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Application of SBA-Pr-SO_3H in the synthesis of benzoxazole derivatives

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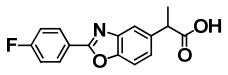
ABSTRACT

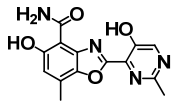
Propylsulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) catalyzed the synthesis of 2-aryl benzoxazoles from 2-aminophenol and benzoyl chloride derivatives in good yields under reflux condition in acetic acid. In solvent free condition, hydroxybenzanilide derivatives were obtained.

1. Introduction

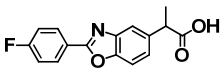
Benzoxazoles and other heterocycles are found in very important classes of bioactive compounds such as antibiotic, antibacterial, antiinflammatory, antistress, antiulcer, and anticancer agents [1-7]. They have recently received considerable attention for their pharmaceutical activities. Flunoxaprofen, benoxaprofen and boxazomycine B are three example of this class of compounds (Figure 1).



Flunoxaprofen



Boxazomycin B



Benoxaprofen

Figure 1. Structure of some benzoxazole drugs.

General methods for the synthesis of benzoxazoles involve two approaches. The first approach is the copper-catalyzed intramolecular *ortho*-arylation of *o*-haloanilides or the intermolecular annulations of *o*-arylhalides with acylamides. The second approach is the condensation of 2-aminophenol with carboxylic acid derivatives in the presence of strong acid/high temperature conditions, or aldehydes with subsequent oxidation using strong oxidants such as $PhI(OAc)_2$, pyridiniumchlorochromate (PCC) [8]. In this reaction, different catalysts such as $ThClO_4$ [9], 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ) and $BaMnO_4$ [10], $In(OTf)_3$ [11], I_2 [12], *N*,*N*'-dibenzyl-1,1' binaphthyl-2,2'-diamine-copper(II) complex [13], *p*-TsOH.H_2O [14], 4-methoxy-2,2,6,6-tetra methyl-1-piperidinyloxy(4-methoxy-TEMPO) [10], CuI/1,10-phenanthroline [15], $Cu(OTf)_3$ [16,17], $FeCl_3$/2,2,6,6-tetra-methyl-3,5 heptanedione (TMHD) [18], $Zn(OAc)_2.2H_2O$ [19], $SiO_2/FeCl_3$ [20] and CuO nano particles [21] were also used. However many of these methodologies have difficulties in recovery and reusability of the catalysts.

Therefore, in this article we used SBA-Pr-SO_3H as heterogeneous nanocatalyst in the one pot synthesis of benzoxazoles. The heterogeneous catalysts can conveniently be removed from the reaction mixture, making the experimental procedure simple and eco-friendly [22]. SBA-Pr-SO_3H has mesoporous silica structure with pore size of 6 nm which can act as reactive nano-reactor in organic synthesis [23].

2. Experimental

2.1. Instrumentation

Electronic ionization GC-MS spectra were recorded on a 5973 network mass selective detector, GC 6890 Agilent spectrometer. IR spectra were obtained with a FT-IR Bruker 500 scientific spectrometer as KBr pellets. The ^1H NMR was run on a Bruker DPX, 250 MHz, in $CDCl_3$. Chemical shifts are reported in δ from TMS. Melting points were measured by the capillary tube method with a 9200-Barnstead electro thermal apparatus. SEM analysis was performed on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV while TEM was carried out on a Tecnai G^2 F30 at 300 kV.

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2.2. Synthesis

2.2.1 Preparation of catalyst

The nanoporous compound SBA-15 was synthesized and functionalizaed according to our previous report and the modified SBA-15-Pr-SO_3H was used as nanoporous solid acid catalyst in the following reaction [24-26]. For the preparation of the catalyst, 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. After this, 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. 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.

2.2.2. General procedure for the synthesis of hydroxybenzanilide derivatives (3)

SBA-Pr-SO_3H (0.02 g) was placed in a flask and activated at 100 °C under vacuum condition for 20 min. Then the catalyst was allowed to cool to room temperature. The reaction mixture of substituted benzoyl chloride (**2a-i**) (3 mmol) and 2-aminophenol (**1**) (3 mmol, 0.33 g) was stirred at 70 °C (Scheme 1, Table 1). The solid benzoyl chlorides (3-nitro-, 4-nitro- and 3,5-dinitro-benzoyl chloride) were kept in 90 °C. After completion of the reaction which was monitored by TLC (*n*-hexane:EtOAC, 1:1), convenient crystallization solvent was added to the reaction mixture for recrystallization of crude product and catalyst was separated by simple filtration.

2.2.3. General procedure for the synthesis of benzoxazoles (4)

Substituted benzoyl chloride (**2a-i**) (3 mmol), 2-aminophenol (**1**) (3 mmol, 0.33 g) and acetic acid (3 mL) was added to activate catalyst (SBA-Pr-SO_3H (0.02 g)) (Scheme 2, Table 2). The mixture was stirred for 8 h under reflux conditions. After completion of the reaction which was monitored by TLC (*n*-hexane:EtOAC, 3:1), the crude product was dissolved in acetone, and catalyst was removed by simple filtration of reaction mixture. The gradual evaporation of acetone, gave the pure crystals of product.

2-Phenyl benzoxazole (**4a**): FT-IR (KBr, cm^{-1}): 3043 ν(C-H) (aromatic), 1693 ν(C=N) (imine), 1579 ν(C=C) (aromatic), 1247 ν(C-O) (ether). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 7.28-7.37 (m, 2H, Ar-H), 7.47-7.58 (m, 4H, Ar-H), 8.22-8.25 (m, 2H, Ar-H). MS (*m/z,* (%)): 195 (100), 63 (53).

2-(2,4-Dichlorophenyl)benzoxazole (**4e**): FT-IR (KBr, cm^{-1}): 3073 ν(C-H) (aromatic), 1700 ν(C=N) (imine), 1647 ν(C=C) (aromatic), 1282 ν(C-O) (ether). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 7.26 (m, 4H, Ar-H), 7.34 (s, 1H, Ar-H), 7.36 (d, 2H, Ar-H). MS (m/z, (%)): 263 (100), 63 (60).

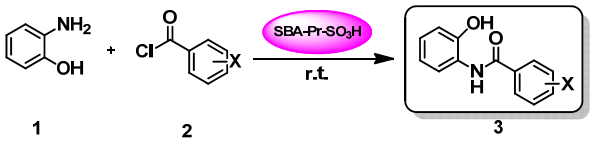
2-(3-Nitrophenyl)benzoxazole (**4f**): FT-IR (KBr, cm^{-1}): 2979 ν(C-H) (aromatic), 1611 ν(C=C), 1613 ν(C=N) (imine), 1527 ν(NO_2), 1360 ν(NO_2). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 9.1 (d, 1H, Ar-H), 8.37-8.61 (m, 3H, Ar-H), 7.26-7.85 (m, 4H, Ar-H). MS (*m/z,* (%)): 240 (100), 194 (44), 139 (16), 63 (13).

2-(4-Nitrophenyl)benzoxazole (**4g**): FT-IR (KBr, cm^{-1}): 3052 ν(C-H) (aromatic), 1608 ν(C=N) (imine), 1508 ν(NO_2), 1246 ν(C-O) (ether). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 6.86-7.06 (m, 4H, Ar-H), 7.7 (d, 1H, Ar-H), 8.1 (d, 1H, Ar-H), 8.2 (d, 1H, Ar-H), 8.5 (d, 1H, Ar-H). MS (*m/z,* (%)): 240 (100), 195 (45), 63 (14).

2-(3,5-Dinitrophenyl)benzoxazole (**4h**): FT-IR (KBr, cm^{-1}): 3181 ν(C-H) (aromatic), 1657 ν(C=N) (imine), 1535 ν(NO_2), 1282 ν(C-O) (ether). ^1H NMR (250 MHz, DMSO-d_6, δ, ppm): 6.88-7.15 (m, 4H, Ar-H), 7.73 (s, 1H, Ar-H), 9.15 (s, 1H, Ar-H), 9.31 (s, 1H, Ar-H).

3. Results and discussion

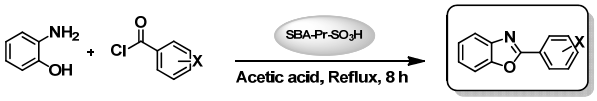
In this investigation the synthesis of 2-hydroxy-benzanilide derivatives (**3**) (Scheme 1) and 2-aryl benzoxazoles (**4**) (Scheme 2) from the condensation of 2-aminophenol (**1**) and benzoyl chlorides (**2a-i**) in the presence of SBA-Pr-SO_3H as heterogeneous and reusable nanocatalyst were studied.



1 2 3

X= H, 2a
2-Cl, 2b
3-Cl, 2c
4-Cl, 2d
2,4-di-Cl, 2e
3-NO_2, 2f
4-NO_2, 2g
3,5-di-NO_2, 2h
2-Me, 2i

Scheme 1



1 2 4

X= H, 2a
2-Cl, 2b
3-Cl, 2c
4-Cl, 2d
2,4-di-Cl, 2e
3-NO_2, 2f
4-NO_2, 2g
3,5-di-NO_2, 2h
2-Me, 2i

Scheme 2

At first, for optimization of reaction conditions, the catalyst free reaction in acetic acid solvent was examined. In this condition, the reaction did not proceed satisfactory and the product was 2-hydroxy-benzanilide derivatives (**3a-i**). Then it was practiced in the presence of SBA-Pr-SO_3H in solvent free condition at 70 °C. In this time, only the acylation product (**3a-i**) was obtained too. The reaction was developed with derivatives of benzoyl chlorides, and the results were demonstrated in Table 1. The demonstrated results were monitored that the more electron withdrawing groups gave the products in shorter reaction time and higher yield (Entry 5-6, Table 1).

When this reaction was refluxed, the product (**3a-i**) was converted to benzoxazole derivatives in good to high yields. The reaction was developed with different benzoyl chloridesthat their results were listed in Table 2. After completion of the reaction (monitored by TLC), the crude product was dissolved in hot convenient crystallization solvent, the insolubility of SBA-Pr-SO_3H in different organic solvents led to very easy work up of catalyst by simple filtration and after cooling of the filtrate, the pure crystals of products were obtained.

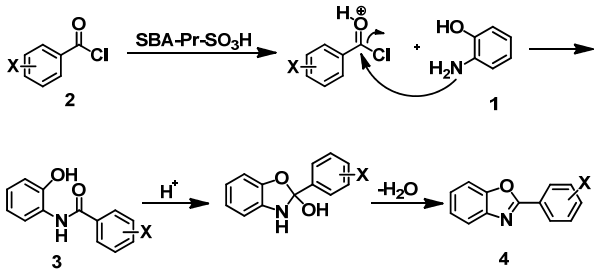
Table 1. Synthesis of hydroxyl-benzanilide derivatives (**3a-i**) catalyzed by SBA-Pr-SO_3H in solvent free conditions.

Entry	Product	X	Temp. (°C)	Time	Yield (%)	M.p. (°C)	M.p. (Lit.)	Crystallization solvent
1	3a	2-Cl	70	1 h	71	190-191	192-193 [27]	EtOH
2	3b	3-Cl	70	1.30 h	52	173-174	171-172 [28]	Acetone
3	3c	2,4-di-Cl	70	1.30 h	46	173-175	173-174 [29]	Acetone
4	3d	3-NO_2	90	2 h	93	205-207	206 [30]	EtOH
5	3e	4-NO_2	90	50 min	72	209-210	206-207 [28]	Acetone
6	3f	3,5-di-NO_2	90	40 min	98	259-260	-	EtOH

Table 2. Synthesis of benzoxazole derivatives (**4a-i**) catalyzed by SBA-Pr-SO_3H.

Entry	Product	R	Time (h)	Yield (%)	M.p. (°C)	M.p. (Lit.)
1	4a	H	8	91	102-103	102-104 [31]
2	4b	2-Cl	8	83	72-74	70-72 [11]
3	4c	3-Cl	8	85	123-125	124-125 [32]
4	4d	4-Cl	8	78	140-142	140-142 [13]
5	4e	2,4-di-Cl	8	82	119-120	118-119 [13]
6	4f	3-NO_2	8	81	205-207	207 [33]
7	4g	4-NO_2	8	75	258-260	257-263 [34]
8	4h	3,5-di-NO_2	8	87	205-207	205-207 [35]
9	4i	2-Me	8	85	66-70	68-69 [10]

A plausible mechanism was shown in Scheme 3. At first, SBA-Pr-SO_3H as a Bronsted nano-catalyst protonates the carbonyl group of benzoyl chloride. Then, the reaction was followed by nucleophilic attack of amino group of 2-aminophenol to carbonyl group of benzoyl chloride. The nucleophilic attack of OH to carbonyl group of compound (**3**), gave the cyclization product (**5**) which converted to benzoxazole derivatives by dehydration.



Scheme 3

The acid catalyst can be 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 2.

For the preparation of the catalyst, at first, the surface of SBA-15 was functionalized and grafted with (3-mercaptopropyl) trimethoxysilane (MPTS), the thiol groups have been incorporated to surface of SBA-15 under reflux condition in dry toluene. Then the thiol groups were oxidized into sulfonic acid groups by hydrogen peroxide (Figure 2) [36,37].

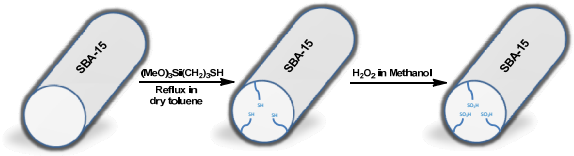


Figure 2. Preparation of SBA-Pr-SO_3H.

Nanopore size about 6 nm of SBA-Pr-SO_3H could act as nano-reactor and catalyzed synthesis of benzoxazole derivatives. A schematic illustration for this activity was shown in Figure 3.

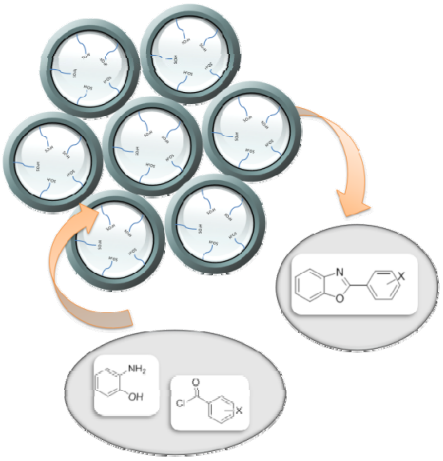
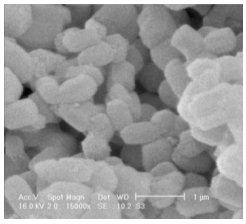
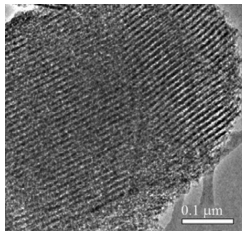


Figure 3. SBA-Pr-SO_3H acts as a nano-reactor.

The SEM and TEM images of SBA-Pr-SO_3H illustrated in Figure 4. Figure 4a shows SEM image of SBA-Pr-SO_3H that indicates uniform particles about 1 μm. The TEM image (Figure 4b) represents the parallel channels that were not collapsed during two step reactions. In general, organic functionalization did not alter the long-range mesoporous arrangement [25,26].



(a)



(b)

Figure 4. SEM (a) and TEM (b) image of SBA-Pr-SO_3H.

4. Conclusion

In summary, we have described the use of nano acid solid catalyst of SBA-Pr-SO_3H in the synthesis of benzoxazole derivatives and 2-hydroxy-benzanilide. Furthermore, operational and experimental simplicity, readily availability, easy work-up procedure and good yields make it, a facile method for the synthesis of these compounds.

Acknowledgements

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