Morita–Baylis–Hillman Route to 8,9,9a,10-Tetrahydrobenzo[b][1,8]naphthyridine-6(7H)-ones and 3,4,4a,5-Tetrahydrodibenzo[b,g][1,8]naphthyridine-1(2H)-ones

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1,8-Naphthyridine, tetrahydro-1,8-naphthyridine and its annelated derivatives are present in many natural and synthetic compounds.1,2 1,8-Naphthyridine derivatives show a broad range of interesting physiological activities such as antiinflammatory,3,4 analgesic,5 antiaggressive,6 anticancer,7 antibacterial,8 antitumor,9 antihypertensive,10 antiallergitic,11 and antimalarial.12 Several synthetic approaches have been developed to the 1,8-naphthyridine derivatives,13 but due to their great importance, the development of new synthetic methods remain an active research area.

The Morita–Baylis–Hillman (MBH) reaction14 has attracted the attention of organic chemists in recent years. This reaction provides synthetically useful multi-functional molecules which have been successfully employed in the preparation of various heterocyclic systems.15 MBH adducts have already been used as substrates for the synthesis of 1,8-naphthyridine skeletons. Basavaiah and Reddy reported an elegant strategy to prepare tri and tetracyclic frameworks containing 1,8-naphthyridine-2-one moiety from the MBH adduct of 2-nitrobenzaldehyde and acrylonitrile.16 Su used an acetylated MBH adduct derived from 2-chloroquinoline-3-carboxaldehyde with acrylic acid esters as a substrate for the synthesis of benzo[b][1,8]naphthyridine-3-carboxylate derivatives.17 Rao and co-worker have reported synthesis of [1,8]naphthyridine-3-carboxylates from the acetics of MBH adducts, derived from substituted 1,8-naphthyridine-3-carboxaldehydes, via the reaction with TsNH2 (or NH2OAc) followed by cyclization or via the treatment with NaN3 followed by reductive cyclization.18 Coelho also reported highly diastereoselective access to 3,4-substituted tetrahydro-1,8-naphthyridines from a silylated MBH adduct derived from 2-chloropyridine-3-carboxaldehyde or 2-chloroquinoline-3-carboxaldehyde with acrylic acid esters.19

Meanwhile, Kim and co-workers reported20 a transformation of the MBH acetates, obtained from 2-halobenzaldehyde or 2-chloroquinoline-3-carboxaldehyde with 2-cyclohexen-1-one, with a base into 2-arylmethylphenol or 2-(quinolone-3-yl)methylphenol, respectively. This reaction proceeded by a base assisted elimination of acetic acid and following keto-enol tautomerization and aromatization by 1,5-hydrogen transfer. Although the acetylated MBH adduct between 2-cyclohexen-1-one and 2-chloropyridine-3-carboxaldehyde or 2-chloroquinoline-3-carboxaldehyde are known,21,22 but the reaction of acetates with primary amines was not studied. In this note we disclose a facile synthesis of 8,9,9a,10-tetrahydrobenzo[b][1,8]naphthyridine-6(7H)-ones and 3,4,4a,5-tetrahydrodibenzo[b,g][1,8]naphthyridine-1(2H)-ones via the successive S2–Ar elimination strategy.

The key starting material MBH adduct 3 was prepared by the reaction of 2-chloropyridine-3-carboxaldehyde (1) with 2-cyclohexen-1-one (2) in the presence of DMAP in aqueous THF at room temperature in 70% yield following the earlier reported procedure.18 Acetylation of 3 with Ac2O/ DMAP gave acetate 4 in 96% yield. The known MBH acetate 7 were prepared in similar manner using 2-chloroquinoline-3-carboxaldehyde.19 The reaction between MBH acetate 4 and several primary amines or NH2OAc in THF in the presence of triethylamine at reflux temperature for 2–7 h afforded the desired 8,9,9a,10-tetrahydrobenzo[b][1,8]naphthyridine-6(7H)-ones 6a-g in 35–57% yields (Table 1, Scheme 1).20 Also, we examined the same reaction with an aromatic amine, aniline, however, the corresponding naphthyridine 6h was not formed in any trace amount, only starting acetate 4 was recovered. Under the same reaction conditions the known

<table>
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<tr>
<th>Entry</th>
<th>Acetate</th>
<th>Time (h)</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>2</td>
<td>-MeOC6H4H2CH2</td>
<td>6a</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2</td>
<td>PhCH2</td>
<td>6b</td>
<td>41</td>
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<td>2</td>
<td>Pr</td>
<td>6c</td>
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<td>6h</td>
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<td>H</td>
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</table>

*The reaction was performed with acetate (1 mmol), amine (1.5 or 3 mmol), and Et3N (2.2 mmol) in THF at reflux temperature. †Isolated yields. 3 mmol of amine was used.
acetate 7 gave 3,4,4a,5-tetrahydrobenzo[b,g][1,8]naphthyridine-1(2H)-ones 8a-d in 33–48% yields (Table 1, Scheme 2). It is worth mentioning that the reactions of the acetates 4 and 7 with isopropyl-, cyclopropyl-, and ethyl amines having low boiling points were achieved with adding same amounts of these amines (1.5 equiv) after refluxing for 2 h as shown in entries 4, 5, 6, and 11 of Table 1. With the aid of Et3N the amine undergoes Michael addition to the exocyclic C=C bond of acetate 4 and subsequent migration of the C=C bond with the simultaneous ejection of the acetic acid to give the allyl amine 5. The intermediate could not be isolated, and subsequently amine moiety can attack in anSnAr reaction at C(2) of the pyridine ring followed by elimination of chloride ion to give 6.

The structures of 6 were elucidated by 1H and 13C NMR and mass spectral analyses. In a DEPT experiment of 6a, four CH2 peaks (δ = 19.7, 30.4, 38.5, 46.7) and seven CH peaks (δ = 58.5, 113.5, 113.9, 128.5, 129.4, 137.0, 150.2) were observed, and we could exclude the possible regioisomeric structure about double bond.

In conclusion, we have successfully elaborated a simple synthetic method for tri and tetracyclic frameworks containing about double bond.

### Experimental Section

2-(2-Chloropyridine-3-yl)(hydroxymethyl)cyclohex-2-en-1-one (3). A mixture of 2-chloropyridine-3-carboxaldehyde (1, 1.42 g, 10 mmol), and DMAP (0.14 g, 2 mmol) in 10 mL of aqueous THF (1:1) was stirred at rt for 24 h. The reaction mixture was diluted with H2O (20 mL) and extracted with CH2Cl2 (3 × 20 mL). The combined organic layers was dried over MgSO4 and the solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting with hexane–EtOAc (1:1) to produce 3 (1.66 g, 70%) as a white solid that was recrystallized (EtO–PE); mp 87–88 °C; IR (KBr): 3392, 1671, 1567, 1405 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 1.97–2.06 (m, 2H, CH2), 2.38–2.53 (m, 4H, 2 × CH2), 3.91 (br s, 1H, OH), 5.83 (s, 1H, CH), 6.59 (t, J = 4.1 Hz, 1H, CH1), 7.33 (dd, J = 7.6 and 4.7 Hz, 1H, aromatic), 8.02 (dd, J = 7.6 and 1.5 Hz, 1H, aromatic), 8.34 (dd, J = 4.7 and 1.8 Hz, 1H, aromatic); 13C NMR (75 MHz, CDCl3) δ 22.3, 25.7, 38.4, 68.8, 122.7, 135.5, 137.4, 138.4, 148.5, 149.3, 200.6; MS m/z 237 (M⁺, 1), 236 (3), 203 (14), 202 (100), 184 (18). Anal. Calcd for C13H12ClNO: C, 60.11; H, 5.04; N, 5.01. Found: C, 59.98; H, 4.84; N, 4.86.

Scheme 1

8a: R = p-MeOC6H4CH3, 8b: R = PhCH2, 8c: R = Pr
8d: R = iso-Pr, 8e: R = cyclo-Pr, 8f: R = Et, 8g: R = H, 8h: R = Ph

Scheme 2

2-[(Acetoxy)(2-chloropyridine-3-yl)methyl]cyclohex-2-en-1-one (4). A mixture of 3 (1.19 g, 5 mmol), acetic anhydride (0.71 mL, 7.5 mmol) and DMAP (0.11 g, 1 mmol) in CH2Cl2 (15 mL) was stirred at rt for 1 h. The mixture was neutralized with a saturated aqueous NaHCO3 solution. The resulting mixture was extracted with CH2Cl2 (2 × 30 mL) and the organic layers were dried over MgSO4 and concentrated in vacuo. The resulting mixture was chromatographed on silica gel eluting with hexane–EtOAc (1:1) to produce 4 (1.33 g, 96%) as a white solid that was recrystallized (EtO–PE); mp 134–135 °C; IR (KBr): 1744, 1676, 1567, 1410, 1370, 1226 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 1.99–2.07 (m, 2H, CH2), 2.13 (s, 3H, CH3), 2.43–2.49 (m, 4H, 2 × CH2), 6.84–6.86 (m, 2H, 2 × CH), 7.27 (dd, J = 4.7 and 2.9 Hz, 1H, aromatic), 7.78 (dd, J = 7.6 and 1.8 Hz, 1H, aromatic), 8.34 (dd, J = 4.7 and 2.1 Hz, 1H, aromatic); 13C NMR (75 MHz, CDCl3) δ 20.8, 22.3, 25.9, 38.3, 69.2, 122.3, 132.9, 135.7, 137.4, 148.8, 149.5, 149.8, 169.2, 196.6; MS m/z 280 (2), 244 (8), 236 (6), 202 (45), 184 (100), 140 (14), 123 (10). Anal. Calcd for C13H11ClNO2C: C, 60.11; H, 5.04; N, 5.01. Found: C, 59.98; H, 4.84; N, 4.86.

8,9,9a,10-Tetrahydrobenzo[b][1,8]naphthyridine-6(7H)-ones (6).

General Procedure: To a stirred solution of MBH acetate 4 (1 mmol) in THF (10 mL) was added either RNH2 (1.5 mmol) or NH2OAc (1.5 mmol) and Et3N (0.31 mL, 2.2 mmol) at rt. The reaction mixture was heated at reflux temperature for 2–7 h. In the case of isopropyl-, cyclopropyl-, and ethyl amines 1.5 mmol of amines was added again after refluxing for 2 h. The mixture was diluted with H2O (10 mL)
and extracted with CHCl₃ (3 × 20 mL). The combined organic layers were dried over MgSO₄ and the solvent was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel eluting hexane–EtOAc (2:1) to produce 6 as an oil.

### 10-Cyclopropyl-8,9,9a,10-tetrahydrobenzo[b]1,8]naphthyridine-6(7H)-one (6d): Reaction time: 5 h; yield: 57%; IR (CHCl₃): 1688, 1620, 1555, 1541 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.01–1.09 (m, 2H, CH₂), 2.29–2.54 (m, 4H, 2 × CH₂); 4.71 and 5.16 (d, J = 6.4 Hz, each 1H, CH₃); 7.01–7.20 (m, 3 × 1H, CH); 8.40–8.50 (d, J = 7.0 and 5.0 Hz, 1H, aromatic); 7.24–7.32 (m, 3 × 1H, aromatic); 12.27 (dd, J = 5.0 and 2.1 Hz, 1H, aromatic); 13C NMR (75 MHz, CDCl₃) δ 19.9, 30.4, 38.6, 47.5, 58.8, 113.6, 114.2, 126.8, 127.8, 130.8, 131.6, 137.0, 137.6, 150.2, 150.9, 162.9, 198.4; MS m/z 274 (26), 277 (100), 199 (46), 183 (12), 170 (13), 150 (2). Anal. Calcd for C₁₈H₁₈N₂O₂: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.76; H, 6.01; N, 9.04.

### 10-Propyl-8,9,9a,10-tetrahydrobenzo[b]1,8]naphthyridine-6(7H)-one (6e): Reaction time: 2 h; yield: 42%; IR (CHCl₃): 1684, 1618, 1554, 1450 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.95 (t, J = 7.3 Hz, 3H, CH₃), 1.66–1.79 (m, 2H, CH₂), 2.03–2.14 (m, 2H, CH₂), 2.35–2.59 (m, 4H, 2 × CH₂); 3.27–3.37 and 3.57–3.67 (m, each 1H, CH), 4.77–4.83 (m, 1H, CH), 6.41 (dd, J = 7.0 and 5.0 Hz, 1H, aromatic), 7.05 (d, J = 2.1 Hz, 1H, CH), 7.10 (dd, J = 7.0 and 1.8 Hz, 1H, aromatic), 7.96 (dd, J = 5.0 and 1.8 Hz, 1H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ 11.4, 19.3, 19.8, 30.8, 38.6, 46.2, 58.7, 112.9, 114.5, 131.2, 131.3, 136.7, 150.2, 150.9, 198.4; MS m/z 242 (M⁺, 35), 241 (16), 240 (27), 214 (32), 213 (26), 199 (36), 187 (42), 186 (100), 172 (24), 171 (25), 170 (37), 144 (43). Anal. Calcd for C₁₈H₁₈N₂O₂: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.56; H, 7.40; N, 11.38.

### 10-(Iso-Propyl)-8,9,9a,10-tetrahydrobenzo[b]1,8]naphthyridine-6(7H)-one (6f): Reaction time: 7 h; yield: 35%; IR (CHCl₃): 1692, 1629, 1591, 1555 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.37 (d, J = 6.7 Hz, 3H, CH₃), 1.41 (d, J = 7.0 Hz, 3H, CH₃), 1.89–2.17 (m, 2H, CH₂), 2.27–2.57 (m, 4H, 2 × CH₂), 4.32–4.41 (m, 1H, CH), 4.84–4.90 (m, 1H, CH), 6.34 (dd, J = 7.0 and 5.0 Hz, 1H, aromatic), 6.79 (d, J = 1.8 Hz, 1H, CH), 6.99–7.02 (m, 1H, aromatic), 7.90 (dd, J = 5.0 and 2.1 Hz, 1H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ 18.7, 19.1, 21.2, 33.7, 38.4, 48.7, 58.0, 112.3, 114.1, 128.8, 133.6, 136.3, 149.5, 155.9, 199.2; MS m/z 242 (M⁺, 31), 214 (47), 200 (20), 199 (28), 188 (32), 186 (82), 145 (32), 144 (100). Anal. Calcd for C₁₈H₁₈N₂O₂: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.16; H, 7.24; N, 11.29.

### General Procedure: To a stirred solution of MBH acetate η²⁻¹ (1 mmol) in THF (10 mL) was added RNH₂ (1.5 mmol) or NH₂OHAc (1.5 mmol) and Et₃N (0.31 mL, 2.2 mmol) at rt. The reaction mixture was heated at reflux temperature for 4–14 h. In the case of ethyl amine 1.5 mmol of amine was added again after refluxing for 2 h. The work-up procedure was the same as described above to give 8 as an oil.

### 5-(p-Methoxybenzyl)-3,4,4a,5-Tetrahydrobenzo[b][1,8]naphthyridine-1(2H)-one (8a): Reaction time: 5 h;
yield: 48%; IR (CHCl₃): 1687, 1614, 1557, 1511 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.87–2.03 (m, 2H, CH₂), 2.32–2.58 (m, 4H, 2 × CH₂), 3.78 (s, 3H, OCH₃), 4.63 and 5.54 (d, J = 15.2 Hz, each 1H, CH₂), 4.70–4.74 (m, 1H, CH), 6.81–6.86 (m, 2H, aromatic), 7.11–7.16 (m, 2H, CH and aromatic), 7.26–7.28 (m, 2H, aromatic), 7.41–7.54 (m, 4H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ 19.8, 30.7, 38.8, 46.7, 55.2, 58.8, 113.8, 116.8, 122.6, 124.1, 126.4, 126.7, 128.9, 129.9, 130.3, 135.0, 136.4, 149.1, 153.4, 158.5, 198.8; MS m/z 339 (4), 325 (4), 281 (14), 265 (32), 249 (47), 210 (26), 208 (100), 193 (10), 191 (16), 163 (14), 146 (16). Anal. Caled for C₂₃H₂₅N₂O: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.65; H, 6.12; N, 7.39.

5-Benzyl-3,4,4a,5-tetrahydridobenz[g]l,8]napthryidine-1(2H)-one (8b): Reaction time: 4 h; yield: 44%; IR (CHCl₃): 1688, 1615, 1558, 1494, 1477 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.83–2.03 (m, 2H, CH₂), 2.31–2.57 (m, 4H, 2 × CH₂), 4.70–4.76 (m, 1H, CH), 4.80 and 5.48 (d, J = 15.8 Hz, each 1H, CH₂), 7.11–7.16 (m, 2H, CH and aromatic), 7.22–7.35 (m, 5H, aromatic), 7.40–7.54 (m, 4H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ 19.8, 30.9, 38.8, 47.6, 59.2, 116.8, 122.6, 124.1, 126.4, 126.9, 127.5, 128.6, 129.2, 130.4, 135.0, 136.5, 138.1, 149.1, 154.3, 198.8; MS m/z 241 (17), 240 (100), 226 (26), 225 (71), 197 (10), 182 (20), 166 (19), 165 (27), 154 (10), 153 (14). Anal. Caled for C₂₁H₂₁N₂O: C, 81.15; H, 5.92; N, 7.83. Found: C, 80.92; H, 5.74; N, 7.96.

5-Ethyl-3,4,4a,5-tetrahydridobenz[g]l,8]napthryidine-1(2H)-one (8c): Reaction time: 14 h; yield: 39%; IR (CHCl₃): 1688, 1615, 1594, 1566, 1495 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.26 (t, J = 7.0 Hz, 3H, CH₃), 1.93–2.03 (m, 2H, CH₂), 2.09–2.64 (m, 4H, 2 × CH₂), 3.60–3.71 and 3.81–3.92 (m, each 1H, CH), 4.76–4.82 (m, 1H, CH), 7.08–7.13 (m, 2H, CH and aromatic), 7.41–7.55 (m, 4H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ 6.21, 19.9, 31.4, 38.9, 39.8, 59.2, 117.1, 122.3, 123.8, 126.4, 127.6, 129.4, 130.2, 134.8, 136.1, 149.4, 153.9, 198.8; MS m/z 278 (M⁺, 39), 276 (24), 251 (41), 249 (44), 235 (35), 222 (100), 194 (38). Anal. Caled for C₂₀H₂₀N₂O: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.48; H, 6.34; N, 9.82.

3,4a,4-benz[g]l,8]napthryidine-1(2H)-one (8d): Reaction time: 7 h; yield: 33%; yellow solid; mp 189–191 °C; IR (KBr): 3228, 1683, 1626, 1593, 1574 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.01–2.68 (m, 6H, 3 × CH₂), 4.90–4.96 (m, 1H, CH), 5.35 (br s, 1H, NH), 7.15–7.21 (m, 1H, aromatic), 7.25 (d, J = 2.4 Hz, 1H, CH), 7.48–7.54 (m, 3H, aromatic, 7.62 (s, 1H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ 19.8, 32.4, 39.3, 54.3, 117.2, 123.0, 124.8, 125.5, 128.1, 129.8, 130.8, 134.3, 136.9, 148.5, 155.3, 198.0; MS m/z 251 (94), 249 (100), 221 (9), 208 (14), 207 (19), 193 (14). Anal. Caled for C₂₁H₁₉N₂O: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.04; H, 5.41; N, 11.32.