One-Step Synthesis of Spiropyridines, a Novel Class of C_2-Symmetric Chiral Ligands, by Cobalt(I)-Catalyzed [2 + 2 + 2] Cycloadditions between *bis*–Alkynenitriles and Alkynes

Jesús A. Varela, Luis Castedo and Carlos Saá*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Facultad de Química, Universidad de Santiago de Compostela, 15706 Santiago de Compostela. SPAIN.

SUPPORTING INFORMATION

Organic Letters

Ms No.: ol991195m

2,2-Di(3-butynyl)malononitrile 1. A suspension of 0.5 g (16.6 mmol) of NaH (80%, dispersion in mineral oil) was washed two times with 10 mL of dry THF. Then, a solution of malononitrile (0.5 g, 7.6 mmol) in dry THF (15 mL) was added with concomitant evolution of hydrogen. Once the gas evolution was ceased, a solution of tosylate of 3-butyn-1-ol (4.24 g, 18.9 mmol, 2.5 eq) and NaI (2.84 g, 18.9 mmol, 2.5 eq) in THF (15 mL) was added and the resulting mixture was refluxed for 4 h. After reaching r.t., an aqueous solution of Na_2CO_3 (30 mL) was added and extracted with ether (3 x 30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography on silica gel with a mixture of hexane/EtOAc 90:10 as eluent. Two products were isolated: dialkylated malononitrile **1** (0.604 g, 47%, R_f= 0.32, hexane/EtOAc 80:20) and monoalkylated malononitrile (0.42 g, 47%, R_f= 0.35, hexane/EtOAc 80:20).

An independent alkylation of the monoalkylated malononitrile (0.57 g, 4.90 mmol) was performed under similar conditions: NaH, 0.33 g (7.65 mmol), tosylate 1.71 g (7.65 mmol), NaI 1.14 g (7.65 mmol) in THF (20 mL) gave **1** in 66% yield.

White crystals (from ether/hexane); mp 51-53 °C, IR (KBr) 3278, 2253, 2122, 1453, 677 cm^{-1}; ^{1}H-NMR (300 MHz) δ: 2.60 (dt, *J*= 7.4, 2.6 Hz, 4H), 2.25 (t, *J*= 7.4 Hz, 4H), 2.12 (t, *J*= 2.6 Hz, 2H); ^{13}C-NMR, DEPT (75 MHz) δ: 114.1 (CN), 79.8 (C), 71.1 (CH), 36.2 (C), 36.1 (CH_2), 15.3 (CH_2); EI MS *m/z* (rel intens %): 170 (M^+, 12), 169 (100), 155 (13), 142 (17), 91 (30); EI HRMS calcd for $C_{11}H_{10}N_2$: 170.081977; found: 170.084398. Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62%; H, 5.92; N, 16.46%. Found: C, 77.29%; H, 6.19%; N, 16.43%.

2,2-Di(4-pentynyl)malononitrile 2. To a solution of malononitrile (0.77 g, 11.7 mmol) and the tosylate of 4-pentyn-1-ol (6.14 g, 25.7 mmol) in dry DMF (6 mL) was added DBU (3.85 mL, 25.8 mmol). The reaction mixture was refluxed for 5 h and, once cooled to r.t., the mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with an aqueous solution of HCl 5N (3 x 20 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography on silica gel with a mixture of hexane/EtOAc 80:20 as eluent giving malononitrile **2** (2.22 g, 95%) as a yellow oil.

IR (NaCl) 3286, 2934, 2246, 2115, 1456, 650 cm^{-1}; ^{1}H-NMR (250 MHz) δ: 2.35 (dt, *J*= 6.5, 2.6 Hz, 4H), 2.10 (m, 4H), 2.03 (t, *J*= 2.6 Hz, 2H), 1.95-1.85 (m, 4H); ^{13}C-NMR, DEPT (63 MHz) δ: 115.2 (CN), 81.9 (C), 70.1 (CH), 37.1 (C), 36.6 (CH_2), 24.2 (CH_2), 17.7 (CH_2); EI MS *m/z* (rel intens %): 198 (M^+, 8), 197 (53), 169 (38), 132 (100); EI HRMS calcd for $C_{13}H_{14}N_2$: 198.115699; found: 198.110737.

CpCo(COD)-catalyzed [2+2+2] cycloaddition between *bis*-alkynenitrile 1 and acetylene (3a).

A solution of **1** (0.6 g, 3.52 mmol) and CpCo(COD) (0.245 g, 1.05 mmol, 30%) in toluene (50 mL) is introduced in a Parr reactor and filled with acetylene until 2.3 Bar. Then the reactor is heated at 137 °C overnight (the internal pressure is raised to 9 Bar). Once the reactor reaches room temperature and the gas pressure is released, the volatiles were removed under vacuum and the residue was chromatographed on neutral alumina (activity IV) using a mixture of hexane/EtOAc 8:2 as eluent. Two products were obtained in order of elution: 0.15 g of pyridine **6** (14%, R_f= 0.87, EtOAc/MeOH 95:5) and 0.25 g of spiropyridine **4a** (32%, R_f= 0.25 (EtOAc/MeOH 95:5).

7-[2-(phenyl)ethyl]-7-(2-pyridyl)-6,7-dihydro-5H-cyclopenta[b]pyiridine **6**. Brown oil; ^{1}H-NMR (250 MHz) δ: 8.56-8.54 (m, 1H), 8.47-8.46 (m, 1H), 7.54-7.46 (m, 3H), 7.23-7.02 (m, 7H), 3.21-3.11 (m, 1H), 2.95-2.89 (m, 2H), 2.72-2.27 (m, 5H); ^{13}C-NMR, DEPT (63 MHz) δ: 167.4 (C), 163.9 (C), 148.4 (CH), 147.6 (CH), 142.5 (C), 137.6 (C), 136.0 (CH), 132.4 (CH), 128.2 (CH), 128.0 (CH), 125.4 (CH), 121.7 (CH), 121.5 (CH), 121.0 (CH), 73.8 (C), 71.3 (CH_2), 72.7 (CH_2), 60.9 (CH_2), 72.1 (CH_2).

[7,7']-spiro-6,6',7,7'-tetrahydro-bi-5H-cyclopenta[b]pyridine **4a**: white cystals (from hexane/EtOAc), mp 116-118 °C; ^{1}H-NMR (300 MHz) δ: 8.35 (d, *J*= 5.1 Hz, 2H), 7.56 (d, *J*= 7.4 Hz, 2H), 7.04 (dd, *J*= 7.4, 5.1 Hz, 2H), 3.26-3.16 (m, 2H), 3.06-2.96 (m, 2H), 2.65-2.56 (m, 2H), 2.34-2.25 (m, 2H); ^{13}C-NMR, DEPT (75 MHz) δ: 168.7 (C), 148.4 (CH), 136.8 (C), 132.5 (CH), 121.6 (CH), 60.4 (C), 37.6 (CH_2), 28.6 (CH_2). EI MS *m/z* (rel intens %): 222 (M^+, 100), 207 (62). EI HRMS calcd for $C_{15}H_{14}N_2$: 222.115699; found: 222.115407. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05%; H, 6.35%; N, 12.60%. Found: C, 81.01%; H, 6.44%; N, 12.74%.

HPLC: *t*R first enantiomer, 17.50 min; *t*R second enantiomer, 22.19 min, (Daicel, Chiralcel OJ, hexane/isopropanol 9:1, 0.5 mL/min). First enantiomer: CD (EtOH) λ (nm): 212 (+), 258 (+), 276 (–), 281 (–). Second enantiomer: CD (EtOH) λ (nm): 212 (–), 258 (–), 276 (+), 281 (+).

Other experiments using the same amounts of **1** but higher or lower acetylene pressure (5 or 1.2 Bar) gave poorer results: **4a**, 20 % and 14%, respectively.

$CpCo(C_2H_4)_2$-catalyzed [2+2+2] cycloaddition between *bis*-alkynenitrile 1 and acetylene (3a).

A solution of **1** (0.1 g, 0.58 mmol) in toluene (7 mL) is placed in a purged Schlenk at –20 °C and then acetylene (**3a**) was bubbled for 30 min. Then, a solution of $CpCo(C_2H_4)_2$ (0.031 g, 0.17 mmol, 30%) in toluene (2 mL) at –20 °C was cannulated into the flask. After stirring 45 min at this temperature (no conversion by tlc monitoring), the solution was allowed to reach rt and stirred for 4 h (an extra amount of catalyst, 0.2 mmol, was needed for completion). After workup as above two products were isolated: **4a** (27 mg, 21%) and **6** (19 mg, 11%).

A variation of experimental conditions, bubbling acetylene atfer having added the catalyst to the solution of **1**, gave poorer results.

General procedure for the $CpCo(CO)_2$-catalyzed [2+2+2] cycloaddition between *bis*-alkynenitriles and alkynes

A solution of *bis*-alkynenitrile (**1** or **2**, 0.1 g, 1 equiv), **3** (see each case below) and $[CpCo(CO)_2]$ (30%) in toluene (10 mL) was irradiated for several hours under Ar in a round-bottomed flask equipped with a reflux condenser. The reaction vessel was irradiated with a Philips PF 808 300W tungsten slide projector lamp placed ca. 5 cm from the center of the flask and operated at 225 W. The volatile components were removed under vacuum and the residue was chromatographed on silica gel.

[7,7']-spiro-6,6',7,7'-tetrahydro-bi-5H-cyclopenta[b]pyridine **4 a**. Conditions: malononitrile **1**, 0.1 g, 0.58 mmol; acetylene **3a**, bubbling 10 min; irradiation time, 5 h.

[7,7']espiro-6,6',7,7'-tetrahydro-2,2',3,3'-tetra(trimethylsilyl)-bi-5H-cyclopenta[b]pyridine **4b**. Conditions: malononitrile**1**, 0.1 g, 0.58 mmol; alkyne **3b**, 5 mL; irradiation time, 4.5 h.

R_f= 0.92 (hexane/EtOAc 90:10); ^{1}H-NMR (250 MHz) δ: 7.40 (s, 2H), 3.33-3.20 (m, 2H), 2.69-2.58 (m, 2H), 2.47-2.38 (m, 2H), 2.05-1.81 (m, 2H), 0.10 (s, 18H), 0.01 (s, 18H); ^{13}C-NMR, DEPT (63 MHz) δ: 170.4 (C), 168.2 (C), 137.7 (C), 136.7 (CH), 133.7 (C), 60.2 (C), 37.2 (CH_2), 29.4 (CH_2), 1.39 (CH_3), 1.29 (CH_3); EI MS* *m/z* (rel intens %): 366 (M^+ - 2 TMS, 100), 351 (43), 235 (43); EI HRMS calcd for $C_{21}H_{30}N_2Si_2$: 366.194756; found: 366.193865.

* This product loses both TMS in α to the nitrogen on standing.

[7,7']-spiro-6,6',7,7'-tetrahydro-2,2',3,3'-tetra(phenyl)-bi-5H-cyclopenta[b]pyridine **4c**. Conditions: malononitrile **1**, 0.1 g, 0.58 mmol; alkyne **3c**, 0.24 g, 1.35 mmol, 2.3 eq; irradiation time, 2 h.

R_f= 0.32 (CH_2Cl_2/hexane 1:1). Pale brown crystals (from CH_2Cl_2/hexane), mp 271-273 °C; ^{1}H-NMR (250 MHz) δ: 7.53 (s, 2H), 7.32-7.11 (m, 20H), 3.51-3.38 (m, 2H), 3.1-2.98 (m, 2H), 2.88-2.78 (m, 2H), 2.44-2.33 (m, 2H); ^{13}C-NMR, DEPT (63 MHz) δ: 168 (C), 155.3 (C), 141 (C), 140.8 (C), 135.5 (C), 134.8 (CH), 134.0 (C), 130.2 (CH), 129.7 (CH), 128.1 (CH), 127.5 (CH), 127.1 (CH), 126.6 (CH), 60.1 (C), 38.0 (CH_2), 28.7 (CH_2); EI MS *m/z* (rel intens %): 526 (M^+, 100), 511 (13), 296 (18), 263 (15); EI HRMS calcd for $C_{39}H_{30}N_2$: 526.240899; found: 526.239842.

Tetramethyl esther of [7,7']-spiro-6,6',7,7'-tetrahydro-bi-5H-cyclopenta[b]pyridine-2,2',3,3'-tetracarboxylic acid **4d.** Conditions: malononitrile **1**, 0.09 g, 0.53 mmol; alkyne **3d**, 0.225 g, 1.58 mmol, 3 eq; irradiation time, 2 h.

R_f= 0.37 (hexane/EtOAc 1:1); IR (KBr): 2955, 1741, 1445 cm^{-1}; ^{1}H-NMR (250 MHz) δ: 8.03 (s, 2H), 3.87 (s, 12H), 3.46-3.33 (m, 2H), 3.07-2.95 (m, 2H), 2.81-2.71 (m, 2H), 2.38-2.23 (m, 2H); ^{13}C-NMR, DEPT (63 MHz) δ: 171.1 (C), 167.4 (CO), 165.9 (CO), 150.6 (C), 138.7 (C), 133.8 (CH), 124.0 (C), 60.2 (C), 52.7 (CH_3), 52.6 (CH_3), 37.5 (CH_2), 28.5 (CH_2); EI MS *m/z* (rel intens %): 454 (M^+, 6), 395 (100); EI HRMS calcd for $C_{23}H_{22}N_2O_8$: 454.137616; found: 454.137456.

[7,7']-spiro-6,6',7,7'-tetrahydro-3,3'-bis(trimethylsilyl)-2,2'-{bis[trimethylsilyl)ethynyl]}bi-5H-cyclopenta[b]pyridine **4e**. Conditions: malononitrile **1**, 0.11 g, 0.58 mmol; alkyne **3e**, 0.05 g , 0.29 mmol; irradiation time, 6 h.

R_f= 0.4 (hexane/EtOAc 95:5). Pale brown crystals (from hexane/EtOAc); mp 256-258 °C; IR (KBr) 2953, 2154, 846 cm^{-1}; ^{1}H-NMR (250 MHz) δ: 7.59 (s, 2H), 3.29 (ddd, *J*=15.8, 8.3, 6.3 Hz, 2H), 2.91 (ddd, *J*=15.8, 8.7, 5.5 Hz, 2H), 2.62 (ddd, *J*=12.9, 8.3, 5.5 Hz, 2H), 2.17 (ddd, *J*=12.9, 8.7, 6.3 Hz, 2H), 0.36 (s, 18H), 0.22 (s, 18H); ^{13}C-NMR, DEPT (63 MHz) δ: 169.3 (C), 145.8 (C), 138.0 (CH), 136.4 (C), 135.6 (C), 106.8 (C), 95.4 (C), 60.5 (C), 37.6 (CH_2), 28.9 (CH_2), -0.4 (CH_3), -1.5 (CH_3); EI MS *m/z* (rel intens %): 558 (M^+, 28), 543 (M^+-CH_3, 13), 485 (M^+-TMS, 19), 149 (100); EI HRMS calcd for $C_{31}H_{46}N_2Si_4$: 558.27381; found 558.274034.

[8,8']-spiro-3,3'-bis(trimethylsilyl)-bitetrahydroquinoline **5b'**. Conditions: malononitrile **2**, 0.1 g, 0.5 mmol; alkyne **3b**, 5 mL; irradiation time, 3 h.

R_f= 0.92* (hexane/EtOAc 90:10); ^{1}H-NMR (300 MHz) δ: 8.39 (s, 2H), 7.46 (s, 2H), 3.05-2.98 (m, 2H), 2.82-2.76 (m, 2H), 2.36-2.25 (m, 2H), 2.13-2.09 (m, 2H), 1.94-1.85 (m, 4H), 0.23 (s, 18H); ^{13}C-NMR, DEPT (75 MHz) δ: 164.6 (C), 151.4 (CH), 142.3 (CH), 131.7 (C), 131.0 (C), 52.9 (C), 36.6 (CH_2), 29.6 (CH_2), 19.2 (CH_2), -1.3 (CH_3).

* This R_f corresponds to the initial bis-TMS spiropyridine **5b**.

[8,8']-spiro-3,3'-bis(trimethylsilyl)-2,2'{bis[trimethylsilyl)ethynyl]}bitetrahydroquinoline **5e**. Conditions: malononitrile **2**, 0.2 g, 1 mmol; alkyne **3e**, 0.2 g, 1 mmol, 1 eq; irradiation time, 6 h.

R_f= 0.45 (hexane/EtOAc 95:5). White crystals (from hexane/EtOAc), mp 256-257 °C; IR (KBr) 2950, 2864, 2150, 1524, 1400, 1248, 842 cm^{-1}; ^{1}H-NMR (250 MHz) δ: 7.40 (s, 2H), 3.12-2.93 (m, 2H), 2.80-2.63 (m, 2H), 2.50-2.30 (m, 2H), 2.00–1.80 (m, 4H), 0.90-0.80 (m, 2H), 0.34 (s, 18H), 0.20 (s, 18H); ^{13}C-NMR, DEPT (63 MHz) δ: 164.2 (C), 144.2 (C), 142.4 (CH), 133.8 (C), 132.0 (C), 107.1 (C), 94.0 (C), 47.0 (C), 37.3 (CH_2), 29.7 (CH_2), 19.1 (CH_2), 0.3 (CH_3), -1.4 (CH_3); EI MS *m/z* (rel intens %): 586 (M^+, 100), 558 (49), 513 (45); EI HRMS calcd for $C_{33}H_{50}N_2Si_4$: 586.305114; found: 586.303436. Anal. Calcd for $C_{33}H_{50}N_2Si_4$: C, 67.51%; H, 8.58%; N, 4.77%. Found: C, 67.39%; H, 8.99%; N, 5.15%.

Cu(I) complex 7. Tetrakis(acetonitrile)copper(I) hexafluorophosphate (17 mg, 0.045 mmol) was added to a stirred solution of 7,7'-spiropyridine **4a** (20 mg, 0.09 mmol) in dry, degassed CH_2Cl_2 (5 mL) and the resulting yellow-green solution was kept at room temperature under Ar overnight. After removal of solvent under reduced pressure, the solid residue was recrystallized from CH_2Cl_2/ diethyl ether to yield 29 mg (98%) of $[Cu^I(\mathbf{4a})_2]PF_6$ **7**: pale yellow powder; FAB+ (m-NBA, rel %): 507 ($[M - PF_6]^+$, 93%), 285 (100%); ^1H NMR (250 MHz, $CDCl_3$) δ: 7.96 (br s, 4H), 7.63 (d, *J*= 7.3 Hz, 4H), 7.11 (br s, 4H), 3.02 (br s, 8H), 2.37-2.28 (m, 4H), 2.19-2.11 (m, 4H); FAB HRMS calcd for $C_{30}H_{28}N_4Cu^{65}$ ($[M–PF_6]^+$): 509.159190; found: 509.157906; FAB HRMS calcd for $C_{30}H_{28}N_4Cu^{63}$ ($[M–PF_6]^+$): 507.160996; found: 507.158720.