Selective synthesis of 5-methyl-2-phenylpyridine from carbonyl compounds and ammonia over zeolite catalysts†

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The vapor-phase cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia was carried out over HZSM-5, Hβ and HY zeolites at 400 °C and 0.5 h^{-1} weight hour space velocity to synthesize 5-methyl-2-phenylpyridine. The cyclization activity follows the order: HY > Hβ > HZSM-5. The influence of catalyst modification with a metal ion, temperature, feed molar ratio, weight hour space velocity, and activity with time on stream parameters were studied. The maximum yield of 5-methyl-2-phenylpyridine was obtained over 3 wt% CoHY zeolite at 400 °C.

Introduction

Phenylpyridine and substituted phenylpyridines are useful intermediates in the synthesis of drugs, agrochemicals, herbicides, insecticides, desiccants, surfactant agents and anti-inflammatory agents.[1,2] They are widely used as ligands in co-ordination complex preparation. 2-Phenylpyridine is a starting material for BMS-232632 and it is a potent azapeptide HIV protease inhibitor that has shown high anti-HIV activity.[3] Traditionally phenylpyridines are synthesized by the arylation of pyridine and picolines with phenyllithium[4,5] and also by Grignard reactions.[6,7] Phenylpyridines were also photocatalytically synthesized from benzonitrile and ethylene in the presence of light using cobalt(I) complex as a catalyst. However these reactions are performed in homogeneous catalysis mode and they suffer from catalyst recovery and end up with tedious work up procedures. A Japanese patent by Shimizu *et al.* describes the synthesis of 6-methyl-2-phenylpyridine from acetophenone, acetone, formaldehyde and ammonia by aluminosilicate catalysts in vapor phase at 350–550 °C.[1] However, the catalysts are not zeolites and the yield of 6-methyl-2-phenylpyridine is only 50%. Zeolites with crystalline and uniform pore structure are proved to be efficient catalysts in acid-mediated reactions. The characteristics that make zeolites as attractive heterogeneous catalysts are their well-defined crystalline structure, a high internal surface area, uniform pores with one or two discrete sizes, the possibility of tuning acidity to a wide range, good thermal stability, shape selectivity and ease of separation. Many pyridine bases such as pyridine, picolines, lutidines and collidines have been synthesized from carbonyl compounds/alcohols with ammonia over zeolite catalysts.[8–14] However, no attempts have been made on the synthesis of large molecular size pyridine bases like phenylpyridine and substituted phenylpyridines. Recently large pore zeolites and mesoporous molecular sieve catalysts have been reported to be excellent catalysts especially for the synthesis of large molecules.[15–19] Earlier studies in our laboratory have also established that the combination of acidity, thermal stability and uniform pore structure of a molecular sieve catalyst provides a good opportunity for the synthesis of large size molecules such as 2-phenylpyridine and 2-methyl-6-phenylpyridine.[20–22] The present synthesis of 5-methyl-2-phenylpyridine from acetophenone, propionaldehyde, formaldehyde and ammonia over molecular sieve catalysts in the vapor phase, to the best of our knowledge, is the first such report.

Experimental

The HZSM-5 (30) zeolite was supplied by Conteka, Sweden, Hβ (20) from Sud-chemie, India and HY (2.6) zeolite from PQ Corporation, USA. The catalyst powder was pelletized, crushed and sieved into 2 mm sized granules. The required amount of metal nitrate in aqueous medium was taken onto the sized catalyst to modify the surface by impregnation followed by calcination in air at 400 °C for 4 h.

Acetophenone (99%) and formaldehyde (30% aqueous solution) (obtained from S. D. Fine Chem.-Ltd, India), propionaldehyde (97%) (from Lancaster, England) and methanol (99.85) (from E-Merck, India) were used in this study. The liquid feed is prepared in the molar ratio of 1:1:1:1 of acetophenone, propionaldehyde, formaldehyde and methanol. The methanol is used as a solvent to provide total miscibility of the feed. The vapor phase cyclization reaction was carried out using a continuous fixed bed Pyrex glass reactor of 20 mm internal diameter. 4 g of catalyst was used in the form of granules and placed in the middle of the reactor. The reactor was placed inside a temperature-controlled furnace with a thermo-

Green Context

This paper describes for the first time the direct synthesis of 5-methyl-2-phenylpyridine from the vapour phase reaction of acetophenone, propionaldehyde, formaldehyde and ammonia using zeolite catalysts. This remarkable multi-step reaction is not surprisingly not 100% selective but the yield of the desired pyridine is improved by the use of larger pore catalysts such as HY. Phenylpyridines are useful intermediates for example, in the preparation of the potent azapeptide HIV protease inhibitor BMS-232632. Their synthesis has traditionally induced acrylation reactions using organometallic reagents which result in high levels of hazardous waste. A single ‘step’ synthesis involving inexpensive substrates and a safe reusable catlyst is a very attractive option. ***JHC***

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couple placed at the center of the catalyst bed for measuring the reaction temperature. The reaction mixture was fed from the top using a B. Brown (Germany) syringe pump. The product was cooled in a water-cooled (ice-cold) condenser, collected in a receiver and analyzed by gas chromatography (Chemito 3865) using 10% SE-30 on chromosorb HIWP packed column and products were confirmed by GC–MS and NMR spectroscopy. The product distribution at different time intervals is given in Tables 2–4.

Temperature programmed desorption (TPD) for ammonia experiments were carried out to measure the acidity of the catalyst as reported earlier.[21] In a typical run, a 0.150 g portion of the catalyst was placed in a quartz tubular reactor and heated at 400 °C under a nitrogen flow of 30 cm^3 min^{-1} for 3 h and the reactor was then cooled to 25 °C and adsorption conducted at that temperature by exposing the sample to ammonia for 2 h. Physically adsorbed ammonia was removed by purging the sample with a nitrogen stream flowing at 30 cm^3 min^{-1} for 1 h at 80 °C. The acid strength distribution was obtained by raising the catalyst temperature (10 °C min^{-1}) from 80 to 600 °C in a flow of nitrogen (10 cm^3 min^{-1}). The NH_3 gas evolved was quantified by gas chromatography using a thermal conductivity detector.

Results and discussion

Physicochemical properties

The frameworks of the modified zeolites were checked by X-ray diffraction and FTIR measurements and the crystallinity was found to be retained after modification. The surface areas of the modified zeolites were measured by the BET method and are listed in Table 1. The decrease in the surface area of the metal modified zeolites relative to the unmodified samples is due to the presence of metal ions and oxide species in the cavities of the zeolite. The surface area of cobalt metal-modified HY zeolite decreases with an increased amount of cobalt. The acidity of the zeolites and modified zeolites were measured by the method of temperature programmed desorption of ammonia and the values are given in Table 1. The total acidity of the catalysts followed the order: CuHY < PbHY < MnHY < CrHY < ZnHY < CoHY < HY < FeHY < LaHY. As reported earlier, HY catalyst modified by rare earth cations such as La, showed higher acidity than unmodified zeolites.[23,24]

Table 1 Physical characteristics of various zeolite catalysts

Catalyst	SiO_2/Al_2O_3	Acidity/ mmol g^{-1}	Surface area/m^2 g^{-1}
HZSM-5	30	1.73	310.0
Hβ	20	1.92	435.8
HY	2.6	2.83	457.2
3-wt % metal ion on HY zeolite			
Cr		2.09	411.4
Mn		1.98	449.0
Fe		3.16	377.3
Co		2.46	447.0
Cu		1.17	432.2
Zn		2.12	427.8
Pb		1.55	448.3
La		3.41	355.7
Co loading on HY zeolite (wt %)			
1			450.8
3			447.5
5			428.0
10			348.4

Catalytic activity

The vapor-phase cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia was carried out over zeolites HZSM-5, Hβ, HY and SiO_2-Al_2O_3 at 400 °C with 0.5 h^{-1} weight hour space velocity to synthesize 5-methyl-2-phenylpyridine and the results are given in Table 2. HZSM-5, Hβ, HY and SiO_2-Al_2O_3 showed conversion of acetophenone of 85.0, 87.0, 99.8 and 96.4% respectively. The yields of 5-methyl-2-phenylpyridine for HZSM-5, Hβ, HY and SiO_2-Al_2O_3 are 23.6, 29.1, 37.9 and 25.4%, respectively. The cyclization activity follows the order: HY > Hβ > SiO_2-Al_2O_3 > HZSM-5. Even though good conversion level on the HZSM-5 catalyst is seen, the low yield of the product observed may be due to inaccessibility or slower diffusion of the product 5-methyl-2-phenylpyridine to diffuse through the pores of ZSM-5 zeolite (5.4 Å). The lower yield of 5-methyl-2-phenylpyridine over Hβ compared to HY is due to secondary reactions and also may be due to slower diffusion of the product through the pores of different geometry (pore size 7.6 × 6.4 and 5.5 × 5.5 Å).[25,26] It is seen that higher yields of 5-methyl-2-phenylpyridine were obtained over zeolites where there is no diffusion limitation of the product. This is also supported by our earlier studies on the synthesis of 2-phenylpyridine[22] and 2-methyl-6-phenylpyridine.[20,21] The pore size of the catalyst must be accessible to reactant and product molecules in order for the reaction to occur.

The reaction was carried out over 3 wt% Cr, Mn, Fe, Co, Cu, Zn, Pb and La metal ion-modified HY zeolites at 400 °C with 0.5 h^{-1} weight hour space velocity and the results are given in Table 3. The cyclization activity for 5-methyl-2-phenypyridine followed the order: CoHY > CuHY ≈ ZnHY > CrHY > MnHY > FeHY > PbHY > LaHY. There is no drastic change in the catalytic activity observed upon varying the metal ion and this may be attributed to the presence of several competitive and parallel reactions in a multi-reactant process. The high acidity of LaHY enhances the formation of side products so showing low selectivity and yield of 5-methyl-2-phenylpyridine (Fig. 1). It is observed that mildly acidic Co, Pb, Cu and Zn modified zeolites

Table 2 Synthesis of 5-methyl-2-phenylpyridine from acetophenone, propionaldehyde, formaldehyde and ammonia over various catalysts[a]

		Product distribution (%)[b]					
Catalyst	Acetophenone conversion (%)	5,2-MPP	2,6-MPP	2-PP	3,5-Lutidine	Other alkylpyridines	Others
HZSM-5 (30)	85.0	23.6	0.9	0.2	32.3	15.0	13.0
Hβ	87.0	29.1	1.2	0.8	14.3	10.8	30.8
HY	99.8	37.9	0.2	0.1	36.0	9.3	21.5
SiO_2-Al_2O_3	96.4	25.4	7.9	3.7	11.2	8.5	39.7

[a] Feed: acetophenone–propionaldehyde–formaldehyde–methanol–ammonia = 1 : 1 : 1 : 1 : 5 (mole ratio); reaction temperature: 400 °C; weight hour space velocity: 0.5 h^{-1}; time on stream: 4 h. [b] 5,2-MPP = 5-methyl-2-phenylpyridine; 2,6-MPP = 2-methyl-6-phenylpyridine; 2-PP = 2-phenylpyridine; other alkylpyridines = pyridine, isomers of picolines, lutidine and collidine; others = isomeric mono- and di-alkylphenylpyridines, 2,6-diphenylpyridine and aldolization products.

Table 3 Synthesis of 5-methyl-2-phenylpyridine over various metal ion modified-HY zeolite[a]

Catalyst	Acetopenone conversion (%)	Product distribution (wt%)[b] 5,2-MPP	2,6-MPP	2-PP	3,5-Lutidine	Others	Selectivity of 5,2-MPP
CrHY	93.0	43.4	2.8	0.1	18.7	28.0	46.7
MnHY	93.3	43.3	2.6	—	23.9	23.5	46.4
FeHY	96.2	44.2	3.1	0.9	19.8	28.2	45.9
CoHY	96.0	48.5	2.1	0.7	16.7	28.0	50.5
CuHY	92.8	44.3	3.0	—	24.6	20.9	47.7
ZnHY	98.7	47.1	2.5	—	22.8	26.3	47.7
LaHY	97.9	34.5	0.2	0.4	15.1	47.7	35.2
PbHY	95.6	43.5	2.9	1.6	24.2	23.4	45.5

[a] Feed: acetophenone: propionaldehyde–formaldehyde–methanol–ammonia = 1 : 1 : 1 : 1:5 (mole ratio); reaction temperature: 400 °C; Weight hour space velocity = 0.5 h^{-1}. [b] 5,2-MPP = 5-methyl-2-phenylpyridine; 2,6-MPP = 2-methyl-6-phenylpyridine; 2-PP = 2-phenylpyridine; others = pyridine, isomers of picolines, lutidine and collidine, isomeric mono- and di-alkylphenylpyridines, 2,6-diphenylpyridine and aldolization products.

led to a slightly higher yield of 5-methyl-2-phenylpyridine. The maximum yield of 5-methyl-2-phenylpyridine was obtained on cobalt metal-modified HY catalyst. Earlier reports on the synthesis of pyridine, picolines and lutidines from carbonyl compounds and ammonia also reveal that cobalt-modified zeolites are active for this type of aminocyclization reaction.[27] In order to gain more insight into the reaction, process parameters such as effect of loading of cobalt on HY zeolite, variation of molar ratio of the reactants, weight hour space velocity and product distribution with time on stream studies, have been studied.

The reaction was studied in the temperature range 300–450 °C for the cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia over 3 wt% CoHY catalyst and the results are given in Table 4. The maximum yield of 5-methyl-2-phenylpyridine was observed at 400 °C. Below 400 °C the conversion of acetophenone and the yield of the product is very low. This may be due to the adsorption of ammonia at lower temperatures, thus blocking the active sites for the reaction to proceed. As the temperature was increased, ammonia starts desorbing making the active sites available for the reaction to occur. Further increase in the temperature above 400 °C decreases the conversion levels and yield of 5-methyl-2-phenylpyridine possibly due to coke formation.

The reaction was studied over 1–10 wt% cobalt ion containing HY zeolite and the results are shown in Fig. 2(a). The optimum percentage of loading was found to be 3 wt%. Further increase in the amount of cobalt decreases the conversion of acetophenone and yield of the 5-methyl-2-phenylpyridine owing to the fall in surface area of the catalyst.

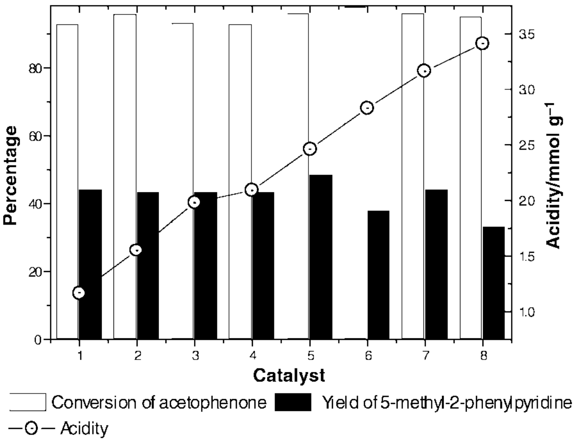
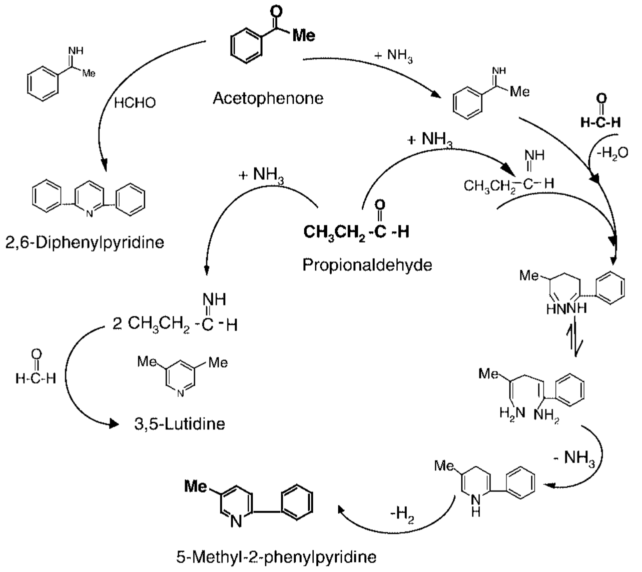


Fig. 1 Effect of acidity of metal ion modified-HY zeolites on the synthesis of 5-methyl-2-phenylpyridine: (1) Cu, (2) Pb, (3) Mn, (4) Cr, (5) Co, (6) HY, (7) Fe (8) La. Feed: acetophenone–propionaldehyde–formaldehyde–methanol–ammonia = 1:1:1:1:5 (mole ratio); reaction temperature: 400 °C: weight hour space velocity: 0.5 h^{-1}; time on stream: 4 h.

The effect of reactant molar ratio for the synthesis of 5-methyl-2-phenylpyridine was studied from 0.5 : 1 to 2 : 1 of acetophenone to propionaldehyde whilst retaining the amounts of formaldehyde and ammonia at a constant level. The maximum yield of 5-methyl-2-phenylpyridine was obtained at a 1 : 1 molar ratio of acetophenone to propionaldehyde as shown in Fig.2(b). An increase of either of the reactants leads to a decrease in the yield of 5-methyl-2-phenylpyridine. An excess of propionaldehyde in the feed increases the formation of pyridine and isomers of picolines and lutidine compounds resulting in a low yield of 5-methyl-2-phenylpyridine. On the other hand, an excess of acetophenone in the feed also decreases the yield of 5-methyl-2-phenylpyridine. This is due to non-availability of required number of propionaldehyde molecules for the cyclization reaction to occur. The formation of aldolization products of acetophenone were also increased.

Variation of weight hour space velocity (WHSV) on the aminocyclization of acetophenone, propionaldehyde, formaldehyde and ammonia was studied in the range 0.25–1 h^{-1} and the results are given in Fig. 2(c). The yield of 5-methyl-2-phenylpyridine decreased with an increase of WHSV due to the decrease in the contact time between reactants and active sites of the catalyst. The maximum yield of 5-methyl-2-phenylpyridine was obtained at a WHSV of 0.5 h^{-1}.

The effect of time on stream on the cyclization reaction was studied for a duration of 10 h over 3 wt% CoHY catalyst at 400 °C and 0.5 h^{-1} weight hour space velocity and the results are given in Fig. 2(d). The catalytic activity was found to be



Scheme 1 A plausible reaction mechanism for the formation of various products during the synthesis of 5-methyl-2-phenylpyridine.

Table 4 Effect of temperature on the synthesis of 5-methyl-2-phenylpyridine over 3 wt% CoHY zeolite[a]

Reaction temperature/°C	TOS/h	Acetophenone conversion (%)	Product distribution (%)[b]				
			5,2-MPP	2,6-MPP	2-PP	3,5-Lutidine	Others
300	2	67.6	25.8	5.0	2.9	6.2	27.7
	4	50.0	15.2	2.9	2.3	4.6	25.0
350	1	56.4	15.7	3.1	3.0	4.4	30.2
	4	55.0	18.4	2.0	3.0	5.8	25.8
400	4	96.0	48.5	2.1	0.7	16.7	28.0
450	1	57.9	17.7	2.8	3.1	4.5	29.8
	4	49.8	16.2	2.5	0.7	5.3	25.1

[a] Feed = acetophenone–propionaldehyde–formaldehyde–methanol–ammonia = 1 : 1 : 1 : 1:5 (mole ratio); Weight hour space velocity = 0.5 h^{-1}. [b] 5,2-MPP = 5-methyl-2-phenylpyridine; 2,6-MPP = 2-methyl-6-phenylpyridine; 2-PP = 2-phenylpyridine; others = pyridine, isomers of picolines, lutidine and collidine, isomeric mono- and di-alkylphenylpyridines, 2,6-diphenylpyridine and aldolization products. TOS = Time on stream.

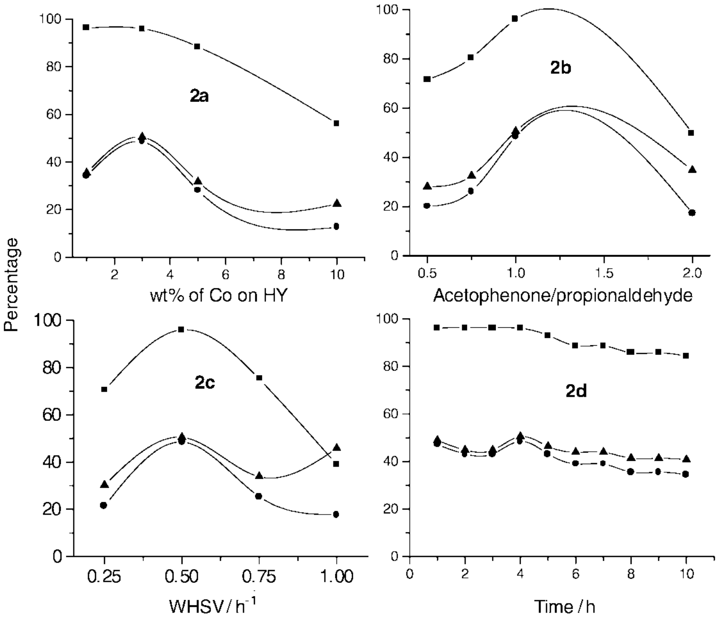


Fig. 2 Effect of reaction parameters on the synthesis of 5-methyl-2-phenylpyridine. (a) Effect of cobalt loading on HY zeolite. (b) Effect of feed mole ratio of acetophenone to propionaldehyde. (c) Effect of weight hour space velocity (WHSV). (d) Effect of time on stream. (■) conversion of acetophenone; (●) yield of 5-methyl-2-phenylpyridine; (▲) selectivity of 5-methyl-2-phenylpyridine.

constant for the first 5 h, with subsequent deactivation probably due to coke formation.

Reaction mechanism

A plausible scheme for the reaction of acetophenone, propionaldehyde, formaldehyde and ammonia over zeolite catalyst is given in Scheme 1. Acetophenone and propionaldehyde react with ammonia forming the corresponding imines. Thus formed, two molecules of imine react with formaldehyde resulting cyclization and dehydrogenation, which leads to the formation of 5-methyl-2-phenylpyridine. The formation of pyridine, picolines and lutidines during the reaction of propionaldehyde, formaldehyde and ammonia has been reported earlier.[14]

Conclusions

Vapor phase cyclization of acetophenone, propionaldehyde, formaldehyde and ammonia over HZSM-5, Hβ and HY zeolites and SiO_2-Al_2O_3 involves multi-step reactions, which leads to the formation of 5-methyl-2-phenylpyridine as the major product and isomeric substituted phenylpyridines, pyridine, picolines and lutidines *etc.* as by-products. The conversion levels of reactants and yield of 5-methyl-2-phenylpyridine increased with pore size of the catalysts. The large pore size of the HY zeolite offers no constraints for the diffusion of the product and gives rise to high activity compared to the medium pore HZSM-5 catalyst. The maximum yield of 5-methyl-2-phenylpyridine was obtained over medium acidic 3 wt% CoHY zeolite at 400 °C. The high acidity/temperatures employed result in catalyst deactivation.

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