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Lewis Acid Mediated Regioselective Ring Opening of Benzylglycidol with Dibenzyl Phosphate: Short and Attractive Synthesis of Dihydroxyacetone Phosphate

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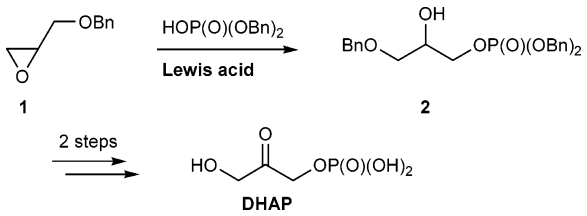
ABSTRACT



A novel, mild, and efficient method was described to introduce a dibenzyl phosphate by ring opening of benzylglycidol mediated by Lewis acids. This methodology was used as a key step for synthesizing the dihydroxyacetone phosphate (DHAP) in only three steps with an overall yield of 74% from the commercially available racemic benzylglycidol.

Epoxides in general, due to their ease of preparation and ready reactivity toward a large variety of reagents such as electrophiles, nucleophiles, acids, bases, reducing agents, and some oxidizing agents, are important starting materials and intermediates in organic synthesis.[1] High reactivity with various nucleophiles leads to high regioselective and trans-stereospecific ring opening products. Therefore, this facile ring opening of epoxides makes them extremely versatile intermediates for organic synthesis. In the course of our investigation of improving the synthesis of dihydroxyacetone phosphate (DHAP), the donor substrate of the aldolases,[2] we were interested in the nucleophilic ring-opening of glycidol derivatives, which possessed widespread synthetic utility as chiral building blocks[3] with a dibenzyl phosphate derivative.

Despite the rich literature on the chemistry of epoxide opening,[1] to the best of our knowledge there are few reports concerning ring-opening of epoxide with phosphate allowing the formation of useful phosphorylated synthons for the synthesis of compounds of biological interest. This methodology was first applied to the synthesis of propanediol phosphate by heating under pressure for 12 h an aqueous K_2HPO_4 solution with propylene oxide.[4] The regioselective opening of epoxide with inorganic phosphate was also used for the preparation of D-glyceraldehyde 3-phosphate[5] and (*2S*)-4,4-diethoxy-2-hydroxybutyl phosphate, an intermediate involved in the synthesis of carbohydrates[6] and used to

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improve the arabinonucleotide synthesis.[7] Recently, this methodology was applied to the chemoenzymatic synthesis of DHAP. The glycidol ring opening with Na_2HPO_4 generated D,L-glycerol 3-phosphate, and DHAP was obtained in 28% overall yield by enzymatic oxidation of L-glycerol 3-phosphate.[8]

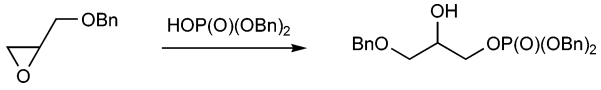
All of of these reactions have been performed in aqueous solution, limiting the application of this procedure in organic synthesis. However, protected phosphates such as dibenzyl or diethyl phosphate have also been used to open polycyclic aromatic hydrocarbon epoxides as a model for the reaction of the carcinogenic epoxy diols derived from benzopyrene diol with nucleic acids.[9] In all cases, the phosphotriesters were formed in benzene or THF with yields around 80% by regiospecific and by stereospecific opening of the epoxide with the phosphate reacting at the benzylic position in an SN_2 mechanism.[9a] A one-pot synthesis using phosphoric acid diesters in the epoxide opening of 1,2-anhydrosugars was investigated for the convenient synthesis of glycosyl phosphates, powerful glycosylating agents.[10]

Phosphorylated dibenzyl conduritol-B derivatives, ideal intermediates for the synthesis of *myo*-inositol phosphates which play key functions in biological systems as free compounds or as part of more complex structures, were also prepared by a double allylic epoxide opening of diepoxycyclohexene with dibenzyl phosphate in dichloromethane with a yield of 55%.[11]

In these examples, the epoxide ring opening occurred either by using inorganic phosphate, or by opening alicyclic epoxide with partially protected phosphates in organic solvents. These features limit the synthetic utility of this reaction.

To optimize our synthesis of DHAP,[12] we investigated the nucleophilic ring opening of the commercially available racemic benzylglycidol **1** with dibenzyl phosphate to prepare the precursor of DHAP **2** (Scheme 1).

Scheme 1. Ring Opening of Benzylglycidol with Dibenzyl phosphate



1 **2**

After oxidation of the secondary alcohol and removal of all protecting groups, DHAP was obtained in three steps.

The ring opening of **1** was first attempted with dibenzyl phosphate in benzene[9] or dichoromethane[11] at room temperature and afforded the desired product **2** in moderate to low yields (Table 1, entries 1 and 4) with the formation of byproducts resulting from the degradation of the starting material.

Table 1. Ring Opening of the Epoxide **1** with Dibenzyl Phosphate in Various Solvents at Room Temperature

entry	solvent	time (h)	yield (%)
1	benzene	96	13
2	toluene	48	20
3	THF	120	9
4	CH_2Cl_2	36	33

These results compared to those described in the literature are probably due to the thermodynamically less favored ring opening of benzylglycidol compared to the strained oxirane ring in the fused systems described in the literature.[9,11] The yield of the reaction was not significantly affected by changing the solvent (toluene, THF) (Table 1, entries 2 and 3), and accordingly, the reactions were performed in dichloromethane.

In all cases, the ring opening reaction appeared to be regiospecific, and the nucleophilic attack occurring at the C-3 position of the benzylepoxide was observed.

To improve the yield of the reaction, we chose to increase the phosphate nucleophilicity by forming in situ the anion of the dibenzyl phosphate with different bases such as NaH, NEt_3, collidine, Na_2CO_3, and Cs_2CO_3 in different solvents such as toluene, THF, and diethyl ether. Under these conditions no reaction occurred, and the starting products were recovered.

To circumvent these problems, we then turned our attention to the use of Lewis acids which have been found to be effective mediators of regio- and stereoselective epoxide openings. Indeed, high regioselectivity (attack at C-3 vs C-2) ring opening of 2,3-epoxy alcohols by nucleophiles has been observed with a catalytic amount of BF_3/Et_2O[13] or CuI[14] and with a stoichiometric amount of $Ti(O\text{-}i\text{-}Pr)_4$.[15] These last results were rationalized by invoking the coordination of the epoxy alcohol to the titanium metal center in the rigid, bidentate manner.[15]

However, when we first examined the ring opening of benzylglycidol **1** in CH_2Cl_2 with 2 equiv of dibenzyl

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phosphate in the presence of 1.5 equiv of Ti(O- *i*-Pr)$_4$, no reaction occurred and the starting materials were recovered (Table 2, entry 1).

Table 2. Ring Opening of the Epoxide **1** with Dibenzyl Phosphate and Titanium(IV) at Room Temperature in CH_2Cl_2

entry	Ti(O-*i*-Pr)$_4$ (equiv)	time (h)	yield (%)
1	1.5	24	0
2	1	17	0
3	0.5	17	16
4	0.25	24	34
5	0.1	17	41
6	0.05	17	52

In contrast, lowering the amount of Ti(O-*i*-Pr)$_4$ from 1.5 to 0.05 equiv resulted in the sole formation of the regioisomer **2** by a C-3 nucleophilic attack in low to moderate yields (Table 2). The best result was obtained by using a catalytic amount of Ti(O-*i*-Pr)$_4$ (Table 2, entry 6) due probably to concurrent chelation of both epoxide and phosphate to the titanium complex. When stoichiometric or an excess amount of titanium(IV) was used, the phosphate should have been completely chelated and thus deactivated.

To improve the ring opening yield, the reaction was tested with a large panel of Lewis acids in a typical procedure.[16] The results are reported in Table 3.

Table 3. Ring Opening of Epoxide **1** with Dibenzyl Phosphate and Various Lewis Acids (1 equiv) in CH_2Cl_2

entry	Lewis acid	*T* (°C)	time (h)	yield (%)	*T* (°C)	time (h)	yield (%)
1	$ZnOTf_2$	rt	15	12	reflux	15	13
2	CsF	rt	24	29	reflux	20	62
3	BF_3/Et_2O	rt	18	31	reflux	3	17
4	Ag_2SO_4	rt	5	32	reflux	3	81
5	$AgBH_4$	rt	4	37	reflux	2	48
6	$AgPF_6$	rt	4	66	reflux	3	52
7	$SnSO_4$	rt	30	65	reflux	16	48
8	$CuOTf_2$	rt	18	18	reflux	17	28
9	$CuSO_4$	rt	24	69	reflux	17	36
10	CuI	rt	24	90	reflux	2.5	22

At room temperature, zinc triflate, cesium fluoride, and BF_3 etherate afforded the opening product **2** in moderate yields (12, 29, and 31%, respectively) (Table 3, entries 1, 2, and 3) accompanied with several byproducts. The use of Ag(I) salts (Ag_2SO_4, $AgBF_4$, and $AgPF_6$) generated the desired product in 31−66% yields (Table 3, entries 4, 5, and 6). Although the isolated yield in epoxide opening reaction with dibenzyl phosphate catalyzed by $AgPF_6$ and $SnSO_4$ was comparable, the reaction was slower with the latter catalyst (Table 3, entry 7).

(16) See the Supporting Information.

When the ring opening was carried out with copper(II) sulfate and triflate, the phosphate **2** was obtained in, respectively, 18 and 69% yield. It is worth noting that the use of LiBr and $ZnCl_2$ as Lewis acids gave a complete formation of the halohydrins,[17] which is due to the ability of halides to open epoxides. Interestingly, the presence of CuI as activator gave the best result, and **2** was isolated in 90% yield (Table 3, entry 10).

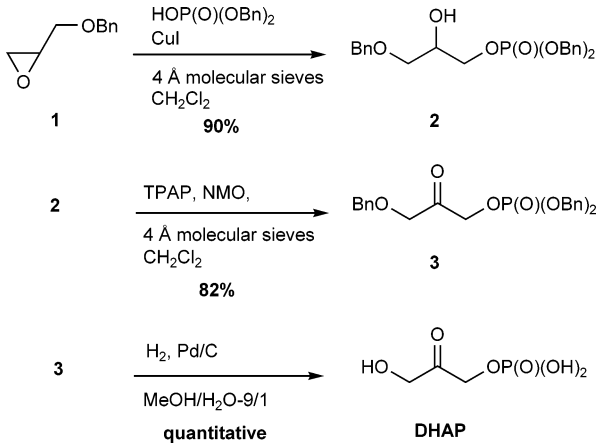
By refluxing the benzylglycidol **1** in dichloromethane in the presence of Lewis acids, the ring opening yield was not significantly affected except for CsF and Ag_2SO_4 showing an increase in the amount of **2** (Table 3, entries 2 and 4). In contrast, with $CuSO_4$ and CuI the yield of the opening dropped (Table 3, entries 9 and 10) with the formation of several byproducts. It is worth noting that all tested Lewis acids are insoluble in dichloromethane excepted for BF_3 etherate and $AgPF_6$. The reaction probably takes place at the liquid−solid interface, i.e., in heterogeneous conditions.

In all reported examples, the oxirane ring opening reaction with dibenzyl phosphate appeared to be regiospecific. Only nucleophilic attack at the C-3 position of the benzylglycidol **1** was observed. This effect is probably due to the intervention of bidentate-chelated structure in which the metal cation is coordinated simultaneously to the oxirane and to the alkoxide oxygens. Moreover, it should be noted that at room temperature the counteranions of the Ag(I) and Cu(II) salts affected the efficiency of the ring opening (Table 3, entries 4, 5, 6 and 8, 9) and did play a significant role in the ring opening epoxy alcohol.

This regioselective ring opening of epoxides by the dibenzyl phosphate mediated by CuI was applied to the synthesis of dihydroxyacetone phosphate (DHAP).

The ring opening of the commercially available benzylglycidol **1** by dibenzyl phosphate at room temperature in dichloromethane with stoechiometric CuI as Lewis acid led in 24 h to the phosphate **2** with a 90% yield (Scheme 2).

Scheme 2. Synthesis of DHAP



The mild oxidation of the secondary alcohol **2** with TPAP/NMO[18] gave rapidly after silica gel chromatography the precursor **3** a stock material of DHAP with a yield of 82%.

Finally, the last step was the deprotection of all of the benzyl groups. This was realized at atmospheric pressure in methanol/water (9/1) with palladium over charcoal (11%). After 1 h, DHAP was obtained in quantitative yield without side products. This step required no purification. The catalyst was simply eliminated by filtration on Celite, and the filtrate was concentrated under vacuum. The residue was dissolved in water and the solution was neutralized by addition of 1M sodium hydroxide. DHAP thus prepared was readily available for coupled aldol reaction.[12]

In conclusion, we have discovered a novel, mild, and efficient method to introduce a dibenzyl phosphate by ring opening of benzylglycidol mediated by CuI. Moreover, this epoxide ring opening is reproducible with excellent yields. This methodology was used as a key step in the synthesis of DHAP and allowed its formation in only three steps with an over yield of 74% from the commercially available racemic benzylglycidol. The simple experimental conditions make this synthesis a reliable and attractive method to access to DHAP with the best yield published up to now.

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Supporting Information Available: Experimental procedure for the key step and characterization data for compounds **2**, **3**, and DHAP. This material is available free of charge via the Internet at http://pubs.acs.org.

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