Stereoselective synthesis of pyrrole phosphonate esters from the reaction of triphenylphosphite and dimethyl acetylenedicarboxylate in the presence of pyrrole in aqueous solution

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The reaction of triphenylphosphite and dimethyl acetylenedicarboxylates (DMAD) in the presence of pyrrole derivatives in an aqueous media led to pyrrole phosphonate esters derivatives.

Keywords: phosphonate ester, stereoselective synthesis, aqueous media, acetylenic ester

The use of water as solvent in organic reactions has been uncommon for several reasons, among them the insolubility of the reactant, the incompatibility of intermediates with water and the competition of the desired reaction with hydrolysis.[1,2] However, one of the main problems in the chemical industry is related to the use of organic solvents in its processes. The manufacture, transport, handling, and disposal of solvents are aspects that demand great care and expense. For these reasons, the replacement of organic solvents by water is of great interest in organic synthesis to minimises the environmental impact, besides lowering cost and decreasing danger.[1,2]

Organophosphorus compounds, *i.e.* those bearing a carbon atom directly bound to phosphorus atom, are synthetic targets of interest, not least because of their value for a variety of industrial, biological and chemical synthetic uses.[3-5] We describe here a synthesis of pyrrole phosphonate esters derivatives in an aqueous media by the Arbuzov reaction.[6]

We report an efficient one-pot synthesis in aqueous media of pyrrole phosphonate ester (**3a**) (see Scheme 1). Phosphonate esters **3a,b** apparently results from the initial addition of triphenylphosphite to the dimethyl acetylenedicarboxylate (DMAD) followed by attack by the pyrrole anion to form an intermediate, which is then hydrolysed to the phosphonato ester **3** (see Scheme 2). Hydrolysis of alkyl triphenoxyphosphonium salts in water has been reported to give diphenyl alkylphosphonates.[7]

The structure of **3a** (see Scheme 3) was assigned from the mass spectrum, which displayed a molecular ion peak at *m/z* 443. Fragmentation involves the loss of the side chains. The ^{1}H NMR spectrum of **3a** displayed signals for vicinal methine protons at δ = 4.18, 4.77 which appear as separate double doublets with $^2J_{HP}$ and $^3J_{HP}$ values of 22.37 and 10.84 Hz, respectively. The phenyl groups of the phosphonate ester fragment, are also diastereotopic and exhibit eight distinct signals in the ^{13}C NMR spectra. The presence of ^{31}P nucleus in **3a**, helps in the assignment of the signals by long range coupling with ^{1}H and ^{13}C nuclei (see Experimental).

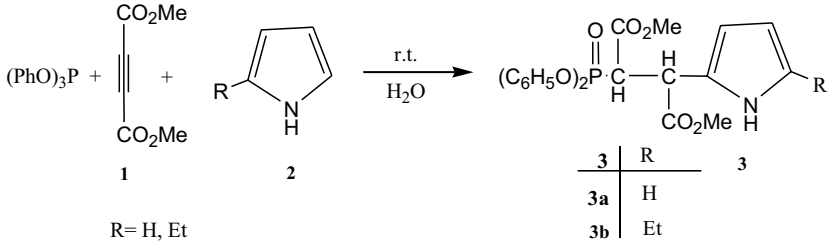
The structure of compound **3b** was confirmed in a similar manner to **3a**. The vicinal proton–proton coupling constant ($^3J_{HH}$) as a function of the torsion angle can be obtained from the Karplus equation.[7] Typically, J_{gauche} and J_{anti} vary between 1.5 Hz and 10–14 Hz respectivily. Observation of $^3J_{HH}$ = 10.9 Hz for the vicinal protons of compounds **3a, 3b** (see Table 1) indicates an anti arrangement for these protons.

Since compounds **3a,b** possess two stereogenic centres, two diastereoisomers for **3a,b** (see Scheme 3) with anti HC–CH arrangement are possible. The three–bond carbon–phosphorus couplings, $^3J_{CP}$, depends on configuration and, as expected, transoid couplings are larger than cisoid ones. The Karplus relationship can be derived from the data for organophosphorus compounds with tetra and pentavalent phosphorus.[7] The observed of $^3J_{CP}$ of 20.13 Hz for the ester C=O group (P–CH–CH–*C*=*O*) (see Table 1) is in agreement with the 2*R*, 3*S*- (**3a**) and its mirror image 2*S*, 3*R*-(**3a'**). This behaviour was also observed for **3b** and its mirror image **3b'** (see Scheme 3).

Experimental

All 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 electrothermal 9100 melting point apparatus. IR spectra were recorded on a shimadzu-IR 470 spetrophotometer. The ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained from a Bruker-500 MHz instrument with $CDCl_3$ as solvent at 500.1, 125.8 and 202.4 MHz, respectively. The mass spectra were recorded on Shimadzu GS/MSQP 1100 EX mass spectrometer operating at an ionisation potential of 70 eV. Elemental analyses were performed for C, H, N using a Heraeus CHN-O-Rapid analyser.

General procedure for preparation of dimethyl 2-(pyrrole-2-yl)-3-(diphenoxyphosphoryl)butanedioate **(3a)**: To a magnetically stirred solution of triphenylphosphite (0.31 g, 1 mmol) and pyrrole (0.067 g, 1 mmol) in 25 ml of water was added, dropwise, solution of dimethyl acetylendicarboxylate (1 mmol) at room temperature over 10 min. The reaction mixture was then stirred for 6 hours. The product was filtered and washed with (3 × 10 ml) mixture of cold *n*-hexane and diethyl ether. The product **3a** was obtained as colourless crystals, yield 90 %, m.p. 133–135 °C, IR (KBr) (ν_{max}, cm^{-1}): 1732 (C=O), 1590 (C =C), MS (*m/z*, %): 443 (M^+) (5), 411(M^+–CH_3OH) (4), 209 (C_4H_4N–$CHCO_2CH_3$–$CHCO_2CH_3$) (15), 177 (209–CH_3OH) (70),



Scheme 1

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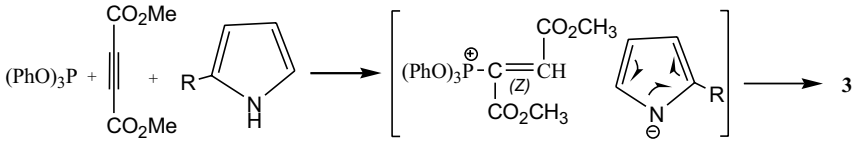
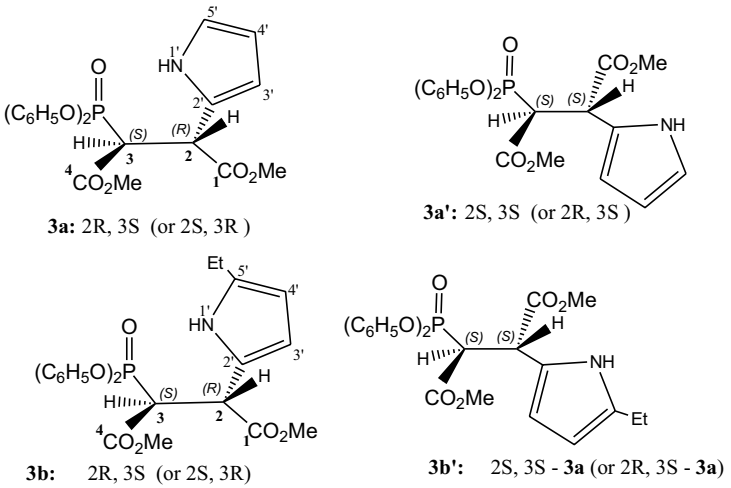


Scheme 2



Scheme 3

Table 1 Selected ^{1}H and ^{13}C NMR chemical shifts (δ in ppm) and coupling constants

		^{1}H NMR spectroscopic data		^{13}C NMR spectroscopic data				
		H-2	H-3	C1	C2	C3	C4	C_2, of pyrrole
Compound	Yield (%)	($^{3}J_{HP}$, $^{3}J_{HH}$)	($^{2}J_{HP}$, $^{3}J_{HH}$)	($^{3}J_{CP}$)	($^{2}J_{CP}$)	($^{1}J_{CP}$)	($^{2}J_{CP}$)	($^{3}J_{CP}$)
3a	90	4.7 10.8, 10.9	4.2 22.4, 10.9	171.7 20.1	52.85 21.2	49.3 136.0	167.9 5.0	123.8 2.3
3b	85	4.8 10.8, 10.9	4.1 22.3, 10.9	171.9 20.3	52.9 26.3	49.6 135.9	167.9 5.0	122.1 2.3

349 (M^{+} –C_6H_5OH) (2), 285 (M^{+} –C_6H_5OH, [P(O)(PhO)$_2$] (50), 94 (C_6H_5OH) (100), 77 (Ph) (100). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.69, 3.73 (2OCH_3), 4.18 (dd, 1H, $^{2}J_{HP}$ 22.4 Hz, $^{3}J_{HH}$ 10.9, P– C*H*), 4.77 (dd, 1H, $^{3}J_{HP}$ 10.8 Hz, $^{3}J_{HH}$ 10.9 Hz, P–C–C*H*), 6.14 (d, 1H, $^{3}J_{HH}$ 2.6 Hz, C_3H of pyrrole), 6.16 (s, 1H, C_4H of pyrrole), 6.7 (d, broad, 1H, $^{3}J_{HH}$ 0.82 Hz, C_5H of pyrrole), 6.9–7.3 (10H, m, Ar), 9.1 (s, 1H, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 43.6, (s, P–CH–^{13}CH) 49.3 (d, $^{1}J_{CP}$ 136.0 Hz P–^{13}CH), 52.7, 53.0 (2×s, 2OCH_3), 108.4 (C_4 of pyrrole), 108.7 (C_3 of pyrrole), 118.5 (C_5 of pyrrole), 120.2, 120.4 (2d, $^{3}J_{CP}$ 4.50 Hz, 2 C_{ortho} of 2C_6H_5), 123.8 (d, $^{3}J_{CP}$ 2.3 Hz, C_2 of pyrrole), 125.3, 125.4 (2 C_{para} of 2C_6H_5), 129.6 (C_{meta} of 2 C_6H_5), 149.7,150.0 (2d, $^{2}J_{CP}$ 9.4 Hz, C_{ipso} of 2C_6H_5), 167.9 (d, $^{2}J_{CP}$ 5.0 Hz, C=O ester), 171.7 (d, $^{3}J_{CP}$ 20.1 Hz, C=O ester). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 13.3 [$(PhO)_2{}^{31}P$ = O]. Anal. Calcd for $C_{22}H_{22}NO_7P$ (443): C, 59.59; H, 5.00; N, 3.16 %. Found: C, 61.8; H, 5.1; N, 3.7 %.

Dimethyl 2-(5-ethylpyrrole-2-yl)-3-(diphenoxyphosphoryl)butanedioate (**3b**): The procedure for preparation of **3b** was similar to that for **3a**. pale orange powder, yield 85 %, m.p. 132–133.2 °C, IR (KBr) (ν_{max}, cm^{-1}): 1728 (C=O),1585 (C=C), MS (*m/z*, %): 439 (M^{+} –CH_3OH) (70), 411(M^{+} –CH_3COOH) (30), 344 (M^{+} –C_6H_5OH–C_6H_5OH) (3), 351(M^{+} –2CH_3COOH) (20), 237 [(C_4H_4N(Et)–CH(CO_2CH_3)–CH(CO_2CH_3)] (10), 94 (C_6H_5OH) (90), 77 (Ph) (80). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.13 (t, 3H, $^{3}J_{HH}$ 7.5 Hz –CH_2–C*H*$_3$), 2.46 (q, 2H, $^{3}J_{HH}$ 7.5 Hz –C*H*$_2$–CH_3), 3.68, 3.72 (2OCH_3), 4.09 (dd, 1H, $^{2}J_{HP}$ 22.3 Hz, $^{3}J_{HH}$ 10.9, P–C*H*), 4.67 (dd, 1H, ^{3} J_{HP} 10.8 Hz, $^{3}J_{HH}$ 10.9 Hz, P– C–C*H*), 5.8 (s, 1H, C_4H of pyrrole), 6.02 (s, 1H, C_3H of pyrrole), 6.86–7.32 (10H, m, Ar), 8.52 (s, 1H, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.6 (CH_2–^{13}C*H*$_3$), 20.7 (–^{13}C*H*$_2$–CH_3), 43.7 (P–CH–^{13}CH), 49.6 (d, $^{1}J_{CP}$ 135.9 Hz P–^{13}CH), 52.8, 53.0 (2×s, 2OCH_3), 104.9 (C_4 of pyrrole), 108.4 (C_3 of pyrrole), 118.5 (C_5 of pyrrole), 120.3, 120.4 (2d, $^{3}J_{CP}$ 4.6 Hz, 2 C_{ortho} of 2 C_6H_5),122.1 (d, $^{3}J_{CP}$ 2.3 Hz, C_2 of pyrrole), 125.4 (2C_{para} of 2C_6H_5), 129.6,129.7 (2C_{meta} of 2C_6H_5), 149.8, 150.1 (2d, $^{2}J_{CP}$ 9.5 Hz, C_{ipso} of 2C_6H_5), 167.9 (d, $^{2}J_{CP}$ 5.0, C=O ester), 171.9 (d, $^{3}J_{CP}$ 20.3 Hz, C=O ester). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 13.6 [$(PhO)_2{}^{31}P$ = O]. Anal.Calcd for $C_{24}H_{26}NO_7P$ (471): C, 61.14; H, 5.56; N, 2.97 %. Found: C, 60.69; H, 5.42; N, 3.26 %.

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