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One-pot synthesis of 1-arylmethylidene-1,2,3,3a-tetrahydro-5*H*-pyrrolo-[1,2-*a*][3,1]benzoxazines and 1-arylmethylidene-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazolines from 5-arylalk-4-ynals and *o*-aminobenzylic alcohol/amine

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Experimental

GLC analysis was performed on a Hewlett-Packard 5890 Series II instrument with a 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 dm^3 min^{-1}. Nebulizer gas was nitrogen (4 dm^3 min^{-1}), the interface temperature was 180 ^{o}C.

Starting aldehydes **1a,b,e** were prepared by alkylation of isobutyraldehyde with 3-aryl-1-chloroprop-2-ynes under phase-transfer catalysis conditions according described procedure.[1] Sonogashira cross-coupling (catalysts $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$) of commercially available 4-bromo-1,2-difluorobenzene and 4-iodobenzotrifluoride with pent-4-yn-1-ol followed by Swern oxidation was used to prepare alkynals **1c,d**.

(1E)-3,3-Dimethyl-1-(2-thienylmethylidene)-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a][3,1]-benzoxazine **4b** was prepared from aldehyde **1b** and amine **2** and isolated in 73% yield, mp 94-96 ^{o}C. ^{1}H NMR, δ: 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 2.77 (d, 1H, =CC*H*H, *J* 15.8 Hz), 2.86 (d, 1H, =CC*H*H, *J* 15.8 Hz), 4.55 (s, 1H, NCHO), 4.98 (s, 2H, OCH_2), 6.39 (br. s, 1H, ThiC*H*=), 6.75 (d.d, 1H, Thi, ^{3}J 3.5 Hz, ^{4}J 1.2 Hz), 6.96 (dd, 1H, Thi, ^{3}J 5.2 Hz, ^{3}J 3.5 Hz), 7.05 (dd, 1H,

Thi, ^{3}J 5.2 Hz, ^{4}J 1.2 Hz), 7.02-7.11 (m, 2H, Ph), 7.24-7.34 (m, 1H, Ph), 7.46 (d, 1H, Ph, ^{3}J 8.0 Hz). ^{13}C NMR, δ: 21.9 (CH_3), 27.7 (CH_3), 38.6 (C^3), 43.9 (C^2), 67.6 (C^5), 92.6 (C^{3a}), 96.1 (Thi*C*H=), 121.1, 122.1, 122.4, 122.9, 125.1, 126.9, 127.0 (C^6, C^7, C^8, C^9, Thi), 126.4 (C^{5a}), 139.1, 143.0, 144.5 (C^{9a}, C^1; C^1, Thi). HRMS, *m/z* 298.1256, calculated for $C_{18}H_{19}NOS$, $[M+H]^+$: *m/z* 298.1260.

(1E)-1-(4-Trifluoromethylbenzylidene)-1,2,3,3a-tetrahydro-5H-pyrrolo[1,2-a][3,1]-benzoxazine **4d** was prepared from aldehyde **1d** and amine **2** and isolated as a brown liquid (purity >90%) in 76% yield. ^{1}H NMR, δ: 1.94-2.13 (m, 1H, =CCH$_2$C*H*HCH), 2.36-2.55 (m, 1H, =CCH$_2$C*H*HCH), 2.83-3.11 (m, 2H, =CC*H*$_2$), 4.97 (d, 1H, OC*H*H, ^{2}J 15.3 Hz), 5.04 (d, 1H, OC*H*H, ^{2}J 15.3 Hz), 5.10 (dd, 1H, NCHO, ^{3}J 6.2 Hz, ^{3}J 3.1 Hz), 6.22 (br. s, 1H, $CF_3C_6H_4C$*H*=), 7.05-7.16 (m, 2H, Ar), 7.23-7.37 (m, 3H, Ar), 7.49-7.58 (m, 3H, Ar). ^{13}C NMR, δ: 28.1, 28.2 (C^2, C^3), 67.3 (C^5), 88.8 (C^{3a}), 96.8 ($CF_3C_6H_4$*C*H=), 122.1, 123.0, 125.1, 126.7 (C^6, C^7, C^8, C^9), 124.6 (q, CF_3, J_{CF} 270 Hz), 125.0 (q, C^3, C^5, $CF_3C_6H_4$, J_{CF} 3.9 Hz), 125.3 (q, C^4, $CF_3C_6H_4$, J_{CF} 32 Hz), 126.1 (C^{5a}), 126.8 (C^2, C^6, $CF_3C_6H_4$), 137.5, 143.0, 146.5 (C^{9a}, C^1; C^1, $CF_3C_6H_4$).

2-(3,4-Difluorobenzyl)-1-(2-hydroxymethylphenyl)-1H-pyrrole **5a** was prepared from aldehyde **1c** and amine **2** and isolated by flash chromatography on silica gel [hexane–dichloromethane (1 : 1) as eluent] in 70% yield. ^{1}H NMR, δ: 1.62 (br. s, 1H, OH), 3.65 (s, 2H, $C_6H_3F_2C$*H*$_2$), 4.10 (d, 1H, C*H*HOH, *J* 13.1 Hz), 4.23 (d, 1H, C*H*HOH, *J* 13.1 Hz), 6.08 (dd, 1H, C^3H, *cyclo*-C_4N, ^{3}J 3.5 Hz, ^{4}J 1.8 Hz), 6.25 (dd, 1H, C^4H, *cyclo*-C_4N, ^{3}J 3.5 Hz, ^{3}J 2.8 Hz), 6.53-6.75 (m, 2H, C^2H, C^6H, $C_6H_3F_2$), 6.66 (dd, 1H, C^5H, *cyclo*-C_4N, ^{3}J 2.8 Hz, ^{4}J 1.8 Hz), 6.93 (ddd, 1H, C^5H, $C_6H_3F_2$, $^{3}J_{HF}$ 10.3 Hz, $^{4}J_{HF}$ 8.2 Hz, ^{3}J 8.2 Hz), 7.08 (dd, 1H, Ph, ^{3}J 7.5 Hz, ^{4}J 1.4 Hz), 7.32 (ddd, 1H, Ph, ^{3}J 7.5 Hz, ^{3}J 7.5 Hz, ^{4}J 2.0 Hz), 7.44 (ddd, 1H, Ph, ^{3}J 7.5 Hz, ^{3}J 7.5 Hz, ^{4}J 1.4 Hz), 7.52 (dd, 1H, Ph, ^{3}J 7.5 Hz, ^{4}J 2.0 Hz). ^{13}C NMR, δ: 32.2 ($C_6H_3F_2$*C*H$_2$), 60.5 (CH_2OH), 108.2, 108.3 (C^3, C^4, *cyclo*-C_4N), 116.6 (d, C^2, $C_6H_3F_2$, J_{CF} 17.1 Hz), 117.3 (d, C^5, $C_6H_3F_2$, J_{CF} 17.3 Hz), 122.7 (C^5, *cyclo*-C_4N), 124.3 (dd, C^6, $C_6H_3F_2$, J_{CF} 6.0 Hz, J_{CF} 3.5 Hz), 127.9, 128.4, 128.6, 128.9 (C^3, C^4, C^5, C^6, Ph), 132.1, 137.6, 138.9 (C^1, C^2, Ph; C^2, *cyclo*-C_4N), 136.6 (dd, C^1, $C_6H_3F_2$, J_{CF} 6.4 Hz, J_{CF} 3.9 Hz), 148.6 (dd, C^3, $C_6H_3F_2$, J_{CF} 246 Hz, J_{CF} 12.6 Hz), 149.8 (dd, C^4, $C_6H_3F_2$, J_{CF} 247 Hz, J_{CF} 12.5 Hz). HRMS, *m/z* 300.1198, calculated for $C_{18}H_{15}F_2NO$, $[M+H]^+$: *m/z* 300.1194.

1-(2-Hydroxymethylphenyl)-2-(4-trifluoromethylbenzyl)-1H-pyrrole **5b** was obtained by heating of solution of compound **4d** in $CDCl_3$ for 15 min at 50 ^{o}C and characterized without isolation. ^{1}H NMR, δ: 1.73 (br. s, 1H, OH), 3.77 (s, 2H, $F_3CC_6H_4C$*H*$_2$), 4.05 (d, 1H, C*H*HOH, *J* 13.2 Hz), 4.21 (d, 1H, C*H*HOH, *J* 13.2 Hz), 6.10 (dd, 1H, C^3H, *cyclo*-C_4N, ^{3}J 3.5 Hz, ^{4}J 1.8 Hz), 6.25 (dd, 1H, C^4H, *cyclo*-C_4N, ^{3}J 3.5 Hz, ^{3}J 2.8 Hz), 6.68 (dd, 1H, C^5H, *cyclo*-C_4N, ^{3}J 2.8 Hz, ^{4}J

1.8 Hz), 7.02 (d, 2H, $CF_3C_6H_4$, *J* 8.1 Hz), 7.09 (dd, 1H, Ph, ^3J 7.5 Hz, ^4J 1.4 Hz), 7.31 (ddd, 1H, Ph, ^3J 7.5 Hz, ^3J 7.5 Hz, ^4J 2.0 Hz), 7.41 (d, 2H, $CF_3C_6H_4$, *J* 8.1 Hz), 7.44 (ddd, 1H, Ph, ^3J 7.5 Hz, ^3J 7.5 Hz, ^4J 1.4 Hz), 7.52 (dd, 1H, Ph, ^3J 7.5 Hz, ^4J 2.0 Hz).^{13}C NMR, δ: 32.9 ($F_3CC_6H_4CH_2$), 60.5 (CH_2OH), 108.3, 108.5 (C^3, C^4, *cyclo*-C_4N), 122.7 (C^5, *cyclo*-C_4N), 125.0 (q, C^3, C^5, $CF_3C_6H_4$, J_{CF} 3.7 Hz), 127.9, 128.4, 128.6, 128.9 (C^3, C^4, C^5, C^6, Ph), 129.0 (C^2, C^6, $CF_3C_6H_4$), 132.0, 137.8, 139.1 (C^1, C^2, Ph; C^2, *cyclo*-C_4N), 143.8 (C^1, $CF_3C_6H_4$), 124.3 (q, CF_3, J_{CF} 272 Hz), 134.1 (q, C^4, $CF_3C_6H_4$, *J* 32 Hz). HRMS, *m/z* 330.1103, 331.1195, 332.1254, calculated for $C_{19}H_{16}F_3NO$, $[M-H]^+$: *m/z* 330.1100, $[M]^+$: *m/z* 331.1178, $[M+H]^+$: *m/z* 332.1257.

(1E)-1-(3,4-Difluorobenzylidene)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline **8b** was prepared from aldehyde **1c** and amine **6** and isolated in 65% yield, mp 106-107^{o}C. ^{1}H NMR, δ: 1.62 (dddd, 1H, =CCH_2CHHCH, ^2J 12.6 Hz, ^3J 9.6 Hz, ^3J 9.6 Hz, ^3J 6.6 Hz), 1.94 (br.s, 1H, NH), 2.41-2.62 (m, 1H, =CCH_2CHHCH), 2.67-2.99 (m, 2H, =CCH_2), 4.11 (d, 1H, NHC*H*H, *J* 17.4 Hz), 4.24 (d, 1H, NHC*H*H, *J* 17.4 Hz), 4.69 (dd, 1H, NCHN, ^3J 6.6 Hz, ^3J 6.6 Hz), 6.13 (br. s, 1H, $C_6H_3F_2CH$=), 6.75-7.30 (m, 6H, Ar), 7.59 (d, 1H, Ar, *J* 8.2 Hz). ^{13}C NMR, δ: 28.1, 29.7 (C^2, C^3), 47.1 (C^5), 73.4 (C^{3a}), 96.5 ($C_6H_3F_2CH$=), 115.2 (d, C^5, $C_6H_3F_2$, J_{CF} 17.5 Hz), 116.8 (d, C^2, $C_6H_3F_2$, J_{CF} 17.3 Hz), 119.9, 121.4, 126.7, 126.8 (C^6, C^7, C^8, C^9), 122.9 (dd, C^6, $C_6H_3F_2$, J_{CF} 6.0 Hz, J_{CF} 3.5 Hz), 125.5 (C^{5a}), 136.8 (dd, C^1, $C_6H_3F_2$, J_{CF} 6.5 Hz, J_{CF} 3.9 Hz), 139.0, 143.8 (C^{9a}; C^1), 147.1 (dd, C^3, $C_6H_3F_2$, J_{CF} 245 Hz, J_{CF} 12.9 Hz), 150.1 (dd, C^4, $C_6H_3F_2$, J_{CF} 246 Hz, J_{CF} 12.5 Hz). HRMS, *m/z* 297.1195, 298.1270, 299.1347, calculated for $C_{18}H_{16}F_2N_2$, $[M-H]^+$: *m/z* 297.1198, $[M]^+$: *m/z* 298.1276, $[M+H]^+$: *m/z* 299.1354.

(1E)-1-(4-Trifluoromethylbenzylidene)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazoline **8c** was prepared from aldehyde **1d** and amine **6** and isolated in 74% yield, mp 109-110 ^{o}C. ^{1}H NMR, δ: 1.63 (dddd, 1H, =CCH_2CHHCH, ^2J 12.6 Hz, ^3J 9.6 Hz, ^3J 9.6 Hz, ^3J 6.6 Hz), 1.91 (br.s, 1H, NH), 2.42-2.62 (m, 1H, =CCH_2CHHCH), 2.74-3.05 (m, 2H, =CCH_2), 4.12 (d, 1H, NHC*H*H, *J* 17.4 Hz), 4.28 (d, 1H, NHC*H*H, *J* 17.4 Hz), 4.70 (dd, 1H, NCHN, ^3J 6.7 Hz, ^3J 6.7 Hz), 6.26 (br. s, 1H, $F_3CC_6H_4CH$=), 6.98 (t, 1H, Ar, *J* 7.4 Hz), 7.06-7.14 (m, 1H, Ar), 7.18-7.28 (m, 1H, Ar), 7.24 (d, 2H, $CF_3C_6H_4$, *J* 8.2 Hz), 7.50 (d, 2H, $CF_3C_6H_4$, *J* 8.2 Hz), 7.63 (d, 1H, Ar, *J* 8.2 Hz). ^{13}C NMR, δ: 28.4, 29.6 (C^2, C^3), 47.0 (C^5), 73.4 (C^{3a}), 97.0 ($F_3CC_6H_4CH$=), 119.9, 121.6, 126.6, 126.7 (C^6, C^7, C^8, C^9), 124.7 (q, CF_3, J_{CF} 270 Hz), 125.1 (q, C^3, C^3, $F_3CC_6H_4$, J_{CF} 3.9 Hz), 125.2 (q, C^4, $F_3CC_6H_4$, J_{CF} 32 Hz), 125.5 (C^{5a}), 126.8 (C^2, C^6, $F_3CC_6H_4$), 138.8, 143.5, 145.1 (C^{9a}, C^1; C^1, $F_3CC_6H_4$). HRMS, *m/z* 329.1268, 330.1338, 331.1420, calculated for $C_{19}H_{17}F_3N_2$, $[M-H]^+$: *m/z* 329.1260, $[M]^+$: *m/z* 330.1338, $[M+H]^+$: *m/z* 331.1417.

(1E)-1-(3,4-Difluorobenzylidine)-3,3-dimethyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]-quinazoline **8d** was prepared from aldehyde **1e** and amine **6** and isolated in 65% yield, mp 100-

102 ^{o}C. ^{1}H NMR, δ: 1.01 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.82 (br. s, 1H, NH), 2.68 (s, 2H, =CCH_2), 4.12 (d, 1H, NHC*H*H, *J* 17.0 Hz), 4.22 (d, 1H, NHC*H*H, *J* 17.0 Hz), 4.32 (s, 1H, NCHN), 6.80-7.32 (m, 6H, Ar), 7.69 (d, 1H, Ar, *J* 8.2 Hz). ^{13}C NMR, δ: 20.7 (CH_3), 25.9 (CH_3), 38.2 (C^3), 44.2, 47.4 (C^2, C^5), 80.9 (C^{3a}), 98.4 ($C_6H_3F_2CH$=), 115.3 (d, C^5, $C_6H_3F_2$, J_{CF} 17.1 Hz), 116.8 (d, C^2, $C_6H_3F_2$, J_{CF} 17.0 Hz), 117.0, 120.3, 126.4, 126.9 (C^6, C^7, C^8, C^9), 122.9 (dd, C^6, $C_6H_3F_2$, J_{CF} 6.1 Hz, J_{CF} 3.3 Hz), 124.3 (C^{5a}), 136.7 (dd, C^1, $C_6H_3F_2$, J_{CF} 6.1 Hz, J_{CF} 4.0 Hz), 139.7, 142.4 (C^{9a}, C^1), 147.1 (dd, C^3, $C_6H_3F_2$, J_{CF} 248.5 Hz, J_{CF} 12.0 Hz), 150.2 (dd, C^4, $C_6H_3F_2$, J_{CF} 248.8 Hz, J_{CF} 12.1 Hz). HRMS, *m/z* 327.1665, calculated for $C_{20}H_{20}F_2N_2$, $[M+H]^+$: *m/z* 327.1667.

References

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