Synthesis of hemiterpene 1-bromo-3-methyl-2-butene derivatives

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Synthesis of hemiterpene 1-bromo-3-methyl-2-butene derivatives

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Abstract. Hemiterpene 1-bromo-2-methyl-2-butene (prenyl bromide) is widely used as a prenyl source for various organic synthesis. One of them is the development of synthetic fragrances for the perfume industry which is growing rapidly for daily consumption. Based on our literature study, most fragrances contain of terpenes. Moreover, terpenes are widely practiced in the flavor and fragrance industry. There are two common groups of terpenes used as fragrances such as oxygenated monoterpenes and sesquiterpenes. Interestingly, hemiterpenes are potential but it is hard to isolate them from natural plant products. In this study, three hemiterpene derivatives have been successfully synthesized with very simple method and obtained in good yields namely prenyl cinnamate **(1)**, prenyl methylbutyrate **(2)**, and prenyl isobutyrate **(3)**. Furthermore, the synthesis method was conducted by two steps. The first step was prepared by acid-base reaction, followed by nucleophilic substitution of prenyl bromide. The hemiterpene derivative structures were confirmed by NMR and mass spectroscopy.

Keywords: *hemiterpene, prenyl bromide, fragrance*

INTRODUCTION

Hemiterpene or isoprene is the simplest terpenoids known as 2-methyl-1,3-butadiena [1]. By head-to-tail condensation, biogenetic relationship of plant isoprenoids and terpenoids which are formed from dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP) [2]. Terpenoid is classified in two big cyclases namely monoterpene and sesquiterpene. They are commonly used to basic ingredient in flavor and fragrance industry [3]. Although hemiterpene is also potential used to however it is rarely founded on natural products [4]. Because it is quite hard to extract or isolate hemiterpene from natural plants. For this reason, synthesis of hemiterpene is important to develop fragrance component particularly. Because of the simple head-to-tail chemical structure, hemiterpene has volatile characteristic in the room temperature. Furthermore, terpenes and their derivatives are not only known as flavor and fragrance component but have been used as potential dietary supplements also [5].

In the past decade, hemiterpene derivatives were gradually developed from either synthetic or isolated compounds. For instance, 3-methyl-2-butene-1-yl-acetate or known as prenyl acetate is one of hemiterpenes which has a strong fruity flavor. So that, it was applied in fragrance, flavor, and medicinal industry [6]. In nature, prenyl acetate has been founded in ylang-ylang oil and produced by some of the prominent industry of fragrance such as Bedoukian and BASF [7]. Recently, hemiterpene derivative known as hemiterpene glycoside was isolated from various plants such as *Securidaca inappendiculata* [8] [9], *Spiraea prunifolia* [10], *Ilex rotunda* [11], *Spiraea canescens* [12], *Megoura crassicauda* [13], and *Ilex pubescens* [14]. Most of them were applied on biological activity assay to drug discovery.

In the previous research, Babler patented synthesis of prenyl acetate. There are five synthetic methods which were patented. The first method was done by using reaction between 2-methyl-1,3-butadiena and acetate acid as well as phosphoric acid as a catalyst at temperature of 60-62 °C for four hours. It was obtained prenyl acetate about 20% in yield [15]. The second method was conducted by using 3-methyl-2-butene-1-yl-dichloromethane synthesized with sodium dichloroacetate in dichloroacetic acid and 2-methyl-1,3-butadiena with dropwise addition for 108 minutes at

room temperature. These result was obtained about 71% in yield. The third is the reaction between potassium dichloroacetate in dichloroacetic acid and 2-methyl-1,3-butadiena with dropwise addition for 39 minutes at room temperature obtained 51% in yield. Then, the reaction between 2-methyl-1,3-butadiena and dichloroacetic acid in the absence of dichloroacetic salts at room temperature for 30 minutes was obtained less than 50% in yield. Moreover, 3-methyl-2-butene-1-yl-formate was synthesized by reaction between 2-methyl-1,3-butadiene and sodium formate in formic acid at room temperature for four hours nevertheless it was obtained about 13% yield [16].

During the past decade, hemiterpene derivatives synthesized from 1-bromo-3-methyl-2-butene are not performed yet. 1-Bromo-3-methyl-2-butene or well-known as prenyl bromide could be used to source of prenyl in various synthesis of organic compounds [17]. Because of bromide as a good leaving group, it makes synthetic reaction easier. In this research, prenyl bromide was used to prenyl source of synthesis three hemiterpene derivatives. They were successfully synthesized by using two steps. Hence, the chemical structures were confirmed by using NMR and mass spectroscopy.

EXPERIMENTAL SECTION

Materials

The chemicals are 1-bromo-3-methyl-2-butene (Fluka, 38925), 3-phenyl-2-propionic acid (Sigma-Aldrich, 133760), 2-methylbutanoic acid (Sigma-Aldrich, 193070), 2-methylpropanoic (Fluka, 58360), *N,N*-dimethylformamide (DMF) (Merck, 103053), dichloromethane (Merck, 106050), sodium bicarbonate (Merck, 106329), aquades, *n*-hexane (Merck, 104367), ethyl acetate (Merck, 109623), magnesium sulfate heptahydrate (Merck, 105886).

Instrumentations

Structure elucidation of the synthesized compounds was performed using GC-MS (Angilenty 19091S-433, HP-5MS), ^{1}H-NMR and ^{13}C-NMR spectrometer (Delta2 Jeol Resonance, 400 MHz; Angilent DD2, 500 MHz).

General Procedure Synthesis of Hemiterpene

Synthesis was conducted using two steps described in Figure 1. The first step was carboxylic acid (1 mmol) dissolved in DMF of 10 mL. The solution was added sodium bicarbonate (2 mmol) and stirred at room temperature for 60 minutes (the monitoring reaction was conducted by using TLC). Next, the reaction product from the first step placed in a cold water bath was added prenyl bromide (1 mmol) with drop wise addition and stirred at room temperature for 500 minutes (the monitoring reaction was conducted by using TLC). The product was dissolved using dichlorometane (25 mL); washed using aquades (25 mL), solution of sodium bicarbonate 0.011 M (100 mL), and aquades (10*x*50 mL). Then, the organic layer was collected and dried using magnesium sulfate heptahydrate and evaporated at room temperature so that hemiterpene was obtained as a light yellow oil. The synthesis product was tested purity using TLC, weighed, and identified using GC-MS and NMR spectrometer.

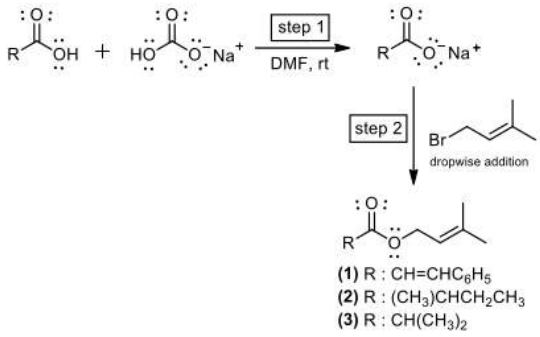

FIGURE 1. Synthesis of three hemiterpenes **(1-3)**

3-methyl-2-butene-1-yl-3-phenyl-2-propenoat or prenyl cinnamate (1)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.73 and 1.77 (6H, s, CH_3), 5.41 (1H, t, C<u>H</u>=), 4.69 (2H, d, CH_2O), 7.66 (1H, d, C<u>H</u>=), 7.35-7.51 (5H, m, Ar<u>H</u>). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 18.16, 25.93 (CH_3), 139.34 ($(CH_3)_2C$=), 118.71 (CH=), 61.56 (CH_2O), 167.12 (C=O), 118.26 (CH=), 144.77 (CH=), 128.15, 128.96, 130.32 (ArCH), 134.53 (ArC); mass spectrum (EI): *m/z* 216 (M, 8%), 201 (10), 171 (35), 147 (50), 131 (100), 103 (45), 85 (5), 77 (30), 69 (40), 51 (10).

3-methyl-2-butene-1-yl-2-methylbutanoat or prenyl methylbutyrate (2)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.66 and 1.70 (6H, s, CH_3), 5.29 (1H, t, C<u>H</u>=), 4.52 (2H, d, CH_2O), 1.09 (3H, d, CH_3), 2.30 (1H, m, C<u>H</u>), 1.41 (2H, q, CH_2), 0.84 (3H, t, CH_3). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 18.03, 25.78 (CH_3), 138.78 ($(CH_3)_2C$=), 118.85 (CH=), 61.15 (CH_2O), 176.87 (C=O), 16.68 (CH_3), 41.11 (CH), 26.90 (CH_2), 11.64 (CH_3); mass spectrum (EI): *m/z* 170 (M, 2%), 155 (1), 142 (1), 128 (1), 114 (1), 103 (2), 85 (25), 69 (100), 57 (55).

3-methyl-2-butene-1-yl-2-methylpropanoat or prenyl isobutyrate (3)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.70 and 1.76 (6H, s, CH_3), 5.32 (1H, t, C<u>H</u>=), 4.55 (2H, d, CH_2O), 2.49-2.58 (1H, m, C<u>H</u>), 1.15 (3H, d, CH_3); mass spectrum (EI): *m/z* 156 (M, 2%), 141 (1), 128 (1), 113 (1), 101 (1), 85 (2), 69 (100), 53 (15).

RESULTS AND DISCUSSION

Synthesis of hemiterpenes was performed using two steps as presented in Figure 1. The first step involved an acid-base reaction between carboxylic acid and sodium bicarbonate in DMF obtained sodium carboxylate and carbonic acid as byproduct. The second step involved a nucleophilic reaction of prenyl bromide which obtained carboxylic acid from the first step as the nucleophile obtained three hemiterpenes: prenyl cinnamate **(1)**, prenyl methylbutyrate **(2)**, and prenyl isobutyrate **(3)** as can be seen in Table 1. Those were conducted at room temperature compared with the previous method (i.e. 60-62 °C) [15]. In general, the synthesis using this step has given good yields (83-91% in yields) compared with the previous method which have yields of 13-71% [15] [16]. The chemical structure of three hemiterpenes **(1-3)** was confirmed by using ^{1}H and ^{13}C-NMR as well as MS spectroscopy analysis.

TABLE 1. Synthesis of three hemiterpenes **(1-3)**

Hemiterpenes	Yield (%)
Prenyl cinnamate **(1)**	91%
Prenyl methylbutyrate **(2)**	83%
Prenyl isobutyrate **(3)**	88%

Prenyl cinnamate **(1)** is a yellow liquid with a yield of 91%. It was obtained by the reaction between 3-phenyl-2-propenoic acid and sodium bicarbonate as well as prenyl bromide in DMF. The mechanism reaction of prenyl cinnamate **(1)** was suggested as Figure 2. That mechanism described that the reaction of 3-phenyl-2-propenoic acid with sodium bicarbonate is an acid-base reaction which produced 3-phenyl-2-propenoate sodium and carbonic acid as byproduct followed by the nucleophilic substitution reaction of prenyl bromide with the nucleophile 3-phenyl-2-propenoic acid. From these reaction, prenyl cinnamate **(1)** was obtained finally with sodium bromide as byproduct. Spectroscopy analysis of GC-MS provided the main peak with a retention time of 16.62 minutes (area of 87.89%), with a mass spectrum as Figure 3. The spectrum showed the molecular ion peak at *m/z* 216 which matched to the relative molecular mass of prenyl cinnamate **(1)**. The release of methane from molecular ions resulted fragment with a peak at *m/z* 201, while the release of isopropyl radicals from molecular ions resulted in fragment with a peak at *m/z* 173 followed by hydrogen resulting in fragment with a peak at *m/z* 171. Moreover, the release of isoprenyl radical was produced with a peak at *m/z* 147, while the release of preniloxy radical resulted in cation which was showed the base peak at *m/z* 131. Then, the release of prenyl formate radical resulted with a peak at *m/z* 103 in cation. Furthermore, molecular ions also experience the release of acyl radicals resulting with a peak at *m/z* 85, while the

release of cinnamic acid radical resulted in isoprene cation with a peak at *m/z* 69. Furthermore, fragmentation of molecular ions also produced phenyl cations with a peak at *m/z* 77, and the 1,3-butadiene cation with a peak at *m/z* 53 followed the release of a hydrogen molecule to present a fragment with a peak at *m/z* 51. The molecular ion fragmentation was described in Figure 4. The ^{1}H-NMR spectrum showed the presence of eight signals with integration ratio of 3:3:2:1:1:3:2:1. The protons of the preniloxy group were indicated two singlet signals at chemical shift of 1.73 and 1.77 ppm with the integration ratio of 3:3 which is a signal of six protons from two methyl groups, a doublet signal with a chemical shift of 4.69 ppm with integration ratio of 2 is a signal from the two protons of the methylene group coupled by a proton of a neighboring methyl group that showed a triplet signal on chemical shift 5.41 ppm with integration ratio of 1. Then, phenyl-2-propenoate group protons were presented with doublet signal at chemical shift of 6.41 and 7.66 ppm which is a signal from two protons of the methine group of the alkene group that are coupled, and the five aromatic protons were showed a multiplet signal on chemical shift of 7.35-7.51 ppm with the integration ratio of 3:2. The ^{13}C-NMR spectrum of prenyl cinnamate **(1)** showed the presence of eleven carbon signals. The preniloxy group carbons presented signal at chemical shift of 18.16 and 25.93 ppm which are the signal for two methyl group carbons, a signal on a chemical shift of 118.71 ppm is a signal for a methane group carbon and 139.34 ppm is a signal for a methane group carbon or alkene, the signal on the chemical shift of 61.56 ppm is a signal of the methylene group carbon, and the carbonyl carbon signals the chemical shift of 167.12 ppm. The phenyl-2-propenoate group carbons was showed with two signals on the chemical shift of 118.26 and 144.77 ppm which are the methine carbon, and the six aromatic carbons on the chemical shift: 134.53; 128.15; 128.15; 128.96; 128.96; and 130.32 ppm.

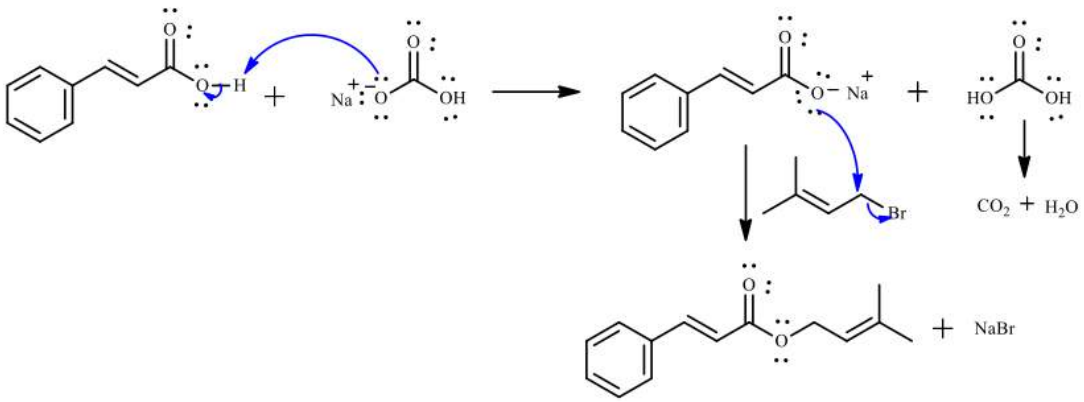

FIGURE 2. Proposed mechanism reaction of prenyl cinnamate **(1)**

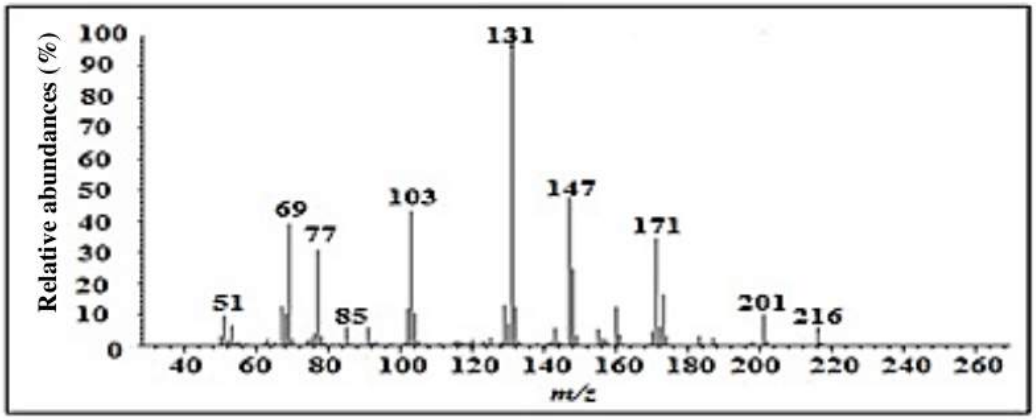

FIGURE 3. Mass spectrum of prenyl cinnamate **(1)**

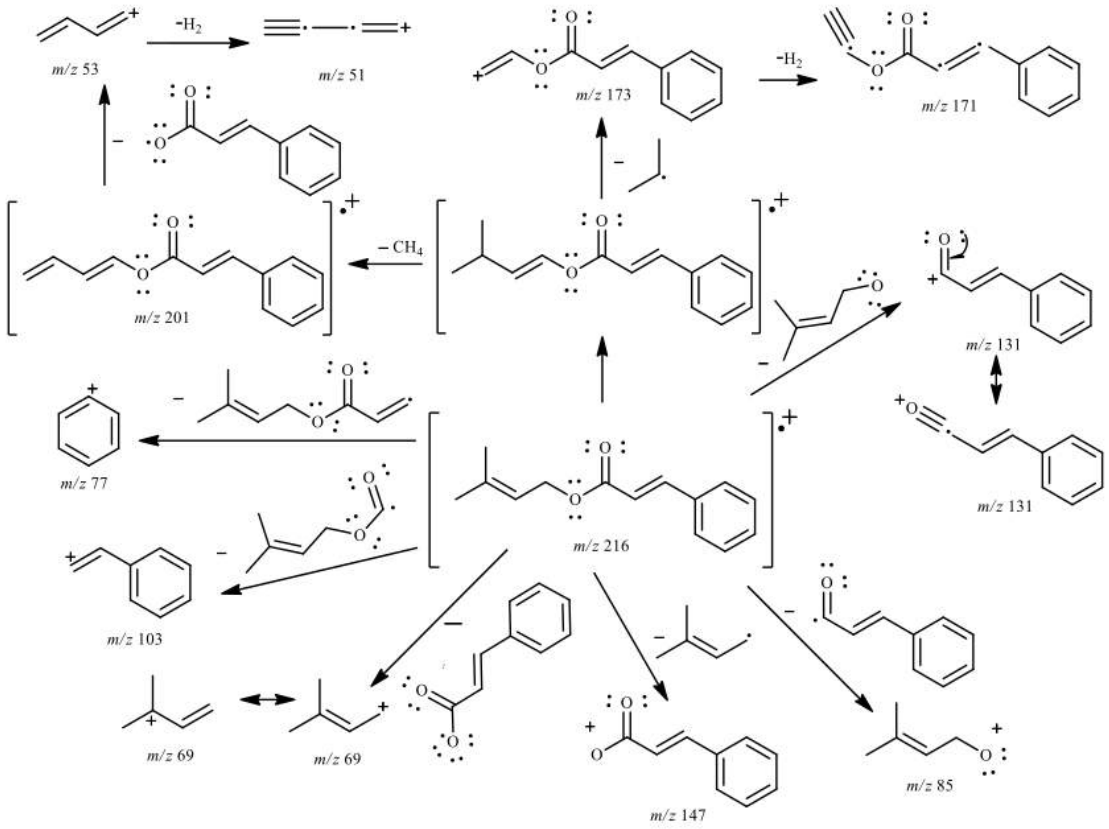

FIGURE 4. Molecular ion fragmentation of prenyl cinnamate **(1)**

Prenyl methylbutyrate **(2)** is a yellow liquid with yield of 83%. The compound was successfully synthesized from the reaction of 2-methylbutanot acid and sodium bicarbonate followed by prenyl bromide in DMF. The synthesis method was carried out the same as for the previous hemiterpene synthesis of **(1)**. The proposed mechanism was presented in Figure 5. Analysis of GC-MS spectroscopy showed a chromatogram with the strong peak of prenyl methylbutyrate **(2)** with a retention time of 7.76 minutes. The mass spectrum can be seen in Figure 6. The mass spectrum showed the molecular ion peak at *m/z* 170 which indicated to the relative molecular mass of prenyl methylbutyrate **(2)**. The release of methyl radicals from the molecular ion resulted in a cation with a peak at *m/z* 155, whereas the release of ethane through McLaferty's rearrangement of the molecular ion resulted in a fragment with a peak at *m/z* 142. Moreover, the release of propene and 2-butene from the molecular ion resulted in fragment with peaks at *m/z* 128 and *m/z* 114. The release of 2-methyl-2,3-butene from the molecular ion resulted in a cation with a peak at *m/z* 103, while the release of prenyloxy radicals resulted in a cation with a peak at *m/z* 85. The radical release of 2-methylbutyric acid from molecular ions produced cation with a peak as the base peak at *m/z* 69. Furthermore, fragmentation of molecular ions was also produced in cations with a peak at *m/z* 57. The molecular ion fragmentation was described in Figure 7. The ^{1}H-NMR spectrum showed the presence of eight signals with integration ratio of 3:3:1:3:3:1:2:1. The protons of the preniloxy group presented two singlet signals at the chemical shift of 1.61 and 1.70 ppm with integration ratio of 3:3 which are the signal of six protons of two methyl groups, a doublet signal at a chemical shift of 4.52 ppm with integration ratio of 2 is a signal from a proton of a methylene group coupled with a neighboring methine group proton, and a triplet signal at a chemical shift of 5.29 ppm with integration ratio of 1 is a signal the methine group. The protons of the acyl group were showed two triplet and doublet signals with an integration ratio of 3:3 at a chemical shift of 0.84 and 1.09 ppm which are the signal of six protons of two methyl groups, a signal quintet with integration of 1 in a chemical shift of 1.41 ppm is the signal of two methylene group protons, the multiplet

signal at 2.30 ppm chemical shift with integration ratio of 1 is the signal of the proton of the methine group. The ^{13}C-NMR spectrum showed the presence of ten carbon signals that correspond to the amount of prenyl methylbutyrate **(2)** carbon. The preniloxy group carbons were presented the signal with the chemical shift of 18.03 and 25.78 ppm which are the signal of two methyl group carbons, a signal for a chemical shift of 138.78 ppm is a signal for methane or alkene carbon, a signal for a chemical shift of 118.85 ppm and 61.15 ppm are the signal for the carbon of the methine and methylene group, respectively. The carbonyl carbon signal is on chemical shift of 176.87 ppm. The acyl group carbons showed the signal with chemical shift of 11.64 and 16.68 ppm which are the signal for two methyl group carbons, a signal with a chemical shift at 26.90 ppm is a signal with a methylene group carbon, and a signal with a chemical shift at 41.11 ppm is the methine group carbon signal.

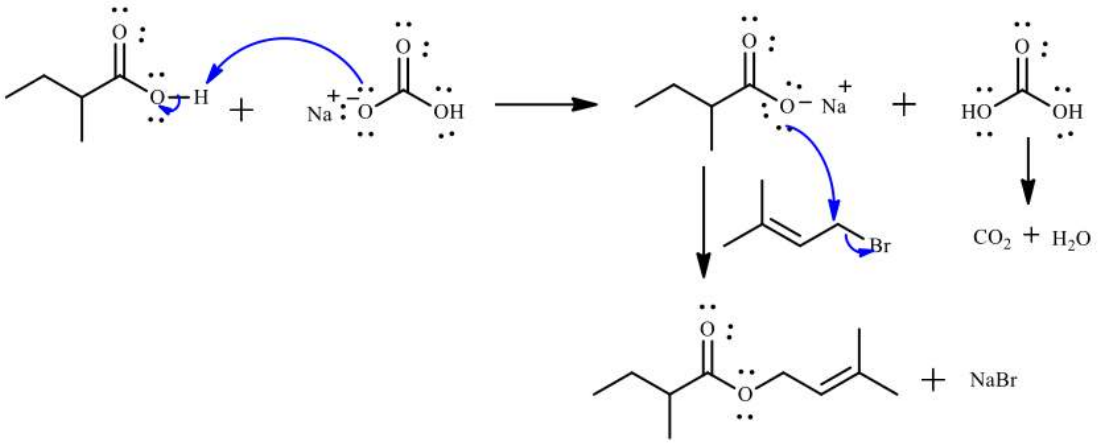

FIGURE 5. Proposed mechanism reaction of prenyl methylbutyrate **(2)**

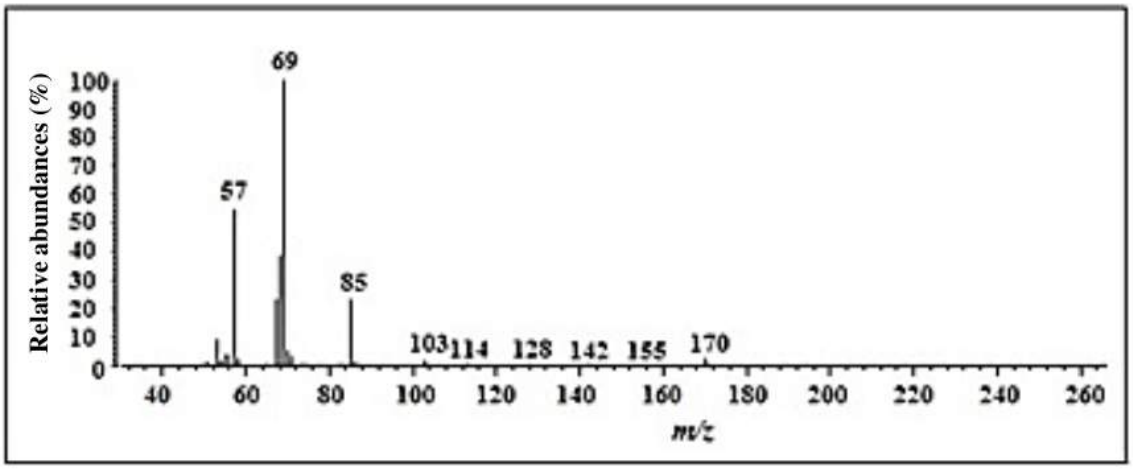

FIGURE 6. Mass spectrum of prenyl methylbutyrate **(2)**

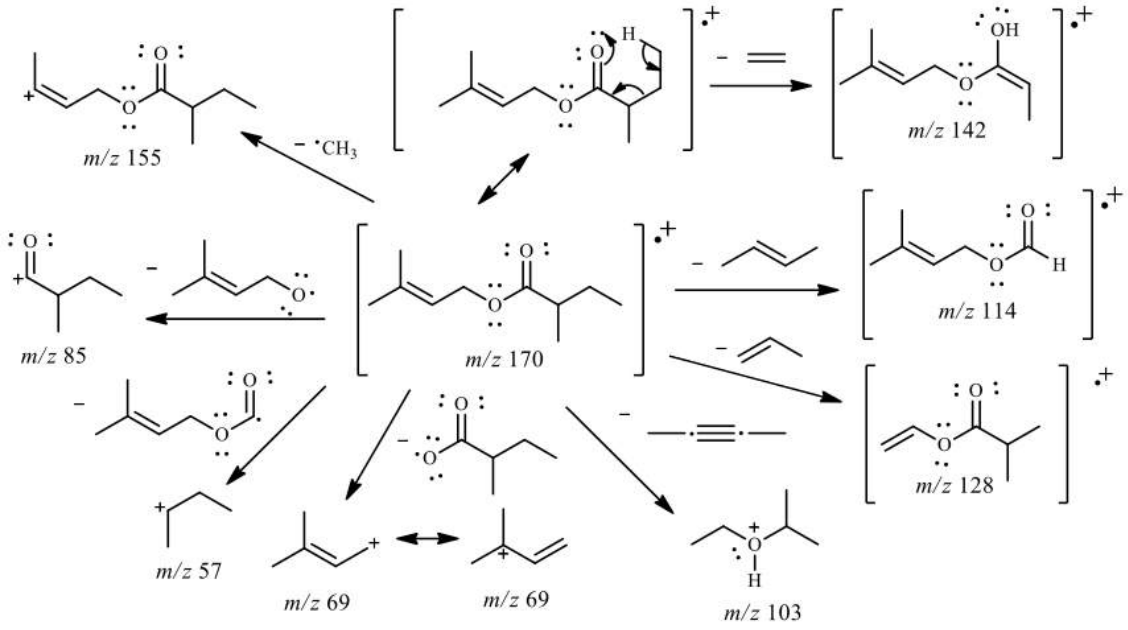

FIGURE 7. Molecular ion fragmentation of prenyl methylbutyrate **(2)**

Prenyl isobutyrate **(3)** is a yellow liquid with yield of 88%. The synthesis method was performed the same as previous hemiterpene synthesis of compound **(1)** and **(2)**. The reaction of 2-methylpropanoic acid and sodium bicarbonate followed by 1-bromo-2-methylbut-2-ene in DMF was resulted prenyl isobutyrate **(3)**. The mechanism reaction was proposed in Figure 8. The spectroscopy analysis of GC-MS provided a strong peak of the hemiterpene **(3)** with a retention time of 6.36 minutes with a mass spectrum as shown in Figure 9. The mass spectrum showed the molecular ion peak at *m/z* 156 which is the relative molecular mass of prenyl isobutyrate **(3)**. The release of methyl and isopropyl radicals from molecular ions resulted in cations with peaks at *m/z* 141 and *m/z* 113, respectively. The release of carbon monoxide from molecular ions resulted in cation radical with a peak at *m/z* 128. Moreover, the release of isoprene radicals from molecular ions produced cation with a peak at *m/z* 101. The release of acyl radicals from molecular ions resulted in cation with a peak at *m/z* 85, while the release of preniloxy radical cation from molecular ions which is as a base peak at *m/z* 69. The molecular ion also experiences the release of 2-methylpropanoic acid so that a 3-methyl-1,2-butadiene cation radical at *m/z* 68 is produced which is hydrogen atoms and methyl radicals at *m/z* 53. The molecular ion fragmentation of isobutyrate **(3)** can be seen in Figure 10. ^{1}H-NMR spectrum analysis showed seven signals with integration ratio of 3:3:3:3:1:2:1. The protons of the preniloxy group presented two singlet signals with the integration ratio of 3:3 at the chemical shift of 1.70 and 1.76 ppm which are the signal of six protons from two methyl groups, a triplet signal at a chemical shift of 5.32 ppm with integration ratio of 1 is a signal of a proton of methine group, and a doublet signal at a chemical shift of 4.55 ppm with integration ratio of 2 is a signal of a proton of the methylene group. Furthermore, the acyl group protons showed a multiplet signal at the chemical shift of 2.49-2.58 ppm with integration ratio of 1 being the proton of the methine group, and the doublet signal at the chemical shift of 1.15 ppm with integration ratio of 3:3 is the signal of the proton of two methyl groups.

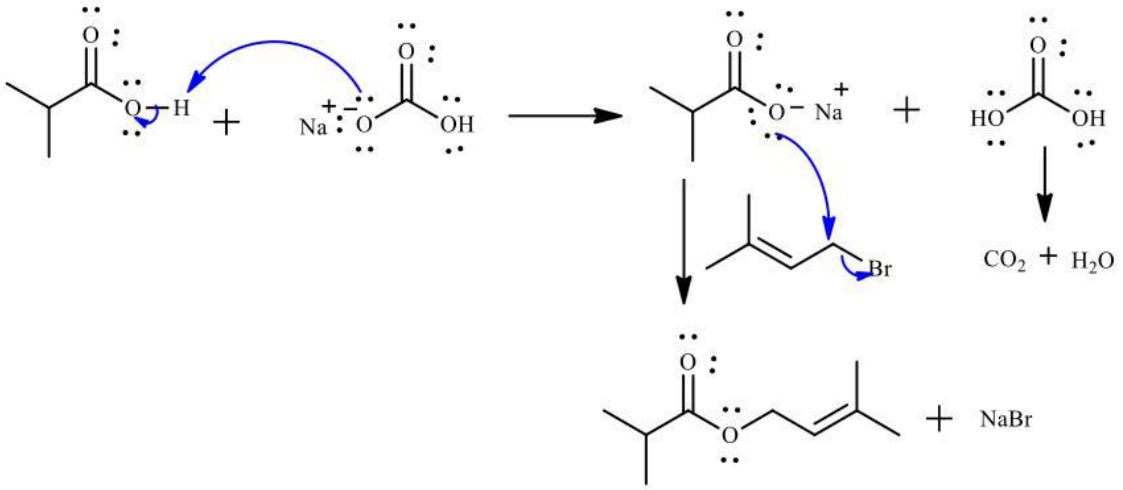

FIGURE 8. Proposed mechanism reaction of prenyl isobutyrate **(3)**

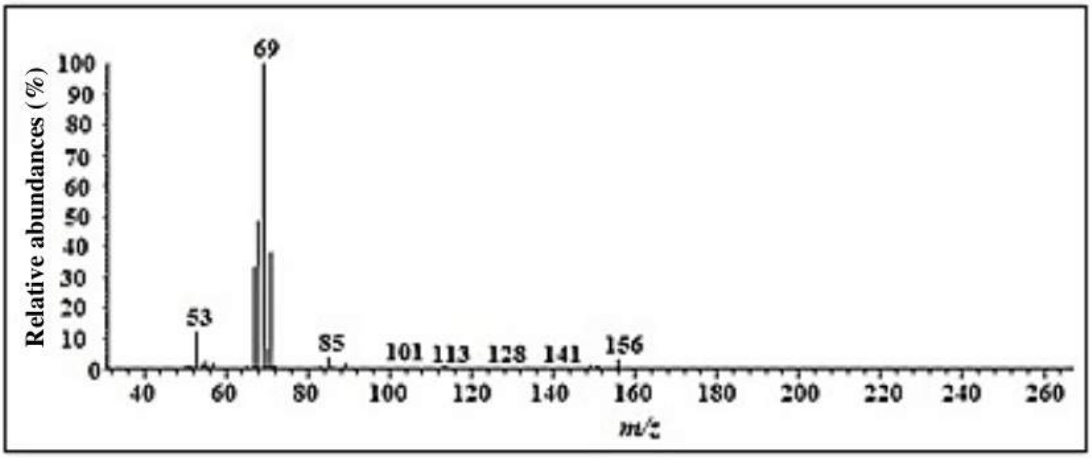

FIGURE 9. Mass spectrum of prenyl isobutyrate **(3)**

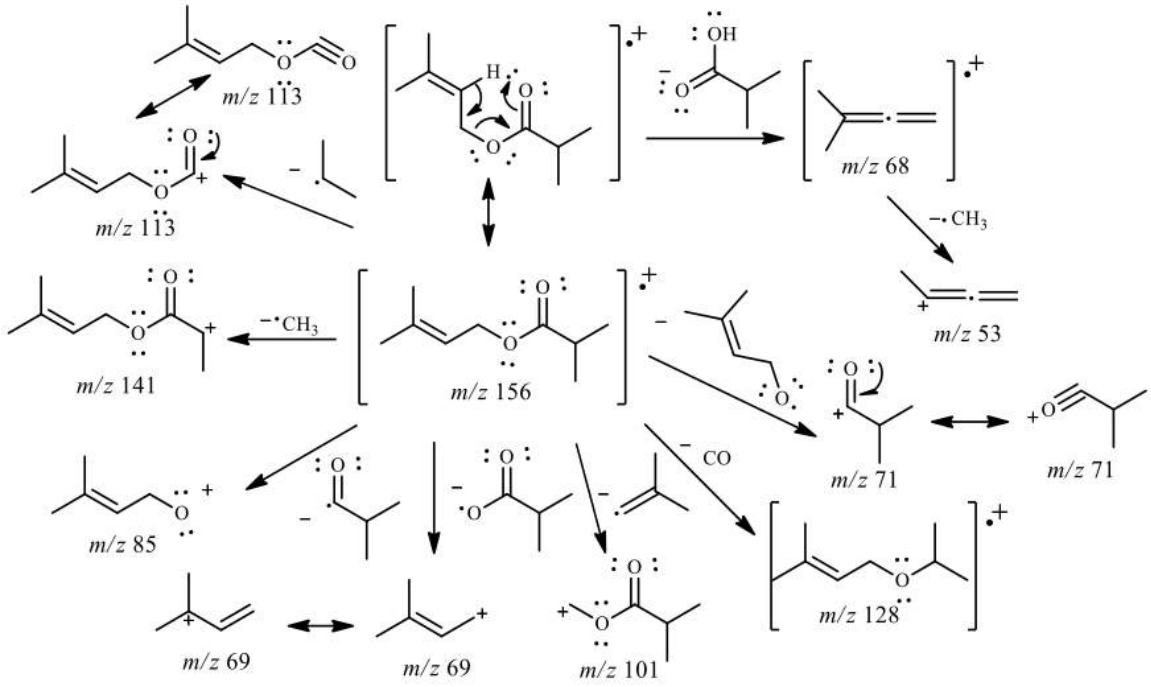

FIGURE 10. Molecular ion fragmentation of prenyl isobutyrate **(3)**

CONCLUSION

Hemiterpene prenyl cinnamate **(1)** was successfully synthesized from the reaction between prenyl bromide and 3-phenyl-2-propenoic acid with yield of 91%. Other hemiterpenes such as prenyl methylbutyrate **(2)** and prenyl isobutyrate **(3)** were also successfully synthesized by the same approach as hemiterpene **(1)** with yield of 83% and 88%, respectively. Furthermore, three hemiterpenes **(1-3)** have been prepared by more convenient method than that of previous study [15] [16].

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