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Mendeleev Commun., 2018, **28**, 398–400

Mendeleev Communications

Synthesis and structure of new 2-aryl-substituted pyrrolidines containing phosphine oxide group

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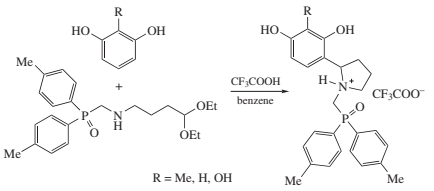
DOI: 10.1016/j.mencom.2018.07.019

2-Aryl-substituted pyrrolidines containing phosphine oxide group have been obtained by the reaction of *P*-(4,4-diethoxybutylaminomethyl)-*P*,*P*-di-*p*-tolylphosphine oxide with polyatomic phenols.



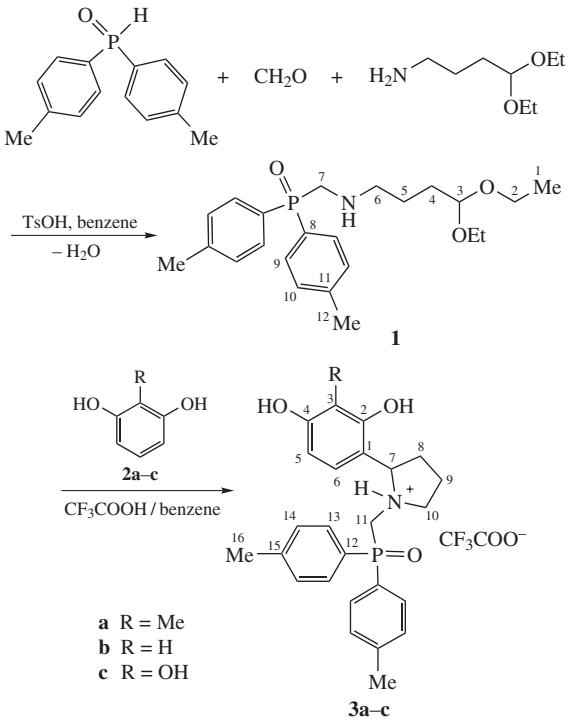
Pyrrolidine ring is included in many biologically active natural products,[1] alkaloids, and compounds that exhibit antitumor,[2] antibacterial,[3] antimicrobal,[4] neurotropic,[5] anti-inflammatory and anti-HIV activities.[6] The presence of a phosphonate group in biologically active molecules enhances their properties.[7] In this context, phosphorylated pyrrolidine derivatives can be of particular interest. Effective inhibitors of HIV protease and dipeptidyl peptidase IV,[8] thymidine phosphorylase,[9] purine nucleoside phosphorylase,[10] and 6-oxopurine phosphoribosyl transferase[11] were discovered among them.

Analysis of literature shows that effective syntheses of phosphorylated pyrrolidines are scarce in spite of their biological potential. The known methods mainly include: (i) direct electrophilic or nucleophilic phosphorylation of heterocyclic system;[12] (ii) ring closing of phosphoryl-functionalized substrates as a result of intramolecular cyclization, cycloaddition[13] and multi-component reactions.[14] Most of the methods relate to the preparation of 1-phosphonopyrrolidines or 2- or 3-phosphoryl substituted pyrrolidines. In spite of this positive background, simple and effective accesses to 2-aryl-substituted pyrrolidinylmethylphosphonates are lacking. At the same time, 2-aryl-substituted pyrrolidines are of interest as non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs).[15] Incorporation of phosphonate moiety into compounds possessing NNRTI activity may improve their solubility and bioavailability.[16]

Assuming these facts, in the present work we aimed at developing novel synthesis of phosphorus-containing 2-aryl-substituted pyrrolidines. Recently, we obtained such compounds by acid-catalyzed intramolecular cyclization of *N*-(4,4-diethoxybutyl)ureas in the presence of phenols as nucleophiles.[17]

Here, the reaction of *P*-(4,4-diethoxybutylaminomethyl)-*P*,*P*-di-*p*-tolylphosphine oxide **1** with polyatomic phenols **2a–c** has been investigated for the first time in order to prepare phosphorylated 2-aryl-substituted pyrrolidines. Previously unknown amino acetal **1**† was synthesized by the reaction of 4,4-diethoxybutylamine with di-*p*-tolylphosphine oxide and paraformaldehyde in benzene in the presence of *p*-toluenesulfonic acid according to the Kabachnik–Fields reaction[18] (Scheme 1).

In the first experiments, amino acetal **1** reacted with 2-methylresorcinol **2a** in chloroform at room temperature in the presence of trifluoroacetic acid giving a hardly separable mixture of products. The MALDI mass spectra of the reaction mixture revealed the signals at *m*/*z* 560 $[M+H]^+$, corresponding to diarylbutylamine derivative, [4,4-bis(2,4-dihydroxy-3-methylphenyl)butylaminomethyl]di-*p*-tolylphosphine oxide, along with signal at *m*/*z* 435 $[M+H]^+$ of the target product **3a**. We have previously reported on the synthesis of diarylbutylamine derivative containing dihexylphosphorylmethyl group by the reaction of 2-methylresorcinol



Scheme 1

† P-*(4,4-Diethoxybutylaminomethyl)*-P,P-*di*-p-*tolylphosphine oxide* **1**. A mixture of di(*p*-tolyl)phosphine oxide (0.86 g, 3.74 mmol), 4,4-diethoxybutan-1-amine (0.6 g, 3.74 mmol), paraformaldehyde (0.11 g, 3.74 mmol) and TsOH (0.01 g) in benzene (50 ml) was heated under reflux in a flask equipped with a Dean–Stark trap for 6 h. When the

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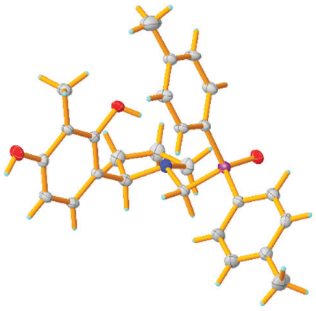

Figure 1 Molecular structure of compound **4** in a crystal.

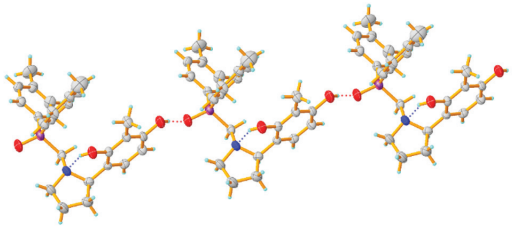

Figure 2 H-bonds in the crystal of compound **4**.

with (4,4-diethoxybutylaminomethyl)dihexylphosphine oxide in excess trifluoroacetic acid.[18]

With the aim to obtain the target phosphorus-containing pyrrolidine **3a** as the only product, we varied the reactant ratio **1**:**2a** from 2:1 to 1:2, the nature of solvent, and the amount of acid. It was found that 2-aryl-substituted pyrrolidines **3a–c**‡ were formed as single products in high yields (67–75%) when phenols **2a–c** and acetal **1** were taken in equimolar amounts and were treated with twofold excess of trifluoroacetic acid in benzene at room temperature (see Scheme 1). According to ^{1}H and ^{13}C NMR spectra, compounds **3a–c** represent salt structures. Note that the signals of protons of methylene groups and pyrrolidine ring in the case of phosphorylated pyrrolidine **3a** are downfield-shifted as compared to analogous signals of non-protonated counterpart **4**, which was formed during spontaneous crystallization of salt **3a** in acetone. The assignment of the signals of ^{1}H and ^{13}C NMR spectra of compound **4** was performed on the basis of 2D homo- and heteronuclear correlation (COSY, NOESY, HSQC, and HMBC) (see Online Supplementary Materials). The molecular structure of compound **4** was confirmed by X-ray analysis (Figure 1).

Investigated crystal is the solvate with the ratio **4**:acetone of 2:1. There are two molecules of pyrrolidine and one molecule of acetone in the independent part of a unit cell. The bond lengths, valence and torsion angles in molecules of compound **4** in a crystal are within the standard values for each type of chemical bond. The crystal structure of compound **4** consists of chains formed by classical O–H···O=P hydrogen bonds (Figure 2) and connected with each other *via* C–H···O and CH–π interactions.‡

In conclusion, we have developed a new efficient synthesis of 2-aryl-substituted pyrrolidines containing phosphine oxide group, which is based on acid catalyzed reaction of phosphorylated aminoacetal with polyatomic phenols. The target products are formed as a result of simultaneous intramolecular cyclization and the formation of C–C bond with the external nucleophile under mild conditions in high yields. These products are promising

reaction was complete, potassium carbonate (250 mg) was added, the mixture was heated for 10 min under reflux and cooled, the precipitate was filtered off. The organic layer was washed with three portions of water, dried over $MgSO_4$, and the solvent was evaporated to dryness. Yield 1.38 g (92%), yellow oil. IR (KBr, ν/cm^{-1}): 1101, 1120 (COC), 1179 (P=O), 1603 (C=C$_{Ar}$), 3317, 3424 (NH). ^{1}H NMR ($CDCl_3$, 400.1 MHz, 30 °C) δ: 1.18 (t, 6H, Me), 1.48–1.54 (m, 2H, CH_2), 1.56–1.60 (m, 2H, CH_2), 2.38 (s, 6H, Me), 2.68 (t, 2H, NCH_2CH$_2$, $^{3}J_{HH}$ 6.9 Hz), 3.41 (d, 2H, PCH_2N, $^{2}J_{PH}$ 8.0 Hz), 3.42–3.47 (m, 2H, CH_2O), 3.56–3.64 (m, 2H, CH_2O), 4.43 (t, 1H, CH, $^{3}J_{HH}$ 5.4 Hz), 7.25–7.27 (m, 4H, ArH), 7.64–7.69 (m, 4H, ArH). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ: 15.27 (C^{1}), 21.47 (C^{12}), 24.78 (C^{4}), 31.12 (C^{5}, $^{4}J_{PC}$ 37.4 Hz), 49.5 (C^{6}, $^{1}J_{PC}$ 80.7 Hz), 51.29 (C^{7}, $^{3}J_{PC}$ 13.2 Hz), 60.97 (C^{7}), 102.71 (C^{3}), 129.19 (C^{8}, $^{1}J_{PC}$ 100.1 Hz), 129.19 (C^{10}, $^{3}J_{CP}$ 12.11 Hz), 131.06 (C^{9}, $^{2}J_{CP}$ 7.33 Hz), 142.2 (C^{11}). ^{31}P NMR (242.9 MHz), δ: 29.4. MS (MALDI), *m*/*z*: 404 [M+H]$^+$. Found (%): C, 68.43; H, 8.52; N, 3.44; P, 7.67. Calc. for $C_{23}H_{34}NO_3P$ (%): C, 68.45; H, 8.49; N, 3.47; P, 7.68.

‡ *[(Pyrrolidin-1-yl)methyl]phosphine oxides* **3a–c** *(general procedure).* Acetal **1** (0.4 g, 1.28 mmol) and trifluoroacetic acid (0.2 ml, 2.5 mmol) were added to appropriate resorcinol **2a–c** (1.27 mmol) dissolved in dry benzene (7 ml). The mixture was stirred at room temperature for 24 h. The benzene layer was decanted, the oily residue was dried *in vacuo*, washed with diethyl ether, filtered off, and dried *in vacuo* to give the desired product.

*2-(2,4-Dihydroxy-3-methylphenyl)-1-[(di-*p*-tolylphosphoryl)methyl]-pyrrolidin-1-ium trifluoroacetate* **3a**. Yield 0.45 g (75%), mp 156–158 °C. ^{1}H NMR (600.1 MHz, acetone-d_6) δ: 2.02 (s, 3H, Me), 2.05–2.23 (m, 4H, CH_2), 2.38 (s, 3H, Me), 2.42 (s, 3H, Me), 2.91–2.98 (m, 1H, CH_2N), 3.52 (dd, 1H, CH_2P, $^{2}J_{PH}$ 6.8 Hz, $^{2}J_{HH}$ 15.2 Hz), 3.78–3.84 (m, 1H, CH_2N), 3.95 (dd, 1H, CH_2P, $^{2}J_{PH}$ 6.5 Hz, $^{2}J_{HH}$ 15.2 Hz), 4.21 (t, 1H, CH, $^{3}J_{HH}$ 8.54 Hz), 6.41 (d, 1H, ArH, $^{3}J_{HH}$ 8.2 Hz), 6.85 (d, 1H, ArH, $^{3}J_{HH}$ 8.2 Hz), 7.32–7.36 (m, 4H, ArH), 7.61–7.66 (m, 4H, ArH). ^{13}C NMR (150.9 MHz, DMSO-d_6), δ: 9.70 (C$^{3'}$), 21.54 (C^{16}), 24.28 (C^{8}), 31.43 (C^{9}), 43.2 (s, C^{11}), 50.03 (s, NCH_2), 70.8 (d, C^{7}, $^{3}J_{CP}$ 13.7 Hz), 107.15 (s, C^{5}), 111.26 (s, C^{3}), 114.42 (q, CF_3, $^{1}J_{CF}$ 292.2 Hz), 123.01 (s, C^{1}), 124.39 (s, C^{6}), 128.75 (d, C^{12}, $^{1}J_{CP}$ 115.0 Hz), 129.9 (d, C^{14}, $^{3}J_{CP}$ 12.5 Hz), 131.18 (d, C^{13}, $^{2}J_{CP}$ 10.3 Hz), 143.35 (s, C^{15}), 153.05 (s, C^{2}), 154.36 (s, C^{4}), 159.98 (q, C=O, $^{2}J_{CF}$ 34.8 Hz). ^{31}P NMR (242.9 MHz), δ: 25.1. MS (MALDI), *m*/*z*: 435 [M+H]$^+$. Found (%): C, 61.15; H, 5.69; N, 2.44; P, 5.66. Calc. for $C_{26}H_{30}NO_3P \cdot CF_3COOH$ (%): C, 61.20; H, 5.69; N, 2.55; P, 5.64.

P-*{[2-(2,4-Dihydroxy-3-methylphenyl)pyrrolidin-1-yl]methyl}*-P,P-*di*-p-*tolylphosphine oxide* **4**. Crystallization of salt **3a** (0.15 g) in acetone during 1 week gives 0.11 g (93%) of **4**, crystals, mp 239–241 °C. IR (KBr, ν/cm^{-1}): 1179 (P=O), 1603 (C=C$_{Ar}$), 3317, 3424 (NH, OH). ^{1}H NMR (600.1 MHz, DMSO-d_6, 30 °C) δ: 1.56 (m, 1H, H-9), 1.75 (m, 2H, H-8), 1.80 (s, 3H, H-3′), 1.98 (m, 1H, H-9), 2.31 (s, 3H, H-16), 2.34 (s, 3H, H-16), 2.36 (m, 1H, C-10), 3.11 (d, 1H, H-11, $^{2}J_{HH}$ 16.3 Hz), 3.46 (m, 1H, H-10), 3.48 (d, 1H, H-11, $^{2}J_{HH}$ 16.3 Hz), 3.53 (m, H-7), 6.20 (d, 1H, $^{3}J_{HH}$ 8.1 Hz), 6.57 (d, 1H, $^{3}J_{HH}$ 8.1 Hz,), 7.24 (dd, 2H, H-14, $^{3}J_{HH}$ 8.1 Hz, $^{4}J_{HP}$ 14.6 Hz), 7.27 (dd, 2H, H-14, $^{3}J_{HH}$ 8.1 Hz, $^{4}J_{HP}$ 14.6 Hz), 7.44 (dd, 2H, H-13, $^{3}J_{HH}$ 8.1 Hz, $^{3}J_{HP}$ 10.9 Hz), 7.52 (dd, 2H, H-13, $^{3}J_{HH}$ 8.1 Hz, $^{3}J_{HP}$ 10.9 Hz), 9.00 (s, 1H, 4-OH), 9.55 (s, 1H, 2-OH). ^{13}C NMR (150.9 MHz, DMSO-d_6, 30 °C) δ: 8.2 (s, C$^{3'}$), 20.9, 21.0 (s, C^{16}), 22.5 (s, C^{8}), 30.9 (s, C^{9}), 52.8 (d, C^{11}, $^{1}J_{CP}$ 82.5 Hz), 54.3 (s, C^{10}), 70.8 (d, C^{7}, $^{3}J_{CP}$ 13.7 Hz), 105.5 (s, C^{5}), 110.8 (s, C^{3}), 115.0 (s, C^{1}), 126.0 (s, C^{6}), 128.4 (d, C^{12}, $^{1}J_{CP}$ 177.8 Hz), 129.1, 129.2 (d, C^{14}, $^{3}J_{CP}$ 11.5 Hz), 130.2, 130.5 (d, C^{13}, $^{2}J_{CP}$ 9.9 Hz), 141.6, 141.7 (d, C^{15}, $^{4}J_{CP}$ 2.2 Hz), 155.0 (s, C^{2}), 155.6 (s, C^{4}). ^{31}P NMR (242.9 MHz) δ: 26.1. ^{15}N NMR (600.1 MHz, DMSO-d_6, 30 °C) δ: 53.3. MS (MALDI), *m*/*z*: 436 [M+H]$^+$. Found (%): C, 71.68; H, 6.99; N, 3.24; P, 7.09. Calc. for $C_{26}H_{30}NO_3P$ (%): C, 71.71; H, 6.94; N, 3.22; P, 7.11.

For detailed experimental procedures and characteristics of compounds **3b**,**c**, see Online Supplementary Materials.

¶ The X-ray diffraction data for the crystal of **4** were collected on a Bruker Apex Smart CCD diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å).

Crystal data for **4**: crystals of $C_{55}H_{66}N_2O_7P_2$ (M = 929.03) are triclinic, space group $P\bar{1}$, at 296 K: a = 10.338(4), b = 15.622(6) and c = 16.489(6) Å, α = 80.468(5), β = 80.247(5) and γ = 79.930(5)°, V = = 2558.6(16) Å^3, Z = 2, d_{calc} = 1.206 g cm^{-3}, μ(MoKα) = 0.138 mm^{-1}, F(000) = 992. Total of 18889 reflections were measured and 8963 independent reflections (R_{int} = 0.1477) were used in a further refinement. The refinement converged to wR_2 = 0.1960 and GOF = 0.803 for all independent reflections [R_1 = 0.0660 was calculated against F for 2698 observed reflections with $I > 2\sigma(I)$].

CCDC 1585981 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

polydentate ligands and potential biologically active substances. Further studies on the scope of this methodology are in progress in our group.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.019.

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Received: 6th February 2018; Com. 18/5470