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Silica Functionalized Sulfonic Acid Catalyzed One-Pot Synthesis of 4,5,8a-Triarylhexahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones under Liquid Phase Catalysis

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Neste trabalho descreve-se a catálise sob fase líquida de 4,5,8a-triarilhexahidropyrimido[4,5-*d*] pyrimidine-2,7(1*H*,3*H*)-diones (**4a-k**) em um pote, catalisada por SiO$_2$-SO$_3$H. O catalisador é preparado facilmente, sendo altamente estável, muito simples de usar e reciclável após cinco vezes sem perda significativa de atividade.

SiO$_2$-SO$_3$H catalyzed one-pot synthesis of 4,5,8a-triarylhexahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones (**4a-k**) is reported under liquid phase catalysis. The catalyst is easily prepared, highly stable, very simple to handle and recycled for five times without loss of significant activity.

Keywords: pyrimido[4,5-*d*]pyrimidine, silica functionalized sulfonic acid, liquid phase catalysis, recyclability, solid acid catalysis

Introduction

Pyrimido[4,5-*d*]pyrimidines are an important class of fused heterocycles since they have close resemblance with purine and pteridine systems.[1] This nucleus is associated with a diverse range of biological activities[2-4] such as anti-allergic, bronchodilators, vasodilators, antihypertensive, and as phosphodiesterase inhibitors. Recently, pyrimido[4,5-*d*]pyrimidine analogues of folic acid were found to show antitumor activity.[5] Thus, the preparation of this heterocyclic nucleus has attracted great attention. Most methods for the preparation of pyrimido[4,5-*d*]pyrimidines are based on the manipulation of uracils.[6] Some patents have also been reported.[2-4] The Biginelli reaction[7] has been employed for the synthesis of hexahydropyrimido[4,5-*d*]pyrimidine-2,7-diones[8] by the one-pot condensation of acetophenone, urea and aldehydes. The most recent method involves the condensation of aldehydes, urea and alkyl arylketones in acetic acid using catalytic amounts of KHSO$_4$ via the Biginelli reaction.[9] Though this method is simple and gives high yield of products, it suffers from the disadvantage of using toxic and environment unfriendly acetic acid as solvent. Thus, a simple, cost-effective and environment-friendly procedure is needed for the synthesis of pyrimido[4,5-*d*]pyrimidines.

Heterogeneous solid acid catalysts[10] for the synthesis of fine chemicals have attracted considerable attention from both environmental and economical perspectives. Recently, more emphasis is made on solid acids containing organic-inorganic hybrids in which acid functionality is covalently anchored onto inorganic support. These solid acids find increased advantages such as easy separation from the reaction medium; reactions are usually clean and selective; procedures are usually cost-effective; and the catalyst is stable and hence can be recycled, which leads to high turn-over numbers. Among various covalently anchored solid acids, silica functionalized sulfonic acid (SiO$_2$-SO$_3$H)[11] finds more utility in organic synthesis.

In this paper, we report a silica functionalized sulfonic acid (SiO$_2$-SO$_3$H) catalyzed synthesis of 4,5,8a-triarylhexahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones by one-pot condensation of aldehydes, urea and alkyl arylketones *via* stirring in acetonitrile at 80 °C using catalytic amounts of KHSO$_4$ under liquid phase catalysis (Scheme 1).

Results and Discussion

For the preparation of silica functionalized sulfonic acid (SiO$_2$-SO$_3$H), activated silica was refluxed with trimethoxy(3-sulfanylpropyl)silane in toluene for 24 h to give 3-sulfanylpropylsilica, which was subjected to oxidation with 30% H$_2$O$_2$ in the presence of concentrated

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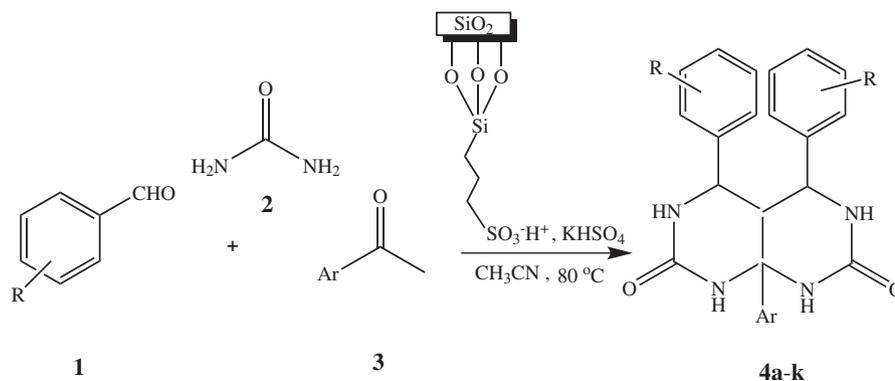
Scheme 1.

sulfuric acid, to give SiO$_2$-SO$_3$H (Scheme 2) according to the literature method with slight modifications.[12] The SiO$_2$-SO$_3$H was characterized by infrared spectroscopy, thermal analysis and elemental analysis. The IR spectra of pure silica shows peak in the range of 3600-3200 cm^{-1} attributed to the hydroxyl stretching of internal silanol groups. The propyl groups attached to the silicon framework in MPS (3-mercaptopropyl silica) are identified by methylene stretching bands at 2925 and 2854 cm^{-1}. The band which appeared at 2575 cm^{-1} due to the –SH group in MPS, disappeared in SiO$_2$-SO$_3$H confirming that –SH was completely oxidized to -SO$_3$H. Further, new bands at 1404 cm^{-1} were due to the asymmetric stretching of SO$_2$ moieties. This confirms the presence of sulfonic acid groups onto the surface of silica. The stability of SiO$_2$-SO$_3$H was determined on the basis of thermogravimetric analysis (TGA). The TGA curve (Figure 1) shows the initial weight loss below 100 °C, which was attributed to residual solvent or water molecules trapped into the silica gel framework. The subsequent weight loss occurs between 300 and 600 °C which was due to the loss of organic functionalities covalently anchored onto the surface of

silica. Thus, the catalyst is stable up to 300 °C and hence it is safe to carry out the reaction at 80 °C. The amount of sulfur content loaded onto the surface of silica was determined by elemental analysis. Typically, a loading of 0.3 mmol g^{-1} (SO$_3$H group) onto the surface of silica was obtained.

4,5,8a-Triarylhexahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones (**4a-k**) were synthesized by stirring a mixture of an aromatic aldehyde, urea, an aromatic ketone, and KHSO$_4$ in acetonitrile at 80 °C in the presence of SiO$_2$-SO$_3$H. To select the optimum conditions for the synthesis of **4**, 4-chlorobenzaldehyde, urea, and 4-fluoroacetophenone were selected as the test substrates. The reaction with test substrates in the ratio of 2:3:1 in the presence of KHSO$_4$ (1 eq.) was carried out under different set of conditions with respect to different catalysts in varied molar concentrations, temperature, and solvents. Firstly, the reaction with test substrates was carried out in the presence of different catalysts like SiO$_2$-HClO$_4$, SiO$_2$-PPA, SiO$_2$-SO$_3$H and without catalyst. The results are summarized in Table 1. SiO$_2$-SO$_3$H was found to be the best catalyst in terms of reaction time, yield and recyclability. Further, the reaction was carried out with
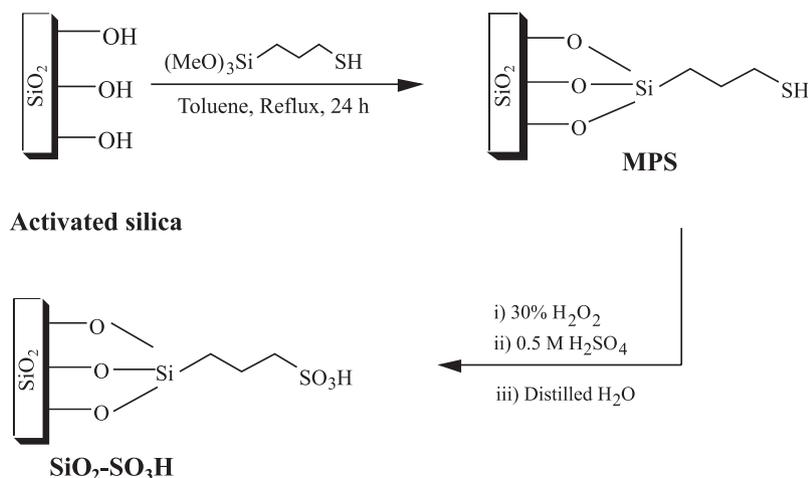
Scheme 2.
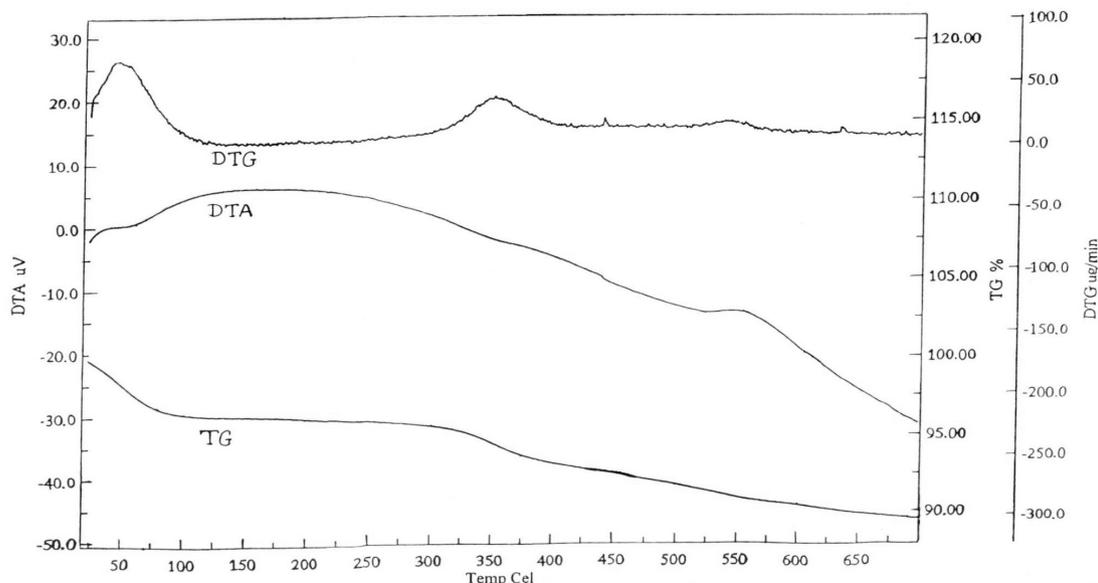
Figure 1. TG-DTG-DTA of silica functionalized sulfonic acid (SiO$_2$-SO$_3$H).

Table 1. Effect of different catalysts for the synthesis[a] of **4c** under liquid phase catalysis

Entry	Catalyst	Time / h	Yield[b] / (%)
1	No catalyst	15	Traces
2	Silica-HClO$_4$	12	56
3	Silica-PPA	12	60
4	SiO$_2$-SO$_3$H	10	95

[a]Reaction conditions: 4-chlorobenzaldehyde (2 mmol), urea (3 mmol), 4-fluoroacetophenone (1 mmol), KHSO$_4$ (1 mmol), catalyst (SiO$_2$-HClO$_4$, 0.25 g; SiO$_2$-PPA, 0.26 g; SiO$_2$-SO$_3$H, 0.3 g, 4.5 mol%) and acetonitrile (8 mL) at 80 °C. [b]Isolated yields.

varied concentrations of SiO$_2$-SO$_3$H and it was found that the catalyst equivalent to 4.5 mol% of SO$_3$H was sufficient for the reaction to proceed in quantitative yield. Secondly, to select the appropriate solvent, the reaction with test substrates was carried out in ethanol, toluene and acetonitrile. It was found that acetonitrile was the optimum solvent since in the case of ethanol and toluene, the reaction did not go to completion even after 20 h of stirring at 80 °C. The non-occurrence of reaction in ethanol and toluene may be due to the poor solubility of the products in these solvents. Further, Shi *et al.*[9] have used KHSO$_4$ as condensing agent for the synthesis of **4** in acetic acid. In order to find out the role of KHSO$_4$ in our protocol, the reaction in the case of test substrates was attempted in the absence and presence of KHSO$_4$ and found that lower yield (25%) was obtained without adding KHSO$_4$, whereas in the presence of KHSO$_4$, **4c** was obtained in 95% isolated yield in 10 h. Thus, the optimum conditions selected are: aldehyde (2 mmol), urea (3 mmol), ketone (1 mmol),

KHSO$_4$ (1 mmol), SiO$_2$-SO$_3$H (0.3 g, 4.5 mol% SO$_3$H), acetonitrile (8 mL) and 80 °C as the reaction temperature.

To demonstrate the versatility of the developed protocol, aldehydes and ketones substituted with different aryl groups possessing both electron-withdrawing and electron-releasing groups were chosen and excellent results were obtained (Table 2).

When using a solid acid catalyst, the most important point is the deactivation and recyclability of the catalyst. To test this, a series of five consecutive runs for the synthesis of **4c** were carried out with the same catalyst and results are shown in Figure 2. The results demonstrate that SiO$_2$-SO$_3$H is highly active, stable and recyclable up to 5th use without loss of significant activity.

Experimental

General

Melting points were determined on a Analab melting point apparatus and are uncorrected. Silica gel (K100, 0.063 - 0.200 mm) was purchased from Merck (Germany) and sulfuric acid and hydrogen peroxide as 30% aqueous solution were purchased from Loba Chemicals Pvt. Ltd (India). ^{1}H NMR spectra were obtained on a Bruker DPX 200 NMR spectrometer (200 MHz) in DMSO-d$_6$ using tetramethylsilane as an internal standard. The IR spectra were recorded using KBr disc on Perkin Elmer FT-IR spectrophotometer and mass spectral data were obtained on ESI-esquires 3000 Bruker Daltonics spectrometer. Thermal analysis was carried out on Perkin Elmer Pyris Diamond Thermal Analyzer with heating rate of 10 °C min^{-1} and elemental analysis was carried out on

Table 2. One-pot synthesis[a] of 4,5,8a-triarylhexahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones (**4a-k**) in the presence of SiO_2-SO_3H by stirring in acetonitrile at 80 °C using $KHSO_4$

Product	R	Ar	Time / h	Yield[b] / (%)	mp /lit. mp[9] / (°C)
4a	H	$4\text{-}FC_6H_4$	12	94	288-289/290-291
4b	4-Cl	2-pyridyl	10	94	>300/>300
4c	4-Cl	$4\text{-}FC_6H_4$	10	95	236-238/238-240
4d	4-Cl	$4\text{-}(OCH_3)C_6H_4$	10	95	>300/>300
4e	4-Br	2-pyridyl	12	96	>300/>300
4f	4-Br	$4\text{-}(CH_3)C_6H_4$	12	95	>300/>300
4g	4-Br	$4\text{-}FC_6H_4$	12	96	234-236/235-238
4h	4-Br	$4\text{-}(OCH_3)C_6H_4$	12	96	>300/>300
4i	$3\text{-}(NO_2)$	$4\text{-}(CH_3)C_6H_4$	12	94	>300/>300
4j	$3\text{-}(NO_2)$	2-pyridyl	12	95	279-281/281-283
4k	$4\text{-}(OH)\text{-}3\text{-}(OCH_3)$	$4\text{-}FC_6H_4$	12	95	185-190

[a]Reaction conditions: The reactions were carried out by stirring a mixture of aromatic aldehyde (2 mmol), urea (3 mmol), aromatic ketone (1 mmol), $KHSO_4$ (1 mmol) and SiO_2-SO_3H (0.3 g, 4.5 mol%) in acetonitrile (8 mL) at 80 °C; [b]Isolated yields.
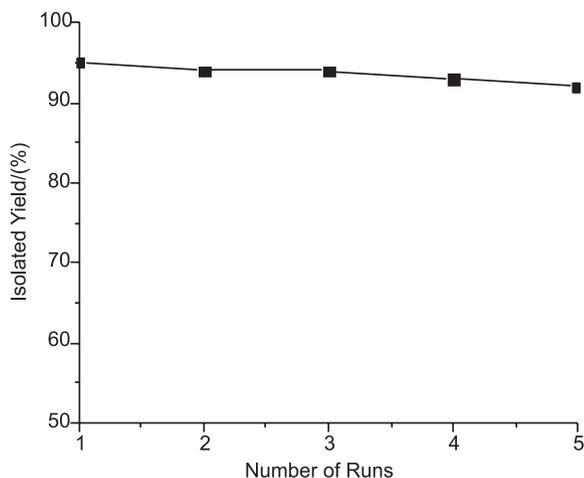
Figure 2. Recyclability of the SiO_2-SO_3H for the one-pot synthesis of **4c** from 4-chlorobenzaldehyde, urea, 4-fluoroacetophenone and $KHSO_4$ by stirring in acetonitrile at 80 °C for 10 h.

Leco-CHNS-932 elemental analyzer manufactured by Leco Corporation, USA Australia. The reactions were monitored qualitatively by TLC.

Preparation of silica functionalized sulfonic acid (SiO₂-SO₃H)

Silica gel (10 g, K 100, 0.063-0.200 mm) was added to a solution of 1:1 conc. HCl and distilled water (200 mL) in a round-bottom flask (500 mL) and the reaction mixture was stirred at 120 °C for 24 h. The activated silica was filtered off, washed with distilled water until the washings were neutral and dried in a hot air oven at 110 °C for 10 h.

Activated silica (10 g) was added to a solution of 3-mercaptopropyl(trimethoxy)silane (10 mmol, 0.982 g)

in dry toluene (150 mL) and refluxed for 24 h. The 3-mercaptopropyl silica (MPS) was filtered off, washed with hot toluene and dried at 110 °C for 5 h. To a mixture of 3-mercaptopropyl silica (MPS, 5 g) and 30% H_2O_2 solution (50 mL), conc. H_2SO_4 (0.078 g, 0.8 mmol) was added and the reaction mixture was stirred at room temperature for 20 h. The solid was filtered off and washed with excess distilled water until the washings were neutral. In order to confirm that all the sulfonic acid groups are protonated, the solid material was further suspended in 0.05 mol L^{-1} H_2SO_4 (30 mL) for 5 h. The solid was then filtered off and washed with excess distilled water until the washings were neutral. Finally, it was dried at 110 °C for 5 h.

*General procedure for the synthesis of 4,5,8a-hexahydro-pyrimido[4,5-d]pyrimidine-2,7(1H,3H)-diones (**4a-k**)*

To a mixture of an aromatic aldehyde **1** (2 mmol), urea **2** (3 mmol), an aromatic ketone **3** (1 mmol), $KHSO_4$ (1 mmol) and SiO_2-SO_3H (0.3 g, 4.5 mol%) in a round-bottom flask (50 mL), acetonitrile (8 mL) was added. The reaction mixture was stirred at 80 °C in an oil-bath for the appropriate time (Table 2). After completion of the reaction (monitored by TLC), the reaction mixture was filtered off at the reaction temperature and washed with hot acetonitrile (3 × 10 mL). The product was obtained after removal of the solvent under reduced pressure and crystallization from EtOH-DMF. The catalyst was washed with distilled water followed by chloroform (2 × 10 mL) and hot acetonitrile (2 × 10 mL). It was dried at 110 °C for 2 h. It could be used further for carrying out the reaction.

The structures of the products were confirmed by IR, ^{1}H NMR, mass spectral data and comparison with authentic samples prepared according to the literature methods.

Spectral data of some selected compounds

8a-(4-Fluorophenyl)-4,5-diphenylhexahydro-pyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (4a)

IR (KBr) ν_{max}/cm^{-1}: 3440, 3230, 1684, 1603, 1508, 1224, 1158, 700. ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 2.90 (m, 1H, CH), 4.26 (d, 2H, CH), 6.72-6.77 (t, 4H, H*arom*), 6.94 (bs, 2H, NH), 6.98-7.13 (m, 8H, H*arom*), 7.18 (bs, 2H, NH), 7.20-7.27 (m, 2H, H*arom*). MS (ESI): 417 (M$^+$+1).

4,5-Bis(4-chlorophenyl)-8a-(4-fluorophenyl)hexahydro-pyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (4c)

IR (KBr) ν_{max}/cm^{-1}: 3413, 3235, 3094, 1685, 1604, 1509, 1337, 1234, 836, 765, 688. ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 2.92-2.96 (m, 1H, CH), 4.20 (d, 2H, CH), 6.76 (t, 2H, H*arom*), 6.88 (bs, 2H, NH), 7.02 (bs, 2H, NH), 7.02-7.25 (m, 10H, H*arom*). MS (ESI): 485 (M$^+$+1).

4,5-Bis(3-nitrophenyl)-8a-(4-tolyl)hexahydro-pyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (4i)

IR (KBr) ν_{max}/cm^{-1}: 3407, 3209, 3081, 1675, 1582, 1526, 1509, 1482, 1250, 1098, 694. ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 2.27 (s, 3H, CH$_3$), 3.02-3.07 (m, 1H, CH), 4.38 (d, 2H, CH), 6.70-6.81 (m, 2H, H*arom* and 2H, NH buried), 7.02-7.08 (d, 2H, H*arom*), 7.12 (bs, 2H, NH), 7.35-7.90 (m, 8H, H*arom*). MS (ESI): 503 (M$^+$+1).

4,5-Bis(4-hydroxy-3-methoxy)-8a-(4-fluorophenyl)hexa-hydropyrimido[4,5-d]pyrimidine-2,7(1H,3H)-dione (4k)

IR (KBr) ν_{max}/cm^{-1}: 3500, 2920, 2846, 1654, 1508, 1384, 1288, 1031, 819, 630. ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 2.94-2.98 (m, 1H, CH), 3.89 (s, 6H, 2xOCH$_3$), 4.22 (d, 2H, CH), 6.86 (bs, 2H, NH), 7.00 (bs, 2H, NH), 7.04-7.30 (m, 10H, H*arom*), 8.80 (s, 2H, OH). MS (ESI): 509 (M$^+$+1).

Conclusions

In conclusion, we have developed a mild and simple procedure for the one-pot synthesis of 4,5,8a-triarylhexahydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones (**4a-k**) by stirring a mixture of aromatic aldehyde, urea and alkyl arylketones at 80 °C using silica functionalized sulfonic acid (SiO$_2$-SO$_3$H) under liquid phase catalysis. The methodology offers several advantages such as: *i)* high yield of products with high purity; *ii)* work-up procedure is simple; *iii)* catalyst can be recovered by simple filtration and reused for five consecutive runs without loss of significant activity; *iv)* tolerates variety of functional groups such as methoxy, nitro, hydroxyl and halides; and *v)* no use of toxic and hazardous reagents.

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