PREPARATION OF DIETHYL 1-(ALKYL/ARYL-2-AMINO-4-OXO-4,5-DIHYDROPYRROL-3-YL)PHOSPHONATES

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The title compounds were prepared starting from diethyl (cyanomethyl)phosphonate by C-acylation with chloroacetyl chloride and subsequent amination with primary amines.
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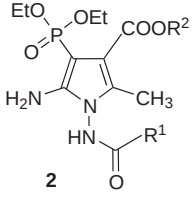
Recently some derivatives of (2-aminopyrrol-3-yl)phosphonic acid have been found to exhibit a high activity against parasitic insects and ectoparasites both in animals and humans[1–3]. For this reason the development of synthetic methods for preparation of amino substituted pyrrolylphosphonates is of interest. However, only one comparatively general procedure of their synthesis is described in the literature[4,5]. It includes an addition-cyclization reaction of diethyl (cyanomethyl)phosphonate (**1**) with conjugated azoalkenes and results in (1,2-diaminopyrrol-3-yl)phosphonic acid derivatives **2**. It is a good method, but the potential of phosphonate **1** for aminopyrrole synthesis does not seem to be limited to the described approach. In our laboratory a convenient two-step protocol for transformation of hetarylacetonitriles into 5-amino-4-hetarylpyrrol-3(2*H*)-ones **3** by C-acylation with chloroacetyl chloride and subsequent amination with pri-



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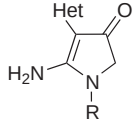

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R = alkyl, aryl; R^1 = OEt, O*t*-Bu, NH_2; R^2 = Me, Et

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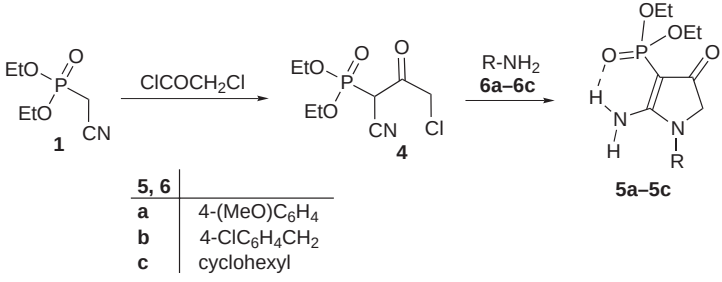
mary amines was elaborated[6–10]. Since the phosphonate **1** can also be considered as a substituted acetonitrile, it seemed interesting to apply our approach to it and to extend the scope of available (aminopyrrolyl)phosphonates by this way. The results of the investigation in this field are reported herein.

An attempt to react the phosphonate **1** with chloroacetyl chloride under the conditions described for hetarylacetonitriles[6,10,11] failed. However, recently an efficient method was reported for C-acylation of phosphorus-containing active methylene compounds under the phase-transfer conditions[12–15]. The method uses solid KOH in anhydrous acetonitrile while the phosphorus-containing compound acts simultaneously as a substrate and a phase-transfer agent. The application of this method to the chloroacetylation of phosphonate **1** allowed to achieve good conversion (*ca* 70% by ^{31}P NMR) of compound **1** to its acyl derivative **4** in 2 h at room temperature (Scheme 1). However, compound **4** undergoes decomposition above 50–55 °C and hence it could not be separated from the unreacted phosphonate **1** by distillation. The decomposition seems to be caused by the P–C bond cleavage that was noted to be a side reaction during acylation



5, 6	
a	4-(MeO)C_6H_4
b	4-Cl$C_6H_4CH_2$
c	cyclohexyl

SCHEME 1

of compounds like **1** (refs[12,15]). To resolve this problem, it was decided to elaborate a one-pot synthesis of the target aminopyrrole derivatives without isolation of the intermediate **4**. The reaction mixture after acylation was evaporated, the residue was treated with water and neutralized, and compound **4** together with unreacted **1** were taken up into benzene. An addition of approximately two-fold excess of a primary amine to the dried extract allowed to obtain pure diethyl (1-alkyl/aryl-2-amino-4-oxo-4,5-dihydropyrrol-3-yl)phosphonates **5a**–**5c** in 50–60% yields based on the starting phosponate **1**. For aliphatic amines **6b** and **6c** the reaction was complete in 3 days at room temperature, whereas for the less reactive aromatic compound **6a** 4 days at 45–50 °C were necessary. Halo- and nitro-

substituted anilines reacted too slowly (by ^{31}P NMR) even at elevated temperature thus making the preparation of the corresponding pyrrole derivatives by this way essentially impossible.

The structure of pyrrolylphosphonates **5** was confirmed by ^{1}H, ^{13}C and ^{31}P NMR data. Thus, their ^{1}H NMR spectra recorded in DMSO-d_6 established a two-proton singlet of the methylene group at 3.5–4.0 ppm and two broad one-proton singlets in the 7.2-7.9 ppm region assigned to the amino group. Magnetic non-equivalence of the amino-group protons is explained by the intramolecular hydrogen bond shown in Scheme 1. Indeed, when ^{1}H NMR spectrum of compound **5a** was recorded in $CDCl_3$, one of these signals remained at 7.8 ppm while the other appeared at 5.1 ppm thus proving the above assumption. It is interesting to note that pyrroles **2** consisting of a similar moiety of vicinal amino and phosphono groups did not exhibit such effect[4]. Probably, amide-like conjugation of amino and carbonyl groups in compounds **5** increases the acidity of NH-protons thus facilitating the hydrogen bond formation. The presence of such conjugation in related systems was reported by us[10] and other researchers[16] on the basis of X-ray investigation. The absence of nitrile absorption both in IR and ^{13}C NMR spectra clearly indicates the ring closure with its participation. The ^{13}C NMR spectrum recorded for compound **5a** was also in good agreement with the assigned structure. The C–H correlations (HMBC and HSQC experiments) were performed to facilitate the signals assignment. First of all, the ^{13}C NMR spectrum exhibited a very characteristic doublet of C-3 at 79.1 ppm (center) split due to interaction with ^{31}P nucleus with the coupling constant 211.3 Hz. The signals of the carbonyl at 190.2 ppm and C-2 at 170.1 ppm were also observed as doublets with $J_{C\text{-}P}$ values 18.9 and 22.6 Hz, respectively. Finally, the signal of the methylene group carbon at 60.3 ppm was also split with the constant 12.5 Hz. The signals from the ethoxy groups appeared at expected δ values both in ^{1}H and ^{13}C NMR spectra. All the prepared compounds displayed a single signal in their ^{31}P NMR spectra near 19 ppm.

To resume, the described investigation has resulted in a one-pot method for the synthesis of a new type of (aminopyrrolyl)phosphonic acid derivatives, namely diethyl (1-alkyl/aryl-2-amino-4-oxo-4,5-dihydropyrrol-3-yl)-phosphonates. The method utilizes stable and readily available starting materials and simple experimental procedures. Unfortunately, the range of amines, which can be used in the synthesis, is limited to aliphatic and highly basic aromatic amines.

EXPERIMENTAL

Melting points were determined on a Thiele apparatus in open capillary tubes and are uncorrected. IR spectra were obtained on a Pye Unicam SP 3-300 apparatus in KBr disks. ^{1}H and ^{31}P NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz for ^{1}H and 120 MHz for ^{31}P) in DMSO-d_6 solutions (if not stated otherwise). Chemical shifts (δ-scale) are given in ppm downfield from internal $SiMe_4$ for ^{1}H or external H_3PO_4 for ^{31}P. Coupling constants *J* are in Hz. For ^{13}C NMR doublet signals, the chemical shifts values for the centers are given. ^{13}C and 2D NMR experiments were performed on a Bruker Avance 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). All reagents were commercially available and were used without additional purification. All reactions were monitored by ^{31}P NMR. The purity of all the compounds prepared was checked by ^{1}H and ^{31}P NMR.

Preparation of Diethyl (1-Alkyl/Aryl-2-amino-4-oxo-4,5-dihydropyrrol-3-yl)-phosphonates (**5a**–**5c**). General Procedure

Powdered KOH (0.67 g, 12 mmol) was added to a solution of phosphonate **1** (0.89 g, 5 mmol) in 20 ml of anhydrous acetonitrile and the resulting mixture was stirred at room temperature for 15 min. After cooling the mixture to 10 °C, chloroacetyl chloride (0.68 g, 6 mmol) was carefully added. The temperature was allowed to increase to room temperature and stirring was continued for 2 h. The solvent was removed *in vacuo* at 40–45 °C. Water (25 ml), benzene (15 ml) and 9% hydrochloric acid (6 ml) were successively added to the residue and the resulting mixture was shaken for 5 min. The organic layer was separated, the aqueous one was extracted with benzene (15 ml) and the combined extract was dried with anhydrous Na_2SO_4. After filtration, an amine (8 mmol) was added to the benzene solution and the resulting mixture was kept at room temperature for 3 days (**5b**, **5c**) or at 45–50 °C for 4 days (**5a**). The precipitated amine hydrochloride was filtered off and benzene was evaporated *in vacuo* to dryness. The residue was treated with ether, filtered and recrystallized from benzene (**5b**) or benzene–hexane (**5a**, **5c**).

Diethyl [2-amino-1-(4-methoxyphenyl)-4-oxo-4,5-dihydropyrrol-3-yl]phosphonate (**5a**). Yield 0.88 g (52%). M.p. 159 °C. For $C_{15}H_{21}N_2O_5P$ (340.3) calculated: 52.94% C, 6.22% H, 8.23% N, 9.10 P; found: 52.88% C, 6.31% H, 8.19% N, 9.12% P. IR: 3305, 3180, 2980, 1595, 1540, 1485, 1245, 1210, 1030, 960, 775. ^{1}H NMR ($CDCl_3$): 1.36 t, 6 H, *J* = 7.0 (CH_3); 3.84 s, 3 H (OCH_3); 3.98 s, 2 H (5-CH_2); 4.14 m, 4 H, *J*(HH) = 7.0, *J*(PH) = 3.0 (OCH_2); 5.11 br s, 1 H (NH); 6.98 d, 2 H, *J* = 9.0 (R); 7.20 d, 2 H, *J* = 9.0 (R); 7.89 br s, 1 H (NH···O). ^{31}P NMR: 19.1. ^{13}C NMR: 16.3 d, *J* = 7.5 (2 CH_3); 55.7 (OCH_3); 60.3 d, *J* = 12.5 (5-C); 62.1 d, *J* = 5.0 (OCH_2); 79.1 d, *J* = 211.3 (3-C); 115.6 (3,5-C_R); 127.3 (2,6-C_R); 128.9 (1-C_R); 159.4 (4-C_R); 170.2 d, *J* = 22.6 (2-C); 190.2 d, *J* = 18.9 (4-C).

Diethyl [2-amino-1-(4-chlorobenzyl)- 4-oxo-4,5-dihydropyrrol-3-yl]phosphonate (**5b**). Yield 1 g (56%). M.p. 157 °C (dec). For $C_{15}H_{20}ClN_2O_4P$ (358.7) calculated: 50.22% C, 5.62% H, 9.88% Cl, 7.81% N, 8.63% P; found: 50.26% C, 5.57% H, 9.94% Cl, 7.79% N, 8.61% P. IR: 3310, 3170, 2980, 1600, 1570, 1485, 1350, 1205, 1025, 960, 800, 770. ^{1}H NMR: 1.19 t, 6 H, *J* = 7.0 (CH_3); 3.57 s, 2 H (CH_2); 3.92 m, 4 H, *J*(HH) = 7.0, *J*(PH) = 3.0 (OCH_2); 4.63 s, 2 H (NCH_2); 7.27 d, 2 H, *J* = 8.4 (R); 7.45 d, 2 H, *J* = 8.4 (R); 7.71 br s, 1 H (NH); 7.90 br s, 1 H (NH···O). ^{31}P NMR: 19.5.

Diethyl (2-amino-1-cyclohexyl-4-oxo-4,5-dihydropyrrol-3-yl)phosphonate (**5c**). Yield 0.9 g (57%). M.p. 174 °C. For $C_{14}H_{25}N_2O_4P$ (316.3) calculated: 53.16% C, 7.97% H, 8.86% N, 9.79% P; found: 53.21% C, 8.00% H, 8.79% N, 9.68% P. IR: 3330, 3160, 2980, 1600, 1580,

1485, 1370, 1215, 1040, 960, 810, 790. ^{1}H NMR: 1.17 t, 6 H, *J* = 7.2 (CH_3); 1.34 m, 5 H (R); 1.72 m, 5 H (R); 3.61 s, 2 H (CH_2); 3.71 m, 1 H (N-CH); 3.89 m, 4 H, *J*(HH) = 7.2, *J*(PH) = 3.0 (OCH_2); 7.56 br s, 2 H (NH_2). ^{31}P NMR: 19.8.

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