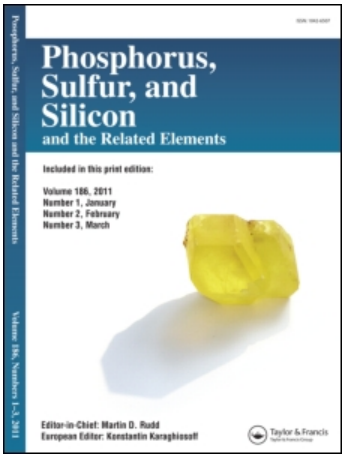

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SUBSTITUENT EFFECTS ON PHOSPHONATION OF γ-CHLOROPROPYL ARYL KETONES WITH TRIETHYL PHOSPHITE

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SUBSTITUENT EFFECTS ON PHOSPHONATION OF γ-CHLOROPROPYL ARYL KETONES WITH TRIETHYL PHOSPHITE

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Phosphonation of γ-chloropropyl aryl ketones **1** with triethyl phosphite yielded oxycyclopentyl phosphonates **2** and δ-ketophosphonates **3**. Formation of **2** was greatly facilitated by the presence of electron-releasing *p*-substituents on the phenyl group, particularly the methoxy group, which may delocalize the electrons of the methoxy oxygen towards carbonyl oxygen through resonance effect. The linear Hammett plots for **2** showed negative ρ value of -2.33 ($r = 0.993$) for the solution with TEP/**1** ratio of 4.5 and -3.09 ($r = 0.999$) for TEP/**1** ratio of 1.5. In contrast, the formation of **3** occurred through a carbonyl group-assisted reaction pathway and the Hammett plot with a positive ρ value of 1.33 ($r = 0.986$) indicated that the reaction was accelerated by the presence of deactivating halogen as substituents, through the inductive effect. The direct replacement of halogen *via* S_N2 mechanism displayed an expected rate constant of 0.67×10^{-6} $Lmol^{-1}s^{-1}$, and the formation of **3** (Y = H) was observed to occur at the rate of 3.83×10^{-6} $Lmol^{-1}s^{-1}$. This result indicates that an S_N2 mechanism was not important for the formation of δ-ketophosphonates.

Keywords: Carbonyl group-assisted mechanism; Oxycyclopentyl phosphonate; δ-Ketophosphonate; Substituent effect; Rate constant

INTRODUCTION

In the reaction of alkyl or aryl γ-chloropropyl ketones **1**, [R-CO-$(CH_2)_3$-Cl, R = alkyl or aryl] with triethyl phosphite (TEP),[1] the formation of 2-alkyl- or 2-aryl-2-tetrahydrofuranylphosphonates **2** and linear alkyl or aryl δ-ketophosphonates **3**, [R-CO-$(CH_2)_3$-$PO(OEt)_2$, R = alkyl or aryl] are known to be in competition, as shown in Scheme 1. Moreover, the product formation has also been found to be sensitive to the substituent effect. In this paper, we present experi-

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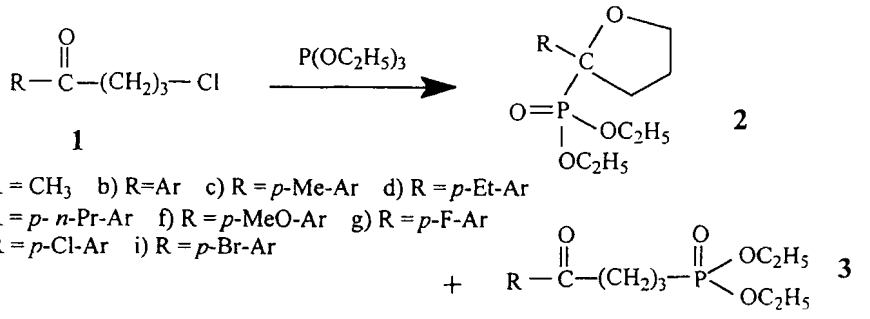


SCHEME 1 The reaction of γ-chloropropyl aryl ketone **1** and TEP

mental evidence showing that formation of these two products occurs through different mechanisms.

Judging from the structure, formation of oxycyclopentyl phosphonate **2** may involve a novel carbonyl oxygen (C-O$^-$) as a nucleophile, which attacks the terminal chlorocarbon in a favorable 5-membered-ring transition state. On the other hand, formation of linear δ-ketophosphonates may proceed either through the S_N2 mechanism, as in the Michaelis-Arbuzov reaction,[2] or through a two-stage transition state in which the carbonyl group-assisted (CGA) transition state (which has also been described as a quasi-3-membered transition state[3]) comprises an initializing step, followed by migration of the phosphorus atom of TEP to the terminal carbon in the second stage. Kinetic study of these *p*-substituted aryl ketones **1** are therefore likely to provide evidence pertaining to the reaction pathways, which lead to the formation of different phosphonates, **2** and **3**. The electronic effects of an electron-releasing methoxy group or deactivating halogens are also likely to alter the electronic nature of the transition state in the phosphonation reaction. For the reaction proceeding *via* the S_N2 mechanism, the reaction rate should not be affected by the substituted aryl groups,[4] especially since the aryl group is three carbons away from the S_N2 reaction site. On the other hand, the rate of the reaction that proceeds through the polarized CGA transition state or novel carbonyl oxygen as the nucleophile, may be greatly affected by the inductive and resonance effects of these substituents.

The aim of this investigation was to study the electronic effects of *p*-substituents in aryl ketones on the formation of oxycyclopentyl and linear phosphonates. The kinetic study involved electron-releasing methoxy, methyl, ethyl groups and deactivating halogens, in order to determine the reaction pathways.

TABLE I Products and rate constants for reactions of **1** with TEP[a]

Y	**2** (%)[b]	**3** (%)[b]	$10^6\ k_{obs}$ ($Lmol^{-1}s^{-1}$)[c]	$10^6\ k$ for **2**[d] ($Lmol^{-1}s^{-1}$)	$10^6\ k'$ for **3** ($Lmol^{-1}s^{-1}$)	k/k'[e]
H	60	40	10.50	6.67 (1.00)[f]	3.83 (1.00)[f]	1.00
Me	82	18	14.60	12.30 (1.84)	2.30 (0.60)	3.07
Et	80	20	13.50	11.03 (1.65)	2.47 (0.65)	2.57
MeO	96	4	40.40	35.33 (5.30)	2.08 (0.54)	9.81
F	32	68	8.25	2.50 (0.37)	5.75 (1.50)	0.25
Cl	24	76	9.00	2.00 (0.30)	7.00 (1.83)	0.17
Br	20	80	8.33	1.67 (0.25)	6.67 (1.74)	0.14

(a) The reaction was carried out at 165.0 ± 0.1 °C using TEP in excess as reactant and solvent. The concentration of **1** and TEP were 1.25 and 5.78 M respectively. The TEP/**1** molar ratio was 4.5. (b) Determined by GLC analysis. (c) All rates were within 95% confidence level. (d) Calculated from total rates and k/k'. (e) From the slope of the plot between concentrations of **2** and **3**, where k/k' for Y = H is 1.74. (f) Relative rates refer to Y = H.

RESULTS AND DISCUSSION

Formation of 2-aryl-2-tetrahydrofuranylphosphonates **2** and linear aryl δ-keto-phosphonates **3** have been known to occur in competition in the reaction of γ-chloropropyl aryl ketones **1** with TEP, which could be monitored by gas chromatography. In order to eliminate unnecessary side reactions of triethyl phosphite, such as hydrolysis, and its conversion to diethyl phosphite and diethyl ethyl phosphonate,[5] the reactions were carried out in excess triethyl phosphite and under dry N_2 atmosphere.[6] The reaction was found to be sensitive to the steric crowding of the transition state. In the reaction involving less the solvated transition state, formation of **2** was favored over **3**. In this less crowded condition with the presence of more solvent molecules, the product was exclusively linear phosphonate **3**. Notably, the pseudo first order kinetic measurements were not possible for formation of **2**, since the dilute condition of **1** in TEP favored the formation of linear phosphonates **3**. Therefore, a more suitable condition, *i.e.* with TEP/**1** molar ratio of 4.5, was used for evaluation of the substituent effects on the formation of both **2** and **3**. The second-order rate, k_{obs} ($k_{obs} = k + k'$) was determined from the linear plots of $ln\ [b_0(a_0 - x)/a_0(b_0 - x)]$ *vs.* reaction time, where a_0 and b_0 are the initial concentrations of **1** and TEP respectively, and x is the consumed concentration.[7] The rates of formation of **2** and **3**, *viz.* k and k' respectively, were calculated from k_{obs} and the k/k' value, where k/k' value is the slope of the plot between concentrations of **2** and **3**.

The kinetic data are presented in Table I. The rates k and k' with various substituent groups in the *para-* position were determined. It can be noted from the variations in k that the substituent effect on **2** is in the order MeO > Alkyl > H > Halogen. In contrast, the reactivity order for **3**, as can be seen from the variations in k', is Halogen > H > Alkyl > MeO, with only a slight

TABLE II Substituent effect on the formation of **2**[a]

Y	10^6 *k for* **2** $(Lmol^{-1}s^{-1})^b$	*Relative rate* (k/k_H)
H	23.89	1.00
Et	52.51	2.20
MeO	161.12	6.74
Cl	3.86	0.16

(a) The reaction was carried out at 165.0 ± 0.1 °C using diglyme as solvent. The concentration of **1** and TEP were 0.5 and 0.75 M respectively. The TEP/**1** molar ratio was 1.5, for which the formation of **3** was not observed. (b) $k_{obs} \cong k$ was determined by the GC analysis, all rates were within 95% confidence level.

variation with the different alkyl groups and among the halogens. These results imply that oxycyclopentyl and linear phosphonates, **2** and **3** are formed through different transition states. The polar transition state induced by the resonance effect is clearly dominant in the formation of oxycyclopentyl phosphonates **2**, while the CGA transition state is involved in the formation of linear phosphonates **3**. The formation of **3** may also proceed *via* the S_N2 mechanism. The contribution of the S_N2 route in the formation of **3** will be discussed later in this paper.

The formation of **2** was also examined by varying the TEP/**1** molar ratio to 1.5. Under this condition, the formation of **3** was not observed, while k_{obs} was noted to be nearly equal to k, from the GC analysis. The values of k with selected *p*-substituents are also presented in Table II. The same order, *viz.* MeO > Et > H > Cl, was observed.

Hammett Plots with σ_p and σ_p^+

Hammett plots were used to differentiate between the transition states, through the substituent effect on the reaction site.[8] The plots of *log* k_{obs} *vs.* σ_p and σ_p^+ are shown in Figure 1. It may be noted here that the Hammett plot of *log* k_{obs} *vs.* σ_p or σ_p^+ is expected to be linear if the formation of these two products involves a common transition state. Moreover, even for the directly competitive reactions without a common transition state, the individual plots of *log k* and *log k' vs.* σ_p should be linear. Therefore, the observed nonlinearity of these plots in Figure 1 confirms the absence of any common transition state, and the formations of oxycyclopentyl and linear phosphonates, **2** and **3** can be concluded to occur through different transition states. Therefore, the assumption of a common transition state for the competitive formations of **2** and **3** may be dismissed.

The individual plots of *log* k/k_H *vs.* σ_p and σ_p^+ are shown in Figure 2, for solutions with TEP/**1** molar ratio of (a) 4.5 and (b) 1.5. The plot with σ_p^+ is more nonlinear, while it exhibits much better linearity with σ_p, for both condi-

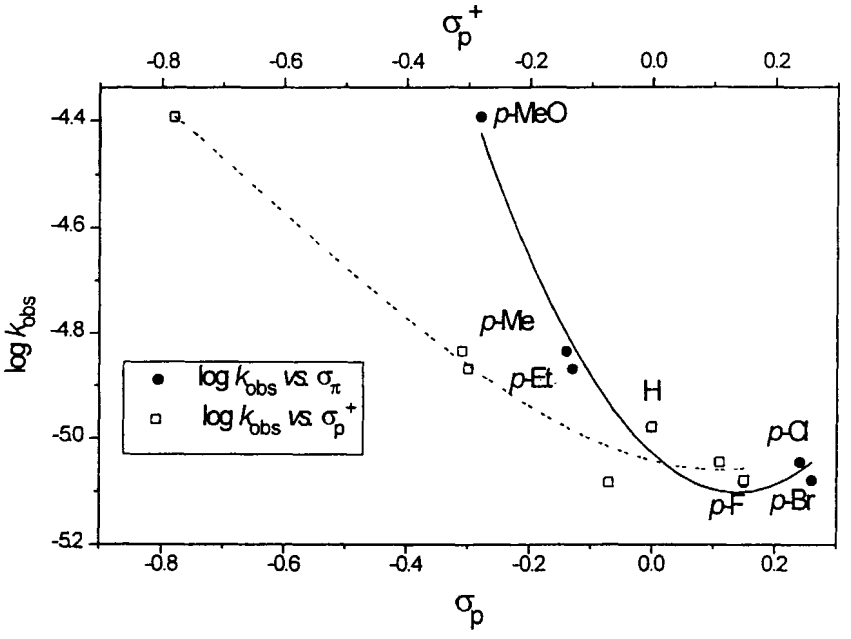


FIGURE 1 The Hammett plot of total rate *vs.* σ_p and σ_p^+

tions. This result indicates that the carbonyl carbon does not develop as an electrophile in the rate determining step in the formation of **2**. The mechanism of the formation of oxycyclopentyl and linear phosphonates were therefore further evaluated as following.

Reaction Pathway for Formation of Oxycyclopentyl Phosphonates 2

The order of reactivity of the substituents for formation of 2-aryl-2-tetrahydrofuranylphosphonates **2** was found to be MeO > alkyl groups > H > F ≅ Cl ≅ Br. This shows that the resonance effect indeed facilitates the nucleophilic attack of carbonyl oxygen on the terminal chlorocarbon, thus resulting in the formation of a favorable 5-membered-ring transition state with γ-chloropropyl sidechain. The reactivity is apparently dependent on the electron density, which delocalized towards the carbonyl oxygen through the resonance effect. The rate of formation of **3** was found to be decreased with the halogen substituents, probably due to the reduction in the electron density of the carbonyl oxygen in some way through the countering effect, since halogens as substituents are known to exert an inductive effect. This behavior is similar to Pasto and Serve's results on the neighboring group participation of carbonyl oxygen[9] in the re-

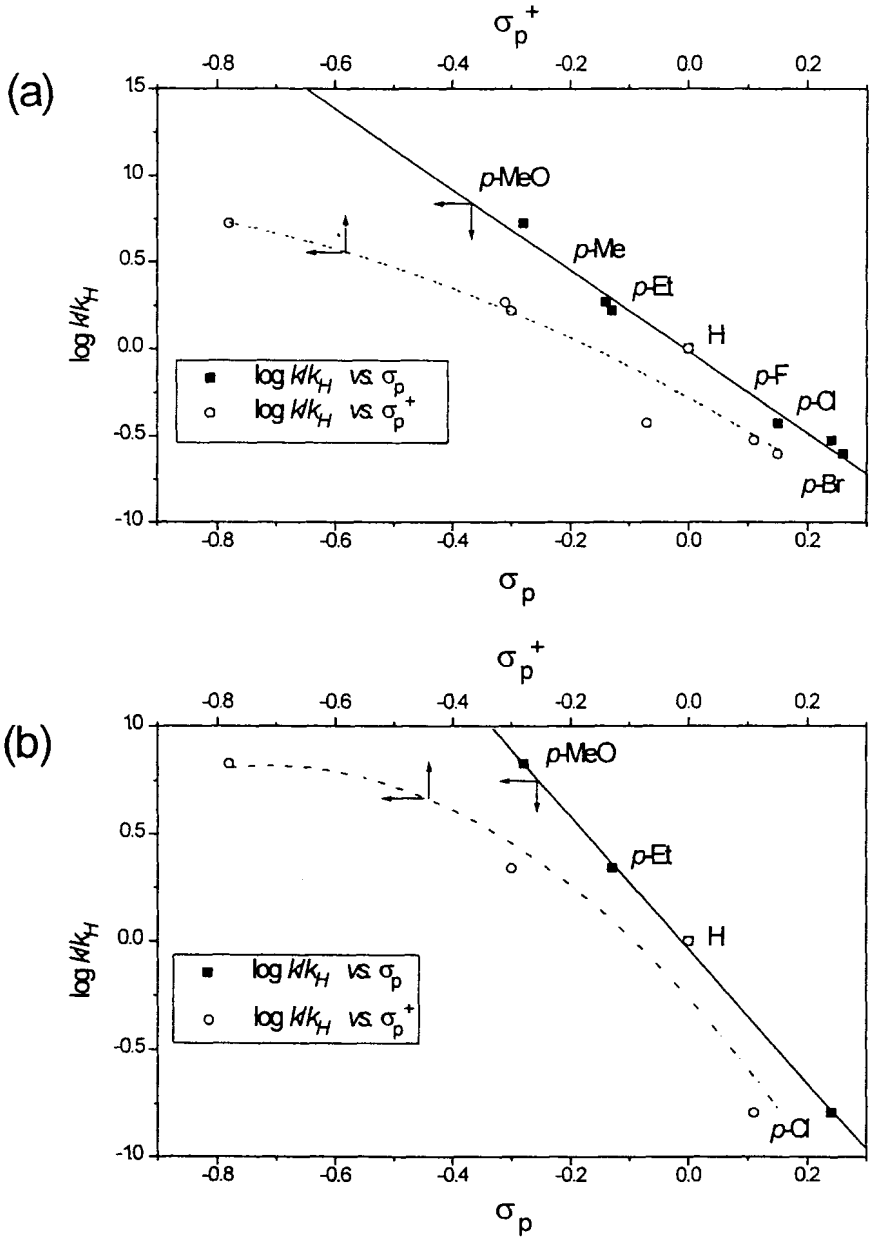
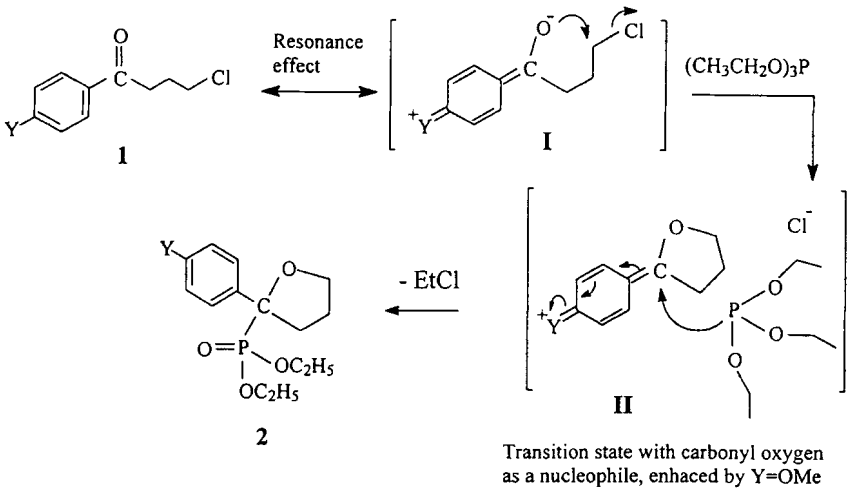


FIGURE 2 The Hammett plots for the formation of **2** (a) $\rho = -2.33$, r = 0.993, s = 0.0654 with TEP/**1** molar ratio of 4.5. (b) $\rho = -3.09$, r = 0.999, s = 0.032 with TEP/**1** molar ratio of 1.5.



SCHEME 2 The reaction pathway for the formation of **2**

actions. Therefore, the resonance effect in the transition state plays an important role in formation of **2** with these aryl groups. If the nucleophilic attack of the phosphorus atom on the carbonyl carbon is the initializing step, then *p*-methoxy group with its resonance effect in **1** may suppress the development of carbonyl carbon as an electrophile and consequently retard the reaction. However, the present results indicate otherwise. Therefore, this nucleophilic attack of TEP on C=O group as initializing step may be excluded from consideration. Additional evidence in support of this statement can be sought from the Hammett plot (ρ = −2.33, r = 0.993, for TEP/**1** = 4.5). The plot of $log\ k/k_H$ does not correlate well with σ_p^+ (largely deviated and scatted), whereas it does correlate well with σ_p values[10] (Figure 2(a)). This clearly suggests that polarization of the carbonyl carbon for subsequent formation of the carbocation on the carbonyl group does not occur in the initializing step.

The dipolar resonance in the transition state [**I**] may be important as it delocalizes the electrons towards the carbonyl oxygen. When the closure of the favorable 5-membered ring, which is formed with the γ-chloropropyl sidechain, occurs, the nucleophilic carbonyl oxygen may first attack the terminal chlorocarbon to form an oxycyclopentyl ring. Then, the subsequent attack of nucleophilic P: of TEP on the carbocation, which is generated by the returning of the electrons to the *p*-substituent group in [**II**], may proceed with simultaneous elimination of the ethyl chloride for formation of phosphonate **2**, as shown in Scheme 2.

Enhancement in the rate of this reaction by polar solvents, for reaction involving neutral starting materials, is well known and has been attributed to the solvation in the polar transition state over the ground state.[11] The reaction of **1** with TEP belongs to this type. The reaction of **1b** with several solvents, *viz.* isobutylbenzene, diglyme and DMSO, was also examined. The preliminary results showed that the rate k (in $Lmol^{-1}s^{-1}$) was 3.3×10^{-3} in DMSO; 2.4×10^{-5} in diglyme and 2.9×10^{-7} in isobutylbenzene. These results imply that the polar solvent such as DMSO stabilizes the polar transition state to a greater extent than diglyme and nonpolar iso-butylbenzene, as this transition state is induced by the resonance effect ([**II**] in Scheme 2). Thus the rate of reaction in DMSO exhibits a two order of magnitude increase over that in diglyme, and is four order of magnitude faster than that in iso-butylbenzene, for the formation of **2**.

Reaction Pathway for Formation of Linear δ-Ketophosphonates 3

The order of reactivity of the substituents for formation of linear aryl δ-ketophosphonates **3** has been found to be F ≅ Cl ≅ Br > H > alkyl > MeO groups (k' in Table I). In order to differentiate the contribution the S_N2 pathway from the CGA mechanism for this reaction, phosphonation of 1-chloro-4-phenyl butane, which does not contain the carbonyl group and is well known to occur *via* the S_N2 mechanism, was carried out with TEP under the same conditions. The rate of this reaction was found to be 0.67×10^{-6} $Lmol^{-1}s^{-1}$, which is 5.7 times slower than that (3.83×10^{-6} $Lmol^{-1}s^{-1}$) for γ-chloropropyl phenyl ketone (Y = H). Since the S_N2 mechanism does not involve the aryl groups[4] separated by 3 carbons from the reaction site, the contribution of the S_N2 mechanism to the k' values for phosphonation of the aryl ketone **1** is assumed to be the same 0.67×10^{-6} $Lmol^{-1}s^{-1}$. The Hammett plot with corrected k's is plotted in Figure 3, which shows a positive ρ value of 1.33. This result indicates that it is the inductive effect and not the resonance effect, that is a dominant factor in formation of **3**, although the S_N2 route may also be in operation for the formation of the same product. The inductive effect arising due to halogen may render the carbonyl group with electron-deficient carbon, thus carbonyl carbon becomes a strong electrophile for the nucleophilic attack of the weak and polarized phosphorus of TEP, and facilitates the formation of CGA transition state which subsequently leads to the formation of linear phosphonate **3** (Scheme 3). This result is consistent with the formation of cyanohydrin[12] from the reaction of *p*-nitrophenyl aldehyde with HCN, where acceleration in the rate of reaction due to the inductive effect is clearly observed. Our previous report on formation of aryl γ-ketophosphonates,[13] $[(EtO)_2P(=O)CH_2CH_2C(=O)Ar]$,

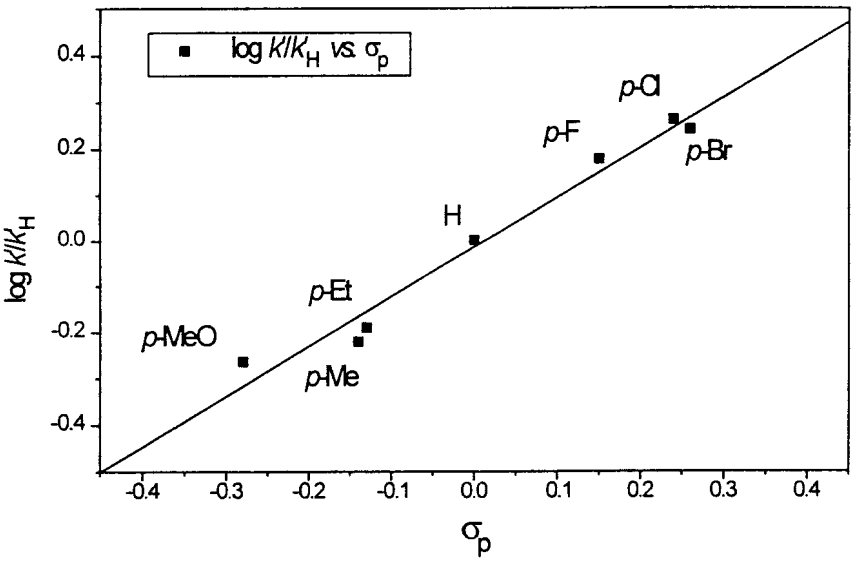
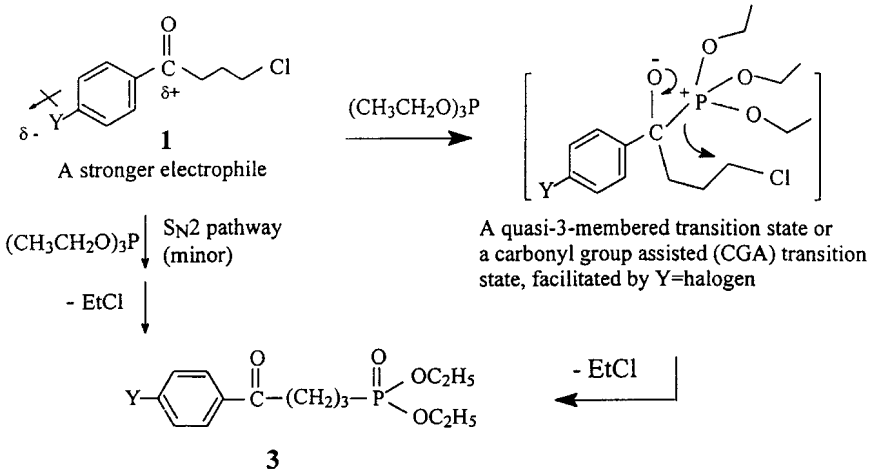


FIGURE 3 The Hammett plot for formation of **3** (ρ = 1.33, r = 0.986, s = 0.051) using the k' values ($k' - 0.67\times10^{-6}$) corrected for the S_N2 mechanism

which consists one carbon less than that of **3**, also supports the argument that the CGA pathway is favored over S_N2 mechanism for the formation of linear aryl δ-ketophosphonates.



SCHEME 3 The reaction pathways for the formation of **3**

EXPERIMENTAL

Commercially available chemicals of reagent grade were used for all the reactions. Triethyl phosphite was redistilled from sodium prior to use.[14] 3-chlorobutyrophenone and its derivatives **1** were prepared following the procedure given by Westeringh and Schliemann *et al.*[15] 1-Chloro-4-phenyl butane was purchased from Lancaster Chemical Co. All reactions were carried out under inert atmosphere of N_2 and in oven dried glassware.

Kinetic measurements were carried out in a thermostatted bath (165.0 ± 0.1°C). 4-chlorobutyrophenone or its derivatives **1** (0.12 mol) were added to triethyl phosphite (24 mL) with vigorous stirring. Aliquots were removed at appropriate intervals of time, and then quickly cooled. GLC analyses[16] were performed on a Varian 3700 chromatograph, equipped with a flame ionization detector, using a capillary column Supelco SPB-5. The column temperature was programmed between 150–220 °C and nitrogen was used as the carrier gas. Experiments were carried out under second order conditions. Linear plots of $ln\ [b_0(a_0 - x)/a_0(b_0 - x)]$ *vs.* reaction time were plotted based on the concentration of products, which were determined from the integrated areas relative to that of the internal standard (biphenyl). Rate constants and values of r and s were calculated by the graphic method, using least-squares.

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References

[1] Jen-Wen Yu and Steve K. Huang, *Phosphorus, Sulfur, and Silicon, and the Related Elements* (in press).
[2] A.K. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, **81**, 415 (1981).
[3] J.F. Allen and O.H. Johnson, *J. Am. Chem. Soc.*, **77**, 2871 (1955); M.S. Kharasch and I.S. Bengelsdorf, *J. Org. Chem.*, **20**, 1356 (1955); F.W. Lichtenthaler, *Chem. Rev.*, 607 (1961).
[4] J. March, *Advanced Organic Chemistry* (John Wiley & Sons, New York, 1992), 4th ed., Chap. 10, pp. 342–344.
[5] I. Petneházy, G. Szakál and L. Töke, *Synthesis* 453 (1983).
[6] I. Petneházy, G. Keglevich, L. Töke and H.R. Hudson, *J. Chem. Soc. Perkin Trans. II* 127 (1988).
[7] K.J. Laidler, *Chemical Kinetics*, (Happer & Row, New York, 1987), 3rd ed., Chap. 2, pp. 23–25.
[8] P. Skyes, *A guidebook to mechanism in organic chemistry* (Longman Group Ltd., New York, 1981), 5th ed., Chap. 13, pp. 345–378; R.A.Y. Jones, *Physical and mechanistic organic*

chemistry (Cambridge University Press, Cambridge, 1979), Chap. 3, pp. 36–58; F.A. Carey and R.J. Sundberg, *Advanced Organic Chemistry* (Plenum Press, New York, 1984), 2nd ed., Chap. 4, pp. 179–190.

[9] D.J. Pasto and M.P. Serve, *J. Am. Chem. Soc.*, **87**, 1515 (1965).

[10] C.G. Swain and E.C. Lupton Jr., *J. Am. Chem. Soc.* **90**, 4328 (1968); L.P. Hammett, *J. Am. Chem. Soc.*, **59**, 96 (1937); H.H. Jaffe, *Chem Rev.*, **53**, 19 (1953).

[11] T.H. Lowry and K.S. Richardson, *Mechanism and Theory in Organic Chemistry* (Happer & Row, New York, 1981), 2nd ed., Chap. 4, pp. 323–337.

[12] W.-M. Ching and R.G. Kallen, *J. Am. Chem. Soc.*, **100**, 6119 (1978).

[13] Jen-Wen Yu, Chien-Keun Chong and Steve K. Huang, *Phosphorus, Sulfur, and Silicon, and the Related Elements*, accepted, 1997.

[14] D.D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals* (Pergamon Press, Oxford 1988), 3rd ed., Chap. 3, pp. 297.

[15] C. van de Westeringh, B. Hermans, F. Raeymaekers and C. Van der Eycken, *Ind. chim. belge*, **25**, 1073 (1960); *Chem. Abstr.* 1960, **55**, 6428b; W. Schliemann, A. Buege and L. Reppel, *Pharmazie*, **35**, 140 (1980).

[16] G. Keglevich, I. Petneházy, L. Töke and H.R. Hudson, *Phosphorus Sulfur*, **29**, 341 (1987).