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Application of sulfonic acid functionalized nanoporous silica (SBA-Pr-SO_3H) in the solvent free synthesis of (*E*)-arylidene-1,3-dihydroindole-2-ones

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ABSTRACT

An efficient and green condensation reaction is developed for the synthesis of (*E*)-arylidene-1,3-dihydroindole-2-ones; (1), using heterogeneous nanoporous acid catalyst of SBA-Pr-SO_3H with pore size, 6 nm in solvent free condition. Arylidene-1,3-dihydroindole-2-ones have many pharmaceutical properties such as Tyrosin kinase inhibiton. This method has the advantages of short reaction time, isolation ease of the products, excellent yields and recyclable catalyst.

1. Introduction

Mesoporous silica SBA-15 was first synthesized by Zhao *et al.* in 1998 [1,2]. These materials have attracted vast interest since then due to their potential applications as catalyst support [3], adsorbents as well as nanoreactors for making an ordered crystalline alumina molecular sieves [4,5]. SBA-15 is nanoporous silica with a hexagonal structure, excellent stability (chemical and thermal), good accessibility due to high surface areas, large pore size, high selectivity, and isolation ease of the products [6,7]. Sulfonic acid functionalized nanoporous silica (SBA-Pr-SO_3H) as a green and heterogeneous nano catalyst with noncorrosive properties was prepared by the functionalization of SBA-15 [8,9]. Homogenous acid catalysts such as H_2SO_4, HF, and $AlCl_3$ have serious hazards in handling, corrosiveness, difficult separation, and production of toxic waste [7]. SBA-Pr-SO_3H has applied in the synthesis of triazoloquinazolinones and benzimidazoquinazolinones [9], polyhydroquinolines [10], Etherification of benzyl alcohols [7], quinoxaline derivatives [11] and esterification of glyceroles for monoglycride production, oxidation of sulfides into sulfoxides [6].

(*Z*)- and (*E*)-arylidene-1,3-dihydroindole-2-ones, **1**, have many pharmaceutical properties such as tyrosin kinase inhibition [12-16], phosphodiesteras inhibition [17], anti-rhematic agent [18], and are also selective inhibitors of *Plasmodium falciparum* cyclin dependent protein kinase [19]. In the literature, some methods for the synthesis of these compounds have been reported using different conditions such as microwave radiation [20], Brønsted acidic ionic liquid [21], piperidine in ethanol [12,14,22,23], and pyrrolidine in benzene [24]. We decided to report the application of SBA-Pr-SO_3H as a highly active nano-acid catalyst in the efficient and green synthesis of arylidene-1,3-dihydroindole-2-ones.

2. Experimental

2.1. Instrumentation

The chemicals employed in this work were obtained from Merck Company and were used with no purifications. IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ^1H NMR (500 MHz) was run on a Bruker DPX. GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent. Weight change curve in nitrogen was measured on a TA instrument of TGA Q50 V6.3 with maximum heating rate of 20 ^oC/min. Nitrogen adsorption and desorption isotherms were measured at -196 ^oC using a Japan Belsorb II system after the samples were vacuum dried at 150 ^oC overnight. SEM analysis was performed on a PhilipsXL-30 field-emission scanning electron microscope operated at 16 kV while TEM was carried out on a Tecnai G^2 F30 at 300 kV.

2.2. Preparation of SBA-15

The synthesis of SBA-15 was carried out in accordance to the earlier reports [1,2]. In a typical synthesis batch, triblock copolymer surfactant as a template (P123 = $EO_{20}PO_{70}EO_{20}$, 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 ^oC. The resulting mixture was transferred into a Teflon-lined stainless steel autoclave and kept at 100 ^oC for 20 h without stirring. The gel composition P123:HCl:H_2O:TEOS was 0.0168:5.854:162.681:1 in molar ratio.

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Table 1. SBA-Pr-SO_3H catalyzed the synthesis of (*E*)-arylidene-1,3-dihydroindole-2-ones under solvent free condition.

No	Product	R	Time (h)	Temp (°C)	Yield (%)	M.p. (°C)	M.p. Lit. (°C)
1	1a	H	1.0	120	90	178-180	175-176 [21,25]
2	1b	2´-OCH_3	1.5	120	65	221-224	221-222 [22]
3	1c	3´-OCH_3	6.0	120	40	150-152	151-152 [22]
4	1d	4´-OCH_3	1.0	120	86	162-165	159-160 [25]
5	1e	2´,3´-$(OCH_3)_2$	2.0	120	81	184-186	New
6	1f	4´-OH	1.0	120	71	295-297	299 [26]
7	1g	4´-$N(CH_3)_2$	1.5	120	50	225-227	230-233 [27]
8	1h	4´-Cl	1.5	120	58	178-181	188-190 [25]
9	1i	2´,3´-$(Cl)_2$	1.0	120	77	220-224	New
10	1j	3´-NO_2	0.5	120	90	203-204	209-210 [21]

Table 2. The optimization of reaction conditions in the synthesis of **1j**.

No	Solvent	Time (h)	Temp (°C)	Yield (%)
1	EtOH	9	80	60
2	H_2O	N.R.	100	-
3	CH_3CN	24	80	27
4	Solvent free	0.5	120	90

N.R. = No Reaction.

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.

2.2.1. Functionalization of SBA-15 with organic group

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 room temperature 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.

2.2.2. General procedure for the preparation of (E)-arylidene-1,3-dihydroindole-2-ones

The SBA-Pr-SO_3H (0.02 gr) was activated in vacuum at 100 °C and then after cooling of catalyst to room temperature, oxindole (0.133 g, 1 mmol) and aryl aldehydes (1 mmol) were added to it. The mixture was heated in oil bath (120 °C) in appropriate time as shown in Table 1. After completion of the reaction which monitored by Thin layer chromatography (TLC), the crude product was dissolved in hot ethanol and then filtered for removing the solid catalyst. Filtrate was cooled to give the pure product. The solid acid catalyst subsequently was washed with diluted acid solution, distilled water and then acetone, dried under vacuum that it can be used for several times without loss of significant activity.

E-3-benzylideneindolin-2-one (**1a**): Color: Yellow. Yield: 90%. M.p.: 178-180 °C. FT-IR (KBr, ν, cm^{-1}): 3150 and 3078 (NH) (amide), 1707 (C=O) (amide), 1614, 1462 and 1361 (C=C). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 6.89 (m, 2H, Ar-H), 7.22 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.48 (m, 3H, Ar-H), 7.65 (dd, *J* = 7.70 Hz, 6.95 Hz, 3H, Ar-H), 7.86 (s, 1H, C=CH-), 8.3 (bs, 1H, NH). MS (EI, *m/z* (%)): 221 (M^+, 100), 220 (75), 193 (30), 165 (25).

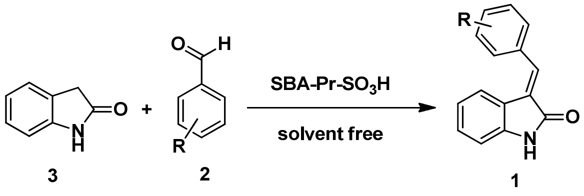
E-3-(2-methoxybenzylidene)indolin-2-one (**1b**): Color: Yellow. Yield: 65%. M.p.: 221-224 °C. FT-IR (KBr, ν, cm^{-1}): 3139 and 3073 (NH) (amide), 2950 and 2834 (CH_3-O), 1699 (C=O) (amide), 1609 and 1461 (C=C), 1228 (C-O-C). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.89 (s, 3H, CH_3), 6.85 (d, *J* = 0.95 Hz, 1H, Ar-H), 6.87 (d, *J* = 0.95 Hz, 1H, Ar-H), 7.00 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.04 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.2 (td, *J* = 1.0 Hz, 7.6 Hz, 1H, Ar-H), 7.27 (s, 1H, C=CH-), 7.44 (td, *J* = 1.8 Hz, 7.8 Hz, 1H, Ar-H), 7.58 (d, *J* = 7.7 Hz, 1H Ar-H), 7.74 (dd, *J* = 7.5 Hz, 1H Ar-H), 7.99 (s, 1H, NH). MS (IE, *m/z* (%)): 252 (15), 251 (M^+, 90), 221(40), 220 (100).

E-3-(2,3-dimethoxybenzylidene)indolin-2-one (**1e**): Color: Yellow. Yield: 81%. M.p.: 184-186 °C. FT-IR (KBr, ν, cm^{-1}): 3183 and 3079 (NH) (amide), 2955 and, 2834 (CH_3-O), 1705 (C=O) (amide), 1611, 1580, 1462 (C=C). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.9 (d, 6H, CH_3), 6.85 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.0 (dd, *J* = 34.7 Hz, 7.65 Hz, 2H, Ar-H), 7.14 (t, *J* =7.8 Hz, 1H, Ar-H), 7.21 (t, *J* = 7.55 Hz, 1H, Ar-H), 7.31 (d, *J* = 7.55 Hz, 1H, Ar-H), 7.53 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.98 (s, 1H, C=CH-), 9.34 (s, 1H, NH). MS (IE, *m/z* (%)): 281 (M^+, 20), 251 (30%), 250 (100), 235 (15).

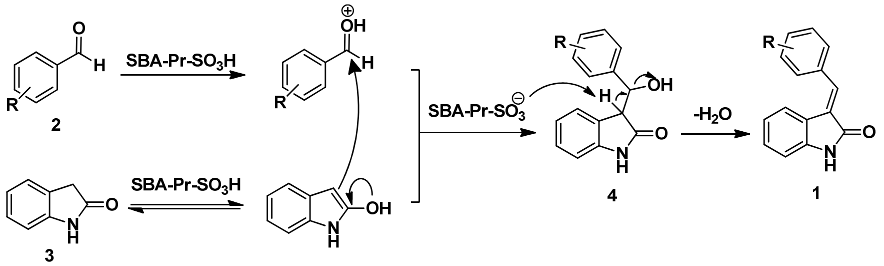
E-3-(2,3-dichlorobenzylidene)indolin-2-one (**1i**): Color: Yellow. Yield: 77%. M.p.: 220-224 °C. FT-IR (KBr, ν, cm^{-1}): 3447 and 3182 (NH) (amide), 1709 (C=O) (amide), 1617, 1553, 1466, 1409 (C=C). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 6.85 (t, *J* = 7.75 Hz, 1H, Ar-H), 6.90 (d, *J* = 7.65 Hz, 1H, Ar-H), 7.3 (m, 3H, Ar-H), 7.6 (dd, *J* = 7.65 Hz, 7.45 Hz, 2H, Ar-H), 7.82 (s, 1H, C=CH-), 8.2 (bs, 1H, NH). MS (IE, *m/z* (%)): 290(M+2, 2), 289 (M+, 5), 256 (30), 254 (100), 219 (5), 190 (8).

3. Result and discussion

In this paper, the condensation of aromatic aldehydes, **2**, with oxindole, **3**, in the presence of nanoporous solid acid catalyst (SBA-Pr-SO_3H) has been studied (Scheme 1). As shown results in Table 2, among the tested solvents such as CH_3CH_2OH, H_2O, CH_3CN and solvent free system, the best results were obtained after 0.5 hour in the solvent free condition in excellent yield. The high yields of reactions are attributed to the effect of nanopore size about 6 nm of solid acid catalyst, which could act as nano-reactor (Figure 1). Therefore, this reaction was developed with different aldehydes and the results were summarized in the Table 1. The reaction time was 0.5-2.0 h and high yields of products were obtained. The acid catalyst was separated from the crude products and reactivated by simple washing subsequently with diluted acid solution, water and acetone, and then reused without noticeable loss of reactivity. The new products were characterized by IR and NMR spectroscopy data. Melting points are compared with reported values in the literature as shown in Table 1.



Scheme 1



Scheme 2

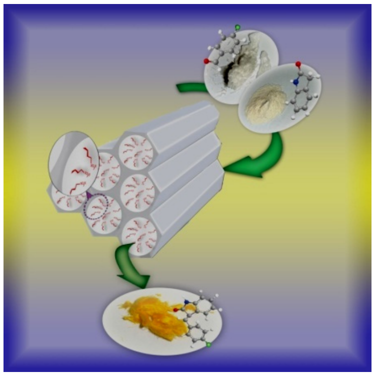


Figure 1. SBA-Pr-SO_3H acts as a nano-reactor.

The suggested mechanism for the SBA-Pr-SO_3H catalyzed condensation was shown in Scheme 2. Concerning the reaction **3** mechanism, we suggest that initially, the solid acid catalyst protonates the carbonyl group of aldehydes, **2**, and then condenses with oxindole **3** to give the adduct product which is converted to target molecule **1** by losing of H_2O.

After finishing of reaction, the filtrated solid acid catalyst was subsequently washed with diluted acid solution, distilled water and then acetone, dried under vacuum. As it is shown in Table 3, after recycling of SBA-Pr-SO_3H, no significant decrease in its activity up to five runs was observed.

Table 3. Reusability of the catalysts in the synthesis of **1j**.

Entry	Number of recycle	Yield (%)
1	First	90
2	Second	90
3	Third	88
5	Forth	86
6	Fifth	86

The synthesis of arylidene-1,3-dihydroindole-2-ones, **1**, have been studied in several conditions in literature as shown in Table 4. In comparison with other existing methods, the present methodology has several advantages such as a greener conditions, simple synthesis, short reaction time, easy work-up, and excellent yields with high purity of products.

3.1. Preparation of catalyst

New nanoporous silica SBA-15 can be obtained by using commercially available triblock copolymer Pluronic P126 as a structure directing agent [1,2]. Functionalizing of SBA-15 with -SO_3H group was usually performed though direct synthesis or post-grafting. As shown in Figure 2, the SBA-15 silica was functionalized with (3-mercaptopropyl)trimethoxysilane (MPTS) then the thiol groups of the product were oxidized to sulfonic acid by hydrogen peroxide. Analyzing of the catalyst surface was performed by various methods such as TGA, BET and CHN methods which demonstrated that the propyl sulfonic acids were immobilized into the pores. Calculating average pore diameter of the surface area was performed by the BET method and pore volume of SBA-Pr-SO_3H are 440 m^2/g, 6.0 nm and 0.660 cm^3/g, respectively, which are smaller than those of SBA-15 due to the immobilization of sulfonosilane groups into the pores [10]. SEM image of SBA-Pr-SO_3H (Figure 3a) shows uniform particles about 1 μm. The same morphology was observed for SBA-15. It can be concluded that morphology of solid was saved without change during the surface modifications. On the other hand, the TEM image (Figure 3b) reveals the parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pore of SBA-Pr-SO_3H was not collapsed during two steps reactions [28].

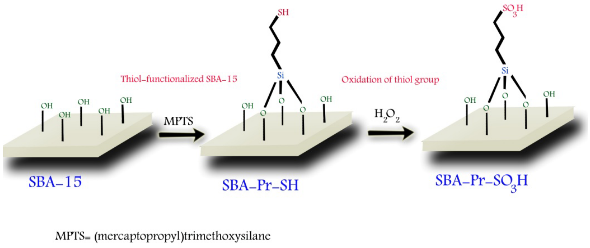


Figure 2. Schematic illustration for the preparation of SBA-Pr-SO_3H.

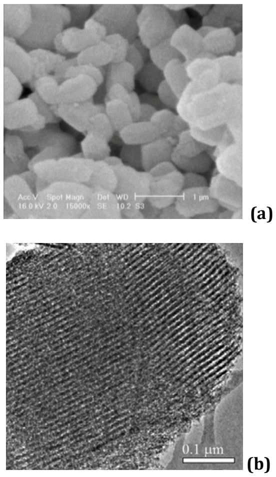


Figure 3. SEM (a) and TEM (b) image of SBA-Pr-SO_3H.

Table 4. Comparison of different condition in the synthesis of arylidene-1,3-dihydroindole-2-ones.

Entry	Catalyst	Solvent	Condition	Time	Yield (%)	Year
1	Piperidine	Ethanol	Reflux	18 h	44-88	2009 [22]
3	Piperidine	Ethanol	Reflux	3-5 h	80	1998 [12]
4	$[(CH_2)_3SO_3Hmim]HSO_4$	-	80 °C	20-120 min	86-97	2008 [21]
5	KF-Al_2O_3	-	MW	3-10 min	69-94	1998 [20]
6	SBA-Pr-SO_3H	-	120 °C	0.5-2 h	31-90	This work
7	No catalyst	-	120 °C	5 h	50	This work

4. Conclusions

A novel and highly efficient method for the synthesis of arylidene-1,3-dihydroindole-2-ones has been developed in the solvent free reaction of aromatic aldehydes and oxindole using recyclable and environmentally benign SBA-Pr-SO_3H as a nano and green solid acid catalyst.

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References

[1]. Zhao, D.; Feng, J.; Huo, Q.; Melosh, N.; Fredrickson, G. H.; Chmelka, B. F.; Stucky, G. D. *Science* **1998**, *279*, 548-552.

[2]. Zhao, D.; Huo, Q.; Feng, J.; Chmelka, B. F.; Stucky, G. D. *J. Am. Chem. Soc.* **1998**, *120*, 6024-6036.

[3]. Hajiaghababaei, L.; Badiei, A.; Ganjali, M. R.; Heydari, S.; Khaniani, Y.; Ziarani, G. M. *Desalination* **2011**, *266*, 182-187.

[4]. Liu, Q.; Wang, A.; Wang, X.; Zhang, T. *Chem. Mater*. **2006**, *18*, 5153-5155

[5]. Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710-712.

[6]. Bahrami, K.; Khodaei, M. M.; Fattahpour, P. *Catal. Sci. Technol.* **2011**, *1*, 389-393.

[7]. Grieken, R. V.; Melero, J. A.; Morales, G. *J. Mol. Catal. A: Chem*. **2006**, *256*, 29-36.

[8]. Margolese, D.; Melero, J. A.; Christiansen, S. C.; Chmelka, B. F.; Stucky, G. D. *Chem. Mater.* **2000**, *12*, 2448-2459.

[9]. Ziarani, G. M.; Badiei, A.; Aslani, Z.; Lashgari, N. *Arabian J. Chem*. **2012**, In Press.

[10]. Ziarani, G. M.; Badiei, A.; Khaniania, Y.; Haddadpour, M. *Iran. J. Chem. Chem. Eng*. **2010**, *29*, 1-10.

[11]. Ziarani, G. M.; Badiei, A.; Haddadpour, M. *Int. J. Chem*. **2011**, *3*, 87-94.

[12]. Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem*. **1998**, *41*, 2588-2603.

[13]. Wood, E. R.; Kuyper, L.; Petrov, K. G.; Hunter, R. N.; Harris, P. A.; Lackey, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 953-958.

[14]. Ölgen, S.; Akaho, E.; Nebioglu, D. *II Farmaco* **2005**, *60*, 497-506.

[15]. Spencer, J.; Chowdhry, B. Z.; Hamid, S.; Mendham, A. P.; Male, L.; Coles, S. J.; Hursthouse, M. B. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2010**, *66*, o71-o78.

[16]. Ölgen, S.; Göze, C.; Jose, J. *Biol. Pharm. Bull*. **2007**, *30*, 715-718.

[17]. Cheng, J. B.; Cooper, K.; Duplantier, A. J.; Eggler, J. F.; Kraus, K. G.; Marshall, S. C.; Marfat, A.; Masamune, H.; Shirley, J. T.; Tickner, J. E.; Umland, J. P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1969-1972.

[18]. Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A. V.; Liston, T. E.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.* **1996**, *39*, 10-18.

[19]. Woodard, C. L.; Li, Z.; Kathcart, A. K.; Terrell, J.; Gerena, L.; Lopez-Sanchez, M.; Kyle, D. E.; Bhattacharjee, A. K.; Nichols, D. A.; Ellis, W.; Prigge, S. T.; Geyer, J. A.; Waters, N. C. *J. Med. Chem*. **2003**, *46*, 3877-3882.

[20]. Villemin, D.; Martin, B. *Synth. Commun*. **1998**, *28*, 3201-3208.

[21]. Hu, Y.; Kang, H.; Zeng, B. W.; Wei, P.; Huang, H. *J. Chem. Res.* **2008**, *2008*, 642-643.

[22]. Zhang, W.; Go, M. L. *Bioorg. Med. Chem*. **2009**, *17*, 2077-2090.

[23]. Pandit, B.; Sun, Y.; Chen, P.; Sackett, D. L.; Hu, Z.; Rich, W.; Li, C.; Lewis, A.; Schaefera, K.; Li, P. K. *Bioorg. Med. Chem.* **2006**, *14*, 6492-6501.

[24]. Walker, G. N.; Smith, R. T.; Weaver, B. N. *J. Med. Chem*. **1965**, *8*, 626-637.

[25]. Xu, T. T.; Wang, S. Y.; Ji, S. J. *Chin. J. Org. Chem.* **2006**, *26*, 1414-1417.

[26]. Chatten, L. G.; Daisley, R. W.; Olliff, C. J. *J. Chem. Soc. , Perkin Trans.* 2 **1973**, 469-473.

[27]. Kniess, T.; Bergmann, R.; Kuchar, M.; Steinbach, J.; Wuest, F. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 7732-7742.

[28]. Lashgari, N.; Ziarani, G. M.; Badiei, A.; Gholamzadeh, P. *Eur. J. Chem.* **2012**, *3(3)*, 310-313.