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SYNTHESIS OF DIMETHYL α-HYDROXY PHOSPHONATES FROM DIMETHYL PHOSPHITE AND PHENACYL CHLORIDE AND CYANIDE

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Abstract– Phenacyl chloride reacts with dimethyl phosphite in several solvents, in the presence of bases e.g. piperidine to yield dimethyl (α-chloromethyl) α-hydroxy benzyl phosphonate. Piperidine hydrochloride and N-piperidinomethyl phenyl ketone were the by products found. Neither dimethyl 1-phenyl vinyl phosphate nor dimethyl epoxyethyl phosphonate was detected in this reaction. The action of sodium ethoxide and amines on the hydroxy phosphonate yield dimethyl 1-phenyl vinyl phosphate.

We have found that phenacyl cyanide also reacts with dimethyl phosphite to give the corresponding dimethyl (α-cyanomethyl) α-hydroxy benzyl phosphonate.

On the other hand, phenacyl bromides yield only acetophenone, piperidine hydrobromide and N-piperidinomethyl phenyl ketone hydrobromide. When dimethyl phosphite was omitted in this reaction, acetophenone was not obtained.

INTRODUCTION

THE nucleophilic addition of dialkyl phosphites to a carbonyl function of haloketones of general structure R—CO—$(CH_2)_n$Cl is typically carried out under anhydrous conditions in the presence of a catalytic amount of base such as amines or alkoxides.[1, 2] The end product is the corresponding α-hydroxyphosphonate ester. Epoxyphosphonate esters have also been reported as products of these reactions.[3]

It is known that reactions between α-haloketones and P(III) compounds are extremely complex and a variety of products have been reported.[1, 4, 5] They may involve attack on the α-C atom, carbonyl C atom, α and β H atoms, carbonyl O atom and halogen atom, depending on the structure of the phosphorus compound, the ketone, the nature of the halogen, the temp and solvent used in the reaction.[6]

We have not found previous reports of the reaction between phenacyl chloride or cyanide and dimethyl phosphite (DMP). Dimethyl (α-chloromethyl) α-hydroxy benzyl phosphonate has only been obtained from the reaction between phenacyl chloride and trimethyl phosphite in methanol in 30% yield.[1, 7] In the presence of aprotic solvents the product of this reaction was mainly dimethyl 1-phenyl vinyl phosphate.[1, 5, 8, 9] With sodium dialkyl phosphites[10] a mixture of two products was obtained, the epoxy phosphonate ester and the isomeric vinyl phosphate. The hydroxy phosphonate was obtained from the mixture with HCl.[5] α-Bromoketones gave mainly ketophosphonates[1, 5] under the same reaction conditions.

No reports exist of the reaction of phosphites with other α-substituted ketones.

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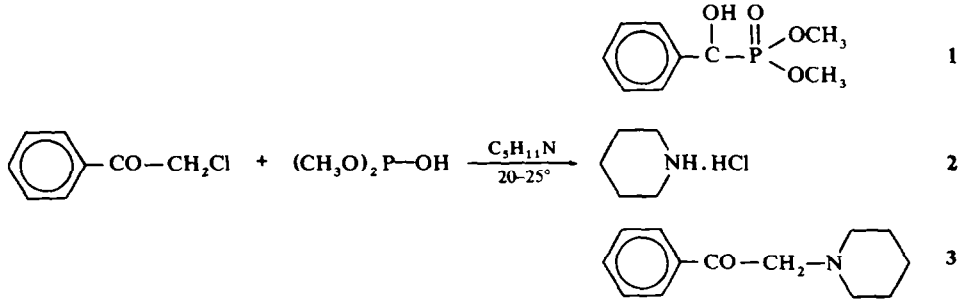
Among these we found that phenacyl cyanide behaves like phenacyl chloride; dimethyl (α-cyanomethyl) α-hydroxy benzyl phosphonate was the main product obtained, following the normal addition to carbonyl group, without side reactions.

This paper is concerned with the formation of dimethyl hydroxy phosphonates from the reaction between phenacyl chloride and cyanide with DMP in protic and aprotic solvents, using amines as catalysts.

RESULTS AND DISCUSSION

The reaction of phenacyl chloride with DMP in the presence of piperidine as catalyst appears to follow Eq. (1).

It yielded a cryst mixture of dimethyl (α-chloromethyl)α-hydroxy benzyl phosphonate (**1**) and piperidine hydrochloride (**2**) which could be separated by recrystallization from hot benzene. In the filtrate another compound was found which was



Equation 1

identified as N-piperidinomethyl phenyl ketone (**3**). The structure of the products was confirmed by elemental analysis, IR and NMR spectroscopy and by comparison with authentic samples. Compound **1** was prepared from phenacyl chloride and trimethyl phosphite and **3** was separated from the solution as an hydrochloride and transformed in its perchlorate salt[11, 12]. An authentic sample was prepared from phenacyl chloride and piperidine.[13]

The reaction carried out in ethyl ether or methanol gave the same products under the same reaction conditions. From methanol **1** was obtained after evaporation of the solvent. When piperidine was omitted phenacyl chloride was recovered unchanged from the mixture.

Neither the vinyl compound (**4**) nor the isomeric oxo compound (**5**) was found in the mixture by NMR or IR spectroscopy.

The reaction temp must be kept between 20–25°, since it is slightly exothermic. At higher temp a lower yield of **1** was obtained. Increasing amounts of base and a temp of about 80° yielded only dimethyl 1-phenyl vinyl phosphate (**4**). The same results were obtained when **1** was heated with piperidine (molar ratio 1:2). An authentic

sample of **4** was prepared from phenacyl chloride and trimethyl phosphite.[8,9] Its identity was confirmed by GLC, IR and NMR spectroscopy.

The experimental results showed that **1** is formed even at high temp but it rearranges to the corresponding vinyl phosphate (**4**), in yields depending on the amount of base added. Only at low temp can **1** be isolated in good yields.

The results are in accordance with the literature. It is known that phenacyl chloride with dialkyl phosphites and triethylamine in equimolar quantities yield vinyl phosphate.[10] Recently[14] it was shown that treatment of dialkyl phosphites with aromatic and alkyl-aryl ketones in the presence of very small amounts of base, at a temp below 30° led to dialkyl (diaryl hydroxy methane) phosphonate and the corresponding alkyl aryl phosphonate in good yield, which rearrange to phosphates at higher concentration of base even at room temp.

Treatment of **1** with sodium ethoxide in ethanol gave dimethyl 1-phenyl vinyl phosphate (**4**) in agreement with the reactions postulated by Meisters *et al.*[5] No epoxy phosphonate ester (**5**) was detected by NMR or IR spectroscopy.

Other amines were also used as catalysts. With primary amines e.g. cyclohexylamine, the hydroxy phosphonate (**1**) and cyclohexylamine hydrochloride were obtained. With tertiary amines e.g. triethylamine, after 24 hr **1** was obtained in good yield; some triethylamine hydrochloride separated from the solution; with pyridine as catalyst the hydroxy phosphonate (**1**) was not obtained.

With phenacyl bromide the reaction follows another course. We isolated a solid identified as piperidine hydrobromide and N-piperidinomethyl phenyl ketone hydrobromide (after transforming it in its perchlorate salt). After evaporation of the solvent NMR spectroscopy showed the presence of acetophenone as main product. This data was confirmed by GLC by comparison with a pure sample. When DMP was omitted, acetophenone was not detected. Other *p*-phenacyl bromides follow the same reaction steps.

Besides, we found that phenacyl cyanide reacts with DMP to give dimethyl (α-cyanomethyl)α-hydroxy benzyl phosphonate, without side products. Other ketones α-substituted by electron withdrawing groups e.g. nitro or ethyl ester did not appear to yield the corresponding hydroxy phosphonates.

Other ketones β- and γ-halosubstituted were found to give α-hydroxy phosphonates but in low yields (10–20%) under the conditions studied. When β-chloropropiophenone or γ-chlorobutyrophenone reacted with DMP in the presence of piperidine, a mixture resulted consisting of piperidine hydrochloride, N-piperidinoethyl or N-piperidinopropyl phenyl ketone hydrochloride and the corresponding α-hydroxy phosphonates, which proved very difficult to separate but was identified by IR spectroscopy.

With other dialkyl phosphites, the corresponding hydroxy phosphonates could not be obtained under the reaction conditions studied.

EXPERIMENTAL

M.ps. were determined with a Buchi apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 spectrometer using TMS as internal standard. GLC was carried out with an Aerograph 1522-B gas chromatograph. IR spectra were measured with a Perkin–Elmer 337 spectrometer using "Fluorolube" and "nujol" mulls. Elemental analysis were performed by the Microanalysis Laboratory of Fac. Cs. Exactas (Universidad de Buenos Aires) and by A. Bernhardt Laboratory (W. Germany).

Solvents were reagent grade. DMP was dried over 4 A molecular sieve (Merck, Darmstadt) and distilled under vacuum b.p. 70°/25 mm Hg. NMR spectra (C_6D_6) showed a doublet at τ 6·8 (J_{P-OCH} 12 c/s). Phenacyl chloride was purified by recrystallization from EtOH-water, m.p. 53–54°. Phenacyl bromide was synthetized from acetophenone and bromine in CCl_4 soln and recryst from EtOH-water, m.p. 47–48°. Phenacyl cyanide was purchased from Eastman Kodak. Piperidine was obtained from Schuchardt, triethylamine from L. Light & Co., pyridine from Fisher Scientific Co., and cyclohexylamine was reagent grade; all were used without further purification.

Reaction of dimethyl phosphite with phenacyl chloride

(a) *In the presence of piperidine—with benzene or ether as solvent.* To a soln of phenacyl chloride (13 mmoles) in 10 ml dry C_6H_6 or ether, freshly distilled DMP (2 ml) and piperidine (4 mmoles) were added. The temp was kept between 20–25°. Precipitation began immediately. After 5–10 min, the solid was separated by filtration and recryst from hot C_6H_6. It consisted of a mixture of **1**, m.p. 149–150° (lit[1] 144–146° (MeOH). (Found: C, 45·36; H, 4·86; Cl, 13·43; P, 11·86. Calc. for $C_{10}H_{14}ClO_4P$: C, 45·36; H, 5·29; Cl, 13·42; P, 11·72%) which separated on cooling with 50–55% yield. Compd **2** remained insoluble in hot C_6H_6, m.p. 243–245°. (Found: C, 49·08; H, 10·2; Cl, 29·06. Calc. for $C_5H_{11}N \cdot ClH$: C, 49·38; H, 9·88; Cl, 29·21%).

The structure of the products was confirmed by IR and NMR spectra and by comparison with authentic samples. IR spectrum of **1** contained bands at 3250 (—OH); 1220 (P=O); 1175 (P—OCH_3); 675 cm^{-1} (CH-Cl); bands due to C=C (1635 cm^{-1}); oxiran ring (1235 cm^{-1}) and C=O (1690–1710 cm^{-1}) were absent. The NMR spectrum (Cl_3CD) showed two sets of doublets at τ 6·45 and τ 6·25 (J_{P-OCH} 13 c/s); due to P—OCH_3 protons; the —CH_2 protons appeared as a weakly resolved pair of doublets at τ 5·85 and τ 5·72 (J_{P-C-CH} 8 c/s); the OH proton signal appeared superimposed with P—OMe protons which was removed from the spectrum on deuteration; a multiplet between τ 2·74 and 2·2 corresponded to five aromatic protons.

An authentic sample of **1**, and identical in all respects, was prepared from equimolar quantities of phenacyl chloride and trimethyl phosphite (TMP) in methanol according to Tieman[7], m.p. 150–151°.

Another product was identified in soln of the reaction mixture. GLC analysis showed a peak with identical retention time as an authentic sample of **3** prepared from phenacyl chloride and piperidine (molar ratio 1:2) in ether or benzene[13]. No vinyl phosphate **4** was found by GLC analysis by comparison with an authentic sample.[8, 9]

GLC analysis was performed using a 6 ft × ⅛ in o.d. S.S. column packed with 5% Silicone 30 on 60/80 Chromosorb W. The instrument operated isothermally at 150°, with N_2 as carrier gas and a Flame ionization detector.

Compd **3** could be isolated from the soln by treatment of the filtrate with HCl. An oil separated which was impossible to crystallize but could be dissolved in water and reprecipitated with $HClO_4$ as its perchlorate salt,[11, 12] m.p. 184–186°. (Found: C, 51·4; H, 6·2; N, 5·05. Calc. for $C_{13}H_{17}NO \cdot HClO_4$: C, 51·4; H, 5·93; N, 4·63%). The IR spectra showed a C=O band at 1690 cm^{-1}.

(b) *In the presence of piperidine—with methanol as solvent.* The same reaction carried out in MeOH gave after evaporation of the solvent a residue which recryst from hot C_6H_6 as **1** yield 48–50%.

(c) *Without catalyst and methanol as solvent.* In the reaction carried out with equimolar quantities of phenacyl chloride and DMP in MeOH, without catalyst the starting materials unchanged, were obtained after evaporation of the solvent.

(d) *In the presence of other amines as catalyst.* (1) *Cyclohexylamine.* To a soln of phenacyl chloride (6 mmoles) in 5 ml C_6H_6, DMP (0·5 ml), cyclohexylamine (2 mmoles) was added. The mixture was worked up as before and after recrystallization of the solid product from hot C_6H_6, **1** and cyclohexylamine hydrochloride, m.p. 207–208° were identified as before (yield 30%).

(2) *Triethylamine.* To a soln of phenacyl chloride (7 mmoles) in 5 ml C_6H_6, 0·5 ml DMP and TEA (2 mmoles) were added. After 24 h at room temp a solid separated, which recryst to give **1** in 80% yield. From the filtrate triethylamine hydrochloride was precipitated, m.p. 252°.

(3) *Pyridine.* Under conditions as before, **1** could not be obtained. The only products isolated were pyridine hydrochloride m.p. 145° and N-pyridinomethyl phenyl ketone hydrochloride, which was transformed in its perchlorate salt m.p. 187–189° (lit[11, 12] 189–190°).

Reaction of DMP and phenacyl chloride in C_6H_6 under reflux

(a) *With piperidine as catalyst.* Working up the mixture as before but maintaining the soln under reflux

for 2 hr, a solid separated which was identified as N-piperidinomethyl phenyl ketone hydrochloride m.p. 209–211° (lit[13] 210–211°). On cooling the soln a small amount of **1** separated (yield 20%). Evaporation of the solvent yielded an oil. NMR (C_6D_6) showed protons due to a vinyl group at τ 4·6 and —CH_2 protons at τ 6·0 probably arising from unreacted phenacyl chloride.

(b) *With excess of piperidine.* To a soln of phenacyl chloride (7 mmoles) in C_6H_6, 0·5 ml of DMP and 15 mmoles piperidine were added. The soln was refluxed for 2 h, but **1** was not obtained. Dimethyl l-phenyl vinyl phosphate was the main product as detected by NMR after evaporation of the solvent. There was a signal due to vinyl protons at τ 4·7 ($J_{C=CH_2}$ 2 c/s; $J_{P-O-C=CH}$ 15 c/s); the P—OMe protons appeared as a doublet at τ 6·5 (J_{P-OCH} 11 c/s); the aromatic protons appeared between τ 3·2–1·8. The product could not be further purified by distillation but was identical with an authentic sample prepared from phenacyl chloride and TMP in ether[8,9] as showed by NMR, IR and GLC. IR bands due to C=C (1640); P=O (1260); P—OCH_3 (1180) were found; C=O (1690–1710) and oxiran ring (1235 cm^{-1}) were absent. GLC analysis was performed with the same column as before.

Reaction of **1** *with piperidine*

Compound **1** (0·2 mmoles) was heated with 10 ml dry C_6H_6 until complete dissolution; 0·4 mmoles piperidine was then added (molar ratio 1:2). Piperidine hydrochloride separated immediately. After heating 5 min the mixture was filtered and the solvent evaporated under vacuum. NMR spectrum of the residual oil showed that it was mainly **4**. A Me signal at τ 7·9 was also detected and identified as corresponding to acetophenone. All the components were identified by GLC. A 10 ft × $\frac{1}{8}$ in o.d. pyrex column packed with 2·5% QF 1 + 2·5% DC 200 on 100/120 Varaport 30, held isothermally at 120°, with N_2 as carrier gas and a flame ionization detector was used to identify acetophenone by comparison with a pure sample.

Reaction of **1** *with sodium ethoxide*

Compound **1** (0·1 mmole) was dissolved in EtOH and the soln was made 0·1 M in EtONa. The soln was heated under reflux for 2 hr; the NaCl filtered off and the solvent evaporated under vacuum. The residue was an oil. Spectroscopic investigation of the product showed the presence of **4**. No epoxy signal could be detected by NMR or IR.

Reaction of DMP with phenacyl cyanide

To a soln of phenacyl cyanide (3·6 mmoles) in C_6H_6, 0·5 ml of DMP, freshly distilled and piperidine (1·2 mmoles) was added. A solid was obtained m.p. 181–182° (Cl_3CH) in 85% yield. It was identified as dimethyl (α-cyanomethyl) α-hydroxy benzyl phosphate. (Found: C, 51·3; H, 5·7; N, 5·6; P, 12·3. Calc. for $C_{11}H_{14}NO_4P$: C, 51·3; H, 5·49; N, 5·49; P, 12·16%).

The structure was confirmed by IR and NMR spectroscopy. The IR spectra contained bands at 3240 (—OH); 1220 (P=O); 1175 (P—OCH_3); 2260 cm^{-1} (CH_2CN) bands due to C=C (1635); oxiran ring (1235) and C=O (1690 cm^{-1}) were absent. The NMR (Cl_3CD) showed two pair of doublets due to P—OMe protons at τ 6·43 and τ 6·29 (J_{P-OCH} 11 c/s); two peaks due to —CH_2 protons at τ 6·93 and τ 6·77 because of coupling to P; the OH proton appeared superimposed with P—OMe and was removed from soln on deuteration; the aromatic protons appeared as a multiplet centred at τ 2·6.

Attempted reaction between DMP and phenacyl bromide

Phenacyl bromide (2·17 g) was dissolved in 10 ml C_6H_6 and 1 ml DMP and 1 ml piperidine was added. A solid separated immediately and was identified as piperidine hydrobromide m.p. 230°. GLC analysis of the filtrate showed the presence of **3**. At room temp until the following day it separated as the hydrobromide as seen from the NMR spectra and by transformation to its perchlorate salt m.p. 185–186°. After evaporation of the solvent the NMR (C_6D_6) showed a signal due to Me protons at τ 7·83. GLC analysis showed the presence of acetophenone by comparison of its retention time with a pure sample. Neither **4** nor **5** nor ketophosphonate was detected by NMR after solvent evaporation. When DMP was omitted in this reaction, acetophenone was not obtained. Only piperidine hydrobromide and **3** were the products identified; according to F. F. Blicke *et al.*[13]

Reaction between DMP and β-chloropropiophenone and γ-chlorobutyrophenone

The reaction carried out as above gave a mixture of piperidine hydrochloride and another solid which in the case of β-chloropropiophenone had m.p. 160–175°. Spectroscopic investigation by NMR (Cl_3CD) and IR data showed evidence of a mixture of dimethyl (α-chloroethyl) α-hydroxy benzyl phosphonate and

N-piperidinoethyl phenyl ketone hydrochloride which was not possible to separate by recrystallization from Cl_3CH, H_2O or C_6H_6. IR bands at 3100 (—OH); 1230 (P=O); 1150 (P—OCH_3); 660–690 (CH—Cl); 1690 (C=C) and 2550–2920 (N^+H).

In the case of γ-chlorobutyrophenone, the solid obtained was mainly the corresponding hydroxyphosphonate m.p. 161–162·5°. IR bands at 3250 cm^{-1} (—OH); 1220 (P=O); 1030 (P—OCH_3); 680–700 (CH—Cl); yield 10–20%.

Attempted reaction between phenacyl chloride and other dialkyl phosphites

The reaction carried out with diethyl phosphite and diisopropyl phosphite under the same conditions gave only piperidine hydrochloride and N-piperidinomethyl phenyl ketone. No hydroxyphosphonate ester was detected by NMR or IR.

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