Partial Synthesis of Farrerol As Antibronchitis Agent from Matteucinol Isolated from The Fern Chingia sakayensis Using Hydrobromic Acid Reagent

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Partial Synthesis of Farrerol As Antibronchitis Agent from Matteucinol Isolated from The Fern *Chingia sakayensis* Using Hydrobromic Acid Reagent.

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ABSTRACT

Partial synthesis of farrerol had been conducted using the starting material of matteucinol isolated from the stem of fern Chingia sakayensis. Synthesis of farrerol was conducted using two methods. In the first method, farrerol was synthesized using hydrobromic acid reagent and refluxed for 10 hours. While in the second method, it was used hydrobromic acid reagent in glacial acetic acid and refluxed for 4 hours. The farrerol resulted from synthesis was purified by recrystallization from chloroform and identified by spectroscopic methods (UV, IR, and MS)and comparing with literature data. Farrerol was obtained as pale yellow needles crystal with a melting point of 224-226 oC. The use of hydrobromic acid reagent in glacial acetic acid was more effective than just using hydrobromic reagent because of its value of percent yield bigger (87.7% vs 63.5%).

Keywords: farrerol, matteucinol, Chingia sakayensis, hydrobromic acid .

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INTRODUCTION

Chingia sakayensis (Zeiller) Holtt, is one of fern belonging to the Thelypteridaceae family, which grow in Thailand, Malaysia, Sarawak, Sumatra, and Java. It is typically grown in the forest, near streams, at an altitude of 150-1200 m above sea level [1]. Young leaves usually are eaten as a vegetable, either raw or cooked. Extracts of the old fronds in the water can be used to treat fever (antipyretics) and its decoction can be used as a tonic after childbirth [2]. Previous work, it had been separated a flavonoid compound namely matteucinol from dichloromethane extract of the *Chingia sakayensis*'s stem [3]. It was known as a major component in dichloromethane extract. Based on its molecular structure, the matteucinol has the potency to be used as a starting material for making farrerol through demethylation reaction of methoxy groups on the atom C-4'. Farrerol is one compound that known to have potential as an active agent of antibronchitis. Moreover it showed activities as expectorant, tyrosinase inhibitory, and cytotoxic against murine leukemia P-388 cells lines [4, 5]. The total synthesis of farrerol had been conducted from m-xylene, acetonitrile, and benzaldehyde as the starting materials [6]. However the partial synthesis farrerol from matteucinol had not been reported. In this paper, we reported the synthesis of farrerol using the matteucinol isolated from the dichloromethane extract of the *Chingia sakayensis*'s stem using reagent hydrobromic acid and hydrobromic acid in glacial acetic acid.

MATERIALS AND METHODS

Matteucinol was isolated from the dichloromethane extract of the *Chingia sakayensis'* stem. The other materials were used analytical grade and purchased from Merck: Hydrobromic acid (47%), glacial acetic acid, chloroform, methanol, ethanol, dichloromethane, sulphuric acid, hydrochloric acid, ferric chloride, sodium hydroxide, sodium acetate, boric acid, alluminium chloride, magnesium ribbon, precoated silica gel 60 F-254 (0.25 mm, 20 x 20 cm) and other materials. The equipments utilized in this experiment were the Fisher John melting point apparatus, UV-Vis spectrophotometer (Shimadzu Pharmaspec UV-1700), infra red spectrophotometer (Perkin Elmer USA 89485), and mass spectrometer (Shimadzu QP-2010S).

Synthesis farrerol from matteucinol using hydrobromic acid reagent

A portion of matteucinol isolates (1.00 g; 3.19 mmol) was inserted in the round bottom flask and added 50 mL of 47% hydrobromic acid. The mixture was refluxed for 4 hours at a temperature of 110 °C. The reaction mixture was allowed to cool at room temperature for 15 minutes, and then carefully poured on to crushed ice (200 g) for 24 hours. The resulting reddish yellow precipitate was filtered and collected. Recrystallization from chloroform afforded farrerol (606 mg; 63.5%).

Synthesis farrerol from matteucinol using hydrobromic acid reagent in acetic acid

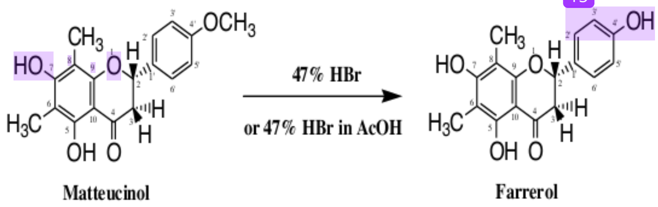
A portion of matteucinol isolates (1.00 g; 3.19 mmol) was inserted in the round bottom flask, then added 10 mL of glacial acetic acid and stirred gently for 1 minute. To this mixture was added 5 mL of 47% hydrogen bromide. The mixture was refluxed for 4 hours at a temperature of 110 °C. The reaction mixture was allowed to cool at room temperature for 15 minutes, and then carefully poured on to crushed ice (200 g) for 24 hours. The resulting reddish yellow precipitate was filtered and collected. Recrystallization from chloroform yielded farrerol (839 mg; 87.7%).

RESULTS AND DISCUSSION

The infra Farrerol had been synthesized from matteucinol using hydrobromic acid reagent and hydrobromic acid reagent in acetic acid. It was obtained as pale yellow needles crystall with melting point of 224-226°C. It was showed one spot at TLC with Rf : 0.38 (chloroform-ethylacetate = 5 : 1); 0.36 (*n*-hexane-ethyl acetate = 3 : 2), and 0.07 (*n*-hexane-ethyl acetate = 4 : 1). Farrerol was showed positive results with ferric chloride reagent and Shinoda test (Mg + HCl) gave pale green and pale red color, respectively. The UV spectrum (MeOH) λ_{max} (log ε) : 297 (3.76), 348 (bh) (3.08) nm; (MeOH + NaOH): 339 (3.96) nm; (MeOH+$AlCl_3$): 297 (3.70), 357 (bh) (3.00) nm; (MeOH+$AlCl_3$+HCl): 299 (3.67), 358 (bh) (2.97) nm; (MeOH+NaOAc): 339 (3.83) nm; (MeOH+NaOAc+H_3BO_3): 297 (3.75), 350 (bh) (3.37) nm. The IR spectrum (KBr) $\bar{\nu}_{max}$: 3425 (OH), 2924 (C-H alkyl), 1636 (chelated C=O), 1520 (aromatic C=C), 1458, 1366, 1234, 1119, 833

cm^{-1}. The mass spectrum (EIMS) showed peaks at *m/z* (rel. int.,%) : 300 (M^+) (82), 282 (3), 271 (1), 257 (3), 207 [$(M-C_6H_5O_3)^+$](6), 194 (12), 180 [$(M-C_8H_8O)^+$] (65), 152 [$(M-C_8H_8O-CO)^+$] (100), 154 (6), 136 (1), 120 [$(M-C_9H_8O_4)^+$] (24), 107 (6), 91 (18), 83 (12), 65 (12), 55 (12).

The positive results of the qualitative test with ferric chloride and test Shinoda supported that farrerol was a flavonoid compound. The EIMS spectrum showed a molecular ion peak at m/z 300, corresponding to farrerol which had a molecular formula $C_{17}H_{16}O_5$ (DBE = 10). The UV spectrum showed absorption characteristic for the flavanone type (DBE = 10) at 297 nm (band II) and 348 nm (bh) (band I) [7]. The CH alkyl absorption band (2924 cm^{-1}), chelated carbonyl (1636 cm^{-1}), and C = C aromatic (1520 cm^{-1}) in the IR spectrum strongly supports that the farrerol was a flavanones [8]. Bathochromic shift of band II (42 nm) on the addition of NaOH and NaOAc reagent showed a hydroxyl group at C-7. As with mateucinol, steric effect caused by the methyl group at C-6 of the hydroxyl group at C-5 is thought to cause a bathochromic shift in the addition of reagent ribbon II $AlCl_3$ + HCl was not significant (2 nm). The absence of a bathochromic shift in the addition of reagent NaOAc + H_3BO_3 support that farrerol compound did not have an ortho-dihydroxy groups on the ring A. Fragmentation pattern shown in the spectrum EIMS supported that the compound synthesized was farrerol.



Matteucinol

Farrerol

The percent yield of farrerol by using reagent 47% hydromic acid in glacial acetic acid was 87,7%, while the use of reagent 47% hydromic acid was produced farrerol with percent yield of 63.5%. Thus the first reagent was more effective than the second. The addition of glacial acetic acid is needed to improve the effectiveness of hydromic acid as reagent on the demetilation reaction. The existence of glacial acetic acid is able to increase the acidity of hydrobromic acid than if it simply mixed with water. The increasing of acidity of hydrobromic acid cause the increasing of its protonated ability so that the $O-CH_3$ bond is weaker and easily broken to produced the hydroxyl group after bromide ion as nucleophile attacks the carbon atom of methyl group that has partially positive charge. The use of glacial acetic acid in demetilation reaction of ether using hydromic acid is supported by several previous studies. The demethylation reaction using 48 % HBr in acetic acid conducted by heating in reflux for 4 hours could produce 4-fluororesorcinol wih percent yield of 87% [9]. In addition the oroxylin A can be obtained by demethylation of 5,6,7-trimethoxyflavone using 47 % HBr in acetic acid (1 : 2) refluxed for 2 hours with percent recovery of 88% [10].

CONCLUSION

Based on the results of this study concluded that the farrerol can be synthesized from a matteucinol isolated from the dichloromethane extract of the *Chingia sakayensis*'s stem using reagent 47% hydrobromic acid and reagent 47% hydrobromic acid in glacial acetic acid. Farrerol compound is obtained as a pale yellow needle crystals with a melting point of 224-226°C. The reagent 47% hydrobromic acid in glacial acetic acid more effective than reagent 47% hydrobromic acid, because produced the bigger percent yield.

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