Vapor-phase alkylation of indole with methanol over zeolites☆

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Abstract

Vapor-phase alkylation of indole with methanol was carried out over HZSM-5 (30), HY, CeHY, LaHY, CrHY and CuHY zeolites in a continuous fixed-bed reactor at atmospheric pressure. Rare earth metal cation-modified HY zeolites are found to be more active for the alkylation of indole than HY zeolites and transition metal-modified HY zeolites. The maximum of 33.6% yield of 3-methylindole at 72.6% indole conversion was obtained over 3 wt.% CeHY catalyst at 300 °C. Furthermore, the activity of pyridine-poisoned and calcined catalysts revealed that either Brønsted or Lewis acid sites of medium strength are the suitable sites for 3-methylindole formation. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Zeolite; Alkylation; Indole; 3-Methylindole

1. Introduction

The synthesis of organic intermediates is an important area in the fine chemical, pharmaceutical drug and dye industries. Friedel–Crafts alkylation is well established in organic reactions. Traditionally, these reactions are carried out using conventional Lewis acid catalysts such as $AlCl_3$, $TiCl_4$, $FeCl_3$ and BF_3, which should be replaced because of their non-reusability, corrosive nature, non-shape selectivity, and non-ecofriendly nature. Zeolite catalysts offer numerous advantages over conventional Lewis acid catalysts, such as reusability, less or no corrosion, high thermal stability and environmentally friendly nature [1–4]. Zeolite-catalyzed alkylation of heterocyclic compounds is important because the alkylated heterocyclic compounds are widely used as intermediates

for many organic processes [5–7]. Indole and its derivatives are extensively used as intermediates in the synthesis of anti-inflammatory agents, antibiotics and dyes [8–10]. 3-Methylindole (3-MI) known as skatole has been reported to promote the dimerization of butadiene and has also found use in photography. It has also been found to have positive biological action as an anti-diuretic, stimulant, anti-hypertensive, muscle relaxant, respiratory inhibitor (inhibits respiration in cancer cells), heart stimulant and tuberculostat. It is also reported to be a plant growth regulator [11].

Traditionally, indole is C-alkylated by alcohols in the presence of sodium or potassium alkoxide [12]. C-alkylation of indole was reported with electron-deficient olefins and epoxides under the influence of a Lewis acid like $Yb(OTf)_3$ to yield 3-alkylated indole [13]. Heterogeneously-catalyzed alkylation of indole was studied using SiO_2, Al_2O_3 or SiO_2-Al_2O_3 as catalyst, yielding 17% of 1-alkylated indole [14]. In this context, it is worth mentioning that zeolites are found to be excellent catalysts for many alkylation and acylation reactions due to their high acidity, thermal stability and shape selectivity.

We are reporting here the vapor-phase alkylation of indole to synthesize 3-methylindole for the first time over zeolite catalysts.

2. Experimental

HY (Si/Al = 2.6) was obtained from PQ Corporation, USA, and HZSM-5 (30) from Conteka, Sweden. The catalyst powder was pelletized, crushed, and sieved into 2 mm size. The HY zeolite is modified by an impregnation method with 3 wt.% metal cations such as La, Ce, Cr, and Cu. The required quantities of zeolite and of metal nitrate were dissolved in distilled water and the mixture was stirred at room temperature and allowed to stand overnight. Then it was dried in an oven at 100 °C to evaporate the residual water. It was calcined in air between 400 and 420 °C for 4 h to obtain the finished catalyst. The impregnated cations are present as oxidized species inside the supercages.

The vapor-phase alkylation reaction was carried out in a continuous fixed-bed glass reactor. An amount of 4 g of 2 mm sized catalyst was placed in the middle of the reactor. The reactants were fed from the top of the reactor using a syringe pump (Perfusor, B. Braun). The products were collected from an ice-cold trap at the bottom of the reactor. The products were analyzed on a gas chromatograph (Chemito 3865) with FID using a SE-30 column and identified by authentic samples and by GC–MS. The conversions were given with respect to indole. The catalytic activity data comparison is made between different catalysts at 4 h duration.

The acidity of all the zeolite catalysts were measured by the stepwise temperature-programmed desorption (STPD) of the ammonia method using a Micromeritics Pulse Chemisorb 2700 unit, as reported earlier [15]. A powdered sample (ca. 0.5 g) was introduced in the sample tube. It was pre-heated in a helium flow for 2 h at 450 °C. Then the sample temperature was brought down to 80 °C. A loop (0.984 cm^3) saturated with ammonia was used to flush several pulses through the sample tube. The sample was thus saturated with ammonia (normally it takes five to six pulses of 30 s duration each). After saturation, the sample is flushed in a helium flow for 30 min to remove any loosely bound ammonia on the sample at 80 °C. The temperature of the sample was then raised to 150 °C and the ammonia was allowed to des-

orb at this temperature. The completion of desorption of ammonia at this temperature region 80–150 °C is taken as physisorbed or weakly chemisorbed ammonia, corresponding to catalytic sites of weak acidic strength. The sample temperature was then raised to 300 °C and the desorbed ammonia is again recorded. The ammonia desorbed in the temperature region of 150–300 °C is considered to represent the catalytic sites of medium acidic strength. The desorption process is repeated by raising the temperature to 450 °C and the ammonia desorbed in this temperature region is considered to represent catalytic sites of strong acidic strength. The qualitative distributions of the relative number and the relative strengths of acid sites are thus evaluated by TPD of ammonia.

The pyridine-poisoning experiments were carried out as reported by Bourdillon and Gueguen [16]. The 3 wt.% CeHY catalyst was pre-treated at 400 °C for 4 h in air and then it was cooled to 150 °C under a nitrogen flow before pyridine was injected (about 2 × 10^{22} molecules of pyridine per gram of the zeolite). After 2 h treatment of pyridine under nitrogen flow at 150 °C, the temperature of the sample was increased to 330 °C under nitrogen flow for the pyridine desorption. The pyridine content of the sample remained constant after a 2 h treatment with nitrogen. The temperature was then lowered to 300 °C and the catalytic reaction was carried out.

3. Results and discussion

Acidity values of the zeolites and of the modified zeolites were measured by the method of stepwise temperature-programmed desorption of ammonia, as reported earlier [15], and the values of the zeolites are given in Table 1. The rare earth metal cation-modified zeolites exhibit slightly higher acidity than those of the parent zeolites [5,15]. The acidity observed decreased in the order LaHY ≥ CeHY > HY > CrHY ≥ CuHY > HZSM-5 (30). The X-ray diffraction patterns of the modified zeolites clearly indicated that the crystallinity was not affected on modification. The surface areas of the modified and unmodified zeolites were measured by N$_2$ adsorption at 77 K (BET method). The surface areas of the zeolite catalysts decreased on modification; the values are shown in Table 1.

Table 1
Acidity and surface area of the zeolite catalysts that are used for alkylation of indole

Catalyst	Acidity (mmol g^{-1}) (desorption temperatures of ammonia)			Total acidity (mmol g^{-1})	Surface area (m^2 g^{-1})
	150–250 °C	250–350 °C	350–450 °C		
HY	0.42	0.19	0.09	0.70	457.2
CeHY	0.48	0.23	0.20	0.91	405.3
LaHY	0.48	0.27	0.22	0.97	355.7
CrHY	0.35	0.15	0.07	0.57	411.4
CuHY	0.32	0.16	0.08	0.56	393.8
HZSM-5 (30)	0.30	0.13	0.10	0.53	427.3

Table 2
Alkylation of indole over HZSM-5 (30), HY and modified HY zeolites[a]

Catalyst	Indole conversion (%)	1-MI yield (%)	3-MI yield (%)	3-MI selectivity (%)	Others yield (%)
HZSM-5 (30)	6.3	1.4	4.4	69.8	0.3
HY	14.7	2.1	11.7	79.6	1.0
CuHY	10.2	0.2	9.6	94.1	0.3
CrHY	12.2	0.3	11.6	95.5	0.9
CeHY	35.1	3.9	30.0	85.5	1.2
LaHY	64.7	7.8	32.2	50.1	22.9

[a] Indole:methanol = 1:6 molar ratio, WHSV = 0.5 h^{-1}, reaction temperature = 300°C, TOS = 4 h. Others: 2-methylindole, 2,3-dimethylindole, 1,2-dimethylindole, 1,3-dimethylindole, 3,3-dimethylindolenine and polymethyl indoles.

The vapor-phase alkylation of indole with methanol was carried out over HZSM-5 (30) and HY zeolites at 300 °C using a feed of indole:methanol 1:6. The results are shown in Table 2. It is observed from the table that the alkylation activity towards the yield of 3-MI decreased in the order: LaHY > CeHY > CrHY > CuHY > HY > HZSM-5 (30). The results indicate that the large pore size HY zeolite shows higher catalytic activity than medium pore size HZSM-5 (30) zeolite. In order to increase the catalytic activity towards 3-MI formation, HY zeolite was modified with various metal ions like Cr, Cu, La and Ce; the results

are given in Table 2. The rare earth cations like (La and Ce)-modified HY zeolite catalysts show higher activity than HY and transition metal-modified HY zeolites. The maximum yield of 33.6% of 3-MI was obtained over 3 wt.% CeHY zeolite catalyst at 300 °C.

The effects of reaction parameters like temperature, weight hour space velocity (WHSV) and time-on-stream (TOS) were studied to get more insight into the mechanism of alkylation and to achieve the highest yield of 3-MI on 3 wt.% CeHY system.

The effect of temperature on alkylation of indole was studied on 3 wt.% CeHY in the temperature range

Table 3
Effect of temperature on alkylation of indole over 3 wt.% CeHY zeolite[a]

Reaction temperature (°C)	TOS (h)	Indole conversion (%)	1-MI yield (%)	3-MI yield (%)	3-MI selectivity (%)	Others yield (%)
200	4	2.5	0.3	2.0	80.0	0.2
250	4	65.4	21.6	23.7	36.2	20.1
300	4	35.1	3.9	30.0	85.7	1.2
350	4	76.9	3.9	29.6	38.5	43.4

[a] Indole:methanol = 1:6 molar ratio, WHSV = 0.5 h^{-1}. Others: 2-methylindole, 2,3-dimethylindole, 1,2-dimethylindole, 1,3-dimethylindole, 3,3-dimethylindolenine and polymethyl indoles.
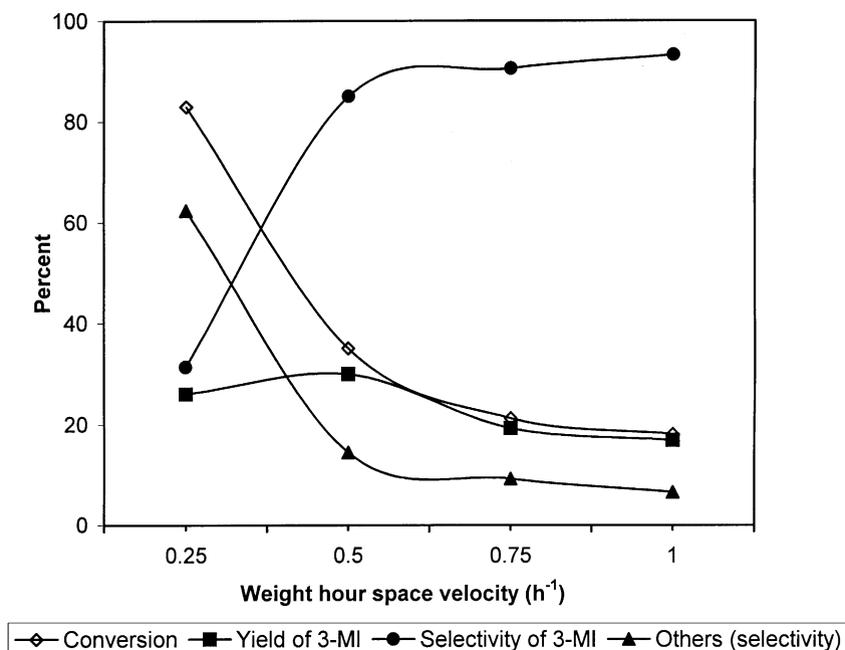
Fig. 1. Effect of WHSV on alkylation of indole over 3 wt.% CeHY catalyst at 300 °C and 1:6 molar ratio of indole to methanol. Time-on-stream = 4 h. Others: 2-methylindole, 2,3-dimethylindole, 1,2-dimethylindole, 1,3-dimethylindole, 3,3-dimethylindolenine and polymethyl indoles.

200–350 °C; the results are shown in the Table 3. The maximum yield of 3-MI was obtained at 300 °C. Below 250 °C, the alkylation activity is very low. At temperatures above 300 °C, the conversion of indole is increasing, but the selectivity of 3-MI is decreasing. This may be due to the generation of strong Lewis acid sites at high reaction temperatures [15–19]; such sites enhance the formation of polyalkylated indoles, thereby decreasing the selectivity of 3-MI.

The effect of WHSV on alkylation of indole was studied over 3 wt.% CeHY catalyst at 300 °C and at 1:6 molar ratio of indole to methanol at 0.25, 0.5, 0.75 and 1 h^{-1} WHSV (Fig. 1). The results shown in Fig. 1 indicate that selectivity of 3-MI increases on increasing WHSV.

Effect of time-on-stream at 300 °C at WHSV of 0.5 h^{-1} and 1:6 molar ratio of indole to methanol on 3 wt.% CeHY is shown in Fig. 2. It could be seen from the figure that the activity of the catalyst decreases with time. This may be due to the formation of coke on the catalyst with time-on-stream. On the other hand, the selectivity of 3-MI is increasing with

time. This selectivity towards 3-MI formation may be due to coke-induced selectivity, which also may reduce the intersection and/or pore diameter so that the polyalkylated products could not diffuse out [20,21].

3.1. Acidity versus alkylation activity

A correlation between the acidity and the activity of the catalysts is shown in Fig. 3. It indicates that the catalytic activity increases with increasing total acidity of the catalyst. The modification of HY with La and Ce increases the acidity of the zeolites. On the other hand, the modification of HY with transition metal cations like Cr and Cu decreases the acidity of HY zeolites, resulting in lower alkylation activity. Earlier reports also suggested that rare earth metal cation-modified HY zeolites were active for alkylation and acylation reactions due to their high acidity [7,17,18]. The high acidity of La- and Ce-modified HY zeolite can be attributed to the coordinating ability of La and Ce with water to generate Brønsted acid sites by dissociation [17,18]. It is known that Brønsted and Lewis acid sites
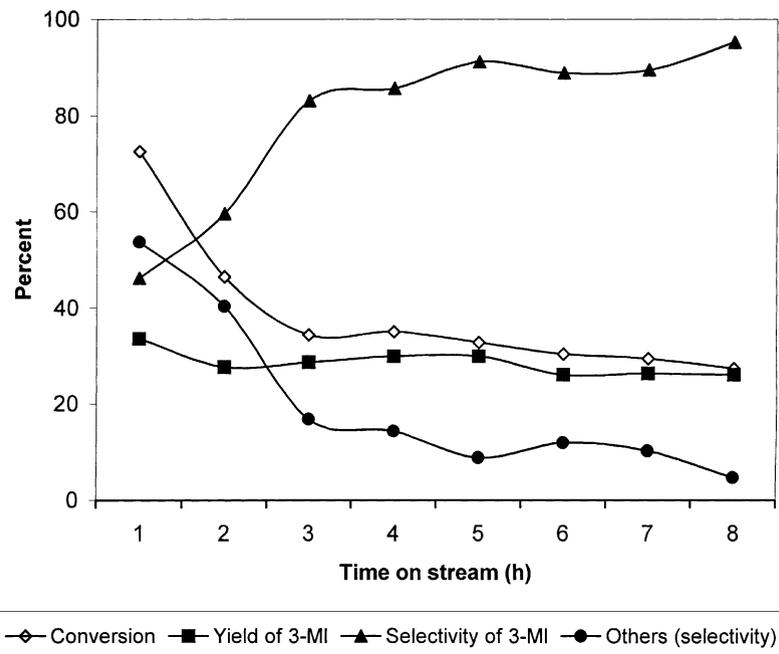
Fig. 2. Effect of time-on-stream on alkylation of indole over 3 wt.% CeHY catalyst. Reaction temperature 300 °C; indole:methanol = 1 : 6 molar ratio; WHSV = 0.5 h^{-1}. Others: 2-methylindole, 2,3-dimethylindole, 1,2-dimethylindole, 1,3-dimethylindole, 3,3-dimethylindolenine and polymethyl indoles.
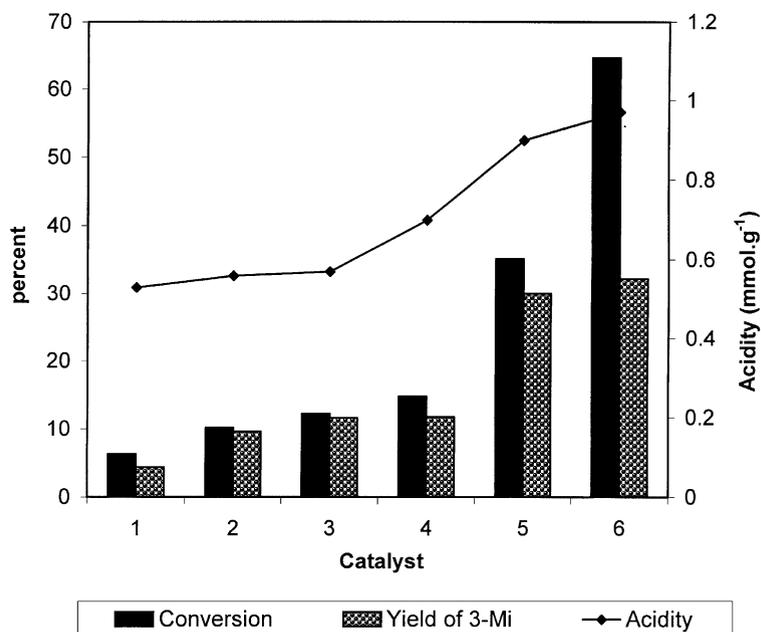
Fig. 3. Acidity vs. catalytic activity for alkylation of indole on (1) HZSM-5 (30); (2) CuHY; (3) CrHY; (4) HY; (5) CeHY and (6) LaHY. Reaction temperature = 400°C; indole:methanol = 1 : 6 molar ratio; WHSV = 0.5 h^{-1}; time-on-stream = 4 h.

are generated during the calcination of the catalyst. Brønsted sites on the catalyst are generated by the dissociation of water molecules and Lewis acid sites are generated by dehydroxylation of hydroxyl groups at higher temperature [18]. The present data on acidity and catalytic activity of the zeolites for 3-MI formation are very much in correlation with our earlier observations on methylation and isopropylation of quinoline [5–7].

3.2. Effect of pyridine poisoning and high temperature calcination of the catalyst

To obtain a correlation between the catalytic activity and the strength of the acid sites, the influence of pyridine poisoning on the catalytic activity was investigated [16]. The catalyst performances were compared, with the sample measured before and after poisoning, as is shown in Fig. 4. The results indicate that the yield of 3-MI over fresh catalyst and the catalyst on which pyridine desorption conducted

is almost the same. This indicates that the strong acid sites that retain pyridine above 330 °C are not active for selective synthesis of 3-MI. The acid sites of medium strength (just able to retain pyridine at 300 °C) are only active in the selective synthesis of 3-MI.

As the nature of the acid sites depends on the thermal pre-treatment, Brønsted acid sites are converted into Lewis acid sites at high temperatures [18]. On this basis, we have calcined the CeHY catalyst at 800 °C for 8 h. It was then subjected to the alkylation at 300 °C; the results obtained are shown in Fig. 4. The high temperature calcination resulted in high initial conversion of indole, but the selectivity for 3-MI is decreased to 13%. The conversion of indole is decreased with time-on-stream and the selectivity towards 3-MI is increased. The yield of 3-MI at the fourth hour is almost the same as that of fresh catalyst. From these observations one can conclude that, even though the reaction on Lewis acid sites increases the conversion of indole, still the formation of
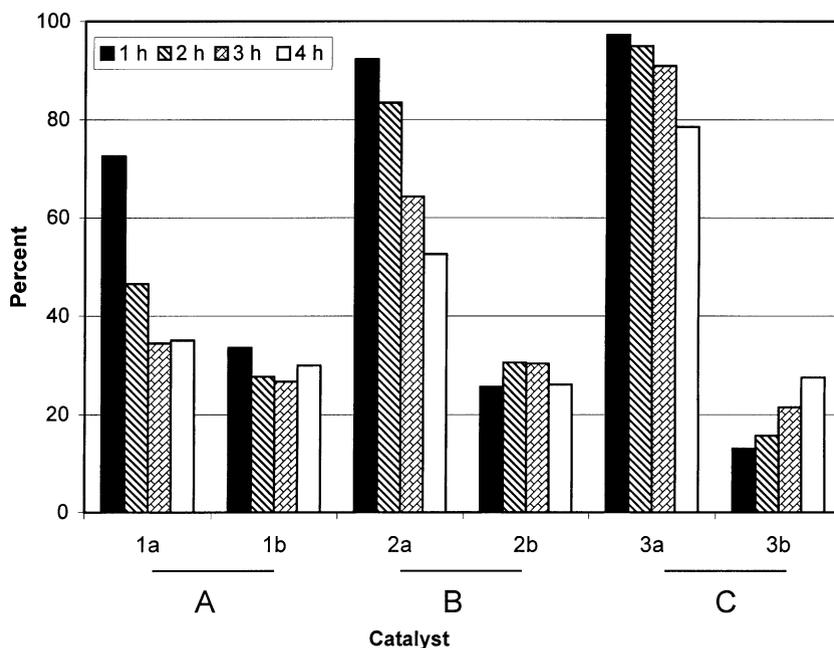
Fig. 4. Catalytic activity for alkylation of indole over 3 wt.% CeHY catalyst. (A) Fresh; (B) pyridine treated and desorbed at 330 °C; (C) calcined at 800 °C. 1a–3a: conversion of indole; 1b–3b: yield of 3-MI; time-on-stream = 1–4 h; reaction temperature = 300 °C; indole: methanol = 1 : 6 molar ratio; WHSV = 0.5 h^{-1}.
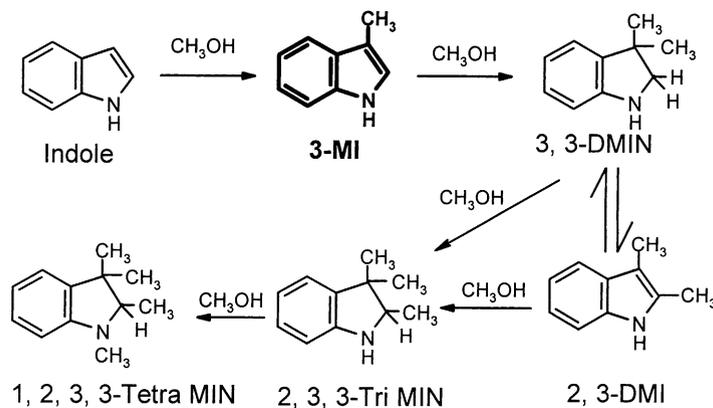
Fig. 5. A possible reaction mechanism for alkylation of indole.

side products (polyalkylated indoles) is unavoidable. Thus, it can be concluded that the strong Lewis acid sites are not active for selective synthesis of 3-MI. The improved yield of 3-MI with time-on-stream may be due to beneficial coking. From the overall observations and the data in Fig. 4, one can conclude that the acid sites of medium strength of either Brønsted or Lewis sites that retain pyridine/ammonia around 300 °C are active for selective alkylation of indole to 3-MI.

A possible reaction mechanism for alkylation of indole based on the product distribution is given in Fig. 5. The π-excessive character of pyrrole ring makes indole ring susceptible to electrophilic attack at 3-position of indole ring to give 3-MI as the major alkylation product [10]. The further alkylation results in the formation of 3,3-dimethylindolenine (3,3-DMIN), 2,3-dimethylindole (2,3-DMI), 2,3,3-trimethylindolenine (2,3,3-TriMIN) and 1,2,3,3-tetramethylindolenine (1,2,3,3-TetraMIN), as is shown in Fig. 5. 1-Methylindole and 2-methylindole are also formed in small amounts either by direct attack of methyl cation at 1- and 2-positions or by rearrangement of 3-MI. Thus, the formation of products of alkylation reaction of indole is complex, because they are subjected to both kinetic and equilibrium controls. Furthermore, a complication normally arises either because of the high reactivity of indole or the relative instability of the selective product (3-MI) [9,10].

In conclusion, rare earth metal cation-modified HY zeolites are active for the alkylation of indole to produce 3-MI. The modification by rare earth metal cations increases the acidity of HY zeolite and in turn the catalytic activity. Acid sites of medium strength of either Brønsted or Lewis sites that retain ammonia around 300 °C during the TPD of ammonia are found to be responsible for this alkylation. The maximum yield of 3-MI of 33.6% at 72.6% indole conversion was obtained over 3 wt.% CeHY catalyst at 300 °C.

References

[1] Y. Ono, Catal. Tech. (1997) 31.
[2] W.F. Holderich, M. Hesse, F. Navmann, Angew. Chem. Int. Ed. Engl. 27 (1998) 226.
[3] R.A. Sheldon, J. Mol. Catal. A 107 (1996) 75.
[4] W.W. Kaeding, C. Chu, L.B. Young, B. Weinstein, S.A. Butter, J. Catal. 67 (1981) 159.
[5] P.R. Reddy, K.V.S. Rao, M. Subrahmanyam, Catal. Lett. 56 (1998) 155.
[6] P.R. Reddy, M. Subrahmanyam, V. Durgakumari, Catal. Lett. 60 (1999) 161.
[7] P.R. Reddy, M. Subrahmanyam, S.J. Kulkarni, Catal. Lett. 54 (1998) 95.
[8] B. Elvers, S. Hawkins, W. Russell, Ullmann's Encyclopedia Ind. Chem. A 14 (1989) 167.
[9] M. Howe-Grant, Kirk-Othmer Encyclopedia of Chemical Technology, 4th Edition, Vol. 14, 1995, p. 161.
[10] M. Howe-Grant, Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition, Vol. 13, 1989, p. 213.

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[11] Lowell R. Smith, Indoles. Part Two. The Chemistry of Heterocyclic Compounds, Wiley/Interscience, New York, 1972, p. 86.

[12] B. Oddo, C. Alberti, Gazz. Chim. Ital. 33 (1993) 236.

[13] A. Kotsuki, M. Teraguchi, N. Shimomoto, M. Ochi, Tetrahedron Lett. 37 (1996) 3727.

[14] J.M. Bakke, H.M. Roholdt, Acta Chem. Scand. Ser. B 33 (1979) 152.

[15] S. Narayanan, K. Deshpande, Appl. Catal. A 135 (1996) 125.

[16] G. Bourdillon, C. Gueguen, Appl. Catal. A 61 (1990) 123.

[17] W. Klading, J. Phys. Chem. 80 (1976) 262.

[18] G. Gauthier, B. Chiche, A. Finiels, P. Geneste, J. Mol. Catal. 50 (1989) 219.

[19] P.A. Jacobs, Carbogenic Activity of Zeolites, Elsevier, Amsterdam, 1997.

[20] B. Gielen, M.G. Parerker, Zeolites 9 (1989) 208.

[21] W.F. Holderich, J. Roseler, G. Heitmann, H.T. Liebens, Catal. Today 37 (1997) 353.