth.,* 1941, **I**, 127–128; (d) J. Klingenberg, *J. Org. Synth.* 1963, **IV**, 112; (e) R.M. Cowper and L.H. Davidson, *Org. Synth.,* 1943, **II**, 480–481; (f) D.I. Pearson, H.W. Poper and W.E. Hargrove, *Org. Synth.,* 1973, **V**, 120.

13 (a) H.M. Meshram, P.N. Reddy, P. Vishnu, K. Sadashiv and J.S. Yadav, *Tetrahedron Lett.,* 2006, **47**, 991–995; (b) S.K. Guha, B. Wu, B.S. Kim, W. Baik and S. Koo, *Tetrahedron Lett.,* 2006, **47**, 291–293; (c) E.I. Sanchez and M.J. Fumarola, *J. Org. Chem.,* 1982, **49**, 1588–1590

14 M.M. Heravi, F. Derikvand, M. Ghassemzadeh and B. Neumuller, *Tetrahedron Lett.,* 2005, **46**, 6243–6245.

15 M.M. Heravi, F. Derikvand and M. Ghassemzadeh, *Synth. Commun.,* 2006, **36**, 581–585.

16 (a) M.M. Heravi, D. Ajami and A.M. Noushabadi, *Iran J. Chem. Eng.,* 1999, **18**(2), 88–90; (b) M.M. Heravi, P. Kazemian, H.A. Oskooie and M. Ghassemzadeh, *J. Chem. Res-S,* 2005, (**2**), 105–106; (c) M.M. Heravi, F. Derikvand, H.A. Oskooie and R. Hekmatshoar, *J. Chem. Res-S,* 2006, 168–169; (d) M.M. Heravi, F. Derikvand, H.A. Oskooie and R. Hekmatshoar, *J. Synth. Commun.,* 2006, **36**, 77–82.

17 (a) www.sigmaaldrich.com; (b) R.W. Wast, *CRC Handbook of Chemistry and Physics,* 69th edn., 1988–1989, c-67; (c) R.P. Edkins and W.H. Linnell, *Quart. J. Pharm. Pharmacol.,* 1936, **9**, 75–109; (d) J. Montagne, *Rec. Trau. Chim.,* 1922, **41**, 703–721.