JOURNAL OF CATALYSIS 147, 349–351 (1994)

NOTE

Intermolecular Cyclization of Diethanolamine and Methylamine to *N*-Methylpiperazine over Zeolites[1]

Piperazine and substituted piperazines are important intermediates in the synthesis of quinolone-type antibacterial drugs (1). Piperazine is used in the synthesis of the norfloxacin, ciprofloxacin, and enofloxacin type of drugs. *N*-methylpiperazine is used in the synthesis of the ofloxacin, amifloxacin, fleroxacin, and difloxacin type of antibacterial drugs (1). Kulkarni *et al.* (2) reported the synthesis of piperazine over zeolites from *N*-hydroxypropylethylenediamine and *N*-2-hydroxyethylethylenediamine (3).

N-Methylpiperazine was prepared from piperazine, formaldehyde, and acetic acid at 100°C in the presence of a Raney Co-catalyst at 280 atm in an autoclave (4). In this process, the yield of *N*-methylpiperazine was 99%. *N*-Methylpiperazine was also prepared from piperazine, formaldehyde, and formic acid in the presence of a catalyst at 150°C in an autoclave with a lower yield (5). The reaction of $MeN(CH_2COOH)_2$ with urea leads to *N*-methylpiperazine in the presence of $LiAlH_4$ (6). The reaction of diethanolamine and methylamine over Ag, Cu, Ni, Cd, or Co on γ-Al_2O_3 leads to *N*-methylpiperazine at 150°C and 250 atm in an autoclave (7, 8).

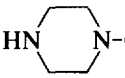
In this Note, we report for the first time the cyclization of diethanolamine and methylamine to *N*-methylpiperazine over zeolites. The reaction was carried out at 250–400°C at 30–80 hydrogen atm under down-flow fixed-bed conditions. The yield of *N*-methylpiperazine was more than 90% based on diethanolamine at ~100% conversion of diethanolamine under certain experimental conditions over a HZSM-5 catalyst.

The HZSM-5 catalysts used in this study were supplied by Conteka (Sweden); they had Si/Al ratios of 30 and 280 and are designated as HZSM-5(30) and HZSM-5(280), respectively. H–mordenite (Si/Al = 6.0) and HY (Si/Al = 3.3) catalysts were supplied by PQ Corporation. The particle size of the catalyst was in the range 18–30 mesh. The reactants used were of analytical grade.

The reactions were carried out using a tubular, down-flow, stainless steel reactor with a 30-mm internal diameter. The hydrogen carrier gas was pressurized at the desired pressure by adjusting the outlet flow. The total system was made up of stainless steel. The pressure was measured with pressure gauges for inlet and outlet points. The reaction mixture was fed through a calibrated burette using the feeder (Lewa, Germany). The product was cooled using ice-cooled water and collected at the bottom. The required number of ice-cooled traps were used at the outlet to collect the total amount. The product was collected every hour. The reaction was carried out in the temperature range 250–400°C. The pressure was varied from 30 to 80 atm of hydrogen. The products were analyzed by gc using SE-30 (5%) and Chromosorb-101 (5%) columns. The analysis was confirmed by mass spectra and gc–ms.

The reaction of diethanolamine and methylamine (1 : 2 mol ratio) was carried out over HZSM-5(30) in the temperature range 250–400°C. The results are collected in Table 1. The yield of *N*-methylpiperazine was highest at 300°C at all pressures. The yields of *N*-methylpiperazine at 300°C and at 30, 50, 65, and 80 atm pressures were 94.0, 93.5, 84.0, and 94.0 wt%. The conversion of diethanolamine was ~100%. The best yield was obtained at 300°C and 80 atom of H_2. Under these experimental conditions, with some variation of temperature or pressure and with time on stream, the yield of *N*-methylpiperazine remained 94.0 wt%. The reaction of diethanolamine was methylamine (1 : 2 molar) was carried out at 300°C with 30 cm^3 per min of hydrogen gas or without hydrogen at 1 atm and 0.5 h^{-1} weight hourly space velocity (W.H.S.V.). The yield of *N*-methylpiperazine was <10 wt% at about ~15% conversion of diethanolamine over HZSM-5(30). At 250°C, the yield of *N*-methylpiperazine increases with increase of H_2 pressure. *N*-Methylpiperazine was the major product with 90–95% selectivity. The major side product (<5%) was piperazine. Due to the presence of hydrogen in the feed, the formation of *N*-methylpyrazine was avoided. The stoichiometry of the reaction may be represented by the following equation:

$$NH(CH_2CH_2OH)_2 + CH_3NH_2 \rightarrow$$



$$+ 2H_2O \ldots. \quad [1]$$

[1] IICT Communication No. 3209.

0021-9517/94 $6.00

TABLE 1

Synthesis of *N*-Methylpiperazine over HZSM-5(30)[a]

H_2 pressure (atm)	Yield of *N*-methylpiperazine[c] at various reaction temperatures							
	TOS (h)[b]	Yield at 250°C (wt%)	TOS (h)	Yield at 300°C (wt%)	TOS (h)	Yield at 350°C (wt%)	TOS (h)	Yield at 400°C (wt%)
30	2	46.0 (~50)[d]	2	94.0 (94)	1	50.5 (~58)	1	8.0 (39.0)
50	3	31.0 (52)	3	93.5 (~94)	1	80.5 (83)	3	14.0 (48.0)
65	3	80.0 (~80)	2	84.0 (~85)	2	57.0 (68)	1	57.0 (62)
80	3	81.0 (~81)	3	94.0 (~95)	3	85.5 (~86)	3	9.0 (58.9)

[a] W.H.S.V. = 0.5 h^{-1}; $HN(C_2H_4OH)_2 : CH_3NH_2$ = 1 : 2 molar.
[b] TOS, time on stream.
[c] Yield based on diethanolamine.
[d] The number in the parenthesis indicates percent selectivity.

The reaction of diethanolamine and methylamine (1 : 2 molar ratio) was carried out over HZSM-5(280), HY, and H–mordenite zeolites and results are given in Table 2. The yields of *N*-methylpiperazine over HZSM-5(280) at 80 atm H_2 pressure and at 250, 300, and 350°C were 6.0, 83.0, and 21.0 wt%. For HY zeolite, the yield of *N*-methylpiperazine at 250°C and at 80 atom pressure was 47.5 wt%. In the case of H–mordenite, at 300°C and 80 and 65 atm pressure the yields were 90.0 and 80.0 wt%. Thus, HZSM-5(30) is the most active catalyst in the synthesis of *N*-methylpiperazine. The HY and HM catalysts showed deactivation. On the other hand, the HZSM-5 catalyst showed a low rate of deactivation, and the activity could be regenerated.

The effect of the molar ratio of diethanolamine and methylamine was studied over HZSM-5(30) and is given

TABLE 2

Synthesis of *N*-Methylpiperazine over Zeolites[a]

Catalyst	H_2 pressure (atm)	Yield of *N*-methylpiperazine[c] at various reaction temperatures							
		TOS (h)[b]	Yield at 250°C (wt%)	TOS (h)	Yield at 300°C (wt%)	TOS (h)	Yield at 350°C (wt%)	TOS (h)	Yield at 400°C (wt%)
HZSM-5(280)	80	3	6.0 (81)[d]	3	83.0 (93)	3	21.0 (92)	—	—
HY zeolite	80	3	47.5 (82)	3	6.0 (83)	—	—	—	—
H–mordenite	80	2	20.0 (42)	2	90.0 (90)	3	30.5 (66)	3	6.0 (50)
	65	2	6.0 (35)	2	80.0 (~85)	1	21.5 (44.8)	3	2.0 (44.4)

[a] W.H.S.V. = 0.5 h^{-1}; $HN(C_2H_4OH)_2 : CH_3NH_2$ = 1 : 2 molar.
[b] TOS, time on stream;
[c] Yield based on diethanolamine.
[d] Number in parentheses indicates the % selectivity.

TABLE 3

Synthesis of *N*-Methylpiperazine over HZSM-5(30): Effect of mol Ratio

mol ratio DEA : MA[a]	Reaction temperature (°C)	Time on stream (h)	H_2 pressure (atm)	Yield (wt%) of *N*-methylpiperazine[b]	*Selectivity (%) of N*-methylpiperazine among the products
2 : 1	300	3	80	44.0	90.0
1 : 1	300	1	80	87.5	96.0
1 : 2	300	3	80	93.0	94.0
1 : 3	300	3	80	16.0	90.0

Note. W.H.S.V. = 0.5 h^{-1}.
[a] DEA : MA, diethanolamine : methylamine.
[b] Yield based on diethanolamine.

TABLE 4

Synthesis of *N*-Methylpiperazine over HZSM-5(30): Effect of W.H.S.V.

W.H.S.V.[a] (h^{-1})	Amount of catalyst	Reaction temperature (°C)	Time on stream (h)	H_2 pressure (atm)	Yield of *N*-methylpiperazine (wt%)	Selectivity (%) of *N*-methylpiperazine (among the products)
1.0	5	300	3	80	81.0	85.0
2.0	5	300	1	80	95.0	96.0
3.0	5	300	3	80	82.0	86.4
4.0	5	300	3	80	88.5	89.0
0.5	10	300	3	80	93.0	95.0
1.0	10	300	(2 + 3)	80	85.0	91.5
1.5	10	300	3	80	88.5	89.5
2.0	10	300	(2 + 3)	80	82.0	82.0

Note. Diethanolamine : methylamine, 1 : 2 molar ratio.
[a] W.H.S.V., weight hourly space velocity.
[b] Yields are based on diethanolamine.

in Table 3. The best yield of *N*-methylpiperazine obtained was 93.0% for 1 : 2 molar ratio. The conversion with respect to diethanolamine was ~99%.

The effect of W.H.S.V. for 5 and 10 g of catalyst was studied in the synthesis of *N*-methylpiperazine over HZSM-5(30). The reaction of diethanolamine and methylamine (1 : 2 molar) was carried out at 300°C and 80 atm H_2 pressure. The results are summarized in Table 4. In the case of 1.0, 2.0, 3.0, and 4.0 h^{-1} W.H.S.V. for 5 g of catalyst, the yields of *N*-methylpiperazine were 81.0, 95.0, 82.0, and 88.5 wt%, respectively. For 10 g of catalyst and 0.5, 1.0, 1.5, and 2.0 h^{-1} W.H.S.V., the yields were 93.0, 85.0, 88.5, and 82.0 wt%, respectively. Thus, HZSM-5(30) showed high activity over a wide range of experimental conditions. The Brønsted acidic centers present at the intersections are assumed to be the active centers in this reaction. Therefore, HZSM-5(30) showed higher activity than HZSM-5(280).

To sum up, *N*-methylpiperazine has been shown to be synthesized from diethanolamine and methylamine over HZSM-5, H–mordenite, and HY, the yield with HZSM-5 being 94% at 300°C and 80 atm H_2 pressure. The synthesis of *N*-heterocycles via intermolecular cyclization of aliphatic compounds over HZSM-5 catalyst has been established.

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K. Nagaiah
A. Sudhakar Rao
S. J. Kulkarni[2]
M. Subrahmanyam
A. V. Rama Rao

Indian Institute of Chemical Technology
Hyderabad 500 007
India

Received April 16, 1993; revised September 20, 1993

[2] To whom correspondence should be addressed.