



A single step synthesis of 2-phenylpyridine from acetophenone, ethanol, formaldehyde and ammonia over molecular sieve catalysts†

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The vapor phase cyclization of acetophenone, ethanol, formaldehyde and ammonia to 2-phenylpyridine was carried out over HZSM-5, H β , HY and modified HY catalysts at 400 °C. The catalytic activity followed the order: HZSM-5 < H β < HY. The influence of catalyst modification, temperature, molar ratio of feed, weight hour space velocity and time on stream on the catalytic activity and selectivity for the cyclization product are investigated. The effect of pore size of the catalyst and acidity of modified zeolites on cyclization activity is discussed. The maximum yield of 2-phenylpyridine was obtained over 3 wt% cobalt-modified HY zeolite.

Introduction

Phenylpyridines are important intermediates in the synthesis of drugs, agrochemicals, herbicides, insecticides, desiccants, surfactant agents and anti-inflammatory agents.^{1,2} 2-Phenylpyridine and its derivatives are widely used as ligands in the preparation of coordination complexes. It is also a starting material for the drug BMS-232632, which is a potent azapeptide HIV protease inhibitor that has shown high anti-HIV activity.³ Traditionally 2-phenylpyridine is synthesized by the arylation of pyridine with phenyllithium^{4,5} and also by the Grignard reaction.⁶ It has also been photocatalytically synthesized from benzonitrile and ethylene in presence of light using a cobalt(i) complex as a catalyst.⁷ However these reactions are performed in homogeneous catalysis mode with problems of catalyst recovery and tedious work up procedures. Zeolites with crystalline and uniform pore structure have proved to be efficient catalysts in acid-mediated reactions. The characteristics that make zeolites as attractive heterogeneous catalysts are a 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 such as phenylpyridine and substituted phenylpyridines. Recently large pore zeolites and mesoporous molecular sieve catalysts are reported to be excellent catalysts especially for the synthesis of large molecules.^{15–19} Previous work in our laboratory has 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-methyl-6-phenylpyridine²⁰ and 5-methyl-2-phenylpyridine.²¹ To the best of our knowledge, this is the first report of the synthesis of 2-phenylpyridine from acetophenone, ethanol, formaldehyde and ammonia over various molecular sieve catalysts in vapor phase reactions.

Experimental

The HZSM-5 (30) zeolite was obtained from Conteka (Sweden), H β (20) was obtained from Sud-chemie (India) and HY (2.6) zeolite was obtained from PQ Corporation (USA). The catalyst powders were pelletized and sized (18–30-mesh). A required amount of metal nitrate in aqueous medium was added to the sized catalyst to modify the surface by impregnation followed by calcination in air at 400 °C for 4 h.

Vapor phase cyclization reactions were carried out using a tubular down flow Pyrex glass reactor with 20-mm internal diameter. The catalyst (4 g) 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 thermocouple 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 a Chromosorb HIWP packed column and products were confirmed by GC–MS and NMR spectroscopy. The best hour and fourth hour values are given in the tables. Comparison is made between different catalysts/conditions at 4 h reaction time.

Temperature programmed desorption (TPD) measurements were carried out to measure the acidity of the catalyst using ammonia as an adsorbate. In a typical run, a 0.150 g portion of catalyst was placed in a quartz tubular reactor and heated at

Green Context

One of the major causes of waste in organic reaction chemistry is multi-stage synthesis. Each step will lead to the production of waste made more damaging by the use of traditional separation methods such as solvent extraction and washing. Thus single step syntheses are very attractive. Here the novel single step synthesis of 2-phenylpyridine using solid catalysts is described. The large pore HY zeolite is particularly effective. Phenylpyridines have widespread uses in areas such as medicine and agriculture. JHC

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400 °C under a nitrogen flow of 30 cm³ 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 cm³ 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 cm³ min⁻¹). The NH₃ gas evolved was quantified by gas chromatography using a thermal conductivity detector.

Results and discussion

Catalyst characterization

The acidity of the modified HY zeolites were measured by temperature programmed desorption of ammonia and values are given in Table 1. The three peaks observed at 150–250, 250–350 and 350–450 °C correspond to desorption of NH₃ gas from weak, medium and strong acid sites, respectively, as observed also by several other groups.^{22–24} The total acidity of the catalysts order followed as CuHY < PbHY < CrHY < CoHY < HY < FeHY < LaHY. As reported earlier, the HY catalyst modified by rare earth cations such as La showed slightly higher acidity than the unmodified zeolite.^{25–27} The framework of the modified zeolites was checked by X-ray diffraction and FTIR measurements and crystallinity found to be retained. The surface areas of the modified zeolites were measured by the BET method and values are given in Table 1. The decrease in the surface area of the metal modified zeolites relative to the unmodified zeolite is due to the presence of metal ion and its oxide species in the cavity of the zeolites. The surface area of cobalt metal-modified HY zeolite decreases with increased loading of cobalt.

Table 1 Physical characteristics of modified HY zeolites

Catalyst	Surface area/ m ² g ⁻¹	Acidity (NH ₃ desorbed) (mmol g ⁻¹)			Total acidity
		150–250	250–350	350–450 °C	
3 wt% metal-modified HY zeolites					
HY	457.19	1.73	0.64	0.45	2.82
CrHY	411.41	1.09	0.38	0.62	2.09
FeHY	377.27	1.81	0.83	0.52	3.16
CoHY	447.16	1.62	0.61	0.23	2.46
CuHY	432.17	0.44	0.68	0.05	1.17
PbHY	448.38	0.89	0.54	0.12	1.55
LaHY	355.71	1.87	0.85	0.69	3.41
Cobalt loading on HY zeolite					
wt %	Surface area/m ² g ⁻¹				
1	450.78				
5	428.00				
10	348.35				

Table 2 Synthesis of 2-phenylpyridine from acetophenone, ethanol, formaldehyde and ammonia over modified HY zeolites. Reaction temperature = 400 °C; WHSV = 0.5 h⁻¹. Feed = acetophenone–ethanol–formaldehyde–ammonia = (1:1:1:5) (mole ratio)

Catalyst	TOS/h	Conversion of acetophenone (wt%)	Yield (wt%)			
			2-PP	Alkylpyridines	5,2-MPP	Others
HZSM-5	2	92.9	19.8	24.2	11.6	37.3
	4	70.4	12.0	28.4	—	30.2
Hβ	1	97.2	20.6	24.7	9.2	42.7
	4	96.5	14.5	29.9	7.7	44.4
HY	1	92.7	31.1	18.3	14.2	28.8
	4	92.0	25.0	22.1	11.2	33.7

2-PP = 2-phenylpyridine; 5,2-MPP = 5-methyl-2-phenylpyridine; alkylpyridines = pyridine, isomers of picoline and lutidine; others = isomers of alkylphenylpyridine, 2,6-diphenylpyridine and acetophenone aldol condensation products. TOS = time on stream (best 1 h and 4 h values).

Catalytic activity

The vapor phase cyclization reaction of acetophenone, ethanol, formaldehyde and ammonia was carried out over HZSM-5, Hβ and HY zeolites at 400 °C with a weight hour space velocity (WHSV) of 0.5 h⁻¹ and the results are given in Table 2. HZSM-5, Hβ and HY showed conversions of acetophenone of 70.4, 96.5 and 92.0% respectively. The yield of 2-phenylpyridine for HZSM-5, Hβ and HY are 12.0, 14.5 and 25.0%, respectively. The catalytic activity order with respect to the yield of 2-phenylpyridine is HZSM-5 < Hβ < HY. The yield of 2-phenylpyridine increased with increase of pore size from HZSM-5 (5.4 Å) to HY (7.4 Å). Even though a good conversion level for the HZSM-5 catalyst is seen, the low yield of the product may be due to inaccessibility or slower diffusion of the product 2-phenylpyridine through the pores of the ZSM-5 zeolite (5.4 Å). Diffusion restriction through the pores is observed only for 2-phenylpyridine with no constraints on the diffusion of other products such as pyridine, picolines and lutidines. On the other hand, the large pore HY zeolite (7.4 Å) shows higher yields of the product compared to HZSM-5, with no diffusion constraint towards 2-phenylpyridine. The lower yield of 2-phenylpyridine over Hβ compared to HY is due to secondary reactions and also may be due to slower diffusion of the product^{28,29} through the pores of different geometry (pore sizes 7.6 × 6.4 and 5.5 × 5.5 Å). The pore size of the catalyst must be accessible to reactant and product molecules in order for the reaction to occur.

Reactions were then carried out over 3 wt% La, Pb Co, Cu, Cr and Fe metal ion-modified HY zeolites at 400 °C at 0.5 h⁻¹ weight hour space velocity and results are given in Table 3. The cyclization activity as reflected in the yield of 2-phenylpyridine followed the order: CoHY > CrHY > FeHY > PbHY > HY > CuHY > LaHY. No drastic change in the catalytic activity was observed upon modification by metal ions which may be attributed to the presence of several competitive and parallel reactions in a multi-reactant process. The high acidity of LaHY and FeHY enhances the formation of side products thus leading to a lower selectivity and yield of 2-phenylpyridine. The maximum yield of 2-phenylpyridine was obtained over medium acidic 3 wt% CoHY catalyst. Earlier reports on the synthesis of pyridine, picolines and lutidines from carbonyl compounds and ammonia also reveal that the cobalt-modified zeolites are active for this type of aminocyclization reaction.^{12,30} In order to gain more insight into the cyclization reaction the process parameters like effect of wt% of metal, variation of molar ratio of the reactants, weight hour space velocity, and time on stream product distribution have been studied over the 3 wt% CoHY catalyst.

The effect of variation of cobalt loading on HY zeolite on the cyclization reaction is shown in Fig. 1. The optimum percentage of loading was found to be 3 wt%.

Further increase in the amount of cobalt decreased the conversion of acetophenone and yield of the 2-phenylpyridine

which may be due the decrease in surface area of the catalyst (Table 1).

The reaction temperature was varied from 300 to 425 °C for the reaction of acetophenone, ethanol, formaldehyde and ammonia over 3 wt% CoHY zeolite and the results are shown in Fig. 2. The maximum yield of 2-phenylpyridine was observed at 400 °C. The yield of 2-phenylpyridine increased with an increase in the reaction temperature from 300 to 400 °C. 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 2-phenylpyridine which may be due to coke formation.

The effect of the molar ratio for the synthesis of 2-phenylpyridine was studied from 0.5:1 to 2:1 molar ratio of acetophenone to ethanol while keeping the formaldehyde and ammonia levels constant, and the results are shown in Fig. 3. The maximum yield of 2-phenylpyridine was obtained at 1:1 molar ratio of acetophenone to ethanol. An increase of either of the reactants leads to decrease in the yield of 2-phenylpyridine. An increase in the molar ratio of acetophenone to ethanol decreases the acetophenone conversion and yield of 2-phenylpyridine due to the non-availability of the required number of ethanol molecules for the cyclization reaction to occur. The decrease in the yield of 2-phenylpyridine is also due to the aldolization of acetophenone giving side products. A decrease in the molar ratio of acetophenone to ethanol in the feed leads to an increase in the formation of pyridine and isomers of picolines and lutidine compounds formation and thus decreases the yield of 2-phenylpyridine.

Variation of weight hour space velocity (WHSV) on the aminocyclization of acetophenone, ethanol, formaldehyde and ammonia was studied in the range 0.25–1 h⁻¹ and the results are given in Fig. 4. The yield of 2-phenylpyridine decreased with an increase of WHSV beyond 0.5 h⁻¹ due to the decrease in the contact time between reactants and active sites of the catalyst. The maximum yield of 2-phenylpyridine was obtained at a WHSV of 0.5 h⁻¹.

The effect of time on stream on cyclization reaction was studied for 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. 5. The catalytic activity was found to be constant for the first 5 h, with subsequent deactivation probably due to coke formation.

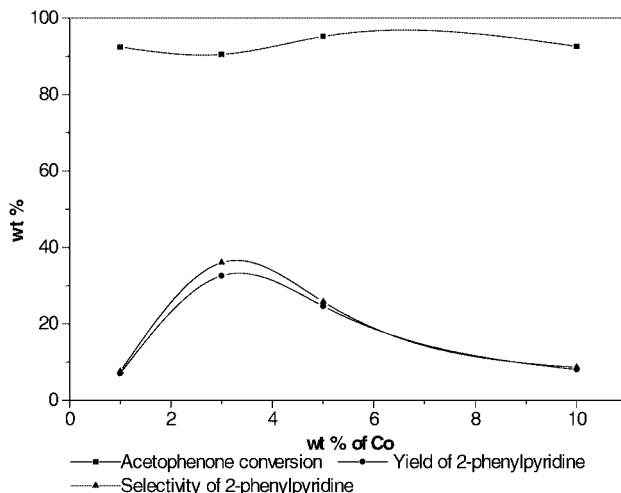


Fig. 1 Effect of wt% of Co in HY zeolite on the synthesis of 2-phenylpyridine. Reaction temperature = 400 °C; WHSV = 0.5 h⁻¹; time on stream = 4 h. Feed = acetophenone–ethanol–formaldehyde–ammonia (1:1:1:5) (mole ratio).

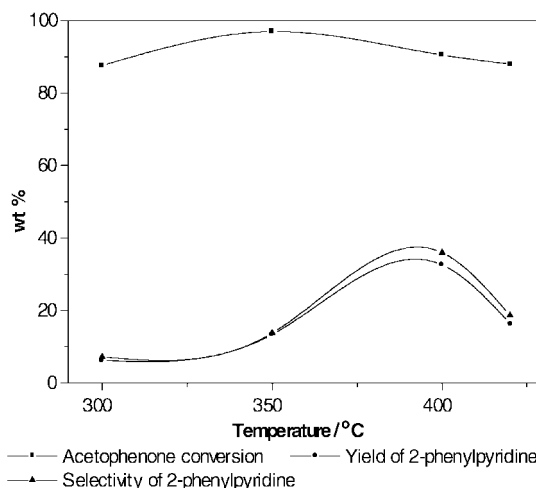


Fig. 2 Effect of temperature on synthesis of 2-phenylpyridine over 3 wt% CoHY zeolite. Feed = acetophenone–ethanol–formaldehyde–ammonia (1:1:1:5) (mole ratio); WHSV = 0.5 h⁻¹; time on stream = 4 h.

Table 3 Synthesis of 2-phenylpyridine over 3 wt% metal-modified HY zeolites. Reaction temperature = 400 °C; WHSV = 0.5 h⁻¹. Feed = acetophenone–ethanol–formaldehyde–ammonia = (1:1:1:5) (mole ratio)

Catalyst	TOS/h	Conversion of acetophenone (wt%)	Yield (wt%)					Selectivity of 2-PP (%)
			2-PP	Alkylpyridines	2,6-MPP	5,2-MPP	Others	
HY	1	92.7	31.1	18.3	0.3	14.2	28.8	33.5
	4	92.0	25.0	22.1	1.9	11.2	21.8	28.3
CrHY	4	91.9	30.1	22.1	1.4	10.5	27.8	32.7
	FeHY	1	91.9	29.1	20.1	0.2	10.1	32.4
4		91.6	26.5	14.5	0.3	10.0	40.6	28.9
CoHY	2	94.5	38.6	16.6	0.1	12.2	27.1	40.8
	4	90.5	32.6	19.1	0.2	8.6	29.9	36.0
CuHY	1	93.2	34.4	10.2	2.9	11.6	34.1	36.9
	4	94.0	24.4	13.6	0.8	11.5	43.7	26.0
PbHY	4	92.2	26.1	14.5	0.2	10.0	41.4	28.3
LaHY	4	94.2	20.8	25.7	2.3	16.7	28.7	22.8

2-PP = 2-phenylpyridine; 2,6-MPP = 2-methyl-6-phenylpyridine; 5,2-MPP = 5-methyl-2-phenylpyridine; alkylpyridines = pyridine, isomers of picoline and lutidine; others = isomers of alkylphenylpyridine, 2,6-diphenylpyridine and acetophenone aldol condensation products. TOS = time on stream (best 1 h and 4 h values).

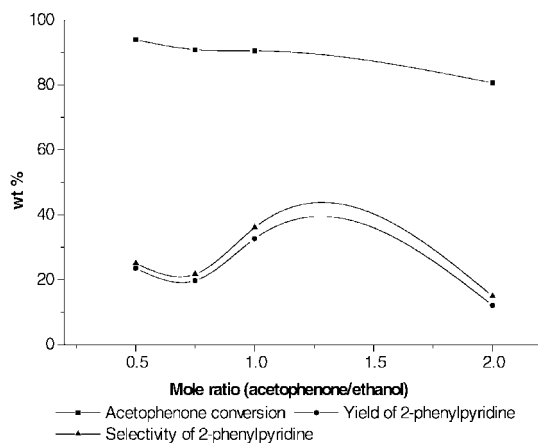


Fig. 3 Effect of molar ratio of acetophenone to ethanol on the synthesis of 2-phenylpyridine over 3 wt% CoHY zeolite. Reaction temperature = 400 °C; WHSV = 0.5 h⁻¹; time on stream = 4 h.

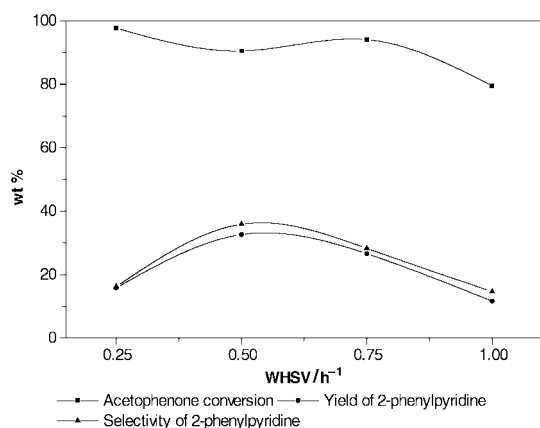


Fig. 4 Effect of weight hour space velocity (WHSV) on the synthesis of 2-phenylpyridine over 3 wt% CoHY zeolite. Feed = acetophenone–ethanol–formaldehyde–ammonia = (1 : 1 : 1 : 5) (mole ratio), reaction temperature = 400 °C; time on stream = 4 h.

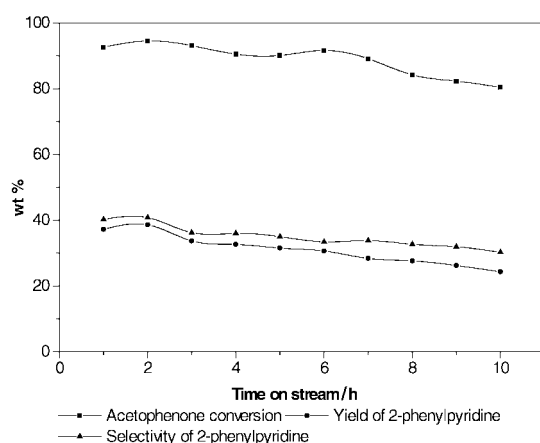
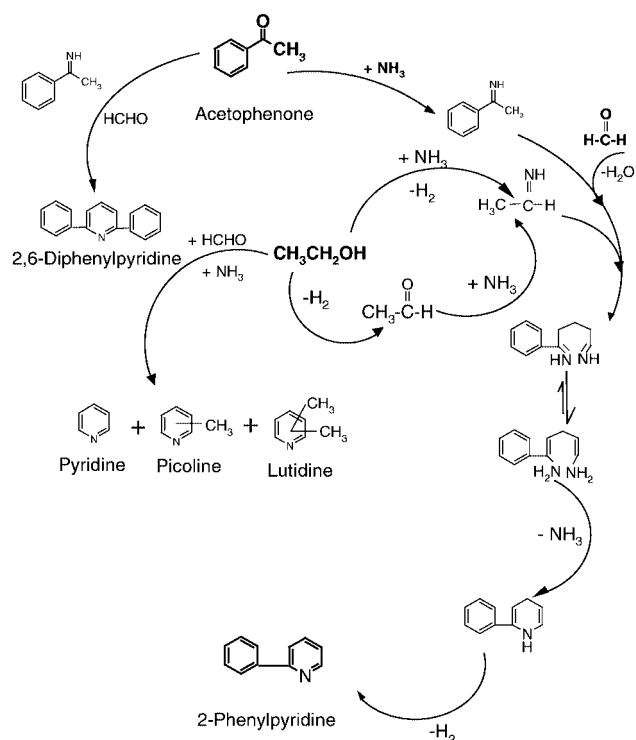


Fig. 5 Effect of time on stream on the synthesis of 2-phenylpyridine over 3 wt% CoHY zeolite. Feed = acetophenone–ethanol–formaldehyde–ammonia = 1 : 1 : 1 : 5 (mole ratio); reaction temperature = 400 °C; WHSV = 0.5 h⁻¹.

Reaction mechanism

A plausible mechanism for the reaction of acetophenone, ethanol, formaldehyde and ammonia over zeolite catalyst is shown in Scheme 1. The reaction of acetophenone with ammonia gives rise to the formation of corresponding imine. Ethanol may be oxidized to acetaldehyde and the subsequent reaction with ammonia results in the formation of the corre-



Scheme 1 A plausible reaction mechanism for the synthesis of 2-phenylpyridine from acetophenone, ethanol, formaldehyde and ammonia over molecular sieve catalysts.

sponding imine. Thus formed, two molecules of imine react with formaldehyde. The resulting cyclization and dehydrogenation lead to the formation of 2-phenylpyridine. The formation of pyridine, picolines and lutidines from the reaction of ethanol, formaldehyde and ammonia has been reported earlier.^{12–14,30}

Conclusions

Vapor phase cyclization of acetophenone, ethanol, formaldehyde and ammonia involves multiple reactions, which leads to the formation of 2-phenylpyridine as the major product as well as other products such as isomeric substituted phenylpyridines, pyridine, picolines and lutidines *etc.* The large pore size of the HY zeolite offers no constraints for the diffusion of the product and thus shows high activity compared to the medium pore HZSM-5 catalyst. High acidity/temperatures result in eventual deactivation. The maximum yield of 2-phenylpyridine was obtained over a medium acidic 3 wt% CoHY catalyst at 400 °C.

References

- 1 S. Shimizu, N. Abe, N. Goto, T. Niwa and A. Iguchi, *Jpn. Pat.*, JP 01261367A, 1998.
- 2 S. Peter, H. Gerhard, H. Elisabeth, K. Ralf, K. Hartmann, H. Albrecht, G. Norbert, W. Helmut, W. Karl-Otto and M. Ulf, *US Pat.*, US 5 733 850, 1998.
- 3 X. Rabasseda, J. Silverstre and J. Castaner, *Drugs Fut.*, 1999, **24**, 375.
- 4 M. T. Dupriest, C. L. Schmidt, D. Kuzmich and S. B. Williams, *J. Org. Chem.*, 1986, **51**, 2021.
- 5 F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020.
- 6 Daniel. Comins and Abdul H. Abdullah, *J. Org. Chem.*, 1982, **47**, 4315.
- 7 B. Heller and G. Oehme, *J. Chem. Soc., Chem. Commun.*, 1995, 179.
- 8 S. E. Golunski and D. Jackson, *Appl. Catal. A*, 1986, **23**, 1.

- 9 S. J. Kulkarni and M. Subrahmanyam, *Indian J. Chem. A*, 1991, **30**, 1041.
- 10 S. J. Kulkarni, *Stud. Surf. Sci. Catal.*, 1998, **113**, 151.
- 11 A. V. Rama Rao, S. J. Kulkarni and M. Subrahmanyam, *Appl. Catal. A*, 1994, **111**, 101.
- 12 S. Shimizu, N. Abe, A. Iguchi, M. Dohba, H. Sato and K. Hirose, *Microporous Mesoporous Mater.*, 1998, **21**, 447.
- 13 S. J. Kulkarni, R. Ramachandra Rao, M. Subrahmanyam and A. V. Rama Rao, *Appl. Catal. A*, 1994, **113**, 1.
- 14 R. Ramachandra Rao, S. J. Kulkarni, M. Subrahmanyam and A. V. Rama Rao, *React. Kinet. Catal. Lett.*, 1995, **56**, 301.
- 15 E. Armengol, M. L. Cano, A. Corma, H. Garcia and M. T. Navarro, *J. Chem. Soc., Chem. Commun.*, 1995, 519.
- 16 Rodriguez, M. J. Climent, S. Iborra, V. Fornes and A. Corma, *J. Catal.*, 2000, **192**, 441.
- 17 A. Corma, V. Fornes, J. Matinez-Triguero and S. B. Pergher, *J. Catal.*, 1999, **186**, 57.
- 18 M. J. Climent, A. Corma, I. Rodriguez, S. Iborra, S. Miquel, J. Primo and F. Rey, *J. Catal.*, 1999, **183**, 76.
- 19 J. P. G. Pater, P. A. Jacobs and J. A. Martens, *J. Catal.*, 1999, **18**, 262.
- 20 D. Venu Gopal, N. Srinivas, B. Srinivas, S. J. Kulkarni and M. Subrahmanyam, *Green Chem.*, 2001, **3**, 65.
- 21 D. Venu Gopal and M. Subrahmanyam, *Green Chem.*, 2001, **3**, 181.
- 22 J. R. Anderson, K. Foger, T. Mole, R. A. Rajadhyaksha and J. V. Sanders, *J. Catal.*, 1979, **58**, 114.
- 23 N. Topsoe, K. Pedersen and E. G. Derouane, *J. Catal.*, 1981, **70**, 41.
- 24 G. P. Babu, S. G. Hegde, S. B. Kulkarni and P. Ratnasamy, *J. Catal.*, 1983, **81**, 471.
- 25 P. Ram Reddy, M. Subrahmanyam and S. J. Kulkarni, *Catal. Lett.*, 1998, **54**, 95.
- 26 P. Ram Reddy, M. Subrahmanyam and V. Durga Kumari, *Catal. Lett.*, 1999, **60**, 161.
- 27 F. O. J. Connor and T. P. Rodney, *Zeolites*, 1985, **5**, 158.
- 28 J. Aguilar, A. Corma, F. V. Melo and E. Sastre, *Catal. Today*, 2000, **55**, 225.
- 29 J. Horniakova, D. Mravec, S. Fabokova, M. Hronec and P. Moreau, *Appl. Catal. A*, 2000, **203**, 47.
- 30 S. Shimizu, N. Abe, A. Iguchi and H. Sato, *Catal. Surv. Jpn.*, 1998, **2**, 71.