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In situ DRIFTS study on the synthesis of *N*-alkylmorpholines

**Chenxi Luo · Hu Luo · Chao Qian · Yunbin Chen ·
Lie Feng · Xinzhi Chen**

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Abstract In situ diffuse reflectance Fourier-transform infrared spectroscopy was used to perform mechanistic investigation on the synthesis of *N*-alkylmorpholines from diethylene glycol (DEG), alcohol and ammonia. The results showed that the synthesis of *N*-alkylmorpholines on a heterogeneous catalyst proceeded along the reaction path between DEG and alkylamine when choosing CuO–NiO/γ-Al_2O_3 as a suitable catalyst. In addition, the yield of methylmorpholine and ethylmorpholine was 86.4 and 76.6 %, respectively.

Keywords In situ DRIFTS · *N*-alkylmorpholines · Mechanism · Synthesis

Introduction

N-Alkylmorpholines play an important role in the production of many chemical compounds including surfactants, dyes, pesticides, preservatives, herbicides, rubber accelerator, lubricants and medicinal intermediates [1–3]. For example, *N*-alkylmorpholines can be used as important blocks in many pharmaceutical compounds such as moclobemide for depression, fominoben for antitussive, morphocycline for infection and the diagnosis of lung cancer, bimolane for psoriasis, and so on (Fig. 1). Given its versatility, exploring more efficient synthesis of *N*-alkylmorpholines is still attracting much attention [4, 5].

There are two main methods of synthesizing *N*-alkylmorpholine. A traditional method is substitution on morpholine with alkyl halides, which is efficient but

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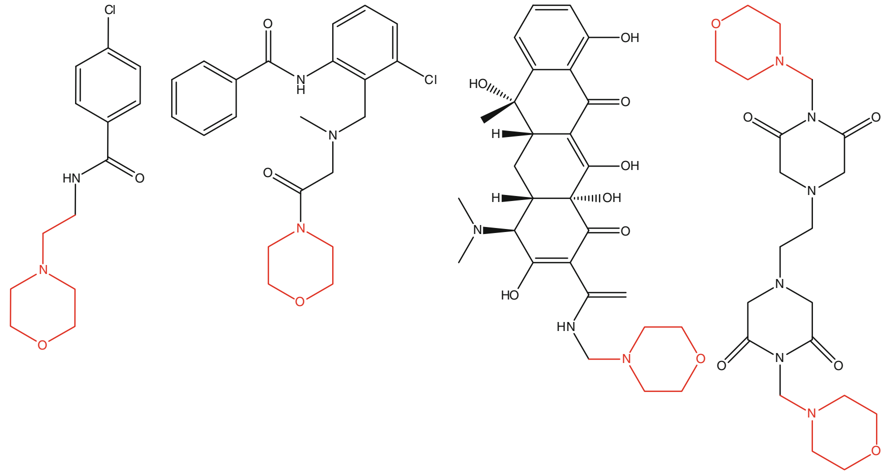
C. Luo · H. Luo · C. Qian · X. Chen (✉)
Department of Chemical and Biological Engineering, Zhejiang University,
Hangzhou 310027, People's Republic of China
e-mail: eric8948@163.com; xzchen@zju.edu.cn

Y. Chen · L. Feng
Zhejiang Jianye Chemical Co., Ltd., Jiande 311600, People's Republic of China

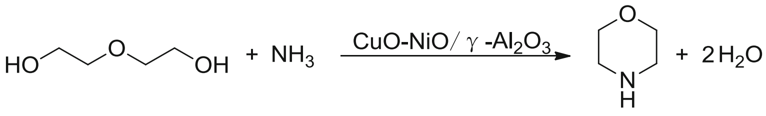


moclobemide fominoben morphocycline bimolane

Fig. 1 *N*-Alkylmorpholines used as important blocks in pharmaceutical compounds

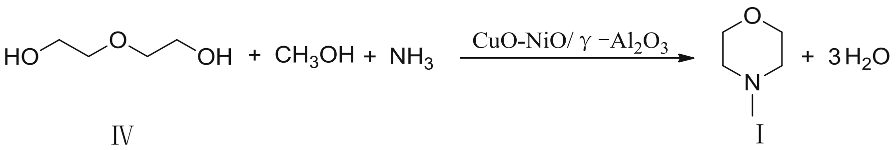
limited by involving mutagenic halides and much effluent. Moreover, polyalkylation decreases the selectivity [6]. In response, metal-catalysed alkylation of amines with alcohols was developed recently, which employs DEG, alcohol and ammonia as the starting materials. Although the mechanism of synthesis of morpholine(III) has been reported, the mechanism of synthesis of *N*-alkylmorpholines remains unknown [7, 8]. Considering that the monoalkylated products can be obtained with high selectivity and that the approach is of less pollution [9], investigation on the mechanism of synthesis of *N*-alkylmorpholines from alcohol, ammonia and DEG is of significant importance. In this work, CuO–NiO/γ-Al_2O_3 [10, 11] was used as catalyst, and a mechanism of synthesizing *N*-alkylmorpholines was proposed on referring previous mechanism of synthesis of morpholine through the study of the mechanism of synthesis of methylmorpholine and ethylmorpholine (Schemes 1, 2, 3).

In situ diffuse reflectance Fourier transform infrared spectroscopy (DRIFTS) was used to explore the mechanism of synthesis of *N*-alkylmorpholines from DEG(IV), alcohol and ammonia. Because of its high sensitivity to surface species [12], the in situ DRIFTS is a powerful tool for the investigation of adsorbed species and active sites [13, 14]. This technique was frequently used in investigating the active sites,

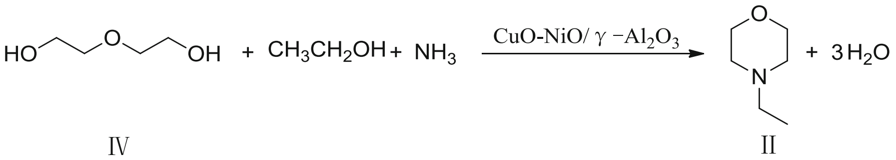


IV III

Scheme 1 Improved synthesis of morpholine(III)



Scheme 2 Improved synthesis of methylmorpholine(I)



Scheme 3 Improved synthesis of ethylmorpholine(II)

the adsorbed species and the intermediates on the catalyst surface under reaction conditions [15, 16]

Theoretical

Diffuse reflectance infrared obeys the Kubelka–Munk theory. While most quantitative analysis assumes that the sample is infinitely thick, so the Kubelka–Munk equation can be simplified as:

$$f(R_\infty) = \frac{(1 - R_\infty)^2}{2R_\infty} = \frac{k}{s}$$

$$k = 2.303\varepsilon c$$

where $f(R_\infty)$ is the function of K–M, R_∞ represents the reflectivity of the infinite thick sample, k represents the molar absorption coefficient of the sample, s represents the scattering coefficient of the sample, ε represents molar absorption rate of the sample, and c represents the molar concentration of the sample. It can be seen from the equation that the function of K–M is proportional to c (the molar concentration of the sample), which provides a basis for quantitative analysis of diffuse reflectance infrared.

Experimental

Catalyst preparation

CuO–NiO/γ-Al_2O_3 was prepared using an impregnation method in a proper Cu/Ni ratio. Firstly, the nitrates aqueous was prepared with Cu and Ni concentration of 17.1 wt.% and 4.3 wt.%, respectively. Secondly, the support, γ-Al_2O_3 ($S_{BET} = 220 \sim 250 m^2 g^{-1}$, $\Phi = 2 \sim 3$ mm) was calcined at 450 °C for 3 h and

850 °C for 6 h in a muffle furnace, then dipped in the nitrates aqueous for 36 h, and the decrement of water volume was measured to determine the pore volume. The measured pore volume density of the calcined γ-Al_2O_3 was 0.9 mL g^{-1}. Then, 4.26 g of $Ni(NO_3)_2 \cdot 6H_2O$, 12.91 g of $Cu(NO_3)_2 \cdot 3H_2O$ and 12 g of H_2O were formulated into a solution. In addition, the 15.72 g of calcined γ-Al_2O_3 was impregnated with the above-mentioned solution for sufficient time for the solution to be absorbed completely, and dried at 60 °C for 3 h under stirring, and then the filtered catalyst was calcined at 280 °C for 6 h, and cooled to room temperature (the suitable volume of carrier was selected in order to ensure that its pore volume was equal to that of the above-mentioned solution). The specific surface area of the compounds was 178.7 m^2 g^{-1}, the pore volume was 0.36 mL g^{-1} and the pore diameter was 17.2 nm.

In situ DRIFTS procedure

As shown in Fig. 2, the in situ DRIFTS spectra were recorded on a Nicolet 5700-FTIR (Fourier transform infrared) equipped with a MCT/A detector cooled by liquid N_2. A gas-handling system was connected to a Spectra-Tech0030-91 high temperature high pressure reaction cell in situ with ZnSe windows, light transmission range of 5,000–500 cm^{-1}. All spectra were measured with a resolution of 8 cm^{-1} and an accumulation of 64 scans. All gas mixtures were fed at a flow rate of 15–25 mL min^{-1} controlled by Brooks 5850E mass flow meter (MFC). A CN8500-type temperature control unit was used for heating and temperature control accuracy of ± 1 °C; the maximum temperature was 900 °C.

At the start, 1.5 g CuO–NiO/γ-Al_2O_3 was placed in a ceramic crucible. Prior to each experiment, the valves of V2 and V4 were opened while the others remained

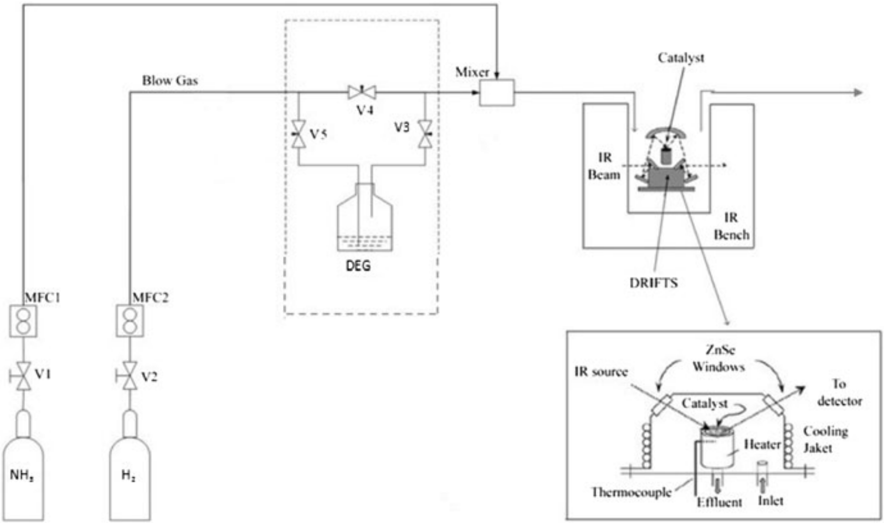


Fig. 2 Diffuse experimental setup

closed. The catalyst was first heated in a flow of 15 mL min^{-1} H_2 for 60 min at 513 K until the infrared absorption signal remained stable, which showed that the activation of the catalyst was completed. Second, the temperature of the ceramic crucible was adjusted to the desired temperature of the reaction. Then, the temperature, atmospheric pressure, the flow of 15 mL min^{-1} H_2 and a desired spectrum of the catalyst in the flow of H_2 serving as the background were recorded. Finally, the valves of V1, V3 and V5 were opened, then the raw materials such as DEG(IV) and alcohols were bubbled into the ceramic crucible by hydrogen and reacted with NH_3; hydrogen was used to protect and activate the catalyst. At the same time, recording IR data was begun based on the background spectrum.

The reaction mixtures were analyzed by gas chromatography [Agilent 1790F fitted with a flame ionization detector (FID) and a SE-30 column (50 cm long); Nanjing Xuxi Apparatus, China) and GC–MS (TRACE G2000/TRACE MS; ThermoQuest, USA] by comparing with the standard sample when nitrogen was used as carrier gas. The GC conditions are shown in Table 1. The yields were determined by an external standard method. To begin with, nine different arithmetic concentration standard samples were prepared around the probable concentration of the analyte. Secondly, the samples were analyzed by GC at the same injection volume. Additionally, a scatter diagram was drawn with the concentration of the standard sample as the x axis and the peak area as the y axis, and a linear regression was made. Finally, the reaction mixture was analyzed by GC at the same injection volume as the standard samples, and the concentration was calculated on basis of the peak area by comparing with the scatter diagram.

Results and discussion

Catalyst activity test

The synthesis of *N*-alkylmorpholines from DEG(IV), methanol and ammonia in gas–solid phase was investigated in a fixed-bed reactor over CuO–NiO/γ-Al_2O_3. The reaction was efficient for primary alcohols with high conversion and selectivity under optimum conditions. The results showed that CuO–NiO/γ-Al_2O_3 was a suitable catalyst for the synthesis of *N*-alkylmorpholines (Table 2).

Effect of the different carrier and gas flow on the reaction

Because of its dark brown color, the CuO-NiO/γ-Al_2O_3 used in the experiment has a strong absorption of infrared radiation, combined with the weak diffuse reflectance

Table 1 The GC conditions

Column head pressure (MPa)	Column temperature (°C)	FID detector with temperature (°C)	Inlet temperature (°C)	Column heating rate (°C min^{-1})
0.1	260	260	100	20

Table 2 The results of the synthesis of *N*-alkylmorpholines

Target product	Molar ratio	Temperature (°C)	Hydrogen pressure (MPa)	LHSV[a] (h^{-1})	Conversion (%)	Selectivity (%)
Methylmorpholine	(DEG):(methanol):(ammonia) = 1:1:6	220–225	1.0	0.25	99.4	86.9
Ethylmorpholine	(DEG):(ethanol):(ammonia) = 1:1:6	220–225	0.9	0.25	98.5	77.8

[a] LHSV represents the liquid hourly space velocity, LHSV $= \frac{\text{Volume flow of raw materials}}{\text{Volume of catalyst}}$ (h^{-1})

infrared signal. The infrared absorption signal becomes so weak that it is necessary to add an appropriate carrier to dilute the catalyst. However, the absorption peak signal of the catalyst which contained Al_2O_3 is stronger and more informative than KBr, so Al_2O_3 is superior as the catalyst carrier.

In addition, determining a reasonable gas flow is all-important. Excessive gas flow will blow the sample powder into the pipe, causing two negative effects: the pipe will be blocked, and the spectral quality will be lowered as the surface of the catalyst is uneven. After a series of tests, the total gas flow was fixed to $15 \sim 25$ mL min^{-1}, in which H_2 flow is 15 mL min^{-1}. The total gas flow was controlled by adjusting the NH_3 flow.

The mechanism of the synthesis of morpholine(III)

In the en suite DRIFTS spectrum of the synthesis of morpholine(III) from DEG(IV) and ammonia (as shown in Fig. 3), the presence of bands in difference spectra at around 3338, 1740, 1710, 1635, 1550 and 1510 cm^{-1} can be observed (Table 3). The sharp and single peak at 3,338 cm^{-1} is attributed to –N–H, therefore the reaction between C and E (Scheme 4) were rapid and the sharp peak was attributed to the compounds D, G and I. The pair bands at 1,740 and 1,710 cm^{-1} are attributed to the aldehyde B and F, whereas the bands are so small that sometimes they are unable to identify. Thus it can be concluded that the intermediate is unstable and prone to convert to the product. Adsorption of C=N (D and H) lead to the appearance of a large and stable band at 1,635 cm^{-1} which is attributed to the imine. The result indicated that the presence of the imine intermediate (D and H) is stable during catalytic amination of alcohol. The dehydrogenation, amination and dehydration are rapid while the hydrogenation of imine is slow. In addition, a double peak at 1,550 and 1,510 cm^{-1} is attributed to the carbon deposition. The size of the absorption peak increased with the reaction time and the temperature (the carbon deposition was formed mainly by two ways, one was the solid carbon enrichment generated through the condensation and dehydrogenation process from hydrocarbons as raw materials. The other was the carbon decomposed from the hydrocarbons directly or the carbon and light hydrocarbons generated through the interaction between reactant and catalyst surface. The phenomenon of carbon deposition has been proved by TGA).

Deriving the mechanism of the synthesis of morpholine(III) from the above analysis:

As C=O (1740, 1710 cm^{-1}) was detected by IR Spectra, aldehyde B was generated through the dehydrogenation reaction from DEG(A) over CuO–NiO/γ-Al_2O_3. Secondly, C was generated through the addition reaction from ammonia and aldehyde B. Adsorption of C=N (1,635 cm^{-1}) and N–H (3,338 cm^{-1}) is attributed to the imine D, which was generated through the dehydration–elimination reaction from intermediate C. In addition, after a series of hydrogenation, dehydrogenation and cyclization reactions, secondary amines G (N–H 3,338 cm^{-1}) was generated from imine D, which generated imine H (C=N 1,635 cm^{-1}) through the dehydration–elimination reaction. Finally, morpholine I (N–H 3,338 cm^{-1}) was generated through the hydrogenation reaction from imine H and hydrogen.

The mechanism of the synthesis of *N*-alkylmorpholines

There are two possible routes in the synthesis of *N*-alkylmorpholines from DEG(IV), alcohol and ammonia. One route proceeds along the path of the reaction between DEG(IV) and alkylamine, and the other is along that between morpholine(III) and alcohol. If the reaction route is the latter one, the spectrum of the synthesis of methylmorpholine(II) from DEG(IV) and methanol should be similar to that of the reaction between morpholine(III) and methanol (Fig. 4), but different from that of the reaction between DEG(IV) and methylamine. However, from Fig. 5, it can be seen that a sharp peak appeared at 3,338 cm^{-1}, and a large and stable band at 1,635 cm^{-1}, which are all attributed to amine. Further, the additional band at 3,440 cm^{-1} that is attributed to the generated hydroxyl in the reaction between morpholine(III) and methanol is not the character of the reaction between DEG(IV), alcohol and ammonia (Fig. 5). Actually, they were just the character of the reaction between morpholine(III) and methanol (Fig. 4). Compared with the

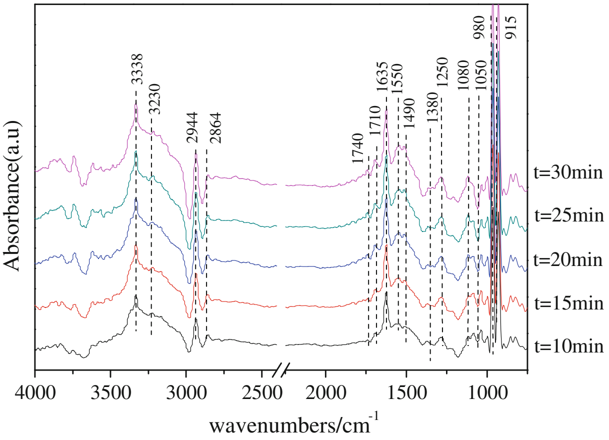
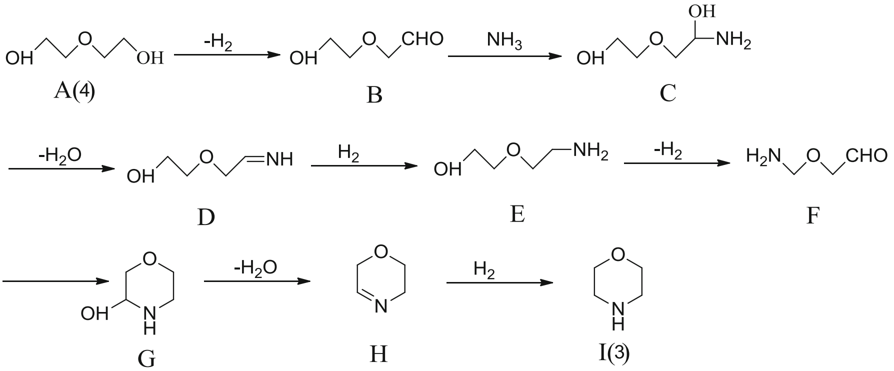


Fig. 3 The in suit DRIFTS spectrum of the synthesis of the morpholine(III) from DEG(IV) and ammonia varies with the reaction time at 220 °C

Table 3 The presented information from Fig. 3

υ/cm^{-1a}	Functional group	Type
3,338	N–H	Attributed to the intermediate products (secondary amines)
3,230	O–H	The hydroxyl of DEG and the intermediate products
2,944, 2,864	C–H	The C–H stretching vibration of methyl and methylene
1,740, 1,710	C=O	Attributed to the intermediate products (aldehyde)
1,635	C=N	Attributed to the intermediate
1,380	C–H	The C–H bending vibration of methyl and methylene
1,280	C–O	Attributed to the alkyl ethers
1,080, 1,050	C–O	Attributed to the hydroxyl of DEG and the intermediate products
980, 915	=C–H	The out-plane bending vibration of =C–H, attributed to the intermediate products (imine)
1,550	The unsaturated hydrocarbons of high carbon hydrogen ratio	Stay on the catalyst's surface because of the carbon deposition
1,510	The unsaturated hydrocarbons of low carbon hydrogen ratio	Stay on the catalyst's surface because of the carbon deposition

[a] υ/cm^{-1} = the frequency of the absorption peak



Scheme 4 The mechanism of the synthesis of morpholine(III) from DEG(IV) and ammonia

single band at 3,338 cm^{-1} (Fig. 3), the trend of the doublet at 3,338 cm^{-1} and 3,230 cm^{-1} (Fig. 3) was strengthened, which was attributed to the increasing of the absorption bands of primary amine. From Fig. 5, it can be seen that the peak appeared in the spectra at 1,635 cm^{-1} attributed to the imine becoming smaller. The reason was that, in the synthesis of morpholine, both amination processes generated imine. On the other hand, only the reaction between methylamine and DEG generated imine in the synthesis of *N*-alkylmorpholines, and the subsequent

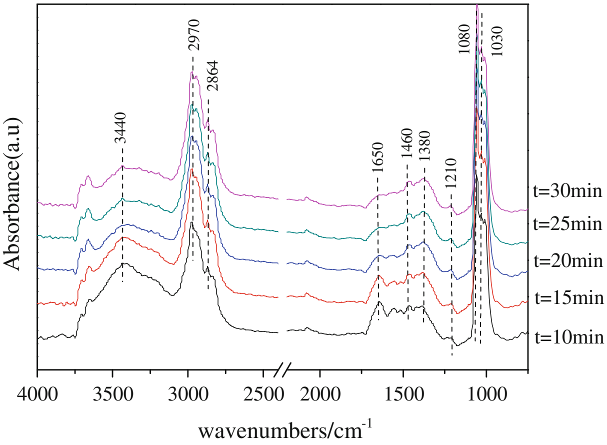


Fig. 4 The in situ DRIFTS spectrum of the synthesis of methylmorpholine(II) from morpholine(III) and methanol varies with the reaction time at 220 °C

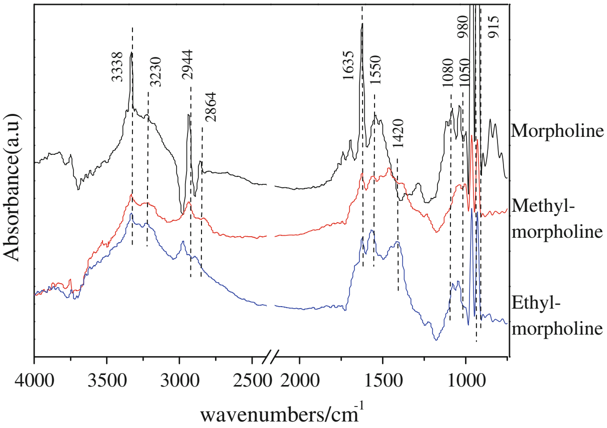


Fig. 5 The in situ DRIFTS spectrum of the synthesis of the morpholine(III), methylmorpholine(II) and ethylmorpholine(II) from DEG(IV), alcohol and ammonia varies with the reaction time at 220 °C

amination reaction generated enamine, thus reducing the intensity of absorption band of the imine. It can be found in the above information that the spectrum from the reaction between DEG(IV) and methanol was similar to that from the reaction between DEG(IV) and methylamine. In addition, if the synthesis of methylmorpholine(II) is along the path of the reaction between morpholine(III) and methanol, then morpholine(III) should exist as an intermediate. However, almost no morpholine(III) was detected in the reaction mixtures which were analyzed by gas chromatography. This fact proved that the synthesis of methylmorpholine(II) proceeds along the path of the reaction between DEG(IV) and methylamine. Taking into account that the spectrum of the reaction between DEG(IV) and methanol and the spectrum of the reaction between DEG(IV) and ethanol were similar, the proposed route can be confirmed.

Conclusions

Compared with reported procedure, Khan [17] synthesized *N*-butylmorpholine from morpholine and 1-chlorobutane (morpholine:choromethane = 1:1.1, mole ratio) at room temperature for 48 h, with a yield of 81 %. Although this method has high yield, low cost and a simple process, the generated hydrogen chloride salified with morpholine which reduced the utility of morpholine. In addition, the hydrogen chloride seriously corroded the reactor. Zhang [18] synthesized *N*- methylmorpholine from morpholine, paraformaldehyde and methanoic acid at 115 °C for 20 min, with a yield of 95 %. The method has high yield, short reaction time and a simple process, but the raw materials were expensive and largely consumed. In addition, the reaction was of low atom economy and had high production costs. In this paper, the synthesis of *N*-alkylmorpholines from DEG(IV), methanol and ammonia in gas–solid phase was investigated in a fixed-bed reactor over CuO–NiO/γ-Al_2O_3 at the temperature of 220–225 °C, hydrogen pressure of 0.9–1.0 MPa and LHSV of 0.25 h^{-1}, with a yield of 86.4 %. Compared to the above methods, this method is of high selectivity, with less pollution, and it is easy to achieve continuous production.

The mechanism of the heterogeneous catalytic reaction of DEG and amination to *N*-alkylmorpholines was investigated via in situ DRIFTS. CuO–NiO/γ-Al_2O_3 was selected as catalyst, and Al_2O_3 was chosen as a suitable carrier. The total gas flow was optimized to $15 \sim 25$ mL min^{-1}, in which H_2 flow was 15 mL min^{-1}, and the NH_3 flow was 5 mL min^{-1}. The mechanism of synthesis of *N*-alkylmorpholines was proposed and proved that it proceeded along the path of the reaction between DEG and alkylamine.

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References

1. K. Fujita, Y. Enoki, R. Yamaguchi, Tetrahedron **64**, 1943 (2008)
2. R.N. Salvatore, C.H. Yoon, K.W. Jung, Tetrahedron **57**, 7785 (2001)
3. V.G. Kozin, A.A. Mukhamadiev, Russ. J. Appl. Chem. **74**, 1289 (2001)
4. S.P. Hanlon, A. Camattari, S. Abad, A. Glieder, M. Kittelmann, S. Lutz, B. Wirz, M. Winkler, Chem. Commun. **48**, 6001 (2012)
5. S.K. Roy, D.A. Eastmood, Mutat. Res-Gen. Toxicol. Environ. Mutagen. **726**, 181 (2011)
6. X. Wang, Z. Tian, Sci. Technol. Chem. Ind. **13**, 63 (2005)
7. G. Guillena, D.J. Ramon, M. Yus, Chem. Rev. **110**, 1611 (2010)
8. W.J. Bartley, R.G. Cook, K.E. Curry, S.K. Mierau, U.S. Pat. 6,534,441, 2003
9. X.Z. Chen, H. Luo, C. Qian, C. He, React. Kinet. Mech. Catal. **104**, 163 (2011)
10. H. Alinezhad, M. Tajbakhsh, R. Zamani, Synth. Commun. **36**, 3609 (2006)
11. S.C. Ghosh, S. Muthaiah, Y. Zhang, X.Y. Xu, S.H. Hong, Adv. Synth. Catal. **351**, 2643 (2009)
12. M.A. Centeno, I. Carrizosa, J.A. Odriozola, Phys. Chem. Chem. Phys. **1**, 349 (1999)

13. D. Alfons, F. Michael, K. Kai, V. Herbert, Chem. Eng. Technol. **23**, 319 (2003)
14. T. Shishido, Z. Song, T. Matsushita, K. Takaki, K. Takehira, Phys. Chem. Chem. Phys. **5**, 2710 (2003)
15. J. Gary, H.D. Burtron, Appl. Catal. A **285**, 43 (2005)
16. W. Qiang, H. Hong, Y. Yunbo, Appl. Catal. B **61**, 107 (2005)
17. K.M. Khan, M.Z. Khan, M. Taha, G.M. Maharvi, Z.S. Saify, S. Parveen, M.I. Choudhary, Nat. Prod. Res. **23**, 479 (2009)
18. X. Zhang, J. Zhang, M. Wu, Chin. J. Appl. Chem. **20**, 917 (2003)