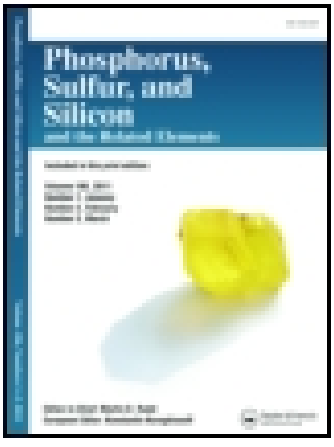

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ELECTRONIC EFFECT OF SUBSTITUENTS AND MECHANISM ON THE FORMATION OF DIETHYL 3-OXO-3-ARYLPROPYL PHOSPHONATES

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ELECTRONIC EFFECT OF SUBSTITUENTS AND MECHANISM ON THE FORMATION OF DIETHYL 3-OXO-3-ARYLPROPYL PHOSPHONATES

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The reaction of aryl β-chloroethyl ketones with triethyl phosphite to give γ-ketophosphonates was studied kinetically. This reaction follows a second order overall and involves a carbonyl group-assisted (CGA) initializing step, followed by a stereoselective pathway to γ-ketophosphonates. A linear Hammett plot reveals that the ρ value is 1.51 (r=0.994), and the transition state is accelerated by the *para*- halogen on the phenyl group. The results confirm the two-stage mechanism and rule out an S_N2 mechanism being responsible for the formation of diethyl 3-oxo-3-arylpropyl phosphonates **3**.

Keywords: Carbonyl group-assisted mechanism; γ-Ketophosphonate; Activation energy; Entropy of activation

INTRODUCTION

The phosphonate group in organic compounds is one of the leaving groups which generates olefinic compounds under mild conditions, especially for synthesis of vinyl compounds as illustrated in the Wittig-Horner reaction.[1] γ-Ketophosphonate (R=CH_3) is particularly useful for conversion to phosphonate intermediates important for the synthesis of biologically active cyclopentanones, a cyclopentenoid antibiotic methylenomycin B.[2] The aryl γ-ketophosphonate **3** (R=Ph-Y), as starting material for this intermediate, may be utilized to synthesize aryl derivatives of methylenomycins. Aromatic and *p*-substituents have been found useful in many biological and medicinal substances such as *p*-chlorophenyl in chlorpheniramine and haloperidol or anisyl group in equol and methoxychlor insecticide, just to name a few.[3]A method that leads to the formation of aryl γ-ketophosphonates with high yield of 87-96% in a simple procedure has been described.[4]

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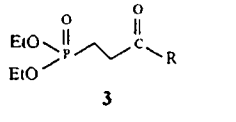
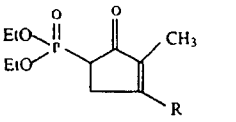




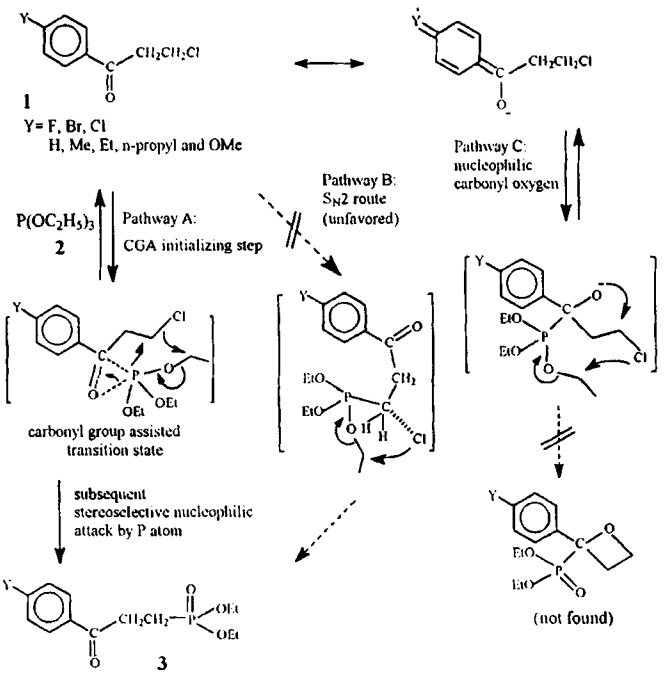
Intermediate of methylenomycin B

In our synthesis of aryl γ-ketophosphonates **3**, the apparent yield was influenced by different *p*-substituents and the reaction mechanism may be different from the Michaelis-Arbuzov reaction.[5] The aims of this investigation were to evaluate reaction pathways and the substituent effects by Hammett plot, accompanied by an AM1 calculation for the formation of **3**. The solvent effect was also measured.

RESULTS AND DISCUSSION

The reaction of β-chloroethyl aryl ketones **1** with triethyl phosphite **2**, TEP is shown in Scheme 1. The reaction has been proposed involving a two-stage transition state with an electronic initializing step and a stereoselective step.[6] At least three pathways for the phosphonation of **1** are possible. Pathway A, a carbonyl group-assisted (CGA) transition state, known as a quasi-3membered ring transition state,[7] Pathway B, a Michaelis-Arbuzov or S_N2 reaction,[5] and Pathway C, a nucleophilic carbonyl oxygen transition state assisted by the resonance effect. The stereoselective step dominates the product formation. In phosphonation of methyl ω-chloroalkyl ketones,[6] $Cl(CH_2)_nC(=O)CH_3$, with TEP, the product was Perkow's vinyl phosphate (90%) through Pathway A and a minor β-ketophosphonate (10 %) at n=1. For n=2, the exclusive product was γ-ketophosphonate (98%) through a CGA mechanism (Pathway A). For n=3, a novel diethyl 2-methyl-2tetrahydrofuranyl phosphonate was formed through a nucleophilic carbonyl oxygen pathway (Pathway C). For n=4 or higher, only ω-ketophosphonates were found through S_N2 mechanism (Pathway B).

The phosphonation of β-chloroethyl aryl ketones **1** gave aryl γ-ketophosphonates **3** as the only product.[4] The product formation with a variety of substituents was monitored by gas chromatography in this study and a plot of the product formation vs. reaction time is shown in Figure 1. The reactivity order of the substituents is F ≅ Cl ≅ Br > alkyl > MeO, indicating that electronic effect plays an important role for this reaction. To understand the energy requirement, some substituents of Y=Cl, Et, H and MeO were selected for kinetic measurement of the



SCHEME 1 Multi-stereoselective pathways for phosphonation of β-chloroethyl aryl ketones **1**

rates and activation parameters. To get a better insight into the nature of the transition state, the different polarity of solvents was evaluated in the kinetic study.

To eliminate the complications arising from the hydrolysis of triethyl phosphite and its conversion to diethyl phosphite and diethyl ethyl phosphonate,[8] the precaution of using dry N_2 as inert gas with the use of a large excess of triethyl phosphite was followed.[9] The rate of disappearance of **1** in the presence of an

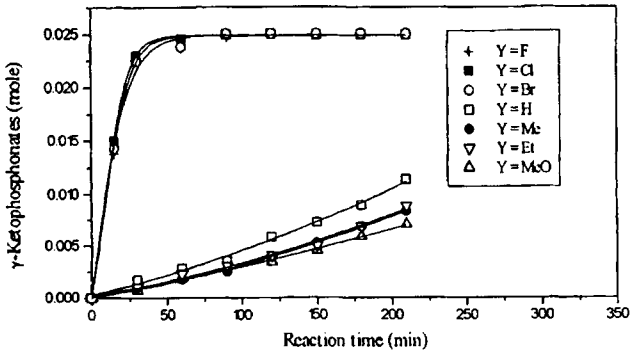
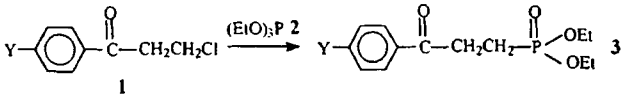


FIGURE 1 The effect of substituents on the formation of aryl γ-ketophosphonates **3** with the same initial mole of β-chloroethyl aryl ketones **1** in 0.025 mole

excess of phosphite was therefore determined and gave a pseudo-first-order rate constant from which the overall second-order rate constant was calculated. Table 1 shows the calculated k values under various temperatures. The *para*- Cl substituent in **1** increases the reaction rate, while the electron-donating substituent, *i.e.* MeO, decreases.

TABLE I Substituent effects on the rate constants and activation parameter[a]



1

Compound	*Temp* ± 0.1°C	10^5k^b M^{-1} sec^{-1}	*Ea* kcal/mol[c]	$\triangle H^{\neq}$ kcal/mol[d]	$\triangle S^{\neq}$ eu[d]	$\triangle G^{\neq}$ kcal/mol[e]
Y=H	85.0	1.12	31.56			
	92.5	2.93		30.83	4.67	29.12
	100.0	6.66				
Y=Et	85.0	0.79	33.58			
	92.5	2.18		31.75	6.60	29.34
	100.0	4.93				
Y=MeO	85.0	0.50	35.64			
	92.5	1.63		34.91	14.67	29.55
	100.0	3.74				
Y=Cl	85.0	3.00	27.37			
	92.5	7.39		26.64	-4.95	28.45
	100.0	14.07				

a) All reactions were proceeded under nitrogen atmosphere. The concentration of **1** is 0.1 M.
b) All rates are within 95% confidence level.
c) Calculated from data at temperature of 85.0, 92.5 and 100.0 °C.
d) At 92.5°C.
e) At 92.5 °C from $\triangle G^{\neq} = \triangle H^{\neq} - T\triangle S^{\neq}$.

The solvent effect on this reaction is shown in Table 2. The reaction rate of **1** (Y=H) with TEP is faster in the polar diglyme than toluene at 92.5 °C. It indicates that the quasi-3-membered transition state with delocalized electrons over

three atoms was solvated and stabilized by the polar solvent, while the nonpolar substrate and reactant were less solvated in the ground state.[10]The increase in rate by the polar diglyme is 1.26 times and the nonpolar toluene decreases the rate to 0.66 in respect to the TEP as solvent.

TABLE II Solvent effect upon rate constant of **1** (Y=H) with TEP

Solvent	*Dipole (Debyes)*[b]	10^5k, $M^{-1}sec^{-1}$	*Relative rate*
Diglyme	0.83	3.68	1.26
TEP	0.38	2.93	1.00
Toluene	0.07	1.93	0.66

a) The rate constants were measured in 92.5 ± 0.1 °C, the concentrations of **1** and TEP are 0.1M and 2M, respectively.
b) Calculated from MINDO/3 method.

The inductive effect of halogen as a substituent is known to deactivate the electrophilic aromatic substitutions in the *ortho-* and *para-* positions on the ring.[11-14] Such inductive effect through the phenyl ring has been observed to predominate over the resonance effect in cyanohydrin formation of *p*-nitrophenyl aldehyde with HCN, where the rate of reaction has been observed to be faster with the *p*-nitro group than the *p*-methoxy group.[15] As seen in this study, the inductive effect arising due to halogen may cause the carbonyl carbon with the electron deficiency thus to become a strong electrophile. Therefore, it facilitates the attack of TEP on the carbon for the formation of the CGA transition state. The subsequent selection of the favored pathway and cleavage of an ethyl group by halide, has been shown to be rapid and not the rate determining step,[16] which quickly led to the formation of product **3.**

A Hammett plot with the rate and the substituent parameters using σ and σ^+ values [17] is shown in Figure 2. The linear correlation with σ but not σ^+indicates that no fullly charged carbonyl carbon has been developed. The reaction parameter, ρ, on the related α-chloromethyl phenyl ketone and its p-substituted phenyl derivatives was 1.36-1.89 as measured by Toke[18] and Borowitz.[19] For the β-chloroethyl aryl ketones, the magnitude and positive sign of the ρ value was found to be 1.51 (r=0.994) and this ρ value supports the quasi-3-membered ring transition state which was accelerated by the inductive effect of the substituents.

The energy requirements for the ground state of the reactants and the transition states for these different pathways, without considering the participation of solvent molecule, were calculated with AM1 calculation using SPARTAN 4.1 software[20] (Figure 3). The formation of **3** is directed by a two-stage CGA-stereo-

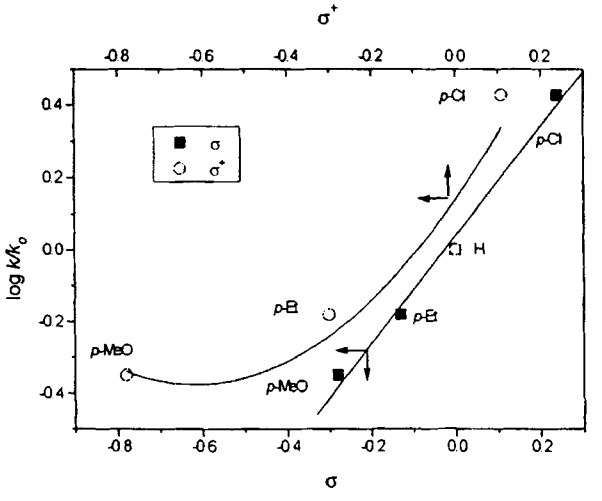


FIGURE 2 Hammett plot of phosphonation of substituted aryl ketones **1** with TEP using σ and σ^+

selective mechanism, although all three pathways considered may be active. Other pathways with higher energy requirements are not likely to result in formation of products. The dipolar transition state, for example, formed by the electron-releasing group may lead to the formation of a nucleophilic carbonyl oxygen at the initializing step. However, the formation of a highly strained product such as oxycyclobutyl phosphonate forces this pathway to return to the starting state. The S_N2 mechanism, with high initial activation energy (about 56 kcal/mol), is out of competition, although it is capable of yielding the same product as that from the two-stage CGA pathway. Therefore, Pathway A, a two-stage CGA pathway, as observed in two steps of about 37 and 14 kcal/mol, possessed the lowest energy requirement among 56 kcal/mol for Pathway B, an S_N2 mechanism, and 37 and 61 kcal/mol for Pathway C involving a nucleophilic attack of the carbonyl oxygen. This result clearly indicates that Pathway A is favored over other pathways for this reaction.

The subsequent release of the phosphorus of TEP and its nucleophilic attack on the terminal CH_2Cl group in the second stage for eventual formation of **3** may depend predominantly on the stereo factor rather than the electronic effect. This may be mainly due to the fact that γ-ketophosphonate **3** formation through this stereoselective pathway does not generate a fully-charged ionic transition state. The transformation of the phosphite group to a phosphonate accompanied by an elimination of ethyl chloride may occur in one continuous but widely spread electronic transition state. The inductive effect of halogen which withdraws electron density from CGA or a quasi-3-membered transition state may not affect

this nucleophilic step significantly. In a Perkow reaction of α-haloalkyl phenones, the negative entropies ($\Delta S^{\neq}$ = -31~ -41 eu) of activation obtained are consistent with an ordered and probably a dipolar transition state.[19] This γ-ketophosphonate formation with the much larger entropies ($\Delta S^{\neq}$ = -4.95~ 14.67 eu) indicates that it requires the breakup of the CGA transition state and moves down to attack on the terminal β-carbon, which results in the increase of the degrees of freedom in the transition state.

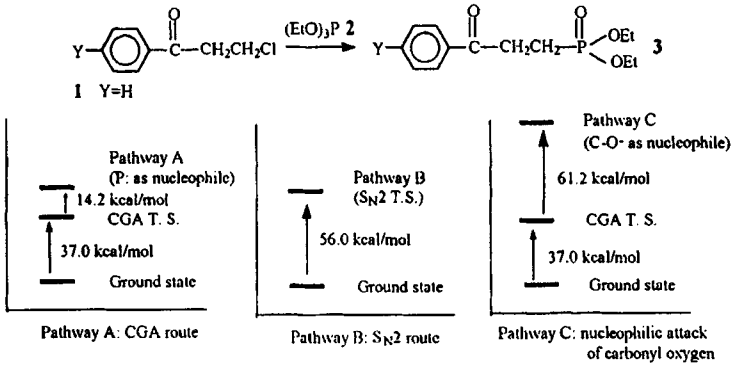


FIGURE 3 Energy requirements for different reaction pathways (Y=H) by AM1 calculation

The mechanism involving S_N2 phosphonation with the direct release of ethyl chloride (Michaelis-Arbuzov mechanism) as Pathway B for the formation of **3** is dismissed from this study. If this were the case, then the effect of substituents should be minimum at best, regardless of their nature, since the S_N2 reaction pathway does not involve the phenyl group and the effects of electron-releasing and/or withdrawing groups as substituents shall bear no effect[21] on the reaction rates. To examine the possible participation of an S_N2 type mechanism in the reaction, the phosphonation of 1-chloro-3phenyl propane with **2** was carried out under the exact same conditions as **1** for measurement of the rate. The rate was found very slow and not detected[22] for 12 h while the rate of **1**, Y=Cl, was 7.39 x 10^{-5} $M^{-1}sec^{-1}$ at 92.5 °C. The result indicates that the phosphonation could not go through an S_N2 type mechanism under these conditions. It also supports the participation of the carbonyl group with TEP at the initializing step is important for this reaction.

EXPERIMENTAL

Commercially available chemicals of reagent grade were used for all the reactions. Triethyl phosphite was redistilled from sodium prior to use.[23]

3chloropropiophenone and its derivatives **1** were prepared from previous report.[4] 1-Chloro-3-phenyl propane was purchased from ACROS Chemical Co. All reactions were carried out under an inert atmosphere of N_2 and in oven dried glassware.

Kinetic measurements were carried out in a thermostatted bath (±0.1 °C). 3-chloropropiophenone or its derivatives **1** (0.002 mol) was added to triethyl phosphite (20 mL) with vigorous stirring. Aliquots were removed at appropriate intervals of time, and then quickly cooled. Experiments were carried out under pseudo-first-order conditions by keeping the triethyl phosphite in a large excess. GLC analyses[24] were performed on a Varian 3700 chromatograph with a flame ionization detector using a capillary column, Supelco SPB-5. The column temperature was programmed between 60-220 °C and nitrogen was used as the carrier gas. Integrated areas were compared with an internal standard using naphthalene or biphenyl. Rate constants and activation parameters were calculated from the graphic method using a least-squares rule for each data.

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