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Amino Acids in Catalytic Synthesis of α-Aminophosphonates

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Abstract—The reaction of acetophenone with chiral α-amino acids and their esters has been studied in catalytic one-pot three-component synthesis of α-aminophosphonates. α-Aminophosphonates are found to form mixtures of diastereomers in high yields.

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Glutamate receptors, neurotransmitters, are essential biological targets in medicinal chemistry. 1-Aminoindane-1,5-dicarboxylic acid is a selective antagonist of metabotropic glutamate receptors. The bioisosteric substitution of a phosphonate group for carboxyl generates ligands of metabotropic glutamate receptors [1, 2], which can have an analogous antagonistic activity. Some oligopeptides are known to improve the cognitive functions of brain [3]; one such oligopeptide (Semax peptide) is used in medical practice.

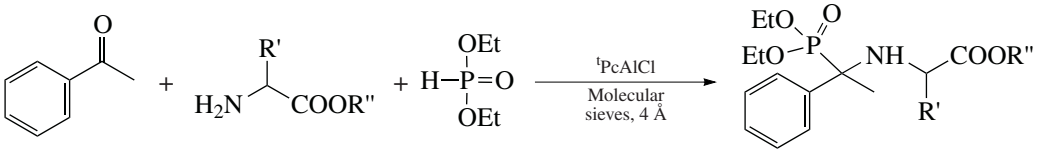
This work was intended to synthesize a potential dual drug that combines oligopeptide and aminophosphonate moieties. To achieve this, we used the previously proposed one-pot three-component (carbonyl compound, amine, and diethyl phosphite) catalytic synthesis of α-aminophosphonates with metal *tert*-butylphthalocyanines as catalysts [4, 5]. Acetophenone was used as an example to study the utility of amino acids and their esters as the amine component in this reaction (Scheme).

α-Aminophosphonate synthesis on the basis of some amino acids have been described [6, 7]. However, the classical Kabachnik–Fields reaction proceeds only for formaldehyde. Attempts to carry out this reaction with aliphatic aldehydes and ketones failed [6, 7].

Some ketones in three-component catalytic synthesis [8] react with amino acid ethyl esters to yield α-aminophosphonates; however, the major process is the cyclization of two amino acid ester molecules to form diketopiperazine. Amino acid *tert*-butyl esters, in which steric hindrances inhibit cyclocondensation, avoid this side process. For acetophenone, this reaction was studied in various solvents, and methylene chloride and methanol were the best solvents. Acetophenone with alanine *tert*-butyl ester or phenylalanine *tert*-butyl ester in methylene chloride at room temperature yields desired aminophosphonates **1** and **2** with 95 and 80% yield, respectively (table).

Not only amino acid esters but also amino acids enter this reaction. However, the reaction of acetophenone with alanine (phenylalanine) and diethyl phosphite was carried out in 2,2,2-trifluoroethanol because of the low solubility of the amino acids in methylene chloride and even in methanol. As a result, the desired α-aminophosphonates **3** and **4**, with a free carboxyl, were obtained. Along with the desired aminophosphonates **3** and **4**, this reaction produces their 2,2,2-trifluoroethyl esters as a result of esterification of the aminophosphonate carboxy group by trifluoroethanol.

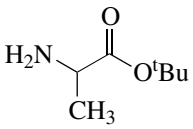
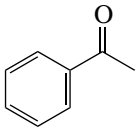
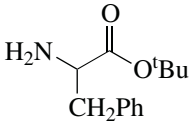
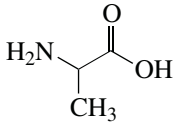
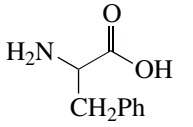
The structures of α-aminophosphonates were verified by IR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra. Because we used chiral amino acid esters, products **1**–**4** were mixtures of diastereomers (table), and all signals in the ^{31}P, ^{1}H, and ^{13}C NMR spectra are doubled.



1 R'=CH_3, R"=t-Bu
2 R'=CH_3, R"=H
3 R'=CH_2Ph, R"=t-Bu
4 R'=CH_2Ph, R"=H

Scheme.

Amino acids (esters) and α-aminophosphonate yields

Amino acid or amino ester	Carbonyl compound	Reaction parameters: solvent, reaction time (h)	α-Aminophosphonate no.	Yield, %
		CH_2Cl_2, 24	**1**	95
		CH_2Cl_2, 48	**2**	80
		CF_3CH_2OH, 120	**3**	60
		CF_3CH_2OH, 120	**4**	55

All α-aminophosphonates synthesized have two signals in the ^{31}P NMR spectra at 25.49–26.24 ppm associated with the dialkylaminophosphate groups of diastereomers.

Thus, it was demonstrated for acetophenone that its three-component reaction with α-amino acids and diethyl phosphite in the presence of ^{t}PcAlCl can serve as a convenient route to phosphorylated derivatives of α-amino acids on the basis of aromatic ketones.

EXPERIMENTAL

^1H NMR spectra (400.13 MHz), ^{13}C NMR spectra (100.61 MHz), and ^{31}P NMR spectra (161.98 MHz) were recorded in $CDCl_3$ on a Bruker Avance 400 instrument relative to internal tetramethylsilane (^1H, ^{13}C) or external 85% H_3PO_4 (^{31}P). IR spectra were measured on a UR-20 instrument in CCl_4. Elemental analysis was carried out on a Vario-II CHN analyzer; chromatographic separation, on columns packed with Merck 60 silica gel (70–230 mesh ASTM).

Synthesis of α-aminophosphonates **1** and **2** (the general procedure) was a follows. To a solution of amino acid ester hydrochloride (3.1 mmol) in water (40 mL), added was sodium hydroxide (3.3 mmol). The mixture was extracted three times with methylene chloride (20-mL increments) in a separatory funnel; the supernatant was separated and stored over anhydrous sodium sulfate. Then, sodium sulfate was filtered; the filtrate was concentrated in vacuo.

To a solution of the amino acid ester prepared as above (3 mmol) in methylene chloride (3 mL), acetophenone (2 mmol), added were 4-Å molecular sieves, and ^{t}PcAlCl (0.1 mmol). The reaction mixture was magnetically stirred for 3 h; then, diethyl phosphite (3 mmol) was added. The reaction course was monitored with thin-layer chromatography (the reaction duration is indicated in the table).

Molecular sieves were filtered off and then washed with CH_2Cl_2–MeOH (10 : 1, 3 × 2 mL). The filtrate was concentrated in vacuo, the residue was dissolved in minimum CH_2Cl_2–MeOH (50 : 1) and chromatographed on a silica gel-packed column (length, 20 cm; diameter, 2.5 cm) with CH_2Cl_2–MeOH (50 : 1) as an eluent.

*tert-Butyl N-{1-(Diethoxyphosphoryl)-1-phenylethyl} Alaninate (**1**)*

Yield: 95%; R_f = 0.62 ($CHCl_3$/MeOH, 10 : 1).

For $C_{19}H_{32}NO_5P$ anal. calcd. (%): C, 59.17; H, 8.39; N, 3.65. Found (%): C, 59.35; H, 8.40; N, 3.65.

^1H NMR spectrum (δ, ppm; *J*, Hz): 1.12, 1.17, 1.27, 1.37 (all t, 6H, 2Me, POEt, *J* = 7.0); 1.21, 1.25 (both d, 3H, Me Ala, *J* = 7.0); 1.31, 1.41 (both s, 9H, 3Me, ^{t}Bu); 1.68, 1.74 (both d, 3H, Me, $^2J_{H,P}$ = 16.3, $^2J_{H,P}$ = 16.7); 2.90 (br m, 1H, NH); 2.97, 3.27 (both q, 1H, Ala, *J* = 6.9), 3.75–4.15 (m, 4H, $2OCH_2$; 7.18–7.36, 7.54–7.61 (both m, 5H, arom.).

^{31}P NMR spectrum (δ, ppm): 25.72.

^{13}C NMR spectrum (δ, ppm; *J*, Hz): 16.18, 16.28 (both d, Me, POEt, $^3J_{C,P}$ = 5.4); 19.89, 20.86 (both s, Me, Ala); 21.29, 22.04 (both s, Me); 27.68, 27.75 (both s, Me, ^{t}Bu); 51.51, 53.30 (both d, CH, Ala, *J* = 13.4, *J* = 13.4); 58.81, 59.99 (both d, C(1), $^1J_{C,P}$ = 150.4, $^1J_{C,P}$ = 155.8); 62.97–63.21 (m, OCH_2), 80.49, 80.53 (both s, C, ^{t}Bu); 127.13, 127.83, 128.27, 140.31 (C_{arom}); 175.24, 175.35 (both s, C=O, Ala).

IR spectrum, ν (cm^{-1}): 1250 (P=O); 1730 (C=O); 3340, 3450 (NH).

*tert-Butyl N-{1-(Diethoxyphosphoryl)-1-phenylethyl} Phenylalaninate (**2**)*

Yield: 80%; R_f = 0.68 ($CHCl_3$/MeOH, 10 : 1).

For $C_{25}H_{36}NO_5P$ anal. calcd. (%): C, 65.03; H, 7.88; N, 3.03. Found (%): C, 65.22; H, 7.92; N, 3.21.

^{1}H NMR spectrum (δ, ppm; *J*, Hz): 1.08, 1.17, 1.19, 1.25 (all t, 6H, 2Me, POEt, *J* = 7.0); 1.15, 1.31 (both d, 9H, 3Me, ^{t}Bu); 1.63, 1.70 (both d, 3H, Me, $^2J_{H,P}$ = 16.7, $^2J_{H,P}$ = 16.3); 2.80 (br m, 1H, NH); 2.82–2.94 (m, 2H, Phe); 3.13, 3.53 (both t, 1H, Phe, *J* = 7.1, *J* = 6.9); 3.63–4.11 (all m, 4H, $2OCH_2$); 7.13–7.18, 7.20–7.33, 7.56–7.58 (all m, 5H, arom.).

^{31}P NMR spectrum (δ, ppm): 25.49, 25.64.

^{13}C NMR spectrum (δ, ppm; *J*, Hz): 16.22–16.48 (m, Me, POEt); 20.15, 21.24 (both s, Me); 27.63, 27.73 (both s, Me, ^{t}Bu); 41.84, 42.06 (both s, CH_2, Phe); 57.45, 57.92 (both d, CH, Phe, $^3J_{C,P}$ = 13.2, $^3J_{C,P}$ = 16.1); 59.79, 60.81 (both d, C(1), $^1J_{C,P}$ = 156.7, $^1J_{C,P}$ = 152.2); 62.91—63.20 (m, OCH_2); 80.78, 80.84 (both s, α-C, ^{t}Bu); 126.46, 127.19, 127.31, 127.87, 128.01, 128.11, 128.42, 129.86, 137.57, 137.90, 138.67, 140.32 (C_{arom}); 174.18, 175.36 (both s, C=O, Phe).

IR spectrum, ν (cm^{-1}): 1250 (P=O); 1730 (C=O); 3340, 3450 (NH).

α-Aminophosphonates **3** and **4** were prepared as follows. To a solution of the carbonyl compound (2 mmol) in a solvent (4 mL), added were amino acid (2.2 mmol), 4-Å molecular sieves (500 mg), ^{t}PcAlCl (0.1 mmol), and the catalytic triethylamine amount (0.2 mmol). The reaction mixture was refluxed for 3 h; then, diethyl phosphite (3 mmol) was added. The reaction course was monitored by thin-layer chromatography (the reaction duration is indicated in the table). Subsequent treatment was as specified in the general procedure.

*N-{1-(Diethoxyphosphoryl)-1-phenylethyl}alanine (**3**)*

Yield: 60%; R_f = 0.46 ($CHCl_3$/MeOH, 10 : 1).

^{1}H NMR spectrum (δ, ppm; *J*, Hz): 1.16, 1.18, 1.32, 1.39 (all t, 6H, 2Me, POEt, *J* = 7.1); 1.37, 1.41 (both d, 3H, Me, Ala, *J* = 7.3); 1.73, 1.81 (both d, 3H, Me, $^2J_{H,P}$ = 16.0, $^2J_{H,P}$ = 16.4); 3.20, 3.48 (both q, 1H, Ala, *J* = 7.1); 3.75–4.12 (m, 4H, OCH_2); 7.09 (br m, 2H, NH, OH); 7.21–7.62 (m, 5H, arom.).

^{31}P NMR spectrum (δ, ppm): 25.93, 26.07.

^{13}C NMR spectrum (δ, ppm; *J*, Hz): 16.18–16.35 (m, Me, POEt); 19.36, 20.13 (both s, Me, Ala); 21.76, 22.24 (both s, Me); 52.29, 54.59 (both d, CH, Ala, *J* = 13.4, *J* = 15.2); 58.71, 59.34 (both d, C(1), $^1J_{C,P}$ = 151.2, $^1J_{C,P}$ = 155.7); 63.13–63.59 (m, OCH_2); 127.31, 127.41, 127.98, 128.21, 139.86, 139.75 (C_{arom}); 177.38, 177.43 (both s, C=O, Ala).

IR spectrum, ν (cm^{-1}): 1250 (P=O); 1720 (C=O); 2400–3500 (OH), 3300, 3420 (NH).

*N-{1-(Diethoxyphosphoryl)-1-phenylethyl}phenylalanine (**4**)*

Yield: 55%; R_f = 0.52 ($CHCl_3$/MeOH, 10 : 1).

^{1}H NMR spectrum (δ, ppm; *J*, Hz): 1.13, 1.19, 1.22, 1.26 (all t, 6H, 2Me, POEt, *J* = 7.0); 1.53, 1.67 (both d, 3H, Me, $^2J_{H,P}$ = 16.6, $^2J_{H,P}$ = 16.3); 2.71–2.83 (m, 2H, Phe); 3.10–3.30 (m, 1H, Phe); 3.63–4.00 (m, 4H, $2OCH_2$); 6.32 (br m, 2H, NH, OH); 7.09–7.51 (m, 10H, arom).

^{31}P NMR spectrum (δ, ppm): 25.76, 26.24.

^{13}C NMR spectrum (δ, ppm; *J*, Hz): 16.20, 16.25 (both d, Me, POEt, $^3J_{C,P}$ = 5.6); 22.14, 22.25 (both s, Me); 41.62, 41.96 (both s, CH_2, Phe); 57.95, 58.32 (both d, CH, Phe, $^3J_{C,P}$ = 14.1, $^3J_{C,P}$ = 16.3); 59.72, 60.81 (both d, C(1), $^1J_{C,P}$ = 151.9, $^1J_{C,P}$ = 156.4); 63.04, 63.44 (both d, OCH_2, $^2J_{C,P}$ = 7.32, $^2J_{C,P}$ = 6.83); 126.92, 127.36, 127.67, 128.20, 128.28, 128.38, 128.43, 129.47, 129.77, 137.80, 138.23, 140.43 (C_{arom}); 177.22, 177.56 (both s, C=O, Phe).

IR spectrum, ν (cm^{-1}): 1250 (P=O); 1720 (C=O); 2400–3500 (OH); 3320, 3420 (NH).

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