SYNTHESIS OF TETRAHYDROFURO[2,3-b][1]BENZO-
PYRANONES BY THE RING-EXPANSION REACTION
OF METHANOCHROMANONE WITH SYMMETRIC
KETONES

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Abstract - In the presence of SnCl₄, 2,3-dimethoxycarbonylmethanochromanone (8) was transformed into a zwitterion which easily reacted with symmetric ketones to give the tetrahydrofuro[2,3-b][1]benzopyranone derivatives in good yields with high diastereoselectivity.

Cyclopropanes having an electron-withdrawing or -donating group are susceptible to ring-opening reactions.¹ Especially, cyclopropanes with donor and acceptor substituents at vicinal positions on the cyclopropane ring are the equivalent of a ring-opened 1,3-zwitterion,² which are expected to react with both nucleophiles³ and electrophiles.⁴ We have recently reported that 2,3-methanochromanone (1), readily prepared from the chromone and dimethyloxosulfonylmethylide, was transformed into a zwitterionic intermediate (2) in the presence of a Lewis acid, and that 2 reacted with silyl enol ethers to give the ring-expanded product (3).⁵ If methanochromanones having a strong electron-acceptor at the methano-position are employed instead of 1, formation of a 1,3-zwitterionic intermediate (5) would be expected (Scheme 1). We report herein the synthesis of tetrahydrofuro[2,3-b][1]benzopyranone derivatives by the Lewis acid-promoted reaction of methanochromanone (8) having two ester groups at the methano-position with symmetric ketones.

EWG = electron-withdrawing group

Scheme 1
Methanochromanone (8) was readily obtained in 80% yield by the reaction of 3-iodochromone (7) with dimethyl malonate in the presence of potassium carbonate in DMF at room temperature (Scheme 2). The reaction pathway for the formation of cyclopropane ring involves the initial Michael reaction of dimethyl malonate to the active site (2-position of the chromone ring) followed by cyclization of the resulting intermediate.

At first, the reactivity of 8 by the action of a Lewis acid was examined. A solution of a stoichiometric amount of SnCl$_4$ in CH$_2$Cl$_2$ was added to a solution of 8 in CH$_2$Cl$_2$ at -78 °C to give the 2-chlorochromanone (10) in 82% yield and no 2-chloro-1-benzoxepinone (11) was detected (Scheme 3). In this result, we considered that methanochromanone (8) is the equivalent of a ring-opened zwitterion (9).

Next the reaction of 8 with symmetric ketones was undertaken. In the presence of SnCl$_4$ (10 mol%), 8 smoothly reacted with acetone in CH$_2$Cl$_2$ at -78 °C to afford the tetrahydrofuro[2,3-b][1]benzopyran-4-one (12a) in quantitative yield with high trans-selectivity (trans : cis = >99 : 1, Table 1, Entry 1). The trans/cis ratio was determined by $^1$H-NMR analysis of the reaction mixture. A similar tendency was observed in the [3+2] cycloaddition reaction of 8 with 3-pentanone and diphenyl ketone (Entries 2 and 3). Cyclic ketones such as cyclopentanone, cyclohexanone, and cycloheptanone also gave the corresponding cycloadducts in good yields with high trans-selectivity (Entries 4~6).

It was also found that the trans-adducts could be easily converted into cis-isomers by treatment with Et$_3$N.
Thus, treatment of the adduct (12a) with Et₃N in CH₂Cl₂ at room temperature gave the cis-isomer (13a) in 86% yield. The stereochemistry of the products was assigned based on NOE experiments. Thus, irradiation of H-9a in cis-isomer (13a) gave a 15.5% enhancement of the signal for H-3a supporting the cis stereochemistry. In comparison, irradiation of H-9a in trans-adduct (12a) resulted in only 3.5% enhancement of the signal for H-3a. The stereochemistry of cycloadducts (12b-f) was established by comparison of the coupling constants between H-3a and H-9a to those of 12a. The adduct (12a) exhibited a coupling constant of 10.1 Hz, while values of 10.4, 10.4, 10.1, 10.1, and 10.1 Hz were observed for 12b, 12c, 12d, 12e, and 12f, respectively.

A plausible reaction mechanism is proposed in Schemes 4 and 5. In the first step, 8 was initially transformed into a zwitterionic intermediate (9) by the action of a Lewis acid and the zwitterion reacted with ketones to form the intermediate (14). In the second step for the diastereoselective cycloaddition reaction, addition of a nucleophile can, in principle, occur at either face of the oxonium ion (14). In each case, either parallel or anti-parallel⁹ (with respect to the axial hydrogen at C3) attack is possible. In general, the intramolecular 5-exo-trig ring closure of cyclohexane derivatives¹⁰ leads to cis-fused products arising from anti-parallel addition via a chair-like transition state¹¹ (Figure 1). In the case of this reaction, C4-C4a, C4a-C8a, and C8a-O bonds in the intermediate (14) should be likely lied in the same plane (Figure 2). In the possible conformations of the intermediate (14), 14A is favored over 14B because of the unfavorable dipole-dipole interactions and/or the steric hindrance between the carbonyl and the ester groups. As a result, trans-fused products would be preferred.

Table 1. Lewis acid-mediated [3+2] cycloaddition of 8 with symmetric ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)ᵃ</th>
<th>trans : cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetone</td>
<td>-78</td>
<td>0.25</td>
<td>12a</td>
<td>99</td>
<td>&gt;99 : 1</td>
</tr>
<tr>
<td>2</td>
<td>3-pentanone</td>
<td>-78 rt -30</td>
<td>4</td>
<td>12b</td>
<td>70</td>
<td>&gt;99 : 1</td>
</tr>
<tr>
<td>3</td>
<td>diphenyl ketone</td>
<td>-78</td>
<td>0.4</td>
<td>12c</td>
<td>80</td>
<td>&gt;99 : 1</td>
</tr>
<tr>
<td>4</td>
<td>cyclopentanone</td>
<td>-78 rt -50</td>
<td>2</td>
<td>12d</td>
<td>88</td>
<td>&gt;50 : 1</td>
</tr>
<tr>
<td>5</td>
<td>cyclohexanone</td>
<td>-78 rt</td>
<td>3.5</td>
<td>12e</td>
<td>88</td>
<td>&gt;99 : 1</td>
</tr>
<tr>
<td>6</td>
<td>cycloheptanone</td>
<td>-10</td>
<td>0.4</td>
<td>12f</td>
<td>67</td>
<td>&gt;50 : 1</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield
In summary, we have demonstrated that the SnCl$_4$-catalyzed ring-opening addition reactions of 8 with symmetric ketones proceeded smoothly to afford the corresponding tetrahydrofuro[2,3-$b$][1]benzopyranones in high yields with high diastereoselectivity.
EXPERIMENTAL

All melting points were determined using a Yanagimoto micro-hot stage and are uncorrected. IR spectra were recorded using a JASCO IR-810 spectrophotometer and NMR spectra were measured using a JEOL JNM-A500 with tetramethylsilane as the internal standard. MS spectra were recorded using a JEOL JMS-700 spectrometer. Column chromatography was done on BW-820 MH (Fuji silysia).

Dimethyl 7,7a-dihydro-7-oxobenzob[2]cyclopropa[e]pyran-1,1-dicarboxylate (8)
To a mixture of 3-iodochromone (5.4 g, 20 mmol) and K$_2$CO$_3$ (11 g, 80 mmol) in DMF (80 mL) was added methyl malonate (2.8 g, 21 mmol) at rt. After being stirred for 3 h, the reaction mixture was deluted with water and extracted with Et$_2$O. The organic layer was dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-AcOEt = 4 : 1) to give 8 (4.4 g, 80%), mp 104-105 °C (from AcOEt-hexane). IR (CHCl$_3$) 1740, 1690, 1620 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$ 3.04 (1H, d, $J = 7.0$ Hz, H-7a), 3.31 (3H, s, OMe), 3.81 (3H, s, OMe), 4.92 (1H, d, $J = 7.0$ Hz, H-1a), 7.01 (1H, dd, $J = 8.5$, 0.9 Hz, H-3), 7.07 (1H, ddd, $J = 8.2$, 7.9, 0.9 Hz, H-5), 7.50 (1H, ddd, $J = 8.5$, 8.2, 1.5 Hz, H-4), 7.87 (1H, dd, $J = 7.9$, 1.5 Hz, H-6); $^{13}$C-NMR (CDCl$_3$) $\delta$ 33.98, 35.24, 52.83, 53.68, 63.70, 117.59, 119.15, 122.71, 126.28, 136.16, 157.52, 162.69, 167.83, 183.35; MS m/z 276 (M$^+$). Anal. Calcd for C$_{14}$H$_{12}$O$_6$: C, 60.87; H, 4.38. Found: C, 60.72; H, 4.46.

Dimethyl (2-chloro-2,3-dihydro-4H-1-benzopyran-3-yl)malonate (10)
To a stirred solution of 8 (138 mg, 0.5 mmol) in CH$_2$Cl$_2$ (6 mL) was dropwise a solution of SnCl$_4$ (1.0 M solution in CH$_2$Cl$_2$, 0.6 mL, 0.6 mmol) at -78 °C under argon atmosphere. After being stirred for 30 min, the reaction was quenched at the same temperature by adding phosphate buffer (Ph 7). The mixture was stirred vigorously for 10 min and allowed to rt. The mixture was extracted with CH$_2$Cl$_2$ (30 mL x 3) and the combined organic layers were dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the residue was recrystallized from Et$_2$O-hexane to give 10 (128 mg, 82%), mp 104-106 °C. IR (CHCl$_3$) 1760, 1740, 1700, 1650, 1620 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$ 3.65 (1H, dd, $J = 8.5$, 2.8 Hz, H-3), 3.72 (3H, s, OMe), 3.74 (3H, s, OMe), 3.81 (1H, d, $J = 8.5$ Hz, COCHCO), 6.72 (1H, d, $J = 2.8$ Hz, H-2), 7.06 (1H, dd, $J = 8.2$, 0.9 Hz, H-8), 7.21 (1H, ddd, $J = 8.2$, 7.9, 0.9 Hz, H-6), 7.59 (1H, td, $J = 8.2$, 8.2, 1.5 Hz, H-7), 7.94 (1H, dd, $J = 7.9$, 1.5 Hz, H-5); High-resolution MS m/z Calcd for C$_{14}$H$_{13}$O$_6$Cl$^{35}$Cl (M$^+$); 312.0401, Found: 312.0371.

General Procedure for [3+2] Cycloaddition Reaction of Methanochromanone (8) with Symmetric Ketones.
To a stirred solution of 8 (138 mg, 0.5 mmol) and a ketone (1 mmol) in CH$_2$Cl$_2$ (4 mL) was dropwise a solution of SnCl$_4$ (0.2 M solution in CH$_2$Cl$_2$, 0.25 mL, 0.05 mmol) at -78--10 °C under argon atmosphere. After being stirred for 0.2--4 h at -78 °C~rt, the reaction was quenched by saturated aqueous NaHCO$_3$. The mixture was stirred vigorously for 10 min and allowed to rt. The mixture was extracted with
CH₂Cl₂ (30 mL x 3) and the combined organic layers were dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane / AcOEt) to afford the cycloadduct (12a-f). The yield is given in Table 1.

Dimethyl trans-2,3,3a,9a-tetrahydro-2,2-dimethyl-4-oxo-4H-furo[2,3-b][1]benzopyran-3,3-dicarboxylate (12a): colorless prism (from AcOEt-hexane), mp 115-117 °C; IR (CHCl₃) 1750, 1730, 1610 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.49 (3H, s, Me), 1.56 (3H, s, Me), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 3.98 (1H, d, J = 10.1 Hz, H-3a), 5.98 (1H, d, J = 10.1 Hz, H-9a), 7.10 (1H, ddd, J = 8.5, 7.3, 1.0 Hz, H-6), 7.12 (1H, dd, J = 8.5, 1.0 Hz, H-8), 7.54 (1H, ddd, J = 8.5, 7.3, 1.8 Hz, H-7), 7.89 (1H, dd, J = 7.9, 1.8 Hz, H-5); MS m/z 334 (M⁺). Anal. Calcd for C₁₇H₁₈O₇: C, 61.07; H, 5.43. Found: C, 60.95; H, 5.36.

Dimethyl trans-2,2-diethyl-2,3,3a,9a-tetrahydro-4-oxo-4H-furo[2,3-b][1]benzopyran-3,3-dicarboxylate (12b): colorless prism (from AcOEt-hexane), mp 108-110 °C; IR (CHCl₃) 1750, 1720, 1620 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.00 (3H, t, J = 7.3 Hz, Me), 1.04 (3H, t, J = 7.3 Hz, Me), 1.68 (1H, dq, J = 14.6, 7.3 Hz, CH₂CH₃), 1.92 (2H, q, J = 7.3 Hz, CH₂CH₃), 1.94 (1H, dq, J = 14.6, 7.3 Hz, CH₂CH₃), 3.81 (6H, s, OMe), 3.93 (1H, d, J = 10.4 Hz, H-3a), 6.00 (1H, d, J = 10.4 Hz, H-9a), 7.10 (1H, ddd, J = 7.9, 7.3, 1.0 Hz, H-6), 7.13 (1H, dd, J = 8.5, 1.0 Hz, H-8), 7.54 (1H, ddd, J = 8.5, 7.3, 1.8 Hz, H-7), 7.88 (1H, dd, J = 7.9, 1.8 Hz, H-5); MS m/z 361 (M⁺-1). Anal. Calcd for C₁₉H₂₂O₇: C, 62.98; H, 6.12. Found: C, 62.75; H, 6.06.

Dimethyl trans-2,3,3a,9a-tetrahydro-4-oxo-2,2-diphenyl-4H-furo[2,3-b][1]benzopyran-3,3-dicarboxylate (12c): colorless prism (from AcOEt-hexane), mp 260-262 °C; IR (CHCl₃) 1745, 1725, 1600 cm⁻¹; ¹H-NMR (CDCl₃) δ 3.37 (3H, s, OMe), 3.47 (3H, s, OMe), 4.46 (1H, d, J = 10.4 Hz, H-3a), 6.28 (1H, d, J = 10.4 Hz, H-9a), 7.14 (1H, ddd, J = 7.9, 7.3, 1.0 Hz, H-6), 7.20-7.29 (4H, m), 7.32 (1H, m), 7.41 (2H, m), 7.48 (2H, m), 7.61 (1H, ddd, J = 8.3, 7.3, 1.8 Hz, H-7), 7.89 (1H, dd, J = 7.9, 1.8 Hz, H-5), 7.90 (2H, m); MS m/z 458 (M⁺). Anal. Calcd for C₂₇H₂₂O₇: C, 70.74; H, 4.84. Found: C, 70.53; H, 4.92.

Dimethyl trans-2,3,3a,9a-tetrahydro-4-oxo-4H-furo[2,3-b][1]benzopyran-2-spirocyclopentane-3,3-dicarboxylate (12d): colorless prism (from Et₂O-hexane), mp 124-126 °C; IR (CHCl₃) 1740, 1610 cm⁻¹; ¹H-NMR (CDCl₃) δ 3.81 (8H, m), 3.83 (3H, s, OMe), 3.95 (1H, d, J = 10.1 Hz, H-3a), 5.92 (1H, d, J = 10.1 Hz, H-9a), 7.09 (1H, ddd, J = 7.9, 7.3, 1.0 Hz, H-6), 7.12 (1H, dd, J = 8.5, 1.0 Hz, H-8), 7.53 (1H, ddd, J = 8.5, 7.3, 1.8 Hz, H-7), 7.88 (1H, dd, J = 7.9, 1.8 Hz, H-5); MS m/z 360 (M⁺). Anal. Calcd for C₁₉H₂₀O₇: C, 63.33; H, 5.59. Found: C, 63.05; H, 5.63.

Dimethyl trans-2,3,3a,9a-tetrahydro-4-oxo-4H-furo[2,3-b][1]benzopyran-2-spirocyclohexane-3,3-dicarboxylate (12e): colorless prism (from Et₂O-hexane), mp 134-136 °C; IR (CHCl₃) 1750, 1730, 1610 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.23 (1H, m), 1.54 (1H, m), 1.65-1.90 (8H, m), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 4.00 (1H, d, J = 10.1 Hz, H-3a), 5.99 (1H, d, J = 10.1 Hz, H-9a), 7.10 (1H, ddd, J = 7.9, 7.0, 1.0 Hz, H-6), 7.14 (1H, dd, J = 8.2, 1.0 Hz, H-8), 7.53 (1H, ddd, J = 8.2, 7.0, 1.8 Hz, H-7), 7.89 (1H, dd, J = 7.9, 1.8 Hz, H-5); MS m/z 374 (M⁺). Anal. Calcd for C₂₀H₂₂O₇: C, 64.16; H, 5.92. Found: C, 64.01; H, 6.01.
Dimethyl trans-2,3,3a,9a-tetrahydro-4-oxo-4H-furo[2,3-b][1]benzopyran-2-spirocycloheptane-3,3-dicarboxylate (12f): colorless prism (from AcOEt-hexane), mp 132-134 °C; IR (CHCl₃) 1750, 1730, 1610 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.44 (1H, m), 1.55-2.08 (11H, m), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 3.92 (1H, d, J = 10.1 Hz, H-3a), 6.00 (1H, d, J = 10.1 Hz, H-9a), 6.99 (1H, ddd, J = 8.2, 7.0, 1.0 Hz, H-6), 7.13 (1H, dd, J = 8.2, 1.0 Hz, H-8), 7.53 (1H, ddd, J = 8.5, 7.0, 1.8 Hz, H-7), 7.88 (1H, dd, J = 7.9, 1.8 Hz, H-5); MS m/z 388 (M⁺). Anal. Calcd for C₂₁H₂₄O₇: C, 64.94; H, 6.23. Found: C, 64.75; H, 6.28.

Dimethyl cis-2,3,3a,9a-tetrahydro-2,2-dimethyl-4-oxo-4H-furo[2,3-b][1]benzopyran-3,3-dicarboxylate (13a): To a solution of 12a (66.8 mg, 0.2 mmol) in CH₂Cl₂ (2 mL) was added Et₃N (101 mg, 1 mmol) at rt. After being stirred for 6 h, 10% HCl was added to the mixture and the whole was extracted with CH₂Cl₂ (20 mL x 3). The organic layer was dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-AcOEt = 10 : 1) to give 13a (57 mg, 86%) as a colorless oil. IR (CHCl₃) 1750, 1690, 1610 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.31 (3H, s, Me), 1.62 (3H, s, Me), 3.48 (3H, s, OMe), 3.86 (3H, s, OMe), 4.18 (1H, d, J = 6.7 Hz, H-3a), 6.12 (1H, d, J = 6.7 Hz, H-9a), 7.04 (1H, dd, J = 8.2, 1.0 Hz, H-8), 7.05 (1H, ddd, J = 7.9, 7.3, 1.0 Hz, H-6), 7.52 (1H, ddd, J = 8.2, 7.3, 1.8 Hz, H-7), 7.82 (1H, dd, J = 7.9, 1.8 Hz, H-5); ¹³C-NMR (CDCl₃) δ 25.05, 26.96, 52.13, 53.10, 54.00, 68.73, 85.48, 100.33, 118.27, 120.24, 122.00, 126.52, 136.50, 157.37, 166.95, 168.12, 188.80; High-resolution MS m/z Calcd for C₁₇H₁₈O₇ (M⁺): 334.1052, Found: 334.1034.

REFERENCE AND NOTES


