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The microwave-assisted synthesis of a 2-carboxyphosphole

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Abstract

Using a one-pot four-step reaction a readily available phospholide was converted efficiently to a 2-carboxyphosphole. This compound can be used as a building block for the synthesis of phosphole-containing peptides, where the phosphole can serve as a coordination site for late transition metals and may affect the secondary structure of the peptide.

Keywords: Phosphorus heterocycles; Sigmatropic rearrangement; P Ligands; Microwave-assisted synthesis

The coordination chemistry of phospholes with late transition metals such as platinum, rhodium or palladium has found widespread application in transition metal catalysis.[1–4] Our research is focussed on the development of new biocompatible catalysts. To achieve this, we are trying to incorporate phospholes into polypeptide chains. Such non-natural polypeptides might find applications in highly specialised, enantioselective catalysis of reactions quite uncommon to native enzymes.[5]

Phospholes can be conveniently synthesised via the McCormack synthesis involving the reaction of an aryldihalophosphine with a diene. This synthesis is however not compatible with many functional group substituents.[6] Functionality is, therefore, more conveniently introduced through nucleophilic or electrophilic substitution reactions at the P atom.[7] Using a nucleophilic substitution reaction, we recently synthesised the first phosphole-containing amino-acid,[8] and incorporated this into a cyclic decamer whose coordination properties are under current investigation.[9]

As an extension of that Letter, we describe the synthesis of a 2-carboxyphosphole inspired by proline. In this design, which is similar to the phospholane carboxylic acid described by Kobayashi and co-workers,[10,11] the five-membered ring of proline is replaced by the phosphole ring. The rigid structure of this molecule, and the bulky phenyl group on the 5-position, could make it a suitable turn-inducer in a polypeptide[12] whilst the lone-pair on the phosphorus makes it a good ligand for late transition metal centres.

Ideally, it should be possible to integrate our phosphole building block into a standard peptide synthesis. We, therefore, designed phosphole **1** (Fig. 1) to be compatible with Fmoc-based peptide synthesis, where the building-blocks possess a free acid functionality and an amine protected by a base-labile protecting group (**2**).[13] For a phosphole, the synthetic equivalent of the deprotonated amine is the phospholide anion. This anion can be masked conveniently through alkylation with bromopropionitrile to give a stable cyanoethyl phosphole.[14] The phospholide can be regenerated with a strong base such as *t*BuOK at room temperature releasing acrylonitrile as the side-product.[15]

The one-pot, four-step synthesis of **7** from readily available **3**, and its subsequent conversion to target compound **1**, is detailed in Scheme 1. We recently reported on the facile, large-scale synthesis of phospholide **3**.[16] On reaction with Boc_2O, this phospholide yields the expected phosphole **4**, which shows a ^{31}P NMR chemical shift at

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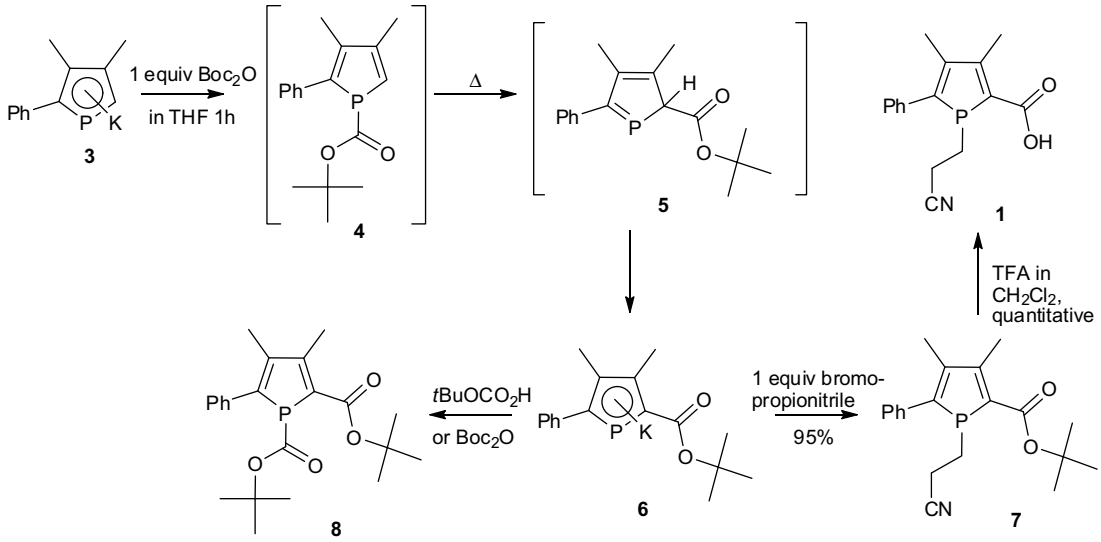


Scheme 1. The four-step, one-pot synthesis of phosphole **7** and its transformation to target compound **1**. Phosphole **8** is formed as a side-product when the heating is not carried out in a microwave or excess Boc_2O is used.

8.7 ppm. Heating the reaction mixture containing compound **4** prompts a[1,5] shift of the ester group, but neither intermediate **5**, nor the cyclodimer formed by a Diels–Alder reaction with itself, were observed. Instead, the reaction proceeded directly to phospholide **6**, which shows a ^{31}P NMR chemical shift at 104 ppm. This is probably because tBuOCO$_2$K, formed in situ in the first step of the reaction, is effecting the deprotonation of **5** to yield **6**.[17] However, when refluxing the reaction mixture in an oil bath a side-product **8**, with a ^{31}P NMR shift at 16.7 ppm, was observed. This compound, which forms even when a deficiency of Boc_2O is employed, can be isolated as the only product when the reaction is carried out using excess Boc_2O. We, therefore, reasoned that it must be formed through a reaction of tBuOCO$_2$H or Boc_2O with phospholide **6**.

To avoid this problem, one could decide to isolate phosphole **4** and then heat it in the presence of tBuOK to yield the desired phospholide. In a more elegant one-pot approach, side-product formation can be prevented when the tBuOCO$_2$K is decarboxylated to give tBuOK and CO_2 in situ. In this case, the tBuOK can act as the base to deprotonate **5**, but the reaction with phospholide **6** to form a side-product cannot take place. We found that when promoting the [1,5]-functional group shift under microwave irradiation (300 W, 100 °C), phospholide **6** was the sole product, and side product **8** was not observed.

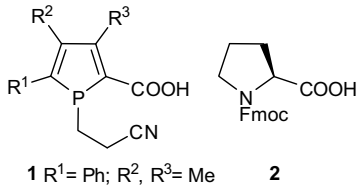


Fig. 1. Phosphole **1** compared to *N*-Fmoc-proline **2**.

It appears that under these conditions the decarboxylation takes place at the same time as the functional group shift.

Quenching phospholide **6** with bromopropionitrile gives the expected phosphole **7** which shows a ^{31}P NMR chemical shift at 6.1 ppm. This phosphole is stable at room temperature and not particularly prone to air oxidation. After filtration through a short silica column, the product was treated with TFA to give the target compound **1**. Since compounds **1** and **7** may be oxidised by air over time they are best stored and handled under nitrogen. Should the oxides, with ^{31}P NMR chemical shifts at 48.2 and 44.6 ppm, respectively, form, they can easily be reconverted to the phospholes by heating in CH_2Cl_2 with excess phenylsilane for several hours,[18] monitoring the progress of the reaction by ^{31}P NMR.

Single crystals of **1** suitable for X-ray analysis were obtained by the slow evaporation of a methanol solution. A displacement ellipsoid plot of a single molecule of **1** is shown in Figure 2 and significant bond lengths are listed in the corresponding legend. Crystal data and structural refinement details are presented in the Supplementary data.

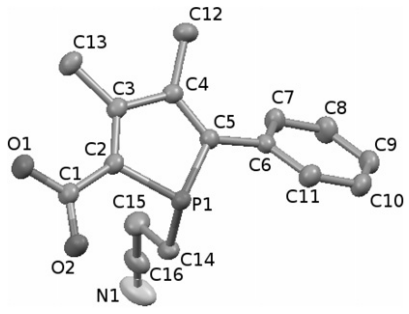
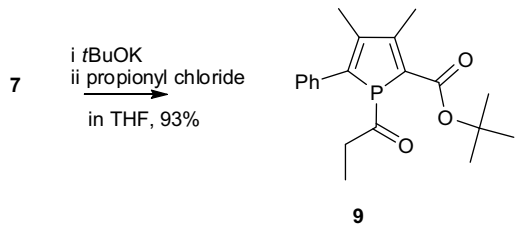


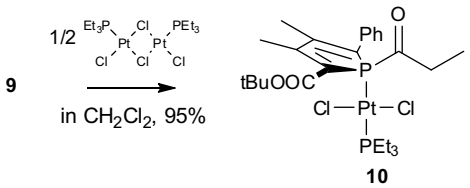
Fig. 2. Displacement ellipsoid plot (50%) of compound **1** CCDC 673227. H omitted for clarity. Significant bond lengths: P(1)–C(2) 1.796(1), P(1)–C(5) 1.800(1), C(2)–C(3) 1.367(2), C(3)–C(4) 1.471(2), C(4)–C(5) 1.364(2) Å.



Scheme 2. Conversion of phosphole **7** to model compound **9**.

Fmoc-based peptide synthesis involves the deprotection of the Fmoc-protected amine followed by reaction with an activated carboxylic acid. To test the suitability of compound **1** for integration into a polypeptide, we studied its reactivity under similar conditions. Unlike the Fmoc protection group, we found that the cyanoethyl moiety was stable towards piperidine. It can however be cleaved with a stronger base. For example, when 1 equiv of *t*BuOK was added to **7** in THF at room temperature, phospholide **6** was rapidly observed by ^{31}P NMR and the reaction was complete within 10 min. Upon reaction with propionyl chloride, product **9**, with a ^{31}P NMR chemical shift at 36.8 ppm, was readily isolated (Scheme 2). This compound is a model for the phosphole integrated in a polypeptide, containing a 1-carbonyl phosphole system as an amide bond surrogate. A reaction between **6** and *N*-Boc glycine, activated using isobutyl chloroformate in the presence of *N*-methylmorpholine, gave a product with a similar ^{31}P NMR chemical shift at 32.1 ppm. Unfortunately, this product was not isolated due to stability problems during purification. Although a strong base such as *t*BuOK may cause racemisation of neighbouring amino acids, these reactions demonstrate the compatibility of phosphole **1** with Fmoc-based solid phase peptide synthesis.

To evaluate the coordination behaviour of the 1-carbonyl phosphole system, compound **9** was reacted with a number of transition metal precursors including palladium, nickel, gold and platinum. For each metal precursor, we observed the disappearance of the free ligand signal and the appearance of new signals assigned to the transition metal complexes. In particular, the Pt(II) complex, formed by reaction with $[PtCl_2(PEt_3)]_2$, demonstrated unambiguously the coordination of the phosphole via its phosphorus atom (Scheme 3). The two resonances, which appeared at 13.6 ppm and 45.9 ppm in the ^{31}P NMR spectrum for the phosphine and the phosphole, respectively, showed a large doublet ($^2J_{pp}$ of 440 Hz), which indicates that the two phosphorus ligands in complex **10** adopt a trans-configuration.[19,20] They also show platinum satellites (J_{PtP} of 2855 Hz), which are quite typical for PEt_3 and a relatively small coupling of 2233 Hz for the phosphole.



Scheme 3. Coordination of $[PtCl_2(PEt_3)]_2$ to ligand **9** yielding complex **10**.

In summary, we have described the synthesis and characterisation of a 2-carboxyphosphole that is suitable for introduction into the backbone of a polypeptide chain. A substituted phosphole moiety in a polypeptide can have a two-fold functionality. Firstly, the phosphorus lone pair can coordinate to a transition metal. This was illustrated by the coordination of several transition metal ions (Pd, Pt, Ni and Au) to model compound **9**. Secondly, and analogous to proline, the rigid structure of the phosphole ring may serve as a folding element, introducing a secondary structure in a polypeptide. Phosphole **1**, therefore, opens up possibilities for the synthesis of new, biocompatible ligands for transition metal catalysts.

Acknowledgement

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Supplementary data

Experimental details and crystallographic tables for **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.075.

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