Synthesis of 1-Alkylthiovinyl- and 1-Arylthiovinyl-phosphonium Salts and Their Use in the Formation of Cyclopentanes

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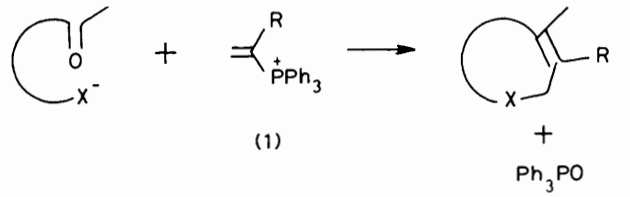
The synthesis of 1-methylthiovinyltriphenyl- and 1-phenylthiovinyltriphenyl-phosphonium salts (1; R = SMe and R = SPh) by introduction of a methylene group α- to the phosphonium centre in Ph_3P^+-CH_2SR is described. The scope and limitations of the method are indicated. The salts (1; R = SMe and R = SPh) are used in the formation of highly functionalised cyclopentanes *via* an intramolecular Wittig reaction.

Vinylphosphonium salts have found considerable use in the synthesis of heterocyclic, carbocyclic, and chain extended systems,[1] much of the pioneering work being carried out by Schweizer. The Scheme shows the general way in which these compounds have been used to synthesise cyclic compounds. Although some vinyl phosphonium salts which are substituted in the vinyl group have been synthesized, they do not generally react according to the Scheme as quickly, or in such high yield, as does the unsubstituted compound. This has been attributed to steric hindrance, probably of the Wittig reaction, caused by the substituent.[2] Those vinylphosphonium salts (1) in which the α-carbon is joined to a heteroatom might be especially useful since the product of the Wittig reaction in the Scheme would be an enol derivative, easily convertible into a ketone. Compound (1; R = OEt) is known [3] but undergoes reaction with α-mercapto ketones to form dihydrothiophenes only in very low yield.[2]

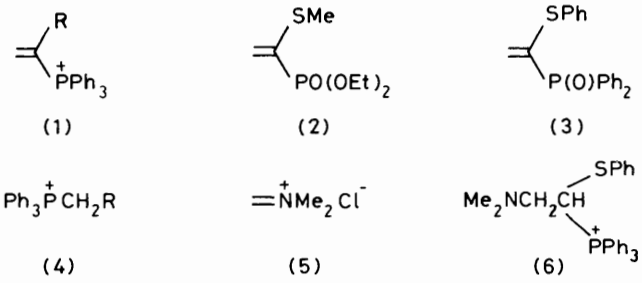
We considered that the salt (1; R = SPh) might be more attractive since the sulphur atom could serve to stabilise the ylide intermediate produced by addition of a nucleophile. We have described our preliminary efforts in this area [4] and now present a full account of the work. Since our preliminary communication appeared, the corresponding phosphonate (2) [5] and phosphine oxide (3) [6] have been reported.

Retrosynthetic analysis suggested that (1; R = SPh) should be available from (4; R = SPh) † by addition of a methylene group to the position α to the phosphorus atom. Recent interest in the chemistry of natural compounds containing the α-methylene carbonyl system has produced a number of methods for such α-methylenations.[7] We attempted first to apply the method of Danishefsky.[8] Thus (4; R = SPh) was treated with butyl-lithium in either tetrahydrofuran (THF) or ether at temperatures ranging from −78 to 25 °C and the resulting phosphorane was allowed to react with *N*,*N*-dimethylmethyleneammonium chloride (5). Only low yields of phosphonium salts were produced and these appeared, from their n.m.r. spectra to be mixtures. This result was confirmed by reaction of other phosphoranes with (5). There is a report of the reaction of iminium salts (formulated as 1-chloroamines) with phosphoranes in which allenes were the eventual product.[9]

One of the methods for reaction of (5) with ketones does not rely on pre-forming the enolate anion but simply involves treating the ketone with (5) in acetonitrile to give the dimethylaminomethyl ketone as its hydrochloride.[10] In view of our failure to obtain the desired product from reaction of phosphoranes with (5) it was decided to investigate the reaction between the phosphonium salt (4; R = SPh) and (5). To our delight when (4; R = SPh) was refluxed in acetonitrile



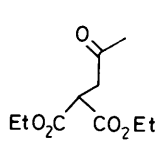
Scheme.



with 2 equivalents of iminium salt (5) n.m.r. monitoring of the reaction mixture showed that within 15 h (4; R = SPh) had disappeared and a new set of signals corresponding to those expected for (1; R = SPh) had appeared. Work-up provided (1; R = SPh) in 89% yield. The mechanism for the conversion presumably involves formation of a small concentration of the anion (phosphorane) from (4; R = SPh) which then reacts with (5). The base forming the anion could be halide ion, which is relatively basic in the dipolar aprotic solvent, or possibly dimethylamine formed by decomposition of (5). The intermediate dimethylaminomethyl compound (6) must then eliminate dimethylamine under the reaction conditions.

Having found this method for generating an α-substituted vinylphosphonium salt we decided to investigate its generality. The methylthiomethylphosphonium salt (4; R = SMe) reacted in the same way as (4; R = SPh) with the iminium salt (5) affording (1; R = SMe) in 84% yield. The only difference was that the reaction took somewhat longer to go to completion. However, in most other cases tried (4; R = Ph, OMe, H, Me, Cl, Br, I) no reaction was observed under a range of reaction times and concentrations. The only exception was on one occasion with the benzyl salt (4; R = Ph) when n.m.r. analysis showed that the desired reaction had taken place, giving (1; R = Ph) [11] to the extent of *ca.* 70%. We were unable to repeat this result initially, but were keen to find conditions which would be reproducible in affording (1; R = Ph). It has now been found that addition of the non-nucleophilic base diazabicyclo[5.4.0]undec-7-ene (DBU)

† The anion of (1) and (4) is omitted for clarity.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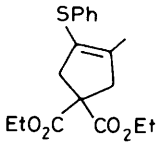
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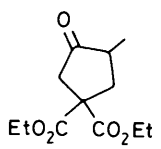
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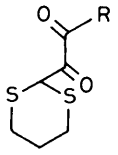
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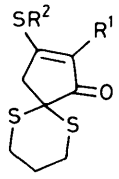
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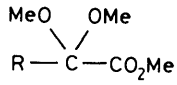
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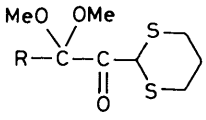
(13)

to a mixture of (4; R = Ph) and (5) in acetonitrile produces (1; R = Ph). The salt was isolated as its fluoroborate since the initial product (probably the chloride) was very hygroscopic. Attempts to apply the DBU method to the other phosphonium salts listed above were not successful. It thus appears that the substituent R in (4) must be one that will stabilise the phosphorane to some extent.

Having succeeded in our initial goal of synthesizing the thio-substituted compounds (1; R = SPh) and (1; R = SMe) we turned our attention to their use in the synthesis of cyclopentanes. The anion of the ketodiester (7) [12] was formed with sodium hydride in THF and (1; R = SPh) was added. Reaction was complete within 2 h and the expected cyclopentene (8) was isolated in 90% yield; it was hydrolysed to the cyclopentanone (9) by heating it under reflux with trifluoroacetic acid (TFA) in chloroform.[13]

For application to the synthesis of cyclopentanoid natural products it was felt that the diketodithiane (10) would be particularly useful since reaction with (1; R = SPh) should give the highly functionalised cyclopentane (11). Compound (10) has been shown to afford cyclopentanes on reaction with simple vinylphosphonium salts.[14] A route to (10) has been described previously from ortho esters. Reaction of an ortho ester with HCN gave α,α-dialkoxynitriles which afforded (10) on treatment with dithiane anion and subsequent acid hydrolysis of the intermediate imine.[14] We were not attracted by the published method, largely because of the hazards associated with HCN. It was felt that a more attractive route would involve the use of α,α-dialkoylesters rather than nitriles. We considered that the dimethoxy esters (12) should be available by alkylation of methyl dimethoxyacetate but while we were in the course of investigating the alkylation procedure, Huet published similar work [15] confirming that esters (12) were readily accessible. Our results for these alkylations were almost identical with those of Huet.

Reaction of the ester (12; R = Me) with the anion of dithiane in the presence of an excess of lithium di-isopropylamide was found to proceed efficiently to give (13; R = Me) which was hydrolysed with aqueous TFA to give the diketodithiane (10; R = Me). In order to demonstrate the formation of the cyclopentane system (11), the diketodithiane (10; R = Me) was converted into its anion by treatment with sodium hydride in THF and then the vinylphosphonium salt (1; R = SPh) was added. The expected product (11; R^1 = Me, R^2 = Ph) was obtained in 75% yield. A similar result was observed with the vinyl phosphonium salt (1; R = SMe) which gave (11; R^1 = R^2 = Me). The application of compounds of the type (11) to natural product synthesis will be described elsewhere.

Experimental

Materials and Techniques.—Dry tetrahydrofuran (THF) was obtained by distillation from potassium. Dry diethyl ether was obtained by distillation from lithium aluminium hydride. Di-isopropylamine was distilled from calcium hydride. Thin layer chromatograms were obtained using Merck '5734' plastic backed plates and short column chromatography was carried out using either Merck '7736' or '7734' silica gel. N.m.r. data were obtained from Jeol-C60 or Perkin-Elmer R-600 FT, or Bruker WP80 instruments. Spectra were recorded in $CDCl_3$ solution with $SiMe_4$ as internal standard. I.r. spectra were obtained from a Pye Unicam SP200 grating i.r. spectrometer as liquid films unless otherwise stated. Light petroleum was of the b.p. range 40—60 °C.

Methylthiomethyltriphenylphosphonium Chloride (4; R = SMe).—A solution of triphenylphosphine (262 g, 1 mol) and methylthiomethyl chloride (96.6 g, 1 mol) in acetonitrile (1 l) was refluxed for 5 h. The solution was allowed to cool to room temperature and the resulting white crystalline solid was filtered off. The filtrate was reduced in volume by half and a second crop of product was obtained on cooling to 0 °C; total yield of salt (293 g, 86.7%), m.p. 218—220 °C (lit.,[16] 219.5—220.5 °C); $\nu_{max.}$ (KBr) 3 050, 2 850, and 2 750 cm^{-1}; δ_H 2.15 (3 H, s, SCH_3), 5.3 (2 H, d, CH_2), and 7.8 (15 H, m, Ph_3P).

Triphenyl(phenylthiomethyl)phosphonium Iodide (4; R = SPh).—This was prepared as for the methylthio derivative (4; R = SMe) above, from triphenylphosphine (262 g, 1 mol) and iodomethylphenyl sulphide (250 g, 1 mol).[17] The product was obtained as a yellow solid (466 g, 91%), m.p. 127—128 °C (from chloroform–ethyl acetate) (Found: C, 58.4; H, 3.95. $C_{25}H_{22}IPS$ requires C, 58.6; H, 4.33%); δ_H 5.38 (2 H, d, CH_2), 7.4 (5 H, m, SPh), and 7.85 (15 H, m, Ph_3P).

1-*Methylthiovinyltriphenylphosphonium Chloride* (1; R = SMe).—To a solution of the phosphonium salt (4; R = SMe) (50 g, 0.14 mol) in dry acetonitrile (250 ml) was rapidly added *N,N*-dimethylmethyleneammonium chloride (5) (28.1 g, 0.3 mol). The mixture was refluxed under nitrogen until n.m.r. analysis indicated complete reaction (*ca.* 60 h). The solvent was removed and the residue was taken up in chloroform (250 ml) and washed with brine (3 × 50 ml). The chloroform layer was dried ($MgSO_4$) and the solvent was removed to afford a pale yellow oil which crystallised on trituration with ether to give (1; R = SMe) (43.5 g, 84%), m.p. 142—144 °C (from chloroform–ethyl acetate); δ_H 2.7 (3 H, s, SCH_3), 6.1—7.2 (2 H, m, CH_2), and 7.8 (15 H, m, Ph_3P). It was analysed as the fluoroborate, m.p. 197—198 °C (from chloroform–ethyl acetate) (Found: C, 59.6; H, 5.05. $C_{21}H_{20}BF_4PS$ requires C, 59.7; H, 4.75%).

Triphenyl-1-phenylthiovinylphosphonium Iodide (1; R = SPh).—This was prepared from (4; R = SPh) as for (1; R = SMe) above. The reaction was complete in *ca.* 15 h. The product was obtained as a yellow solid (89%), m.p. 145—146 °C (from acetonitrile–ethyl acetate) (Found: C, 59.35; H, 4.15. $C_{26}H_{22}IPS$ requires C, 59.5; H, 4.2%); δ_H 6.35—7.0 (2 H, m, CH_2), 7.55 (5 H, m, SPh), and 7.95 (15 H, m, Ph_3P).

Triphenyl-1-phenylvinylphosphonium Tetrafluoroborate (1; R = Ph).—Benzyltriphenylphosphonium bromide (433 mg,

1 mmol) was dissolved in dry acetonitrile (10 ml). *N,N*-Dimethylmethyleneammonium chloride (5) (187 mg, 2 mmol) was added followed by DBU (304 mg, 2 mmol), and the mixture was refluxed for 16 h. The acetonitrile was removed and the residue was partitioned between chloroform and water. The chloroform layer was dried ($MgSO_4$) and evaporated. The residue was triturated with ether (3 × 10 ml) and the washings discarded. The residue was dissolved in water and treated with aqueous $NaBF_4$ to give the solid product (270 mg, 60%), m.p. 159—160 °C (from chloroform–ethyl acetate) (Found: C, 69.05; H, 5.3. $C_{26}H_{22}BF_4P$ requires C, 69.05; H, 4.90%); δ_H 6.35 (1 H, d, CH), and 6.55—7.90 (21 H, m, Ph and CH).

Diethyl 3-Methyl-4-phenylthiocyclopent-3-ene-1,1-dicarboxylate (8).—The ketodiester (7) [12] (540 mg, 2.5 mmol) was dissolved in dry THF (20 ml) and a 50% sodium hydride dispersion (120 mg, 2.5 mmol) was added portionwise. The mixture was stirred for 10 min after which the phosphonium salt (1; R = SPh) (1.31 g, 2.5 mmol) was added all at once. The mixture was stirred for 3 h after which the THF was removed and the residue partitioned between ether and water. The ether layer was dried ($MgSO_4$) and evaporated. Chromatography with ethyl acetate–light petroleum, 5 : 95 afforded the product (8) (750 mg, 90%) as a pale yellow oil (Found: C, 64.4; H, 6.4. $C_{18}H_{22}O_4S$ requires C, 64.6; H, 6.6%); $\nu_{max.}$ 1 745 cm^{-1}; δ_H 1.2 (6 H, t, 2 × CH_3), 1.85br (3 H, s, CH_3), 3.1 br (4 H, s, ring CH_2's), 4.25 (4 H, q, OCH_2), and 7.4 (5 H, s, SPh).

Diethyl 3-Methyl-4-oxocyclopentane-1,1-dicarboxylate (9).—Vinyl sulphide (8) (185 mg) was refluxed in trifluoroacetic acid (5 ml) and chloroform (5 ml) for 5 days. The trifluoroacetic acid was neutralised by the addition of aqueous sodium hydrogencarbonate after which the layers were separated. The aqueous layer was extracted with chloroform (2 × 10 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was chromatographed with ethyl acetate–light petroleum (1 : 9) to give the product (9) as a colourless oil (73 mg, 56%); $\nu_{max.}$ 1 750 cm^{-1}; δ_H 1.3 (9 H, m, 3 × CH_3), 2.0—3.1 (5 H, m, ring H's), 4.35 (4 H, q, 2 × CH_2). The compound was analysed as the dinitrophenylhydrazone derivative, m.p. 93—95 °C (from EtOH) (Found: C, 51.25; H, 5.3; N, 13.05. $C_{18}H_{22}N_4O_8$ requires C, 51.2; H, 5.2; N, 13.2%).

Methyl Dimethoxyacetate (12; R = H).—To a solution of glyoxylic acid hydrate (50 g, 0.544 mol) in trimethyl orthoformate (543 g, 2.72 mol) contained in a spinning-band column distillation flask (1 l) was added toluene-*p*-sulphonic acid (10 g). After 3 h anhydrous potassium carbonate (10 g) was also added and the contents of the flask were distilled through the spinning band column. The product was obtained as a colourless liquid (57.4 g, 79%), b.p. 64—67 °C at 20 mmHg (lit.,[18] b.p. 60—61 °C at 18 mmHg); $\nu_{max.}$ 2 860 and 1 760; δ_H 3.54 (6 H, s, ether OCH_3), 3.93 (3 H, s, ester OCH_3), and 4.97 (1 H, s, CH).

Alkylation of methyl dimethoxyacetate. The method used was essentially that described by Huet.[15]

1-(1,3-Dithian-2-yl)-2,2-dimethoxypropan-1-one (13; R = Me).—Under nitrogen, 1,3-dithiane (14.95 g, 0.125 mol) and di-isopropylamine (17.44 ml, 0.125 mol) were added to THF (1.2 l). The mixture was cooled to −78 °C and n-butyllithium in hexane (242 ml, 0.249 mol) was added dropwise with stirring during 20 min. After being stirred at −78 °C for a further 20 min, a solution of methyl 2,2-dimethoxypropanoate (12; R = Me) (18.53 g, 0.125 mol) in dry THF was added dropwise during 30 min. After being stirred for a further 20 min the solution was quenched with water and the layers were separated. The aqueous layer was extracted with ether (2 × 100 ml) and the combined organic layers washed with brine (200 ml) and dried ($MgSO_4$). The solvent was removed to give a light brown oil which crystallised. Recrystallisation from light petroleum gave (13; R = Me) as a white crystalline solid (26.8 g, 91%), m.p. 46—48 °C (Found: C, 45.7; H, 6.7. $C_{19}H_{16}O_3S_2$ requires C, 45.8; H, 6.8%); $\nu_{max.}$ 2 850 and 1 715 cm^{-1}; δ_H 1.55 (3 H, s, CH_3), 2.0—2.5 (4 H, m, dithiane 4- and 6-CH_2), 2.5—2.8 (2 H, m, dithiane 5-CH_2), 3.33 (6 H, s, OCH_3), and 4.88 (1 H, s, dithiane CH).

1-(1,3-Dithian-2-yl)propane-1,2-dione (10; R = Me).—The acetal (13; R = Me) (4.45 g, 19 mmol) was dissolved in 5% aqueous trifluoroacetic acid and stirred at room temperature for 10 min. The mixture was diluted with ether (150 ml) and poured into water (100 ml). The organic layer was washed with water (3 × 50 ml) and then saturated aqueous sodium hydrogencarbonate (to neutrality), dried ($MgSO_4$), and evaporated to give the product (10; R = Me) as a bright yellow solid, m.p. 43—45 °C (from light petroleum) (Found: C, 44.15; H, 5.15. $C_7H_{10}O_2S_2$ requires C, 44.2; H, 5.3%); $\nu_{max.}$ 1 710 cm^{-1}; δ_H 1.75—2.8 (4 H, m, dithiane 4- and 6-axial H and 5-CH_2), 2.48 (3 H, s, CH_3), 2.95—3.55 (2 H, m, dithiane 4- and 6-equatorial H), and 5.1 (1 H, s, dithiane CH).

2-Methyl-3-phenylthio-6,10-dithiaspiro[4.5]dec-2-en-1-one (11; R^1 = Me, R^2 = Ph).—The diketodithiane (10; R = Me) (1.19 g, 6.26 mmol) was dissolved in dry THF (25 ml) under nitrogen and cooled to 0 °C. A 50% sodium hydride dispersion (0.34 g, 7 mmol) was added in portions with vigorous stirring and then after 30 min the phosphonium salt (1; R = SPh) (3.1 g, 6.9 mmol). After being stirred for 30 min the mixture was poured into water (100 ml) and extracted with chloroform (3 × 25 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography with ethyl acetate–light petroleum, 1 : 9 gave (11; R^1 = Me, R^2 = Ph) as a colourless crystalline solid (1.45 g, 75%), m.p. 162.5—163 °C (from light petroleum) (Found: C, 58.2; H, 5.6. $C_{15}H_{16}OS_3$ requires C, 58.2; H, 5.2%); $\nu_{max.}$ ($CHBr_3$) 1 680 cm^{-1}; δ_H 1.6 (2 H, m, 8-CH_2), 1.78 (3 H, t, CH_3), 2.1 (2 H, dt, 7- and 9-equatorial H's), 2.52 (2 H, dd, 4-CH_2), 3.99 (2 H, m, 7- and 9-axial H's), and 6.8—7.1 (5 H, m, SPh).

2-Methyl-3-methylthio-6,10-dithiospiro[4.5]dec-2-en-1-one (11; R^1 = R^2 = Me).—The method used was as for (11; R^1 = Me, R^2 = Ph) above. The product was obtained as a colourless crystalline solid (75%), m.p. 163—166 °C (Found: C, 48.95; H, 5.7. $C_{10}H_{14}OS_3$ requires C, 48.75; H, 5.75%); $\nu_{max.}$ (KBr) 1 690 cm^{-1}; δ_H 1.7 (3 H, t, CH_3), 1.5—3.0 (4 H, m, 7- and 9-equatorial H's and 8-CH_2), 2.34 (3 H, s, SCH_3), 2.79 (2 H, dd, 4-CH_2), and 3.97 (2 H, dt, 7- and 9-axial H's).

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