SYNTHESIS OF 1,4-DIHYDROPIRIDINE WITH AROMATIC OF CINNAMALDEHYDE COMPOUND USING NiFe$_2$O$_4$ MNPs CATALYST AND THE ACTIVITY TEST AS ANTIOXIDANT

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ABSTRACT

1,4-dihydropyridine (DHPs) is a class of compounds that are significantly present in a variety of natural products and commercial medicines such as felodipine. This study aims to modify cinnamaldehyde to become derivatives of 1,4-dihydropyridine using NiFe$_2$O$_4$ MNPs as the catalyst. NiFe$_2$O$_4$ MNPs were synthesized by the co-precipitation method using a 2:1 molar ratio between ferrite nitrate and nickel nitrate and analyzed by XRD and SEM-EDX. The results of the characterization support that NiFe$_2$O$_4$ MNPs were successfully synthesized. After that, NiFe$_2$O$_4$ was tested for its ability as a catalyst in the synthesis of 1,4 dihydropyridine. The synthesis results are confirmed with MP apparatus, UV/Vis Spectrophotometry, FT-IR and GC-MS, and obtained three 1,4-dihydropyridine compounds, namely 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (compound 1), 2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (compound 2), and 4-(4-Hydroxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (compound 3). The ability NiFe$_2$O$_4$ as catalyst gives a significant difference yield between the reaction with and without the catalyst.

Keywords: 1,4-Dihydropyridine, Cinnamaldehyde, NiFe$_2$O$_4$, Nanocatalyst, Antioxidant.

INTRODUCTION

Nowadays, the use of Spinel ferrites with the MFe$_2$O$_4$ formula is of concern and is widely used in the chemical field because of its advantages. The MFe$_2$O$_4$, M is divalent metal ions such as Mn, Cu Mg, Co, Zn, and Ni, has attractive electrical, magnetic and optical properties. NiFe2O4 is one of the most exciting ferrite spinels due to the high saturation magnetization of a typical crystal, high magnetocrystalline anisotropy, and magnetic structure. NiFe$_2$O$_4$ MNPs catalysts can be used in synthesis under extreme conditions and require relatively low costs in preparation. This catalyst has a spinel structure in which Fe$^{3+}$ occupies the tetrahedral site while Ni$^{2+}$ and Fe$^{3+}$ both occupy the octahedral site. As heterogeneous catalyst, the form of solids make it easier to separate it from the reactions so that this catalyst can be reused for several times. The derivatives of 1,4-dihydropyridine can be synthesized through the Hantschz multi-component reaction. This reaction method is usually used to synthesize pharmacologically useful compounds such as antitumor and antidiabetic. Multi-components used in synthesis include aromatic aldehydes, β-ketoesters (such as ethyl acetocetate), and ammonium sulfate. One of the aromatic aldehydes that can be used in this synthesis is the cinnamaldehyde compound. This compound can be isolated from cinnamon plant bark, which is one of Indonesia's biodiversity. Previous research has proven that 1,4-dihydropyridine derivatives have antioxidant activity by giving electrons from one of the hydrogen atoms in the dihydropyridine ring to free radical molecules to neutralize the harmful nature of these free radicals. One method commonly used to test antioxidant activity is the DPPH method (2,2 diphenyl-1-piricydradazil). This method is based on spectrophotometric measurements of changes in DPPH concentration resulting from the reaction of DPPH with antioxidants. Therefore, this research presents the synthesis of 1,4-dihydropyridine derivatives that support by a catalyst of NiFe$_2$O$_4$ MNPs and use the...
compound cinnamaldehyde isolated from cinnamon as a variation of aromatic aldehyde precursors and the compound will be tested its antioxidant activity.

**EXPERIMENTAL**

**Materials**

The chemicals were used for analytical grade without any further purification and obtained from Merck or Sigma-Aldrich Chemical Company, such as ferrite nitrate, nickel nitrate, deionized water, NaOH, cinnamaldehyde, benzaldehyde, 4-hydroxybenzaldehyde, ammonium carbonate, ethyl acetoacetate, ethanol, and DPPH.

**Preparation of NiFe$_2$O$_4$ MNPs Catalyst**

NiO NP as a Catalyst Control is synthesized by the co-precipitation method by dissolving 0.01 mole of nickel nitrate (Ni (NO$_3$)$_2$) into distilled water until the concentration reaches 0.1 mol/L. The solution was then added to 0.03 mol/L NaOH until the pH of the mixture reached 9. Then the solution was filtered then washed with distilled water until the pH of the filtrate was equal to 7. The solid phase obtained from the filtering was dried overnight at 110°C and calcined for 4 hours at temperature 550°C. NiFe$_2$O$_4$ MNPs catalysts were synthesized by the co-precipitation method with a 2:1 molar ratio between ferrite nitrate and nickel nitrate. Both are dissolved with deionized water, then add NaOH slowly until the pH of the solution becomes 10-11. After that, it is stirred for one hour at 80°C and cooled at room temperature. Then washed with de-ionized water until the filtrate pH becomes 7. Finally, it is dried overnight at room temperature, mashed, and then calcined at 450°C for 3 hours.

**Synthesis of 1,4-Dihydropyridine Derivatives**

Variations of aldehyde used were 3 mmol aromatic aldehydes (benzaldehyde, cinnamaldehyde, and 4-hydroxybenzaldehyde), 3 mmol ammonium sulfate, 6 mmol ethyl acetoacetate, ethanol 5 mL, two drops of H$_2$O. The synthesis was carried out under conditions of optimization of catalyst concentration, temperature, and reaction time. The result of the reaction was monitored and evaluated by TLC. After completion, the mixture was allowed at room temperature, and the catalyst was decanted from the outside of the reaction flask. Then, the products were recrystallized with ethanol.

**Antioxidant Activity Test (DPPH method)**

Antioxidant activity testing was carried out by dissolving 10 mg of DPPH powder in a 25 mL volumetric flask with ethanol. This solution is then referred to as a DPPH stock solution. After that, make a control solution by diluting the DPPH stock solution in ethanol in a ratio of 1: 2. Decreasing of absorbance was measured at 517 nm after the solution was incubated for 30 minutes in the darkroom. The sample solution was prepared in a series of concentrations of 10000 ppm, 8000 ppm, 6000 ppm, 4000 ppm, and 2000 ppm in ethanol. Then mix the sample solution with stock solution and ethanol in a ratio of 2: 1: 2. Then homogeneous using vortex and incubated in a dark room for half an hour. Then the absorbance is evaluated by a UV-Vis spectrophotometer at 517 nm. Percentage of inhibition (% inhibition) is calculated using the equation:

$$\% \text{ inhibition} = \frac{Ac - As}{Ac} \times 100$$

Ac is the control absorbance, and As is the sample absorbance.

**RESULTS AND DISCUSSION**

**Characterization of NiO NP dan NiFe$_2$O$_4$ Catalyst**

The formation of NiO NP and NiFe$_2$O$_4$ catalysts is proven by several instruments. Characterization with XRD was carried out to determine the structure of the catalyst that was formed. Figure-1a and 1b illustrate the diffraction pattern of NiO and NiFe$_2$O$_4$, respectively. NiO has several peaks, namely 43.32°; 63.04°; 75.46°; and 79.40. The value of 20 is compatible with NiO's Crystallography Open Database (COD entry number 961526381), and it was successfully synthesized with Miller index (102), (110), (201) and (202). Then the NiFe$_2$O$_4$ diffractogram (Fig.-1b) showed several diffraction peaks of 20 at
35.53°; 53.82°; 62.89°; and 75.27°. These data match the data in the Open Database Crystallography (COD entry number 965910065) of NiFe₂O₄. The catalyst of NiFe₂O₄ MNPs was successfully synthesized with the Miller index (311), (422), (404), and (622). The characterization results showed the presence of NiO, NiFe₂O₄, Fe₂O₃, and Fe₃O₄ phases on the prepared catalyst.

The Scanning Electron Microscope (SEM) characterization is shown in Fig.-2a that NiO NP has an irregular shape with a granule-like surface. While in Fig.-2c, it is seen that NiFe₂O₄ MNPs are not uniform in size as well. The presence of white granules is caused by the induction of Fe in Ni. Based on the EDX characterization of NiO (Fig.-2(b)), the weight percent values of the elements O and Ni are 26.56% and 73.44%, which shows that the mole percent values of the elements O and Ni are 1.66% and 1.24%. So the mol ratio of O: Ni obtained is 1.66: 1.24, which is close to the actual proportion of 1: 1. So from this data, it is expected that the nickel oxide compound formed is NiO. Then, the EDX of NiFe₂O₄ shows the weight percent values of elements O, Fe, and Ni, respectively, by 27.29%, 43.34%, and 29.37%. The weight percent value indicates the amount of mole percent of each element O, Fe, and Ni, namely 1.70%, 0.77%, and 0.49%. So the mole ratio of O: Fe: Ni is 1.70: 0.77: 0.49, which is close to the actual ratio of 4:2:1. Then from this data, it is expected that the compound formed is NiFe₂O₄.

**Catalytic Application of NiFe₂O₄ in the Synthesis of 1,4-Dihydropyridine Compounds**

Synthesis process to produce dihydropyridine derivatives, two equivalents of β-ketoester from ethyl acetooacetate, will be condensed with aromatic aldehyde compounds. While the presence of ammonia from...
ammonium sulfate as a component of nitrogen in forming pyridine rings. In general, the reaction of the formation of 1,4-dihydropyridine derivatives can be seen in Fig.-3. Aldehyde compounds used for this study were benzaldehyde (compound 1), cinnamaldehyde (compound 2), and 4-hydroxybenzaldehyde (compound 3).

![Fig.-3: Formation of 1,4-dihydropyridine Derivatives](image)

Optimization of the reaction conditions is carried out as in Table-1 which was carried out on compound 3. Based on the information in the Table-1, optimum conditions of the formation of 1,4-dihydropyridine derived compounds obtained in the reaction with a catalyst concentration of 0.3% mol, for 3.5 h at room temperature (Entry 9) with a yield of 83.23%. Under that condition, compound 1 and compound 2 was synthesized with a yield of 55.73% and 51.11% (Table-2).

| Entry | Catalyst (% mol) | Temperature (°C) | Reaction Time (h) | Yield (%) |
|-------|------------------|------------------|-------------------|-----------|
| 1     | 0                | Room temperature | 3.0               | 14.24     |
| 2     | 0.3              | Room temperature | 3.0               | 81.91     |
| 3     | 0.7              | Room temperature | 3.0               | 80.23     |
| 4     | 1.3              | Room temperature | 3.0               | 69.91     |
| 5     | 1.5              | Room temperature | 3.0               | 67.80     |
| 6     | 0.3              | Room temperature | 1.5               | 2.42      |
| 7     | 0.3              | Room temperature | 2.0               | 10.82     |
| 8     | 0.3              | Room temperature | 2.5               | 35.08     |
| 9     | 0.3              | Room temperature | 3.5               | 83.23     |
| 10    | 0.3              | Room temperature | 4.0               | 81.13     |
| 11    | 0.3              | 50°C             | 3.5               | 31.01     |
| 12    | 0.3              | 70°C             | 3.5               | 27.26     |

Table-2: Analysis of Products Characterization and Yield

| Comp | Product Structure | Characterization Analysis | Yield  |
|------|------------------|---------------------------|--------|
| 1    | ![Product Structure](image) | White solid. MP: 162.73°C. IR (cm⁻¹): 3320 (N-H), 2924 (C-H sp³), 2850 (C-H sp²), 1725 (C=O), 1256 (C-N), and 1196 (C-O). UV-Vis (nm): 227.5. MS (m/z): 329.1. | 55.73% |
| 2    | ![Product Structure](image) | Yellow solid. MP: 299.76°C. IR (cm⁻¹): 3271 (N-H), 3007 (C-H sp³), 2893 (C-H sp²), 1722 (C=O), 1228 (C-N), and 1152 (C-O). UV-Vis (nm): 330. MS (m/z): 355. | 51.11% |
Experimental evidence in support of the formation of 1,4-dihydropyridine was obtained through the Melting Point apparatus, Fourier-transform infrared spectroscopy (FTIR), UV-Vis Spectrophotometer, and GCMS that have been illustrated in Table-2. The compounds obtained are named 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (compound 1), 2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (compound 2), and 4-(4-Hydroxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (compound 3). The confirmation and evaluation of product structures were conducted by mass spectrometry. Figure-4a is the mass spectrometry of compound 1, which has an m/z of 329.1 as a parent peak. This value corresponds to the molecular weight of the compound synthesized by the molecular formula C_{19}H_{22}NO_{4}. Then there are peaks at m/z 269.0, 252.9, 172.9, and 73.1, which are peak fragments of compound 1. The proposed fragments of compound 1 based on their mass spectrum are depicted in the Fig.-4b.

![Mass Spectrometry and Fragments](image)

**Fig.-4: Mass Spectrometry (a) and Fragments (b) of Compound 1**
Reusable catalyst testing is carried out by using catalysts repeatedly in the same reaction. This magnetic catalyst is decanted with a magnet from the outside, which is then washed with ethanol. Later used for the next reaction. Figure-5 is a yield obtained from the repetition of 5 times usage. According to the table, the NiFe$_2$O$_4$ catalyst can still be used until the fourth month, with a yield of 40.82%.

**Fig.-5: Reusability of NiFe$_2$O$_4$ as the Catalyst (Compound 3)**

**DPPH Radical Scavenging Activity**

Based on the percent inhibition values obtained from several compound concentrations (Table-3), the curve between the % inhibition as the y-axis and the test solution concentration as the x-axis to determine the IC$_{50}$ value of each test solution. This value is calculated using the linear equation $y = ax ± b$. The calculation results in the IC$_{50}$ value of compound 1 are more significant than compound 2. So it can be said that compound 2 has better antioxidant activity than compound 1. This is possible because when the test compound inhibits radicals from DPPH compounds, the radicals formed in compound 2 are more stable than those formed in compound 1.

**Table-3: Antioxidant Activity Test With DPPH Method**

| Sample | % Inhibition | IC$_{50}$ (ppm) |
|--------|--------------|-----------------|
|        | 10000 ppm    | 8000 ppm        | 6000 ppm        | 4000 ppm        | 2000 ppm        | 2099.76          | 310.66           |
| Comp. 1| 79.53        | 75.93           | 70.17           | 58.64           | 46.54           | 2099.76          |                  |
| Comp. 2| 90.11        | 88.17           | 81.0            | 60.27           | 58.92           | 310.66           |                  |

**CONCLUSION**

NiFe$_2$O$_4$ MNPs catalyst was successfully synthesized by the co-precipitation method, and further analysis needs to be carried out on the allegation that the Ni element plays an active role as a catalyst while Fe as a supporting magnetic property. Reaction optimization was conducted by reacting benzaldehyde precursors (compound 1), cinnamaldehyde (compound 2), and 4-hydroxybenzaldehyde (compound 3), ammonium sulfate and ethyl acetoacetate with 0.3% mol of NiFe2O4 MNPs catalyst during 3.5 hours at room temperature. Percent yields of the product are 55.73%, 51.11%, and 83.23%, respectively. Compound 1 has IC$_{50}$ values of 2099.76 and 310.66 in compound 2. The catalytic activity decreases with repeated use of catalysts.

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