General Synthesis of 2-, 3-, and 4-Hydroxyalkylphosphonium Salts by the Reaction of Triphenylphosphine with Cyclic Ethers in the Presence of Strong Acids

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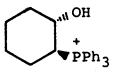
Synopsis. Cyclic ethers were efficiently converted to the corresponding hydroxyalkylphosphonium salts by the reaction with triphenylphosphine and trifluoromethanesulfonic or trifluoroacetic acid. The reaction of these salts with bases afforded the corresponding phosphonium inner salts which reacted with carbonyl compounds to give homoallylic alcohols.

2-Hydroxyalkylphosphonium salts (**1**) are an important class of compounds because of their use in the mechanistic investigation of the Wittig reaction and their versatile synthetic utility.[1] However, there are only a few reports regarding the synthesis of **1**.[2-4] While triphenylposphine (**2**) has been found to react with epoxides (**3**) to afford olefins via betaine intermediates,[5] there is, to our knowledge, no report on the synthesis of **1** from epoxides and triphenylphosphine. Recently, we reported the convenient synthesis of (hydroxyalkyl)dimethylsulfonium salts from cyclic ethers, acid, and dimethyl sulfide.[6] This result, in turn, prompted us to investigate the possibility of the synthesis of hydroxyalkylphosphonium salts. We report here a new general and convenient method for the preparation of **1**, 3- (**4**), and 4-hydroxyalkylphosphonium salts (**5**) by the reaction of **2** with **3**, oxetane (**6**), or tetrahydrofuran (**7**) in the presence of trifluoromethanesulfonic acid (**8a**) or trifluoroacetic acid (**8b**).

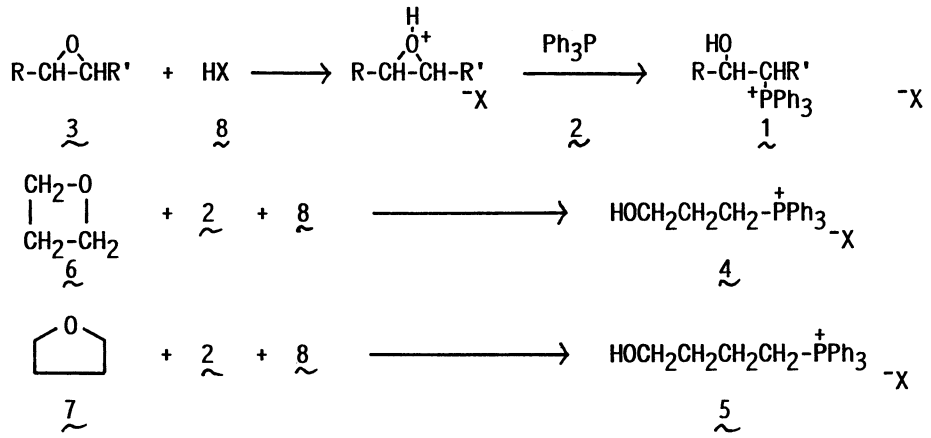
Results and Discussion

We first tried the reaction of epoxides with triphenylphosphine. Treatment of 1,2-epoxycyclohexane (**3a**) with **2** in the presence of **8a** afforded corresponding 2-hydroxycyclohexylphosphonium triflate (**1a**) in 65.0% yields. As shown in Table 1, phosphonium salts **1** were prepared in good yields. Previously, com-

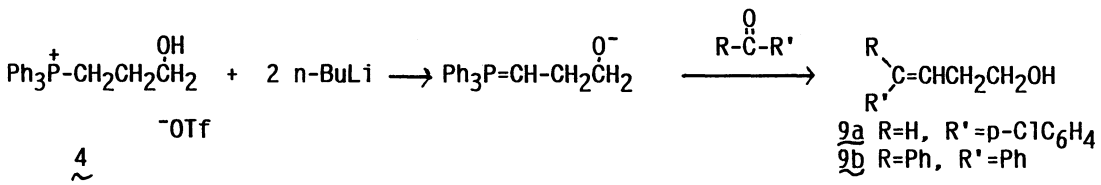
Table 1. Preparation of Hydroxyalkylphosphonium Salts

Cyclic ether	Acid		Phosphonium salt[a]	Anion	Yield/%	Mp/°C
1,2-Epoxycyclohexane	**8a**	**1a**		$^-$OTf	65.0	184—185
	8b	**1a′**		$^-$BPh$_4$	37.8[b]	219—220
2-Metyloxirane	**8a**	**1b**	$Ph_3\overset{+}{P}$-$CH_2CH(Me)OH$	$^-$BPh$_4$	78.0	172—173
	8b	**1b**			80.4	
2-Ethyloxirane	**8a**	**1c**	$Ph_3\overset{+}{P}$-$CH_2CH(Et)OH$	$^-$BPh$_4$	75.7	161—162
	8b	**1c**			69.5	
Oxetane	**8a**	**4**	$Ph_3\overset{+}{P}$-$CH_2CH_2CH_2OH$	$^-$BPh$_4$	90.0	178—179
	8b	**4′**		$^-$OCOCF$_3$	84.3	162—163
Tetrahydrofuran	**8a**	**5**	$Ph_3\overset{+}{P}$-$CH_2CH_2CH_2CH_2OH$	$^-$BPh$_4$	65.0	197—198

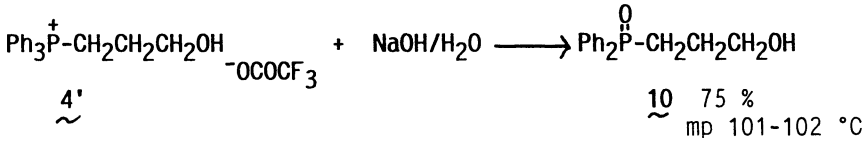
a) Since most of the products were oils, yields and elemental analyses were determined by their tetraphenylborates except **1a** and **4′**. When styrene oxide was used as epoxide, corresponding phosphonium salt could not be isolated. b) Triphenylphosphine was recovered in 34% yield



Scheme 1.



Scheme 2.



Scheme 3.

pounds **1** were obtained from the corresponding 2-hydroxyalkyl halides and triphenylphosphine,[2] by the reaction of the more nucleophilic 2,6-disubstituted triphenylphosphine with epoxides,[3] or by the reaction of phosphonium ylides with aldehydes followed by the addition of acids.[7] The reaction is stereospecific and regiospecific. The present method requires only one step and good yields were generally obtained.

Reactions of **2** with **3** have long been known to demand much more severe conditions. Products of these reactions in protic solvents are complex mixtures of triphenylphosphine oxide and alkenes formed directly from betaine or oxaphosphetane intermediates.[5] The present method will provide a much more precise mechanistic view of these reactions.

Corey and Yamamoto reported that the reaction of Wittig reagents with aldehydes gave the corresponding adducts at low temperature, which further reacted with a base to afford 2-phosphonio-1-alkanolates.[8] They also reported the reaction of phosphonium ylide anions with epoxides to give 3-phosphino-1-alkanolates.[9] Schlosser et al. and Maryanoff et al. also reported the stereoselective synthesis of alkenols from **1**.[10] The present method may be an alternative approach for the synthesis of the above alcohols. To confirm this possibility, we investigated the reaction of **4** with two equivalents of a base followed by the addition of carbonyl compounds. As expected, the corresponding homoallyl alcohols (**9a**, **b**) were obtained in good yields.

Recently, Warren and co-workers reported the stereoselective synthesis of homoallylic alcohols by the reactions of (hydroxyalkyl)diphenylphosphine oxide (**10**) with aldehydes.[11] So, we tried the preparation of **10** from **4**. As shown in Scheme 3, compound **10** was obtained in good yields.[12]

Within the current synthetic effort in organic chemistry, hydroxyalkylphosphonium salts play an important role in the total synthesis of many conventional natural products containing double bonds.[13] There is therefore a requirement for a simple preparative method for this key intermediate. This synthesis should afford many applications in olefin synthesis.

Experimental

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-90Q and a JEOL JNM-60 SI spectrometers with Me_4Si as the internal standard.

Synthesis of 1 and 4. General Procedure. To a solution of triphenylphosphine (**2**) (5 mmol) and a solution of corresponding acids (**8**) (5.2 mmol) in dichloromethane (10 mL) was added a solution of cyclic ether (**3**, **6**) (5.5 mmol) in dichloromethane (10 mL) at room temperature. After refluxing for 8 h, the reaction mixture was evaporated to give a pale yellow oil. The residue was washed with ether (20 mL) for several times to yield color less crystals. Recrystallization from dichloromethane-ether gave pure salts. **1a**: mp 184—185 °C. ^{1}H NMR ($CDCl_3$) δ=3.42 (1H, m, CH), 4.00 (1H, m, CH), 4,87 (1H, d, OH), 7.78 (15H, m, Ph). Calcd for $C_{25}H_{24}F_3O_4PS$: C, 59.05; H, 4.76%. Found: C, 59.05; H, 5.01%. **4'**: mp 162—163 °C. ^{1}H NMR ($CDCl_3$) δ=1.83 (2H, m, CH_2), 3.53 (2H, m, CH_2), 3.78 (2H, t, CH_2), 5.64 (1H, br, OH) 7.76 (15H, d, Ph). Calcd for $C_{23}H_{22}F_3O_3P$: C, 63.59; H, 5.10%. Found: C, 63.98; H, 4.80%.

Other salts were obtained as colorless oils. These compounds were converted to their tetraphenylborates for elemental analysis: To a solution of the resulting oil in acetone (5 mL) was added a solution of sodium tetraphenylborate (5.20 mmol) in acetone (5 mL). Colorless crystals of tertaphenylborates were precipitated by addition of ether (50 mL). Recrystallization from dichloromethane gave pure tetraphenylborate salts. **1a'**: mp 219—220 °C. ^{1}H NMR (DMSO-d_6) δ=3.52 (1H, m, CH), 4.76 (1H, m, CH), 5.12 (1H, br, OH), 7.66 (15H, m, Ph). Calcd for $C_{48}H_{46}BOP$: C, 84.70; H, 6.81%. Found: C, 84.90; H, 6.96%. **1b**: mp 172—173 °C. ^{1}H NMR (DMSO-d_6) δ=0.95 (3H, t, CH_3), 3.95 (3H, m, CH-CH_2), 4.70 (1H, d, OH), 7.73 (15H, m, Ph). Calcd for $C_{43}H_{42}BOP$: C, 84.37; H, 6.61%. Found: C, 84.74; H, 6.36%. **1c**: mp 161—162 °C. ^{1}H NMR (DMSO-d_6) δ=0.92 (3H, q, CH_3), 1.59 (2H, m, CH_2), 3.68 (3H, m, CH-CH_2), 5.32 (1H, br, OH), 7.72 (15H, m, Ph). Calcd for $C_{44}H_{44}BOP$: C, 84.40; H, 6.77%. Found: C, 84.78; H, 6.48%. **4**: mp 178—179 °C. ^{1}H NMR (DMSO-d_6) δ=1.64 (2H, m, CH_2), 3.51 (2H, t, CH_2), 3.72 (1H, br, OH), 7.72 (15H, m, Ph). Calcd for $C_{43}H_{42}BOP$: C, 84.37; H, 6.61%. Found: C, 84.26; H, 6.81%.

Synthesis of 5. To a solution of triphenylphosphine (**2**) (1.32 g, 5.03 mmol) in THF (10 mL) was added trifluoromethanesulfonic acid (**8a**) (0.787 g, 5.25 mmol) at room temperature. After refluxing for 8 h, reaction mixture was evaporated to give a pale yellow oil. A solution of sodium tetraphenylborate (1.80 g, 5.25 mmol) in acetone (5 mL) was added to a solution of this oil in acetone (5 mL). When ether (50 mL) was added to the mixture, colorless crystals were precipitated. Recrystallization from dichloromethane gave pure phosphonium salts (2.20 g, 65.0%). Mp 197—198 °C. ^{1}H NMR δ=1.59 (4H, m, CH_2-CH_2), 3.18 (2H, m, CH_2), 3.39

(2H, m, CH_2), 4.46 (1H, br, OH), 7.74 (15H, d, Ph). Calcd for $C_{46}H_{44}BOP$: C, 84.40; H, 6.77%. Found: C, 84.29; H, 6.87%.

Synthesis of 9. To a suspension of **4** (2.35 g, 5.00 mmol) in THF (15 mL) was added a solution of two equimolar amounts of butyllithium in THF (5 mL) at −78 °C. After stirring for 1 h, a solution of *p*-chlorobenzaldehyde (0.744 g, 5.29 mmol) or benzophenone (1.00 g, 5.47 mmol) in THF (10 mL) was added to the mixture at 0 °C. After stirring for 10 h at 30 °C, water (5 mL) was added to the mixture and the solvent was evaporated. Aq. NH_4Cl was added to neutralize the mixture. The aqueous mixture was extracted with dichloromethane (25 mL×2). The combined extracts were dried over $MgSO_4$ and evaporated to give a pale yellow oil. The resulting residue was extracted with hexane (20 mL×3). The combined extracts were evaporated to give a yellow oil. The corresponding homoallyl alcohol **9** was isolated from this oil by column chromatography on silica gel by elution with dichloromethane. **9a** was obtained as a mixture of *E*- and *Z*-isomers. Yield 74% (0.673 g). ^{1}H NMR ($CDCl_3$) δ=2.47 (2H, q, CH_2), 3.74 (2H, t, CH_2), 4.63 (1H, br, OH), 5.97—6.53 (2H, m, CH=CH), 7.25 (4H, s Ph). M^+_{found}=182.0497, $C_{11}H_{11}OCl$ (^{35}Cl) requires 182.0498. **9b**: Yield 56% (0.627 g). ^{1}H NMR ($CDCl_3$) δ=2.39 (2H, q, CH_2), 3.50 (2H, t, CH_2), 3.71 (1H, br, OH), 6.12 (1H, t, CH), 7.21 (10H, s, PH). M^+_{found}=224.1181, $C_{16}H_{16}O$ requires 224.1201.

Synthesis of 10. A suspension of **4'** (1.30 g, 3.00 mmol) in 30% aqueous NaOH (20 mL) was refluxed for 3 h. The reaction mixture was extracted with 20 mL of dichloromethane for three times. The combined extracts was dried over $MgSO_4$ and evaporated to give yellow oil. When the yellow oil was washed with ether (20 mL×3), the crystals were obtained. Recrystallization from ethyl acetate gave pure crystals (0.585 g, 2.25 mmol, 75%). Mp 101—102 °C. ^{1}H NMR ($CDCl_3$) δ=1.85 (2H, m, CH_2), 2.36 (2H, m, CH_2), 3.68 (2H, q, CH_2), 4.38 (1H, t, OH), 7.48 (10H, m, Ph). Calcd for $C_{15}H_{17}O_2P$: C, 69.22; H, 6.58%. Found: C, 69.14; H, 7.07%.

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