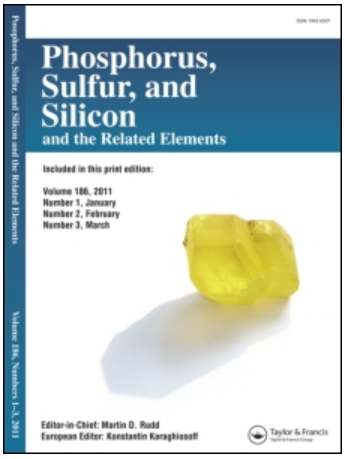

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A New Route to 3-Phosphonylpyrazoles

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A NEW ROUTE TO 3-PHOSPHONYLPYRAZOLES

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The regioselective synthesis of 3-diethoxyphosphonopyrazoles has been accomplished through the addition of aryl or alkyl hydrazines to (3-ethoxyacryloyl)phosphonic acid diethyl ester. An example of hydrolysis of the pyrazolephosphonic ester to the corresponding acid is described.

Keywords Aminophosphonic acids; cycloaddition reactions; phosphonylpyrazoles

INTRODUCTION

Organophosphorus compounds have found a wide range of applications in the areas of biological, medicinal, and synthetic chemistry.[1–3] Their biological activity is often enhanced by their association with various heterocycles, which are themselves biologically active.[4] Among the numerous methods developed to synthesise pyrazoles,[5] the most often applied protocols are the reaction of hydrazines with β-difunctional compounds, and the 1,3-dipolar cycloaddition of diazocompounds or nitrileimines to alkenes and alkynes. By these methods, several phosphonylpyrazoles have already been prepared.[4,6,7] However, in most cases, the synthesis involves multistep reaction sequences.[8,9]

In this article, we describe a regioselective synthesis of 1-substituted or unsubstituted pyrazoles **2a–d** bearing diethylphosphonic ester moiety at the 3-position. An example of transformation of phosphonylpyrazole **2b** into the corresponding phosphonic acid is also reported.

RESULTS AND DISCUSSION

It has been reported that 1-benzoyl-2-ethoxyvinylphosphonic acid diethyl ester can be cyclized with hydrazine hydrate to form 4-phosphonylpyrazole.[10] In this article, we report on a facile strategy for the synthesis of 3-phosphonylpyrazoles from a similar β-ethoxyenone system. The starting 3-ethoxyprop-2-enoylphosphonic acid diethyl ester (**1**) was synthesised by a two-step procedure as shown in Scheme 1. The Arbuzov reaction of acetyl chloride and triethylphosphite gave acetylphosphonic acid diethyl ester,[11] which was then refluxed with triethyl orthoformate in acetic anhydride as solvent for 16 h. The

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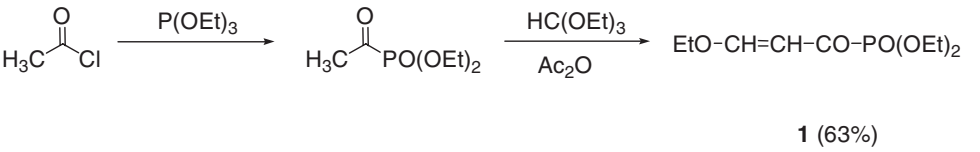
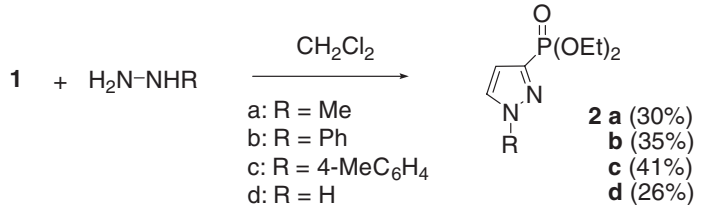


Scheme 1

pure product was separated by distillation at reduced pressure in 63% yield. A similar 3-ethoxyprop-2-enoylphosphonic acid dimethyl ester has been described in literature as a product of Arbuzov reaction of 3-ethoxyprop-2-enoyl chloride with trimethylphohosphite.[12]

Finally we investigated the reaction of β-ethoxyenone **1** with four hydrazines (Scheme 2). The reaction was carried out in dichloromethane as a solvent, and we observed a mild heat evolution. In all cases, we obtained the 3-phosphonylpyrazoles **2a–d**, which were purified by column chromatography. The structures of compounds **2a–d** were confirmed by analytical and spectroscopic data. In the case of **2b–d** they are in accordance with literature,[8,13,14] while products **2a,c** are new.



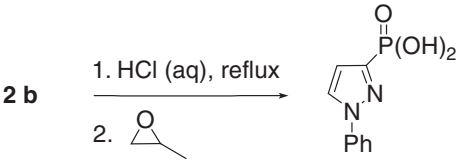
Scheme 2

The pure pyrazolephosphonic acid **3** was obtained by refluxing **2b** with 20% HCl (aq.) solution for 10 h and subsequent treatment with propylene oxide (Scheme 3).

In summary, a new and simple method for the synthesis of 1-*H* or 1-substituted 3-phosphonylpyrazoles has been developed, which is based on the reaction of easily available 3-ethoxyacryloylphosphonic acid diethyl ester and hydrazines.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained with a Bruker DPX 250, a Varian Gemini 200, and a Tesla BS 687 spectrometer operating at 250, 200, and 80 MHz for ^{1}H (TMS), at 63 and 50 MHz for ^{13}C, and at 101 and 80 MHz for ^{31}P (H_3PO_4), respectively. MS-ESI spectra were recorded with a Bruker Esquire-LC instrument. The elemental analyses were performed by the Laboratory of Microanalysis of the Centre of Molecular and



Scheme 3

Macromolecular Studies, Polish Academy of Science in Łódź, Poland. Acetylphosphonic acid diethyl ester was obtained according to the method described in literature.[11]

3-Ethoxyprop-2-enoylphosphonic Acid Diethyl Ester (1)

A solution of acetylphosphonic acid diethyl ester (18.0 g, 0.1 mol) and triethyl orthoformate (30.0 g, 0.2 mol) in acetic anhydride (30.0 g) was refluxed for 16 h. Then the solvent was evaporated, and the residue was fractionated under reduced pressure to yield the pure product as a pale yellow oil (59.6 g, 63%), bp 118–150 °C/0.4 mm Hg. ^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.27–1.47 (m, 9H, CH_3), 3.95–4.38 (m, 6H, CH_2O), 5.98 (dd, $^{3}J_{PH}$ = 14.9 Hz, $^{3}J_{HH}$ = 12.5 Hz, 1H, CH), 8.26 (d, $^{3}J_{HH}$ = 12.5 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 13.5 (CH_3), 15.4 (d, $^{3}J_{PC}$ = 5.7 Hz, CH_3), 62.6 (d, $^{2}J_{PC}$ = 6.9 Hz, CH_2), 67.5 (CH_2), 107.2 (d, $^{2}J_{PC}$ = 68.1 Hz, C-2), 167.4 (d, $^{3}J_{PC}$ = 2.8 Hz, C-3), 195.3 (d, $^{1}J_{PC}$ = 173.7 Hz, C-1). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = –2.3. Anal. Calcd. for $C_9H_{17}O_5P$: C, 45.76; H, 7.25%. Found: C, 45.36; H, 7.38%.

3-Phosphonylpyrazoles 2a-d: General Procedure

To a solution of **1** (10.0 mmol) in CH_2Cl_2 (50 mL), substituted hydrazine or hydrazine hydrate (10.5 mmol) was added and mild heat evolution was observed. The mixture was stirred for 1 h, then the solvent was evaporated, and the products **2a–d** were purified by chromatography on SiO_2 (hexane–ethyl acetate, gradient 50 to 100% ethyl acetate).

1-Methyl-1*H*-pyrazol-3-ylphosphonic acid diethyl ester (2a). Yellow oil (0.65 g, 30%). ^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.25–1.43 (m, 6H, CH_3), 3.99 (s, 3H, CH_3), 4.04–4.37 (m, 4H, CH_2), 6.69–6.74 (m, 1H, CH), 7.42–7.48 (m, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 15.6 (d, $^{3}J_{PC}$ = 6.4 Hz, CH_3), 38.8 (CH_3N), 61.8 (d, $^{2}J_{PC}$ = 5.5 Hz, CH_2), 111.4 (d, $^{2}J_{PC}$ = 23.5 Hz, C-4), 130.7 (d, $^{3}J_{PC}$ = 10.0 Hz, C-5), 140.8 (d, $^{1}J_{PC}$ = 232.9 Hz, C-3). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = 9.9. Anal. Calcd. for $C_8H_{15}N_2O_3P$: C, 44.04; H, 6.93%. Found: C, 43.82; H, 6.93%.

1-Phenyl-1*H*-pyrazol-3-ylphosphonic acid diethyl ester (2b). Yellow oil (0.98 g, 35%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.38 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, CH_3), 4.17–4.32 (m, 4H, CH_2), 6.91–6.92 (m, 1H, CH), 7.35–7.76 (m, 5H, C_6H_5), 7.99–8.01 (m, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 16.0 (d, $^{3}J_{PC}$ = 6.6 Hz, CH_3), 62.5 (d, $^{2}J_{PC}$ = 5.5 Hz, CH_2), 113.0 (d, $^{2}J_{PC}$ = 23.2 Hz, C-4), 119.7 (CH_{arom}), 127.4 (CH_{arom}), 127.8 (d, $^{3}J_{PC}$ = 9.4 Hz, C-5), 129.3 (CH_{arom}), 139.4 (C_{arom}), 143.1 (d, $^{1}J_{PC}$ = 231.5 Hz, C-3). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = 9.6. Anal. Calcd. for $C_{13}H_{17}N_2O_3P$: C, 55.71; H, 6.11%. Found: C, 55.60; H, 5.92%.

1-(4-Tolyl)-1*H*-pyrazol-3-ylphosphonic acid diethyl ester (2c). Yellow oil (1.21 g, 41%). ^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.36 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, CH_3), 2.38 (s, 3H, CH_3), 4.05–4.41 (m, 4H, CH_2), 6.86–6.90 (m, 1H, CH), 7.19–7.69 (m, 4H, C_6H_4), 7.92–7.98 (m, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 15.9 (d, $^{3}J_{PC}$ = 6.5 Hz, CH_3), 20.5 (CH_3), 62.4 (d, $^{2}J_{PC}$ = 5.6 Hz, CH_2), 112.7 (d, $^{2}J_{PC}$ = 23.2 Hz, C-4), 119.5 (CH_{arom}), 127.6 (d, $^{3}J_{PC}$ = 9.5 Hz, C-5), 129.6 (CH_{arom}), 137.0 (C_{arom}), 137.1 (C_{arom}), 142.5 (d, $^{1}J_{PC}$ = 231.3 Hz, C-3). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = 9.7. Anal. Calcd. for $C_{14}H_{19}N_2O_3P$: C, 57.14; H, 6.51%. Found: C, 57.11; H, 6.65%.

1*H*-Pyrazol-3-ylphosphonic acid diethyl ester (2d). Colorless crystals (0.53 g, 26%), mp 64–66 °C (lit.[8,13] mp 63–64 °C). ^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.32 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, CH_3), 3.98–4.26 (m, 4H, CH_2), 6.71–6.76 (m, 1H, CH), 7.85–7.91

(m, 1H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 15.8 (d, $^3J_{PC}$ = 6.1 Hz, CH_3), 62.2 (d, $^2J_{PC}$ = 5.0 Hz, CH_2), 110.2 (d, $^2J_{PC}$ = 23.3 Hz, C-4), 131,0 (d, $^3J_{PC}$ = 9.4 Hz, C-5), 139.2 (d, $^1J_{PC}$ = 230.1 Hz, C-3). ^{31}P NMR ($CDCl_3$, 80 MHz): δ = 10.3. ESI-MS (MeOH): 205 (30%, $[M+H]^+$), 227 (100%, $[M+Na]^+$).

1-Phenyl-1*H*-pyrazol-3-ylphosphonic Acid (3)

The ester **2b** (1.40 g, 0.005 mol) was dissolved in HCl (aq.) solution (8 mol/L, 55 mL) and EtOH (5 mL) was added. The mixture was refluxed for 12 h, and then the solvent was evaporated. The residue was dissolved in MeOH (10 mL), propylene oxide was added, and the mixture was left for 10 h. Then the solvent was evaporated, and the residue was crystallized from water to yield aminoacid **3** as colorless crystals (0.17 g, 15%), mp 159–160 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 6.57–6.58 (m, 1H, CH), 7.10–7.39 (m, 5H, C_6H_5), 7.80–7.82 (m, 1H, CH). ^{13}C NMR (D_2O/NaOD, 63 MHz): δ = 111.0 (d, $^2J_{PC}$ = 20.7 Hz, C-4), 120.1 (CH_{arom}), 127.4 (CH_{arom}), 129.3 (CH_{arom}), 129.4 (CH_{arom}), 139.1 (C_{arom}), 150.0 (d, $^1J_{PC}$ = 212.0 Hz, C-3). ^{31}P NMR (D_2O/NaOD, 101 MHz): δ = 4.9. Anal. Calcd. for $C_8H_9N_2O_3P$: C, 48.23; H, 4.05%. Found: C, 48.11; H, 4.09%.

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