A facile synthesis of norathyriol

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In this paper, norathyriol has been synthesised from 2-bromo-4,5-dimethoxybenzoic acid and 1,3,5-trimethoxybenzene by a three-step sequence of transformations involving a Friedel–Crafts acylation with cyclisation and demethylation. The procedure was facile and should be easily scaled-up. The overall yields reached approximately 70%.

Keywords: norathyriol, synthesis, Friedel–Crafts acylation, cyclisation, demethylation, xanthone

Norathyriol (**1**, see Fig. 1), also known as 1,3,6,7-tetrahydroxyxanthone, is a naturally-occurring polyphenolic xanthone which was found present in various herbal plants.[1–4] It is attracting more and more the attention of organic and medicinal chemists for its wide range of biological and pharmacological properties and it is believed to be the important active component in some traditional medicinal plants.[3–6] Related studies on the chemical modifications and structure–activity relationships of **1** are on-going.[7–8] Although Ueno[3] first reported the synthesis of **1** from a mixture of 2,4,5-trihydrobenzoic acid, phloroglucinol, fused $ZnCl_2$ and an excess of $POCl_3$ by one-pot reaction in 1962, the yield was very poor and the product was difficult to isolate and purify. In 1992, Lin *et al.*[9] reported a synthesis from the corresponding benzophenone as precursor by Friedel–Crafts acylation and base-catalysed cyclisation to give **1**. However, the key benzophenone intermediate was not easily available and the yield was poor. The absence of efficient preparation of **1** has encouraged further studies on synthetic procedures. In 2011, Li *et al.*[10] have reported the synthesis of **1** with 2-bromo-4,5-dimethoxybenzoic acid and 3,5-dimethoxyphenol as the key precursors by Ullmann condensation followed by Friedel–Crafts acylation cyclisation and complete demethylation. The yield was still very poor and the precursors were difficult to prepare and the Ullmann reaction conditions were very harsh. In 2011, Hu *et al.*[8] reported a synthetic route in four steps to give **1** with 2,4,5-trimethoxybenzoic acid and 1,3,5-trimethoxy-benzene as the starting materials. The yield was still unsatisfactory and open to improvement.

In our studies of the structure–activity relationships of active compounds from natural sources,[11–13] we had also established the efficient preparation of **1** by an alternative procedure, which has been patented in China.[14] Our team has continued further investigations of the procedure, which has resulted in improvements in the preparation of **1**. Here, we report our preparation of **1** using the commercially available starting materials, which features an improved procedure and better yields, and should be better for the scaled-up preparation of **1** (see Scheme 1).

Results and discussion

As shown in Scheme 1, the title compound **1** has been synthesised with good overall yield from 2-bromo-4,5-dimethoxybenzoic acid **2** and 1,3,5-trimethoxybenzene **3**. In our patent, the compound **2** was condensed with compound **3** to give the compound **4** in the presence of a Lewis acid such as PPA, $POCl_3$, BF_3, *etc*. Then, compound **4** was demethylated selectively with BCl_3 at approximately 0 °C to produce the compound **5**, which was smoothly cyclised to provide **6** in hot, strong alkali solution with good yield. Lastly, compound **6** was demethylated completely in excess pyridine hydrochloride at 180 °C for 5h to afford the title compound **1** in high yield. However, further investigations suggested that compound **4** could also be demethylated selectively with BF_3 at 80–90 °C to produce compound **5** in good yield. Thus, compound **2** could be condensed with 1,3,5-trimethoxybenzene by Friedel–Crafts acylation followed by demethylation selectively at 80–90 °C in the presence of a little excess of a Lewis acid such as BF_3 in a one pot reaction to produce the key intermediate **5**. Hence, our patented procedure was improved by removing one reaction step.

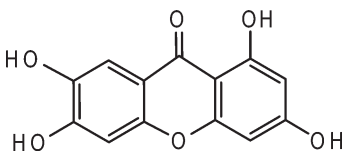

Fig. 1 Structure of norathyriol (**1**).

In conclusion, a convenient and efficient synthesis of **1** has been achieved using only three reaction steps. The overall yield is approximately 70% and satisfactorily high. All the starting materials and reagents are commercially available and inexpensive. Each step of reaction was carried out to give the product easily. Hence, we believe that this improved procedure could be an efficient synthetic approach for scaled-up synthesis 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. ^{1}H NMR spectroscopic data were recorded on a Bruker DRX 500 NMR spectrometer and chemical shift are reported in ppm (δ) relative to TMS as internal standard. Mass spectra were determined on a VG Auto Spec-3000 spectrometer and reported as *m/z*.

2-Bromo-4, 5, 2', 4', 6'-pentamethoxyl benzophenone (**4**): To the mixture of the compound **2** (5.7 g, 22 mmol) and the compound 3 (3.3 g 20 mmol) in chlorobenzene (15 mL), $POCl_3$ (4.8 mL, 50 mmol) was added dropwise. After the reaction mixture was stirred at 80 °C for 4 h, H_2O (100 mL) was added and the mixture was kept heating and stirring for another 1h. Then, the mixture was cooled to room temperature and extracted with 1,2-dichloroethane twice (2×100 mL). The organic layers were combined and washed sequentially with H_2O (100 mL×2), saturated sodium bicarbonate (100 mL×2) and H_2O (100 mL×1) and then dried with anhydrous sodium sulfate overnight. Removal of the solvent under reduced pressure gave a solid residue, which was recrystallised from ethanol to afford the compound **4** as white crystals (7.00 g), yield: 85.0%, m.p. 129–130 °C (lit.[14] 129–130 °C), ^{1}HNMR (500 MHz $CDCl_3$) δ: 7.26 (s, 1H), 7.01 (s, 1H), 6.13 (s, 2H), 3.91 (s, 3H), 3.85 (s, 6H), 3.70 (s, 6H). MS (*m/z*): 412, 410 (M^+).

2-Bromo-2'-hydroxy-4, 5, 4', 6'-tetramethoxyl benzophenone (**5**): *Method A*: To the solution of the compound **4** (4.1 g, 10 mmol) in dichloromethane (30 mL) at approximately 0 °C, 1 mol L^{-1} BCl_3 in dichloromethane (12 mL, 12 mmol) was added dropwise for about 1 h, and then the reaction mixture were stirred at room temperature for another 3 h. H_2O (100 mL) was added, the mixture was stirred for another hour and extracted with dichloromethane twice (100 mL×2). The organic layers were combined and washed sequentially with

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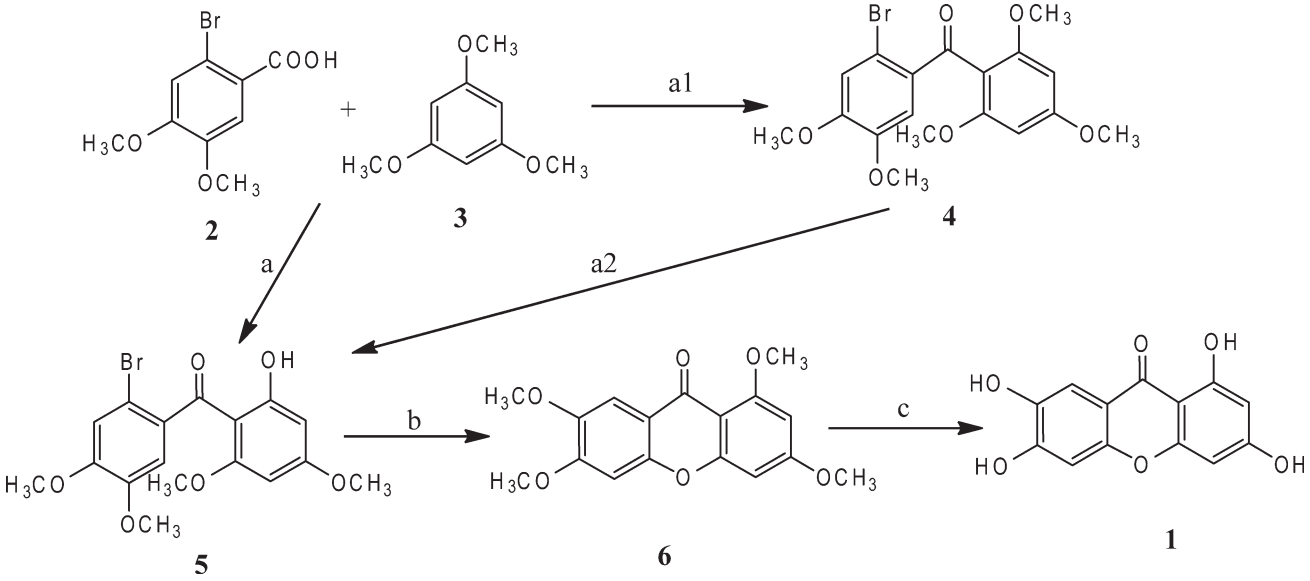

Scheme 1 Reagents and conditions:(a) BF_3–Et_2O, $ClCH_2CH_2Cl$, 90 °C, 6h, 85% (a1) $POCl_3$, $ClCH_2CH_2Cl$, 70–80 °C, 4h, 85% (a2) BCl_3, CH_2Cl_2, 0 °C r.t., 4h, 90% (b) KOH, H_2O, reflux, 15h, 95% (c) pyridine HCl, 180 °C, 5h, 85%.

H_2O (100 mL×2), saturated sodium bicarbonate (100 mL×2) and H_2O (100 mL×1) and then dried with anhydrous sodium sulfate overnight. Removal of the solvent under reduced pressure gave a solid residue, which was recrystallised from ethanol to afford the compound **5** as white crystals (3.56 g), yield: 90.0%, m.p. 153–154 °C (lit.[14]153–154 °C), ^{1}H NMR (500 MHz $CDCl_3$) δ: 7.00 (s, 1H), 6.77 (s, 1H), 6.14 (s, 1H), 5.85 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.46 (s, 3H). MS (*m/z*): 398, 396 (M^+).

2-Bromo-2′-hydroxy-4, 5, 4′, 6′-tetramethoxyl benzophenone (**5**): *Method B*: To the mixture of the compound **2** (5.7 g, 22 mmol) and the compound **3** (3.3 g 20 mmol) in chlorobenzene (10 mL), BF_3–Et_2O solution (7.0 mL, 47%, 50 mmol) was added dropwise. The reaction mixture was heated at 90 °C for 6 h. H_2O–methanol (100 mL, V/V = 1/1) was added and the mixture was stirred for another 1 h. Then, the mixture was extracted with 1,2-dichloroethane twice (2×100 mL). The organic layers were combined and washed sequentially with saturated sodium bicarbonate (100 mL×2), H_2O (100 mL) and dried with anhydrous sodium sulfate overnight. Removal of the solvent under reduced pressure gave a solid residue, which was recrystallised from ethanol to afford the compound **5** as white crystals (6.73 g), yield: 85.0%, m.p. 153–154 °C (lit.[14]153–154 °C), ^{1}HNMR (500 MHz $CDCl_3$) δ: 7.00 (s, 1H), 6.77 (s, 1H), 6.14 (s, 1H), 5.85 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.46 (s, 3H). MS (*m/z*): 398, 396 (M^+).

1,3,6,7-Tetramethoxyxanthone (**6**): The mixture of the compound **5** (4.0 g, 10 mmol) and potassium hydroxide (1.12 g, 20 m mol) in H_2O (60 mL) was heated under reflux for 15 h. The mixture was cooled to room temperature and neutralised with dilute hydrochloric acid (1M). The precipitate was filtered off, washed with water, and the aqueous phase was extracted with 1,2-dichloroethane twice (2×100 mL). The organic layers were combined and washed with H_2O (100 mL) once and dried with anhydrous sodium sulfate overnight. Removal of the solvent under reduced pressure gave a solid residue. The solid was combined with the above precipitate and recrystallised from ethanol to give the compound **6** as white crystals (2.60 g), yield: 95%, m.p. 202–203 °C (lit.[15] 206–207 °C), ^{1}H NMR (500 MHz $CDCl_3$) δ: 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 **5** (1.6 g, 5 mmol) and an excess of pyridine hydrochloride (6.4 g, 50 mmol) was heated at 180 °C for 4.5h under an N_2 atmosphere. Then the mixture was cooled to room temperature and dilute hydrochloric acid (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 recrystallised from 75% ethanol to give the compound **1** as yellow crystals (1.10 g), yield: 85%, m.p. >320 °C (decomp.) (lit.[3] >320 °C), ^{1}H NMR (500 MHz DMSO) δ: 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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