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Selective one-pot synthesis of 11-arylmethylidene-11*H*-isoindolo[2,1-*a*]-benzimidazoles and 6-arylbenzimidazo[2,1-*a*]isoquinolines from *o*-alkynylbenzaldehydes and *o*-diaminobenzenes

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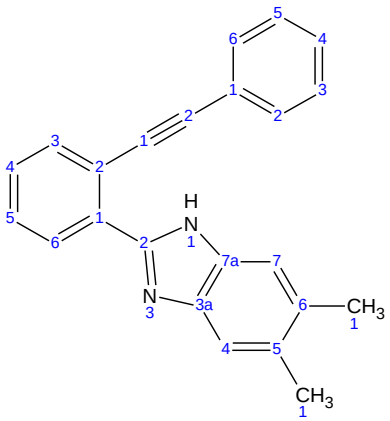
Experimental

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 using the solutions of test compounds in $CDCl_3$ and 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 dm^3 min^{-1}. Nebulizer gas was nitrogen (4 dm^3 min^{-1}), the interface temperature was 180 °C.

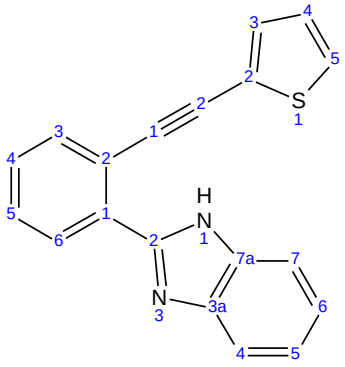
Quantum chemical calculations of structure, vibrational frequencies, and potential energy surfaces (PESs) were carried out on using the Gaussian 09, revision D.01, software package[1] at B3LYP level with 6/31+G (d,p) basic set. All found structures were verified by examination of their Hessian matrix as minima (all frequencies real) or transition states (one imaginary frequency). The identities of transition states to particular reactions were established by IRC calculations. Solvent effects from the DMSO environment were included using the polarizable continuum model (PCM).

Starting aldehydes **1a-c** were prepared by palladium-catalyzed cross-coupling of commercially available 2-bromobenzaldehyde with the corresponding arylacetylenes (phenylacetylene[2], (2-thienyl)acetylene and (4-*tert*-butylphenyl)acetylene[3]) in Et_3N.

Synthesis of 2-[2-(alk-1-ynyl)phenyl]benzimidazoles **3b,c** *from* o-*alkynylbenzaldehydes* **1a,b** *and* o-*diaminobenzenes* **2a,b** *(general procedure).* To a solution of aldehyde **1** (2 mmol) in DMSO (3 ml), a solution of the corresponding *o*-diaminobenzene **2** (2 mmol) in anhydrous DMSO (3 ml) was slowly added. Then NH_4Br (39 mg, 0.4 mmol) was added, and the resulting mixture was stirred for 24 h at room temperature in the contact with dry air. Then water (30 ml) and CH_2Cl_2 (30 ml) 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 light petroleum – THF mixture to give a target products **3b,c**.

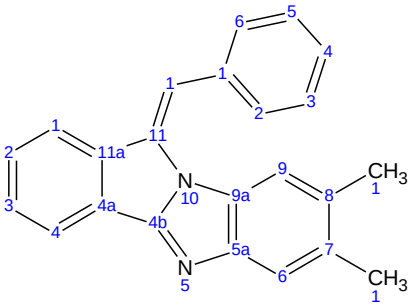


*5,6-Dimethyl-2-[2-(phenylethynyl)phenyl]-1*H-*benzimidazole* **3b** was prepared from aldehyde **1a** and diamine **2b** with 67% yield. ^{1}H NMR, δ: 2.61 (s, 6H, $2CH_3$), 7.36-7.53 (m, 5H, C^3H, C^4H, C^5H, Ph; C^7H, C^4H), 7.54-7.73 (m, 5H, C^2, C^6, Ph; C^3, C^4, C^5, *o*-phenylene), 8.52-8.60 (m, 1H, C^6H, *o*-phenylene), 10.82 (br. s, 1H, NH). ^{13}C NMR, δ: 20.4 ($2CH_3$), 89.0, 94.4 (C≡C), 115.2 (broad, C^4, C^7), 119.2, 122.2 (C^2, *o*-phenylene; C^1, Ph), 128.7, 128.8, 129.1, 132.2 (C^3, C^4, C^5, C^6, *o*-phenylene), 129.1, 129.4, 131.4 (C^2, C^3, C^4, C^5, C^6, Ph), 130.7 (C^1, *o*-phenylene), 133.6 (C^5, C^6), 137.2 (broad, C^{3a}, C^{7a}), 149.6 (C^2).

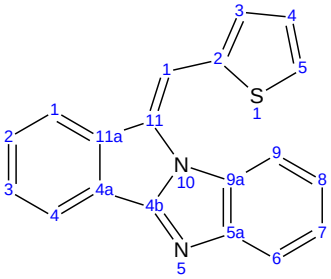


*2-[2-(2-Thienylethynyl)phenyl]-1*H-*benzimidazole* **3c** was prepared from aldehyde **1b** and diamine **2a** with 78% yield. ^{1}H NMR (DMSO-d_6), δ: 7.10 (dd, 1H, C^4H, Thi, ^3J 5.2 Hz, ^3J 3.6 Hz), 7.20-7.30 (m, 2H, C^5H, C^6H), 7.36 (dd, 1H, C^5H, Thi, ^3J 3.6 Hz, ^4J 1.2 Hz), 7.52-7.61 (m, 2H, C^4H, C^5H, *o*-phenylene), 7.62-7.76 (m, 4H, C^3H, *o*-phenylene; C^3H, Thi; C^4H, C^7H), 7.91-8.02 (m, 1H, C^6H, *o*-phenylene), 10.30 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6), δ: 86.7, 95.5 (C≡C), 115.4 (broad, C^4, C^7), 120.8, 122.2 (C^2, *o*-phenylene; C^2, Thi), 122.3 (C^5, C^6), 127.7, 129.1, 129.5, 129.8, 129.9, 132.6, 132.7 (C^3, C^4, C^5, C^6, *o*-phenylene; C^3, C^4, C^5, Thi), 132.4 (C^1, *o*-phenylene), 139.4 (broad, C^{3a}, C^{7a}), 150.4 (C^2).

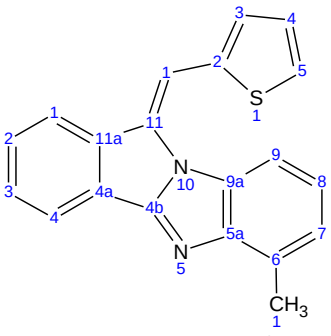
Characterization data for compounds **4b-e** *and* **5b-e**



*(11*Z*)-11-Benzylidene-7,8-dimethyl-11*H*-isoindolo[2,1-a]benzimidazole* **4b** was prepared from aldehyde **1a** and diamine **2a** and isolated in 52% yield by double recrystallization from hexane-THF mixture. ^{1}H NMR, δ: 1.97 (s, 3H, 8-CH_3), 2.28 (s, 3H, 7-CH_3), 5.38 (s,1H, C^{9}H), 7.07 (s, 1H, C*H*Ph), 7.39-7.54 (m, 8H, C^{2}H, C^{3}H, C^{6}H; Ph), 7.72-7.79 (m, 1H, C^{1}H), 7.95-8.02 (m, 1H, C^{4}H). ^{13}C NMR, δ: 20.0 (CH_3), 20.1 (CH_3), 109.2 (*C*HPh), 114.8 (C^{9}), 120.4, 120.6, 121.4 (C^{1}, C^{4}, C^{6}), 127.2 (C^{11a}), 128.1, 129.5 [doubled intensity, two overlapped signals] (C^{2}, C^{3}; C^{4}, Ph), 128.5, 130.3 (C^{2}, C^{3}, C^{5}, C^{6}, Ph), 128.9, 132.8, 135.4, 140.4 (C^{11}, C^{4a}, C^{9a}; C^{1}, Ph), 131.6, 131.7 (C^{7}, C^{8}), 147.1 (C^{5a}), 157.1 (C^{4b}). HRMS, *m/z* 323.1537, calculated for $C_{23}H_{18}N_2$, $[M+H]^+$: *m/z* 323.1543.

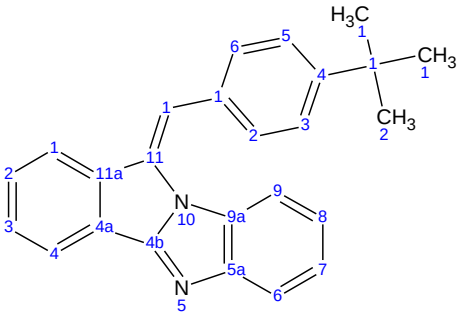


*(11*Z*)-11-(2-Thienylmethylidene)-11*H*-isoindolo[2,1-a]benzimidazole* **4c** was prepared from aldehyde **1b** and diamine **2a** and isolated in 69% yield by column chromatography [hexane–THF (3:1) as eluent]. ^{1}H NMR, δ: 5.98 (d,1H, C^{9}H, ^{3}J 8.2 Hz), 6.96 (s, 1H, C*H*Thi), 6.97 (dd, 1H, C^{8}H, ^{3}J 8.2 Hz, ^{3}J 7.5 Hz), 7.07 (d, 1H, C^{3}H, Thi, ^{3}J 3.5 Hz), 7.16 (dd, 1H, C^{4}H, Thi, ^{3}J 5.3 Hz, ^{3}J 3.5 Hz), 7.19 (dd, 1H, C^{7}H, ^{3}J 8.0 Hz, ^{3}J 7.5 Hz), 7.44-7.56 (m, 3H, C^{2}H, C^{3}H; C^{5}H, Thi), 7.68—7.80 (m, 2H, C^{6}H, C^{1}H), 7-96-8.04 (m, 1H, C^{4}H). ^{13}C NMR, δ: 101.7 (*C*HThi), 113.3 (C^{9}), 119.4, 120.3 120.6 (C^{1}, C^{4}, C^{6}), 122.2, 122.3 (C^{7}, C^{8}), 125.8 (C^{11a}), 126.7, 127.0, 128.9, 129.0, 129.3 (C^{2}, C^{3}; C^{3}, C^{4}, C^{5}, Thi), 127.8, 132.8, 135.2, 139.4 (C^{11}, C^{4a}, C^{9a}; C^{2}, Thi), 147.8 (C^{5a}), 157.7 (C^{4b}). HRMS, *m/z* 301.0798, calculated for $C_{19}H_{12}N_2S$, $[M+H]^+$: *m/z* 301.0794.

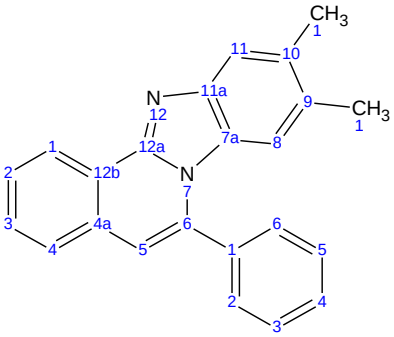


*(11*Z*)-6-Methyl-11-(2-thienylmethylidene)-11*H*-isoindolo[2,1-a]benzimidazole* **4d** was prepared from aldehyde **1b** and diamine **2c** and isolated in 62% yield by column chromatography [hexane–THF (3:1) as eluent]. ^{1}H NMR, δ: 2.71 (s, 3H, CH_3), 5.86 (d, 1H, C^{9}H, ^{3}J 8.1 Hz), 6.87 (dd, 1H, C^{8}H, ^{3}J 8.1 Hz, ^{3}J 7.5 Hz), 6.94 (s, 1H, C*H*Thi), 7.01 (d, 1H, C^{7}H, ^{3}J 7.5 Hz), 7.07 (d, 1H, C^{3}H, Thi, ^{3}J 3.5 Hz), 7.17 (dd, 1H, C^{4}H, Thi, ^{3}J 5.3 Hz, ^{3}J 3.5 Hz), 7.43-7.57 (m, 3H, C^{2}H, C^{3}H; C^{5}H, Thi), 7.70-7.77 (m, 1H, C^{1}H), 8.03-8.10 (m, 1H, C^{4}H). ^{13}C NMR, δ: 17.1 (CH_3), 102.2 (*C*HThi), 111.9 (C^{9}), 120.8, 122.0, 123.0, 123.9 (C^{1}, C^{4}, C^{7}, C^{8}), 127.6, 127.7, 129.7, 129.9 [doubled intensity, two overlapped signals] (C^{2}, C^{3}; C^{3}, C^{4}, C^{5}, Thi), 129.0, 130.3, 133.8, 136.2, 140.3 (C^{6}, C^{11}, C^{4a}, C^{9a};

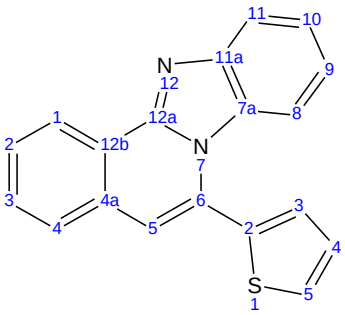
C^2, Thi), 147.7 (C^{5a}), 157.1 (C^{4b}). HRMS, *m/z* 315.0946, calculated for $C_{20}H_{14}N_2S$, $[M+H]^+$: *m/z* 315.0950.



*(11*Z*)-11-(4*-tert-*Butylbenzylidene)-11*H-*isoindolo[2,1*-a*]benzimidazole* **4e** was prepared from aldehyde **1c** and diamine **2a** and isolated in 48% yield by column chromatography [hexane–THF (5:1) as eluent]. ^{1}H NMR, *δ*: 1.42 (s, 9H, $3CH_3$), 5.64 (d,1H, C^9H, ^3J 8.4 Hz), 6.80 (dd, 1H, C^8H, ^3J 8.4 Hz, ^3J 7.8 Hz), 7.10 (s, 1H, C*H*C_6H_4t-Bu), 7.15 (dd, 1H, C^7H, ^3J 7.8 Hz, ^3J 8.0 Hz), 7.32-7.43 (m, 2H, C_3H, C_5H in C_6H_4), 7.46-7.60 (m, 4H, C_2H, C_3H; C_2H, C_6H in C_6H_4), 7.74 (d,1H, C^6H, ^3J 8.0 Hz), 7.79-7.86 (m, 1H, C^1H), 7.98-8.05 (m, 1H, C^4H). ^{13}C NMR, *δ*: 31.4 ($3CH_3$), 34.9 ($C(CH_3)_3$), 110.3 (CHC_6H_4t-Bu), 114.4 (C^9), 120.3, 120.7, 121.8 (C^1, C^4, C^6), 122.7, 122.9 (C^7, C^8), 125.7 (C^3, C^5 in C_6H_4), 127.0 (C^{11a}), 129.6, 129.9 (C^2, C^3), 130.1 (C^2, C^6 in C_6H_4), 130.5, 132.7, 137.6, 140.7 (C^{11}, C^{4a}, C^{9a}; C^1 in C_6H_4), 148.7 (C^{5a}), 152.0 (C^4 in C_6H_4), 158.0 (C^{4b}). HRMS, *m/z* 351.1855, calculated for $C_{25}H_{22}N_2$, $[M+H]^+$: *m/z* 351.1856.

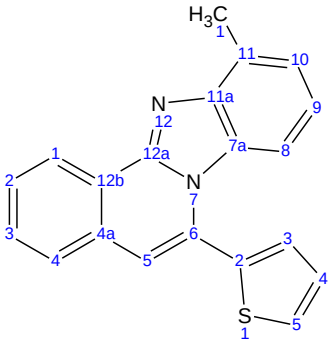


9,10-Dimethyl-6-phenylbenzimidazo[2,1-a*]isoquinoline* **5b** was prepared from aldehyde **1a** and diamine **2b** in 84% yield. ^{1}H NMR, *δ*: 2.15 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.22 (s, 1H, C^8H), 6.87 (s, 1H, C^5H), 7.56-7.73 (m, 8H, C^2H, C^3H, C^4H, Ph), 7.75 (s, 1H, $C^{11}H$), 8.82-8.91 (m, 1H, C^1H). ^{13}C NMR, *δ*: 20.4 (CH_3), 20.8 (CH_3), 112.1, 114.3 (C^5, C^8), 119.7 (C^{11}), 123.2 (C^{12b}), 125.0, 126.6, 127.7, 129.7, 129.8 (C^1, C^2, C^3, C^4; C^4, Ph), 128.9, 129.6 (C^2, C^3, C^5, C^6, Ph), 129.3, 130.3, 131.5, 133.4, 135.0 (C^9, C^{10}, C^{7a}, C^{11a}; C^1, Ph), 137.6 (C^6), 142.9 (C^{4a}), 147.8 (C^{12a}). HRMS, *m/z* 323.1546, calculated for $C_{23}H_{18}N_2$, $[M+H]^+$: *m/z* 323.1543. These spectra are in good agreement with previously published data[4].

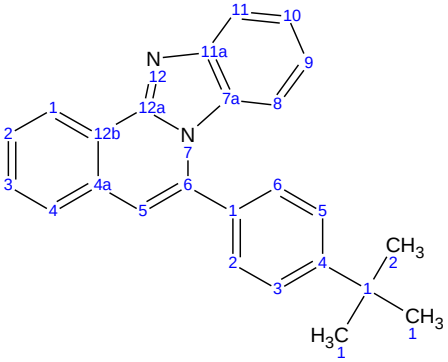


6-(2-Thienyl)benzimidazo[2,1-a*]isoquinoline* **5c** was prepared from aldehyde **1b** and diamine **2a** in 78% yield. ^{1}H NMR, *δ*: 6.53 (d, 1H, C^8H, ^3J 8.0 Hz), 7.06 (s, 1H, C^5H), 7.07 (dd, 1H, C^9H, ^3J 8.0 Hz, ^3J 7.7 Hz), 7.24 (dd, 1H, C^4H, Thi, ^3J 5.3 Hz, ^3J 3.3 Hz), 7.34 (d, 1H, C^3H, Thi, ^3J 3.3 Hz), 7.39 (dd, 1H, $C^{10}H$, ^3J 8.2 Hz, ^3J 7.7 Hz), 7.59 (d, 1H, C^5H, Thi, ^3J 5.3 Hz), 7.61-7.73 (m, 3H, C^2H, C^3H, C^4H), 7.98 (d, 1H, $C^{11}H$, ^3J 8.2 Hz),8.82-8.91 (m, 1H, C^1H). ^{13}C NMR, *δ*: 113.8, 115.4 (C^5, C^8), 119.6 (C^{11}), 121.6, 124.4 (C^9, C^{10}), 123.2 (C^{12b}), 125.1, 126.8, 127.6, 128.1, 128.4, 129.8, 130.2 (C^1, C^2, C^3, C^4; C^3, C^4, C^5, Thi), 130.5, 131.1 [doubled

intensity, two overlapped signals], 134.5 (C^6, C^{7a}, C^{11a}; C^2, Thi), 143.9 (C^{4a}), 148.0(C^{12a}). HRMS, *m/z* 301.0790, calculated for $C_{19}H_{12}N_2S$, $[M+H]^+$: *m/z* 301.0794. These spectra are in good agreement with previously published data.[4]



11-Methyl-6-(2-thienyl)benzimidazo[2,1-a]isoquinoline **5d** was prepared from aldehyde **1b** and diamine **2c** in 65% yield. ^{1}H NMR, *δ*: 2.87 (s, 3H, CH^3), 6.40 (d, 1H, C^8H, ^3J 8.4 Hz), 7.00 (dd, 1H, C^9H, ^3J 8.2 Hz, ^3J 7.2 Hz), 7.07 (s, 1H, C^5H), 7.23 (d, 1H, $C^{10}H$, ^3J 7.5 Hz), 7.27 (dd, 1H, C^4H, Thi, ^3J 5.2 Hz, ^3J 3.5 Hz), 7.37 (dd, 1H, C^3H, Thi, ^3J 3.5 Hz, ^4J 1.2 Hz), 7.62 (dd, 1H, C^5H, Thi, ^3J 5.2 Hz, ^4J 1.2 Hz), 7.65-7.73 (m, 3H, C^2H, C^3H, C^4H), 8.91-9.00 (m, 1H, C^1H). ^{13}C NMR, *δ*: 17.2 (CH_3), 111.2, 115.3 (C^5, C^8), 121.5, 124.5 (C^9, C^{10}), 123.5 (C^{12b}), 125.3, 126.7, 127.5, 128.0, 128.3, 129.8, 130.0 (C^1, C^2, C^3, C^4; C^3, C^4, C^5, Thi), 129.6 (C^{11}), 130.2, 130.9 [doubled intensity, two overlapped signals], 134.6 (C^6, C^{7a}, C^{11a}; C^2, Thi), 143.4 (C^{4a}), 147.4(C^{12a}). HRMS, *m/z* 315.0942, calculated for $C_{20}H_{14}N_2S$, $[M+H]^+$: *m/z* 315.0950.



*6-(*tert*-Butylphenyl)benzimidazo[2,1-a]isoquinoline* **5e** was prepared from aldehyde **1c** and diamine **2a** in 72% yield. ^{1}H NMR, *δ*: 1.48 (s, 9H, $3CH_3$), 6.55 (d, 1H, C^8H, ^3J 8.2 Hz), 6.93 (s, 1H, C^5H), 7.06 (dd, 1H, C^9H, ^3J 8.2 Hz, ^3J 7.7 Hz), 7.42 (dd, 1H, $C^{10}H$, ^3J 8.2 Hz, ^3J 7.7 Hz), 7.52-7.73 (m, 7H, C^2H, C^3H, C^4H; C_6H_4), 8.03 (d, 1H, $C^{11}H$, ^3J 8.2 Hz),8.80-8.90 (m, 1H, C^1H). ^{13}C NMR, *δ*: 31.5 ($3CH_3$), 35.1 ($C(CH_3)_3$), 113.1, 114.1 (C^5, C^8), 119.5 (C^{11}), 121.5, 124.5 (C^9, C^{10}), 122.3 (C^{12b}), 125.3, 126.7, 127.7, 128.1 (C^1, C^2, C^3, C^4), 125.9 (C^3, C^5 in C_6H_4), 129.1 (C^2, C^6 in C_6H_4), 130.6, 131.6, 131.8 (C^{7a}, C^{11a}; C^1 in C_6H_4), 137.6 (C^6), 143.6 (C^{4a}), 148.3 (C^{12a}), 153.4 (C^4 in C_6H_4). HRMS, *m/z* 351.1852, calculated for $C_{25}H_{22}N_2$, $[M+H]^+$: *m/z* 351.1856. These spectra are in good agreement with previously published data.[5]

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