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Synthesis of Myristicin Ketone (3,4-Methylenedioxy-5-Methoxyphenyl)-2-Propanone from Myristicin

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Abstract: The synthesis of myristicin ketone from myristicin has been achieved through conversion of allyl group to ketone. Myristicin was isolated from nutmeg oil. The reaction of myristicin with mercury acetate in aqueous tetrahydrofuran, followed by in situ reduction of the mercurial intermediate by alkaline solution sodium borohydride produced myristicin alcohol. Myristicin alcohol was oxidized with PCC at 40 0C for 90 minutes, followed by purified with saturated potassium disulphite yield myristicin ketone (3-methoxy-4,5-methylenedioxyphenyl)-2-propanone (68.32%).

Keywords: Myristicin Ketone, Myristicin, Nutmeg Oil

1. Introduction

Myristicin (1-allyl-3,4-methylenedioxy-5-methoxybenzene, or methoxylsafrole, is a natural aromatic alkenylbenzene constituent found in the nutmeg, the dried ripe seed of *Myritica fragrans*, Houtt [1-2]. Myristicin is one of the main components in nutmeg oil that can be isolated by distillation under reduced pressure. Myristicin has allyl groups which can be converted into a ketone group. Research on the conversion of allyl groups in safrole to ketones can be done through isomerization, epoxidation and epoxide ring opening [3]. Conversion safrole into its compounds has been done is safrole to be safrylalcohol and synthesis of 3,4-methylenedioxy phenyl-2-propanone, [4-5]. Another method is the conversion of the allyl group of metileugenol through the addition of formic acid and then hydrolyzed to produce secondary alcohols which were subsequently oxydized with PCC to produces ketones [6]. Synthesis of secondary alcohols can be also through methods of oxymercuration-demercuration of olefin using mercury acetate and $NaBH_4$ according *in situ* [7-8]. Method for synthesis of ketones is through oxidation of secondary alcohols with PCC which is a reagent that is selective in the preparation of citronellal from citronellol [9] and the oxidation of subtitued homoallylic alcohols with PCC the corresponding carbonyl compound were formed [10]. Myristicin is the major constituent of the higher-boiling fractions of nutmeg and mace oils. This structure was confirmed by the synthesis of myristicinaldehyde [11], and convertion of myristicin to isomyristicin has been reported. Myristicin was treated with either metallic sodium or boiled with alcoholic KOH undergoes isomerism to yield isomyristicin [11-12], but the syntheses of ketone from myristicin are not yet fully reported. This research studied the synthesis of 3,4-methylenedioxy-5-methoxy phenyl) -2-propanone from myristicin through oxymercuration-demercuration allyl group into a secondary alcohol and oxidation of secondary alcohols with PCC (Figure 1).

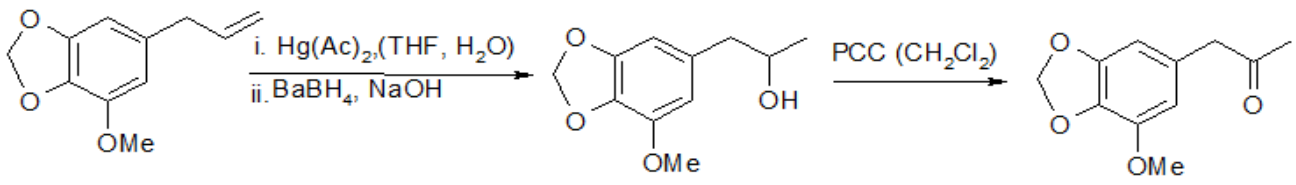

Figure 1. *Synthetic route to myristicin ketone (3,4-methylenedioxy-5-methoxy phenyl) -2-propanone.*

2. Materials and Methods

2.1. Chemical and Equipment

The chemical in the study are: Nutmeg oil obtained from steam distillation of nutmeg from Moluccas, diethyl ether p.a (E.merck), dichloromethane pa (E.Merck), ethanol pa (E.Merck), potassium bisulfite p.a (E. Merck), anhydrous sodium sulfates p.a (E.Merck), tetrahydrofuran p.a (E.Merck), pyridine p.a (E. Merck), Chromium trioxyde p.a (E.Merck), K_2CO_3 p.a (E.Merck), NaCl p.a (E.Merck), HCl 30% p.a (E.Merck),$Hg(OCOCH_3)_2$ p.a(E.Merck), $NaBH_4$ p.a(E.Merck). The tools used in this study are, a set of fractional distillation under reduced pressure, electric heaters, evaporators and tools Buchi laboratory glassware, Gas Chromatography (GC-2010 Shimadzu), an Infra Red spectrophotometer (FTIR-8400S, Shimadzu),^{1}H-NMR Spectrophotometer (JEOL-MY 500), Mass Spectrophotometer (GC-MS QP-2010 Plus, Shimadzu).

2.2. Isolation of Myristicin from Nutmeg Oil

A total of 239 g of nutmeg oil obtained from steam distillation of nutmeg was placed in a in round bottom flask 500 mL and equipped with vigroux column, thermometer, condensor and containment pressure distillation carried out at 153 ^{0}C/10 mmHg. The purity of the products was determined using GC, whereas their structures were elucidated using FTIR, ^{1}HNMR and MS.

2.3. Oymercuration-Demercuration Myristicin

Into a three neck flask (500 mL) that has been equipped with a magnetic stirrer, a thermometer, a cooling ball and funnel dropper included 32.0g (0.10 mole) of Hg (II) acetate, 100 mL of water and stir until dissolved, then add 100 ml of tetrahydrofuran, the solution color changed to light yellow and was stirred for 15 minutes. Then, by using dropper funnel 19.2 g (0.10 mole) of myristicin dropwise at a temperature of 25 ^{0}C and stirred until the yellow color disappeared. Stirring was continued for 2 hours and 100 mL of 3 M NaOH, followed by 100 mL of NaBH4 solution of 1.90 g (0.05 mole) in 3 M NaOH was added at a temperature of 25 ^{0}C. The mixture was refluxed at room temperature for 3 hours. Mercury was allowed to settle and put in a separating funnel and left overnight. Mercury was separated from the aqueous layer and an organic layer. Saturated NaCl solution was added to the aqueous layer and extracted twice with 100 mL of diethyl ether. The ether layer was separated and the organic layers were pooled.

The organic layer was then separated by an evaporator to form two layers and added with 100 mL of diethyl ether and washed with water until neutral. Product was dried over Na_2SO_4 anhydrous and diethyl ether was separated by the evaporator. The purity of the product was determined using GC, whereas their structures were elucidated using FTIR, and MS.

2.4. Synthesis of 3-Methoxy-4,5-Methylendioxy Phenyl)-2-Propanone from Myriticin Alcohol

Into a three-neck flask of 500 mL size that has been equipped with a magnetic stirrer, thermometer, condensor containing blue silica gel included 21.0 g (0.0975 mole) pyridinium chlorochromate in 50 mL of anhydrous CH_2Cl_2 and 3.75 g (0.017 mole) of 1- (3,4-methylenedioxy phenyl) - 2-propanol in 20 mL of CH_2Cl_2 was added. The mixture was refluxed at 40 ^{0}C for 90 minutes to form a black paste and decanted. Black paste residue was extracted three times with 20 mL of diethyl ether and the filtrates were pooled. Results were dried with anhydrous Na_2SO_4 and dichloromethane was separated by the evaporator. The result obtained was added 25 mL with diethyl ether and 4.0 g of potassium bisulfites in 20 mL of water and stirred for 2 hours. The precipitate that formed was filtered and washed with 25 mL of ethanol and 25 ml of ether and dried in the air. Ketone bisulfite precipitates were reacted with 4 mL of 10% potassium carbonate, and added 20 mL of water and extracted twice with 40 mL of dichloromethane, which was then washed with water until neutral and the solvent dichloromethane separated by the evaporator to obtain myristicin ketone (68.32%). The purity of the product was determined using GC, whereas their structures were elucidated using FTIR, ^{1}HNMR and MS.

3. Results and Discussion

3.1. Isolation of Myristicin from Nutmeg Oil

Isolation of myristicin from nutmeg oil by distillation under reduced pressure at the temperature of 153 ^{0}C / 10 mmHg obtained myristicin (17.08%). Identification of obtained myristicin by Gas Chromatography with purity (100%). The properties of the resulting myristicin was a clear liquid form, fragrant, insoluble in water but soluble in ethanol, chloroform and ether. Infra red spectrum of myristicin showed absorption band in the region 3077-2923cm^{-1} which is the absorption C_{sp3}-H, this was confirmed by the appearance of absorption at 1431 cm^{-1} for $–CH_2$-(methylene). Untake range of C=C alifatic absorption appeared at 1632 cm^{-1} absorption at 1631 cm^{-1} for C=C aromatic and supported by absorption at 2973-2778 cm^{-1} which is absorption bands for $=C_{sp2}$-H (aliphatic/aromatic). Absorption band at 1131 cm^{-1} and 1090 cm^{-1} region showed the range of C-O-C (ether). The ^{1}H-NMR spectrum (500 MHz, $CDCl_3$): δ 3.29 ppm (*d*, $-CH_2$-, *J* = 6.5 Hz), 3.87 ppm (s, $-OCH_3$-), 5.08 ppm (*d*, $=CH_2$), 5.89 ppm (*m*, -CH=, *J* = 6.5 Hz)), 5.91 ppm (*s*, $-OCH_2O$-), 6.32 ppm (s, $-H_1$-Ar-), 6.35 ppm (s, $-H_6$-Ar-). Mass spectrum (m/z): 30, 39, 53, 65, 77, 91, 103, 119, 131. 147, 161, 177, 192 (base peak) $[C_{11}H_{12}O_3]^{+\cdot}$.

3.2. Oxymercuration-Demercuration of Myristicin

The oxymercuration-demercuration of myristicin was done with $Hg(OAc)_2$-$NaBH_4$, followed by distillation under reduced pressure to obtain myristicin alcohol (48.33%).

Identification by Gas Chromatography obtained myristicin alcohol with purity (85.2%). This product is smaller than oxymercuration-demercuration of olefin (1-hexene) which produced 99.5% 2-hexanol [7] and the allyl group attached to 3,4-substitution on the aromatic ring produces 66-72% [4-5]. This is due to the steric effect on the process oxymercuration allyl group attached to the benzene ring with substituents when compared with a lot of straight chain. Infra red spectrum of myristicin alcohol showed abrorption at area 3447-3415 cm^{-1} which is –OH absorption. Absorption range of C=C aromatic appeared at 1628 cm^{-1} . Absorption bands $=C_{sp2}$-H (aromatic) appeared in the area 2965-2878 cm^{-1}. Absorption at 1136 to1045 cm^{-1} showed the range of the C-O-C. The mass spectrum (m/z); 45, 77, 108, 135, 151, 165 (base peak), 166, 210 (M +.). The obtained myristicin alcohol can be proved through the presence of the -OH absorption at 3447 cm^{-1} in the IR spectrum, m/z = 165 (base peak) and m/z = 210 in the Mass spectrum of the molecular weight of myristicin alcohol. The mechanism of the oxymercuration-demercuration of myristicin is estimated as follows (Figure 2).

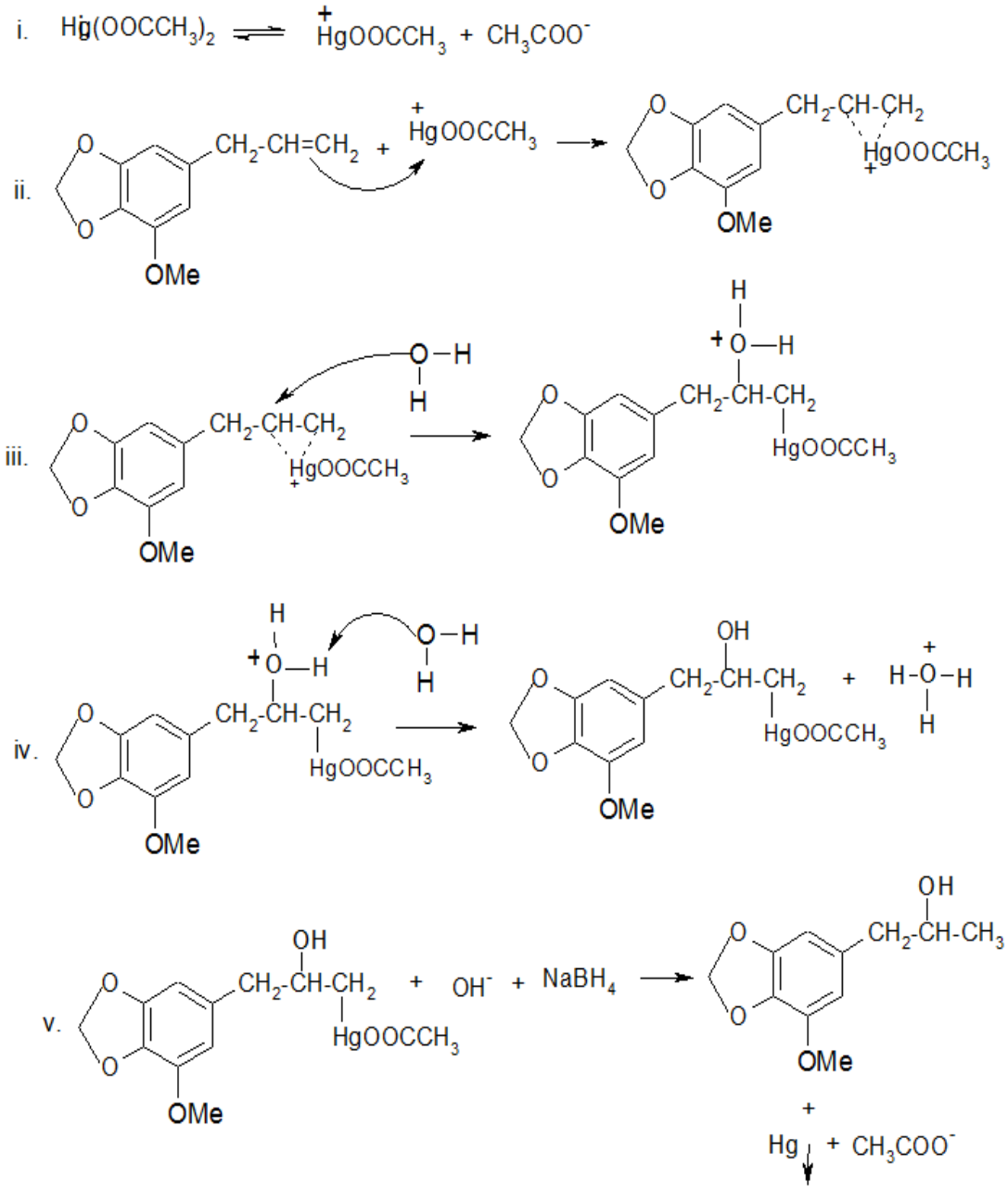

Figure 2. *The mechanism of the oxymercuration-demercuration of Myristicin.*

3.3. Synthesis of 3,4-Methylendioxy-5-Methoxyphenyl)-2-Propanone from Myrysticin Alcohol

PCC has been prepared according to the literature [9]. Oxidation of myristicin alcohol was done with PCC in CH_2Cl_2 dry as solvent and refluxed for 90 minutes and purified with potassium bisulfites to obtain 3-methoxy-4,5-

methylenedioxy phenyl)-2-propanone (68.32%). Purification of ketones with potassium bisulfite is a new method that is most appropriate to the small number of samples that can not be done by the method of distillation. The properties of the resulting myristicin ketone is a clear liquid form, insoluble in water but soluble in ethanol, chloroform and ether. Infra red spectrum of myristicin ketone showed abrorption at area 1706 cm^{-1} which is C=O absorption. Absorption range of C=C aromatic appeared at 1634 cm^{-1}. Absorption bands $=C_{sp2}$-H (aromatic) appeared in the area 2975-2896 cm^{-1}. Absorption at 1134 to1133 cm^{-1} showed the range of the C-O-C. .The ^{1}H-NMR spectrum (500 MHz), δ 2.12 ppm (s, -CH_3), 3.55 ppm (s, -CH_2 -), 3.85 ppm (s, -OCH3), 5.92 ppm (s, -OCH_2O -), 6.31 ppm (s, -H1-Ar), 6.35 ppm (s, -H6-Ar -). The mass spectrum (m/z); 43, 77, 92, 120, 135, 150, 165 (base peak), 208 (M +.). The compound 3,4-methylenedioxy-5-methoxyphenyl)-2-propanone can be proved through the presence of the C=O absorption at 1706 cm^{-1} in the IR spectrum, the presence of a singlet signal, δ = 2.12 ppm in the ^{1}H-NMR spectrum and m/z = 208 in the Mass spectrum of the molecular weight of myristicin ketone (3,4-methylenedioxy-5-methoxy phenyl)-2-propanone. The mechanism of the oxidation of Myristicin ketone with PCC is estimated as follows (Figure 3).

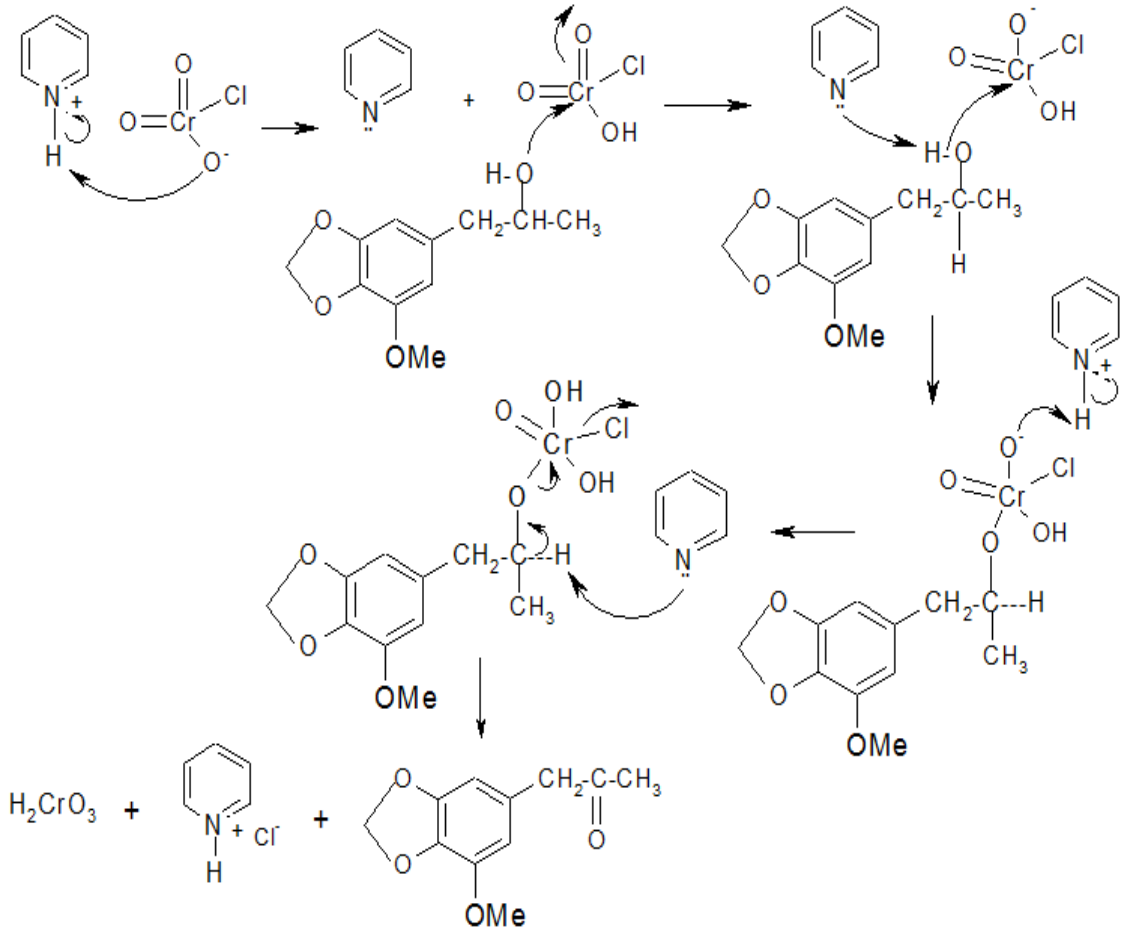

Figure 3. *The mechanism of the oxidation of Myristicin alcohol.*

4. Conclusion

1. The steric effect of substituted groups affect the oxymercuration-demercuration of myristicin causing the yield of alcohol produced was smaller than the straight chain and 3,4-substitution on the aromatic ring.
2. Oxydation of 3-methoxy-4,5-methylenedioxyphenyl)-2-propanol (myristicin alcohol) with PCC produced good results although it was not pure compound and methods of separation of ketones with potassium bisulfite is an easy and simple method for the compounds in small quantities.

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