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Notes

H-beta zeolite catalysed synthesis of N-benzylbenzamide from benzonitrile and benzyl alcohol

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Amides have been synthesized from the reaction of alcohols with various nitriles using a heterogeneous H-beta zeolite catalyst with 91% isolated yield. The H-beta zeolite can be easily separable and recycled several times without considerable loss of its catalytic activity. The scale up trial on 1 g (benzyl alcohol) batch is reported under the optimized reaction condition.

Keywords: Catalysts, Heterogeneous catalyst, H-beta zeolite, Ritter reaction, Amides

Amide bond formation has very important role in synthetic chemistry and in biosynthesis. In nature, amide bond plays a vital role in protein chemistry. Also its formation is very important in pharmaceuticals, fine chemicals and potent drugs including number of nucleosides antibiotic and HIV protease antimicrobial and antiviral activity. Amides are present in ~25% of top-selling pharmaceutical drugs and other medically important compounds[1-4]. Amide bonds are typically formed from amines and pre-activated carboxylic acid derivatives such as acid chlorides, e. g., thionyl or oxalyl chloride, anhydrides e. g., carbonic anhydrides and esters like phosphonic esters, etc., or by using the carboxylic acid directly with coupling reagents such as carbodiimides[5]. However, these methods have considerable disadvantages such as use of hazardous and/or expensive reagents in stoichiometric amount and generation of harmful by products[5, 6].

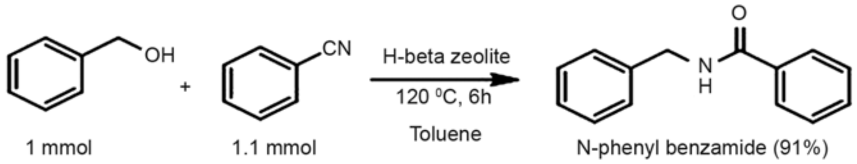
Ritter reaction is a classical and extensively studied method for the synthesis of a variety of amides[3,7]. The first report on Ritter reaction published in the year 1948, involved the condensation of the alcohols or suitable alkenes with nitriles in presence of stoichiometric amount of sulfuric acid and glacial acetic acid[8]. The main disadvantage of the classical Ritter reaction is harsh reaction conditions involving the use of corrosive and hazardous sulfuric acid and acetic acid[9]. Tremendous efforts were made to overcome these drawbacks by replacing sulfuric and acetic acid with other materials and many reports are available in literature. To list some of these, catalysts such as magnetic $CoFe_2O_4$ nanoparticle[3], triflic anhydride[10], Fe^{3+} montmorillonite K-10[11], heteropolyacids ($H_3PW_{12}O_{40}$, $H_7PMo_{12}O_{42}$, and $H_4SiW_{12}O_40_{13}$[12], $Ca(HSO_4)_2$[13], 2,4-nitrobenzenesulfonic acid[14], (P_2O_5/SiO_2) [15], $FeCl_3 \cdot 6H_2O$[16, 17], ionic liquids ([NSPTEA][OTF] and [BMIM(SO_3H)][OTF][18, 19]), magnetic nanoparticles (γ-Fe_2O_3@SiO_2-$HClO_4$[20], I_2/H_2O[21]), sulfated tungstate[22], pentafluorophenyl ammonium triflate (PFPAT)[23], silica boron–sulphuric acid nanoparticles[24], trifluoromethane sulfonic anhydride[25], $ZnCl_2/SiO_2$[26], $BF_3 \cdot OEt_2$[27], heteropolyanion-base [MIMPS]$H_2PMo_{12}O_{40}$][28], magnetite-sulfonic acid (Nanocat-Fe-OSO_3H)[29], and silica based sulfuric acid[30] have been studied. Moreover, H-ZSM-5 and HY-zeolite were reported for Ritter reaction with acetonitrile and alcohol at 150 °C for 24 h with 62.2% and 7.4% product yields respectively[31]. Ritter reaction (with acetonitrile and isopropyl alcohol) has been also reported using beta-zeolite catalyst at 150 °C for 24 h with very low 8.5% yield [32, 33].

Herein, we report the Ritter reaction involving benzonitrile and benzyl alcohol to yield N-benzylbenzamide using environmentally benign H-beta zeolite catalyst and also one gram scale up experiment for N-benzylbenzamide in toluene.

Experimental

H-beta zeolite was prepared by ion exchange method. The Na-beta zeolite was converted to the NH_4^+ form by treating with 1 *M* NH_4Cl aqueous solution three times at 90 °C for 4 h. The resulting NH_4^+-beta zeolite was further converted to H^+-beta zeolite by calcination in air at 550 °C for 4 h[34].

All reactions were carried out in oven-dried glassware under standard reaction conditions. Ethyl acetate, acetonitrile, hexane and toluene were purchased from SD Fine Chemical Ltd., India. Commercially available Na-beta zeolite (SiO_2/Al_2O_3 = 25)



Ritter reaction between benzyl alcohol and benzonitrile.

Scheme 1

was procured from Zeochem AG, Switzerland, and used without further purification. Thin layer chromatography was performed on pre-coated silica gel 60 F_{254} plates (Merck). Visualization on TLC was achieved by UV light (254 nm). Flash column chromatographic purification of the compounds was carried out by gradient elution using ethyl acetate in light hexane unless stated otherwise. The conversion of alcohol and selectivity of amide product was calculated on the basis of its weight percent using GC data. The product was also identified by GC–MS (Shimadzu, GCMS-QP 2010). ^{1}H / ^{13}C NMR was recorded on 200/50 and 500/125 MHz NMR spectrometer (Bruker, Avance II (500 MHz) Bruker, DPX-200 (200 MHz)) in $CDCl_3$ unless otherwise stated, using either TMS or the undeuterated solvent residual signal as the reference.

Powder X-ray diffraction analysis of the beta zeolite samples was done on a Rigaku Miniflex-II (FD 41521) powder diffractometer. The samples were scanned in the 2θ range of 2-80° using Cu-Kα (λ = 1.54178 Å) radiation and Ni filter with a scan speed of 2° s^{-1}. The surface area, total pore volume, and the average pore diameter were measured by N_2 adsorption-desorption method using ASAP 2020 (Micromeritics Inc., USA) at −196 °C after degassing the sample under vacuum (10−2 Torr) at 300 °C for 4 h. The surface area was determined by Brunauer-Emmett-Teller (BET) equation. Pore size distributions were determined using Barrett-Joyner-Halenda (BJH) model. Temperature-programmed desorption of ammonia (TPD-NH_3) measurements were conducted on Autochem-2920II Chemisorption analyser (Micromeritics Inc. USA) by placing 85 mg of the sample in a sample tube and pre-treated in helium flow (35 cm^3 min^{-1}) at 300 °C for 2 h and then cooled to 100 °C. Ammonia gas (100 torr, 25 mL/m) was allowed to adsorb on the sample for 1 h. The physisorbed ammonia was removed by flushing the sample with helium for 1 h. NH_3-TPD measurements were carried out in the temperature range of 100–800 °C.

Benzyl alcohol (1 mmol) and benzonitrile (1.1 mmol) were taken in 1 mL toluene in a glass tube and stirred (300 rpm) on a hot plate. H-beta zeolite (50 mg) was added as a catalyst. The mixture was heated at 120 °C for 6 h (Scheme 1). Progress of the reaction was monitored by TLC of the sample. After completion of the reaction, the reaction mixture was cooled at room temperature and resulting mixture was extracted with EtOAc (5×10 mL) to collect the product in the organic layer. Then the organic layer was concentrated and the crude product was purified by column chromatography (EtOAc/hexane) using silica gel (100-200 mesh from HIMEDIA) to get the pure product which was analysed by NMR. ^{1}H and ^{13}C NMR data of all the isolated product are given in supplementary data.

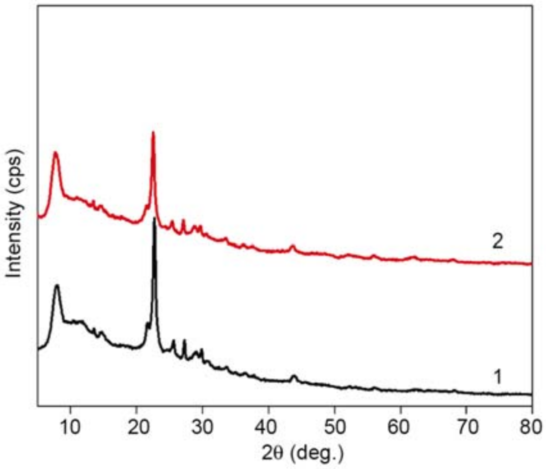


Fig. 1 — PXRD patterns of Na-beta zeolite (1) and H-beta zeolite (2).

Results and discussion

Crystallinity and phase purity of the Na-beta and H-beta-zeolite samples were identified from their respective X-ray diffraction patterns (Fig. 1). The diffraction peaks located at ~2θ values of 7.8° and 22.4° are characteristic diffraction peaks of the H-beta zeolite structure indicating no significant change in the framework structure on cation exchange and calcination during converting Na-beta-zeolite to H-beta-zeolite.

N_2 adsorption and desorption isotherms of the Na-beta zeolite and H-beta zeolite samples (Fig. 2)

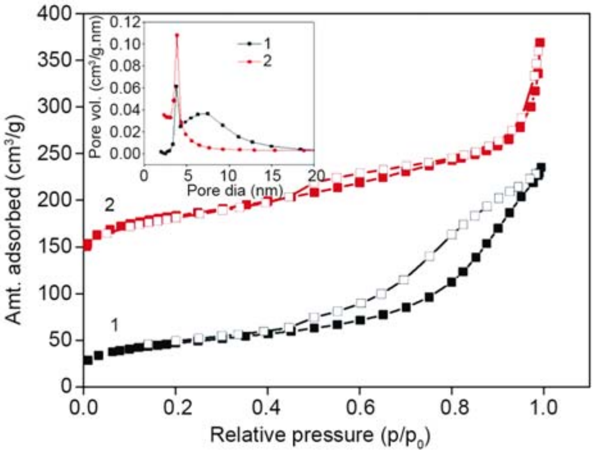


Fig. 2 — N_2-sorption isotherms of Na-beta zeolite (1) and H-beta zeolite (2).

was measured in the partial pressure (P/P_0) range of 0.1-0.9. The BET surface area of H-beta zeolite was higher (546 m^2/g) as compared to that of Na-beta (407 m^2/g). The total pore volume and pore diameter were analysed from the amount of nitrogen adsorbed. Pore volume was higher for H-beta zeolite (0.40 cm^3/g) as compared to that of Na-beta zeolite (0.26 cm^3/g), which may be due to lower atomic volume of H atom (Table 1).

NH_3-TPD profiles of H-beta zeolite and Na-beta zeolite are shown in Fig. 3. The amount and strength of acidic sites were determined by amount of ammonia desorbed and peak position respectively. H-beta zeolite exhibits two desorption peaks at ~100 °C and 400 °C. The peak at ~100 °C observed for H-beta zeolite and Na-beta zeolite arises due to the weakly held (probably hydrogen bonded) NH_3 molecules. It has been suggested that the extra framework alumina species such as $Al(OH)^{2+}$ could be the absorbed sites of a weak Lewis acid[34]. The peak at ~400 °C may be assigned to desorption of NH_3 molecules, which implies the presence of strong Brönsted acid sites in H-beta zeolite having acidity 1.83 mmol NH_3/g zeolite. On the other hand Na-beta zeolite does not show any peak in the higher temperature region, indicating very low acidity.

During the optimization studies for high yield and purity of the amide product, the H-beta zeolite was employed as a catalyst for Ritter reaction between benzyl alcohol and benzonitrile, a simple model reaction to evaluate the effects of temperature, time, mole ratio and the dose of catalyst. Experimental conditions and isolated yields are shown in Table 2.

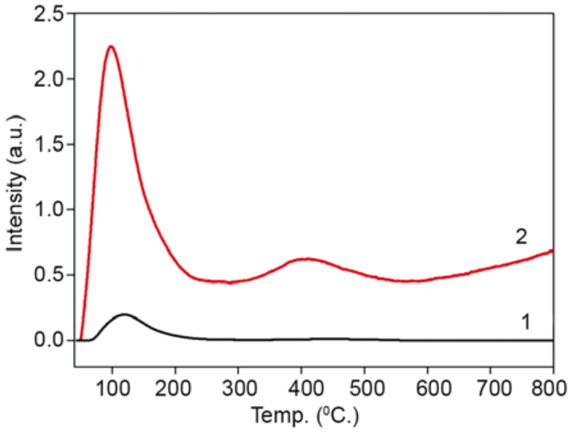


Fig. 3 — NH_3-TPD analysis of Na-beta zeolite (1) and H-beta zeolite (2).

Table 1 — Specific surface area and pore volume of H-beta zeolite and Na-beta zeolite

Sample	S_{BET} (m_2/g)	Pore vol. (cm_3/g)	Pore dia. (nm)
Na-beta zeolite	407	0.26	5.91
H-beta zeolite	546	0.40	6.72

Table 2 — Optimization of the reaction conditions for H-beta zeolite (50 mg) mediated Ritter reaction. [Catalyst: 50 mg; toluene (solvent): 1 mL]

No.	Mole ratio[a] ($ph\text{-}CH_2OH$:ph-CN)	React. cond.	Isolated yield (%)
1	1:1.5	80 °C, 10 h	50
2	1:1.5	100 °C, 10 h	82
3	1:1.5	120 °C, 10 h	91
4	1:1.2	120 °C, 10 h	91
5	1:1.1	120 °C, 10 h	91
6	1:1.0	120 °C, 10 h	85
7	1:1.1	120 °C, 8 h	91
8	1:1.1	120 °C, 6 h	91
9	1:1.1	120 °C, 4 h	73
10[b]	1:1.1	120 °C, 6 h	70
11[c]	1:1.1	120 °C, 6 h	91
12[d]	1:1.1	120 °C, 6 h	87

[a]Mole ratio of benzyl alcohol:benzonitrile, [b]Catalyst: 30 mg, [c]Catalyst: 70 mg, [d] Solvent free.

Effect of reaction temperature was studied by varying reaction temperature for achieving highest yield. The increase in yield of amide product is associated with increase in the reaction temperature (Table 2, Entries, 1, 2 and 3). This may be due to the formation of undesired benzamide product via competitive hydration of benzonitrile at lower reaction temperature. The yield of N- benzylbenzamide (91%)

at 120 °C was significantly higher than that of observed at 80 °C and 100 °C. Therefore, 120 °C temperature was selected as optimum reaction temperature.

The Ritter reaction of benzyl alcohol and benzonitrile to N-benzylbenzamide was performed at 120 ºC for 10 h using 50 mg catalyst by varying mole ratios of benzyl alcohol to benzonitrile in the range of 1:1.0 to 1:1.2 (Table 2 entries, 4, 5 and 6). Interestingly, the 1:1.1 mole ratio of benzyl alcohol and benzonitrile showed good reactivity with 91% isolated yield for N-benzylbenzamide.

The effect of reaction time on the formation of N-benzylbenzamide product was carried out by varying the reaction time in the range of 4-10 h (Table 2 entries 5, 7, 8 and 9) at a mole ratio of reactants 1:1.1 using 50 mg H-beta zeolite catalyst. Highest isolated yield (91%) of N-benzylbenzamide was obtained within 6 h by reacting benzyl alcohol and benzonitrile. It has been observed that, with the decrease in reaction time formation of N-benzylbenzamide also decreased as evidenced by very low (73%) yield for reaction time of 4 h, as observed from Table 2 (entry 9).

The effect of the amount of catalyst (H-beta zeolite) on isolated yield for the Ritter reaction of benzonitrile with benzyl alcohol at 120 °C was studied. Monitoring of the reactions (Table 2) showed that use of 30 mg H-beta zeolite (entry 10) resulted in lower yield (70%) of N-benzylbenzamide due to non-availability of sufficient and essential acid sites for the reaction to proceed, whereas 50 mg and 70 mg of catalyst H-beta zeolite provided sufficient acid sites to give excellent yield of 91% (entries 8 and 11). Of these, 50 mg catalyst loading was considered as optimum dose of catalyst for further studies with various derivatives of amide. In the case of solvent free condition, Ritter reaction with benzyl alcohol and nitrile yielded the product in 87% isolated yield (Table 2, entry 12).

Conclusively, the optimum reaction conditions for Ritter reaction of benzyl alcohol (1 mmol) and benzonitrile (1.1 mmol) in presence of toluene solvent with H-beta zeolite (50 mg) catalyst was established as 120 °C for 6 h. As per the obtained GC_MS analysis, a 95.4 % conversion of benzyl alcohol with 95.3 % selectivity of product (N- benzylbenzamide, Table S1) has been observed. The reaction was also studied under the solvent free condition using the same optimized parameters and benzyl alcohol conversion has found to be 90.9 % as per the GC_MS analysis. The GC_MS analysis also showed 5 % side product as ether and dicumene (Table S1).

Subsequently, the Ritter reaction of benzyl alcohol and benzonitrile was extended to various aromatic nitriles and alcohols. Products were isolated in excellent yields (Table 2).

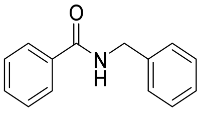
The effects of both, the nature and the position of the substituent, on the aromatic ring have been observed upon changing the nitrile derivatives. The nitrile derivatives containing electron-donating (-Me, -OMe) and electron-withdrawing (-CF_3, -Cl) groups has resulted in good yield under optimized conditions. However, in the case of N-benzyl-4-nitrobenzamide, the yield was very low (product 3t). This may be due to the presence of strong electron withdrawing group (–NO_2) at *para* position (p) which does not stabilize the carbon cation. The presence of a methyl group at *ortho* position (o) to the nitrile group resulted in 60% yield (Table 3, product 3j) due to steric hindrance. The reaction with heterocyclic derivative, thiophene-2-carbonitrile, gave 71% yield (product 3q). The reaction of 1-adamantanol with benzonitrile did not proceed with H-beta zeolite as catalyst (product 3r).

In order to check the performance of the prepared catalyst, the reaction between benzyl alcohol and benzonitrile at 120 °C for 8 h in 3 mL toluene on 1 g batch scale was carried out in the presence of H- beta zeolite as the catalyst. The crude reaction mass was concentrated via rota-evaporator and separated by column chromatography. After separation by column chromatography (10% ethyl acetate/90% hexane), the product N-benzylbenzamide yield was obtained in 87% yield with 5% side product as ether and dicumene.

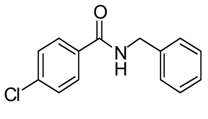
The possibility of recycling the catalyst was tested using the reaction of benzyl alcohol with benzonitrile under optimized conditions (benzyl alcohol (1 mmol), benzonitrile (1.1 mmol)) in the presence of toluene as solvent with H-beta zeolite (50 mg) at 120 °C for 6 h. The recovered catalyst was regenerated by washing with EtOAc and activating at 100 °C for 2 h. The catalyst could be reused up to five cycles without any significant loss of the catalytic activity.

The proposed reaction mechanism, in presence of H-beta zeolite catalyst is shown in Scheme 2. The carbocation from benzyl alcohol is generated by the acid catalyst, H-beta zeolite, which further reacts with the corresponding nitrile compound. The resulting nitrilium ion is hydrolysed by water to give the desired amide product.

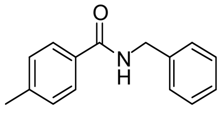
Table 3 — Reaction of benzyl alcohol with nitrile derivatives containing electron-donating and electron-withdrawing group[a]



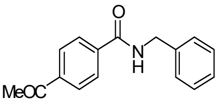
3a (91%)



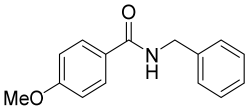
3b (79%)



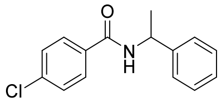
3c (91%)



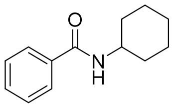
3d (76%)



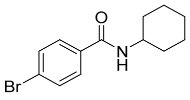
3e (89%)



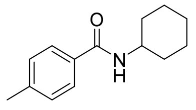
3f (70%)



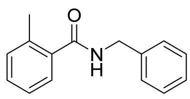
3g (81%)



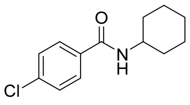
3h (82%)



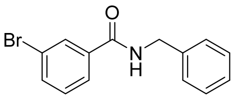
3i (84%)



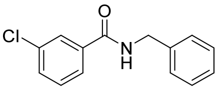
3j (60%)



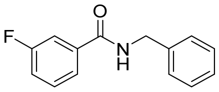
3k (79%)



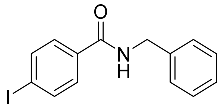
3l (78%)



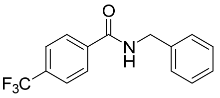
3m (78%)



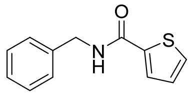
3n (80%)



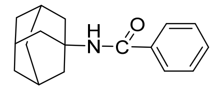
3o (81%)



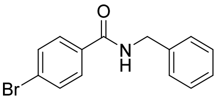
3p (75%)



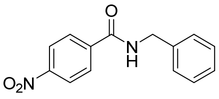
3q (71%)



3r trace

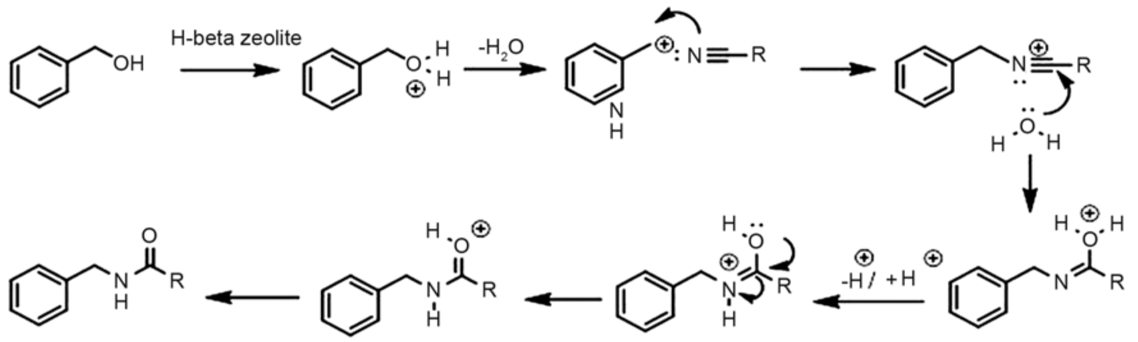


3s (81%)



3t (5-7%)

[a] Alcohol (1 mmol) and nitrile (1.1 mmol) were mixed with H-beta zeolite (50 mg) and heated at 120 °C for 6 h. Toluene: 1 mL.



Proposed mechanism for H-beta zeolite mediated preparation of amides from benzyl alcohol

Scheme 2

In conclusion, the present work successfully establishes the H-beta zeolite as a very effective catalyst for the Ritter reaction between various nitriles and alcohols with 95.4% conversion and 91% isolated yield in toluene. The catalyst is reusable and efficient for a wide range of substrates. Moreover, it has the potential for large scale applications and paves the greener way to synthesize amides.

Supplementary data

Supplementary data associated with the article, viz., Table S1, GC_MS data of Ritter reaction and NMR of the products, are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_56A (02)220-225_SupplData.pdf.

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