



A novel single step synthesis of 2-methyl-6-phenylpyridine from non-heterocyclic compounds over molecular sieve catalysts†

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The industrially important 2-methyl-6-phenylpyridine is synthesized for the first time in a single step by reacting acetophenone, acetone, formaldehyde and ammonia in the vapor phase over microporous and mesoporous molecular sieve catalysts.

Introduction

Conventional homogeneous acid catalysts such as H_2SO_4 , HF, $AlCl_3$, $FeCl_3$ etc., show several disadvantages such as high corrosiveness, tedious work-up, requirement of stoichiometric quantities, the presence of several undesirable side products, and non-recycling of catalyst, and thus are highly non-ecofriendly. The major goals of 'Green chemistry' are to increase process selectivity, maximize the use of starting materials, and to replace hazardous and stoichiometric reagents with eco-friendly catalysts in order to facilitate easy separation of the final reaction mixture, including recovery of the catalyst. Microporous aluminosilicate molecular sieves have been studied extensively in the area of acid catalysis and cyclization reactions, and these materials have contributed greatly to hydrocarbon processing and the chemical industry.¹ Mesoporous MCM-41 materials have well defined pore sizes of 15–100 Å, *i.e.* larger than the pore size constraint of 15 Å characteristic of microporous zeolites. The large pore size (relative to that of microporous zeolites) reduces diffusional restriction of reactants and products and so enables reactions involving bulky molecules to occur.^{2–4} Although extensive research efforts have been undertaken to explore the catalytic applications of modified MCM-41 materials in the field of catalytic oxidations,^{5,6} acid catalysis⁷ and alkylation reactions⁸ applications in a variety of fields of organic chemistry still remain limited.

Among heterocyclic compounds, alkyl substituted phenylpyridines are extensively used as intermediates in the synthesis of drugs, pharmaceuticals, herbicides and agrochemicals.⁹ A substituted phenylpyridine 2-(4-carboxyphenyl)pyridine is a starting material for BMS-232632, a potent azapeptide HIV protease inhibitor which has shown high anti-HIV activity.¹⁰ Among various synthetic routes for pyridine and its derivatives, aldehyde/ketone and ammonia condensation is a commercially proven success.

The synthesis of 2-methyl-6-phenylpyridine over molecular sieve catalysts has not been reported. 2-Phenylpyridine and substituted 2-phenylpyridines are generally synthesized from the reaction of aryllithium with pyridine and picolines in homogenous conditions.¹¹ Regioselective alkylation of 2-phenylpyridine with olefins in the presence of Rh(i) as a catalyst gave 3-methyl-2-phenylpyridine¹² and 2-(4-methylphenyl)pyridine,¹³ but not 2-methyl-6-phenylpyridine. It was reported that 2-methyl-6-phenylpyridine can be synthesized by a homo-

neous photocatalytic reaction from benzonitrile and ethylene using a Co(i) complex as a photocatalyst.¹⁴ A Japanese patent⁹ reported that acetophenones catalytically react with symmetric ketones, formaldehyde and ammonia using a metal-modified amorphous silica-alumina catalyst in the vapor phase at 350–550 °C, however, the amorphous silica-alumina catalyst is prone to deactivation with time on stream.

Here, we report for the first time, the synthesis of 2-methyl-6-phenylpyridine over a novel mesoporous MCM-41 catalyst in a continuous fixed bed using simple and inexpensive raw materials, *i.e.* acetophenone, acetone, formaldehyde and ammonia.

Results and discussion

The heterocyclization reaction of acetophenone, acetone, formaldehyde and ammonia for the synthesis of 2-methyl-6-phenylpyridine was carried out over HZSM-5, HM, H β , HY and MCM-41 catalysts and the results are shown in Table 1 and in Fig. 1. The order of catalytic activity for 2-methyl-6-phenylpyridine was found to be MCM-41 > HY > H β > HM \geq HZSM-5. It is assumed that the small pore size (5.4 Å) of the HZSM-5 zeolites imposes diffusion control through which the bulky product 2-methyl-6-phenylpyridine can not diffuse out, with the formation of the small amount of the product probably through a surface reaction. The intermediate activity of HY zeolite (pore size 7.4 Å) indicates that diffusion control is reduced compared to HZSM-5 for the large size product 2-methyl-6-phenylpyridine. The lower catalytic activity of H β relative to HY may be due to its geometry of two

Green Context

The ability to carry out clean synthetic transformations over solid catalysts has been transformed by the advent of MCM type materials. While initial attempts to use the larger pores showed that the acidity of the materials is much lower than that of most zeolites of similar composition, this can often be advantageous. Here, for example, a multicomponent condensation is carried out using the large pore dimensions and mild acidity of these materials. It is shown that yields of this gas phase (no-solvent) reaction are much better than found with a range of zeolites.

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types of pores (pore sizes: 5.4 and 7.6 Å) in the intersecting channel system. It is observed that mesoporous Al-MCM-41 (pore size 30 Å) shows high catalytic activity for 2-methyl-6-phenylpyridine formation with no diffusional constraint. It is evident from the data shown in Fig. 1 that the pore size of the catalyst plays a major role during the synthesis of 2-methyl-6-phenylpyridine, a large molecule. Fig. 1 summarizes the important relation between pore size and molecular size of the reactant/product. The pore size of the catalyst must be accessible to reactant and product molecules in order to take part in the reaction.

A plausible reaction mechanism based on the product distribution is given in Scheme 1, which involves a multi-reactant system leading to several competitive and parallel reactions. Acetophenone and acetone upon reacting with ammonia form the corresponding imines. Thus, the two molecules of imine which form react with formaldehyde and subsequently undergo cyclization and dehydrogenation reactions leading to the formation of 2-methyl-6-phenylpyridine.

Similarly, cyclization between two imine molecules of acetone and formaldehyde resulted the formation of 2,6-lutidine as a major side product. In similar manner, the reaction between two molecules of imine deriving from acetophenone and formal-

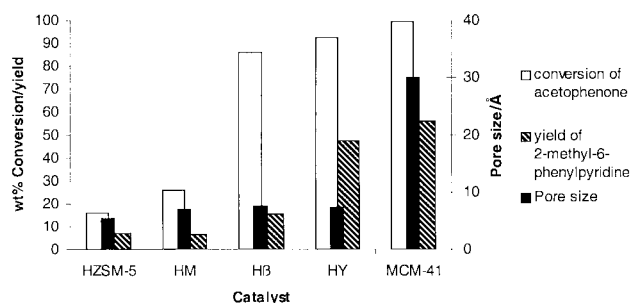
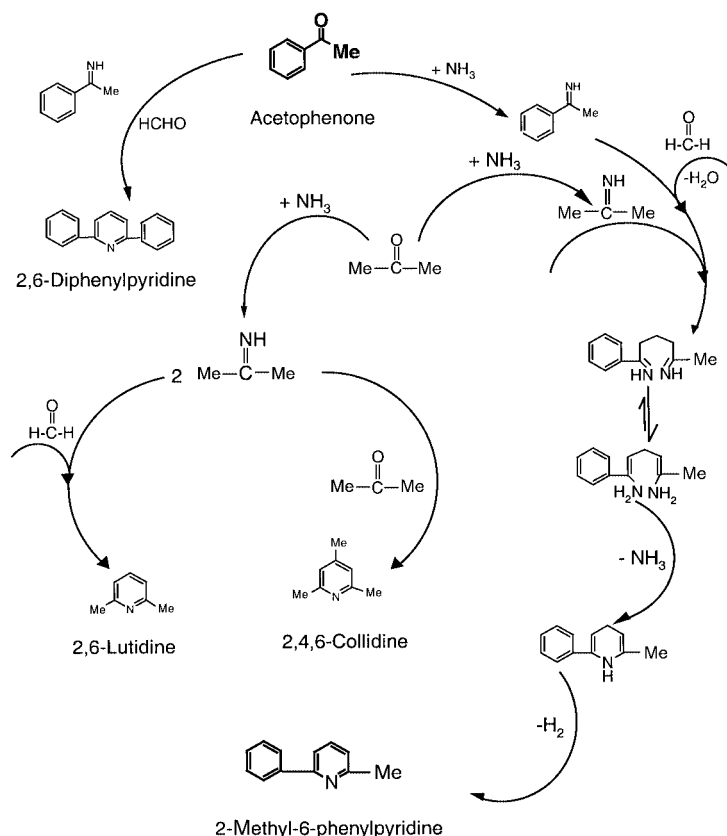


Fig. 1 Effect of pore size on the synthesis of 2-methyl-6-phenylpyridine.

Table 1 Synthesis of 2-methyl-6-phenylpyridine over molecular sieve catalysts

Catalyst	SiO ₂ /Al ₂ O ₃	TOS/h	Conversion of acetophenone (wt%)	Yield of 2-methyl-6-phenylpyridine (wt%) ^a	Pore size/Å
HZSM-5	30	1	50.6	15.7	5.4
		4	16.0	7.2	
HM		4	25.9	6.3	7.1
		4	86.2	15.6	
Hβ	20	1	83.0	28.0	7.6, 5.4
		4	86.2	15.6	
HY	2.9	1	99.1	48.0	7.4
		4	92.3	47.5	
MCM-41	25	3	99.4	58.6	30
		4	99.3	56.0	
SiO ₂ -Al ₂ O ₃	4	4	86.1	21.5	—
		4	86.1	21.5	

Feed = acetophenone:acetone:formaldehyde:ammonia = 1:1.5:1:5 (molar ratio); reaction temperature = 400 °C; weight hour space velocity (WHSV) = 0.5 h⁻¹. ^a The yields are calculated based on the acetophenone conversion.



Scheme 1 A plausible reaction mechanism for the formation of various products during the synthesis of 2-methyl-6-phenylpyridine.

dehyde lead to the formation of 2,6-diphenylpyridine. Furthermore, 2- and 4-picoline were observed as minor products. The isomers of alkylated and mono- and di-methyl-phenylpyridines result from the cyclization of acetone with acetophenone in different mol ratios in the presence of formaldehyde and ammonia. Aldol condensation products of acetophenone and acetone are also observed in trace amounts. Ethylbenzene, trace amounts of styrene, α -methylstyrene and cumene were also observed. The internal acidity of the zeolites is responsible for the various transformations. It is clear that the acidic strength of the sites depends on the chemical composition of the zeolite and is related to the framework topology. It was observed that medium strength acid sites are favored for the required specific heterocyclization product.

Conclusion

In conclusion, this work shows that mesoporous molecular sieves such as MCM-41 are active catalysts for heterocyclization reactions, especially in the present case, for the synthesis of 2-methyl-6-phenylpyridine. It is also shown that the large pore mesoporous MCM-41 catalyst is more active than microporous aluminosilicates like HZSM-5, HM, H β and HY zeolites for the synthesis of 2-methyl-6-phenylpyridine which is a large molecule. The data also substantiate the phenomenon of diffusion control of reactants, products and shape selectivity with respect to pore size of the catalysts.

Experimental

Al-MCM-41 was prepared as reported by Ortlam *et al.*¹⁵ and calcined at 500 °C in air for 12 h. The BET surface area was determined by N₂ adsorption at 77 K and also characterized by XRD, IR and MAS-NMR spectroscopic techniques. The HZSM-5 zeolite was obtained from Conteka (Sweden), H β was obtained from Sud-chemie (India) and HM, HY zeolites were obtained from PQ Corporation (USA).

The cyclization reaction was carried out in a continuous fixed-bed down-flow Pyrex glass reactor of internal diameter 18 mm, using 4 g of the sized catalyst (18–30 mesh) in the middle of the reactor, with an electrically heated furnace. The reaction was carried out at 400 °C. The feed (acetophenone:acetone:formaldehyde:ammonia = 1:1.5:1:5 mol ratio) was fed from the top of the reactor using a B. Braun (Germany) syringe pump. The products were collected through an ice-cold water trap and analyzed by GC (10% SE-30, 20% Carbowax in 1.8 meter S.S. packed columns) and identified by GC-MS and ¹H NMR spectroscopy.

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