

# Solid silica-based sulfonic acid: A remarkably efficient heterogeneous reusable catalyst for the one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

S. Mohammad Sajadi<sup>1\*</sup>, Ali Reza Faraji<sup>2</sup>, Sarbast Ahmad Mahmud<sup>3</sup>, Fereshteh Zeidali<sup>4</sup>

1. Department of Petroleum Geoscience, Faculty of Sciences, University of Soran, PO box 624, Soran, Kurdistan Regional Government, Iraq, [Tel:+9647503714550](tel:+9647503714550)
2. Iran Oilseeds and Vegetable Processing Factories Cooperative Company Applied Science and Technology Academic Center, Iran
3. Department of Petroleum Geoscience, Faculty of Sciences, University of Soran, PO box 624, Soran, Kurdistan Regional Government, Iraq
4. Ilam petrochemical Complex, Ilam, Iran

\* E-mail of the corresponding author: [smohammad.sajadi@gmail.com](mailto:smohammad.sajadi@gmail.com), [mohammad.s@soranu.com](mailto:mohammad.s@soranu.com)

## Abstract

A novel, efficient and one-pot method for preparation of 2*H*-indazolo [2,1-*b*] phthalazine-trione derivatives is reported using solid silica-based sulfonic acid as an effective heterogeneous catalyst under thermal and solvent-free conditions. This method has the advantages of high yields, a cleaner reaction, simple methodology, easy work-up and greener conditions. The catalyst is easily prepared, stable (up to 300 °C), reusable and efficient under the reaction conditions.

**Keywords:** Dimedone, 2*H*-indazolo[2,1-*b*]phthalazine-trione, indazolophthalazine, solid silica-based sulfonic acid

## 1. Introduction

One of the most important objectives now is to adapt classical processes so that pollution effects are kept to a minimum, with both a reduction in energy and consumption of raw materials. Solid acid catalysts play a prominent role in organic synthesis under heterogeneous conditions (Nasrollahzadeh 2009; Sajadi 2011; Habibi 2011; Modarresi-Alam 2008). In general, solid acid catalysts are mainly based on clay and silica (Nasrollahzadeh 2009; Habibi 2010; Modarresi-Alam 2007; Das 2007; Bahulayan 1999). In terms of convenience, silica-based catalysts are inexpensive, easy to prepare, and insoluble in most of the organic solvents, which means they have the advantage of recovery and recycle from various reactions.

Multi-component reactions (MCRs) are a promising and vital field of chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient, and timesaving manner without the isolation of any intermediate. As a result, it requires minimum effort, which minimizes the environmental loading and is acceptable from a 'Green Chemistry' point of view. In recent years, the discovery of novel MCRs has become an increasingly active area of research, yielding novel chemical scaffolds for drug discovery. Thus, the development of new multi-component reactions is a popular area of research in current organic chemistry (Menendez 2006).

In the past few decades, the synthesis of new heterocyclic compounds has been a subject of great interest due to their wide applicability. Heterocyclic compounds occur very widely in nature and are essential to life (Nasrollahzadeh 2011). Among a large variety of heterocyclic compounds, heterocycles containing phthalazine moiety are of interest because they show some pharmacological and biological

activities (Jain 2004; Carling 2004). Phthalazine derivatives were reported to possess anticonvulsant (Grasso 2000), cardiotoxic (Nomoto 1990), and vasorelaxant (Watanabe 1998) activities.

Recently the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones has been reported by Bazgir and co-workers using *p*-TSA (2008). The development of a *catalytic* synthetic method for 2*H*-indazolo[2,1-*b*]phthalazine-triones still remains an active research area.

We herein report a new protocol for preparation of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives using a catalytic amount of recyclable solid silica-based sulfonic acid under solvent-free conditions (Scheme 1, Table 1).

Solid silica-based sulfonic acid behaves as an organic–inorganic hybrid (interphase) catalyst wherein a Bronsted acid site has been selectively created (Fig. 1). Recently, solid silica-based sulfonic acid as heterogeneous solid acid catalyst has been used to catalyze a variety of reactions (Karimi 2005; Das 2006; Shylesh 2004). Recently, Nasrollahzadeh and co-workers reported the synthesis of 1,4-dihydropyridines using Sulfonic acid-functionalized silica as a heterogeneous catalyst (2010).

## 2. Experimental

### 2.1. General

All reagents were purchased from Merck and Aldrich and used without further purification. <sup>13</sup>C NMR and <sup>1</sup>H NMR spectra were recorded on Bruker, 300 and 500 MHz using TMS as an internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. IR spectra were recorded on a Shimadzu 470 spectrophotometer. TLC was performed on Merck-precoated silica gel 60-F254 plates.

### 2.2. Preparation of 3-mercaptopropylsilica (MPS)

Mesoporous amorphous silica gel (average pore diameter 60 Å) was activated by refluxing in concentrated hydrochloric acid (6 M) for 24 h and then washed thoroughly with the deionized water and dried before undergoing chemical surface modification. Refluxing the activated silica gel (10 g) with 3-mercaptopropyltrimethoxysilane (MPTMS, 5 mmol) in dry toluene for 18 h. The solid materials were filtered off and washed with hot toluene for 12 h in a continuous extraction apparatus (Soxhlet) and then dried in oven at 110 °C overnight to give the surface-bound thiol (MPS) group.

### 2.3. Preparation of solid silica-based sulfonic acid (Karimi 2005)

The thiol groups of the modified silica (MPS, 5 g) were oxidized with a 30% H<sub>2</sub>O<sub>2</sub> solution (50 ml) and concentrated H<sub>2</sub>SO<sub>4</sub> (two drops) in methanol (15 ml) for 12 h at room temperature and the solid was filtered off and washed three times with deionized water (50 ml). In order to ensure that all the sulfonic acid groups were protonated, the solid was suspended in 10 wt.% H<sub>2</sub>SO<sub>4</sub> solution (30 ml) for 4 h. The solid was then filtered off and washed thoroughly with deionized water and dried at 120 °C overnight (Scheme 2).

### 2.4. Catalyst characterization

The organic composition of the solid sulfonic acid was quantitatively determined by thermogravimetric analysis (TGA) and ion-exchange pH analysis (Karimi 2005). Typically a loading of ca. 0.35 mmol/g was obtained. The catalyst shows high thermal stability (up to 300 °C) (Karimi 2005).

### 2.5. General Procedure for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

To a mixture of dimedone (10 mmol), phthalhydrazide (10 mmol) 3-chlorobenzaldehyde (12 mmol) and solid silica-based sulfonic acid (0.8 g) was heated at 100 °C for the appropriate time (Table 1). Completion of the reaction was indicated by TLC. After completion, the reaction mass was cooled to 25 °C, then H<sub>2</sub>O was added and the mixture stirred for 5 min. The solid residue was isolated and dissolved in ethyl acetate. The solid silica-based sulfonic acid was filtered; solvent was evaporated

from the reaction mixture. The solid product was purified by recrystallization procedure in aqueous EtOH. [M.p.: 205-207 °C]  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.21 (6H, s), 2.33 (2H, s), 3.20 (1H, d,  $J$  = 19.0 Hz), 3.40 (1H, d,  $J$  = 19.0 Hz), 6.41 (1H, s), 7.23-7.88 (6H, m), 8.24-8.39 (2H, m) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.4, 28.5, 34.6, 38.0, 50.8, 64.3, 117.9, 125.9, 127.1, 127.7, 128.1, 128.9, 129.0, 129.9, 133.7, 134.6, 138.4, 151.3, 154.4, 156.0, 192.0 ppm. Anal. Calcd for  $\text{C}_{23}\text{H}_{19}\text{ClN}_2\text{O}_3$ : C, 67.90; H, 4.71; N, 6.89%. Found: C, 67.84; H, 4.78; N, 6.81%.

The desired pure product(s) was characterized by comparison of their physical data with those of known *2H*-indazolo[2,1-*b*]phthalazine-triones (Sayyafi 2008).

### 3. Result and Discussion

In the first set of experiments, the catalytic potential of some catalysts were investigated for the preparation 3,4-dihydro-3,3-dimethyl-13-(4-chlorophenyl)-*2H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione under solvent-free thermal conditions at 100 °C (Table 2) and the most efficient catalyst was solid silica-based sulfonic acid. Next, we optimized the amount of solid silica-based sulfonic acid as catalyst in the reaction between 5,5-dimethylcyclohexane-1,3-dione (dimedone), phthalhydrazide and aromatic aldehydes. The amount of solid silica-based sulfonic acid was chosen to be 0.08 g.

The effect of temperature was studied by carrying out the reactions at different temperatures [room temperature, 50 °C, 80 °C, 100 °C and 125 °C]. As it shown in Table 3, by raising the reaction temperature from room temperature to 100 °C the yield of reactions increased, but increasing the reaction temperature above 100 °C (120 °C) had no effect on yield of reactions. From these results, it was decided that 100 °C temperature would be the best temperature for all reactions.

Thus, we continued preparation of *2H*-indazolo[2,1-*b*]phthalazine-triones in an optimum model experiment: dimedone (1 mmol), phthalhydrazide (1 mmol), aldehyde (1.2 mmol) in the presence of solid silica-based sulfonic acid (0.08 g) at 100 °C (Scheme 1, Table 1). As shown in Table 3, benzaldehyde and aromatic aldehydes containing electron-withdrawing groups or electron-donating groups were employed and gave the corresponding *2H*-indazolo[2,1-*b*]phthalazine-triones without the formation of any side products, in high to excellent yields and in short reaction times under thermal and solvent-free conditions (Table 1, entries 1-8).

The simplicity, together with the use of inexpensive, non-toxic and environmentally benign catalyst under solvent free condition are other remarkable features of the procedure. All the products obtained were fully characterized by spectroscopic methods such as IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and also by comparison of the spectral data with those reported.

Under the same conditions, this reaction almost could not be observed when the aliphatic aldehyde was used as a starting material.

#### 3.1. Catalyst reuse and stability

Solid silica-based sulfonic acid works under heterogeneous conditions but its reaction centres are highly mobile, as in a homogeneous catalyst. It is an inexpensive and non-hazardous solid acid catalyst. It can easily be handled and removed from the reaction mixture by simple filtration. The recovered catalyst was reused consecutive five times with a minimum variation of the yields of the products (Table 4). After completion of the reaction, catalyst was filtered, thoroughly washed with ethanol and dried at 100 °C for 2 h and use for subsequent runs. Moreover, even after five uses of the solid silica-based sulfonic acid, there is no decrease in the reaction conversion of the product indicating high activity of the catalyst. This reusability demonstrates the high stability and turnover of solid silica-based sulfonic acid under operating condition. The reusability of the catalyst is important for large-scale operation and an industrial point of view.

### 4. Conclusion

Solid silica-based sulfonic acid, which can be prepared simply from commercially available and relatively cheap starting materials, is an efficient, thermally stable (up to 300 °C), and recoverable catalyst for the synthesis of *2H*-indazolo[2,1-*b*]phthalazine-triones under solvent-free and thermal

conditions. The present procedure provides a novel, efficient, and recyclable methodology for the preparation of 2*H*-indazolo[2,1-*b*]phthalazine-triones in a high yield with an easy work-up procedure. To the best of our knowledge, this protocol is the first example of synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones using solid silica-based sulfonic acid in which the catalyst can be recovered and reused over several reaction cycles without considerable loss of reactivity.

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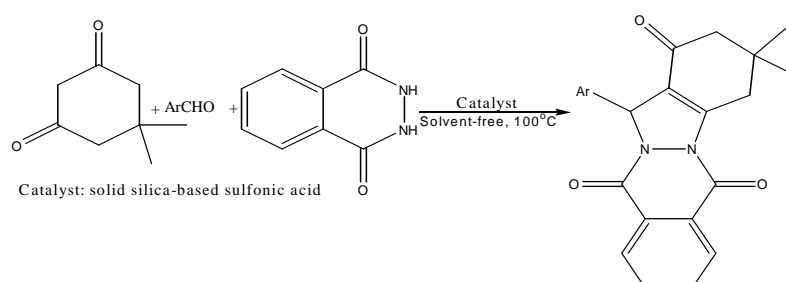
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Scheme 1. 2H-indazolo[2,1-b]-phthalazine-trione derivatives using the solid silica-based sulfonic acid under solvent-free conditions

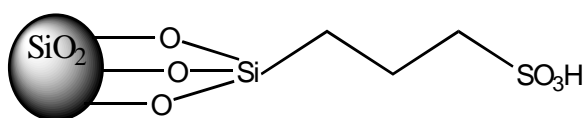
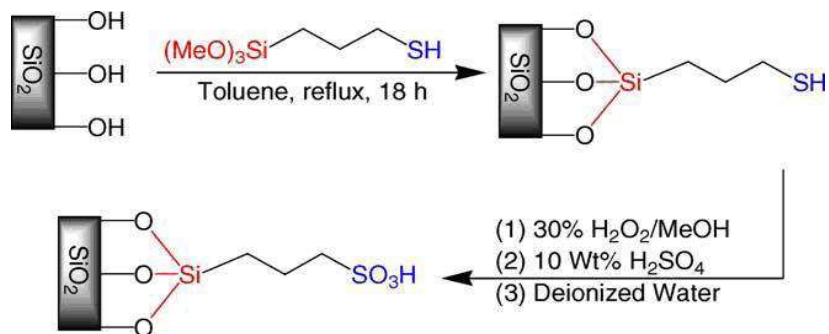


Figure 1. 1,4-dihydropyridines using Sulfonic acid-functionalized silica as a heterogeneous catalyst



Scheme 2. Preparation of solid silica-based sulfonic acid

Table 1. Effect of catalytic loading on the reaction<sup>a</sup>

Entry	Catalyst	Time (min)	Yield (%) <sup>b</sup>
1	None	90	-
2	Al <sub>2</sub> O <sub>3</sub>	70	-
3	Natrolite zeolite	70	-
4	solid silica-based sulfonic acid (0.1 g)	10	90
5	solid silica-based sulfonic acid (0.08 g)	10	90
6	solid silica-based sulfonic acid (0.06 g)	14	87
7	solid silica-based sulfonic acid (0.04)	18	79

<sup>a</sup>Reaction conditions: dimedone (1 mmol), phthalhydrazide (1 mmol) 4-chlorobenzaldehyde (1.2 mmol) and solid silica-based sulfonic acid (0.08 g) was reacted at 100 °C under solvent-free conditions.

<sup>b</sup>Isolated yield.

Table 2. Effect of temperature on reaction<sup>a</sup>

Entry	Catalyst	Time (min)	Yield (%) <sup>b</sup>
1	Room temperature	35	-
2	55	65	79
3	80	15	86
4	100	10	90
5	130	7	90

<sup>a</sup>Reaction conditions: dimedone (1 mmol), phthalhydrazide (1 mmol) 4-chlorobenzaldehyde (1.2 mmol) and solid silica-based sulfonic acid (0.08 g) was reacted at 100 °C under solvent-free conditions.

<sup>b</sup>Isolated yield.

Table 3. Preparation of indazolo[2,1-*b*]phthalazine-triones

Entry	Ar	Time (min)	Yield (%) <sup>a</sup>	Mp (Lit. mp) <sup>ref</sup>
1	C <sub>6</sub> H <sub>5</sub>	15	81	187-189 (188-190) <sup>11</sup>
2	4-ClC <sub>6</sub> H <sub>4</sub>	15	90	172-174 (173-175) <sup>11</sup>
3	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	15	84	127-129 (126-128) <sup>11</sup>
4	3-BrC <sub>6</sub> H <sub>4</sub>	15	83	174-176 (174-176) <sup>11</sup>
5	3-ClC <sub>6</sub> H <sub>4</sub>	17	82	205-207
6	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	15	85	176-178 (175-177) <sup>11</sup>
7	4-BrC <sub>6</sub> H <sub>4</sub>	15	86	185-187 (184-186) <sup>11</sup>
8	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	20	83	159-161 (160-162) <sup>11</sup>

<sup>a</sup>Yield refer to the pure isolated products.

Table 4. Reusability of solid silica-based sulfonic acid

Entry	No of cycles	Yield (%) <sup>a</sup>
1	0	90
2	1	90
3	2	89
4	3	87
5	4	86
6	5	85

<sup>a</sup>Isolated yield.



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