Synthesis of 1,2,3,4-tetrahydrocarbazole over zeolite catalysts

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1,2,3,4-tetrahydrocarbazole (CAR) has been synthesized over H-ZSM-12, H-beta, H-mordenite, H-Y, H-ZSM-22, H-EU-1, H-ZSM-5 and acetic acid by Fisher's method using phenylhydrazine and cyclohexanone. H-Y is more active than the other zeolites studied for the synthesis of CAR. The influence of different parameters such as the duration of the run, catalyst concentration, reaction temperature and molar ratios of the reactants in the synthesis of CAR are also studied. A number of arylhydrazines such as *o*-tolylhydrazine, *p*-tolylhydrazine and 1,1-diphenylhydrazine and cyclic ketones such as cyclopentanone, cyclohexanone and 3-methylcyclohexanone have also been taken to study the effect of substitution in phenylhydrazine and the size of the cyclic ketones in the reaction. The yields of indoles correlated with the degree of substitution of the reactants and products, and the limitations imposed on diffusion through zeolite pores.

Keywords: arylhydrazines, cyclic ketones, Fisher indole synthesis, 1,2,3,4-tetrahydrocarbazole, zeolites

1. Introduction

The synthesis of substituted and condensed indoles has attracted considerable attention due to their importance as building blocks for many therapeutically useful materials and the wide ranging biological activity of both synthetic and naturally occurring derivatives [1–3]. The Fisher indole synthesis (FIS) is one of a large number of methods available for the synthesis of indoles from arylhydrazines and ketones. It involves a complex series of acid-catalyzed reactions and rearrangements in which the generally accepted key steps are (i) the condensation of arylhydrazines with ketones to form arylhydrazones, (ii) rearrangement of these to form ene-hydrazines, and (iii) acid-catalyzed [3,3] sigmatropic rearrangement followed by intramolecular displacement of NH_3 to produce indoles [4]. The acidity of the medium and the steric effect of the intermediate therefore play an important role in FIS. Zeolites have been shown to be viable catalysts for these reactions [5–7]. Most of the previous works were related to the shape-selective FIS over different zeolites using phenylhydrazine and unsymmetrical ketones. The condensation of phenylhydrazine and 3-heptanone produced two products, the bulky 2-ethyl-3-propylindole and linear 2-butyl-3-methylindole over HNaX [7]. Among the two possible products (linear and bulky), the linear isomer was predominantly produced over most of the zeolites suggesting that the constraints in the molecular sieve pores favor the product with smaller kinetic diameter [7].

In this study, our objective is to investigate extending the scope for the zeolite-catalyzed reaction to the synthesis of carbazoles (I, scheme 1) and condensed indoles (II, scheme 1). We report the results of the effect of different zeolite catalysts, duration of the run, catalyst concentration, reaction temperature, and molar ratios of the reactants on the yield of CAR. It was anticipated that the steric demands of product molecules would possibly inhibit the rate of the reaction over zeolites. We have accordingly investigated the reactions with various arylhydrazines such as phenylhydrazine (PH), *o*-tolylhydrazine (OTPH), *p*-tolylhydrazine (PTPH) and 1,1-diphenylhydrazine (DPH) and cyclic ketones such as cyclopentanone (CP), cyclohexanone (CH) and 3-methylcyclohexanone (MCH) (scheme 1). H-Y was used for detailed study on effects of parameters such as catalyst concentration, reaction temperature and molar ratios of the reactants on the yield of CAR. The catalytic activity of H-Y was compared with H-ZSM-5 for the reactions of various arylhydrazines and MCH.

2. Experimental

Zeolites H-Y, H-beta and H-ZSM-5 were obtained from Suedchemie, Germany. H-mordenite was obtained from Laporte Inorganics, Cheshire, UK. Zeolites ZSM-12, ZSM-22 and EU-1 were synthesized by known procedures [8–10]. Organic templates of the zeolites were removed by calcining in air at 823 K for 16 h. The resulting zeolites were converted into their protonic form by repeated exchanges with a solution of NH_4NO_3 (1 M, 10 ml/g zeolite, 353 K, 6 h, pH = 7–8, three exchanges) followed by calcination at 823 K for 8 h. The chemical analysis of the zeolites was carried out by a combination of wet and atomic absorption spectroscopy (Hitachi 800) methods. The average particle sizes of the zeolites were determined using a Shimadzu (model UV-2101 PC) scanning electron microscope. The surface areas of the zeolites were determined by sorption of nitrogen at liquid-nitrogen temperature using an Omnisorb 100CX apparatus. In addition, temperature-

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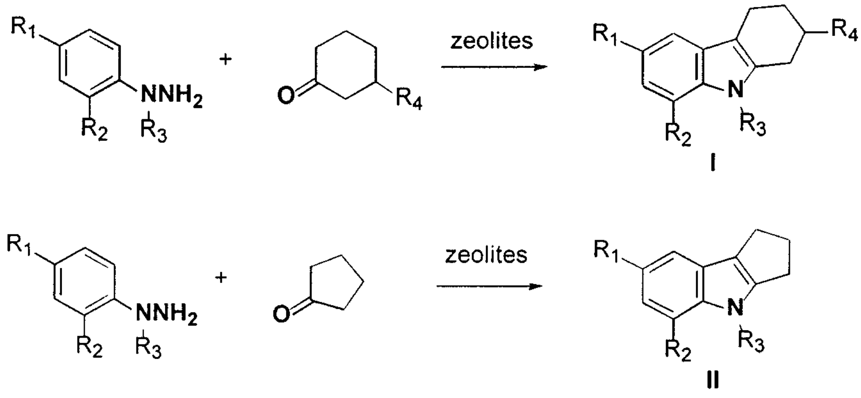

Scheme 1. Generalized reaction of arylhydrazines with cyclic ketones. The arylhydrazines include PH ($R_1 = R_2 = R_3 = H$), PTPH ($R_1 = CH_3$, $R_2 = R_3 = H$), OTPH ($R_2 = CH_3$, $R_1 = R_3 = H$), DPH ($R_1 = R_2 = H$, R_3 = phenyl); cyclic ketones include cyclohexanone ($R_4 = H$), 3-methylcyclohexanone ($R_4 = CH_3$), and cyclopentanone.

Table 1
Physico-chemical properties of the catalysts used for the synthesis of CAR.

Catalyst	SiO_2/Al_2O_3	Surface area[a] (m^2/g)	Micropore volume[a,b]	Mesopore volume[a]	Total acid sites[c]	Crystal size (μm)
H-ZSM-5	34.2	452	0.151	0.009	1.2	0.5
H-ZSM-22	22.0	275	0.138	0.011	0.82	0.5
H-EU-1	28.0	300	0.141	0.008	0.89	0.7
H-ZSM-12	100.1	456	0.169	0.051	0.26	0.6
H-beta	28.8	745	0.265	0.074	0.78	0.6
H-mordenite	22.2	552	0.126	0.021	0.71	1.0
H-Y	5.1	615	0.209	0.038	1.40	1.0

[a] N_2 adsorption.

[b] Obtained from De Boer plot.

[c] NH_3 chemisorbed at 303 K (mmol/g).

programmed desorption (TPD) of ammonia was carried out to evaluate the acidic properties of the zeolites. Details of the methods were described elsewhere [11]. The main properties of the catalysts used are summarized in table 1.

Before reaction, all the catalysts were calcined in air at 823 K. The reagents PH, PTPH, OTPH, DPH, CP, CH and MCH were obtained from Aldrich and used without further purification. OTPH, PTPH and DPH were used as hydrochloride forms in the reactions. In a typical experiment, cyclohexanone (5.5 mmol), methanol (10 ml) and powdered catalyst (1 g) were stirred together in a three-necked round-bottom flask fitted with a reflux condenser and a calcium chloride guard tube, and heated in an oil bath maintained at a temperature of 333 K. After 1 h, phenylhydrazine (2.7 mmol) was added dropwise through a syringe over 30 min. The reaction was monitored at fixed intervals over 18 h by withdrawing samples from the reaction mixture and analysing these by GC (Varian 3400 gas chromatograph) equipped with a flame ionization detector and a 50 m × 0.2 mm HP-1 capillary column, using toluene as an internal standard. After 18 h, the catalyst was removed by filtration and the filtrate concentrated under vacuum. The used catalysts were then extracted with methanol in a soxhlet apparatus to recover adsorbed materials. In a typical adsorption measurement, a mixture of phenylhydrazine (0.3 g) and methanol (10 ml) was added to H-Y (1 g) and the mixture stirred at 333 K for 18 h. After 18 h, the catalyst was separated from the reaction mixture and the concentration of phenylhydrazine in the mixture determined by GC. All the products were characterized by IR spectroscopy (Perkin–Elmer 137 IR spectrophotometer), GC-MS (Hewlett–Packard), ^{1}H- and ^{13}C-NMR spectroscopy (Varian VXR-200 spectrometer, $CDCl_3$ solutions), microanalysis and by determination of melting points. Samples of all the indoles and carbazoles were prepared independently using acetic acid, characterized by NMR and used as reference samples for GC and NMR analysis of products for the zeolite-catalyzed reactions. The sizes of the carbazoles were calculated by optimizing structures using GAUSSIAN94, supplied by MSI molecular simulation, USA, in a Silicon Graphics workstation Indigo 2.

3. Results and discussion

3.1. Duration of the run

The yields of CAR over different catalysts versus reaction time are presented in figure 1. All the arylhydrazines are strongly basic compounds which adsorb over acidic zeolites. A separate adsorption study of arylhydrazines over all the catalysts has been done to correct the conversions of arylhydrazines. After reaction, the cat-

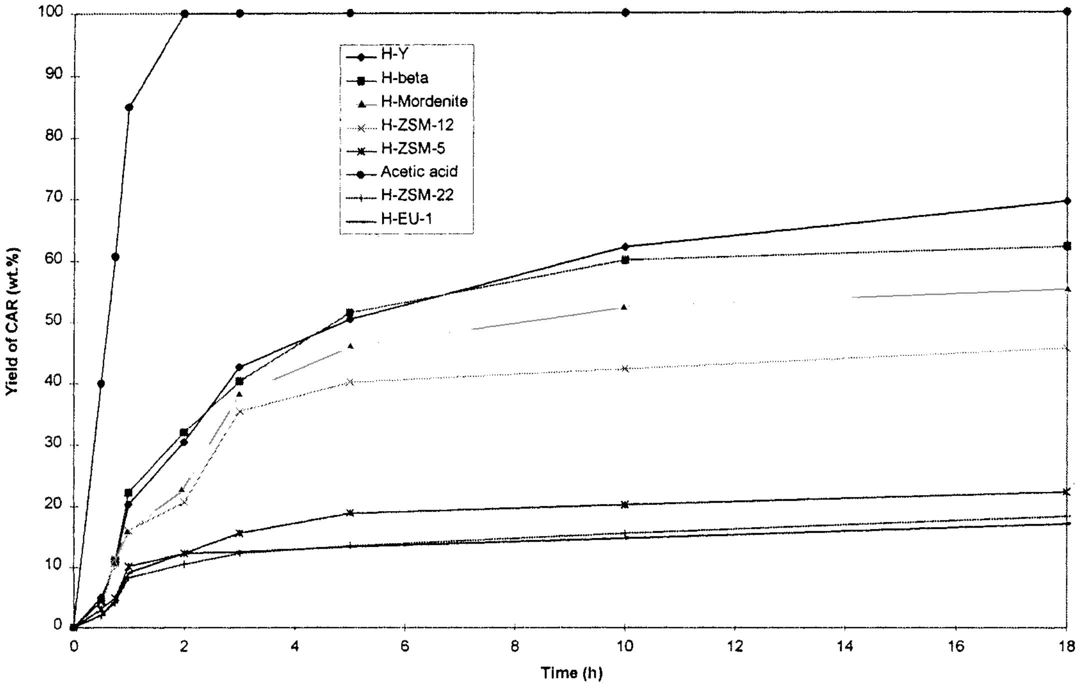

Figure 1. Effect of reaction time on the yield of CAR over various zeolite catalysts.

alysts were treated with soxhlet extraction and the recovered products were added to calculate the exact yields of CAR. In all cases, the reactions were 100% selective towards CAR with no evidence of substituted anilines which have been reported as by-products arising from N–N bond cleavage during the reaction over mineral acids [12]. H-Y is found to be the best catalyst for the synthesis of CAR (figure 1). H-beta shows slightly lower activity compared to H-Y under identical conditions (figure 1). The higher activity of H-Y and H-beta may be attributed to their stronger acid sites and mesoporous system (table 1). The lower yield of CAR over H-ZSM-12 may be due to its higher SiO_2/Al_2O_3 ratio and, hence, the lower number of acid sites. All the three medium-pore zeolites H-ZSM-5, H-ZSM-22 and H-EU-1 showed lower activity than the large-pore zeolites used (figure 1). The total numbers of acid sites of H-ZSM-5, H-ZSM-22 and H-EU-1 are 1.2, 0.82 and 0.89 mmol/g, respectively, which are comparable with H-beta (0.78 mmol/g). No significant change in the adsorption capacity (mmol/g) of phenylhydrazine has been observed among the four catalysts under experimental conditions. However, the yields of CAR over H-beta, H-ZSM-5, H-ZSM-22 and H-EU-1 were 69.5, 22.4, 18.4, and 17.2%, respectively. So the diffusional limitation of CAR through the pores of H-ZSM-5, H-ZSM-22 and H-EU-1 is expected to play an important role in FIS. Figure 1 shows that the rate of indolization is fast during the first phase of the reaction (0–4 h). After 4 h, the rate of the reaction slowed down for all the catalysts. The effect was more pronounced over medium-pore zeolites. The reason may be the slower diffusion of CAR through the pores of H-ZSM-5, H-ZSM-22 and H-EU-1. In presence of SiO_2–Al_2O_3 and without catalyst, mainly hydrazones were formed. Small amounts of CAR such as 4 and 2 wt% were formed over SiO_2–Al_2O_3 and without catalyst, respectively, after 18 h of reaction.

Table 2
Effect of catalyst concentration, reaction temperature and CH/PH ratio on the yield of CAR over zeolite H-Y.

Entry	CH/PH (mol/mol)	PH/catalyst (wt/wt)	Reaction temperature (K)	Product yield (wt%)
1	2	0.3	333	69.3
2	2	0.4	333	53.5
3	2	0.6	333	35.7
4	2	1.2	333	15.6
5	2	0.3	323	45.6
6	2	0.3	313	23.1
7	2	0.3	303	15.1
8	5	0.3	333	55.6
9	10	0.3	333	48.3
10	20	0.3	333	30.1

3.2. Effect of catalyst concentration

The PH to catalyst ratio was changed by keeping the PH concentration constant in the reaction mixture. When PH/catalyst decreased from 1.2 to 0.3, the yield of CAR increased from 15.6 to 69.3%, respectively (table 2, entries 1–4). Below this ratio (0.3) the yield of CAR labeled off. Table 2 (entries 1–4) shows a very good correlation between the yield of CAR and the amount of catalyst, hence the number of acid sites. Therefore, the number of acid sites play an important role in this reaction.

3.3. Effect of reaction temperature

The yield of CAR over H-Y was examined in the temperature range 303–333 K. The results obtained are sum-

Table 3
Product yield of the reactions of arylhydrazines with cyclic ketones over H-Y.[a]

Reactant	Product yield (wt%)		
	Cyclopentanone	Cyclohexanone	3-methylcyclohexanone
Phenylhydrazine (PH)	75.1	69.3	58.5
p-tolylhydrazine (PTPH)	68.3	45.9	41.0
o-tolylhydrazine (OTPH)	63.6	41.3	39.6
1,1-diphenylhydrazine (DPH)	40.6	34.6	29.3

[a] Reaction conditions: temperature = 333 K; arylhydrazine/catalyst = 0.3; cyclic ketones/arylhydrazine = 2; methanol = 10 ml.

marized in table 2 (entries 5–7). Lower temperature does not favor the formation of CAR, however the yield of CAR increased sharply with the increase in reaction temperature and reached a value as high as 69.3% at 333 K. The apparent activation energy over H-Y was found to be 60.2 kJ/mol.

3.4. Effect of CH to PH molar ratio

The mole ratio of CH to PH was varied between 2 and 20 maintaining the amount of PH constant (table 2, entries 8–10). It is seen from table 2 that the yield of CAR decreases quite significantly with increasing CH/PH mole ratio.

3.5. Effect of reactant structure in the yield of carbazoles and condensed indoles

The trends in the recorded yields by the reactions of arylhydrazines and cyclic ketones over H-Y are presented in table 3. Table 3 shows that with increasing the size of the arylhydrazines (table 3) the yield of indole decreases. Similarly, the yield of corresponding indoles decreases with increasing the size of the ketones as expected. Both for substituted and unsubstituted arylhydrazines, a significant difference in the yield of condensed products is observed on changing the ketone structure from cyclopentanone to cyclohexanone, whereas a minor effect in the yield of indoles has been observed by introducing a methyl group in the cyclohexanone ring (table 3). Methyl-substituted cyclohexanone produces selectively the 2-substituted rather than 3-substituted tetrahydrocarbazoles or condensed indoles, a result consistent with published observations [12] in the reaction carried out in liquid acids. This outcome is therefore not attributed to shape selectivity in zeolite H-Y, but presumably mainly due to stereoelectronic effects in the transition state of the [3,3] sigmatropic rearrangement step of the reaction. As expected, further restriction of the pore geometry in zeolite H-ZSM-5 results in even lower yields of the products derived from 3-methylcyclohexanone (table 4). The dimensions of the products are clearly significantly larger than the pore dimensions of H-ZSM-5 (0.53 × 0.56 mm; 0.51 × 0.55 nm).

Table 4
Yield of substituted tetrahydrocarbazoles from the reaction of 3-methylcyclohexanone and arylhydrazines over H-Y and H-ZSM-5.[a]

Reactant	Dimensions of the products (nm)	Product yield (wt%)	
		H-Y	H-ZSM-5
Phenylhydrazine (PH)	0.93 × 0.55 × 0.85	58.5	25.3
p-tolylhydrazine (PTPH)	1.01 × 0.72 × 0.84	41.0	18.9
o-tolylhydrazine (OTPH)	0.94 × 0.84 × 0.84	39.6	12.3
1,1-diphenylhydrazine (DPH)	0.92 × 0.88 × 1.00	29.3	6.7

[a] Reaction conditions: temperature = 333 K; arylhydrazine/catalyst = 0.3; 3-methylcyclohexanone/arylhydrazine = 2; methanol = 10 ml.

4. Conclusions

In conclusion, acidic zeolites are active and selective catalysts for FIS. The results show that H-Y is the best catalyst for the synthesis of carbazoles and condensed indoles by the reaction of arylhydrazines and cyclic ketones. The limited diffusion of the products inhibits the yield of CAR over medium-pore zeolites such as H-ZSM-5, H-ZSM-22 and H-EU-1. Good conversions are possible with unsubstituted phenylhydrazine and cyclic ketones, while the substitution by methyl groups either in the phenylhydrazine or cyclic ketones induces significant lowering of the conversions of corresponding arylhydrazines. The change of the values of different parameters such as duration of the run, catalyst concentration, reaction temperature and molar ratios of the reactants changes the yield of carbazoles. However, the absence of side reactions and the successful production of a range of variously substituted tetrahydrocarbazoles and condensed indoles are evidence for the potential of zeolite catalysis of this and other heterocyclic condensation reactions.

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