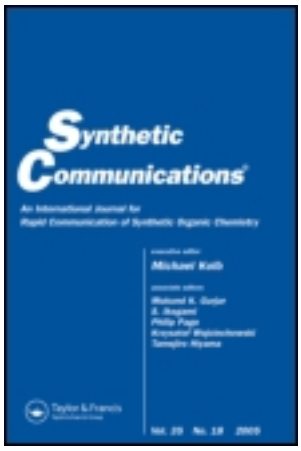

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Facile Total Synthesis of Xanthotoxol

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Facile Total Synthesis of Xanthotoxol

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Abstract: Xanthotoxol, a biologically active linear furocoumarin, has been efficiently synthesized from 7-hydroxycoumarin in six steps. The key steps included two efficient rearrangements—Fries rearrangement and Claisen rearrangement—and a Baeyer–Villiger oxidation process. The overall yield of xanthotoxol was 29%. This approach also provided a new strategy to furnish easily furocoumarins with a hydroxyl group in the framework.

Keywords: Baeyer–Villiger oxidation, Claisen rearrangement, Fries rearrangement, furocoumarins, total synthesis, xanthotoxol

INTRODUCTION

Xanthotoxol (**1**) is a natural furocoumarin that occurs in a large number of plants.[1] It exhibits a wide range of biological properties, such as antioxidative activity,[2] 5-HT antagonistic effect,[3] and central nervous system activity.[4]

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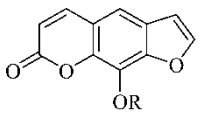
Recently, it was reported that xanthotoxol had a cytotoxic effect on transitional cell carcinoma (TCTC) cells,[5] and they could be used as biological probes to investigate the structure and function of nucleic acid in molecular biology.[6] Besides the isolation from natural sources, the preparation of xanthotoxol was often established by a semisynthetic method from xanthotoxin (Fig. 1), which is also a natural product usually isolated from some plants.[7]

Although several approaches for the O-demethylation of xanthotoxin have been described in the literature, such as pyridine–HCl,[6a] BBr_3,[6b] Mg/I_2,[8a] Me_3SiI,[8b] and $AlCl_3$,[8c] the difficulties obtaining natural xanthotoxin have limited the application of xanthotoxol. In the context of our continuing interest in the important biological properties of furocoumarins, we report herein an efficient strategy for the total synthesis of xanthotoxol.

RESULTS AND DISCUSSION

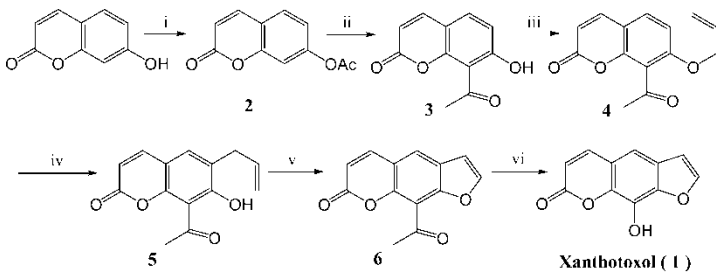
The general approach to synthesize xanthotoxol is outlined in Scheme 1. At first, commercially available 7-hydroxycoumarin was easily converted into 7-acetoxycoumarin **2** by acetylation in 98% yield. Acetyl migration was carried out under Fries rearrangement with $AlCl_3$ as usual to predominately afford isomer 8-acetyl-7-hydroxycoumarin **3** in 72% yield.[9] When refluxed overnight in acetone, compound **3** was then converted into the desired allyl ether **4** in 96% yield by an allylation reaction with allyl bromide in the presence of anhydrous K_2CO_3. The Claisen rearrangement of **4** was performed in refluxing N,N-diethylaniline and allowed for isolation of pure **5** in 73% yield. With 6-allyl derivative **5** in hand, the furocoumarin **6**[10] could be obtained through an oxidation reaction with osmium tetroxide–potassium periodate and cyclization with a phosphoric acid sequence in one pot in 71% yield.

It is well known that aryl ketone derivatives can be easily converted to phenolic derivatives by the Baeyer–Villiger oxidation.[9] When **6** is transformed by the usual oxidation procedure, 30% H_2O_2 in 2 M NaOH, the desired title compound xanthotoxol **1** was isolated in 82% yield. All the compounds mentioned previously were consistent with the structures described in Scheme 1 and have been confirmed by melting point, IR, ^1H NMR, MS, or elemental analysis.



R= CH_3 Xanthotoxin
R= H Xanthotoxol (**1**)

Figure 1. Structures of xanthotoxin and xanthotoxol.



Scheme 1. Route for synthesis of Xanthoxol. Reagents and conditions: (i) Ac_2O, pyridine, rt, 24 h; (ii) $AlCl_3$, 160°C, 2 h; (iii) allyl bromide, K_2CO_3, adcetone, refluing overnight; (iv) N,N-diethylaniline, refluing 3.5 h; (v) (1) KIO_4, cat. OsO_4, MeOH-H_2O, rt, 16 h; (2) 85%H_3PO_4, 0.5 h; and (vi) H_2O_2, NaOH.

In conclusion, a facile, efficient method for the total synthesis of xanthotoxol has been demonstrated. This process has afforded concise synthesis of xanthotoxol through six steps in 29% overall yield. In addition to providing the desired xanthotoxol for biological activity testing, this approach also allows the generation of new furocoumarin derivatives for drug research. Syntheses of these natural-product-like compounds are under investigation in our research group.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded with KBr disks on Nicolet Magna 750 spectrometer and only characteristic absorptions were reported. NMR spectra were recorded on Bruker AM-400 spectrometer, using tetramethylsilane as the internal standard. Mass spectra were performed on a Varian MAT-711 spectrometer. Element analyses were obtained using a Foss-Heraeus Vario EL instrument. All the solvents and chemicals were obtained from commercial sources and were used without further purification unless otherwise stated.

7-Acetoxycoumarin, 2

Acetic anhydride (2.8 mL, 30 mmol) was added to a chilled, stirred solution of 7-hydroxycoumarin (2.43 g, 15 mmol) in pyridine (40 mL) at such a rate as to keep the temperature below 20°C. After stirring at room temperature for 24 h, the reaction mixture was poured into ice water and then extracted with EtOAc (3×50 mL). The combined organic layer was washed with 5% HCl and brine. After drying over anhydrous sodium sulfate and evaporating in vacuo, the residue was flash chromatographed using petroleum ether and acetone (4:1, v/v) as eluent to afford 7-acetoxycoumarin (3.02 g, yield 98%).

Mp 142 − 143°C [lit.[9] yield 97%; mp 143 − 145°C]. ^{1}H NMR (400 M, $CDCl_3$) δ 7.74 (d, $J = 9.4$ Hz, 1H), 7.52 (d, $J = 8.2$ Hz, 1H), 7.12 (s, 1H), 7.10 (d, $J = 8.2$ Hz, 1H), 6.43 (d, $J = 9.4$ Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 M, $CDCl_3$) δ 169.2, 160.9, 155.2, 153.6, 143.4, 129.0, 119.6, 117.1, 116.5, 110.9, 21.6; EI-MS m/z (%) 204 (M^+, 100), 162 (70), 105 (25); IR (KBr): 1751, 1742, 1615, 1204, 746 cm^{-1}.

Fries Rearrangement for the Synthesis of 8-Acetyl-7-hydroxycoumarin, 3

The mixture of compound **2** (2.65 g, 13 mmol) and anhydrous aluminium chloride (6.40 g, 48 mmol) was heated to 160°C and stirred for 2 h at the same temperature. When the reaction mixture was cooled to room temperature, 5% HCl (30 mL) was added. The resulted mixture was stirred for 1 h at room temperature and then heated under a steam bath for another 0.5 h. The solution was cooled and extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. After evaporating in vacuo, the residue was purified by flash chromatograph using petroleum ether and acetone (5:1, v/v) as eluent to give 1.92 g of product (yield 72%). Mp 166–167°C [lit.[9] yield 79%; mp 165 − 167°C]. ^{1}H NMR (400 M, $CDCl_3$) δ 13.65 (s, 1H), 7.65 (d, $J = 9.4$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 6.90 (d, $J = 8.8$ Hz, 1H), 6.28 (d, $J = 9.4$ Hz, 1H), 2.97 (s, 3H); ^{13}C NMR (100 M, $CDCl_3$) δ 200.1, 162.2, 161.1, 151.4, 143.6, 133.2, 118.2, 115.3, 111.4, 111.3, 31.4; EI-MS m/z (%) 204 (M^+, 100), 161 (55), 105 (30); anal. calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.95; found: C, 64.74; H, 3.90. IR (KBr): 3161, 1720, 1632, 1205, 764 cm^{-1}; IR (KBr): 1738, 1721, 1380, 752 cm^{-1}.

8-Acetyl-7-allyloxycoumarin, 4

A mixture of **3** (1.60 g, 8 mmol), allyl bromide (4.0 mL), and anhydrous potassium carbonate (3.30 g, 24 mmol) in acetone (80 mL) was stirred and refluxed overnight under N_2. After cooling to room temperature, the reaction mixture was filtered, washed with acetone, and concentrated to dryness in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether–acetone = 3:1, v/v) to afford **4** (1.87 g, yield 96%). Mp 89 − 90°C; ^{1}H NMR (400 M, $CDCl_3$) δ 7.62 (d, $J = 9.6$ Hz, 1H), 7.43 (d, $J = 9.0$ Hz, 1H), 6.86 (d, $J = 9.0$ Hz, 1H), 6.27 (d, $J = 9.6$ Hz, 1H), 6.01 (m, 1H), 5.42–5.30 (m, 2H), 4.65 (d, $J = 5.1$ Hz, 2H), 2.61 (s, 3H); ^{13}C NMR (100 M, $CDCl_3$) δ 199.9, 161.0, 158.2, 151.4, 143.4, 133.4, 132.9, 118.1, 115.1, 113.5, 111.3, 110.4, 69.6, 31.2; EI-MS m/z (%) 244 (M^+, 100), 215 (45), 201 (35), 189 (85); anal. calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95; found: C, 68.86; H, 4.91. IR (KBr): 3161, 1720, 1632, 1205, 764 cm^{-1}; IR (KBr): 1742, 1708, 1645, 758 cm^{-1}.

Claisen Rearrangement for the Synthesis of 8-Acetyl-6-allyl-7-hydroxycoumarin, 5

A solution of **4** (1.22 g, 5 mmol) in N,N-diethylaniline (5 mL) was heated under refluxing for 3.5 h. After cooling to room temperature, EtOAc (100 mL) was added, and the mixture was washed several times with 0.5 M HCl and then brine. After drying over anhydrous sodium sulfate, the organic phase was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel to furnish **5** (0.89 g, yield 73%). Mp 130 − 132°C; ^{1}H NMR (400 M, $CDCl_3$) δ 13.00 (s, 1H), 7.80 (s, 1H), 7.64 (d, $J = 9.6$ Hz, 1H), 6.32 (d, $J = 9.6$ Hz, 1H), 5.99 (m, 1H), 5.15 ∼ 5.01 (m, 2H), 3.62 (d, $J = 5.6$ Hz, 2H), 2.69 (s, 3H); ^{13}C NMR (100 M, $CDCl_3$) δ 200.1, 161.7, 161.1, 146.2, 144.5, 137.2, 132.7, 125.2, 118.2, 116.9, 114.6, 111.7, 39.2, 30.2; EI-MS m/z (%) 244 (M^+, 100), 201 (25), 189 (25); anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95; found: C, 68.80; H, 4.92. IR (KBr): 3161, 1720, 1632, 1205, 764 cm^{-1}; IR (KBr): 3340, 1720, 1612, 1204 cm^{-1}.

9-Acetyl-7H-furo[3,2-*g*]chromen-7-one, 6

A solution of osmium tetroxide (7 mg) in water (3 mL) was added to a vigorously stirred mixture of potassium periodate (1.24 g, 5.8 mmol) and **5** (0.7 g, 2.9 mmol) in methanol (20 mL). After stirring for 16 h, the mixture was diluted with dichloromethane and washed with saturated brine. The dichloromethane layer was dried over sodium sulfate and evaporated in vacuo. Without further purification of the residue, 85% phosphoric acid (10 mL) was added, and the mixture was heated on a steam bath with stirring for 0.5 h. When cooling to room temperature, the mixture was poured into water and extracted three times with EtOAc. After drying over anhydrous sodium sulfate and evaporating in vacuo, the residue was purified by flash chromatography on silica gel to afford the product 0.46 g (yield 71%). Mp 206 − 208°C [lit.[10] mp 207 − 208°C].; ^{1}H NMR (400 M, $CDCl_3$) δ 7.79 (d, $J = 9.0$ Hz, 1H), 7.73 (s, 1H), 7.70 (d, $J = 2.2$ Hz, 1H), 6.81 (d, $J = 2.2$ Hz, 1H), 6.30 (d, $J = 9.0$ Hz, 1H), 2.79 (s, 3H); ^{13}C NMR (100 M, $CDCl_3$) δ 201.0, 161.8, 161.1, 147.1, 146.9, 144.3, 125.3, 122.4, 114.6, 114.1, 113.2, 107.0, 29.3; EI-MS m/z (%) 228 (M^+, 100), 144 (10), 115 (25); anal. calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.53; found: C, 68.36; H, 3.60. IR (KBr): 3161, 1720, 1632, 1205, 764 cm^{-1}.

Baeyer–Villiger Oxidation for the Synthesis of Xanthotoxol, 1

A suspension of **6** (0.45 g, 2 mmol) in 2 M NaOH (10 mL) and dioxane (15 mL) was heated for 10 min and then cooled to 0°C in an ice bath.

Aqueous H_2O_2 (30%, 15 mL) was added dropwise within 30 min. The resulting solution was stirred until the reaction was complete (about 2 h, thin-laser chromatography: petroleum ether–acetone 2:1). The reaction was quenched at 0°C by the addition of 2 M HCl, and the aqueous mixture was extracted three times with EtOAc. The combined extracts were dried over sodium sulfate and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether–acetone 3:1) to afford the title compound (0.33 g) in 82% yield. mp 242 − 243°C (crystallization in acetone) [lit. [6b] 244 − 246°C]; ^{1}H NMR (400 M, $CDCl_3$) δ 7.81 (d, $J = 9.8$ Hz, 1H), 7.72 (d, $J = 2.2$ Hz, 1H), 7.28 (s, 1H), 6.83 (d, $J = 2.2$ Hz, 1H), 6.38 (d, $J = 9.8$ Hz, 1H), 6.20 (s, br, 1H); ^{13}C NMR (100 M, $CDCl_3$) δ 160.1, 147.4, 145.4, 145.3, 139.9, 130.3, 125.4, 116.4, 113.9, 110.2, 107.1; EI-MS m/z (%) 202 (M^+, 100), 174 (70), 157 (30), 146 (10); anal. calcd. for $C_{11}H_6O_4$: C, 65.35; H, 2.99; found: C, 65.36; H, 3.03. IR (KBr): 3341, 1712, 1629, 1235, 765 cm^{-1}.

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