Synthesis and structural elucidation of (±)-3,4-dihydrocoumarins by 2D-NOESY spectrum

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(±)-3,4-Dihydrocoumarins have been synthesized in high yield and the structures are confirmed by 2D-NOESY spectrum.

Dihydrocoumarins are well-known for fragrance in cosmetics, food flavouring and in perfumery industries. However, only few methods are reported in the literature with limitations of low yield and side products.

Chaturvedi et al. had claimed the formation of benzofuranones by the condensation of substituted phenols and cinnamic acids with trifluoroacetic acid (TFA). They had recorded 1H NMR and IR spectra of benzofuranones. The IR values for these compounds were reported to be 1760 cm⁻¹. According to Kirtany, the IR values for benzofuranones should appear between 1800-1820 cm⁻¹, so he suggested the product to be dihydrocoumarin. This prompted us to reinvestigate correct structure of above synthesised compounds by NOESY spectrum.

To discriminate between the two products, we have carried out the condensation of m-methoxyphenol with p-methoxycinnamic acid by refluxing in TFA. The high resolution 1H NMR spectrum of the product 3c (Scheme I) displayed a multiplet at δ 2.98 for two protons and unsymmetrical triplet-at δ 4.23 for single proton. The reported, 1H chemical shifts are matching with our values. However, this was not enough to differentiate the structures 3 and 4 (Scheme I) as chemical shifts are expected to be very close for both the structures, also the spectrum seems to be deceptive simple ABX type. The intensity pattern shows nucleus X, is coupled differently with two nuclei, A and B, which are strongly coupled to each other. The coupling patterns are calculated by the standard analysis. The results are compiled in Table I.

Discrimination between structures 3 and 4 is obtained from 2D-NOESY spectrum of compound 3c (Figure 1). Presence of cross peak A, due to the ortho protons and with proton at C-4 characterize the specificity of structure 3. Due to rigid structure of 3, cross peak B is seen from the geminal protons of C-3 and with the ortho protons of phenyl ring. In structure 4, there is free rotation about two C-C single bonds due to methylene spacer (>CH=CH₂-C₆H₄), therefore cross peak A due to proton at C-3 and ortho protons is unlikely to be seen.

From the above discussion it is clear that the condensation of substituted phenol and cinnamic acid gives (±)-dihydrocoumarin (six-membered) 3 and not benzofuranone (five membered) 4.

Several substituted (±)-dihydrocoumarins 3 have been synthesized by condensation of substituted
phenols and substituted cinnamic acids (Scheme I) by modified procedure using TFA and toluene. Interestingly, the yield of the reaction was improved by the addition of toluene into the reaction mixture and time of the reaction was reduced by two hours. (±)-dihydrocoumarins 3 displayed characteristic band at 1760 cm⁻¹ in IR spectra. The same have been characterized by ¹H NMR, IR and elemental analysis. The results are compiled in Table I.

Experimental Section

Melting points were taken in open capillaries in an electrical metal bath and are uncorrected. ¹H NMR spectra and NOESY spectrum in CDCl₃ were recorded on a Brucker AMX-500 spectrometer using TMS as internal standard (chemical shifts in δ, ppm). 2D-NOESY spectrum was recorded with a mixing time of 400 ms.

General method for preparation of (±)-dihydrocoumarins. To the mixture of phenol (0.01 mole) and cinnamic acid (0.01 mole) in 10 mL toluene, 1 mL TFA was added with stirring. The clear solution was gently refluxed for 30 min. After the completion of the reaction, TFA and toluene were removed under reduced pressure. The mixture was extracted with CH₂Cl₂(3×20 mL). The organic extract
Table I — Spectral data of dihydrocoumarins (3a–n)

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>(^1)H NMR δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>78</td>
<td>70</td>
<td>3.02 (1H, dd, J\textsubscript{AB}=15.9 Hz, J\textsubscript{AX}=8.0 Hz, 3-CH\textsubscript{A}), 3.08 (1H, dd, J\textsubscript{AB}=15.7 Hz, J\textsubscript{AX}=5.7 Hz, 3-CH\textsubscript{A}), 4.35 (1H, unsym, t, J\textsubscript{AX}+J\textsubscript{EX}=13.7 Hz, 4-CH\textsubscript{A}), and 7.0-7.5 (m, 9H, Ar-H)</td>
</tr>
<tr>
<td>3b</td>
<td>83(\uparrow)</td>
<td>82</td>
<td>2.18 (3H, s, CH\textsubscript{3}), 3.00 (1H, dd, J\textsubscript{AB}=15.7 Hz, J\textsubscript{AX}=7.9 Hz, 3-CH\textsubscript{A}), 3.05 (1H, dd, J\textsubscript{AB}=15.7 Hz, J\textsubscript{AX}=5.5 Hz, 3-CH\textsubscript{A}), 4.30 (1H, unsym, t, J\textsubscript{AX}+J\textsubscript{EX}=13.3 Hz, 4-CH\textsubscript{A}) and 6.7-7.5 (m, 8H, Ar-H)</td>
</tr>
<tr>
<td>3c</td>
<td>130(\uparrow)</td>
<td>65</td>
<td>2.95 (1H, dd, J\textsubscript{AB}=15.7 Hz, J\textsubscript{AX}=7.9 Hz, 3-CH\textsubscript{A}), 3.02 (1H, dd, J\textsubscript{AB}=15.7 Hz, J\textsubscript{AX}=5.5 Hz, 3-CH\textsubscript{A}), 3.80 (3H, s, -OCH\textsubscript{3}), 3.81 (3H, s, -OCH\textsubscript{3}), 4.23 (1H, unsym, t, J\textsubscript{AX}+J\textsubscript{EX}=13.3 Hz, 4-CH\textsubscript{A}), 6.63 (1H, dd, J\textsubscript{AB}=8.5 Hz, J\textsubscript{AX}=2 Hz, H-6), 6.68 (1H, d, J\textsubscript{AB}=8 Hz, H-5), 6.87 (2H, d, J\textsubscript{AB}=2 Hz, H-2', H-6') and 7.06 (2H, d, J\textsubscript{AB}=9 Hz, H-2', H-6')</td>
</tr>
<tr>
<td>3d</td>
<td>120(\uparrow)</td>
<td>80</td>
<td>2.26 (3H, s, -CH\textsubscript{3}), 2.96 (1H, dd, J\textsubscript{AB}=15.8 Hz, J\textsubscript{AX}=7.7 Hz, 3-CH\textsubscript{A}), 3.02 (1H, dd, J\textsubscript{AB}=15.8 Hz, J\textsubscript{AX}=5.7 Hz, 3-CH\textsubscript{A}), 3.80 (3H, s, -OCH\textsubscript{3}), 4.25 (1H, unsym, t, J\textsubscript{AX}+J\textsubscript{EX}=13.4 Hz, 4-CH\textsubscript{A}), 6.63 (1H, dd, J\textsubscript{AB}=8.5 Hz, J\textsubscript{AX}=2 Hz, H-7), 6.85 (1H, d, J\textsubscript{AB}=8.5 Hz, H-8), 6.68 (1H, d, J\textsubscript{AB}=2 Hz, H-5), 6.86 (2H, d, J\textsubscript{AB}=9 Hz, H-3', H-5') and 7.06 (2H, d, J\textsubscript{AB}=9 Hz, H-2', H-6')</td>
</tr>
<tr>
<td>3e</td>
<td>92(\uparrow)</td>
<td>79</td>
<td>2.18 (3H, s, CH\textsubscript{3}), 2.95 (1H, dd, J\textsubscript{AB}=15.8 Hz, J\textsubscript{AX}=7.2 Hz, 3-CH\textsubscript{A}), 3.02 (1H, dd, J\textsubscript{AB}=15.8 Hz, J\textsubscript{AX}=5.3 Hz, 3-CH\textsubscript{A}), 3.80 (3H, s, -OCH\textsubscript{3}), 4.25 (1H, unsym, t, J\textsubscript{AX}+J\textsubscript{EX}=12.5 Hz, 4-CH\textsubscript{A}), 6.63 (1H, dd, J\textsubscript{AB}=8.5 Hz, J\textsubscript{AX}=2 Hz, H-6), 6.68 (1H, d, J\textsubscript{AB}=2 Hz, H-3), 6.86 (1H, d, J\textsubscript{AB}=8.5 Hz, H-3), 6.87 (2H, d, J\textsubscript{AB}=9 Hz, H-3', H-5') and 7.06 (2H, d, J\textsubscript{AB}=9 Hz, H-2', H-6')</td>
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<tr>
<td>3f</td>
<td>127</td>
<td>76</td>
<td>2.95 (1H, dd, J\textsubscript{AB}=15.7 Hz, J\textsubscript{AX}=7.9 Hz, 3-CH\textsubscript{A}), 3.03 (1H, dd, J\textsubscript{AB}=15.7 Hz, J\textsubscript{AX}=5.5 Hz, 3-CH\textsubscript{A}), 3.80 (3H, s, -OCH\textsubscript{3}), 3.81 (3H, s, -OCH\textsubscript{3}), 4.26 (1H, unsym, t, J\textsubscript{AX}+J\textsubscript{EX}=13.4 Hz, 4-CH\textsubscript{A}), 6.63 (1H, dd, J\textsubscript{AB}=8.5 Hz, J\textsubscript{AX}=2 Hz, H-6), 6.66 (1H, d, J\textsubscript{AB}=2 Hz, H-6), 6.67 (1H, d, J\textsubscript{AB}=8.5 Hz, H-3), 6.68 (1H, d, J\textsubscript{AB}=2 Hz, H-2'), 6.81 (1H, dd, J\textsubscript{AB}=8 Hz, J\textsubscript{AX}=2.4 Hz, H-6') and 6.88 (1H, d, J\textsubscript{AB}=8.5 Hz, H-5)</td>
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<tr>
<td>3g</td>
<td>132</td>
<td>74</td>
<td>2.98 (1H, dd, J\textsubscript{AB}=15.8 Hz, J\textsubscript{AX}=7.8 Hz, 3-CH\textsubscript{A}), 3.04 (1H, dd, J\textsubscript{AB}=15.8 Hz, J\textsubscript{AX}=5.3 Hz, 3-CH\textsubscript{A}), 3.80 (6H, s, -OCH\textsubscript{3})</td>
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</tbody>
</table>
Table 1 — Spectral data of dihydroucoumarins (3a-n), (— Contnd.)

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p.</th>
<th>Yield</th>
<th>$^1$H NMR δ (ppm)</th>
</tr>
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<tr>
<td></td>
<td>°C</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>3n</td>
<td>118</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\text{-OCH}<em>3$, 4.23 (IH, unsym, t, $J</em>{AX}+J_{BX}=13.4$ Hz, 4-CH$<em>2$), 6.65 (1H, d, $J</em>{d}=2$Hz, H-7), 6.87 (1H, d, $J_{d}=2$Hz, H-5), 6.67 (1H, d, $J_{d}=8.5$Hz, H-5), 6.68 (1H, d, $J_{d}=2$Hz, H-2') and 6.80 (1H, dd, $J_{d}=8$Hz, $J_{d}=2.4$Hz, H-6')</td>
</tr>
</tbody>
</table>

Elemental analysis for C, H and N were found to be satisfactory ($\pm$ 0.3).

was washed with saturated sodium bicarbonate, dried (Na$_2$SO$_4$) and concentrated. The product was crystallised from ethyl acetate-light petroleum (60-80°C).

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References