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Synthesis of the first pseudo-phosphonopeptides derived from (ferrocenyl)aminomethanephosphonous acids

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Abstract—The first example of the condensation of (ferrocene)-*N*-benzhydrylamino-methanephosphonous acid (**1**) with α-amino acids **2a**–**d** and several model dipeptides **4a**–**d** and the tripeptide DL-alanyl-DL-leucinyl-glycine (**4e**) in the presence of DCC resulted in pseudo-phosphono-dipeptides **3a**–**d** and pseudo-phosphono-oligopeptides **5a**–**d**. The probable chiral assistance of the incoming amino acid or peptide in the formation of the new chiral center on phosphorus was also a feature of this method.
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Phosphonopeptides have been discussed significantly in the literature.[1,2] It has been demonstrated that they are of interest as plant protection agents[3] and as antibiotics.[4] On the other hand, ferrocene-derived compounds are characterized by their ability to form metal-centered redox systems to generate oxidized or reduced forms with different properties and they have been widely employed in various fields such as molecular recognition as biosensors,[5–9] in polymer science as redox active dendrimers[10] and in pharmacology.[11] Successful syntheses of amino acids bearing a ferrocene moiety have also been accomplished.[12–14] Ferrocenyl amino acids have found application in food chemistry as a possible substitute for phenylalanine in the commercial sweetener aspartame.[13]

In our studies concentrating on ferrocenes bearing phosphonyl groups, we were interested in ferrocene-derived alkylaminomethanephosphonous acids.[15,16] Their properties are very interesting, and we condensed them with various alcohols or amines such as cholesterol and adenosine,[16] as well as polyglycols and polyamines.[17] Good results from these condensations prompted us to investigate the synthesis of pseudo-peptides of ferrocene-derived alkylaminomethanephosphonous acids bearing a P(O)–N bond.

To our knowledge, this is the first example of the condensation of α-aminophosphonous acids with α-amino acids in the presence of DCC, however, some examples of similar condensations with aminophosphonic acids have been noted.[18–23]

We chose (ferrocene)-*N*-benzhydrylaminomethanephosphonous acid (**1**) for this synthesis, for the reasons discussed in detail in our previously reported work[16] and this compound was synthesized following the method described therein.

The condensation was initially performed with esters of several amino acids; as model compounds we employed glycine methyl ester (**2a**), alanine methyl ester (**2b**), phenylalanine ethyl ester (**2c**) and leucine methyl ester (**2d**) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) was used as the condensing agent (Scheme 1). The reactions were carried out in dichloromethane and gave the corresponding pseudo-dipeptides **3a**–**d** in satisfactory yields. The results are collected in Table 1. Amino acid esters **2a**–**d** are commercially available as their hydrochlorides, thus triethylamine was added to their solutions in dichloromethane to convert them into the free esters. The precipitated triethylammonium chloride was removed by filtration. When the reactions were complete, traces of triethylammonium chloride were removed by washing with dilute aqueous hydrochloric acid.

Keywords: Condensation; (Ferrocene)aminomethanephosphonous acid; Amino acids; Dipeptides.

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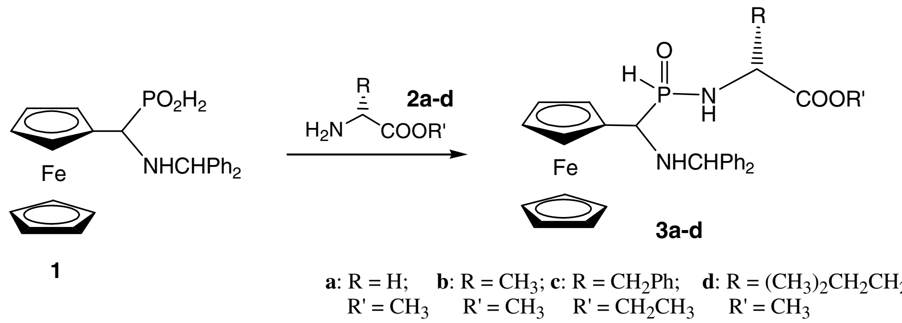


Scheme 1.

Table 1. Reaction of (ferrocene)-*N*-benzhydrylaminomethanephosphonous acid (**1**) with α-amino acids esters **2a**–**d** and oligopeptides **4a**–**e** in the presence of DCC

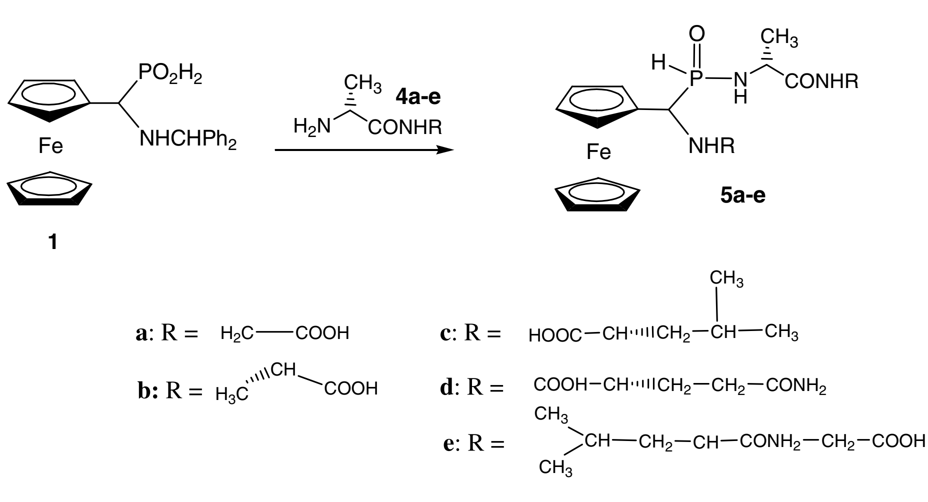
Product	Yield (%)	^{31}P NMR data[a]	Method[18]
3a	69	24.36; 22.32	Acid **1** + DCC in CH_2Cl_2 then **2a**
3b	75	25.34; 24.14; 23.57; 21.96 (2:2:1:1)	Acid **1** + DCC in CH_2Cl_2 then **2b**
3c	84	25.96; 24.30; 23.60; 21.84 (2:2:1:1)	Acid **1** + DCC in CH_2Cl_2 then **2c**
3d	86	25.75; 24.86; 23.93; 21.92 (2:2:1:1)	Acid **1** + DCC in CH_2Cl_2 then **2d**
5a	68	24.45; 23.83	Acid **1** + DCC in MeCN then **4a**
5b	61	24.45; 23.77	Acid **1** + DCC in MeCN then **4b**
5c	60	24.09; 23.73	Acid **1** + DCC in MeCN then **4c**
5d	85	24.47; 23.81	Acid **1** + DCC in MeCN then **4d**
5e	89	24.29 (very large signal)	Acid **1** + DCC in MeCN then **4e**

[a] ^{31}P NMR recorded in $CDCl_3$ at 81 MHz.

The condensation was then performed with several model dipeptides: alanyl-glycine (Ala-Gly) (**4a**), alanyl-alanine (Ala-Ala) (**4b**), alanyl-leucine (Ala-Leu) (**4c**), alanyl-glutamine (Ala-Gln) (**4d**) and the tripeptide DL-alanyl-DL-leucinyl-glycine (**4e**) in acetonitrile with DCC as the condensing agent (Scheme 2). As a result, pseudo-oligopeptides **5a**–**e** were obtained in fair yields. The results are collected in Table 1.

The pseudo-peptides **3a**–**d** and **5a**–**e** obtained were too sensitive toward silica gel or aluminum oxide, so that column chromatography could not be used as a purification method. However, slow crystallization from an ethyl acetate–hexane mixture enabled pure pseudo-peptides to be obtained.

The starting acid **1** used for the reaction was a racemic mixture. In the course of the reaction, a new chiral center at phosphorus was formed. All optically active amino acid esters **2b**–**d** and dipeptides **4a**–**d** demonstrated chiral induction, so that the reactions were diastereoselective. In the case of pseudo-peptides **3b**–**d**, four diastereoisomers were formed, two in excess (dr ratio 2:2:1:1). In the case of pseudo-peptides **5a**–**d**, only two diastereoisomers were formed in a 1:1 ratio, however, four were expected. The reaction of glycine methyl ester



Scheme 2.

2a resulted in the formation of the two expected diastereoisomers **3a** but as a racemic mixture.

In conclusion, we have developed the first example of the condensation of α-aminophosphonous acids with α-amino acids in the presence of DCC.[24] Investigations toward separation of the diastereomers are now being undertaken in this laboratory.

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24. *General procedure for the preparation of* **3a**–**d**. Acid **1** (2.5 mmol) was suspended in CH_2Cl_2 and then DCC (3 mmol) was added and the mixture stirred for 0.5 h. Simultaneously, a solution of amino acid ester **2a**–**d** (2.5 mmol) in CH_2Cl_2 was mixed with triethylamine (2.5 mmol) and the salt formed was removed by filtration. The filtrate was then added to the suspension. The whole mixture was refluxed for 3–4 days, then filtered to remove dicyclohexyl urea and the filtrate was washed with dilute aqueous HCl to remove traces of triethylammonium chloride. The organic fractions were dried and then evaporated and the residue was recrystallized from EtOAc–hexane mixture (10:1).