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Alkylation of pyrazoles with alcohols over zeolites

Yoshio Ono, Yuriko Izawa and Zhi-Hua Fu

Department of Chemical Engineering, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan

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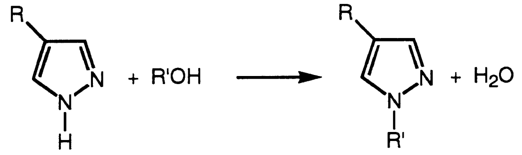
HY zeolite is a highly active catalyst for the vapor-phase N-alkylation of pyrazoles with alcohols. For example, the reactions of pyrazole and 4-methylpyrazole with methanol over HY afford N-methylpyrazole and 1,4-dimethylpyrazole, respectively, in a 100% yield at 573 K.

Keywords: methylation, alkylation, pyrazole, alcohol, zeolite

1. Introduction

N-alkylpyrazoles are important chemicals as intermediates for the syntheses of pharmaceuticals and agrochemicals. They are commonly obtained by the alkylation of pyrazoles in liquid phase using alkyl halides or dialkyl sulfate as the alkylating agents [1], though several other methods of the alkylation were also known [2,3]. However, alkyl halides and alkyl sulfates are highly toxic and corrosive. Moreover, more than stoichiometric amount of a strong base like $NaNH_2$ and NaOH is required. This results in the formation of a stoichiometric amount of metal salts as byproducts. Alkylations with phase-transfer catalysts are also reported [4,5]. The catalytic alkylation with alcohols in vapor phase over heterogeneous catalysts may offer a more convenient way than that with homogeneous catalysts in liquid phase, since the work-up after the reaction is much easier in the former case. Moreover, methanol is a much less toxic and corrosive methylating agent than methyl halide or dimethyl sulfate. In fact, phosphoric acid supported on alumina was reported to be an effective catalyst for vapor-phase alkylation of pyrazoles [6]. We have reported that acidic zeolites are very active catalysts for alkylation of imidazoles [7,8]. Here, we report that pyrazoles are effectively N-alkylated with alcohols in vapor phase over acidic zeolites.



2. Experimental

NaY zeolite ($SiO_2/Al_2O_3 = 5.6$) was obtained from Tosoh. It was ion-exchanged with NH_4^+, La^{3+}, and Ca^{2+} ions in conventional procedures. ZSM-5 ($SiO_2/Al_2O_3 = 43.5$), obtained in its Na^+ form from Tosoh, was converted into its NH_4^+ form by a conventional ion-exchange procedure. A portion of NH_4-ZSM-5 was converted into H-ZSM-5 in the reactor by heating at 773 K in an dry air stream for 1 h prior to the reaction. Beta zeolite ($SiO_2/Al_2O_3 = 25$), SAPO-5, and MAPO-36 were synthesized according to the method described in literature, and they were calcined to obtain their protonic form. Phosphoric acid supported on silica was also used.

Reactions were carried out in a fixed-bed flow reactor (10 mm i.d.) at atmospheric pressure. The catalysts were pretreated under an air stream at 773 K for 1 h prior to the reaction. The mixture of pyrazole and alcohol was fed by a motor-driven syringe to the preheating zone of the catalyst bed. The products were collected in an ice trap and identified by ^{1}H-NMR and a gas chromatograph. The yields of alkylated products were expressed based on the starting pyrazole. The contact time W/F was defined as the weight of the catalyst used (g) divided by the flow rate of the feed (pyrazole + methanol + nitrogen, in mol h^{-1}).

3. Results and discussion

3.1. *Activities of various catalysts*

Catalytic activities of various catalysts for alkylation of 4-methylpyrazole with methanol were examined at 573 K and the results are shown in table 1. Among the catalysts studied, HY was found most active and gave a 100% yield of 1,4-dimethylpyrazole. NaY showed a very low activity, indicating that the active sites for the methylation are Brønsted sites. Other acidic materials, SAPO-5, MAPO-36 and phosphoric acid supported on silica also showed reasonable activities, though their activities were lower than that of HY.

Table 1
Yield of 1,4-methylpyrazole in the alkylation of 4-methylpyrazole (4-MP) with methanol over various catalysts [a]

Catalyst	Yield (%)
HY	100
LaY	41
CaY	17
NaY	2
H-beta	85
SAPO-5	69
MAPO-36	35
H_3PO_4/SiO_2	69 [b]

[a] Conditions: 573 K ([b] 543 K), 4-MP = 25.3 kPa, MeOH/4-MP = 1, $W/F = 18.8\,g\,h\,mol^{-1}$ ([b] $24.1\,g\,h\,mol^{-1}$).

3.2. Effect of reaction conditions

HY was also active for alkylation of pyrazole with methanol. Figure 1 shows the change in the yield of N-methylpyrazole with contact time at 513, 543, and 573 K. A 100% yield of N-methylpyrazole was obtained at 543 and 573 K at relatively low contact time. Under any conditions, products other than N-methylpyrazole were not observed. Thus, HY is a highly active and selective catalyst for alkylation of pyrazole.

Figure 2 shows the effect of the molar ratio of methanol to pyrazole on the yield of N-methylpyrazole in the methylation of pyrazole over HY. The yield increased with the ratio and reached 100% at the molar ratio of 3 at 543 K. Though not shown in figure 2, the yield reached 100% at the molar ratio of 2 at 573 K.

3.3. Methylation of 3(5)-methylpyrazole

3-methylpyrazole and 5-methylpyrazole are in tautomeric equilibrium. Therefore, the methylation of the tautomeric mixture resulted in the formation of the mixtures of 1,3-dimethylpyrazole (1,3-DMP) and 1,5-dimethylpyrazole (1,5-DMP). The distribution of the two isomers in the vapor-phase alkylation of 3(5)-methylpyrazole with methanol depended on the catalyst used, as shown in table 2. H-beta and H-ZSM-5 favored 1,3-DMP, while SAPO-5 favored 1,5-DMP. HY showed the highest activity and gave the two isomers to an almost equal extent. Figure 3 shows the change in the yield of dimethylpyrazoles with contact time. The yield increased with contact time, but the ratio of the two isomers did not change with contact time, indicating that the two isomers are formed in parallel.

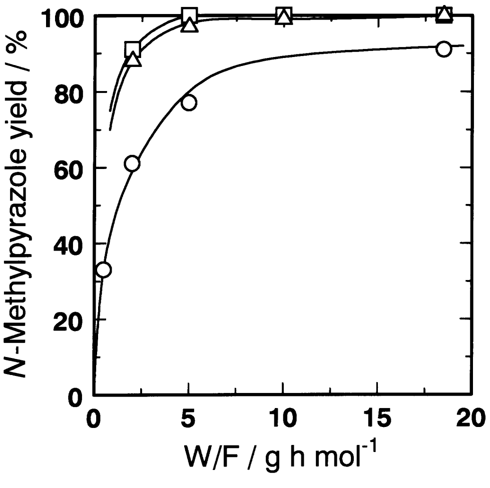


Figure 1. Change in the yield of N-methylpyrazole with contact time at 513 K (○), 543 K (△) and 573 K (□) in the methylation of pyrazole over HY with methanol. Reaction conditions: pyrazole = 16.9 kPa, CH_3OH/pyrazole = 2.

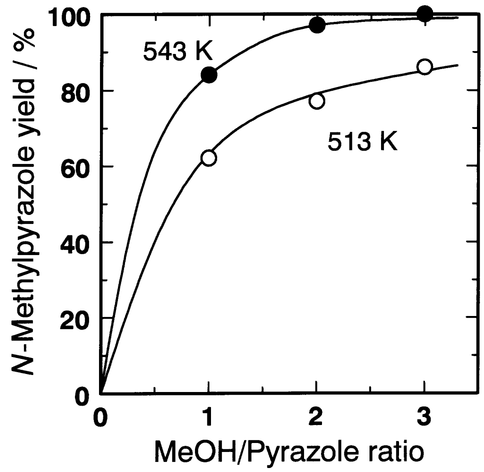


Figure 2. Effect of methanol to pyrazole molar ratio on the yield of N-methylpyrazole over HY. Reaction conditions: pyrazole = 16.9 kPa, $W/F = 5\,g\,h\,mol^{-1}$.

3.4. Alkylation of pyrazole with various alcohols

The reaction of pyrazole with various alcohols was carried out at 573 K. The results are shown in table 3. In every case, the alkylation proceeded to give exclusively the N-alkylation products in high yields. In the case of 1-propanol, only N-propylpyrazole was obtained. Similarly, in the case of 2-propanol, only N-isopropylpyrazole was obtained. These results indicate that free carbenium ions are not intermediates in the alkylation.

Table 2
Alkylation of 3(5)-methylpyrazole (3(5)-MP) with methanol to 1,3- and 1,5-dimethylpyrazole (DMP) [a]

Catalyst	3(5)-MP conversion (%)	Selectivity (%)	
		1,3-DMP	1,5-DMP
HY	97	44	56
H-beta	58	71	29
H-ZSM-5	37	75	25
SAPO-5	27	26	74

[a] Conditions: 513 K, 3(5)-MP = 16.9 kPa, MeOH/3(5)-MP = 2, $W/F = 18.5\,g\,h\,mol^{-1}$.

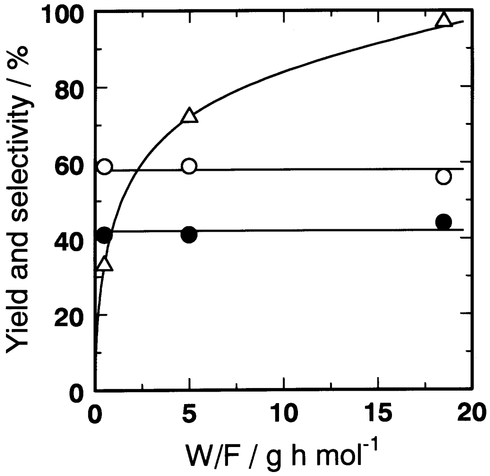


Figure 3. Change in the yield and selectivity with contact time in the methylation of 3(5)-methylpyrazole with methanol over HY. (△) Yield of N-methylated product, (○) selectivity for 1,5-dimethylpyrazole, (●) selectivity for 1,3-dimethylpyrazole. Reaction conditions: 513 K, 3(5)-methylpyrazole = 16.9 kPa, methanol/3(5)-methylpyrazole = 2.

3.5. Reaction mechanism

The base-catalyzed alkylation of pyrazoles is generally accomplished by the treatment of pyrazoles with an appropriate base followed by the treatment of the resulting salt with an alkylating agent.

The alkylation of pyrazole over zeolites proceeds on acidic sites. Therefore, the mechanism is different from that in the basic media and may be expressed as follows:

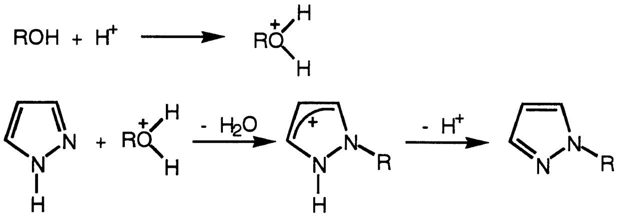


Table 3
N-alkylation of pyrazole with alcohols over HY [a]

Alcohol	Yield (%)
methanol	100
ethanol	96
1-propanol	81
2-propanol	51

[a] Conditions: 573 K, pyrazole = 16.9 kPa, MeOH/pyrazole = 2, $W/F = 5\,\mathrm{g\,h\,mol^{-1}}$.

The attack of a proton at the O-atom of an alcohol molecule and the transfer of the alkyl group to the N-atom of pyrazole are probably concerted, since the *n*-propyl derivative is exclusively formed and the isopropyl derivative is not formed in the reaction of pyrazole with propyl alcohol.

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