Microwave-Enhanced Synthesis of N-Shifted Buflavine Analogues via a
Suzuki - Ring Closing Metathesis Protocol Prasad Appukkuttan, Wim
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Supporting Information

General Remarks: ^1H , ^{13}C and DEPT NMR spectra were recorded on a Bruker 300 Avance instrument. The ^1H chemical shifts are reported in ppm relative to tetramethylsilane, using the residual solvent signal as an internal reference and ^{13}C with CDCl_3 as internal standard, unless otherwise stated. The low resolution mass spectra were obtained with a HP5989A MS instrument. High resolution mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150-250°C as required. High resolution EI-mass spectra were performed with a resolution of 10000. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV₂₅₄ and 70-230 mesh silica gel (E. M. Merck)) were used. All compounds have been characterized by ^1H , ^{13}C and DEPT NMR as well as LR and HR EI-MS. All commercially available compounds were purchased from Aldrich and used without any further purification. Purity of all new compounds has been determined based on the NMR experiments.

Microwave Irradiation Experiments: All microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with an aluminum/Teflon crimp top. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (60-120 s) to ambient temperature by air jet cooling.

Representative procedure for the bromination of aldehydes 3a-b

2-Bromo-4,5-dimethoxybenzaldehyde 3a

3,4-Dimethoxybenzaldehyde **2a** (1.66 g, 10.0 mmol) was dissolved in dry, degassed MeOH (50 mL) and stirred under argon. To this was added bromine (0.54 mL, 11.0 mmol) and the resultant solution was stirred at r.t. for 3 h. After the completion of the reaction, as noted by TLC and CI-MS, solvent was evaporated and the resultant mixture was partitioned between DCM (50 mL) and a sat. soln of Na₂S₂O₃ (50 mL). The aqueous layer was once extracted with DCM (50 mL) and the combined organic layers were washed with brine (25 mL) and water (25 mL) respectively. Solvent was removed under reduced pressure to furnish the bromoaldehyde **3a**, which was used without further purification.

¹H NMR (300 MHz, CDCl₃): δ = 3.92 (s, 3H), 3.96 (s, 3H), 7.04 (s, 1H), 7.39 (s, 1H), 10.17 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 56.0, 56.4, 110.3, 115.3, 120.2, 126.4, 148.7, 154.3, 190.5 ppm. DEPT (75 MHz, CDCl₃): δ = 56.0, 56.4, 110.3, 115.3, 190.5 ppm. EI-MS [M⁺]: 244 (100%).

Representative procedure for the synthesis of styrenes 4a-b

1-Bromo-4,5-dimethoxy-2-vinylbenzene 4a

To a stirred solution of methyl(triphenyl)phosphonium bromide (0.89 g, 2.5 mmol) in dry, degassed THF (20 mL) at r.t. under argon atmosphere, was added *n*-BuLi (2.5 M in hexanes, 1 mL) in a slow manner. The resultant yellowish solution was stirred for an additional 15 min till the deep yellow color of the ylide was developed. 2-Bromo-4,5-dimethoxybenzaldehyde **3a** (0.61 g, 2.5 mmol) in dry THF (10 mL) was added to the

mixture via a hypodermic syringe and the colour of the reaction mixture was soon found to fade. The resultant off-white solution was stirred at r.t. for an additional 3h, before the TLC and CI-MS has indicated the completion of the reaction. After NH_4Cl work-up, the organic components were extracted with DCM (3×25 mL) and the combined organic layers were washed with brine (25 mL) and water (25 mL) and finally dried on MgSO_4 . Removal of the solvents under reduced pressure has generated the styrene **4a** as a thick yellow oil, which was further purified by column chromatography [silica gel, heptane-diethyl ether (3:2)] to furnish the pure product (0.54 g, 89%).

General procedure - Microwave-enhanced Suzuki-Miyaura reaction for the synthesis of biaryl-anilines 6a-b

Styrene **4a-b** (0.25 mmol), 2-pivaloylaminoophenylboronic acid **5** (0.325 mmol, 1.30 equiv.), NaHCO_3 (0.75 mmol, 3.0 equiv.) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (5 mol%) were suspended in DMF (1.5 mL) and water (1.5 mL) and vial was sealed tightly. The mixture was irradiated for 15 min at a pre-selected temperature of 150 °C, using a maximum irradiation power of 150 W. After the reaction, the vial was cooled to 60 °C by air jet cooling. The crude mixture was partitioned between diethyl ether (25 mL) and water (25 mL) and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were dried on magnesium sulphate and solvents were removed under reduced pressure to yield the crude product as yellow oil. Column chromatography [silica gel, heptane-diethyl ether] afforded biaryls **6a-b** as yellowish oily materials.

Synthesis of 4,5-dimethoxy-2-vinyl-2'-pivaloylamino-biphenyl (6a)

Biaryl **6a** was synthesized following the general procedure for the microwave-enhanced Suzuki-Miyaura reactions from styrene **4a** (0.06 g, 0.25 mmol). After chromatographic

purification (silica gel, heptane-diethyl ether 1:1), analytically pure product **6a** was isolated as a yellow oily material (0.079 g, 93%).

^1H NMR (300 MHz, CDCl_3): δ = 1.09 (s, 9H), 3.83 (s, 3H), 3.89 (s, 3H), 5.20 (dd, 1H, J = 11.3, 1.7 Hz), 5.56 (dd, 1H, J = 17.8, 1.7 Hz), 6.93 (bs, 1H), 7.09 (s, 1H), 7.14 (t, 1H, J = 7.2 Hz), 7.20 (s, 1H), 7.51 (t, 1H, J = 7.9 Hz), 7.69 (d, 1H, J = 7.9 Hz), 8.10 (d, 1H, J = 7.9 Hz), 8.44 (dd, 1H, J = 17.9, 11.3 Hz) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 27.1, 39.2, 55.9, 56.0, 113.3, 114.85, 115.2, 116.9, 126.3, 126.9, 128.9, 129.3, 133.6, 134.5, 134.6, 141.7, 146.9, 151.2, 176.4 ppm. DEPT (75 MHz, CDCl_3): δ = 27.1, 55.9, 56.0, 113.3, 114.9, 115.2, 116.9, 126.3, 126.9, 133.6, 134.6 ppm. EI-MS $[\text{M}^+]$: 339, 282, 254 (100%), 239. HR (EI) – MS: $\text{C}_{21}\text{H}_{25}\text{NO}_3$ found = 339.18356, Anal. calcd. 339.18344.

Synthesis of 4,5,6-trimethoxy-2-vinyl-2'-pivaloylamino-biphenyl (**6b**)

Biaryl **6b** was synthesized following the general procedure from styrene **4b** (0.07 g, 0.25 mmol). After chromatographic purification (silica gel, heptane-diethyl ether 1:1), analytically pure product **6b** was isolated as a yellow oily material (0.08 g, 91%).

^1H NMR (300 MHz, CDCl_3): δ = 1.10 (s, 9H), 3.76 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 5.15 (dd, 1H, J = 11.2, 1.7 Hz), 5.61 (dd, 1H, J = 17.7, 1.7 Hz), 6.72 (s, 1H), 6.89 (bs, 1H), 7.29 (t, 1H, J = 7.7 Hz), 7.66 (t, 1H, J = 7.9 Hz), 7.85 (d, 1H, J = 8.0 Hz), 8.38 (d, 1H, J = 8.0 Hz), 8.50 (dd, 1H, J = 17.7, 11.3 Hz) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 27.3, 39.3, 56.2, 61.1, 61.3, 105.3, 115.1, 118.9, 120.8, 126.1, 128.5, 128.9, 129.3, 132.1, 134.7, 138.4, 142.3, 148.3, 152.5, 175.5 ppm. DEPT (75 MHz, CDCl_3): δ = 27.3, 56.2, 61.1, 61.3, 105.3, 115.1, 118.9, 126.1, 128.9, 129.3, 134.7 ppm. EI-MS $[\text{M}^+]$: 369, 312, 284 (100%), 269. HR (EI) – MS: $\text{C}_{22}\text{H}_{27}\text{NO}_4$ found = 369.19409, Anal. calcd. 369.19401.

Synthesis of *N*-allyl-*N*-(4',5'-dimethoxy-2'-vinyl[1,1'-biphenyl]-2-yl)-2,2-dimethylpropanamide (**7a**)

Biaryl **6a** (0.08 g, 0.25 mmol) was dissolved in dry, degassed THF (5.0 mL) and stirred under inert atmosphere. To this was added NaH (80% suspension on mineral oil, 0.01 g, 0.30 mmol) and the mixture was refluxed for 30 min. After 30 min, allyl bromide (0.033 g, 0.275 mmol) was added to the refluxing mixture and the temperature was maintained for an additional 5.5 h when the TLC and CI-MS indicated the completion of the reaction. The mixture was cooled to r.t., and sat. NH_4Cl soln was added to it, and the mixture was allowed to stir for 15 min. It was then extracted with DCM (3×20 mL) and the combined organic layers were washed with brine (20 mL), sat. NaHCO_3 soln (20 mL) and finally with water (20 mL) and dried over MgSO_4 . Solvents were removed under reduced pressure to furnish the N-allyl derivative **7a**, which was further purified by column chromatography [silica gel, heptane-diethyl ether 3:2] to furnish the analytically pure product (0.09 g, 96%) as a yellow oily material.

^1H NMR (300 MHz, CDCl_3): δ = 1.27 (s, 9H), 3.82 (s, 3H), 3.84 (s, 3H), 4.58-4.69 (m, 1H), 5.16 (d, 2H, J = 5.6 Hz), 5.40 (dd, 2H, J = 13.6, 0.4 Hz), 5.54 (d, 2H, J = 15.4 Hz), 6.65 (s, 1H), 6.89 (t, 1H, J = 8.0 Hz), 7.21 (d, 1H, J = 8.1 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.84 (t, 1H, J = 8.0 Hz), 8.13 (dd, 1H, J = 14.3, 0.3 Hz), 8.23 (s, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 23.2, 38.4, 52.2, 55.9, 56.2, 111.8, 114.9, 115.2, 118.4, 118.9, 125.6, 127.4, 127.6, 128.6, 131.6, 131.9, 132.2, 133.6, 14.40, 150.2, 151.3, 173.9 ppm. DEPT (75 MHz, CDCl_3): δ = 23.2, 52.2, 55.9, 56.2, 111.8, 114.9, 115.2, 118.4, 118.9, 125.6, 128.6, 131.6, 131.9, 133.6 ppm. EI-MS [M^+]: 379, 338, 294 (100%), 280. HR (EI) – MS: $\text{C}_{24}\text{H}_{29}\text{NO}_3$ found = 379.21476, Anal. calcd. 379.21474.

Synthesis of N-allyl-2,2-dimethyl-N-(2',3',4'-trimethoxy-6'-vinyl-[1,1'-biphenyl]-2-yl) propanamide (7b)

N-allyl analogue **7b** was synthesized from biaryl **6b** (0.092 g, 0.25 mmol) following the same procedure for the synthesis of **7a**. Column chromatography [silica gel, heptane-diethyl ether 3:2] furnished the analytically pure product **7a** (0.10 g, 94%) as a yellow oily material.

^1H NMR (300 MHz, CDCl_3): δ = 1.24 (s, 9H), 3.77 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 4.39 (d, 2H, J = 5.1 Hz), 4.88 (dd, 1H, J = 17.1, 3.2 Hz), 5.15 (dd, 1H, J = 11.2, 1.7 Hz), 5.42 (dd, 1H, J = 10.1, 3.2 Hz), 5.61 (dd, 1H, J = 17.7, 1.7 Hz), 6.05-6.17 (m, 1H), 6.84 (s, 1H), 7.50-7.61 (m, 3H), 7.68 (t, 1H, J = 7.9 Hz), 8.39 (d, 1H, J = 8.1 Hz) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 29.1, 39.7, 52.2, 56.2, 61.0, 61.1, 105.4, 115.1, 118.9, 120.3, 120.4, 127.3, 127.4, 127.6, 128.7, 130.4, 131.9, 134.7, 142.4, 145.8, 149.6, 151.1, 179.8 ppm. DEPT (75 MHz, CDCl_3): δ = 29.1, 52.2, 56.2, 61.0, 61.1, 105.4, 115.1, 118.9, 120.4, 127.4, 127.6, 128.7, 131.9, 134.7 ppm. EI-MS $[M^+]$: 409, 368, 324 (100%), 310. HR (EI) – MS: $\text{C}_{25}\text{H}_{31}\text{NO}_4$ found = 409.22542, Anal. calcd. 409.22531.

General procedure for the Synthesis of dihydrodibenzo[*b,d*]azocines **8a-b** via Ring Closing Metathesis under conventional heating conditions

N-allyl derivative **7a-b** (0.25 mmol) was dissolved in dry, degassed solvent (Table 1, 5 mL) in a 25 mL round-bottomed flask and kept stirring under inert atmosphere. To this was added the catalyst (Table 1, 3 mol%) and the mixture was stirred at the temperature (Table 1) till the completion of the reaction was monitored by TLC and CI-MS (Table 1). This mixture was then diluted with DCM (25 mL) and washed with brine (10 mL), sat. NaHCO_3 soln (10 mL) and H_2O (10 mL), and dried on MgSO_4 . After removal of the solvent, the crude mixture was purified by column chromatography [silica gel, heptane-DCM (1:1)] to furnish pure products **8a-b** in yields noted in Table 1.

General procedure for the Synthesis of dihydrodibenzo[*b,d*]azocines **8a-b** via Ring Closing Metathesis under microwave irradiation

N-allyl derivative **7a-b** (0.25 mmol) was dissolved in dry, degassed solvent (Table 1, 3 mL) in a 10 mL glass vial and to this was added the catalyst (Table 1, 3 mol%). The vial was tightly sealed and the mixture was irradiated at a maximum power level of 150W, for the time and temperature described in Table 1. The mixture was then diluted with DCM (25 mL) and washed with brine (10 mL), sat. NaHCO₃ soln (10 mL) and H₂O (10 mL), and dried on MgSO₄. After removal of the solvent, the crude mixture was purified by column chromatography [silica gel, heptane-DCM (1:1)] to furnish pure products **8a-b** in yields noted in Table 1.

5-(2,2-dimethylpropanoyl)-10,11-dimethoxy-5,6-dihydrodibenzo[*b,d*]azocine (**8a**)

¹H NMR (300 MHz, CDCl₃): δ = 1.26 (s, 9H), 3.69 (d, 2H, J = 8.0 Hz), 3.81 (s, 3H), 3.83 (s, 3H), 5.73 (dt, 1H, J = 8.0 Hz), 6.86 (d, 1H, J = 8.5 Hz), 7.27 (dd, 1H, J = 7.8 Hz), 7.34 (s, 1H), 7.61-7.66 (m, 2H), 7.73 (s, 1H), 7.91 (d, 1H, J = 7.9 Hz) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 29.2, 39.2, 39.7, 55.8, 55.9, 113.3, 115.7, 120.4, 121.6, 123.4, 126.2, 126.8, 129.7, 130.5, 130.7, 139.9, 148.1, 149.1, 150.1, 179.8 ppm. DEPT (75 MHz, CDCl₃): δ = 29.2, 39.2, 55.8, 55.9, 113.3, 115.7, 120.4, 121.6, 123.4, 126.2, 126.8, 130.7 ppm. EI-MS [M⁺]: 351 (100%), 294, 266. HR (EI) – MS: C₂₂H₂₅NO₃ found = 351.18355, Anal. calcd. 351.18344.

5-(2,2-dimethylpropanoyl)-10,11,12-trimethoxy-5,6-dihydrodibenzo[*b,d*]azocine (**8b**)

^1H NMR (300 MHz, CDCl_3): δ = 1.24 (s, 9H), 3.69 (d, 2H, J = 8.0 Hz), 3.79 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 5.73 (dt, 1H, J = 8.0 Hz), 6.77 (d, 1H, J = 8.2 Hz), 6.78 (s, 1), 7.21 (d, 1H, J = 8.1 Hz), 7.36 (t, 1H, J = 8.0 Hz), 7.64 (t, 1H, J = 8.0 Hz), 8.17 (d, 1H, J = 8.0 Hz) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 29.1, 39.2, 39.7, 56.0, 60.4, 60.9, 110.1, 116.4, 117.7, 121.4, 121.6, 125.4, 127.8, 128.8, 129.6, 30.6, 142.7, 143.1, 144.9, 152.6, 179.8 ppm. DEPT (75 MHz, CDCl_3): δ = 29.1, 39.2, 56.0, 60.4, 60.9, 110.1, 117.7, 121.4, 121.6, 125.4, 127.8, 130.6 ppm. EI-MS $[\text{M}^+]$: 381 (100%), 324, 296. HR (EI) – MS: $\text{C}_{23}\text{H}_{27}\text{NO}_4$ found = 381.19405, Anal. calcd. 381.19401.

Synthesis of 5-(2,2-dimethylpropanoyl)-10,11-dimethoxy-5,6,7,8-tetrahydrodibenzo[*b,d*]azocine (**9a**)

8a (0.25 mmol) was dissolved in dry, degassed MeOH (25 mL) and transferred to a high-pressure Parr[®]-hydrogenation bottle. To this was added 10% Pd-C (10 mol%) and the mixture was repeatedly evacuated and flushed with hydrogen gas ($\times 4$). The mixture was then kept under hydrogen pressure (30 atm.) for 8h, when TLC and CI-MS has shown the completion of the reaction. Contents were then filtered through a small pad of Celite[®] and the pad was repeatedly washed with DCM (3×25 mL). Solvents were removed under reduced pressure to furnish the crude product **9a**, which was further purified by column chromatography [silica gel, heptane-DCM (1:1)] to furnish the pure product **9a** (0.083 g, 94%) as pale yellow oil.

^1H NMR (300 MHz, CDCl_3): δ = 1.24 (s, 9H), 1.70-1.77 (m, 2H), 2.77 (t, 2H, J = 5.8 Hz), 3.45 (t, 2H, J = 5.3 Hz), 3.80 (s, 3H), 3.84 (s, 3H), 6.64 (s, 1H), 7.26 (t, 1H, J = 7.9 Hz), 7.56 (d, 1H, J = 7.9 Hz), 7.63 (t, 1H, J = 7.8 Hz), 7.84 (d, 1H, J = 7.8 Hz), 7.90 (s, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 28.1, 29.1, 32.9, 39.9, 49.2, 55.8, 56.0, 113.3, 114.9, 118.5, 122.4, 125.5, 129.7, 131.0, 136.1, 136.4, 148.2, 148.6, 151.1, 180.5 ppm. DEPT (75 MHz, CDCl_3): δ = 28.1, 29.1, 32.9, 49.2, 55.8, 56.0, 113.3, 114.9, 118.5, 122.4, 125.5, 129.7 ppm. EI-MS $[\text{M}^+]$: 353 (100%), 296, 268. HR (EI) – MS: $\text{C}_{22}\text{H}_{27}\text{NO}_3$ found = 353.19911, Anal. calcd. 353.19909.

5-(2,2-dimethyl-propanoyl)-10,11,12-trimethoxy-5,6,7,8-tetrahydridibenzo-[b,d]azocine (9b)

Compound **9b** was synthesized from the cyclized compound **8b** following the above-mentioned procedure for the synthesis of **9a**. Column chromatography [silica gel, heptane-DCM (1:1)] afforded the pure product **9b** (0.09 g, 91%) as pale yellow oil.

^1H NMR (300 MHz, CDCl_3): δ = 1.18 (s, 9H), 1.66-1.75 (m, 2H), 2.22 (dt, 2H, J = 7.0, 0.3 Hz), 3.55 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.96 (t, 2H, J = 7.0 Hz), 6.27 (t, 1H, J = 8.1 Hz), 6.63 (d, 1H, J = 8.0 Hz), 6.81 (t, 1H, J = 8.3 Hz), 7.25 (s, 1H), 7.87 (d, 1H, J = 7.9 Hz) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 23.5, 28.1, 33.2, 41.0, 50.3, 56.1, 61.0, 61.1, 113.7, 117.1, 120.7, 124.4, 125.2, 129.3, 129.6, 136.1, 142.0, 143.5, 148.4, 153.2,

174.5 ppm. DEPT (75 MHz, CDCl_3): δ = 23.5, 28.1, 33.2, 50.3, 56.1, 61.0, 61.1, 113.7, 117.1, 120.7, 124.4, 129.6 ppm. EI-MS $[\text{M}^+]$: 383 (100%), 326, 298. HR (EI) – MS: $\text{C}_{23}\text{H}_{29}\text{NO}_4$ found = 383.20975, Anal. calcd. 383.20966.