

Synthesis of *N*-Methylmorpholine from Morpholine and Dimethyl Carbonate

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The synthesis of *N*-methylmorpholine from morpholine and dimethyl carbonate was investigated. The effects of reaction variables upon the formation of the compounds were also examined. Under the optimized conditions, higher yield of *N*-methylmorpholine 83 % was obtained and the selectivity of *N*-methylmorpholine was 86 %. The mechanism on formation of product and undesired product was proposed based on the experimental results.

Key Words: *N*-Methylation, Dimethyl carbonate, Morpholine, *N*-Methylmorpholine.

INTRODUCTION

N-Methylmorpholine (NMM) is one kind of heterocyclic amine, it is significantly important in the bulk and fine chemical industry as versatile building blocks for pesticide, herbicide, fungicide, coolant lubricant, surfactant¹. *N*-Methylmorpholine is also used as an extractive solvent and anticorrosive agent². And its derivative *N*-methylmorpholine-*N*-oxide (NMMO) is used in transition metal-catalyzed oxidations of various organic structures and can possibly be regarded as the most important amine *N*-oxide in organic synthesis and *N*-methylmorpholine-*N*-oxide has found major interest due to its ability to dissolve cellulose, it is nowadays used as a bulk solvent in industrial fiber-making processes (Lyocell process)^{3,4}.

With the growing wide range of applications, the development of efficient methods for the synthesis of *N*-methylmorpholine continues to be a challenging and active area of research. The conventional process is *via* methylating of morpholine with methyl halides but this process is limited due to the storage of the toxic methyl halides and byproduct waste salts¹. The *N*-methylation of morpholine by methanol was carried out by Zotto *et al.*⁵ and Chen *et al.*¹ who used ruthenium complexes or CuO-NiO/ γ -Al₂O₃ catalyst.

Dimethyl carbonate (DMC) is a green chemical reagent, it can be used as a valuable methylating reagent which can replace methyl halides and dimethyl sulfate in the methylation⁶⁻¹³. *N*-Methylation of morpholine by dimethyl carbonate was studied by Borredon *et al.*¹⁴ they used a reactor equipped

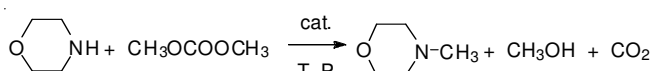
with stirring system, thermometer and surmounted by a distillation column and reflux condenser. The yield of *N*-methylmorpholine was 43 %.

In this paper, a green route for the synthesis of *N*-methylmorpholine from morpholine and dimethyl carbonate is investigated (**Scheme-I**), the possible side reaction was *N*-carboxymethylation of morpholine (**Scheme-II**). Compared with other method, this route is becoming an attractive one. The other byproducts are methanol and carbon dioxide. In addition, the byproduct methanol can be used to produce DMC by the oxidation carbonylation. The reaction conditions were examined, higher yield of *N*-methylmorpholine 83 % was obtained and the selectivity of *N*-methylmorpholine was 86 %. The mechanism on formation of product and byproducts was proposed based on the experimental results.

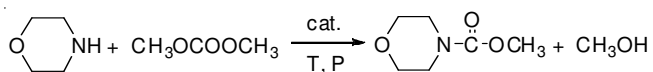
EXPERIMENTAL

Morpholine (98.5 %) was purchased from Shanghai Lingfeng Chemical Regent Co., Ltd. (Shanghai, China). Dimethyl carbonate (99.7 %) was purchased from Hebei Tangshan Chaoyang Chemical Co. Ltd. (Hebei, China). Methanol (99.9 %) was purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). *N*-Ethylmorpholine (99.0 %) was purchased from Aladdin Chemistry Co. Ltd. (Shanghai, China). All of the chemicals were used as received without further treatment.

General procedure: All the reactions were carried out in a 250 mL stainless autoclave with magnetic stirrer. The reactants



Scheme-I: A green route for the synthesis of *N*-methylmorpholine from morpholine and dimethyl carbonate



Scheme-II: The possible side reaction of morpholine with dimethyl carbonate: *N*-carboxymethylation of morpholine

and the catalyst were charged into the reactor. The mixture was then stirred constantly and heated to a desired temperature for certain time. When the reaction was completed, the autoclave was cooled down to room temperature then the reaction mixture was removed from the autoclave for analysis.

Analysis method: The products were identified by GC-MS (SHIMADZU GCMS-QP2010 Ultra). The product solution was analyzed by GC (Shanghai GC-112 A) with a flame ionization detector and a column of SPBTM-50 (30 m × 0.25 mm × 0.25 μm), *N*-ethylmorpholine was used as an inner standard agent. The conversion of morpholine (C_M), the yield and selectivity of *N*-methylmorpholine (Y_{NMM} , S_{NMM}) were calculated from the results of GC analysis.

RESULTS AND DISCUSSION

Qualitative analysis and quantitative analysis: In order to qualitatively analyze the undesired products, the reacted liquid was analyzed by GC-MS, the reconstruct ion chromatogram of product was shown in Fig. 1. According to the GC-MS results, the residence time = 3.976 min (RT = 3.976 min) (the main ion peaks of characteristic fragment in Fig. 2) was *N*-methylmorpholine; the RT = 4.057 min (the main ion peaks of characteristic fragment in Fig. 3) was morpholine; the RT = 9.017 min (the main ion peaks of characteristic fragment in Fig. 5) was methyl morpholine-4-carboxylate; the RT = 4.283 min (the main ion peaks of characteristic fragment in Fig. 4) and the RT = 13.827 min (the main ion peaks of characteristic fragment in Fig. 6) were probably the products of ring-opening reaction of morpholine.

The quantitative analysis of products were detected by GC, using internal standard analysis method, the internal standard material is *N*-ethylmorpholine (NEM).

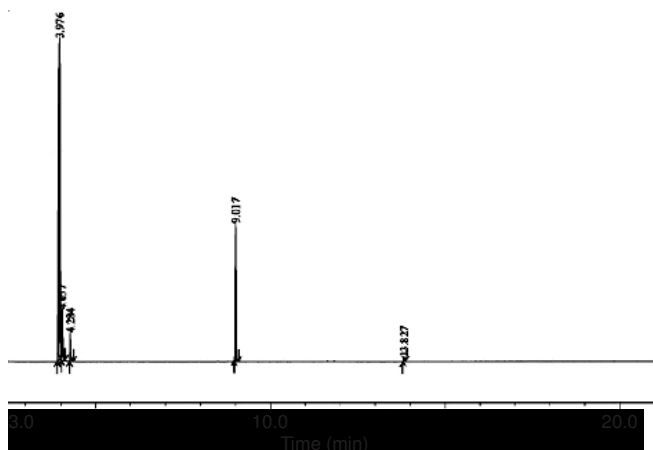


Fig. 1. Reconstruct ion current chromatogram of the product

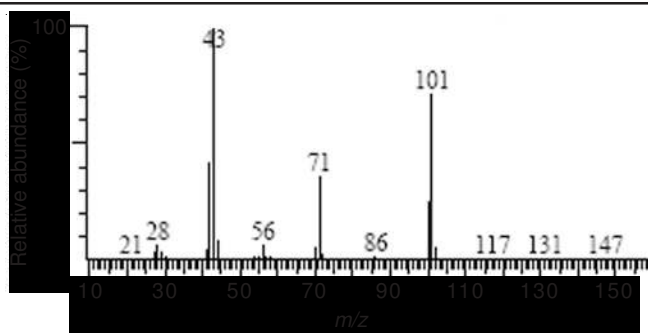


Fig. 2. The spectra of RT = 3.976 min

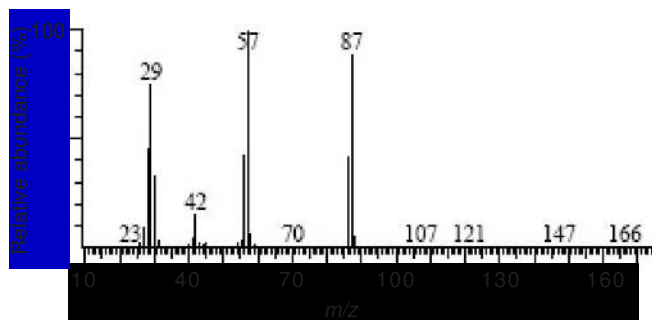


Fig. 3. The spectra of RT = 4.057 min

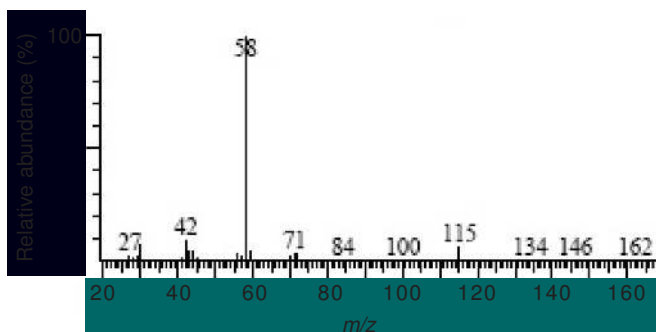


Fig. 4. The spectra of RT = 4.283 min

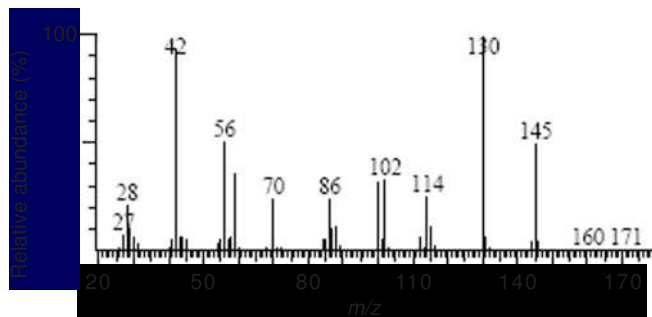


Fig. 5. The spectra of RT = 9.017 min

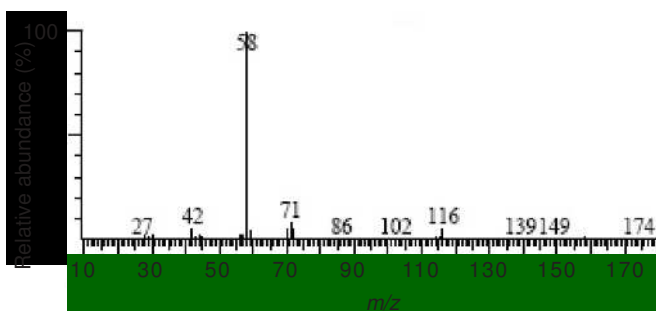


Fig. 6. The spectra of RT = 13.827 min

Effect of reactors: In order to obtain the effect of different reactors on the property of reaction, the atmospheric pressure device (reflux unit) and high-pressure device (autoclave) were studied (Fig. 7). The methylation performance of morpholine with dimethyl carbonate which occurred in autoclave had greatly improved than that in the reflux unit. So, subsequent experiments were carried out in the autoclave.

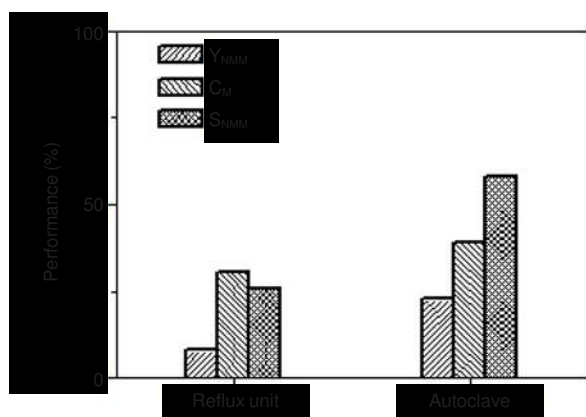


Fig. 7. Effect of different reactors on the property of reaction, experimental conditions: morpholine 0.50 mol, n(dimethyl carbonate):n(morpholine) = 1:1, without catalyst, reaction temperature: 100 °C, reaction time: 1 h

Effect of methylating agents: As the reaction of dimethyl carbonate and morpholine can produce methanol and methanol can be used as a methylating reagent, in order to examine whether the methylation reaction of morpholine and dimethyl carbonate was effected by produced methanol under the reaction condition, the two agents, dimethyl carbonate and methanol were respectively reacted with morpholine under the same conditions (Fig. 8). The yield of *N*-methylmorpholine was 72 % when using dimethyl carbonate as methylating agent, the yield of *N*-methylmorpholine was only 0.24 % when using methanol as methylating agent. The methylation performance of morpholine with dimethyl carbonate was obviously superior to that with methanol, the effective methylating agent was dimethyl carbonate under the reaction condition.

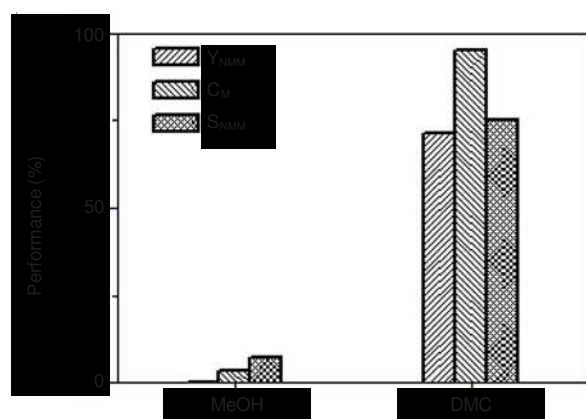


Fig. 8. Effect of different methylating agents on the property of reaction, experimental conditions: morpholine 0.50 mol, n(dimethyl carbonate):n(morpholine)=1:1, n(MeOH):n(morpholine)=1:1, without catalyst, reaction temperature: 160 °C, reaction time: 1 h

Effect of dimethyl carbonate/morpholine molar ratio: The effect of dimethyl carbonate/morpholine molar ratio on

conversion of morpholine, yield of *N*-methylmorpholine and selectivity of *N*-methylmorpholine at 160 °C was presented in Fig. 9. The results show that the ratio of n(dimethyl carbonate)/n(morpholine) impacted greatly on the reaction results, with n(dimethyl carbonate)/n(morpholine) ratio increased, the yield of *N*-methylmorpholine declined. Mainly because when dimethyl carbonate content increased, there would be more undesired product generated. Therefore, as the reaction temperature maintained at 160 °C, when dimethyl carbonate/morpholine molar ratio closes to the stoichiometric ratio (1:1) was regarded as optimum.

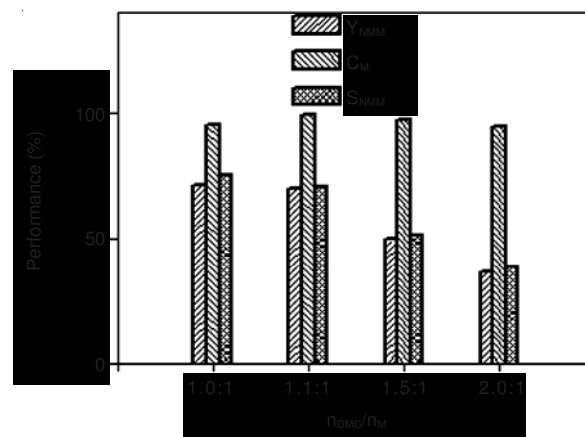


Fig. 9. Effect of n(dimethyl carbonate)/n(morpholine) ratio on the property of reaction, experimental conditions: morpholine 0.50 mol, without catalyst, reaction temperature: 160 °C, reaction time: 1 h

Effect of reaction time: The effect of reaction time on conversion of morpholine, yield of *N*-methylmorpholine and selectivity of *N*-methylmorpholine at 160 °C is presented in Fig. 10. The results show that with the extension of reaction time, the conversion of morpholine changed a little, but the yield of *N*-methylmorpholine and the selectivity of *N*-methylmorpholine increased gradually. It can be conducted methyl morpholine-4-carboxylate can transfer to *N*-methylmorpholine with increasing the times. When morpholine reacted with dimethyl carbonate for 8 h, the yield of *N*-methylmorpholine was 83 % and the selectivity of *N*-methylmorpholine was 86 %.

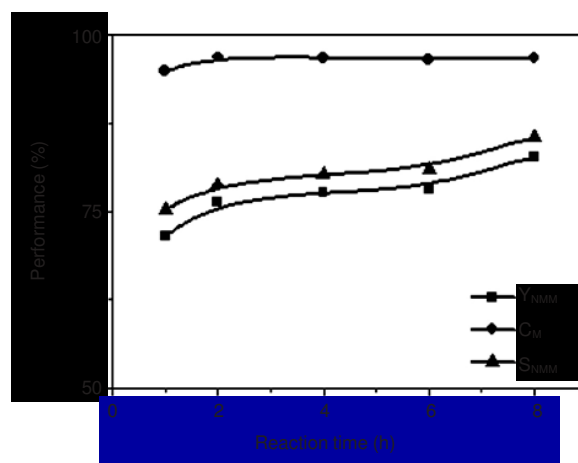


Fig. 10. Effect of reaction time on the property of reaction, experimental conditions: morpholine 0.50 mol, without catalyst, n(dimethyl carbonate)/n(morpholine) = 1:1, reaction temperature: 160 °C

Effect of reaction temperature: As the reactions were carried out in autoclave, the reaction temperature higher than the boiling point of dimethyl carbonate (90 °C) was able to be obtained. Fig. 8 shows the effect of reaction temperature on conversion of morpholine, yield of *N*-methylmorpholine and selectivity of *N*-methylmorpholine at a dimethyl carbonate/morpholine molar ratio of 1.0. From Fig. 11, we can see that the yield of *N*-methylmorpholine and the selectivity of *N*-methylmorpholine gradually increased with the reaction temperature increased, the high temperature (≥ 140 °C) was beneficial to the methylation reaction of morpholine with dimethyl carbonate, low temperature was beneficial to *N*-carboxymethylation. The result is consistent with that reported by Tundo *et al.*⁶⁻⁸, high temperatures is beneficial to methylation reaction of dimethyl carbonate.

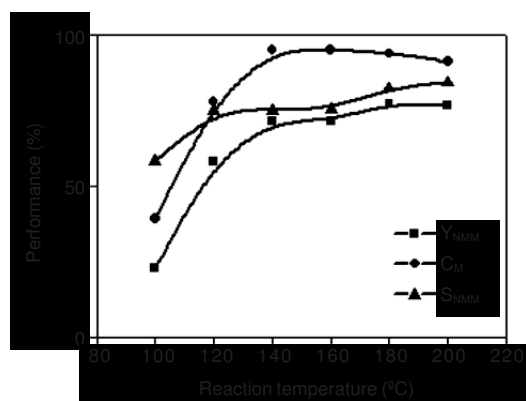
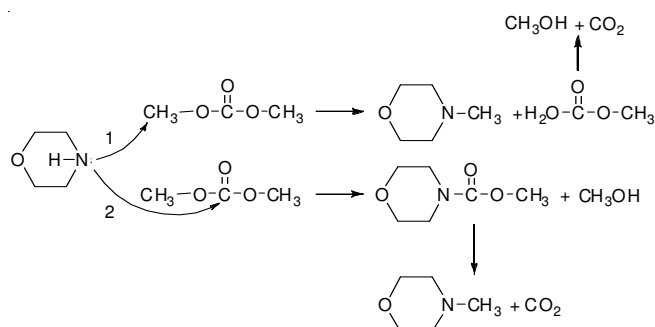


Fig. 11. Effect of reaction temperature on the property of reaction, experimental conditions: morpholine 0.50 mol, without catalyst, $n(\text{dimethyl carbonate})/n(\text{morpholine}) = 1:1$, reaction time: 1 h

Proposed reaction mechanism: The reactions mentioned above were carried out without catalyst and the reactions were also studied in the presence of catalysts (not shown here), but the performance of reaction was not obviously improved. This is mainly due to the self-catalysis of morpholine. Because morpholine is a weak base, the lone pair electrons of the N atom of morpholine is nucleophilic and it can attack the methoxy carbon atom of dimethyl carbonate to form *N*-methylmorpholine or it can attack the methoxy carbonyl carbon atom of dimethyl carbonate to form morpholine-4-carboxylic acid methyl, then morpholine-4-carboxylic acid methyl can transfer to *N*-methylmorpholine. The plausible mechanism of formation of *N*-methylmorpholine by using morpholine reacted with dimethyl carbonate could be represented as shown in **Scheme-III**.



Scheme-III: The plausible mechanism of formation of *N*-methylmorpholine by using morpholine reacted with dimethyl carbonate

Conclusion

Morpholine can be *N*-methylated by dimethyl carbonate to yield heterocyclic *N*-methylmorpholine. The experimental results revealed that the methylation performance of morpholine with dimethyl carbonate which occurred in autoclave had greatly improved than that in the reflux unit. Compared with methanol, dimethyl carbonate was the effective methylating agent under the reaction conditions. The reaction conditions including molar ratio of starting materials and reaction temperature evidently influenced the formation of *N*-methylmorpholine. When $n(\text{dimethyl carbonate})/n(\text{morpholine})$ closes to the stoichiometric ratio (1:1) was regarded as optimum. The yield and the selectivity of *N*-methylmorpholine gradually increased with the reaction temperature increased, the high temperature (≥ 140 °C) was beneficial to the methylation reaction of morpholine with dimethyl carbonate. Based on these experiments, the plausible mechanism of formation of *N*-methylmorpholine by using morpholine reacted with dimethyl carbonate were proposed.

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