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Synthesis of isocyanide derivatives of α-aminoalkylphosphonate diphenyl esters

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Abstract—This letter describes the first example of the synthesis of isocyanide derivatives of α-aminoalkylphosphonate diphenyl esters. This method produces the title compounds in high purity and in very good yields. It also permits the generation of an α-aminophosphonate-based library of biologically active phosphonopeptides. Preliminary experiments demonstrate their application as substrates for the Ugi-type multicomponent condensation.

For several years α-aminoalkylphosphonates—phosphonic analogues of amino acids—have interested biochemists, due to their broad spectrum application as herbicides, apoptosis inducers and neuroactive agents.[1] Special attention has been paid to their activity as enzyme inhibitors, especially serine proteases inhibitors.[2] To date, many phosphonate diphenyl esters and their peptide derivatives have been used as potent and selective enzyme inhibitors.[3] The synthesis of phosphonopeptides uses classical coupling procedures such as mixed carboxylic-carbonic anhydride (MCA), dicyclohexylcarbodiimide (DCC), and active ester and active chloride methods.[4] Very little attention has been paid to the four-component condensation, formally known as the Ugi reaction for the preparation of phosphonopeptides in one step.[5] We have found only two reports in the literature describing such an approach which uses commercially available 1-isocyanomethanephosphonate diethyl ester.[6] This is the first example of the synthesis of pseudopeptides with an α-aminoalkylphosphonate diphenyl ester moiety at the C-terminus in one step using isocyanide derivatives as the substrates.

The possibility of using isocyanide derivatives of α-aminophosphonate diphenyl esters in multicomponent condensation reactions opens the way for the synthesis of large numbers of new biologically active compounds. It also provides a powerful tool for one-pot syntheses of diverse and complex peptides with aminophosphonate moieties at the C-terminus in great numbers. No other single method enables chemists to create such large numbers of chemicals as is provided by multicomponent reactions combining simple raw materials, such as carbonic acids, amines, aldehydes and isocyanides.[7] 'If for example, 40 each of different components are reacted with one another, the result is $40^4 = 2{,}560{,}000$ reaction products.'[8] Here we present a simple method for the preparation of isocyanide derivatives of α-aminoalkylphosphonate diphenyl esters. We also report our preliminary results of their application for phosphonopeptide synthesis in the Ugi-type multicomponent condensation.[9]

The synthetic approach is outlined in Scheme 1. The starting Cbz-N-protected α-aminophosphonate diphenyl esters **1a**–**j** were prepared using the method described in the literature.[10] Compounds **1a**–**j** were obtained as racemic mixtures upon condensation of triphenyl phosphite, benzyl carbamate and an aldehyde. The synthesis of Phth-N-protected 5-amino-1-pentanal began with the protection of the amino group of 5-amino-1-pentanol with phthalic anhydride. Subsequent oxidation under Swern conditions gave the desired aldehyde.[11] The synthesis of *N*-phthaloyl-4-amino-1-butanal started with the protection of the amino group of 4-aminobutyraldehyde diethyl acetal with *N*-ethoxycarbonylphthalimide,

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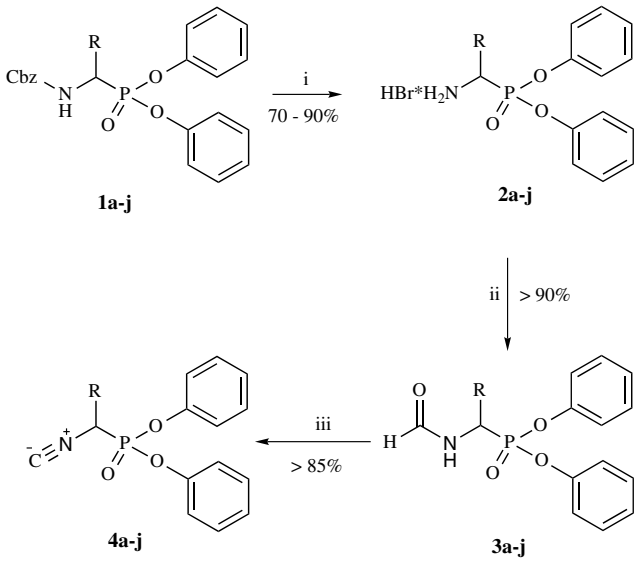


Scheme 1. Preparation of 1-isocyanoalkylphosphonate diphenyl esters **4a**–**j**. R is an aromatic or aliphatic side–chain. Reagents and conditions: (i) 33% HBr/AcOH; (ii) Et_3N, acetic formic anhydride, CH_2Cl_2; (iii) Et_3N, $POCl_3$, CH_2Cl_2, N_2, −20 °C.

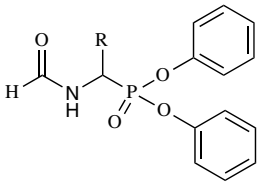
followed by acidic hydrolysis in THF.[12] Deprotection of α-aminoalkylphosphonate diphenyl esters **1a**–**j** using 33% HBr in acetic acid gave the corresponding hydrobromide salts of the α-aminoalkylphosphonates **2a**–**j**.

The typical method for preparing N-formylated α-aminophosphonates is a two-step process, with a total yield of about 70%.[13] First, hydrobromide salts are transformed into hydrochloride salts. Formylation is then achieved using EDC/formic anhydride in dichloromethane at 0 °C in the presence of *N*-methylmorpholine. The duration of the reaction is rather long, and the temperature needs to be kept constant throughout the duration.

Here we present a fast, efficient and simple method for the synthesis of N-formylated α-aminoalkylphosphonate diphenyl esters. To a suspension of **2a**–**j** (1 equiv) in dichloromethane, Et_3N (1.2 equiv) was added at room temperature. After the hydrobromide salt had dissolved completely, acetic formic anhydride[14] was added as the formylating agent (2.0 equiv). The reaction was complete within 30 min. The reaction mixture was then evaporated to dryness, dissolved in ethyl acetate, and the hydrobromide salt of triethylamine, which usually precipitates, was filtered off. The organic phase was washed with 5% $NaHCO_3$, dried with Na_2SO_4 and evaporated, giving **3a**–**j** in very high yields.[15] The structures of the *N*-formyl derivatives **3a**–**j** are presented in Table 1.

For the synthesis of isocyanides **4a**–**j**, N-formylated derivatives **3a**–**j** were dissolved in dichloromethane. After adding Et_3N (5 equiv), the reaction mixture (N_2 atmosphere) was cooled to −22 °C and $POCl_3$ (2 equiv) was added slowly.[16] The reaction was complete within 2 h. α-Aminoalkylphosphonate diphenyl esters are quite stable under strongly acidic conditions.[2] After washing the organic phase with saturated $NaHCO_3$ and brine, it was dried with Na_2SO_4 and evaporated to give **4a**–**j** as oils with a characteristic isocyanide odour in yields greater than 85% (see Table 2).[17]

Table 1. The *N*-formyl derivatives of α-aminoalkylphosphonate diphenyl esters

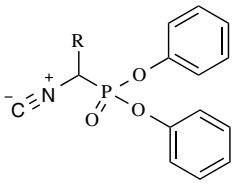


Compound	R	Yield (%)
3a	–CH_3	95
3b	–$CH_2CH_2CH_3$	91
3c	–$CH(CH_3)_2$	97
3d	–$CH_2CH(CH_3)_2$	99
3e	–Ph	96
3f	–CH_2Ph	99
3g	–CH_2CH_2Ph	99
3h	–$CH_2CH_2CH_2$NPhth	99
3i	–$CH_2CH_2CH_2CH_2$NPhth	93
3j	–$CH_2CH_2SCH_3$	90

Initial experiments clearly demonstrated the application of 1-isocyanoalkylphosphonate diphenyl esters in the Ugi-type multicomponent condensation for the preparation of phosphonic pseudopeptides. The yields were in the range of 44–70% as diastereomeric mixtures.[18] We are currently at advanced stages in the synthesis of a phosphonopeptide-based library using the multicomponent condensations. Complete data for the condensation products obtained as well as their biological activities will be published in due course.

In conclusion, we have presented a very efficient route for the synthesis of *N*-formyl-1-aminoalkylphosphonate diphenyl esters compared to the method described in the literature.[13] We have also shown that *N*-formyl derivatives can be easily dehydrated, giving their isocyanide derivatives—a new class of compounds, which could be used in the preparation of very large number of phos-

Table 2. The isocyanide derivatives of α-aminoalkylphosphonate diphenyl esters



Compound	R	Yield (%)
4a	–CH_3	95
4b	–$CH_2CH_2CH_3$	87
4c	–$CH(CH_3)_2$	85
4d	–$CH_2CH(CH_3)_2$	98
4e	–Ph	85
4f	–CH_2Ph	91
4g	–CH_2CH_2Ph	99
4h	–$CH_2CH_2CH_2$(NPhth)	86
4i	–$CH_2CH_2CH_2CH_2$(NPhth)	94
4j	–$CH_2CH_2SCH_3$	85

phonic pseudopeptides designed to inhibit enzyme activity or to examine enzyme specificity.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.058.

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15. ^{1}H, ^{13}C NMR and ^{31}P NMR spectra were recorded at 600.58, 151.03 and 243.11 MHz, respectively. Spectroscopic data of all synthesized N-formylated α-aminoalkylphosphonate diphenyl esters can be found in the Supplementary data.
    Compound **3a**: White crystals, mp 75 °C; ^{31}P NMR ($CDCl_3$): 18.10 (s); ^{1}H NMR ($CDCl_3$): 1.52 (dd, $J = 7.8$, 18.3 Hz, 3H), 4.95–5.03 (m, 1H), 7.09–7.37 (m, Ar–H, NH, 11H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$): 16.63, 40.17 (d, $J = 161.6$ Hz), 120.49 (d, $J = 4.5$ Hz), 125.49, 125.62, 129.93 (d, $J = 6.0$ Hz), 149.98. (d, $J = 10.6$ Hz), 150.26 (d, $J = 10.6$ Hz), 160.70 (d, $J = 7.6$ Hz). IR (KBr, cm^{-1}): 3430, 3255, 3035, 2880, 1685, 1590, 1535, 1490, 1380, 1255, 1210, 1185, 1165, 1070, 950, 930, 780, 690. MS (ESI) $m/z = 328.8$ (M^{+}+Na).
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17. ^{1}H, ^{13}C NMR and ^{31}P NMR spectra were recorded at 600.58, 151.03 and 243.11 MHz, respectively. Spectroscopic data of all synthesized isocyanide derivatives of α-aminoalkylphosphonate diphenyl esters can be found in the Supplementary data.
    Compound **4a**: Amber oil; ^{31}P NMR ($CDCl_3$): 9.70 (s); ^{1}H NMR ($CDCl_3$): 1.82 (dd, $J = 7.2$, 16.8 Hz, 3H), 4.23–4.29 (m, 1H), 7.26–7.38 (m, Ar–H, 10H); ^{13}C NMR ($CDCl_3$): 16.48 (d, $J = 4.5$ Hz), 45.77 (d, $J = 161.6$ Hz), 120.41 (dd, $J = 4.5$, 12.1 Hz), 125.96 (d, $J = 13.6$ Hz), 130.06 (d, $J = 9.1$ Hz), 149.68 (d, $J = 9.1$ Hz), 149.94 (d, $J = 9.1$ Hz), 161.06 (d, $J = 4.5$ Hz). IR (neat, cm^{-1}): 3285, 3070, 2935, 2139, 1685, 1595, 1590, 1490, 1455, 1390, 1320, 1270, 1250, 1200, 1160, 1070, 1025, 1010, 930. MS (ESI) $m/z = 310.5$ (M^{+}+Na).
18. ^{1}H and ^{31}P NMR spectra were recorded at 600.58 and 243.11 MHz, respectively. Spectroscopic data of the derivative of **4d**—*N*-Cbz-Ala-(*N*-*n*-butyl)-Val-Leu^{P}$(OPh)_2$ obtained by Ugi-type condensation as the diastereoisomeric mixture: Yield 48%; colourless oil; ^{31}P NMR ($CDCl_3$): 19.69 (26%), 19.79 (20%), 20.07 (26%), 20.45 (28%); ^{1}H NMR ($CDCl_3$): 0.71–0.87 (m, 15H), 1.05–1.15 (m, 2H), 1.17–1.27 (m, 4H), 1.49–1.62 (m, 3H), 1.68–1.81 (m, 2H), 2.43 (s, 1H), 3.12–3.27 (m, 2H), 4.14–4.30 (m, 1H), 4.46–4.61 (m, 1H), 4.77–4.97 (m, 1H), 5.00–5.15 (m, 2H), 5.77 (s, 1H), 6.95–7.23 (m, Ar–H, 15H). MS (ESI) $m/z = 702.5$ (M^{+}+Na).