

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

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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),

cardiotonic (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. ¹³C NMR and ¹H 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% H₂O₂ solution (50 ml) and concentrated H₂SO₄ (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.% H₂SO₄ 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 H₂O

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] ¹H NMR (300 MHz, CDCl₃): δ = 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; ¹³C NMR (75 MHz, CDCl₃): δ = 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 C₂₃H₁₉ClN₂O₃: 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 2*H*-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)-2*H*-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 2*H*-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 2*H*-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, ¹H NMR, ¹³C 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 2*H*-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.

References

- Bahulayan, D., Sukumar, R., Sabu, K. R., Lalithambika, M. (1999), "An easy synthesis of 4,4'-di-aminodiphenylmethanes on natural kaolinites", *Green Chemistry* **1**, 191-193.
- Carling, R. W., Moore, K. W., Street, L. J., Wild, D., Isted, C., Leeson, P. D., Thomas, S., O'Connor, D., McKernan, R. M., Quirk, K., Cook, S. M., Attack, J. R., Waftord, K. A., Thompson, S. A., Dawson, G. R., Ferris, P., Castro, J. L. (2004), "3-Phenyl-6-(2-pyridyl)methoxy-1,2,4-triazolo[3,4-*a*]phthalazines and analogues: high-affinity α -aminobutyric acid-A benzodiazepine receptor ligands with 2, 3, and 5-subtype binding selectivity over 1 α ", *Journal of Medicinal Chemistry* **47**, 1807-1822.
- Das, B., Laxminarayana, K., Ravikanth, B. (2007), "Application of heterogeneous catalysts for an efficient synthesis of α -keto enol ethers", *Journal of Molecular Catalysis A: Chemical* **271**, 131-133.
- Das, B., Damodar, K., Chowdhury, N., Kumar, R. A. (2007), "Application of heterogeneous solid acid catalysts for Friedlander synthesis of quinolines", *Journal of Molecular Catalysis A: Chemical* **274**, 148-152.
- Das, B., Venkateswarlu, K., Holla, H., Krishnaiah, M. (2006), "Sulfonic acid functionalized silica: A remarkably efficient heterogeneous reusable catalyst for α -monobromination of carbonyl compounds using *N*-bromosuccinimide", *Journal of Molecular Catalysis A: Chemical* **253**, 107-111.
- Das, B., Venkateswarlu, K., Krishnaiah, M., Holla, H. (2006), "A highly chemoselective Boc protection of amines using sulfonic-acid-functionalized silica as an efficient heterogeneous recyclable catalyst", *Tetrahedron Letters* **47**, 7551-7556.
- Grasso, S., DeSarro, G., Micale, N., Zappala, M., Puia, G., Baraldi, M., Demicheli, C. (2000), "Synthesis and anticonvulsant activity of novel and potent 6,7-methylenedioxyphthalazin-1(2*H*)-ones", *Journal of Medicinal Chemistry* **43**, 2851-2859.
- Habibi, D., Nasrollahzadeh, M., Kamali, T. A. (2011), "Green synthesis of the 1-substituted 1*H*-1,2,3,4-tetrazoles by application of the Natrolite zeolite as a new and reusable heterogeneous catalyst", *Green Chemistry* **13**, 3499-3504.
- Habibi, D., Nasrollahzadeh, M., Bayat, Y. (2011), "AlCl₃ as an effective Lewis acid for the synthesis of arylaminotetrazoles", *Synthetic Communications* **41**, 2135-2145.
- Habibi, D., Nasrollahzadeh, M. (2010), "Silica-supported ferric chloride (FeCl₃-SiO₂): an efficient and recyclable heterogeneous catalyst for the preparation of arylaminotetrazoles", *Synthetic Communications* **40**, 3159-3167.
- Jain, R. P., Vederas, J. C. (2004), "Structural variations in keto-glutamines for improved inhibition against hepatitis A virus 3C proteinase", *Bioorganic & Medicinal Chemistry Letters* **14**, 3655-3658.
- Karimi, B., Khalkhali, M. (2005), "Solid silica-based sulfonic acid as an efficient and recoverable interphase catalyst for selective tetrahydropyranylation of alcohols and phenols", *Journal of Molecular Catalysis A: Chemical* **232**, 113-117.
- Karimi, B., Zareyee, D. (2005), "A high loading sulfonic acid-functionalized ordered nanoporous silica as

an efficient and recyclable catalyst for chemoselective deprotection of tert-butyldimethylsilyl ethers, *Tetrahedron Letters* **46**, 4661-4665.

Menendez, J. C. (2006), *Multicomponent reactions*, *Synthesis* 2624.

Modarresi-Alam, A. R., Nasrollahzadeh, M., Khamooshi, F. (2008), *Al(HSO₄)₃ Mediated for the preparation of primary carbamates under solvent-Free conditions*, *Scientia Iranica* **15**, 452-455.

Modarresi-Alam, A. R., Nasrollahzadeh, M., Khamooshi, F. (2007), *Solvent-free preparation of primary carbamates using silica sulfuric acid as an efficient reagent*, *Arkivoc* (**xvi**), 234-245.

Modarresi-Alam, A. R., Khamooshi, F., Nasrollahzadeh, M., Amirazizi, H. A. (2007), *Silica supported perchloric acid (HClO₄-SiO₂): an efficient reagent for the preparation of primary carbamates under solvent-free conditions*, *Tetrahedron* **63**, 8723-8726.

Mohammadi, B., Hosseini Jamkarani, S. M., Kamali, T. A., Nasrollahzadeh, M., Mohajeri, A. (2010), *Sulfonic acid-functionalized silica: a remarkably efficient heterogeneous reusable catalyst for the one-pot synthesis of 1,4-dihydropyridines*, *Turkish Journal of Chemistry* **34**, 613-619.

Nasrollahzadeh, M., Sajadi, S. M., Maham, M., Salaryan, P., Enayati, A., Sajjadi, S. A., Naderi, K. (2011), *Optimal extraction method of phenolics from the root of Euphorbia condylocarpa*, *Chemistry of Natural Compounds* **47**, 434-435.

Nasrollahzadeh, M., Habibi, D., Shahkarami, Z., Bayat, Y. (2009), *A general synthetic method for the formation of arylaminotetrazoles using natural natrolite zeolite as a new and reusable heterogeneous catalyst*, *Tetrahedron* **65**, 10715-10719.

Nasrollahzadeh, M., Bayat, Y., Habibi, D., Moshaei, S. (2009), *FeCl₃-SiO₂ as a reusable heterogeneous catalyst for the synthesis of 5-substituted 1H-tetrazoles via [2+3] cycloaddition of nitriles and sodium azide*, *Tetrahedron Letters* **50**, 4435-4438.

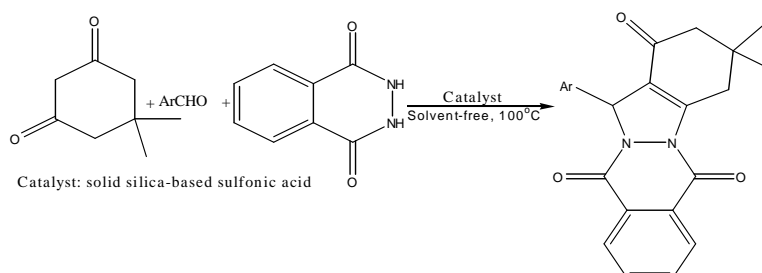
Nomoto, Y., Obase, H., Takai, H., Teranishi, M., Nakamura, J., Kubo, K. (1990), *Studies on cardiogenic agents.2. synthesis of novel phthalazine and 1,2,3-benzotriazine derivatives*, *Chemical & Pharmaceutical Bulletin (Tokyo)* **38**, 2179-2183.

Sajadi, S. M., Khalaj, M., Hosseini Jamkarani, S. M., Maham, M., Kashefi, M. (2011), *Aluminum (III) hydrogensulfate: An efficient solid acid catalyst for the preparation of 5-substituted 1H-tetrazoles*, *Synthetic Communications* **41**, 3053-3059.

Sayyafi, M., Seyyedhamzeh, M., Khavasi, H. R., Bazgir, A. (2008); *One-pot, three-component route to 2H-indazolo[2,1-b]phthalazine-triones*, *Tetrahedron* **64**, 2375-2378.

Shylesh, A., Sharma, S., Mirajkar, S. P., Sing, A. P. (2004), *Silica functionalised sulphonic acid groups: synthesis, characterization and catalytic activity in acetalization and acetylation reactions*, *Journal of Molecular Catalysis A: Chemical* **212**, 219-228.

Watanabe, N., Kabasawa, Y., Takase, Y., Matsukura, M., Miyazaki, K., Ishihara, H., Kodama, K., Adachi, H. (1998), *4-Benzylamino-1-chloro-6-substituted phthalazines: synthesis and inhibitory activity toward phosphodiesterase*, *Journal of Medicinal Chemistry* **41**, 3367-3372.



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

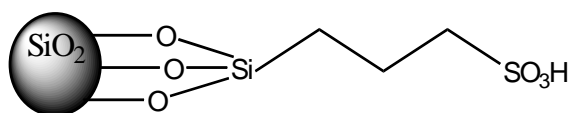
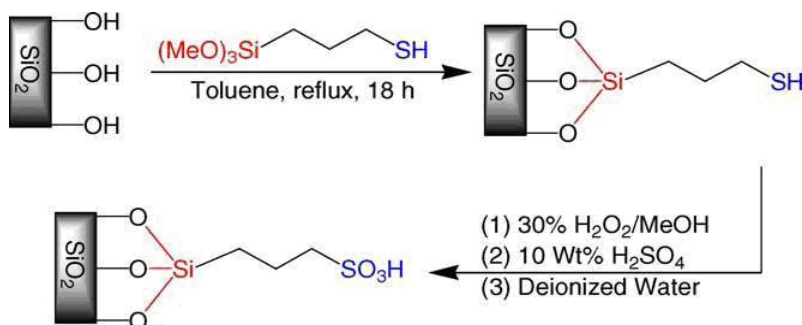


Figure 1. 1,4-dihydropyridines using Sulfonic acid-functionalized silica as a heterogeneous catalyst



Scheme 2. Preparation of solid silica-based sulfonic acid

Table 1. Effect of catalytic loading on the reaction^a

Entry	Catalyst	Time (min)	Yield (%) ^b
1	None	90	-
2	Al ₂ O ₃	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

^aReaction 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.

^bIsolated yield.

Table 2. Effect of temperature on reaction^a

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

^aReaction 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.

^bIsolated yield.

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

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

^aYield refer to the pure isolated products.

Table 4. Reusability of solid silica-based sulfonic acid

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

^aIsolated yield.