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A MILD AND GENERAL SYNTHESIS OF MIXED ORTHOESTERS

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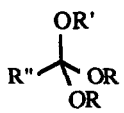
Summary: Mixed orthoesters which contain two structurally simple and one complex alkoxy group may be synthesized in high yield and purity by an exchange process catalyzed by magnesium chloride. The reaction is procedurally straightforward, general and provides crude products requiring minimal or no subsequent purification.

Our studies in cation-olefin cyclization chemistry recently required the preparation of mixed orthoesters of general structure I wherein the group R is some simple disposable entity such as ethyl or methyl and the group R' is structurally more complex, usually containing unsaturation or other functionality. Mixed orthoester syntheses



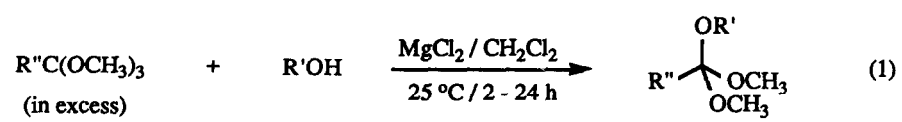
R = ethyl or methyl

R' = functionalized unit

I

are relatively rare and no general methods exist to our knowledge.[1,2] We desired a method which would be mild enough such that cyclization to tetrahydropyran derivatives[3] (with unsaturated substrates) or elimination reactions would not occur. In addition, we wanted to obviate the need for further purification of the crude product since orthoesters are easily hydrolyzed and are known to undergo eliminations to vinyl ethers when heated or distilled in the presence of traces of acid. In essence, an absolutely clean conversion was sought.

Acid-catalyzed transesterification of simple orthoesters with an excess of a less volatile alcohol is a well-known method for synthesizing "higher" orthoesters with three identical alkoxy groups.[1] It was found that the desired mono-exchange product could be obtained by transorthoesterification if the starting orthoester was used in excess and the exchange mediated by $MgCl_2$ (eqn. 1). The mixed orthoesters (I) were obtained uncontaminated with byproducts of further exchange, hydrolysis or elimination. The use of other salts of magnesium ($Mg(OTf)_2$,



(1)

R" = H, methyl

I

$MgBr_2$ or MgI_2) led to tetrahydropyran formation with unsaturated alcohols. Not unexpectedly, the use of near stoichiometric quantities of starting materials in this process provided mixtures of products derived from mono-, bis- and tris-exchange.

The results shown in Table I illustrate the generality of the reaction. Primary and secondary alcohols undergo the exchange readily, although tertiary alcohols are somewhat sluggish (entry 8). Yields are generally high and no products other than the one desired can be observed spectroscopically. Note also that substrates like 3-methyl-3-buten-1-ol (entry 3) do not undergo cyclization to tetrahydropyran derivatives as we have observed when other Lewis acids are used.[3]

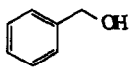
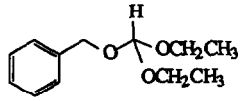
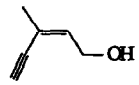
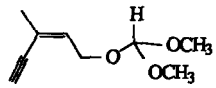
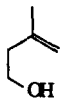
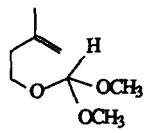
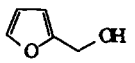
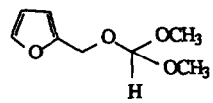
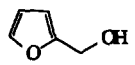
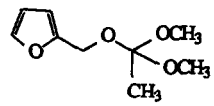
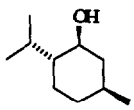
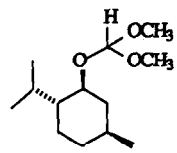
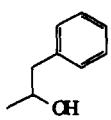
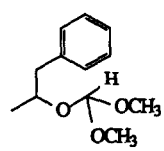
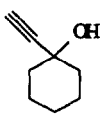
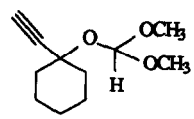
This is clearly an acid-catalyzed equilibrium exchange process in which production of the desired mono-exchange product can be favored by using a large excess of an inexpensive, readily removable reactant. The utility of the method lies in its ability to generate a mixed orthoester cleanly such that subsequent purification is unnecessary. This is essential since one generally wishes to manipulate an orthoester as little as possible due to their relative chemical instability.

Some further comments regarding practical points are in order. We have found that the reaction can be carried out on a moderate scale (producing up to at least 5 grams of mixed orthoester) with very little effect on yield. The orthoesters are stable for several weeks when stored in a closed container and kept at -25 °C. They undergo rapid (< 5 minutes) equilibration to several orthoester exchange products when dissolved in chloroform containing traces of HCl. The mixed orthoesters are unstable to chromatography on silica (hexane elution) using flash column or HPLC techniques. However, bulb-to-bulb distillation under vacuum at less than 150 °C is not accompanied by significant decomposition. At this point we are not ready to recommend the orthoester functionality as a general protecting group[4] for alcohols, despite the facility of this exchange process. Orthoesters are simply too sensitive to Lewis acidic reagents[5] to be satisfactory in this regard. In certain undemanding scenarios, however, their use might be advantageous.

A representative procedure is as follows: a flame-dried round bottom flask under a nitrogen atmosphere is charged with the orthoester (10-30 equiv) and dichloromethane (*ca.* 3 mL/mmol of alcohol, dried over CaH_2). Anhydrous magnesium chloride (0.25 equiv) is added as a solid followed 10 minutes later by the alcohol (1.0 equiv). The reaction is allowed to stir at room temperature until thin-layer chromatography indicates consumption of the starting alcohol. Occasionally the starting material will not show complete disappearance by TLC. This may be due to partial hydrolysis on silica TLC plates. The reaction is quenched by dilution with aqueous 10% NaOH solution. The aqueous layer is extracted 2-3 times with fresh dichloromethane and the extracts are combined with the original CH_2Cl_2 layer. The combined CH_2Cl_2 solution is washed with brine, dried (Na_2SO_4) and evaporated to give the crude product, usually a colorless liquid. NMR analysis (C_6D_6) normally indicated a product greater than 95% pure with no traces (by TLC, ^1H or ^{13}C NMR) of multiple exchange products or esters derived by hydrolysis of the orthoester.[6]

Acknowledgments Acknowledgment is made to the donors of the Petroleum Research Fund of the American Chemical Society for partial support of this work. We also acknowledge the support of the American Cancer Society, the National Institutes of Health (Biomedical Research Support Grant) and the Wayne State University Research Committee. F. P. thanks the Toyota Corporation for a graduate Fellowship.

Table I. Results of Mono-Orthoesterification of Alcohols

Entry	Alcohol	Orthoester (no. of equiv.)	Product (% Yield)	Reaction Conditions
1		$HC(OCH_2CH_3)_3$ (20)	 (94)	2 h / 25°C
2		$HC(OCH_3)_3$ (20)	 (96)	2 h / 25°C
3		$HC(OCH_3)_3$ (20)	 (87)	2 h / 25°C
4		$HC(OCH_3)_3$ (20)	 (82)	2 h / 25°C
5		$CH_3C(OCH_3)_3$ (20)	 (65)	4 h / 25°C
6		$HC(OCH_3)_3$ (30)	 (88)	12 h / 25°C
7		$HC(OCH_3)_3$ (20)	 (89)	12 h / 25°C
8		$HC(OCH_3)_3$ (40)	 (56)[b]	36 h / 25°C

[a] All compounds exhibited satisfactory ^1H and ^{13}C NMR, IR and mass spectral data.
[b] Contaminated with ca. 28% starting alcohol (estimated by proton NMR).

References

1) For two leading reviews on the preparation of orthoesters, see DeWolfe, R. H. *Synthesis* **1974**, 153 and DeWolfe, R. H. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970.

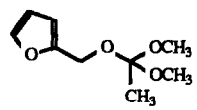
2) The Pinner reaction is a well-known classical method for forming symmetrical orthoesters. There are two reports of mixed orthoester synthesis using this method (Pinner, A. *Chem Ber.* **1883**, *16*, 1643 and Sah, P. P. T. *J. Chinese Chem. Soc.* **1933**, *1*, 100; *Chem. Abstr.* **1933**, *27*, 5729.

3) Perron, F., Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128.

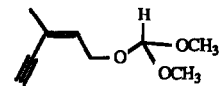
4) Cyclic orthoesters of diols are well known and have been utilized somewhat successfully as protecting groups. See Greene, T. "Protecting Groups in Organic Synthesis"; Wiley Interscience: New York, 1981; pp 82-86.

5) Orthoesters react readily with Grignard reagents and many other organometallics to provide acetals. See Bachman, G. B. *Org. Synth., Coll. Vol. II*, **1943**, 323; Dornfeld, C. A.; Coleman, G. H. *Org. Synth., Coll. Vol. III*, **1955**, 710 and references cited therein.

6) Spectral data on typical mixed orthoesters:



i



ii

i) Colorless liquid - ^{1}H NMR (300 MHz, C_6D_6) δ 7.05 (br s, 1H), 6.07 (d, J = 3 Hz, 1H), 6.01 (br s, 1H), 4.46 (s, 2H), 3.09 (s, 6H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 152.5, 142.1, 114.6, 110.1, 108.3, 56.3, 49.4, 18.9; IR (neat, cm^{-1}) 3149, 3119, 3003, 2949, 2838, 1728 (w), 1609 (w), 1503, 1469, 1436, 1383, 1150 (br), 1050 (br), 925, 892, 812, 739; low resolution electron impact m.s. - (M^+ not observed); major fragments at m/e 112, 97, 89, 81, 53.

ii) Colorless liquid - ^{1}H NMR (300 MHz, C_6D_6) δ 5.76 (br t, J = 6 Hz, 1H), 4.93 (s, 1H), 4.35 (d, J = 6 Hz, 2H), 3.10 (s, 6H), 2.78 (s, 1H), 1.60 (br s, 3H) ; ^{13}C NMR (75 MHz, C_6D_6) δ 135.1, 119.7, 113.6, 82.3, 81.5, 62.6, 50.5, 22.4 ; IR (neat, cm^{-1}) 3289, 2950, 2887, 2840, 2096, 1638, 1449, 1379, 1350, 1 322, 1276, 1221, 1196, 1106 (br), 990, 927, 911, 841, 646; low resolution electron impact m.s. - (M^+ not observed); major fragments at m/e 110, 95, 79, 75.

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