SYNTHESIS OF 1-(3,4-METHYLENEDIOXYPHENYL)-1-BUTENE-3-ONE FROM SAFROLE

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ABSTRACT

The synthesis of 1-(3,4-methylenedioxyphenyl)-1-butene-3-one from Safrole has been done through conversion of allyl group to double bonds conjugated-ketone. Safrole was isolated from *culilawan* oil. The isomerization of safrole with KOH free solvent yielded isosafrole (72.82%), followed by oxidation of isosafrole with $KMnO_4$ and the application of Tween 80 as catalyst yielded piperonal (72.30%). The Condensation reaction of piperonal with acetone by the molar ratio of piperonal and acetone 1:6 and KOH as a catalyst and reaction time 2 hours followed by recrystalisation in methanol yielded yellow solid (84.21%).

Keywords: 1-(3,4-methylenedioxyphenyl)-1-butene-3-one, piperonal, isosasafrole, safrole, *culilawan* oil.

INTRODUCTION

Benzalacetone and its derivatives are known to have potent anti-oxidant activity (Waylon et al, 2005), and inhibit tumor promotion (Motohashi, et al, 1998). Thirty-six compounds were reported as antimutagenic activities (Yamagami and Motohashi, 2002, Yuliana et al, 2004). Monosubstituted benzalacetone and o-dehydrozingerone (2-hydroxy-3-methoxy-benzalacetone) were prepared by an aldol-type condensation as previously described. 4-Dimethoxybenzalacetone was prepared by Williamson ether synthesis from dehydrozingerone (Motohashi et al 1998, Pranowo et al, 2008, Handayani et al, 2012). A simple and direct method for the Claisen-Schmidt reaction to prepare functionalized α, β-unsaturated ketones has been developed. Microwave irradiation of aldehydes with acetone produces benzalacetones (Rayar et al. 2015). *Culilawan* oil obtained from steam-distillation of the bark of *Cinnamomum culilawan* revealed that this oil contained three main constituents, namely; eugenol, safrole and methylegenol. Two main compounds, safrole and eugenol were isolated from culilawan oil (Sohilait and Kainama, 2016). In this study, we report the synthetic strategy details for 1-(3,4-methylenedioxyphenyl)-1-butene-3-one from safrole via isomerization of safrole to isosafrol, oxidation of isosafrole to piperonal and aldol condenzation reaction of piperonal with acetone. Safrole was treated with either metallic sodium or boiled with alcoholic KOH, or without solvent undergoes isomerism to yield isosafrole (Nagase et al, 1974, Sohilait, 2013). Conversion of safrole into its derivated compounds, isosafrole and piperonal has also been done (Sohilait at al, 2013, Kapelle et al, 2015). The reaction of piperonal with acetone by the molar ratio of piperonal and acetone 1:6 and KOH as catalyst and reaction time 2 hours to molecule target (Figure 1).

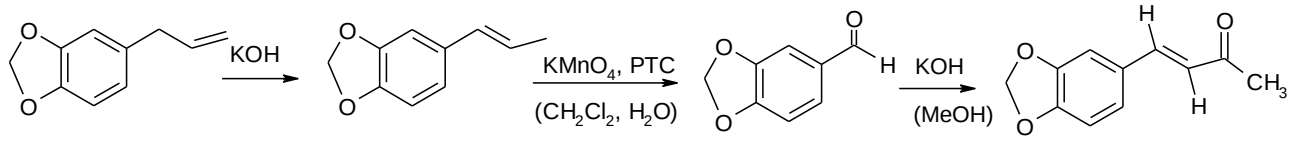

Figure 1. *Synthetic route to produce 1-(3,4-methylenedioxyphenyl)-1-butene-3-one*

MATERIALS AND METHODS

Chemicals and Equipment

The chemicals in the study are: Culilawan Oil obtained from steam distillation of *Cinnamomum culilawan* collected from Sorong, West Papua, Indonesia, sodium hydoxide p.a (E.Merck), petrolium ether 35-60 ^{0}C p.a (J.T. Baker), anhydrous sodium sulfate p.a (E.Merck), sodium chloride p.a (E.Merck), KOH p.a(E.Merck), Acetone GR (E.Merck), dichloromethane GR (E.Merck), $KMnO_4$ (E.Merck), tween 80, acetic acid. The tools used in study were a set of fractional distillation under reduced pressure, electric heaters, Buchi evaporators and tools laboratory glassware, Gas Chromatography GC-2010, Shimadzu, an Infra Red spectrophotometer (FTIR-8400S, Shimadzu),^{1}H-NMR, Spectrophotometer (JEOL-MY 500, MHz), ^{13}C-NMR, Spectrophotometer (JEOL-MY 125, MHz), Mass Spectrophotometer (GC-MS QP-2010 Plus, Shimadzu).

Isolation of Safrole from Cullilawan Oil

In a 1000 mL flask, NaOH (80.0 g), aquades (300 mL) and culilawan oil (300.0 g) were charged and the mixture were strired until forming two layers. The upper layer (A) was separated from the bottom layer (B). The upper layer was extracted with 100 mL of 20% NaOH and the aquous layer was combined to bottom layer (B). The organic layer (A) was washed with water until neutral and dried with Na_2SO_4 anhydrous and the residue was distilled under reduced pressure at 120°C/15 mmHg. The purity of compounds was tested by GC and the elucidation of the structures employed FTIR ,^{1}H-NMR,^{13}C-NMR and GC-MS methods.

Isomerization of Safrole to Isosafrole

KOH has been ground before using. Into a three neck flask (250 mL) that has been equipped with a magnetic stirrer, a thermometer, and a condenser containing blue silica gel included 32.40 g (0.2 mol) safrole and 22.4 g (0,4 mol) KOH. The mixture was refluxed at 120^{0}C for 4 hours. After cooling the mixture was added with unsaturated NaCl solution, followed by twice extraction with 100 mL of CH_2Cl_2, which was then washed with water until neutral. Product was dried over Na_2SO_4 anhydrous and dichlorometane was separated by the evaporator, followed by distilling under pressure at the temperature 120-130^{0}C/10 mmHg yielding 72.82% . The purity of the product was analyzed using GC, whereas their structures were elucidated using FTIR,^{1}H-NMR and MS.

Preparation of Piperonal from Isosafrole

Into a 500 mL three-neck flask that has been equipped with a magnetic stirrer, thermometer and condenser included 3,24 g (0.02 mol) isosafrole, 100 mL dichlorometana, 100 mL aquades, 2 mL acetic acid, 15 mL H_2SO_4 50% and 100 mg Tween 80, followed by the addition of 9.79 g (0.062 mol) $KMnO_4$ which was droped about 500 mg per minute at 30^{0}C and the stirring was continued again until change of colour from purple to clear. The mixture was filtrated by Buchner containing silica gel, followed by separation of organic layer and aquoes layer. Aquoes layer was extracted twice with 50 mL dichloromethane. The dichorometane layer was`combined to organic layer, which was then washed with water until neutral. Product was dried over Na_2SO_4 anhydrous and dichlorometane was separated by the evaporator. The residue was recrystazation in methanol yield 72,3%. The structures were elucidated using FTIR, ^{1}H-NMR and MS.

Synthesis of piperonylacetone from piperonal

Into a three neck flask (50 mL) that has been equipped with a magnetic stirrer, a thermometer, and a condenser included 3.24 g (0.02 mol) isosafrole and 6.96 g (0,12 mol) acetone, followed 1.12 g (0.02 mol) KOH in 5 mL water was added and the mixture was refluxed at room temperature for 120 minutes. the mixture was extracted twice 100 mL of CH_2Cl_2, which was then washed with water until neutral. Product was dried over Na_2SO_4 anhydrous and dichlorometane was separated by the evaporator. The residue was recrystalyzed in methanol yield 98,1% The structures were elucidated using FTIR, ^{1}H-NMR and MS.

RESULTS AND DISCUSSION

Isolation of Safrole from Cullilawan Oil

Isolation of safrole from *culilawan* oil was processed as follows; The upper layer (A) was separated from the bottom layer (B), (procedure 2.2). The uper layer was washed with water until neutral followd by drying over anhydrous Na_2SO_4. After removing petroleum ether, the residue was distilled under reduced pressure 15 mmHg/120^{0}C yield (21.86%). This product yielded was larger than that isolated from culilawan oil grown in Amboina island wich produced 6.571% (Sohilait et al, 2016). Spectrum IR (cm^{-1}): 2977, 2842, 1639, 1608, 1432, 1246, 1034. Spectrum ^{1}H-NMR (500 MHz, $CDCl_3$, ppm), ∂ : 3.32 (*d* –CH_2-, *J* = 7.1Hz), 5.06 (d, =CH_2), 5.92 (s, -OCH_2O-), 5.95 (m, -CH=, *J* = 7.1 Hz), 6.67 (d, H-C5Ar), 6,74 (s, C3-Ar), 6.84 (d, H-C6-Ar. Spectrum ^{13}CNMR (100 MHz, CDCl3) : ∂: 40.06 (-$\underline{C}H_2$-), 100.95(-O$\underline{C}H_2$O-), 108.30 (C3-Ar), 109.23 (C5-Ar), 115.82 (=$\underline{C}H_2$), 121.44 (C6-Ar), 133.96 (C1-Ar), 137.80 (-$\underline{C}$H=), 145,99 (C4-Ar), 147.90 (C3-Ar). Mass spectrum (m/z): 51, 63, 77, 91, 104, 131, 162 [$M^{+\cdot}$], (base peak). The spectral data matched to that given in previous reports [11, 12]. The Infra-red spectra of safrole showed absorption bands in the region 2977 cm^{-1} which is the absorption Csp^3-H, this was confirmed by the appearance of absorption at 1432 cm^{-1} for –CH_2- (methylene). Untake range of C=C aliphatic absorption appeared at 1639 cm^{-1}, absorption at 1608 cm^{-1} for C=C aromatic and supported by absorption at 2977-2842 cm^{-1} which is absorption bands for =Csp^2-H (aliphatic/aromatic). Absorption band at 1246 cm^{-1} and 1034 cm^{-1} region showed the range of C-O-C (ether). The ^{1}H-NMR spectrum, signal doublet at 3.32 ppm(-CH_2-, *J* = 7.1Hz) and signal multiplet at 5.95 ppm (–CH=, *J* = 7.1 Hz), signal singlet at 5.92 ppm of one methylenedioxy group. The ^{13}C-NMR spectrum showed 10 nonequivalent carbon resonances and the MS spectrum showed a molecular ion peak [M+.] at *m/z* 162, $C_{10}H_{10}O_2$.

Isomerization of Safrole to Isosafrole

Isomerization of safrole by KOH, without solvent at the 140^{0}C for 4 hours yielded isosafrole (72.82%). The compound was identified by GC yield *cis*- isosafrole (7.11%) and *trans*-isosafrole (92.89%). IR Spectra (cm^{-1}): 2977, 2842, 1639, 1608, 1432, 1246, 1034. ^{1}H-NMR Spectra (500 MHz, $CDCl_3$, ppm), ∂ : 1.87 (d –CH_3, J = 6.8Hz), 5.10 (m, =CH_2-), 5.92 (s, -OCH_2O-), 6.07 (m, =CH-, J = 6.8 MHz), 6.34 (-CH=, J = 14.4 Hz), 6.6-6.9 (m, 3H-Ar). Mass spectra (m/z): 51, 63, 77, 91, 104, 131, 162 [$M^{+\cdot}$], (base peak). The obtained isosafrole could be proved through the presence of the signal doublet at ∂ = 1.87 ppm (s, CH_3-) in ^{1}H-NMR spectrum.

Preparation of Piperonal from Isosafrole

Oxidation of isosafrol with $KMnO_4$ and tween 80 (PTC) as catalysts in two phase: organic phase and aquoes phase, followed by recrystalization in methnol yield 72,3%. IR Spectra (cm^{-1}): 2915, 2720, 1690, 1623, 1252. ^{1}H-NMR Spectra (500 MHz, $CDCl_3$, ppm), ∂ : 6.06 (s, -OCH_2O-), 6.90-7.40 (m, 3H-Ar), 9.79 (s, CHO). Mass spectra (m/z): 29, 53, 63, 91, 121, 149 (base peak), 150 [$M^{+\cdot}$]. The obtained piperonal can be proved through the presence of the -CHO absorption at 2720 cm^{-1} and absorption at 1690 Cm^{-1}(C=O) in the IR spectrum, the presence of a singlet signal, ∂ = 9.79 ppm (s, CHO) in the ^{1}H-NMR spectrum and m/z = 150 in the Mass spectrum indicated the molecular weight of piperonal.

Synthesis of piperonylacetone from piperonal

Condensation reaction of piperonal with acetone by the molar ratio of piperonal and acetone 1:6 and KOH as a catalyst and reaction time 2 hours followed by recrystalisation in methanol yield yellow solid (84.21%). IR Spectra (cm^{-1}): 2991, 2906, 1670, 1645, 1624, 1038. ^{1}H-NMR Spectra (500 MHz, $CDCl_3$, ppm), ∂ : 2.35 (s, -CH_3), 6.01 (s, -OCH_2O-), 6.54 (d, =CH-, J = 16.2 Hz), 6.81-7.05 (m. 3H-Ar), 7.41 (d, Ar-CH=, J = 16.2 Hz). ^{13}C-NMR Spectra (125 MHz, $CDCl_3$) : ∂: 27.49 (-$\underline{C}H_3$), 101.67(-O$\underline{C}H_2O$-), 106.56 (C2-Ar), 108.61 (C4-Ar), 125.08 (C6-Ar), 125.25 (=$\underline{C}$H-), 128.78 (C2-Ar), 143.23 (Ar-$\underline{C}$H=), 148.43 ((C4-Ar), 149.86 (C3-Ar), 198.26 ($\underline{C}$=O). Mass spectra (m/z): 39, 43, 63, 73, 89, 117, 145 (base peak), 175, 190 [$M^{+\cdot}$]. The obtained piperonylacetone can be proved through the presence of the –C=C- aliphatic absorption at 1645 cm^{-1} and absorption at 1670 Cm^{-1}(C=O) in the IR spectrum, the presence of a singlet signal, ∂ = 2.35 ppm (s, -CH_3), signal doublet, ∂ = 6.54 ppm (=CH-, J = 16.2 Hz), signal doublet, ∂ = 7.41 ppm (=CH-, J = 16.2 Hz) in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum showed 11 nonequivalent carbon resonances and the Mass spectrum showed a molecular ion peak [M+.] at *m/z* 190, $C_{11}H_{10}O_3$, of the molecular weight of piperonylacetone. Concerning stereochemistry, the olefinic 3.4-methylenedoxy phenyl-butandiene-3-ones were obtained in E-form, since the coupling constants of the two protons attached to the double bonds are around 16.2 Hz. The E-configuration for sterical reasons since in the Z-isomers the phenyl rings have to turn out of the plane of the olefinic double bond because of interaction of the H-atoms with the carbonyl O-atom. Consequently there is a decrease in resonance energy, making the Z-isomer less favourable. The mechanism of the reaction between piperonal, acetone, and KOH is estimated as follows (Figure 2):

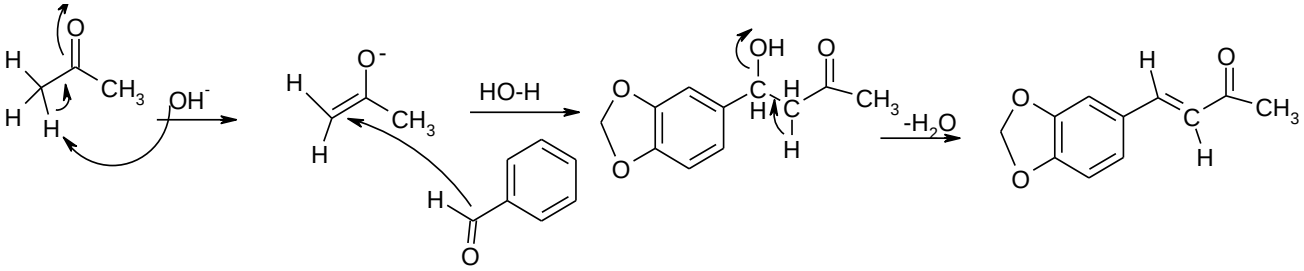

Figure 2. *The mechanism of the aldol condensation reaction of pipernal and acetone*

CONCLUSIONS

Synthesis of 1-(3,4-methylenedioxyphenyl)-1-butene-3-one from Safrole trough isomerization, oxidation and aldol condenzation produces E –form isomer of molecule target.

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