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PHOSPHONATE REAGENTS FOR THE SYNTHESIS OF ENOL ETHERS AND ALDEHYDE HOMOLOGATION[1]

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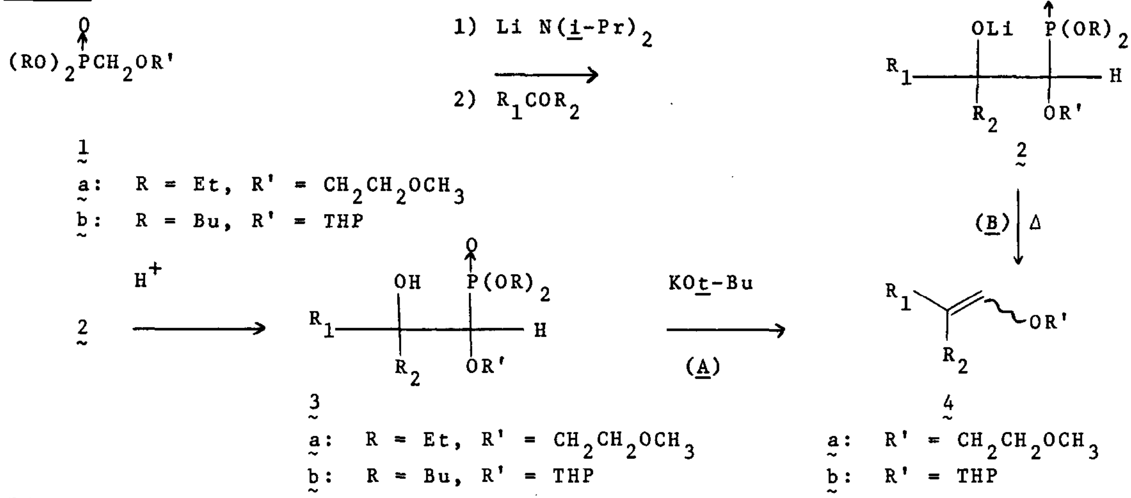
Homologation techniques for the preparation of aldehydes form a considerable body of synthetic methodology. Among these techniques are the Darzens method[2], the alkoxymethylene-[3,4] and aryloxymethylenetriphenylphosphoranes[5], phenylthiomethylenetriphenylphosphorane[6], diethyl methylthiomethylphosphonate[7], methoxymethyl diphenylphosphine oxide[8], bis(ethylenedioxyboryl)methide[9], α-aminophosphonates[10], and α-chloro-α-trimethylsilyl carbanion.[11]

In connection with a problem in total synthesis we required an enol ether synthesis that would lead to aldehyde homologation. We required a reagent that would modify several of the characteristics and shortcomings of the existing triphenylphosphorane reagents[3,4,5] in three points: (1) eliminate triphenylphosphine oxide as a by-product, (2) reduce side reactions with enolizable aldehydes and ketones, (3) incorporate functionality which would permit mild hydrolysis of the enol ether.

Certain facts in the literature pointed towards difficulties in the development of such a phosphonate analogy to the existing triphenylphosphorane reagents. Lithio diethyl methylphosphonate was known to give 1,2-adducts with carbonyl compounds, but no conditions were found to achieve four-centered elimination to give olefins.[12] Also, it was reported that diethyl methoxymethylphosphonate was recovered unchanged after attempted reaction with benzaldehyde and sodium hydride.[7] With these considerations in mind we decided to further investigate the potential of phosphonate reagents for homologation to aldehydes

Two reagents were developed for the desired enol ether synthesis. Reagent **1a**[13] (b.p. 90-91°, 0.2 mm) was prepared in 77% yield by the reaction of methoxyethoxymethyl(MEM) chloride[14] with triethyl phosphite (3 hr. at 155°). Reagent **1b**[13] (b.p. 140°, 0.1 mm) was prepared in 63% yield from tetrahydropyranylation of dibutyl hydroxymethylphosphonate.[15,16] Reaction of **1a** or **1b** with lithium diisopropylamide (LDA)[17] (THF-hexane, 2:1, -78°, argon) followed by addition of an aldehyde or ketone at -78° or -100°[18] gave high yields of 1,2-adducts **3a** and **3b**. Two methods were used to prepare enol ethers **4a** and **4b**: (*A*) the adduct **3a** or **3b** was treated with 2 eq. KO*t*-Bu (50°, 5 min.), and (*B*) the reaction mixture was heated at reflux until tlc analysis indicated completion (**2** → **4**).

SCHEME

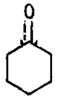
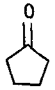
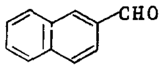


1
a: R = Et, R' = $CH_2CH_2OCH_3$
b: R = Bu, R' = THP

3
a: R = Et, R' = $CH_2CH_2OCH_3$
b: R = Bu, R' = THP

4
a: R' = $CH_2CH_2OCH_3$
b: R' = THP

Table 1,2-Adducts, Enol Ethers, and Homologated Aldehydes[13]

Substrate	Reagent	**3** % Yield (temp)	**4** % Yield (A)	**4** % Yield (B)	Homologated Aldehyde % Yield[a,b]
Ph_2CO	**1a**	92 (-78°)	79	90	20[c]
	1b	86 (-78°)	78	85	89
$PhCOCH_3$	**1a**	66 (-78°)	85	--	72[c]
	1b	60 (-78°)	87	65[d]	90
	1b	95 (-100°)	--	--	--
	**1a**	83 (-78°)	73	86	80[e]
	1b	99 (-100°)	85	97	87[e]
	**1a**	38 (-78°)	--	--	--
	1b	36 (-78°)	88	36[d,f]	92[e]
	1b	90 (-100°)	--	--	--
	**1a**	80 (-78°)	60	--	50[c]

a) isolated yield unless otherwise stated

b) 0.2 M HCl, THF, argon, 2-4 hr. room temp. unless otherwise stated

c) 2% $HClO_4$, THF, argon, 60°, 6 hr

d) ketone added at -100°

e) vpc yield

f) reaction 40% complete after 72 hr. at reflux

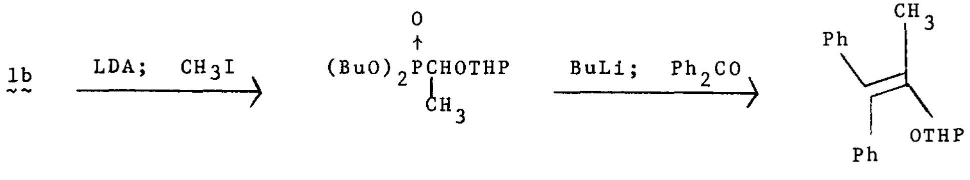
Two main points of interest follow from these results (Table).

1) Reagent 1b gives high yields of 1,2-adducts, even with enolizable substrates such as cyclopentanone and acetophonone. This result with cyclopentanone at -100° is in contrast to the reaction of cyclopentanone with methoxymethylenetriphenylphosphorane.[5]

2) The use of 1b to incorporate a tetrahydropyranyloxy function in the enol ether allows for more facile hydrolysis[4] than was encountered with enol ethers 4a. The ease of hydrolysis of THP-enol ethers makes 1b the reagent of choice for aldehyde homologation. Further development of such a phosphonate reagent could conceivalby occur with the use of MEM[14] or methylthiomethyl[19] in lieu of THP. These groups would allow enol ether hydrolysis to occur under very mild conditions.

The successful thermal decomposition of 2 is in contrast with the report for the unsubstituted phosphonate.[12] Apparently the inductive effect exerted by the alkoxy function in 2 stabilizes the buildup of negative charge α to phosphorus in the transition state for olefin formation. Successful olefinations are reported for chlorinated phosphonates[20] where there is inductive stabilization of negative charge α to phosphorus in the transition state for olefin formation.

Preliminary experiments indicate some potential for the adaptability of 1b to ketone homologation. Reaction of lithio 1b with 1 eq. CH$_3$I followed in succession by (a) addition of 1 eq. n-BuLi, (b) addition of 1 eq. benzophenone, and (c) heating at reflux for 18 hr. gave a 67% yield of 5[13], m.p. 66-67°. Reagents produced by alkylation of lithio 1b might serve as a compliment to the "acyl anion" alkylation method for enol ether synthesis developed by Schlosser.[21] Moreover, the present synthesis of THP-enol ethers represents a convenient source of starting materials for the Schlosser method.



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References and Notes

1. Contribution No. 517 from the Institute of Organic Chemistry.

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13. Satisfactory spectra and elemental analyses were obtained for all new compounds.

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16. The dibutyl hydroxymethylphosphonate was used without distillation. Volatiles were removed at 100° (0.1 mm). Phosphorus oxychloride was used to catalyze the tetrahydropyranylation. Prior to distillation the crude product was filtered through SiO_2 with 80% Et_2O-hexane.

17. Use of n-BuLi gave no useful product.

18. A -100° temperature was conviently obtained by adding liquid N_2 to a methanol bath (Dewar) already at -78°.

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