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SiO_2-$NaHSO_4$ as an Efficient Reusable Heterogeneous Catalyst for the One-Pot Three-Component Synthesis of Octahydro-quinazolin-2,5-diones in Water

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Abstract: An environmentally benign method for the synthesis of octahydro-quinazolin-2,5-diones by the reaction of aromatic aldehydes, dimedone, and urea in the presence of SiO_2-$NaHSO_4$ is reported. SiO_2-$NaHSO_4$ acts as an efficient, mild, and recyclable heterogeneous catalyst to give excellent yields within a short reaction time in water at 60–80 °C.

Key words: octahydro-quinazolin-2,5-dione; aromatic aldehyde; dimedone; urea; water

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Multicomponent reactions (MCRs) are very important for the construction of many heterocyclic compounds [1] and this strategy has been used effectively in the synthesis of many biologically active substances and natural products [2]. The synthesis of octahydro-quinazolin-2,5-diones has attracted the attention of chemists because of their highly potent antibacterial activity against many kinds of bacteria including *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* [3]. Furthermore, they have demonstrated calcium antagonist activity [4–6]. Several methods have been reported for the synthesis of octahydro-quinazolin-2,5-diones from aromatic aldehydes, dimedone, and urea, involving the use of catalysts such as NH_4VO_3 [7], TMSCl [8], Nafion-H [9], conc. H_2SO_4 [10], conc. HCl [11], heteropolyacids [12–13], bakers' yeast [14], and ionic liquids [15,16]. They can also be synthesized via a Biginelli multicomponent reaction using cyclo-β-diketones [17]. Many of the reported methods suffer from one or more disadvantages including harsh reaction conditions, long reaction times, poor yields, and the use of hazardous and expensive catalysts with limited reusability.

Herein, we have attempted to develop a clean and environment friendly approach to the synthesis of octahydro-quinazolin-2,5-diones with high yields using SiO_2-$NaHSO_4$ as a catalyst. SiO_2-$NaHSO_4$ acts as highly efficient heterogeneous catalyst for the synthesis of octahydro-quinazolin-2,5-diones from aromatic aldehydes, dimedone, and urea, providing the product in excellent yields in a water solvent at temperature in the range of 60–80°C. The catalyst can be easily recovered and reused several times with good efficiency.

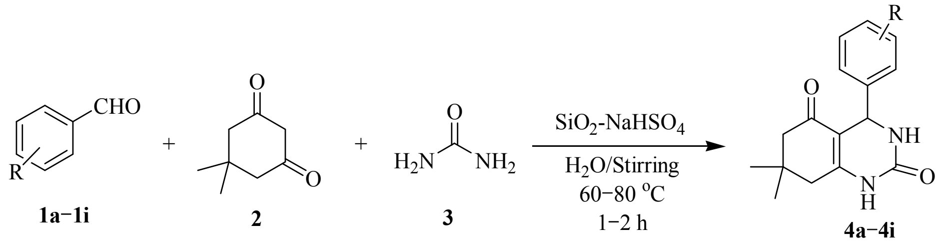
1 Experimental

1.1 Preparation of the catalyst

SiO_2-$NaHSO_4$ catalyst was prepared by the reported method [18]. Silica gel (15 g, 100–200 mesh) was added to a magnetically stirred solution of $NaHSO_4.H_2O$ (6.9 g, 50 mmol) in distilled water (100 ml) at 25 °C over a 30 min period. The mixture was stirred for a further 30 min allowing for the sodium bisulfate to adsorb onto the surface of the silica gel. The water was removed in vacuo to give a powder which was dried in an oven at 120 °C for 2–3 h.

1.2 Synthesis of octahydro-quinazolin-2,5-diones

All reactions were carried out in a 50 ml RB flask in water. During a general procedure (Scheme 1), a mixture of dimedone (1 mmol), urea (1.2 mmol), SiO_2-$NaHSO_4$ (0.1 g), and water (10 ml) was taken in a 50 ml round bottom flask and heated at 60–80 °C for 30 min. An aromatic aldehyde (1 mmol) was then added and heating was continued with stirring for a period of time. Ethyl acetate (10 ml) was then added and the solid catalyst filtered from the mixture, washed with chloroform, and recycled. The filtrate was evaporated to give the crude product which was recrystallized from methanol-water (2:1) to afford the pure product.



R = -H, -OMe, -Cl, -OH, $-NO_2$, -2-OMe, $-N(CH_3)_2$, -[4-OH, 3-OMe]

Scheme 1. Synthesis of octahydro-quinazolin-2,5-diones from aromatic aldehydes, dimedone, and urea catalyzed by SiO_2-$NaHSO_4$.

During the course of the reaction, the product formation was monitored by thin layer chromatography (TLC) analysis and compared with the authentic samples. Melting points were determined on a RAAGA system (Chennai, India). Infrared (IR) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer from KBr discs. The ^1H and ^{13}C NMR spectra were recorded from DMSO-d_6 solvent on 400 and 100 MHz Bruker instruments, respectively. Elemental analysis was done using a vario MICRO CHN analyzer.

4-(2-hydroxyphenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4b**). Mp 184–186 °C. IR (KBr, cm^{-1}): *v* 498 (br), 3298 (br), 2954 (s), 1705 (s), 1654 (s), 1610 (vs), 1463 (w), 1350 (s), 1220 (s). ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 0.98 (s, 6H, 2Me), 2.1(s, 2H, CH_2), 2.3 (s, 2H, CH_2), 3.4 (s, 1H, OH), 5.3 (s, 1H, CH), 6.9–7.3 (m, 4H, Ph), 9.8 (br, 2H, 2NH). ^{13}C NMR (100MHz, $CDCl_3$ + DMSO-d_6): δ 196.6 (*C*=O), 5.3 (N*C*=O),150.6 (N*C*=C), 129.6, 126.8, 124.4, 118.2, 115.8, 112.7 (all Ar*C*), 112.7 (OC-*C*=C), 51.6 (*C*-NH), 48 (*C*H_2), 32.5 (*C*H_2), 32.3 (>*C*<), 29.8, 28.7(*C*H_3). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.1328; H, 6.29; N, 9.79. Found: C, 67.20; H, 6.29; N, 9.83.

4-(3,4-dimethoxyphenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**4g**). Mp 154–156 °C. IR (KBr, cm^{-1}): *v* 3433 (br), 3228 (br), 2954 (s), 1705 (s), 1668(s), 1615 (vs), 1498 (s), 1400 (s), 1244 (s), 1135 (vs), 1022 (s). ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 0.99 (s, 6H, 2Me), 2.3 (s, 2H, CH_2), 2.4 (s, 2H, CH_2), 3.6 (s, 3H, CH_3), 3.7 (s, 3H, CH_3), 5.7 (s, 1H, CH), 6.5–6.8 (m, 3H, Ph), 9.8 (br, 2H, 2NH). ^{13}C NMR (100MHz, $CDCl_3$ + DMSO-d_6): δ 195.5 (*C*=O) , 177.7(N*C*=O), 148.6 (N*C*=C), 146.3, 138.8, 119.7, 115.6, 112.3, 111.9 (all Ar*C*), 111.9 (OC-*C*=C), 56.4 (O-*C*H_3), 55.8 (O-*C*H_3), 51.3 (*C*-NH), 48 (*C*H_2), 31.9 (CH_2), 30.7 (>*C*<), 30.5, 27.9 (*C*H_3). Anal. Calcd for $C_{18}H_{23}N_2O_4$: C, 65.256, H, 6.94, N, 8.45. Found: C, 65.32, H, 6.97, N, 8.43.

2 Results and discussion

2.1 Catalytic performance of SiO_2-$NaHSO_4$

Recently, SiO_2-$NaHSO_4$ catalyzed organic reactions have gained much attention, because of their commercial availability, moisture stability, and recyclability. A literature survey revealed that the use of SiO_2-$NaHSO_4$ for the synthesis of xanthenediones [19], β-enaminones, and 2-methylquinolin-4(1*H*)-ones [20]. Furthermore, SiO_2-$NaHSO_4$ has been used in the protection of aldehydes with 2-mercaptoethanol [18]. In a continuation of our work into the synthesis of biologically active heterocyclic compounds using readily available, inexpensive, and environment friendly catalysts [21–26], herein we are report the synthesis of octahydro-quinazolin-2,5-diones by the one-pot multi-component reaction of aromatic aldehydes, dimedone, and urea using SiO_2-$NaHSO_4$ as an efficient catalyst in water. We have found that SiO_2-$NaHSO_4$ catalyzes the reaction between aromatic aldehydes, dimedone, and urea in an aqueous medium efficiently to afford the desired products in excellent yield within 1–2 h. The catalyst can be easily prepared [18] and safely handled, making the method more advantageous over other conventional methods and catalysts.

The efficiency of SiO_2-$NaHSO_4$ as a catalyst for the synthesis of the model compound 7,7-dimethyl-4-phenyl-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione (**4a**), was compared with that of other catalysts reported in the literature (Table 1). It is clear from this table that SiO_2-$NaHSO_4$ is an efficient, cost-effective, and environmentally benign catalyst which could be useful in the synthesis of a series of octahydro-quinazolin-2,5-diones. From a practical perspective, the catalyst can be easily prepared from readily available reagents and can also be recycled.

In order to optimize the reaction conditions, reactions between benzaldehyde, dimedone, and urea in the presence

Table 1 Comparison of the efficiency of SiO_2-$NaHSO_4$ with other catalysts for the synthesis of **4a**

Catalyst	Time (h)	Yield (%)	Ref.
TMSCl	1.5	93	[8]
Ionic liquids	2.5	91	[16]
conc. H_2SO_4	3.0	85	[10]
conc. HCl	6.5	—	[11]
SiO_2-$NaHSO_4$	1.5	95	—

Table 2 Synthesis of octahydro-quinazolin-2,5-diones catalyzed by SiO_2-$NaHSO_4$

Aldehyde	Product[a]	Time (h)	Yield[b] (%)	Melting point (°C)	
				Reported	Found
C_6H_5CHO **1a**	**4a**	1.5	95	290–292	292–295
2-OH-C_6H_4CHO **1b**	**4b**[c]	1.0	88	—	184–186
4-Cl-C_6H_4CHO **1c**	**4c**	1.5	90	>300	297
3-OMe,4-OH-C_6H_3CHO **1d**	**4d**	1.0	85	192–194	189–191
4-OMe-C_6H_4CHO **1e**	**4e**	2.0	92	284	278–280
3-NO_2-C_6H_4CHO **1f**	**4f**	2.0	85	298–300	297
3,4-$(OCH_3)_2C_6H_3CHO$ **1g**	**4g**[c]	1.0	95	—	154–156
4-NO_2-C_6H_4CHO **1h**	**4h**	2.0	90	302–304	296–298
4-$N(CH_3)_2C_6H_4CHO$ **1i**	**4i**	1.5	90	231–232	229

[a] All the products are known and were characterized by IR (KBr) spectral analysis. Products **4a**, **4b**, **4c**, **4g**, and **4i** were also characterized by ^1H NMR spectral analysis and by comparing on TLC with the samples prepared by reported methods.

[b] Isolated yield.

[c] **4b** and **4g** are new compounds and were also characterized by ^{13}C NMR and CHN analyses.

of catalytic amounts of SiO_2-$NaHSO_4$ were conducted under various reaction conditions including the ‘grinding’ of the solid reagents and catalyst in a mortar and pestle, heating of the reaction mixture on a preheated hot plate at 120 °C without solvent and by stirring in water at 60–80 °C. It was found that grinding of the reactants and the catalyst did not afford the product in good yield. Similarly, heating the materials neat on a hot-plate at 120 °C provided only a moderate increase in yield, whereas, stirring in water at 60–80 °C was found to be ideal for the present reaction.

In a typical experiment, dimedone, urea, SiO_2-$NaHSO_4$, and water were taken in a 50 ml RB flask and the mixture was heated in an oil bath at 60–80 °C for 30 min. Benzaldehyde was then added and the heating was continued with stirring until **4a** was obtained in maximum yield (typically 1.5 h for a 95% yield). In order to illustrate the versatility of the present method, a variety of aromatic aldehydes were treated with dimedone and urea. The results of the study are presented in Table 2. The products obtained were characterized by spectral and elemental analysis.

The possibility of recycling the catalyst was then examined. After completion of the reaction (1.5 h), ethyl acetate (10 ml) was added to the reaction mixture and the catalyst was filtered and washed with chloroform, ready for further use. This process of recycling was completed four times (with washing every time). From Fig. 1 it can be seen that, in the first two runs, the activity remained the same. After two runs, however, the activity started decreasing, which may be due to the degradation of the catalyst under mechanical stirring and heating. The yields for the four runs were found to be 93%, 91%, 85%, and 75%, respectively.

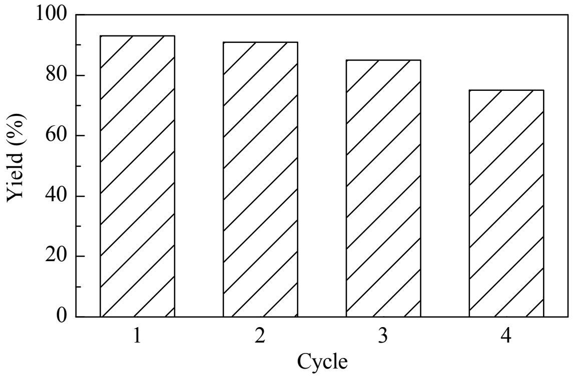
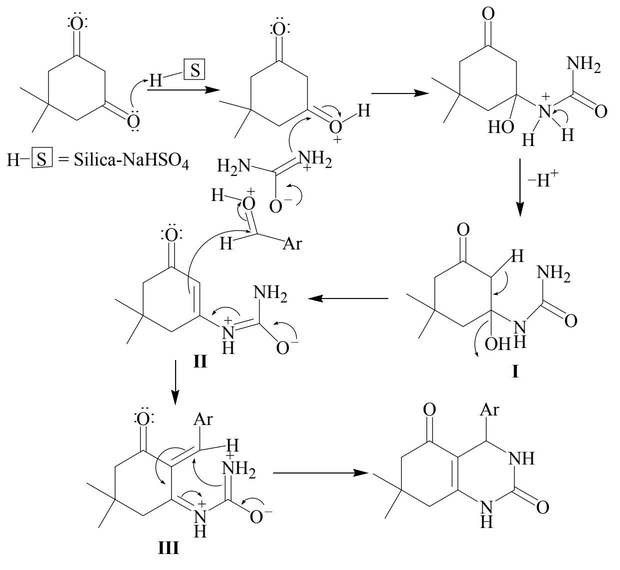


Fig. 1. Reusability of SiO_2-$NaHSO_4$ in the synthesis of **4a**.

2.2 Mechanism

A plausible mechanism for the formation of 7,7-dimethyl-4-aryl-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione is presented in Scheme 2. The activation of dimedone may take place by the protonation of one of the oxygens by the catalyst. A nucleophilic reaction may then occur between activated dimedone and urea resulting in the formation of



Scheme 2. A plausible mechanism for the formation of 7,7-dimethyl-4-aryl-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione.

intermediate (**I**) which may lose a molecule of water to give intermediate (**II**). Intermediate (**II**) may then attack the activated aldehyde forming intermediate (**III**), which may undergo cyclization through an internal nucleophilic attack to form 7,7-dimethyl-4-aryl-4,6,7,8-tetrahydro-1*H*,3*H*-quinazoline-2,5-dione, as shown in the scheme (Scheme 2).

3 Conclusions

SiO_2-$NaHSO_4$ is a heterogeneous, easy to prepare, inexpensive, and efficiently catalyst for the synthesis of octahydro-quinazolin-2,5-diones. The advantages offered by this method include simple reaction condition, short reaction time, involvement of an environment friendly procedure, ease of product isolation, excellent yields, and reusability of the catalyst. To the best of our knowledge, this method is the first reported procedure for the synthesis of tetrahydro-1*H*,3*H*-quinazoline-2,5-dione molecules using a heterogeneous recyclable catalyst.

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