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Synthesis of α-amino phosphonates by diastereoselective addition of diethyl phosphite sodium salt to aldimines derived from Betti base

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General remarks

^{1}H NMR spectra were recorded on a Bruker AVANCE-400 and AVANCE-500 (Germany, Karlsruhe) instrument with the working frequency of 400.13 and 500.13 MHz correspondingly relative to the signals of residual protons of deuterated solvent ($CDCl_3$), ^{31}P NMR spectra were obtained on a Bruker AVANCE-400 and AVANCE-500 (Germany, Karlsruhe) instrument with the working frequency of 161.97 and 202.45 MHz correspondingly relative to the external standard (85% H_3PO_4). IR spectra were recorded on Bruker Vector 22 Fourier spectrometer (Germany, Karlsruhe) from KBr pellets. Melting points were measured on a Boetius melting point microscope.

Experimental details

1,3-Diphenylnaphthoxazine (**1e**) was synthesized according to known procedure.[1]

1-(a-Aminobenzyl)-2-naphthol was obtained by the hydrolysis of 1,3-diphenylnaphthoxazine (**1e**) as described earlier[2] with subsequent liberation of the free base by the reaction with sodium carbonate.

3-Alkyl-1-phenylnaphthoxazines (**1a-d**) were obtained by the condensation of 1-(a-aminobenzyl)-2-naphthol with the corresponding aliphatic aldehydes.[3] Compound **1b** was obtained for the first time.

3-Butyl-1-phenyl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1b**) was isolated by recrystallization from methanol in 75% yield, mp 127-129°C. Compound **1b** is a mixture of *trans*- and *cis*-oxazine tautomers in 85:15 ratio in the solution. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.93 (t, 2.55H, CH_3, $^{3}J_{HH}$ = 7.3 Hz, *trans*-tautomer); 0.97 (t, 0.45H, CH_3, $^{3}J_{HH}$ = 7.3 Hz, *cis*-tautomer); 1.30-1.62 (m, 4H, $CH_3CH_2CH_2$, *trans*- and *cis*-tautomers); 1.68-1.88 (m, 2H, CH_2CH, *trans*- and *cis*-tautomers); 4.68 (t, 0.85H, NHC*H*O, $^{3}J_{HH}$ = 5.7 Hz, *trans*-tautomer); 4.79 (t,

0.15H, NHC*H*O, $^3J_{HH}$ = 5.7 Hz, *cis*-tautomer); 5.56 (s, 0.85H, PhC*H*NH, *trans*-tautomer); 5.80 (s, 0.15H, PhC*H*NH, *cis*-tautomer); 7.13-7.39 (m, 9H, H_{arom}, *trans*- and *cis*-tautomers); 7.71-7.80 (m, 2H, H_{arom}, *trans*- and *cis*-tautomers) ppm. IR (KBr), ν = 3320, 1620, 1597 cm^{-1}. Found (%): C, 83.30; H, 7.31; N, 4.45. Calcd. for $C_{22}H_{23}NO$ (%):C, 83.24; H, 7.30; N, 4.41.

*α-Amino phosphonates **2** (general procedure).* Sodium metal (3.96 mmol) was dissolved in diethyl phosphite (10.56 mmol) at vigorous stirring under dry argon atmosphere and the resulting solution was added to naphthoxazines **1a-e** (1.32 mmol). The mixtures were stirred at room temperature under argon for 6 h, then were diluted with 96% aqueous ethanol (5 ml) and were vigorously stirred for 1 h. Reaction mixtures were analyzed by ^{31}P NMR for d.e. determination by the integration of diastereoisomer signals (d.e. = 90% (for **2a**), 80% (for **2b**), 82% (for **2c**), 86% (for **2d**), 92% (for **2e**)). Then the volatiles were removed *in vacuo* using an oil pump. Dense residues were dissolved in 6 ml of hot hexane and the solid precipitated on cooling was filtered off and washed with 3 ml of cyclohexane. In the case of **2a** and **2d**, the mother liquor was allowed to stand at −10 °C for several days. Resulting crystals were filtered off and dried. In the case of **2b** and **2c** mother liquor was evaporated, and the residues were analyzed by NMR and IR-spectroscopy. In the case of **2e**, the mother liquor was evaporated, the residue was dissolved in toluene (2 ml), and the solution was allowed to stand at −10 °C for several days. The resulting crystals of were filtered off and dried.

Diethyl (R,R/S,S)-1-[(2-hydroxynaphthalen-1-yl)(phenyl)methylamino]-2-phenylethyl-phosphonate (from **2a** mixture) was isolated after recrystallization in 68% yield, mp 131-132 ºC. ^1H NMR (500 MHz, $CDCl_3$), *δ*: 1.33, 1.35 (2t, 6H, C*H*$_3$CH$_2$OP, $^3J_{HH}$ = 7.1 Hz); 2.91-3.00 (m, 1H, PCH); 3.31-3.39 (m, 2H, CH_2Ph); 4.08-4.20 (m, 4H, CH_3CH_2OP); 6.12 (s, 1H, PhC*H*NH); 7.11-7.73 (m, 16H, H_{arom}) ppm. ^{31}P NMR (500 MHz, $CDCl_3$), *δ*: 28.21 ppm. IR (KBr), ν = 3330, 1232, 1057, 1033. Found (%): C, 71.32; H, 6.72; N, 2.97; P, 6.15. Calcd. for $C_{29}H_{32}NO_4P$ (%): C, 71.25; H, 6.59; N, 2.86; P, 6.23.

Diethyl 1-[(2-hydroxynaphth-1-yl)(phenyl)methylamino]penthylphosphonate (**2b**) was obtained as pale yellow viscous oil, which is a mixture of diastereomers in 90:10 molar ratio. ^1H NMR (500 MHz, $CDCl_3$), *δ*: 0.88 (t, 0.3H, C*H*$_3$CH$_2$, $^3J_{HH}$ = 7.2 Hz, minor diastereomer [**D₂**]); 0.92 (t, 2.7H, C*H*$_3$CH$_2$, $^3J_{HH}$ = 7.3 Hz, major diastereomer [**D₁**]); 1.26-1.39 (m, 8H, CH$_3$C*H*$_2$CH$_2$+C*H*$_3$CH$_2$OP, **D₁**+**D₂**); 1.40-1.47 (m, 1H, CH$_2$C*H*$_2$CH$_2$, **D₁**+**D₂**, H_a); 1.50-1.57 (m, 1H, CH$_2$C*H*$_2$CH$_2$, **D₁**+**D₂**, H_b); 1.69-1.80 (m, 1H, CH$_2$C*H*$_2$CH, **D₁**+**D₂**, H_a); 1.87-1.99 (m, 1H, CH$_2$C*H*$_2$CH, **D₁**+**D₂**, H_b); 3.02-3.07 (m, 1H, PCH, **D₁**+**D₂**); 4.09-4.23 (m, 4H, CH$_3$C*H*$_2$OP, **D₁**+**D₂**); 6.12 (s, 0.9H, PhC*H*NH, **D₁**); 6.41 (br.s, 0.1H, PhC*H*NH, **D₂**); 7.17-7.86 (m, 11H, H_{arom}, **D₁**+**D₂**) ppm. ^{31}P NMR (500 MHz, $CDCl_3$), *δ*: 26.89 (**D₁**); 27.93 (**D₂**) ppm. IR (KBr), ν = 3320, 1237, 1058, 1025.

Diethyl 1-[(2-hydroxynaphth-1-yl)(phenyl)methylamino]-3-methylbutylphosphonate (**2c**) was obtained as pale yellow viscous oil, which is a mixture of diastereomers in 91:9 molar ratio. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.68, 0.80 (2d, 5.46H, $(CH_3)_2CH$, $^{3}J_{HH}$ = 6.6 Hz, major diastereomer [**D$_1$**]); 0.76, 0.82 (2d, 0.54H, $(CH_3)_2CH$, $^{3}J_{HH}$ = 6.5 Hz, minor diastereomer [**D$_2$**]); 1.29 (t, 0.54H, CH_3CH_2OP, $^{3}J_{HH}$ = 7.0 Hz, **D$_2$**); 1.38 (t, 5.46H, CH_3CH_2OP, $^{3}J_{HH}$ = 6.9 Hz, **D$_1$**); 1.52-1.60 (m, 0.09H, $CHCH_2CH$, **D$_2$**, H_a); 1.62-1.75 (m, 1H, $CHCH_2CH$, **D$_1$**+**D$_2$**, H_a+H_b); 1.80-1.90 (m, 0.91H, $CHCH_2CH$, **D$_1$**, H_b); 1.91-2.02 (m, 1H, $(CH_3)_2CH$, **D$_1$**+**D$_2$**); 2.97-3.05 (m, 1H, PCH, **D$_1$**+**D$_2$**); 4.10-4.26 (m, 4H, CH_3CH_2OP, **D$_1$**+**D$_2$**); 6.24 (s, 0.91H, PhC*H*NH, **D$_1$**); 6.51 (br.s, 0.09H, PhC*H*NH, **D$_2$**); 7.16-7.89 (m, 11H, H_{arom}, **D$_1$**+**D$_2$**) ppm. ^{31}P NMR (400 MHz, $CDCl_3$), δ: 27.75 (**D$_1$**); 28.36 (**D$_2$**) ppm. IR (KBr), ν = 3333, 1193, 1051, 1025.

Diethyl (R,R/S,S)-1-[(2-hydroxynaphth-1-yl)(phenyl)methylamino]-2-methylpropyl-phosphonate (from **2d** mixture) was isolated after recrystallization in 62% yield, mp 119-121 ºC. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.03, 1.09 (2d, 6H, $(CH_3)_2CH$, $^{3}J_{HH}$ = 6.9 Hz); 1.37, 1.38 (2t, 6H, CH_3CH_2OP, $^{3}J_{HH}$ = 7.1 Hz); 2.27-2.37 (m, 1H, $(CH_3)_2CH$); 2.93 (dd, 1H, PCH, $^{2}J_{PH}$ = 17.5 Hz, $^{3}J_{HH}$ = 2.7 Hz); 4.12-4.23 (m, 4H, CH_3CH_2OP); 6.22 (s, 1H, PhC*H*NH); 7.18-7.90 (m, 11H, H_{arom}) ppm. ^{31}P NMR (500 MHz, $CDCl_3$), δ: 27.03 ppm. IR (KBr), ν = 3291, 1236, 1053, 1020. Found (%): C, 68.15; H, 7.47; N, 3.23; P, 7.18. Calcd. for $C_{25}H_{32}NO_4P$ (%): C, 68.01; H, 7.31; N, 3.17; P, 7.02.

Diethyl (R,R/S,S)-1-[(2-hydroxynaphth-1-yl)(phenyl)methylamino]-1-phenylmethyl-phosphonate (from **2e** mixture) was isolated after recrystallization in 85% yield, mp 141-142 ºC. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.02, 1.43 (2t, 6H, CH_3CH_2OP, $^{3}J_{HH}$ = 7.1 Hz); 3.58-3.66 (m, 1H, CH_3CH_2OP, H_a); 3.84-3.92 (m, 1H, CH_3CH_2OP, H_b); 4.08 (d, 1H, PCH, $^{2}J_{PH}$ = 22.4 Hz); 4.19-4.26 (m, 2H, CH_3CH_2OP); 5.53 (s, 1H, PhC*H*NH); 7.18-7.76 (m, 16H, H_{arom}) ppm. ^{31}P NMR (500 MHz, $CDCl_3$), δ: 22.21 ppm. IR (KBr), ν = 3326, 1237, 1047, 1019. Found (%): C, 70.84; H, 6.26; N, 2.84; P, 6.35. Calcd. for $C_{28}H_{30}NO_4P$ (%): C, 70.72; H, 6.36; N, 2.95; P, 6.51.

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