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Short Communication

Synthesis of Piceatannol (Trans-3,5,3’,4’-Tetrahydroxystilbene)

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Abstract

Piceatannol was synthesized from 3,5-dimethoxyaniline through diazotization, reduction, and acetylation reactions followed by the Mizoroki-Heck coupling reaction with 3,4-dimethoxystyrene and demethylation with boron tribromide, with an overall yield of approximately 32.0%. Its structure is characterized by infra-red spectroscopy, hydrogen nuclear magnetic resonance spectroscopy, and mass spectrometry.

Keywords: Piceatannol; 3,5,3’,4’-tetrahydroxy-stilbene; Mizoroki-Heck coupling reaction; 3,4-dimethoxystyrene

Introduction

Resveratrol (Res) is a polyphenolic organic compound, a phytoalexin produced by many plants in response to stress, with the chemical name 3,4’,5-trihydroxy-1,2-diphenylethylene (the structure is shown in Figure 1). It possesses a variety of important physiological functions, such as anti-cancer, antibacterial, reducing blood lipids, and preventing cardiovascular and cerebrovascular diseases [1,2]. *In vitro* experiments and animal experiments have shown that resveratrol can help to reduce cholesterol, to prevent thrombosis and to protect cardiovascular health. In recent years, as a lead compound with great development potential [3], resveratrol has attracted the attention of researchers who have been modifying its structure and resynthesizing it in hopes of obtaining resveratrol derivatives with higher activity for the treatment of various diseases.

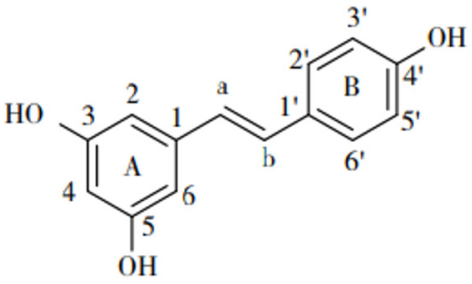

Figure 1: Structure of Resveratrol

Piceatannol (trans-3,5,3’,4’-tetrahydroxystilbene) (structure shown in Figure 2) is a naturally occurring small molecule compound with antileukemia activity [4,5]. It has been widely used clinically to treat a variety of malignant tumors, such as breast cancer, ovarian cancer, non-small cell lung cancer, etc. [6,7]. It can block the mitosis of tumor cells, thereby inhibiting tumor growth. In addition, it also has anti-inflammatory, anti-viral and immunomodulatory effects.

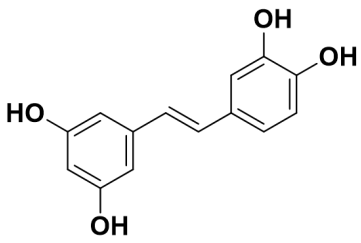

Figure 2: Structure of Piceatannol (1).

Several synthetic methods for Resveratrol derivatives have been developed. Piceatannol (3,5,3',4'-Tetrahydroxy-stilbene) has been prepared previously [8-11]. They simply use different materials and methods.

In this study, Piceatannol was synthesized from 3,5-dimethoxyaniline through diazotization, reduction, and acetylation reactions followed by the Mizoroki-Heck coupling reaction with 3,4-dimethoxystyrene and de-methylation with boron tribromide.

Results

By referencing the literature method, piceatannol was synthesized from 3,5-dimethoxyaniline (2) and 3,4-dimethoxystyrene as starting materials. 3,5-Dimethoxyaniline (2) was first treated with sodium nitrite and hydrochloric acid to yield 3,4-dimethoxybenzenediazonium chloride, which was reduced to 3,5-dimethoxyphenylhydrazine hydrochloric acid salt (3). After treatment with acetic anhydride in the presence of triethylamine, 3,5-dimethoxyphenylhydrazine hydrochloric acid salt (3) was acetylated to produce *N'*-(3,5-dimethoxyphenyl) acetohydrazide (4). Under the co-catalysis of $PdCl_2$ and CuI, the acetohydrazide (4) reacted with 3,4-dimethoxystyrene through a Mizoroki-Heck coupling reaction to yield the tetramethylated Piceatannol product (5). Finally, the tetramethyl-protected compound (5) was demethylated using boron tribromide (BBr_3) to afford piceatannol (1), trans-3,4',3,5-tetrahydroxystilbene. The synthetic route is depicted in Figure 3.

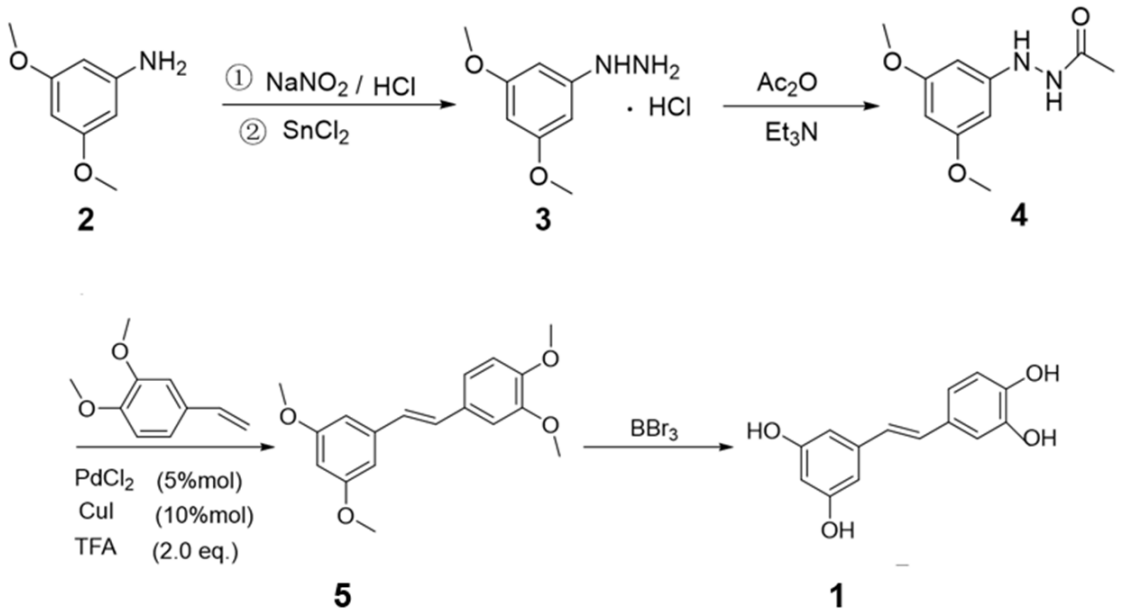

Figure 3: Synthetic Route.

Materials and Methods

Generals

All reagents used were of commercial chemical purity or analytical purity grade. ^1H and ^{13}C NMR analyses were performed using a Bruker ASCEND™ 400 MHz AVANCE III in deuterated chloroform ($CDCl_3$) as solvent with tetramethyl-silane (TMS) as an internal standard or in DMSO-d_6.

Synthesis of piceatannol [11]

Synthesis of 3,5-dimethoxyphenylhydrazine hydrochloric acid salt (3)

In a round-bottom flask equipped with a dropping funnel, a magnetic stirrer, and a thermometer, 6.0g (39.0mmol) of 3,5-dimethoxyaniline was added followed by 60ml of 6.0mol/L HCl. The resulting solution was stirred at room temperature. The temperature was controlled to less than 0 °C (in a 95% ethanol cool bath). A 15.0mL aqueous solution of 2.76g (40.0mmol) $NaNO_2$ was slowly added dropwise over approximately 20 minutes under stirring at below 0 °C for 1 hour. After the disappearance of the raw material by using thin-layer chromatography (TLC), a solution of 20.80g (109.7mmol) $SnCl_2$ in 120ml of 6mol/L HCl was added dropwise over approximately 30 minutes, during which a whitish solid gradually formed. After the addition was complete, the reaction proceeded at room temperature for about 16 hours. The reaction solution was then vacuum filtered, affording brown solid (5.7g, crude product). After recrystallization, 3.72g of pure product were obtained. The melting point was in the range (97-101) °C.

[1]HNMR (400 MHz, DMSO-d6) δ: 10.01 (s, 2H), 8.16 (s, 1H), 6.20~6.11 (m, 2H), 6.10 (t, J = 2.1Hz, 1H), 3.71(s, 6H); HRMS-ESI (m/z): C8H12N2O2 [M + H]+, Calculated molar mass: 169.0977g/mol, Found molar mass: 169.0950 g/mol.

Synthesis of N'-(3,5-dimethoxyphenyl) acetohydrazide (4)

In a 250ml round-bottom flask equipped with a dropping funnel, a magnetic stirrer, and a thermometer, 3.0g (15mmol) of 3,5-dimethoxyphenylhydrazine hydrochloric acid salt (3) prepared as described before and 60ml of dichloromethane were added. The solution was stirred at room temperature. Then, 5.00g (49.5mmol) of triethylamine were added. With the temperature controlled around 10 °C under a nitrogen atmosphere, 11.5g (113mmol) of acetic anhydride were slowly added dropwise. After the addition completed, the reaction mixture was further stirred at room temperature for 24 hours.

After the reaction was completed, 60ml of CH_2Cl_2 and 60ml of water were added for extraction. After allowing the mixture to stand until the layers separated, the lower organic phase was separated and washed successively with 60ml of saturated $NaHCO_3$ solution and with 60ml of saturated NaCl solution. The organic phase was then dried over anhydrous Na_2SO_4 overnight. After filtration and removal of the solvent, brown oily crude product was then purified using silica gel column chromatography technique, affording pure product 3.32g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.50 (d, *J*=2.1 Hz, 2H), 6. 44 (s, 1H), 3.76 (s, 6H), 2.16 (s, 3H); HRMS-ESI (*m/z*): $C_{10}H_{15}N_2O_3$ [M + H]+, Calculated molar mass: 211.1083g/mol, Found molar mass: 211.1090g/mol.

Synthesis of 3,4,3',5'-tetramethoxystilbene (5)

N'-(3,5-Dimethoxyphenyl)acetohydrazide (4) (4.00g, 23.8mmol) was dissolved in 30ml of DMSO. 0.210g (1.19mmol) of $PdCl_2$, 0.450g (2.37mmol) of CuI, and 3.50ml (45.4mmol) of TFA were then added into the solution. 3.50ml (21.5mmol) of 3,4-dimethoxystyrene was added to the reaction mixture. The reaction mixture was heated to 80 °C and maintained at this temperature for 12 hours. The progress of the reaction was monitored using thin-layer chromatography (TLC) with a solvent system of petroleum ether to ethyl acetate (3:1) until completion. After cooling the reaction system to room temperature and addition of water (60ml), the mixture was extracted with ethyl acetate (60ml × 2). The combined organic phase was washed with 60ml of saturated NaCl solution and 60ml of water. The organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified using silica gel column chromatography with a solvent system of petroleum ether to ethyl acetate (5:1), affording colorless crystals 4.6g, 77.2% yield and m.p. 53-55 °C (literature m.p. 54~57 °C) .

^{1}H NMR (600MHz, $CDCl_3$) δ: 7.05 (m, 1H), 7.03 (m, 1H), 7.00 (m, 1H), 6. 91 (m, 1H), 6.86 (m, 1H), 6.65 (d, J=2. 2Hz, 2H), 6. 38 (t, J=2. 2Hz, 1H), 3. 94 (s, 3H), 3.90 (s, 3H), 3. 83 (s, 6H); HRMS-ESI (m/z): $C_{18}H_{20}O_4$ [M + H]+ , Calculated molar mass: 300.348g/mol, Found molar mass: 300.349g/mol.

Synthesis of Piceatannol (trans-3,5,3',4'-tetrahydroxystilbene) (1)

Using intermediate (5) as the raw material, toluene as the solvent, and BBr3 for demethylation, piceatannol (1) is obtained. Synthetic route was shown in Figure 3. 0.500g (1.67mmol) of 3,4,3',5'-tetramethoxystilbene (5) was added into a round-bottom flask containing 5ml of toluene. The solution was stirred and the temperature was controlled to be below than 0 °C. Under nitrogen protection, 0.58ml (6.0mmol) of BBr3 was added via a syringe under good ventilation, and the mixture was stirred at the same temperature for 0.5 hour and continued stirring at room temperature for of saturated $NaHCO_3$ solution was slowly added dropwise. After standing, the organic layer was separated after 1.5 hours. After the reaction was complete, the reaction system was cooled to below 0 °C, and then raised to 15 °C to be melted, and the aqueous phase was extracted with ethyl acetate (2 × 15ml). The organic layers were combined and activated carbon (50mg) and an appropriate amount of anhydrous Na_2SO_4 were added. The resulting solution was stirred at room temperature for 0.5 hour. After filtration and removal of the solvent, a white solid was obtained. Pure product Piceatannol was obtained by recrystallization from acetonitrile. 0.31g was obtained with 62% yield and m.p. in the range 221–225 °C (literature m.p. range 223–228 °C).

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.20 (s, 2H, 3,5-OH), 9.08 (s, 1H, OH), 8.91 (s, 1H, OH), 6.95 (d, J=2.4 Hz, 2H), 6.84 (d, J=16.0 Hz, 1H), 6.83 (dd, J=8.0, 2.0 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.71 (d, J=16.0 Hz, 1H), 6.36 (d, J=2.4 Hz, 2H), 6.11 (t, J=2.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 158.1, 145.1, 145.0, 139.1, 128.6, 128.0, 125.5, 118.5, 115.5, 113.2, 104.2, 101.8.

Conclusion

With 3,5-dimethoxyaniline and 3,4-dimethoxystyrene as starting materials, 3,5-dimethoxyaniline was converted to N'-(3,5-dimethoxyphenyl)acetohydrazide, which further underwent the Mizoroki-Heck reaction with 3,4-dimethoxystyrene, generating tetramethyl-protected piceatannol. The target product piceatannol can be achieved by subsequent demethylation. This route has fewer reaction steps, relatively mild conditions, simple operation, relatively short reaction time and adheres to the principles of green chemistry.

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