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A novel and efficient synthesis of norathyriol using Pd(II) as a catalyst

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Abstract A facile and simple procedure for the synthesis of norathyriol using Pd(II) as a catalyst via two steps under mild conditions is described. The major advantages of this method are the use of a commercially available catalyst, short reaction times, and the simplicity of the reaction and work-up. The overall yield of 36.6 % is acceptable.

Keywords Synthesis · Norathyriol · Catalyst · Transition metal

Introduction

Norathyriol (Fig. 1) is a naturally-occurring polyphenolic xanthone which has received considerable attention because of its wide range of biological and pharmacological properties [1–3]. Human exposure to norathyriol occurs primarily through the consumption of chamomile and through its presence as a glycoside in many folk medicinal plants [4–7]. Norathyriol, like most xanthones, has antioxidant [8], anti-inflamrnatory [9], and anticholinesterase activities [10]. Recently, norathyriol has been synthesized by Hu et al. [11] in four steps with an overall yield of 45.5 %. In addition, norathyriol has also been prepared by other authors [6, 12, 13], but most of the published synthesis methods report low yields and use starting materials that are not easily accessible.

Here, we report a novel and efficient procedure to synthesis **1** with the commercially available 4,6-dimethoxy-2-hydroxybenzaldehyde and 4,5-dibromo-1,2-dimethoxybenzene as the starting material. (Scheme 1).

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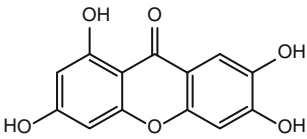
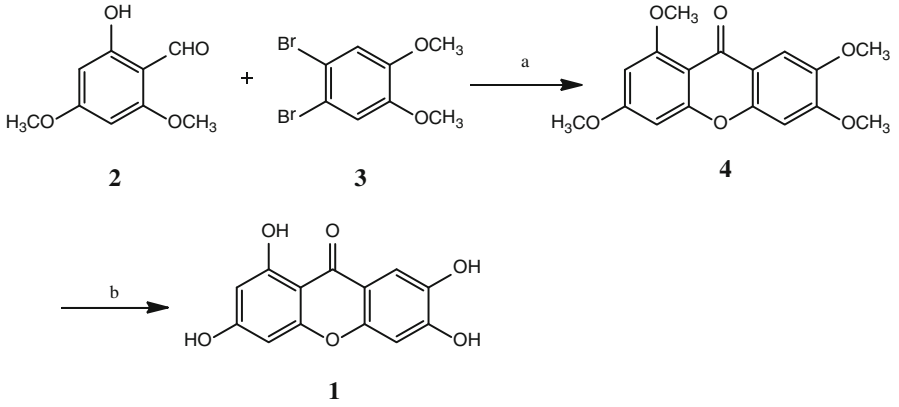
Fig. 1 Structure of norathyriol (**1**)





Scheme 1 Reagents and conditions: **a** 5 mol% $PdCl_2(PPh_3)_2$, DMF, K_2CO_3, 130 °C, 12 h, 43 %, **b** pyridine HCl, 180 °C, 5 h, 85 %

Results and discussion

As shown in Scheme 1, norathyriol has been synthetized with good total yields from 4,6-dimethoxy-2-hydroxybenzaldehyde **2** in two steps. Firstly, 4,6-dimethoxy-2-hydroxybenzaldehyde **2** was reacted with 4,5-dibromo-1,2-dimethoxybenzene **3** in DMF at 130 °C in the presence of 5 mol% of $PdCl_2(PPh_3)_2$ and K_2CO_3 (2 equiv.) to obtain the compound **4** in mild yield. Secondly, the compound **4** was demethylated completely in excess pyridine hydrochloride at 180 °C for 5 h to afford the title compound **1** in high yield.

In conclusion, a convenient and efficient synthesis of **1** has been achieved via only two steps in a very high overall yield (36 %). The starting material is commercially available and the intermediate is sufficiently stable to permit isolation. We believe that this new procedure could be an efficient synthetic approach for scaling-up of **1** and be a useful addition to the reported methods for the preparation of the xanthone.

Experimental

All reactions were monitored by TLC and TLC was performed on silica gel GF_{254}. Melting points were measured on a YRT-3 temperature apparatus and are uncorrected. ^1H NMR spectral data were recorded on a Bruker DRX 500 NMR spectrometer and chemical shifts are reported in ppm(δ) relative to TMS as internal

standard. Mass spectra were determined on VG Auto Spec-3000 spectrometer and reported as *m*/*z*. All reagents were purchased from Aladdin-reagent, China, and used without further purification.

1,3,6,7-tetramethoxyxanthone(**4**)

To a mixture of compound **2** (364 mg, 2 mmol) and compound **3** (1.17 g 2 mmol), K_2CO_3 (560 mg, 4 mmol), $(PPh_3)_2PdCl_2$ (75 mg, 0.11 mmol) and 10 mL DMF were added. The mixture was heated to 130 °C under N_2 atmosphere for 12 h. Then the mixture was cooled to room temperature and diluted with diethyl ether (50 mL) and washed with water and brine. The aqueous layer was extracted with diethyl ether (2 × 80 mL). The organic layers were combined and dried with $NaSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 50/1) to afford the desired product **4** as white crystals (271 mg), yield: 43 %, m.p. 202–203 °C ([14], 206–207 °C); ^{1}H NMR (500 MHz, $CDCl_3$) (δ, ppm): 7.65 (s, 1H), 6.82 (s, 1H), 6.47 (s, 1H), 6.34 (s, 1H),3.99 (s, 3H), 3.97 (s, 6H),3.91 (s, 3H); MS (*m*/*z*): 316 (M^+).

1,3,6,7-tetrahydroxyxanthone(**1**)

The mixture of the compound **4** (1.6 g, 5 mmol) and excess pyridine hydrochloride (6.4 g, 50 mmol) were heated at 180 °C for 4.5 h under an N_2 atmosphere. Then the mixture was cooled to room temperature and dilute hydrochloride (1.0 M × 100 mL) was added. The mixture was stirred for another 40 min and cooled at approximately 0 °C for several hours. The precipitate was filtered off, washed with water, and recrystallized from 75 % ethanol to give the compound **1** as yellow crystals (1.10 g), yield: 85 %, m.p. >320 °C (decomp.) (lit.[6] > 320 °C); ^{1}H NMR (500 MHz DMSO) (δ, ppm): 13.15 (s, 1H), 9.60–10.79 (br, 3H), 7.35 (s, 1H), 6.84 (s, 1H), 6.31 (s, 1H), 6.13 (s, 1H); MS (*m*/*z*): 260 (M^+).

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