IMPROVED SYNTHESIS OF 2',6'-DIHYDROXY-3,4-DIMETHOXY CHALCONE BY GRINDING TECHNIQUE TO SYNTHESIZE 5-HYDROXY-3',4'-DIMETHOXY FLAVONE

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ABSTRACT

5-hydroxy-3',4'-dimethoxy flavone can be efficiently synthesized in two steps via the formation of 2',6'-dihydroxy-3,4-dimethoxy chalcone with good results. 2',6'-dihydroxy-3,4-dimethoxy chalcone as reactants for synthesis of flavones was prepared through Claisen-Schmidt condensation reaction between 2,6-dihydroxyacetophenones,3,4-dimethoxybenzaldehyde and solid NaOH in mortar for 15 min. The yield of the product (70%) is higher than conventional method (65%). This chalcone then oxidatively cyclized with iodine to form 5-hydroxy-3',4'-dimethoxy flavone (yield 62%). Compounds synthesized were characterized by spectroscopic (IR, ^{1}H-NMR, and ^{13}C-NMR).

Keywords: *chalcone; flavone; Claisen-Schmidt; grinding*

ABSTRAK

5-hidroksi-3',4'-dimetoksi flavon dapat disintesis dengan efesien dalam dua tahap melalui pembentukan 2',6'-dihidroksi-3,4-dimetoksi kalkon dengan hasil yang baik. Senyawa 2',6'-dihidroksi-3,4-dimetoksi kalkon sebagai reaktan untuk sintesis flavon disiapkan dari reaksi kondensasi Claisen-Schmidt antara 2,6-dihidroksiasetofenon, 3,4-dimetoksibenzaldehid dan NaOH padat dalam mortar selama 15 menit. Rendemen produk baik (70%) dibandingkan dengan metode konvensional (65%). Kalkon ini kemudian disiklisasi secara oksidatif dengan adanya iodin untuk membentuk 5-hidroksi-3',4'-dimetoksi flavon (rendemen 62%). Senyawa hasil sintesis dikarakterisasi secara spektroskopi (IR, ^{1}H-NMR, dan ^{13}C-NMR).

Kata Kunci: *kalkon; flavon; Claisen-Schmidt; grinding*

INTRODUCTION

Flavone is a class of flavonoids, the important group of plant secondary metabolites that occur naturally in fruits, vegetables, nuts, flowers, and bark. The flavone has been extensively investigated due to posses' varied biological and pharmacological activities, such as antioxidant [1], antiinflammatory [2], and antibacterial [3].

The flavone can be obtained from nature mainly and synthesis secondly. Different strategies are used for the synthesis of flavones, such as the Kostanecki reaction, the Baker-Venkataraman rearrangement, and synthesis via chalcones. The synthesis of flavone is carried out mostly by oxidative cyclisation of 2'-hydroxy chalcone, an important route for the synthesis of flavones with oxidizing agents such as SeO_2, DDQ, oxalic acid, I_2-DMSO, Sodium periodate, $FeCl_3$, etc. Many flavone derivatives have been synthesized using I_2-DMSO and give good yield [4-6].

The chalcone is an important group of natural product, as on starting materials in the synthesis of various heterocyclic compounds. This compounds well known to exhibit various pharmacological activities such as antioxidant [7], anticancer [8], antimicrobial [9-10], and insecticide [11]. The chalcone was synthesized from 2-hydroxyacetophenone and benzaldehyde under Claisen–Schmidt condensation. The Claisen–Schmidt condensation has played an important role in synthetic organic compound. The reaction are classically catalyzed by aqueous bases like KOH, NaOH, $Ba(OH)_2$. These reactions suffer from the use of strong bases, long reaction time and low yields. In a previous study found that the synthesis of 2',4'-dihydroxy-3,4-dimethoxy chalcone and 2',5'-dihydroxy-3,4-dimethoxy chalcone using conventional methods require a base with a high concentration (up to 50%, w/v), longer reaction (24-48 h) and a small yield (40-50%) [12-13]. Therefore, the grinding

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technique for efficient synthesis of chalcone is really wanted to develop, environmentally friendly organic reaction methods.

In grindstone technique, reactions are initiated by grinding, occurs through generation of local heat by grinding of crystals of substrate and reagent by mortar and pestle. The reaction are simple, reduce pollution, shorter reaction, and better yield. This method has been successful in synthesizing some new chalcone of 2-acetyl-1-naphthol and benzaldehyde substituted with high yields (84-95%) in short reaction times (4-8 min) [14].

The problem of the research is whether the synthesis of 2',6'-dihydroxy-3,4-dimethoxy chalcone can be improved by grinding method. We focus on developing the novel procedure for synthesis of 2',6'-dihydroxy-3,4-dimethoxy chalcone by condensation of 2,6-dihydroxyacetophenone and 3,4-dimethoxybenzal dehyde under grinding technique. We wish to report the synthesis due to the importance of the 2',6'-dihydroxy-3,4-dimethoxy chalcone as precursor for various natural product like 5-Hydroxy-3',4'-dimethoxy flavone.

EXPERIMENTAL SECTION

Materials

2,6-dihydroxyacetophenone, 3,4-dimethoxybenzal dehyde, sodium hydroxide, sodium thiosulphate, HCl, anhydrous Na_2SO_4, silica gel 60-F254, Iodine, ethanol, ether, dimethylsulfoxide, EtOAc, $CDCl_3$, TMS, KBr pellets, *n*-hexane, acetone. General chemicals were purchased from Merck or Aldrich, and were used without further purification. All solvents (Merck) were used without further purification.

Instrumentation

IR spectra was recorded on a Fourier-transform infrared spectrometer (Shimadzu FTIR-8201 PC) in KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were performed JEOL JNM ECA500 instrument using $CDCl_3$ as solvent and Tetramethylsilane (TMS) as internal reference.

Procedure

Synthesis of 2',6'-dihydroxy-3,4-dimethoxy chalcone using grinding method

A mixture of 2,6-dihydroxyacetophenones (5 mmol), 3,4-dimethoxybenzaldehyde (10 mmol) and solid pallete of NaOH 20 mmol) was ground with a mortar and pestle for 15 min at room temperature. The obtained solid mixture was diluted with cold water, acidified with cold HCl (10%), and extracted with ether. The ether layer was washed with water, followed by drying over anhydrous Na_2SO_4 and the solvent was evaporated. The reaction mixture was purified by Column chromatography on a silica gel column (*n*-hexane:acetone, 6:4), followed by recrystallization. Characterization used by UV-Vis, IR, NMR Spectroscopy.

Synthesis of 2',6'-dihydroxy-3,4-dimethoxy chalcone using conventional method

A mixture of 2,6-dihydroxyacetophenones (10 mmol), 3,4-dimethoxybenzaldehyde (10 mmol) were stirred in ethanol (15 mL) and then 12 mL sodium hydroxide (50%, w/v) were added. The reaction mixture was stirred at room temperature and left at room temperature for 24 h. The mixture was poured into iced water, acidified with cold HCl (10%), extracted with ether. The ether layer was washed with water, followed by drying over anhydrous Na_2SO_4 and the solvent was evaporated. The reaction mixture was purified by Column chromatography on a silica gel column (*n*-hexane:acetone, 6:4), followed by recrystallization.

Synthesis of 5-hydroxy-3',4'-dimethoxy flavone

2',6'-dihydroxy-3,4-dimethoxy chalcone (0.01 mmol) was suspended in 10 mL DMSO and then I_2 (250 mg) were added. The mixture was reflux for 1 h and poured into water, and the resulting syrup was extracted with EtOAc. The organic phase was washed with sodium thiosulphate solution (20%) and water. The mixture was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The compound purified by column chromatography and recrystallization. The product was characterized by IR, NMR Spectroscopy.

RESULT AND DISCUSSION

2',6'-dihydroxy-3,4-dimethoxy Chalcone

The synthesis of 2',6'-dihydroxy-3,4-dimethoxy chalcone involves the grinding of a mixture of 2,6-dihydroxyacetophenones with 3,4-dimethoxybenzal dehyde, and sodium hydroxide in a mortar and pestle for 15 min at room temperature. The yield of the product is good (70%), after purification by column chromatography and recrystallization. On the other hand, synthesis of 2',6'-dihydroxy-3,4-dimethoxy chalcone by conventional require organic solvent, a base with a high concentration (50%, w/v), longer reaction (24 h) and a small yield (65%).

Synthesis of chalcone using grinding technique has been carried out for the synthesis of 2',4'-dihydroxy-3,4-dimethoxy chalcone and 2',5'-dihydroxy-3,4-dimethoxy chalcone. The technique is simple, reduce pollution, requires no special apparatus, the procedures are more economical and environmentally friendly. The grinding technique does not use organic

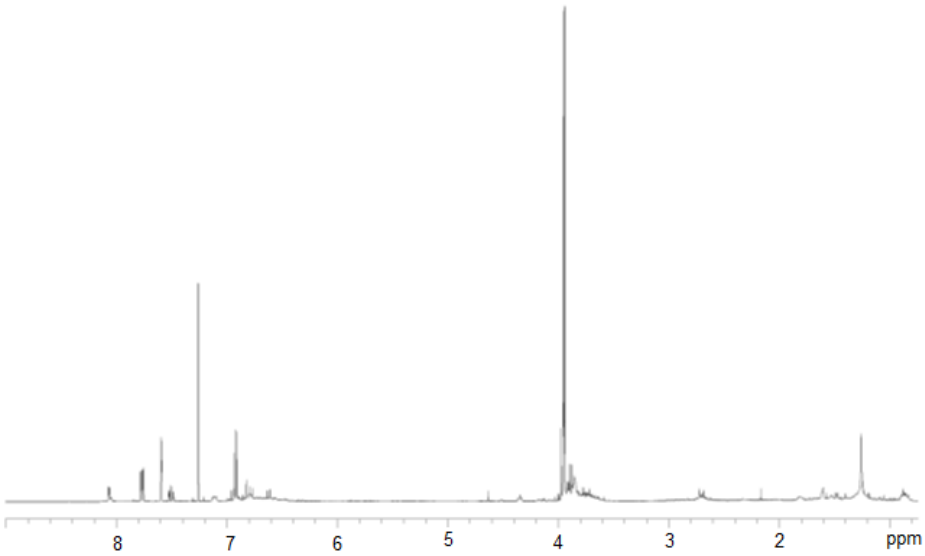


Fig 1. [1]H-NMR spectrum of 2',6'-dihydroxy-3,4-dimethoxy chalcone

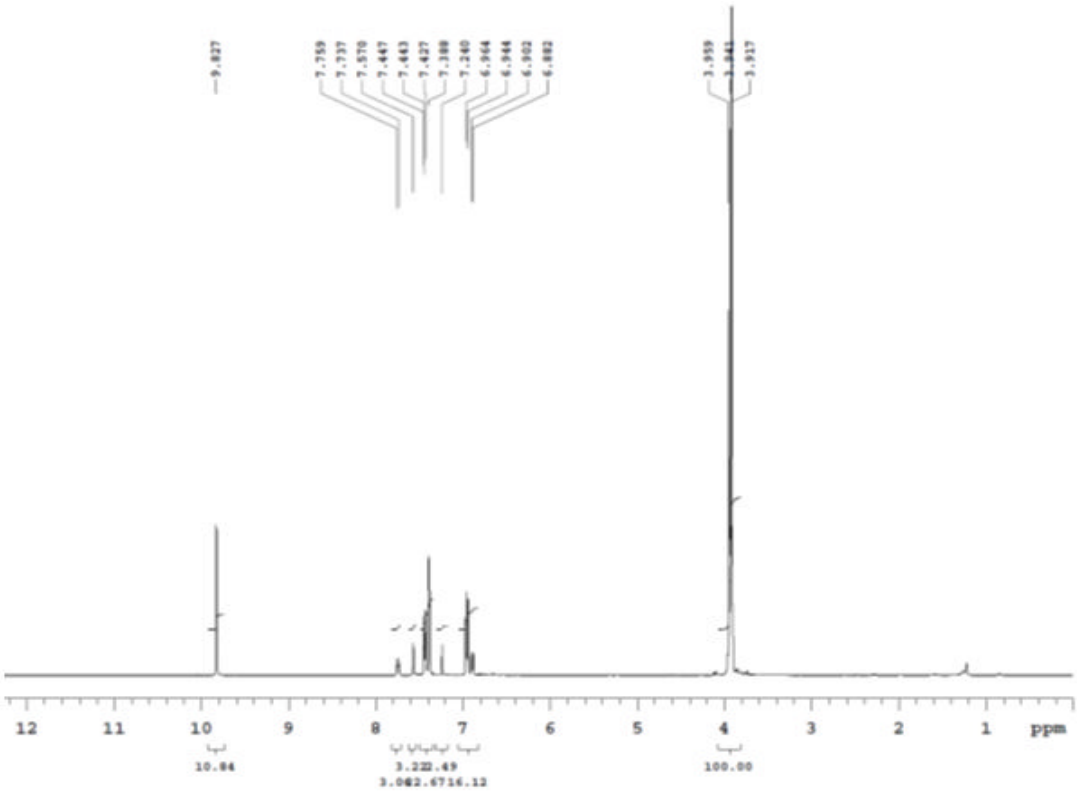


Fig 2. [1]H-NMR spectrum of 5-hydroxy-3,4-dimethoxy flavone

solvents, the reaction starts with the grind, with a small amount of energy through friction, generating local heat when grinding crystal substrates and reagents with a mortar and pestle. The synthesis using the grinding requires a low base concentration, shorter reaction (15 min) and higher yield (70-84%). Synthesis of this chalcone using grinding method is better than the conventional method [15].

The compounds synthesized in the form of giving a yellow orange color with Mg/HCl, showed positive flavonoids. Structures of the synthesized compounds were confirmed by spectral data. The IR spectrum of the compound displayed stretching bands for hydroxyl group at 3425 cm^{-1} and carbonyl group at 1674 cm^{-1}. Its IR spectrum also showed bands for C-H aliphatic at 2939 cm^{-1}, C=C group at 1427 cm^{-1}, and C-0 stretching

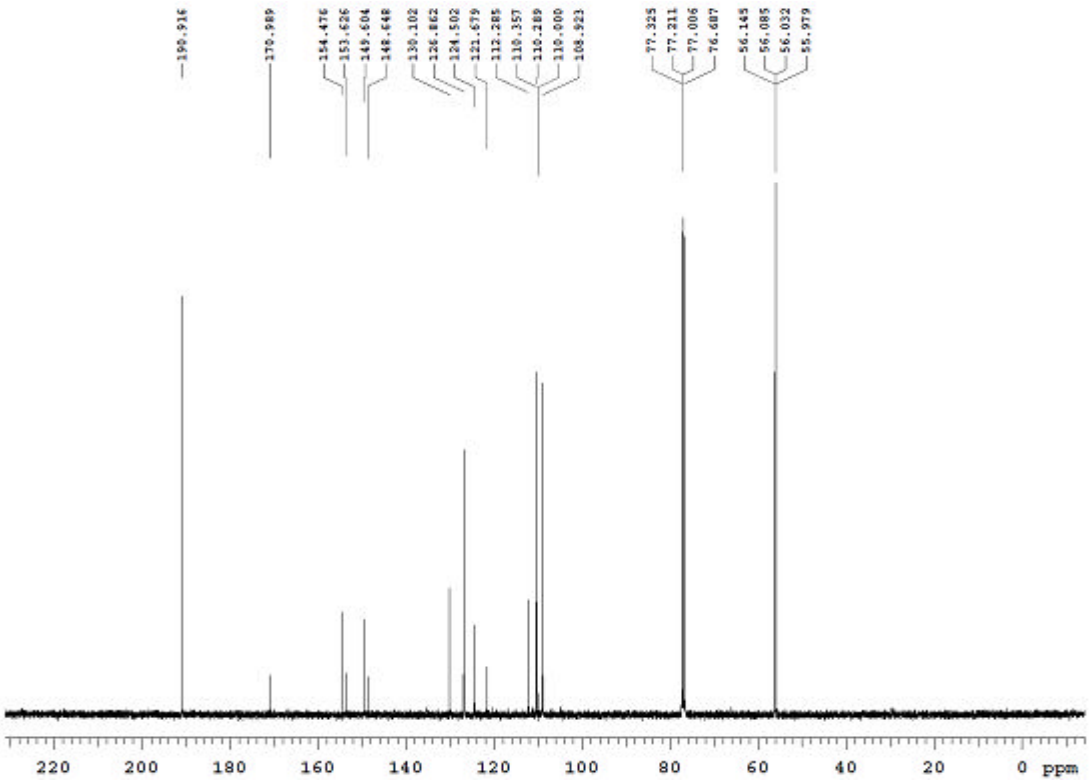
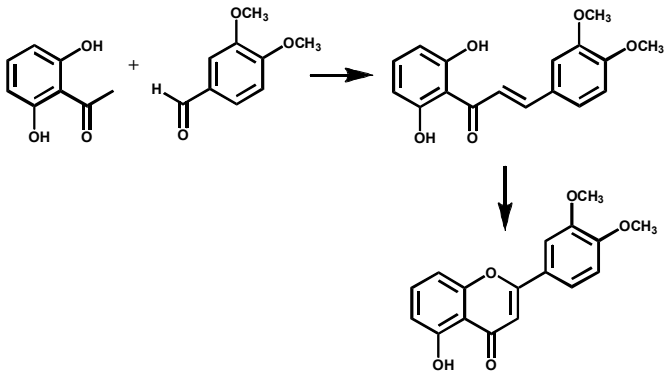


Fig 3. ^{13}C-NMR spectrum of 5-hydroxy-3,4-dimethoxy flavone



Scheme 1. Route to synthesis of 5-hydroxy-3',4'-dimethoxy flavones

at 1026 cm^{-1}. The ^{1}H-NMR spectrum of the chalcone (Fig. 1) explained the presence of two methoxyl groups in the B ring at δ 3.8 and 3.9 integrating for 6 protons. The olefinic proton of α,β-unsaturated ketone were clearly observed at δ 7.77 (1H, H-α) and δ 7.75 (1H, H-β) corresponding to H-α and H-β. Based on the above spectral evidences, it can be concluded that synthesized compound characterized as 2',6'-dihydroxy-3,4-dimethoxy chalcone.

5-hydroxy-3',4'-dimethoxy Flavone

Cyclisation of 2',6'-dihydroxy-3,4-dimethoxy chalcone into 5-hydroxy-3',4'-dimethoxy flavone was carried by using iodine in DMSO. The compound has reacted completely after one hour when the reaction was checked on TLC (Scheme 1). IR spectrum of the compound showed characteristics of carbonyl (1681 cm^{-1}), aromatic C=C (1589 and 1465 cm^{-1}), and C-O (1273 cm^{-1}) functionalities. The presence of hydroxyl group was indicated by band at 3464 cm^{-1}. The ^{1}H-NMR spectrum of flavone (Fig. 2) showed the presence of proton methoxy at δ 3.9. The aromatic protons of A ring at δ 7.7 (1H, C-7), 7.2 (H, C-6) and 6.9 (1H, C-8), whereas the three aromatic proton of the ring B appeared at δ 7.5 (1H, C-6'), 7.4 (1H, C-2') and 7.3 (1H, C-5'). The ^{13}C-NMR spectrum of flavone (Fig. 3) showed the presence of 17 different carbons. The signals for one carbonyl at δ 190.9, and signals for methyl carbons at δ 56.0. The spectrum indicated the presence seven quaternary carbon at δ 170.9 (C-8a), 154.4 (C-5), 153.6 (C-2), 149.6 (C-3^{1}), 148.6 (C-4^{1}), 126.8 (C-1^{1}), 110.3 (C-4a), and seven methine carbons at δ 130.1 (C-7), 124.5 (C-6^{1}), 121.6 (C-2^{1}), 112.2 (C-5^{1}), 110.2 (C-6), 110.0 (C-8), and 108.9 (C-3). Based on the above spectral evidences, it could be concluded that synthesized compound characterized as 5-hydroxy-3',4'-dimethoxy flavone.

CONCLUSION

2',6'-dihydroxy-3,4-dimethoxy chalcone has been synthesized by grinding technique, which may be used

an alternative to the existing methods because a simple reaction condition and higher yield. The grinding method for synthesis of 2',6'-dihydroxy-3,4-dimethoxy chalcone better than conventional methods. Cyclisation of the compound have formed 5-hydroxy-3',4'-dimethoxy flavone. The synthesized compounds were characterized by UV-Vis, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

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