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Efficient synthesis of 5,6,7-trisubstituted 1*H*-pyrrolizines

Issa Yavari* and Mehdi Adib

Department of Chemistry, University of Tarbiat Modarres, P.O. Box 14155-4838, Tehran, Iran

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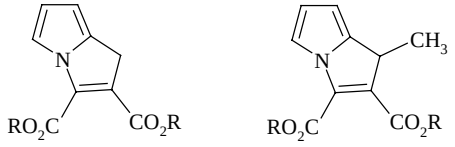
Abstract—Crystalline phosphorus ylides are obtained in excellent yields from the 1:1:1 addition reaction between triphenylphosphine, dialkyl acetylenedicarboxylates and strong NH-acids, such as 2-pyrrolylglyoxalate or *N*-benzyl-2-pyrrolylglyoxamate. These phosphoranes undergo a smooth intramolecular Wittig reaction in boiling toluene to produce 5,6,7-trisubstituted 1*H*-pyrrolizine derivatives in quantitative yields. Dynamic NMR effects are observed in the ^{1}H NMR spectra of stabilized ylides **6a** and **6d** ($\Delta G^{\neq}$=67.6 and 69.5 kJ mol^{-1}, respectively) and are attributed to restricted rotation around the carbon–carbon partial double bond resulting from conjugation of the ylide moiety with the adjacent carbonyl group.

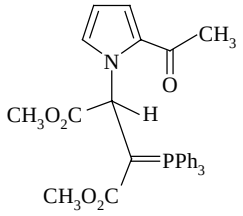
1. Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[2–4] The interest in bicyclic 5–5 systems with one ring junction nitrogen atom and no extra heteroatoms, stems from the appearance of saturated and partially saturated pyrrolizine ring systems in many alkaloids.[5,6] Consequently, there has been an ongoing interest in synthesis of pyrrolizine ring structures.[7–10]

We have recently described[11] the synthesis of functionalized 1*H*-pyrrolizine derivatives **1** from the reaction of triphenylphosphine, dialkyl acetylenedicarboxylates and pyrrole-2-carboxaldehyde using an intramolecular Wittig reaction.[12–14] With the purpose to prepare 1*H*-pyrrolizines having a methyl group at position 4, such as **2**, 2-acetylpyrrole was treated with dimethyl acetylenedicarboxylate and triphenylphosphine. However, the pyrrolizine derivative **2** was not observed and dimethyl 2-(2-acetyl-1*H*-pyrrole-1-yl)-3-(triphenylphosphanylidene)butanedioate **3** was isolated in quantitative yield. This stable ylide, was recovered unchanged after refluxing in toluene for 24 h.



1 **2**



3

Since vicinal dicarbonyl compounds are more reactive than alkyl ketones in the Wittig reaction,[15–20] we turned to ethyl 2-pyrrolylglyoxalate (**5a**) and *N*-benzyl-2-pyrrolyl-glyoxamate (**5b**). These compounds undergo a smooth reaction with dialkyl acetylenedicarboxylates **4** and triphenylphosphine in dichloromethane at ambient temperature to produce dialkyl 2-(ethyl 2-pyrrolglyoxalate-1-yl)-3-(triphenylphosphoran-ylidene)butanedioate **6** in 95–100% yield. Phosphorus ylides **6** undergo intramolecular Wittig reaction in boiling toluene to produce 1*H*-pyrrolizine derivatives **7** in quantitative yield (Scheme 1).

2. Results and discussion

On the basis of the well established chemistry of trivalent phosphorus nucleophiles,[12–19] it is reasonable to assume that phosphorus ylide **6** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent

Keywords: 5,6,7-trisubstituted 1*H*-pyrrolizines; 2-pyrrolylglyoxalate; *N*-benzyl-2-pyrrolylglyoxamate.

* Corresponding author. Fax: +98-21-8006544; e-mail: isayavar@yahoo.com

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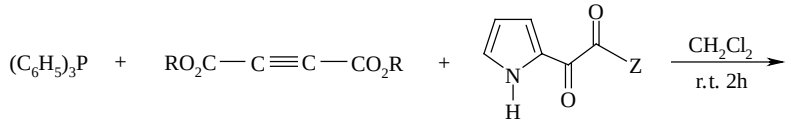
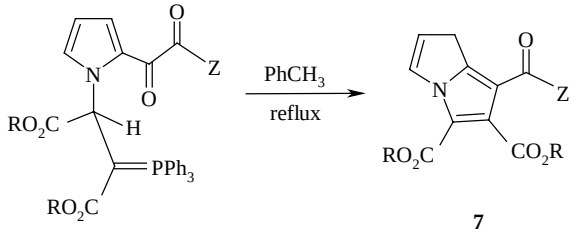


4	R
a	Me
b	Et
c	^{i}Pr

5	Z
a	OEt
b	NHCH$_2$Ph



6 **7**

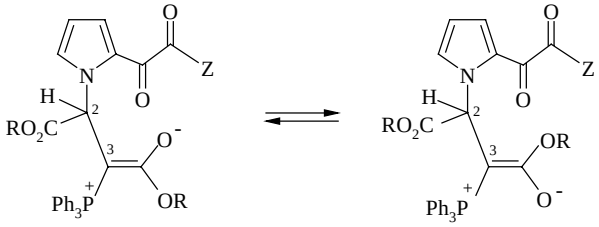
6, 7	R	Z	%Yield of **6**
a	Me	OEt	100
b	Et	OEt	100
c	^{i}Pr	OEt	95
d	Me	NHCH$_2$C$_6$H$_5$	100

Scheme 1.

protonation of the 1:1 adduct by the NH-acid **5**. Then the positively charged ion is attacked by the nitrogen atom of the conjugate base of the NH-acid to form phosphoranes **6**.

The structures of compounds **6a**–**d** were deduced from their elemental analyses and their high-field ^{1}H-, ^{13}C-, and ^{31}P NMR and IR spectral data. The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra which displayed molecular ion peaks at m/z=571, 599, 627, and 632, respectively. Initial fragmentations involve loss from or complete loss of the side chains and scission of the heterocyclic ring system.

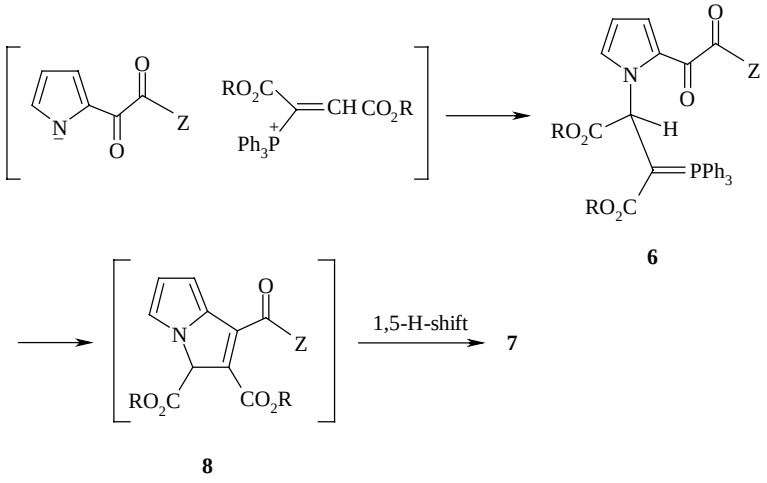
Table 1. Selected ^{1}H, ^{13}C, and ^{31}P NMR chemical shifts (δ in ppm) and coupling constants (Jin Hz) for H-2, CO$_2$R, COR, C-2, C-3, and P in the major (M) and minor (m) geometrical isomers of compounds **6a**–**d**



6-(*Z*) **6**-(*E*)

Compound	Isomer (%)	^{1}H NMR spectroscopic data			^{13}C NMR spectroscopic data		^{31}P
		H-2 ($^{3}J_{PH}$)	OR	CO$_2$R	C-2 ($^{2}J_{PC}$)	C-3 ($^{1}J_{PC}$)	
6a	M(52)	5.71 (17.6)	3.21	3.72	61.83 (17.5)	44.28 (126)	24.39
	m(48)	5.65 (19)	3.59	3.71	61.74 (16.8)	44.55 (134)	25.23
6b	M(60)	5.71 (18)	–	–	61.75 (17.5)	43.10 (126)	24.42
	m(40)	5.65 (19.4)	–	–	61.65 (16.5)	43.50 (130)	25.39
6c	M(64)	5.70 (18.3)	4.79[a]	5.06[a]	61.10 (17.5)	42.98 (126)	24.27
	m(36)	5.55 (19.8)	4.93[a]	4.95[a]	60.85 (16.7)	43.50 (128)	25.54
6d	M(55)	5.63 (17.1)	3.21	3.74	61.02 (17.5)	43.75 (126)	24.45
	m(45)	5.59 (18.1)	3.61	3.72	60.92 (17.3)	43.92 (134)	25.35

[a] The methine group of the OR moiety.



6 **8** **7**

Scheme 2.

The ^{1}H-, ^{13}C-, and ^{31}P NMR spectra of ylides **6a–d** are consistent with the presence of two isomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the partial double bond in **6**-(*E*) and **6**-(*Z*) geometrical isomers is slow on the NMR timescale at ambient temperature. 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 **6a–d** are shown in Table 1.

Phosphorus ylides **6** undergo a smooth reaction in boiling toluene to produce triphenylphosphine oxide and 1*H*-pyrrolizine derivatives **7** (see Scheme 1). Structure **7** was assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H-, and ^{13}C NMR and mass spectral data. NMR spectroscopy was used to distinguish structure **7** from the primary product, 5*H*-pyrrolizine derivative **8** (see Scheme 2). Thus the ^{1}H NMR spectrum of each of the isolated products exhibited a methylene proton signal at about δ=4.6–4.8. Further evidence was obtained from the ^{13}C NMR spectra, which displayed a methylene carbon resonance at about δ=53–55. The mass spectra of 1*H*-pyrrolizine derivatives **7a–d** are similar, as expected, and confirm their molecular weights. Partial assignments of the ^{1}H- and ^{13}C resonances in the ^{1}H- and ^{13}C NMR spectra of **5a–d** are given in the experimental section.

Several examples are known in which a heterocyclic alkene is produced from a phosphorane connected to a carbonyl group by a chain containing a heteroatom.[12,13] Thus, pyrrolizine derivative **7** may be regarded as a product of an intramolecular Wittig reaction. Such cyclization reaction produces 5*H*-pyrrolizine derivative **8** (see Scheme 2). Compound **8** apparently isomerizes, under the reaction conditions, to produce the 1*H*-pyrrolizine isomer **7**.

The most noteworthy feature of the ^{1}H NMR spectrum of **6a** in $CDCl_3$ at room temperature (25°C) is the methoxy region which exhibits two sharp singlets (δ=3.72 and 3.71 ppm) for the CO_2CH_3 groups of (*E*)-**6a** and (*Z*)-**6a** and two fairly broad singlets (δ=3.59 and 3.21) for the methoxy groups (see Table 1). Near 5°C the broad lines become sharper. The ^{1}H NMR spectrum of **6a** in 1,2-dichlorobenzene at 5°C is similar to that in $CDCl_3$. Increasing the temperature results in coalescence of the methoxy resonances (T_c=50±1°C). At 90°C, a fairly broad singlet was observed, while the CO_2CH_3 protons appear as a sharp single resonance.

Although an extensive line-shape analysis in relation to the dynamic ^{1}H NMR effect observed for **6a** was not undertaken, the variable temperature spectra allowed to calculate the free energy barrier (if not the enthalpy and entropy of activation) for the dynamic NMR process in **6a**. From coalescence of the methoxy proton resonances and using the expression, $k = \pi\Delta\nu/\sqrt{2}$, we calculate that the first-order rate constant (k) for dynamic NMR effect in **6a** is 75 s^{-1} at 323 K (see Table 2). Application of the absolute rate theory with a transmission coefficient of 1 gives a free-energy of activation ($\Delta G^{\neq}$) of 67.6±2 kJ mol^{-1}, where all known sources of errors are estimated and included.[21] The experimental data available are not suitable for obtaining meaningful values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the errors in $\Delta G^{\neq}$ are not large.[22]

Similar dynamic ^{1}H NMR effect was observed for compound **6d**. From coalescence of the methoxy proton resonances, the first-order rate constant for dynamic NMR

Table 2. Selected proton chemical shifts (at 90 MHz, in ppm, Me_4Si) and activation parameters (kJ mol^{-1}) for **6a** and **6d** in 1,2-dichlorobenzene

Compound	Temp (°C)	Resonance (OCH_3)		$\Delta\nu$ (Hz)	k (s^{-1})	T_c (K)	$\Delta G^{\neq}$
6a	5	3.24	3.62	34	75	323	67.6±2
	90	3.39					
6d	5	3.27	3.66	35	78	332	69.5±2
	90	3.43					

in **6d** is 78 s^{-1} at 332 K. The calculated free-energy of activation for the dynamic process in **6d** is 69.5±2 kJ mol^{-1}, which is slightly higher than that for compound **6a** (see Table 2).

3. Conclusion

The present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.[7–10,23] Dynamic NMR effects are observed in the ^{1}H NMR spectra of compounds **6a** and **6d** and are attributed to restricted rotation around the carbon–carbon partial double bond resulting from conjugation of the phosphorus ylide carbon atom with the adjacent carbonyl group.

4. Experimental

Dialkyl acetylenedicarboxylates and triphenylphosphine were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Ethyl 2-pyrrolylglyoxalate and *N*-benzyl-2-pyrrolylglyoxamate were prepared by known methods.[24,25] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H-, ^{13}C- and ^{31}P NMR spectra were measured ($CDCl_3$ solution) with a Brucker DRX-500 AVANCE spectrometer at 500.13, 125.77 and 202.45 MHz, respectively. Dynamic NMR studies were carried out using a JEOL-EX 90 Fourier transform spectrometer at 89.45 MHz. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Aldrich silica gel 70–230 mesh.

4.1. General procedure for preparation of compounds 6a–d

4.1.1. Dimethyl 2-(ethyl 2-pyrrolylglyoxalate-1-yl)-3-(triphenylphosphoranylidene)butanedioate 6a. The process for the preparation of the above-mentioned compound is described as an example. To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol) and ethyl 2-pyrrolylglyoxalate **5a** (0.334 g, 2 mmol) in dichloromethane (4 mL) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.284 g, 2 mmol) in dichloromethane (2 mL) at −5°C for 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 2 h. The solvent was removed under reduced pressure and the residual solid recrystallized from hexane as colorless crystals, mp 149–150°C (dec), yield 1.14 g, 100%. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1627, 1630 (C=O). MS, *m*/*z* (%): 571 (M^+, 1), 277 (100), 183 (48), 152 (31), 94 (57), 77(56). Anal. Calcd for $C_{32}H_{30}NO_7P$ (571.56): C, 67.24; H, 5.29; N, 2.45. Found: C, 67.4; H, 5.3; N, 2.5%.

Major isomer, **6a**-(*Z*) (51%), ^{1}H NMR: δ 1.34 (3H, t, J=7 Hz, CH_3), 3.21 and 3.72 (6H, 2s, $2OCH_3$), 4.27 (2H, q, J=7 Hz, OCH_2), 5.71 (1H, d, $^3J_{PH}$=17.6 Hz, P–C–CH), 6.24 (1H, br t, N–CH=C*H*), 7.08 (1H, dd, $^3J_{HH}$=4 Hz and $^4J_{HH}$=1.4 Hz, N–C=CH), 7.4–7.6 (15H, m, $3C_6H_5$), 7.89 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 14.48 (CH_3), 44.28 (d, $^1J_{PC}$=126 Hz, P=C), 49.77 and 53.05 ($2OCH_3$), 61.83 (d, $^2J_{PC}$=17.5 Hz, P–C–*C*H), 62.03 (OCH_2), 110.14 (pyrrole C^4H), 125.15 (pyrrole C^3H), 126.62 (d, $^1J_{PC}$=91.5 Hz, C^{ipso}), 128.87 (pyrrole C^5H), 129.31 (d, $^3J_{PC}$=12.3 Hz, C^m), 132.45 (pyrrole C^2), 132.73 (C^p), 133.79 (d, $^2J_{PC}$=9.9 Hz, C^o), 164.01 ($CO_2C_2H_5$), 170.97 and 172.31 (2d, $^2J_{PC}$=13 Hz and $^3J_{PC}$=18.2 Hz, 2C=O ester), 173.88 (pyrrole-C=O). ^{31}P NMR: δ 24.39 (Ph_3P^+–C).

Minor isomer, **6a**-(*E*) (49%), ^{1}H NMR: δ 1.33 (3H, t, J=6.9 Hz, CH_3), 3.59 and 3.71 (6H, 2s, $2OCH_3$), 4.27 (2H, q, J=6.9 Hz, OCH_2), 5.65 (1H, d, $^3J_{PH}$=19 Hz, P–C–CH), 6.24 (1H, br t, N–CH=C*H*), 7.14 (1H, dd, $^3J_{HH}$=4 Hz and $^4J_{HH}$=1.4 Hz, N–C=CH), 7.4–7.6 (15H, m, $3C_6H_5$), 7.80 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 14.48 (CH_3), 44.55 (d, $^1J_{PC}$=134 Hz, P=C), 50.76 and 52.85 ($2OCH_3$), 61.74 (d, $^2J_{PC}$=16.8 Hz, P–C–*C*H), 61.98 (OCH_2), 109.99 (pyrrole C^4H), 125.34 (pyrrole C^3H), 126.01 (d, $^1J_{PC}$=91.4 Hz, C^{ipso}), 128.96 (pyrrole C^5H), 129.35 (d, $^3J_{PC}$=12.1 Hz, C^m), 132.53 (pyrrole C^2), 132.73 (C^p), 133.87 (d, $^2J_{PC}$=10 Hz, C^o), 163.89 ($CO_2C_2H_5$), 170.42 and 172.32 (2d, $^2J_{PC}$=13 Hz and $^3J_{PC}$=13.2 Hz, 2C=O ester), 173.97 (pyrrole-C=O). ^{31}P NMR: δ 25.23 (Ph_3P^+–C).

4.1.2. Diethyl 2-(ethyl 2-pyrrolylglyoxalate-1-yl)-3-(triphenylphosphoranylidene) butanedioate 6b. Colorless crystals, mp 125–127°C, yield 1.18 g, 100%. IR (KBr) (ν_{max}/cm^{-1}); 1747, 1724, 1638 (C=O). MS, *m*/*z* (%): 599 (M^+, 2), 278 (54), 183 (100), 108 (54), 94 (76), 77 (43). Anal. Calcd for $C_{34}H_{34}NO_7P$ (599.62): C, 68.10; H, 5.71; N, 2.33. Found: C, 68.5; H, 5.8; N, 2.3%.

Major isomer, **6b**-(*Z*) (60%), ^{1}H NMR: δ 0.51, 1.24 and 1.33 (9H, 3 t, J=7 Hz, $3CH_3$), 3.77, 4.13 and 4.28 (6H, 3q, J=7 Hz, $3ABX_3$, $3OCH_2CH_3$), 5.71 (1H, d, $^3J_{PH}$=18 Hz, P–C–CH), 6.24 (1H, dd, $^3J_{HH}$=4.0 Hz and $^3J_{HH}$=2.6 Hz, N–CH=C*H*), 7.08 (1H, dd, $^3J_{HH}$=4.0 Hz and $^4J_{HH}$=1.4 Hz, N–C=CH), 7.4–7.6 (15H, m, $3C_6H_5$), 7.91 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 13.55, 13.58 and 13.60 ($3CH_3$), 43.1 (d, $^1J_{PC}$=126 Hz, P=C), 57–61 ($3OCH_2$), 61.75 (d, $^2J_{PC}$=17.5 Hz, P–C–*C*H), 109.17 (pyrrole C^4H), 124.26 (pyrrole C^3H), 126.03 (d, $^1J_{PC}$=93.4 Hz, C^{ipso}), 126.41 (pyrrole C^5H), 128.41 (d, $^3J_{PC}$=12.1 Hz, C^m), 131.75 (C^p), 132.54 (pyrrole C^2), 132.97 (d, $^2J_{PC}$=9.6 Hz, C^o), 163.21 ($CO_2C_2H_5$), 170.15 and 170.6 (2d, $^2J_{PC}$=13.2 Hz and $^3J_{PC}$=13.3 Hz, 2C=O ester), 173.07 (pyrrole-C=O). ^{31}P NMR: δ 24.42 (Ph_3P^+–C).

Minor isomer, **6b**-(*E*) (40%), ^{1}H NMR: δ 1.16, 1.29 and 1.34 (9H, 3t, J=7 Hz, $3CH_3$), 4.06, 4.23 and 4.30 (6H, 3q, J=7 Hz, $3ABX_3$, $3OCH_2CH_3$), 5.65 (1H, d, $^3J_{PH}$=19.4 Hz, P–C–CH), 6.25 (1H, dd, $^3J_{HH}$=4.0 Hz and $^3J_{HH}$=2.6 Hz, N–CH=C*H*), 7.15 (1H, dd, $^3J_{HH}$=4.0 Hz and $^4J_{HH}$= 1.4 Hz, N–C=CH), 7.4–7.6 (15H, m, $3C_6H_5$), 7.84 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 13.61, 13.67 and 13.69 ($3CH_3$), 43.5 (d, $^1J_{PC}$=130 Hz, P=C), 57–61 ($3OCH_2$), 61.65 (d, $^2J_{PC}$=16.5 Hz, P–C–*C*H), 108.96 (pyrrole C^4H), 124.43 (pyrrole C^3H), 125.41 (d, $^1J_{PC}$=91.5 Hz, C^{ipso}),

126.60 (pyrrole C^5H), 128.31 (d, $^3J_{PC}$=12.1 Hz, C^m), 131.75 (C^p), 132.95 (pyrrole C^2), 132.98 (d, $^2J_{PC}$=9.6 Hz, C^o), 163.10 ($CO_2C_2H_5$), 168.15 and 170.6 (2d, $^2J_{PC}$=12.6 Hz and $^3J_{PC}$=13.4 Hz, 2 C=O ester), 172.99 (pyrrole-C=O). ^{31}P NMR: δ 25.39 (Ph_3P^+–C).

4.1.3. Diisopropyl 2-(ethyl 2-pyrrolylglyoxalate-1-yl)-3-(triphenylphosphoranylid-ene)butanedioate 6c. Colorless crystals, mp 123–126°C, yield 1.25 g, 95%. IR (KBr) (ν_{max}/cm^{-1}): 1739, 1634 (C=O). MS, *m/z* (%): 627 (M^+, 2), 288 (7), 278 (12), 262 (28), 183 (100), 108 (96), 77 (21). Anal. Calcd. for $C_{36}H_{38}NO_7P$ (627.67): C, 68.89; H, 6.10; N, 2.23. Found: C, 69.1; H, 6.05; N, 2.3%.

Major isomer, **6c**-(*Z*) (64%), ^{1}H NMR: δ 0.50, 0.69, 1.24 and 1.28 [12H, 4d, *J*=6 Hz, 4OCH(CH_3)$_2$], 1.32 (3H, t, *J*=7 Hz, OCH$_2$CH_3), 4.24 (2H, m, ABX_3 system, OCH_2CH$_3$), 4.79 and 5.06 [2H, 2 septet, *J*=6 Hz, 2OC*H*(CH$_3$)$_2$], 5.70 (1H, d, $^3J_{PH}$=18.3 Hz, P–C–CH), 6.23 (1H, dd, $^3J_{HH}$=4.0 Hz and $^3J_{HH}$=2.6 Hz, N–CH=C*H*), 7.09 (1H, dd, $^3J_{HH}$=4.0 Hz and $^4J_{HH}$=1.4 Hz, N–C=CH), 7.4–7.65 (15H, m, 3C_6H_5), 7.92 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 13.59 (CH$_2$*C*H$_3$), 21.19, 21.24, 21.43 and21.60 [2CH(*C*H$_3$)$_2$], 42.98 (d, $^1J_{PC}$=126 Hz, P=C), 60.99 (OCH$_2$), 61.10 (d, $^2J_{PC}$=17.5 Hz, P–C–*C*H), 64.37 and 67.99 [2O*C*H(CH$_3$)$_2$], 109.13 (pyrrole C^4H), 124.21 (pyrrole C^3H), 126.24 (d, $^1J_{PC}$=92 Hz, C^{ipso}), 126.40 (pyrrole C^5H), 128.2 (d, $^3J_{PC}$=12.4 Hz, C^m), 131.67 (d, $^4J_{PC}$=2.6 Hz, C^p), 132.69 (pyrrole C^2), 133.1 (d, $^2J_{PC}$=9.6 Hz, C^o), 163.21 ($CO_2C_2H_5$), 170.18 and 170.7 (2d, $^2J_{PC}$=13.1 Hz and $^3J_{PC}$=13.3 Hz, 2C=O ester), 172.88 (pyrrole-C=O). ^{31}P NMR: δ 24.27 (Ph_3P^+–C).

Minor isomer, **6c**-(*E*) (36%), ^{1}H NMR: δ 1.12, 1.21, 1.23 and 1.29 [12H, 4d, *J*=6 Hz, 4OCH(CH_3)$_2$], 1.34 (3H, t, *J*=7 Hz, OCH$_2$CH_3), 4.25 (2H, m, ABX_3 system, OCH_2CH$_3$), 4.93 and 4.95 [2H, 2 septet, *J*=6 Hz, 2OC*H*(CH$_3$)$_2$], 5.55 (1H, d, $^3J_{PH}$=19.8 Hz, P–C–CH), 6.24(1H, dd, $^3J_{HH}$=4.0 Hz and $^3J_{HH}$=2.6 Hz, N–CH=C*H*), 7.13 (1H, br. t, N–C=CH), 7.4–7.65 (15H, m, 3C_6H_5), 7.83 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 13.60 (CH$_2$*C*H$_3$), 21.44, 21.45, 21.88 and 21.89 [2CH(*C*H$_3$)$_2$], 43.50 (d, $^1J_{PC}$=128 Hz, P=C), 60.85 (d, $^2J_{PC}$=16.7 Hz, P–C–*C*H), 61.15 (OCH$_2$), 65.07 and 68.19 [2O*C*H(CH$_3$)$_2$], 108.73 (pyrrole C^4H), 124.35 (pyrrole C^3H), 125.75 (d, $^1J_{PC}$=92 Hz, C^{ipso}), 126.60 (pyrrole C^5H), 128.32 (d, $^3J_{PC}$=12.9 Hz, C^m), 131.60 (d, $^4J_{PC}$=2.6 Hz, C^p), 132.95 (pyrrole C^2), 133.85 (d, $^2J_{PC}$=12.4 Hz, C^o), 163.29 ($CO_2C_2H_5$), 168.37 and 170.7 (2d, $^2J_{PC}$=12.5 Hz and $^3J_{PC}$=13.2 Hz, 2C=O ester), 172.91 (pyrrole-C=O). ^{31}P NMR: δ 25.54 (Ph_3P^+–C).

4.1.4. Dimethyl 2-(*N*-benzyl 2-pyrrolylglyoxamate-1-yl)-3-(triphenylphosphoran-ylidene)butanedioate 6d. Pale orange crystals, yield 1.25 g, 100%, mp 160–162°C (from 1:2 hexane–ethyl acetate) (melted and decomposed). IR (KBr) (ν_{max}/cm^{-1}): 3365 (N–H), 1738, 1674, 1620 (C=O). MS, *m/z* (%): 632 (M^+, 1), 277 (56), 183 (51), 106 (100), 91 (69), 77 (34). Anal. Calcd for $C_{37}H_{33}N_2O_6P$ (632.65): C, 70.24; H, 5.26; N, 4.43. Found: C, 70.4; H, 5.3; N, 4.5%.

Major isomer, **6d**-(*Z*) (55%), ^{1}H NMR: δ 3.21 and 3.74 (6H, 2s, 2 CH$_3$), 4.33 and 4.51 (2H, 2dd, $^2J_{HH}$=14.8 Hz, $^3J_{HH}$=5.2 Hz and $^3J_{HH}$=5.3 Hz, ABX system, NHCH_2), 5.63 (1H, d, $^3J_{PH}$=17.1 Hz, P–C–CH), 6.28 (1H, dd, $^3J_{HH}$=5.2 Hz, NH), 7.25–7.35 (6H, m, C_6H_5 and N–CH=C*H*), 7.35–7.56 (15H, m, 3C_6H_5), 7.87 (1H, br t, N–C=CH), 7.95 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 42.67 (NHCH$_2$), 43.57 (d, $^1J_{PC}$=126 Hz, P=C), 49.94 and 52.19 (2OCH$_3$), 61.02 (d, $^2J_{PC}$=17.5 Hz, P–C–*C*H), 109.61 (pyrrole C^4H), 125.76 (d, $^1J_{PC}$=91.2 Hz, C^{ipso}), 126.07 (pyrrole C^3H), 126.65 (pyrrole C^5H), 127.15 (C^p of NHCH$_2$$C_6H_5$), 127.37 ($C^m$ of NHCH$_2$$C_6H_5$), 128.21 ($C^o$ of NHCH$_2$$C_6H_5$), 128.39 (d, $^3J_{PC}$=12.1 Hz, C^m), 131.76 (C^p), 132.81 (pyrrole C^2), 132.94 (d, $^2J_{PC}$=10 Hz, C^o), 137.37 (C^{ipso} of NHCH$_2$$C_6H_5$), 161.57 ($CO_2C_2H_5$), 169.47 and 171.82 (2d, $^2J_{PC}$=13.1 Hz and $^3J_{PC}$=13.4 Hz, 2C=O ester), 173.71 (pyrrole-C=O). ^{31}P NMR: δ 24.45 (Ph_3P^+–C).

Minor isomer, **6d**-(*E*) (45%), ^{1}H NMR: δ 3.61 and 3.72 (6H, 2s, 2OCH$_3$), 4.33 and 4.51 (2H, 2dd, $^2J_{HH}$=14.8 Hz, $^3J_{HH}$=5.2 Hz and $^3J_{HH}$=5.3 Hz, ABX system, NHCH_2), 5.59 (1H, d, $^3J_{PH}$=18.1 Hz, P–C–CH), 6.27 (1H, dd, $^3J_{HH}$=5.2 Hz, NH), 7.25–7.35 (6H, m, C_6H_5 and N–CH=C*H*), 7.35–7.56 (15H, m, 3C_6H_5), 7.87 (1H, br t, N–C=CH), 7.95 (1H, br t, N–C*H*=CH). ^{13}C NMR: δ 42.69 (NHCH$_2$), 43.92 (d, $^1J_{PC}$=134 Hz, P=C), 48.91 and 52.01 (2OCH$_3$), 60.92 (d, $^2J_{PC}$=17.3 Hz, P–C–*C*H), 109.51 (pyrrole C^4H), 125.14 (d, $^1J_{PC}$=91.6 Hz, C^{ipso}), 126.37 (pyrrole C^3H), 126.86 (pyrrole C^5H), 127.16 (C^p of NHCH$_2$$C_6H_5$), 127.38 ($C^m$ of NHCH$_2$$C_6H_5$), 128.22 ($C^o$ of NHCH$_2$$C_6H_5$), 128.45 (d, $^3J_{PC}$=12.1 Hz, C^m), 131.77 (C^p), 132.01 (pyrrole C^2), 133.02 (d, $^2J_{PC}$=10.2 Hz, C^o), 137.29 (C^{ipso} of NHCH$_2$$C_6H_5$), 161.49 ($CO_2C_2H_5$), 170.09 and 171.85 (2d, $^2J_{PC}$=13.4 Hz and $^3J_{PC}$=18.2 Hz, 2C=O ester), 173.54 (pyrrole-C=O). ^{31}P NMR: δ 25.35 (Ph_3P^+–C).

4.2. General procedure for preparation of compounds 7a–d

4.2.1. Dimethyl 6-ethoxycarbonyl 1*H*-pyrrolizine-4,5-dicarboxylate 7a. The process for the preparation of the above mentioned compound is described as an example. A mixture of **6a** (0.57 g, 1 mmol) in toluene (10 mL) was refluxed for 24 h. The solvent was removed under reduced pressure and the product was purified by column chromatography using hexane–ethyl acetate (2:1) as eluent. The solvent was removed under reduced pressure and the product **7a** was obtained as pale orange crystals, mp 101–103°C, yield 0.29 g, 100%. IR (KBr) (ν_{max}/cm^{-1}): 1730, 1700 (C=O). MS, *m/z* (%): 293 (M^+, 6), 262 (32), 233 (30), 201 (68), 159 (90), 131 (51), 103 (56), 77 (47), 42 (100). Anal. Calcd for $C_{14}H_{15}NO_6$ (293.28): C, 57.33; H, 5.15; N, 4.77. Found: C, 56.9; H, 5.1; N, 4.8%. ^{1}H NMR: δ 1.34 (3H, t, *J*=7.1 Hz, CH$_3$), 3.78 and 3.95 (6H, 2s, 2OCH$_3$), 4.29 (2H, q, *J*=7.1 Hz, OCH$_2$), 4.76 (2H, dd, $^3J_{HH}$=1.9 Hz and $^4J_{HH}$=1.7 Hz, CH$_2$), 6.77 (1H, dt, $^3J_{HH}$= 6 Hz and $^4J_{HH}$=1.7 Hz, CH), 6.98 (1H, dt, $^3J_{HH}$=6 Hz and $^3J_{HH}$=1.9 Hz, CH). ^{13}C NMR: δ 13.81 (CH$_2$*C*H$_3$), 51.75 and 52.26 (2OCH$_3$), 54.85 (CH$_2$), 59.84 (OCH$_2$), 104.13 and 117.70 (2C), 122.63 (N–CH=*C*H), 126.24 (C), 135.68 (N–*C*H=CH), 147.61 (C), 159.62, 162.19 and 165.29 (3C=O).

4.2.2. Diethyl 6-ethoxycarbonyl 1*H*-pyrrolizine-4,5-dicarboxylate 7b. Pale orange crystals, yield 0.315 g, 100%, mp 93–94°C, IR (KBr) (ν_{max}/cm^{-1}): 1739 and 1690 (C=O). Ms, *m*/*z* (%): 321 (M^+, 9), 275 (10), 201 (100), 158 (30), 131 (22), 103 (20), 77 (8). Anal. Calcd for $C_{16}H_{19}NO_6$ (321.33): C, 59.81; H, 5.96; N, 4.36. Found: C, 59.4; H, 5.86; N, 4.29%. ^{1}H NMR: δ 1.27, 1.28 and 1.34 (9H, 3t, J=7.1 Hz, $3CH_3$), 4.23, 4.26 and 4.34 (6H, 3q, J=7.1 Hz, $3OCH_2$), 4.68 (2H, dd, $^3J_{HH}$=1.9 Hz and $^4J_{HH}$=1.6 Hz, CH_2), 6.71 (1H, dt, $^3J_{HH}$=6 Hz and $^3J_{HH}$=1.9 Hz, N–CH=C*H*), 6.89 (1H, dt, $^3J_{HH}$=6 Hz and $^4J_{HH}$=1.6 Hz, N–C*H*=CH). ^{13}C NMR: δ 13.60, 13.66 and 13.76 ($3CH_3$), 54.78 (CH_2), 59.74, 60.33 and 61.04 ($3OCH_2$), 103.84 and 117.79 (2C), 122.39 (N–CH=*C*H), 126.36 (C), 135.72 (N–*C*H=CH), 147.48 (C), 159.10, 162.11 and 164.69 (3C=O).

4.2.3. Diisopropyl 6-ethoxycarbonyl 1*H*-pyrrolizine-4,5-dicarboxylate 7c. Pale orange crystals, yield 0.33 g, 100%, mp 53–57°C. IR (KBr) (ν_{max}/cm^{-1}): 1728, 1702 (C=O). MS, *m*/*z* (%): 349 (M^+, 7), 247 (40), 201 (100), 175 (36), 131 (20), 94 (42), 77 (8). Anal. Calcd for $C_{18}H_{23}NO_6$ (349.38): C, 61.88; H, 6.63; N, 4.01. Found: C, 61.4; H, 6.5; N, 4.1%. ^{1}H NMR: δ 1.29 [6H, d, J=6.3 Hz, $OCH(CH_3)_2$], 1.36 (3H, t, J=7.2 Hz, CH_3), 1.37 [6H, d, J=6.3 Hz, $OCH(CH_3)_2$], 4.26 (2H, q, J=7.2 Hz, OCH_2), 4.69 (2H, dd, $^3J_{HH}$=1.8 Hz and $^4J_{HH}$=1.6 Hz, CH_2), 5.16 [1H, septet, J=6.3 Hz, $OCH(CH_3)_2$], 5.22 [1H, septet, J=6.3 Hz, $OCH(CH_3)_2$], 6.7 (1H, dt, $^3J_{HH}$=6 Hz and $^4J_{HH}$=1.6 Hz, N–CH=C*H*), 6.92 (1H, dt, $^3J_{HH}$=6 Hz and $^3J_{HH}$=1.8 Hz, N–C*H*=CH). ^{13}C NMR: d 13.88 (OCH_2CH_3), 21.29 and 21.43 [$2OCH(CH_3)_2$], 54.83 (CH_2), 59.65 (OCH_2), 68.23 and 68.74 [$2OCH(CH_3)_2$], 103.79 and 117.98 (2C), 122.52 (N–CH=*C*H), 126.47 (C), 135.57 (N–*C*H=CH), 147.47 (C), 158.81, 162.21 and 164.24 (3C=O).

4.2.4. Dimethyl 7-[(benzylamino)carbonyl] 1*H*-pyrrolizine-4,5-dicarboxylate 7d. Pale orange crystals, yield 0.34 g, 100%, mp 84–86°C. IR (KBr) (ν_{max}/cm^{-1}): 3335 (NH), 1730 and 1695 (C=O). MS, *m*/*z* (%): 354 (M^+, 4), 278 (4), 249 (35), 190 (15), 131 (62), 106 (100), 91 (85), 77 (11). Anal. Calcd for $C_{19}H_{18}N_2O_5$ (354.36): C, 64.40; H, 5.12; N, 7.91. Found: C, 64.5; H, 5.2; N, 7.9%. ^{1}H NMR: δ 3.80 and 3.82 (6H, 2 s, $2OCH_3$), 4.54 (2H, d, J=5.7 Hz, NCH_2), 4.62 (2H, dd, $^3J_{HH}$=1.8 Hz and $^4J_{HH}$=1 Hz, CH_2), 6.60 (1H, dt, $^3J_{HH}$=6 Hz and $^3J_{HH}$=1.8 Hz, N–CH=C*H*), 7.07 (1H, dt, $^3J_{HH}$=6 Hz and $^4J_{HH}$=1 Hz, N–C*H*=CH), 7.2–7.3 (5H, m, C_6H_5), 7.95 (1H, t, J=5.7 Hz, NH). ^{13}C NMR: δ 42.82 ($NHCH_2$), 51.5 and 52.27 ($2OCH_3$), 53.02 (N–C–CH_2), 108.9 (N–CH=*C*H), 119.89 and 120.53 (2C), 123.11 (N–*C*H=CH), 126.64 (C^p), 126.98 (C^m), 128.05 (C^o), 134.33 (C^{ipso}), 138.15 and 147.33 (2N–*C*=C), 159.81, 162.46 and 167.03 (3C=O).

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