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## Novel Reaction of Methylenetriphenylphosphorane with Epichlorohydrin Leading to Alkylidenecyclobutanols

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Abstract: The reaction of methylenetriphenylphosphorane with epichlorohydrin followed by the addition of butyllithium and aldehydes in toluene afforded unusual four-membered cyclic alkylidenecyclobutanols.

Wittig reagents (1) form an important class of compounds because of their versatile synthetic utility.<sup>1</sup> Much attention has been recently paid to the synthesis of allylic and homoallylic alcohols.<sup>2</sup> We have also prepared optically active homoallylic alcohols from 1.<sup>3</sup> Alkylidenecyclopropylcarbinols (2) were prepared by the reaction of methylenetriphenylphosphorane (1a) with epichlorohydrin followed by the addition of aldehydes.<sup>4</sup> Recently, we have also reported the synthesis of enantiomerically pure methylenecyclopropylcarbinol from methylenetriphenylphosphorane and optically active epichlorohydrin.<sup>5</sup> Exoalkyldene cyclobutanes and substituted cyclobutanols are important class of compounds for their synthetic and structural point of view.<sup>6</sup> Recently, many reports on the synthesis concerning to these compounds are appeared.<sup>7</sup> However, there is no report on the direct synthesis of alkylidenecyclobutanols (3) from 1. We report herein a novel one-pot synthesis of 3 which utilizes a totally different strategy from that applied to the Wittig synthesis of alkylidenecyclopropylcarbinols.

Treatment of 1a derived from methyltriphenylphosphonium iodide and butyllithium with epichlorohydrin followed by the addition of butyllithium and benzaldehyde at -40 °C resulted in the formation of the corresponding benzylidenecyclobutanol (3a) in 62 % yield. Other reactions were shown in Table 1.



Scheme 1.

Generally, good yields were obtained by the use of aromatic aldehydes as starting aldehydes (Entry 1, 2). When aldehydes were used as substrates, the yields were better than that of cyclohexanone (Entry 5).

En	try RR'C=O	Conditions Base Temp./°C		Solvent	Time/hr	Product (Yield/%) 9 3		
1	Benzaldehyde	BuLi	-40	toluene	1	3a	62	
2	4-Chlorobenzaldehyde	BuLi	-40	toluene	1	3b	70	
3	Propionaldehyde	BuLi	-40	toluene	1	3 c	58	
4	Hexanal	BuLi	40	toluene	1	3d	55	
5	Cyclohexanone	BuLi	-40	toluene	1	3 e	27	

Table 1. The Reaction of 1a with Epichlorohydrin and Carbonyl Compounds.<sup>8</sup>

Previously, Turcant and Le Corre reported that the reaction of epichlorohydrin with 2 eq. of 1a afforded five-membered oxaphospholane (4), which further reacted with aldehydes to give three-membered cyclic homoallylic alcohols (2) (Scheme 2).<sup>4</sup> However, they could not synthesize four-membered cyclic homoallylic alcohols. They also reported that four-membered cyclic alcohols such as 3 were not obtained by the reaction of 3,4-epoxybutyltriphenylphosphonium ylide with aldehydes.<sup>10</sup>



The present result is quite different from theirs. We then tried the reaction of methylenetriphenylphosphorane, 1a, prepared from sodium hydride or potassium *tent*-butoxide with epichlorohydrin followed by the addition of aldehydes under several conditions. A similar reaction occurred, whereas the obtained products were mixtures of 2 and 3 in low yields. Additionally, when the reaction was carried out in THF as a solvent, a mixture of 2a and 3a was obtained in 15 % and 6 % yields, respectively (Table 2). Thus, bases and solvents used play important roles in this reaction.

Aldehyde	Conditions Base Temp./°C	Solvent	<b>2</b> <sup>a)</sup>		3	
Benzaldehyde	NaH 0	THF	2a	20	3a	0
Benzaldehyde	BuLi -40	THF	2a	15	3a	6
Propionaldehyde	BuLi <sup>9</sup> -78	THF	2 c	12	3 c	5
Propionaldehyde	NaH room temp.	toluene	2 c	5	3c	0
Propionaldehyde	tert-BuOK room temp.	toluene	2 c	5	3c	0

Table 2. Preparation of Homoallylic Alcohols under Several Conditions.

a) E- and Z-mixtures of 2a and 2c were obtained.

First we thought that the reaction might proceed through 3,4-epoxybutylphosphonium iodide (5). However, the reaction of 5 with butyllithium followed by the addition of benzaldehyde only afforded 2a in 55% yield.



Thus, the reaction might proceed as follows: Initial attack of 1 to epichlorohydrin resulted in the formation of betaine 6, which was changed into  $\gamma$ -oxide ylide (7) by  $\alpha$ -proton abstraction of 6. Since lithium ion is tightly combined with oxy anion in toluene, intramolecular substitution on  $\delta$ -carbon gave the corresponding cyclobutylidenephosphorane, which finally reacted with aldehyde to afford 3 (Scheme 4).



Scheme 4.

To confirm this possibility, preparation of 3-hydroxy-4-iodobutyltriphenylphosphonium iodide (8) which would be the precursor of  $\gamma$ -oxide ylide 7 was carried out independently<sup>12</sup> and reacted with butyllithium followed by the addition of benzaldehyde which resulted in the formation of four-membered alcohol, **3a** in 48 % yield (Scheme 5). Thus, the reaction would proceed through  $\gamma$ -oxide ylide 7.



Scheme 5.

On the other hand, when the reaction was carried out in THF, oxy anion of **6** further attacked to  $\delta$ -carbon in intramolecular manner to afford **5**, which further reacted with butyllithium followed by the addition of aldehydes to afford finally 3-membered cyclic alkylidenecyclopropylcarbinols, **2**.

1-Propylidenecyclobutan-2-ol was previously prepared by the solvolysis of 1-iodo-1cyclopropylpropene. However, a lot of side products were obtained, <sup>13</sup> The present method provides a new convenient synthesis of alkylidenecyclobutanols.

In summary, the reaction of **1a** with epichlorohydrin followed by the addition of butyllithium and aldehydes gave the alkylidenecyclobutanols, **3** when toluene was used as a solvent. This is the first example of the one-pot synthesis of **3** from Wittig reagents.

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- **Typical One-pot Procedure for Preparation of 3a:** To a solution of methyltriphenyl-phosphonium iodide (2.01 g, 5.0 mmol) in dry toluene (30 mL) was added butyllithium (1.6 M in hexane, 3.2 mL, 5.1 mmol) via syringe at 0 °C. After stirring for 20 min, epichlorohydrin (0.46 g, 5 8) mmol) in toluene (5 mL) was added slowly via syringe to this yellow suspension. After stirring for 30 min at 0 °C, butyllithium (1.6 M in hexane, 6.4 mL, 10.2 mmol) was added dropwise to this suspension. The yellow suspension turned into brown and finally reddish orange. At this stage, the suspension was cooled to -40 °C and benzaldehyde (0.80 g, 7.5 mmol) in toluene (5 mL) was added dropwise via syringe to this suspension. After stirring for 1 h at this temperature, the orange suspension turned into pale yellow and warmed up to room temperature. The reaction was stopped by adding water, neutralized by 1 N HCl, and extracted with dichloromethane. The reaction mixture was chromatographed over silica gel by elution with hexane-dichloromethane (1:1) to give **3a** (0.50 g, 3.1)mmol).
- Satisfactory microanalytical data or HRMS were obtained for all new compounds. Spectral data for the 9) reported compounds are as follows: (3a): Mp. 52-54 °C, <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =2.85 (dddd, 1H, The product compounds are as follows. (3a). Mp. 32-54 °C, <sup>1</sup>H NMR (CDCI<sub>3</sub>) 6=2.85 (dddd, <sup>1</sup>H,  $J_{gem}=16$ ,  $J_{vic}=6$ , J=3, J=2 Hz, CH<u>H</u>), 3.13 (m, 1H,  $J_{gem}=16$ ,  $C_{HH}$ ), 3.28 (m, 1H,  $J_{gem}=16$  Hz, CH<u>H</u>), 4.55 (quintet, 1H,  $J_{vic}=6$  Hz, CH<u>H</u>), 3.28 (m, 1H,  $J_{gem}=16$  Hz, CH<u>H</u>), 4.55 (quintet, 1H,  $J_{vic}=6$  Hz, C<u>H</u>OH) 6.23 (br quintet, 1H, J=2Hz, =CH), 7.15-7.35 (m, 5H, Ar-H). <sup>13</sup>C NMR (CDCI<sub>3</sub>)  $\delta=43.31$  (CH<sub>2</sub>), 43.84 (CH<sub>2</sub>), 64.51 (CH), 122.59 (=CH), 126.14 (p-C), 127.05 (m-C), 128.35 (o-C), 134.33 (ipso-C), 137.66 (=C). (3b): Mp.  $112-113^{\circ}$ C, <sup>1</sup>H NMR (CDCI<sub>3</sub>)  $\delta=1.91$  (d, 1H, OH, J=5.5 Hz), 2.86(m, 1H, CHH), 2.98 (m, 1H, CHH), 3.14 (m, 1H, CHH), 3.28 (m, 1H, CHH), 4.51 (q, CHOH, J=5.5 Hz),  $\overline{6.18}$  (br s, 1H, =CH),  $\overline{7.11}$  (d, 2H, J=8.5 Hz, Ar-H),  $\overline{7.26}$  (d, 2H, J=8.5 Hz, Ar-H).  $\overline{13C}$ NMR (CDCl<sub>3</sub>)  $\delta$ =43.22 (CH<sub>2</sub>), 43.88 (CH<sub>2</sub>), 64.50 (CH), 121.59 (=CH), 128.26, 128.50, 131.66, 135.21, 136.13 (Ar) (**3**c): colorless oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =0.92 (t, 3H, J=7.3 Hz), 1.86 (q, 2H, J=7.3 Hz), 2.45 (m, 2H, CH<sub>2</sub>), 2.95 (m, 2H, CH), 4.36 (m, 1H, CHOH), 5.19 (m, 1H, =CH). (3d): colorless oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=0.88 (t, 3H), 1.23-1.33 (m, 6H, CH<sub>2</sub> × 3), 1.87 (q, 2H, CH<sub>2</sub>), 2.55 (m, 2H, CH<sub>2</sub>), 2.98 (m, 2H, CH<sub>2</sub>), 4.35 (quintet, 1H, C<u>H</u>OH), 5.20 (m, 1H, =CH). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ =14.13 (CH<sub>3</sub>), 22.59 (CH<sub>2</sub>), 28.74 (CH<sub>2</sub>), 29.34 (CH<sub>2</sub>), 31.46 (CH<sub>2</sub>), 40.35 (cyclobutyl CH<sub>2</sub>), 42.22 (cyclobutyl CH<sub>2</sub>), 63.98 (CHOH), 122.83 (CH=C), 129.63 (CH=C). (**3e**): colorless oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =1.40–1.75 (m, 6H, CH<sub>2</sub> × 3) 1.90–2.02 (m, 4H, CH<sub>2</sub> × 2), 2.48 (m, 2H, CH<sub>2</sub>), 2.96 (m, 2H, CH<sub>2</sub>), 4.35 (q, 1H, J=6.4 Hz, CHOH). 10) A. Turcant and M. Le Corre, *Tetrahedron Lett.*, **1977**, 789. A. Hercoute and M. Le Corre, *Tetra*-
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- 11) When tert-butyllithium was used as a base, (2-hydroxymethyl)cyclopropyltriphenylphosphonium iodide was obtained in 24% yield.
- 12) 8: Mp 166-168 °C, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=1.82-1.96 (m, 1H, C<u>H</u>H), 2.02-2.14 (m, 1H, CH<u>H</u>), 3.30 (dq, 2H, CH<sub>2</sub>I), 3.80 (m, 2H, P-CH<sub>2</sub>), 4.14 (br m, 1H, CH-OH), 4.56 (d, 1H, J=7.2 Hz, OH), 7.60-7.90 (m, 15H, Ar).
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