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OPTIMIZATION AND VALIDATION OF PARA AMINOPHENOL SYNTHESIS FROM NITROBENZENE USING HOMOGENEOUS ACID CATALYST

Eriawan Rismana[1,✉], Didik Sudarsono[2], Muhammad Irfan Fakhruddin[1], Ni Luh Indah Puspayani[1], Maya Damayanti Rahayu[1] and Susi Kusumaningrum[1]

[1]Research Center for Pharmaceutical Ingredients and Traditional Medicine, National Research and Innovation Agency, Cibinong, West Java, 16911, Indonesia
[2]Directorate of Regional Research and Innovation Policy, National Research and Innovation Agency, Jakarta, 10340, Indonesia
✉Corresponding author: Eria001@brin.go.id

ABSTRACT

Para-aminophenol (PAP) was synthesized from nitrobenzene through a two-step homogeneous acid catalyst reaction. In the first step, the intermediate of phenyl hydroxylamine was synthesized from the reduction of nitrobenzene with zinc. Next, the intermediate undergoes a Bamberger rearrangement in the presence of sulfuric acid into PAP. The PAP was purified with toluene extraction, an adsorption process with activated carbon, and crystalized by adjusting the pH solution. The reaction temperature, H_2SO_4 concentration, and reaction time on PAP yield were also optimized and validated. The process validation result showed that about 46.60 % PAP yield and 80 % PAP purification were obtained within the conditional process, such as a reaction temperature of 70°C, H_2SO_4 concentration of 1.5 M, reaction time of 150 min, and crystallization temperature of 5°C. Furthermore, the PAP product was identified with FT-IR and UPLC-MS. FT-IR spectrum showed pattern similarity with the standard of PAP, and the molar mass of the PAP synthesized measured by UPLC-MS was 109.23 g/mole, similar to PAP in the literature.

Keywords: *p*-Aminophenol; Nitrobenzene; Homogeneous Acid Catalyst; Phenyl hydroxylamine, Optimization, Validation

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INTRODUCTION

Para-aminophenol (PAP) is an intermediate chemical substance used in the production of antipyretic and analgesic drugs such as paracetamol in the pharmaceutical industry[1-3] and also used in photographic, chemicals, corrosion inhibitors, fragrances, and dyestuffs industries.[4] Para-nitrophenol can be reduced using the Fe-HCl reagent to produce PAP. This route has the disadvantage of producing a large amount of Fe-FeO sludge (1.2 kg/kg product) and difficulty controlling the reaction rate.[5-6]

This sludge causes significant disposal issues and makes it difficult to separate the reaction. Para-aminophenol can be synthesized by hydrogenating nitrobenzene using various supported noble catalysts in pressurized hydrogen gas.[7-10] This route has low selectivity with aniline as a by-product and high cost due to high temperature and pressure. Para-aminophenol was also synthesized via the transfer hydrogenation of nitrobenzene over a Pd/AC + SO_4^{2-}/ZrO_2 catalyst using formic acid as the hydrogen source.[11] Para-aminophenol can be synthesized by nitrobenzene involving a two-step reaction using Zn powder to become phenyl hydroxylamine as an intermediate and undergo a Bamberger rearrangement in the presence of a sulfuric acid. A significant side reaction is the production of aniline via further hydrogenation of phenyl hydroxylamine. It is the most promising route in the chemical industry, with the cheapest nitrobenzene reagent, high yield, and the lowest energy consumption. This study focused on optimizing PAP synthesis from nitrobenzene using a two-step reaction.

Nitrobenzene as a raw material is the result of product synthesis in an internal laboratory from the nitration process of benzene. The effect of reaction temperature, sulfuric acid concentration, and reaction time was evaluated to get the optimum conditions and discuss the production of PAP with homogeneous acid catalyst in detail. The PAP was characterized by Fourier Transform Infra-Red (FT-IR) and Ultra Performance Liquid Chromatography-Mass Spectrophotometry (UPLC-MS). The PAP synthesis technology is required due to Indonesia's high demand for paracetamol, which reaches 8,000

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tons annually. Until now, there has been no para-aminophenol industry in Indonesia, so the research aims to study and provide para-aminophenol production technology on a laboratory scale.

EXPERIMENTAL

Materials

Ammonium chloride (Merck), petroleum ether (Fulltime), and zinc (Merck) with pro-analysis grade were used for the synthesis of phenyl hydroxylamine from nitrobenzene. Nitrobenzene used for synthesis resulted from the nitration process of benzene (PT. TPPI Cilacap Indonesia). In addition, sulfuric acid (Merck), toluene (Merck), activated carbon (Merck), and ammonia solution (Merck) with pro-analysis grade were applied to research the synthesis of PAP from phenyl hydroxylamine.

Synthesis of Para-Aminophenol

In the glass reactor, 10 g nitrobenzene was added to 0.0550 M ammonium chloride solution, and 12 g of zinc powder was added to the solution under stirring for 30 minutes. The zinc reduction of nitrobenzene occurred with a rising temperature reaction until 60 – 65ºC. The mixture was filtered, and the filtrate was crystalized by saturating the aqueous solution with sodium chloride and cooling until 3ºC. The formed phenyl hydroxylamine crystal was separated and purified with petroleum ether. In the next step, phenyl hydroxylamine was added to 1.50 M H_2SO_4 solution in a glass reactor. The solution was mixed at 70ºC and stirred continuously for 2 hours. After the reaction, adjust the pH with the ammonia solution until pH 3. The residue was extracted using 100 mL toluene, and the extract was purified using 2 g of activated carbon. The clear solution was crystalized by adjusting the pH to pH 8 and cooling the solution. The PAP formed was filtered and dried in a vacuum oven for 2 hours at 60ºC.

Characterization

Para-aminophenol was analyzed using FT-IR and UPLC-MS. FT-IR with the brand Themo Scientific Nicolet iS10 was utilized to evaluate the chemical bond characteristic of the PAP with a spectrum range between 100 – 4,000 cm^{-1}. UPLC-MS with brand Waters Acquity has identified the molecular weight of the PAP using a PDA detector, C18 column packing, flowrate 0.4 mL/min, column temperature 35ºC, and mobile phase with formic acid and acetonitrile. The purity of PAP was determined using HPLC.

RESULTS AND DISCUSSION

Effect of Reaction Temperature

Fig-1 shows the effect of reaction temperature on the yield of PAP, which varied from 60ºC to 90ºC using a homogeneous acid catalyst and keeping the other condition reaction constant. The yield of PAP obtained using a reaction temperature at 60ºC, 70ºC, 80ºC, and 90 was respectively 46.58%, 48.04%, 45.56%, and 43.87% within an H_2SO_4 concentration of 1.5 M, a reaction time of 2 hours, and a crystallization temperature 5ºC. Based on the data, the optimum reaction temperature was 70ºC. Before reaching the optimum point, increasing the reaction temperature would increase the yield of PAP. After passing the optimum point, the higher the reaction temperature for PAP synthesis, the lower the PAP yield obtained. The reaction temperature significantly affected the synthesis of PAP because Bamberger rearrangement could switch to a full hydrogenation process from phenyl hydroxylamine to aniline, the main observed by-product with high temperature. In a low-temperature reaction, only part of the phenyl hydroxylamine reacted to PAP because it requires high energy for a high yield. Rode *et al*. also observed that increasing the reaction temperature would increase the rate constant parameter and the selectivity of PAP at temperatures up to 80ºC in PAP synthesis from nitrobenzene.[9] The further increase in reaction temperature from 80ºC to 100ºC would give a constant value for the reaction rate parameter and decrease the selectivity of PAP.

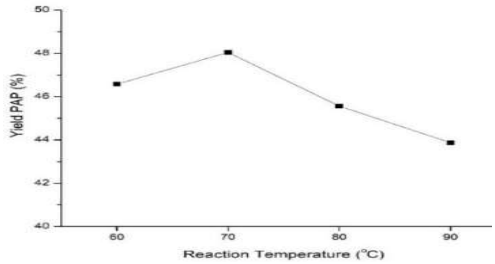


Fig.-1: Effect of Reaction Temperature on Yield of PAP

The higher the reaction rate constant, the higher the intermediate of phenyl hydroxylamine conversion, where phenyl hydroxylamine as an intermediate could transform into PAP as a product and aniline as a by-product.

Effect of Sulfuric Acid Concentration

In a Bamberger rearrangement of intermediate phenyl hydroxylamine to PAP, which is acid-catalyzed, it is essential to investigate the acid concentration effect on the yield and selectivity of PAP. Fig-2 shows the effect of sulfuric acid concentration on the yield of PAP while keeping the other condition reaction constant. The yield of PAP obtained with sulfuric acid concentrations varied from 0.80 M, 1.50 M, 2.20 M, and 2.90 M, respectively 36.31%, 48.04%, 47.37%, and 42.63% within a reaction temperature of 70ºC, a reaction time of 2 hours, and a crystallization temperature of 5ºC. The results suggest that the optimum sulfuric acid concentration was 1.5 M, with a PAP yield of 48.04%. Before reaching the optimum point, increasing sulfuric acid concentration would increase the yield of PAP because PHA could react with more sulfuric acid molecules. This could result from protons being more mobile at lower than higher acid concentrations. After passing the optimum point, the yield of PAP would decrease with increased sulfuric acid concentration. The amount of NH_4OH solution needed to raise the pH solution caused the total volume of the solution to be more significant. The amount of crystallized PAP would reduce as the solubility of PAP increased in the solution.

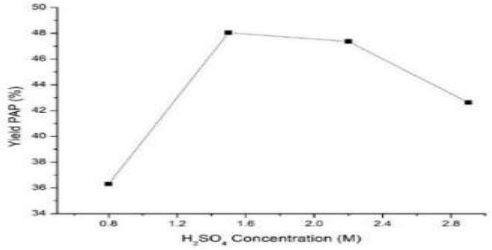


Fig.-2: Effect of H_2SO_4 Concentration on Yield of PAP

Effect of Reaction Time

Fig-3 shows the effect of reaction time on the PAP yield from the reduction of nitrobenzene using the same conditions reaction. The yield of PAP obtained using reaction time at 60 min, 90 min, 120 min, and 150 min was respectively 36.20%, 45.56%, 48.04%, and 50.52% within a sulfuric acid concentration of 1.50 M, a reaction temperature of 70ºC, and a crystallization temperature of 5ºC. The longer the reaction time of PAP synthesis, the higher the PAP yield produced. The synthesis of PAP takes a long time, which is required for the synthesis of PAP from PHA, up to 150 minutes.

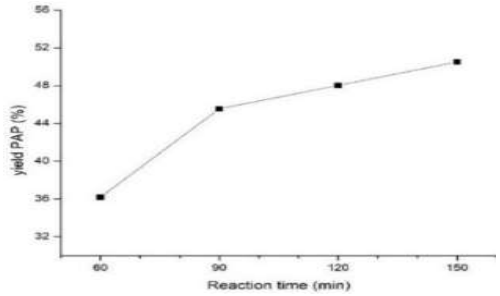


Fig.-3: Effect of Reaction Time to Yield of PAP

Validation Process

The validation process is carried out by applying the synthesis parameters under the optimization results, namely under reaction temperature 70ºC, H_2SO_4 concentration 1.5 M, and reaction time 150 minutes with crystalization temperature 5ºC. Validation was carried out with 3 repetitions. The yield of PAP synthesis validation is 45.19%, 46.69%, and 47.93%.

Characterized of Para-Aminophenol Product

The PAP was recovered as a solid product. Fig.- 4 shows the crystal of PAP. Qualitative analysis was carried out using the FT-IR spectrometry method to determine the quality of PAP. Fig.-5 shows the FT-IR spectrum of the PAP produced in this synthesis, while Fig.-6 shows the FT-IR spectrum of the standard PAP and PAP compound synthesized using a solid catalyst.

Fig.-4: PAP Synthesized Product

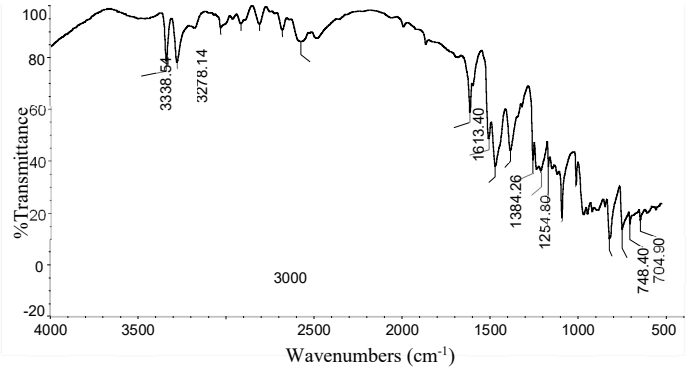


Fig.-5 : FT-IR Spectrum of PAP Synthesized Product

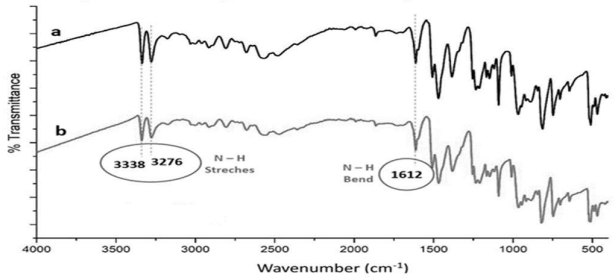


Fig.-6: FTIR Spectrum (a.) The Standard of PAP, (b.) PAP Synthesized Using a Solid Catalyst [12]

This characterization aims to compare the FT-IR test results of synthesized PAP products with USP grade PAP standards and PAP products with other synthesis methods. It can be seen that the two spectra have similarities in the peak patterns at specific wave numbers produced. This indicates that the synthesized PAP crystal product is qualitatively PAP product. The spectrum shows the presence of several peaks which are characteristic of PAP, namely having amine groups. The synthesized PAP has absorption peaks at wave numbers 3,278 cm^{-1} and 3,338 $cm^{-1,}$ which indicate the presence of stretching vibrations from amine bonds (N-H), and also has an absorption peak at wave number 1,613 $cm^{-1,}$ which means the presence of vibrations bending of the amine bond (N-H).[12] Apart from that, there is also absorption at wave numbers 1,310 cm^{-1} to 1,390 cm^{-1}, which indicates phenol compounds, and absorption at wave numbers 700 ± 20 cm^{-1}, which indicates benzene compounds.[13] This is because the structures of these two compounds are in the PAP structure. The molecular weight and purity of PAP were analyzed using UPLC and HPLC, respectively. The analysis has been carried out using the HPLC method to determine the purity of the synthesized PAP product. The chromatogram of the test results is shown in Fig.-7 and Fig.-8. Table-1 shows the HPLC test results that the PAP 1, PAP 2, and PAP 3 content from validation results, respectively, are 77.92%, 82.83%, and 82.65%.

Table-1: Purity of PAP

Sample Code	Content (%)		
	Test 1	Test 2	Mean
PAP 1	80.24	75.59	77.92
PAP 2	82.67	82.98	82.83
PAP 3	82.98	82.31	82.65

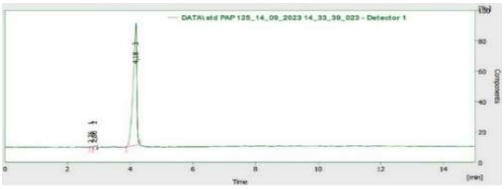


Fig.-7: Chromatogram of PAP Standard Compound

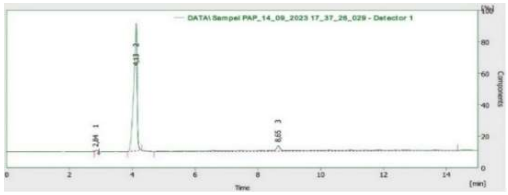
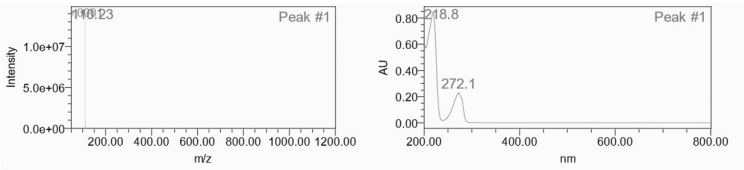


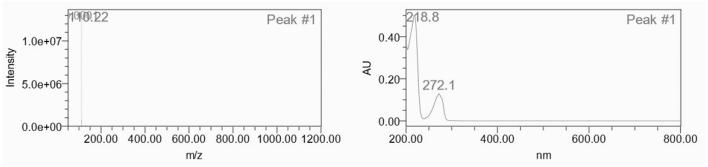
Fig.-8: Chromatogram of Synthesized PAP

UPLC Analysis

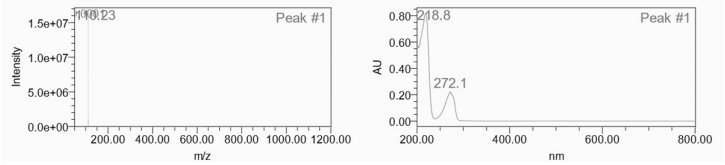
UPLC-MS will be used to identify the molecular weight of the synthesized PAP. After that, the molecular weight of the UPLC-MS test results will be compared with the literature, where the molecular weight of PAP is 109.13 g/mol. Fig.-9 is a graph of the UPLC-MS characterization test results for the PAP samples that have been synthesized. It can be seen that all samples show one highest peak at a retention time of 0.730 minutes with a lambda = 218.8 nm. After data integration, the observed molecular weight value is 109.23 g/mol. This value is the same as the molecular weight PAP in the literature, 109.13 g/mol. The results of the characterization data using UPLC-MS prove that the crystalline solid produced is PAP.



UPLC - MS of PAP 1



UPLC - MS of PAP 2



UPLC - MS of PAP 3

Fig.-9: Spectrum UPLC - MS of PAP Samples

CONCLUSION

This study shows that the conditions that produce optimum yield in the synthesis of para-aminophenol from nitrobenzene as raw materials using acid catalysts are at a reaction temperature of 70ºC, sulfuric acid concentration of 1.5 M, and synthesis reaction time takes up to 150 minutes. The validation results of para amino phenol production show that product yield and purity are 46.60 % and 80.00 %, respectively. Based on the FT-IR spectrum, synthesized PAP indicates the stretching vibration and has the bending vibration of the amine (N-H) bond, phenol bond, and benzene bond because the three compound structures are in the PAP structure. The results of determining the molecular weight of the para-amino phenol sample using UPLC show Mr = 109.23, similar to the standard molecular weight of para-aminophenol.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in research, wrote, reviewed/edited, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

E. Rismana http://orchid.org/0000-0002-7601-0673
D.Sudarsono http://orchid.org/0000-0002-5847-8715
S. Kusumaningrum http://orchid.org/0000-0002-5388-6285
M. D. Rahayu http://orchid.org/0009-0009-0807-952X
Muhammad Irfan Fakhruddin https://orcid.org/0009-0008-0176-3719
Ni Luh Indah Puspayani https://orcid.org/0009-0000-3751-0520

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