



## Synthesis of 5-Hydroxy-4-methoxy- $\alpha$ -methyl-(1,2-benzobutane sultone) from Eugenol and Eugenil Acetate

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The purpose of this study was to develop an efficient synthesis route to pharmacologically interesting sultone derivatives from readily accessed natural products. Synthetic approach of 5-hydroxy-4-methoxy- $\alpha$ -methyl-(1,2-benzobutane sultone) *via* eugenol (**1**) produced only in moderate yield (64 %). On the other hand synthetic approach *via* eugenil acetate (**2**) gave 5-hydroxy-4-methoxy- $\alpha$ -methyl-(1,2-benzobutane sultone) in high yield (96 %). Eugenol approach involved only one step reaction due to direct reaction of eugenol with chlorosulfonic acid but in eugenil acetate approach involved two-step reactions due to its preparation of eugenol before reaction with chlorosulfonic acid. Eugenil acetate was prepared smoothly in good yield by esterification of phenolic group of eugenol with acetic anhydride in the presence of sodium bicarbonate. A variety of bicarbonate catalysts such as NaHCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub> were investigated in O-acetylation of eugenol to afford eugenil acetate (84 %), (72 %) and (88 %), respectively. Structures of all the products have been established by spectral and GC-MS analysis data.

**Keywords:** Comparison reaction, Eugenol, Eugenil acetate, Cyclic sulfonic ester, Sultone, Markovnikov.

### INTRODUCTION

Eugenol (4-allyl-2-methoxyphenol) (**1**), a constituent of clove, has been used as a fine chemical for further chemical transformation [1-4]. Eugenol (**1**) has three reactive functional groups namely: alcohol as a phenol, phenyl and alkene as an allyl. These reactive functional groups can compete each other and will disturb further reaction such as on reaction of eugenol with chlorosulfonic acid to form sultone derivative.

In continuation of our work to increase the yield of sultone derivative (**3**), which previously prepared directly from eugenol, synthesis of this compound *via* Markovnikov addition of chlorosulfonic acid to eugenil acetate (**2**) was reported. This synthesis involved two steps reaction: firstly direct protection of phenolic group of eugenol by acetic anhydride to form eugenil acetate and secondly Markovnikov addition of chlorosulfonic acid to eugenil acetate.

Phenols are potentially reactive towards electrophilic aromatic substitution. This is because the hydroxy group, -OH, is a strongly activating, *ortho*- or *para*- directing substituent. Protection of phenols is one of the most common synthetic

strategies utilized to mask hydroxyl functionalities during multistep synthetic procedures. In addition, O-acetylation procedures are widely employed for the protection and purification of various natural and synthetic products. Solvent-free O-acetylation of alcohols, phenols and thiols using catalytic amounts of sodium acetate trihydrate gave good yields [5]. A variety of primary alcohols and phenols were reacted with acetic anhydride at room temperature in the presence of sodium bicarbonate to produce corresponding esters and eugenol was reacted with acetic anhydride at room temperature in the presence of sodium bicarbonate to produce corresponding esters in good to excellent yields [6]. A series of eco-friendly solid acid catalysts including: Preyssler, Wells-Dowson and Keggin HPAs have been used as catalysts for acetylation of alcohols, phenols and salicylic acid with acetic anhydride [7]. Acylation of eugenol with Ac<sub>2</sub>O/Py/DMAP in dichloromethane at room temperature gave eugenil acetate in high yield (98 %) [8].

Eugenil acetate (4-allyl-2-methoxyphenyl acetate) has an asymmetrically substituted alkenes which can undergoes Markovnikov addition by strong acid such as chlorosulfonic

acid (H-O-SO<sub>2</sub>Cl), which states that when a strong acid is added to an asymmetrically substituted alkene, the major product results from the addition of hydrogen atom to double-bonded carbon that is attached to more hydrogen atoms [9]. Furthermore, a sultone derivative (**3**) was formed from this addition. Sultones are heterocyclic compounds and are internal esters of the corresponding hydroxy sulfonic acids [10]. Sultones are reactive intermediates having commercial applications in detergents, polymers, antistatics and other industrial applications [11].

In the present work, an effort for design and synthesis of biologically active sultone derivative from eugenol and eugenil acetate will be discussed.

## EXPERIMENTAL

The material used included: clove, dichloromethane, hexane, methanol, acetonitrile, acetate anhydride, ethanol, sodium hydroxide pellet, hydrochloric acid, sodium hydrogen carbonate anhydrous, ethyl acetate, sodium carbonate anhydrous, chlorosulfonic acid, analytical thin layer chromatography, silica gel chromatography.

**General procedure:** Dried clove buds were ground into fine particles (powder) for extraction. Clove powder (150 g) were percolated with dichloromethane (1 L) and stored away from light for 2 × 24 h. The result then filtered and the filtrate was evaporated with rotary evaporator to obtain the brownish clove oil (32 g; 21 %).

**Isolation of eugenol (1):** Clove oil (21 g) were dissolved in dichloromethane (65.7 mL). The mixture was added with NaOH (5.36 g), which had been dissolved with H<sub>2</sub>O (39 mL). Mixture was stirred with magnetic stirrer for 60 min in room temperature. Two layers were formed where the aqueous phase in the top layer was separated from the organic phase in the bottom layer. The aqueous phase that contains eugenol salt was acidified with concentrated HCl to pH 3. The organic layer was then separated from the aqueous layer with separation funnel. The remaining aqueous layer then extracted with dichloromethane (15 mL, 3x). The crude eugenol then filtered with dichloromethane: *n*-hexane (1:1) through silica gel mixture and evaporated with rotary evaporator to afford yellowish oil (18.3 g, 83.7 %). The oil was analyzed by TLC. TLC analyses showed eugenol sample R<sub>f</sub> 0.72 and eugenol standard R<sub>f</sub> 0.72 (eluent: CH<sub>2</sub>Cl<sub>2</sub>).

**Synthesis of eugenil acetate (2):** This reaction was conducted by adopting method from Lugenwa *et al.* [6]. A mixture of eugenol (1 g, 6.10 mmol), acetate anhydride (3 g, 30 mmol), K<sub>2</sub>CO<sub>3</sub> (1 g, 12 mmol), ethyl acetate (75 mL) was stirred at room temperature for the 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the filtrate was evaporated by rotary evaporator. The residue was added dichloromethane (25 mL) and water (10 mL) and the phases separated. The organic layer was dried (Na<sub>2</sub>CO<sub>3</sub>) and concentrated to afford syrup (1.1 g, 5.34 mmol, 87.5 %). The syrup was analyzed by TLC and GC-MS. TLC analyses showed eugenil acetate sample R<sub>f</sub> 0.78 (eluent: CH<sub>2</sub>Cl<sub>2</sub>). GC-MS: M<sup>+</sup> 206, cal for C<sub>12</sub>H<sub>14</sub>O<sub>3</sub>, major fragments : 164 (base peak), 149, 131, 121, 103, 91, 77.

**Synthesis of cyclic sulfonic ester or sultone derivative (3):** This reaction was conducted by adopting method from

Sudarma *et al.* [1]. To stirred solution of eugenil acetate (**2**) (500 mg, 2.43 mmol) in dichloromethane (25 mL) was added chlorosulfonic acid (2.5 mL) drop by drop. The solution was stirred at room temperature for 30 min then refluxed for 15 min. The solution was evaporated and water (15 mL) then added, basified to pH 8 with 1 M sodium hydroxide, then extracted with dichloromethane. The organic phase was dried and evaporated to dryness to give an amorphous brown solid (96 %). Compound (**3**), GC-MS: M<sup>+</sup> 244, cal for C<sub>10</sub>H<sub>12</sub>SO<sub>5</sub> Major fragments: 200, 183, 165, 151, 136 (base peak). IR (film), ν<sub>max</sub>, cm<sup>-1</sup>: 3232 (O-H), 3084 (C=CH-Ar), 2936, 2829, 1399, 1327, 1260 (C-O), 1127 (C-O), 1066, 999, 912, 764. <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>): δ 1.62 (3H, d, *J* 6.6 Hz, -CH<sub>3</sub>); 2.16 (1H, s, OH); 2.85 – 2.31 (2H, m, -CH<sub>2</sub>-); 3.93 (3H, s, -OCH<sub>3</sub>); 5.20 (1H, m, -CH-); 6.60 (1H, s, ArH); 7.33 (1H, s, ArH). <sup>13</sup>C NMR (400.1 MHz, CDCl<sub>3</sub>): δ 21.3 (-CH<sub>3</sub>); 35.6 (-CH<sub>2</sub>); 56.4 (-CH-); 110.1 (ArCH); 110.6 (ArCH); 126.8 (ArC); 127.2 (ArC); 145.4 (ArC); 150.1 (ArC).

## RESULTS AND DISCUSSION

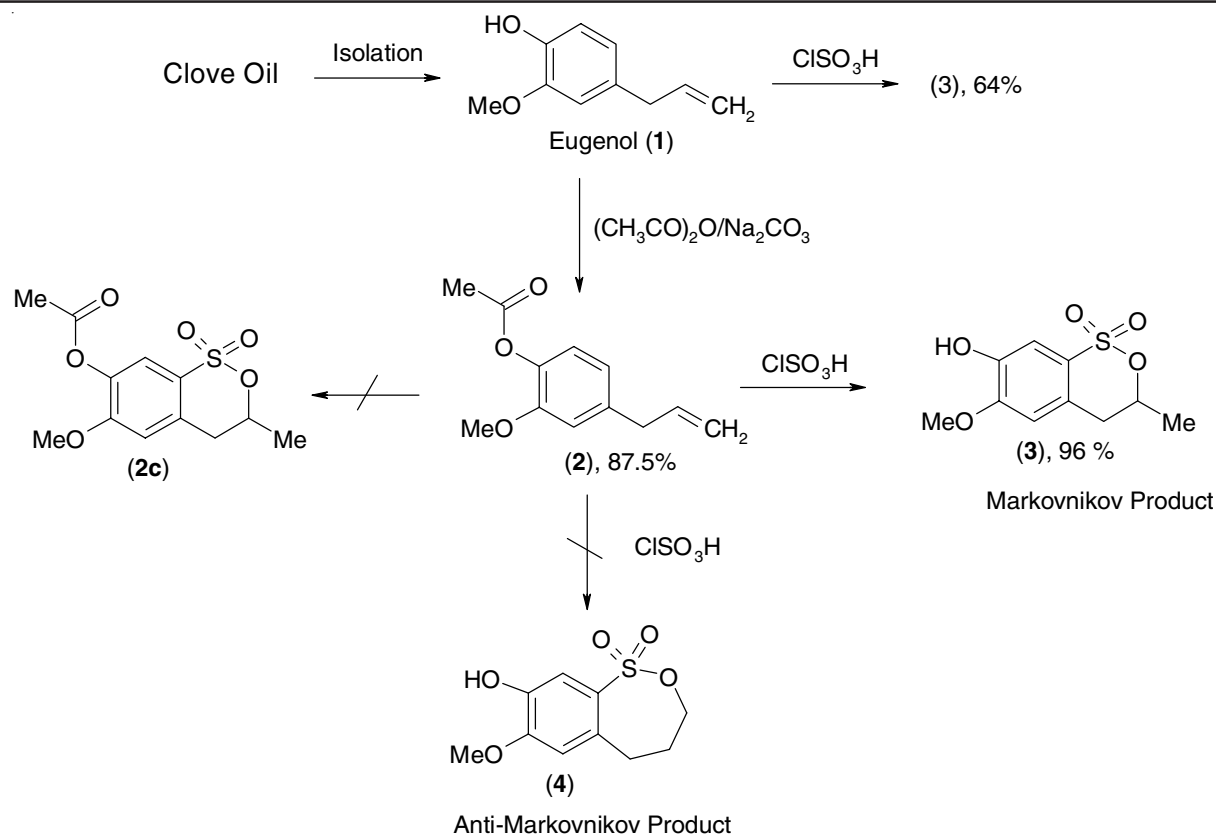
Eugenol (**1**) was extracted and isolated from clove oil in good yield (83.7 %). The presence of -OH group as a phenol in eugenol (**1**) is potentially decreased the yield of sultone because this functional group is very reactive towards electrophilic aromatic substitution, oxidation, *etc.* To increase the yield of sultone, presumably the -OH group of eugenol (**1**) has to be protected. Protection of hydroxyl is one common synthetic strategies utilized to mask hydroxyl functionalities during further step synthetic procedures. Esterification is one way to protect the -OH of eugenol. A varies of catalyst were employed to increase the yield of esterification of eugenol by acetate anhydride. Eugenol was reacted with acetic anhydride at room temperature in the presence of bicarbonate catalyst to produce corresponding esters or eugenil acetate (**2**) in moderate to good yield (Table-1).

TABLE-1  
ACETYLATION OF EUGENOL (**1**)  
TO BE EUGENIL ACETATE (**2**)

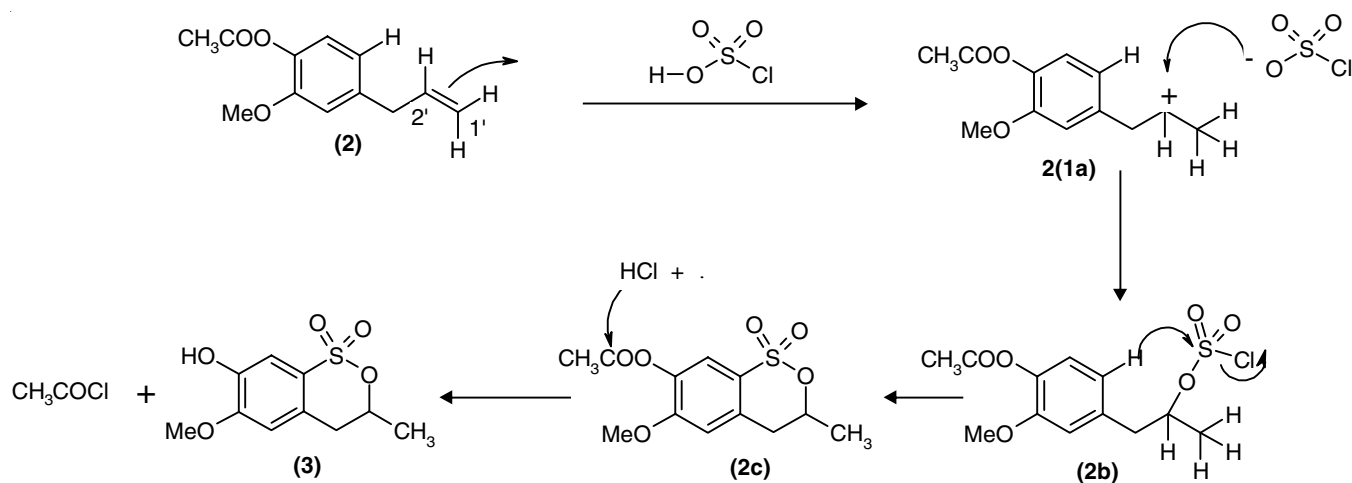
No.	Catalyst and its condition	Yield of compd. <b>2</b> (%)
1	NaHCO <sub>3</sub> /(CH <sub>3</sub> CO) <sub>2</sub> O, ethyl acetate, r.t., 24 h	84
2	NaHCO <sub>3</sub> /(CH <sub>3</sub> CO) <sub>2</sub> O, acetonitrile, r.t., 24 h	72
3	Na <sub>2</sub> CO <sub>3</sub> /(CH <sub>3</sub> CO) <sub>2</sub> O, ethyl acetate, r.t., 24 h	88
4	K <sub>2</sub> CO <sub>3</sub> /(CH <sub>3</sub> CO) <sub>2</sub> O, ethyl acetate, r.t., 24 h	88

It has been reported that eugenol (**1**) reacted with chlorosulfonic acid to form sultone derivative (**3**) in moderate yield (64 %) [1]. After protection of the -OH group of eugenol (**1**) to be eugenil acetate (**2**) and further reaction with chlorosulfonic acid, presumably will afford sultone derivative (**2c**), but this hypothesis was not correct. These reaction gave the same product as reaction of eugenol (**1**) with chlorosulfonic acid (**Scheme-I**).

In the first stage, the chemical basis for Markovnikov's rule is the transformation of the most stable carbocation during the addition process (**Scheme-II**) [1,9]. The addition of the hydrogen from H-OSO<sub>2</sub>Cl to one carbon atom in the double bond of allyl group of eugenil acetate (**2**) creates a positive



**Scheme-I:** Synthesis route of sultone derivative (3) from eugenol (1) and eugenil acetate (2)



**Scheme-II:** Formation mechanism of sultone derivative (3) from eugenil acetate

charge on the other carbon, forming a carbocation intermediate (2a). The more substituted the carbocation the more stable it is, due to induction and hyperconjugation effects [9]. The carbocation C2' is more stable than carbocation C1' and  $^-\text{OSO}_2\text{Cl}$  will attack the carbocation C2' leads to the formation of intermediate (2b). However, the other less substituted C1' or less stable carbocation C1' will still be formed and will proceed to form the minor product with the opposite attachment of  $^-\text{OSO}_2\text{Cl}$  but such intermediate is not detected from the GC-MS and NMR analyses [1]. In the second stage of the reaction, a base donates electrons to the hydrogen atom and generated the losses of HCl to afford cyclic product (2c). Final stage, cleavage of ester by HCl produced sultone derivative (3).

On the basis of spectroscopic evidence and mechanistic considerations, the structure of sultone derivative (3) was proposed for Markovnikov product and excluded the Anti-Markovnikov product (4) as proposed in Scheme-I. Additional methyl group as a doublet at  $\delta$  1.58 in  $^1\text{H}$  NMR spectrum gave appropriate information about cyclic sulfonic ester derivative (3) compare to (4). This analysis was supported by  $^{13}\text{C}$  NMR and DEPT, which gave 4 quaternary carbons, 3 methine carbons, 1 methylene carbon and 2 methyl carbons. Generally, the  $^1\text{H}$  NMR spectrum supported the proposed structure (3).

### Conclusion

Reaction of eugenol (1) with chlorosulfonic acid gave cyclic sulfonic ester or sultone derivative (3) in moderate yield

(64 %), on the other hand reaction of eugenil acetate (**2**) with chlorosulfonic acid also gave sultone derivative (**3**) in high yield (96 %). Both reactions occurred *via* Markovnikov rule.

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#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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