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Stereoselective one-pot synthesis of (1*Z*)- and (1*E*)-1-arylmethylidene-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazoles by cyclization of alk-4-ynals with *o*-diaminobenzene

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Experimental

GLC analysis was performed on a Hewlett-Packard 5890 Series II instrument with an HP-1 capillary column (30 m × 0.153 mm) and a Hewlett-Packard 3396A automated integrator. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200p spectrometer in $CDCl_3$ with TMS as an internal standard. High resolution mass spectra were recorded on a Bruker micrOTOF II instrument with electrospray ionization (ESI). The measurements were performed on the positive ions (capillary voltage 4500 V). Masses were scanned in the range of m/z from 50 to 3000 Da, using an external or an internal calibration (Electrospray Calibrant Solution, Fluka). Solutions of compounds in acetonitrile were injected using a syringe, the flow rate 3 L min^{-1}. Nebulizer gas was nitrogen (4 L min^{-1}), the interface temperature was 180 ^{o}C.

Starting aldehydes **1a,b,d,f** were prepared by the interaction of isobutyraldehyde or cyclohexanecarbaldehyde with the corresponding 1-aryl-3-chloroprop-1-ynes under phase-transfer catalysis conditions according to the procedure described[1]. Palladium-catalyzed [$Pd(PPh_3)_2Cl_2$- or $Pd(PPh_3)_4$] cross-coupling of commercially available aryl halides (iodobenzene and 4-bromo-1,2-difluorobenzene) with pent-4-yn-1-ol followed by Swern oxidation was used to prepare α-unsubstituted aldehydes **1c,e**.

Synthesis of 2-(alk-3-ynyl)benzimidazoles **2a,b** *from ynals* **1a,b** *and o-diaminobenzene (general procedure).* To a solution of 2 mmol of aldehyde **1** in 3 ml of DMSO was slowly added solution of 216 mg (2 mmol) of *o*-diaminobenzene in 3 ml of anhydrous DMSO. Then, 39 mg (0.4 mmol) of NH_4Br was added, and the resulting mixture was stirred for 24 h at room temperature in the presence of dry air. Then, 30 ml of water and 30 ml of CH_2Cl_2 were added,

and the organic layer was separated. The aqueous layer was additionally extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were washed three times with water, dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was subjected to recrystallization from petroleum ether–THF mixture to give a target products **2a,b**.

2-(1,1-Dimethyl-4-phenylbut-3-yn-1-yl)-1H-benzimidazole **2a** was prepared from aldehyde **1a** and isolated in 68% yield, mp 250-251 °C. ^{1}H NMR, δ: 1.55 (s, 6H, $2CH_3$), 2.90 (s, 2H, CH_2), 7.05-7.15 (m, 2H, C^5H, C^6H), 7.20-7.25 (m, 5H, Ph), 7.45-7.55 (m, 2H, C^4H, C^7H), 11.90 (br. s, 1H, NH). ^{13}C NMR, δ: 25.0 ($2CH_3$), 30.9 (CH_2), 35.4 ($C(CH_3)_2$), 81.0, 85.8 (C≡C), 113.1 (broad, C^4, C^7), 119.9 (C^5, C^6), 121.8 (C^1, Ph), 126.2 (C^4, Ph), 126.7, 129.7 (C^2, C^3, C^5, C^6, Ph), 136.8 (broad, C^{3a}, C^{7a}), 158.8 (C^2). HRMS, *m/z* 275,1549, calculated for $C_{19}H_{18}N_2$, $[M+H]^+$: *m/z* 275.1543.

2-[1-(3-Phenylprop-2-yn-1-yl)cyclohexyl]-1H-benzimidazole **2b** was prepared from aldehyde **1b** and isolated in 74% yield, mp 238-239 °C. ^{1}H NMR, δ: 1.23-1.96 (m, 8H, *cyclo*-C_6), 2.52-2.67 (m, 2H, *cyclo*-C_6), 2.86 (s, 2H, CH_2C≡C), 7.14-7.25 (m, 2H, C^5H, C^6H), 7.25-7.41 (m, 5H, Ph), 7.58-7.70 (m, 2H, C^4H, C^7H), 12.08 (br. s, 1H, NH). ^{13}C NMR, δ: 22.1 (C^3, C^5, *cyclo*-C_6), 25.0 (C^4, *cyclo*-C_6), 32.3 (C≡C*C*H_2), 33.9 (C^2, C^6, *cyclo*-C_6), 40.7 (C^1, *cyclo*-C_6), 82.6, 86.9 (C≡C), 114.0 (broad, C^4, C^7), 120.6 (C^5, C^6), 123.0 (C^1, Ph), 127.3 (C^4, Ph), 127.8, 130.9 (C^2, C^3, C^5, C^6, Ph), 135.9 (broad, C^{3a}, C^{7a}), 158.3 (C^2). HRMS, *m/z* 315,1851, calculated for $C_{22}H_{22}N_2$, $[M+H]^+$: *m/z* 315.1856.

Characterization data for compounds ***E*****-3b** *and* ***Z*****-3b-f**

(1'E)-1'-Benzylidene-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[1,2-a]benzimidazole] ***E*****-3b** was prepared from aldehyde **1b** in 48% yield, mp 119-120 °C. ^{1}H NMR, δ: 1.40-1.83 (m, 6H, *cyclo*-C_6), 1.85-2.16 (m, 4H, *cyclo*-C_6), 3.15 (d, 2H, CH_2, ^4J 1.6 Hz), 5.77 (d, 1H, benzimidazole, ^3J 8.2 Hz), 6.16 (br.s, 1H, PhC*H*=), 6.77-6.87 (m, 1H, benzimidazole), 7.09-7.18 (m, 1H, benzimidazole), 7.14-7.40 (m, 5H, Ph), 7.71 (d, 1H, benzimidazole, ^3J 8.0 Hz). ^{13}C NMR, δ: 22.7 (C^3, C^5, *cyclo*-C_6), 25.3 (C^4, *cyclo*-C_6), 35.8 (C^2, C^6, *cyclo*-C_6), 40.5 ($C^{1,3'}$), 44.3 ($C^{2'}$), 108.5 (Ph*C*H=), 111.4, 120.1, 122.8, 123.1 ($C^{5'}$, $C^{6'}$, $C^{7'}$, $C^{8'}$), 126.4, 127.9, 128.7 (Ph), 129.5, 148.7 ($C^{4a'}$, $C^{8a'}$), 135.8, 136.1 (C^1, Ph; $C^{1'}$), 166.8 ($C^{3a'}$). HRMS, *m/z* 315,1852, calculated for $C_{22}H_{22}N_2$, $[M+H]^+$: *m/z* 315.1856.

(1'Z)-1'-Benzylidene-1',2'-dihydrospiro[cyclohexane-1,3'-pyrrolo[1,2-a]benzimidazole] ***Z*-3b** was prepared from aldehyde **1b** as yellow oil in 52% yield. ^{1}H NMR, δ: 1.40-1.83 (m, 6H, *cyclo*-C_6), 1.85-2.16 (m, 4H, *cyclo*-C_6), 3.15 (d, 2H, CH_2, ^{4}J 1.6 Hz), 5.77 (d, 1H, benzimidazole, ^{3}J 8.2 Hz), 6.16 (br.s, 1H, PhC*H*=), 6.77-6.87 (m, 1H, benzimidazole), 7.09-7.18 (m, 1H, benzimidazole), 7.14-7.40 (m, 5H, Ph), 7.71 (d, 1H, benzimidazole, ^{3}J 8.0 Hz). ^{13}C NMR, δ: 22.8 (C^3, C^5, *cyclo*-C_6), 25.4 (C^4, *cyclo*-C_6), 35.0 (C^2, C^6, *cyclo*-C_6), 40.5 ($C^{1,3'}$), 47.4 ($C^{2'}$), 108.1 (Ph*C*H=), 114.3, 119.3, 121.8, 122.3 ($C^{5'}$, $C^{6'}$, $C^{7'}$, $C^{8'}$), 127.0, 128.0, 129.5 (Ph), 129.9, 147.8 ($C^{4a'}$, $C^{8a'}$), 133.8, 135.9 (C^1, Ph; $C^{1'}$), 168.6 ($C^{3a'}$). HRMS, *m/z* 315,1850, calculated for $C_{22}H_{22}N_2$, $[M+H]^+$: *m/z* 315.1856.

(1Z)-1-Benzylidene-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole ***Z*-3c** was prepared from aldehyde **1c** in 37% yield, mp 152-154 ^{o}C. ^{1}H NMR, δ: 3.12-3.23 (m, 2H, CH_2), 3.29-3.41 (m, 2H, CH_2), 5.75 (d, 1H, benzimidazole, ^{3}J 8.1 Hz), 6.18 (br.s, 1H, PhC*H*=), 6.78-88 (m, 1H, benzimidazole), 7.09-7.19 (m, 1H, benzimidazole), 7.17-7.27 (m, 2H, Ph), 7.26-7.39 (m, 3H, Ph), 7.65 (d, 1H, benzimidazole, ^{3}J 8.1 Hz). ^{13}C NMR, δ: 23.1 (C^3), 34.7 (C^2), 107.6 (Ph*C*H=), 114.4, 119.2, 121.9, 122.5 (C^5, C^6, C^7, C^8), 127.2, 128.2, 129.7 (Ph), 130.5, 148.4 (C^{4a}, C^{8a}), 135.0, 136.0 (C^1, Ph; C^1), 163.0 (C^{3a}). HRMS, *m/z* 247.1231, calculated for $C_{17}H_{14}N_2$, $[M+H]^+$: *m/z* 247.1230.

(1Z)-1-(3,4-Difluorobenzylidene)-3,3-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]-benzimidazole ***Z*-3d** was prepared from aldehyde **1d** in 57% yield, mp 124-126 ^{o}C. ^{1}H NMR, δ: 1.58 (s, 6H, $2CH_3$), 3.12 (d, 2H, CH_2, ^{4}J 1.5 Hz), 5.87 (d, 1H, benzimidazole, ^{3}J 8.2 Hz), 6.07 (br.s, 1H, $C_6H_3F_2C$*H*=), 6.86-6.97 (m, 1H, benzimidazole), 7.11-7.21 (m, 1H, benzimidazole), 6.83-7.12 (m, 3H, $C_6H_3F_2$), 7.69 (d, 1H, benzimidazole, ^{3}J 8.1 Hz). ^{13}C NMR, δ: 26.4 ($2CH_3$), 36.6 (C^3), 51.3 (C^2), 106.3 (Ph*C*H=), 113.9, 119.7, 122.4, 122.9 (C^5, C^6, C^7, C^8), 117.1 (d, C^5, $C_6H_3F_2$, J_{CF} 17.1 Hz), 118.3 (d, C^2, $C_6H_3F_2$, J_{CF} 17.1 Hz), 125.9 (dd, C^6, $C_6H_3F_2$, J_{CF} 6.1 Hz, J_{CF} 3.3 Hz), 130.1, 148.0 (C^{4a}, C^{8a}), 132.8 (dd, C^1, $C_6H_3F_2$, J_{CF} 6.1 Hz, J_{CF} 4.1 Hz), 134.7 (C^1), 149.3 (dd, C^3, $C_6H_3F_2$, J_{CF} 248.5 Hz, J_{CF} 12.1 Hz), 149.9 (dd, C^4, $C_6H_3F_2$, J_{CF} 248.8 Hz, J_{CF} 12.1 Hz), 168.8 (C^{3a}). HRMS, *m/z* 311.1344, calculated for $C_{19}H_{16}F_2N_2$, $[M+H]^+$: *m/z* 311.1354.

(1Z)-1-(3,4-Difluorobenzylidene)-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole ***Z*-3e** was prepared from aldehyde **1e** in 32% yield, mp 126-128 ^{o}C. ^{1}H NMR, δ: 3.12-3.24 (m, 2H, CH_2), 3.28-3.40 (m, 2H, CH_2), 5.85 (d, 1H, benzimidazole, ^{3}J 8.2 Hz), 6.06 (br.s, 1H, $C_6H_3F_2C$*H*=), 6.83-7.30 (m, 5H, benzimidazole, Ph), 7.66 (d, 1H, benzimidazole, ^{3}J 8.1 Hz). ^{13}C NMR, δ: 23.1 (C^3), 34.9 (C^2), 105.4 ($C_6H_3F_2$*C*H=), 113.9, 119.5, 122.3, 123.0 (C^5, C^6, C^7, C^8), 117.1 (d, C^5, $C_6H_3F_2$, J_{CF} 17.3 Hz), 118.4 (d, C^2, $C_6H_3F_2$, J_{CF} 17.1 Hz), 126.0 (dd, C^6, $C_6H_3F_2$, J_{CF} 5.7 Hz, J_{CF} 3.3 Hz), 130.3, 148.5 (C^{4a}, C^{8a}), 132.9 (dd, C^1, $C_6H_3F_2$, J_{CF} 6.1 Hz, J_{CF} 4.1 Hz), 135.9 (C^1), 149.2

(dd, C^3, $C_6H_3F_2$, J_{CF} 248.5 Hz, J_{CF} 12.1 Hz), 149.8 (dd, C^4, $C_6H_3F_2$, J_{CF} 248.8 Hz, J_{CF} 12.1 Hz), 163.0 (C^{3a}). HRMS, *m/z* 283.1042, calculated for $C_{17}H_{12}F_2N_2$, $[M+H]^+$: *m/z* 283.1041.

(1Z)-3,3-Dimethyl-1-(2-thienylmethylidene)-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole ***Z*-3f** was prepared from aldehyde **1f** in 78% yield, mp 83-85 ^oC. ^1H NMR, δ: 1.55 (s, 6H, $2CH_3$), 3.11 (d, 2H, CH_2, ^4J 1.7 Hz), 5.91 (d, 1H, benzimidazole, ^3J 8.1 Hz), 6.07 (br.s, 1H, ThiC*H*=), 6.76 (br.d, 1H, Thi, ^3J 3.5 Hz), 6.87-6.98 (m, 1H, benzimidazole), 7.00 (dd, 1H, Thi, ^3J 5.2 Hz, ^3J 3.5 Hz), 7.12-7.22 (m, 1H, benzimidazole), 7.31 (dd, 1H, Thi, ^3J 5.2 Hz, ^4J 1.2 Hz), 7.67 (d, 1H, benzimidazole, ^3J 8.1 Hz). ^{13}C NMR, δ: 26.4 ($2CH_3$), 36.4 (C^3), 50.8 (C^2), 100.3 (Thi*C*H=), 114.2, 119.4, 122.3, 122.7 (C^5, C^6, C^7, C^8), 125.5, 127.0, 128.3 (Thi), 130.2, 148.0 (C^{4a}, C^{8a}), 135.9, 137.0 (C^1, Ph; C^1), 168.7 (C^{3a}). HRMS, *m/z* 281.1105, calculated for $C_{17}H_{16}N_2S$, $[M+H]^+$: *m/z* 281.1107.

References

1. J. Cossy and D. Belotti, *Tetrahedron*, 1999, **55**, 5145.