ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Asai, M. Kato, Y. Monguchi, H. Sajiki and Y. Sawama, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC01514C.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C7CC01514C

Journal Name

COMMUNICATION

Cyclic Ether Synthesis from Diols using Trimethyl Phosphate

Shota Asai, Maho Kato, Yasunari Monguchi, Hironao Sajiki* and Yoshinari Sawama*

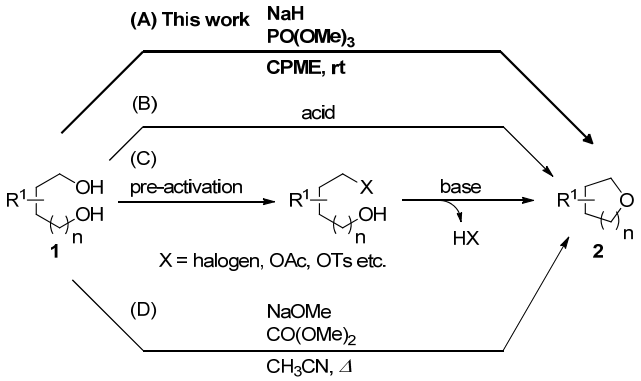
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Cyclic ethers have been effectively synthesized via the intramolecular cyclization of diols using trimethyl phosphate and NaH. The present cyclization could proceed at room temperature to produce 5-7 membered cyclic ethers in good to excellent yields. Substrates possessing a chiral secondary hydroxy group were transformed into the corresponding chiral cyclic ethers along with the retention of their stereochemistries.

Cyclic ethers are fundamental heterocycles of bioactive compounds (i.e., tegafur, griseofulvin, tocopherol and isosorbide), natural products, etc. [1-3] Although cyclic ethers can be directly synthesized from readily available diols by the acid-catalyzed intramolecular cyclization, harsh reaction conditions, such as strong acidic and heating conditions, are required to activate the less reactive free hydroxy groups as a leaving group (Scheme 1: route B).[4] Therefore, a stepwise procedure via the selective transformation of one hydroxyl group into a good leaving group using moisture sensitive reagents (e.g., tosyl chloride, thionyl chloride and phosphorus tribromide) and the subsequent intramolecular nucleophilic substitution of the other hydroxyl group is generally adopted to convert the diol into the corresponding cyclic ether (route C).[5] A direct and efficient synthesis of cyclic ethers from diols was recently reported using sodium methoxide and dimethyl carbonate as an activator of the hydroxy groups under the basic and heating conditions (route D).[6] We have recently developed a novel activation method of the hydroxy group using trimethyl phosphate [$PO(OMe)_3$] as an inexpensive and stable reagent for the conversion of allenols into eneynes.[7] We now report that $PO(OMe)_3$ and NaH efficiently facilitates the intramolecular cyclization of various diols into cyclic ethers at room temperature in cyclopentyl methyl ether (CPME) as a process chemistry-friendly ether type solvent (route A).[8] Furthermore, the stereoselective cyclization could also be accomplished with retention of the stereochemistry using chiral diols.



Scheme 1. Synthesis of cyclic ethers from diols

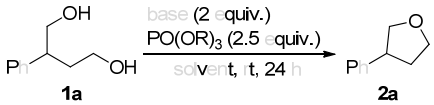
2-Phenylbuta-1,4-diol (**1a**) as a substrate was smoothly transformed into 3-phenyltetrahydrofuran (**2a**) in 86% isolated yield using $PO(OMe)_3$ (2.5 equiv.) and NaH (2 equiv.) in CPME at room temprature for 24 h (entry 1). Other bases, such as KH, NaOH, $NaNH_2$, NaOMe, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave low yields (entries 2-6). The use of relatively bulky phosphates possessing the more bulky residues [e.g., $PO(OEt)_3$, $PO(On\text{-}Bu)_3$ and $PO(OPh)_3$] were inadequate (entries 7-9). Although THF is also a good solvent for the present reaction, CPME is a more favorable solvent by virtue of its quite low productivity of a peroxide[8] (entries 1 *vs.* 10). Meanwhile, the reaction in hexane, CH_3CN, toulene or DMF for 24 h was incomplete (entries 11-14) and no reaction was observed in $(CH_2Cl)_2$ (entry 15). The reduced use of NaH or $PO(OMe)_3$ caused a significant decerase in reaction efficiency (the details are described in Supporting Information).

Laboratory of Organic Chemistry, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan, E-mail: sajiki@gifu-pu.ac.jp: sawama@gifu-pu.ac.jp; Fax: +81-58-230-8109

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Optimization

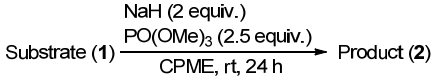


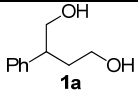
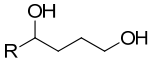
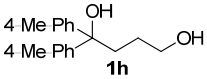
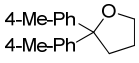
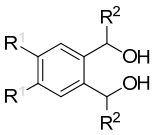
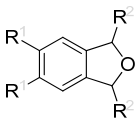
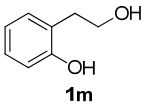
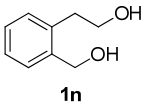
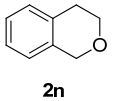
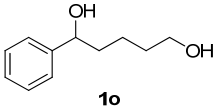
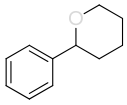
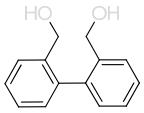
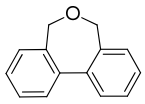
entry	base	R	solvent	yield (%)[a]	
				1a	**2a**
1	NaH	Me	CPME	0	88 (86%)[b]
2	KH	Me	CPME	18	66
3	NaOH	Me	CPME	56	35
4	$NaNH_2$	Me	CPME	60	34
5	NaOMe	Me	CPME	79	13
6	DBU	Me	CPME	98	0
7	NaH	Et	CPME	56	40
8	NaH	*n*-Bu	CPME	63	27
9	NaH	Ph	CPME	complex mixture	
10	NaH	Me	THF	0	88
11	NaH	Me	hexane	5	85
12	NaH	Me	CH_3CN	9	85
13	NaH	Me	toluene	3	79
14	NaH	Me	DMF	2	72
15	NaH	Me	$(CH_2Cl)_2$	98	0

[a] The yield was determined by ^{1}H NMR using 1,1,2,2,-tetrachloroethane as the internal standard. [b] Isolated yield.; CPME: cyclopentyl methyl ether

The present reaction conditions using $PO(OMe)_3$ and NaH in CPME at room temperature could be applied to the intramolecular cyclization of various diols (**1a**-**1o**) into the corresponding cyclic ethers (**2**, Table 2). Various 1-arylbutan-1,4-diols (**1b**-**1f**) bearing a 1,4-diol functionality were smoothly transformed into the corresponding 2-aryltetrahydrofuran products (**2b**-**2f**) in moderate to excellent yields (entries 2-6). Dodecan-1,4-diol (**1g**) as an aliphatic substrate underwent the present cyclization to give the corresponding 2-octyltetrahydrofuran (**2g**) in 79% yield (entry 7). The sterically-hindered diols (**1h**) possessing a tertiary hydroxy group were also good substrates to produce the 2,2-disubstituted tetrahydrofuran (**2h**) in 76% yield (entry 8). Phthalan derivatives are also useful compounds.[9,10] A variety of phthalan derivatives (**2i**-**2l**) could also be constructed from the 1,2-benzenedimethanol derivatives (**1i**-**1l**) (entries 9-12). Phenolic and primary hydroxy groups in 2-hydroxyethyl phenol (**1m**) could be effectively condensed to give 2,3-dihydrobenzofuran (**2m**) in 90% yield (entry 13). 1,5- and 1,6-Diol derivatives (**1n**-**1p**) were also transformed into 6 and 7-membered cyclic ethers (entries 14-16).[11-13]

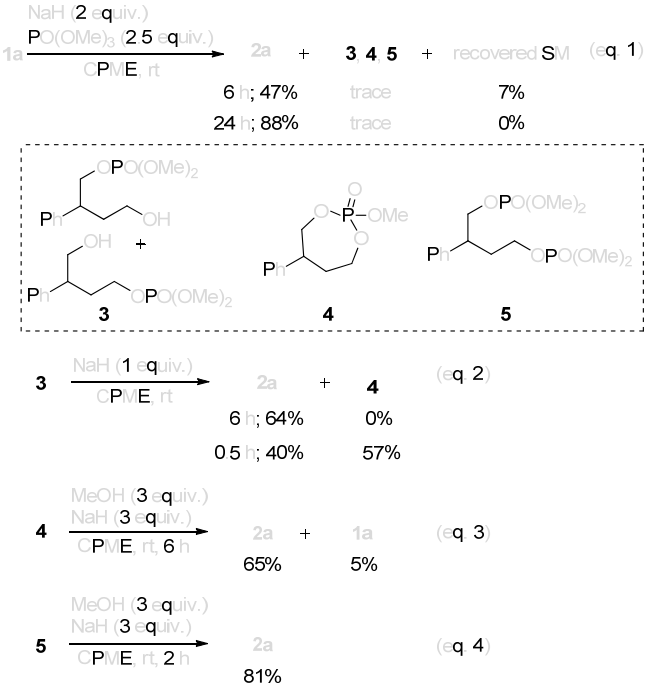
Table 2. Scope of substrates



entry	substrate	product	Yield[a]
1	 **1a**	 **2a**	86%
2	 **1b**; R = Ph	 **2b**	91%
3	**1c**; R = 4-MeO-Ph	**2c**	78%
4	**1d**; R = 4-Me-Ph	**2d**	68%
5	**1e**; R = 4-Cl-Ph	**2e**	68%
6	**1f**; R = 4-F-Ph	**2f**	53%
7	**1g**; R = *n*-octyl	**2g**	79%
8	 **1h**	 **2h**	76%
9	 **1i**; R^1, R^2 = H	 **2i**	67%
10[b]	**1j**; R^1 = MeO, R^2 = H	**2j**	46%
11	**1k**; R^1 = Cl, R^2 = H	**2k**	50%
12	**1l**; R^1 = H, R^2 = Me (*dr* = 69/31)	(*cis*/*trans* = 64/36)	39%
13	 **1m**	 **2m**	90%
14	 **1n**	 **2n**	45%
15	 **1o**	 **2o**	26%
16	 **1p**	 **2p**	76%

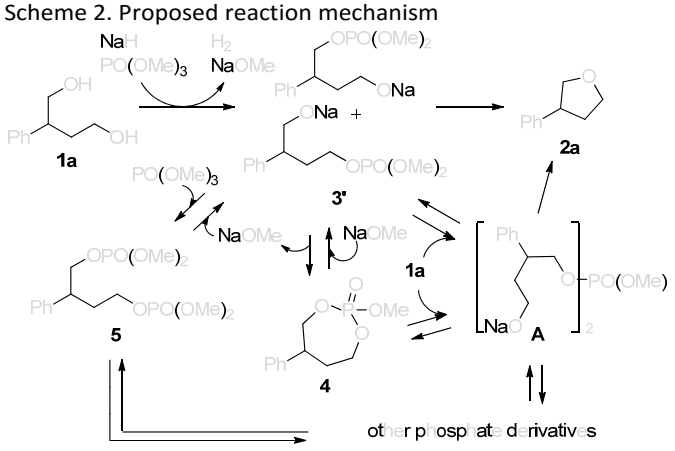
[a] Isolated yield. [b] THF was used instead of CPME.

While the desired product (**2a**) was efficiently obtained in 88% NMR yield (86% isolated yield) for 24 h (Table 1, entry 1 and Table 2, entry 1), the reaction suspended at 6 h under the same reaction conditions gave only 47% of **2a** and 7% of the unchanged **1a** together with a trace amount of the phosphate derivatives as expected reaction intermediates, such as monophosphates (**3**), cyclic phosphate (**4**) and diphosphate (**5**) as shown in eq. 1. **3** were easily transformed into **2a** via the formation of **4** in the presence of NaH (eq. 2), while **4** and **5** could also be converted to **2a** in the presence of MeOH as a nucleophilic reagent (eqs. 3 and 4).[14,15] These results indicated that monophosphates (**3**) are the principal reaction intermediates for **2a**.



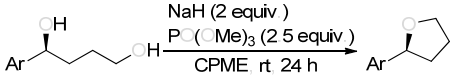
2-Phenylbutan-1,4-diol (**1a**) was initially transformed into the monophosphate sodium salts (**3'**) in the presence of NaH and $PO(OMe)_3$ and **2a** could be produced by the intramolecular nucleophilic substitution accompanied with the elimination of dimethylphosphate (Scheme 2). Otherwise, **4** could be produced by the nucleophilic attack of the hydroxyl anion of **3'** to the intramolecular phosphate in association with elimination of the methoxide ion, and **5** is also generated by the second phosphorylation of **3'**. **4** and **5** could be reconverted into **3'** by the nucleophilic attack of the *in situ*-generated methoxide ion. Various types of phosphate derivatives could probably be formed during the reaction as an undetectable amount of side products (e.g., **A**), which were all transformed into **2a**. Consequently, a single product (**2a**) was obtained via various intermediates after stirring for 24 h.

Scheme 2. Proposed reaction mechanism

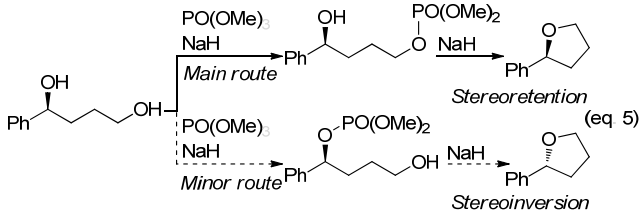


The cyclization of the chiral (*S*)-1-arylbutan-1,4-diol derivatives as 1,4-diols bearing a (*S*)-secondary benzylic alcohol moiety was investigated. The acid-mediated cyclization of chiral 1,4-diols generally gives the corresponding cyclic ethers with stereoinversion due to the high leaving-group ability of the secondary hydroxy group.[4f] On the other hand, the stereoretentive cyclization of chiral diols using sodium methoxide and dimethyl carbonate was also reported.[6] We have investigated the stereoselective cyclization of diols bearing a secondary benzylic alcohol moiety within the molecule. The reaction of (*S*)-2-phenylbuta-1,4-diol (**1a**: 97% ee) in the presence of NaH and $PO(OMe)_3$ efficiently proceeded at room temperature with perfect stereoretention to give (*S*)-**2a** in 81% yield with 96% ee (Table 3, entry 1). 1-(4-Fluorophenyl)butan-1,4-diol was also stereo-selectively converted into the corresponding (*S*)-**2f** in a stereoretentive manner of 67% yield and 92% ee (entry 2). Meanwhile, a slight loss of enantioselectivity was observed during the cyclization of 1-(4-methoxyphenyl)butan-1,4-diol [(*S*)-**1c**; 77% ee] into (*S*)-**2c** (71% ee) (entry 3). The primary hydroxy group of the substrate is preferentially phosphorylated and the following intramolecular nucleophilic attack by the chiral secondary hydroxyl anion produces the corresponding chiral cyclic ether in a stereoretentive manner (eq. 5).

Table 3. The cyclization with stereoretention



entry	Ar	substrate	product	
		ee	yield	ee
1	Ph	**1a**: 97% (*S*)	81%	96% (*S*)
2	4-F-Ph	**1f**: 94% (*S*)	67%	92% (*S*)
3	4-MeO-Ph	**1c**: 77% (*S*)	61%	71% (*S*)



In conclusion, we have accomplished the efficient cyclic ether synthesis via the intramolecular cyclization of diol derivatives using an inexpensive and easily handled trimethylphosphate/NaH combination. The present cyclization of diols could efficiently proceed in CPME at room temperature and 5-7 membered cyclic ethers were smoothly constructed. Furthermore, diols bearing a chiral secondary benzylic alcohol moiety within the molecule could be transformed into the corresponding chiral cyclic ethers with complete stereoretention.

Acknowledgement

We thank the Zeon Corporation for the kind gift of CPME.

Notes and references

1 For example, see: 5 membered cyclic ether derivatives; (a) C.-C. Liaw, F.-R. Chang, Y.-C. Wu, H.-K. Wang, Y. Nakanishi, K. F. Bastow and K.-H. Lee, *J. Nat. Prod.*, 2004, **67**, 1804-1808; (b) M. A. Lawson, M. Kaouadji and A. J. Chulia, *Tetrahedron Lett.*, 2008, **49**, 2407-2409; (c) G.-H. Tang, Z.-W. Chen, T.-T. Lin, M. Tan, X.-Y. Gao, J.-M. Bao, Z.-B. Cheng, Z.-H. Sun, G. Huang and S. Yin, *J. Nat. Prod.*, 2015, **78**, 1894-1903.

2 For example, see: 6 membered cyclic ether derivatives; (a) L. Ghribi, P. Waffo-Téguo, S. Cluzet, A. Marchal, J. Marques, J.-M. Mérillon and H. B. Jannet, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3825-3830; (b) S. A. Ahmed, S. A. Ross, D. Slade, M. M. Radwan, I. A. Khan and M. A. Elsohly, *Phytochemistry*, 2015, **117**, 194-199; (c) J. Le, W. Lu, X. Xiong, Z. Wu and W. Chen, *Molecules*, 2015, **20**, 18496-18510.

3 For example, see: 6 membered cyclic ether derivatives; K. Li, X.-M. Li, N.-Y. Ji and B.-G. Wang, *J. Nat. Prod.*, 2008, **71**, 28-30.

4 (a) T. Shibata, R. Fujiwara and Y. Ueno, *Synlett*, 2005, 152-154; (b) X. Jiang, E. K. London, D.J. Morris, G. J. Clarkson and M. Wills, *Tetrahedron*, 2010, **66**, 9828-9834; (c) I. Čorić, J. H. Kim, T. Vlaar, M. Patil, W. Thiel and B. List, *Angew. Chem. Int. Ed.*, 2013, **52**, 3490-3493; (d) J. Kim, D.-H. Lee, N. Kalutharage and C. S. Yi, *ACS catal.* , 2014, **4**, 3881-3885; (e) M. Hellal, F. C. Falk, E. Wolf, M. Dryzhakov and J. Moran, *Org. Biomol. Chem.*, 2014, **12**, 5990-5994; (f) A. Bunrit, C. Dahlstrand, S. K. Olsson, P. Srifa, G. Huang, A. Orthaber, P. J. R. Sjöberg, S. Biswas, F. Himo and J. S. M. Samec, *J. Am. Chem. Soc.*, 2015, **137**, 4646-4649.

5 (a) H. Aikawa, S. Tago, K. Umetsu, N. Haginiwa and N. Asao, *Tetrahedron*, 2009, **65**, 1774-1784; (b) K. Yoshikawa, T. Nagata, T. Yoshino, Y. Nakamoto, N. Haginoya, R. Muto, A. Mochizuki, H. Kanno and T. Ohta, *Heterocycles*, 2012, **85**, 1711-1720; (c) B. D. Kelly and T. H. Lambert, *Org. Lett.*, 2011, **13**, 740-743; (d) P. H. Huy and A. M. P. Koskinen, *Org. Lett.*, 2013, **15**, 5178-5181.

6 F. Aricò, P. Tundo, A. Maranzana and G. Tonachini, *ChemSusChem*, 2012, **5**, 1578-1586.

7 S. Asai, M. Kato, Y. Monguchi, H. Sajiki and Y. Sawama, *ChemistrySelect*, 2017, **2**, 876-878.

8 (a) K. Watanabe, N. Yamagiwa and Y. Torisawa, *Org. Process Res.*, 2007, **11**, 251-258; b) Y. Monguchi, K. Kitamoto, T. Ikawa, T. Maegawa and H. Sajiki, *Adv. Synth. Catal.*, 2008, **350**, 2767-2777; (c) K. Watanabe, N. Kogoshi, H. Miki and Y. Torisawa, *Synth. Commun.*, 2009, **39**, 2008-2013; d) V. Antonucci, J. Coleman, J. B. Ferry, N. Johnson, M. Mathe, J. P. Scott and J. Xu, *Org. Process Res.*, 2011, **15**, 939-941; e) S. Kobayashi, H. Kuroda, Y. Ohtsuka, T. Kashihara, A. Masuyama and K. Watanabe, *Tetrahedron*, 2013, **69**, 2251-2259; f) K. Watanabe, *Molecules*, 2013, **18**, 3183-3194.

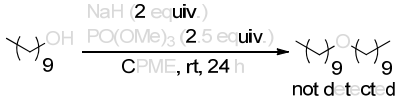
9 (a) X. Xu, F. Song, S. Wang, S. Li, F. Xiao, J. Zhao, Y. Yang, S. Shang, L. Yang and J. Shi, *J. Nat. Prod.*, 2004, **67**, 1661-1666; (b) M. Otomo, K. Takahashi, H. Miyoshi, K. Osada, H. Nakashima and N. Yamaguchi, *Biol. Pharm. Bull.*, 2008, **31**, 1489-1495; (c) R. Khan, A. Malik, M. I. Qadir, A. Adhikari and M. I. Choudhary, *Chem. Nat. Compd.*, 2010, **46**, 722-725.

10 (a) J. D. Harden, J. V. Ruppel, G.-Y. Gao and X. P. Zhang, *Chem. Commun.*, 2007, 4644-4646; (b) X. Guo, S. Pan, J. Liu and Z. Li, *J. Org. Chem.*, 2009, **74**, 8848-8851; (c) M. V. Pham and N. Cramer, *Angew. Chem. Int. Ed.*, 2014, **53**, 3484-3487; (d) S. Asai, Y. Yabe, R. Goto, S. Nagata, Y. Monguchi, Y. Kita, H. Sajiki and Y. Sawama, *Chem. Pharm. Bull.*, 2015, **63**, 757-761; (e) N. M. Weldy, A. G. Schafer, C. P. Owens, C. J. Herting, A. Varela-Alvarez, S. Chen, Z. Niemeyer, D. G. Musaev, M. S. Sigman, H. M. L. Davies and S. B. Blakey, *Chem. Sci.*, 2016, **7**, 3142-3146; (f) W. Yuan and K. J. Szabó, *ACS Catal.*, 2016, **6**, 6687-6691.

11 The reaction of **1n** and **1o** resulted in low yields. A small amount of starting material remained unchanged, and phosphorylated reaction intermediates were probably formed.

12 The cyclization of **1n** or **1o** at 80 °C gave 53% of **2n** or 35% of **2o**. The elebvated reaction temperature slightly improved the yields, but they are unsatisfactory.

13 The reaction of 1-decanol in the presence of $PO(OMe)_3$ and NaH never produced didecyl ether as a symmetric ether formed by the intermolecular coupling.



14 Compounds **3**, **4** and **5** could be alternatively prepared using $POCl(OMe)_2$. See Supporting Information.

15 The use of NaH in the absence of MeOH also gave **2a** in low yields (10-14%). The contaminated H_2O probably facilitates the conversion of **4** and **5** into **3'** derivative as shown in Scheme 2.