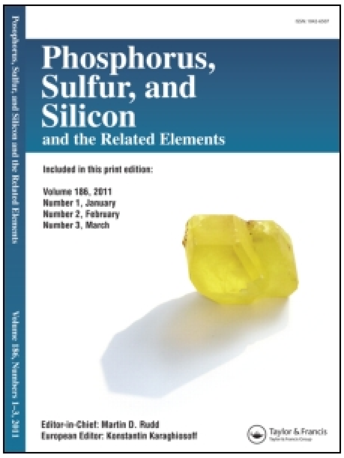

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Silica Sulfuric Acid-Mediated Synthesis of β-Enaminones and β-Enaminoesters Under Microwave Irradiation

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SILICA SULFURIC ACID–MEDIATED SYNTHESIS OF β-ENAMINONES AND β-ENAMINOESTERS UNDER MICROWAVE IRRADIATION

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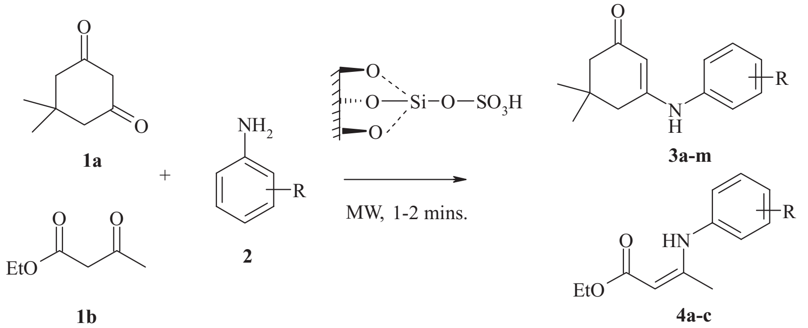
GRAPHICAL ABSTRACT



Abstract *Silica sulfuric acid, a heterogeneous reagent, has been found to be an efficient catalyst for the synthesis of β-enaminones and β-enaminoesters under microwave irradiation in a microwave reactor within 2 min. The experimental procedure is simple and environment-friendly, and results in excellent yields of the products. Further, the catalyst is recyclable, and the reaction is 60 times faster than the reaction at room temperature.*

Keywords β-Enaminoesters; β-enaminones; microwave irradiation; recyclable catalyst; silica sulfuric acid

INTRODUCTION

Solid phase synthesis[1] has become one of the most important applications in organic synthesis. The solid phase chemistry concept includes substrates becoming chemically bound to the surface of the solid support, then being converted into the product, and, after the completion of the reaction, released from the solid support.[2] The solid-phase

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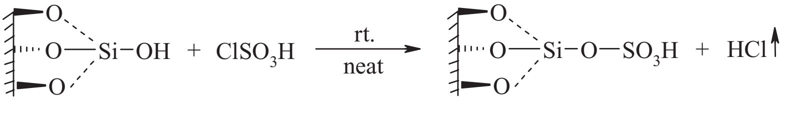
reagents can be either functionalized organic polymers[3] or silica gel grafted catalysts.[4] The wide application of solid-supported catalysts is enhanced rate, higher yields, easy work-up procedures, safety, and economy. There are cases in which solid-phase catalysts can be recycled with very minor changes in activity and selectivity.[5] In this view, several types of solids have been synthesized and applied as very efficient catalysts in chemical transformations,[6a] and one such catalyst is silica sulfuric acid (Scheme 1),[6b,c] which can be synthesized by treating silica with chlorosulfonic acid.[7] The use of silica sulfuric acid is more advantageous over conventional homogenous acid catalysts because the catalyst can be handled safely and it is nonhygroscopic.



Scheme 1 Synthesis of silica sulfuric acid from chlorosulfonic acid and silica gel.

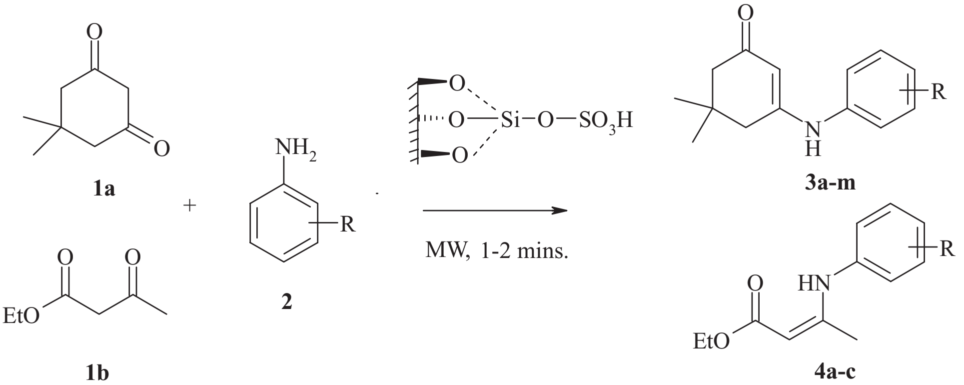
In the recent past, in our laboratory, we have been actively engaged in the synthesis of various heterocyclic compounds under different reaction conditions.[8] As part of our ongoing search program on the synthesis of some important pharmaceutical chemicals[9a] and bioactive heterocycles,[9b] we have aimed to synthesize some useful synthons such as β-enaminones and β-enaminoesters. β-Enaminones are useful in the synthesis of unsymmetrical 4-arylacridinediones.[10] β-Enaminones containing the structural unit N—C═C—C═O find application in the synthesis of many therapeutic agents such as antibacterial,[11a,b] anticonvulsant,[11b] anti-inflammatory,[11b] and antitumor agents.[11b,c] β-Enaminones are also important as intermediates for the synthesis of several amino acids,[12a] aminols,[12b] peptides,[12c] and alkaloids.[12d]

The method for the synthesis of β-enaminones involves the direct condensation of β-dicarbonyls with amines under reflux in an aromatic solvent with azeotropic removal of water.[13] The other reported methods involve use of a number of catalysts.[14–25] Although these catalysts improve the yields and the reaction rates, they still require drastic conditions such as high temperatures or use of solvents. Non-availability or use of very expensive reagents is another disadvantage. Moreover, some of the catalysts cannot be recycled, which limits their use.

Recently, microwave irradiation was used for this conversion in water,[26] and without any catalyst and solvent[27] in the reactor. However, in these methods, the condensation of aromatic amines takes a longer amount of time, and the reactions are possible at high temperatures. Subsequently, a solid-state synthesis using $KHSO_4.SiO_2$ [28] has been reported that also requires longer time (10–120 mins) for the complete conversion. Hence, there is still a need to develop a simpler and "greener" method for the condensation of amines and β-dicarbonyl compounds to obtain β-enaminones and β-enaminoesters.

Since the introduction of microwave-induced organic reaction enhancement (MORE) chemistry,[29a,b] microwave-assisted organic reactions have emerged as an important tool in organic synthesis owing to its uniform heating effect.[29c] Microwave-induced reactions require open vessels with no or very little solvents; the method is free of risk of explosion and can be scaled up. Despite the attractiveness of silica sulfuric acid, to the best of our knowledge there are no reports in the literature on the applicability of silica sulfuric acid for the enamination of β-dicarbonyls.

In continuation of our work on the development of efficient and environmentally friendly methods for the synthesis of various organic molecules under different reaction conditions, synthesis of a series of β-enaminones and β-enaminoesters from dimedone and ethyl acetoacetate, respectively, in the presence of a minimum amount of acetonitrile is being reported in Scheme 2.



Scheme 2 Silica sulfuric acid–catalyzed synthesis of β-enaminones and β-enaminoesters.

RESULTS AND DISCUSSION

Initially we carried out the reaction between aniline (5 mmol) and dimedone (5 mmol) with a catalytic amount of silica sulfuric acid (0.1 g equal to 0.26 mmol of H^+) at room temperature in acetonitrile, as this condensation works well in polar solvents, and the yield of the product was found to be around 60% after 30 min. After acknowledging the advantages of MORE, we executed the same reaction under MW irradiation in a microwave reactor in the presence of a minimum amount of acetonitrile to get β-enaminone in 98% yield within 30 sec (which is 60 times faster than reaction conditions at room temperature). A minimum amount of solvent was required for reflux in the microwave reactor. Reactions in solvents such as THF, CH_2Cl_2, DMF, and EtOAc were also carried out, but they gave lower yields of the desired product after prolonged reaction time.

To examine the catalytic activity of the reagent, a mixture of aniline and dimedone was irradiated with varying amount of silica sulfuric acid in a microwave reactor for 30 sec. It was found that the best results were obtained when 0.1 g of the catalyst was loaded with the substrates. The excellent yield obtained led us to expand this protocol for the synthesis of β-enaminones and β-enaminoesters by MW irradiation of a variety of substituted amines with dimedone or ethylacetoacetate along with a small amount of acetonitrile (2 mL) in the presence of a catalytic amount of silica sulfuric acid. Quantitative conversions were obtained within 2 min of irradiation, and the results are presented in Table 1.

Anilines containing electron-donating groups such as $-CH_3$ and $-OCH_3$ (entries **3b–3d**, **3j**, **3k**) and electron-withdrawing substituents such as $-NO_2$ and $-Cl$ (entries **3f**–**3i**, **4c**) afforded the corresponding β-enaminone in excellent yield. It is noteworthy that substituents such as &bond;COOH (entry **3m**) were tolerated, and benzyl amine (entries **3e** and **4b**) was also shown to be a good substrate for the reaction. After applying this protocol for the synthesis of β–enaminone from cyclic β-dicarbonyl, dimedone, we

Table 1 β-Amination of dimedone (**1a**) or ethylacetoacetate (**1b**) with amines (**2**) using silica sulfuric acid under solvent-free MWI

Product[a] (**3**)	(**1**)	(**2**)	Time (Sec)	Yield[b] (%)	Melting point* (°C)
3a	**1a**	$C_6H_5NH_2$	30	98	181[181–183][22]
3b	**1a**	$4\text{-}CH_3C_6H_4NH_2$	70	96	201[203–204][22]
3c	**1a**	$3\text{-}CH_3C_6H_4NH_2$	50	95	Oil[17c]
3d	**1a**	$4\text{-}CH_3OC_6H_4NH_2$	60	97	185[186–188][22]
3e	**1a**	$C_6H_5CH_2NH_2$	40	97	130[130–131][22]
3f	**1a**	$4\text{-}NO_2C_6H_4NH_2$	95	89	241[242–245][22]
3g	**1a**	$4\text{-}ClC_6H_4NH_2$	50	95	209[208–210][22]
3h	**1a**	$3\text{-}ClC_6H_4NH_2$	60	93	Oil[17c]
3i	**1a**	$2\text{-}ClC_6H_4NH_2$	80	90	142[142–144][17c]
3j	**1a**	$2\text{-}CH_3C_6H_4NH_2$	60	95	130[130–132][18]
3k	**1a**	$2\text{-}CH_3OC_6H_4NH_2$	80	93	126[126–128][17b]
3l	**1a**	$\alpha\text{-}C_{10}H_7NH_2$	70	90	185[185][22]
3m	**1a**	$2\text{-}HOOCC_6H_4NH_2$	120	93	187[188–189][26]
4a	**1b**	$C_6H_5NH_2$	50	96	Oil[Oil][22]
4b	**1b**	$C_6H_5CH_2NH_2$	60	97	Oil[Viscous liquid][22]
4c	**1b**	$4\text{-}ClC_6H_4NH_2$	65	91	57[57–58][18]

[a] All reactions were performed using amine (5 mmol), dimedone/ethylacetoacetate (5 mmol), and silica sulfuric acid (0.26 mmol of $H^+ = 100$ mg).

[b] Isolated yield; all the compounds are known, and physical properties agree with the reported values. Mass spectral data of all the products match with the reported data.

*Observed melting point [lit. melting point][ref].

wanted to prepare β-enaminoesters from aliphatic dicarbonyl compounds. Hence, we took ethylacetoacetate (5 mmol) and treated it with an amine (5 mmol) in the presence of 0.1 g of silica sulfuric acid and irradiated it at 400 W in a microwave oven for the appropriate time as indicated by the TLC. Since the yield of the products was extremely high, we continued the reaction with a variety of amines. The structures of all the products were confirmed by mass spectral analysis and their melting points, which were found to be comparable with the authentic samples.

Comparison of the present method with the reported methods was done in order to determine the efficacy of our work, and the results are represented in Table 2. It is evident from this table that the present method is superior to the existing methods.

Table 2 A comparative study of the present system with the reported methods

Entry	Reagent	Conditions	Time	Yield[a] (Ref.)
1	CAN	Acetonitrile/RT	9 min	75[22]
2	$ZrCl_4$	Solvent-free/RT	40 min	95[25]
3	$HClO_4\text{-}SiO_2$	Solvent-free/RT	8 min	95[18]
4	I_2	Solvent-free/RT	2.5 min	81[20]
5	Silica gel	Solvent-free/RT	24 h	86[21]
6	**Silica sulfuric acid[b]**	**Acetonitrile/MW**	**50 sec**	**96***

[a] Isolated yield.

[b] Present method.

*Reaction conditions: Dimedone (5 mmol), amine (5 mmol), silica sulfuric acid (100 mg), and acetonitrile (2 mL) in a MW reactor at 400 W.

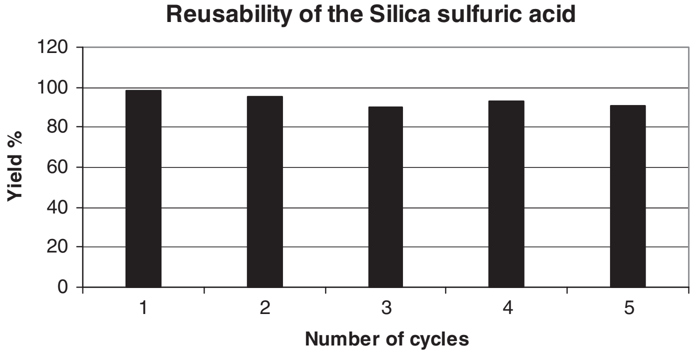


Figure 1 Reusability of silica sulfuric acid (0.1 g) in the condensation of aniline (5 mmol) with dimedone (5 mmol) for 30 sec.

Finally, the possibility of recycling the catalyst was examined. For this, the reaction of aniline and dimedone under the optimized conditions was studied in the presence of 0.1 g of silica sulfuric acid. When the reaction was complete, the mixture was filtered; the residue was washed with warm ethanol and recycled 4 times. The results of five runs showed that more than 90% of the catalyst was recovered, and it retained its activity in terms of product yields: 98%, 95%, 90%, 93%, and 91% respectively (Figure 1).

EXPERIMENTAL

Materials and Methods

All amines and β-dicarbonyl compounds were commercial products and were used without further purification. Yields refer to isolated products. Melting points were measured on a Raaga (Chennai, India) melting point apparatus; GC-Mass spectra were recorded on a Shimadzu GC-MS QP 5050A instrument. Infrared spectra were recorded using a Shimadzu FT-IR-8400s spectrophotometer as KBr pellets for solids, and liquids/oils as thin films between NaCl pellets. All microwave reactions were conducted in a MILESTONE microwave reactor at 400 W.

Typical Experimental Procedure

A mixture of amine (5 mmol), dimedone or ethylacetoacetate (5 mmol), and silica sulfuric acid (0.1g, equal to 0.26 mmol of H^+) was taken in a Pyrex glass tube. A minimum amount of acetonitrile (2 mL) was added, homogenized, and placed in a microwave reactor, and the mixture was irradiated (400 W) for a period of 1–2 min with 20 sec intervals (Table 1). After completion of the reaction, as indicated by the TLC, EtOAc (3 mL) was added to the reaction mixture. The solid catalyst was removed by filtration and washed with warm ethanol for reuse. The reaction mixture was then washed with hot water (5 mL) followed by dil. HCl (5 mL) to remove any unreacted amine and dried over $MgSO_4$. The solvent was removed under vacuum to get the product. Analytical grade samples were then obtained by recrystallization from aq. alcohol. Yields and physical constants of all the products prepared by this procedure are presented in Table 1.

CONCLUSIONS

In conclusion, silica sulfuric acid has been proven to be an active and excellent catalyst for the effective amination of β-dicarbonyls by a variety of amines under microwave irradiation. The ready availability and cost of the reagents, reusability of the catalyst, and easy procedure and work-up make this method attractive for large-scale operations.

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