

Highly selective and single step vapor phase synthesis of 2,6-bis(4-methylphenyl)pyridine over Al-MCM-41 molecular sieves[☆]

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Abstract

Vapor phase synthesis of 2,6-bis(4-methylphenyl)pyridine (2,6-BP), an important drug intermediate, was carried out by the cyclization of 4-methyl acetophenone (4-MAP), ethanol, formaldehyde and ammonia over different classes of molecular sieves, viz. HY, HZSM-5, H β and Al-MCM-41. The predominant product of cyclization 2,6-BP was obtained on Al-MCM-41 with high selectivity. To understand the mechanism and to identify the suitable acid sites, we further studied the reaction by varying the Si/Al ratio and feed composition on Al-MCM-41. A plausible mechanism leading to the formation of 2,6-BP along with the other major by-products 2-(4-methylphenyl)pyridine (2-P) and 2,6-bis(4-methylphenyl)4-methyl pyridine (2,6-MBP), is proposed.

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1. Introduction

In recent years, environmental and economic considerations have created great interest in designing catalysts for specific products in which multi-step processes are avoided and generation of a large amount of waste is minimized. Zeolites and mesoporous molecular sieves are the immediate choices to synthesize products with high selectivity as the knowledge and range of materials available for this class allows designing of catalysts easily for a product of specific interest.

For the past few years, IICT-Hyderabad has been specializing in synthesis of pyridine derivatives as important drug intermediates using zeolites and modified zeolites [1–6]. The present investigation is a part of the on-going research describing the synthesis of 2,6-bis(4-methylphenyl)pyridine (2,6-BP) with very high selectivity in a single step over Al-MCM-41 molecular sieves.

Aryl pyridines are important intermediates for the synthesis of drugs, agrochemicals, pesticides, prolongators, insecticides and avia-repellents [7–8]. 2,6-BP is also used as a

ligand for the synthesis of metal complexes [9]. Aryl pyridines are finding their use as aromatase inhibitors, in which pyridinic nitrogen of the derivatives interacts with heme iron via ligation. Such a phenomenon is used for treating cancerous cells. The use of substituted pyridines as nonsteroidal inhibitors of human placental aromatase is reported [10].

Aryl pyridines are conventionally prepared either by replacing the alkoxysulphonyl groups in the second position of pyridine nucleus with aryl lithium [11] or from pyridine N-oxide conversion into 2-aryl pyridines by the reaction with aryl magnesium bromide, followed by acetylation (Ac₂O) and spontaneous elimination of acetic acid [12]. All such processes are multi-step, homogenous and require tedious work-up procedures. Based on the data generated, the present route for the synthesis of 2,6-BP with high selectivity may be seen as a suitable method for the production of drug intermediates on a large scale as an eco-friendly process. Further research is in progress.

2. Experimental

Commercial zeolites HY (Si/Al = 2.6) from PQ Corporation (USA), HZSM-5 (Si/Al = 15) from Conteka (Sweden) and H β (20) from Sud-Chemie (India) were procured. 4-Methyl acetophenone and formaldehyde were obtained

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from Spectrochem Ltd. (India). Ethanol was obtained from Changshu Yangyuan Chemicals China.

Al-MCM-41 (with Si/Al ratio ~ 15 –150) was synthesized in the laboratory, as described earlier [13]. An aqueous solution of aluminium isopropoxide (0.76 g) and sodium hydroxide was added in a 50 ml beaker and stirred while heating till a clear solution appeared. Then 9.4 ml of tetra ethyl ammonium hydroxide (TEAOH) was added to the solution while cooling under stirring (solution A). Simultaneously the required amount of tetraethylorthosilicate was taken in another beaker in 50 ml water (solution B) and then solution A was added slowly to solution B with stirring. After stirring for 2 h, hexadecyltrimethyl ammonium bromide (HDTAB) 10.55 g was added slowly to the above mixture. Finally the gel mixture having the molar composition of $\text{SiO}_2 : x\text{Al}_2\text{O}_3 : 2.2\text{HDTAB} : 3.16\text{TEAOH} : 1.89\text{Na}_2\text{O} : 615\text{H}_2\text{O}$ (x varies with Si/Al ratio) was transferred into an autoclave and heated at 100°C for 24 h. The recovered product was calcined at 500°C in air for 12 h to expel the imprisoned template.

The vapor phase cyclization reaction was carried out using a fixed bed tubular down-flow glass reactor (i.d. 20 mm and length 45 cm) at atmospheric pressure. The reaction mixture was fed from the top of the reactor by using a syringe pump (profuse, B. Braun, Germany) to the catalyst placed in the middle of the reactor. The solid product in the down-stream was collected by washing with dichloromethane at the bottom of the reactor and in the condenser. The cumulative sample (4 h) containing the solid and liquid products that were dissolved in dichloromethane was analyzed using gas chromatography (Hewlett-Packard 6890) with a flame ionization detector using 10% SE-30 column. The products were confirmed by GC-MS, ^1H NMR and EIMS spectroscopies.

3. Results and discussion

The heterocyclization of 4-MAP, ethanol, formaldehyde and ammonia was carried out over HY, HZSM-5, H β and Al-MCM-41; the results are shown in Table 1. The catalytic activity in terms of 4-MAP conversion follows the order

Table 1
Synthesis of aryl pyridines from 4-MAP, ethanol, formaldehyde and ammonia^a

Catalyst (Si/Al ratio)	4-MAP conversion (%)	Selectivity (wt.%) ^b			
		2-P	2,6-BP	2,6-MBP	Others
HY (2.6)	84	11	56	29	5
HZSM-5 (15)	96	12	49	7	29
H β (20)	96	14	42	3	38
MCM-41 (15.5)	70	6	72	19	3

^a Feed mole ratio = 1:1:1:5; temperature = 300°C ; WHSV = 0.5.

^b 2-P, 2-(4-methylphenyl)pyridine; 2,6-BP, 2,6-bis(4-methylphenyl)pyridine; 2,6-MBP, 2,6-bis(4-methylphenyl)-4-methyl pyridine; others, pyridine, isomeric mono and di-alkyl tolyl pyridines.

HZSM-5 \approx H β > HY > Al-MCM-41. The cyclization reaction is forming 2,6-BP as the major product of the reaction independent of the zeolite used, along with 2-P and 2,6-MBP as by-products in considerable amounts. Though conversions are high on HZSM-5 and H β , high selectivity is observed towards 2,6-BP on Al-MCM-41. This may be due to the pore size of HZSM-5 and H β that might be restricting the formation and diffusion of bigger molecules leading the reaction into side products lowering the selectivity. Meanwhile, Al-MCM-41 having mesopores is showing high selectivity towards 2,6-BP. Further experiments were planned to study Al-MCM-41 as this zeolite is forming 2,6-BP with high selectivity at reasonable conversions with minimum by-products; amounts of other products are low. Thus the effect of temperature, Si/Al ratio, the feed composition and WHSV were studied on Al-MCM-41.

3.1. Effect of temperature

Fig. 1 shows the effect of temperature on cyclization of 4-MAP over Al-MCM-41 (15.5). Conversions as high as 70–74% are observed in the temperature range of 300 – 350°C ; conversion decreased with further increase in temperature. 2,6-BP also follows the same trend as that of conversion, showing maximum selectivity around 300°C . Increase in temperature decreased the formation of 2,6-BP and 2,6-MBP, whereas the formation of 2-P is maintained more or less at the same level in the temperature range studied. Thus a reaction temperature of 300°C is chosen for studying the other effects.

3.2. Effect of WHSV

The variation of weight hourly space velocity on cyclization was studied in the range of 0.25 – 1 h^{-1} and the results are shown in Fig. 2. The effect of WHSV on cyclization

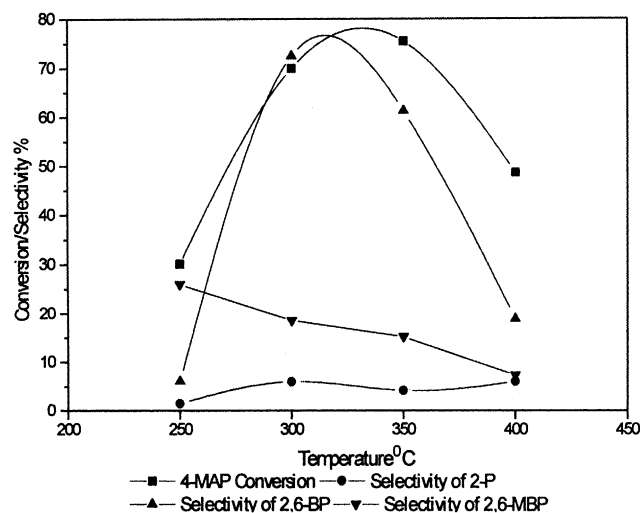


Fig. 1. Effect of temperature on the synthesis of aryl pyridines over Al-MCM-41 (15.5). Feed mole ratio = 1:1:1:5; WHSV = 0.5.

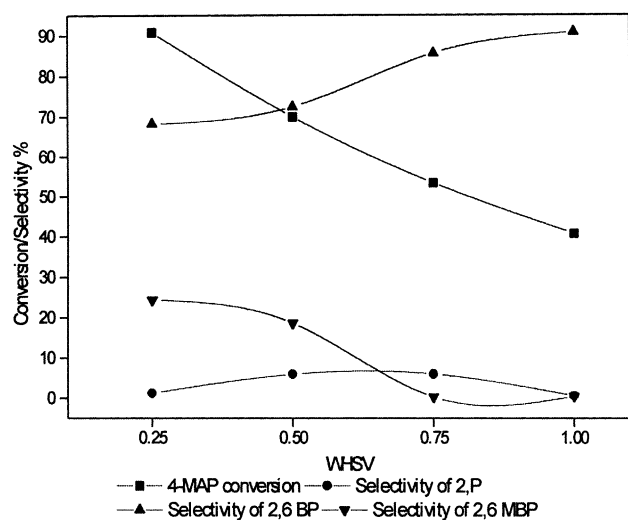


Fig. 2. Effect of weight hourly space velocity (WHSV) on the synthesis of aryl pyridines over MCM-41 (15.5). Feed mole ratio = 1:1:1:5; temperature = 300°C.

of 4-MAP at 300°C shows that, with decrease in contact time, conversion decreased, increasing the 2,6-BP selectivity. It is observed in our experiments that high contact time results into side products and coking. At moderate conversions ($\approx 70\%$), the reaction forms 2,6-BP as the predominant product. Thus the cyclization reaction was studied at WHSV of 0.5 conveniently with steady conversion and selectivity for more than 10 h with minimum coking (Table 4).

3.3. Effect of variation of feed composition

Effect of variation of feed composition on cyclization reaction is studied over Al-MCM-41 (15.5) and results are shown in Table 2. It is very clear from the results that, in the absence of ethanol and the presence of formaldehyde, 4-MAP conversion and selectivity of 2,6-BP are high. In the presence of ethanol and absence of formaldehyde, however, conversions are low and the selectivity is shifted to 2,6-MBP, indicating the role of ethanol in the main reaction as well as in the side reactions that form other products (pyridine, isomeric mono and di alkyl tolylpyridines). Further experiments were carried out in the absence of ethanol to

Table 2
Effect of variation of feed composition over MCM-41 (15.5)^a

Feed	4-MAP conversion (%)	Selectivity ^b			
		2-P	2,6-BP	2,6-MBP	Others
4-MAP + EtOH + HCHO + NH ₃	70.0	6	72.0	19.0	3.0
4-MAP + HCHO + NH ₃	83.8	–	84.2	–	15.8
4-MAP + EtOH + NH ₃	32	5	–	48.2	41.8

^a Temperature = 300°C; WHSV = 0.5.

^b 2-P, 2-(4-methylphenyl)pyridine; 2,6-BP, 2,6-bis(4-methylphenyl)pyridine; 2,6-MBP, 2,6-bis(4-methylphenyl)4-methyl pyridine; others, pyridine, isomeric mono and di-alkyl tolyl pyridines.

Table 3
Synthesis of 2,6-BP over MCM-41 with different Si/Al ratios^a

Catalyst	4-MAP conversion (%)	Selectivity (%) ^b			
		2-P	2,6-BP	2,6-MBP	Others
Al-MCM-41 (15.5)	83.8	–	84.2	–	15.8
Al-MCM-41 (37.5)	76.3	–	98.0	–	2.0
Al-MCM-41 (75)	48.6	–	96.2	–	4.8
Al-MCM-41 (150)	30.4	–	97.4	–	2.6

^a Feed mole ratio, 4-MAP; for NH₃, 2:1:5; temperature = 300°C; WHSV = 0.5.

^b 2-P, 2-(4-methylphenyl)pyridine; 2,6-BP, 2,6-bis(4-methylphenyl)pyridine; 2,6-MBP, 2,6-bis(4-methylphenyl)4-methyl pyridine; others, pyridine, isomeric mono and di-alkyl tolyl pyridines.

obtain 2,6-BP with maximum selectivity (98%), as shown in Table 3.

3.4. Effect of variation of Si/Al ratio of Al-MCM-41

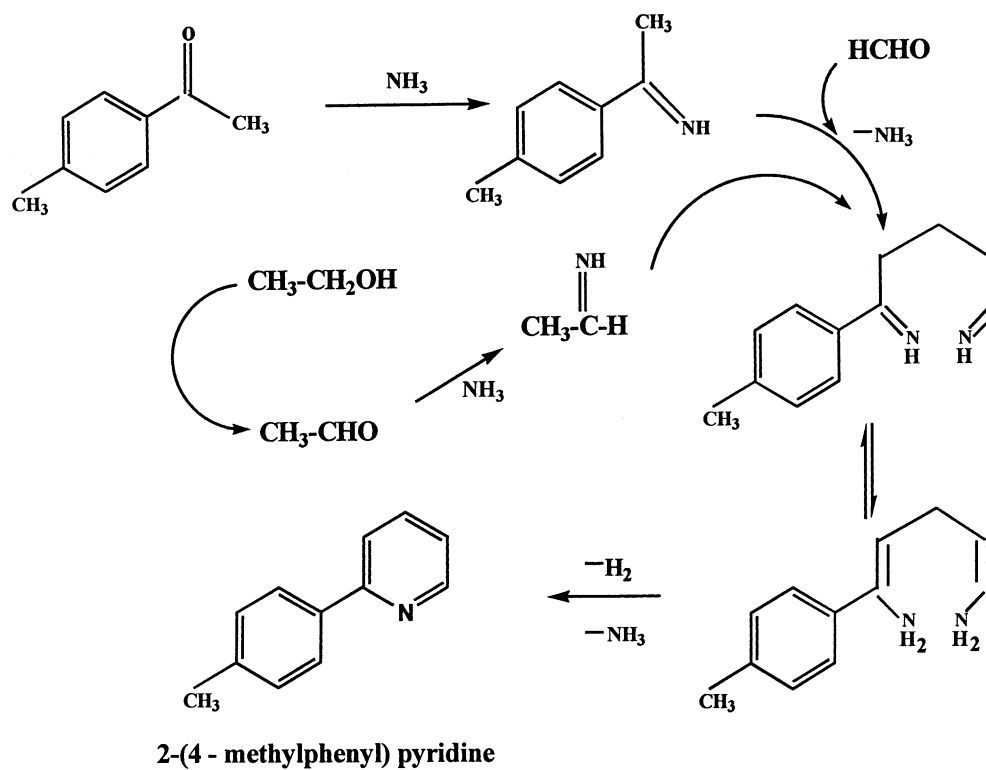
The cyclization reaction was also studied by varying the Si/Al ratio of Al-MCM-41 (Table 3). These results clearly show that, with increasing Si/Al ratio and without ethanol, the cyclization reaction is very smooth and forms 2,6-BP as the major product of the reaction. The formation of other by-products is seen only on Al-MCM-41 with Si/Al ratio 15.5, as the total acidity and the number of acid sites of different strength (weak, medium and strong) are expected

Table 4
Time on stream activity of cyclisation reaction over Al-MCM-41 (37.5)^a

Feed ^a	TOS (h)	4-MAP conversion (%)	Selectivity (%) ^b			
			2-P	2,6-BP	2,6-MBP	Others
4-MAP + HCHO + NH ₃	4	76.3	–	98.0	–	2
4-MAP + HCHO + NH ₃	10	75.6	–	97.3	–	3.7
4-MAP + EtOH + NH ₃	4	22.0	–	–	43.5	56.5
4-MAP + EtOH + NH ₃	10	21.2	–	–	35.8	64.2

^a Temperature = 300°C; WHSV = 0.5.

^b 2-P, 2-(4-methylphenyl)pyridine; 2,6-BP, 2,6-bis(4-methylphenyl)pyridine; 2,6-MBP, 2,6-bis(4-methylphenyl)4-methyl pyridine; others, pyridine, isomeric mono and di-alkyl tolyl pyridines.

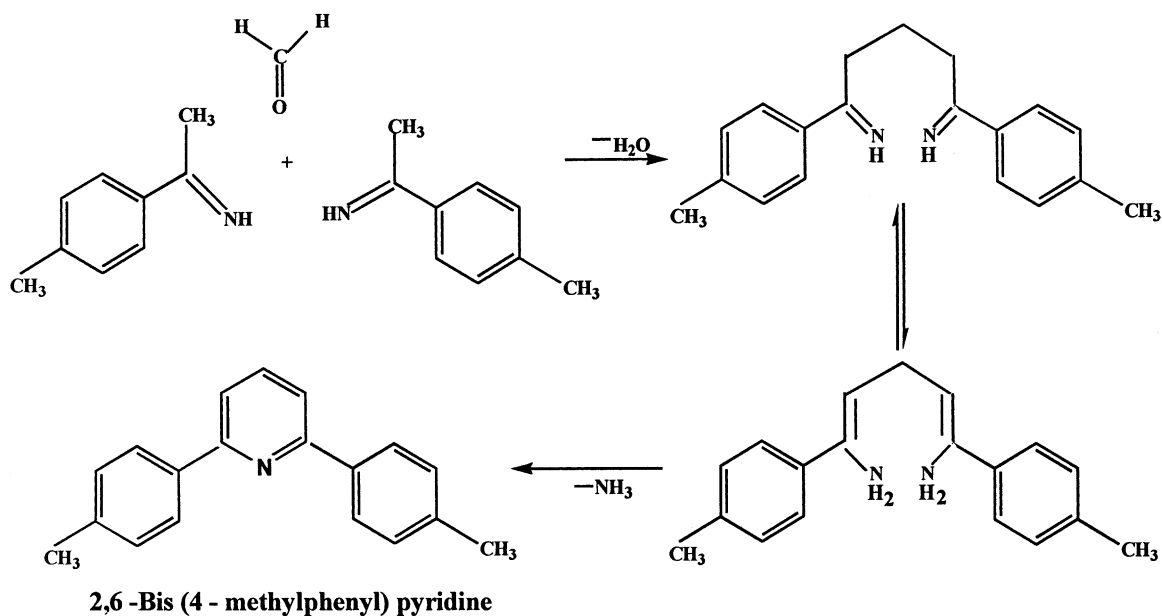


Scheme 1.

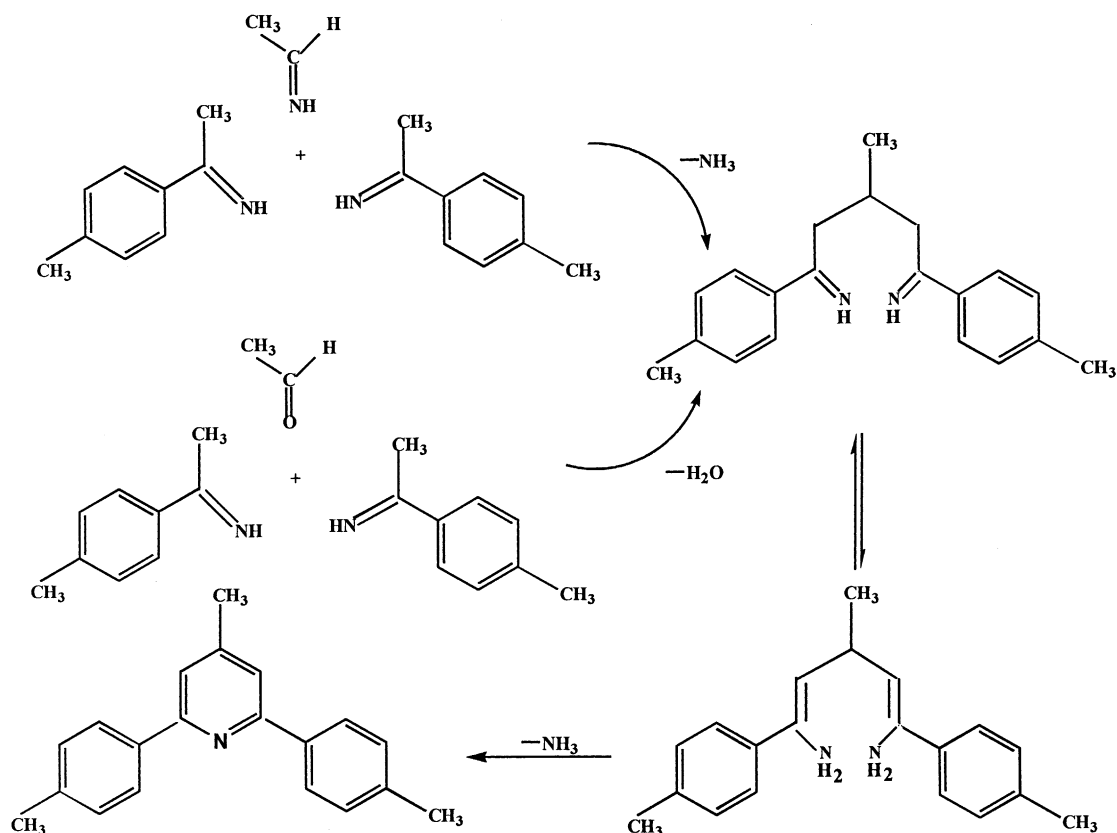
to be high on this molecular sieve. The effect of Si/Al ratio highlights 2,6-BP formation selectively on Al-MCM-41 with Si/Al ratio 37.5, indicating the presence of suitable acid site strength necessary for the cyclization reaction on this catalyst.

3.5. Effect of time on stream

Finally, the reaction was studied for time on stream activity, as shown in Table 4. The cumulative samples collected at 4 and 10 h show more or less the same level of conversion



Scheme 2.



2,6-Bis(4 -methylphenyl) 4 -methyl pyridine

Scheme 3.

and product distribution, indicating minimum or no deactivation during the course of the reaction.

3.6. Reaction mechanism

Based on the product distribution in the cyclization of 4-MAP, formaldehyde, ammonia and alcohol over Al-MCM-41, the plausible reaction mechanism leading to the formation of major products is discussed now. The product formation may depend on the relative activity and stability of the imine \leftrightarrow amine intermediates that are formed in situ during the course of the reaction. The formation of 2-P is observed when all the reactants are involved in the ratio of 1:1:1:5, and is not observed by eliminating one of the reactants: ethanol or formaldehyde. The reactants 4-MAP and alcohol spontaneously form imines with ammonia. The possible conversion of the imine in the presence of formaldehyde may lead to another set of imine \leftrightarrow amine intermediates which, on further dehydrogenation and deamination, form a cyclized product 2-P as shown in Scheme 1. A second possibility of this reaction is seen through the conversion of 2 mol of 4-MAP imine and formaldehyde to a imine \leftrightarrow amine intermediate which on

further dehydrogenation and deamination yields a bigger cyclized product 2,6-BP, as shown in Scheme 2. This is further confirmed by observing the reaction in the absence of ethanol, in which 2,6-BP is selectively formed. Similarly the reaction may end up in 2,6-MBP in the absence of formaldehyde, if the condensation takes place between 2 mol of 4-MAP imine with aldehyde or by the direct condensation of 4-MAP imine and aldehyde, as shown in Scheme 3.

4. Conclusions

Vapor phase cyclization of 4-MAP, ethanol, formaldehyde and ammonia at 300°C over Al-MCM-41 involves the formation of imine \leftrightarrow amine intermediates, which on further dehydrogenation and deamination form 2,6-BP as major product and 2-P, 2,6-MBP as by-products. The cyclization reaction in the absence of ethanol forms 2,6-BP selectively. The molecular sieve Al-MCM-41 with Si/Al ratio of 37.5 has suitable acidity for selective formation of 2,6-BP. The observed product distribution supports the mechanism proposed.

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