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A NEW STABLE WITTIG REAGENT SUITABLE FOR THE SYNTHESIS OF α,β-UNSATURATED PHOSPHONATES[a]

G. H. Jones, E. K. Hamamura, and J. G. Moffatt
Institute of Molecular Biology, Syntex Research, Palo Alto, California

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In recent years several laboratories have studied the synthesis of phosphonic acid analogs of naturally occurring phosphate esters such as nucleotides,(1) phospholipids,(2) nucleoside polyphosphates(3) and sugar phosphates.(4) These compounds have generally been prepared via an Arbusov reaction between an alkyl halide and a trialkyl phosphite, the phosphonate ester groups being subsequently removed by vigorous acidic hydrolysis,(2) hydrogenolysis(1a,b) or elimination.(1c) Perhaps the most interesting of these analogs are those in which the normal ester oxygen bridge of the phosphate is replaced by an essentially isosteric methylene group.(5) Recently Hullar(5b) has described the synthesis of an isosteric phosphonic acid analog of pyridoxol phosphate via reaction of the anion of tetraethylmethylene-bis-phosphonate(6) with an appropriate aldehyde followed by catalytic reduction and vigorous acidic hydrolysis. While we have successfully applied this reaction to both suitably protected sugar aldehydes and ketones,(7) it has, in our hands, been far from satisfactory when applied to protected nucleoside 5'-aldehydes.(8)

The facile synthesis of α,β-unsaturated carbonyl compounds using stabilized Wittig reagents(9) has prompted us to attempt the preparation of the related phosphonate stabilized ylids such as I. Attempts to prepare the phosphonium salt IIa by reaction of triphenylphosphine with diethyl iodomethylphosphonate(10) led only to intractable gums and the isolation of a low yield of ethyltriphenylphosphonium iodide presumably formed via the dealkylation of an ethyl ester by iodide ion.(11) Similarly reaction of methylenetriphenylphosphorane with diethyl phosphorochloridate led to the isolation of none of the desired phosphonium salt II or ylid I. The reaction of two equivs. of methylenetriphenylphosphorane with diphenyl phosphorochloridate in tetrahydrofuran at 22°, however,

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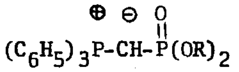
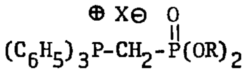
led to the instantaneous precipitation of methyltriphenylphosphonium chloride. Extraction of the filtered solution with 3 N hydrochloric acid followed by neutralization of the extracts with sodium hydroxide gave crystalline diphenyl triphenylphosphoranylidenemethylphosphonate (Ib) in 60% yield. The synthesis of Ib on a large scale was more conveniently carried out via quaternization of triphenylphosphine with diphenyl chloromethylphosphonate[b] at 175° for 4 hours giving IIb of m.p. 210-222°. Neutralization of an aqueous solution of the latter gave the desired ylid Ib which was recrystallized from ethyl acetate with m.p. 149-150° in an overall yield of 77%.[c] The n.m.r. spectrum of Ib in deuteriochloroform showed the aliphatic proton as a broad, one proton singlet at 1.50 ppm. In trifluoroacetic acid, however, the methylene group of the resulting phosphonium salt appeared as a 2-proton quartet at 4.45 ppm with phosphorus-proton couplings of 16 and 22 Hz. The mass spectrum of Ib showed a molecular ion at m/e 508 together with some interesting peaks due to rearrangements which further substantiate the proposed structure.$^{(12)}$ Issleib, et al.,$^{(13)}$ have recently described the preparation and reactions of some phosphonium ylids stabilized by diarylphosphine oxide and related groups.



$(C_6H_5)_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}H\text{-}\overset{\overset{O}{\|}}{P}(OR)_2$

I(a) R = Et

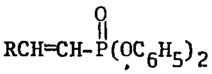
(b) R = C_6H_5



$(C_6H_5)_3\overset{\oplus}{P}\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{P}(OR)_2 \quad X^{\ominus}$

II(a) R = Et, X = I

(b) R = C_6H_5, X = Cl



$RCH{=}CH\text{-}\overset{\overset{O}{\|}}{P}(OC_6H_5)_2$

III

The ylid Ib proved to be very stable towards storage at room temperature but reacted smoothly with a variety of simple aromatic and aliphatic aldehydes at 100-110° (see Table I). The reactions were considerably more rapid in dimethyl sulfoxide than in toluene and were, as expected, also accelerated with aldehydes bearing electron withdrawing substituents. Suitably protected nucleoside$^{(14)}$ and sugar$^{(7)}$ aldehydes were considerably more reactive and condensed with Ib at room temperature in dimethyl sulfoxide. The products, which were isolated in high yields by crystallization from ethanol, were shown to be exclusively the trans isomers of the appropriate diphenyl vinylphosphonates (III). The n.m.r. spectra of these compounds showed the vinyl

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[b] M.p. 42-43°, b.p. 150-152°/0.05 mm. See U. S. Patent 2,900,405, Chem. Abstr. 54, 416d (1960).

[c] All compounds gave satisfactory elemental analyses.

protons as quartets ($J_{H,H}$ = 17-18 Hz; $J_{P,H,gem}$ = 18-21 Hz; $J_{P,H,vic}$ = 22-24 Hz). No indication of the formation of the corresponding cis isomers, which would show different coupling constants,(15) was observed.

TABLE I

Aldehyde	Solvent	Time	Temp.	Yield	m.p.
2-Naphthaldehyde	Toluene	44 hrs	110°	66%	154-155°
2-Naphthaldehyde	DMSO	21 hrs	100°	72%	154-155°
p-Chlorobenzaldehyde	Toluene	48 hrs	110°	84%	107-108°
p-Nitrobenzaldehyde	Toluene	18 hrs	110°	92%	116-117°
Valeraldehyde	Neat	6 hrs	100°	95%	b.p. 148-150°/10^{-3} mm

The use of stabilized ylids such as Ib for the synthesis of vinyl phosphonates is thus complementary to the Wadsworth-Emmons procedure,(5b,6) but offers the distinct advantage of not requiring the use of strongly basic reagents for carbanion formation. The ease of removal of the phenyl esters from the final condensation products(14) opens the way to the synthesis of phosphonic acids derived from sensitive molecules such as nucleosides and sugars. A detailed account of our studies on the synthesis and reactions of other ylids related to I will be reported shortly.

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