REACTION OF DIOLS AND TRIOLS WITH TRIALKYL ORTHOESTERS: FACILE ONE-POT FORMATION OF OXACYCLIC COMPOUNDS FROM TRIOLS†

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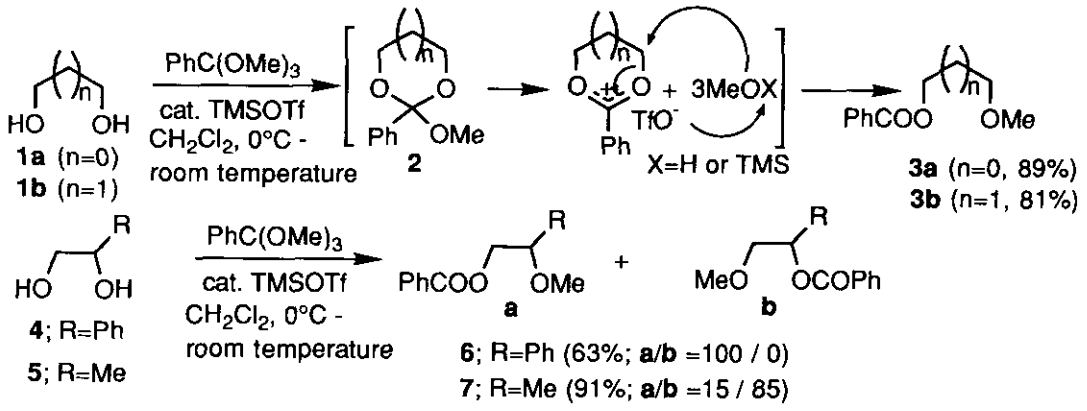
Abstract-Reaction of diols and triols with trialkyl orthoesters was studied and facile one-pot formation of oxacyclic compounds from triols was developed.

Substituted oxacyclic molecules, such as tetrahydrofurans and tetrahydropyrans, are found widely in polyether antibiotics[1] and marine *Laurencia metabolites*.[2] Although many methods have been devised for constructing them so far,[3] a new strategy is still strongly desirable. We present here a facile one-pot formation of substituted oxacyclic molecules by reaction of triols and trialkyl orthoesters.

Orthoesters are versatile agents and work as superior electrophiles by forming dioxenium cations.[4] 1,3-Dioxolan-2-ylium ions formed by treatment of 2-alkoxy-1,3-dioxolane type orthoesters react with nucleophiles at the 2 or 4 position, depending on the nature of the nucleophiles, and also when the 2-substituted 2-alkoxy-1,3-dioxolanes were treated with a catalytic amount of BF_3 to give the corresponding 1-acyloxy-2-alkoxyethanes.[5] These results suggest that direct conversion of diols to the corresponding alkoxyalkyl esters is possible in one-pot operation. In fact, the reactions of ethylene glycol (**1a**) and propanediol (**1b**) with trimethyl orthobenzoate [$PhC(OMe)_3$] in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) proceeded to give the

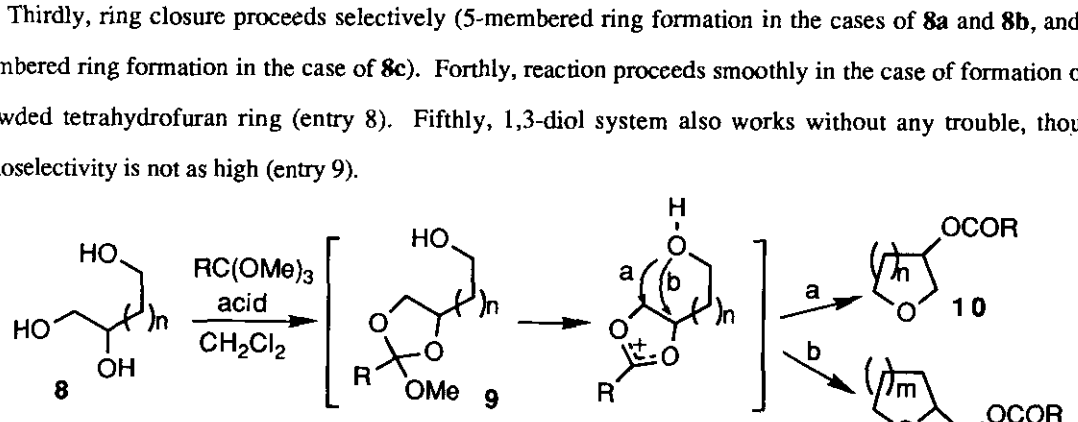
†This paper is dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

corresponding methoxyalkyl benzoates (**3a**) and (**3b**), respectively, *via* cyclic orthoester (**2**) then dioxenium cation. A similar reaction was also observed in cases of compounds (**4**) and (**5**): the ratios of the products (a / b) were determined by ^{1}H-nmr spectroscopy (Scheme 1).



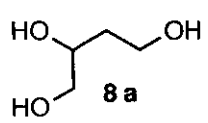
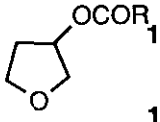
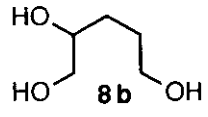
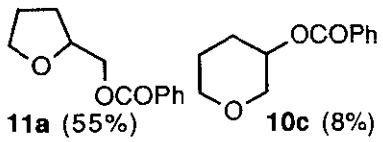
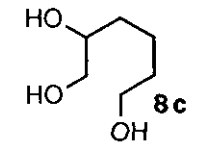
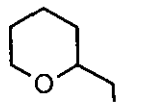
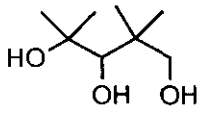
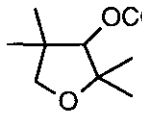
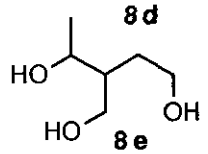
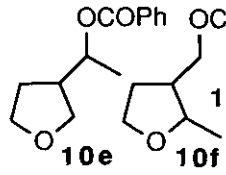
Scheme 1

From these results, one can easily imagine that the triols (**8**), with a suitably positioned hydroxy group, give the cyclic ethers *via* dioxenium cation intermediates from cyclic orthoesters (**9**) as depicted in Scheme 2. Reactions of triols (**8**) and 1.1 equivalent of trialkyl orthoesters in the presence of a catalytic amount of acid in CH_2Cl_2 were carried out to obtain the oxacyclic compounds (**10**) or (**11**). The results are summarized in the Table. Several aspects are noteworthy. First, TMSOTf is a superior choice as an acid (runs 1 and 5 *vs* runs 2 and 6). Secondly, $PhC(OMe)_3$ gave better results than trimethyl ortho acetate [$MeC(OMe)_3$] (runs 1 and 5 *vs* runs 3 and 7). Thirdly, ring closure proceeds selectively (5-membered ring formation in the cases of **8a** and **8b**, and 6-membered ring formation in the case of **8c**). Forthly, reaction proceeds smoothly in the case of formation of a crowded tetrahydrofuran ring (entry 8). Fifthly, 1,3-diol system also works without any trouble, though regioselectivity is not as high (entry 9).



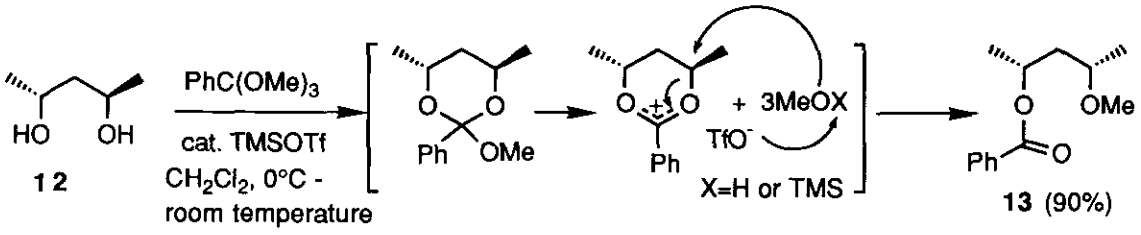
Scheme 2

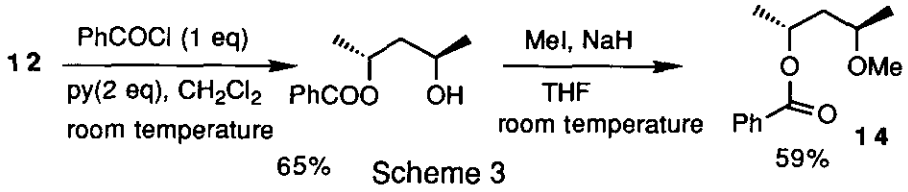
Table. Reaction of Triols with Trimethyl orthoesters in the Presence of Acid

Run	Triols	Reaction Conditions	Products (Yields) a)
1	 **8a**	$PhC(OMe)_3$, cat. TMSOTf, 0°C,2 h	 **10a**; R=Ph (99%)
2		$PhC(OMe)_3$, cat. p-TsOH, 0°C,2 h	**10a** (95%)
3		$MeC(OMe)_3$, cat. TMSOTf, 0°C,2 h	**10b**; R=Me (44%)
4	 **8b**	$PhC(OMe)_3$, cat. TMSOTf, 0°C,2 h	 **11a** (55%) **10c** (8%)
5	 **8c**	$PhC(OMe)_3$, cat. TMSOTf, 0°C,2 h	 **11b**; R=Ph (89%)
6		$PhC(OMe)_3$, cat. p-TsOH, 0°C,3 h	**11b** (68%)
7		$MeC(OMe)_3$, cat. TMSOTf, 0°C,2 h	OCOR **11c**; R=Me (57%)
8	 ***8d***	$PhC(OMe)_3$, cat. TMSOTf, 0°C,0.5 h	 **10d** (84%)
9	 **8e**	$PhC(OMe)_3$, cat. TMSOTf, 0°C,2 h	 **10e/10f**=1/2 b) (94%) c) **10e** **10f**

a) Yields are not optimized. b) The ratio was determined by ^{1}H-nmr spectroscopy.
c) Total yield of **10e** and **10f**.

The reaction using chiral diol and orthoester was found to give an inversion product. Thus, reaction of (-)-(2*R*,4*R*)-2,4-pentanediol (**12**) with $PhC(OMe)_3$ in the presence of a catalytic amount of TMSOTf provided (-)-(2*R*,4*S*)-2-benzoyloxy-4-methoxypentane (**13**) in excellent yield. The stereochemistry of **13** and complete inversion by SN2 attack of MeO^- at the 4-position of dioxenium cation intermediate were ascertained by comparison with (-)-(2*R*,4*R*)-2-benzoyloxy-4-methoxypentane (**14**), which was prepared by monobenzoylation and successive methylation of **12**[6] (Scheme 3).





Scheme 3

In conclusion, we found that direct formation of methoxyalkyl esters and oxacyclic compounds was caused by reaction of several diols and triols with trimethyl orthoesters. Although the synthetic methodology of substituted tetrahydrofurans *via* the cyclic dioxenium cations formed by oxidation of benzylidene acetals with a suitable positioned hydroxyl group has been reported,[7] our methodology can give the cyclic ether compounds from the unprotected triols in one-pot operation and has a great advantage in a practical point of view.

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4. For recent review, see: U. Pindur, J. Muller, C. Flo, and H. Witzel., *Chem. Soc. Rev.*, 1987, **16**, 75 and references cited therein.

5. H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Liebigs Ann. Chem.*, 1960, **632**, 38.

6. Spectroscopic data of **13**: $[\alpha]_D$ -35° (*c*=3.0, $CHCl_3$). ^{1}H-Nmr (200M Hz, $CDCl_3$) δ : 1.19 (3H, d, *J*=6.2 Hz), 1.38 (3H, d, *J*=6.4 Hz), 1.6-1.7 (1H, m), 2.9-2.1 (1H, m), 3.30 (3H, s), 3.4-3.5 (1H, m), 5.2-5.4 (1H, m), 7.4-7.6 (3H, m), 8.0-8.1 (2H, m). Spectroscopic data of **14**: $[\alpha]_D$ -80° (*c*=0.8, $CHCl_3$). ^{1}H-Nmr (200M Hz, $CDCl_3$) δ : 1.17 (3H, d, *J*=6.0 Hz), 1.36 (3H, d, *J*=6.4 Hz), 1.7-1.9 (2H, m), 3.28 (3H, s), 3.3-3.5 (1H, m), 5.3-5.5 (1H, m), 7.3-7.6 (3H, m), 7.9-8.1 (2H, m).

   Compounds (**13**) and (**14**) are easily distinguishable to each other by ^{1}H-nmr spectra, since the signals of methylene groups of them appear in completely different regions.

7. D. R. Williams, Y. Harigaya, J. L. Moore, and A. D'sa, *J. Am. Chem. Soc.*, 1984, **106**, 2641.

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