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Pseudo six-component stereoselective synthesis of 2,4,6-triaryl-3,3,5,5-tetracyanopiperidines

Anatoly N. Vereshchagin, Kirill A. Karpenko, Michail N. Elinson, Evgeniya O. Dorofeeva, Alexander S. Goloveshkin and Mikhail P. Egorov

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM300 at ambient temperature in DMSO-d_6 solutions. Chemical shifts values are given in δ scale relative to Me_4Si. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass-spectra (EI = 70 eV) were recorded with a Finningan MAT INCOS 50 spectrometer. All starting materials were obtained from commercial sources and used without purification.

General procedure. A mixture of aromatic aldehyde **1a,c-g** (9 mmol), malononitrile (396 mg, 6 mmol) and ammonium acetate (6 mmol) was refluxed in methanol (5 ml) for 2 h. In the case of *p*-tolualdehyde **2b**, ammonia (25% aq., 6 mmol) was used instead of NH_4OAc, reaction temperature 25°C, reaction time 6 h. Then reaction mixture was cooled to -10 °C for 15 min. The solid precipitate was filtered and dried to afford pure products **2a-g**.

***cis*,*cis*-2,4,6-Triphenylpiperidine-3,3,5,5-tetracarbonitrile (2a)**. White solid, yield 1.05 g, 85%, mp = 191-192 °C (lit. [S1] mp 178-179 °C). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 4.79 (s, 2H, CH), 4.82 (s, 1H, CH), 4.99 (s, 1H, NH), 7.45-7.77 (m, 13H, Ar), 7.85-7.95 (m, 2H, Ar).

***cis*,*cis*-2,4,6-Tris(4-methylphenyl)piperidine-3,3,5,5-tetracarbonitrile (2b).** White solid, yield 1.05 g, 72%, mp = 161-162 °C (lit. [S1] mp 159–160 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 2.38 (s, 9H, 3 CH_3), 4.64 (s, 1H, CH), 4.71 (s, 2H, CH), 4.88 (s, 1H, CH), 7.30 (d, J = 8.6 Hz, 4H, Ar), 7.40 (d, J = 8.5 Hz, 2H, Ar), 7.58 (d, J = 8.6 Hz, 4H, Ar), 7.76 (d, J = 8.5 Hz, 2H, Ar).

***cis*,*cis*-2,4,6-Tris(2-fluorophenyl)piperidine-3,3,5,5-tetracarbonitrile (2c).** White solid, yield 0.98 g, 70%, mp = 175-176 °C. IR (ν_{max}/cm^{-1}): 3333, 2968, 1617, 1589, 1494, 1461, 1378, 1283, 1241, 813. MS, m/z (%): [M^+] (1), 230 (86), 201 (7), 183 (21), 172 (44), 145 (47), 124 (24), 123 (100), 122 (75). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 4.81 (s, 1H, CH), 5.56 (s, 1H, NH), 5.61 (s, 2H, CH), 7.28–7.59 (m, 9H, Ar), 8.01 (t, J = 7.3 Hz, 2H, Ar), 8.29 (t, J = 7.3 Hz, 1H, Ar). ^{13}C NMR (75.47 MHz,

DMSO-d6) δ: 43.5, 57,4 (2C), 58.1 (2C), 112.0 (2C), 112.1 (2C), 115.1 (d, $J^4_{C–F}$ = 4.4 Hz) (2C), 115.7 (d, $J^4_{C–F}$ = 4.4 Hz), 116.1 (d, $J^3_{C–F}$ = 8.8 Hz) (2C), 116,3 (d, $J^3_{C–F}$ = 7.7 Hz), 127.7, (d, $J^3_{C–F}$ = 21.0 Hz) (2C), 129.1 (d, $J^2_{C–F}$ = 28.9 Hz), 129.2 (d, $J^2_{C–F}$ = 26.5 Hz) (2C), 129.3 (d, $J^2_{C–F}$ = 24.8 Hz), 131.1 (d, $J^2_{C–F}$ = 8.9 Hz) (2C), 131.8 (d, $J^2_{C–F}$ = 7.7 Hz), 159.3 (d, $J^1_{C–F}$ = 247.7 Hz) (2C), 159.5 (d, $J^1_{C–F}$ = 245.5 Hz). Anal. Calcd. for $C_{27}H_{16}F_3N_5$: C, 69.37; H, 3.45; N, 14.98. Found: C, 69.32; H, 3.48; N, 14.96.

***cis,cis*-2,4,6-Tris(4-fluorophenyl)piperidine-3,3,5,5-tetracarbonitrile (2d).** White solid, yield 1.16 g, 83%, mp = 187-188 °C. IR (ν_{max}/cm^{-1}): 3569, 3338, 2255, 2232, 1608, 1512, 1431, 1239, 1162, 842. MS, m/z (%): [M$^+$–CN] (0.2), 414 (0.3) 295 (99), 231 (27), 230 (99), 183 (33), 173 (21), 172 (100), 145 (49), 123 (98), 122 (72). ^{1}H NMR (300.13 MHz, DMSO-d6) δ: 4.80 (s, 2H, CH), 4.91 (s, 1H, NH), 5.08 (s, 1H, CH), 7.39 (t, *J* = 8.7 Hz, 4H, Ar), 7.53 (t, *J* = 8.7 Hz, 2H, Ar), 7.75–7.82 (m, 4H, Ar), 7.94–8.12 (m, 2H, Ar). ^{13}C NMR (75.47 MHz, DMSO-*d*$_6$) δ: 44.8, 47.9 (2C), 65.2 (2C), 111.8 (2C), 112.6 (2C), 115.7 (d, $J^2_{C–F}$ = 21.7 Hz) (4C), 116.9 (d, $J^2_{C–F}$ = 21.9 Hz) (2C), 128.7 (d, $J^4_{C–F}$ = 3.2 Hz) (2C), 130.5 (d, $J^3_{C–F}$ = 8.6 Hz) (4C), 131.1 (d, $J^4_{C–F}$ = 2.9 Hz), 131.4 (d, $J^3_{C–F}$ = 8.7 Hz) (2C), 161.3 (d, $J^1_{C–F}$ = 25.4 Hz) (2C), 164.7 (d, $J^1_{C–F}$ = 27.6 Hz). Anal. Calcd. for $C_{27}H_{16}F_3N_5$: C, 69.37; H, 3.45; N, 14.98. Found: C, 69.30; H, 3.45, N, 14.94.

***cis,cis*-2,4,6-Tris(3-bromophenyl)piperidine-3,3,5,5-tetracarbonitrile (2e).** White solid, yield 1.83 g, 94%, mp = 180-181 °C. IR (ν_{max}/cm^{-1}): 3340, 2253, 1720, 1572, 1476, 1436, 1021, 1075, 783, 691. MS, m/z (%): [M$^+$–$C_{10}H_5BrN_2$] 354 (11), 352 (23), 234 (51), 232 (55), 185 (32), 183 (40), 153 (100), 126 (39), 75 (37). ^{1}H NMR (300.13 MHz, DMSO-d6) δ: 3.75 (d, *J* = 5.0 Hz, 3H, CH_3 from methanol), 40.10 (q, *J* = 5.5 Hz, 1H, OH from methanol), 4.78 (s, 2H, CH), 5.06 (s, 1H, CH), 5.12 (s, 1H, NH), 7.51 (m, 2H, Ar), 7.70 (m, 6H, Ar), 7.91 (m, 3H, Ar), 8.04 (s, 1H, Ar). ^{13}C NMR (75.47 MHz, DMSO-*d*$_6$) δ: 30.6, 44.2 (2C), 47.9 (2C), 65.2 (2C), 111.6 (2C), 112.3 (2C), 121.6 (2C), 122.5 (2C), 127.8 (2C), 127.9 (2C), 130.7, 130.8, 132.1 (2C), 132.9 (2C), 133.9, 134.5, 136.9 (2C). Anal. Calcd. for $C_{27}H_{16}Br_3N_5$: C, 49.88; H, 2.48; Br, 36.87; N, 10.77. Found: C, 49.85; H, 2.53; Br, 36.80; N, 14.91.

***cis,cis*-2,4,6-Tri(3-pyridyl)piperidine-3,3,5,5-tetracarbonitrile (2f).** White solid, yield 1.15 g, 92%, mp = 174-175.5 °C. IR (ν_{max}/cm^{-1}): 3310, 3150, 2929, 2251, 1578, 1485, 1434, 1150, 1029, 722. MS, m/z (%): [M$^+$–$C_{12}H_5N_5$] (49), 155 (100), 128 (44), 106 (29), 105 (20), 104 (76), 101 (39), 100 (20), 75 (47). ^{1}H NMR (300.13 MHz, DMSO-d6) δ: 4.94 (s, 2H, CH), 5.23 (s, 1H, NH), 5.26 (s, 1H, CH), 7.60 (d, *J* = 4,4 Hz, 2H, Ar), 7.74 (d, *J* = 4,4 Hz, 1H, Ar), 8.18 (d, *J* = 7,7 Hz, 2H, Ar), 8.39 (d, *J* = 8,5 Hz, 1H, Ar), 8.72 (d, *J* = 4,4 Hz, 2H, Ar), 8.84 (d, *J* = 4.4 Hz, 1H, Ar), 8.88 (s, 2H, Ar), 8.99 (s, 1H, Ar). ^{13}C NMR (75.47 MHz, DMSO-*d*$_6$) δ: 44.3 (2C), 46.3, 48.6 (2C), 111.6 (2C),

112.3 (2C), 123.7 (2C), 124.8, 128.2, 130.3 (2C), 135.8, 136.2 (2C), 149.3 (2C), 150.3, 151.3 (2C), 152.2. Anal. Calcd. for $C_{24}H_{16}N_8$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.17; H, 3.89; N, 26.87.

Single crystals of $C_{25}H_{20}N_8O$ (**2f** solvate with MeOH) were grown from MeOH. A suitable crystal was selected and kept on a 'Bruker APEX-II CCD' diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [S2], the structure was solved with the XS [S3] structure solution program using Direct Methods and refined with the XL [S3] refinement package using Least Squares minimisation. Final crystal structure were deposited in CCDC (CCDC 1812779).

***cis,cis*-2,4,6-Tri(4-pyridyl)piperidine-3,3,5,5-tetracarbonitrile (2g).** White solid, yield 0.77 g, 62%, mp = 139-140 °C. IR (ν_{max}/cm^{-1}): 3394, 3156, 2963, 2255, 1604, 1563, 1421, 1144, 831, 813. MS, m/z (%): [M^+ - $C_9H_5N_3$] (0,3), 196(3), 155(100), 128(47), 106(27), 104(42), 101(32), 79(20), 76(20), 75(27), 63(13). ^{1}H NMR (300.13 MHz, DMSO-d6) δ: 4.88 (s, 2H, CH), 5.19 (s, 1H, CH), 5.22 (s, 1H, NH), 7.73 (d, *J* = 5.8 Hz, 4H, Ar), 7.86 (d, *J* = 5.8 2H, Ar), 8.77 (d, *J* =5.8 Hz, 4H, Ar), 8.91 (d, *J* = 5.8, 1H, Ar). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 43.0 (2C), 47.6, 64.4 (2c), 111.2 (2C), 112.0 (2C), 123.2 (4C), 123.7 (2C), 140.1, 142.7 (2C), 150.4 (4C), 151.4 (2C). Anal. Calcd. for $C_{24}H_{16}N_8$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.19; H, 3.93; N, 26.94.

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