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A HORNER-WITTIG SOLUTION TO THE SYNTHESIS OF KETENE O,O-ACETALS.

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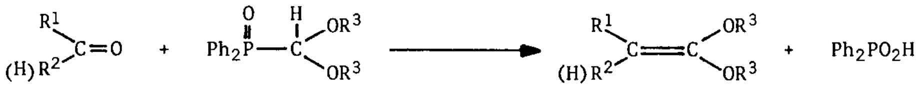
Summary: Aldehydes as well as ketones can be converted into their homologous ketene O,O-acetals by a Horner-Wittig reaction with dialkoxymethyl diphenylphosphine oxides.

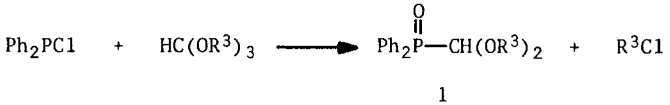
Ketene O,O-acetals are highly valued intermediates in organic synthesis. They can be easily converted into a number of carboxylic acid derivatives[1] and also enter into a variety of cycloaddition reactions.[2] Despite the work that has been carried out by McElvain[1,3] and by others[4,5] on the preparation of ketene O,O-acetals, their use is still seriously hampered by lack of a generally applicable synthetic method.

Two methods that have been exploited with great success in the synthesis of other heteroatom substituted olefins are the Horner-Wittig reaction[6] and the Peterson olefin synthesis.[7] Thusfar, attempts to establish either of these methods as a useful synthetic procedure for the preparation of ketene O,O-acetals have failed.[8] This appears to be due to the impossibility to obtain the required lithiated nucleophiles of adequate stability. E.g., it was reported that diethyl diethoxymethylphosphonate did not undergo metallation, even if *t*-butyllithium was used as a base.[5]

The excellent properties of phosphine oxides with regard to stabilization of a heteroatom substituted carbanionic center[9] have led us to investigate the possibility to carry out the Horner-Wittig reaction with dialkoxymethyl diphenylphosphine oxides. In this communication we report that, by careful control of the reaction conditions, these reagents are eminently suitable to effect conversion of both aldehydes and ketones of a wide range of reactivities into homologous ketene O,O-acetals:



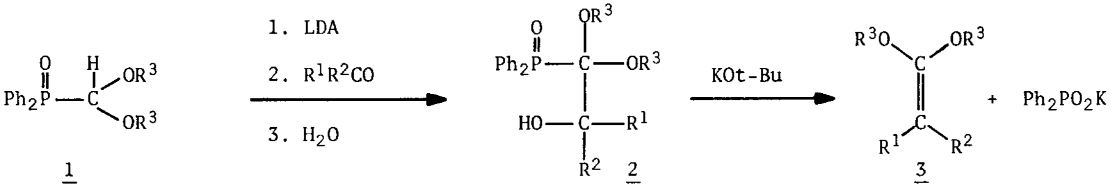
The requisite phosphine oxides 1 are easily accessible by an Arbusov reaction of chlorodiphenylphosphine with orthoformates.[10,11]



$$Ph_2PCl + HC(OR^3)_3 \longrightarrow Ph_2P(=O)-CH(OR^3)_2 + R^3Cl$$

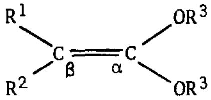
1

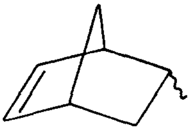
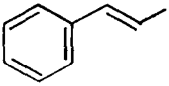
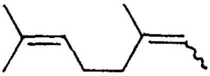
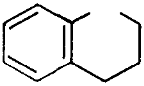
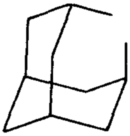
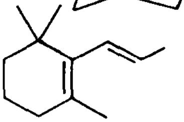
When these phosphine oxides are treated with lithium diisopropyl amide (LDA) at -100°C they are rapidly converted into their lithiated anions. These anions are thermally unstable at temperatures exceeding -90°C. Subsequent reactions were therefore carried out between -100° and -95°C. A mixture of diethyl ether/tetrahydrofuran (THF) (1/3 v/v) proved satisfactory to prevent solidification of the reaction mixture and maintain adequate solubility for the phosphine oxides. Even at these low temperatures, the reaction with carbonyl compounds is almost instantaneous. Although it is possible to complete the Horner-Wittig reaction with the lithiated adducts thus formed by simply allowing the temperature to rise, far better results are obtained by first isolating the protonated adducts. Quenching the reaction mixture at low temperature with water and work-up affords the adducts 2 in almost quantitative yields.[12] Subsequent treatment of these adducts in THF solution at room temperature with a slight excess of potassium *t*-butoxide then completes the Horner-Wittig reaction. By applying a water-free work-up procedure the ketene O,O-acetals 3 are obtained in the yields listed in the Table. In most cases these products are sufficiently pure for synthetic purposes. Analytically pure ketene acetals can be obtained by distillation (yields in parenthesis). Because of their thermal instability this is accompanied by appreciable loss of product.



The results outlined in the Table illustrate the generality of this method. Not only aldehydes - saturated as well as α,β-unsaturated and aromatic - give good results, also ketones of various structural types are easily converted into homologous ketene O,O-acetals. Only in the case of cyclopentanone, the starting materials were recovered unchanged, probably as a result of enolisation. The method also provides an easy way to vary the nature of the ketene alkoxy groups. The strikingly high melting points of the cyclic ketene acetals with $-R^3, R^3 = -CH_2CMe_2CH_2-$ (entries C, O, and Q) allows their convenient purification by crystallization.

TABLE Conversion of carbonyl compounds R^1R^2CO into ketene O,O-acetals [a]:



	R^1	R^2	R^3	Yield(%)	δ_H	$\delta_{C\alpha}$	$\delta_{C\beta}$	n_D / mp
A.*[1]	Ph	H	Et	85 (48)	4.62	158.5	80.4	n_D^{22} = 1.5373
B.*[1]	Ph	H	Me	(67)	4.54	160.3	79.1	n_D^{22} = 1.5662
C.	Ph	H	$-CH_2CMe_2CH_2-$	69	4.92	155.5	86.2	mp = 78-79°C
D.	*p*-MeO-Ph	H	Et	80 (69)	4.66	157.6	80.6	n_D^{21} = 1.5368
E.	$c-C_6H_{11}$	H	Et	68 (43)	3.41	156.8	87.8	n_D^{22} = 1.4518
F.	$Ph(CH_2)_2$	H	Et	65 (32)	3.68	158.0	79.6	n_D^{22} = 1.4939
G.		H	Et	(50)	3.30	156.9	86.5	n_D^{22} = 1.4761
H.		H	Et	65 (25)	4.62	159.9	82.4	n_D^{26} = 1.5924
I.		H	Et	75 (38)	4.50	157.8	79.3	n_D^{23} = 1.4864
J.	Ph	Me	Et	50 (20)	--	153.3	98.9	n_D^{24} = 1.5129
K.			Et	58 (29)	--	152.4	99.3	n_D^{23} = 1.5478
L.	$Me_2C=CH(CH_2)_2$	Me	Et	76 (27)	--	151.6	98.8	n_D^{22} = 1.4457
M.	$-(CH_2)_5-$		Et	90 (66)	--	148.7	103.7	n_D^{22} = 1.4530
N.*[14]	$-(CH_2)_5-$		Me	(60)	--	151.6	101.9	n_D^{25} = 1.4586
O.	$-(CH_2)_5-$		$-CH_2CMe_2CH_2-$	68	--	147.5	98.6	mp = 56-58°C
P.			Et	45	--	145.6	111.4	n_D^{24} = 1.4896
Q.			$-CH_2CMe_2CH_2-$	50	--	145.0	107.2	mp = 68°C
R.		Me	Et	(39)	--	153.8	100.1	n_D^{26} = 1.5099

a) Ketene acetals that have been previously described are marked with an asterisk.

General Procedure: To a solution of 10 mmol of phosphine oxide 1[10] in 200 ml of a mixture of THF/diethyl ether (3:1) cooled to -100°C, is added 1.1 equiv of LDA in 25 ml of THF. After stirring for 1 min, a solution of 10 mmol of the carbonyl compound in 20 ml of THF is added at such a rate to the deeply coloured solution that the temperature is kept at all times below -90°C. After stirring for an additional 5 min at this temperature the mixture is quenched by the addition of 40 ml of water. After warming to room temperature, solid potassium carbonate is added and the organic layer is separated and dried. Evaporation of the solvent affords the adduct 2, usually in quantitative yield. To complete the Horner-Wittig reaction, a solution of 11 mmol potassium *t*-butoxide in 50 ml of THF is added in one portion to a solution of the adduct in 50 ml of THF. After stirring for 1 h at room temperature, the solvent is removed at temperatures not exceeding 40°C. The residue is taken up in hexane (100 ml) and transferred into centrifuge tubes. After centrifugation the hexane solution is decanted. The residue is extracted once with a second portion of hexane. Upon evaporation of the solvent the ketene O,O-acetal is obtained as a pale yellow oil.[13]

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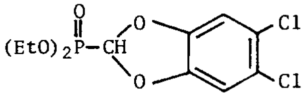
2. R.W. Aben, R. Hofstraat and J.W. Scheeren, Recl.Trav.Chim.Pays-Bas 100, 355 (1981); J. Bitter *et al.*, Ber. 113, 1020 (1980) and references cited therein.
3. S.M. McElvain and Philip L. Weyna, J.Am.Chem.Soc. 81, 2579 (1959).
4. J.W. Scheeren, R.W. Aben and R.J.F. Nivard, J.Org.Chem. 42, 3128 (1977) and references cited therein; D.W. Cameron *et al.*, Aust.J.Chem. 31, 1335 (1978).
5. M. Mikołajczyk, S. Grzejsczak, A. Zatorski, B. Mlotkowska, H.Gross and B. Costisella, Tetrahedron 34, 3081 (1978).
6. See, i.a.:M. Mikołajczyk, S. Grzejsczak and P. Lyżwa, Tetrahedron Lett. 23, 2237 (1982)
7. See, i.a.:David J. Ager, Tetrahedron Lett. 22, 2923 (1981).
8. The only limited success that has been reported was obtained with the cyclic acetal:



From diethyl ketone and benzophenone the corresponding Horner-Wittig products were obtained in yields of 19 and 32%, respectively. It should be realized that these compounds may not display the pattern of reactivity normally associated with ketene O,O-acetals.

9. N.L.J.M. Broekhof, F.L. Jonkers and A. van der Gen, Tetrahedron Lett. 20, 2433 (1979); J.I. Grayson and S. Warren, J.Chem.Soc.Perkin Trans.I, 1977, 2263.
10. W. Dietsche, Ann. 712, 21 (1968).
11. Another route to these compounds is described by B. Costisella and H. Gross, J.Prakt.Chem. 319, 8 (1977).
12. Isolation of the adducts 2 also allows investigation of their decomposition under acidic conditions. The results of this study will be reported separately.
13. Spectral properties of all compounds listed in the Table (IR, UV, MS, ^{1}H- and ^{13}C-NMR) are fully in agreement with the indicated structures.
14. S.M. McElvain and R.E. Starn, J.Am.Chem.Soc. 77, 4571 (1955).

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