

GREEN ORGANIC SYNTHESIS OF N-METHYLPYRROLIDINE

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ABSTRACT

N-methylpyrrolidine was successfully synthesized in an aqueous medium by using methylamine and 1,4-dibromobutane in the presence of catalyst K_2CO_3 at a moderated temperature. Here, N-methylpyrrolidine was firstly synthesized via the green chemistry process, in which both the water solvent and potassium carbonate catalyst were inexpensive and environmentally friendly. Also, the reaction temperature was quite moderated at 90 °C. As a result, the current synthesis process was highly potential to implement in practice. Since the product yield directly depended on the operating conditions, the catalysts, temperature, ratio of reactants and solvent would be critical factors. In the present study, the structure of N-methylpyrrolidine product was confirmed by using the IR, 1H -NMR, ^{13}C -NMR and Gas Chromatography-Mass spectroscopy (GC-MS).

Keywords: tertiary amines, alkylation, aqueous media.

1. INTRODUCTION

N-methylpyrrolidine is a versatile intermediate used mainly in the synthesis of pharmaceuticals cefepime. This heterocycle is an important component of the cefepime which determines pharmacokinetic parameters and the exchange of drugs in the human body [1]. The pyrrolidine ring structure is also present in many natural alkaloids such as nicotine and hygrine, etc. Since the N-methylpyrrolidine product is significant and has a wide application, many studies have already paid much attention to it in order to achieve the highest yield product.

According to Champion et al [2], the N-methylpyrrolidine is synthesized via the reaction of N-methylpyrrolidone and hydrogen gas at a high pressure of 1000 - 5000 psig in the presence of copper chromite catalyst. The less than 50 % yield product of N-methylpyrrolidine is then isolated by extraction with an aliphatic hydrocarbon solvent. Subba Rao et al [3] also reported that the N-methylpyrrolidine could be synthesized via the cyclization reaction of 1,4-butanediol and methylamine as using the modified ZSM-5 catalysts. The results revealed that the yield product of N-methylpyrrolidine was only 10 % when the operating temperature was less than 300 °C. Also, the yield product was impossibly enhanced as increasing the temperature, because the side product of this synthesis process such as aromatics was remarkably facilitated when the temperature was over 300 °C. According to the Hofmann-Löffler-Freytag reaction [4], the N-

pyrrolidine derivatives are also synthesized from the N-alkyl-N-chloroamine, where the acid is used as regards the solvent of this synthesis process. N-methylpyrrolidine is also produced via pyrrolidine intermediate before methylation [5]. In industry, pyrrolidine can be synthesized from butanediol and ammonia over an aluminum thorium oxide catalyst at 300 °C or over a nickel catalyst at 200 °C and 20 Mpa under hydrogenation conditions [5]. Moreover, it can also be produced from THF and ammonia over aluminum oxide at 275 - 375 °C [5].

In Vietnam, it is definitely noted that there are not any studies of N-methylpyrrolidine synthesis as using the water solvent. In foreign countries, the previous studies indicated that the N-methylpyrrolidine synthesis was often carried out at a high temperature and pressure combined with a toxic solvent and an expensive catalyst, where the yield product of N-methylpyrrolidine was always less than 50 %. Therefore, a new synthesis process for the N-methylpyrrolidine product was essential to develop. In the present study, a green chemistry process with high efficiency, economic and environmental friendliness was developed to synthesize the N-methylpyrrolidine product, in which the water solvent and an inexpensive potassium carbonate catalyst were firstly applied in this synthesis process.

2. EXPERIMENTAL

The methylamine and 1,4-dibromobutan were purchased from Sigma-Aldrich and Acros Company, respectively, while the other reagents were commercial grade and purified according to the established procedures. The reactions were monitored by using the TLC on silica gel 60 F254 (0.25 mm). The molecules structure of N-methylpyrrolidine was confirmed by using the NMR, FT-IR and GC-MS spectra. Here, the NMR spectra were recorded in D₂O with tetramethylsilane as the internal standard for ¹H NMR (500 MHz) and D₂O solvent for ¹³C NMR (125 MHz). The FT-IR spectra were detected by the Bruker Tensor 27 spectrometer, while the GC-MS were recorded by using a capillary column (30 × 0.25 mm, 0.25 μm) in EI mode.

The reactants including methylamine and 1,4-dibromobutane combined with the catalyst were taken up in water and heated at 90 °C in a tube reactor for a period of 5.0 hours. The alkylation product was separated by distillation at 81 - 82 °C. The product as a clear colorless liquid was then identified by IR, NMR and GC-MS analysis. The NMR spectrum of N-methylpyrrolidine product in current work was illustrated as shown below:

¹H-NMR (500 MHz, D₂O/TMS) δppm 2.38 (s, 4H), 2.17 (s, 3H), 1.65 (s, 4H). ¹³C-NMR (125 MHz, D₂O/TMS) δppm 54.5 (-CH₂-CH₂-N), 40.1 (CH₃-N), 22.8 (-CH₂-CH₂-N). The DEPT-90 spectrum shows no signal, the DEPT-135 shows one positive CH₃ signal (δ 40.1), and two negative CH₂ signals (δ 54.5, 22.8). Satisfactory ¹H and ¹³C NMR data was consistent with those found in literature.

3. RESULTS AND DISCUSSION

3.1. Characteristic of N-methylpyrrolidine product

As shown in Fig.1, it was clearly indicated that the IR spectroscopy of N-methylpyrrolidine product (2964 – 2769 cm⁻¹: CH₂, CH₃) in current work obviously matched with the standard product, in which the structure of N-methylpyrrolidine was defined by the NMR spectrum that was described in above experimental section. Moreover, the structure of N-methylpyrrolidine was confirmed by GC-MS spectroscopy, where it has only one peak at 3.87 min of mean residence time corresponding to the 85.16 molecular weight fragment of N-methylpyrrolidine

product, as depicted in Fig. 2. As such, the current synthesis process was successful to synthesis the N-methylpyrrolidine product.

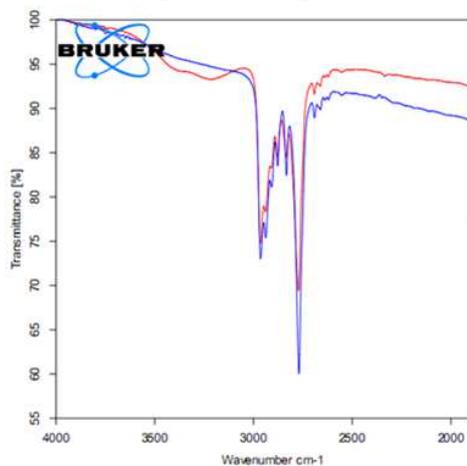


Figure 1. IR spectroscopy of N-methylpyrrolidine product in current work (red line) and standard one (blue line).

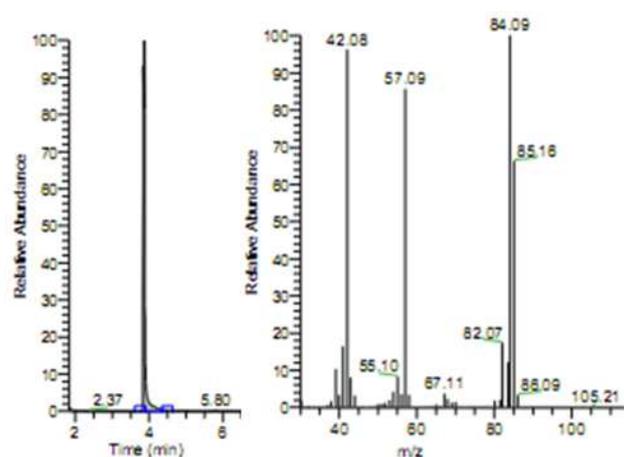


Figure 2. GC-MS spectroscopy of N-methylpyrrolidine product.

3.2. Synthesis of N-methylpyrrolidine product

The dissolution ability of methylamine in an aqueous medium provided a high potential to perform the N-alkylation reaction in aqueous media. As shown in Fig.3, the synthetic protocol includes a two-step alkylation of a primary amine with an alkyl dihalide to assemble two C-N bonds, where the structure of the substrate is a primary alkyl halide which has relatively unhindered sites, so the product was formed in a simple S_N2 -like sequential heterocyclization. In present study, the cyclization reaction of N-methylpyrrolidine was investigated in various operating conditions, where the temperature, inorganic base, solvent and ratio of reactants were considered as the key factors which impacted on the N-methylpyrrolidine yield product.

The typical transient behavior of the reaction was monitored in terms of the N-methylpyrrolidine yield product, as shown in Fig. 4. Here, the N-methylpyrrolidine yield product increased rapidly from 0.0 % to 50.3 % as the reaction time varied from 0.0 to 3.0 hours. After 3.0 hours, the yield product was almost invariant, implying a steady state of the N-alkylation reactions. As such, the N-methylpyrrolidine product could be harvested at the steady state after 3.0 hours of the reaction time. From the steady state of reaction, the influence of operating conditions including temperature, solvent, catalyst and ratio of reactants on the yield product was investigated. As shown in Fig. 5, the yield product gradually increased from 48.1 % to 50.3 % as increasing temperature from 80 °C to 100 °C and reached the highest yield at 90 °C. This result was expected in terms of the kinetic of the nucleophilic substitution (S_N^2) reaction, where it was normally promoted as increasing the temperature. However, further increasing the temperature over 100 °C, the yield product decreased dramatically. Here, the yield product quickly decreased from 50.3 % to only 39.4 % as increasing temperature from 100 °C to 160 °C. The decreasing yield product as further increasing the temperature was explained in term of the competition between the reduction reaction and the nucleophilic substitution (S_N^2) reaction, in which the reduction reaction was more facilitated than the nucleophilic substitution (S_N2) reaction at a higher temperature, so the product yield was certainly decreased as increasing

temperature at above 100 °C. Plus, when the temperature was over 100 °C as known the boiling point of water solvent, the liquid solvent transformed to the gas phase, so the kinetic of the nucleophilic substitution (S_n^2) reaction might be reduced, which resulted in decreasing the product yield of N-methylpyrrolidine. Accordingly, the temperature of the current synthesis process was chosen as 90 °C and fixed it in all later experiments.

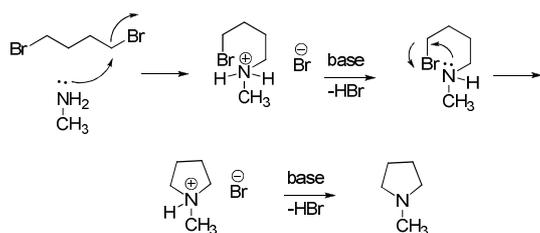


Figure 3. Reaction pathway of synthesis of N-methylpyrrolidine product.

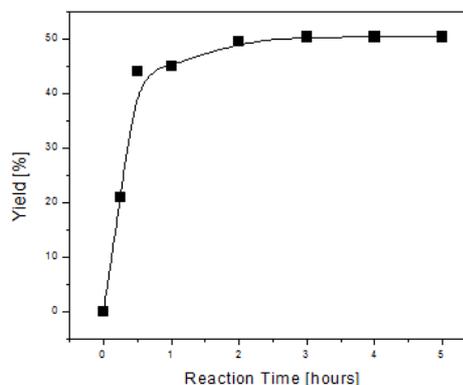


Figure 4. Transient profile of N-methylpyrrolidine yield product with the reaction time.

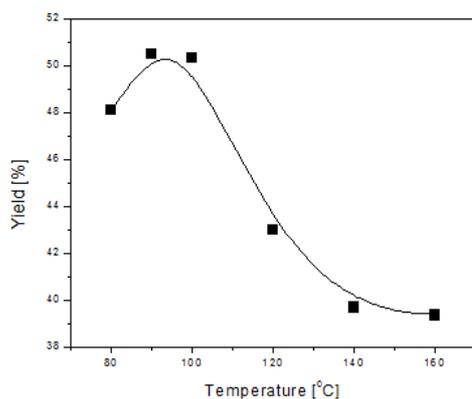


Figure 5. Influence of temperature on the N-methylpyrrolidine yield product.

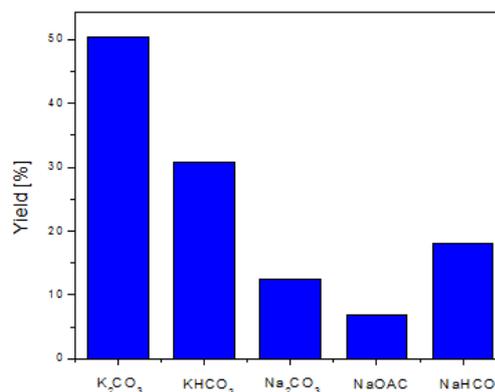


Figure 6. Influence of catalyst on the N-methylpyrrolidine yield product.

The N-methylpyrrolidine yield product was also investigated with different inorganic catalysts including K_2CO_3 , $KHCO_3$, Na_2CO_3 , $NaOAC$ and $NaHCO_3$, as shown in Fig. 6. The result indicated that the synthesis of N-methylpyrrolidine was performed in strong base conditions without any rapid hydrolysis of alkyl halide. Here, the highest yield product was 50.3 % as using the potassium carbonate (K_2CO_3) catalyst. The yield product with different catalysts flowed the order $K_2CO_3 > KHCO_3 > NaHCO_3 > Na_2CO_3 > NaOAC$, as depicted in Fig.6. The effect of these catalysts on the N-methylpyrrolidine synthesis mechanism was very complicated and unreported in any previous researches, so the mechanism should be further deeply studied. However, this result might be partly explained based on the pH and solubility of each catalyst. Here, the effect of catalyst on order of product yield as mentioned above might be explained in term of the order of pH and solubility, where the catalyst would provide a higher

yield product as it has a higher pH and solubility. For example, the potassium carbonate (K_2CO_3) catalyst had a higher pH (pH = 10.57) and solubility ($C_{eq} = 52.7$ g/L) compared to other catalysts, so it would provide a higher yield product. In present study, the potassium carbonate (K_2CO_3) was considered as the appropriate catalyst for the current synthesis process.

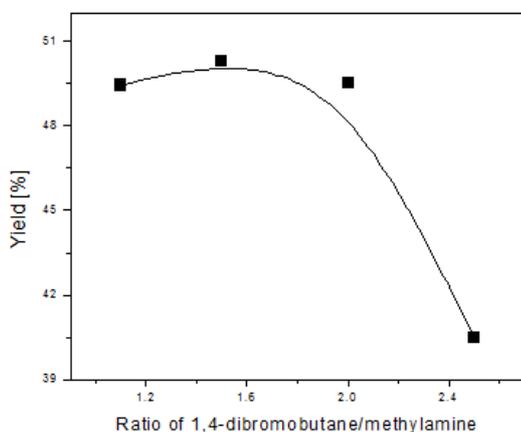


Figure 7. Influence of the ratio of 1,4-dibromobutane and methylamine on the yield product.

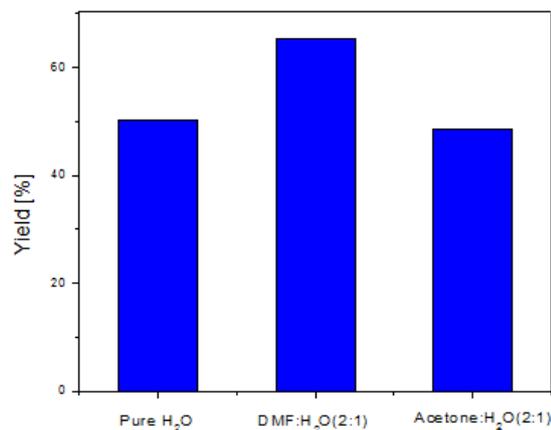


Figure 8. Influence of various solvent on the yield product of *N*-methylpyrrolidine.

The influence of ratio reactants of methylamine and 1,4-dibromobutane on the yield product was also demonstrated, as shown in Fig. 7. Here, the yield product slightly increased from 49.5 % to 50.3 % as increasing the ratio of 1,4-dibromobutane and methylamine from 1.0 to 1.5. However, further increasing the ratio of 1,4-dibromobutane and methylamine to 2.5, the yield product quickly dropped to 40.5 %. This result was expected in term of the alcohol derivative formation, where it was facilitated as increasing the ratio of 1,4-dibromobutane reactant, resulting in decreasing the the *N*-methylpyrrolidine yield product. Thus, the highest yield product in current work was found as 50.3 % when the ratio of 1,4-dibromobutane and methylamine was 1.5

The influence of different solvents on the yield product of *N*-methylpyrrolidine was also investigated, as shown in Fig.8. It was indicated that the yield product of *N*-methylpyrrolidine was 50.3 % as using the water solvent, while it was only 48 % and 65 % as using the acetone and DMF solvent at the same operating conditions, respectively. This result implied that the yield product in water solvent was more facilitated compared to that in other toxic and expensive solvent. As such, according to the green chemistry, the water solvent was an appropriate solvent for the synthesis *N*-methylpyrrolidine product.

4. CONCLUSIONS

The present study demonstrated that the green chemical process as using the water solvent, inexpensive catalyst (K_2CO_3) and moderate temperature (90 °C) was successfully applied for the *N*-methylpyrrolidine synthesis. Here, the yield product of *N*-methylpyrrolidine was obtained as 50.3 %, which was high and efficient compared to that in other toxic and expensive solvent. As such, the present synthesis process had more advantages over the conventional synthesis process in term of the efficiency, economic and environmental friendliness. Since the present synthesis

process was simplicity, low cost and environmental friendliness, it had a highly potential to implement in practice.

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TÓM TẮT

TỔNG HỢP N-METHYLPYRROLIDIN THEO PHƯƠNG PHÁP HÓA HỌC XANH

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N-methylpyrrolidine đã được tổng hợp thành công trong môi trường nước với tác chất phản ứng ban đầu là methylamin và 1,4-dibromobutan trong sự hiện diện của xúc tác K_2CO_3 tại nhiệt độ trung bình. Trong nghiên cứu này N-methylpyrrolidin lần đầu tiên được tổng hợp theo con đường hóa học xanh, trong đó cả dung môi nước và xúc tác K_2CO_3 đều kinh tế và thân thiện với

môi trường. Bên cạnh đó nhiệt độ thực hiện phản ứng trung bình khoảng 90 °C. Do đó quá trình tổng hợp này có tính khả thi cao khi ứng dụng trong thực tế. Khi hiệu suất của phản ứng phụ thuộc trực tiếp vào các điều kiện vận hành thì xúc tác, nhiệt độ, tỉ lệ giữa các tác chất và dung môi sẽ đóng vai trò then chốt. Cấu trúc của sản phẩm N-methylpyrrolidin được xác định bởi các loại phổ IR, ¹H-NMR, ¹³C-NMR và GC-MS.

Từ khóa: amin tam cấp, phản ứng alkyl hóa, phản ứng trong môi trường nước.