Direct Cyclopropanation of 1-Alkynylphosphonates by Cp_2ZrCl_2 / 2EtMgBr / 2AlCl_3 to Afford Cyclopropylmethylphosphonates.

Abed Al Aziz Quntar and Morris Srebnik*

Department of Medicinal Chemistry and Natural Products, School of Pharmacy,
Hebrew University in Jerusalem 99120 Israel

Supporting Information

General comments and General experimental method	S1
Spectroscopic data of 3a	S2
Spectroscopic data of 3c	S2
Spectroscopic data of 3d	S2
Spectroscopic data of 3e	S3
Procedure and Spectroscopic data of 3f	S3
Spectroscopic data of 3g	S4
Spectroscopic data of 3h	S4
Spectroscopic data of 3i	S4

General comments: General comments: All reactions were carried out under a nitrogen atmosphere vacuum line and glove box techniques. Solvents were purified by distillation from appropriate drying agents under a nitrogen atmosphere. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in CDCl_3 , ^{31}P NMR (121.4 MHz) was recorded in CDCl_3 . GCMS equipped with an EI detector and 30m methyl silicone column.

General procedure for the synthesis of 3. To 0.306 g (1.05 mmol) of zirconocene dichloride dissolved in 7 ml of dry THF at -78°C was added 1.05 ml of 2M EtMgBr (2.1 mmol) dropwise in a 25 ml round-bottom flask. After stirring for 5 min at -78°C , 1 mmol of 1-alkynylphosphonate was added. The reaction was gradually warmed to 25°C and stirred for 1 hr. The reaction was cooled to -30°C and maintained at -30 - 40°C while 2 equiv. of AlCl_3 were added. The reaction was stirred for 1 hr at -30°C and

was worked up with dilute HCl. The product was extracted with diethyl ether (2 X 15ml), separated on silica gel column (70% petroleum ether: 30% diethyl ether), and analyzed by GCMS, elemental analysis, and NMR spectroscopy.

(3a). Diethyl (1-propylcyclopropyl)methylphosphonate. ^1H NMR (300 MHz): δ 0.34 (m, 2H), 0.41 (m, 2H), 0.87 (t, 3H, $J_{\text{HH}} = 6.6$ Hz), 1.30 (dt, 6H, $J_{\text{HH}} = 6.9$, $^4J_{\text{PH}} = 0.2$ Hz), 1.32-1.47 (overlap, 4H), 1.77 (d, 2H, $^2J_{\text{PH}} = 18.0$ Hz), 3.98-4.18 (m, 4H). ^{31}P NMR (121.4 MHz): δ 31.88. ^{13}C NMR (75.5 MHz): δ 12.7, 12.8, 14.1, 15.0 (d, $^2J_{\text{PC}} = 4.2$ Hz), 16.42 (d, $^3J_{\text{PC}} = 6.0$ Hz), 22.8, 32.3 (d, $^1J_{\text{PC}} = 140.0$ Hz), 36.7, 61.3 (d, $^2J_{\text{PC}} = 6.6$ Hz). MS m/z : 234 (32.2), 219 (55.5), 205 (27.5), 191 (26.7), 163 (47.8), 149 (45.3), 138 (40.3), 125 (33.2), 111 (70.3), 81 (72.4), 67 (40.1), 57 (39.2), 41 (68.8), 28 (100). Anal. Calcd for $\text{C}_{11}\text{H}_{23}\text{O}_3\text{P}$: C, 56.39; H, 9.90; P, 13.22. Found: C, 56.47; H, 9.84; P, 13.08.

(3c). Diethyl (1-pentylcyclopropyl)methylphosphonate. ^1H NMR (300 MHz): δ 0.34 (m, 2H), 0.42 (m, 2H), 0.84 (t, 3H, $J_{\text{HH}} = 6.6$ Hz), 1.28 (dt, 6H, $J_{\text{HH}} = 6.9$, $^4J_{\text{PH}} = 0.2$ Hz), 1.35-1.47 (overlap, 8H), 1.71 (d, 2H, $^2J_{\text{PH}} = 17.7$ Hz), 3.97-4.17 (m, 4H). ^{31}P NMR (121.4 MHz): δ 31.64. ^{13}C NMR (75.5 MHz): δ 12.7, 12.8, 14.0, 16.1 (d, $^2J_{\text{PC}} = 6.9$ Hz), 16.4 (d, $^3J_{\text{PC}} = 6.0$ Hz), 22.6, 26.2, 31.9, 32.3 (d, $^1J_{\text{PC}} = 140.1$ Hz), 36.9, 61.2 (d, $^2J_{\text{PC}} = 6.6$ Hz). MS m/z : 262 (50.0), 247 (14.7), 233 (57.8), 219 (59.8), 207 (35.3), 191 (25.5), 177 (21.6), 163 (36.0), 149 (40.2), 138 (34.3), 124 (32.3), 111 (60.8), 81 (61.8), 67 (32.4), 57 (39.2), 41 (46.7), 28 (100). Anal. Calcd for $\text{C}_{13}\text{H}_{27}\text{O}_3\text{P}$: C, 59.52; H, 10.37; P, 11.81. Found: C, 59.59; H, 10.41; P, 11.70.

(3d). Diethyl (1-(2-(benzyloxy)ethylcyclopropyl)methylphosphonate. ^1H NMR (300 MHz): δ 0.44 (m, 2H), 0.47 (m, 2H), 1.27 (dt, 6H, $J_{\text{HH}} = 6.9$, $^4J_{\text{PH}} = 0.2$ Hz), 1.74 (t, 2H, $J_{\text{HH}} = 6.6$ Hz), 1.76 (d, 2H, $^2J_{\text{PH}} = 17.7$ Hz), 3.58 (t, 2H, $J_{\text{HH}} = 6.6$ Hz), 3.92-4.15 (m, 4H), 4.47 (s, 2H), 7.20-7.35 (m, 5H). ^{31}P NMR (121.4 MHz): δ 31.38.

^{13}C NMR (75.5 MHz): δ 12.6, 12.8, 16.1 (d, $^2J_{\text{PC}} = 6.6$ Hz), 16.4 (d, $^3J_{\text{PC}} = 6.0$ Hz), 25.5, 32.7 (d, $^1J_{\text{PC}} = 139.8$ Hz), 36.4, 61.2 (d, $^2J_{\text{PC}} = 6.6$ Hz), 67.9, 127.4, 127.5, 127.5, 127.6, 128.2, 138.5. MS m/z : 226 (1.0), 296 (2.0), 281 (1.0), 267 (1.0), 235 (12.7), 220 (32.4), 161 (15.7), 149 (5.9), 129 (14.7), 91 (100), 77 (4.9), 65 (15.7), 41 (7.8), 29 (5.9). Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{O}_4\text{P}$: C, 62.56; H, 8.34; P, 9.49. Found: C, 62.45; H, 8.48; P, 9.42.

(3e). Diethyl 2[^2H] (1-butylcyclopropyl)methylphosphonate. ^1H NMR (300 MHz): δ 0.37 (m, 2H), 0.44 (m, 2H), 0.84 (t, 3H, $J_{\text{HH}} = 6.3$ Hz), 1.31 (dt, 6H, $J_{\text{HH}} = 7.2$, $^4J_{\text{PH}} = 0.3$ Hz), 1.40-1.8 (overlap, 6H), 4.06-4.14 (m, 4H). ^{31}P NMR (121.4 MHz): δ 31.77. ^{13}C NMR (75.5 MHz): δ 12.7, 12.8, 14.1, 14.9 (d, $^2J_{\text{PC}} = 4.0$ Hz), 16.5 (d, $^3J_{\text{PC}} = 6.0$ Hz), 22.8, 28.8, 31.0 (d, $^1J_{\text{PC}} = 145.1$ Hz), 36.7, 61.2 (d, $^2J_{\text{PC}} = 6.9$ Hz). MS m/z : 250 (37.3), 235 (10.8), 221 (100), 207 (14.7), 193 (29.4), 165 (91.2), 138 (29.5), 111 (59.8), 97 (25.5), 81 (49.0), 80 (49.0), 69 (29.5), 41 (29.5), 29 (34.3). Anal. Calcd for $\text{C}_{12}\text{H}_{23}\text{D}_2\text{O}_3\text{P}$: C, 57.58; H, 10.87; P, 12.37. Found: C, 57.71; H, 10.77; P, 12.30.

(3f). Diphenyl (1-pentylcyclopropyl)methylphosphonate. The synthesis is identical to the procedure for synthesis of compounds **3**, except that Cp_2ZrEt_2 and diphenyl hex-1-ynylphosphonate were stirred overnight.

^1H NMR (300 MHz): δ 0.41 (m, 2H), 0.50 (m, 2H), 0.91 (t, 3H, $J_{\text{HH}} = 7.5$ Hz), 1.20-1.60 (overlap, 4H), 1.43 (d, 2H, $^2J_{\text{PH}} = 14.7$ Hz), 1.86 (m, 2H), 2.35 (m, 2H), 6.40-7.46 (overlap, 10H). ^{31}P NMR (121.4 MHz): δ 25.91. ^{13}C NMR (75.5 MHz): δ 13.4, 14.1, 19.2 (d, $^2J_{\text{PC}} = 4.3$ Hz), 21.9, 22.8, 28.9, 29.6, 31.0 (d, $^1J_{\text{PC}} = 140.0$ Hz), 36.9, 116.4, 116.5, 116.5, 120.5, 125.1, 130.0. MS m/z : 358 (6.9), 343 (5.7), 329 (7.4), 281 (4.5), 269 (5.0), 253 (18.6), 239 (63.7), 225 (100), 211 (70.6), 197 (42.2), 183 (53.9), 157 (90.2), 143 (16.7), 129 (65.7), 116 (56.9), 81 (58.8), 79 (39.2), 77 (39.2), 41

(92.2). Anal. Calcd for $C_{21}H_{27}O_3P$: C, 70.37; H, 7.59; P, 8.64. Found: C, 70.25; H, 7.64; P, 8.71.

(3g). Diethyl (1-(3-chloropropyl)cyclopropyl)methylphosphonate. 1H NMR (300 MHz): δ 0.30 (m, 2H), 0.47 (m, 2H), 1.05 (t, 3H, $J_{HH} = 7.5$ Hz), 1.30 (dt, 6H, $J_{HH} = 6.9$, $^4J_{PH} = 0.2$ Hz), 1.36 (m, 2H), 1.71 (d, 2H, $^2J_{PH} = 18.0$ Hz), 3.52 (t, 2H, $J_{HH} = 7.5$ Hz), 3.98-4.15 (m, 4H). ^{31}P NMR (121.4 MHz): δ 31.92. ^{13}C NMR (75.5 MHz): δ 12.7, 12.8, 15.0 (d, $^2J_{PC} = 4.3$ Hz), 16.4 (d, $^3J_{PC} = 6.3$ Hz), 17.9, 32.4 (d, $^1J_{PC} = 140.1$ Hz), 41.0, 61.3 (d, $^2J_{PC} = 6.6$ Hz). MS m/z : 270 (0.3), 268 (1.0), 233 (70.6), 231 (66.7), 219 (28.4), 205 (44.1), 177 (46.0), 163 (46.0), 149 (63.7), 148 (40.2), 125 (38.2), 111 (100), 99 (92.2), 97 (92.2), 81 (91.8), 67 (60.8), 41 (68.6), 29 (53.9). Anal. Calcd for $C_{11}H_{22}ClO_3P$: C, 49.17; H, 8.25; Cl, 13.19; P, 11.53. Found: C, 49.08; H, 8.31; Cl, 13.29; P, 11.43.

(3h). Diethyl (1-cyclopropylcyclopropyl)methylphosphonate. 1H NMR (300 MHz): δ 0.26 (m, 2H), 0.25-0.35 (overlap, 6H), 1.29 (dt, 6H, $J_{HH} = 7.2$, $^4J_{PH} = 0.2$ Hz), 1.84 (d, 2H, $^2J_{PH} = 17.7$ Hz), 4.00-4.12 (m, 4H). ^{31}P NMR (121.4 MHz): δ 31.7. ^{13}C NMR (75.5 MHz): δ 2.8, 8.6, 9.7, 9.9, 15.1 (d, $^2J_{PC} = 4.2$ Hz), 16.4 (d, $^3J_{PC} = 6.0$ Hz), 35.5 (d, $^1J_{PC} = 140.0$ Hz), 61.3 (d, $^2J_{PC} = 6.6$ Hz). MS m/z : 232 (7.8), 217 (11.8), 203 (10.8), 175 (20.6), 161 (29.4), 148 (12.7), 137 (14.7), 124 (10.8), 111 (33.3), 94 (88.2), 93 (100), 78 (71.6), 65 (23.5), 41 (21.6), 29 (18.6). Anal. Calcd for $C_{11}H_{21}O_3P$: C, 56.88; H, 9.11; P, 13.34. Found: C, 57.02; H, 9.07; P, 13.26.

(3i). Diethyl (1-(4-methylpentyl)cyclopropyl)methylphosphonate. 1H NMR (300 MHz): δ 0.36 (m, 2H), 0.45 (m, 2H), 0.83 (d, 2H, $J_{HH} = 5.4$), 1.31 (dt, 6H, $J_{HH} = 6.9$, $^4J_{PH} = 0.2$ Hz), 1.25-1.47 (overlap, 7H), 1.74 (d, 2H, $^2J_{PH} = 18.0$ Hz), 4.02-4.12 (m, 4H). ^{31}P NMR (121.4 MHz): δ 31.88. ^{13}C NMR (75.5 MHz): δ 11.4, 12.7, 12.9, 15.6 (d, $^2J_{PC} = 4.2$ Hz), 16.5 (d, $^3J_{PC} = 6.0$ Hz), 19.1, 29.4, 32.2 (d, $^1J_{PC} = 146.0$ Hz), 33.2,

34.5, 61.2 (d, $^2J_{\text{PC}} = 6.6$ Hz). MS m/z : 276 (24.5), 261 (10.8), 247 (39.2), 219 (100), 207 (14.7), 191 (22.5), 163 (30.4), 152 (23.5), 137 (16.7), 125 (13.7), 111 (21.6), 81 (24.5), 67 (12.7), 55 (13.2), 41 (22.1). Anal. Calcd for $\text{C}_{14}\text{H}_{29}\text{O}_3\text{P}$: C, 60.85; H, 10.58; P, 11.21. Found: C, 61.00; H, 10.45; P, 11.13.