

Reactions of Triethyl Phosphite with 2-Haloacetyl-furan, -thiophene, -pyrrole and -*N*-methylpyrrole (1)

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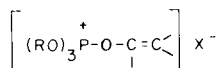
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Trialkyl phosphites react with α -haloketones to give enol phosphates $(RO)_2P(O)-O-C=C$ (Perkow reaction), β -ketophosphonates $(RO)_2P(O)-CH_2-CO-$ (Michaelis-Arbuzov reaction) or a mixture of both isomers. The course of the two competitive reactions depends on the nature of the halogen atom, on the structure of the carbonyl compound and on the reaction conditions (temperature, solvent) (2-4).

The Michaelis-Arbuzov reaction mechanism has been widely studied and involved an attack of the phosphorus atom to the saturated carbon atom (5).

For the Perkow reaction several mechanisms have been proposed (6), the most likely ones involve the initial attack by the nucleophilic phosphorus at the carbonyl carbon atom, the saturated carbon atom, the carbonyl oxygen atom, or the halogen. In every case an enol phosphonium halide is formed from which alkyl halide is eliminated with the formation of an enol phosphate (6).



In our previous work the reaction of triethyl phosphite (TEP) with substituted α -haloacetophenones has been reported (4).

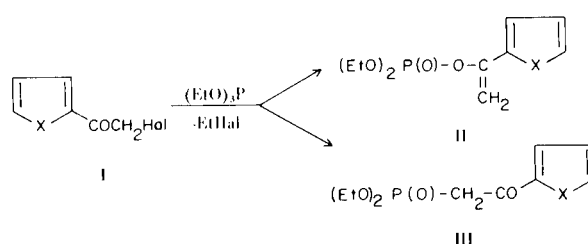
Recently, moreover, we reported a kinetic study of the Perkow reaction between some *p*-substituted α -chloroacetophenones and TEP (7). The results were in agreement with the mechanism involving the rate-determining addition of the phosphorus atom to the carbonyl carbon atom followed by rearrangement to enol phosphate.

These results have also been supported by a kinetic study of a series of aryl-substituted α -chloroisobutyrophenones and α -bromoisobutyrophenones with TEP (8).

Following this research work, the present paper reports the reaction between TEP and some heterocyclic five-membered α -halo ketones in order to study the effect of a heteroaromatic ring system on the two competitive reactions (Scheme I).

The results, listed in Table I, show that TEP reacts with

Scheme I



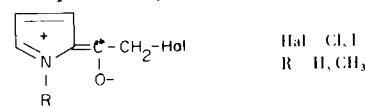
Ia: X = O	Hal: Cl	IIa: X = O
Ib: O	Br	Ib: S
Ic: O	I	
Id: S	Cl	
Ie: S	Br	IIIa: X = O
If: S	I	Ib: S
Ig: NH	Cl	Ic: NH
Ih: NH	I	Id: NCH ₃
Ii: NCH ₃	Cl	

2-chloroacetyl-furan and -thiophene to give quantitative yields of enol phosphates (reactions 1 and 8); with 2-bromoacetyl derivatives, instead, TEP give both enol phosphates and β -ketophosphonates, the latter in higher percentages (reactions 2-4 and 9-11). The furan and thiophene iodo derivatives give mainly β -ketophosphonates (reactions 5-7 and 12-14).

As observed in reactions of TEP with α -halo acetophenones, the nature of the halogen atom influences the course of the reaction (4). The comparison of the results with those of the corresponding benzene derivatives shows that the heterocyclic rings produce only small changes in the percentage of the two isomeric esters II and III. As previously noted, higher reaction temperatures increase the amount of β -ketophosphonate (2).

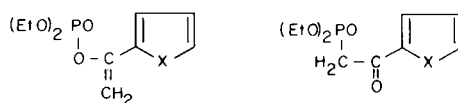
With 2-chloro- and iodoacetyl pyrrole (reactions 15 and 16) and 2-chloroacetyl-*N*-methylpyrrole (reaction 17) only β -ketophosphonate esters are obtained.

This can be explained by a strong mesomeric release of



(IV)

TABLE I

Reactions of $(\text{EtO})_3\text{P}$ and $\text{C}_4\text{H}_3\text{X}-\text{COCH}_2\text{Hal}$ 

No.	X	Hal	temp.	% yield	% yield
1	O	Cl	70	100	—
2	O	Br	20	32	68
3	O	Br	50	18	82
4	O	Br	70	16	84
5	O	I	20	26	74
6	O	I	50	6	94
7	O	I	70	6	94
8	S	Cl	70	100	—
9	S	Br	20	33	67
10	S	Br	50	24	76
11	S	Br	70	22	78
12	S	I	20	5	95
13	S	I	50	5	95
14	S	I	70	4	96
15	NH	Cl	70	—	100
16	NH	I	70	—	100
17	NCH ₃	Cl	70	—	100

TABLE II

Spectroscopic Characteristics of Enol Phosphates (II) and β -Ketophosphonates (III).

	Ir Spectra (cm^{-1})				Nmr Spectra (ppm, δ)	
	C=C	C=O	PO	POR	=CH ₂	-CH ₂ -
$(\text{EtO})_2\text{P}(\text{O})-\text{O}-\text{C}(\text{O})-\text{C}_4\text{H}_3\text{X}$ CH ₂						
IIa: X = O	1644		1270	1020	5.15	
b: S	1630		1270	1030	5.22	
$(\text{EtO})_2\text{P}(\text{O})-\text{CH}_2-\text{CO}-\text{C}_4\text{H}_3\text{X}$						
IIIa: X = O		1682	1255	1025		3.56
b: S		1655	1250	1025		3.46
c: NH		1645	1250	1025		3.54
d: NCH ₃		1645	1255	1025		3.52

electrons from the pyrrole ring to the carbonyl group (IV).

The carbonyl carbon atom is, thus, deactivated and, therefore, the phosphorus nucleophilic attack takes place on the saturated carbon atom to give β -ketophosphonate.

The same behaviour of the *N*-methyl derivative (Ii) leads us to exclude hypotheses such as hydrogen bonding, keto-enol equilibria, intermolecular association, etc. (9).

In addition, the infrared spectra (9), dipole moment values (10) and kinetics of alkaline hydrolysis of esters (11) confirm the presence of a similar mesomeric interaction in pyrrole carbonyl compounds.

In order to study the effect of the heteroaromatic nucleus (7) on reactivity of the Perkow reaction, we have undertaken a kinetic study of the reaction between TEP

and 2-chloroacetyl furan and -thiophene and such a study is currently under way.

Preliminary results show that the furan derivative reacts faster than α -chloroacetophenone and 2-chloroacetylthiophene (least reactive).

The same reactivity sequence was also found in other reactions in which the rate determining step is the attack of a nucleophile on the carbonyl carbon atom, e.g. alkaline hydrolysis of ester (11), reaction of acid chlorides with aniline (12), and Wittig reaction between stable ylids and aldehydes (13).

Structure for enol phosphates and β -ketophosphonates were established by spectral analysis (ir and nmr).

Enol phosphoric esters show the characteristic ir stretch-

TABLE III
Boiling Points, Analytical and Uv Data of Enol Phosphates and β -Ketophosphonates

	B. p. °C/mm	Formula	P %		Uv Spectra (a) (nm)	
			Calcd.	Found	λ max	log ϵ
$(\text{EtO})_2\text{P}(\text{O})-\text{C}-\text{C}_4\text{H}_3\text{X}$ CH ₂	IIa: X = O	C ₁₀ H ₁₅ O ₅ P	12.58	12.51	259	4.16
	b: S	C ₁₀ H ₁₅ O ₄ PS	11.81	11.69	273	4.33
$(\text{EtO})_2\text{P}(\text{O})-\text{CH}_2-\text{CO}-\text{C}_4\text{H}_3\text{X}$	IIIa: X = O	C ₁₀ H ₁₅ O ₅ P	12.58	12.38	255 270 (c)	4.32 4.25
	b: S	C ₁₀ H ₁₅ O ₄ PS	11.81	11.65	265 280 (c)	4.29 4.22
	c: NH	C ₁₀ H ₁₆ NO ₄ P	12.63	12.50	260 (c) 295	3.73 4.23
	d: NCH ₃	C ₁₁ H ₁₈ NO ₄ P	11.95	11.77	260 (c) 293	3.63 4.14

(a) In ethanol 95%. (b) Distilled with little decomposition; purified from a silica-gel column. (c) Inflection.

ing frequency of the vinyl group, located at 1630-1644 cm^{-1} , while β -ketophosphonate show that of the carbonyl group, located at 1642-1682 cm^{-1} (Table II). Moreover in both esters II and III the absorption bands characteristic of the phosphoric group (PO, POEt) are present.

The nmr spectra (Table II) of enol phosphates exhibit a multiplet centered at 5.10-5.22 ppm (14) while those of β -ketophosphonates show the typical doublet centered at 3.46-3.56 ppm (16).

EXPERIMENTAL

Starting Materials.

2-Chloroacetyl furan (Ia).

This compound was obtained by the method of Burger and Harnest (16) from 2-furoyl chloride with an ether solution of diazomethane followed by decomposition of the diazocompound with dry hydrogen chloride (50% yield), m.p. 30-31° from benzene-petroleum ether.

2-Bromoacetyl furan (Ib).

A solution of bromine (0.2 mole) in 50 ml. of carbon tetrachloride was added to a mixture of 2-acetyl furan (0.1 mole), in 150 ml. of carbon tetrachloride, and a few iron filings. The solution was refluxed for thirty minutes at the end of which time evolution of hydrogen bromide had ceased. The solvent was removed by distillation and the residue was fractionated (yield 50%), b.p. 76°/0.3 mm., m.p. 34° from petroleum ether (17).

2-Iodoacetyl furan (Ic).

This compound was obtained from Ia (6.4 g., 0.05 mole) by treatment with sodium iodide (20 g., 0.12 mole) in 100 ml. of acetone. The mixture after standing at 20° for ca. 30 minutes, was poured into water. The product was extracted with ether and the solution evaporated. The residue was purified by distillation (50% yield), b.p. 100°/1 mm. The compound underwent decomposition during distillation and storage.

2-Chloroacetylthiophene (Id).

A mixture of thiophene (25 g., 0.3 mole) and chloroacetyl chloride (33.6 g., 0.3 mole) in 50 ml. of carbon disulfide was added during one hour with stirring to a mixture of aluminum chloride (52.8 g., 0.4 mole) in 100 ml. of carbon disulfide. After one hour the solvent was removed by distillation and the residue was treated with 300 ml. of dilute hydrochloric acid and the mixture was heated for ca. 30 minutes. The cold mixture was extracted with ether and after evaporation of the solvent the product was collected (55% yield), m.p. 47° from petroleum ether, coincident to that of the product obtained from 2-acetylthiophene chlorination (18). The ir spectrum in carbon tetrachloride is the same as that reported in the literature (19).

2-Bromoacetylthiophene (Ie).

This compound was obtained following the method for Ib from bromination (25.5 g., 0.28 mole of bromine in carbon tetrachloride) of 2-acetyl thiophene (20 g., 0.14 mole) with a few iron filings (60% yield), b.p. 95°/1.5 mm (20).

2-Iodoacetylthiophene (If).

This compound was obtained from Id and sodium iodide in acetone, as for the Ic synthesis (55% yield), b.p. 115°/1 mm.

Anal. Calcd. for C₆H₅IOS: 1, 50.36. Found: 50.22.

2-Chloroacetylpyrrole (Ig).

Chloroacetyl chloride (22.2 g., 0.2 mole) in 50 ml. of benzene was added dropwise during one hour to a mixture of pyrrole (13.4 g., 0.2 mole) and aluminum chloride (34.3 g., 0.20 mole) in 200 ml. of benzene. After standing for 2 hours at room temperature, the product was isolated using the same procedure as for Id (40% yield), m.p. 118° from petroleum ether (21).

2-Iodoacetylpyrrole (Ih).

This compound was obtained by the method of Blicke *et al.* (21) from Ig with sodium iodide in acetone (90% yield), m.p. 130-131° from benzene.

2-Chloroacetyl-N-methylpyrrole (Ii).

This compound was prepared following the method for Ig (35%

yield), m.p. 47-48° from petroleum ether (22).

Synthesis of Phosphonate Esters.

Halo ketone (1) (0.1 mole) was added to TEP (0.12 mole) at the appropriate temperature. The reactions (yields and percentages) were followed by glc analysis (SE₃₀25% on Chromosorb P 30-60 mesh). The esters were purified by distillation at reduced pressure. The compounds underwent little thermal decomposition. The purity of the esters was verified by glc analysis.

In Table III boiling points, analytical and uv data of esters II and III are listed.

Spectroscopy.

Uv spectra were recorded on a Hitachi-Perkin Elmer model EPS 3T spectrometer in ethanol solutions (1.10^{-5} mole l⁻¹).

Ir spectra were recorded as liquid films on sodium chloride plates with a Perkin Elmer model 237 spectrometer. Nmr spectra were obtained with a Varian A-60 D spectrometer in carbon tetrachloride, using TMS as internal standard.

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