COMMUNICATION

New and efficient approach to the synthesis of pentacoordinate spirobicyclic phosphoranes

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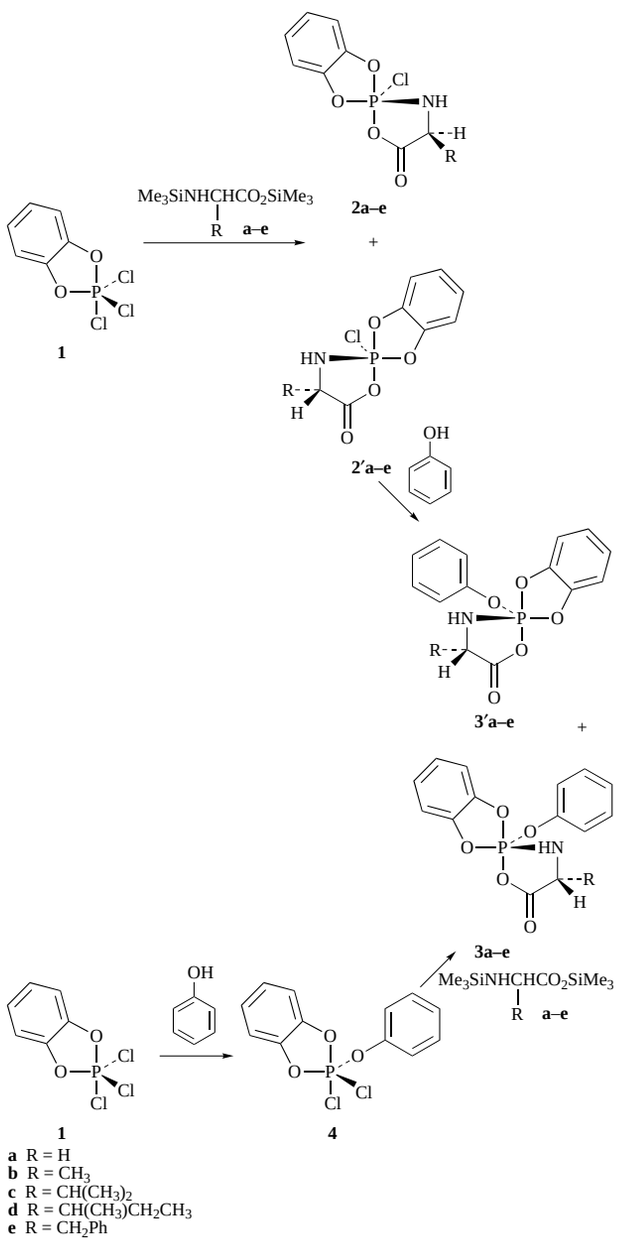
Pentacoordinate spirobicyclic 2-phenoxy-1,3-phenylenedioxo-1,3,2-imino(alkyl)acetoxyphosphoranes are synthesized through a new and efficient method whereby phosphorus pentachloride is displaced stepwise by catechol, an *N*,*O*-bis(trimethylsilyl)amino acid and phenol (pathway A) or catechol, phenol and an *N*,*O*-bis(trimethylsilyl)amino acid (pathway B); this method has advantages of high yields, rapid reaction times and easy operation, which might provide a new route for the synthesis of other pentacoordinate phosphoranes.

Since the 1960s, much attention has been paid to pentacovalent phosphorus compounds due to the stereochemistry and chemical reactivity associated with their biologically important phosphate esters.[1,2] For example, it was postulated that five-membered cyclic acyl phosphates could be intermediates in the reactions of phosphoenolpyruvate esters.[3,4] In our research group, a series of *N*-phosphoryl amino acids have been synthesized.[5–9] Previously, it was found that *N*-phosphoryl amino acids could catalyze many interesting bioorganic reactions under mild conditions.[10,11] For example, phosphoryl amino acids could autocatalyze to give peptides, esters, phosphoryl exchanged esters and phosphoryl group migration products—their reactivity being dependent on the amino acid side chains. An intramolecular pentacoordinate phosphoric–carboxylic mixed anhydride intermediate was considered as an important transient species.[10,11] In 1995, an interesting experiment involving silicon chemistry was applied to trap the pentacoordinate phosphorus moiety.[12] Since Lipmann had also proposed that the biosynthesis of proteins proceeded through a mixed phosphoric–carboxylic anhydride intermediate,[13] we thought it might be significant to synthesize the stable compounds. To our knowledge, the synthesis and characterization of the pentacoordinate spirobicyclic imino(alkyl)acetoxyphosphoranes have not been reported. In this paper, a series of these compounds was synthesized using phosphorus pentachloride.

Two synthetic pathways leading to the pentacoordinate spirobicyclic 2-phenoxy-1,3-phenylenedioxo-1,3,2-imino(alkyl)-acetoxyphosphoranes† are shown in Scheme 1. Pathway A: under a nitrogen atmosphere at 25 °C 1 equiv. of the *N*,*O*-bis(trimethylsilyl)amino acid **a**–**e**[14] in benzene or dichloromethane respectively, was added dropwise to a benzene or dichloromethane solution of 2,2,2-trichloro-1,3,2-benzodioxaphosphole[15] and stirred continuously. A few minutes later, the 2-chloro-1,3-phenylenedioxo-1,3,2-imino(alkyl)acetoxyphosphorane **2**,**2′a**–**e** was obtained. The reaction could be traced by ^{31}P NMR spectroscopy. For example, the starting material **1** showed a signal at δ_P −26.23 which quickly changed into two peaks at δ_P −29 and −31 (diastereoisomers **2** and **2′**) because of the introduction of the amino acid chiral carbon atom. When **1** completely disappeared, 1 equiv. of phenol was added dropwise



Scheme 1 Synthetic pathways to pentacoordinate spirobicyclic imino(alkyl)acetoxyphosphorane

† IUPAC name: 2-phenoxy-2.7[5]-spiro[1,3,2-benzodioxaphosphole-2,2′-1,3,2-oxazaphospholan]-5′-one.

into the reaction mixtures to give **3**,**3′a–e** quantitatively. Because **1** has a five-membered ring, reaction to form a spirobicycle system was favored.

Pathway B: under a nitrogen atmosphere at 25 °C 1 equiv. of phenol in benzene or dichloromethane was added dropwise to a benzene or dichloromethane solution of 2,2,2-trichloro-1,3,2-benzodioxaphosphole and stirred continuously. A few minutes later, 2,2-dichloro-2-phenoxy-1,3,2-benzodioxaphosphole **4** was quantitatively obtained, showing one peak in the ^{31}P NMR spectrum at δ −34.13. Then an *N*,*O*-bis(trimethylsilyl)amino acid **a–e** was added to the reaction mixture to give **3**,**3′a–e**. Compounds **3**,**3′a–d** were crystallized from dichloromethane–diethyl ether (1:5) while **3**,**3′e** was recrystallized from benzene, to give the products, in some cases, as white solids; yields: 63–71% (pathway A); 74–83% (pathway B).

Since the P–O bond of the anhydride P–O–CO moiety was longer than expected in the pentacoordinate phosphorane,[16] it implies that this is the apical bond. Indeed, each of the compounds **3**,**3′a–e** had a large $^{2}J_{\mathrm{P-OCO}}$-value. Because glycine has no chiral carbon, **2a**,**2′a** only showed one peak in the ^{31}P NMR spectrum at δ_{P} −27.89, and their derivatives **3a**,**3′a** also showed only one peak at δ_{P} −42.02. The anhydride POC=O bond is of high energy,[17] and consequently yields a peptide bond when the amino group of an amino acid attacks the carboxy group of the anhydride. Hence, the pentacoordinate imino(alkyl)acetoxyphosphoranes might be intermediates in protein biosynthesis and could have potential in polypeptide synthesis. In summary, the high yields, rapid reactions and easy availability of the starting materials and reagents render this synthesis an efficient process.

Experimental

^{1}H, ^{13}C, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY NMR spectra were recorded on a Bruker AM-500 spectrometer at 500 MHz in $CDCl_3$ solvent with chemical shifts referenced to $CDCl_3$ ($\delta_{\mathrm{H}} = 7.24$, $\delta_{\mathrm{C}} = 77$). *J* Values are given in Hz. ^{31}P NMR spectra were determined by a Bruker AM-200 spectrometer at 200 MHz using 85% H_3PO_4 ($\delta_{\mathrm{P}} = 0$) as an external standard. Elemental analyses were carried out on a Carlo Erba 1106 CHN analyzer. Field desorption mass spectra were obtained on a Finnigan MAT 90 double-focusing mass spectrometer.

The preparation of compound **3**,**3′c** is given as an example.

Pathway A

To a stirred solution of **1** (1.23 g, 5 mmol) in anhydrous benzene (15 ml) at room temperature under a nitrogen atmosphere was added dropwise *N*,*O*-bis(trimethylsilyl)valine (1.31 g, 5 mmol) in benzene (10 ml). After 10 min, 0.5 ml of the mixture was withdrawn and its ^{31}P NMR spectrum was taken (δ_{P} **1**: −26.23; **2c**,**2′c**: −29.39, −29.92). Phenol (0.47 g, 5 mmol) in benzene (10 ml) was then added dropwise to the mixture. After 10 min the precipitate was filtered off, the solvent and trimethylchlorosilane were removed by rotary evaporation, and the remaining solution (*ca.* 1 ml), was diluted with dry diethyl ether (5 ml). A white precipitate appeared which was filtered off, and the filtrate was washed three times with dry diethyl ether and dried *in vacuo* over P_2O_5 at 39 °C for 5 h to afford **3**,**3′c** (2.32 g, 67%).

Pathway B

To a stirred solution of 2,2,2-trichloro-1,3,2-benzodioxaphosphole (1.23 g, 5 mmol) in anhydrous benzene (15 ml) at room temperature under a nitrogen atmosphere was added dropwise phenol (0.47 g, 5 mmol) in benzene (10 ml). After 10 min, 0.5 ml of the mixture was withdrawn and its ^{31}P NMR spectrum was taken (δ_{P} **1**: −26.23; **4**: −34.13). *N*,*O*-Bis(trimethylsilyl)valine (1.31 g, 5 mmol) in benzene (10 ml) was then added dropwise to the mixture. After 10 min the reaction was worked-up as for Pathway A. Isolated yields and purities were similar to pathway A. Yield of **3**,**3′c**: 2.56 g, 74%; mp 148–150 °C (Found: C, 58.75; H, 5.18; N, 4.05. $C_{17}H_{18}NO_5P$ requires C, 58.79; H, 5.19; N, 4.03%); δ_{H} 0.92 (d, 3 H, 17-CH_3), 0.99 (d, 3 H, 18-CH_3), 1.10 (m, 6 H, 17′- and 18′-CH_3), 2.18 (m, 1 H, 16-CH), 2.26 (m, 1 H, 16′-H), 3.76 (d, 1 H, 13-NH, $^{2}J_{\mathrm{PNH}}$ 16.19), 3.81 (d, 1 H, 13′-NH, $^{2}J_{\mathrm{PNH}}$ 16.19), 3.87 (m, 1 H, 14-CH), 3.88 (m, 1 H, 14′-CH), 6.56–6.68 (dd, 2 H, 1,1′-Ph), 6.81–6.94 (m, 8 H, 2,2′,3,3′-Ph, 7,7′,11,11′-Ph), 7.07–7.13 (m, 4,4′-Ph, 9,9′-Ph) and 7.21–7.23 (m, 8,8′,10,10′-Ph); δ_{C} 16.21 (17-CH_3), 16.86 (17′-CH_3), 18.61 (18-CH_3), 19.15 (18′-CH_3), 31.04 (d, 16-CH), 31.12 (d, 16′-CH), 60.45 (14-CH), 60.54 (14′-CH), 109.92 (d, 1-Ph), 110.08 (d, 1′-Ph), 111.47 (d, 4-Ph), 111.60 (d, 4′-Ph), 120.78 (3,3′,7,7′,11,11′-Ph), 123.51 (2,2′-Ph), 124.89, 125.10 (9,9′-Ph), 129.26, 129.47 (8,8′,10,10′-Ph); 142.22 (5,5′-Ph), 144.96 (6,6′-Ph), 152.06 (12,12′-Ph), 167.99, 168.17 (dd, 15,15′-CO-, $^{2}J_{\mathrm{P-C}}$ 17.95); δ_{P} −44.64 and −44.83; *m*/*z* (FDMS) 347 (M^+).

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