ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 8, pp. 1237–1238. © Pleiades Publishing, Inc. 2006.
Original Russian Text © E.D. Matveeva, N.S. Zefirov, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 8, pp. 1254–1255.

SHORT COMMUNICATIONS

Amino Acids in a Three-Component Synthesis of α-Aminophosphonates Derivatives

E.D. Matveeva and N.S. Zefirov

Moscow State University, Moscow, 119992 Russia
e-mail: matveeva@org.chem.msu.ru

Received May 11, 2006

DOI: 10.1134/S1070428006080240

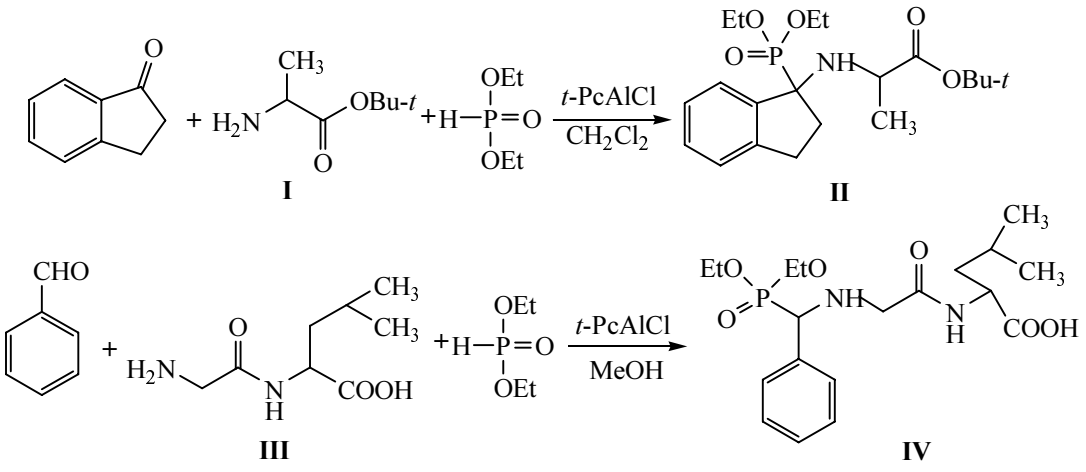
α-Aminophosphonic acids are bioisosteric phophorus analogs of α-amino acids. Their biological activity, the existence of natural phosphonates, the proved interaction of phosphonates with numerous enzymes and receptors [1–5] prompt the researchers to look for new synthetic approaches to the α-aminophosphonates [6–11].

It is known that the formaldehyde reacts with some α-amino acids and under the conditions of Kabachnik–Fields reaction in the presence of diethyl phosphite gives rise to α-amino acids containing a phosphonate group [12]. However the attempts to extend this reaction to the other aldehydes and ketones were unsuccessful. We have demonstrated in the present study that: (1) Both amino acids and their esters, and also dipeptides can be brought into this reaction; (2) In this reaction can be involved aliphatic and aromatic aldehydes and ketones under the catalysis with tetra(*tert*-butyl)phthalocyanine aluminum chloride (*t*-PcAlCl).

Indan-1-one in reaction with L-alanine *tert*-butyl ester (**I**) in the presence of diethyl phosphite and *t*-PcAlCl as catalyst led to the formation of α-amino acid derivatives **II** in a 65% yield. Likewise**,** the benzaldehyde reacted with dipeptide, glycyl-leucine of the L series (**III**), in the presence of diethyl phosphite and *t*-PcAlCl as catalyst and formed dipeptide **IV** in a 70% yield. The structure of compounds **II** and **IV** was confirmed by ^{1}H, ^{13}C, ^{31}P NMR, and IR spectra.

We are actively investigating the application limits and synthetic opportunities of the catalytic version of this reaction with amino acids.

General procedure. To a solution of 1.5 mmol of amino acid ester hydrochloride in 40 ml of water was added 0.00165 mol of sodium hydroxide, and the mixture was vigorously shaken in a separatory funnel for 1 min. Then the mixture was extracted with dichloromethane (3×10 ml). The organic layer was separated, dried over



I II III IV

anhydrous magnesium sulfate, and the solvent was removed on a rotary evaporator. To 1.5 mmol of thus obtained amino acid ester **I** (or dipeptide **III**) was added 2 ml of dichloromethane (or methanol), 0.001 mol of a carbonyl compound, molecular sieves 4A, and 0.5 mmol of *t*-PcAlCl. The reaction mixture was stirred for 3–4 h, then 1.5 mmol of diethyl phosphite was added. The completion of the process was monitored by TLC. The dehydrating agent was removed and washed with dichloromethane. The solvent was evaporated on a rotary evaporator, the residue was dissolved in a minimal amount of a mixture chloroform–methanol, 50:1, and subjected to a column chromatography on silica gel (15×2–3 cm; eluent a mixture chloroform–methanol, 50:1).

***N*-(1-Diethylphosphinylindan-1-yl)-L-alanine *tert*-butyl ester (II).** Yield 65%. IR spectrum, ν, cm^{-1}: 980, 1180 (P–O–Alk), 1250 (P=O), 1730 (C=O), 3320, 3470 (NH). ^1H NMR spectrum, δ, ppm: 1.12 t, 1.15 t, 1.22 t, 1.24 t (6H, $2CH_3$ of ethyl), 1.16 d (3H, CH_3 Ala), 1.31 s (9H, *t*-Bu), 1.91–2.11 m, 2.50–2.67 m (2H, C^2H_2 of ring), 2.63 br.m (1H, NH), 2.86–2.98 m (2H, C^3H_2 of ring), 3.19 q, 3.40 q (1H, CH Ala), 3.59–4.15 m (4H, $2OCH_2$), 7.10–7.18 m, 7.42–7.45 m ($4H_{arom}$). ^{13}C NMR spectrum, δ, ppm: 16.23–16.43 m (CH_3, of ethyl), 21.76 s, 22.00 s (CH_3 Ala), 27.81 s (CH_3, *t*-Bu), 30.23 s (C^3H_2 of ring), 33.36 C, 34.16 c (C^2H_2 of ring), 51.80 d, 52.01 d (CH Ala, *J* 12.2, 9.5 Hz), 62.51 d, 62.83 d, 62.88 d, 63.23 d ($2OCH_2$ $^2J_{CP}$ 6.7, $^2J_{CP}$ 4.0, $^2J_{CP}$ 8, $^2J_{CP}$ 6.8 Hz), 68.81 d, 68.90 d (α-C, $^1J_{CP}$ 160.6, $^1J_{CP}$ 162.0 Hz), 80.52 s, 80.60 s (C, *t*-Bu), 124.53, 125.78, 126.29, 128.25, 140.10, 141.16, 144.60, 145.7 (C_{arom}), 175.80, 175.95 (C=O, Ala). ^{31}P NMR spectrum, δ, ppm: 23.84, 24.07. Found, %: C 60.44; H 8.13; N 3.45. $C_{20}H_{32}NO_5P$. Calculated, %: C 60.44; H 8.12; N 3.52.

[*N*-(α-Diethylphosphinylbenzyl)glycyl]-L-leucine (IV). Yield 70%. IR spectrum, ν, cm^{-1}: 980, 1190 (P–O–Alk), 1250 (P=O), 1690 (C=O, amide), 1745 (C=O, acid), 3280 (NH). ^1H, δ, ppm: 0.94 d, 0.99 d (6H, $2CH_3$ Leu), 1.07–1.13 t, 1.27–1.36 t (6H, $2CH_3$, of ethyl), 1.16 d (3H, CH_3); 1.57–1.81 m [3H, CH_2, $\underline{CH}(CH_3)_2$], 3.13 (H_A), 3.40 (H_B) (2H, Gly *AB* system, $^2J_{HH}$ 17.0 Hz); 3.30 d (α-CH, J_{HP} 11.3 Hz), 3.64–3.78 m, 3.87–3.97 m, 4.06–4.30 m (4H, $2OCH_2$), 4.50–4.55 m [1H, $\underline{CH}$(COOH)], 7.34–7.43 m ($5H_{arom}$). ^{31}P NMR spectrum, δ, ppm: 23.13, 23.41. Found, %: C 55.05; H 7.53; N 6.66. $C_{19}H_{31}N_2O_6P$. Calculated, %: C 55.06, H 7.54; N 6.76.

^1H, ^{31}P, and ^{13}C NMR spectra were registered on a spectrometer VXR-400 (400 MHz) in $CDCl_3$ using TMS as internal reference. IR spectra were recorded on spectrophotometers UR-20 and Specord IR75 from solutions in tetrachloromethane. Elemental analysis was carried out on a CHN analyzer Vario-II. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Silufol UV-254 plates.

The study was carried out under a financial support by grants of the Russian Academy of Sciences: 10-OKhNM, 1-OKhNM; RNP.2.1.1.7779, RFFI-05-03-33054.

REFERENCES

1. Bioulac, B., Tingui, E.De., Vincent, J.D., and Neuzil, E., *Gen. Pharmacol.,* 1978, vol. 10, p. 121.
2. Murakawa, T., Sakamoto, H., Fukada, S., Konishi, T., and Nishida, M., *Antimicrob. Agents Chemother.,* 1982, vol. 21, p. 224.
3. Allen, J.G., Atherton, F.R., Hall, M.J., Hassall, C.H., Holmes, S.W., Lambert, L.W., Nisbet, L.J., and Ringrose, P.S., *Nature,* 1978, vol. 272, p. 56.
4. Atherton, F.R., Hall, M.J., Hassall, C.H., Lambert, L.W., Lloyd, W.J., Lord, A.V., Ringrose, P.S., and Westmacott, D., *Antimicrob. Agents Chemother*., 1983, vol. 24, p. 552.
5. Lambert, M.P. and Neuhaus, F.C., *J. Bacteriol.,* 1972, vol. 110, p. 978.
6. Kukhar, V.P. and Hudson, H.R., *Aminophosphonic and Aminophosphinic Acids,* V.P.Kukhar. and Y.R.John, Ed., Wiley & Sons, 2000.
7. Uziel, J. and Genet, J.P., *Zh. Org. Khim*., 1997, vol. 33, p. 1605.
8. Cherkasov, R.A. and Galkin, V.I., *Usp. Khim.,* 1998, vol. 67, p. 940.
9. Pavlov, V.Y., Kabachnik, M.M., Zobnina, E.V., Timofeev, V., Konstantinov, I.O., Kimel, B.G., Ponomarev, G.V., and Beletskaya, I.P., *Synlett.,* 2003, no. 14, p. 2193.
10. Kabachnik, M.M., Zobnina, E.V., and Beletskaya, I.P., *Zh. Org. Khim*., 2005, vol. 41, p. 517.
11. Matveeva, E.D., Podrugina, T.A., Tishkovskaya, E.V., and Zefirov, N.S., *Synlett.,* 2003, vol. 15, p. 2321.
12. Prishchenko, A.A., Novikova, O.N., Livantsov, M.V., Grigor'ev, E.V., and Goncharova, Zh.Yu., *Zh. Obshch. Khim*., 1995, vol. 65, p. 1751.