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A competent pot and atom-efficient synthesis of Betti bases over nanocrystalline MgO involving a modified Mannich type reaction

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ABSTRACT

A simple, efficient, and eco-friendly method for the synthesis of 1-(α-aminoalkyl) naphthols, the Betti bases, has been carried out over a basic nanocrystalline MgO catalyst in aqueous condition. The method has been applied for the synthesis of a range of compounds with variable functionalities in excellent yield and selectivity.

In recent years multicomponent reactions (MCR) have become a powerful tool for atom efficient and waste-free synthesis of complex building blocks of 'drug-like' motifs.[1] Generally MCR strategy affords time and cost advantageous, environmentally benign pathways leading to the synthesis of a library of compounds. In the history of multicomponent one-pot reactions, the Strecker synthesis was the first to be studied leading to α-aminonitriles.[2] Subsequently, there has been a stupendous development of this MCR protocol. Mention may be made of the Biginelli,[3] Passerini,[4] Ugi[5] and Mannich[6] reactions.

Compounds bearing 1,3 arrangements of amino and oxygenated functional groups are frequently found in various biologically active natural products.[7] The importance lies in their capacity to bind Lewis acidic sites making a stable six membered ring. Another important class of such compounds is the 1-(α-aminoalkyl)-2-naphthols, the 'so-called' Betti bases (Fig. 1).[8] These compounds can be transformed into derivatives having antibacterial, hypotensive, and bradycardiac activities.[9] The phenolic hydroxyl, and amino groups can be utilized in developing several synthetic building blocks.[10] Optically active Betti bases can be used as ligands to chelate with organometallic reagents in different reactions to provide highly efficient asymmetric induction.[11] Reaction of Betti bases with aldehydes produces 1,3-oxazines, an important biologically active scaffold.[10,12]

The classical synthesis of Betti bases generally involves a modified Mannich pathway by the condensation of 2-naphthol, aldehydes, and ammonia. However, modifications have been made to prepare Betti base derivatives by using other naphthols, quilinols, and akylamines replacing ammonia.[13] Addition of naphthols to preformed iminium salts has also been carried out.[14] However, these reported methods either take longer reaction time or involve heating conditions. Moreover the catalysts used in these methods are not user friendly and non-recoverable. Recently, Kumar et al. reported an efficient method for the preparation of *N,N*-dialkyl derivatives of Betti bases in a surfactant mediated condition in water.[15] However, there are no reports available for the synthesis of Betti bases over heterogeneous catalysts.

Nanocrystalline metal oxides find excellent application as active adsorbent for gases, for destruction of hazardous chemicals,[16] and as catalyst in various organic reactions.[17] In continuation of our efforts for the development of synthetic methodologies for the

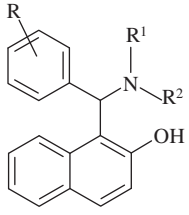

Figure 1. Structure of a general Betti base.

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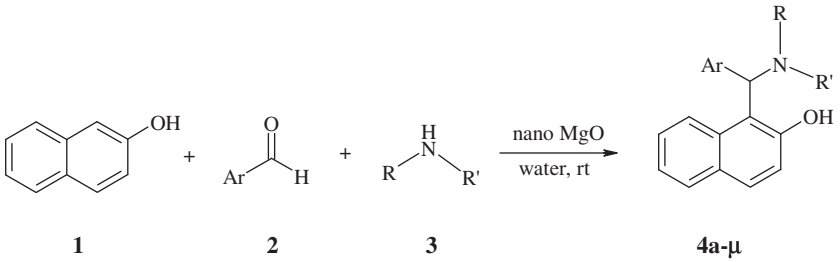


Scheme 1. Synthesis of Betti bases over nanocrystalline MgO catalyst.

Table 1
Screening of solvents in the synthesis of Betti bases[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	THF	8	33
2	CH_3CN	8	72
3	CH_2Cl_2	8	65
4	Toluene	12	57
5	Hexane	12	n.r.
6	Water	2	88

[a] Reactions and conditions: benzaldehyde/pyrrolidine/2-naphthol = 1.2:1.0:1.0, 50 mg catalyst, room temperature.
[b] Isolated yield.

Table 2
Synthesis of Betti bases over nanocrystalline MgO catalyst[a]

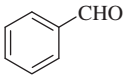
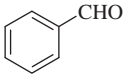
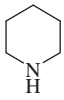
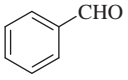
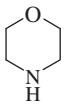
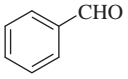
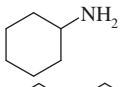
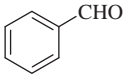
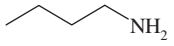
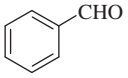
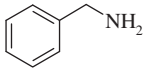
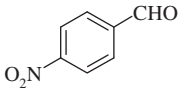
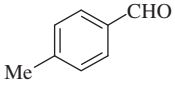
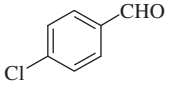
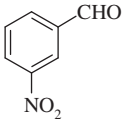
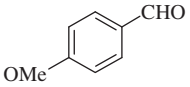
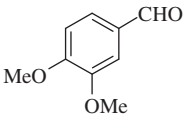
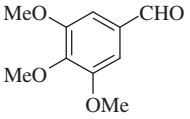
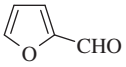
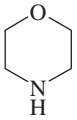
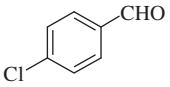
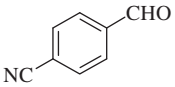
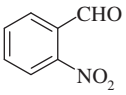
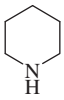
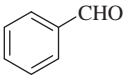
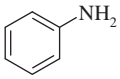
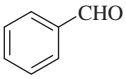
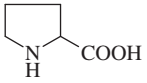
Entry	Aldehyde	Amine	Product	Time (h)	Yield[b] (%)
1			**4a**	2	88
2			**4b**	3	90
3			**4c**	2.5	90
4			**4d**	3.5	85
5			**4e**	3	78
6			**4f**	3	81
7			**4g**	2.5	87
8			**4h**	3.5	84
9			**4i**	3	88
10			**4j**	2	92

Table 2 (*continued*)

Entry	Aldehyde	Amine	Product	Time (h)	Yield[b] (%)
11			**4k**	4	86
12			**4l**	3.5	82
13			**4m**	3	85
14			**4n**	2	90
15			**4o**	3	88
16			**4p**	3	89
17			**4r**	2.5	87
18			**4s**	4	<20
19			**4u**	6	n.r

[a] Reaction and conditions: aldehyde/amine/2-naphthol = 1.2:1.0:1.0, 50 mg MgO, water; rt.
[b] Isolated yield.

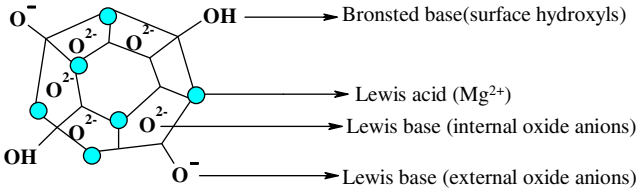


Figure 2. Reactive sites of nanocrystalline MgO.

production of various biologically important moieties using mesoporous heterogeneous catalysts,[18] we wish to report for the first time the use of nanocrystalline MgO catalyzed one-pot three component synthesis of Betti bases and their derivatives in water at ambient conditions (Scheme 1).

A very simple protocol was followed in the reaction process.[19] A mixture of pyrrolidine (1.0 mmol), benzaldehyde (1.2 mmol) and 2-naphthol (1.0 mmol) was stirred in water at room temperature over nanoporous MgO catalyst. The progress was checked by TLC and after work-up excellent yields of the product were obtained. No other additive was necessary to promote the reaction.

However, prior to this generalization, feasibility of the reaction conditions was investigated. Optimization was done with variation of the reaction medium. The results have been summarized in Table 1. The difference in results indicated the influence of solvent on reaction mechanism. Different conventional organic solvents like

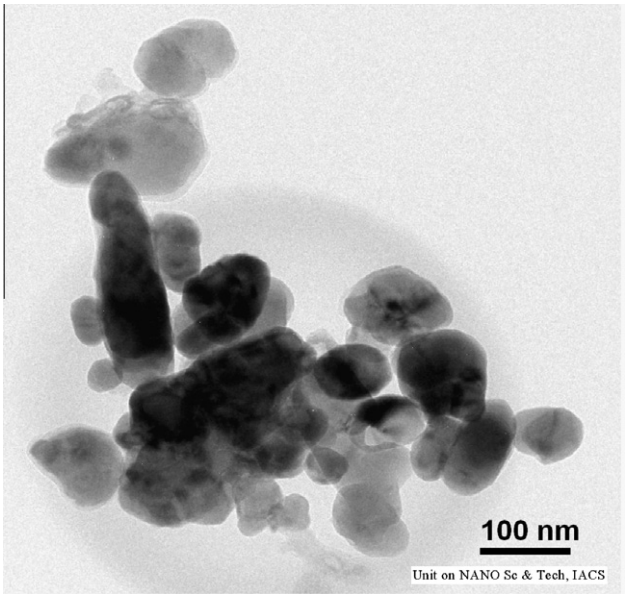


Figure 3. TEM image of the nano MgO.

THF, CH_3CN, CH_2Cl_2, and toluene afforded low to moderate yields (33–72%). In hexane no reaction was observed. The best result was achieved in aqueous condition when it furnished the coupled product in high yield (88%). The reaction failed in the absence of any catalyst. Notably, there was no need for creating an inert atmosphere and the reactions were done at ambient conditions only.

In order to study the scope and limitations of this procedure, a series of reactions were carried out with 2-naphthol using variety of aromatic aldehydes and aliphatic amines. The results have been shown in Table 2. The reactions worked well with almost all the aldehydes. However, aromatic aldehydes bearing groups like $-NO_2$, –CN, –OMe, and –Cl showed better reactivity and the reactions were completed in shorter time. Even the heteroaryl aldehyde, 2-furfural, afforded the desired product in high yield. The same course of the reactions continued with the aliphatic amines which showed excellent reactivity affording very good yields. Surprisingly, the reaction was not successful with aromatic amines which might be due to its reduced nucleophilicity. Similarly, proline also failed to produce the corresponding Betti base. After the reaction the crude reaction mixtures were purified through column chromatography using neutral alumina and appropriate mixtures of EtOAc/hexane as eluent. The isolated products were then characterized from ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis.

Nanocrystalline MgO has a polyhedral crystalline structure containing a number of anionic oxidic Lewis basic (O^{2-}, O^-) and hydroxylic Bronsted basic (OH) sites along with Mg^{2+} as Lewis acid site (Fig. 2). Moreover, the high surface concentrations of edge/corner and various exposed crystal planes (such as 0 0 2, 0 0 1 and 1 1 1), lead to inherently high surface reactivity per unit area. The crystalline nature of the material is evident from the TEM image (Fig. 3). Particle size of the nano MgO[20] was found to be around 20–22 nm. The enhanced surface area due to small particle size is an added advantage for its reactivity. All these important factors are responsible for the high accessibility of the substrate molecules on the catalyst surface. The reaction involves the initial formation of imines by condensation of aldehydes and amines and these then react with 2-naphthol at the α-position following a Mannich type pathway to produce the 1-(α-aminoalkyl)-2-naphthols.

From the context of green chemistry this reaction is highly significant as the reactions are extremely atom-efficient and have been performed in water avoiding the use of harmful organic solvents.

An efficient, clean, step economic, and one-pot procedure for the synthesis of Betti bases has been developed by the three-component coupling of aldehyde, amine, and 2-naphthol over the high surface area of nanocrystalline MgO catalyst under aqueous condition. Mild reaction conditions, short reaction time, excellent yields of the products make this methodology highly significant.

Acknowledgments

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References and notes

1. (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123; (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
2. Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
3. Bose, A. K.; Pednekar, S.; Ganguly, S. N.; Chakraborty, G.; Manhas, M. S. *Tetrahedron Lett.* **2004**, *45*, 8351.
4. Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842.
5. Kobayashi, K.; Matoba, T.; Irisawa, S.; Matsumoto, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1998**, 551.
6. Zhao, G.; Jiang, T.; Gao, H.; Han, B.; Huang, J.; Sun, D. *Green Chem.* **2004**, *6*, 75.
7. Knapp, S. *Chem. Rev.* **1995**, *95*, 1859.
8. Cardellicchio, C.; Capozzi, M. A. M.; Naso, F. *Tetrahedron: Asymmetry* **2010**, *21*, 507.
9. Shen, A. Y.; Tsai, C. T.; Chen, C. L. *Eur. J. Med. Chem.* **1999**, *34*, 877.
10. (a) Szatmari, I.; Hetenyi, A.; Lazar, L.; Fulop, F. *J. Heterocycl. Chem.* **2004**, *41*, 367; (b) Heydenreich, M.; Koch, A.; Klod, S.; Szatmari, I.; Fulop, F.; Kleinpeter, E. *Tetrahedron* **2006**, *62*, 11081.
11. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685.
12. (a) Betti, M. *Gazz. Chim. Ital.* **1900**, *30*, 310; (b) Smith, H. E.; Cooper, N. E. *J. Org. Chem.* **1970**, *35*, 2212.
13. (a) Phillips, J. P.; Barrall, E. M. *J. Org. Chem.* **1956**, *21*, 692; (b) Phillips, J. P. *Chem. Rev.* **1956**, *56*, 271; (c) Saidi, M. R.; Azizi, N.; Naimi-Jamal, M. R. *Tetrahedron Lett.* **2001**, *42*, 8111; (d) Mukhopadhyay, C.; Rana, S.; Butcher, R. J. *ARKIVOC* **2010**, *x*, 291.
14. Katrizky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Belyakov, S. A.; Ghiviriga, I.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 6071.
15. Kumar, A.; Gupta, M. K.; Kumar, M. *Tetrahedron Lett.* **2010**, *51*, 1582.
16. (a) Lucas, E.; Decker, S.; Khaleel, A.; Seitz, A.; Fultz, S.; Ponce, A.; Li, W.; Carnes, C.; Klabunde, K. J. *Chem. Eur. J.* **2001**, *7*, 2505; (b) Schlogl, R.; Abd Hamid, S. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 1628; (c) Bell, A. T. *Science* **2003**, *299*, 1688; (d) Carnes, C. L.; Klabunde, K. J. *Langmuir* **2000**, *16*, 3764.
17. (a) Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahendar, k.; Sreedhar, B. *J. Am. Chem. Soc.* **2004**, *126*, 3396; (b) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167; (c) Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Kantam, M. L. *Tetrahedron Lett.* **2005**, *46*, 1369; (d) Choudary, B. M.; Mahendar, K.; Ranganath, K. V. S. *J. Mol. Catal. A: Chem.* **2005**, *234*, 25; Choudary, B. M.; Mahendar, K.; Kantam, M. L.; Ranganath, K. V. S.; Athar, T. *Adv. Synth. Catal.* **2006**, *348*, 1977; (f) Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K.; Chakrapani, L.; Choudary, B. M. *Tetrahedron Lett.* **2007**, *48*, 7646.
18. (a) Karmakar, B.; Nayak, A.; Chowdhury, B.; Banerji, J. *ARKIVOC* **2009**, *xii*, 209; (b) Postole, G.; Chowdhury, B.; Karmakar, B.; Pinki, K.; Banerji, J.; Auroux, A. *J. Catal.* **2010**, *269*, 110; (c) Karmakar, B.; Chowdhury, B.; Banerji, J. *Catal. Commun.* **2010**, *11*, 601; (d) Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2010**, *51*, 3855; (e) Karmakar, B.; Sinhamahapatra, A.; Panda, A. B.; Banerji, J.; Chowdhury, B. *Appl. Catal. A: Gen.* **2010**, *392*, 111.
19. *Representative experimental procedure*: A mixture of 2-naphthol (1.0 equiv), amine (1.0 equiv), and aldehyde (1.2 equiv) was stirred at room temperature in water in presence of 50 mg MgO catalyst for certain period as indicated in Table 2. After completion of the reaction as indicated by TLC (After elusion the silica gel precoated aluminum plates were visualized under UV light and charred in alkaline $KMnO_4$ solution), the reaction mixture was extracted with ethyl acetate (3×10 mL). The extract was concentrated under reduced pressure and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (6–10%) as eluent. The isolated compounds were characterized by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (C, H, and N). Spectral data of some representative products are provided below.
l-(α-N-pyrrolidobenzyl)-2-naphthol (**4a**, entry1, Table 2). White solid; mp 180 °C; IR (KBr): 3449.9, 2967.0, 1841.3, 1510.3, 1591.8, 1456.9, 1236.0, 1095.6, 950.5, 823.5, 748.8, 699.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.83 (br s, 4H), 2.3–2.5 (m, 4H), 5.11 (s, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.16–7.25 (m, 5H), 7.34 (1H, J = 7.7 Hz, 1H), 7.58 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.67 (d, J = 9.3 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.4, 53.5, 70.8, 116.6, 119.9, 121.09, 122.36, 126.37, 127.85, 128.49, 128.59, 128.69, 128.87, 129.5, 131.87, 141.15, 155.5; Anal. Calcd for $C_{21}H_{21}NO$: C, 83.17; H, 6.93; N, 4.62. Found: C, 83.08; H, 6.87; N, 4.69.
l-(α-N-butylaminobenzyl)-2-naphthol (**4e**, entry 5, Table 2). Crystalline white solid; mp 131–133 °C; IR (KBr): 3311.9, 3054.6, 2922.9, 1592.9, 1460.3, 1238.1, 1085.8, 975.8, 827.9, 747.8, 698.8 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (m, 3H), 1.39 (m, 2H), 1.55–1.66 (m, 2H), 2.8–2.86 (m, 2H), 3.64 (m, 1H), 5.68 (s, 1H), 7.14 (d, J = 9.04 Hz, 1H), 7.24–7.29 (m, 5H), 7.31 (m, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.47–7.74 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.85, 20.32, 48.96, 64.42, 109.4, 113.4, 120.12, 121.14, 122.35, 123.32, 126.39, 127.73, 128.06, 128.26, 128.6, 128.82, 129.09, 129.63, 130.54, 141.7, 156.84; Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.71; H, 7.53; N, 4.51.
20. *Procedure for the synthesis of nanocrystalline MgO*: The catalyst was prepared by non-hydrothermal sol-gel approach. Anhydrous $MgCO_3$ was used as the Mg source. The salt was dissolved in triethanolamine solvent with stirring at room temperature. Deionised water was added dropwise to form a gel. Then triethyl ammonium hydroxide was added to the mixture to maintain a pH of 12. This was aged at room temperature for 24 h to obtain a white gel. The gel was dried at 120 °C for another 24 h and finally the cake was calcined at 600 °C for 12 h to obtain a fine white powder.