Supporting Information

Reaction of 2*H*-Azirine-phosphine oxide and - phosphonates with nucleophiles. Stereoselective synthesis of functionalized aziridines and α - and β - aminophosphorus derivatives

Francisco Palacios, Ana M. Ochoa de Retana, and José M. Alonso*

Departamento de Química Orgánica I. Facultad de Farmacia. Universidad del País Vasco, Apartado
450, 01080 Vitoria (Spain)

Telephone 34-945-013103. Fax 34-945-013049. E-mail: francisco.palacios@ehu.es

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General Methods. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use: CH_2Cl_2 (P_2O_5); *n*-hexane, diethyl ether and THF (sodium, benzophenone ketyl); ethyl acetate (K_2CO_3); ethanol (EtMgI). All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light and KMnO_4 solution. Flash chromatography was carried out using silica gel 60 (230–400 mesh). Melting points are uncorrected. ^1H (400, 300 MHz), ^{13}C (100, 75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded using tetramethylsilane (TMS) (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in CDCl_3 solutions for ^1H NMR spectra or chloroform (77.0 ppm) as an internal reference in CDCl_3 solutions for ^{13}C NMR, and phosphoric acid (85%) for ^{31}P NMR spectra. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet) or m (multiplet). Coupling constants (J) are reported in Hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EI) or chemical ionization (CI). Data are reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were taken on a IRFT spectrometer, and were obtained as solids in KBr or as neat oils in NaCl. Peaks are reported in cm^{-1} . Azirines **1** and **4** were prepared according to literature procedures.^{1,2}

General Procedure for the Preparation of Aziridines 3 and 5. To a solution of 2*H*-azirine **1** or **4** (5 mmol) in THF (15 ml) cooled to $-78\text{ }^\circ\text{C}$, was added a solution of Grignard reagent **2** (15 mmol) in diethyl ether under nitrogen atmosphere. The mixture was stirred for one hour at $-78\text{ }^\circ\text{C}$ and then was allowed to warm to room temperature (15 hours). After the reaction was complete, the mixture was quenched with a saturated NH_4Cl solution (15 ml). The crude reaction was extracted three times with CH_2Cl_2 (3 x 15 ml). Organic layer was dried over anhydrous MgSO_4 , filtered and the solvent was

evaporated under vacuum. The crude residue was then purified by flash chromatography (silica gel, AcOEt) affording derivatives **5** as white solids and derivatives **3** as pale yellow oils.

Diethyl trans-3-benzyl-3-methylaziridin-2-ylphosphonate 3ab. The general procedure was followed using 2*H*-azirine-2-phosphonate **1a** (0.96 g, 5 mmol) and benzylmagnesium bromide 1M **2b** (15 ml, 15 mmol). Chromatographic purification eluting AcOEt afforded 0.93 g, (66 %) of compound **3ab** as a yellow pale oil: R_f 0.27 (AcOEt); ^1H NMR (CDCl_3) δ 7.35-7.16 (m, 5H), 4.21 (m, 4H), 2.45 (d, $^4J_{\text{PH}} = 2.8$ Hz, 2H), 2.05 (s, 1H), 1.75 (s, 3H), 1.40 (m, 6H) ppm; ^{13}C NMR (CDCl_3) δ 135.9-126.2 (m), 63.1, 62.7 (d, $^2J_{\text{PC}} = 6.0$ Hz), 62.5 (d, $^2J_{\text{PC}} = 6.0$ Hz), 43.5, 36.4 (d, $^1J_{\text{PC}} = 192.8$ Hz), 21.3, 19.1, 16.7 (d, $^3J_{\text{PC}} = 5.5$ Hz) ppm; ^{31}P NMR (CDCl_3) δ 25.2 ppm; IR (NaCl) 3416, 2985, 1633, 1447, 1241 cm^{-1} ; MS (EI) m/z 283 (M^+ , 6), 145 ($\text{M}^+ - \text{HP}(\text{O})(\text{OEt})_2$, 100); Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{NO}_3\text{P}$: C, 59.35; H, 7.83; N, 4.94. Found: C, 59.47; H, 7.82; N, 4.96.

Diethyl cis-3-allyl-3-phenylaziridin-2-ylphosphonate 3bc. The general procedure was followed using 2*H*-azirine-2-phosphonate **1b** (1.27 g, 5 mmol) and allylmagnesium bromide 1M **2c** (15 ml, 15 mmol). Chromatographic purification eluting AcOEt afforded 1.28 g, (87 %) of compound **3bc** as a yellow pale oil: R_f 0.28 (AcOEt); ^1H NMR ($\text{CDCl}_3 + \text{D}_2\text{O}$) δ 7.69-7.18 (m, 5H), 5.70 (ddt, $^3J_{\text{HH}} = 7.3$ Hz, $^3J_{\text{HHcis}} = 10.2$ Hz, $^2J_{\text{HHgem}} = 17.1$ Hz, 1H), 5.06 (dd, $^3J_{\text{HHcis}} = 10.2$ Hz, $^3J_{\text{HHtrans}} = 17.1$ Hz, 2H), 3.92 (m, 2H), 3.72 (m, 1H), 3.36 (m, 1H), 2.67 (dd, $^3J_{\text{HH}} = 7.1$ Hz, $^2J_{\text{HHgem}} = 14.0$ Hz, 1H), 2.46 (dd, $^3J_{\text{HH}} = 7.1$ Hz, $^2J_{\text{HHgem}} = 14.0$ Hz, 1H), 2.22 (d, $^2J_{\text{PH}} = 15.5$ Hz, 1H), 1.21 (m, 3H), 1.05 (m, 3H) ppm; ^{13}C NMR (CDCl_3) δ 132.3-127.3 (m), 119.4, 61.7 (d, $^2J_{\text{PC}} = 6.0$ Hz), 61.6 (d, $^2J_{\text{PC}} = 6.0$ Hz), 46.8, 46.5, 34.8 (d, $^1J_{\text{PC}} = 202.5$ Hz), 16.1 (d, $^3J_{\text{PC}} = 5.5$ Hz), 16.0 (d, $^3J_{\text{PC}} = 5.5$ Hz) ppm; ^{31}P NMR (CDCl_3) δ 21.9 ppm; IR (NaCl) 3243, 1725, 1639, 1447, 1241 cm^{-1} ; MS (CI) m/z 295 ($\text{M}^+ + 1$, 100); Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{NO}_3\text{P}$: C, 61.01; H, 7.51; N, 4.74. Found: C, 60.93; H, 7.49; N, 4.75.

***trans*-3-Allyl-3-methylaziridin-2-yl diphenylphosphine oxide 5ac.** The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **4a** (1.28 g, 5 mmol) and allylmagnesium bromide 1M **2c** (15 ml, 15 mmol). Chromatographic purification eluting AcOEt afforded 1.01 g, (68 %) of compound **5ac** as a white solid: mp 109-108 °C; ¹H NMR (CDCl₃) δ 7.82-7.26 (m, 10H), 5.75 (ddt, ³*J*_{HH} = 7.3 Hz, ³*J*_{HH_{cis}} = 7.3 Hz, ²*J*_{HH_{gem}} = 14.5 Hz, 1H), 5.07 (dd, ³*J*_{HH_{cis}} = 7.3 Hz, ³*J*_{HH_{trans}} = 10.1 Hz, 2H), 2.37 (dd, ³*J*_{HH} = 7.3 Hz, ²*J*_{HH_{gem}} = 14.5 Hz, 1H), 2.15 (d, ²*J*_{PH} = 22.7 Hz, 1H), 2.13 (dd, ³*J*_{HH} = 7.3 Hz, ²*J*_{HH_{gem}} = 14.5 Hz, 1H), 1.60 (s, 1H), 1.44 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 133.9-128.6 (m), 118.1, 44.8, 41.6 (d, ²*J*_{PC} = 1.5 Hz), 37.4 (d, ¹*J*_{PC} = 95.4 Hz), 18.0 (d, ³*J*_{PC} = 2.5 Hz) ppm; ³¹P NMR (CDCl₃) δ 27.4 ppm; IR (KBr) 3217, 3051, 1639, 1434, 1182 cm⁻¹; MS (CI) *m/z* 297 (M⁺+1, 100); Anal. Calcd. for C₁₈H₂₀NOP: C, 72.71; H, 6.78; N, 4.71. Found: C, 72.89; H, 6.80; N, 4.70.

***trans*-3-(2-[1,3]-Dioxolan-2-ylethyl)-3-methylaziridin-2-yl diphenylphosphine oxide 5ad.** The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **4a** (1.28 g, 5 mmol) and 2-ethyl-[1,3]dioxolanylmagnesium bromide **2d** (15 mmol). This organometallic was prepared according to literature procedures: Tsantali, G.G.; Takakis, I. M. *J. Org. Chem.*, **2003**, 68, 6455–6458. Chromatographic purification eluting AcOEt afforded 1.16 g, (65 %) of compound **5ad** as a white solid: mp 101-100 °C; ¹H NMR (CDCl₃) δ 7.94-7.42 (m, 10H), 4.80 (t, ³*J*_{HH} = 7.2 Hz, 1H), 3.93 (m, 2H), 3.81 (m, 2H), 2.16 (d, ²*J*_{PH} = 23.2 Hz, 1H), 1.62 (m, 5H), 1.43 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 134.2-128.5 (m), 103.8, 64.9, 64.8, 41.5 (d, ²*J*_{PC} = 2.0 Hz), 38.2 (d, ¹*J*_{PC} = 95.2 Hz), 34.6, 30.0, 17.5 (d, ³*J*_{PC} = 2.5 Hz) ppm; ³¹P NMR (CDCl₃) δ 27.7 ppm; IR (KBr) 3239, 3051, 1674, 1434, 1122 cm⁻¹; MS (CI) *m/z* 358 (M⁺+1, 100); Anal. Calcd. for C₂₀H₂₄NO₃P: C, 67.21; H, 6.77; N, 3.92. Found: C, 67.14; H, 6.76; N, 3.93.

***cis*-3-Allyl-3-phenylaziridin-2-yl diphenylphosphine oxide 5bc.** The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **4b** (1.59 g, 5 mmol) and allylmagnesium

bromide 1M **2c** (15 ml, 15 mmol). Chromatographic purification eluting AcOEt afforded 1.13 g, (63 %) of compound **5bc** as a white solid: mp 139-138 °C; ^1H NMR (CDCl_3) δ 7.63-6.88 (m, 15H), 5.52 (ddt, $^3J_{\text{HH}} = 7.3$ Hz, $^3J_{\text{HH}_{\text{cis}}} = 11.6$ Hz, $^2J_{\text{HH}_{\text{gem}}} = 16.6$ Hz, 1H), 4.83 (dd, $^3J_{\text{HH}_{\text{cis}}} = 11.6$ Hz, $^3J_{\text{HH}_{\text{trans}}} = 16.6$ Hz, 2H), 2.84 (d, $^2J_{\text{PH}} = 19.5$ Hz, 1H), 2.78 (m, 1H), 2.26 (dd, $^3J_{\text{HH}} = 7.3$ Hz, $^2J_{\text{HH}_{\text{gem}}} = 14.7$ Hz, 1H), 1.80 (s, 1H) ppm; ^{13}C NMR (CDCl_3) δ 138.4-128.2 (m), 119.3, 49.1, 46.8, 39.8 (d, $^1J_{\text{PC}} = 109.3$ Hz) ppm; ^{31}P NMR (CDCl_3) δ 26.6 ppm; IR (KBr) 3211, 3051, 1633, 1434, 1162 cm^{-1} ; MS (CI) m/z 360 ($\text{M}^+ + 1$, 100); Anal. Calcd. for $\text{C}_{23}\text{H}_{22}\text{NOP}$: C, 76.86; H, 6.17; N, 3.90. Found: C, 76.95; H, 6.18; N, 3.89.

General Procedure for Hydrogenation Ring Opening of Aziridines 3 and 5. To a solution of aziridine **3** or **5** (5 mmol) in EtOH (15 ml) was added under nitrogen atmosphere, Pd/C (20 %), and then ammonium formate (75 mmol). The mixture was kept at reflux for 8 hours. Then, NH_4OH solution (25 %) was added until pH 8, and the aqueous layer was extracted three times with CH_2Cl_2 . The combined organic layers were dried over anhydrous MgSO_4 , and the solvent was evaporated. The crude mixture was purified by flash column chromatography to afford amino phosphorus derivatives **6**, **7** or **8** as white solids or colorless oils.

2-Amino-2-methylpenthyldiphenylphosphine oxide 6ac. The general procedure was followed using aziridine-2-diphenylphosphine oxide **5ac** (1.50 g, 5 mmol). Chromatographic purification eluting AcOEt afforded 0.87 g, (58 %) of compound **6ac** as a white solid: mp: 56-55 °C; ^1H NMR (CDCl_3) δ 7.82-7.43 (m, 10H), 2.53 (d, $^2J_{\text{PH}} = 10.4$ Hz, 2H), 2.11 (s, 2H), 1.48 (t, $^3J_{\text{HH}} = 8.5$ Hz, 2H), 1.28 (m, 2H), 1.17 (s, 3H), 0.76 (t, $^3J_{\text{HH}} = 7.2$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) δ 135.2-128.6 (m), 53.7 (d, $^2J_{\text{PC}} = 4.9$ Hz), 47.0 (d, $^3J_{\text{PC}} = 8.4$ Hz), 40.7 (d, $^1J_{\text{PC}} = 70.4$ Hz), 29.2 (d, $^3J_{\text{PC}} = 6.9$ Hz), 17.4, 8.2 ppm; ^{31}P NMR (CDCl_3) δ 29.5 ppm; IR (KBr) 3434, 3045, 1590, 1434, 1187 cm^{-1} ; MS (EI) m/z 302 ($\text{M}^+ + 1$, 50), 285 ($\text{M}^+ - \text{NH}_2$, 100); Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{NOP}$: C, 71.74; H, 8.03; N, 4.65. Found: C, 71.89; H, 8.04; N, 4.64.

2-Amino-2-phenylpenthyldiphenylphosphine oxide 6bc. The general procedure was followed using aziridine-2-diphenylphosphine oxide **5bc** (1.81 g, 5 mmol). Chromatographic purification eluting AcOEt afforded 0.98 g, (65 %) of compound **6bc** as a white solid: mp: 158-157 °C; ^1H NMR (CDCl_3) δ 7.76-6.99 (m, 15H), 3.34 (s, 1H), 3.14 (s, 1H), 2.96 (dd, $^2J_{\text{HHgem}} = 15.0$ Hz, $^2J_{\text{PH}} = 11.6$ Hz, 1H), 2.82 (dd, $^2J_{\text{HHgem}} = 15.0$ Hz, $^2J_{\text{PH}} = 8.2$ Hz, 1H), 1.88 (ddq, $^2J_{\text{HHgem}} = 15.0$ Hz, $^3J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 6.4$ Hz, 2H), 1.24 (m, 2H), 0.73 (t, $^3J_{\text{HH}} = 6.7$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3) δ 145.6-125.8 (m), 58.4 (d, $^2J_{\text{PC}} = 4.9$ Hz), 47.8 (d, $^3J_{\text{PC}} = 9.4$ Hz), 43.9 (d, $^1J_{\text{PC}} = 70.1$ Hz), 16.7, 7.1 ppm; ^{31}P NMR (CDCl_3) δ 29.5 ppm; IR (KBr) 3396, 3310, 1600, 1434, 1175 cm^{-1} ; MS (EI) m/z 364 ($\text{M}^+ + 1$, 64), 347 ($\text{M}^+ - \text{NH}_2$, 100); Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{NOP}$: C, 76.01; H, 7.21; N, 3.85. Found: C, 76.16; H, 7.22; N, 3.84.

Diethyl 1-amino-2-phenylpenthylphosphonate 8bc. The general procedure was followed using aziridine-2-phosphonate **3bc** (1.49 g, 5 mmol). Chromatographic purification eluting AcOEt afforded 0.81 g, (54 %) of compound **8bc** as a colorless oil: R_f 0.26 (AcOEt); ^1H NMR (CDCl_3) δ 7.33-7.20 (m, 10H), 4.11 (m, 8H), 3.25 (dd, $^3J_{\text{HHanti}} = 6.6$ Hz, $^2J_{\text{PH}} = 13.1$ Hz, 1H), 3.15 (dd, $^3J_{\text{HHsin}} = 5.0$ Hz, $^2J_{\text{PH}} = 14.7$ Hz, 1H), 3.05 (2d, $^3J_{\text{HHanti}} = 6.6$ Hz, $^3J_{\text{HHsin}} = 4.9$ Hz, 2H), 1.94 (m, 2H), 1.78 (m, 2H), 1.64 (s, 4H), 1.25 (m, 12H), 1.16 (m, 4H), 0.79 (m, 6H) ppm; ^{13}C NMR (CDCl_3) δ 142.3-126.5 (m), 61.9 (d, $^2J_{\text{PC}} = 4.0$ Hz), 61.7 (d, $^2J_{\text{PC}} = 7.1$ Hz), 54.5 (d, $^1J_{\text{PC}} = 146.6$ Hz, *anti*), 53.4 (d, $^1J_{\text{PC}} = 151.0$ Hz, *syn*), 46.8, 46.2 (d, $^3J_{\text{PC}} = 3.0$ Hz), 35.2 (d, $^3J_{\text{PC}} = 7.6$ Hz, *syn* and *anti*), 31.2 (d, $^3J_{\text{PC}} = 5.0$ Hz, *syn* and *anti*), 20.4 (d, $^3J_{\text{PC}} = 3.5$ Hz), 16.4 (d, $^5J_{\text{PC}} = 2.0$ Hz), 16.3 (d, $^5J_{\text{PC}} = 4.0$ Hz), 13.9 (d, $^5J_{\text{PC}} = 8.1$ Hz) ppm; ^{31}P NMR (CDCl_3) δ 28.0, 27.9 ppm; IR (NaCl) 3397, 1462, 1228, 1066 cm^{-1} ; MS (EI) m/z 299 (M^+ , 8), 222 ($\text{M}^+ - \text{P}(\text{O})(\text{OEt})_2$, 20); Anal. Calcd. for $\text{C}_{15}\text{H}_{26}\text{NO}_3\text{P}$: C, 60.18; H, 8.75; N, 4.68. Found: C, 60.29; H, 8.77; N, 4.67.

Procedure for the synthesis of *trans*-3-imidazolyl-3-methylaziridin-2-ylidiphenylphosphine oxide 10ab. To a 0 °C solution of 2*H*-azirine **4a** (1.28 g, 5 mmol) in benzene (15 ml), imidazole (0.34 g, 5.5 mmol) was added slowly under a nitrogen atmosphere and with continuous stirring. The reaction mixture stirred at room temperature for 48 hours. The crude reaction was then washed three times with H₂O (3 x 5 ml). The organic layer was dried over anhydrous MgSO₄ and filtered and the solvent was evaporated under reduced pressure. Crude reaction was purified by crystallization from diethyl ether/hexane 2/1 affording 1.34 g (83 %) of compound **10ab** as a white solid: mp: 119-118 °C; ¹H NMR (CDCl₃) δ 7.86-7.46 (m, 11H), 7.01 (d, ³*J*_{HH} = 1.1 Hz, 1H), 7.00 (t, ³*J*_{HH} = 1.4 Hz, ⁴*J*_{HH} = 1.2 Hz, 1H), 2.56 (d, ²*J*_{PH} = 22.3 Hz, 1H), 2.32 (s, 1H), 1.95 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 134.8-128.6 (m), 116.4, 52.8, 40.2 (d, ¹*J*_{PC} = 87.6 Hz), 19.5 ppm; ³¹P NMR (CDCl₃) δ 24.4 ppm; IR (KBr) 3442, 3190, 1586, 1367, 1175 cm⁻¹; MS (CI) *m/z* 324 (M⁺+1, 85), 256 (M⁺- C₃H₃N₂, 100); Anal. Calcd. for C₁₈H₁₈N₃OP: C, 66.86; H, 5.61; N, 13.00. Found: C, 66.72; H, 5.60; N, 12.93.

References and Notes

- (1) Palacios, F. Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213–3217.
- (2) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I. *Tetrahedron Lett.* **2000**, *41*, 5363–5366.