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RESEARCH NOTE

Intermolecular Cyclization of Diethanolamine and Methylamine to *N*,*N*′-Dimethylpiperazine over Zeolites under High Pressure

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Synthesis of *N*,*N*′-dimethylpiperazine via intermolecular cyclization of diethanolamine and methylamine has been investigated under high pressure conditions using zeolites and montmorillonite K10 for the first time. The HZSM-5(30) is particularly effective for *N*,*N*′-dimethylpiperazine formation and the catalyst can be reused many times without significant loss of activity. © 2001 Academic Press

Key Words: **zeolites; cyclization; autogeneous pressure; *N*,*N*′-dimethylpiperazine; autoclave.**

INTRODUCTION

The catalytic formation and cleavage of a carbon–nitrogen (C–N) single bond is of considerable importance for numerous areas of chemistry because of the ubiquitous presence of nitrogen-containing compounds in nature. For example, the catalytic formation of C–N bonds plays a significant role in the synthesis of pharmacologically active molecules (1–6).

We have reported a number of cyclization reactions of C_2 to C_7 aliphatics in the presence of formaldehyde and ammonia over modified zeolites (7–11). McAteer and Scriven (12) published a review on the synthesis of *N*-heterocyclics. In the reaction of ethanol, or acetaldehyde in the presence of formaldehyde and ammonia over zeolites, pyridine and picolines were formed. Products such as 3,5- and 2,6-lutidines were formed from propanol, isopropanol, or propionaldehyde in the presence of formaldehyde and ammonia. Collidines were obtained from 2-butanol and methyl ethyl ketone. These heterocyclics are intermediates in the synthesis of drugs and agrochemicals. In the reaction of diethanolamine and methylamine over zeolites, *N*-methylpiperazine was formed at 30–80 H_2 atm pressure and 250–350°C (11). The yield of *N*-methylpiperazine was >90% at 300°C and 30–80 H_2 atm pressure over HZSM-5 ($SiO_2/Al_2O_3 = 30$). At atmospheric pressure the yield of *N*-methylpiperazine and *N*,*N*′-dimethylpiperazine was <10% at 300°C. The reaction was carried out using a fixed bed flow reactor system.

Piperazine and substituted piperazines are important intermediates in the synthesis of quinoline-type antibacterial drugs (13). The substituted piperazines are used in the treatment of intestinal worms, e.g., anthelmintics, chemotherapeutics.

A supercritical fluid has liquid-like density and solvation strength, and it has the ability to homogenize reaction substrates, while possessing transport properties, i.e., viscosities and diffusivities, that are more like gases (14, 15). Methylamine has a critical temperature of 156.9°C and a critical pressure of 73.6 atmosphere both of which are readily achievable.

N,*N*′-Dimethylpiperazine was prepared from piperazine and methanol over H_3PO_4–SiO_2 at 160°C (16), and over H_3PO_4–TiO_2 at 280°C/13.8 atm (17). In this process the yield of *N*,*N*′-dimethylpiperazine was >80%. *N*,*N*′-Dimethylpiperazine was also prepared by cyclodehydration of $HO(CH_2)_2NHCH_3$ over activated alumina at 268°C (18), and over H_3PO_4–TiO_2 at 250–350°C/34.5–138 atm (19).

In this paper, we report for the first time the cyclization of diethanolamine and methylamine to *N*,*N*′-dimethylpiperazine over zeolites under high pressure conditions, similar to supercritical conditions with respect to methylamine. The reaction was carried out in an autoclave under high pressure in a batch mode in the liquid phase.

EXPERIMENTAL

Synthesis of N,N′-Dimethylpiperazine

Catalyst (15 g, 20 wt%), diethanolamine (71.88 ml, 0.75 mol) and 30% methylamine (129.125 ml, 1.5 mol) were placed (loaded) in a 500-ml (capacity) stainless steel autoclave at room temperature. The autoclave was sealed and the temperature was increased to 300°C under stirring (autogeneous pressure 100 atm). Agitation was maintained at this temperature for 10 h. After completion

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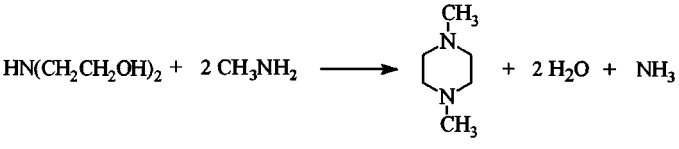
of the reaction, the temperature was cooled down to room temperature, the pressure was released slowly. When atmospheric pressure was reached, the autoclave was opened, the reaction mixture was filtered, and the product N,N'-dimethylpiperazine was identified by ^{1}H NMR and GC/mass spectroscopy and quantified by GC.

RESULTS AND DISCUSSION

The reaction of diethanolamine and methylamine was carried out over HZSM-5 (30) in the 200–300°C temperature range in an autoclave. The results are given in Table 1. The yields of N,N'-dimethylpiperazine were 40.5, 65.0, and 68% with conversions >90% at 290, 296, and 300°C reaction temperatures and 30–100 atm autogeneous pressure, respectively in autoclave (batch mode). The highest yield was obtained at 300°C. On the other hand, the yield of N,N'-dimethylpiperazine was <10% at 66 atm pressure and 285°C, when the reaction was carried out using water as a solvent and not under supercritical conditions. The stoichiometry of the reaction may be represented by the following equation:



SCHEME 1

The reaction of diethanolamine and methylamine (1:2 molar ratio) was carried out at 300°C and ~100 atm autogeneous pressure over several solid acid catalysts in autoclave (batch mode). The weight of the catalyst was 20 wt% with respect to the weight of the diethanolamine. The yields of N,N'-dimethylpiperazine were 68.0, 36.0, 33.0, 9.3, and 28.0 over HZSM-5 (30), HZSM-5 (280), H-mordenite, HY, and montmorillonite K10, respectively, as given in Table 2. Thus, HZSM-5 (30) was the best catalyst among the various zeolites in the cyclization reaction under identical reaction conditions.

TABLE 2

Synthesis of N,N'-Dimethylpiperazine over Molecular Sieves and a Clay

Entry	Catalyst	Reaction[a] temp. (°C)	Time (h)	Conversion of diethanolamine (%)	Yield[b] (%)
1.	HZSM-5(30)	300	10	96	68.0
2.	HZSM-5(280)	300	10	84	36.0
3.	H-Mordenite	300	10	72	33.0
4.	HY	300	10	46	9.3
5.	Montmorillonite K10	300	10	88	28.0
6.	—	300	10	78	8.6

[a] Autogeneous pressure = 100 atm.
[b] Yield of N,N'-dimethylpiperazine based on diethanolamine.

The effect of the molar ratio of diethanolamine and methylamine was studied over HZSM-5 (30) and the results are given in Table 3. Best yields of N,N'-dimethylpiperazine were 68.0 and 70.0% for 2.0 and 3.0 molar ratios of diethanolamine and methylamine, over HZSM-5 (30) at 300°C reaction temperature, respectively.

Similarly the weight of the catalyst was varied and the yields of N,N'-dimethylpiperazine varied from 9–68% for 0 to 20% of the HZSM-5 (30) (Table 4). Thus, HZSM-5 (30) showed high activity over a wide range of experimental conditions. The Brønsted acidic centers present at the channel intersections are assumed to be the active centers in this reaction. Therefore, HZSM-5 (30) showed higher activity than HZSM-5 (280). A tentative mechanism for the formation of N,N'-dimethylpiperazine is shown in Scheme 2.

The high yields under high pressure similar to the supercritical conditions with respect to methylamine are mainly due to the drastic increase in the reactive collisions and miscibility. The selectivity is also strongly influenced by the

TABLE 1

Synthesis of N,N'-Dimethylpiperazine over HZSM-5(30): Effect of Temperature

Entry	Reaction temp. (°C)	Autogeneous pressure (Atm.)	Time (h)	Conversion of diethanolamine (%)	Yield[a] (%)
1.	200	32	10	5	0.0
2.	250	59	10	22	0.0
3.	270	80	10	41	10.3
4.	290	90	10	90	40.5
5.	296	95	10	93	65.0
6.	300	100	10	96	68.0

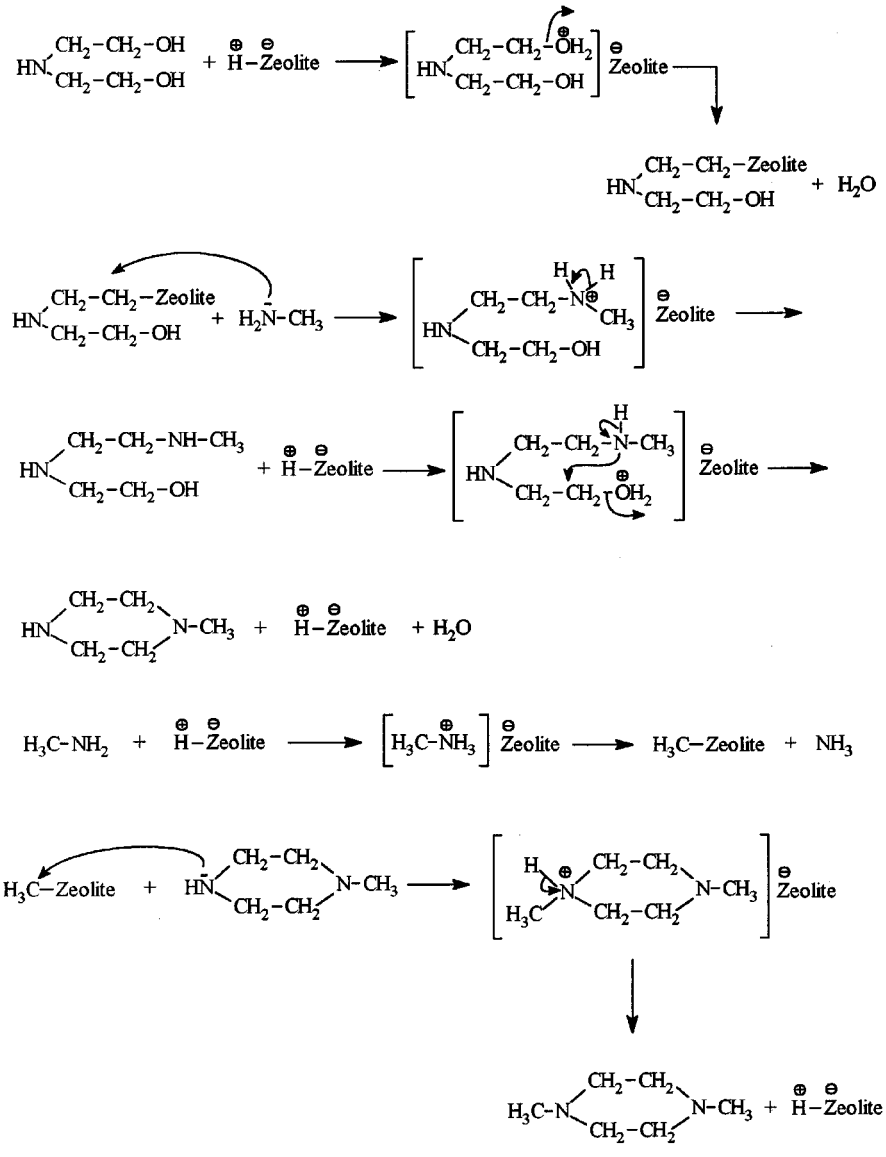
[a] Yield of N,N'-dimethylpiperazine based on diethanolamine.

TABLE 3

Synthesis of N,N'-Dimethylpiperazine over HZSM-5(30): Effect of Molar Ratio

Entry	Mol. ratio[a] DEA : MA	Reaction temp. (°C)[b]	Time (h)	Conversion of diethanolamine (%)	Yield[c] (%)
1.	1:1	300	10	90	37
2.	1:1.5	300	10	95	45
3.	1:2	300	10	96	68
4.	1:3	300	10	95	70

[a] DEA : MA, diethanolamine : methylamine.
[b] Autogeneous pressure = 100 atm.
[c] Yields of N,N'-dimethylpiperazine based on diethanolamine.



SCHEME 2

TABLE 4

Synthesis of *N*,*N*′-Dimethylpiperazine over HZSM-5(30): Effect of Amount of Catalyst

Entry	Amount of catalyst (wt%)	Reaction temp. (°C)[a]	Time (h)	Conversion of diethanolamine (%)	Yield[b] (%)
1.	—	300	10	78	9
2.	2.5	300	10	83	32
3.	5	300	10	85	41
4.	10	300	10	90	46
5.	20	300	10	96	68

[a] Autogeneous pressure = 100 atm.
[b] Yields of *N*,*N*′-dimethylpiperazine based on diethanolamine.

reactor design. We also studied the reduction in the coke deposit, i.e., deactivation of the catalyst. The strategy is presently being extended to other cyclization reactions.

CONCLUSIONS

The present study demonstrates the potential of HZSM-5 (30) catalyst (zeolite) exercising a unique activity in the synthesis of *N*,*N*′-dimethylpiperazine via intermolecular cyclization of aliphatic compounds. The catalyst can be reused without any loss of activity, when the reaction was carried out in liquid phase, batch mode in an autoclave. It is interesting to note that the selectivity and/or the nature of

products formed was different in the case of the autoclave and fixed-bed flow systems (11).

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REFERENCES

1. Singer, T. P., Von Korff, R. W., and Murphy, D. L., "Monoamine Oxidase, Function and Altered States." Academic Press, New York, 1979.
2. Kapeller-Alder, R., "Amine Oxidases and Methods for Their Study." Wiley, New York, 1970.
3. Gibson, M. S., *in* "The Chemistry of the Amino Group" (S. Patai, Ed.), p. 37. Wiley, New York, 1968.
4. Gribble, G. W., Jasinski, J. M., Pellicore, J. T., and Panetta, J. A., *Synthesis* 766 (1978).
5. Bruice, T. C., *Acc. Chem. Res.* **13**, 256 (1980).
6. Katritzky, A. R. (Ed.), "Comprehensive Heterocyclic Chemistry." Vol. 1–8. Pergamon Press, New York, 1984.
7. Kulkarni, S. J., *Stud. Surf. Sci. Catal.* **113**, 151 (1998).
8. Kulkarni, S. J., Subrahmanyam, M., and Rama Rao, A. V., *Indian J. Chem. A* **32**, 28 (1993).
9. Subba Rao, Y. V., Kulkarni, S. J., Subrahmanyam, M., and Rama Rao, A. V., *J. Chem. Soc. Chem. Commun.* 1456 (1993).
10. Subba Rao, Y. V., Kulkarni, S. J., Subrahmanyam, M., and Rama Rao, A. V., *J. Org. Chem.* **59**, 3998 (1994).
11. Nagaiah, K., Sudhakar Rao, A., Kulkarni, S. J., Subrahmanyam, M., and Rama Rao, A. V., *J. Catal.* **147**, 349 (1994).
12. McAteer, C. H., and Scriven, E. F. V., *in* "Fine Chemicals through Heterogeneous Catalysis" (R. A. Sheldon and H. van Bekkum, Eds.), p. 275. Wiley–VCH, New York, 2001.
13. Grohe, K., *Chem. Bri.* **28**, 35 (1992).
14. Clifford, A. A., "Fundamentals of Supercritical Fluids." Oxford University Press, London, 1998.
15. Clifford, A. A., *in* "Supercritical Fluids" (E. Kiran and J. M. H. Levelt Sengers, Eds.), p. 449. Kluwer, Dordrecht, 1994.
16. Dockner, T., Toussaint, H., and Decker, M., Ger. Offen. 2, 205, 597 (cl. C.07d), 16 Aug. 1973, Appl. p 22 05 597.6, 07 Feb. 1972, 8 pp.; Chem. Abstr. **79**, 115626g.
17. Vanderpool, H., Steven, M., and Peter, S., U.S. Patent 4, 727, 143 (cl. 544-404, C07D295/02), 23 Feb. 1988, Appl. 871, 941, 09 Jun. 1986, 4 pp.; Chem. Abstr. **108**, 188918f.
18. Blustein, R., Bernard, S., and Jack, M. U.S. Patent 3,647,795 (cl. 260-268SY, C08d), 07 May. 1972, Appl. 696, 707, 10 Jan. 1968, 311; Chem. Abstr. **76**, 140880f.
19. Zimmerman, L., Robert, V., and Steven, H., U.S. Patent 4, 698, 428 (cl. 544-404, C07D241/04). 06 Oct. 1987, Appl. 871, 954, 09 Jun. 1986, 3pp.; Chem. Abstr. **108**, 7897e.