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Highly efficient synthesis of buflavine: a unique *Amaryllidaceae* alkaloid

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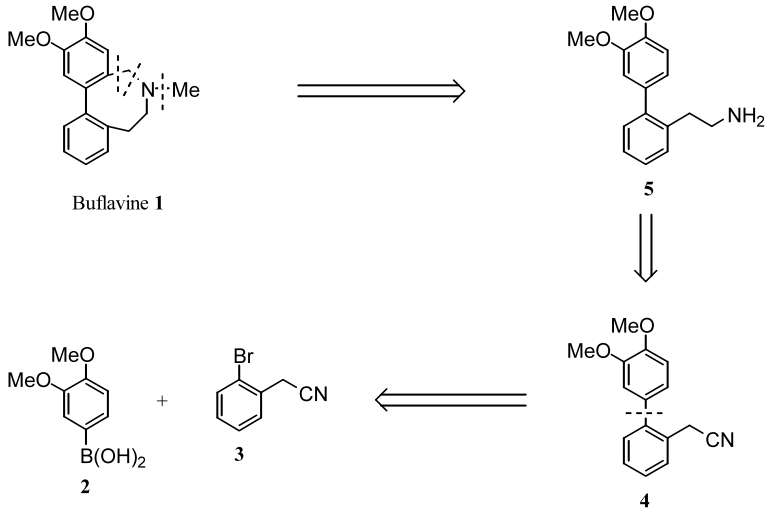
Abstract—The *Amaryllidaceae* alkaloid buflavine **1** has been synthesized in three steps by Suzuki–Miyaura cross coupling, reduction and the cascade reactions of Pictet–Spengler type and Eschweiler–Clarke *N*-methylation.

Buflavine **1** belongs to a group of natural *Amaryllidaceae* alkaloids isolated from *Boophane flava* bulbs.[1] It possesses a very rare 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine skeleton composed of a biaryl ring system linked via an eight-membered *N*-heterocyclic ring. Such compounds have been shown to exhibit potential α-adrenolytic and anti-serotonin activities.[2] The unique structure of buflavine and its interesting biological activities have prompted our efforts to synthesize this alkaloid. All previous synthetic routes[3,4] including the most recent publication[5] firstly involve formation of the biaryl ring by three different standard procedures (Ullmann, Suzuki–Miyaura and Meyer's biaryl coupling) followed by construction of the eight-membered *N*-heterocyclic ring via condensation of a C_1 side-chain with the remaining side-chain. Herein, we are pleased to report an efficient three-step total synthesis of buflavine **1** based on the retrosynthetic analysis outlined in Scheme 1.



Scheme 1. Retrosynthetic analysis of buflavine **1**.

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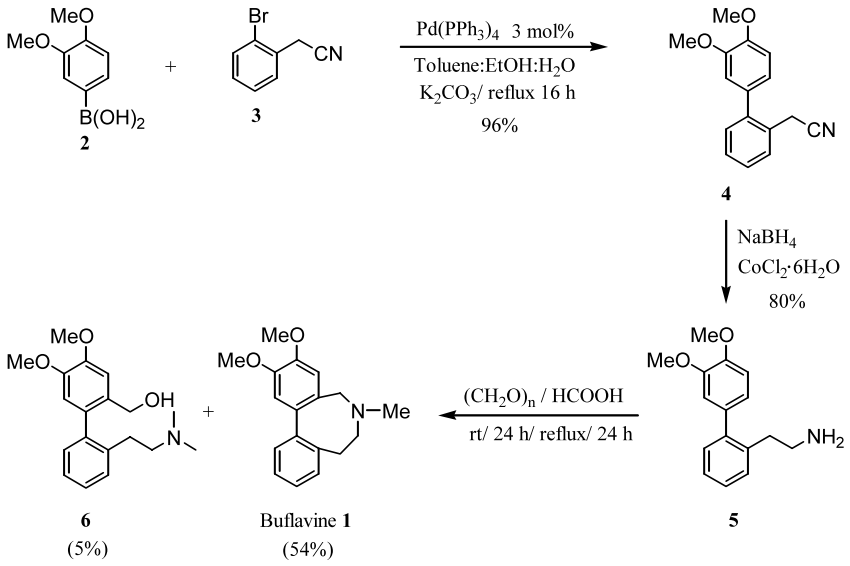

Scheme 2. Synthetic route of buflavine **1**.

The eight-membered *N*-heterocyclic ring could be simply formed by a cascade of Pictet–Spengler type reaction then *N*-methylation under the reaction conditions employed. The biarylethylamine precursor **5** is derived from biarylacetonitrile **4** which is easily prepared via Suzuki–Miyaura cross coupling of the commercially available 3,4-dimethoxyphenylboronic acid **2** and *o*-bromophenyl acetonitrile **3** (Scheme 2).

Suzuki–Miyaura cross coupling[6] of **2** and **3** using 3 mol% $Pd(PPh_3)_4$ and K_2CO_3 in a mixture of toluene, ethanol and H_2O (3:3:2) gave the expected biarylacetonitrile **4** in 96% yield. Conversion of biarylacetonitrile **4** to the key intermediate, biarylethylamine **5**, was accomplished by reduction with $NaBH_4$ in the presence of cobalt chloride hexahydrate[7] in 80% yield. We have previously exploited the tandem reaction of the Pictet–Spengler reaction[8a–d] and Eschweiler–Clarke reaction[9] in the synthesis of various alkaloids by performing the reaction in formic acid.[10a–c] It was gratifying to find that the formation of the eight-membered *N*-heterocyclic ring and *N*-methylation could indeed be carried out by reacting the biarylethylamine with paraformaldehyde in formic acid. To complete the ring formation and suppress the non-cyclized *N*,*N*-dimethylbiarylethylamine product, the mixture of biarylethylamine **5** and 5 equiv. of paraformaldehyde in formic acid was first stirred at room temperature for 24 h and subsequently an additional 5 equiv. of paraformaldehyde was added and the mixture was then heated at reflux for another 24 h to give buflavine **1** as a viscous oil in 54% yield accompanied by biarylalcohol-amine **6**[11] in 5% yield after preparative thin layer chromatography (10% MeOH–CH_2Cl_2). The biarylalcohol-amine **6** was presumably derived from electrophilic substitution of the aryl ring with paraformaldehyde in parallel with *N*,*N*-dimethylation. The spectroscopic data of our synthetic compound corresponded well with those reported for the natural product.[1] As far as we are aware, this is the first report on the successful application of the Pictet–Spengler type reaction in the formation of an eight-membered heterocyclic ring.

In conclusion, we have developed a concise and highly efficient route for the synthesis of buflavine **1** in three steps in 44% overall yield from commercially available starting materials using a Suzuki–Miyaura cross coupling to form a biaryl ring in conjunction with a cascade of Pictet–Spengler then *N*-methylation of the biarylethylamine in a one-pot reaction to construct the eight-membered heterocyclic ring.

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11. All compounds were fully characterized. Biarylacetonitrile (**4**) pale yellow crystals, mp (EtOAc) 87.0–87.5°C. IR (KBr) 2250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.64 (s, 2H), 3.90, 3.94 (2s, 2×3H), 6.85 (broad s, 2H), 6.95 (d, 1H, $J=8.8$ Hz), 7.26–7.44 (m, 3H), 7.46–7.56 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.02, 55.92, 111.31, 112.30, 118.34, 121.11, 127.94, 128.11, 128.98, 130.45, 132.51, 141.75, 148.66, 148.93. EIMS (m/z, % relative intensity) 254 (M^++1, 25), 253 (M^+, 100), 210 (54), 192 (16), 182 (15), 180 (11), 166 (11), 165 (17). HRMS (FAB+) calcd for $C_{16}H_{16}NO_2$, 254.1181. Found 254.1179. Anal. calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.51; H, 5.74; N, 5.26%. Biarylethylamine (**5**) viscous oil, mp (HCl salt) 209–210°C, mp (oxalate salt) 148–149°C. IR (neat) 3345, 2934, 1605, 1585, 1520, 1485, 1246, 1027 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 2H), 2.78 (s, 4H), 3.88, 3.93 (2s, 2×3H), 6.80–6.95 (m, 3H), 7.2–7.4 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.43, 110.62, 112.33, 120.88, 125.59, 126.79, 129.09, 129.81, 134.0, 136.59, 141.60, 147.62, 148.09. EIMS (m/z, % relative intensity) 258 (M^++1, 6), 257 (M^+, 24), 240 (45), 228 (100), 213 (17), 209 (12). HRMS (FAB+) calcd for $C_{16}H_{20}NO_2$, 258.1494. Found 258.1496. Buflavine **1** viscous oil, mp (oxalate salt) 194.0–194.5°C. IR (neat) 2931, 1606, 1520, 1452, 1357 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.49–2.80 (m, 3H), 3.07 (d, 1H, $J=13.5$ Hz), 3.26 (t, 1H, $J=9.5$ Hz), 3.54 (d, 1H, $J=13.5$ Hz), 3.90, 3.96 (2s, 2×3H), 6.80 (s, 1H), 6.91 (s, 1H), 7.31 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.45, 45.82, 55.89, 58.24, 58.62, 112.06, 113.51, 126.08, 127.88, 129.01, 129.43, 129.58, 132.92, 139.96, 141.19, 147.84, 148.34. EIMS (m/z, % relative intensity) 284 (M^++1, 37), 283 (M^+, 99.8), 268 (100), 240 (67), 225 (71), 197 (76), 179 (47), 178 (28), 165 (38), 153 (22), 152 (27). HRMS (FAB+) calcd for $C_{18}H_{22}NO_2$, 284.1651. Found 284.1649. Biarylalcohol-amine **6** viscous oil, IR (neat) 3364, 2936, 1607, 1515, 1465 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.00 (s, 6H), 2.40–2.9 (m, 4H), 3.20 (broad s, 1H), 3.85, 3.95 (2s, 2×3H), 4.24 (d, 1H, $J=12$ Hz),), 4.48 (d, 1H, $J=12$ Hz), 6.67 (s, 1H), 7.08 (s, 1H), 7.20–7.38 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.15, 44.74, 55.95, 56.01, 60.81, 62.49, 112.37, 112.94, 125.94, 127.73, 129.57, 130.29, 131.92, 132.54, 138.52, 140.01, 147.76, 148.35. EIMS (m/z, % relative intensity) 316 (M^++1, 26), 315 (M^+, 14), 270 (56), 239 (100), 240 (28), 238 (23), 211 (23), 196 (27), 195 (24), 181 (33), 165 (48), 153 (33), 152 (44), 58 (88). HRMS (FAB+) calcd for $C_{19}H_{26}NO_3$, 316.1913. Found 316.1909.