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A THREE COMPONENT KETONE SYNTHESIS FROM A PHENYLTHIOVINYLPHOSPHINE OXIDE

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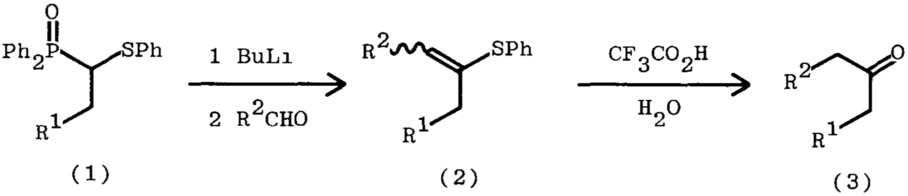
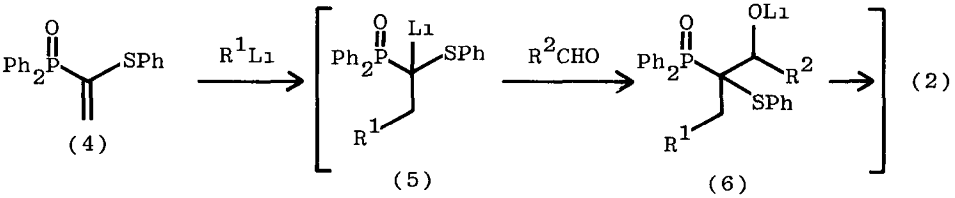
The anion formed by addition of an alkyl-lithium to the vinyl phosphine oxide (4) reacts with aldehydes to give vinyl sulphides, easily hydrolysed to ketones.

Phosphine oxides with an α-PhS group (1) behave as acyl anion equivalents, the Wittig-Horner reaction giving vinyl sulphides (2) which are hydrolysed to ketones (3) in trifluoroacetic acid[2] (TFA)



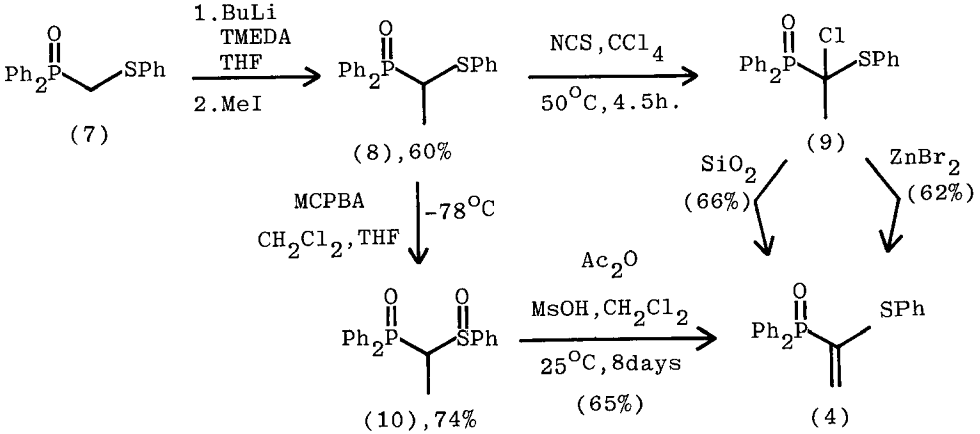
(1) (2) (3)

We now report that a third component may be built into this ketone synthesis. Addition of an alkyl-lithium to 1-(phenylthio)vinyldiphenylphosphine oxide (4) produces the anion (5). Quenching this anion with an aldehyde gives vinyl sulphides (2) in one step from (4) since the electron-withdrawing PhS group accelerates the elimination of $Ph_2PO_2^-$ from (6) The vinyl sulphides (2) are formed as mixtures of geometrical isomers, both giving the same ketone on hydrolysis in TFA

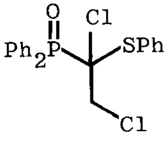


(4) (5) (6)

Trapping the intermediate (5) with aqueous ammonium chloride gives the sulphenylated phosphine oxides (1). Sample results are compared with those from the two-step procedure in the table. The anion (5) does not give a vinyl sulphide with ketones : proton transfer occurs instead and (1) is again isolated (entry 5, table). The two step method[2] is effective with ketones if MeS replaces PhS in (1).



The reagent[3] (4) is prepared from the saturated sulphide (8). Chlorination gives (9) contaminated with (11). Chromatography (SiO_2) converts (9) into (4) and removes (7). Alternatively, treatment with anhydrous $ZnBr_2$ gives (4) and chromatography separates the minor product (12). The Pummerer dehydration route[4] via sulphoxide (10) is efficient but very slow.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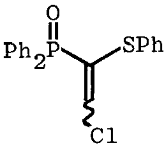
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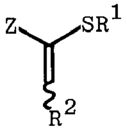
(13)

Nucleophilic addition of alkyl-lithiums to the silicon analogue (13, R^1=Ph, R^2=H, Z=$SiMe_3$) has been used in an aldehyde synthesis by D. J. Ager.[5] The phosphonate ester (13, R^1=Me, R^2=Ph, Z=$(EtO)_2PO$) has been made,[6] and the phosphonium salt (13, R^1=Ph, R^1=H, Z=Ph_3P^+) has been used in a cyclopentanone synthesis.[7] In this last example, as in our work, the reagent behaves as the synthon $+CH_2CO^-$ having umpolung at both carbon atoms.

Table Synthesis of Ketones and α-(PhS)-Alkyldiphenylphosphine Oxides

Entry	R^1	Electrophile	Route[a]	Yield (1)	Yield $(2)^b$	Yield (3)
1	Me	H^+	A	71	-	-
2	Me	PhCHO	A	-	54(8 1)	78
3	Me	PhCHO	B	73	93	
4	n-Bu	H^+	A	85	-	-
5	n-Bu	$(CH_2)_5CO$	A	55[c]	-	-
6	s-Bu	H^+	A	72	-	-
7	Ph	n-HexylCHO	B	84	93	93
8	Me	i-PrCHO	A	-	25(3 1)	48

a. Route A (4) + R^1Li + electrophile
Route B (1) → (2), see ref 2

b. Figures in parenthesis give E Z ratio of vinyl sulphide (2) determined by NMR

c See text

1-(Phenylthio)vinyldiphenylphosphine oxide (4) -

Chlorination method. Finely powdered N-chlorosuccinimide (1.80g, 13 5 mmol) was added to a solution of 1-(phenylthio)ethyldiphenylphosphine oxide[2] (8) (4.47g, 13.2 mmol) in CCl_4 (150 ml). The mixture was stirred at 50°C for about 4 5h until all the precipitate floated. The reaction mixture was washed (10% NaOH), dried ($MgSO_4$) and the solvent evaporated. The crude product (9) was dehydrochlorinated by one of two methods (a) *Silica Method:* The colourless syrup was dissolved in ethyl acetate and stirred with silica gel (ca. 10g) for 16 h Chromatography on silica (eluted with EtOAc) gave the *reagent*[3] (4) (1.57g, 66%). (b) *Zinc Bromide Method.* The crude (9) from (8) (4.47g) was dissolved in CH_2Cl_2 (50 ml) and anhydrous zinc bromide (25 mg) added. The mixture was stirred for 16h at room temperature, washed with 10% NaOH, and dried ($MgSO_4$) Chromatography on silica eluted with ethyl acetate light petroleum, b p. 30 - 40°C (9 1) gave the *reagent*[3] (4) (2.75g, 62%).

Sample Procedure for the three-component ketone synthesis -

The reagent (4) (673 mg, 2 mmol) in THF (10 ml) was cooled to - 78°C and methyl-lithium (1.5 ml as LiBr complex, 1.45M in Et_2O, 2 18 mmol) added. The yellow solution was stirred for 15 minutes and the aldehyde (3 mmol, then 1 mmol) added in two portions. The solution was allowed to warm to room temperature and, after 18h, quenched with saturated NH_4Cl. Water was added and the mixture was extracted with CH_2Cl_2 (3 x 50 ml). The extracts were washed (5% NaOH) and the solvents were removed Chromatography (silica, CH_2Cl_2) gave the vinyl sulphide (2)

References and Footnotes

1 Present address Département de Chimie Organique, 30, quai Ernest Ansermet, 1211 Genève 4, Switzerland

2 J I Grayson and S Warren, *J Chem. Soc , Perkin Trans. 1*, 1977, 2263

3 Reagent (4) is an oil, ν_{max} 1596 (ν C=C), 901 (δ $C{=}CH_2$) cm^{-1}, δ ($CDCl_3$) 8 25 - 7.15 (15H, m, PhS, Ph_2PO), 6 16 (1H, d, J 17 2 Hz, *cis* PC=CH), 5 63 (1H, d, J 34 4 Hz, *trans* PC=CH), M^+ 336 0741, $C_{20}H_{17}OPS$ requires *M*, 336 0738, *m/e* 336 (M^+, 100%), 277 (42), 227 (*M* - PhSH, 15), 202 (Ph_2PO_2H, 31), 201 (Ph_2PO^+, 62), 123 (42%) (Found C, 71 6, H, 5 30, P, 9 05 $C_{20}H_{17}OPS$ requires C, 71 4, H, 5 09, P, 9 21%)

4 cf H J Monteiro and A L. Gemal, *Synthesis*, 1975, 437

5 D J Ager, *Tetrahedron Lett* , 1981, **22**, 587

6 B Venugopalan, A. B Hamlet and T Durst, *Tetrahedron Lett* , 1981, **22**, 191

7 A T Hewson, *Tetrahedron Lett* , 1978, 3267.

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