Natural Product Chemistry. Part 154 [1]. Biomimetic Synthesis of 3,3'-Umbelliferone

Johannes Reisch* and Johannes Zappel [2]

Institut für Pharmazeutische Chemie der
Westfälischen Wilhelms-Universität Münster,
Hittorfstr 58-62, 4400 Münster, Germany

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3,3'-Umbelliferone has been synthesized by oxidation in one step reaction from umbelliferone.

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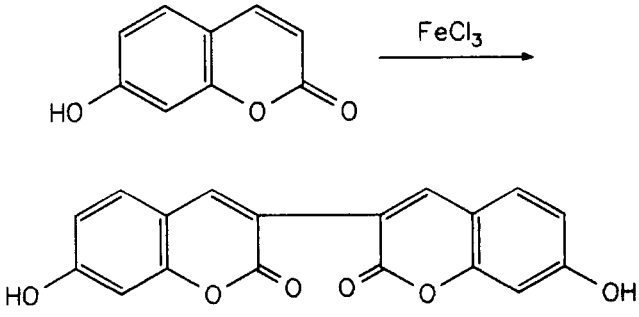
In the past di- and tricoumarins have been isolated from different plants [3-8]. Most of these coumarin dimers and trimers are bridged through oxygen (C-O-C) even some have a carbon-carbon linkage. Oxidative coupling reactions of phenols and 2-naphthol with ferric chloride have been investigated [9,10]. Using several copper(II)-amine complexes as oxidants, 2-naphthol has also been oxidatively dimerised [11].

In continuation of our studies on the synthesis of coumarin derivatives [12-15], it was planned to have a simple biomimetic way to synthesize the 7,7'-dimer with ferric chloride by oxidation of umbelliferone. By virtue of the mesomerism, the 3-position was more reactive so that the only product obtained was the 3,3'-umbelliferone dimer. The mechanism of this reaction is probably due to the formation of a radical intermediate, as Fe^{3+} is reduced to Fe^{2+} by accepting one electron each from the 3-position of umbelliferone and consequently yielding the dimer. The oxidation of other related monomers to umbelliferone could also be possible.



A mixture of **1** and ferric chloride hexahydrate in water was stirred at 50° for 2 hours, then dissolved in acetone and heated under reflux for 48 hours. This reaction gave, after purification, an 18% yield of **2**. The 3,3'-umbelliferone was unequivocally characterized by its ir, nmr, and ms spectral data. The absence of 3-H in its ^{1}H-nmr indicates that the linkage is between C-3 and 3'. In addition, the 4-H appeared as a singlet at δ 8.60 as against a doublet at δ 7.96 in the starting material. The molecular weight of **2** was obtained as M^+ = 322 and confirmed by high resolution mass spectrometry as 322.0472.

EXPERIMENTAL

The melting point was determined on a Kofler hot-stage apparatus and is uncorrected. The ir spectrum was recorded on a Pye Unicam Sp3-200 spectrophotometer. The ^{1}H- and ^{13}C-nmr spectra were obtained on a Varian Gemini 200 MHz spectrometer, with tetramethylsilane as the internal standard. The mass spectrum was recorded on a Varian MAT 44S spectrometer. High resolution mass spectra were recorded on Finnigan MAT 312 spectrometer. Preparative thin layer chromatography was carried out on E. Merck (Darmstadt) Kieselgel 60 F_{254} plates and column chromatography with E. Merck (Darmstadt) Kieselgel 60 (70-230 mesh). Compound **1** (0.2 g, 3.1 mmoles) was suspended in 20 ml of hot water and a solution of 1.1 g of ferric chloride hexahydrate (3.7 mmoles) in 5 ml of water was added slowly. Then the mixture was stirred at 50° for 2 hours, 50 ml of acetone was added and it was heated under reflux for 48 hours. The reaction mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was dried under reduced pressure. Column chromatography with dichloromethane:ethyl acetate (85:15) gave **2**, which was further purified by preparative thin-layer chromatography using the same solvent system; yield was 18%, mp 129°; ir (potassium bromide): ν 3535 (br OH), 2915 (CH arom), 1729 (C=O), 1596 (C=C) cm^{-1}; ^{1}H-nmr (acetone-d_6): δ 8.60 (s, 2H, 3-H), 7.73 (d, 2H, 5-H, J = 8.6 Hz), 6.93 (dd, 2H, 6-H, J = 2.18, 8.63 Hz), 6.79 (d, 2H, 8-H, J = 2.14 Hz); ^{13}C-nmr (acetone-d_6): δ 102.93 (C-8 and C-8'), 107.97 (C-4a and C-4a'), 111.87 (C-3 and C-3'), 114.67 (C-6 and C-6'), 132.56 (C-5 and C-5'), 149.55 (C-4 and C-4'), 189.49 (C-8a and C-8a'), 163.95 (C-7 and C-7'), 164.63 (C-2 and C-2'); ms: m/e 322 (10.7% M^+), 234 (38, M^+-C_6O), 189 (100, 234-COOH), 162 (93, 189-C_2H_3), 134 (31, 162-CO), 105 (56, 134-CH_2CH_3); hrms: m/e Calcd. for M^+ = $C_{18}H_{10}O_6$ 322.047740. Found: 322.0472076 and Calcd for M^+-C_6O = $C_{12}H_{10}O_5$ 234.052825. Found: 234.0524414.

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