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Silica Bonded S-Sulphonic Acid as a Green Catalyst in the Synthesis of Functionalized Pyrimidine under Solvent-Free Microwave Irradiation Conditions

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Abstract : ***Microwave irradiated synthesis of pyrimidine derivatives was performed using benzaldehyde, a 1,3-diketone with ammonium acetate and urea under solvent free condition in the presence of Silica bonded sulphur sulphonic acid (SBSSA) as a solid acid catalyst. Prominent yield was obtained within a short reaction time. The structure of the pyrimidine derivatives was characterized by spectral techniques like NMR and FT-IR. The catalyst was recovered and reused thrice in the synthesis of pyrimidine derivatives without any change in the product yield.***

Keywords: Silica bonded-S-sulphonic acid, Solvent- free, Microwave irradiation, Pyrimidine derivatives.

1.Introduction

Nowadays, industries and academics are in search to carry out eco-friendly organic synthesis for chemical and biological applications. Thus, the use of heterogeneous catalyst in green synthesis is a primary area of interest. Easy retrieval, reusability and proficient inclusion of reactors makes heterogeneous catalyst a prospective one than homogeneous systems [1]. In addition, reduced reactor usage, plant corrosion effects, easy handling and safer disposal enable a facile solid acid catalyst treatment in organic transformations [2].

Pyrimidine ring compounds posses significant pharmacological value [5,6] such as antiseptic, antifungal, antimalarial and anticonvulsant activities [3,4]. It inhibits hyperthyroidism, acute leukemia in children and adult granulocytic leukemia. Pyrimidine derivatives also plays a major role in polymer and supramolecular chemistry [8,9]. Conjugated molecules containing pyrimidine core are used in light emitting devices [10] and molecular wires [11].

Synthesis of bioactive pyrimidines via green chemistry is currently attempted in various reactions like the one-pot, three-component reaction of halides, terminal propargyl alcohols and amidinium salts based upon a coupling-isomerization–cyclocondensation sequence[12], Suzuki coupling reaction[13], microwave-assisted reaction [14], sequential assembly of aryl groups onto a pyrimidine core [15], HeteroPolyAcid under refluxing [16], inorganic solid supported microwave irradiation [17], ionic liquid [18], solid Supported Preyssler Nanoparticles [19], Piperidine under refluxing [20] and Liquid Phase Catalysis [21]. Though these methods have appropriate reaction conditions, there exist some drawbacks such as long reaction time, expensive reagents, low yield of products and high amount of catalyst, corrosive reagents and solid support. All these would eventually result in the generation of a large amount of toxic waste. Hence, solid acid catalysts with attractive properties such as low cost, less toxicity, easy availability, air-stable, recyclable and water-tolerant are required for organic synthesis [22].

Earlier studies reported the use of silica bonded-S-sulphonic acid (SBSSA) as catalyst for the preparation of 2,3-Dihydroquinazolin-4(1*H*)-ones[23],Quinoxalines[24],pyrazol[25], α-aminonitriles[26],Bis-Indolylmethanes[27], coumarins[1] and benzimidazole [28] under different reaction conditions. This is the first report on the synthesis of pyrimidine derivatives in the presence of SBSSA under microwave, solvent-free condition.

2. Experimental

2.1 General

All the analytical grade chemicals and solvents were purchased from Alfa Aesar (India). IR Spectra was recorded from KBr disk using IR-AFFINITY- 1 SHIMADZU equipment. The phase formation was monitored by X-ray diffraction method with Cu-K radiation on X'pert Pro, PANalytical(λ = 1.5425 Å),. The ^{1}H and ^{13}C NMR obtained from 300 MHz, BRUKER instrument. TLC was taken using LuxPlate® Silica gel 60 F_{254} plates to monitor the reaction.

2.2 Preparation of Silica Bonded S-Sulphonic Acid (SBSSA)

2.2.1Preparation of Activated Silica**:**

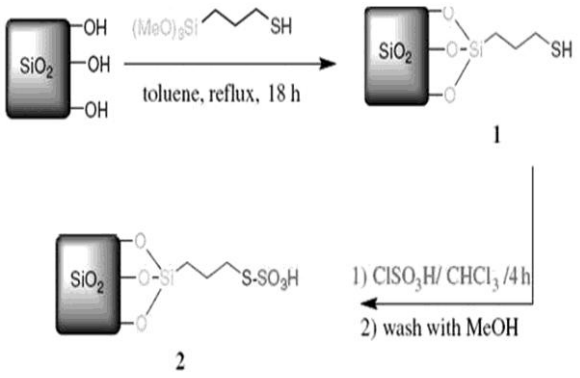
Silica gel (0.03 mol) was activated using 1:1 conc. HCl and distilled water in a round-bottom flask. The mixture was stirred for 24h at 80°C, filtered off, washed and neutralized using deionized water and dried in hot air oven at 110°C [29].

2.2.2Preparation of 3-Mercapto propyl Silica (MPS) 1

Activated Silica (0.03mol) was added to 5mL of (3mercaptopropyl) trimethoxysilane in dry toluene, under refluxing for 18 hrs, 3-MercaPtopropylSilica (MPS)1 was obtained which was then dried in a hot air oven at 110°C [26].

2.2.3 Preparation of Silica bonded Sulphur Sulphonic Acid 2:

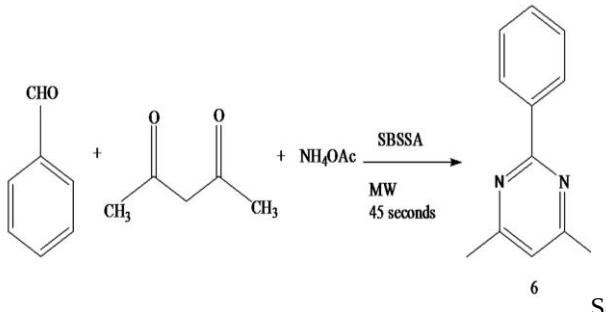
3-mercaptopropylsilica 1 (1g) in $CHCl_3$ (10mL) was stirred with drop wise addition of chlorosulfonic acid (0.3ml) at 0°C. To remove the HCl from the reaction vessel, the mixture was stirred for 2h. Then it was filtered, washed with methanol and dried at room temperature to obtain silica-bonded functionalized sulfonic acid 2 (SBSSA) as a sandal colored powder (scheme 1)[24].



Scheme1: Preparation of Silica bonded S-sulphonic acid catalyst

2.3 General Synthesis of 4,6-dimethyl 2-phenyl pyrimidine:

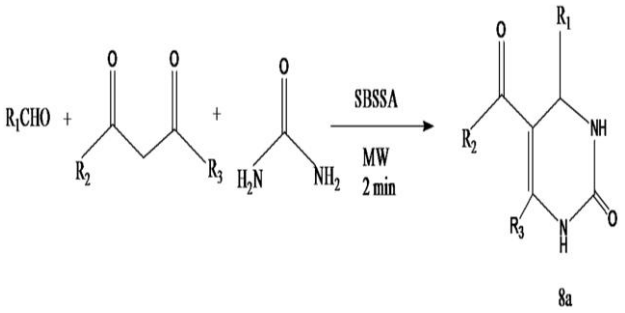
Ammonium acetate (20 mmol) was added to the mixture of benzaldehyde (10 mmol), acetyl acetone (10 mmol). The mixture was subjected to microwave irradiation of 100W in the presence of (0.01g) Silica bonded Sulphur Sulphonic Acid catalyst. The reaction completion was monitored by performing TLC. A brownish orange colored colloidal product of 4,6-dimethyl 2-phenyl- pyrimidine 6 was obtained . The catalyst was filtered off and impurities were removed by dissolving the product in acetone. The recovered catalyst was washed with dichloromethane and reused after drying [30] (scheme



2) Scheme 2: Synthesis of 4,6-dimethyl- 2-phenyl pyrimidine using SBSSA

2.4 General Synthesis of 5-acetyl 6-methyl 4-phenyl 1,2,3,4-tetrahydropyrimidin-2-one dervatives:

Benzaldehyde (10 mmol) and acetyl acetone (10 mmol) was added to urea crystals (20 mmol). Then the catalyst silica bonded sulphur sulphonic acid (0.01g) was added. This reaction mixture was subjected to microwave irradiation of 100W for 2 min. TLC was performed to monitor the progress of reaction. A brownish orange colored solid product of 5-acetyl 6-methyl 4-phenyl-1,2,3,4-tetrahydropyrimidin-2-one 8**(a-f)** was obtained (Table 1). It was then dissolved in acetone and the solid catalyst was separated by filtration. Dichloromethane was used to wash and recover the catalyst [31] (scheme 3).



Scheme 3:Synthesis of 5-acetyl-6-methyl- 4-phenyl 1,2,3,4-tetrahydropyrimidin2-one using SBSSA

Where R_1,R_2,R_3 are indicated in table1

[a]All reactions were performed on 10 mmols of aromatic aldehyde , 10 mmols of 1,3-diketonederivative and 20 mmols of urea using 0.01 g of SBSSA. [b]All products were characterized using ^{1}H-NMR and ^{13}C-NMR.Higher [c]yields were obtained for all products

2.5 Spectral characterization of Pyrimdine derivatives(6,8a-f):

3.2 4,6-dimethyl 2-phenyl pyrimidine(6) (CID 239976) : brownish orange(42%) ,^{1}H NMR ($CDCl_3$, 300 MHZ) δ 2.67(s,3H, CH_3),6.56(s,1H, C_5H of pyrimidine ring) , 7.22-7.48(m ,5H,Ar H.).^{13}C NMR ($CDCl_3$) δ 22.1, 95.5, 127.9, 128.5, 128.9,152.6, 163.5.

5-acetyl- 6-methyl- 4-phenyl- 1,2,3,4-tetra hydropyrimidine-2-one (8a): brownish orange(91%)**,** IR (KBr ,cm^{-1}): 778 (C-C bend), 1452 (Ar C=C str), 1713 (C=O), 3035 (C-H str), 3212 (N-H str) [32]. ^{1}H NMR ($CDCl_3$) δ 6.52(s,1H, NH),4.55(dd,1H, C_4H of pyrimidine ring),1.45(s,3H, CH_3)2.69(s,3H, CH_3),7.13-7.45(m, 5H-Ar-H). ^{13}CNMR($CDCl_3$)δ 19.4,30.8,40.2,110.1,126.933,127.8,128.7,129.0,144.7,152.6,194.7

5-acetyl- 4-(4-chlorophenyl)-6-methyl- 1,2,3,4-tetrahydropyrimidin-2-one (8b): Yellowish orange colour (98%) ^{13}CNMR($CDCl_3$) δ24.2,35.1, 45.4,114.7, 133.0, 133.4,138.5, 133.7,147.0,152.8,196.5.

5-acetyl- 4-(4-bromophenyl)-6-methyl- 1,2,3,4-tetrahydropyrimidin-2-one(8c): Scarlet red(92%),^{13}C NMR ($CDCl_3$) δ 24.2,24.4, 45.4,114.7, 117.5, 126.1,133.3,136.4, 147.6, 152.7,199.6.

5-acetyl- 4-(4-nitrophenyl)-6-methyl- 1,2,3,4-tetrahydropyrimidin-2-one(8d): Brown crystals(74%), ^{13}C NMR ($CDCl_3$) δ24.3, 35.2, 45.4, 128.1,128.5, 131.2, ,133.2, 154.9, 157.6, 198.0.

5-acetyl- 6-methyl- 4-(napthalen-1-yl) -1,2,3,4-tetrahydropyrimidin-2-one (8e): Orange colour(98%), ^{13}C NMR ($CDCl_3$) δ 18.5,29.1, 39.5, 125.1, 125.4,126.4,126.9, 127.6, 131.0,131.6, 132.0,155.1,111.7, 132.0, 155.1,196.4.

5-benzoyl-6-methyl- 4-phenyl- 1,2,3,4-tetrahydropyrimidin2one (8f): Yellowish red colour (87%), ^{13}C NMR ($CDCl_3$) δ 17.7,55.3,109.6,118.0,126.7,127.3,127.6, 127.9, 130.6, 140.0, 143.0,149.2,152.3, 166.9.

2.6 spectral determination of SBSSA catalyst:

The structure of SBSSA was analyzed using FT-IR technique which showed the S-S stretching peak at 450 cm^{-1} , the S-O stretching frequency appeared at 577 cm^{-1} and

the silica (SiO_2) symmetric Si-O-Si stretching peak near 762 cm^{-1}. The major peak was a broad asymmetric Si-O-Si stretching which lies at 1080 $cm^{-1.}$ For the sulfonic acid functional group, the O=S=O asymmetric stretching mode appeared at 1182cm^{-1}. The H-C-H stretching band appeared at 2928 cm^{-1}. The spectrum also showed a broad OH stretching absorption at 3431 cm^{-1}. The SBSSA structure was confirmed with XRD which showed 2θ peaks at 20.80, 26.69, 50.11, 59.79, and 67.93 [27].

3. Results and Discussion:

While the reaction was carried out with ammonium acetate as a reactant, poor yield (42%) was obtained compared to urea (91%). Therefore the synthesis of pyrimidine derivatives was performed via urea instead of ammonium acetate using substituted ethylacetoacetate and the aldehydes in the presence of SBSSA catalyst(Table 1). Among the six compounds synthesized, 5-acetyl- (4-napthalen-1-yl)-6-methyl -1,2,3,4-tetrahydropyrimidin-2-one produced higher yield (98%) compared to the parent compound (91%). In particular, the presence of bulkier group in the 4th position of the compound (6e), improves the product yield than the compound containing the electron withdrawing group. Based on the substituents, product yield and purity varied due to their change in conformation and configuration[32].

The catalyst reusability was monitored in this framework using dichloromethane. The recycled catalyst was reused thrice without any further treatment. During the 4th run, catalytic activity was decreased. Thus, SBSSA could be used as a efficient catalyst for the first 3 cycles of the reaction (Fig 1 and Fig 2).

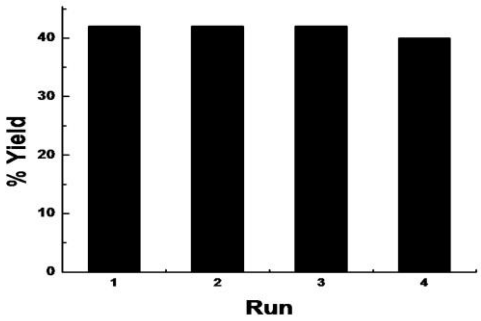


Fig1:Recyclability of SBSSA (0.01 g) in the reaction of benzaldehyde (10 mmols) ,acetyl acetone (10mmols)and ammonium acetate (20 mmols)
Reactiontime=45seconds

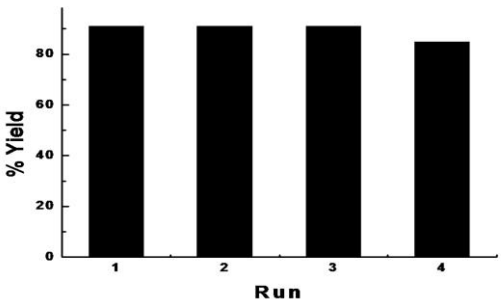


Fig 2:Recyclability of SBSSA (0.01 g) in the reaction of benzaldehyde (10 mmols) ,acetyl acetone (10 mmols)and urea (20 mmols) Reaction time = 2 min.

Table 2:Comparison of efficiency of various catalysts in synthesis of pyrimidine derivatives

Catalyst	Solvent	Reaction Condition	Reaction time	Yield (%)	References
HPA	CH_3CN	Refluxing	5 hrs	67	(31)
SiO_2-SO_3H	CH_3CN	80^oC	10hrs	95	(21)
Ionic liquid	-	80^oC	30 min	90	(18)
Piperidine	Water	Refluxing -100^o C	3hrs	95	(20)
SBSSA	-	MW	2 min	91	Synthesized in this study

In this study, efficacy of our prepared SBSSA was compared with the reported catalysts in the synthesis of pyrimidine derivatives (Table 2). Though silica functionalized sulphonic acid and Piperidine showed 95% yield, reaction time was too long. In the presence of SBSSA, 91% yield was obtained with very short reaction time (2min) using microwave irradiation under solvent free condition. Since SBSSA has acidic character, there is no need to add acidic solvents like sulphuric acid, hydrochloric acid for the synthesis of pyrimidine derivatives. Addition of these solvents possess solvent removal problem from the product, which harm and pollute the environment during its disposal. If such solvents are used in microwave irradiation, the boiling point of the solvent hinders the reaction (Table 2).

4. Conclusion

Green synthesis of pyrimidine derivatives has been achieved by reacting an aromatic aldehyde, a 1,3-diketone and ammonium acetate/urea under microwave irradiation in the presence of eco friendly silica bonded s-sulphonic acid as a solid acid and recyclable catalyst. The solvent free condition, high product yield, low reaction time and environmentally safe procedure enable this method to be a part in green chemistry.

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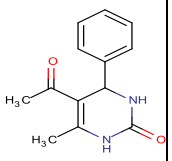
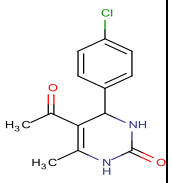
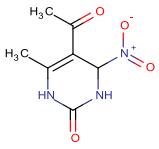
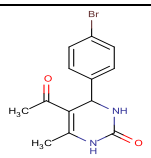
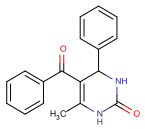
Entry[a]	Product[b]		R_1	R_2	R_3	Time / mins	Yield (%)[d]
1	**8a**		- C_6H_5	- CH_3	- CH_3	2	91
2	**8b**		*p*- C_6H_4Cl	- CH_3	- CH_3	2	98
3	**8c**		*p*- $C_6H_4No_2$	- CH_3	- CH_3	2	92
4	**8d**		*p*- C_6H_4Br	- CH_3	- CH_3	2	74
5	**8e**		- $C_{10}H_9$	- CH_3	- CH_3	2.45	98
6	**8f**		- C_6H_5	- CH_3	- C_6H_5	2	87

Table 1:Comparision of the result of microwave synthesis of pyrimidine derivatives under solvent free conditions using SBSSA with other reported catalysts