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Research Article

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Synthesis of (*E*)-3,5-dihydroxy-4-isopropylstilbene under microwave irradiation

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ABSTRACT

(E)-3,5-dihydroxy-4-isopropylstilbene is a new kind of anti-inflammatory drug for the treatment of anaphylactic disease such as psoriasis and eczema. The synthesis of (E)-3,5-dihydroxy-4-isopropylstilbene from (E)-3,5-dimethoxy-4-isopropylstilbene under microwave irradiation was investigated. Compared with the traditional heating method, microwave irradiation has the advantage that the demethylation reaction of (E)-3,5-dimethoxy-4-isopropylstilbene can be finished rapidly at relatively lower temperature with a higher yield and provides a new idea for the synthesis of stilbenes.

Key words: (E)-3,5-dihydroxy-4-isopropylstilbene , Demethylation, Microwave irradiation, Synthesis

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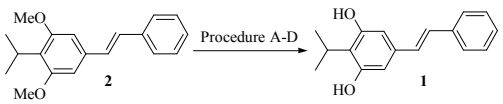
INTRODUCTION

Stilbenes usually refer to the compounds containing two benzene rings connected by a vinyl [1, 2]. With typical conjugate structure, this kind of compounds has a wide range of applications in the pharmaceutical, food, cosmetics, electronics, optics, dye, materials science and other fields. *(E)-3,5-dihydroxy-4-isopropylstilbene* (DHPS, Scheme 1.1), as a derivative of stilbenes, was first discovered in the metabolites of the *Photorhabdus* sp. [3]. Subsequent studies found that DHPS exist in a genus of bacteria symbionts which live in the parasitic nematodes guts [4, 5], from *Photorhabdus luminescens*, a bacterial symbiont of the entomopathogenic nematode *Heterorhabditis megidis* [6]. Further studies showed DHPS has a variety of physiological activity and pharmacological effects, such as significant antibacterial and anti-inflammatory effect on T lymphocytes, neutrophils, macrophages and regulatory effect on associated cytokines [7].



Scheme 1. Synthetic route for DHPS

The synthetic methods of DHPS mainly include Perkin reaction, Wittig-Horner reaction, Heck reaction, Condensation reaction of carbanion and carbonyl compound [8, 9]. Of them, Wittig-Horner route with simple operation and high yield is used frequently, and demethylation is inevitable after the Wittig-Horner reaction [10]. The shortcomings of conventional demethylation methods are as follows: Strong reaction conditions such as

ultralow or high temperature could easily cause the change of chemical structure and the three-dimensional configuration and also lead to the side reactions; Long reaction time reduces the yield of product; Tedious operation results in the control difficult. However, in the demethylation of DHPS′ s synthesis, by-products would be produced with increasing reaction temperature and time, and which led to the reduction of yield [11]. Therefore, it not only has theoretical significance, but also has practical value to explore a simple, mild, efficient and rapid demethylation method.

Microwave technology, as early as 1987, had been used as a rapid method for hydrolysing of peptide and protein [12, 13], has many advantages such as clean process, high efficiency, low energy consumption and less pollution [14, 15]. It not only opens up a new field of organic synthesis, but also has been widely used in various branches of chemistry [16-18]. Compared with traditional methods of heating, organic reaction under microwave radiation improves times or even thousands of times. Meanwhile it has advantages of high yield, reaction selectively, simple post-processing, less byproducts as well as saving energy consumption, so the microwave has been widely used in organic synthesis and developed rapidly [19, 20].

In this paper, DHPS **1** was synthetized from *3,5-dihydroxyl-4-isopropyl benzoic acid* which was used as the raw material, treated by methylation, reduction, chlorination and Wittig-Horner reaction to give the precusor **2**. The demethylation of **2** with $AlCl_3$ and *N,N-dimethyl anilineaniline*, or *pyridine hydrochloride* under microwave irradiation was conducted to give the product DPHS (as shown in Scheme 1). The yield was improved obviously compared to that with conventional heating. This method was never reported in previous literatures and this article focused on the demethylation reaction and the optimal reaction condition of that was determined.

EXPERIMENTAL SECTION

General

Solvents and reagents were commercially available and used without further purification. The *toluene, N,N-dimethyl aniline, $AlCl_3$, pyridine hydrochloride* and *ethyl acetate* were provided by Hebei Yongda Chemical Ltd. Co. The microwave oven (NJL07-3) was manufactured in Nanjing Jiequan Microwave Equipment Ltd. Co. The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained using a Bruker Avance (DRX-500) spectrometer operating at 500.13 MHz. HPLC was performed by using Aligen LC-20AT systems at the wavelength of 318 nm. The column was Hypersil BDS C18 (5 μm, 250× 4.6 mm) and the column temperature was 25 °C. The mobile phase was a mixture of acetonitrile/water (60/40, *V/V*) at a flow rate of 1.0 mL·min^{-1} and the injection volume was 5 μL. Good linearity and precision were obtained for DHPS and the linear concentration of DHPS ranged from 1.05 mg·L^{-1} to 157.5 mg·L^{-1} (r=0.99995).

General Procedure

Synthesis of 2: The synthesis process was reported in literature [8].

Synthesis of DHPS (1)

General Procedure A

A mixture of *(E)-3,5-dimethoxy-4-isopropylstilbene* (300 mg, 0.01 mol) and *toluene* (15 mL) was placed into a 50 mL round bottom flask fitted with stoppers and the temperature was kept at 0± 2 ºC. *N,N-dimethyl aniline* (0.06 mol) was introduced into the mixture with stirring. 10 min later, $AlCl_3$ (0.06 mol) was added in three batches with 10 min between each interval. After stirring for 15 min, the ice bath was removed out and the temperature of reaction mixture was automatically rising to room temperature, then the mixture was heated to 110 ºC for several hours. After completed, the mixture was cooled to room temperature acidified with *HCl* (10%, 15 mL) and extracted with *ethyl acetate* (3× 20 mL). The combined organic layer was washed with water to neutral and evaporated to remove the solvent under vacuum to obtain the crude product. The content of DHPS was determined by HPLC and the yield was calculated according to the content. (Scheme 1)

General Procedure B

To the solution of *(E)-3,5-dimethoxy-4-isopropylstilbene* (300 mg, 0.01 mol) and *toluene* (15 mL), was added *N,N-dimethyl aniline* (0.06 mol). The mixture was stirred and the temperature was kept at 0±2 ºC. Then $AlCl_3$ (0.06 mol) was added in three batches with 10 min between each interval. After that stirring for 15 min, the reaction mixture was taken out from the ice bath and cooled to room temperature. Then the mixture was subjected to microwave irradiation at various powers and temperatures for the designated time intervals. The workup was the same as the procedure A. (Scheme 1)

General Procedure C

(E)-3,5-dimethoxy-4-isopropylstilbene (300 mg) and *pyridine hydrochloride* (1500 mg) were weighed then mixed.

The mixture was heated to 180 °C and lasted for several hours. Following that, the reaction mixture was cooled to room temperature acidified with *HCl* (10%, 15 mL) and extracted with *ethyl acetate* (3× 20 mL). The combined organic layer was washed with water to neutral and evaporated to remove the solvent under vacuum to obtain the crude product. The content of DHPS was determined by HPLC and the yield was calculated according to the content. (Scheme 1)

General Procedure D

(E)-3,5-dimethoxy-4-isopropylstilbene (300 mg) and *pyridine hydrochloride* (1500 mg) were weighed then mixed. The mixture was subjected to microwave irradiation at various powers and temperatures for the designated time intervals. The workup was the same as the procedure C. (Scheme 1)

DHPS, ^{1}H NMR ($CDCl_3$): δ 7.46, 2H, d, *J*=7 Hz; 7.25, 3H, m; 7.00, 1H, d, *J*= 16 Hz; 6.90, IH, d, *J*=16 Hz; 6.50, 2H, s; 4.90, 2H; 3.45, 1H, heptet, *J*=7 Hz; 1.30, 6H, d, *J*=7 Hz.

RESULTS AND DISCUSSION

The influencing factors such as microwave power, reaction temperature and time on demethylation of *(E)-3,5-dimethoxy-4-isopropylstilbene* with microwave irradiation were investigated in detail, and the optimal condition of reaction was established.

***$AlCl_3$* and *N,N-dimethyl aniline* as demethylation reagent**

High power microwave radiation is benificial to the reaction attribute to the rapid rise of temperature can promote the intermolecular vibration. However, exceedingly high temperature also promotes the side reaction resulting in the decrease of the yield. In the same way, when the reaction time is overlong, the yield of DHPS will be reduced due to the occurrence of polymerization. As shown in Fig. 1~3, at a certain microwave power, with the temperature increasing, the yields appear to have a decline trend after an initial ascent for a certain time. (Note: The microwave oven can not rise over 170 °C at the power of 400 W.)

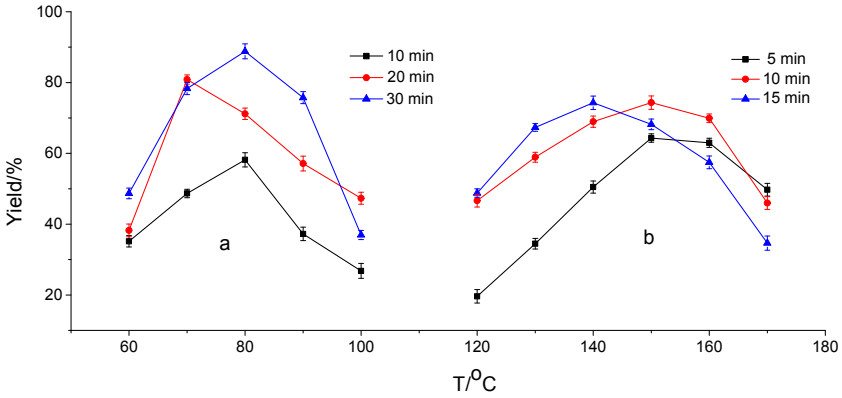


Fig. 1 Effects of temperature and time on the yield under 400 W: (a) *$AlCl_3$, N,N-dimethyl aniline;* (b) *Pyridine hydrochloride*; n=3

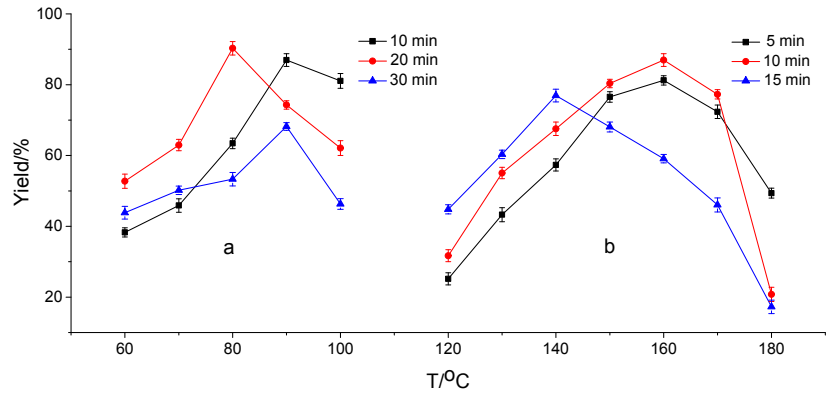


Fig. 2 Effects of temperature and time on the yield under 500 W: (a) *$AlCl_3$, N,N-dimethyl aniline;* (b) *Pyridine hydrochloride*; n=3

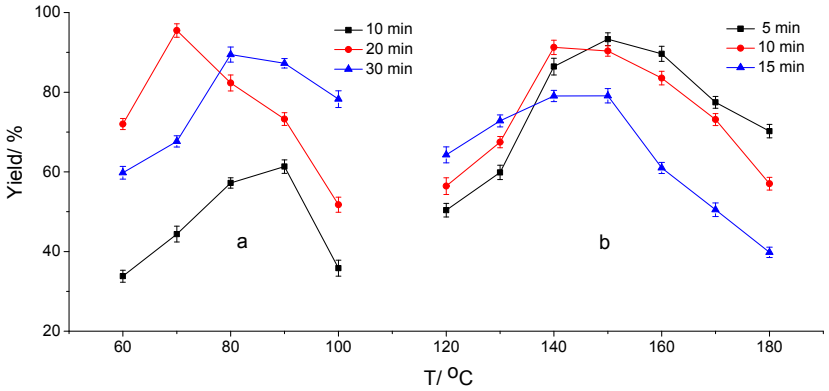


Fig. 3 Effects of temperature and time on the yield under 600 W: (a) *AlCl₃, N,N-dimethyl aniline;* (b) *Pyridine hydrochloride*; n=3

Tab. 1 Yields of demethylation by conventional heating

Demethylation reagents	T/ °C	* t/h	** Yield/%
AlCl₃ and *N,N-dimethyl aniline*	110	3	49.63
		4	59.72
		5	60.48
		6	54.22
		7	44.91
Pyridine hydrochloride	180	1	24.37
		2	49.60
		3	62.38
		4	55.95
		5	50.58

**Yield of DHPS.*
***Timed from reaching to the required temperature.*

The results of the experiments indicated that the optimal condition of demethylation for sythesis of DHPS using *AlCl₃* and *N,N-dimethyl aniline* as demethylation reagents is as follows: The microvewave power is 600 W, the reaction temperature is 70 °C and time is 20 min, and the yield of DHPS is 95.49 % corresponding to 60.48 % with conventional heating for 5 h at 110 °C (Tab. 1).

***Pyridine hydrochloride* as demethylation reagent**

By using pyridine hydrochloride as demethylation reagent, the yield of DHPS is relatively poor at lower temperature under microwave irradiation, because pyridine hydrochloride cannot melt at low temperature. However, the high temperature can also promote the side reactions, resulting in the decrease of the yield. Similarly, the overlong time leads to the polymerization and the decrease the yield. Under microwave irradiation, the yield increases with the temperature increasing at first, then shows a downward trend (shown in Fig. 1~3). (Note: The maximum limit of the microwave power is 700 W. For security reasons, the maximum power we employed was not exceed 600 W.)

As seen from the results above, the optimal synthesis condition of DHPS using *pyridine hydrochloride* as demethylation reagent is as follows: Under microwave irradiation, 600 W, 150 °C and 5 min is the best choice for the demethylation and the yield of DHPS is 93.33 %. In addition, compared with the microwave irradiation method, the best yield of DHPS is 62.38 % with conventional heating for 3 h at 180 °C (Tab. 1).

CONCLUSION

A rapid and efficient method for the synthesis of *(E)-3,5- dihydroxy-4-isopropylstilbene* using microwave irradiation by *AlCl₃* and *N,N-dimethyl aniline,* or *pyridine hydrochloride* as demethylation reagents has been described here. The experiment results indicate that microwave irradiation in contrast to conventional heating, could significantly shorten reaction time and reduce reaction temperature. And above all, desired products are obtained in excellent yields.

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