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Synthesis of N-Benzenesulfonyl-*p*-Coumaramide from *p*-Coumaric Acid

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Abstract: *N-Benzenesulfonyl-p-Coumaramide has been synthesized from p-qumarid acid. This research aimed to synthesized N-Benzenesulfonyl-p-Coumaramide from p-qumarid acid. Targeted coumpound obtained from two steps reaction. Which were amidation and asilation. Synthesized product was identified and characterized by melting point, thing Layer Chromatography analysis, FTIR Spectrhophotometer, ^{1}H-NMR, dan ^{13}C-NMR. The result showed the obtained N-Benzenesulfonyl-p-Coumaramide was white solid (yield 78.58 %) with melting point was 145-147 ^{o}C and KLT (SiO_2, n-hexane : cloroform = 6 : 4 v/v, Rf = 0.45).*

Keywords*: asilation, amidation, N-Benzenesulfonyl-p-Coumaramide, p-qumarid acid.*

1. INTRODUCTION

The *p*-coumaramide compound (Fig. 1) has been isolated from the root bark of Paliasa *Kleinhovia hospita* Linn and has a biological activity against shrimp larvae *Artemia salina* Leach with LC_{50} = 180.53 µg/mL (Ilyas, 2008). The results of this research indicate that *p*-coumaramide compound have the potential to be developed as anticancer and antibacterial drugs.

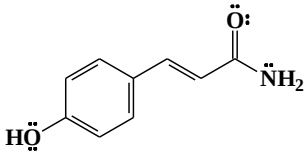

Figure 1. Structure of *p*-coumaramide compound (Ilyas, 2008)

Based on the results of this study, Firdaus et al (2009) has synthesized *p*-coumaramide compound from *p*-coumaric acid and tested its biological activity against leukemia cancer cell P-388. The result of *p*-coumaramide compound test against leukemia cancer cell P-388 showed that *p*-coumaramide compound has biological activity with IC_{50} = 44 µg/mL. According to Anderson et al (1990), the compound has strong anticancer activity if the IC_{50} value < 20 µg/mL. Therefore, *p*-coumaramide compounds deserve to be the basic framework for obtaining more active compounds.

The biological activity of *p*-coumaramide compounds can be increased by modifying the molecular structure (Tang, 2005). For this reason, Firdaus et al (2011) has synthesized and tested the biological activity of P-388 leukemia cancer cell of 3 *p*-coumaramide derived compounds, *N*,*N*-diethyl-*p*-coumaramide (IC_{50} = 23.50 µg/mL), *N*-propyl-*p*-coumaramide (IC_{50} = 53.56 µg/mL), and piperidinyl-*p*-coumaramide (IC_{50} = 5.34 µg/mL). Rasyid (2014) has also synthesized and tested the biological activity of P-388 tumor cells from 2 *p*-coumaramide derivatives, namely methyl *β*-(*p*-hydroxyphenyl) acrylate (IC_{50} = 16.51 µg/mL) and methyl *β*-(*p*-methoxyphenyl) acrylate (IC_{50} = 21.18 µg/mL).

Similarly, Dali and Dali (2017) have also succeeded in synthesizing *N*-*p*-methylbenzyl-*p*-coumaramide (Fig. 2) from *p*-coumaric acid.

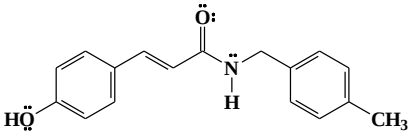

Figure 2. Structure of *N*-*p*-methylbenzyl-*p*-coumaramide compound (Dali and Dali, 2017)

The search for other *p*-coumaramide derivated compounds can be performed by choosing a secondary or primary amine group that is less polar, making it easier for these compounds to pass through cell membranes containing lipid compounds (Shargel et al., 2004). Besides the group polarity factor, the efficacy factor of the group is also used as the basis for consideration in determining the selection of group on N atom that bound to the basic framework. For example, amide compounds derived from sulfonic acid (RSO_3H) are efficacious as antibiotic or antibacterial drugs (Matta et al., 1996). Both of these reasons underlie the selection of target synthesis compounds in this research.

2. MATERIALS AND METHOD

Tools

Spectrometer FTIR Prestige-21 (Shimadzu), ^{1}H-NMR and ^{13}C-NMR (FTNMR JEOL ECX500), melting point meter (Electrothermal 9100), analytical balance (Ohaus), Celsius thermometer, magnetic stirrer of 1 cm, heating mantle, three neck flask of 100 mL, spherical cooler, desicator, refrigerator, oven, and glassware.

Materials

The *p*-coumaric acid, benzene, thionyl chloride, pyridine, commercial nitrogen, tetrahydrofuran, benzenesulfonamine, triethylamine, dichloromethane, *n*-hexane, chloroform, aquabidest (Onelab Waterone), anhydrous sodium sulfate, sodium iodide, potassium carbonate, hydrogen chloride, sodium chloride, and TLC plate. These chemicals are ordered from Merck and or Sigma Aldrich.

Procedures

Synthesis of p-coumaroyl chloride from p-coumaric acid

The *p*-coumaric acid compound of 0.44 g (0.5 mmol) is introduced into a round bottom three neck flask of 100 mL equipped with a spherical cooler. Subsequently 25 mL of dry benzene, 5 mL $SOCl_2$, and 3 drops of pyridine were added to a round bottom three neck flask. The mixture is stirred and refluxed for 8 hours at room temperature while flowed with nitrogen gas. Every 2 hours the mixture was tested by TLC method. The excess of thionyl chloride is separated by distillation (bp 71°C). The liquid formed is the *p*-coumaroyl chloride. The *p*-coumaroyl chloride solution is unstable, so this compound is used directly without further purification (Dali, 2016).

Synthesis of N-benzenesulfonyl-p-coumaramide from p-coumaroyl chloride

Chloride acid solution (0.3 g, 0.4147 mmol) in dry tetrahydrofuran (5 mL) was added dropwise under nitrogenous atmosphere conditions into a benzenesulfonamine solution (0.21 mL, 1.51 mmol) and triethylamine (0.21 mL, 1.51 mmol) in dry tetrahydrofuran (10 mL). The mixture is stirred with a magnetic stirrer for 24 hours at room temperature while flowing nitrogen gas. Every 8 hours the mixture is tested on TLC. Next the mixture is filtered and the filtrate is concentrated. The residue was dissolved in dichloromethane and the solution was washed with cold water (-5 ^{o}C), dried with Na_2SO_4 anhydrous. The product solution is filtered and the solvent evaporated. The formed solids are recrystallized with methanol-dichloromethane. The white solid formed is the target compound (Dali, 2016). The target compound is then dried in the desiccator and then characterized by KLT test, melting point, FTIR, ^{1}H-NMR, and ^{13}C-NMR.

3. RESULTS AND DISCUSSION

Results

The *N*-benzenesulfonyl-*p*-coumaramide target compound is a white solid (yield 78.57%) with a melting point of 145-147 ^{o}C and TLC (SiO_2, *n*-hexane : chloroform = 6 : 4 v/v, Rf = 0.45). This target compound is obtained through two stages of the synthesis reaction. The first stage is an acylation reaction between *p*-coumaric acid as a starting material with thionyl chloride in a dry benzene solvent and produce *p*-coumaroyl chloride. In this acylation reaction stage there is a conversion of carboxylic acid group (RCO_2H) to acyl chloride group (RCOCl) (Fig. 3). This conversion reaction is supported by changes in Rf values of the reactant (0.75) to product (0.37). This is consistent with the expected product in which the product have a higher polarity than the reactant. The *p*-coumaroyl chloride is not spectroscopically analyzed because it is highly reactive to water vapor.

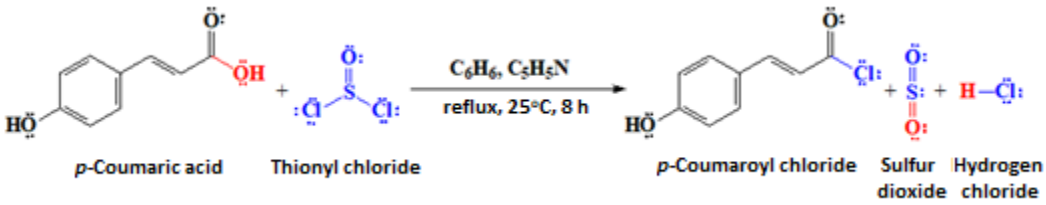

Figure 3. Synthesis reaction of *p*-coumaroyl chloride from *p*-coumaric acid

The second stage is an amidation reaction between *p*-coumaroyl chloride and benzene sulfonamine in a dry tetrahydrofuran solvent and we obtained the targeted molecul, namely a *N*-benzenesulfonyl-*p*-coumaramide target compound. At this stage of the amidation reaction there is conversion of the acyl chloride group (RCOCl) to the amide group (R'CONHR) (Fig. 4). This conversion reaction is supported by changes in Rf values of the reactant (0.37) to product (0.45). This is as expected, namely the product has a lower polarity compared to the reactant.

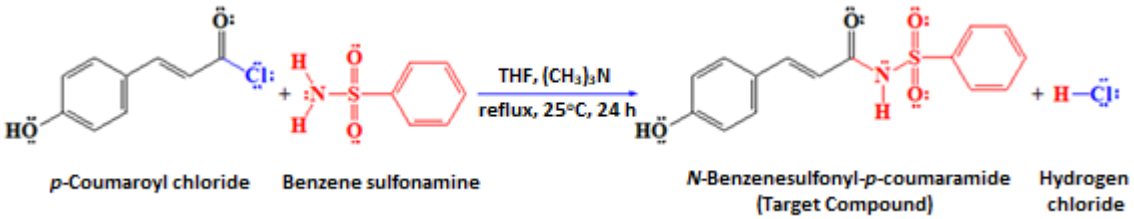

Figure 4. Synthesis reaction of *N*-benzenesulfonyl-*p*-coumaramide from *p*-coumaroyl chloride

Discussion

The FTIR spectrum of the target compound shows that two very strong absorption bands at 3377.36 cm^{-1} and 1687.71 cm^{-1} derived from the stretching of OH and C=O groups of *p*-coumaric acid as a starting materials are no longer visible. This indicates that the acylation and amidation reactions have occurred. This data is also reinforced by the appearance of three strong absorption bands at 3437.50, 1651.07, and 1510.26 cm^{-1} respectively derived from a stretching of N-H group of secondary amides, C=O group of secondary amides (amide I band), and C-N group of secondary amides (amide II band). Other supporting data are the appearance of three strong absorption bands at 1150.21, 1170.79, and 551.64 cm^{-1} respectively derived from the stretching of SO_2 group, SO_2 symmetry, and SO_2 scissor. Thus, from the FTIR data the target compound shows that the conversion reaction of the carboxylic acid group (RCO_2H) in *p*-coumaric acid as a starting material has changed to the amide group (R'CONHR) in *N*-benzenesulfonyl-*p*-coumaramide.

The success of the *N*-benzenesulfonyl-*p*-coumaramide synthesis reaction of *p*-coumaric acid is also supported by ^{1}H-NMR spectra data (Fig. 5).

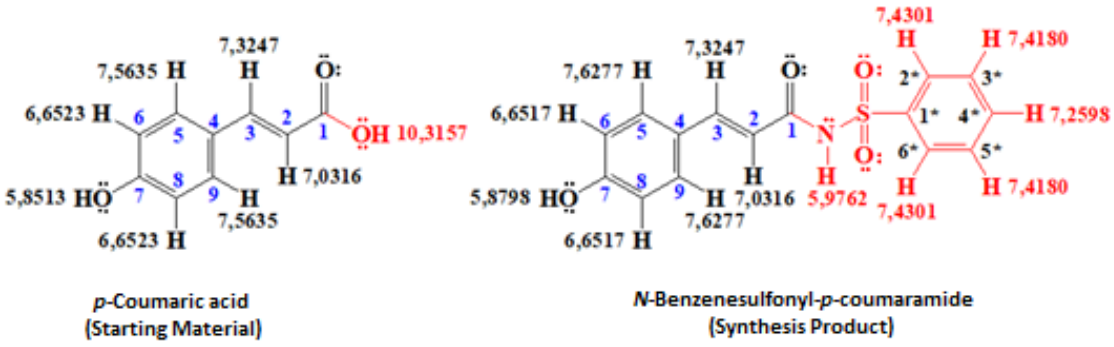

Figure 5. Interpretation of ^{1}H-NMR (500 MHz, $CDCl_3$) spectrum data of *p*-coumaric acid and *N*-benzenesulfonyl-*p*-coumaramide synthesis product

The ^{1}H-NMR spectrum of the target compound did not show any signal at δ_H 10.3157 ppm (1**H**, *s*, 1) derived from a proton of the *p*-coumaric acid (O**H**-1). This data is also reinforced by the appearance of a signal at δ_H 5.9762 ppm (1**H**, *s*) derived from proton amide (N**H**).

Other supporting data are the appearance of three signals at δ_H 7.4301 ppm (1**H**, *d*, 2* and 6*), 7.4180 ppm (1**H**, *t*, 3* and 5*), and 7.2598 ppm (1**H**, *t* , 4*) derived from aryl protons (Ar**H**) in *ortho*, *meta*, and *para* positions. Thus, the signals appearing in the ^{1}H-NMR spectrum of the target compound are in accordance with the proton character of the *N*-benzenesulfonyl-*p*-coumaramide compound (Fig. 5).

The interpretation of ^{13}C-NMR spectrum data (500 MHz, $CDCl_3$) of the target compound (Fig. 6) also strengthens the results of FTIR and ^{1}H-NMR spectrum analysis above.

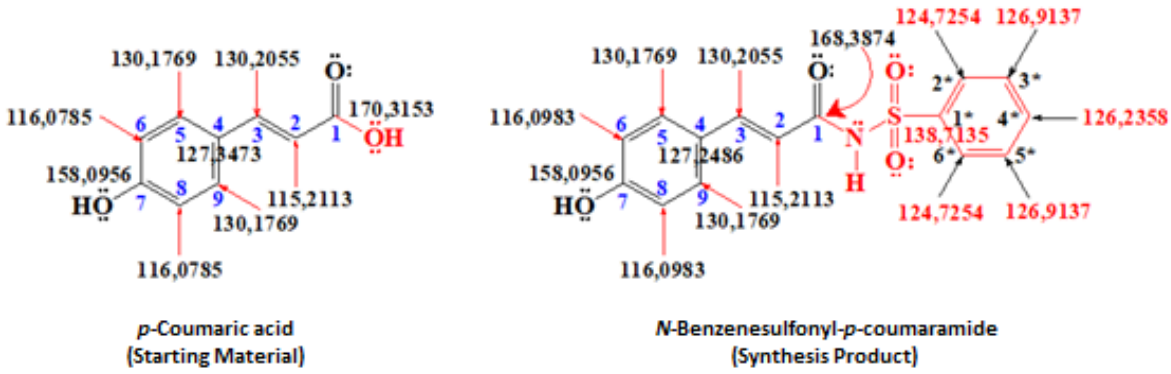

Figure 6. Interpretation of ^{13}C-NMR spectrum data (500 MHz, $CDCl_3$) *p*-coumaric acid and *N*-benzenesulfonyl-*p*-coumaramide synthesis product

The ^{13}C-NMR spectrum data of the target compound shows the presence of the aryl carbon signals (**C**-aryl) not found in the spectrum of *p*-coumaric acid as a starting material. The signals of the aryl carbon atoms (**C**-aryl) are dispersed into four δ_C values, ie δ_C 138.7135 ppm [(**C**-terminal aryl) (**C**-SO_2)], δ_C 124.7254 ppm (**C**-*o* aryl), δ_C 126.9137 ppm (**C**-*m* aryl), and δ_C 126.2358 ppm (**C**-*p* aryl). While the signals of other carbon atoms that emerge from the target compound are in accordance with the signals of carbon atoms from *p*-coumaric acid (Fig. 6). Therefore, the signals appearing in the ^{13}C-NMR spectrum of the target compound are in accordance with the carbon skeleton of the *N*-benzenesulfonyl-*p*-coumaramide (Fig. 7).

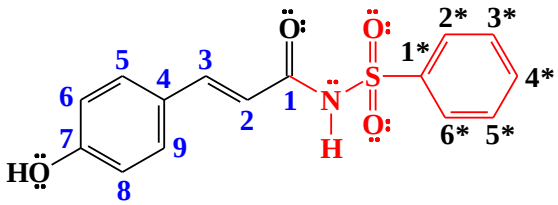

Figure 7. The carbon framework of the *N*-benzenesulfonyl-*p*-coumaramide

4. CONCLUSION

The *N*-benzenesulfonyl-*p*-coumaramide has been successfully synthesized from *p*-coumaric acid through acylation and amidation reaction steps. The *N*-benzenesulfonyl-*p*-coumaramide is a white solid (yield 78.57%) with a melting point of 145-147 °C and TLC (SiO_2, *n*-hexane : chloroform = 6 : 4 v/v, Rf = 0.45).

Suggestion

Biological activity of *N*-benzenesulfonyl-*p*-coumaramide needs to be tested further so that these compounds can be used as raw materials for anticancer and antibacterial drugs.

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