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Synthesis of β-Receptor Blocker and Antihypertensive Drug Using (SBA-Pr-SO_3H) as an Eco-Friendly, Inexpensive and Efficient Nano-Catalyst

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Abstract: In this method, at first the synthesis of 2,3-dihydro-1*H*-carbazol-4(9*H*)-one product by the condensation of (Z)-3-(2-phenylhydrazono)cyclohexanone in the presence of (SBA-Pr-SO_3H) as nanoporous solid acid catalyst, acid acetic glacial and ethanol as solvent under reflux conditions is reported. (SBA-Pr-SO_3H) nanoporous solid acid catalyst was used as an effective catalyst for the synthesis of Carvedilol from the reaction of 4-oxiranylmethyoxy-9*H*-carbazole and 2-(2-methoxyphenoxy)ethanamine in the presence of monoglyme solvent. This synthesis afforded under ring opening of 4-oxiranylmethyoxy-9*H*-carbazole with 2-(2-methoxyphenoxy)ethanamine by above nano-catalyst. Heterogeneous reaction conditions, easy procedure, short reaction time, and high yields are some important advantages of this method.

Keywords: Carvedilol, Nano-Catalyst, Carbazole, Heterogeneous, (SBA-Pr-SO_3H), Synthesis

1. Introduction

β-adrenoreceptor plays a role in many diseases of the heart and the brain. They have been shown to be altered in the brains of patients suffering from Alzheimer's disease, panic disorder, anxiety, depression and stress [1]. Carvedilol (Figure 1) an adrenergic antagonist with nonselective β and α1 receptor blocking agent and a vasodilatation drug with antioxidant activity [2]. Carvedilol has demonstrated significant clinical benefits in the management of patients with heart failure and in the post-myocardial infarction setting. It also possesses unique ancillary properties that may account for positive results in a number of clinical trials. It appears to offer particular advantages in the treatment of co-morbid conditions, including coronary artery disease, stroke hypertension, renal failure, diabetes and arterial fibrillation [3] that can independently contribute to the progression of heart failure.

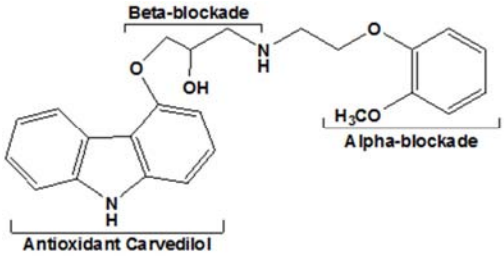


Figure 1. *Carvedilol.*

The high ordered nanoporous silica, such as MCM-41 [4], LUS-1 [5] and SBA-15 [6] are unique inorganic solid supports that have very high surface area with controllable pore sizes between 2 to 30 nm. They can be employed as catalysts [7], for the preconcentration of metals [8], and as modified carbon electrodes [9]. The SBA-15 is new nanoporous silica with hexagonal structure, large pore, high surface area, high thermal stability and also diffusion free due to thicker pore walls and larger pore size respectively.

This can be prepared by using commercially available triblock copolymer pluronic P126 as a structure directing agent [6]. Integration of acidic functional groups (e.g.,-SO_3H) into SBA-15 has been explored to produce promising solid acids. The sulfonic acid functionalized SBA-15 were usually synthesized through direct synthesis or post-grafting [10]. There have been only a few reports about the application of several types of sulfonic acid functionalized ordered mesoporous silicas as nano acid catalyst in chemical transformations [11]. For example, SBA-Pr-SO_3H has been used in the synthesis of chromenes from chromanols [12], and the *von Pechmann* reaction [13].

2. Experimental

2.1. Chemicals

All the chemicals were obtained from Merck (Darmstadt, Germany) and used as received. All solvents were purchased from commercial sources.

2.2. Instruments

Melting points were measured using Electro thermal IA 9100 digital melting point apparatus. Yields are based on GC/mass analysis using an Agilent (Denver, CO, USA) 6890 GC system Hp-5 capillary 30 m×530 μm×1.5 μm nominal. The IR spectra were recorded on a Shimadzu model impact 400D FT-IR spectrophotometer using KBr pellets. ^{1}H NMR were recorded on a Bruker AC-300F 400 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard with ^{1}H resonant frequency of 400 MHz. Optical rotation values were considered on Bellingham Stanly polarimeter.

2.3. Catalyst Synthesis Procedure

2.3.1. Preparation of SBA-15 Catalyst

At First, pluronic P123 triblock copolymer surfactant ($EO_{20}PO_{70}EO_{20}$, M_{ac} =5800) (4.0 g) was dissolved in 30 g of water and 120 g of 2 M HCl solution. Then, TEOS (tetraethyl orthosilicate) (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 distillated 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 copolymer template [14].

2.3.2. Preparation of the Pr-SO_3H as Nanoporous Solid Acid Catalyst

Functionalization of the SBA-15 catalyst was performed according to Fig. 3. 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 6h 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 reaction.

2.4. Synthesis of Compounds (3-5)

To a solution of Cyclohexane-1,3-dione (1) (1 g, 8.47 mmol) and phenyl hydrazine (2) (1.77 mL, 12.71 mmol) was added 15 mL of ethanol. The resultant mixture was stirred at 25°C for 3 h and then gave compound 3. The compound 3 was refluxed in the presence nano sulfonic acid (SBA-Pr-SO_3H as nanoporous solid acid) catalyst (0.5 g), ethanol (20 mL) and glacial acetic acid (10 mL) for 3 h and the mixture afforded compound 4. The cyclized compound 4 was reduced for 2 h with Raney nickel gave 4-hydroxy carbazole (5).

2.5. Synthesis of 4-(2,3-Epoxyprpoxy) Carbazole (6)

To a stirred solution of 300 mL water and sodium hydroxide (5.75 g, 0.143 mol), 4-Hydroxy carbazole (5) (5 g, 0.027 mol) is added over a period of 15-20 min. The reaction mass is cooled to 10-15°C and added 100 mL DMSO drop wise for 55 min. After stirring for 15 min, epichlorohydrin (18.9 g, 0.204 mol) is added over 1 h duration by maintain the temp at 10-15°C. The reaction mass temperature is slowly raised to 50°C and the suspension is maintained for 5 h under stirring. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude compound. The obtained crude product is recrystallized in methanol to afford pure 4-oxiranylmethyoxy-9*H*-carbazole (6) as an off white crystalline powder.

M. P.: 121-126°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.3 (s, J = 8.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.3 (m, J = 8.1 Hz, 1H), 7.3 (m, J = 8.1 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.1 (d, J = 7.2 Hz 1H), 6.9 (d, J = 7.2 Hz 1H), 4.1 (m, J = 7.2 Hz, 2H), 3.3 (m, J = 6.6 Hz, 1H), 3.0 (m, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 50.0, 52.51, 56.22, 69.17, 111.10, 111.80, 119.0, 114.9, 115.40, 120.10, 120.70, 121.4, 121.71, 124.15, 146.62, 149.00, 149.0. MS: *m/z* (M^++1) 240; Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48, N, 5.85%. Found: C, 75.39; H, 5.56, N, 5.92 %. HRMS (EI) Calcd. for $C_{15}H_{13}NO_2$ $[M]^+$, 239.1000, Found 239.0979.

2.6. Synthesis of 2-(2-Methoxyphenoxy) Ethanamine (7)

The 2-(2-methoxyphenoxy)ethanamine was synthesized in according to pervious literature [15].

2.7. Synthesis of 1-(9H-Carbazol-4-Yloxy)-3-(2-(2-Methoxyphenoxy) Ethylamino) Propan-2-ol, Carvedilol (8)

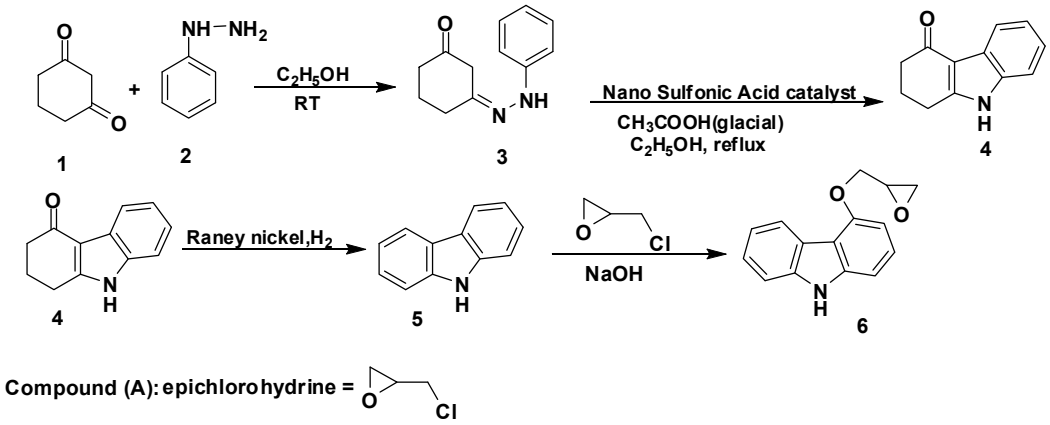
Methanol (25 mL) added into a round-bottom flask and started stirring at 25 ^{o}C. Compound (6) (3 g), monoglyme (30

mL), compound (7) (3 g) and SBA-Pr-SO_3H as nanoporous solid acid catalyst (0.5 g) was added and their mixture was cooled to 0°C. Concentrated HCl (15 mL) was added slowly drop wise over a period of 30-45 minutes at the same temperature. Reaction mass allowed to ambient temperature and progress of the reaction was monitored by TLC. Reaction completed after 5 h of maintenance and distilled off methanol completely under vacuum to get the material as a residue. Residue was purified by column chromatography by eluting with 5-15% ethyl acetate in hexane to get pure impurity (8).

Yield 96%, M. P.: 114-116 °C; IR (KBr, cm^{-1}): 3344, 2923, 1590, 1504, 1452, 1217, 1099. 1H NMR (400 MHz, $CDCl_3$): δ_H 11.2 (s, *J* = 8.1 Hz, 1H), 8.2 (s, *J* = 8.1 Hz, 1H), 7.4 (d, *J* = 8.1 Hz, 1H), 7.3 (m, *J* = 8.1 Hz, 1H), 7.3 (m, *J* = 8.1 Hz, 1H), 7.1 (m, 1H), 7.1 (m, 1H), 6.9 (m, 1H), 6.9 (m, 1H), 6.9 (m, 1H), (6.9, 1H), 6.7 (d, 1H), 5.2 (s, *J* = 7.2 Hz, 1H), 4.2 (d, *J* = 7.2 Hz, 2H), 4.1 (m, *J* = 7.2 Hz, 2H), 4.0 (s, *J* = 7.2 Hz, 1H), 3.75 (s, *J* = 6.6 Hz, 3H), 2.97 (m, *J* = 6.6 Hz, 2H), 2.8 (m, J = 6.6 Hz, 2H), 2.0 (s, 1 *J* = 6.6 Hz, H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 50.0, 52.51, 56.22, 69.17, 111.10, 111.80, 119.0, 114.9, 115.40, 120.10, 120.70, 121.4, 121.71, 124.15, 146.62, 149.00, 149.0. MS: m/z (M^++1) 276;. Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45, N, 6.89%. Found: C, 70.96; H, 6.56, N, 6.94%. HRMS (EI) Calcd. for $C_{24}H_{26}N_2O_4$ $[M]^+$, 416.1900, Found 416.1889.

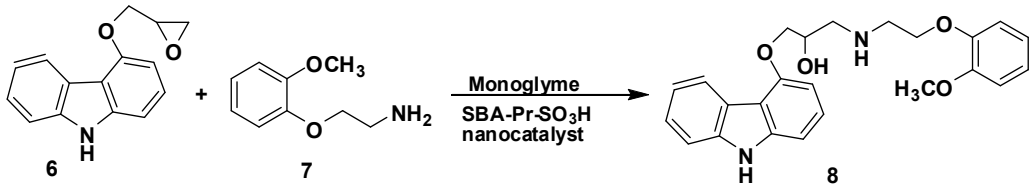
3. Results and Discussion

In this work, we would like to explore the catalytic activity of the Sulfonic acid functionalized (SBA-Pr-SO_3H) as a highly efficient heterogenous nanoporous acid catalyst towards the one-pot synthesis of Carvedilol (96%) (8). The synthetic approach for the preparation of Carvedilol (8) describes the opening of oxirane ring of 4-(2,3-epoxyprpoxy) carbazole (6) with 2-(2-methoxyphenoxy) ethanamine (7) in monoglyme solvent (Schemes 1 and 2).



Scheme 1. *Synthesis of 4-(oxiran-2-ylmethoxy)-9H-carbazole (4) using (SBA-Pr-SO_3H) as a highly efficient heterogenous nanoporous acid catalyst.*

4-Oxiranylmethyoxy-9*H*-carbazole (6) was prepared according to the method described in the experimental section. Thus, Cyclohexane-1,3-dione (1) was condensed with phenyl hydrazine (2) in ethanol gave compound (3). Cyclization of compound (3) in the presence SBA-Pr-SO_3H nanocatalyst and glacial acetic acid afforded compound (4). The cyclized compound (4) was reduced with Raney nickel gave 4-hydroxy carbazole (5). 4-Hydroxy carbazole (5) was treated with epichlorohydrine (compound (A)) gave 4-oxiranylmethyoxy-9*H*-carbazole (6) (Scheme 1). 4-Oxiranylmethyoxy-9*H*-carbazole (6) on condensation with 2-(2-methoxyphenoxy)ethanamine (7) in the presence of monoglyme and SBA-Pr-SO_3H, nanoporous solid acid catalyst at 0 °C gave compound 8 (Scheme 2).



Scheme 2. *Synthesis of 1-(9H-carbazol-4-yloxy)-3-(2-(2-ethoxyphenoxy)ethylamino)propan-2-ol (8), Carvedilol using SBA-Pr-SO_3H as a highly efficient heterogenous nanoporous acid catalyst.*

The catalytic activity of catalysts using Fe_2O_3, SiO_2, HCl, $H_3[PW_{12}O_{40}]$, HY-Zeolite, H_2SO_4 and CuO, was less than SBA-Pr-SO_3H nanoporous solid acid. The yields of the synthesis of 1-(9*H*-carbazol-4-yloxy)-3-(2-(2-ethoxyphenoxy) ethylamino)propan-2-ol (8), Carvedilol using SBA-Pr-SO_3H nanoporous solid acid with various catalysts are given in Table 1. When, SBA-Pr-SO_3H nanoporous solid acid catalyst was used in the reaction, the yield for compound 8 was 96%, but the yield was lower when using Fe_2O_3, SiO_2, HCl, $H_3[PW_{12}O_{40}]$, HY-Zeolite, H_2SO_4 and CuO (Table 1, entries 1-7).

The yield of the product (8), Carvedilol was very good by using SBA-Pr-SO_3H nanoporous solid acid catalyst (Table 1, entry 8).

Table 1. *The yields of Synthesis of 1-(9H-carbazol-4-yloxy)-3-(2-(2-ethoxyphenoxy)ethylamino)propan-2-ol (8), Carvedilol using using different catalysts.*

Entry	Catalyst	[a]Yield (%)
1	Fe_2O_3	53
2	SiO_2	45
3	HCl	63
4	$H_3[PW_{12}O_{40}]$	71
5	HY-Zeolite	66
6	H_2SO_4	73
7	CuO	51
8	SBA-Pr-SO_3H	96

[a]Isolated yields

Monoglyme is a high purity dimethylether ethylene glycol primarily used as a solvent for pharmaceutical applications. Monoglyme is used as a solvent for chemical reactions for industrial and pharmaceutical applications. It is used preferentially for reaction processes involving reagents containing or generating cations such as sodium, sodium borohydride, Grignards and organometallics. It is also stable with halogenated compounds. Monoglyme is used as a process solvent in the production of high-purity granulated polysylicon, as a solvent for teflon etching compounds, in the production of pharmaceutical protease inhibitors, anti-histamines, synthetic hormones. Monoglyme is a very stable, polar, aprotic recyclable reaction solvent. The addition of BHT as a stabilizer reduces the product's sensitivity to air oxidation.

3.1. Plausible Mechanism for Preparation of SBA-Pr-SO_3H, Nanoporous Solid Acid Catalyst

Pure Nanoporous compound SBA-15 (SBA-Pr-SO_3H nanoporous solid acid) was synthesized according to the well-established method designed by *Zhao & coworkers* [6] with triblock poly(ethylene oxide)-b-poly(propylene oxide)-bpoly(ethylene oxide)copolymer (Pluronic, $EO_{20}PO_{70}EO_{20}$, P123) as the template. A schematic illustration for the preparation of SBA-Pr-SO_3H nanoporous solid acid catalyst was shown in Figure 2. First, the calcined SBA-15 silica was functionalized with (3-mercaptopropyl) trimethoxysilane (MPTS) and then, the thiol groups were oxidized to sulfonic acid by hydrogen peroxide.

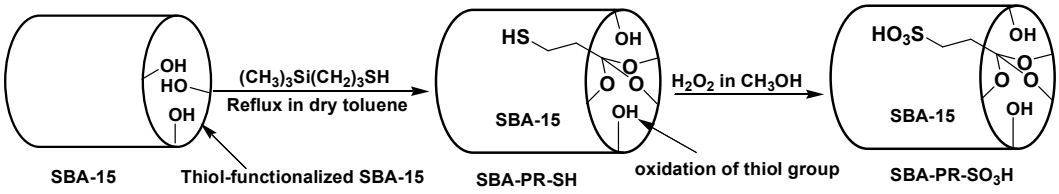


Figure 2. *Schematic illustration for the preparation of SBA-Pr-SO_3H, nanoporous solid acid.*

3.2. Characterization of Catalyst

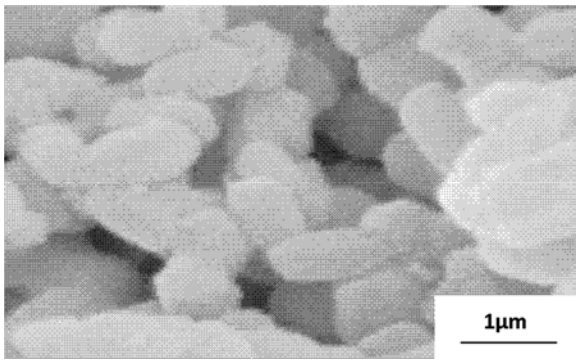


Figure 3. *SEM of SBA-Pr-SO_3H nanoporous solid acid.*

Functionalizing of SBA-15 with -SO_3H group was usually performed through direct synthesis of post-grafting. As shown in Figure 2, the SBA-15 silica was functionalized with (3-mercaptopropyl)timethoxysilane (MPTS) and then the diol groups of the product were oxidized to sulfunic acid by hydrogen peroxide. Analyzing of the catalyst surface was performed by various methods such as BET wich demonstrated that the propyl sulfonic acids were immobilized into the pores. Calculating average pore diameter calculated by the BET method and pore volume of SBA-Pr-SO_3H are 440 m^2g^{-1}, 6.0 nm and 0.660 cm^3g^{-1}, respectively, which are smaller than those of SBA-15 due to the immobilization of sulfonosilane groups into the pores.Wich they are smaller than those of SBA-15 due to the immobilization of sulfonosilane groups into the pores [16]. SEM image of SBA-Pr-SO_3H nanoporous solid acid (Figure 3) shows uniform particles.

4. Conclusion

In conclusion, we reported a novel and highly efficient method for the synthesis of 1-(9*H*-Carbazol-5-yloxy)-3-chloropropan-2-ol (8) using recyclable and environmentally benign Sulfonic acid functionalized nanoporous silica (SBA-Pr-SO_3H).

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