

Sulfonic acid-functionalized silica: a remarkably efficient heterogeneous reusable catalyst for the one-pot synthesis of 1,4-dihydropyridines

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An efficient one-pot method for the synthesis of 1,4-dihydropyridines from β -dicarbonyl compounds, aldehyde, and ammonium acetate is reported using sulfonic acid-functionalized silica at 90 °C under solvent-free conditions with good to excellent yields. The catalyst is easily prepared, stable (up to 300 °C), reusable, and efficiently used under reaction conditions.

Key Words: 1,4-Dihydropyridine, β -dicarbonyl compounds, solid acid, SiO₂-R-SO₃H, heterogeneous catalyst.

Introduction

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are well known as Ca²⁺ channel blockers and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension.^{1,2} 1,4-Dihydropyridines possess a wide range of biological activities, being vasodilators, bronchodilators, geroprotectives, hepatoprotectives, and antitumor, antiatherosclerotic, and antidiabetic agents.^{3a-e}

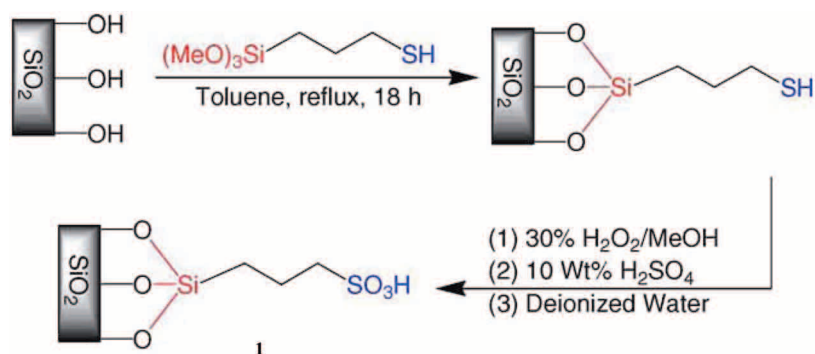
Recent studies have revealed that 1,4-DHPs exhibit several other medicinal applications, including neuroprotectant^{4a} and platelet antiaggregator activity,^{4b} in addition to acting as cerebral antiischemic agents

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in the treatment of Alzheimer's disease^{4c} and as a chemosensitizer in tumor therapy.^{4d} A recent computational analysis of the comprehensive medicinal chemistry database showed the DHP framework to be among the most prolific chemo types found. Development of drug resistance, both intrinsic drug resistance and acquired drug resistance, remains a clinical obstacle in the chemotherapy of many cancers.^{5,6} Among the possible resistance modifiers, the dihydropyridines, calcium antagonists, have been studied extensively as the analogue of verapamil.⁷ Furthermore, the photocatalytic oxidation of these compounds to pyridines has been intensively investigated.⁸

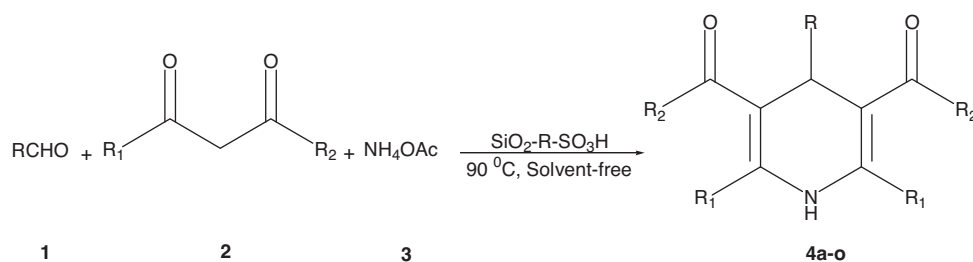
More than 100 years ago, the first 1,4-DHPs were synthesized by Hantzsch.⁹ The classical method involves a one-pot condensation of an aldehyde with 1,3-dicarbonyl compounds and ammonia, either in acetic acid or in a refluxing alcohol for a longer period.

An important objective of chemistry is to adapt classical processes so that pollution effects are kept to a minimum, with both reductions in energy usage and consumption of raw materials. Solid acid catalysts play a prominent role in organic synthesis under heterogeneous conditions. In general, solid acid catalysts are mainly based on clay¹⁰ or silica.^{11,12} In terms of convenience, silica-based catalysts are inexpensive, easy to prepare, and insoluble in all organic solvents. Hence, they can be recovered and recycled from reactions. Among various silica-based heterogeneous catalysts, sulfonic acid-functionalized silica has the advantages of being low cost, easy to prepare, and able to be recycled.¹³ Sulfonic acid-functionalized silica behaves as an organic-inorganic hybrid (interphase) catalyst, wherein a Brønsted acid site has been selectively created. Recently, silica-functionalized sulfonic acid has been used to catalyze a variety of reactions.¹⁴ The catalyst (**1**) was prepared^{14d} by the immobilization of propyl thiol on silica using 3-mercaptopropyltrimethoxysilane, followed by the selective oxidation of the thiol groups by aqueous H₂O₂ to the sulfonic acid groups (Scheme 1). The catalyst shows high thermal stability (up to 300 °C).^{14d}



Scheme 1.

In continuation of our recent work on the synthesis of heterocycles¹⁵ and application of heterogeneous reagents for the development of synthetic methodologies,¹² we report a new protocol for the preparation of 1,4-dihydropyridines from a wide variety of aromatic aldehydes using sulfonic acid-functionalized silica (**1**)^{14d} under thermal and solvent-free conditions (Scheme 2 and Table).



Scheme 2.

Experimental section

General

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. The NMR spectra were recorded on Bruker Avance DRX 250, 300, and 500 MHz instruments. The chemical shifts (δ) are reported in ppm relative to the TMS as the internal standard. J values are given in Hz. The IR spectra were recorded on a Shimadzu 470 spectrophotometer. TLC was performed on silica gel polygram SIL G/UV 254 plates.

Preparation of 3-mercaptopropylsilica (MPS)^{14d}

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. The activated silica gel (10 g) was refluxed 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 an oven at 110 °C overnight to give the surface-bound thiol (MPS) group.

Preparation of solid silica-based sulfonic acid **1**^{14d}

The thiol groups of the modified silica (MPS, 5 g) were oxidized with a 30% H₂O₂ solution (50 mL) and concentrated H₂SO₄ (2 drops) in methanol (15 mL) for 12 h at room temperature. The solid was filtered off and washed 3 times with deionized water (50 mL). In order to ensure that all of 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, washed thoroughly with deionized water, and dried at 120 °C overnight.

The organic composition of the solid sulfonic acid was quantitatively determined by thermogravimetric analysis (TGA), acid-base titration, and ion exchange pH analysis.^{14d} Typically, a loading of approximately 0.35 mmol/g was obtained. When the washed sulfonated product **1** was placed in an aqueous NaCl solution, the solution pH dropped virtually instantaneously to approximately pH 2, as ion exchange occurred between protons and sodium ions (proton exchange capacity: 0.33 mmol/g of sulfonic acid **1**, which is in good agreement with

the results obtained from TGA and titration). This result also shows that more than 94% of the surface-bound thiol groups were converted to the corresponding sulfonic acid group.^{14d}

General procedure for the synthesis of 1,4-dihydropyridines

A mixture of aldehyde (1 mmol), β -dicarbonyl compounds (2 mmol), NH_4OAc (1.5 mmol), and $\text{SiO}_2\text{-R-SO}_3\text{H}$ (0.1 g) was heated at 90 °C with stirring for 60 min. After completion of the reaction (as indicated by TLC), the reaction mixture was washed with ice-cold water and extracted with EtOAc, followed by a water and brine solution, and dried with anhydrous Na_2SO_4 . The solution was concentrated in a vacuum to afford the crude product, and then the crude product was purified by using column chromatography. All of the products were known compounds, and the spectral data and melting points were identical to those reported in the literature.

Catalyst reuse and stability

Sulfonic acid-functionalized silica works under heterogeneous conditions, but its reaction centers are highly mobile, as in a homogeneous catalyst. It is an inexpensive and nonhazardous solid acid catalyst. It can easily be handled and removed from the reaction mixture by simple filtration. The recovered catalyst was reused consecutively 5 times with a minimum of variation of the yields of the products (Table, entry 2). This reusability demonstrates the high stability and turnover of solid silica-based sulfonic acid under operating conditions. The simplicity, together with the use of an inexpensive, nontoxic, and environmentally benign catalyst under solvent-free conditions, is another remarkable feature of the procedure.

Results and discussion

However, the yields of 1,4-DHPs obtained by the Hantzsch method are generally low. Due to some disadvantages of this method, several efficient methods have been developed for the synthesis of 1,4-DHPs, which comprise the use of microwaves, ionic liquid, high temperatures in refluxing solvents, TMSCl-NaI , and metal triflates.¹⁶ However, the use of large quantities of volatile organic solvents, high temperatures, expensive metal precursors, longer reaction times, stoichiometric use of reagents and catalysts, and unsatisfactory yields limit these methods. Additionally, the clean handling of some anhydrous metal halides is not easy enough in the laboratory apart from their hygroscopic nature, due to the strong tendency for hydrolysis. Therefore, it is desirable to develop a more efficient and convenient method for the synthesis of 1,4-dihydropyridines.

First, we optimized the amount of $\text{SiO}_2\text{-R-SO}_3\text{H}$ catalyst required in the reaction between aldehyde, 1,3-dicarbonyl compounds, and ammonium acetate. The optimum amount of $\text{SiO}_2\text{-R-SO}_3\text{H}$ was found to be 0.1 g in the presence of aldehydes (1 mmol), 1,3-dicarbonyl compound (2 mmol), and ammonium acetate (1.5 mmol). As shown in the Table, benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as the nitro or halide groups) or electron-donating groups (such as the alkoxy group) were employed and gave the corresponding 1,4-dihydropyridine. The nature of the substituent on the benzaldehyde did not affect the reaction time. This is a new method for the synthesis of these compounds, and in all cases the reaction gives the products in good yields (86%-93%) and prevents problems that many associate with solvent use, such as cost, handling, safety, and pollution.

Table. One-pot synthesis of 1,4-dihydropyridines under solvent-free conditions using SiO₂-R-SO₃H.

Entry	R	R ₁	R ₂	Product	Yield ^a %	Reference
1	C ₆ H ₅	CH ₃	OMe	4a	93	17
2	C ₆ H ₅	CH ₃	OEt	4b	93,90 ^b	17, 18
3	2-OMeC ₆ H ₄	CH ₃	OMe	4c	88	17
4	2-NO ₂ C ₆ H ₄	CH ₃	OMe	4d	90	17
5	2-NO ₂ C ₆ H ₄	CH ₃	OEt	4e	90	17
6	2-BrC ₆ H ₄	CH ₃	OEt	4f	91	17
7	4-ClC ₆ H ₄	CH ₃	OEt	4g	90	17
8	4-NO ₂ C ₆ H ₄	CH ₃	OEt	4h	89	17, 18
9	4-BrC ₆ H ₄	CH ₃	OEt	4i	90	17, 18
10	4-MeC ₆ H ₄	CH ₃	OMe	4j	88	17
11	4-MeC ₆ H ₄	CH ₃	OEt	4k	89	17
12	4-OMeC ₆ H ₄	CH ₃	OMe	4l	87	16i
13	4-OMeC ₆ H ₄	CH ₃	OEt	4m	89	17
14	3,4-(OMe) ₂ C ₆ H ₃	CH ₃	OEt	4n	86	16i
15	3,4-Cl ₂ C ₆ H ₃	CH ₃	OEt	4o	87	16i

^aYields refer to the pure isolated products.^bYield after the fifth cycle.

Conclusions

We have developed a novel and highly efficient method for the synthesis of 1,4-dihydropyridines by treatment of aromatic aldehydes with a 1,3-dicarbonyl compound in the presence of silica solid sulfonic acid as a catalyst. The significant advantages of this methodology are high yields, a simple work-up procedure, cleaner reaction, and easy preparation and handling of the catalyst. The catalyst can be recovered by filtration and reused.

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References

1. Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762-769.
2. (a) Nakayama, H.; Kasoaka, Y. *Heterocycles* **1996**, *42*, 901-909; (b) Şafak, C.; Doğan, E.; Erol, K. *Turk. J. Chem.* **2006**, *30*, 109-117.
3. (a) Godfraid, T.; Miller, R.; Wibo, M. *Pharmacol. Rev.* **1986**, *38*, 321-416; (b) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269-289; (c) Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H. *Drug Design Discovery*

- 1992, 8, 273-289; (d) Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; SchraVan, K. *Eur. J. Med. Chem.* **1992**, 27, 229-235; (e) Ayhan Kılıçgil, G.; Tunçbilek, M.; Ertan, R.; Erol, K.; Yıldırım, E. *Turk. J. Chem.* **2000**, 24, 255-260.
4. (a) Klusa, V. *Drugs Fut.* **1995**, 20, 135-138; (b) Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Am. J. Kidney. Dis.* **1993**, 21, 53-64; (c) Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Drugs Fut.* **1992**, 17, 465-468; (d) Boer, R.; Gekeler, V. *Drugs Fut.* **1995**, 20, 499-509.
 5. Davis, H. L.; Davis, T. E. *Cancer Treat. Rep.* **1979**, 63, 809-815.
 6. Pastan, I.; Gottesman, M. M. N. *Engl. J. Med.* **1987**, 316, 1388-1393.
 7. Tanabe, H.; Tasaka, S.; Ohmori, H.; Gomi, N.; Sasaki, Y.; Machida, T.; Lino, M.; Kiue, A.; Naito, S.; Kuwano, M. *Bioorg. Med. Chem.* **1998**, 6, 2219-2227.
 8. Zhang, D.; Wu, L. Z.; Zhou, L.; Han, X.; Yang, Q. Z.; Zhang, L. P.; Tung, C. H. *J. Am. Chem. Soc.* **2004**, 126, 3440-3441.
 9. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, 215, 1-82.
 10. (a) Bahulayan, D.; Narayan, G.; Sreekumar, V.; Lalithambika, M. *Synth. Commun.* **2002**, 32, 3565-3574; (b) Bahulayan, D.; Sukumar, R.; Sabu, K.R.; Lalithambika, M. *Green. Chem.* **1999**, 1, 191-193.
 11. (a) Das, B.; Laxminarayana, K.; Ravikanth, B. *J. Mol. Catal. A: Chem.* **2007**, 271, 131-133; (b) Das, B.; Damodar, K.; Chowdhury, N.; Kumar, R. A. *J. Mol. Catal. A: Chem.* **2007**, 274, 148-152; (c) Bigdeli, M. A.; Heravi, M. M.; Mahdavinia, G. H. *J. Mol. Catal. A: Chem.* **2007**, 275, 25-29.
 12. (a) Modarresi-Alam, A. R.; Nasrollahzadeh, M.; Khamooshi, F. *Arkivoc* **2007**, xvi, 238-245; (b) Modarresi-Alam, A. R.; Khamooshi, F.; Nasrollahzadeh, M.; Amirazizi, H. A. *Tetrahedron* **2007**, 63, 8723-8726; (c) Modarresi-Alam, A. R.; Nasrollahzadeh, M.; Khamooshi, F. *Scientia Iranica* **2008**, 15, 452-455.
 13. (a) Mbaraka, I. K.; Radu, D. R.; Lin, V. S.; Shanks, B. H. *J. Catal.* **2003**, 219, 329-336; (b) Diaz, I.; Marquez-Alvarez, C.; Mohino, F.; Perez-Pariente, J.; Sastre, E. *J. Catal.* **2000**, 193, 283-295; (c) Diaz, I.; Marquez-Alvarez, C.; Mohino, F.; Perez-Pariente, J.; Sastre, E. *J. Catal.* **2000**, 193, 295-302; (d) Wilson, K.; Lee, A. F.; Macquarrie, D. J.; Clark, J. H. *Appl. Catal. A* **2002**, 228, 127-133; (e) Das, D.; Lee, J. F.; Cheng, S. *Chem. Commun.* **2001**, 2178-2179; (f) Melero, J. A.; Stucky, G. D.; Van Grieken, R.; Morales, G. *J. Mater. Chem.* **2002**, 12, 1664-1670; (g) Clark, J. H. *Acc. Chem. Res.* **2002**, 35, 791-797; (h) Margolese, D.; Melero, J. A.; Christiansen, S. C.; Chmelka, B. F.; Stucky, G. D. *Chem. Mater.* **2000**, 12, 2448-2459; (i) Van Rhijn, W. M.; De Vos, D. E.; Sels, B. F.; Bossaert, W. D.; Jacobs, P. A. *Chem. Commun.* **1998**, 317-318; (j) Lim, M. H.; Blanford, C. F.; Stein, A. *Chem. Mater.* **1998**, 10, 467-470; (k) Yang, Q.; Kapoor, M. P.; Inagaki, S. *J. Am. Chem. Soc.* **2002**, 124, 9694-9695; (l) Das, B.; Suneel, K.; Venkateswarlu, K.; Ravikanth, B. *Chem. Pharm. Bull.* **2008**, 56, 366-368.
 14. (a) Karimi, B.; Zareyee, D. *Tetrahedron Lett.* **2005**, 46, 4661-4665; (b) Zareyee, D.; Karimi, B. *Tetrahedron Lett.* **2007**, 48, 1277-1280; (c) Das, B.; Venkateswarlu, K.; Krishnaiah, M.; Holla, H. *Tetrahedron Lett.* **2006**, 47, 7551-7556; (d) Karimi, B.; Khalkhali, M. J. *J. Mol. Catal. A: Chem.* **2005**, 232, 113-117; (e) Das, B.; Venkateswarlu, K.; Holla, H.; Krishnaiah, M. *J. Mol. Catal. A: Chem.* **2006**, 253, 107-111; (f) Shylesh, A.; Sharma, S.; Mirajkar, S. P.; Singh, A. P. *J. Mol. Catal. A: Chem.* **2004**, 212, 219-228.
 15. (a) Habibi, D.; Nasrollahzadeh, M.; Faraji, A. R. Bayat, Y. *Tetrahedron* **2010**, 66, 3866-3870; (b) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. *Tetrahedron* **2009**, 65, 10715-10719; (c) Nasrollahzadeh, M.; Bayat, Y.; Habibi, D.; Moshatee, S. *Tetrahedron Lett.* **2009**, 50, 4435-4438; (d) Modarresi-Alam, A. R.; Nasrollahzadeh, M. *Turk. J. Chem.* **2009**, 33, 1-14; (e) Kamali, T. A.; Habibi, D.; Nasrollahzadeh, M. *Synlett* **2009**, 2601-2604; (f) Kamali, T. A.; Bakherad, M.; Nasrollahzadeh, M.; Farhangi, S.; Habibi, D. *Tetrahedron Lett.* **2009**, 50, 5459-5462;

- (g) Modarresi-Alam, A. R.; Khamooshi, F.; Rostamizadeh, M.; Keykha, H.; Nasrollahzadeh, M.; Bijanzadeh, H. R.; Kleinpeter, E. *J. Mol. Struc.* **2007**, *841*, 61-66; (h) Bakherad, M; Keivanloo, A; Bahramian, B; Kamali, T. A. *J. Braz. Chem. Soc.* **2009**, *20*, 907-912; (i) Bakherad, M; Keivanloo, A; Tajbakhsh, M; Kamali, T. A. *Synth. Commun.* **2010**, *40*, 173-178.
16. (a) Khadikar, B. M.; Gaikar, V. G.; Chitnavis, A. A. *Tetrahedron Lett.* **1995**, *36*, 8083-8086; (b) Ohberg, L.; Westman, J. *Synlett* **2001**, 1296-1298; (c) Agarwal, A.; Chauhan, P. M. S. *Tetrahedron Lett.* **2005**, *46*, 1345-1348; (d) Ji, S. J.; Jiang, Z. Q.; Lu, J.; Loh, T. P. *Synlett* **2004**, 831-835; (e) Sridhar, R.; Perumal, P. T. *Tetrahedron* **2005**, *61*, 2465-2470; (f) Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S.; Bertoasi, V. *J. Org. Chem.* **2003**, *68*, 6172-6183; (g) Dondoni, A.; Massi, A.; Minghini, E.; Bertoasi, V. *Tetrahedron* **2004**, *60*, 2311-2326; (h) Tewari, N.; Dwivedi, N.; Tripathi, R. P. *Tetrahedron Lett.* **2004**, *45*, 9011-9014; (i) Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129-4131.
17. Maheswara, M.; Siddaiah, V.; Rao, Y. K.; Tzeng, Y. M.; Sridhar, C. *J. Mol. Catal. A: Chem.* **2006**, *260*, 179-180.
18. Arslan, M.; Faydali, C.; Zengin, M.; Küçükislamoglu, M.; Demirhan, H. *Turk. J. Chem.* **2009**, *33*, 769-774.