Catalysis by materials for fine chemicals production

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Abstract

Liquid phase alkylation of phenol with 4-hydroxybutan-2-one, cyclisation of (phenylthio)acetaldehyde diethylacetal and elcectrophilic substitution of indole with a variety of aromtic aldehydes were investigated over Hβ, HY, H-ZSM-5, ion-exchanged β and Y zeolites and modified zeolites. Raspberry ketone was obtained regioselectively over Hβ (Si/Al=10) catalyst in 77 % yield. This product is formed not only by direct alkylation but also by the facile rearrangment of O-alkylated product. Zn^{2+} ion-exchanged β and Y zeolites showed better activity than its H-form counterpart owing to its higher Lewis acidity in the formation of benzo[b]thiophene and bis(indolyl)methanes respectively.

Keywords: Raspberry ketone; Benzo[b]thiophene;Bis(indolyl)methanes; Zeolites.

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1. Introduction

The fine and speciality chemicals are low volume and high gain / price chemicals which cover a wide range of products like flavours, fragrances, drug intermediates, cosmetics, bioactive, surfactants etc. These chemicals possess high growth rate and the Indian market for these chemicals is currently estimated to be US dollar 1.2 billion, which constitutes 2.5 % of the global market. The traditional synthesis route of most of these chemicals includes homogeneous catalysts. The usage of these conventional mineral acid catalysts leads to handling and disposal problems. These catalysts also tend to generate large quantities of wastes like wash water stream, metal salts and heavy metals that pose environmental threat. Further the post reaction neutralization of acid residues forms large amount of salts which is to be retreated and disposed. Most of these catalysts are not recyclable and reusable. Hence the development of new generation ecofriendly catalysts, designing a robust process and preventing scale-up problems in fine chemical industries are now challenging problems. The new catalysts should improve atom efficiency, product selectivity and minimise waste generation in chemical industries. Since more and more green processes in the future will require heterogeneous catalysts, where control of synthetic conditions and process variables are so critical, the design of environmentally friendly catalysts, processes and effluent minimization and control are the key factors in fine and speciality chemicals production.

The exhaustive overviews exhibit the capability of zeolites as catalyst in fine and speciality chemicals synthesis [1-4]. They have many advantages over mineral acids. They are non-corrosive, eco-friendly, reusable and have no disposal problems. Their separation from the products is much easier and they can be designed to give high activity, selectivity and longer catalyst life. In the recent years, the use of zeolites, the so-called microreactors, in the manufacture of fine chemicals and chemical intermediates has attracted increasing interest owing to the special features such as shape selectivity, controlled variability, thermal stability and above all reusability and eco-friendly nature, the characters most sought after in green chemistry [5]. In the present article synthesis of raspberry ketone, benzo[b]thiophene and bis(indolyl)methanes, the important fine and speciality chemicals, using zeolites and modified zeolites under liquid phase condition and the influence of various parameters are discussed.

2. Catalysts preparation

Na form of Y zeolite ($SiO_2/Al_2O_3=3$), β zeolites ($SiO_2/Al_2O_3=3$, 10, 15 and 25) and ZSM-5 ($SiO_2/Al_2O_3=53$) were supplied by United Catalysts India and S*ü*d-Chemie India Ltd., India. Zeolite β with $SiO_2/Al_2O_3=25$ was prepared in our laboratory by following the reported procedure [6]. Na form of zeolites were converted into NH_4^+ form by repeated ion exchange with 1M ammonium nitrate solution at 80 °C for 6h. NH_4^+ form of the catalysts were converted into H form by calcination at 500°C for 6h.The H form of zeolites Y and β ($SiO_2/Al_2O_3=10$) were repeatedly ion exchanged with 0.1N zinc nitrate and ferric nitrate solutions to get Zn^{2+} and Fe^{3+} ion exchanged catalysts. The percentage of ion exchange was determined by ICP-AES (ICP 1000 III, Shimadzu I). The XRD patterns of the catalysts were recorded on Rigaku, D-Max/II- VC model using CuKα radiation. The surface area of the catalysts was measured by BET nitrogen adsorption method. The thermally dealuminated zeolite (HBDA) was obtained by calcinations of the parent zeolite (HB) at 850°C for 8 h at a high rate of heating. The sample HBDA0.1a was prepared by the treatment of HBDA with 0.1N HCl for 24 h at room temperature. The catalysts HB0.1a and HB1a were obtained by the treatment of HB with 0.1 and 1N HCl, respectively. The surface-passivated zeolite beta (SPHB) was obtained by following the method described by Andy et al. [7] HB (0.25g) with 3 mil of hexane was stirred under an argon atmosphere to which 0.1 ml of tetraethyl orthosilicate (TEOS) was added and the stirring was continued for 3 h. then the zeolite was filtered and washed with hexane. In this method, the surface of the zeolite became coated with silica [8]. Before added to the reaction flask the catalysts were heated to 200 °C in a flow of nitrogen to remove the adsorbed water and other impurities and then cooled in a desiccator.

3. Catalytic reaction

The alkylation reaction was carried out in a double-necked RB flask fitted with a reflux condenser. A typical reaction condition was as follows: To phenol 5.34g (56.7 mmol) 1g of the catalyst was added at 40 °C and stirred for 10 minutes. The temperature of the mixture was raised to the desired value and then 1g (11.3 mmol) of 4-

hydroxybutan-2-one was added dropwise in 5 minutes. The reaction mixture was stirred at the same temperature. Samples were collected periodically and analysed by GC (Shimadzu GC-17A, DB-5 capillary column, 30m) and GC-MS (Shimadzu QP 5000 equipped with GC-17A).

4. Results and discussion

4.1. Synthesis of raspberry ketone

4-(4-Hydroxyphenyl)butan-2-one, otherwise known as raspberry ketone due to its characteristic raspberry odour, is an important aroma chemical used in the food and perfume industries [9,10]. It also exhibits biological activity, such as inhibition of melanin formation [11] and promotion of lipid degradation. Therefore it is used in skin lightening and weight-reducing cosmetics [12-14]. Commercially, raspberry ketone is produced by alkylation of phenol with methyl vinyl ketone or 4-hydroxybutan-2-one using hazardous acid catalysts such as H_2SO_4, H_3PO_4 and aqueous HCl [15] or cation-exchanged resin Dowex-50W [16]. Tateiwa et al. reported facile *para* alkylation of phenol with 4-hydroxybutan–2-one over Zr^{4+} ion-exchanged montmorillonite clay [17]. In this manuscript we are presenting the liquid phase Friedel-Crafts alkylation of phenol which served both as reactant and solvent with 4-hydroxybutan-2-one over β and Y zeolites to produce the expected raspberry ketone [18,19]. The effect of various parameters such as temperature, reactants mole ratio, SiO_2/Al_2O_3 ratio and catalyst weight is studied.

In the alkylation of phenol with 4-hydroxybutan-2-one one can expect different products like O-alkylated product (4-phenoxybutan-2-one), *para*-alkylated product [4-(4- hydroxyphenyl) butan-2-one], *ortho*-alkylated product [4-(2-hydroxyphenyl)butan-2-one] and other polyalkylated and polymeric compounds (Scheme 1). But we obtained *para* product (**b**) regioselectively in 77% GC yield along with some unidentified polymeric compounds over HBEA1 catalyst at 100°C after a period of 48h and no O-alkylated product (**a**) and *ortho* product (**c**) were not obtained. HY and ion-exchanged zeolites showed less selectivity towards **b** (Table 1).

Scheme 1

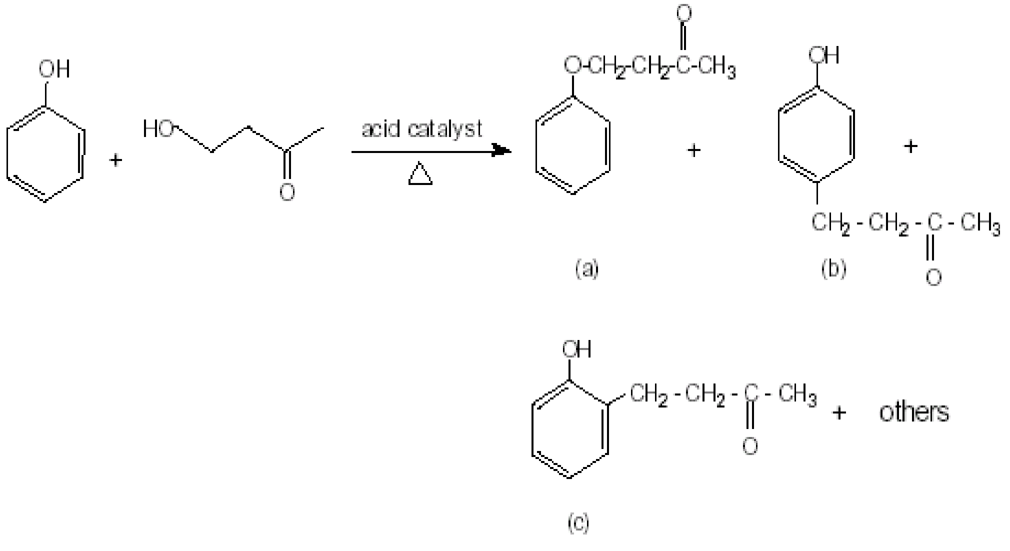


Table 1
Alkylation of phenol with 4-hydroxybutan-2-one

Run	Catalyst	Conversion of 4-hydroxybutane-2-one	Product distribution (Wt.%)†				
			MVK	**a**	**b**	**c**	Others
1.	HBEA1	100	-	-	77	-	23
2.	HY	95	24	26	25.5	5	14.5
3.	ZnHB	99	3	33	50	4	9
4.	FeHB	98	2	30	51	4	11
5.	ZnHY	92	33	30	13	6	10
6.	FeHY	85	22	28.5	20.5	3.5	10.5
7.	Blank	21	15	6	-	-	-
8.	HBEA1*	72	10.5	56.5	3.5	1.5	-

Temperature = 100 ^{o}C; Catalyst = 1g; Phenol = 5.34 g; 4-Hydroxybutan-2-one = 1 g
*Catalyst + Pyridine (1 mmol)
†With respect to 4-hydroxybutane-2-one

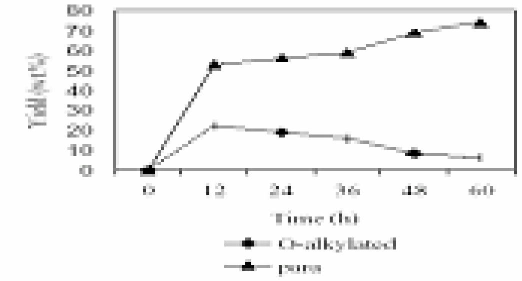


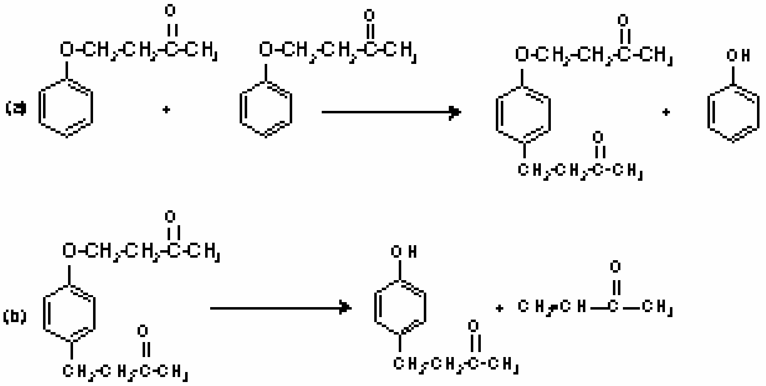
Figure 1. Distribution of **a** & **b** Vs time

In the alkylation reaction over HBEA2 the distribution of **a** and **b** Vs time (Figure1) indicated gradual disappearance of **a** and gradual increase of **b** during the course of the reaction. The results already reported on alkylation of phenol with alcohols it is shown that both O-alkylation and C-alkylation are competitive reactions [20-22]. Hence it is reasonable to conclude that during the alkylation **a** and **b** are competitively formed and **a** gradually rearranged to give **b** under the reaction conditions.

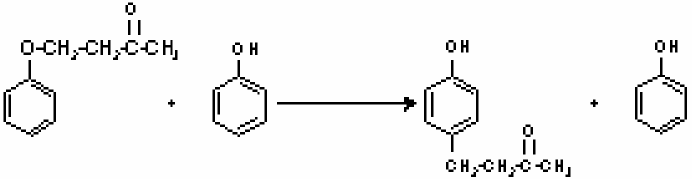
4.1.1. Rearrangement of 4-phenoxybutan-2-one

In order to confirm the rearrangement of O-alkylated product into *para* alkylated product, the O-alkylated product was synthesised separately and its rearrangement was studied using HB catalyst. The experimental results revealed 57 wt % conversion of O-alkylated product with the formation of *para* alkylated product (30.5 wt%), MVK (17.5 wt %) and other products (19 wt%). The studies clearly revealed the regioselective rearrangement of O-alkylated product into *para* alkylated product. Overgaag et al. studied rearrangement of alkyl phenyl ethers over dealuminated HY zeolite in liquid phase and they proposed different possible pathways. According to them, alkyl phenols were obtained either by an intramolecular rearrangement of ether or by dealkylation of intermediate alkoxy alkyl benzenes or by direct alkylation of phenol by alkoxy benzene [23]. The intramolecular rearrangement of alkoxy benzene is known to lead preferentially to the *ortho* alkylated product [24]. In our study on rearrangement, the *ortho* alkylated product was not obtained. Hence we ruled out the intramolecular rearrangement of the O-alkylated product. The possibility of self alkylation of O-alkylated product to give dialkylated product (Scheme 2(a)) and its dealkylation to give *para* alkylated product (Scheme 2(b)) was ruled out since no dialkylated product was observed during the reaction. Further, it was found that the rearrangement took place only in the presence of phenol. When the reaction was carried out in toluene alone, only the decomposition of O-alkylated product is observed. Similar results were observed by Tateiwa et al. in the presence of ion-exchanged montmorillonite clay catalysts [25]. Even if a small amount of dialkylated product is formed, due to its bulky nature it must be formed on the surface of the catalyst rather than inside the pores. Hence, the alkylation reaction was carried out on surface passivated beta zeolite (HBSP) and the *para* to O-alkyl ratio was observed to be almost the same as that of the parent zeolite (Table 1). So the rearrangement takes place mainly inside the pores of the catalyst, and this could also be the reason why *para* alkylated product, rather than *ortho* alkylated product, is formed selectively; the latter experiences steric hindrance inside the pores. On considering all these facts we propose that during the rearrangement, phenol is directly alkylated by O-alkylated product to give *para* alkylated product (Scheme 3).

Scheme (2)



Scheme (3)



4.1.2. Effect of SiO_2/Al_2O_3 ratio

The effect of SiO_2/Al_2O_3 ratio over the reaction is shown in Table 3. When the SiO_2/Al_2O_3 ratio increases conversion and *para* selectivity decreases. It is well known fact that when the Al content of the zeolite increases the Bronsted acidity increases [26]. From this it is evident that Bronsted acidic sites are needed for the formation of **b**.

Table 2 : Effect of SiO_2/Al_2O_3 over the reaction

Catalyst	SiO_2/Al_2O_3	Conversion of 4-hydroxybutane-2-one (Wt. %)	Product distribution (Wt. %)†				
			MVK	a	b	c	Others
HBEA1	10	100	-	-	77	-	23
HBEA2	15	97	3	8.5	68	1.5	16
HBEA3	25	92	10	12.5	56.5	1	12

Temperature = 100 °C; Catalyst = 1 g; Phenol = 5.34 g; 4-Hydroxybutane-2-one =1 g
†With respect to 4-hydroxybutane-2-one

4.1.3. Effect of reactants mole ratio

The reaction was carried out with different phenol to 4-hydroxybutan-2-one mole ratio over HBEA1 (Figure 2). The results showed that the *para* product formation decreases when phenol to alkylating agent mole ratio was changed from 5:1 to 5:3. From this it can be suggested that in case of higher concentration of the alkylating agent, it preferentially adsorbs on the active (acidic) sites of the catalyst and minimize the chances of adsorption of **a** thereby minimize the rearrangement of **a** to **b**. It is also evident from the experimental observation that when the reaction is carried out in the presence of small quantity of added pyridine (Table 1, run 8) **a** is obtained selectively. This may be due to the blocking of the acidic sites of the catalyst by pyridine which minimize the chances of adsorption of **a** and hence the rearrangement.

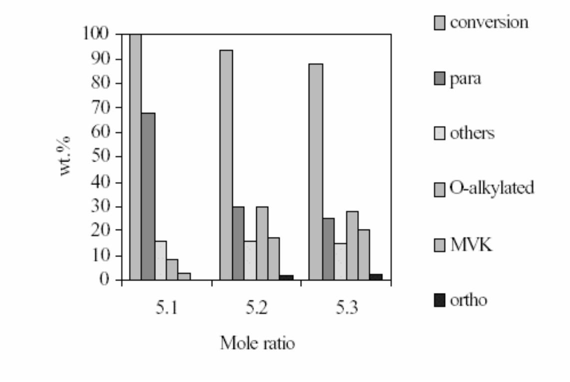


Figure 2. Effect of mole ratio over the reaction (HBEA2=1 g, Temperature = 100 °C)

4.1.4. Effect of temperature

The effect of temperature over the reaction was shown in Table 3 As expected higher temperature increases the conversion and yield of *para* product. C-alkylation is favoured at high temperature as it requires higher activation energy [27]. Increase in temperature also increases the yield of polyalkylated and polymeric compounds.

Table 3 : Effect of temperature over the reaction

Temperature (°C)	Catalyst	Conversion of 4-hydroxybutane-2-one	Product distribution (Wt.%)*					
			Time (h)	MVK	**a**	**b**	**c**	Others
75	HBEA2	97	48	12	33	38.5	2.5	11
	HY	87	48	28	23	21	5	10
100	HBEA2	100	48	3	8.5	68	1.5	16
	HY	95	48	24	26	25.5	3	14.5
125	HBEA2	100	24	-	6	74	-	20
	HY	100	36	-	36	47	1	16

Catalyst = 1 g; Phenol = 5.34 g; 4-Hydroxybutan -2-one = 1 g
*With respect to 4-hydroxybutane-2-one

4.1.5. Effect of catalyst weight

Figures 3 and 4 indicate the effect of catalyst weight on the alkylation of phenol with 4-hydroxybutan-2-one and MVK, respectively. An increase in the catalyst weight increases the *para* product selectivity and decreases the *ortho* and O-alkylated product selectivity. This indicates the possible rearrangement of *ortho* and O-alkylated products into *para* alkylated product. The possibility of the conversion of the whole of the O-alkylated product into secondary products is ruled out because there is only a slight increase in the selectivity of the bulkier products. The heats of formation of O-alkyl, *para* and *ortho* products were calculated and are found to be –58.7, -72.2 and –73.9 kcal/mol respectively. Since the heat of formation of O-alkylated product is about 13.5 kcal/mol higher than that of *para* alkylated product, the rearrangement of O-alkyl to *para* product is predicted to be thermodynamically favourable. Therefore, a decrease in the *ortho* product selectivity may be due to its secondary reaction, which gives rise to the side products.

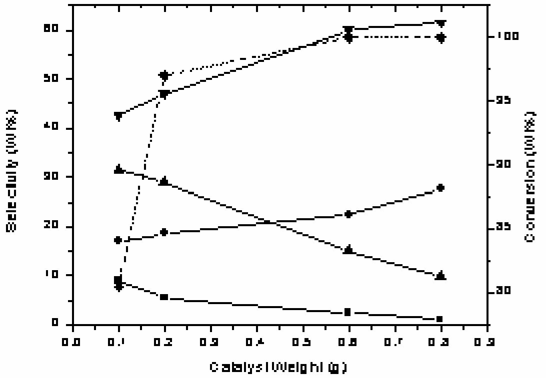


Figure 3. Conversion of 4-hydroxybutan-2-one and selectivity of the products as a function of catalyst

weight (Temperature: 100°C, Time: 48h, Phenol/4-hydroxybutan-2-one mole ratio: 5:1) (◆: conversion of 4-hydroxybutan-2-one, ▲: O-alkyl, ▼: para, ■ ortho, ●: others).

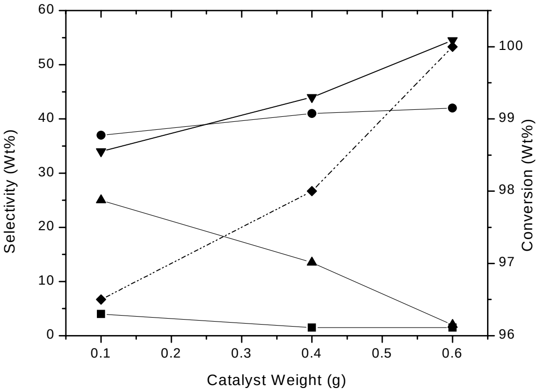


Figure 4. Conversion of MVK and selectivity of the products as a function of catalyst weight (Temperature: 100°C, Time: 48h, Phenol/MVK mole ratio: 5:1) (◆: conversion of 4-hydroxybutan-2-one, ▲: O-alkyl, ▼: para, ■ ortho, ●: others).

4.1.6. Catalytic activity of different catalysts

Table 4 shows the results of alkylation of phenol with 4-hydroxybutan-2-one over various modified beta zeolites. The materials obtained were *para*-alkylated product (4-(4-hydroxyphenyl)butan-2-one), *ortho*-alkylated product (4-(2-hydroxyphenyl)butan-2-one, O-alkylated product (4-phenoxybutan-2-one), methyl vinyl ketone and others (oligomers and polyalkylated products). The results clearly demonstrated that the modification of the H-beta zeolite affected both the conversion and the selectivity of the products. The decrease in conversion over acid-treated samples (HB0.1a and HB1a) is attributed to the increase in Si/Al ratio and to the resulting decrease in their acid site density. In the case of HB0.1a and HB1a, even though the overall selectivity of the products seemed to be altered, the ratio of *para* to O-alkyl products remained almost constant. The increase in the selectivity of other products in the presence of HB0.1a and HB1a is due to the enhancement of catalytic activity of the external surface. The acid treatment increases the catalytic activity of the external surface due to the extraction of extra framework and framework aluminium species out of the micropores and further generates new defect sites [28-30] that might have helped the formation of bulky oligomers and polyalkylated products. Hence the selectivity of the remaining products decreased. Another interesting aspect is the increase in conversion of 4-hydroxybutan-2-one over the thermally dealuminated and subsequently acid-washed sample (HBDA0.1a) (Table 3). This increase in conversion and *para* product selectivity could be due to the reversal of the effects of severe calcination and the reappearance of lost silanol groups. Heinichen and Holderich showed that the acid treatment of the severely calcined sample causes the internal as well as the hydrogen-bonded silanol groups to reappear [30,31].

Since Lewis acid sites are not found to be suitable active sites for the selective formation of *para* alkylated product, it is predicted that Bronsted acid sites must be suitable. In order to ascertain this, the same reaction was carried out over Cs^+ ion exchanged β zeolite (CsB). As shown in Table 3, the conversion of 4-hydroxybutane-2-one decreased to 43wt% and the selectivity of the O-alkylated product increased to 46wt%. During ion exchange, Bronsted acidic protons were replaced by Cs^+

ions. Due to this, acidity was weakened and basicity was introduced in the catalyst, which improved the O-alkylated product formation. Obviously the formation of O-alkylated product is favoured over weak acid sites. Kim et al. reported that anisole was exclusively formed over Cs^+-exchanged zeolite X [32]. Park et al. found that O-alkylation is favoured during the alkylation of phenol with propylene over Na^+ ion-exchanged H-ZSM 5 catalyst [33]. In order to confirm the role of Bronsted acid sites, we carried out the reaction over sulphated zirconia, which is known as a super acid due to its strong Bronsted acid sites. The conversion and selectivity of the products observed over sulphated zirconia are given in the Table 3. The higher *para* alkylated product to O-alkylated product ratio observed over sulphated zirconia supported our assumption of the necessity of Bronsted acid sites for the formation of *para* alkylated product. The increase in the other product selectivity is expected to be the result of side reactions catalysed by the strong acid sites of sulphated zirconia.

Table 4

Results of alkylation of phenol over different catalysts

Catalyst	Conv. (wt.%)	Selectivity (Wt.%)				para /O-alkyl ratio	MVK (wt.%)
		O-alkyl	ortho	para	others		
HB	80.5	31.5	8	42.5	18	1.34	13.5
HB0.1a	71.5	30.5	10.5	40	19.5	1.31	15
HB1a	54	29	9.5	39.5	21	1.36	16.5
HBDA	65.5	35	9	36	20	1.0	18.5
0HBDA0.1a	68	28	9.5	39	23	1.39	16.5
γ-alumina[a]	46.5	59.5	3	13.5	24	0.18	28.5
CsB[b]	43	46	1.5	12.5	40	0.27	29
Sulphated Zirconia	75	25	5	45	25	1.8	15
SPHB	71	32	9.5	43	15.5	1.34	17

(Temperature: 100°C; Time: 48h; phenol:4-hydroxybutan-2-one molar ratio: 5:1)
([a]Catalyst weight: 0.3g) ([b]Rection time 60h)

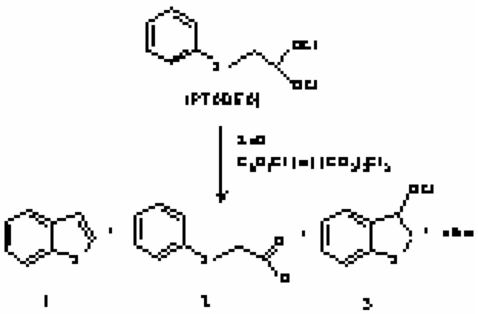
4.1.7. Comparison of alkylation of phenol with 4-hydroxybutan-2-one and methyl vinyl ketone (MVK)

The formation of methyl vinyl ketone as by-product during alkylation of phenol with 4-hydroxybutan-2-one showed the dehydration of 4-hydroxybutan-2-one over acidic sites. Further, it suggests that the carbonium ion, produced from MVK, attacks phenol to give alkylated products. Hence the alkylation was also carried out using MVK. The results were compared with the results obtained from the alkylation of phenol with 4-hydroxybutan-2-one. When MVK is used as an alkylating agent, the selectivity of the O-alkyl, *para* and *ortho* alkylated products decreases and the selectivity of unwanted side products increases in comparison with 4-hydroxybutan-2-one. This shows that the highly reactive MVK undergoes oligomerisation to give oligomers, and further, that mono alkylated phenols react with MVK to give secondary products.

4.2. Synthesis of benzo[b]thiophene

Benzo[b]thiophene and its derivatives are important heterocycles which find use in pharmaceuticals, pesticides and in general organic synthesis [34,35]. Sulphur-containing crude petroleum is the main source of these compounds. However, separation of these compounds from crude petroleum is a tedious process and hence the demand for these compounds is mainly met by synthetic methods. One of the methods followed for the synthesis of these compounds is cyclisation of the corresponding (arylthio)-acetaldehyde diethylacetal or dimethylacetal in the presence of polyphosphoric acid [36-38]. The main problem associated with this method is the low yields due to acid-catalysed side reactions which lead complex mixture of by-products [39-41]. Clark et al. [42] reported cyclisation of (phenylthio)acetaldehyde diethylacetal in the presence of K-10 clay impregnated with $ZnCl_2$ in both liquid- and vapour-phase conditions. They were able to achieve a good yield only in vapour-phase condition, which requires temperatures as high as 300°C, vacuum, and specialised apparatus to carry out the reaction. Further a high catalyst to reagent ratio (10 to 15) is required for effective cyclisation [42]. Cyclisation of (phenylthio)acetaldehyde diethylacetal in the presence of beta zeolites, keeping in mind the eco-friendly nature of the zeolites and their restricted pore system, which can limit the unwanted polymerised by-products. We report herein [43] a successful and relatively simple method for the cyclisation of (phenylthio)acetaldehyde diethylacetal in the liquid phase which require temperature as low as 90°C and a catalyst to reagent ratio as low as 0.4. The major products in the cyclisation process were benzo[b]thiophene (**1**), thiophenyl acetaldehyde (**2**), 2,3-dihydro-3 ethoxybenzo[b]thiophene (**3**) and others (diphenyl disulphide and unidentified by-products) (Scheme 4).

Scheme 4



The results of cyclisation of PTADEA are summarised in Table 5. The reaction in 1,2-dichloroethane requires a slightly higher amount of catalyst and longer reaction time. The decrease in concentration of **2** and **3** with increase in reaction time (Figures 5 and 6) and catalyst amount, as shown in figure 7, reveals that the products **2** and **3** are the intermediates formed in the reaction which yield benzo[b]thiophene by different pathways. On comparing figures 1 and 2 it was observed that the yield of **2** is higher in 1,2-dichloroethane than in chlorobenzene. A Similar trend was observed when the reaction was carried out in dichloromethane at even lower temperature (Table 5). From the experimental results it is obvious that on going from lower to higher temperature the yield of **3** increases. Based on these observations it is suggested that at lower temperature deacetalisation that yields the aldehyde **2** is favoured over cyclisation that yields the ether **3**. Considering these facts, it is proposed that at lower temperature the cyclisation proceeds predominantly via pathway (scheme 5) in which first the PTADEA undergoes deacetalisation in the presence of acid sites and water present in the catalyst to give the aldehyde **2** and in the second step the carbonyl oxygen coordinates with the acid sites to give the intermediate **4** which further gives rise to benzo[b]thiophene. The small amount of 2,3-dihydro-3-hydroxybenzo[b]thiophene observed in the GC-MS analysis confirms this mechanism. At higher temperature both deacetalisation and cyclisation are possible. Hence the reaction proceeds via both of the pathways as shown in schemes 5 and 6. The formation of diphenyl disulphide is due to the intermolecular attack of one reactant molecule over the other as suggested by Clark et al [42].

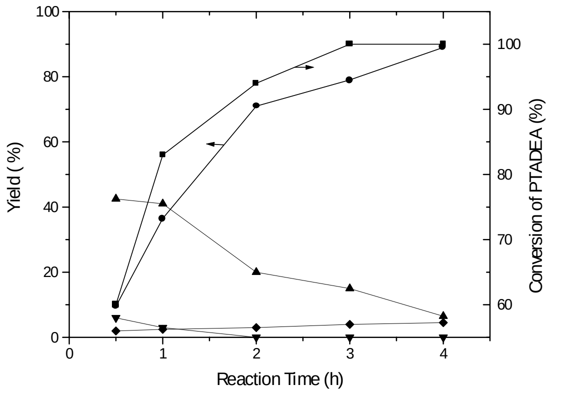


Figure 5. Conversion and products yield as a function of reaction time in 1,2-dichloroethane over ZnB catalyst (Catalyst wt: 150 mg, Temperature : 85°C); (■ Conversion of PTADEA, ●: 1, ▲: 2, ▼: 3, ◆: others)

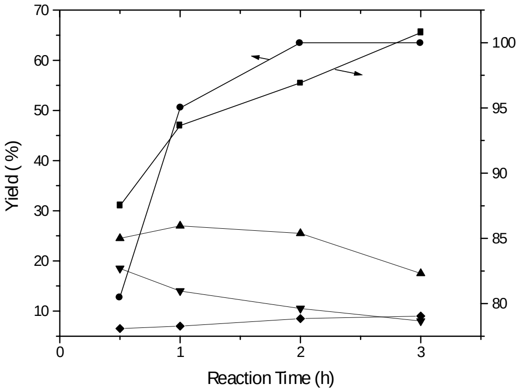


Figure 6. Conversion and products yield as a function of reaction time in chlorobenzee over ZnB catalyst (Catalyst weight: 50 mg, Temperature: 135°C); (■ Conversion of PTADEA, ●: 1, ▲: 2, ▼: 3, ◆: others)

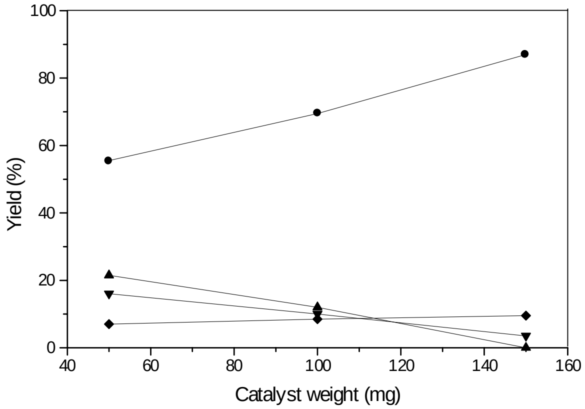


Figure 7. Effect of catalyst weight (ZnB) over products yield (Solvent: C_6H_5Cl, Temperature: 135°C, Reaction Time: 1 h) (●: 1, ▲: 2, ▼: 3, ◆: others)

The *in situ* DRIFT spectra of pyridine adsorbed catalysts are presented in Figure 8. It can be seen that in the spectrum of ZnB there is an increase in the intensity of the peaks at 1450 cm^{-1} and 1612 cm^{-1} which corresponds to coordinately bound pyridine Lewis acid sites [44,45]. Lewis acidity of the catalysts was calculated from the

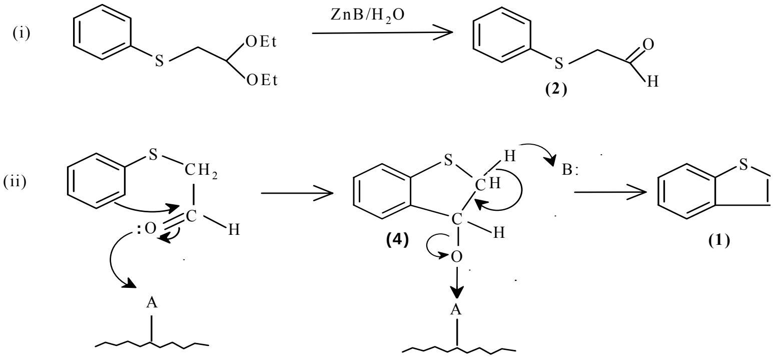
Table 5

Results of Cyclisation of PTADA

Catalyst	Catalyst to PTADEA ratio	Solvent	Temp (°C)	Time (h)	Conversion of PTADEA (%)	Products yield (%)			
						1	**2**	**3**	Others
ZnB	0.4	$(CH_2)_2Cl_2$	90	4	100	89	6.5	-	4.5
	0.3	C_6H_5Cl	135	1	100	87	-	3.5	9.5
	0.4	CH_2Cl_2	45	2	40	4	30	2	4
HB	0.4	$(CH_2)_2Cl_2$	90	4	85	27	51.5	3.5	3
	0.3	C_6H_5Cl	135	1	98	43.5	6	40.5	8

absorbance value of the peak at 1450 cm^{-1} using an extinction coefficient (ε) of $1.5x10^6$ cm^{-1} per mol, and it was found to be 0.227 mmol/g for HB and 0.437 mmol/g for ZnB [46,47]. This increase in Lewis acidity reveals that new Lewis acid sites are created upon Zn^{2+} ion-exchange in the parent zeolite.

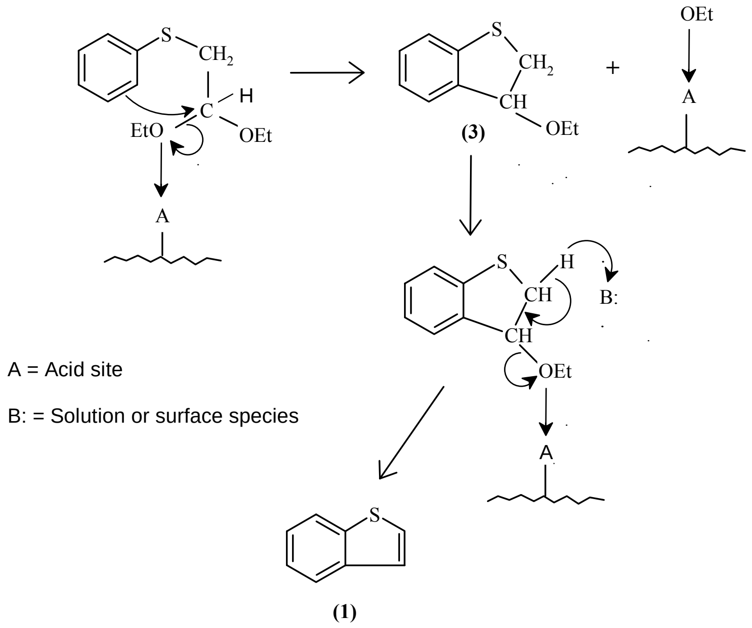
Scheme 5



A = Acid site

B: = Solution or surface species

Scheme 6



This newly generated Lewis acid sites may be responsible for the enhanced catalytic activity of the ZnB catalyst compared with the parent HB catalyst. After the end of the reaction the catalyst was filtered, washed with acetone, and regenerated at 500°C in the presence of moisture-free air and reused. The catalytic activity of the catalyst was found to be retained even after three recycles.

4.3. Synthesis of bis(indolyl)methanes

Indole derivatives are found abundantly in a variety of naturally occurring compounds. They exhibit various physiological properties and are potentially bioactive compounds.

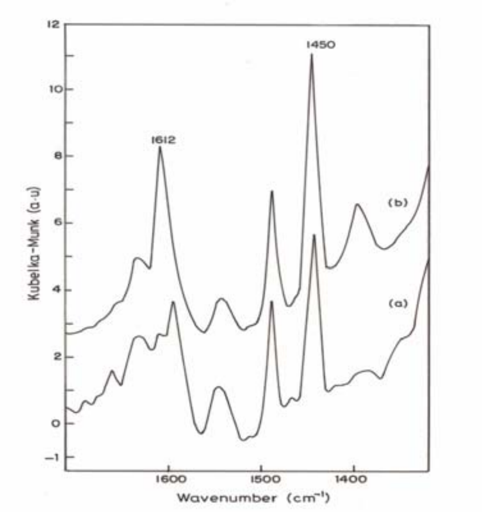
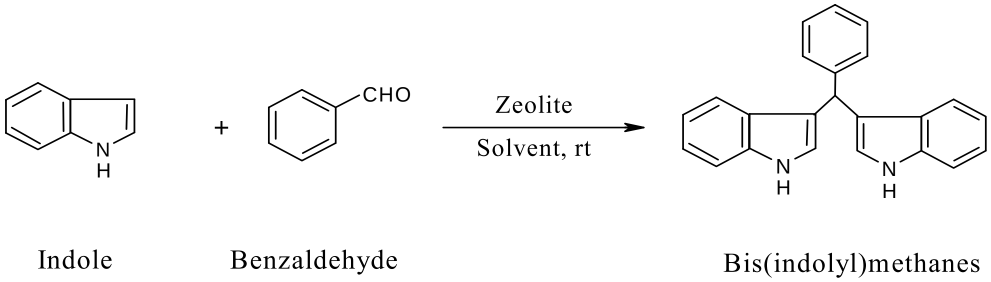


Fig. 8. The *in situ* DRIFT spectra of pyridine adsorbed catalysts (a) HB and (b) ZnB

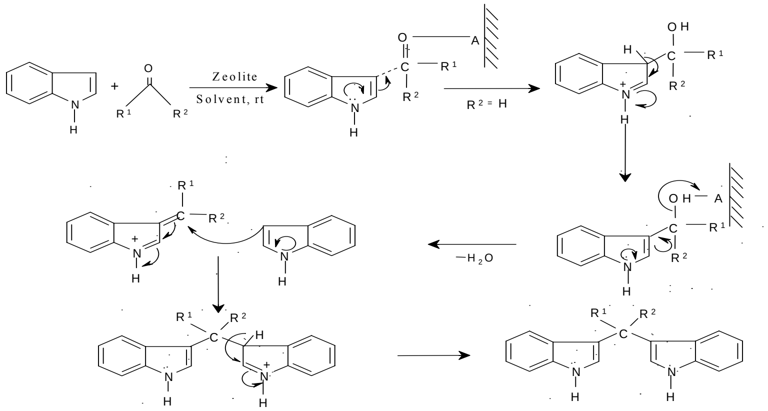
Diindolylmethanes (DIM) or bis(indolyl)methanes (BIM) are the most cruciferous substances for promoting beneficial estrogen metabolism in men and women [48]. DIM is effective in the prevention of cancer due to its ability to modulate certain cancer causing estrogen metabolites [49]. DIM induces apoptosis in human cancer cells [50] and may also normalize abnormal cell growth associated with cervical dysplasia [51]. As bis(indolyl)methanes derivatives are being important compounds in pharmaceutical chemistry, their synthesis have received increasing attention. Several methods have been reported in the literature for the synthesis of bis(indolyl)methanes using protic acids [52] and Lewis acids [53,54]. Many Lewis acids like trifluoroboron etherate, aluminium chloride promote this type of reaction but they generate large amount of harmful wastes. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required because the acids are trapped by nitrogen [55]. Recently, lithium perchlorate [56] and lanthanide triflates [57] are also used as Lewis acid catalysts for the reaction of indole with aldehydes or ketones affording bis(indolyl)methanes. But the reaction requires high reaction time and the process involves high cost. Hence there is a need for a new, efficient, recyclable and ecofriendly catalysts for the synthesis of bis(indolyl)methanes. We report herein [58] the use of zeolite as a catalyst in the reaction of indole with aldehydes at room temperature for good to excellent yields of bis(indolyl)methanes. Furthermore we report a successful and relatively simple method for the synthesis of bis(indolyl)methanes, and the catalyst is found to be highly efficient, economical and recyclable.

4.3.1. Catalytic activity

When indole was treated with benzaldehyde in the presence of zeolite catalyst in dichloromethane as the solvent, bis(indolyl)methanes were obtained in excellent yield. The electrophilic substitution reaction of indole with aromatic aldehydes proceeded smoothly at room temperature to afford the corresponding bis(indolyl)methane in high yield. The reaction is illustrated in scheme 7 and the proposed mechanism of the reaction is given in scheme 8. The influence of catalyst, solvent and substituent in the aromatic ring of the aldehyde on the yield of bis(indolyl)methanes was investigated and the results are discussed.



Scheme 7. Zeolite catalyzed reaction of indole with benzaldehyde



Scheme 8. Mechanism of the zeolite catalyzed reaction of indole with aromatic aldehyde A = Acid sites of the zeolites

4.3.2. Effect of catalyst

The effect of catalyst on the yield of bis(indolyl)methane is given in Table 6. The reaction of indole with benzaldehyde was carried out over Hβ, HY and H-ZSM-5 zeolites. The yield of bis(indolyl)methane increases in the order H-ZSM-5 < Hβ < HY, which is the same order of the increasing acid sites of the catalysts. Zn^{+2} ion-exchange Y zeolite showed better activity than parent HY zeolite owing to its higher Lewis acidity. These results are in good agreement with DRIFT (pyridine adsorption) measurements (Figure 9). The product might be formed on the external surface of the catalyst due to its bulky nature rather than inside the pores of the zeolites. In order to confirm this, the reaction was carried out on the surface passivated HY (SPHY) and Hβ (SPHβ) zeolites. The yield of bis(indolyl)methane was drastically suppressed on the surface passivated zeolites (Table 6). These results show that almost all the acid sites on the external surface are passivated by the amorphous silica layer. The nature of surface passivated zeolites was also confirmed by FT-IR. These results suggest that the reaction probably takes place mainly on the external surface or external acid sites of the zeolites. The reaction was also performed by varying the amount of catalyst. The increase in the yield of bis(indolyl)methanes was linear when the amount of the catalyst was increased from 100 to 500 mg. Above this, there was no increase in the yield.

Table 6: Effect of catalyst[a] on the yield of bis (indolyl) methanes

S. No.	Catalyst[b]	Time (h)	Yield (%)[c]
1	Hβ	2.5	75
2	HY	2.0	80
3	ZnY	2.0	90
4	H-ZSM-5	4.5	40
5	SPHβ	4.0	20
6	SPHY	4.0	15

[a] The reaction was carried out according to typical experimental procedure

[b] Catalyst wt - 0.5 g; Solvent - Dichloromethane

[c] Isolated yield after purification

4.3.3. *Effect of solvent*

The effect of solvent on the yield of bis(indolyl)methane is given in Table 7.

The reaction of indole with benzaldehyde was chosen as a model reaction for investigating the effect of solvent. Among the solvents examined, dichloromethane was found to be the most effective solvent. The reaction proceeded equally well in acetonitrile, diethyl ether and methanol whereas in all other solvents the reaction proceeded slowly.

Table 7: Effect of solvents[a] on the yields of bis(indolyl)methanes

S. No.	Solvent	Time (h)	Yield (%)[b]
1	CH_2Cl_2	2.0	80
2	CH_3CN	2.0	75
3	$C_2H_5OC_2H_5$	2.0	70
4	CH_3OH	2.5	70
5	C_2H_5OH	4.0	65
6	i-PrOH	5.0	30

[a] The reaction was carried out according to typical experimental procedure;[b] Isolated yield after purification;Catalyst wt (HY zeoliote) - 0.5 g.

4.3.4. Effect of substituent

The effect of substituents in the aromatic ring of aldehyde was investigated. The effect of various substituted aromatic aldehydes on the yield of bis(indolyl)methane derivatives in the presence of HY are summarized in Table 8. It is seen that chloro and nitro substituted aldehydes required longer reaction time to produce comparable yield than those of their electron-donating counterparts. Aldehydes like 4-methoxy benzaldehyde and 4-hydroxy-3-methoxy benzaldehyde (vanillin) reacted rapidly with indole to give the products in excellent yield and the reaction was completed within 1.5 h.

5. Conclusions

The studies revealed that raspberry ketone, benzo[b]thiophene and bis(indolyl)methanes can be conveniently synthesised employing zeolites and modified zeolites. The strength and type of acidic sites of the catalyst is important to obtain the desired product selectivity and in good yield. The essential advantage in the use of zeolites in the liquid phase reaction is the easy separation of the catalyst from the reaction mixture. The catalyst is readily recyclable and it can be reused more than four times without any loss of catalytic activity. The present studies demonstrate that zeolites and modified zeolites could be a viable, ecofriendly and economical alternative to mineral acid catalysts in the synthesis of raspberry ketone, benzo[b]thiophene and bis(indolyl)methanes.

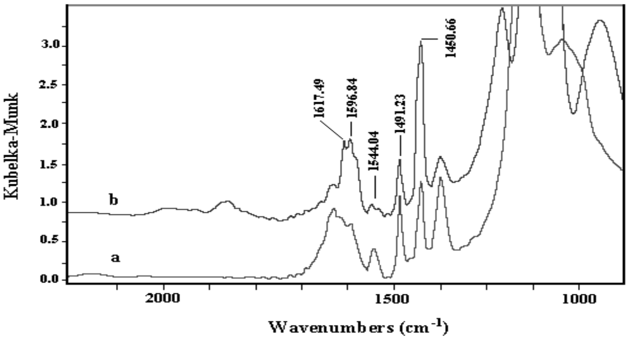
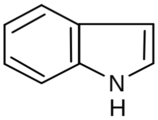
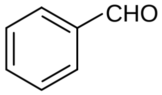
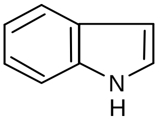
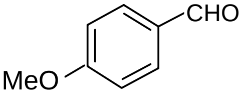
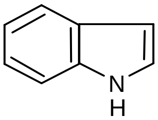
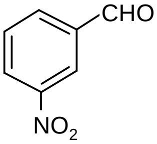
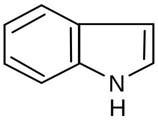
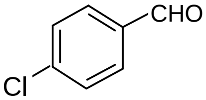
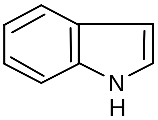
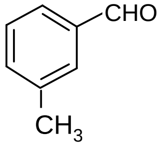
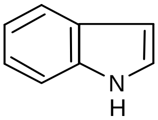
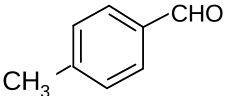
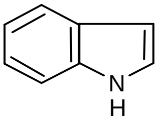
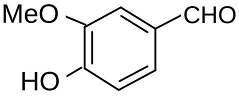


Figure 9. DRIFT (pyridine adsorption) spectra of zeolite catalysts. (a) HY and (b) ZnY.

Table 8: Effect of various substituted aromatic aldehydes on the yield of bis(indolyl) methanes darivatives[a]

S. No.	Indole	Aldehydes	Time (h)	Yield (%)[b]
1			2.0	80
2			1.5	85
3			4.0	72
4			5.0	64
5			2.0	75
6			1.5	80
7			1.5	85

[a] All the products were characterized by FT-IR,^{1}H & ^{13}C NMR and GC-MS.
[b] Isolated yield after purification.
Catalyst wt (HY zeolite) - 0.5 g; Solvent - Dichloromethane.

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