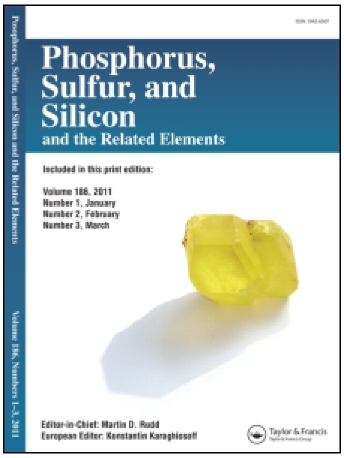

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Chemoselective Synthesis of Stable Phosphorus Ylides from 6-Azauracil and Mechanistic Investigation of the Reaction by UV Spectrophotometry

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Stable crystalline phosphorus ylides were obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine and dialkyl acetylenedicarboxylates, in the presence of NH-acids such as 6-azauracil. These stable ylides exist in solution as a mixture of two geometrical isomers as a result of restricted rotation around the carbon–carbon partial double bond resulting from conjugation of the ylide moiety with the adjacent carbonyl group. To determine the kinetic parameters of the reactions, they were monitored by UV spectrophotometry. The second order fits were automatically drawn, and the values of the second order rate constants (k_2) were automatically calculated using standard equations. At the temperature range studied, the dependence of the second order rate constant (Ln k_2) on reciprocal temperature was in agreement with the Arrhenius equation. This provided the relevant plots to calculate the activation energy of all the reactions. Furthermore, useful information was obtained from studies of the effect of solvent, structure of reactants (different alkyl groups within the dialkyl acetylenedicarboxylates), and also concentration of reactants on the rate of reactions. The proposed mechanism was confirmed according to the obtained results, and a steady-state approximation and first step (k_2) of the reaction was recognized as a rate-determining step on the basis of experimental data.

Keywords Kinetic parameters; NH-acid; stable phosphorus ylides; triphenylphosphine; UV spectrophotometry

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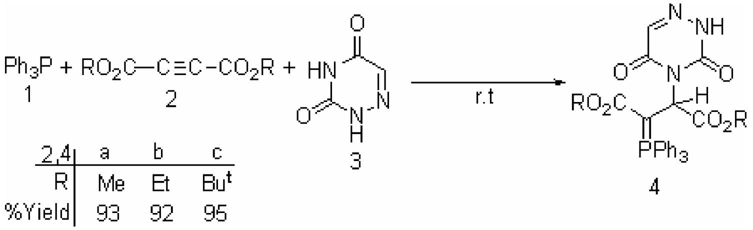
INTRODUCTION

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic chemistry.[1,2] Phosphorus ylides are reactive systems that take part in many valuable reactions of organic synthesis,[3–11] and they are most often prepared by treatment of a phosphonium salt with a base. Most of the phosphonium salts are prepared from the reaction of a phosphine and an alkyl halide,[3–7] though they can be obtained also by the Michael addition of phosphorus nucleophiles to activated olefins.[2,3] Herein, we describe an efficient synthetic route to, and kinetic study of, stable phosphorus ylides using triphenylphosphine, dialkyl acetylenedicarboxylates, and NH-acids such as 6-azauracil. As noted in the literature,[12] the 6-azauracil moiety and its derivatives are widely used in the preparation of medicines; hence, the present work was undertaken for the generation of stable phosphoranes. Accordingly, the reaction of triphenylphosphine **1** with dialkyl acetylenedicarboxylates **2** (**2a**, **2b**, or **2c**) in the presence of a NH-acid 3 led to the corresponding stable heterocyclic phosphorus ylides **4** (**4a**, **4b** or **4c**) in excellent yields (see Figure 1).

RESULTS AND DISCUSSION

The reactions of 6-azauracil **3** with dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine **1** were carried out in ethylmethylketone at room temperature and were completed within a few hours. The ^{1}H and ^{13}C NMR spectra of the crude products indicated clearly the formation of stable phosphorus ylides **4**. Any product other than **4** could not be detected by NMR spectroscopy. The structures of compounds **4a–c** were deduced from their IR, ^{1}H, ^{13}C, and ^{31}P NMR



2,4	a	b	c
R	Me	Et	Bu^t
%Yield	93	92	95

FIGURE 1 The reaction between triphenylphosphine **1**, dialkyl acetylendicarboxylate **2** (**2a**, **2b**, or **2c**), and 6-azauracil **3** for generation of stable phosphorus ylides **4** (**4a**, **4b**, or **4c**).

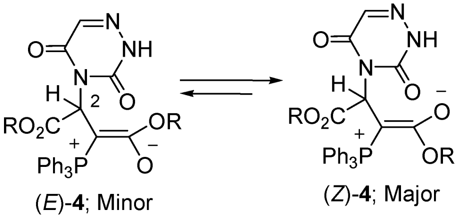


FIGURE 2 Two geometrical isomers (minor and major) of stable phosphorus ylides **4** (**4a** or **4b**).

spectra. Their mass spectra displayed molecular ion peaks at appropriate m/z values, and initial fragmentations involved the loss of parts or complete side chains and scission of the heterocyclic ring system. The 1H, ^{13}C, and ^{31}P NMR spectra of ylides **4a** and **4b** are consistent with the presence of two isomers. The ylide moieties of these compounds are strongly conjugated with the adjacent carbonyl group, and rotation around the partial double bond in (E)-**4** and (Z)-**4** geometrical isomers is slow on the NMR timescale at ambient temperature (see Figure 2). Selected ^{1}H, ^{13}C, and ^{31}P NMR chemical shifts and coupling constants in the major (M) and minor (m) geometrical isomers of compounds **4a** and **4b** are shown in Table I. As can be seen, only one geometrical isomer was observed for **4c**, presumably because of the bulky tert-butyl groups.

The structural assignment of (E)-**4** and (Z)-**4** rotamers as the major or minor form in phosphorus ylides have been previously established and reported in the literature.[14–17] Herein, the ^{1}H NMR spectrum of compound **4a** exhibits two single sharp lines (δ 3.14 and 3.75) arising from the methoxy group in the E rotamer and two single sharp

TABLE I Selected ^{1}H, ^{13}C, and ^{31}P NMR Chemical Shifts (δ in ppm) and Coupling Constants (J in Hz) for H-2, OR, CO_2R, C-2, and C-3, in the Major (M) and Minor (m) Geometrical Isomers of Compounds 4a–c

		^{1}H NMR spectroscopy data			^{13}C NMR data		
Compound	Isomer (%)	H-2 ($^{3}J_{PH}$)	OR	CO_2R	C-2 ($^{2}J_{PC}$)	C-3 ($^{1}J_{PC}$)	^{31}P NMR
4a	M (62)	5.27 (16.1)	3.14	3.75	62.69 (16.5)	38.70 (130.4)	23.01
4a	m (38)	5.32 (16.6)	3.56	3.70	62.17 (16.8)	39.78 (138.8)	23.12
4b	M (67)	5.28 (17.5)	4.01	4.22	62.74 (16.4)	39.84 (138.8)	23.01
4b	m (33)	5.22 (16.1)	3.70	4.15	62.12 (16.1)	38.63 (130.6)	23.39
4c	M	5.01 (17.0)	0.93	1.54	63.35 (17.3)	39.43 (137.6)	22.46

resonances at 3.56 and 3.70 ppm for methoxy groups in the Z rotamer. The shift at 3.14 of methoxy group of the Z rotamer is shielded, due to the anisotropic effect of phenyl group of triphenylphosphine. This effect confirms why the (E)-**4** and (Z)-**4** rotamers could appear as the minor and major forms, respectively, with respect to the experimental abundance percentages of both isomers, which have been reported in Experimental section. Also, signals for the methine protons at $\delta = 5.27$ and 5.32 ppm, appear as two doublets for the N-CH group, respectively, for the major and minor geometrical isomers. The ^{13}C NMR spectrum of **4a** exhibited 26 distinct resonances that are in a good agreement with the mixture of two rotational isomers. Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of **4a**, it helps in the assignment of the signals by long-range couplings with the ^{1}H and ^{13}C nuclei (see the Experimental section). The ^{1}H and ^{13}C NMR spectra of 4b–c are similar to those of **4a**, except for the ester groups, which exhibited characteristic resonances with appropriate chemical shifts (see the Experimental section). The ^{1}H and ^{13}C NMR spectral data for compounds **4a–b** are consistent with the geometrical isomers. The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **4a–c** were supported by the IR spectra. The carbonyl region of the spectra exhibited two distinct absorption bands for each compound (see the Experimental section). Of special interest is the ester absorption at 1735–1624 cm^{-1} for these compounds. Conjugation with the negative charge appears to be a plausible factor in the reduction of the wave numbers of the carbonyl absorption bands.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[2–6] it is reasonable to assume that phosphorus ylide **4** results from the initial addition of triphenylphosphine **1** to the acetylenic ester **2** (rate constant k_2) and subsequent protonation of the 1:1 adduct (I_1) by the NH-acid **3** (rate constant k_3) to form phosphoranes **4** (rate constant k_4) (see Figure 3).

EXPERIMENTAL

Melting points, IR, and UV spectra of all compounds were measured on an Electrothermal 9100 apparatus, a Shimadzu IR-460 spectrometer, and a Cary UV/VIS spectrophotometer model Bio-300 with a 10 mm light-path quartz spectrophotometer cell, respectively. In addition, the ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained from a Bruker DRX-300 Avance instrument with $CDCl_3$ as solvent at 300.1, 121.4, and 75.5 MHz, respectively. The mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a

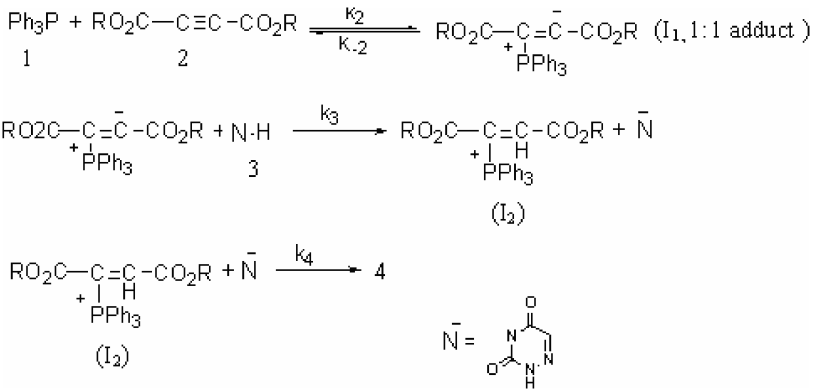


FIGURE 3 Proposed mechanism for the reaction between **1**, **2** (**2a**, **2b**, or **2c**), and **3** on the basis of literature[14–31] for generation of phosphorus ylides **4** (**4a**, **4b**, or **4c**).

Heraeus CHM-O-Rapid analyzer. Dialkyl acetylenedicarboxylates, triphenylphosphine, and 6-azauracil were purchased from Fluka (Buchs, Switzerland) and used without further purification.

Preparation of Dimethyl 2-(6-Azauracil-3-yl)-3-(triphenylphosphoranylidene)-butanedioate (4a)

To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol), 6-azauracil (0.11 g, 1 mmol), and ethylmethylketone (10 mL), a solution of dimethyl acetylenedicarboxylate (0.14 g, 1 mmol) and ethylmethylketone (4 mL) was added dropwise at –5°C over 10 min. After approximately 5 h stirring at room temperature, the product was filtered and recrystallized from ethylmethylketone.

Colorless crystals, mp 197–199°C, 0.48 g, yield 93%. IR (ν_{rnax}, cm^{-1}): 1618, 1643, 1708 and 1723 (4C=O). MS (m/z,%): 334 (M-PPh_2, 18), 303 (M-PPh_2 and OCH_3, 41), 262 (PPh_3, 86), 183 (PPh_2, 86), 108 (PPh, 57). Anal. Calcd for $C_{27}H_{24}N_3O_6P$ (517): C, 62.67; H, 4.64; N, 8.12, Found: C, 62.52; H, 4.71; N, 8.03.

Major isomer (Z)-**4a** (62%): ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 3.14 and 3.75 (6H, 2s, 2OMe), 5.27 (1H, d, $^3J_{HP}$ = 16.1 Hz, P–C–CH), 7.48–7.69 (16H, m, 3C_6H_5 and N=CH), 9.83 (1H, s, N-NH). ^{3}C NMR (75.5 MHz, $CDCl_3$): δ_C 38.7 (d, $^1J_{PC}$ = 130.4 Hz, P=C), 49.3 and 52.9 (2s, 2OMe), 62.7 (d, $^2J_{PC}$ = 16.5 Hz, P–C–CH), 126.3 (d, $^1J_{PC}$ = 92.1 Hz, C_{ipso}), 128.9 (d, $^3J_{PC}$ = 12.4 Hz, C_{meta}), 132.2 (C_{para}), 133.5 (d, $^2J_{PC}$ = 9.6 Hz, C_{ortho}), 147.9, 156.6 and 165.4 (3C, $C_3H_2N_3O_2$), 169.9 (d, $^3J_{PC}$ =

12.8 Hz, C=O ester), 170.8 (d, $^2J_{PC}$ = 13.9 Hz, P−C=C). ^{3}P NMR (121.5 MHz, CDCl$_3$): δ_P 23.0 (Ph_3P^+–C).

Minor isomer (E)-**4a** (38%): ^{1}H NMR (300.1 MHz, CDCl$_3$):δ_H 3.56 and 3.70 (6H, 2s, 2OMe), 5.32 (1H, d, $^3J_{PH}$ = 16.6 Hz, P–C–CH), 7.48–7.69 (16H, m, 3C_6H_5 and N=CH), 9.87 (1H, s, N-NH). ^{3}C NMR (75.5 MHz, CDCl$_3$): δ_C 39.8 (d, $^1J_{PC}$ = 138.8 Hz, P=C), 50.5 and 52.7 (2s, 2OMe), 62.2 (d, $^2J_{PC}$ = 16.8 Hz, P–C–CH), 125.7 (d, $^1J_{PC}$ = 91.3 Hz, C_{ipso}), 128.5 (d, $^3J_{PC}$ = 12.1 Hz, C_{meta}), 131.2 (C_{para}), 132.6 (d, $^2J_{PC}$ = 9.7 Hz, C_{ortho}), 147.9, 156.6 and 165.5 (3C, $C_3H_2N_3O_2$), 171.0 (d, $^3J_{PC}$ = 13.7 Hz, C=O ester), 171.1 (d, $^2J_{PC}$ = 14.2 Hz, P−C=C). ^{3}P NMR (121.5 MHz, CDCl$_3$):δ_P 23.1 (Ph_3P^+–C).

Diethyl 2-(6-Azauracil-3-yl)-3-(triphenylphosphoranylidene)-butanedioate(4b)

Colorless crystals, mp 183.5–185.5°C, yield 0.51 g, 92%. IR (KBr) ($\nu_{max,}$ cm^{-1}): 1730, 1620, 1647, 1713 and 1730 (4C=O). MS (m/z,%): 545 (M, 5), 433 (M-$C_3H_2N_3O_2$, 38), 262 (PPh_3, 69), 238 (M-PPh_3 and OEt, 24), 183 (PPh_2, 79), 108 (PPh, 48). Anal. Calcd. for $C_{29}H_{28}N_3O_6P$ (545): C, 63.85; H, 5.14; N, 7.71%. Found: C, 63.72; H, 5.08; N, 7.75%.

Major isomer (Z)-**4b** (67%): H NMR (300.1 MHz, CDCl$_3$): δ_H 0.41 and 1.27 (6H, 2t, $^3J_{HH}$ = 7.1 Hz, 2O–C–CH_3), 4.01 and 4.22 (4H, 2m, 2ABX$_3$ systhem, 2O–CH_2–C), 5.28 (1H, d, $^3J_{HP}$ = 17.5 Hz, P–C–CH), 7.47–7.70 (16H, m, 3C_6H_5 and N=CH), 10.15 (1H, s, N-NH). ^{3}C NMR (75.5 MHz, CDCl$_3$): δ_C 13.9 and 14.2 (2s, 2O-C-CH_3), 39.8 (d, $^1J_{PC}$ = 138.8 Hz, P=C), 57.8 and 61.6 (2s, 2O–CH_2-C), 62.7 (d, $^2J_{PC}$ = 16.4 Hz, P–C–CH), 126.6 (d, $^1J_{PC}$ = 92.0 Hz, C_{ipso}), 128.8 (d, $^3J_{PC}$ = 12.4 Hz, C_{meta}), 132.3 (C_{para}), 133.6 (d, $^2J_{PC}$ = 9.7 Hz, C_{ortho}), 148.1, 156.8 and 165.0 (3C, $C_3H_2N_3O_2$), 169.4 (d, $^3J_{PC}$ = 12.9 Hz, C=O ester), 170.3 (d, $^2J_{PC}$ = 13.1 Hz, P-C=C). ^{3}P NMR (121.5 MHz, CDCl$_3$): δ_P 23.0 (Ph_3P^+–C).

Minor isomer (E)-**4b** (33%): H NMR (300.1 MHz, CDCl$_3$): δ_H 1.13 and 1.30 (6H, 2t, $^3J_{HH}$ = 7.0 Hz, 2O–C–CH_3), 3.70 and 4.15 (4H, 2m, 2ABX$_3$ systhem, 2O–CH_2–C), 5.22 (1H, d, $^3J_{HP}$ = 16.1 Hz, P–C–CH), 7.47–7.70 (16H, m, 3C_6H_5 and N=CH), 10.17 (1H, s, N-NH). ^{3}C NMR (75.5 MHz, CDCl$_3$): δ_C 14.2 and 14.8 (2s, 2O-C-CH_3), 38.6 (d, $^1J_{PC}$ = 130.6 Hz, P=C), 58.5 and 61.4 (2s, 2O–CH_2-C), 62.1 (d, $^2J_{PC}$ = 16.1 Hz, P–C–CH), 125.9 (d, $^1J_{PC}$ = 92.2 Hz, C_{ipso}), 128.9 (d, $^3J_{PC}$ = 12.2 Hz, C_{meta}), 132.3 (C_{para}), 133.6 (d, $^2J_{PC}$ = 9.8 Hz, C_{ortho}), 148.2, 156.8 and 165.1 (3C, $C_3H_2N_3O_2$), 170.4 (d, $^3J_{PC}$ = 13.7 Hz, C=O ester), 171.0 (d, $^2J_{PC}$ = 18.0 Hz, P-C=C). ^{3}P NMR (121.5 MHz, CDCl$_3$): δ_P 23.4 (Ph_3P^+–C).

Di-tert-butyl 2-(6-Azauracil-3-yl)-3-(triphenylphosphoranylidene)-butanedioate (4c)

Powder, mp 204–206°C, 0.57 g, yield 95%. IR (ν_{rnax}, cm^{-1}): 1640, 1677, 1708 and 1721 (4C=O). Mz (m/z,%): 489 (M-$C_3H_2O_2N_3$, 41) 455 (M-2OCMe$_3$, 36), 343 (M-$C_3H_2O_2N_3$ and 2OCMe$_3$, 27), 262 (PPh$_3$, 86), 183 (PPh$_2$, 86), 108 (PPh, 57); Anal. Cacld for $C_{33}H_{36}N_3O_6P$ (601): C, 65.89; H, 5.99; N, 6.99, Found: C, 66.07; H, 6.11; N, 6.87.

Major isomer (Z)-**4c**: H NMR (300.1 MHz, CDCl$_3$): δ_H 0.93 and 1.54 (18H, 2s, 2CMe$_3$), 5.01 (1H, d, $^3J_{HP}$ = 17.0 Hz, P–C–CH), 7.48–7.73 (16H, m, 3C$_6$H$_5$ and N=CH), 9.41 (1H, s, N-NH). ^{3}C NMR (75.5 MHz, CDCl$_3$): δ_C 28.3 and 28.7 (2s, 2OCMe$_3$), 39.4 (d, $^1J_{PC}$ = 137.6 Hz, P=C), 63.4 (d, $^2J_{PC}$ = 17.3 Hz, P–C–CH), 77.3 and 81.4 (2s, 2OCMe$_3$), 127.2 (d, $^1J_{PC}$ = 91.7 Hz, C$_{ipso}$), 128.5 (d, $^3J_{PC}$ = 12.1 Hz, C$_{meta}$), 132.2 (C$_{para}$), 133.6 (d, $^2J_{PC}$ = 9.7 Hz, C$_{ortho}$), 147.6, 156.5 and 164.5 (3C, $C_3H_2N_3O_2$), 168.5 (d, $^3J_{PC}$ = 13.3 Hz, C=O ester), 169.3 (d, $^2J_{PC}$ = 13.6 Hz, P-C=C). ^{3}P NMR (121.5 MHz, CDCl$_3$): δ_P 22.5 (Ph$_3$P$^+$–C).

KINETIC STUDIES

The synthetic reactions between triphenylphosphine **1**, dialkyl acetylenedicarboxylates **2**, and CH, SH, or NH-acids have been reported earlier,[13–31] but a few kinetic studies of these reactions have been investigated.[32,33] Herein, we wish to describe a kinetic investigation of the current synthesis. Numerous kinetic investigations over a large area of different reactions have been reported previously using UV analysis.[34–44] In order to gain further insight into the reaction mechanism, a kinetic study of the reactions was undertaken by UV spectrophotometeric technique. First it was necessary to find the appropriate wavelength in order to follow the kinetic study of the reaction. For this purpose, in the first experiment, 3 × 10^{-3} M solution of compounds **1**, **2c**, and **3** was prepared in 1,4-dioxane as a solvent. An approximately 3 mL aliquot from each reactant was pipetted into a 10 mm light path quartz spectrophotometer cell, and the relevant spectra were recorded over the wavelength range 190–400 nm. Figures 4, 5, and 6 show the ultraviolet spectra of compounds **1**, **2c**, and **3**, respectively. In a second experiment, a 1 mL aliquot from the 3 × 10^{-3} M solutions of each compound of **1** and **3** was pipetted first into a quartz spectrophotometer cell (as there is no reaction between them). Later 1 mL aliquot of the 3 × 10^{-3} M solution of reactant **2c** was added to the mixture, and the reaction was monitored by recording scans of the entire spectra every 13 min over the whole reaction time at ambient temperature. The ultraviolet spectra shown in Figure 7 are typical.

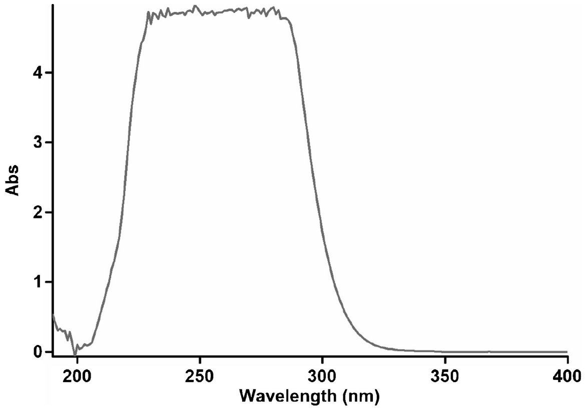


FIGURE 4 The UV spectrum of 10^{-3} M di-tert-butyl acetylenedicarboxylate **2c** in 1,4-dioxane.

From this, the appropriate wavelength was found to be 330 nm (corresponding mainly to product **4c**). At this wavelength, compounds **1**, **2c**, and **3** have relatively no absorbance value. This then provided us with the opportunity to fully investigate the kinetics of the reaction between triphenylphosphine **1**, di-tert-butyl acetylenedicarboxylate **2c**, and 6-azauracil 3 at 330 nm in the presence of 1,4-dioxane as solvent. Since the spectrophotometer cell of the UV instrument had a 10 mm light-path cuvette, the UV/Vis spectra of compound **4c** were measured over the concentration range (2×10^{-4} M $\leq M_{4c} \leq 10^{-3}$M) to check for a linear relationship between absorbance values and concentrations. With

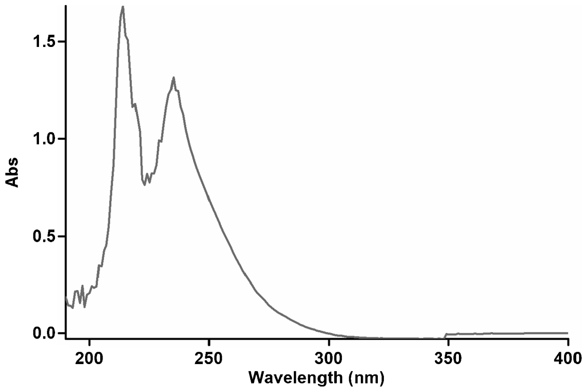


FIGURE 5 The UV spectrum of 10^{-3} M triphenylphosphine **1** in 1,4-dioxane.

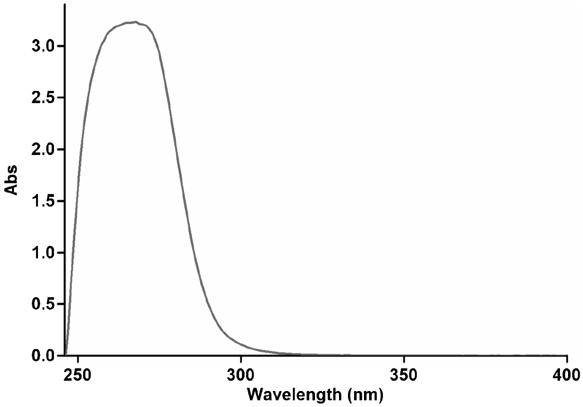


FIGURE 6 The UV spectrum of 10^{-3} M 6-azauracil **3** in 1,4-dioxane.

a suitable concentration range and wavelength identified, the following procedure was employed.

For each kinetic experiment, a 1 mL aliquot from each freshly made 3×10^{-3} M solution of compounds **1** and **3** in 1,4-dioxane was pipetted into a quartz cell, and then a 1 mL aliquot of the 3×10^{-3} M of solution of reactant **2c** was added to the mixture, keeping the temperature at 12.0°C. The reaction kinetics was followed by plotting UV absorbance against time. Figure 8 shows the absorbance change (dotted line) versus time for the 1:1:1 addition reaction between compounds **1**, **2c**, and

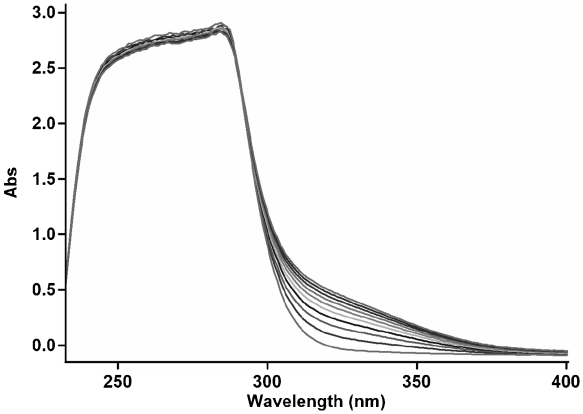


FIGURE 7 The UV spectra of the reaction between **1**, **2c**, and **3** with 10^{-3} M concentration of each compound as the reaction proceeds in 1,4-dioxane with10 mm light-path cell.

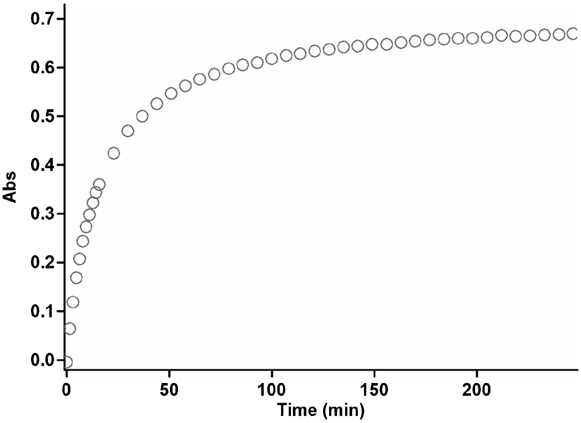


FIGURE 8 The experimental absorbance changes (dotted line) against time at 330 nm for the reaction between compounds **1**, **2c**, and **3** at 12°C in 1,4-dioxane.

3 at 12.0°C. The infinity absorbance (A_∞), that is the absorbance at reaction completion, can be obtained from Figure 8 at t = 214 min. With respect to this value, zero, first, or second curve fitting could be drawn automatically for the reaction by the software[46] associated with the UV instrument. Using the original experimental absorbance versus time data provided a second order fit curve (solid line) that fits exactly the experimental curve (dotted line) as shown in Figure 9. Thus, the reaction between triphenylphosphine **1**, di-tert-butyl acetylenedicarboxylate **2c**, and 6-azauracil **3** follows second-order kinetics. The second-order rate constant (k_2) is then automatically calculated using a standard equation[45] within the program at 12.0°C. It is reported in Table II.

Further kinetic studies were carried out using the same concentration of each reactant in the continuation of experiments with concentrations of 5×10^{-3} M and 7×10^{-3} M. As expected, the second order rate constant was independent of concentration, and its value was the same as in the previous experiment. In addition, the overall order of reaction was also two.

Effect of Solvents and Temperature

To determine the effect of change in temperature and solvent environment on the rate of reaction, we elected to perform various experiments

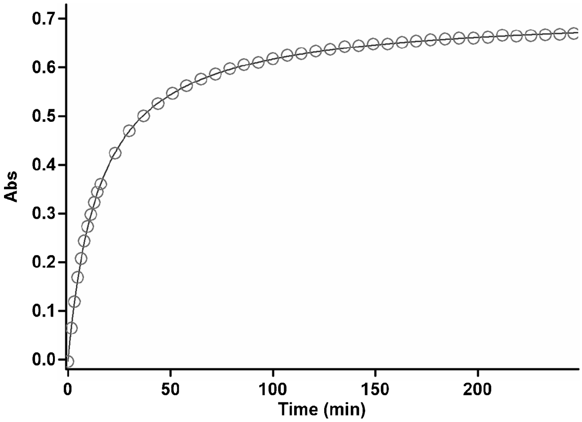


FIGURE 9 Second order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between compounds **1**, **2c**, and **3** at 330 nm and 12.0°C in 1,4-dioxane.

at different temperatures and solvent polarities, but otherwise under the same conditions as for the previous experiment. For this purpose, ethyl acetate with a dielectric constant ($\varepsilon = 6$) was chosen as suitable solvent, since it not only dissolved all compounds but also did not react with them. The effects of solvents and temperature on the rate constant are given in Table II. The results show that the rate of reaction in each case was increased at higher temperature. In addition, the rate of reaction between **1**, **2c**, and **3** was accelerated in a higher dielectric constant environment (ethyl acetate) in comparison with a lower dielectric constant environment (1,4-dioxane) at all temperatures investigated. In the temperature range studied, the dependence of the

TABLE II The Values of Overall Second Order Rate Constant for the Reaction Between 1, 2, and 3 in the Presence of Solvents Such as Ethyl Acetate and 1,4-Dioxane at All Temperatures Investigated

			k_2 $M^{-1}.min^{-1}$			
2	Solvent	ε	12.0°C	17.0°C	22.0°C	27.0°C
2c	1,4-dioxane	2	52.3	61.5	72.0	86.4
	Ethyl acetate	6	77.1	88.9	104.6	124.0
2b	1,4-dioxane	2	276.5	300.1	335.9	380.1
	Ethyl acetate	6	337.6	365.3	403.0	449.3
2a	1,4-dioxane	2	415.2	443.7	483.1	532.8
	Ethyl acetate	6	572.6	613.8	655.2	713.7

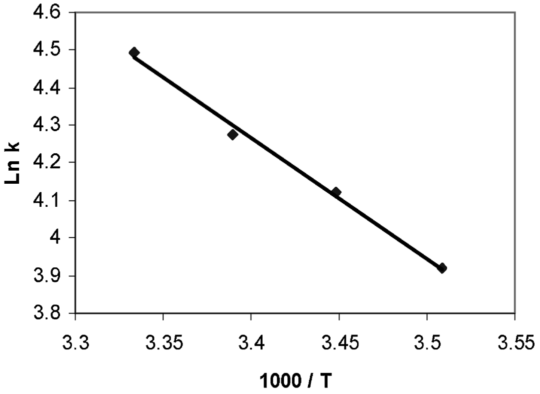


FIGURE 10 Dependence of second order rate constant (Ln k_2) on reciprocal temperature for the reaction between compounds **1**, **2c**, and **3** measured at wavelength 330 nm in 1,4-dioxane in accordance with the Arrhenius equation.

second-order rate constant (Ln k_2) of the reactions on reciprocal temperature is consistent with the Arrhenius equation, giving activation energy of reaction between **1**, **2c**, and **3** (23.6 kJ/mol) from the slope of the Figure 10.

Effect of Concentration

To determine reaction order with respect to triphenylphosphine **1** and dialkyl acetylenedicarboxylate **2** (**2c**), in the continuation of experiments, all kinetic studies were carried out in the presence of an excess of **3**. Under this condition the rate equation may therefore be expressed as

$$\text{rate} = k_{obs}[1]^{\alpha}[2]^{\beta} \quad k_{obs} = k_2[3]^{\gamma} \quad \text{or} \quad \text{Ln}k_{obs} = \text{Ln}k_2 + \gamma\text{Ln}[3] \qquad (1)$$

In this case, 3×10^{-2} M of **3** instead of 3×10^{-3} M using the original experimental absorbance versus time data provides a second order fit curve (solid line) against time at 330 nm that exactly fits the experimental curve (Figure 11). The value of the rate constant was the same as that of obtained from the previous experiment (3×10^{-3} M). Repeating the experiments with 5×10^{-2} M and 7×10^{-2} M concentrations of **3** gave separately the same fit curve and rate constant. In fact the experimental data indicated that the observed pseudo second-order rate constant (k_{obs}) is equal to the second-order rate constant (k_2); this is possible when γ is zero in Equation (1). It appears, therefore, that the reaction is zero and second order with respect to **3** (NH-acid) and

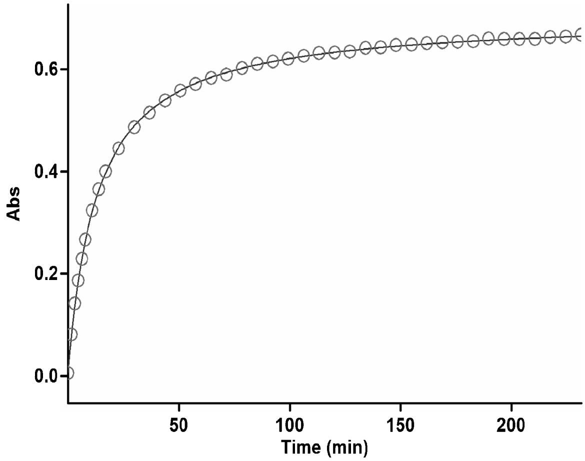


FIGURE 11 Pseudo second order fit curve (solid line) for the reaction between **1** and **2c** in the presence of excess **3** (10^{-2} M) at 330 nm and 12.0C in 1,4-dioxane.

the sum of **1** and **2** (**2c**) ($\alpha + \beta = 2$), respectively. To determine the reaction order with respect to dialkyl acetylenedicarboxylate 2 (2c), a continuation of the experiment was performed in the presence of an excess of **1**:

$$\text{rate} = \text{k}'_{\text{obs}}[3]^{\gamma}[2]^{\beta}, \text{k}'_{\text{obs}} = \text{k}_2[1]^{\alpha} \tag{2}$$

The original experimental absorbance versus time data provide a pseudo first-order fit curve at 330 nm, which exactly fits the experimental curve (dotted line) as shown in Figure 12.

As a result, since $\gamma = 0$ (as determined previously), it is reasonable to accept that the reaction is first order with respect to compound **2** (**2c**) ($\beta = 1$). Because the overall order of reaction is **2** ($\alpha + \beta + \gamma = 2$), it is obvious that $\alpha = 1$ and the order of triphenylphosphine **1** must be equal to one. This observation was obtained also for reactions between (**1**, **2b**, and **3**) and (**1**, **2a**, and **3**). Based on the above results, a simplified proposed reaction mechanism (Figure 3) is shown in Figure 13. The experimental results indicate that the third step (rate constant k_3) is possibly fast. In contrast, it may be assumed that the third step is the rate-determining step for the proposed mechanism. In this case the rate law can be expressed as follows:

$$\text{rate} = \text{k}_3[\text{I}_1][3] \tag{3}$$

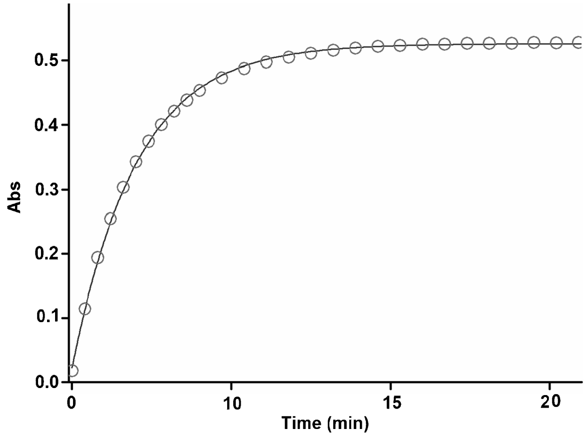


FIGURE 12 Pseudo first order fit curve (solid line) for the reaction between **2c** and **3** in the presence of excess **1** (10^{-2} M) at 330 nm and 12.0°C in 1,4-dioxane.

The steady-state assumption can be employed for $[I_1]$, which generates the following equation,

$$[I_1] = \frac{k_2[1][2]}{k_{-2} + k_3[3]}$$

The value of $[I_1]$ can be replaced in equation (3) to obtain this equation:

$$\text{rate} = \frac{k_2 k_3[1][2][3]}{k_{-2} + k_3[3]}$$

Since it was assumed that k_3 is relevant to the rate-determining step, it is reasonable to make the following assumption:

$$k_{-2} \gg k_3[3]$$

$$1 + 2 \xrightarrow{k_2} I_1 \text{ (Intermediate 1)}$$

$$I_1 \xrightarrow{k_{-2}} 1 + 2$$

$$I_1 + 3 \text{ (NH-acid)} \xrightarrow{k_3} N^- + I_2 \text{ (Intermediate 2)}$$

$$I_2 + N^- \xrightarrow{k_4} 4 \text{ (product, ylide)}$$

FIGURE 13 The simplified scheme for the proposed reaction mechanism.

so the rate law becomes:

$$\text{rate} = \frac{k_2k_3[1][2][3]}{k_{-2}}$$

The final equation indicates that the overall reaction order is three, which is not compatible with the experimental overall reaction order (two). In addition, according to this equation, the order of reaction with respect to 6-azauracil **3** is one, whereas it was actually shown to be equal to zero. For this reason, it appeared that the third step is fast. If we assume that the fourth step (rate constant k_4) is the rate-determining step for the proposed mechanism, in this case, there are two ionic species to consider in the rate-determining step, namely phosphonium ion (I_2) and 6-azauracil ion (N^-). The phosphonium and 6-azauracil ions, as we see in Figure 3, have full positive and negative charges and form very powerful ion dipole bonds to the ethyl acetate, the high dielectric constant solvent. However, the transition state for the reaction between the two ions carries a dispersed charge, which here is divided between the attacking 6-azauracil and the phosphonium ions. Bonding of solvent (ethyl acetate) to this dispersed charge would be much weaker than to the concentrated charge of 6-azauracil and phosphonium ions. The solvent thus would stabilize the species ions more than it does in the transition state, and therefore E_a would be higher, slowing down the reaction. However, in practice, ethyl acetate speeds up the reaction and for this reason, the fourth step, which is independent of the change in the solvent medium, could not be the rate-determining step. Furthermore, the rate law of formation of the product (fourth step) for a proposed reaction mechanism with application of steady-state assumption can be expressed by

$$\text{rate} = k_4[I_2][N^-]$$

By application of steady-state for $[I^-]$ and $[N^-]$, and replacement of their values in the above equation, the following equation is obtained:

$$\text{rate} = \frac{k_2k_3[1][2][3]}{k_{-2} + k_3[3]} \tag{4}$$

This equation is independent of the rate constant of the fourth step (k_4) and shows why the fourth step would not be affected by a change in the solvent medium. In addition, it has been suggested earlier that the kinetics of ionic species' phenomena (e.g., the fourth step) are very fast.[47,48] If the first step (rate constant k_2) were the rate-determining step, in this case, two reactants (triphenylphosphine **1** and dialkyl acetylenedicarboxylate **2**), as we see (Figure 3), have no charge and could not form strong ion-dipole bonds to the high dielectric constant solvent, ethyl acetate. However, the transition state carries a dispersed charge, which here is divided between the attacking **1** and **2**, and, hence bonding of solvent to this dispersed charge is much stronger than to the reactants, which lack charge. The solvent thus stabilizes the transition state more than it does the reactants, and, therefore, E_a is reduced, which speeds up the reaction. Our experimental results show that the solvent with the higher dielectric constant exerts a powerful effect on the rate of reaction (in fact, the first step has rate constant k_2 in the proposed mechanism), but the opposite occurs with the solvent with lower dielectric constant (1,4-dioxane, see Table II). The results of the current work (effects of solvent and concentration of compounds) have provided useful evidence for steps 1 (k_2), 3 (k_3), and 4 (k_4) of the reactions between triphenylphosphine **1**, dialkyl acetylenedicarboxylate **2** (**2a**, **2b**, or **2c**), and 6-azauracil **3**. Two steps involving 3 and 4 are not rate-determining steps, although the discussed effects, taken together, are compatible with the first step (k_2) of the proposed mechanism and would allow it to be the rate-determining step. However, a good kinetic description of the experimental result using mechanistic scheme based upon the steady-state approximation is frequently taken as evidence of its validity. By application of this, the rate formation of product **4** from the reaction mechanism (Figure 13) is given by:

$$\frac{\mathrm{d[4]}}{\mathrm{dt}} = \frac{\mathrm{d[ylide]}}{\mathrm{dt}} = \mathrm{rate} = \mathrm{k_4[I_2][N^-]} \tag{5}$$

We can apply the steady-state approximation to $[I_1]$ and $[I_2]$:

$$\frac{\mathrm{d[I_1]}}{\mathrm{dt}} = \mathrm{k_2[1][2] - k_{-2}[I_1] - k_3[I_1][3]}$$

$$\frac{\mathrm{d[I_2]}}{\mathrm{dt}} = \mathrm{k_3[I_1][3] - k_4[I_2][N^-]}$$

To obtain a suitable expression for $[I_2]$ to put into Equation (5), we can assume that, after an initial brief period, the concentrations of $[I_1]$ and $[I_2]$ achieve a steady state with their rates of formation and rates of disappearance just balanced. Therefore, $\frac{d[I_1]}{dt}$ and $\frac{d[I_2]}{dt}$ are zero, and we can obtain expressions for $[I_2]$ and $[I_1]$ as follows:

$$\frac{\mathrm{d[I_2]}}{\mathrm{dt}} = 0 \quad \mathrm{[I_2]} = \frac{\mathrm{k_3[I_1][3]}}{\mathrm{k_4[N^-]}} \tag{6}$$

$$\frac{\mathrm{d[I_1]}}{\mathrm{dt}} = 0 \quad \mathrm{[I_1]} = \frac{\mathrm{k_2[1][2]}}{\mathrm{k_{-2} + k_3[3]}} \tag{7}$$

We can now replace $[I_1]$ in Equation (6) to obtain this equation:

$$[I_2] = \frac{k_2k_3[1][2][3]}{k_4[N^-]\left[k_{-2} + k_3[3]\right]}$$

The value of $[I_2]$ can be put into Equation (5) to obtain the rate Equation (8) for the proposed mechanism:

$$\text{rate} = \frac{k_2k_3k_4[1][2][3][N^-]}{k_4[N^-]\left[k_{-2} + k_3[3]\right]} \quad \text{or} \quad \text{rate} = \frac{k_2k_3[1][2][3]}{\left[k_{-2} + k_3[3]\right]} \tag{8}$$

Since experimental data have indicated that steps 3 (k_3) and 4 (k_4) are fast but step 1 (k_2) is slow, it is therefore reasonable to make the following assumption:

$$k_3[3] \gg k_{-2}$$

So the rate equation becomes

$$rate = k_2[1][2] \tag{9}$$

This equation, which was obtained from a mechanistic scheme (shown in Figure 13) by applying the steady-state approximation, is compatible with the results obtained by UV spectrophotometry.

Further Kinetic Investigations: Effect of Structure of Dialkyl Acetylenedicarboxylates

To confirm the above observations, further experiments were performed with diethyl acetylene dicarboxylate **2b** and dimethyl acetylenedicarboxylate **2a** under the same conditions used in the previous experiments. The values of the second-order rate constant (k_2) for the reactions between (**1**, **2b**, and **3**) and (**1**, **2a**, and **3**) are reported in Table II for all solvents and temperatures investigated. The original experimental absorbance curves (dotted line) accompanied by the second order fit curves (solid line), which exactly fit experimental curves (dotted line) for both reactions, are shown in Figures 14 and 15 at 12.0°C and 330 nm.

As can be seen from Table II, the behavior of diethyl acetylenedicarboxylate **2b** and dimethyl acetylenedicarboxylate **2a** are the same as for the di-tert-butyl acetylenedicarboxylate **2c** with respect to the reaction with triphenylphosphine **1** and 6-azauracil **3**. The rates of the former reactions were also accelerated in a higher dielectric constant environment and with higher temperatures; however these rates under the same conditions are approximately 5 to 7 times greater than for the reaction with di-tert-butyl acetylenedicarboxylate **2c**

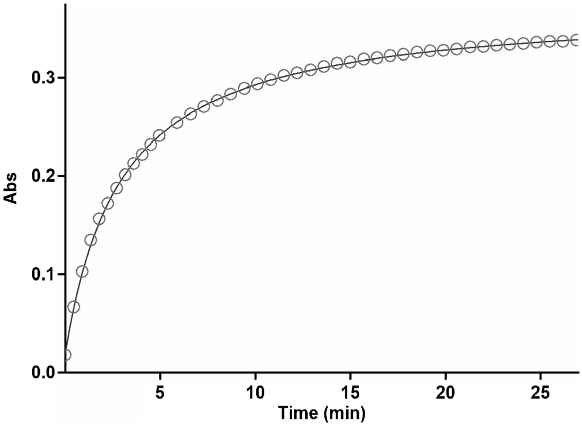


FIGURE 14 Second order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between compounds **1**, **2b**, and **3** at 330 nm and 12.0°C in 1,4-dioxane.

(see Table II). It seems that both inductive and steric factors for the bulky alkyl groups in **2c** tend to reduce the overall reaction rate (see Equation 9). In the case of dimetyl acetylenedicarboxylate **2a**, the lower steric and inductive effects of the dimethyl groups exert a powerful effect on the rate of reaction.

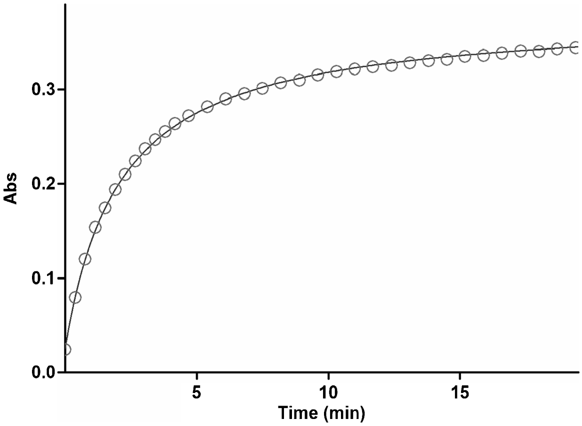


FIGURE 15 Second order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between compounds **1**, **2a**, and **3** at 330 nm and 12.0°C in 1,4-dioxane.

CONCLUSION

Briefly, we have prepared novel phosphorus ylides using a one-pot reaction between triphenylphosphine 1 and dialkyl acetylenedicarboxylates **2** (**2a**, **2b**, **2c**) in the presence of a NH-acid such as 6-azauracil. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modifications. The stable phosphorus ylides **4** (**4a**, **4b**, or **4c**) are potentially useful synthetic intermediates, and the procedure described here may be acceptable for the preparation of phosphoranes with variable functionalities. In addition, kinetic investigations of these reactions were undertaken using UV spectrophotometry. The results, which are similar to previous work,[33] can be summarized as follows:

1. The appropriate wavelengths and concentrations were determined in order to follow the reaction kinetics.
2. The overall reaction order followed second-order kinetics, and the reaction orders with respect to triphenylphosphine, dialkyl acetylenedicarboxylate and 6-azauracil were one, one, and zero, respectively.
3. The values of the second-order rate constants of all reactions were calculated automatically with respect to the standard equation using the software associated with the Cary-300 UV equipment.
4. The rates of all reactions were accelerated at higher temperatures. Under the same conditions, the activation energy of the reaction with di-tert-butylacetylenedicarboxylate **2c** (23.6 kJ/mol) was higher than that for the both reactions that were followed by the diethyl acetylenedicarboxylate **2b** (15.1 kJ/mol) and dimethyl acetylenedicarboxylate **2a** (11.8 kJ/mol).
5. The rates of all reactions were increased in solvents of higher dielectric constant, and this can be related to differences in stabilization by the solvent of the reactants and the activated complex in the transition state.
6. Increased steric bulk in the alkyl groups of the dialkyl acetylenedicarboxylates, accompanied by the correspondingly greater inductive effect, reduced the overall reaction rate.
7. With respect to the experimental data, the first step of the proposed mechanism was recognized as a rate-determining step (k_2), and this was confirmed based upon the steady-state approximation.

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