

Synthesis of 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one from *Tessmannia densiflora*

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ABSTRACT

The synthesis of 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (1) isolated from the stem and root bark extracts of *Tessmannia densiflora* has been described. The reaction of 3,5-dimethoxyhomophthalic anhydride (2) with hexanoyl chloride in the presence of 1,1,3,3-tetramethylguanidine and triethylamine afforded 6,8-dimethoxy-3-pentylisocoumarin (3). Regioselective demethylation of the latter using anhydrous aluminum chloride furnished the title isocoumarin (1).

1. Introduction

Isocoumarins (1*H*-2-benzopyran-1-ones) are natural lactones that are isolated from a wide range of natural sources (microbes, plant, and insects) and possess an array of biological activities including nephrotoxic, hepatotoxic, protease inhibitory, antifungal, cytotoxic, immunomodulatory, antiallergic, and antimalarial activities [1-6]. Isocoumarins are isomeric to coumarins with an inverted lactone ring. Most of the natural isocoumarins possess a 3-alkyl (C₁-C₁₇) or a substituted 3-phenyl ring and 6,8-dioxygenation due to their typical biosynthetic origin [7].

During investigations for botanical insecticides for the control of malaria-transmitting *Anopheles gambiae* mosquitoes, Nkunya and coworkers [8] isolated a number of compounds from the stem and root bark extracts of *Tessmannia densiflora* Harms (family Caesalpiniaceae) that showed mosquito larvicidal activity. The isolated compounds were identified as nor-halimane diterpenoid tessmannic acid and its methyl, 2-methylisopropyl and 1-methylbutylesters, 5-pentyl-3-methoxy-N-butylaniline, and two unusual isocoumarins. The structures of the new isocoumarins were established unambiguously as 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (Figure 1) and 7-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin, respectively, by analysis of spectroscopic data [8].

As a continuance of our focusing on the synthesis, characterization, crystal structure, and bioevaluation of this important class of secondary metabolites [9-14], a simple and efficient synthesis of the title compound was undertaken. The structural simplicity, coupled with the bioactivity associated with this molecule, makes it an attractive target for synthesis. The synthesis not only confirms the structural assignment but also makes it accessible for comprehensive evaluation of its bioactivity.

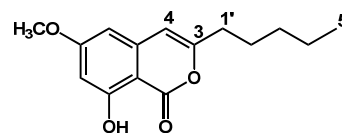


Figure 1. Isocoumarin (8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one) from *Tessmannia densiflora*.

2. Experimental

2.1. Instrumentation

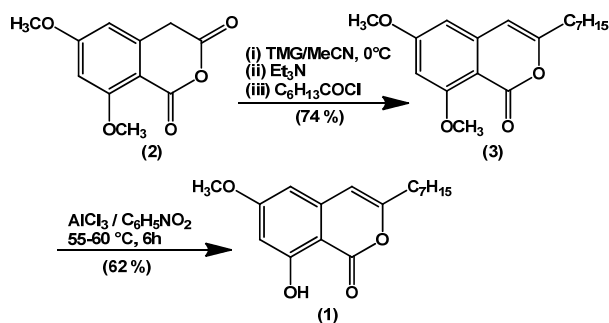
Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were determined in CDCl₃ solutions at 300 MHz and 75 MHz respectively using a Bruker AM-300 spectrophotometer. FT-IR spectra were recorded using an FTS 3000 MX spectrophotometer, Mass spectra (EI, 70 eV) on a GC-MS instrument and elemental analyses with a LECO-183 CHNS analyzer. All compounds were purified by thick layer chromatography using silica gel from Merck (Darmstadt, Germany).

2.2. Synthesis

2.2.1. 6,8-Dimethoxy-3-pentylisocoumarin (3)

A solution of 3,5-dimethoxyhomophthalic anhydride (2, 1.0 g, 4.50 mmol) in acetonitrile (30 mL) was added slowly to a solution of 1,1,3,3-tetramethylguanidine (TMG) (0.62 mL, 4.95 mmol) in acetonitrile (12 mL), while maintaining the internal temperature ≤ 0 °C. Triethylamine (1.0 mL, 9.0 mmol) was

added in a single portion followed by dropwise addition of hexanoyl chloride (1.23 mL, 7.20 mmol). The reaction mixture was further stirred for 20 minutes, allowed to warm to ambient temperature and then quenched by addition of 1 M HCl (15 mL). The organic layer was separated, washed with saturated brine dried and concentrated. The crude compound was purified by thick layer chromatography followed by recrystallization from methanol to yield isocoumarin **3** (0.42 g, 1.53 mmol, 74 %) (Scheme 1). As a colorless oil; IR (KBr, ν , cm^{-1}): 2913, 2849, 1722, 1605, 1575, 1510, 860, 835, 810. ^1H NMR (CDCl_3 , δ , ppm): 0.88 (t, $J=7.12$ Hz, 3H, H-5'), 1.30 (m, 2H, H-4'), 1.35 (quin, $J=3.5$ Hz, 2H, H-3'), 1.67 (quin, $J=3.5$ Hz, 2H, H-2'), 2.47 (2H, t, $J=7.1$ Hz, H-1'), 3.85 (s, 3H, MeO), 3.95 (s, 3H, MeO), 6.09 (s, 1H, H-4), 6.39 (d, $J=2.2$ Hz, 1H, H-7), 6.47 (d, $J=2.1$ Hz, 1H, H-5). ^{13}C NMR (CDCl_3 , δ , ppm): 168.1 (C=O), 167.3 (C6), 163.7 (C8), 159.6 (C3), 141.8 (C9), 103.4 (C4), 102.2 (C5), 100.9 (C7), 99.9 (C10), 55.3 (MeO), 56.6 (MeO), 33.3 (C1'), 31.1 (C3'), 26.4 (C2'), 22.3 (C4'), 14.1 (C5'). MS (m/z): 276 (16), 219 (18), 206 (52), 191 (15), 177 (27), 165 (14), 164 (98). Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_4$: C, 69.54; H, 7.30. Found: C, 69.71; H, 7.15.



Scheme 1

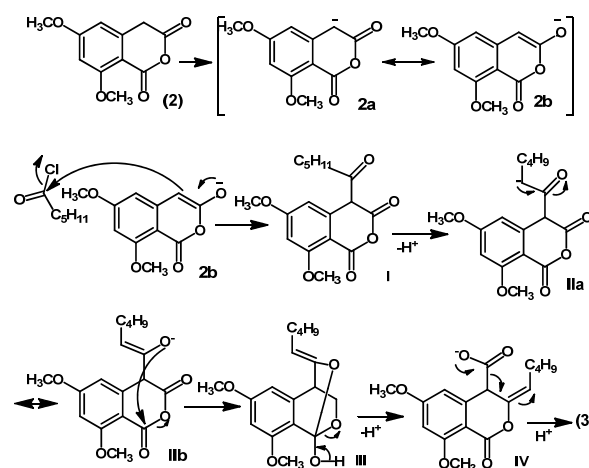
2.2.2. 6-Methoxy-8-hydroxy-3-pentylisocoumarin (1)

Aluminum chloride (0.83 g, 6.24 mmol) was added to a stirred solution of **3** (0.35 g, 1.26 mmol) in freshly distilled dry nitrobenzene (10 mL). The reaction mixture was stirred at 50-60 °C for 6 h, then poured into ice water and acidified with 0.5 N HCl. The acidic solution was extracted with diethyl ether (3x50 mL) and stirred for 10 min. The layers were separated and the aqueous layer extracted with dichloromethane (2x50 mL) and then the combined organic extracts washed with 2.5 M NaOH (2x60 mL). The basic solution was extracted with diethyl ether, acidified and again extracted with diethyl ether. The last extract was evaporated and residue purified by thick layer chromatography (petroleum ether:ethyl acetate (8:2)) to afford (**1**) (0.20 g, 0.8 mmol, 62%). M.p.: 76-78 °C (Lit. [8]: 79-80 °C). ^1H NMR (CDCl_3 , δ , ppm): 0.89 (t, $J=7.12$ Hz, 3H, H-5'), 1.31 (m, 2H, H-4'), 1.39 (quin, $J=3.5$ Hz, 2H, H-3'), 1.68 (quin, $J=3.5$ Hz, 2H, H-2'), 2.49 (t, $J=7.61$ Hz, 3H, H-1'), 3.85 (s, 3H, MeO), 6.18 (s, 1H, H-4), 6.39 (d, $J=2.2$ Hz, 1H, H-7), 6.47 (d, $J=2.2$ Hz, 1H, H-5), 11.2 (1H, br s, OH). ^{13}C NMR (CDCl_3 , δ , ppm): 164.4 (C=O), 163.7 (C8), 163.3 (C6), 159.7 (C3), 142.4 (C9), 103.1 (C4), 102.9 (C5), 100.3 (C7), 98.7 (C10), 56.3 (MeO), 33.3 (C1'), 31.1 (C3'), 26.4 (C2'), 22.3 (C4'), 13.9 (C5'). MS (m/z): 262 (37), 206 (52), 191 (15), 177 (27), 164 (100), 149 (29). Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_4$: C, 68.68; H, 6.92; found C, 68.12; H, 7.01.

3. Results and discussion

3,5-Dimethoxyhomophthalic acid [15] was efficiently converted into corresponding anhydride (**2**) by refluxing with acetic anhydride in dry toluene. The anhydride **2** in acetonitrile was added to a solution of 1,1,3,3-tetramethyl guanidine (TMG) in the same solvent at 0 °C followed by addition of triethylamine [16]. Treatment of the reaction mixture with

hexanoyl chloride furnished the 6,8-dimethoxy-3-pentylisocoumarin (**3**) in 74% yield. Isocoumarin **3** exhibited the characteristic singlet for H-4 olefinic proton at 6.09 ppm, the triplet for H-1' at 2.46 ppm ($J=7.1$ Hz) and the carbon signals at 103.5 (C-4) and 159.3 (C-3) and 168.1 (C=O) ppm. The δ -lactonic carbonyl stretching in the IR spectrum appeared at 1725 cm^{-1} . The construction of isocoumarin **3** from the anhydride **2** may be visualized by the loss of a benzylic proton to base to afford the resonance stabilized anionic species (**2a** and **2b**), which attacks the hexanoyl chloride to give the 4-hexanoyl-6,8-dimethoxyisochroman-1,3-dione intermediate I. Loss of proton to the base affords the species II a, b, which upon intramolecular *O*-acylation furnishes the tricyclic intermediate III, which under basic influence undergoes ring opening to afford IV. Decarboxylation followed by isomerization of the latter provided the isocoumarin **3** (Scheme 2).



Scheme 2

The C-8 methoxyl in 6,8-dimethoxy-3-methylisocoumarin (**3**) was regioselectively demethylated using anhydrous aluminum chloride in dry nitrobenzene [17-18], due to hydrogen bonding of the resulting hydroxyl with the periplanar lactonic carbonyl to yield the 8-hydroxy-6-methoxy-3-pentylisocoumarin (**1**). In addition to the disappearance of the C-8 methoxy group at 3.95 ppm, the downfield shift of singlet for H-4 and the triplet for H-1' to 6.15 and 2.48 ppm ($J=7.6$ Hz), respectively, was detected. A similar shift for C-4 and C-3 (104.0 and 156.2 ppm, respectively) was also noted. The lactonic carbonyl absorption was also lowered to 1685 cm^{-1} due to chelation with C-8 hydroxyl which appeared at 11.2 ppm.

4. Conclusion

An efficient synthesis of a natural isocoumarin has been achieved. A likely pathway for formation of isocoumarin **3** from anhydride **2** has also been proposed.

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