J Wood Sci (2006) 52:90–92
DOI 10.1007/s10086-005-0727-6

NOTE

Toshiyuki Takano · Tomomi Kondo · Fumiaki Nakatsubo

Facile synthesis of rubiadin by microwave heating

Received: August 2, 2004 / Accepted: March 25, 2005 / Published online: February 1, 2006

Abstract Rubiadin (**4**) (1,3-dihydroxy-2-methylanthraquinone), which is one of the natural dyes from the roots of Rubiaceae, was synthesized from phthalic anhydride (**1**) and 2,6-dihydroxytoluene (**3**) by two reaction steps, that is, a Friedel-Crafts reaction with $AlCl_3$ and a cyclization with H_2SO_4/HBO_2. Microwave heating resulted in remarkable acceleration of the reaction rate in the first reaction, and had an effect in reducing the reaction time and increasing the yield of rubiadin (**4**) in the second reaction.

Key words Synthesis · Rubiadin · Hydroxyanthraquinone · Microwave · Friedel-Crafts acylation

Introduction

The natural dyes from the roots of Rubiaceae, such as *Prismatomeris malayana* and *Morinda elliptica,* have been traditionally used in Southeast Asia. It is well known that the dyes contain anthraquinones, such as rubiadin, rubiadin 1-methyl ether, lucidin, damnacanthal, nordamnacanthal, and their glycosides.[1–3] However, the color development properties of the individual ingredients have not been investigated well, because the isolation and purification of the ingredients are not easy. Among them, rubiadin (1,3-dihydroxy-2-methylanthraquinone) (**4**) is important as an intermediate for the synthesis of the other anthraquinones.

Several synthetic methods for rubiadin (**4**) have been reported so far.[4–8] Hirose[4] reported the synthesis of rubiadin (**4**) from phthalic anhydride (**1**) and 2,6-dihydroxytoluene (**2**) by two reaction steps. In the first step, the condensation of **1** and **2** with $AlCl_3$ in $CHCl_2CHCl_2$ was carried out at 125°C for 3 h to give 2-(2′,4′-dihydroxy-3′-methyl) benzoylbenzoic acid (**3**). The second step of cyclization via dehydration of the compound **3** was performed in concentrated H_2SO_4, which acted as solvent, in the presence of fused boric acid at 100°C for 25 min. However, the yields of the both reaction steps were low (33% and 54%, respectively). In addition the reproducibility of this method was very poor, although we made many efforts to reproduce the experimental data.

Chari et al.[5] reported the synthetic method for rubiadin via 2-methylpurpurin (1,3,4-trihydroxy-2-methylanthraquinone). However, this method required five steps, and the yield of each reaction step was low. Courchesne and Brassard[6] and Boisvert and Brassard[7] described the syntheses of rubiadin derivatives by using Diels-Alder reactions involving halogenated naphthoquinones and dienes. Zhao and Biehl[8] reported the preparation of rubiadin by the condensation of 3-bromo-2,6-dimethoxytoluene with a phthalide. In these reports, the key intermediates are not commercially available, and must be synthesized by many reaction steps. On the other hand, it has been accepted that microwave heating has major advantages of reducing reaction time or increasing yield of products when compared with conventional heating.[9]

Herein, this report describes the modification of synthesis of rubiadin by the method of Hirose[4] and the application of microwave heating to it.

Experimental

Microwave heating was conducted using a CEM Discover Synthesis Unit (CEM, Matthews, NC, USA). The apparatus consists of a continuous focused microwave power delivery system with power output from 0 to 300 W at 2.45 GHz. The reaction temperature of the contents in the flasks was monitored using a calibrated infrared temperature control of this

T. Takano (✉) · T. Kondo · F. Nakatsubo
Division of Forest and Biomaterials Science, Graduate School of Agriculture, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan
Tel. +81-75-753-6257; Fax +81-75-753-6300
e-mail: takatmys@kais.kyoto-u.ac.jp

This report was presented at the 54th Annual Meeting of the Japan Wood Research Society, Sapporo, August 2004

apparatus. The control temperature was used as the reaction temperature, because the difference between control temperature of the apparatus and monitored temperature of the contents was within 4°C in this experiment. The reaction time was expressed as the sum of ramp time from room temperature to control temperature and hold time at control temperature.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Varian INOVA300 FT-NMR (300 MHz) spectrometer, and ultraviolet (UV) spectra were recorded with a Jasco V-560 UV/VIS spectrophotometer. All reagents except HBO_2 (metaboric acid) were purchased from Nacalai Tesque (Kyoto, Japan), and used without further purification. HBO_2 was prepared by heating commercial boric acid at 80°C in vacuo for 3 days.[10]

2′,4′-Dihydroxy-3′-methyl-2-benzoylbenzoic acid (**3**)

Phthalic anhydride (**1**, 600 mg, 4.05 mmol) and 2,6-dihydroxytoluene (**2**, 600 mg, 4.83 mmol) were dissolved in CH_2ClCH_2Cl (50 ml) or in $CHCl_2CHCl_2$ (50 ml). $AlCl_3$ (1.2 g, 9.0 mmol) was added to the solution. The reaction mixture was treated by conventional heating (oil bath) or by microwave heating under the reaction conditions shown in Table 1. After cooling, 1N HCl (20 ml) was added to the reaction mixture. The mixture was extracted with ethyl acetate (EtOAc). The organic layer was washed with distilled water, and extracted with 5% $NaHCO_3$ solution. The aqueous $NaHCO_3$ layer was washed with EtOAc, acidified with 1*N* HCl, and extracted with EtOAc again. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give compound **3**.

Data for compound **3**. ^{1}H-NMR (acetone-d_6) δ(ppm) 12.79 (1H, s), 8.12 (1H, dd, J = 7.4, 1.2 Hz), 7.75 (1H, dd, J = 7.4, 1.2 Hz), 7.67 (1H, dd, J = 7.4, 1.2 Hz), 7.44 (1H, dd, J = 7.4, 1.2 Hz), 6.85 (1H, d, J = 8.7 Hz), 6.38 (1H, d, J = 8.7 Hz), 2.11 (3H, s). UV λ_{max} (methanol) (nm) 217, 293. Melting point: 223°C (lit: 223°C).[4]

1,3-Dihydroxy-2-methyl anthraquinone (rubiadin) (**4**)

Compound **3** (108 mg, 0.4 mmol) and HBO_2 (247 mg, 5.6 mmol) were suspended in concentrated H_2SO_4 (1.3 ml). The reaction mixture was heated by conventional heating (oil bath) or by microwave heating under the reaction conditions listed in Table 1. After cooling, the reaction mixture was extracted with EtOAc, and the organic layer was successively washed with distilled water, saturated $NaHCO_3$ solution, and brine, dried over anhydrous Na_2SO_4, and passed through a silica gel column [3/1 EtOAc/*n*-hexane (v/v) as eluent]. The eluent was concentrated to give compound **4**.

Data for compound **4**. ^{1}H-NMR (acetone-d_6) δ 13.23 (1H, s), 8.30 (1H, m), 8.22 (1H, m), 7.92 (2H, m), 7.37 (1H, s), 2.19 (3H, s). UV λ_{max} (methanol) (nm) 209, 246, 278, 411.

Results and discussion

The synthetic route for rubiadin (**4**) from phthalic anhydride (**1**) and 2,6-dihydroxytoluene (**2**) is shown in Fig. 1. The first reaction is a Friedel-Crafts type reaction with $AlCl_3$. The results are shown in Table 1.

First, CH_2ClCH_2Cl was used as a solvent, because of the high boiling point of $CHCl_2CHCl_2$. However, the yields of compound **3** by both heating methods were moderate. Next, the reaction was performed by conventional heating under the same reaction conditions ($AlCl_3$/$CHCl_2CHCl_2$/125°C/180 min) reported by Hirose.[4] The yield of compound **3** was

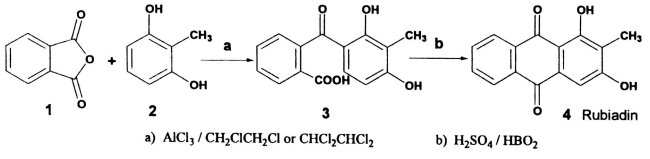

Fig. 1. Synthetic route for rubiadin (**4**) from phthalic anhydride (**1**) and 2,6-dihydroxytoluene (**2**)

Table 1. Reaction conditions and the yields of products in steps a and b in Fig. 1

Reaction step	Heating method	Solvent	Irradiation power (W)	Reaction temperature (°C)	Reaction time (min)	Yield (%)
a	Oil bath	CH_2ClCH_2Cl	–	80	180	53
a	MW	CH_2ClCH_2Cl	30	80	13	56
a	Oil bath	$CHCl_2CHCl_2$	–	125	180	90
a	MW	$CHCl_2CHCl_2$	120	125	13	95
b	Oil bath	H_2SO_4	–	100	25	2
b	MW	H_2SO_4	20	100	1	3
b	MW	H_2SO_4	20	120	1	7
b	MW	H_2SO_4	20	140	1	14
b	MW	H_2SO_4	20	160	1	60
b	MW	H_2SO_4	20	170	1	59
b	MW	H_2SO_4	20	180	1	18
b	Oil bath	H_2SO_4	–	160	25	32

MW, Microwave heating

90% in this experiment, although it has been reported to be 33%. On the other hand, by microwave heating, compound **3** was obtained in a 95% yield after only 13 min (ramp time 3 min, hold time 10 min). Microwave heating was effective for reducing reaction time in this reaction, although there was little difference in the yields of compound **3** obtained by conventional heating and by microwave heating.

The second reaction is a cyclization via dehydration with concentrated H_2SO_4 and HBO_2 (metaboric acid). The results are shown in Table 1.

The reaction was carried out by conventional heating under the same reaction conditions (H_2SO_4/HBO_2/100°C/25 min) reported by Hirose.[4] However, compound **4** was obtained in only 2% yield. The reproducibility of the Hirose method was very poor. Even with microwave heating at 100°C for 1 min (ramp time 20 s, hold time 40 s), the yield of compound **4** was only 3%. Consequently, it was found that this reaction was strongly influenced by the reaction temperature. By microwave heating, the optimal reaction temperature was 160°–170°C. That is, the yield of compound **4** was increased to 60% by microwave heating at 160°C for 1 min (ramp time 30 s, hold time 30 s), whereas the yield was only 32% after conventional heating at 160°C for 25 min. In the case of microwave heating above 180°C, the yield of compound **4** was reduced, and many by-products were observed by thin-layer chromatography analysis.

In summary, microwave heating has an effect on shortening reaction time and increases the yield of compound **4.** Our microwave heating procedure provides an easy and practical way to prepare rubiadin (**4**) from phthalic anhydride (**1**) and 2,6-dihydroxytoluene (**2**), which are commercially available and inexpensive.

References

1. Lee HH (1969) Coloring matters from *Prismatomeris malayana*. Phytochemistry 8:501–503
2. Jasril, Lajis NH, Abdullah MA, Ismail NH, Ali AM, Marziah M, Ariff AB, Kitajima M, Takayama H, Alimi N (2000) Anthraquinones from cell suspension culture of *Morinda elliptica*. Nat Prod Sci 6:40–43
3. Ali AM, Ismail NH, Mackeen MM, Yazan LS, Mohamed SM, Ho ASH, Lajis NH (2000) Antiviral cyototoxic and antimicrobial activities of anthraquinones isolated from the root of *Morinda elliptica*. Pharm, Biol 38:298–301
4. Hirose Y (1960) Syntheses of damnacanthal, damnacanthol, norjuzunal and norjuzunol, the coloring matters of *Damnacanthus* spp. Chem Pharm Bull 8:417–426
5. Chari VM, Neelakantan S, Seshadri TR (1966) A convenient synthesis of rubiadin. Indian J Chem 4:330–331
6. Courchesne M, Brassard P (1993) Identification and characterization of naturally occurring rubiadins. J Nat Prod 56:722–730
7. Boisvert L, Brassard P (1989) Naturally occurring rubiadins. Chem Lett 1055–1058
8. Zhao H, Biehl E (1995) Preparation of naturally occurring anthraquinones using the aryne reaction. J Nat Prod 58:1970–1974
9. Lidstrom P, Tierney J, Wathey B, Westman J (2001) Microwave assisted organic synthesis – a review. Tetrahedron 57:9225–9283
10. Nakahara H (1976) Boric acid (in Japanese). In: The Chemical Society of Japan (ed) Shi-Jikkenkagaku Koza 8-I. Maruzen, Tokyo, p 364