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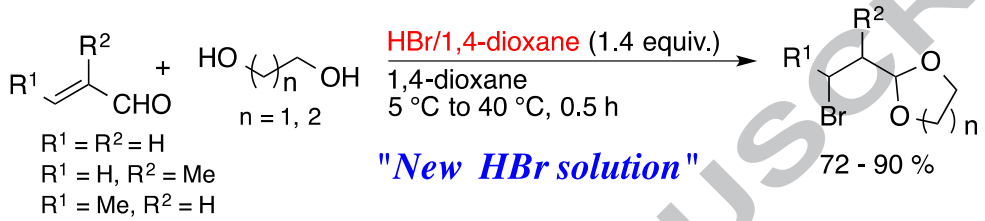

Highlights

- A novel solution of HBr in 1,4-dioxane was prepared.
- Bromination of ROH and hydrobromination of alkenes were examined with the solution.
- The novel solution provided equal or superior results to HBr_{aq} and HBr/AcOH.
- Preparation of dioxolanes and dioxanes was achieved using the novel solution.
- The novel solution is a liquid alternative to HBr gas without protic solvents.

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Preparation and properties of a novel solution of hydrogen bromide (HBr) in 1,4-dioxane: An alternative reagent to HBr gas without protic solvents

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ABSTRACT

A solution of hydrogen bromide (HBr) in 1,4-dioxane was prepared and investigated for its ability to brominate alcohols, and hydrobrominate alkenes. This study revealed that the brominating ability of this HBr/1,4-dioxane solution is equal or superior to that of hydrobromic acid or HBr in acetic acid. The solution of HBr in 1,4-dioxane is robust, exhibiting no decomposition of the solvent, and retaining 97% of its original concentration, when kept at -25 °C for 30 days. This solution is a liquid alternative to HBr gas without protic solvents.

1. Introduction

The introduction of bromine atoms into organic compounds, to afford organic bromides, is an important process in organic synthesis, since bromides are versatile intermediates for the preparation of various chemicals, including natural products and functional materials. Molecular bromine (Br_2) is a typical reagent that is often employed in bromination reactions. While many other brominating reagents, such as NBS,[1,2] BDMS,[3,4] and DBI,[5,6] are known, hydrogen bromide (HBr)[7] is the simplest and most atom-economical reagent among them. The hydrobromination of alkenes with HBr[8] is one of the basic reactions in organic chemistry. Indeed, most organic chemistry textbooks discuss the addition of HBr to alkenes under ionic or radical conditions, to afford alkyl bromides through Markovnikov- or anti-Markovnikov-type processes, respectively.[9] Another typical reaction using HBr is the bromination of alcohols.[10] This reaction produces water as the only by-product, and its atom-economy is superior to that using any other brominating reagent. Despite its atom-economy and low cost, the use of HBr is problematic, leading to hesitation in its use. In particular, HBr is a corrosive, poisonous gas.[11] Through the use of special HBr lines, this problem has largely been solved by the chemical industry; however, this solution is not as easily applied to laboratories, due to cost. In addition, the maintenance of HBr lines is more tedious than those of other gases, like N_2 or O_2. Therefore, in laboratories, HBr solutions are usually used as alternatives to the gas. HBr dissolves well in polar solvents; HBr in water (hydrobromic acid, HBr_{aq}, **1a**)[12] and HBr in acetic acid (HBr/AcOH, **1b**)[13] are commercially available. However, the use of these solutions in chemical syntheses has associated limitations. Bromination using **1a** is sometimes ineffective due to the immiscibility of **1a** with organic solvents. In addition, the strongly acidic properties of **1a** can cause the hydrolysis of functional groups such as esters and urethanes. On the other hand, the acetic acid in **1b** can react with alcohols or amines to afford acetylated compounds. To solve these problems, and as part of our on-going interest in bromination chemistry,[14] we began to explore new HBr solutions. Consequently, the solubility of HBr in a variety of organic solvents, and the durability of the prepared HBr solutions, were investigated; 1,4-dioxane was found to be the best solvent for these HBr solutions. In addition, the brominating ability of the HBr/1,4-dioxane solution **1c** was investigated using alkenes and alcohols. A comparison between the brominating ability of **1c** with that of **1a** and **1b** is also presented.

2. Results and discussion

2.1. Preparation of HBr solutions

The preparation of the various HBr solutions was achieved by dissolving HBr gas in the required organic solvent. However, as HBr is highly acidic, it can decompose many organic solvents. Therefore, the choice of appropriate solvent is important. With this in mind, we focused on three points for the development of a new HBr solution: (1) concentration of dissolved HBr, (2) durability of the solvent, and (3) reactivity of the solution. Candidates for these solutions were prepared by bubbling HBr gas (50 mL/min) for 30 min at 25 °C into the organic solvent (10 mL). The concentrations of HBr in the various solvents, and the durability of each solution are summarized in Table 1. Ethylene glycol (EG), ethanol, and 2-methoxyethanol dissolved HBr well (19–25%) and decomposition of the solvent was not detected, while 1,3-propanediol showed significant decomposition after 30

min. (entries 1–4). Tetrahydropyran (THP)[15] and cyclopentyl methyl ether (CPME)[16] also dissolved HBr well (18 and 23%, respectively). Although no decomposition (< 1%) was detected by GC analysis of these solutions, the colours of the solutions changed to pale brown (entries 5 and 7), indicating that trace amounts of these solvents are being decomposed. Tetrahydrofuran (THF), ethyl acetate and acetonitrile decomposed with HBr (entries 8, 10 and 11). 1,4-Dioxane and *N*,*N*-dimethylformamide (DMF) showed high HBr solubility (17 and 22%, respectively) and stability (entries 6 and 9). As a result, ethylene glycol, ethanol, 2-methoxyethanol, 1,4-dioxane, and DMF were selected as candidates for the new HBr solvent.

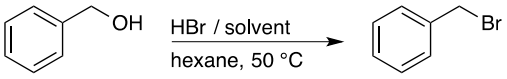
Table 1. Choice of solvent for the HBr solution[a]

Entry	Solvent	Concentration of HBr (wt%)[b]	Decomposition of solvent[c]
1	Ethylene glycol	20	–
2	Ethanol	25	–
3	2-Methoxyethanol	19	–
4	1,3-Propanediol	21	+
5	THP	23	±
6	1,4-Dioxane	17	–
7	CPME	18	±
8	THF	7.8	+
9	DMF	22	–
10	Ethyl acetate	24	+
11	Acetonitrile	3.1	+

[a]Preparation conditions: solvent (10 mL), HBr gas (flow rate: 50 mL min^{-1}) bubbled for 30 min., 25 °C. [b]Determined by titration. [c]Detected by GC.

Next, we investigated the reactivity of these selected HBr solutions and HBr/THP toward the bromination of benzylalcohol as a model reaction (Table 2). The reaction using HBr/EG solution afforded benzyl bromide in 65% yield (entry 1). Using HBr in ethanol, 2-methoxyethanol or DMF afforded lower yields of the brominated product (entries 2, 3 and 6). On the other hand, HBr solution in THP or 1,4-dioxane afforded the desired product in 91 or 71% yields, respectively (entries 4 and 5). In addition, no by-product was observed during the reaction using HBr/THP or HBr/1,4-dioxane. These results encouraged us to investigate HBr/1,4-dioxane (**1c**) and HBr/THP (**1d**) in detail; the ability of each solution to retain HBr was monitored over 5 days at 5 °C (Figure S1, Supplementary Material). Retention was determined by titration using a 0.5 M solution of sodium hydroxide. Concentrations of HBr in fresh **1c** and **1d** were determined to be 2.50 mol kg^{-1} (17 wt%) and 3.75 mol kg^{-1} (23 wt%), respectively. After two days, the concentrations of HBr in **1c** and **1d** at 5 °C had decreased to 93 and 80% of the original concentrations, respectively, and after five days while the concentration of HBr in **1d** had decreased to 67%, **1c** was still at 84%. Based on its reactivity during the bromination of benzyl alcohol, and its ability to retain HBr, we concluded that 1,4-dioxane is the most suitable solvent for our novel HBr solution. Furthermore, the HBr retaining ability of **1c** at 5 °C and -25 °C was measured. As shown in Figure S2 (Supplementary Material), while the concentration of HBr in **1c** decreased to 93% of the original concentration, at 5 °C, the level of HBr was determined to be > 99% at -25 °C after 7 days. After 30 days the HBr levels in **1c**, at 5 °C and -25 °C, were observed to be 64 and 97%, respectively, indicating that when kept at -25 °C, **1c** can be stored for long periods of time with almost no loss of HBr.[17]

Table 2. Bromination of benzyl alcohol with HBr solution



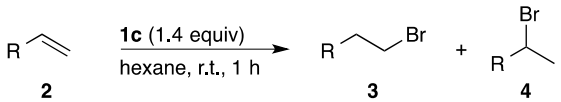
Entry	Solvent	HBr (wt%)	Time (h)	Isolated yield (%)
1	Ethylene glycol	20	3	65
2	Ethanol	25	3	33
3	2-Methoxyethanol	19	3	42
4	THP	23	0.5	91
5	1,4-Dioxane	17	2	71
6	DMF	22	3	38

*2.2. Assessment of the brominating ability of HBr/1,4-dioxane (**1c**)*

2.2.1 Hydrobromination of alkenes

To evaluate the brominating ability of **1c**, we carried out the hydrobromination of a variety of alkenes using this HBr solution. Hence, alkene **2** (2 mmol) was reacted with **1c** (1.4 equiv.), in hexane at room temperature, for 1 h to give the anti-Markovnikov product **3**, as the major product[18,19] (Table 3). The hydrobromination of 1-tetradecene **2a** and 10-undecenoic acid **2b**, with **1c**, afforded the corresponding bromides **3a** and **3b** in almost quantitative yields (entries 1 and 2). Reactions using the ester-bearing alkenes **2c** and **2d**, which normally would be hydrolysed, also afforded the corresponding bromides **3c** and **3d** in excellent yields (entries 3 and 4). However, alkenes **2e** and **2f**, bearing *tert*-butyldimethylsilyl (TBDMS) and methoxymethyl group (MOM) groups, respectively, afforded only trace amounts of bromides **3e** and **3f**, respectively, presumably because these compounds easily discompose under acidic conditions (entries 5 and 6). These results indicate that **1c** is reactive enough to be used as the HBr source for hydrobromination of alkenes.

Table 3. Hydrobromination of alkenes using **1c**[a]



2 **3** **4**

Entry	Substrate		Isolated Yield(%)	**3**/**4**[b]
1	$C_{12}H_{25}$	**2a**	98	19:1
2	$HO_2C(CH_2)_8$	**2b**	>98	19:1
3	$EtO_2C(CH_2)_8$	**2c**	>98	>20:1
4	*n*-BuO_2C	**2d**	96	>20:1
5	TBDMS-$O(CH_2)_8$	**2e**	< 1	-
6	MOM-$O(CH_2)_8$	**2f**	< 1	-

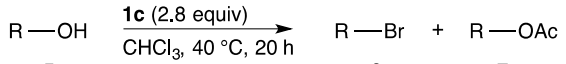
[a]Reaction conditions: substrate (2 mmol), **1c** (17 wt%, 2.7 mmol), hexane (2 mL), r.t., 1 h. [b]Determined by ^{1}H-NMR.

2.2.2 Bromination of alcohols

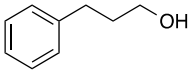
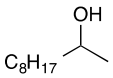
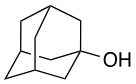
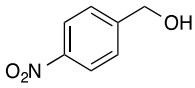
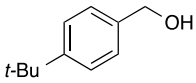
We next turned our attention to the bromination of alcohols **5** with **1c**. For comparison of reactivities, the bromination of alcohols using HBr/AcOH (**1b**) was also carried out. Accordingly, alcohol **5** (2.0 mmol) was reacted with **1b** or **1c** (2.8 equiv.) in chloroform at 40 °C for 20 h, to afford the

corresponding bromide **6** or acetate **7**. As shown in Table 4, the primary alcohol **5a** reacted with **1c** to give the bromide **6a** in 60% yield. On the other hand, bromination of **5a** with **1b** did not afford **6a** but acetate **7a** in 97% yield. Similarly, secondary alcohol **5b**, when reacted with **1b**, gave the corresponding acetate **7b** as the major product, in 67% yield, while bromination of **5b** using **1c** yielded exclusively bromide **6b** in 60% yield. On the other hand, tertiary alcohol **5c** afforded bromide **6c** in high yields, with either **1b** or **1c**. These results clearly show that **1c** is a better brominating reagent than **1b** for the bromination of alcohols. Benzyl alcohols **5d** and **5e** also reacted with **1c** to afford the corresponding bromides, **6d** and **6e**, in good yields.

Table 4. Bromination of alcohols using **1c**[a]



5 **6** **7**

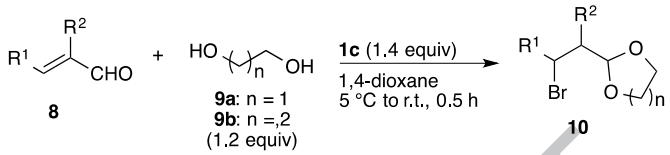
Entry	Substrate		Isolated yield (%)	
			6	**7**
1		**5a**	60[d]	-
2[b]			< 1	97
3		**5b**	60[e]	-
4[b]			16	67
5		**5c**	90	-
6[b]			89	< 1
7		**5d**	83	-
8[c]		**5e**	96	-

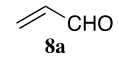
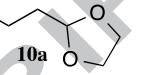
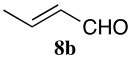
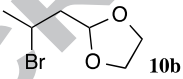
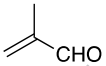
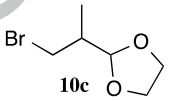
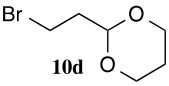
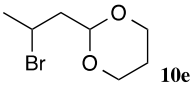
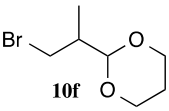
[a]Reaction conditions: substrate (2 mmol), **1c** (17 wt%, 5.7 mmol), CH_3Cl (2 mL), 40 °C, 20 h. [b]Using **1b**. [c]Reaction time: 2 h. [d]30% of **5a** was recovered. [e]32% of **5b** was recovered.

2.3. Synthesis of 2-(2-bromoalkyl)-1,3-dioxolanes and 2-(2-bromoalkyl)-1,3-dioxanes

Since HBr is a highly acidic brominating reagent, with pK_a = -9[20] (cf. pK_a of HCl = -7),[20] we examined whether acid-catalysed acetalisation and bromination would be accomplished simultaneously; preparation of 2-(2-bromoalkyl)-1,3-dioxolanes and 2-(2-bromoalkyl)-1,3-dioxanes (**10**),[21] which are useful synthetic C3 bromide intermediates containing masked formyl groups, were carried out (Table 5). Acrolein derivatives **8** were reacted with **1c** (1.4 equiv.) and ethylene glycol **9a** or trimethylene glycol **9b** (1.2 equiv.), at 5 °C to room temperature, for 0.5 h to afford the corresponding bromide **10** in good yields. Reactions using **8a** and **8b** gave **10a** and **10b** in 82 and 72% yields, respectively (entries 1 and 4). Since **10c** was obtained in 76% yield, the α-branch in acrolein **8c** appears to have little influence on reactivity (entry 5). When trimethylene glycol was employed in these reactions, dioxanes **10d-f** were obtained in 83–90% yields (entries 6–8). The preparation of dioxolane **10a** was also performed using the traditional HBr solutions **1a** and **1b** for comparison; reactions using **1a** and **1b** furnished the desired product in only 10 and 58% yields, respectively, significantly lower than that using **1c** (entries 2 and 3).

Table 5. Synthesis of 2-(2-bromoalkyl)-1,3-dioxolanes and 2-(2-bromoalkyl)-1,3-dioxanes[a]



Entry	Substrate	Diol	Product	Isolated yield (%)
1	 **8a**	**9a**	 **10a**	82
2[b]				10
3[c]				58
4	 **8b**	**9a**	 **10b**	72
5	 **8c**	**9a**	 **10c**	76
6	**8a**	**9b**	 **10d**	83
7	**8b**	**9b**	 **10e**	90
8	**8c**	**9b**	 **10f**	83

[a]Reaction conditions: substrate (6 mmol), diol (7.4 mmol), **1c** (8.4 mmol), 1,4-dioxane (5 mL), 5 °C to r.t., 0.5 h. [b]Using **1a**. [c]Using **1b**.

3. Conclusions

We have developed **1c** as a new HBr solution using 1,4-dioxane as a solvent. The ability of **1c** to retain HBr was investigated by GC analysis, revealing that 97% of the initial HBr is retained over 30 days at -25 °C, without any decomposition of the 1,4-dioxane. Hydrobromination of alkenes, and bromination of alcohols, using **1c** provided superior results than two traditional HBr solutions, HBr_{aq} (**1a**) and HBr/AcOH (**1b**). In addition, the synthesis of 2-bromoalkyl-1,3-dioxolanes and 2-bromoalkyl-1,3-dioxolanes **10** using **1c** was achieved in good yields and without any by-products.[22] Since HBr solution **1c** does not contain a polar protic solvent, this solution is a useful alternative to HBr gas for many organic syntheses.

Typical procedure for the preparation of 2-(2-bromoalkyl)-1,3-dioxolanes with HBr/1,4-dioxane (1c)

To a mixture of acrolein (90%, 374 mg, 6.0 mmol), ethylene glycol (460 mg, 7.4 mmol) in 1,4-dioxane (5 mL), **1c** (17%, 4.0 g, 8.4 mmol) was added at 5 °C. The mixture was then warmed to room temperature for 30 min with stirring. The resulting mixture was quenched with saturated aq. $NaHCO_3$ (20 mL) and extracted with diethyl ether (15 mL × 3). The combined organic layer was washed with brine (25 mL × 3), dried over Na_2SO_4 (10 g) and concentrated in vacuo. The crude residue was purified by column chromatography on florisil (eluent: pentane) to afford **10a** (890 mg, 82%) as a colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (dt, *J* = 4.6 Hz, *J* = 7.4 Hz, 2H), 3.47 (t, *J* = 7.1 Hz, 2H),

3.88 (m, 2H), 3.96 (m, 2H), 5.01 (t, J = 4.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.14, 36.97, 64.78 (2C), 102.34.

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17. Van Cleave *et al.* reported that 1,4-dioxane reacts slowly with anhydrous HBr at room temperature to afford 2,2'-dibromodiethyl ether (Van Cleave, A. B.; Blake, R. I. *Can. J. Chem.* **1951**, *29*, 785–789). We confirmed that no 1,4-dioxane decomposition products were observed by GC analysis after treatment with HBr gas at 25 °C for 30 min. They also reported that the HBr/1,4-dioxane solution, initially at 0.821 M in HBr, was determined to be 0.301 M after 30 days at 25°C. In other words, the HBr level decreased to 37% of the initial concentration over that period, which does not contradict our HBr retention tests results.
18. Although the outcomes in Table 3 are counterintuitive, it is known that anti-Markovnikov addition of HBr takes place without peroxide[9a,23] Interestingly, the origin of this "abnormal" addition is still unclear.[23,24] To suppress the formation of radical species, we carried out hydrobromination of tetradecene (**2a**) with HBr/1,4-dioxane solution (**1c**) in the presence of 10 mol% of a radical inhibitor, BHT, under N_2.[24] However, the anti-Markovnikov-type product, 1-bromotetradecane (**3a**), was still obtained in 90% yield.
19. Solvents can influence regioselectivity in the hydrobromination of alkenes with HBr.[23] We also demonstrated that the hydrobromination of **2a** with **1c** in CH_2Cl_2 or 1,2-dichloroethane afforded the Markovnikov product, 2-bromotetradecane (**4a**), in 95% or 90% yields, together with a trace amount (< 1%) or 10% of the anti-Markovnikov product **3a**, respectively.
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22. To examine the scalability of reactions with HBr solution **1c**, we have prepared 2-(2-bromoethyl)-1,3-dioxolane (**10a**) from 1.68 g (30 mmol) of acrolein, obtaining 5.18 g (95%) of the desired product. This demonstrates that preparation of the dioxolane on even a 5-g scale can be successfully performed using **1c**.
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Supplementary Material

All compounds prepared in this study are known compounds. Supplementary data (Tables S1 and S2, Experimental details, ^{1}H and ^{13}C NMR data of compounds prepared in this study) can be found in the online version, at http://