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TRIMETHYLALUMINUM PROMOTED CONJUGATE ADDITIONS OF DIMETHYLPHOSPHITE TO α,β-UNSATURATED ESTERS AND KETONES

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ABSTRACT: The effective conjugate addition of a dimethyl phosphonate moiety to α,β-unsaturated esters and ketones is described. This addition is promoted specifically by trimethylaluminum and does not occur with other Lewis acids which have been examined to date.

The installation of a phosphonate moiety β to a carbonyl carbon could, in principle, be accomplished via conjugate addition of the appropriate trialkyl phosphite to an α,β-unsaturated carbonyl compound. However, because of the reversibility of this reaction, trialkyl phosphites will not effectively add in a conjugate manner to α,β-unsaturated ketones or esters. This predilection was, to some extent, overcome when organosilicon tervalent phosphorous esters (X_2POSiR_3, X= alkoxy) were used in which a transfer of silicon to oxygen could occur with the concomitant formation of a silyl-ketene acetal or silyl-enol ether.[1] Accordingly, dimethyl trimethylsilyl phosphite adds to acrolein exclusively via a 1,2-addition pathway at 25° C over a 12h period. This same reagent adds to methyl vinyl ketone and 3-pentene-2-one in a 1,4 manner at 50° C (6h) and 80° C (24h) respectively. No detectable 1,4-addition occurs to cyclic enones unless the reactions are performed in acetonitrile under equilibrating conditions (i.e. for 2-cyclohexene-1-one , 180° C /12h to obtain a 16:1 1:4/1:2 ratio). Even with these conditions, the relative amounts of 1,4-adducts decrease with increasing hindrance around the β-carbon.[2] It is pertinent to note that the more forcing conditions required for cyclic enones only resulted in adduct formation when diethyl trimethylsilyl phosphite was employed. Reactions involving the dimethyl phosphite derivative failed.

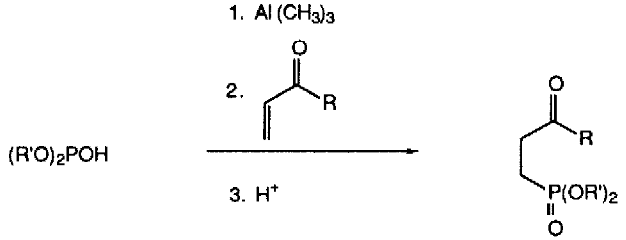
With respect to α,β–unsaturated carboxylates, only one report could be found describing the 1,4-addition of $(RO)_2POSi(CH_3)_3$ (R = CH_3,Et,nBu) to simple systems.[3] The conditions employed were 110-120° C for 2h. Yields decreased significantly with substitution at the β–carbon of the unsaturated system or increased bulk on the phosphite. The reaction failed with methyl cinnamate and methyl methacrylate and resulted in polymer formation in the latter case.

It is known that upon reaction of thiols or selenols with trimethylaluminum, a loss of methane occurs to provide complexes which will effect a conjugate addition of the sulfur or selenium group to α,β-unsaturated ketones via an aluminum enolate intermediate.[4] Additionally, reactions between trimethylaluminum and phosphinic acids are known to occur, with loss of methane, to form dimethylaluminum complexes.[5] Based on these observations, the reaction between trimethylaluminum and a dialkylphosphite was considered.

Suprisingly, it was discovered that upon admixture of trimethylaluminum and dimethylphosphite, no loss of methane occurred. Even after stirring for a period of 24 hours at room temperature. However, upon addition of ethylacrylate at 0^oC, a high yield of the conjugate addition product was obtained.Interestingly, other Lewis acids examined (i.e. BF_3,$TiCl_4$, $SnCl_4$) did not promote the addition.

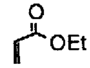
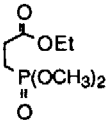
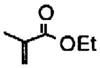
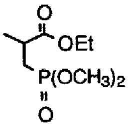
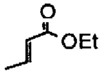
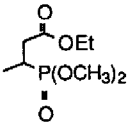
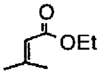
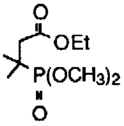
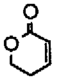
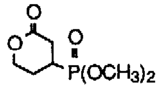
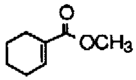
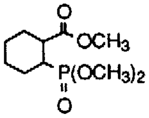
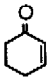
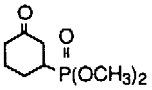
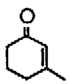
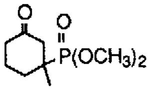
That the addition is not mediated by an aluminum enolate is based on the observation that quenching the reaction with DCl/D_2O produced none of the deuterated addition product as evidenced by MS and 300MHz ^1H-NMR. However. the aluminum enolate and resultant deuterated product could be obtained when use was made of the "ate" complex of dimethylphosphite and trimethylaluminum.[6]

As shown in the table, the indicated mixture provides a mild and efficient method for effecting the installation of a phosphonate moiety to α,β–unsaturated ketones and esters.



Two aspects concerning the scope of this method which become clear are (a) accommodation of increasing substitution at the α or β carbons of the enone with exclusive delivery of the phosphonate moiety in a 1,4 fashion (b) exclusive 1,4 delivery of the phosphonate moiety with cyclic α,β–unsaturated ketones or esters, even with substitution on the β carbon.

TABLE : Phosphonates From Ketone/Esters With Dimethylphosphite and Trimethylaluminum [a]

Starting Material	Product	Yield
		95%
		93%
		94%
		82%
		32%
		89% [b]
		87%
		84%

[a] All reactions were run according to the general procedure described. Products were fully characterized by 300 Mhz ^{1}H NMR, IR, Mass Spectra and/or Combustion Analysis data.

[b] Obtained as a 3:1 mixture of isomers as determined from ^{13}C-NMR

General Procedure . To a solution of dimethylphosphite (19.2mmol) in 50 mL of dichloromethane at 0° C is added a toluene solution of trimethylaluminum (2.0 M, 19.2 mmol) dropwise. After stirring for 20 min., the α,β–unsaturated ester or ketone (19.2 mmol) is added dropwise. The resulting solution is allowed to warm to room temperature over one hour and stir overnight . The solution is poured onto 5% HCl (aq) and extracted with dichloromethane. The combined extracts are dried over Na_2SO_4. For those cases cited, purification was performed via bulb to bulb distillation (P= 0.1 Torr, T= 100° C).

References and Notes :

1. For a description of various tervalent phosphorous-silicon reagents see: Borisov,S.N.;Voronkov,M.G.;Lukevits,E.Ya."Organosilicon Derivatives of Phosphorous and Sulfur", Plenum Press; New York, N.Y., 1971, Chapter 1. Evans, D.A.; Hurst,K.M.; Takacs,J.M. *J. Am. Chem. Soc.* **1978**,*100*, 3467.
2. Liotta,D.; Sunay,U.; Ginsberg, S. *J. Org. Chem.***1982**, *47*, 2227.
3. Okamota, T.; Sakura,H. *Synthesis* **1982**, 497.
4. (a) Leonard,W.R.; Livinghouse,T. *Tett. Lett.* **1985**, *26*, 6431. (b) Itoh,A.; Ozawa,S.; Oshima,K.; Nozaki,H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274.
5. (a) Coates, G. E. ; Mukherjee, R. N. *J. Chem. Soc.* , 1295 (1964) . (b) For a description of the complexes between trialkylaluminums and various organophosphorous species see; Mole,T.; Jefferey, E.A. "*Organoaluminum Compounds*", Elsevier; Amsterdam, **1972**, pp 256-261.
6. In a manner analogous to thiols and selenols, nBuLi (1 eq.) is added to a solution of diethylphosphite (1 eq.) in tetrahydrofuran at 0°C and then trimethylaluminum is added to produce the "ate" complex. When ethyl acrylate is added, an aluminum enolate intermediate is produced which can be quenched with deuterium or condensed with aldehydes. Details on the condensation with aldehydes will be reported in a forthcoming publication .
7. Some preliminary experiments indicate that this process also occurs when a catalytic amount of trimethylaluminum is employed. For the case of ethyl acrylate, the yield is not affected. However, for other more substituted examples the yield is significantly reduced. Further details on this work will reported at a later date.

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