

Vasu Amrutham¹ · Naresh Mameda^{1,2} · Srujana Kodumuri¹ · Durgaiah Chevella¹ · Rammurthy Banothu^{1,2} · Krishna Sai Gajula^{1,2} · Nellya Gennadievna Grigor'eva³ · Narender Nama^{1,2}

Received: 22 June 2017 / Accepted: 15 September 2017 © Springer Science+Business Media, LLC 2017

Abstract A simple approach for the formation of imines by condensation of ketones and anilines over heterogeneous catalyst (H β zeolite) has been successfully developed. The present catalytic system scope was explored for various aromatic ketones and anilines. Furthermore, H β zeolite can be easily separable and recycled several times (five times) without considerable loss of its catalytic activity.

Graphical Abstract



Keyword Condensation · Heterogeneous catalyst · Imines · Aromatic ketones · Zeolites

1 Introduction

The C–N bond-formation reaction is one of the most important transformations in modern synthetic chemistry and

Electronic supplementary material The online version of this article (doi:10.1007/s10562-017-2196-0) contains supplementary material, which is available to authorized users.

Narender Nama narendern33@yahoo.co.in; nama.iict@gov.in

- ¹ I&PC Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, Telangana 500 007, India
- ² Academy of Scientific and Innovative Research, CSIR-Indian Institute of Chemical Technology, Hyderabad, Telangana 500 007, India
- ³ IPC RAS, 141 prosp, Oktyabrya, 450075 Ufa, Russian Federation

plays a vital role in biological and chemical systems [1-3]. In particularly, due to their diverse reactivity, imines and their derivatives have become crucial intermediates in the synthesis of biologically active nitrogen compounds and have been broadly used in the preparation of pharmaceuticals, dyes, fragrances, fungicides and agricultural chemicals [4, 5]. Imines also serve as versatile components in nucleophilic addition with organometallic reagents [6], cycloaddition reactions [7, 8] and have potential for the rapeutic applications [9-12]. Several methods have been described in the literature for their synthesis, such as condensation of amines with the carbonyl compounds [13–16], self-condensation of primary amines upon oxidation [17-19], oxidative coupling of alcohols and amines [20, 21], hydroamination of alkynes with amines [22–25], oxidation of secondary amines and the partial hydrogenation of nitriles followed by coupling with the amines [26, 27]. Among the all approaches for the synthesis of imines, the condensation of amines with the carbonyl compounds is a well-established, direct and attractive synthetic route to prepare imines, although problems still remain to achieve this chemical transformation economically. Therefore, given the importance of imines as intermediates in organic synthesis, the development of convenient procedures for their preparation is of interest.

Recently, growth of new processes that reduce pollution in the chemical industry has received substantial consideration due to growing environmental concerns. In this route, heterogeneous catalysis has appeared as a convenient tool to diminish waste production with regard to the simplicity of the process and separation and recycling of the catalysts [28–31]. Catalysis by zeolites and related materials has become an attractive research area over the past decades in the heterogeneous catalysis and green chemistry [32, 33]. As an important type of solid acids, zeolites have been broadly used as replacement for highly toxic and corrosive mineral



acids or inorganic Lewis acids in synthesis of fine chemicals [34, 35]. This is mainly due to the fact that zeolites have well defined porous structures with large amount of acid sites (both Bronsted and Lewis type) present on the inner surface of the pores. One of the paramount properties of zeolites is the great variety of topologies and pore architectures. The acidic properties of zeolites are mainly dependent on the Si/ Al molar ratio as well as the temperature of activation [36, 37]. All the characteristics of zeolite-acidity such as, distribution of Lewis and Bronsted sites, strength, density of the acid sites can be modified by a large number of treatments. For example, the treatment at high temperature of protonic zeolites causes the transformation of Bronsted acid sites into Lewis acid sites. Yet the protonic sites of the dehydroxylated zeolites are stronger than those of the starting zeolites. On the other hand, dealumination decreases the acid site density but can increase the acid strength and modify the porosity. Therefore, the catalytic activity of zeolites could be tailored for special chemical transformations. Additionally, their environmentally benign nature, high surface area and adsorption capacity, as well as outstanding chemical and thermal stability, make them ideal candidates for heterogeneous catalysis. In continuation of our efforts toward the development of novel and eco-friendly synthetic protocols using zeolites [38-42], we herein report the H β zeolite catalyzed synthesis of imines from aromatic ketones and anilines.

2 Experimental Section

2.1 General Information

All chemicals were acquired from Sigma-Aldrich and used as received without further purification. The catalyst H_β Zeolite (Si/Al=19) was procured from Alfa Aesar, England. ¹HNMR spectra were recorded at 300, 400 or 500 MHz and ¹³CNMR spectra at 75, 100 or 125 MHz in CDCl₂. The chemical shifts (δ) are reported in ppm units relative to TMS as an internal standard for ¹HNMR and CDCl₃ for ¹³CNMR spectra. Coupling constants (J) are reported in hertz (Hz) and multiplicities are indicated as follows: s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet). The GC analysis were carried out using GC Shimadzu (GC-2014) gas chromatograph equipped with FID detector and capillary column (EB-5, length 30 m, inner diameter 0.25 mm, film 0.25 mm). TLC inspections were performed on Silica gel 60 F254 plates. Column chromatography was performed on silica gel (100-200 mesh) using n-hexane-EtOAC as eluent. The XRD patterns of the samples were obtained on a Regaku miniflex X-ray Diffractometer using Ni filtered CuK α radiation at $2\theta = 2^{\circ} - 80^{\circ}$ with a scanning rate of 2° min⁻¹ and the beam voltage and currents of 30 kV and 15 mA, respectively.

2.2 General Procedure

Hβ zeolite (100 mg) was added to the well stirred solution of aromatic ketone (2 mmol), aniline (2 mmol) and toluene (1 mL) in a 15 mL sealed tube and the reaction mixture was allowed to stir at 120 °C. After 24 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The catalyst was separated by simple filtration and the exclusion of solvent in vacuo yielded the crude which was further purified by column chromatography using silica gel (100–200 mesh) to afford pure products. All the products were identified on the basis of ¹H and ¹³C NMR spectral data.

3 Results and Discussion

In the preliminary investigation, a typical reaction of acetophenone with p-anisidine to give

 Table 1 Optimization of reaction conditions-the condensation of acetophenone with *p*-anisidine



Entry	Catalyst	Tem- perature (°C)	Conver- sion 1a (%) ^a	Selectiv- ity 3a (%) ^a	Yield (%) ^b
1	Нβ	120	92	98	90
2	NaY	120	70	99	69
3	HZSM-5 (150)	120	65	99	64
4	H-Mordenite	120	74	98	72
5	HY	120	66	99	65
6	Montmorillonite K10	120	64	99	63
7	HMCM-41	120	67	99	66
8	Absence of catalyst	120	20	99	20
9	Нβ	100	72	99	71
10	Нβ	80	52	99	52
11	Нβ	120	61	99	60 ^c
12	Ηβ	120	91	99	90 ^d

Reaction conditions: **1a** (2 mmol), **2a** (2 mmol), toluene (1 mL), catalyst (100 mg), 120 °C, 24 h, sealed tube

^aConversion and selectivity based on GC

^bIsolated yields

^c50 mg

^d150 mg

2r-2aa

Table 2 Scope of the condensation reaction of acetophenone with various substituted anilines over H β zeolite



1a-1q





Entry	R	Ar	Conversion $1a-1q$ (%) ^a	Selectivity 3a–3aa (%) ^a	Yield (%) ^b
1	4-MeO	C ₆ H ₅	92	98	3a; 90
2	Н	C ₆ H ₅	57	97	3b ; 55
3	4-Me	C ₆ H ₅	79	98	3c ; 77
4	2-Me	C ₆ H ₅	85	97	3d; 82
5	2-Et	C_6H_5	54	98	3e ; 50
6	4- <i>i</i> -Pr	C ₆ H ₅	46	97	3f; 45
7	4-t-Bu	C ₆ H ₅	53	98	3g; 50
8	2,6-Me,Me	C_6H_5	59	97	3h; 69
9	2,4-Me,Me	C_6H_5	75	98	3i ; 73
10	4-F	C ₆ H ₅	64	99	3j; 63
11	4-Cl	C ₆ H ₅	61	97	3k; 60
12	4-Br	C ₆ H ₅	68	98	3l ; 66
13	3,4-Cl,Cl	C ₆ H ₅	73	96	3m; 70
14	4-NO ₂	C ₆ H ₅	00	_	3n; –
15	4-COOH	C ₆ H ₅	00	_	30 ; –
16	4-CONH ₂	C_6H_5	00	-	3p; –
17	$2-CH_2C_6H_5$	C ₆ H ₅	52	97	3q ; 50
18	4-MeO	4-MeOC ₆ H ₅	79	98	3r; 77
19	4-MeO	3-MeOC ₆ H ₅	90	97	3s ; 88
20	4-MeO	$3-\text{MeC}_6\text{H}_5$	89	98	3t ; 87
21	4-MeO	$4-NO_2C_6H_5$	94	97	3u ; 92
22	4-MeO	$4-FC_6H_5$	97	97	3v; 95
23	4-MeO	3-ClC ₆ H ₅	94	98	3w ; 92
24	4-MeO	4-ClC ₆ H ₅	92	97	3x; 90
25	4-MeO	3-BrC ₆ H ₅	79	98	3y; 75
26	4-MeO	4-BrC ₆ H ₅	89	97	3z; 86
27	4-MeO	2-Napthyl	92	98	3aa; 90

Reaction Conditions: 1a-1q (2 mmol), 2r-2aa (2 mmol), toluene (1 mL), Hβ (100 mg), 120 °C, 24 h, sealed tube

^aConversion and selectivity based on GC

^bIsolated yields

(E)-4-methoxy-*N*-(1-phenylethylidene)aniline (**3a**) was chosen as a model system to elevate the best reaction conditions for this transformation. To get the best catalyst, the reaction was carried out over various zeolites, MCM-41 and montmorillonite K10 using toluene as solvent at 120 °C in sealed tube for 24 h (Table 1, entries 1–7). Among the catalysts surveyed, H β zeolite exhibited a higher catalytic activity and gave the corresponding imine **3a** in 90% yield due to its strong acidic sites (higher acid strength) and special

three-dimensional large size porous structure¹² (Table 1, entry 1). In the absence of a catalyst, the yield of **3a** was only 20% (Table 1, entry 8) and this observation obviously indicates the role of catalyst in the reaction (the influence of the catalyst on the reaction).

The influence of temperature was studied, after H β catalyst was found as the best catalyst for this reaction. A gradual improvement was observed in the reaction yield of **3a** (52–90%) by varying the reaction temperature from 80 to

120 °C and further increase of temperature did not have any accountable effect on the yield (Table 1, entries 1, 9 and 10). The present reaction was also conducted using different amounts of catalyst and found that 100 mg of catalyst gave the best results (Table 1, entries 1, 11 and 12). Next, various solvents were studied under similar reaction condition over H β and the results were suggested that toluene was the best medium for this transformation (see the ESI Tables S1). From the above obtained results, the optimized reaction conditions to acquire the highest yield for this reaction are 1:1 mol ratio of acetophenone to *p*-anisidine in toulene (1 mL) at 120 °C over H β zeolite (100 mg) (Table 1, entry 1).

After optimizing the reaction conditions, we then turned our attention to explore the versatility of this condensation reaction by reacting the various anilines with aromatic ketones and the results are summarized in Table 2. Various electron-donating and electron-withdrawing groups were well tolerated with the present catalytic system and gave the desired products 3a-3m and 3q-3aa in low to excellent yields (Table 2, entries 1–13 and 17–27). The condensation of acetophenone with aniline afforded the corresponding imine 3b in 55% yield (Table 2, entry 2). Aniline substituted with activating groups reacted efficiently and produced the respective imine products 3c-3i in 45-82% yields under these reaction conditions (Table 2, entries 3–9). However, higher alkyl chain substituted anilines (Table 2, entries 5–7) gave the desired products in lower yields compared to methyl substituted anilines (Table 2, entries 3, 4, 8 and 9). Halo substituted anilines, such as 4-fluoroaniline (3j), 4-chloroaniline (3k), 4-bromoaniline (3l) and 3,4 dichloroaniline (3m) could be transformed into the corresponding imines 3j-3m in 60–70% yields (Table 2, entries 10–13). Unfortunately, aniline with strongly electron-withdrawing groups (i.e. NO₂, COOH and CONH₂) were unsuccessful under the present conditions (Table 2, entries 14–16). 2-Benzylaniline yielded the respective imine **3q** in 50% yield (Table 2, entry 17).

To further extend the scope of this reaction, a variety of aromatic ketones were employed to react with *p*-anisidine under optimal conditions (Table 2, entries 18–27) and were found to be tolerable in this process. Acetophenones having electron-donating and withdrawing groups reacted smoothly under optimized conditions to give the corresponding products 3r-3u in good to excellent yields (Table 2, entries 18–21). Halo substituted acetophenones were also provided respective imines 3v-3z in 75–95% yields (Table 2, entries 22–26). Reaction of polyaromatic ketone *i.e.* 2-acetonaphthone with *p*-anisidine yielded the respective imine **3aa** in 90% yield (Table 2, entry 27).

For environmental considerations and commercial applications, the reusability of the catalyst is one of the most important feature. The possibility of recycling the catalyst was tested using the condensation reaction between acetophenone with *p*-anisidine under standard reaction conditions. The catalyst was easily separated from the reaction mixture by simple filtration and the collected catalyst was calcined at 450 °C to use in the next cycle. No obvious loss of the catalytic activity was discovered even after five cycles (Fig. 1). The XRD analysis of reused catalyst matched well with fresh catalyst, thus suggesting that the crystallinity of the reused catalyst is comparable to the original material (Fig. 2).

The plausible reaction mechanism for the formation of imines (ketimines) from aromatic ketones and anilines over $H\beta$ zeolite is illustrated in Scheme 1. It is assumed that aromatic ketone(I) adsorbs on the Bronsted acid sites of zeolite, which subsequently reacts with aniline to give the intermediate II, finally, dehydration of the resulting intermediate II leads to the respective imines (ketimines) III.



Fig. 1 Recyclable study of $H\beta$ zeolite on the condensation of acetophenone with *p*-anisidine



Fig. 2 XRD patterns of H β zeolite: *a* before reaction, *b* after reaction

Scheme 1 Plausible mechanism for the formation of imines (ketimines) from aromatic ketones and anilines





In summary, a simple heterogeneous catalytic system for the synthesis of imines involving the condensation of aromatic ketones with anilines over H β zeolite developed successfully. The scope and limitations of this protocol were investigated with various anilines and acetophenones. Prominent advantages obtainable by this catalytic strategy are use of nonhazardous and reusable catalyst, mild reaction conditions and simple work-up procedures.

Acknowledgements We thank the DST, New Delhi for financial support under Indo-Russia (DST-RSF) (No. INT/RUS/RSF/P-7) programme. M. N, Ch. D and G. K. acknowledge the CSIR, India and K. S. and B. R. acknowledge the UGC, India for financial support in the form of fellowship.

References

- 1. Ricci A (2000) Modern amination reactions. Wiley, Weinheim
- Hartwig JF (2002) In: Negishi E, Meijere A (eds) Handbook of organopalladium chemistry for organic synthesis, vol 1. Wiley, New York
- Lawrence SA (2004) Amines synthesis properties and application. Cambridge University Press, Cambridge
- 4. Rappoport ZJ, Liebman F (2009) The chemistry of hydroxylamines oximes and hydroxamic acids. Wiley, New York, p 609
- Hadjipavlou-Litina DJ, Geronikaki AA (1998) Drug Des Discov 15:199–206
- Kuznetsov VV, Palma AR, Aliev AE, Varlamov AV, Prostakov NS, Zh (1991) Org Khim 127:1579–1581
- 7. Tsuge O, Kanemasa R (1989) Adv Heterocycl Chem 45:231-349
- Aly MF, Younes MI, Matwally SAO (1994) Tetrahedron 50:3159–3168
- Hadjipavlou-litina DJ, Geronikaki AA (1996) Drug Des Discov 15:199–206
- Cushman M, Nagarathnam D, Gopal D, Chakraborti AK, Lin CM, Hamel EJ (1991) Med Chem 34:2579–2588
- 11. Cushman M, He HM, Lin CM, Hamel E (1993) J Med Chem 36:2817–2821

 Vicini P, Geronikaki A, Incerti M, Busonera B, Poni G, Cabras CA, Colla PL (2003) Bioorg Med Chem 11:4785–4789

(III)

- 13. Patil RD, Adimurthy S (2013) Asian J Org Chem 2:726-744
- 14. Angelici RJ (2013) Catal Sci Technol 3:279-296
- 15. Qin W, Long S, Panunzio M, Biondi S (2013) Molecules 18:12264–12289
- 16. Ryland BL, Stahl SS (2014) Angew Chem Int Ed 53:8824-8838
- Su F, Mathew SC, Mohlmann L, Antonietti M, Wang X, Blechert S (2011) Angew Chem Int Ed 50:657–660
- Chen B, Wang L, Dai W, Shang S, Lv Y, Gao S (2015) ACS Catal 5:2788–2794
- 19. Chen B, Wang L, Gao S (2015) ACS Catal 5:5851-5876
- 20. Blackburn L, Taylor RJK (2001) Org Lett 3:1637-1639
- 21. Tamura M, Tomishige K (2015) Angew Chem Int Ed 54:864-867
- 22. Pohlki F, Doye S (2001) Angew Chem Int Ed 40:2305–2308
- 23. Johnson JS, Bergman RG (2001) J Am Chem Soc 123:2923-2924
- 24. Li Y, Shi Y, Odom AL (2004) J Am Chem Soc 126:1794–1803
- 25. Ryken SA, Schafer LL (2015) Acc Chem Res 48:2576-2586
- Srimani D, Feller M, Ben-David Y, Milstein D (2012) Chem Commun 48:11853–11855
- 27. Chakraborty S, Berke H (2014) ACS Catal 4:2191-2194
- 28. Sheldon RA, Dakka J (1994) Catal Today 19:215–246
- 29. Clark JH (1995) Chemistry of waste minimisation. Chapman and Hall, London
- 30. Hoelderich WF, Heitmann G (1997) Catal Today 8:227-233
- Anastas PT, Bartlett LB, Kirchhoff MM, Williamson TC (2000) Catal Today 55:11–22
- Cejka J, Centi G, Perez-Pariente J, Roth WJ (2012) Catal Today 179:2–15
- 33. Martinez C, Corma A (2011) Coord Chem Rev 255:1558-1580
- 34. Gupta P, Paul S (2014) Catal Today 236:153-170
- 35. Clark JH (2002) Acc Chem Res 35:791–797
- 36. Lok BM, Marcus BK, Angell CL (1986) Zeolites 6:185–194
- Scherzer J (1990) Octane-enhancing zeolitic FCC catalysts. Marcel Dekker, New York
- Mohan KVVK, Reddy KSK, Narender N, Kulkarni SJ (2009) J Mol Catal A 298:99–102
- Mohan KVVK, Narender N, Kulkarni SJ (2007) Micropor Mesopor Mater 106:229–235
- Mohan KVVK, Narender N, Kulkarni SJ (2006) Green Chem 8:368–372
- Naresh M, Swamy P, Reddy MM, Srujana K, Durgaiah C, Narender N (2015) Appl Catal A 505:213–216
- 42. Narender N, Srinivasu P, Kulkarni SJ, Raghavan KV (2000) Green Chem 2:104–105