Reaction of \( o-(\text{oxiranylmethyl}) \)benzonitriles with sodium borohydride or Grignard reagent/CuI: a new synthesis of substituted 3-alkyl-3,4-dihydroisocoumarins

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Abstract. A new method for the synthesis of substituted 3-alkyl-3,4-dihydroisocoumarins is described. \( o-(\text{Oxiranylmethyl}) \)benzonitriles, prepared from isovanillin in five steps, when reacted with nucleophiles such as sodium borohydride or phenylmagnesium chloride/CuI, undergo an intramolecular cyclization to yield the target compounds in good yields, in one pot.

Keywords: Isovanillin, oxiranes, benzonitriles, intramolecular cyclization, 3,4-dihydroisocoumarins

Introduction

3,4-Dihydroisocoumarins (DHIC), otherwise named 3,4-dihydroisochromen-1-ones, are abundantly distributed in a wide range of natural sources. For examples, DHIC isolated from \textit{Kigelia pinnata},\(^1\) \textit{Hydrangea macrophylla},\(^2\) Cape aloe,\(^3\) \textit{Montrouziera sphaeroidea},\(^4\) \textit{Aloe hildebrandtii},\(^5\) \textit{Cassia siamea},\(^6\) \textit{Caryocar glabrum},\(^7\) as well as others have been reported. Furthermore, certain DHIC from natural sources have broadly biological activities. DHIC such as isolated from \textit{Xyris pterygoblephara} exhibiting antifungi activity,\(^8\) from \textit{Aloe vera} exhibiting binding activity with human serum albumin,\(^9\) from \textit{Fusarium verticillioides} exhibiting antimalarial, antitubercular and antifungal activities,\(^10\) as well as others. On the other hand, DHIC also play an important core structure for many biologically active compounds. For instance, AI-77-B, a naturally-occurring DHIC which chemically belongs to the amicoumacin family, was isolated from different \textit{Bacillus} genera exhibiting an antiulcerogenic activity without common side effects.\(^11\) Because of diverse biological activities, a number of synthetic strategies for DHIC have been developed. The major methods reported include the use of the Heck-Matsuda reaction,\(^12\) radical cyclization mediated by titanocene(III) chloride,\(^13\) cyclization of \( \alpha-\)
lithiated 2-toluene-carboxylates,\textsuperscript{14} coupling of vinylic halides or triflates with \textit{o-}(1-alkenyl)-benzoic acids,\textsuperscript{15} the successive lateral and \textit{ortho}-lithiations of 4,4-dimethyl-2-(\textit{o}-toyl)oxazoline,\textsuperscript{16} as well as others. However, those reported methods have some disadvantages including tedious reaction conditions, inaccessible starting materials or reagents, and low yields. Therefore, the development of a mild and efficient method for DHIC is requisite and of interest. On the other hand, the ring-opening of epoxides by various nucleophiles to yield diverse organic compounds has been well documented in organic synthesis.\textsuperscript{17} The addition of various nucleophiles to cyano groups has also been well described.\textsuperscript{18} However, studies on the addition of various nucleophiles to aryl compounds with an adjacent epoxy and cyano substituents has seldom been examined. In our previous study, we reported the reaction of \textit{o-}(oxiranylmethyl)benzonitrile intermediates with TBAB/NaCN to yield various substituted 3,4-dihydroisoquinolin-1-ones.\textsuperscript{19} Continuing our work on benzoheterocycles,\textsuperscript{20} here we herein report the synthesis of substituted 3-alkyl-3,4-dihydroisocoumarins from the reaction of \textit{o-}(oxiranylmethyl)benzonitriles with nucleophiles such as sodium borohydride and Grignard reagent in the presence of copper iodide (Scheme 1).

\begin{center}

\textbf{Scheme 1.} Synthesis of 3-alkyl-3,4-dihydroisocoumarins from \textit{o-}(oxiranylmethyl)benzonitriles with NaBH$_4$ and C$_6$H$_5$MgCl/CuI nucleophiles.

\end{center}

\begin{center}

\textbf{Results and Discussion}

\end{center}

In order to optimize the reaction conditions, compound 2a used as a model reaction was allowed to react with NaBH$_4$ under various conditions. The given results showed that 5,6-dimethoxy-3-methyl-dihydroisochroman (3a) together with 1-(2,3-dimethoxy-6-cyanophenyl)-2-propanol (5a) were formed in varying ratios. Compound 3a was produced through a domino sequence, involving ring-opening of the epoxide, followed by the intramolecular cyclization of the forming alkoxide anion with the cyano functional group, and then hydrolysis. Compound 5a was formed by simple ring opening of the epoxide by NaBH$_4$. The results of this model reaction are compiled in Table 1.
Table 1. The reaction of compound 2a with NaBH₄ under various conditions to yield 3a and 5a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. NaBH₄</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time (hr)</th>
<th>3a (%)</th>
<th>5a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>EtOH</td>
<td>rt</td>
<td>24</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>EtOH</td>
<td>reflux</td>
<td>1</td>
<td>59</td>
<td>33²⁰⁻a</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>EtOH</td>
<td>reflux</td>
<td>1</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>4⁻b</td>
<td>1.5</td>
<td>EtOH</td>
<td>reflux</td>
<td>1</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>MeOH</td>
<td>reflux</td>
<td>1</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>6⁻b</td>
<td>1.5</td>
<td>MeOH</td>
<td>reflux</td>
<td>1</td>
<td>18</td>
<td>42</td>
</tr>
<tr>
<td>7⁻b</td>
<td>3.0</td>
<td>EtOH</td>
<td>reflux</td>
<td>1</td>
<td>80</td>
<td>-</td>
</tr>
</tbody>
</table>

⁻a Determined by isolated yields; ⁻b Anhydrous solvent was used.

Based on the results reported in Table 1, we concluded that ethanol (entries 1–4) is a better solvent than methanol (entries 5–6) and anhydrous ethanol (entries 4, 7) is the best solvent for the reaction. Three equivalents of NaBH₄ (entry 7) is better than 1 or 1.5 equivalents of NaBH₄ (entries 1–6), and heating under reflux is better than reaction at room temperature for the production of 3. Thus, the use of excess NaBH₄ (3.0 equiv.) in refluxing ethanol (entry 7) gives a high yield (80%) of 3a from 2a. Based on these conditions, o-(oxiranylmethyl)benzonitriles 2a-d gave the target compounds 3a-d in high yields (80–87%), in the one pot procedure.

All spectral data, such as IR, ¹H-NMR, ¹³C-NMR, EI-MS, and HRMS or EA, are consistent with the 3-methyl-3,4-dihydroisocoumarin structures (3a-d). The IR spectrum of compound 3a, for example, showed absorption at 1707 cm⁻¹ (C=O) and the ¹H-NMR spectrum exhibited a doublet signal of methyl group bonded to C-3 (J 6.2 Hz at δ 1.46); two double doublet signals at δ 2.66 and 3.13 which respectively have coupling constants J 16.8, 11.4 and 16.8, 3.2 Hz assigned to H-4a and H-4b; two singlet methoxy signals at δ 3.78 and 3.89; a one proton signal at δ 4.59 coupled to neighboring protons assigned as H-3; and two aromatic protons at δ 6.88, and 7.82 with the same coupling constant J 8.4 Hz indicating their ortho relationship. In the ¹³C-NMR twelve lines are observed consistent with that required for the structure. The HRMS (m/z 222.0887) and EA (C, 65.01; H, 6.41) are consistent with the structure. To increase the diversity, o-(oxiranylmethyl)benzonitriles (2a-d) were allowed to react with Grignard reagent phenylmagnesium chloride/CuI. At the start of this study, 2a was reacted with phenylmagnesium
chloride under various conditions to yield the desired 3-benzyl-5,6-dimethoxydihydroisocoumarins 4a and the results are shown in Table 2.

**Table 2.** The reaction of compound 2a with C₆H₅MgBr under various conditions to yield 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu⁻</th>
<th>Additive</th>
<th>Temp</th>
<th>Time (hr)</th>
<th>4a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅MgCl (1.2 equiv)</td>
<td>-</td>
<td>0°- r.t.</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅MgCl (1.2 equiv)</td>
<td>CuI (0.25 equiv)</td>
<td>0°-r.t.</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅MgCl (1.2 equiv)</td>
<td>CuI (0.50 equiv)</td>
<td>0°- r.t.</td>
<td>24</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅MgCl (1.2 equiv)</td>
<td>CuI (1.0 equiv)</td>
<td>0°- r.t.</td>
<td>24</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>C₆H₅MgCl (1.2 equiv)</td>
<td>CuI (1.0 equiv)</td>
<td>reflux</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>C₆H₅MgCl (2.4 equiv)</td>
<td>CuI (0.5 equiv)</td>
<td>reflux</td>
<td>24</td>
<td>86</td>
</tr>
</tbody>
</table>

aIsolated yield from column chromatography, other by products being neglected.

As shown in Table 2, in the absence of CuI, 4a was formed in the low yield (16%) (entry 1) with the exception of entry 5 (11%) which was carried out for a shorter reaction time. This suggests the importance of CuI. A lower amount of Grignard reagent C₆H₅MgCl (entries 1-5) gave 4a in low to modest yields (11-66%). On the other hand the reaction of 2a with excess C₆H₅MgCl (2.4 equiv)/CuI (0.5 equiv) in refluxing THF (entry 6) for 24 hr provided the highest yield for 4a (86%). These conditions were employed for the synthesis of 3-benzyl-3,4-dihydroisocoumarins 4a-d from o-(oxiranylmethyl)benzonitriles 2a-d, in yields of 85-90%.

The spectral data including IR, ¹H-NMR, ¹³C-NMR, EI-MS, and HRMS or EA are all consistent with those required for the proposed 5-alkoxy-3-benzyl-6-methoxy-3,4-dihydroisocoumarin structures 4a-d. The IR spectrum of compound 4a, for example, shows absorption at 1717 cm⁻¹ (C=O) indicating the presence of carbonyl group. The ¹H-NMR spectrum exhibits two double doublet signals at δ 2.75 (dd, J 16.4, 11.2 Hz, 1H) and δ 3.11 (dd, J 16.4, 3.2 Hz, 1H) indicating the presence of H₄-a and H₄-b; other two double doublet signals at δ 3.04 (dd, J 14.0, 6.8 Hz, 1H, Ha-9) and δ 3.21 (dd, J 14.0, 6.0 Hz, 1H, Hb-9) indicating the presence of H-9a and H-9b (two benzylic protons), two-protons singlet signals, each at δ 3.77, 3.93 indicating two OCH₃ groups, and one proton multiplet at δ 4.69 indicating H-3; two one-proton doublet aromatic protons at δ 6.91 and 7.88 with ortho-coupling constant J 8.4 Hz indicating the presence of H-7 and H-8 and one multiple signals of five protons at δ 7.30 indicating the presence of aromatic protons of benzyl group. In the ¹³C-NMR spectrum of
compound 4a shows sixteen lines which is consistent with carbon numbers required for the structure 4a. Besides, the data of HRMS (m/z 298.1204) and elemental analysis (C, 72.19; H, 6.03), all data are correct and consistent with the data required for compound 4a.

Conclusions

We have successfully prepared diverse 3-substituted 3,4-dihydroisocoumarins from the reaction of o-(oxiranylmethyl)benzonitriles with nucleophiles (NaBH₄ or Grignard reagent/CuI). This reaction demonstrates that epoxide ring of o-(oxiranylmethyl)benzonitrile opened by nucleophile to give alkoxide anion which attacks the neighboring nitrile to effect the intramolecular cyclization, and this is followed by hydrolysis to yield a series of substituted 3-alkyl-3,4-dihydroisocoumarins.

Experimental Section

General. Melting points were measured with Yanaco micro melting-point apparatus. ¹H-NMR and ¹³C-NMR spectra were obtained on a Varian Unity plus 400 Spectrometer. Chemical shifts were measured in parts per million with respect to TMS. IR spectra were run on a Perkin-Elmer spectrometer (System 2000 FT-IR, series No. 35575). Elemental analyses were recorded on a Heraeus CHN-O Rapid analyzer. Mass spectra were recorded on a Chem/HP/middle spectrometer connected to a Hewlett Packard series II model gas-liquid chromatography. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230-400 mesh) for column chromatography and the pre-coated silica gel plates (60 F-254) for TLC were purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

General preparation of 5-alkoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarins (3a-d). 3-Alk oxy-4-methoxy-2-(oxiranylmethyl)benzonitriles (2a-d) (2.0 mmol) dissolved in EtOH (50 mL) was stirred and added NaBH₄ (0.23 g, 6.0 mmol) in portions. Then, the reaction mixture was heated to the reflux for 1 hr (monitoring by TLC). The given mixture was quenched with H₂O (50 mL), and concentrated in vacuo to remove EtOH. The obtained residue was poured into separating funnel and extracted with CH₂Cl₂ (50 mL x 3). The extracted solution was combined and washed with brine (30 mL x 2), dried with MgSO₄, and filtered in sequence. The resulting residue was purified from silica gel column chromatography (ethyl acetate: n-hexane = 1: 5) to give pure 3a-d. Under the same reaction condition but with insufficient amount of NaBH₄ (1 mmol), for example, 5a was obtained.

5,6-Dimethoxy-3-methyl-3,4-dihydroisocoumarin (3a). Compound 3a (0.35 g, 80%) was obtained as colorless crystals, mp 110-111 °C (EtOAc + n-hexane) (lit.⁹ mp 127-128 °C), Rf = 0.31 (ethyl acetate: n-hexane = 1: 5); IR (neat) νmax: 1707 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 200
MHz) δ 1.46 (d, J 6.2 Hz, 3H, H-9), 2.66 (dd, J 16.8, 11.4 Hz, 1H, Hb-4), 3.13 (dd, J 16.8, 3.2 Hz, 1H, Ha-4), 3.78, 3.89 (each s, 2 × 3H, 2 × OCH3), 4.59 (m, 1H, H-3), 6.88 (d, J 8.4 Hz, 1H, ArH), 7.82 (d, J 8.4 Hz, 1H, ArH); 13C-NMR (CDCl3, 50 MHz) δ 20.9, 29.0, 55.8, 60.5, 74.6, 110.7, 117.8, 127.2, 133.0, 144.5, 156.7, 165.3; EIMS (70eV) m/z (rel. intensity, %) 222 (M+, 72), 179 (16), 178 (38), 163 (18), 151 (10), 150 (100), 135 (17), 91 (13), 79 (9); HRMS Calcd for C12H14O4: 222.0892. Found: 222.0887; Anal. Calcd for C12H14O4: C, 64.85; H, 6.35. Found: C, 65.01; H, 6.41.

Under the same reaction condition but with insufficient amount of NaBH4 (1 mmol), for example, 3a was obtained in 59% yield as well as by-product 5a was obtained in 33% yield.

2-(2-Hydroxypropyl)-3,4-dimethoxybenzonitrile (5a) (0.15 g, 33%) was obtained as a colorless liquid, Rf = 0.28 (ethyl acetate: n-hexane = 1: 1); IR (neat) cm⁻¹: 2217 (CN), 3407 (OH); 1H-NMR (CDCl3, 400 MHz) δ 1.30 (d, J 6.4 Hz, 3H, H-3'), 2.00 (d, J 5.2 Hz, 1H, OH), 3.02 (d, J 6.8 Hz, 2H, H-1'), 3.87, 3.93 (each s, 2 × 3H, 2 × OCH3), 4.12 (m, 1H, H-2'), 6.86, 7.41 (each d, J 8.4 Hz, 1H, H-5 and H-6); 13C-NMR (CDCl3,100 MHz) δ 23.56, 38.50, 55.92, 60.75, 68.49, 105.8, 110.9, 129.7, 131.5, 136.5, 150.8, 156.4; EI-MS (70eV) m/z (rel. intensity, %) 221 (M+, 6), 178 (10), 177 (62), 163 (12), 162 (100), 134 (14), 131 (15), 106 (10); HRMS (El, m/z) Calcd for C13H14N2O3: 221.1052. Found: 221.1053.

5-Ethoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (3b). Compound 3b (0.40 g, 87%) was obtained as colorless liquid, Rf = 0.39 (ethyl acetate: n-hexane = 1: 5); IR (neat) νmax: 1713 cm⁻¹ (C=O); 1H-NMR (CDCl3, 200 MHz) δ 1.33 (t, J 7.0 Hz, 3H, OCH2CH3), 1.48 (d, J 6.2 Hz, 3H, H-9), 2.68 (dd, J 16.8, 11.4 Hz, 1H, Hb-4), 3.16 (dd, J 16.8, 3.2 Hz, 3H, Ha-4), 3.89 (s, 3H, OCH3), 4.01 (q, J 7.0 Hz, 2H, OCH2-CH3), 4.56 (m, 1H, H-3), 6.88 (d, J 8.8 Hz, 1H, ArH), 7.84 (d, J 8.8 Hz, 1H, ArH); 13C-NMR (CDCl3, 50 MHz) δ 15.6, 21.0, 29.4, 55.4, 68.8, 74.7, 110.7, 117.9, 127.1, 133.4, 143.6, 156.9, 165.4; EIMS (70eV) m/z (rel. intensity, %) 236 (M+, 58), 208 (27), 165 (17), 164 (100), 163 (18), 136(32), 135(28); HRMS Calcd for C13H16O4: 236.1049. Found: 236.1043.

5-Isopropoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (3c). Compound 3c (0.41 g, 83%) was obtained as colorless crystals, mp 83-84 °C, Rf = 0.45 (ethyl acetate: n-hexane = 1: 5); IR (neat)νmax: 1718 cm⁻¹ (C=O); 1H-NMR (CDCl3, 200 MHz) δ 1.21 (d, J 6.2 Hz, 6H, OCH(CH3)2), 1.44 (d, J 6.2 Hz, 3H, H-9), 2.64 (dd, J 16.8, 11.4 Hz, 1H, Hb-4), 3.14 (dd, J 16.8, 3.2 Hz, 1H, Ha-4), 3.85 (s, 3H, OCH3), 4.41 (hept, J 6.2 Hz, 1H, OCH(CH3)2), 4.51 (m, 1H, H-3), 6.85 (d, J 8.8 Hz, 1H, ArH), 7.78 (d, J 8.8 Hz, 1H, ArH); 13C-NMR (CDCl3, 50 MHz) δ 20.9, 22.4, 29.8, 55.7, 74.6, 74.8, 110.5, 117.8, 126.7, 133.7, 142.4, 156.9, 165.4; EIMS (70eV) m/z (rel. intensity, %) 250 (M+, 7), 208 (50), 165 (17), 164 (100), 137 (9), 136 (33), 135 (17), 93 (5); HRMS Calcd for C14H15O4: 250.1205. Found: 250.1200; Anal. Calcd for C14H15O4: C, 67.18; H, 7.25. Found: C, 67.19; H, 7.25.

5-Butoxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (3d). Compound 3d (0.42 g, 81%) was obtained as colorless liquid, Rf = 0.46 (ethyl acetate: n-hexane = 1: 5); IR (neat)νmax: 1715 cm⁻¹ (C=O); 1H-NMR (CDCl3, 200 MHz) δ 0.95 (t, J 7.4 Hz, 3H, OCH2-CH2CH2CH3), 1.47 (sixin, J 7.4 Hz, 2H, OCH2-CH2CH2CH3), 1.48 (d, J 6.2 Hz, 3H, H-9), 1.71 (quint, J 7.4 Hz, 2H,
OCH₂CH₂CH₂CH₃), 2.66 (dd, J 16.8, 11.4 Hz, 1H, Hb-4), 3.15 (dd, J 16.8, 3.2 Hz, 1H, Ha-4), 3.88 (s, 3H, OCH₃), 3.91 (t, J 7.4 Hz, 2H, OCH₂CH₂CH₂CH₃), 4.55 (m, 1H, H-3), 6.87 (d, J 8.4 Hz, 1H, ArH), 7.83 (d, J 8.4 Hz, 1H, ArH); ¹³C-NMR (CDCl₃, 50 MHz) δ 13.8, 19.1, 20.9, 29.2, 32.2, 55.7, 72.9, 74.7, 110.6, 117.7, 127.1, 133.2, 143.7, 156.9, 165.5; EIMS (70eV) m/z (rel. intensity, %) 264 (M⁺, 20), 208 (39), 165 (22), 164 (100), 136 (29), 135 (14), 93(5); HRMS Calcd for C₁₅H₂₀O₄: 264.1362. Found: 264.1356.

**General preparation of 3-benzyl-5-alkoxy-6-methoxy-3,4-dihydroisocoumarins (4a-d).**

3-Alkoxyl-4-methoxy-2-(oxiranylmethyl)benzonitriles (2a-d) (2.0 mmol) dissolved in THF (20 mL) was stirred and added copper (I) iodide (0.22 g, 1.17 mmol) and then added phenylmagnesium chloride (2.0 M in THF) (5.6 mmol) dropwise at room temperature. The reaction mixture was continually stirred and heated to the reflux for 1 day (monitoring by TLC). Then, the reaction mixture was quenched with saturated NH₄Cl solution (30 mL), and concentrated in vacuo to remove THF. The residue was extracted with CH₂Cl₂ (50 mL × 3). The extracted solution was combined and washed with brine (30 mL × 2), dried with MgSO₄, and filtered. The filtrate was concentrated in vacuo. The resulting residue was purified from silica gel column chromatography (ethyl acetate: n-hexane = 1: 8) to give pure 4a-d.

**3-Benzyl-5,6-dimethoxy-3,4-dihydroisocoumarin (4a).** Compound 4a (0.50 g, 86%) was obtained as colorless crystals, mp 141-142 °C, Rf = 0.31 (ethyl acetate: n-hexane = 1: 5); IR (neat) νmax cm⁻¹: 1717 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 400 MHz) δ 2.75 (dd, J 16.4, 11.2 Hz, 1H, Ha-4), 3.04 (dd, J 14.0, 6.8 Hz, 1H, Ha-9), 3.11 (dd, J 16.4, 3.2 Hz, 1H, Hb-4), 3.21 (dd, J 14.0, 6.0 Hz, 1H, Hb-9), 3.77, 3.93 (each s, 2 × 3H, 2 × OCH₃), 4.69 (m, 1H, H-3), 6.91 (d, J 8.4 Hz, 1H, ArH), 7.30 (m, 5H, ArH), 7.88 (d, J 8.4 Hz, 1H, ArH); ¹³C-NMR (CDCl₃, 100 MHz) δ 26.5, 41.2, 55.9, 60.6, 78.8, 110.8, 118.0, 126.9, 127.5, 128.6, 129.6, 132.9, 136.2, 144.7, 156.9, 165.3; EIMS (70eV) m/z (rel. intensity, %) 298 (M⁺, 19), 208 (9), 207 (73), 180 (11), 179 (100), 136 (7), 91 (11); HRMS Calcd for C₁₈H₁₁O₄: 298.1205. Found: 298.1204; Anal. Calcd for C₁₈H₁₁O₄: C, 72.47; H, 6.08. Found: C, 72.19; H, 6.03.

**3-Benzyl-5-ethoxy-6-methoxy-3,4-dihydroisocoumarin (4b).** Compound 4b (0.55 g, 90%) was obtained as colorless liquid, mp 77-78 °C, Rf = 0.32 (ethyl acetate: n-hexane = 1: 5); IR (neat) νmax cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 400 MHz) δ 15.5, 26.9, 41.2, 55.8, 68.8, 78.8, 110.7, 118.0, 126.8, 127.3, 128.5, 129.6, 133.2, 136.3, 143.7, 157.0, 165.3; EIMS (70eV) m/z (rel. intensity, %) 312 (M⁺, 29), 222 (13), 221(97), 194 (22), 193(100), 165(21), 107(12), 91(8); HRMS Calcd for C₁₉H₂₀O₄: 312.1362. Found: 312.1360.

**3-Benzyl-5-isopropoxy-6-methoxy-3,4-dihydroisocoumarin (4c).** Compound 4c (0.55 g, 85%) was obtained as colorless crystals, mp 77-78 °C, Rf = 0.32 (ethyl acetate: n-hexane = 1: 5); IR (neat) νmax cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 400 MHz) δ 1.20 (d, J 6.4 Hz, 3H, OCH(CH₃)₂), 2.69 (dd, J 16.8, 11.2 Hz, 1H, Ha-4), 3.02 (dd, J 14.0, 6.8 Hz, 1H, Ha-9), 3.15 (dd, J 16.8, 3.2
Hz, 1H, Hb-4), 3.21 (dd, J 13.6, 6.0 Hz, 1H, Hb-9), 3.90 (s, 3H, OCH₃), 4.37 (hept, J 6.4 Hz, 1H, OCH(CH₃)₂), 4.66 (m, 1H, H-3), 6.89 (d, J 8.8 Hz, 1H, ArH), 7.31 (m, 5H, ArH), 7.85 (d, J 8.4 Hz, 1H, ArH); ¹³C-NMR (CDCl₃, 100 MHz) δ 22.3, 22.5, 27.5, 41.2, 55.8, 75.2, 78.9, 110.6, 118.0, 126.8, 127.0, 128.5, 129.5, 133.1, 136.3, 142.5, 157.1, 165.5; EIMS (70eV) m/z (rel. intensity, %) 326 (M⁺, 5), 250 (7), 208 (99), 193 (37), 165 (70), 164 (100), 136 (37), 135 (21); HRMS Calcd for C₂₀H₂₂O₄: 326.1518. Found: 326.1520. Anal. Calcd for C₂₀H₂₂O₄: C, 73.60; H, 6.79. Found: C, 73.28; H, 6.78.

3-Benzyl-5-butoxy-6-methoxy-3,4-dihydroisocoumarin (4d). Compound 4d (0.60 g, 89%) was obtained as colorless crystals, mp 115-116 °C, Rf = 0.31 (ethyl acetate: n-hexane = 1: 5); IR (neat) νmax: 1719 cm⁻¹ (C=O); ¹H-NMR (CDCl₃, 400 MHz) δ 0.93 (t, J 7.2 Hz, 3H, OCH₂CH₂CH₂CH₃), 1.40 (sextet, J 7.2 Hz, 2H, OCH₂CH₂CH₂CH₃), 1.63 (quint, J 7.2Hz, 2H, OCH₂CH₂CH₂CH₃), 2.71(dd, J 16.8, 11.2 Hz, 1H, Ha-4), 3.02 (dd, J 13.6, 7.2 Hz, 1H, Ha-9), 3.11 (dd, J 16.8, 3.2 Hz, 1H, Hb-4), 3.23 (dd, J 13.6, 6.0 Hz, 1H, Hb-9), 3.88 (t, J 7.2Hz, 2H, OCH₂CH₂CH₂CH₃), 3.90 (s, 3H, OCH₃), 4.66 (m, 1H, H-3), 6.89 (d, J 8.4 Hz, 1H, ArH), 7.29 (m, 5H, ArH), 7.86 (d, J 8.4Hz, 1H, ArH); ¹³C-NMR (CDCl₃, 100 MHz) δ 13.8, 19.1, 26.8, 32.2, 41.3, 55.8, 73.0, 78.8, 110.7, 118.0, 126.8, 127.2, 128.6, 129.6, 133.1, 136.2, 143.9, 157.0, 165.4; EIMS (70eV) m/z (rel. intensity, %) 340 (M⁺, 22), 250 (8), 249 (52), 194 (11), 193 (100), 166 (9), 165 (34), 91 (6); HRMS Calcd for C₁₉H₂₀O₄: 340.1675. Found: 340.1677; Anal. Calcd for C₂₁H₂₄O₄: C, 74.09; H, 7.11. Found: C, 73.88; H, 7.11.

Acknowledgements

We are grateful to National Science Council of Taiwan (NSC-99-2113-M-037-007) and Kaohsiung Medical University (N-843) for financial support.

References


http://dx.doi.org/10.1016/S0031-9422(99)00442-2

http://dx.doi.org/10.1016/S0031-9422(00)94814-3

http://dx.doi.org/10.1016/S0031-9422(00)81245-5

http://dx.doi.org/10.1016/j.phytochem.2007.05.011, PMid:17618658

http://dx.doi.org/10.1016/j.phytochem.2007.08.002, PMid:17870137

http://dx.doi.org/10.1016/j.molstruc.2008.03.005

http://dx.doi.org/10.1021/np0205598, PMid:12762815

http://dx.doi.org/10.1016/S0040-4039(98)01977-7

http://dx.doi.org/10.1016/j.tetlet.2011.09.014

http://dx.doi.org/10.1016/j.tet.2008.09.075

http://dx.doi.org/10.1055/s-1997-1538

[http://dx.doi.org/10.1016/j.tet.2007.04.092](http://dx.doi.org/10.1016/j.tet.2007.04.092)

[http://dx.doi.org/10.1002/ejoc.201001693](http://dx.doi.org/10.1002/ejoc.201001693)
(b) Schneider, C. *Synthesis* **2006**, 3919-3944; and references cited therein. 

[http://dx.doi.org/10.1016/0010-8545(94)01128-1](http://dx.doi.org/10.1016/0010-8545(94)01128-1)

[http://dx.doi.org/10.1016/j.tet.2012.02.023](http://dx.doi.org/10.1016/j.tet.2012.02.023)

[http://dx.doi.org/10.1021/ol302256y](http://dx.doi.org/10.1021/ol302256y), PMid:22934626