

SULFONIC ACID FUNCTIONALIZED NANOPOROUS SILICA (SBA-PR-SO₃H) AS AN EFFICIENT CATALYST FOR THE ONE-POT SYNTHESIS OF 2H-INDAZOLO[1,2-*b*]PHTHALAZINE-TRIONES

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ABSTRACT

Sulfonic acid functionalized SBA-15 (SBA-Pr-SO₃H) with a pore size of 6 nm is an efficient catalyst in the green three-component condensation of phthalhydrazide, dimedone and aldehydes to give 2H-indazolo[1,2-*b*]phthalazine-triones under solvent-free conditions in excellent yields and short reaction times.

Keywords: Sulfonic acid functionalized SBA-15; Phthalhydrazide; Dimedone; Nano-reactor; One-pot reaction.

1. INTRODUCTION

In recent years, heterogeneous catalysts have gained great importance due to economic and environmental considerations.¹⁻³ Among the various heterogeneous catalysts, particularly, Santa Barbara Amorphous (SBA-15) is significant mesoporous silica with exclusive and important properties such as thick walls, profusely large surface area, huge pore volume and hydrothermal stability which render it as a promising catalyst for wide applications.⁴ Moreover, functionalization and modification of SBA-15 could enhance and optimize its catalytic activity.⁴ Applications of these nano catalysts in organic synthesis and one-pot reactions under green conditions are significant and growing. In continuation of our studies, on the application of nanoporous heterogeneous solid catalysts to organic synthesis,⁵⁻⁹ herein, we want to report a suitable method for the preparation of 2H-indazolo[1,2-*b*]phthalazine-trione derivatives using SBA-Pr-SO₃H as a nanoporous heterogeneous acid catalyst.

The development of simple synthetic routes for construction of complex organic molecules from readily available reagents is an important task in organic synthesis. Multi-component reactions (MCRs) are powerful and valuable tools for the rapid and efficient synthesis of a wide variety of organic molecules.^{10, 11}

In the past few decades, the synthesis of nitrogen-containing heterocyclic compounds has gained prominence as they are widespread in nature.¹² Among a large variety of N-containing heterocyclic compounds, heterocycles containing hydrazine moiety as 'fusion site' have received considerable attention due to their pharmacological properties and clinical applications.¹³ Moreover, fused phthalazine derivatives were found to possess multiple biological activities such as anticonvulsant,¹⁴ cardiotoxic,¹⁵ vasorelaxant,¹⁶ antifungal,¹⁷ and anticancer¹⁸ activities. Many methods are available for the synthesis of phthalazine derivatives,¹⁹⁻²² however, some of these methods suffered from several drawbacks such as hazardous organic solvents, high cost, long reaction times, excess amounts of acids, and harsh reaction conditions with non-recyclable catalysts. Therefore, the development of a new, efficient, and environmentally benign procedure which allows the simple synthesis of heterocycles containing phthalazine ring fragment is necessary. In this paper, we want to report the application of SBA-Pr-SO₃H as a highly active nanoporous heterogeneous acid catalyst in the preparation of 2H-indazolo[1,2-*b*] phthalazine-trione derivatives.

2. EXPERIMENTAL

Materials and Methods

All chemicals were obtained commercially and used without further purification. The 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 spectra was run on a Bruker DPX, at 400 MHz using TMS as an internal standard. GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, Gc 6890 Agilent. 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 G² F30 at 300 kV.

Synthesis and Functionalization of SBA-15

The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report⁸ and the modified SBA-15-Pr-SO₃H was used

as nanoporous solid acid catalyst in the following reaction.

General Procedure for the Synthesis of 2H-Indazolo[1,2-*b*]phthalazine-trione Derivatives (4a-k)

The SBA-Pr-SO₃H (0.02 g) was activated in vacuum at 100 °C. After cooling to room temperature, phthalhydrazide **1** (1 mmol, 0.16 g), aromatic aldehyde **2** (1 mmol), and dimedone **3** (1 mmol, 0.14 g) were added to it. The mixture was heated at 80 °C under solvent-free condition until the reaction was completed. After completion of the reaction (monitored by TLC), the solid product was dissolved in hot ethanol (2 × 10 mL) and the heterogeneous solid catalyst was removed by simple filtration. Then, the filtrate was cooled to give the pure products **4a-k**.

Selected Spectral Data

3,4-Dihydro-3,3-dimethyl-13-(2-methoxyphenyl)-2H-indazolo[1,2-*b*]phthalazine-1,6,11(13H)-trione (4i)

Color: Yellow. Yield: 79%. M.p.: 240-242 °C. FT-IR (KBr, v, cm⁻¹): 2895, 1661, 1600, 1555, 1494, 1328, 1218, 1078, 788. MS (EI, m/z): 402 (M⁺, 7), 371 (11), 327 (31), 295 (27), 274 (25), 162 (52), 130 (21), 104 (100), 76 (94), 55 (60).

3,4-Dihydro-3,3-dimethyl-13-(2,3-dimethoxyphenyl)-2H-indazolo[1,2-*b*]phthalazine-1,6,11(13H)-trione (4j)

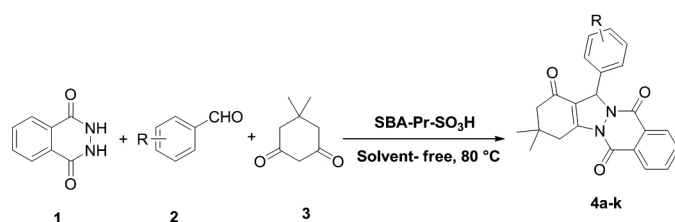
Color: Yellow, Yield: 88%. M.p.: 230-232 °C. FT-IR (KBr, v, cm⁻¹): 3165, 3016, 3894, 1661, 1599, 1556, 1489, 1369, 1224, 751. ¹H NMR (400 MHz, CDCl₃, δ, ppm): 6.86-8.38 (m, 7H, ArH), 6.67 (s, 1H, CHN), 3.84 (s, 6H, 2OMe), 3.27-3.41 (AB system, J = 19.2 Hz, 2H, CH₂H₂CO), 2.33 (s, 2H, CH₂C), 1.13 (s, 6H, 2Me). MS (EI, m/z): 432 (M⁺, 20), 401 (49), 312 (31), 257 (30), 162 (100), 132 (20), 104 (85), 76 (43), 51 (26).

3,4-Dihydro-3,3-dimethyl-13-(2,6-dichlorophenyl)-2H-indazolo[1,2-*b*]phthalazine-1,6,11(13H)-trione (4k)

Color: Yellow. Yield: 80%. M.p.: 264-266 °C. FT-IR (KBr, v, cm⁻¹): 3445, 3067, 2965, 2929, 1745, 1661, 1623, 1600, 1309, 1267, 1168, 705. ¹H NMR (400 MHz, CDCl₃, δ, ppm): 7.29-8.41 (m, 7H, ArH), 7.19 (s, 1H, CHN), 3.24-3.42 (AB system, J = 19.2 Hz, 2H, CH₂H₂CO), 2.36 (s, 2H, CH₂C), 1.24 (s, 6H, 2Me). MS (EI, m/z): 440 (M⁺, 3), 405 (2), 295 (19), 162 (100), 132 (22), 104 (99), 76 (42), 50 (22).

RESULTS AND DISCUSSION

In this paper, an efficient, one-pot, three-component condensation of phthalhydrazide **1**, aromatic aldehydes **2** and dimedone **3** in the presence of SBA-Pr-SO₃H for the preparation of 2H-indazolo[1,2-*b*]phthalazine-trione derivatives **4a-k** under solvent-free conditions has been studied (Scheme 1). We initially investigated the solvent effects in this reaction. As shown results in Table 1, among the tested solvents such as H₂O, EtOH, EtOH/H₂O (1:1), MeCN, and solvent-free system, the best result was obtained after 5 min under solvent-free condition at 80 °C in excellent yield. Therefore, this reaction condition was developed with different aldehydes and the results were summarized in the Table 2. It was reported that in the absence of any catalyst and under solvent-free conditions, this reaction afforded compound **4a** after 60 hours in trace amount.²³



Scheme 1. Synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione derivatives in the presence of SBA-Pr-SO₃H.

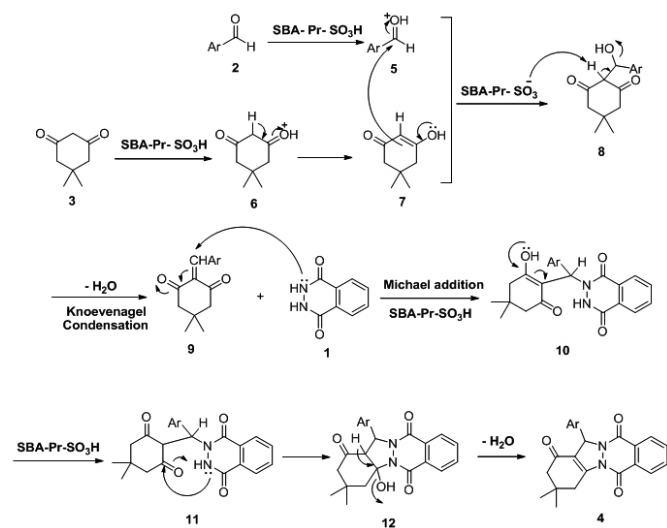
Table 1. Influence of different solvents on the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione derivatives.

No.	Solvent	Time (h)	Yield of 4a (%)
1	EtOH	2	78
2	EtOH/H ₂ O (1:1)	4	70
3	H ₂ O	3	67
4	MeCN	1	75
5	neat (80 °C)	5 min	90

Table 2. SBA-Pr-SO₃H Catalyzed the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione derivatives 4a-k under solvent-free condition.

Entry	R	Product	Time (min)	Yield (%)	M.p (°C)	M.p (Lit.)
1	H	4a	5	90	200-202	204-206 ²¹
2	4-Cl	4b	10	75	260-262	262-264 ²¹
3	3-NO ₂	4c	15	80	267-269	270-272 ²¹
4	2,3-Cl ₂	4d	5	70	263-265	266-268 ²⁴
5	2,4-Cl ₂	4e	7	88	216-218	219-221 ²⁴
6	4-N(Me) ₂	4f	15	70	250-252	256-258 ²⁵
7	2-OH	4g	15	80	180-182	185-187 ²³
8	4-OH	4h	10	81	261-263	265-266 ²⁵
9	2-OMe	4i	10	79	240-242	New
10	2,3-(OMe) ₂	4j	10	88	230-232	New
11	2,6-Cl ₂	4k	15	80	264-266	New

We propose a (plausible) mechanism for this reaction (Scheme 2). The reaction is thought to proceed in a stepwise manner. Firstly, we assume that the solid acid catalyst protonates the carbonyl group of aldehyde and then a Knoevenagel condensation between compounds 5 and 7 results in the intermediate 9 which immediate Michael addition of phthalhydrazide 1 to the C=C bond of this compound leads to the formation of intermediate 11. Cyclocondensation through of amino and carbonyl groups of the compound 11, followed by elimination of water produces the desired products 4a-k in excellent yields. The effect of nano pore size about 6 nm of solid acid catalyst enables it to act as a nano-reactor in which the reaction proceeds faster (Fig. 1).



Scheme 2. Proposed mechanism.

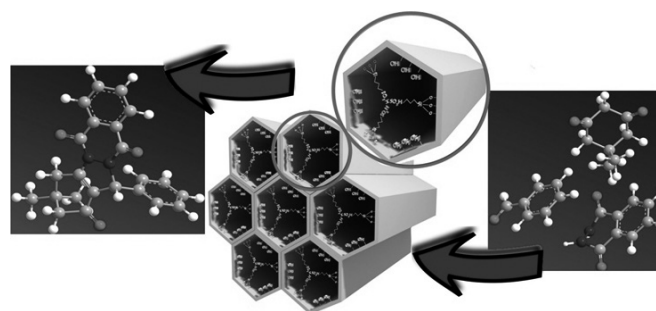


Fig. 1. SBA-Pr-SO₃H acts as a nano-reactor.

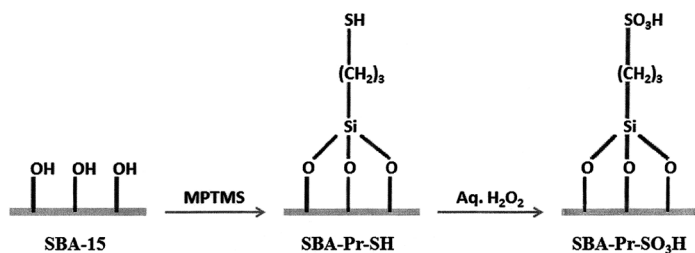
The synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-trione derivatives has been reported under different conditions with several catalysts and solvents in the literature as shown in Table 3. The high yield and shortest reaction time in this table is attributed to the high efficiency of the nano catalyst of SBA-Pr-SO₃H.

A schematic illustration for the preparation of SBA-Pr-SO₃H was shown in Fig. 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.

Table 3. Comparison of different conditions in the synthesis of 4a.

Entry	Catalyst	Solvent	Condition	Temp. (°C)	Time (min)	Yield (%)	Year
1	<i>p</i> -TSA ^a	-	Heating	80	10	86	2008 ²¹
2	Silica-SO ₃ H	-	Heating	100	8	87	2008 ²⁶
3	Mg(HSO ₄) ₂	-	Heating	100	10	85	2009 ²⁷
4	H ₂ SO ₄	H ₂ O/EtOH	Reflux	80	30	86	2009 ²⁵
5	TMSCl ^b	MeCN/DMF	Reflux	80	30	95	2009 ²⁸
6	PPA-SiO ₂ ^c	-	Heating	100	8	92	2009 ²⁹
7	H ₄ SiW ₁₂ O ₄₀	-	Heating	100	16	92	2010 ²²
8	H ₃ PW ₁₂ O ₄₀	[bmim]BF ₄ ^d	Reflux	r.t	10	90	2010 ³⁰
9	PMA-SiO ₂ ^e	-	Heating	80	30	85	2010 ³¹
10	TCT ^f	-	Heating	100	15	96	2010 ³²
11	TBBDA ^g	-	Heating	100	10	89	2011 ²⁴
12	PBBS ^h	-	Heating	100	25	65	2011 ²⁴
13	I ₂	EtOH	Reflux	80	20	93	2011 ³³
14	S-CSA ⁱ	-	Heating	80	15	90	2011 ³⁴
15	DPA ^j	-	Heating	80	10	96	2012 ²³
16	SBA-Pr-SO ₃ H	-	Heating	80	5	90	This work

^a*p*-Toluenesulfonic acid; ^bTrimethylsilyl chloride; ^cSilica supported polyphosphoric acid; ^d1-Butyl-3-methyl imidazolium tetrafluoroborate; ^ePhosphomolybdic acid; ^f2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride); ^gN, N, N', N'-Tetrabromobenzene-1,3-disulfonamide; ^hPoly(N-bromo-N-ethylbenzene-1,3-disulfonamide); ⁱ(S)-Camphorsulfonic acid; ^jDodecylphosphonic acid

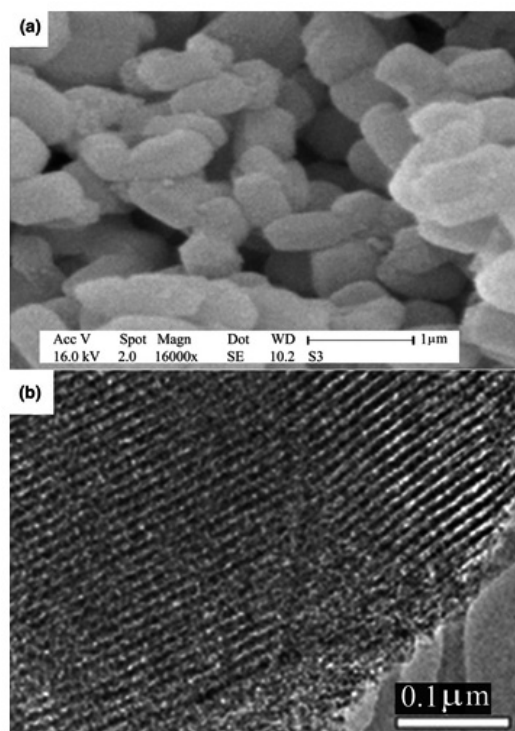
**Fig. 2.** Schematic illustration for the preparation of SBA-Pr-SO₃H.

The surface area, average pore diameter calculated by the BET method and pore volume of SBA-Pr-SO₃H are 440 m²g⁻¹, 6.0 nm and 0.660 cm³ g⁻¹, respectively (Table 4) which are smaller than those of SBA-15 because of the stabilization of sulfonosilane groups into the pores.⁸

Table 4. Porosimetry values for SBA-15 and functionalized SBA-15.

	Surface area (cm ² g ⁻¹)	Pore volume (cm ³ g ⁻¹)	Pore diameter (nm)
SBA-15	649	0.806	6.2
SBA-SO ₃ H	440	0.660	6.0

Fig. 3 illustrates the SEM and TEM images of SBA-Pr-SO₃H. SEM image (Fig. 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 (Fig. 3b) reveals the parallel channels, which resemble the pores configuration of SBA-15. This indicates that the pore of SBA-Pr-SO₃H was not collapsed during two-steps reactions.

**Fig. 3.** SEM (a) and TEM (b) images of SBA-Pr-SO₃H.

3. CONCLUSION

In summary, we have developed a solvent-free reaction for the synthesis of 2*H*-indazolo[1,2-*b*] phthalazine-triones via one-pot, three-component condensation reaction of aromatic aldehydes with dimedone and phthalhydrazide using the reusable and environmentally benign sulfonic acid

functionalized nanoporous silica (SBA-Pr-SO₃H) as a green solid acid catalyst. The merits of this protocol are high product yields, shorter reaction times, solvent-free condition, and simple workup.

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