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Synthesis of 1,2-Disubstituted Benzimidazoles in the Presence of SBA-Pr-SO_3H as a Nano Solid Acid Catalyst

G. Mohammadi Ziarani,[*1] A. Badiei,[2] M. Shakiba Nahad,[1] S. Ghadim Alizadeh[1]

[1]*Department of Chemistry, Alzahra University, Tehran, Iran*

[2]*School of Chemistry, College of Science, University of Tehran,Tehran, Iran*

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**Corresponding author:*
E-mail address*:*
gmziarani@hotmail.com,
gmohammadi@alzahra.ac.ir.

Phone: 98 88041344
Fax: +98 2188041344

Abstract

In this article, simple, convenient synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzimidazole (1,2-disubstituted benzimidazoles) via condensation of 1,2-phenylenediamine and aromatic aldehydes using SBA-Pr-SO_3H as a nanoporous solid acid catalyst in green protocol was reported.

1. Introduction

Synthesis of benzimidazole ring system has attracted a great deal of attention because of its biological activities such as local anesthetic, antipyretic, antihistaminic [1], fungicidal, antihypertensive, antidiabetic, sedative, antimicrobial, antifungal, antiparkinson, anticancer, antibiotic [2]. They can act as lowering blood sugar level, inhibitor of kasin kinase-2 (CK-

2) and phosphodiesterase-5 (PDE-5). Also some anthelmintic drugs such as albendazole [3] and mebendazole [4] have benzimidazole scaffold. Tilomisole as a thiabenzimidazole derivative has demonstrated immunomodulatory, anti-inflammatory and antimetastatic activity (Fig. 1) [5].

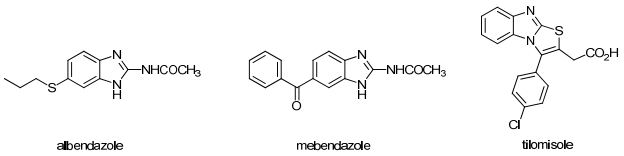


Fig. 1. Some benzimidazole drugs

Conventionally 1,2-disubstituted benzimidazoles are synthesized by the condensation of *o*-phenylendiamine and a carboxylic acid or its derivatives (nitriles, amidates, orthoesters) under harsh dehydrating conditions [6]. Other synthetic protocols involve N-alkylation of 2-substituted benzimidazole [7] and N-alkylation of *o*-nitroanilides followed by reductive cyclization [8]. Various catalyst such as YCl_3 [9], oxalic acid [10], $FePO_4$ [11], bismuth trifluoromethanesulphonate [12], silica sulfuric acid [6], silica phenyl sulfonic acid [13], HCl-Treated trans-3,5-Dihydroperoxy-3,5-dimethyl-1,2-dioxolane [14], TsOH/graphite, *N,N*-dimethylaniline/graphite [15], SBA-15-supported poly (4-styrenesulfonyl-perfluorobutylsulfonyl) imide [7], Amberlite IR-120 [16], P_2O_5/SiO_2 [17] were used in this synthesis. In this paper, we want to report the application of SBA-Pr-SO_3H as a highly active, nanoporous heterogeneous acid catalyst in the preparation of 1,2-disubstituted benzimidazoles. The heterogeneous catalysts can conveniently be removed from the reaction mixture, making the experimental procedure simple and ecofriendly [18]. SBA-Pr-SO_3H has mesoporous silica structure with pore size of 6 nm which can act as reactive nanoreactor in organic synthesis [19]. We have been used SBA-Pr-SO_3H in the synthesis of polyhydroquinolines derivatives [20], quinoxaline derivatives [21], Triazoloquinazolinones and benzimidazoquinazolinones [18].

2. Experimental procedure

General information

2.1. General procedure for the synthesis of SBA-15

In a typical synthesis batch, triblock copolymer surfactant as a template (P123 = EO20PO70EO20, Mac = 5800) (4.0 g) was dissolved in 30 g of water and 120 g of 2 M HCl solution. Then, TEOS (tetraethylorthosilicate) (8.50 g) was added to reaction mixture which was stirred for 8 h at 40 °C. The resulting mixture was transferred into a Teflon-lined stainless steel autoclave and kept at 100 °C for 20 h without stirring. The gel composition P123 : HCl : H_2O : TEOS was 0.0168:5.854:162.681:1 in molar ratio. After cooling down to room temperature, the product was filtered, washed with distilled water and dried overnight at 60 °C in air. The as-synthesized sample was calcinated at 550 °C for 6 h in air atmosphere to remove the template.

2.2. Functionalization of SBA-15 by organic groups

Functionalization of the SBA-15 catalyst was schematically shown in Fig 2. The calcinated SBA-15 (2 g) and (3-mercaptopropyl) trimethoxysilane (10 ml) in dry toluene (20 ml) were refluxed for 24 h. The product was filtered and extracted for 6 h in CH_2Cl_2 using a soxhlet apparatus, then dried under vacuum. The solid product was oxidized with H_2O_2 (excess) and one drop of H_2SO_4 in methanol (20 ml) for 24 h at rt and then the mixture was filtered and washed with H_2O, and acetone. The modified

SBA-15-Pr-SO_3H was dried and used as nanoporous solid acid catalyst in the following reactions [21].

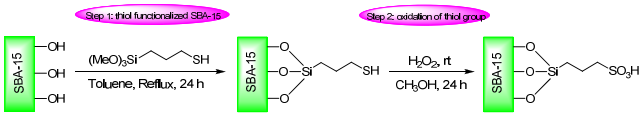


Fig. 2. Schematic illustration for the preparation of SBA-Pr-SO_3H

2.3. General procedure for the preparation of 2-aryl-1-arylmethyl-1-H-1,3-benzimidazoles

The SBA-Pr-SO_3H (0.02 g) was activated in vacuum at 100 °C and then after cooling to room temperature, an aromatic aldehyde (2 mmol) and 1,2-phenylendiamine (1 mmol, 0.11gr) was added. The mixture was stirred at room temperature under solvent free conditions for an appropriate time according Table 1. After completion of reaction that was indicated by TLC (n-hexane/EtOAc, 3/1), the crude product was dissolved in hot convenient solvent (Table 1), the heterogeneous solid catalyst was removed easily by simple filtration and after cooling of the filtrate, the pure crystals of products were obtained. The acid catalyst can be reactivated by simple washing subsequently with diluted acid solution, water and acetone, dried under vacuum and re-used for several times without loss of significant activity.

2.4. Spectral data of products

1 -(4-Hydroxybenzyl)-2-(4-hydroxyphenyl)-1H-1,3-benzimidazole ***(3g):*** IR (KBr):3295, 1610, 1513, 1441, 1391, 1245 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ = 7.67-7.70 (d, 2H), 7.50-7.54 (d, 2H), 6.70-6.91 (m, 4H), 5.37 (s, 2H), 4.20 (s, 1H), 3.51-3.59 (q, 1H).

1-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-1H-1,3-benzimidazole ***(3i):*** IR (KBr):1607, 1588, 1513, 1377, 1258 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ = 7.78-7.87 (d, 2H), 7.69-7.73 (d, 1H), 7.54 (s, 1H), 7.15-7.41 (m, 4H), 6.65-6.90 (d, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H).

2.5. Instruments

GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 egilent. IR spectra were obtained with a brucker 500 scientific spectrometer. Products were recorded on a FT-NMR Bruker 250 MHz. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. SEM analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at16 kV while TEM was carried out on a Tecnai G^2 F30 at 300 kV.

3. Results and discussion

In this paper, the condensation of 1,2-phenylendiamine **(1)** with aromatic aldehydes **(2)** in the presence of SBA-Pr-SO_3H as nanoporous solid acid catalyst in solvent free conditions at room temperature for the preparation of some 1,2-disubstituted benzimidazoles **(3)** has been studied (Fig. 3). The reactions were completed in 10-52 min. After completion of the reaction (monitored

Table 1: SBA-Pr-SO_3H catalyzed the synthesis of 1,2-disubstituted benzimidazoles under solvent free condition.

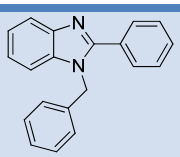
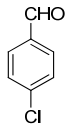
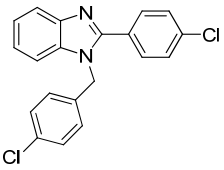
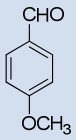
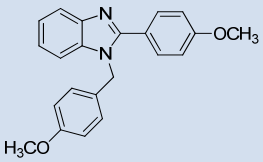
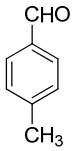
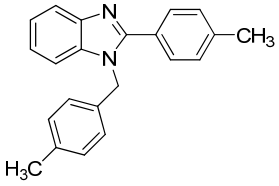
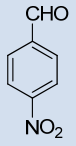
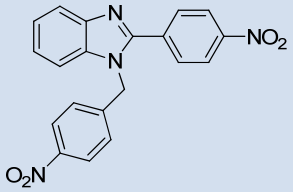
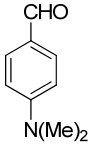
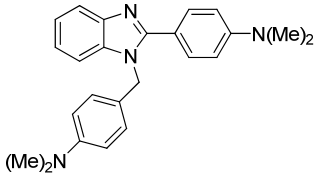
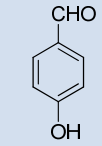
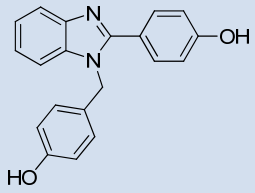
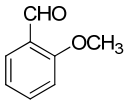
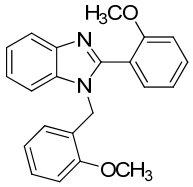
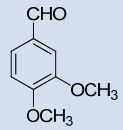
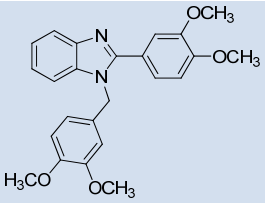
Entry	Aldehyde	Product	Time (min)	Yield %	Crystallization solvent	mp (°C)	mp (Lit)	Ref.
1		 **3a**	25	88	MeOH/ EtOAc	130-132	132	[22]
2		 **3b**	20	85	EtOAc	262-265	262-265	[23]
3		 **3c**	15	75	EtOAc	129-131	129-130	[24]
4		 **3d**	35	75	MeCN	128-130	128-130	[24]
5		 **3e**	17	80	EtOH	191-193	190-192	[17]
6		 **3f**	52	87	EtOAc	252-253	250-252	[24]

Table 1: SBA-Pr-SO_3H catalyzed the synthesis of 1,2-disubstituted benzimidazoles under solvent free condition (continued).

Entry	Aldehyde	Product	Time (min)	Yield %	Crystallization solvent	mp (°C)	mp (Lit)/Ref
7		 **3g**	10	90	EtOH	250-252	250-253 [25]
8		 **3h**	10	85	MeOH	149-151	149-152 [26]
9		 **3i**	40	75	EtOH	235	235-236 [23]

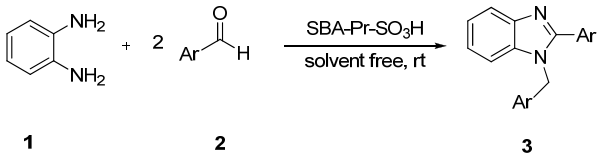


Fig. 3. Synthesis of 2-aryl-1-arylmethyl-1-H-1,3-benzimidazoles using SBA-Pr-SO_3H.

by TLC), the crude product was dissolved in convenient solvent (Table 1) and the heterogeneous solid catalyst was removed easily by simple filtration, and after cooling of the filtrate, the pure crystals of products were obtained. In all the studied cases, the 1,2-disubstituted benzimidazoles were selectively obtained in good to excellent yields by the reaction with various aromatic aldehydes in the presence of SBA-Pr-SO_3H under solvent free condition. The reaction results were reported in Table 1. We examined various aldehydes with electron-donating and electron-withdrawing substituent. Results indicated that the reaction time was decreased with more electron withdrawing substituent such as $–NO_2$ (Table 1, entries 5) and increased with more electron-donating substituent such as $–N(Me)_2$ and $–OCH_3$ (Table 1 entries 6, 9).

The products were characterized by IR and NMR spectroscopy data. Melting points are compared with reported values in literature.

The suggested mechanism (Fig. 4) for the SBA-

Table 2: Efficiency Comparison of various catalysts in the synthesis of 1,2-di substituted benzimidazoles.

Entry	Catalyst	Solvent	Conditions/ Tem (°C)	Time (min)	Yield	Ref.
1	Mesoporous mixed metal oxide nano catalyst of Al_2O_3-Fe_2O_3, Al_2O_3-V_2O_5, Al_2O_3-CuO	Free	M.W/109	0.75-1.5	88-94	[27]
2	Mesoporous mixed metal oxide nano catalyst of Al_2O_3-Fe_2O_3, Al_2O_3-V_2O_5, Al_2O_3-CuO	CH_3CN	r.t.	10-45	78-90	[28]
3	TsOH-SiO_2	EtOAc	60-70	5-30	76-99	[28]
4	Acetic acid/O_2	-	M.W/50	4-8	75-98	[25]
5	Acetic acid/O_2	-	Reflux/80	20-60	52-92	[26]
6	[Hmim]TFA	free	r.t.	1-5 h	78-93	[24]
7	[Hmim]TFA	water	r.t.	10-20	76-95	[25]
8	Silica Sulphoric acid	ethanol	r.t./20	1-2 h	67-95	[6]
9	Silica Sulphoric acid	water	r.t./20	1.5-3h	60-90	[6]
10	**SBA-Pr-SO_3H**	**free**	**r.t.**	**10-52 min**	**75-90**	**This work**

TsOH-SiO_2: *p*-toluenesulfonic acid adsorbed on silica gel
[Hmim]TFA:1-methylimidazoliumtriflouroacetate

Pr -SO_3H catalyzed transformation is shown in Fig. 2. At first, the solid acid catalyst protonates the carbonyl group of aromatic aldehyde **(2)** which then condense with 1,2-phenylendiamine **(1)** to produce dibenzylidene-1,2-phenylenediamine **(4)**. In the presence of catalyst, ring closure produces five membered ring **(5)** which produced 1,2-disubstituted benzimidazoles **(3)** by deprotonation and [1, 3] hydrid shift [23, 29].

The synthesis of 1,2-disubstituted benzimidazoleswere reported with several catalysts and solvents in literature as shown in Table 2. In contrast with other existing methods, the present methodology offers several advantages such as excellent yields, easy synthesis, a simple procedure, simple work-up and greener conditions.

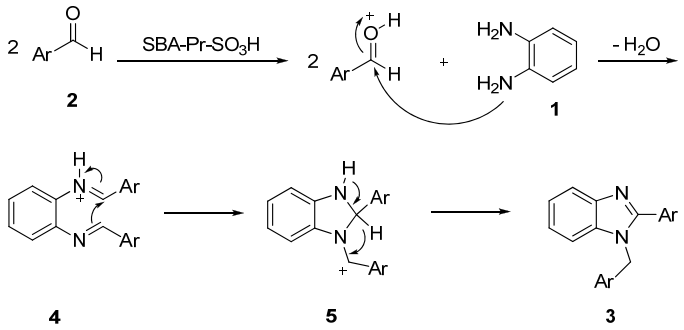
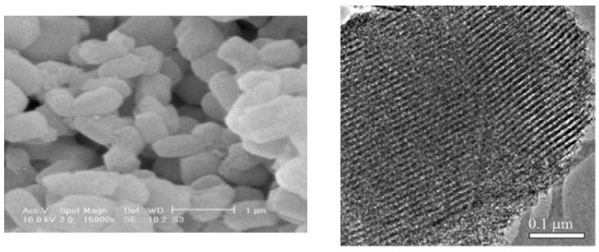


Fig. 4. Proposed mechanism for the synthesis of 2-aryl-1-arylmethyl-1-H-1,3-benzimidazoles.

Preparation of catalyst: The SBA-15 as a new nanoporous silica can be prepared by using commercially available triblock copolymer Pluronic P126 as a structure directing agent. Integration of acidic functional groups (e.g., –SO_3H) into SBA-15 has been explored to produce promising solid acids. The calcined SBA-15 silica

was functionalized with (3-mercaptopropyl)tri-methoxysilane (MPTS) and then, the thiol groups were oxidized to sulfonic acid by hydrogen peroxide. The surface of catalyst was analyzed by different methods such as TGA, BET and CHN methods which demonstrated that the organic groups (propyl sulfonic acid) were immobilized into the pore [18]. The SEM and TEM images of SBA-Pr-SO_3H illustrate in Figure 5. Figure 5 (a) shows SEM image of SBA-Pr-SO_3H that indicates uniform particles about 1 µm. The TEM image (Figure 5 (b)) represents the parallel channels which were not collapsed during two step reactions. In general, organic functionalization did not alter the long-range mesoporous arrangement.



a b

Fig.5. SEM image (a) TEM image (b) of SBA-Pr-SO_3H

The efficiency of SBA-Pr-SO_3H is attributed to the nanoporous structure of this solid acid catalyst, which could act as nano-reactor (Fig. 6).

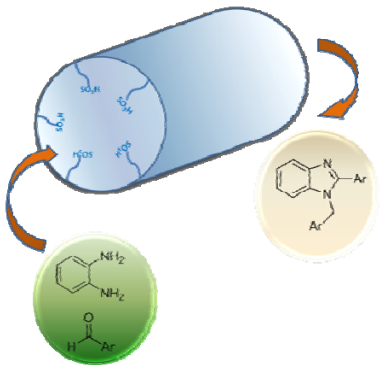


Fig. 6. SBA-Pr-SO_3H acts as a nano-reactor.

4. Conclusion

In summary, this paper describes clean and simple one-pot reaction for the synthesis of synthesis of 2-aryl-1-aryl-methyl-1-H-1,3-benzimi-dazole derivativescatalyzed by SBA-Pr-SO_3H as a solid nano catalyst in green conditions.It is worthy of mention thatoperational simplicity, simple separation of catalyst, high yields and short reaction time are the notable features of these one-pot reactions leading to the synthesis of heterocyclic compounds.

Acknowledgment

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References

1. S. Perumal, S. Mariappan, S. Selvaraj. ARKIVOK, viii (2004) 46-51.
2. P. Sharma, A. Kumar, M. Sharma. Catalysis Communications, 7 (2006) 611-617.
3. F. Hernández-Luis, R. Castillo, L. Yépez-Mulia, R. Cedillo-Rivera, G. Martínez-Vázquez, R. Morales-Hurtado, H. Jung, M. Sánchez, A. Hernández-Campos, N. Viveros, O. Muñoz. Bioorganic and Medicinal Chemistry Letters, 6 (1996) 2231-2236.
4. G. Navarrete-Vázquez, L. Yépez, A. Hernández-Campos, A. Tapia, F. Hernández-Luis, R. Cedillo, J. González, A. Martínez-Fernández, M. Martínez-Grueiro, R. Castillo. Bioorganic and Medicinal Chemistry, 11 (2003) 4615-4622.
5. S. C. Gilman, R. P. Carlson, J. F. Daniels, L. Datko, P. R. Berner, J. Chang, A. J. Lewis. International Journal of Immunopharmacology, 9 (1987) 9-16.

6. P. Salehi, M. Dabiri, M. A. Zolfogol, S. Otokesh, M. Baghbanzadeh. Tetrahedron Letters, 47 (2006) 2557-2560.
7. Z.-H. Ma, S. Lin, J. Nie. Synthetic Communications, 42 (2011) 506-515.
8. K. Takeuchi, J. A. Bastian, D. S. Gifford-Moore, R. W. Harper, S. C. Miller, J. T. Mullaney, D. J. Sall, G. F. Smith, M. Zhang, M. J. Fisher. Bioorganic and Medicinal Chemistry Letters, 10 (2000) 2347-2351.
9. L.-J. Zhang, J. Xia, Y.-Q. Zhou, H. Wang, S.-W. Wang. Synthetic Communications, 42 (2011) 328-336.
10. N. D. Kokare, J. N. Sangshetti, D. B. Shinde. Synthesis, 2007 (2007) 2829,2834.
11. F. K. Behbahani, P. Ziaei. Chinese Journal of Chemistry, 30 (2012) 65-70.
12. J. S. Yadav, B. V. S. Reddy, K. Premalatha, K. S. Shankar. Canadian Journal of Chemistry, 86 (2008) 124-128.
13. H. Veisi, A. Sedrpoushan, M. A. Zolfigol, F. Mohanazadeh. Journal of Heterocyclic Chemistry, 48 (2011) 1448-1454.
14. D. Azarifar, K. Khosravi, Z. Najminejad, K. Soleimani. Heterocycles, 81 (2010) 2855-2863.
15. H. Sharghi, O. Asemani, S. M. H. Tabaei. Journal of Heterocyclic Chemistry, 45 (2008) 1293-1298.
16. S. D. Sharma, D. Konwar. Synthetic Communications, 39 (2009) 980-991.
17. H. R. Shaterian, N. Fahimi, K. Azizi. Chinese Journal of Chemistry, 29 (2011) 2389-2393.
18. G. Mohammadi Ziarani, A. Badiei, Z. Aslani, N. Lashgari. Arabian Journal of Chemistry, *IN PRESS*.
19. K. Bahrami, M. M. Khodaei, P. Fattahpour. Catalysis Science and Technology, 1 (2011) 389-393.
20. G. Mohammadi Ziarani, A. R. Badiei, Y. Khaniania, M. Haddadpour, Iranian Journal of Chemistry and Chemical Engineering, 29 (2010) 1-10.
21. G. M. Ziarani, A. Badiei, M. Haddadpour. International Journal of Chemistry, 3 (2011) 87-94.
22. N. Iravani, N. Safikhani Mohammadzade, K. Niknam. Chinese Chemical Letters, 22 (2011) 1151-1154.
23. G. Mohammadi Ziarani, A. Badiei, M. Hassanzadeh. International Journal of Applied Biology and Pharmceutical Technology, 2 (2011) 48-54.
24. M. Dabiri, P. Salehi, M. Baghbanzadeh, M. Shakouri Nikcheh. Synthetic Communications, 38 (2008) 4272-4281.
25. D. Azarifar, M. Pirhayati, B. Maleki, M. Sanginabadi, R. Nejat Yami. Journal of the Serbian Chemical Society, 75 (2010) 1181-1189.
26. Y. S. Beheshtiha, M. M. Heravi, M. Saeedi, N. Karimi, M. Zakeri, N. Tavakoli-Hosseini. Synthetic Communications, 40 (2010) 1216-1223.
27. P. Bandyopadhyay, M. Sathe, G. K. Prasad, P. Sharma, M. P. Kaushik. Journal of Molecular Catalysis A: Chemical, 341 (2011) 77-82.
28. M. Chakrabarty, R. Mukherjee, S. Karmakar, Y. Harigaya. Monatshefte fur Chemie, 138 (2007) 1279-1282.
29. R. D. Viirre, G. Evindar, R. A. Batey. Journal of Organic Chemistry, 73 (2008) 3452-3459.