Synthesis of Pyrrole Phosphonate Esters: Emphasis on Pyrrole NH Acids and Dialkylacetylenic Esters Substitution

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ABSTRACT: *Reaction of dialkyl acetylenedicarboxylates **1a-c** and pyrrole derivatives **2a-e** in the presence of triphenylphosphite (TPP) was investigated and the effect of the pyrrole substitution was established. Diastereoselectivity is observed with pyrroles, **2a**,**b**, yielding phosphonate ester derivatives **3a-f** and **4**, and their relative configuration is determined by $^{1}H/^{13}C$ and ^{31}P NMR and confirmed by single X-ray diffraction. Similar reactions with higher degree of substitution of the pyrrole, **2c**,**e** showed no diastereoselectivity.*

KEY WORDS: *Organophosphorus compounds, Acetylenic diesters, Substituted pyrrole, Phosphonate esters, Diastereoisomers.*

INTRODUCTION

The incorporation of phosphorus into organic compounds is of importance in biology amongst many other technical applications [1,2]. Recent biological applications include phosphonate diesters as probes for nucleophiles presence in displayed antibodies and in non-antibody serine proteinases [3,4]. In addition phosphonate monoester transition state analogues have been employed for the isolation of certain esterase antibody [5]. Moreover, the biological activity of phosphonate ester enatiomers is deployed in the agrochemical industry as pesticides. The presence of chiral carbon center in these class of compounds give arise to stereoisomers which have pronounce differences in biological activity and toxicological effects [6,7]. In this context, we and others have established synthetic methodology for the preparation of phosphonato esters from reaction of dialkyl acetylendicarboxylates with triphenylphosphite in the presence of NH and CH acids [8-12].

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In continuation with our investigation of preparing pyrrole phosphonato-ester compounds, we extended our research to phosphonate ester derivatives **3a**-**f** and **4** involving substituted pyrroles, and examined the effects of substitution of the pyrrole on this condensation reaction in non polar solvents. Non protic solvent diethyl ether was used to avoid interference with the acid/base chemistry of the pyrrole. Under non polar conditions and by tuning the basicity of the pyrrole we anticipate stereoselectivity and possibly the formation of the elusive phosphonate ylides. Pyrroles have low basicity due to the delocalization of the lone pair on the nitrogen taking part in the formation of an aromatic 6π-electron system, and under acidic conditions result in protonation of the 2-position. The resulting pyrrylium cation is very reactive and can readily undergo electrophilic substitutions preferentially at the 2-position [13].

The reported pyrrole phosphonate ester compounds herein are obtained through the above-mentioned mechanism. Herein we report the synthesis of new diastereomers of pyrrole derivatives phosphonate esters in non-polar solvent media, diastereomers separation, and relative stereochemistry determination. Also the research is aimed at establishing a rationale on the reactivity and activation of pyrrole derivatives in this condensation reaction. Structural charaterisation of the obtained pyrrole phosphonate esters is determined by NMR techniques and the relative sterochemistry corroborated by single X-ray diffraction technique such as for **3a** and **4**. The use of pyrrole and ethyl pyrrole, **2a** and **b** in the reaction resulted in diastereoseltivity of the pyrrole phosphonate ester derivatives while the use of highly substituted of the pyrroles, **2c** and **d** resulted in no diastreoselectivity. Phosphonate ylides are not observed and conversely the reaction resulted in forming pyrrole phosphonate esters products similar to the previously reported from aqueous media [9].

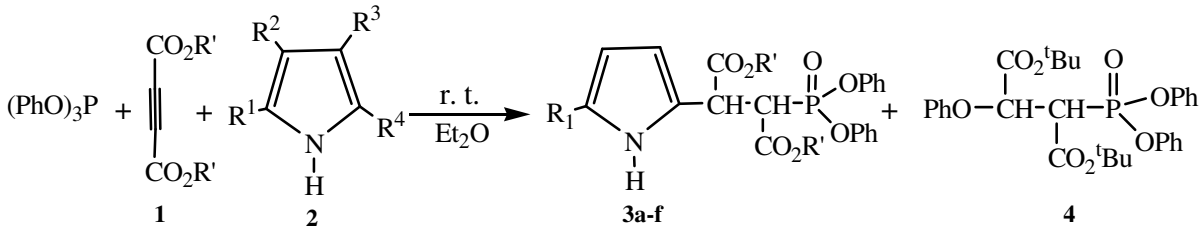
RESULTS AND DISCUSSION

This contribution reports the synthesis of pyrrole derivatives and phenoxy phosphonate esters **3a**-**f** and **4**, respectively, from reaction of dialkyl acetylene-dicarboxylates (DAAD), **1a**-**c** with triphenylphosphite (TPP) in the presence of pyrrole derivatives **2a**,**b** at room temperature in diethyl ether (scheme 1). The resulting compounds **3a**-**f** are produced from the initial addition of TPP to the dialkyl acetylenedicarboxylates **1a**-**c** and concomitant protonation of the reactive 1:1 adduct by the pyrrole derivatives. Then the vinyl phosphonium salt intermediate is attacked by the pyrrole anion, which then is hydrolyzed to produce phosphonate ester **3a**-**f** and **4** (scheme 1).

The resulting product from this condensation reaction has two chiral centers and hence expecting product distribution of four diastereoisomers. However, the outcome of this condensation reaction yielded either one or two diastereoisomers products depending on the pyrrole used. For example the reaction of TPP with dimethyl acetylenedicarboxylate (DMAD) **1a** in the presence of pyrrole derivatives **2a**,**b** is diastereoselective affording mainly one isomer **3a** and **3b** respectively (scheme 1).

Moreover, we were able to authenticate the structure of **3a** in the solid state. The ^{1}H NMR spectrum of **3a** displayed signals for the vicinal methine protons appearing as separate double doublets. The vicinal proton-proton coupling constant ($^3J_{HH}$) as a function of the torsion angle can be obtained from the Karplus equation [14]. Typically, J_{gauche} and J_{anti} vary between 1.5-5 Hz and 10-14 Hz respectively [14,15]. Observation of $^3J_{HH}$ = 10.9 Hz for the vicinal protons of compound **3a** confirms an anti arrangement for these protons. Moreover, since compound **3a** possesses two stereogenic centers, two diastereomers with anti C_H-C_H arrangement are possible. The presence of ^{31}P nucleus in compound **3a** and **4** was of great assistance in identifying the stereo-configuration by analyzing the long range coupling signals of phosphorus ^{31}P nuclei with proton ^{1}H and carbon ^{13}C nuclei (table 1 and Figs. 1 and 2). Although the synthesis of **3a** was reported earlier by our group from aqueous media [9], the present method in non polar solvent provided the product with both higher yield and diastereoselectivity.

The carbon-phosphorus three bond range coupling constants $^3J_{PC}$ is related to the stereo configuration with the transoid coupling being larger than cisoid coupling [16,17]. The Karplus relationship can be derived from literature data for organophosphorus compounds for tetra and penta-valent phosphorus [14, 15]. The observation of $^3J_{PC}$ = 20.1 Hz (δ 171.7 ppm) for the distal carbonyl group of the ester in **3a** is in agreement with an anti arrangement of the phosphonate group in respect to the



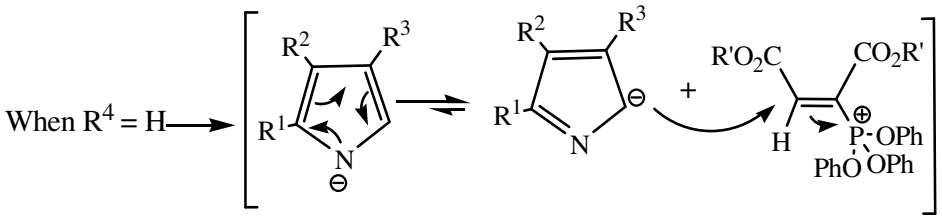
1	R′
a	Me
b	Et
c	*tert*-By

2	R^1	R^2	R^3	R^4
a	H	H	H	H
b	Et	H	H	H
c	Me	Et	Me	H
d	Me	Ac	Me	H
e	CO_2Et	H	H	CO_2Et

3	R^1	R′
a	H	Me
b	Et	Me
Diastereoismer c	H	Et
Diastereoismer d	H	Et
e	H	*tert*-Bu
f	H	*tert*-Bu

For products **3a-f**, $R^2 = R^3 = R^4 = H$

When R^4 = -CO_2Et, there is no reaction and when it is H, the products **3a-f** and **4** are resulted



Scheme 1.

distal ester group (P-CH-CH-C(O)). Similar coupling of the phosphorus to the carbonyl of the proximal ester gives a smaller coupling constant $^2J_{PC}$ = 5.0 Hz (δ 167.9 ppm) (table 1). Structural determination by single X-ray diffraction for compound **3a** and **4** confirms the configuration assigned by ^{1}H and ^{13}C NMR, (Fig. 1). The structure of phosphonate ester **3a** was devoid of solvent molecules with the asymmetric unit containing a complete molecule, and the hydrogens on the streogenic centers are in transoid arrangement. In contrast analogous hydrogen's in compound **4** are in a cisoid arrangement while the phosphonate group is in a transoid arrangement to the distal ester group (Fig. 2).

The reaction between phosphorus reagent TPP and diethyl acetylenedicarboxylate (DEAD) **1b** or di-tertbutyl acetylenedicarboxylate (DTAD) **1c** in the presence of pyrrole **2a** generated a mixture of two diastereomers **3c** and **3d** (60:40) or **3e** and **3f** (80:20) respectively. The structure and the ratio of the two diastereoisomers **3c**, **3d** and **3e**, **3f** were established by ^{1}H, ^{13}C and ^{31}P NMR based on their distinctive chemical shifts. The diastereomers were separated by column chromatography and preparative TLC techniques. The phosphorus NMR was very helpful in ascertaining the *cis* and *trans* configuration of the methine protons. The value of carbon-phosphorus coupling constant $^3J_{PC}$, is related to *cis* or *trans* configuration. The observation of large $^3J_{PC}$ values for P-C coupling of 20.0 and 21.1 Hz in **3c** and **3e**, respectively, is consistent with the anti arrangement of the phosphonate to the ester group. In addition, the smaller coupling constants of pyrrole C_2 carbon with phosphorus nuclei $^3J_{PC}$ is also supporting the gauche arrangement for **3c** and **3e** (table 1). However, the observed smaller coupling constant $^3J_{PC}$ of 8.1 and 7.4 Hz for **3d** and **3f** are in good agreement with the gauche arrangement for the phosphonate and ester groups. A larger coupling constant $^3J_{PC}$ for phosphorus with C_2 carbon of the pyrrole moiety is also observed which

Table 1: Selected spectroscopic data, ^{1}H and ^{13}C NMR chemical shifts (δ/ ppm) and coupling constants (J in Hz) for H-2, H-3, C-1, C-2, C-3, C-4 and C-2 of pyrrole derivatives in 3a-f and 4 in $CDCl_3$ as solvent (25 °C).

^{1}H NMR Coupling constants σ: H_2 ($^{3}J_{PH}$, $^{3}J_{HH}$) H_3 ($^{2}J_{PH}$, $^{3}J_{HH}$)	^{13}C NMR Coupling constants σ: C_1 ($^{3}J_{PC}$), C_2 ($^{2}J_{PC}$), C_3 ($^{1}J_{PC}$), C_4 ($^{2}J_{PC}$), C_2 of pyrrole ($^{3}J_{PC}$)	Configuration
4.8 10.8, 10.9 4.2 22.4, 10.9	171.7 43.6 49.3 167.9 123.8 20.1 0 136.0 5.3 2.3	2*R*,3*S*-**3a** or mirror image (2*S*,3*R*)
4.7 10.8, 10.9 4.1 22.3, 10.9	171.9 43.7 49.6 167.9 122.1 20.3 0 135.9 5.0 2.3	2*R*,3*S*-**3b** or mirror image (2*S*,3*R*)
4.7 11.1, 10.9 4.1 22.1, 10.9	171.1 43.7 49.7 167.2 124.1 20.0 0 135.0 5.0 3.0	2*R*,3*S*-**3c** or mirror image (2S,3R)
4.6 9.1, 9.1 4.2 22.2, 9.1	170.8 43.3 48.7 167.0 124.0 8.1 2.4 132.8 5.0 13.0	2*S*,3*S*-**3d** or mirror image (2*R*,3*R*)
4.5 11.1, 11.2 3.9 21.8, 11.2	170.4 44.7 50.7 166.4 124.8 21.1 0 134.7 5.0 1.9	2*R*,3*S*-**3e** or mirror image (2*S*,3*R*)
4.4 9.0, 9.0 4.1 22.6, 9.0	169.8 44.3 49.7 166.1 124.9 7.4 0 132.3 5.0 14.1	2*S*,3*S*-**3f** or mirror image (2*R*,3*R*)
5.2 6.0, 7.5 4.2 22.8, 7.2	167.9 75.9 50.4 164.4 - 7.4 5.3 141.0 5.2 -	2*R*,3*R*-**4** or mirror image (2*S*,3*S*)

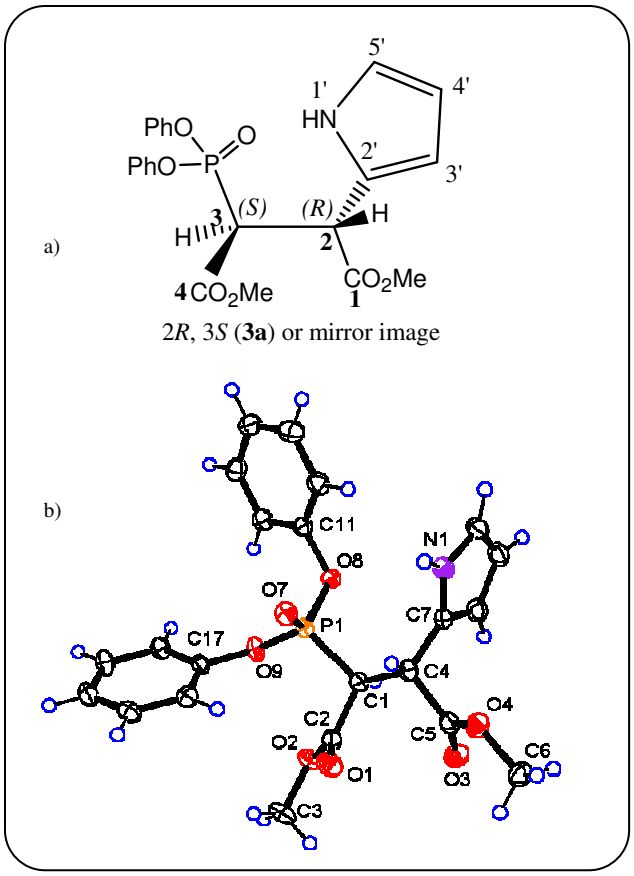


Fig. 1: a) Stereochemistry assignment and b) X-ray crystal structure for 3a.

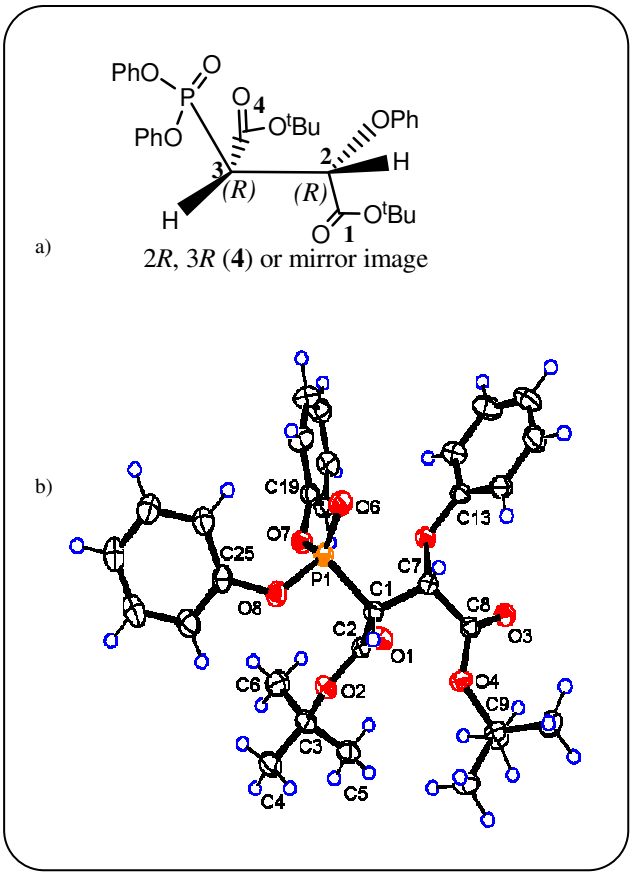
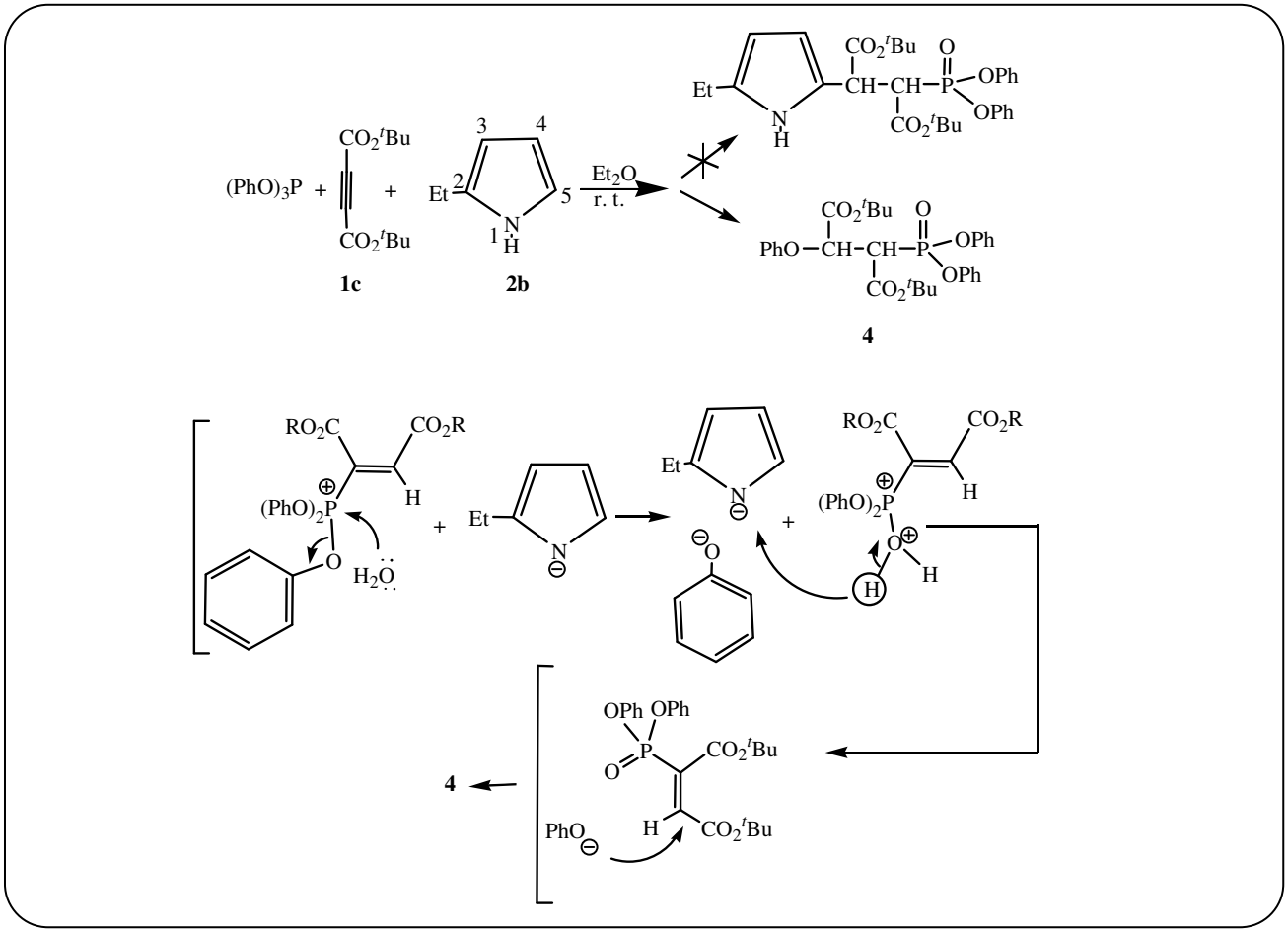


Fig. 2: a) Stereochemistry assignment and b) X-ray crystal structure for 4.



Scheme 2.

corresponds to an anti arrangement (table 1). The obtained coupling constants are compatible with the configuration assignments and are summarized in table 1.

Similar condensation reaction of DTAD involving ethyl pyrrole under the same conditions failed to yield the desired product and afforded compound **4** (scheme 2). Compound **4** was characterized by NMR and its stereochemistry established by single X-ray diffraction. The possible rationale behind this outcome could be explained by the electronic effect of the ethyl substituent on the pyrrole as an electron-donating group preventing the formation of a stable intermediate anion. The resulting ethyl pyrrole anion is more reactive, hence circumventing the ring resonance to form stable anion at C_5 center required for the preparation of the targeted compound **3**, as shown in scheme 2. In this reaction we have competition of two nucleophiles, namely the ethyl pyrrole anion and the phenoxide derived from the hydrolysis of the phosphonium cation intermediate. The high reactivity of the ethyl pyrrole prevents its incorporation into the molecule and is replaced by the phenoxide as a moderate nucleophile to form compound **4** (scheme 2).

Polysubstituted pyrrole **2c**,**d** reactions with acetylenic ester, **1a** yielded pyrrole phosphonate ester analogues, albeit no diastreosecltivity was observed.

Highly substituted pyrrole also participated in this condensation reaction but obviously the reaction is greatly influenced by the electronic effects of the group substituents. The presence of electron donating alkyl groups, as in **2c** (3-ethyl-2, 4-dimethyl pyrrole), able to produce a more reactive anion intermediate undermines the stereoselectivity including the formation of N-pyrrole adducts. In contrast, with the electron withdrawing groups, as in **2d** (3-acetyl-2, 4-dimethyl pyrrole), a stable pyrrole carbanion is formed and thus the obtained product pyrrole phosphonate ester derivatives exhibit certain degree of diastereoselectivity.

The stereochemistry for compound **3a** as a model for phosphonate ester compounds was confirmed by single X-ray diffraction analysis and was established to be 2R, 3S. Whereas, compound **4** with 2R, 3R configuration was also confirmed by single X-ray diffraction (table 1 and Fig. 1).

In conclusion, we have successfully developed a facile diastereoselective synthesis for pyrrole phosphonate ester analogues, R,S or mirror image S,R (**3a**-**f**), and a phenoxy phosphonate ester, **4** (R,R). The present procedure is simple and good yielding, and carried out under mild conditions. The stereochemistry of pyrrole phosphonates involving pyrrole derivatives, dialkyl acetylenedicarboxylates, and triphenylphosphite has been examined, and the effect of the pyrrole substituents established. Investigation of the reactivity of substituted pyrroles with electron-donating groups showed less diastereoselectivity, while electron-withdrawing groups showed enhanced diastereoselectivity. The effect of the bulkiness of the esters groups in this condensation reaction is yet to be established. The formation of compound **4** is interesting resulting from the competition of two nucleophiles, ethyl pyrrole and the in situ formed hydrolysis by-product phenoxide. Overall and with limited examples reported herein, we believe we established a proof of concept that the adjusting of the electronics of the pyrrole is of great importance in accessing diastereoselectivity in pyrrole phosphonate ester preparation.

EXPERIMENTAL SECTION

All the materials and solvents were obtained from Merck chemical company (Germany) and Fluka (Switzerland) and used without further purification. Melting points were determined in open capillary tubes on an Electrotermal 9100 melting point apparatus. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer in $CDCl_3$ at 500.1, 125.8 and 202.4 MHz, respectively. Mass spectrometry performed on Shimadzu GC/MSQP 1100 EX mass spectrometer operating at an ionization potential of 70 eV.

X-ray diffracted intensities were measured at 100 K on an Oxford Diffraction Gemini-R Ultra CCD diffractometer using monochromatized Cu-K_α (λ = 1.54178 Å). Elemental analysis (CHN) was performed on a Thermo Finigan Flash EA1112. Column chromatography separation was run on silica gel 60, 230-400 mesh.

General Procedure

To a magnetically stirred solution of triphenylphosphite (0.26 ml, 1mmol) and pyrrole **2** (0.07 mL, 1mmol) in diethylether (5 mL), dimethyl acetylenedicarboxylate **1** (1 mmol) in 5 mL diethyl ether was added dropwise at room temperature over 10 minutes. The reaction mixture was then allowed to stir for 12 hours at room temperature. The solvent was removed under reduced pressure to afford compounds **3** purified by column chromatography using EtOAc-petroleum ether 1:10 as eluents or crystallization from diethyl ether.

Diethyl - 2 - (pyrrole-2-yl) - 3 - (diphenoxyphosphoryl) butanedioate [major diastereomer] (3c)

Red-brown oil, 0.43 g, yield 91 % (**3c**:**3d**; 3:2); IR (thin film): 3285 (NH), 1735 (C=O), 1594 (C=C) Cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.2 (m, 6H, $2CH_3$), 4.1 (dd, 1H, $^{2}J_{PH}$ = 22.1 Hz, $^{3}J_{HH}$ = 10.9 Hz, P- C*H*), 4.7 (t, 1H, $^{3}J_{PH}$ = 11.1 Hz, $^{3}J_{HH}$ = 10.9 Hz , P-C-C*H*), 6.14 (d, 1H, $^{3}J_{HH}$ = 2.8. Hz, C_4-H of pyrrole), 6.2 (s, 1H, C_3-H of pyrrole), 7.1-7.3 (m, 10H, Ar), 8.89 (s, 1H, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.9 ($2OCH_2$-$^{13}CH_3$), 43.7 (s, P- CH-^{13}CH) 49.7 (d, $^{1}J_{PC}$ = 135.0 Hz P-^{13}CH), 62.1 (s, CH_2), 62.2 (s, CH_2), 108.3 (C_4 of pyrrole), 108.7 (C_3 of pyrrole), 118.4 (C_5 of pyrrole), 120.3 (d, $^{3}J_{PC}$ = 4.5 Hz, C_{ortho} of C_6H_5), 120.5 (d, $^{3}J_{PC}$ = 4.5 Hz, C_{ortho} of C_6H_5), 124.1 (d, $^{3}J_{PC}$ = 3.0 Hz, C_2 of pyrrole), 125.3 (s, C_{para} of C_6H_5), 125.4 (s, C_{para} of C_6H_5), 129.6 ($2C_{meta}$ of 2 C_6H_5), 149.7 (d, $^{2}J_{PC}$ = 9.4 Hz, C_{ipso} of C_6H_5), 150.1 (d, $^{2}J_{PC}$ = 9.4 Hz, C_{ipso} of C_6H_5), 167.2 (d, $^{2}J_{PC}$ = 5.3. Hz, C=O ester), 171.07 (d, $^{3}J_{PC}$ = 20.0 Hz, C=O ester); ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 13.71 [-$(PhO)_2{}^{31}$P=O]; MS (EI, 70eV): *m/z* (%) = 471 (5) [M^+] and Calcd. for $C_{24}H_{26}NO_7P$ (471): C, 61.76; H, 6.15; N, 3.38 %. Found: C, 61.76; H, 6.15; N, 3.38 %.

Diethyl -2- (pyrrole-2-yl) -3- (diphenoxyphosphoryl) butanedioate [minor diastereomer] (3d)

Red-brown oil, 0.43 g, yield 91 % (**3c**:**3d**; 3:2); IR (thin film): 3285 (NH), 1735 (C=O), 1594 (C=C) Cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.2 (m, 6H, 2× CH_3), 4.15 (m, 4H, $2CH_2$), 4.19 (dd, 1H, $^{2}J_{PH}$ = 22.2 Hz, $^{3}J_{HH}$ = 9.1 Hz, P- C*H*), 4.6 (t, 1H, $^{3}J_{PH}$ = 9.1 Hz, $^{3}J_{HH}$ = 9.1. Hz ,

P-C-C*H*), 6.1 (d, 1H, $^3J_{HH}$ = 2.9 Hz, C_4H of pyrrole), 6.15 (s, 1H, C_3H of pyrrole), 6.86-7.32 (m, 10H, Ar), 9.0 (s, 1H, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.85 (s, CH_3), 13.88 (s, CH_3), 43.3 (d, $^2J_{PC}$ = 2.4 Hz, P-CH-^{13}CH), 48.7 (d, $^1J_{PC}$ = 132.8 Hz P-^{13}CH), 61.7 (s, CH_2), 61.8 (s, CH_2), 108.2 (C_4 of pyrrole), 109.5 (C_3 of pyrrole), 118.6 (C_5 of pyrrole), 120.6 (d, $^3J_{PC}$ = 4.7 Hz, one of C_{ortho} of $2C_6H_5$), 120.6 (d, $^3J_{PC}$ = 4.5 Hz, other C_{ortho} of C_6H_5), 124.0 (d, $^3J_{PC}$ = 13.0 Hz, C_2 of pyrrole), 125.3 (s, C_{para} of C_6H_5), 125.4 (s, C_{para} of C_6H_5), 129.7 ($2C_{meta}$ of 2 C_6H_5), 149.7 (d, $^2J_{PC}$ = 9.4 Hz, C_{ipso} of C_6H_5), 149.9 (d, $^2J_{PC}$ = 9.4 Hz, C_{ipso} of C_6H_5), 167.0 (d, $^2J_{PC}$ = 5.0. Hz, C=O ester), 170.8 (d, $^3J_{PC}$ = 8.1 Hz, C=O ester); ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 12.5 [-$(PhO)_2{}^{31}$P=O]; MS (EI, 70eV): *m/z* (%) = 471 (5) [M^+] and Calcd. for $C_{24}H_{26}NO_7P$ (471): C, 61.76; H, 6.15; N,3.38 %. Found: C, 61.76; H, 6.15; N, 3.38 %.

Di-*tert*-Butyl -2- (pyrrole-2-yl) -3- (diphenoxyphosphoryl) butanedioate[major diastereomer] (3e)

Separation of diastereomer **3e** was performed by column chromatography (silica gel, EtOAc-petroleum ether 1:10). 0.5 g, total yield 70 % (**3e**:**3f**, 4:1), The compound **3e** was obtained as a viscous red-brown oil; IR (thin film): 3290 (NH), 1732 (C=O), 1590 (C=C) Cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.43 (s, 18H, $C(Me)_3$), 1.47 (s, 18H, $C(Me)_3$), 3.9 (dd, 1H, $^2J_{PH}$ = 21.8 Hz, $^3J_{HH}$ = 11.2 Hz, P- C*H*), 4.5 (t, 1H, $^3J_{PH}$ = 11.1 Hz, $^3J_{HH}$ = 11.2 Hz, P-C-C*H*), 6.10 (d, 1H, $^3J_{HH}$ = 2.8 Hz C_4 of pyrrole), 6.13 (s, 1H, C_3H of pyrrole), 6.64 (d, broad, 1H, $^3J_{HH}$ = 1.7 Hz C_5 of pyrrole) 6.8-7.3 (m, 10H, Ar), 8.89 (s, 1H, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.8 (s, 6 ^{13}CH$_3$ of 2^{t}Bu), 44.7 (s, P-CH-^{13}CH), 50.7 (d, $^1J_{PC}$ = 134.7 Hz P-^{13}CH), 82.1 (s, O-^{13}C of ^{t}Bu), 83.0 (s, O-^{13}C of ^{t}Bu), 107.9 (C_4 of pyrrole), 108.6 (C_3 of pyrrole), 118.1 (C_5 of pyrrole), 120.5 (d, $^3J_{PC}$ = 4.2 Hz, 2 C_{ortho} of $2C_6H_5$), 124.8 (d, $^3J_{PC}$ = 1.9 Hz, C_2 of pyrrole), 125.25, 125.29 (2 C_{para} of $2C_6H_5$), 129.68 (s, C_{meta} of C_6H_5), 129.72 (s, C_{meta} of C_6H_5), 149.9 (d, $^2J_{PC}$ = 9.3. Hz, C_{ipso}, C_6H_5), 150.1 (2d, $^2J_{CP}$ = 9.6 Hz, C_{ipso}, C_6H_5), 166.4 (d, $^2J_{PC}$ = 5.0, C=O ester), 170.4 (d, $^3J_{PC}$ = 21.1 Hz, C=O ester); ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 15.3 [- $(PhO)_2{}^{31}$P=O]. MS (EI, 70eV): *m/z* (%) = 527 (15) [M^+], Calcd. for $C_{28}H_{34}NO_7P$ (527): C, 63.75; H, 6.45; N, 2.65 %. Found: C, 63.96; H, 6.40; N, 3.04 %.

Di-*tert*-Butyl -2- (pyrrole-2-yl) -3- (diphenoxyphosphoryl) butanedioate[minor diastereomer] (3f)

The compound **3f** was obtained as a pale brown oil, 0.5 g, total yield 70% (**3e**:**3f**, 4:1), IR (thin film): 3290 (NH), 1732 (C=O), 1590 (C=C) Cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.38 (s, 18H, $C(Me)_3$), 1.40 (s, 18H, $C(Me)_3$), 4.1 (dd, 1H, $^2J_{PH}$ = 22.6 Hz, $^3J_{HH}$ = 9.0 Hz, P-C*H*), 4.4 (t, 1H, $^3J_{PH}$ = 9.0. Hz, $^3J_{HH}$ = 9.0 Hz, P-C-C*H*), 6.1 (d, 1H, $^3J_{HH}$ = 2.8 Hz $C_4$of pyrrole), 6.2 (s, 1H, C_3H of pyrrole), 6.7 (d, broad, 1H, $^3J_{HH}$ = 2.6 Hz C_5 of pyrrole) 6.8-7.3 (m, 10H, Ar), 9.0 (s, 1H, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.75 (s, 3*C*H$_3$ of ^{t}Bu), 27.85 (s, 3*C*H$_3$ of ^{t}Bu), 44.3 (s, P-CH-^{13}CH), 49.7 (d, $^1J_{PC}$ = 132.3 Hz P-^{13}CH), 82.2 (s, $^{13}C(CH_3)_3$), 83.0 (s, $^{13}C(CH_3)_3$), 108.0 (C_4 of pyrrole), 109.4 (C_3 of pyrrole), 118.2 (C_5 of pyrrole), 120.8 (d, $^3J_{PC}$ = 4.2 Hz, 2 C_{ortho} of $2C_6H_5$), 124.9 (d, $^3J_{PC}$ = 14.1 Hz, C_2 of pyrrole), 125.29 (s, C_{para} of C_6H_5), 125.34 (s, C_{para} of C_6H_5), 129.7 (s, C_{meta} of C_6H_5), 129.9 (s, C_{meta} of C_6H_5), 149.9 (d, $^2J_{PC}$ = 9.3 Hz, C_{ipso} of C_6H_5), 150.1 (2d, $^2J_{PC}$ = 6.3 Hz, C_{ipso} of C_6H_5), 166.1 (d, $^2J_{PC}$ = 5.0, C=O ester), 169.8 (d, $^3J_{PC}$ = 7.4 Hz, C=O ester); ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 13.9 [-$(PhO)_2{}^{31}$P=O]; MS (EI, 70eV): *m/z* (%) = 527 (15) [M^+], Calcd. for $C_{28}H_{34}NO_7P$ (527): C, 63.75; H, 6.45; N, 2.65 %. Found: C, 63.96; H, 6.40; N, 3.04 %.

i-tert-Butyl -2- (phenoxy) -3- (diphenoxyphosphoryl) butanedioate (4)

Pale orange powder, 0.51 g, yield 92 %, m.p. 115-117 ^{o}C; IR (KBr): 1751 (C=O), 1728 (C=O), 1599 and 1590 (C=C) Cm^{-1}; ^{1}H NMR (400 MHz Varian, $CDCl_3$): δ 1.4, 1.5 (2×s, 18H, O-$C(CH_3)_3$), 4.1 (dd, 1H, $^3J_{HH}$ = 7.2 Hz, $^2J_{PH}$ = 22.8 Hz, $(PhO)_2$PO-C*H*), 5.2 (dd, 1H, $^3J_{HH}$ = 7.5, $^3J_{PH}$ = 6 Hz, P-CH-C*H*), 6.9-7.3 (15H, m, Ar). ^{13}C NMR (100.54 MHz, $CDCl_3$): δ 28.1, 28.2 (2×s, $(CH_3)_3$ of 2 ^{t}Bu), 50.4 (d, $^1J_{PC}$ = 141 Hz, P-^{13}CH), 75.9 (d, $^2J_{PC}$ = 5.3 Hz, P-CH-^{13}CH), 83.3, 83.5 (2×s, 2O-C), 116.5 (s, C_{ortho} of CH-O-Ph), 121.1 (s, $2C_{ortho}$ of $2C_6H_5$), 122.5 (s, C_{meta} of CH-O-Ph), 125.7 (2×s, $2C_{para}$ of $2C_6H_5$),129.6 (s, C_{meta} of CH-O-C_6H_5), 130 (2×s, $2C_{meta}$ of O=P$(C_6H_5)_2$), 150.4 (2d, $^2J_{PC}$ = 9.7 Hz, $2C_{ipso}$ of C_6H_5), 158.3 (s, C_{ipso} of CH-O-Ph), 164.4 (d, $^2J_{PC}$ = 5.2, C=O ester), 167.9 (d, $^3J_{PC}$ = 7.4 Hz, C=O ester); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 11.9 [- $(PhO)_2{}^{31}$P=O]; MS (EI, 70eV): *m/z* (%) = 554 (M^+- CH_3OH) (10), 350 (M^+-2CO-2^{t}BuOH) (30), 165 (PhO-CCPO) (90), 114 (M^+-2CO_2H) (30).

CRYSTALLORGAPHY

Crystal data/refinement details for compound 3a

The X-ray diffracted intensities were measured from a single crystal 0.29 × 0.22 × 0.14 mm at about 100 K on an Oxford Diffraction Xcalibur-S CCD diffractometer using monochromatized Cu-K_α (λ = 0.71073 Å). Data were corrected for Lorentz and polarization effects and absorption correction applied using multiple symmetry equivalent reflections. The structure were solved by direct method and refined on F^2 using SHELX-97 crystallographic package. A full matrix least-squares refinement procedure was used, minimizing w F_o^2 - F_c^2), with w =[σ^2 (f_o^2) + $(AP)^2$ + BP]$^{-1}$, where P=(F_o^2+2F_c^2)/3. Agreement factors (R=Σ||F_O|-|F_C||/Σ|F_O|, wR2 = {Σ[w(F_o^2-F_c^2)^2]/ Σ[w(F_o^2)^2]}$^{1/2}$ and GOF = {Σ[w(F_o^2-F_c^2)^2]/(n-p)}$^{1/2}$ are cited, where n is the number of reflections and p the total number of parameters refined). All non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms were localized from difference Fourier synthesis and their atomic parameters were constrained to the bonded atoms during the refinement.

$C_{22}H_{22}NO_7P$, M = 548.41, F(000) = 443.38 e, triclinic, P-1 (No. 2), Z = 2, T = 100(2) K, a = 10.6164(7), b = 10.7929(6), c = 10.8244(8) Å, α = 60.786(6), β = 80.013(6), γ = 78.350(5) °, V = 1056.14(14) Å^3; D_c = 1.394 g cm^{-3}; μ_{Mo} = 0.175 mm^{-1}; sinθ/λ_{max} = 0.7035; N(unique) = 6139 (merged from 29685, R_{int} = 0.0798, R_{sig} = 0.0494), N_o (I > 2σ(I)) = 4474; R = 0.0484, wR2 = 0.1310 (A,B = 0.1, 0.3), GOF = 1.004; $|\Delta\rho_{max}|$ = 0.62(8) e Å^{-3}. CCDC 654645.

Crystal data/refinement details for compound 4

The X-ray diffracted intensities were measured from a single crystal 0.31 × 0.29 × 0.23 mm at about 100 K on an Oxford Diffraction Gemini-R Ultra CCD diffractometer using monochromatized Cu-K_α (λ = 1.54178 Å). Data were corrected for Lorentz and polarization effects and absorption correction applied using multiple symmetry equivalent reflections. The structure were solved by direct method and refined on F^2 using SHELX-97 crystallographic package. A full matrix least-squares refinement procedure was used, minimizing w(F_o^2-F_c^2), with w=[σ^2(F_o^2)+$(AB)^2$+BP]$^{-1}$, where P=(F_o^2+2F_c^2)/3. Agreement factors (R = Σ||F_O|-|F_C||/Σ|F_O|, wR2 = {Σ[w(F_o^2-F_c^2)^2]/Σ[w(F_o^2)^2]}$^{1/2}$ and GOF = {Σ[w(F_o^2-F_c^2)^2]/(n-p)}$^{1/2}$ are cited, where n is the number of reflections and p the total number of parameters refined). All non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms were localized from difference Fourier synthesis and their atomic parameters were constrained to the bonded atoms during the refinement.

$C_{26}H_{22}F_3O_9PS$, M = 598.47, F(000) = 4928 e, monoclinic, Cc (No. 9), Z = 16, T = 100(2) K, a = 25.5100(5), b = 31.3207(6), c = 18.2700(4) Å, β= 134.105(3) °, V = 10482.0(4) Å^3; D_c = 1.517 g cm^{-3}; sinθ/λ_{max} = 0.7035; N(unique) = 15282 (merged from 144564, R_{int} = 0.0394, R_{sig} = 0.0345), N_o (I > 2σ(I)) = 11742; R = 0.0424, wR2 = 0.1085 (A,B = 0.084, 0.0), GOF = 1.004; $|\Delta\rho_{max}|$ = 0.72(7) e Å^{-3}. CCDC 656625.

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