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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Bingbing Han, Zubiao Zheng, Fang Wu & Aidong Wang (2017): One-pot synthesis of α-bromoacetals of ketones from secondary alcohols and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in ethylene glycol, Synthetic Communications, DOI: 10.1080/00397911.2017.1378681

To link to this article: http://dx.doi.org/10.1080/00397911.2017.1378681

One-pot synthesis of α-bromoacetals of ketones from secondary alcohols and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in ethylene glycol

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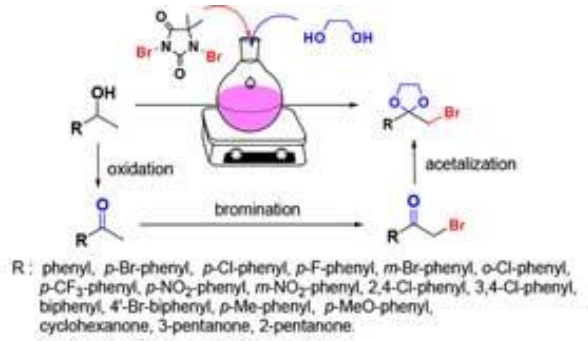
ABSTRACT

α-Bromoacetals of ketones were prepared from various secondary alcohols with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and ethylene glycol through oxidation, bromination

and acetalization in one pot without the use of other catalysts under mild conditions. The effects of DBDMH, the solvent and *N*-bromosuccinimide (NBS) on the reaction were investigated. Under the optimal conditions, most α-bromoacetals of ketones were obtain in 90-98% yields.

GRAPHICAL ABSTRACT



R: phenyl, *p*-Br-phenyl, *p*-Cl-phenyl, *p*-F-phenyl, *m*-Br-phenyl, *o*-Cl-phenyl, *p*-CF_3-phenyl, *p*-NO_2-phenyl, *m*-NO_2-phenyl, 2,4-Cl-phenyl, 3,4-Cl-phenyl, biphenyl, 4'-Br-biphenyl, *p*-Me-phenyl, *p*-MeO-phenyl, cyclohexanone, 3-pentanone, 2-pentanone.

An easy and mild method was reported that could directly prepare α-bromoacetal of ketones from various secondary alcohols with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and ethylene glycol through oxidation, bromination and acetalization in one-pot without any other catalyst.

An easy and mild method was reported that could directly prepare α-bromoacetal of ketones from various secondary alcohols with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and ethylene glycol through oxidation, bromination and acetalization in one-pot without any other catalyst.

KEYWORDS: 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), one pot, oxybromoacetalization, secondary alcohol, α-bromoacetals of ketones

Introduction

The development of facile and efficient methods for the preparation of valuable intermediates from readily available reagents is a challenge in organic synthesis.[1] The conversion of α-bromoacetals of ketones is an important transformation in synthetic organic chemistry

because the resulting products are very useful as intermediates in the synthesis of biologically active compounds specially for triazole fungicides (propiconazole and difenoconazole)[2], α,β-unsaturated ketones[3], and enol ethers[3d], for pharmaceuticals and agrochemicals. Several methods have been described for the preparation of α-bromoacetals. Additionally, the conversion of ketones to α-bromoacetals of ketones can operate via two pathways to reach the target molecules, i.e., bromination and acetalization, employing a catalyst, such as liquid bromine[4], copper(II) bromide[5], poly(diallyldimethylammonium chloride)[6], iodobenzene dichloride[7], an *N*-bromo reagent[8] and an expensive metallic or strong protic acid.[9] Recently, many reports have focused on the one-pot formation of α-bromoacetals from various acetophenones. However, few reports have focused on the direct selective synthesis of α-bromoacetals (through ketones) from alcohols using the same reagents due to the challenges accompanying oxidation and bromoacetalization, such as using hazardous reagents[4,5,10], strong oxidation conditions[11] and excessive bromination.

N-Bromo reagents represent a larger group of substances that have been widely used in organic synthesis and the chemical manipulations of natural compounds.[12] 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH), as an *N*-bromo reagent, is stable, commercially available and low cost and thus has attracted much attention. The application of DBDMH in the bromination of ketones to prepare α-bromoketones has been investigated under various reaction conditions[13], including some methods described by our group[13b,c]. The latest research further indicated that DBDMH is also a mild, highly selective and environmentally friendly oxidation reagent[14] in the

oxidation of alcohols to ketones[15], aldehydes[14a,16], and esters[16] under suitable reaction conditions to substitute high-valent metal salts and metal oxides. Herein, we developed and optimized a one-pot method for the synthesis of α-bromoacetals (through ketones) from secondary alcohols and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in ethylene glycol (oxybromoacetalization).

Results and Discussion

In the preliminary experiments, 1-phenylethanol (**1a)**, as the simplest secondary aromatic alcohol, was chosen as a model for the one-pot preparation of α-bromoacetal (through acetophenone). Upon treating compound **1a** with 1.0 equiv (2 mmol) of DBDMH in 6 mL of ethylene glycol without another catalyst under room temperature, 2-bromomethyl-2-phenyl-1,3-dioxolane (**2a**) was obtained as a white precipitate in 96% yield (entry 2, **Table 1**). In addition, the effect of the molar ratio of DBDMH to **1a** was investigated (**Table 1**), and the results are summarized in **Table 1**. Upon adding 1.0 mmol (0.5 equiv) of DBDMH to the reaction system, the yield of **2a** was only 35% (entry 1, **Table 1**), and acetophenone and 2-methyl-2-phenyl-1,3-dioxolane were the main byproducts determined by gas chromatography (GC). Increasing the amount of DBDMH to 2.4 mmol (1.2 equiv) resulted in an increased yield up to 98% (entry 3, **Table 1**). However, a larger amount of DBDMH did not further facilitate the reaction.

The effect of the amount of ethylene glycol on the oxybromoacetalization of **1a** was also investigated (**Table 2**). A lower amount of ethylene glycol (1 mL) resulted in a low yield of **2a**

(83%) (entry 1, **Table 2**). When the volume of ethylene glycol was increased to 4 mL, the yield increased to 98% (entry 4, **Table 2**). This result may be attributed to the ketone-ketal chemical equilibrium diluting the amount of ethylene glycol in water that formed during the oxidation and acetalization processes. Upon further increasing the amount of ethylene glycol, the product yield was nearly unchanged (entry 5, and 6, **Table 2**). However, when the reaction was performed with 1 mmol (0.5 equiv) of DBDMH in methanol under the same conditions, the reaction mainly proceeded through oxidation, and acetophenone was isolated in 78% yield (entry 7, **Table 2**). Upon increasing the amount of DBDMH to 2.4 mmol (1.2 equiv), 2-bromo-1-phenylethanone was isolated as the oxybromination product in 80% yield (entry 8, **Table 2**). Therefore, 4 mL of ethylene glycol (4 mL) was initially chosen for the acetalization.

The optimal reaction conditions to obtain the highest yield required 2 mmol of **1a**, 2.4 mmol of DBDMH, 4 mL of ethylene glycol at room temperature for 24 h. To further examine the scope of this protocol, the optimized conditions were then applied to the synthesis of a variety of α-bromoacetal of substituted ketones from secondary aromatic alcohols and aliphatic alcohols. The results are listed in **Table 3**. When **1b**, **1c**, **1d** and **1e** with a halogen atom (-X) or a trifluoromethyl group ($-CF_3$) on the *para*-position of the benzene ring were selected, the corresponding yields of **2b**, **2c**, **2d**, and **2e** were 99%, 96%, 94%, and 84% (entries 2, 3, 4, and 5, **Table 3**), respectively. When 3-bromoacetophenone (**1f**) and 3,4-dichloroacetophenone (**1g)** were tested as substrates, high yields of 92% and 90% (entries 6, and 7, **Table 3**), respectively, were also obtained. However,

when **1h** and **1i** were used, yields of only 19% and 9% (entry 8, and 9 **Table 3**), respectively, were achieved, which could be attributed to the steric effect of the *ortho*-chlorine atom. Under the same conditions, **2g** and **2h**, which contain a nitro group on the benzene ring, were obtained in low yields (entry 10, and 11, **Table 3**). When **1l** and **1m** with bulky groups on the benzene ring were tested, the yields of **2l** and **2m** reached 96% and 94% (entries 12 and 13, **Table 3**), respectively. Product **2n** with a methyl group on the benzene ring was isolated in 92% yield (entry 14, **Table 3**). Substrates with a strong electron-donating group (-OCH_3), such as **1o** furnished 2-bromomethyl-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane (**2o**) as the target product in only 36% yield (entry 15, **Table 3**). Cyclohexanone (**1p**), 3-pentanone (**1q**), and 2-pentanone (**1r**), as aliphatic ketones, were selected as test substrates, and the yields of **2p**, **2q**, and **2r** were 99%, 86%, and 70% (entry 16, 17 and 18, **Table 3**), respectively. Product **2r** was a 3:2 mixture of 2-(bromomethyl)-2-propyl-1,3-dioxolane and 2-(1-bromopropyl)-2-methyl-1,3-dioxolane, as determined by ^{1}H NMR spectroscopy. 1,2-Propanediol produced the two isomers of 2-bromomethyl-4-methyl-2-phenyl-1,3-dioxolane in 96% yield (entry 19, **Table 3**) in a 3:2 ratio, as determined by ^{1}H NMR spectroscopy.

N-Bromosuccinimide (NBS), an analogue of DBDMH, has been studied widely in bromination under various reaction conditions. The effect of NBS on the oxybromoacetalization of **1a** was further investigated as a reference (**Table 4**). When 2.0 mmol (1.0 equiv) of NBS was added to the reaction system, **2a** was isolated in only 52% yield (entry 1, **Table 3**). Increasing the

amount of NBS to 4.6 mmol (2.3 equiv) resulted in an increased yield of 97% (entry 4, **Table 3**). Then, various secondary alcohols were also tested for oxybromoacetalization with 4.6 mmol of NBS in 4 mL of ethylene glycol at room temperature, showing similar results to those of the DBDMH reactions, as summarized in **Table 4**. Compared to NBS, DBDMH is a widely used industrial product and is much cheaper. For example, in 2017, the price of DBDMH was approximately two times lower than that of NBS, according to the Alfa Aesar product catalogue (China). The bromine content of DBDMH is also higher than NBS.

Chen et al. developed a mechanism of the keto-enol tautomerism in the chlorination of acetophenones using DCDMH.[17] Analogously, we propose the following oxybromoacetalization mechanism: the oxidation of 1-phenylethanol to the ketone generates HBr in situ, which catalyses the bromo ketal formation (Scheme 1).

In summary, we developed a simple, effective, mild and one-pot method to directly synthesize α-bromoacetals of ketones from various secondary alcohols by the application of DBDMH in glycols as a reaction reagent and solvent without the use of other catalysts. The major advantages of the present protocol include a wide range of tolerable substrates, mild reaction conditions, ease and safety of operation, and high yields, which provided a novel route to α-bromoacetals of ketones, furthering the developments of organic synthesis.

Experimental Section

Representative procedure for the preparation of α-bromoacetals of ketones from secondary alcohols

A mixture of 2 mmol of the substrate and 4 mL of ethylene glycol was stirred for 5 min, and then, 2.4 mmol of DBDMH or 4.6 mmol of NBS was added in 5 additions over one hour. The mixture was stirred 24 h at room temperature. Afterward, the mixture was extracted with ether (10 mL × 3). The combined organic layer was washed twice with water (20 mL) and was dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was treated with alumina chromatography (petroleum ether/AcOEt = 20/1, v/v) to generate the product. **2-Bromomethyl-2-phenyl-1,3-dioxolane (2a)**: Yield: 98%, white solid. M.p.: 56-58 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.66 (s, 2H, CH_2Br), 3.88-3.91 (m, 2H, OCH_2CH_2O), 4.17-4.20 (m, 2H, OCH_2CH_2O), 7.32-7.38 (m, 3H, ArH), 7.52 (d, 2H, J = 7.5 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.2, 65.8, 107.3, 126.0, 128.3, 128.7, 139.8. IR (KBr, cm^{-1}): 3011, 2885, 1627, 1485, 1470, 1447, 1220, 1169, 1039, 1029, 997.

Acknowledgement

The authors thank the Education Department of the Anhui Province for financial support (No. KJ2016A684, KJHS2017B13).

The supplementary material is available. Supporting Information: experimental details, yields, melting points, ^{1}H and ^{13}C NMR spectra, and IR spectra.

References

[1] (a) Palash, P.; Gayen, K. S.; Khamarui, S.; Chatterjee, N.; Maiti, D. K. *Chem. Comm.* **2011**, *47*, 6933–6935; (b) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471–17482.

[2] (a) Baldwin, B. C.; Wiggins, T. E. *Pestic. Sci.* **1984**, *15*, 156–166; (b) Li, J. M.; Tang, H.; Zu, Z. B.; Li, F. M.; Xu, W. T.; Wu, J. Q. *Agr. Res. & App.* **2009**, *13*, 18–21; (c) Bu, Y. L.; Weng, J. Q. *Fine Chem. Intermed.* **2007**, *37*, 25–27.

[3] (a) Wilson, A. M.; Allinger, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 1999–2001; (b) Johnson, W. S.; Bass, J. D.; Williamson, K. L. *Tetrahedron* **1963**, *19*, 861–867; (c) Warnhoff, E. W.; Marshall, D. R. *J. Org. Chem.* **1967**, *32*, 2000–2003; (d) Park, H. S.; Kim, S. H.; Park, M. Y.; Kim, Y. H. *Tetrahedron Lett.* **2001**, *42*, 3729–3732; (e) Kimpe, N. D.; Stevens, C. *Tetrahedron* **1995**, *51*, 2387–2402; (f) Kimpe, N. D.; Keppens, M. *J. Agric. Food Chem.* **1996**, *44*, 1515–1519.

[4] Akihiro, I.; Masatomi, K.; Yokusu, K.; Manabu, Y.; Kenjin, I.; Takashi, O.; Koji, U. WO2004014887.

[5] Sathob, J. Y.; Yokoyama, C. T.; Haruta, A. M.; Nishicawa, K.; Hirose, M.; Hagitani, A. *Chem. Lett.* **1974**, *3*, 1521–1522.

[6] Massein, M.; Kachiei, Z. *Chin. J. Chem.* **2010**, *28*, 2221–2225.

[7] Yu, J.; Zhang, C. *Synthesis* **2009**, 2324–2328.

[8] (a) Zhou, B.; Chen, Z. Z.; Zheng, Z. B.; Han, B. B.; Zou, X. Z. *Synth. Commun.* **2012**, *42*, 1147–1453; (b) Zheng, Z. B.; Li, Z. Z.; Han, B. B.; He, Z. M.; Shi, T. F.; Cheng, P. *Tetrahedron Lett.* **2015**, *56*, 2219–2222; (c) Zheng, Z. B.; Han, B. B.; Wu, F.; Shi, T. F.; Liu, J.; Zhang, Y.; Hao, J. L. *Tetrahedron* **2016**, *72*, 7738–7743.

[9] (a) Vražič, D.; Jereb, M.; Laali, K.; Stavber, S. *Molecules* **2013**, *18*, 74–96; (b) Yadav, G. D.; Katole, S. O. *Catal. Today* **2014**, *237*, 125–135; (c) Mallesham, B.; Sudarsanam, P.; Raju, G.; Reddy, B. M. *Green Chem.* **2013**, *15*, 478–489; (d) Salama, T. A.; Novák, Z. *Tetrahedron Lett.* **2011**, *52*, 4026–4029.

[10] Sarrafi, Y.; Sadatshahabi, M.; Alimohammadi, K. *Chin. Chem. Lett.* **2009**, *20*, 393–396.

[11] (a) He, X. J.; Shen, Z. L.; Mo, W. M.; Sun, N.; Hu, B. X.; Hu, X. Q. *Adv. Synth. Catal.* **2009**, *351*, 89–92; (b) Yamaoka, H.; Moriya, N.; Ikunaka, M. *Org. Process Res. Dev.* **2004**, *8*, 931–938.

[12] (a) Reddy, B. M.; Kumar, V. V. R.; Reddy, N. C. G.; Rao, S. M. *Chin. Chem. Lett.* **2014**, *25*, 179–182; (b) Kolvari, E.; Ghorbani-Choghamarani, A.; Salehi, P.; Shirini, F.; Zolfigol, M. A. *J. Iran. Chem. Soc.* **2007**, *4*, 126–174.

[13] (a) Radaram, B.; Levine, M. *Tetrahedron Lett*. **2015**, *55*, 4905–4908; (b) Gao, G. R.; Guan, X. X.; Zou, X. Z. *Chin. J. Org. Chem.* **2007**, *27*, 109–111; (c) Zhu, W.; Li, Z. Z.; Yao, L. L.; Zheng, Z. B.; Zou, X. Z. *Chin. J. Org. Chem.* **2012**, *32*, 1146–1149.

[14] (a) Chaudhuri, S.; Zaki, H.; Levine, M. *Synth. Commun.* **2016**, *46*, 636–644; (b) Kumar, B. N. P.; Mohana, K. N. *Int. J. Drug Des. Discov.* **2013**, *4*, 1188–1192.
[15] Khazaei, A.; Abbasi, F.; Kianiborazjani, M.; Saednia, S. *J. Braz. Chem. Soc.* **2014**, *25*, 361–364.
[16] Li, Z. Z.; Zhu, W.; Bao, J. L.; Zou, X. Z. *Synth. Commun.* **2014**, *44*, 1155–1164.
[17] Chen, Z. Z.; Zhou, B.; Cai, H. H.; Zhu, W.; Zou, X. Z. *Green Chem.* **2009**, *11*, 275–278.

Table 1. Effect of DBDMH on oxybromoacetalization of **1a** with ethylene glycol[a].

Entry	DBDMH (mmol)	Yield[b] (%)
1	1.0(0.5 equiv)	35
2	2.0(1.0 equiv)	96
3	2.4(1.2 equiv)	98
4	3.0(1.5 equiv)	98
5	4.0(2.0 equiv)	97

[a]The reaction was performed with 2 mmol of 1-Phenylethanol (**1a**), and 6 mL of ethylene glycol at room temperature for 24 h;

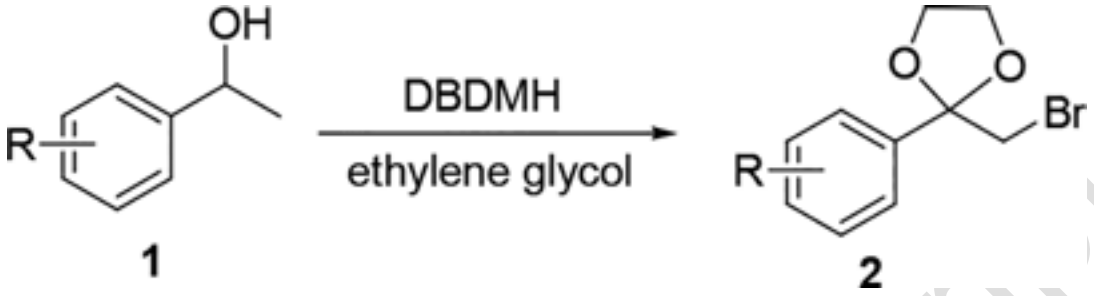
[b]The α-bromoacetal of acetophenone (**2a**) was filtrated directly from the reaction system as a white solid.

Table 2. Effect of solvents on the oxybromoacetalization of **1a** with DBDMH[a].

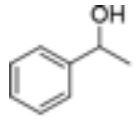
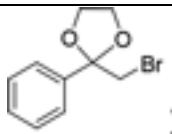
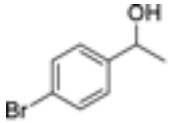
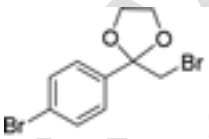
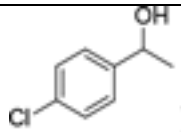
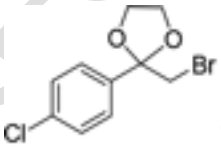
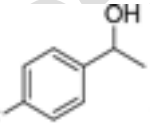
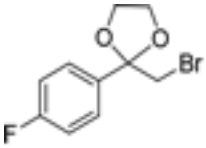
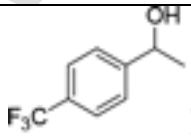
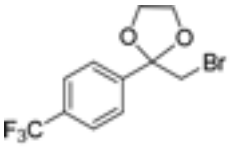
Entry	Solvent	Volume (mL)	Yield (%)
1	ethylene glycol	1	83[b]
2	ethylene glycol	2	95
3	ethylene glycol	3	96
4	ethylene glycol	4	98
5	ethylene glycol	5	98
6	ethylene glycol	7	98
7	methanol	5	0(78[b])
8	methanol	5	0(80[c])

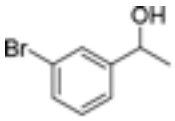
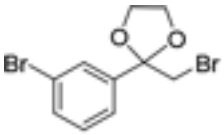
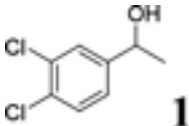
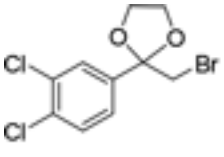
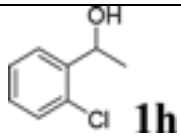
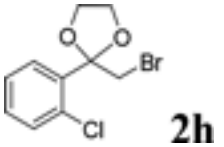
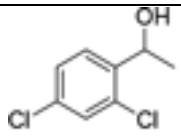
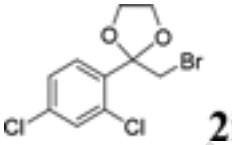
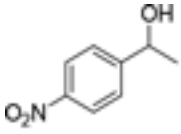
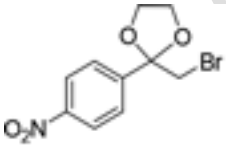
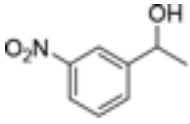
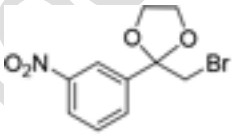
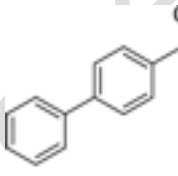
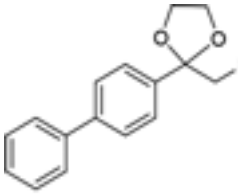
[a]The reaction was performed with 2 mmol of 1-Phenylethano l(**1a**), 2.4 mmol of DBDMH(1.2 equiv), at room temperature for 24 h; [b]The reaction was performed with 1.0 mmol of DBDMH (0.5 equiv) for 1 h, and then acetophenone was obtained with 78% yield; [c]The reaction was performed with 2.4 mmol of DBDMH (1.2 equiv) for 3 h, and then 2-bromo-1-phenylethanone was obtained with 80% yield.

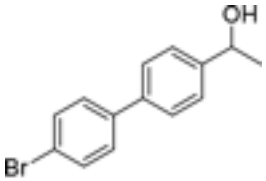
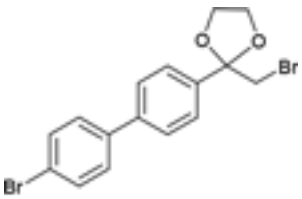
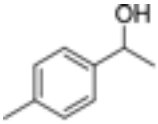
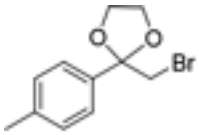
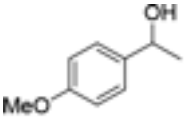
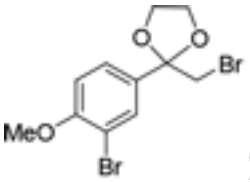
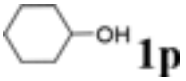
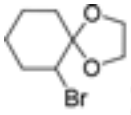
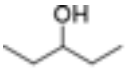
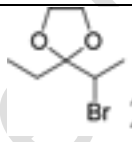
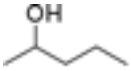
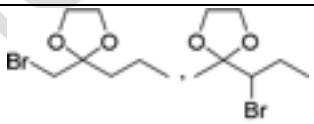
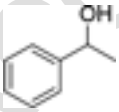
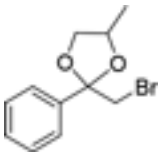
Table 3. Oxybromoacetalization of various secondary alcohols with DBDMH/NBS in ethylene glycol[a].



1 2

Entry	Substrate	Product	Yield[b](%, DBDMH)	Yield[b](%, NBS)
1	 **1a**	 **2a**	98	97
2	 **1b**	 **2b**	99	82
3	 **1c**	 **2c**	96	93
4	 **1d**	 **2d**	94	92
5	 **1e**	 **2e**	84	80

6	 **1f**	 **2f**	92	95
7	 **1g**	 **2g**	90	88
8	 **1h**	 **2h**	19	8
9	 **1i**	 **2i**	9	2
10	 **1j**	 **2j**	50	42
11	 **1k**	 **2k**	34	43
12	 **1** **l**	 **2l**	96	94

13	 **1m**	 **2m**	94	94
14	 **1n**	 **2n**	92	83
15[c]	 **1o**	 **2o**	36	23
16	 **1p**	 **2p**	99	97
17	 **1q**	 **2q**	86	92
18	 **1r**	 **2r**	70[d]	72
19			96	94

[a]The reaction was performed with 2 mmol of ketone, 2.4 mmol (1.2 equiv) of DBDMH or 4.6 mmol (2.3 equiv) of NBS, and 4 mL of ethylene glycol at room temperature for 24 h; [b]isolated yield; [c]2-bromomethyl-2-(3-bromo-4-methoxyphenyl)-1,3-

dioxolane(**2o**) was isolated as the main product; [d]a mixture of 2-(bromomethyl)-2-propyl-1,3-dioxolane and 2-(1-bromopropyl)-2-methyl-1,3-dioxolane was obtained, and the ratio determined by ^{1}H NMR was 3: 2.

Table 4. Effect of NBS on the oxybromoacetalization of **1a** with ethylene glycol[a].

Entry	NBS (mmol)	Yield of **2a** (%)
1	2	52
2	3	78
3	4	92
4	4.6	97
5	5	91
6	6	90

[a]The reaction was performed with 2 mmol of acetophenone (1a), and 6 mL of ethylene glycol at room temperature for 24 h.

Scheme 1. Possible mechanism for one-pot oxybromoacetalization of **1a** with DBDMH in ethylene glycol.