Silica gel supported sodium hydrogen sulfate as an efficient and reusable heterogeneous catalyst for the synthesis of imines in solvent-free conditions under microwave irradiation

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This synthesis of imines has been carried out efficiently by the condensation of carbonyl compounds with amines in the presence of silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$) as a heterogeneous catalyst under microwave irradiation in solvent-free conditions. $NaHSO_4.SiO_2$ can be recovered and re-used up to ten times by simple washing with diethyl ether after each use and activated in an oven at 120 °C for 1 h, thus rendering the process more economical.

Keywords: silica gel supported sodium hydrogen sulfate, imines, solvent-free conditions

Novel approaches to ecofriendly chemistry include the coupling of dry media synthesis with microwave activation. There is an increasing interest in the use of environmentally benign reagents and conditions[1-3] and particularly in solvent-free procedures.[4] Imines or Schiff bases have attracted great attention recently in synthetic organic chemistry due to their pharmacological and therapeutic uses such as lipoxygenase inhibitors, anti-inflammatory agents[5] and anti-cancer agents.[6] The condensation of carbonyl compounds with amines plays a pivotal role in chemical transformation[7] as the resultant imines are used as diverse and versatile components in the formation of optically active α-alkyl aldehydes,[8] in the preparation of secondary amines by hydrogenation,[6] in nucleophilic addition with organometallic reagents,[10] and in cycloaddition reactions.[11] The first procedure for the synthesis of imines, reported by Schiff[12] more than a century ago, makes use of the condensation of a carbonyl compound with an amine under azeotropic distillation[13] to separate the liberated water. This has led to the development of several new synthetic strategies involving Lewis acids[14] and molecular sieves in ionic liquids[15] which gave better yields of imines. However, all these methods have some limitations with regard to generality and efficiency. As imines are versatile intermediates in medical and organic chemistry, development of an alternative synthetic methodology is of importance. Silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$),[16] a non-toxic and inexpensive catalyst, has been used for a number of organic reactions such as the one pot conversion of ketones into amides[17] and single-step synthesis of 4(3H)-quinazolinones.[18]

Microwave (MW) irradiation has proved to be highly efficient for the rapid synthesis of a variety of compounds.[19] Chemical reactions are accelerated essentially because of selective absorption of microwave energy by polar molecules which are inert to the microwave dielectric loss. Among them, heterogeneous reactions facilitated by supported reagents on various mineral oxides have received special attention in recent years.[20] While planning to select a suitable mild acid for catalysing imine formation, we thought that a catalyst known for activation of an electrophile should serve the purpose.

During the course of our studies aimed at developing solvent-free procedures we found that the use of silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$) catalysed nucleophilic attack on the carbonyl group by the amine and served as a dehydrating agent to facilitate the removal of water in the final step both under MW irradiation and thermal conditions. $NaHSO_4.SiO_2$ catalyses the reactions of structurally diverse carbonyl compounds and various amines under mild conditions to give the corresponding imines in excellent yield. $NaHSO_4.SiO_2$ catalyst was shown to be one of the most efficient MW absorbers with a very high specificity to MW heating. It was able to reach a temperature of 110 °C after 3 min of irradiation in a domestic oven (320 W).

The $NaHSO_4.SiO_2$ catalyst can be reused by simple washing with diethyl ether after each use and followed by activation in an oven at 120 °C for 1 h, thus rendering the process more economical. This constitutes a green and efficient alternative to the MW assisted method described by Varma *et al.*[14b] using K-10 clay as catalyst.

$NaHSO_4.SiO_2$ catalyst was shown to have a remarkable high activity for the condensation of carbonyl compounds with amines to give the corresponding imines in high yields, without any of the environmental disadvantages of using toxic drying reagents such as $TiCl_4$.[14b] Several substituted imines have been prepared by this method and the resulting data are summarised in Table 1.

Experimental conditions have been carefully monitored to regulate the use of the $NaHSO_4.SiO_2$ catalyst, the irradiation time and the power level of the microwave oven to get the maximum yield. The 1:1 ratio of $NaHSO_4.SiO_2$ catalyst to substrate is the most acceptable ratio in terms of efficiency, and a power level of 320 W is the most suitable one.

To establish the scope and limitations of $NaHSO_4.SiO_2$ as a catalyst for imine formation, a model reaction was performed by condensing 3,4-dimethoxybenzaldehyde with 4-nitroaniline, since the presence of the methoxy group in the carbonyl compound reduces the electrophilicity of the carbonyl compound through resonance and the strong electron withdrawing property of the nitro group in the amine decreases the nucleophilicity of the amine group. In order to evaluate the synergy between dry media and MW irradiation in this reaction, several experiments were tried. As shown in Table 2, the reaction of 3,4-dimethoxybenzaldehyde and 4-nitroaniline without irradiation is unsuccessful and no imine is formed after 600 s grinding in a mortar (entry 2). When $NaHSO_4.SiO_2$ is used as a catalyst (660 s, Δ), the corresponding imine is obtained in 82% yield (entry 4). The condensation of 3,4-dimethoxybenzaldehyde with 4-nitroaniline in the presence of $NaHSO_4.SiO_2$ catalyst without irradiation is unsuccessful and the yield of corresponding imine after 300 s grinding in a mortar at 40 °C is only 32% (entry 3). Similarly when we used irradiation without $NaHSO_4.SiO_2$ catalyst for 300 s the condensation proceed in only 10% yield (entry 5). Only in the case of dry media coupled with MW irradiation taking advantage of the synergy between both methodologies is the imine produced in excellent yield (entry 1).

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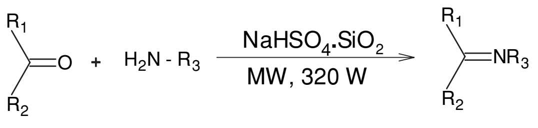
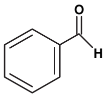
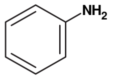
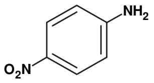
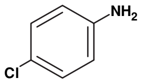
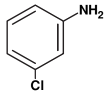
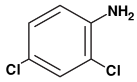
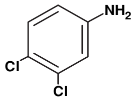
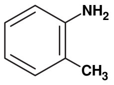
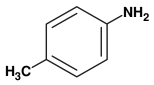
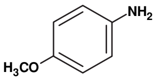
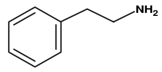
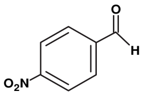
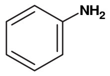
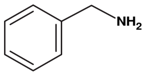
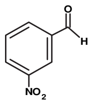
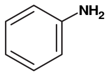
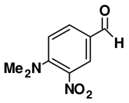
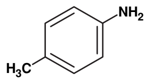
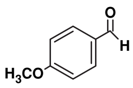
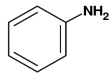
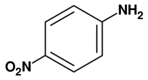
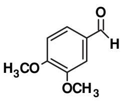
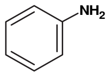
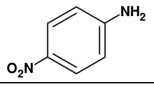
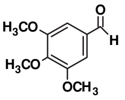
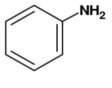
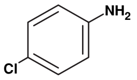
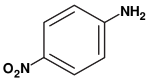
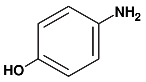
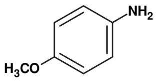
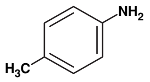
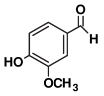
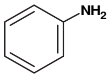
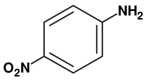
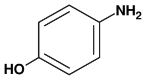
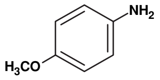
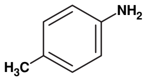
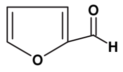
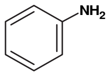
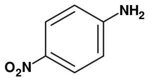
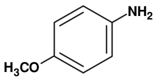
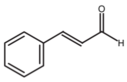
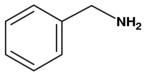
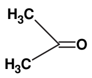
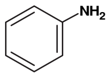
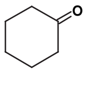
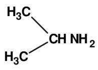
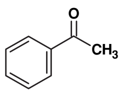
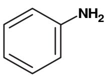
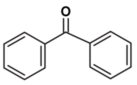
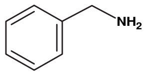
Table 1 Microwave-induced synthesis of imines[14,15] using $NaHSO_4.SiO_2$ catalyst (Power = 320W)



1 **2** **3**

Entry	Substrate	Amine	Reaction temp.[a] /°C	Time/s	Yield[b]/%
1			50–52	40	98
2			52–54	80	95
3			62–64	75	96
4			58–60	70	95
5			64–66	85	90
6			60–62	65	92
7			52–54	55	92
8			50–52	60	94
9			62–64	75	91
10			62–64	75	91
11			64–66	85	94
12			58–60	78	95
13			60–62	80	90
14			64–66	85	92
15			58–60	70	92
16			64–66	90	96
17			56–58	80	95
18			58–60	90	93

Entry	Substrate	Amine	Reaction temp.[a] /°C	Time/s	Yield[b]/%
19			60–62	90	94
20			58–60	90	93
21			60–62	85	96
22			58–60	80	95
23			60–62	75	92
24			64–66	85	93
25			58–60	75	96
26			64–66	85	93
27			56–58	82	95
28			60–62	80	98
29			54–56	85	91
30			56–58	88	98
31			58–60	85	96
32			60–62	78	95
33			64–66	90	95
34			50–52	120	75
35			54–56	95	82
36			48–50	240	78
37			58–60	260	83

[a] Reaction temperature was measured by immersing a glass thermometer into the reaction mixture immediately after exposure to MW irradiation.

[b] Yields of isolated products.

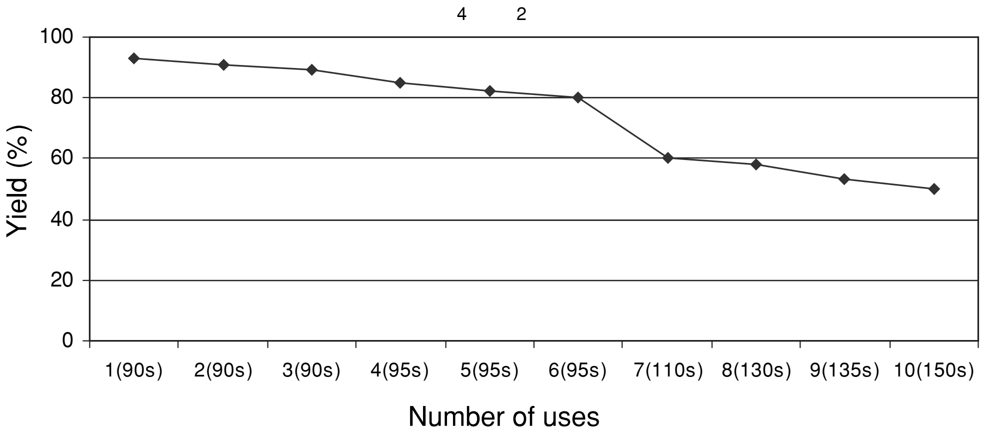


Fig. 1 Re-use studies on the $NaHSO_4.SiO_2$ catalyst mediated synthesis of imines using 10 mmol of 3,4-dimethoxybenzaldehyde and 10 mmol of 4-nitroaniline. The reaction was carried out in a microwave oven at 320W. In parenthesis the irradiation reaction time is given.

Table 2 Condensation of 3,4-dimethoxybenzaldehyde with 4-nitroaniline

Entry	Catalyst	*T* or MW power	Time/s	Imine[a]/%
1	$NaHSO_4.SiO_2$	320W	90	93
2	$NaHSO_4.SiO_2$	r.t.	600	0
3	$NaHSO_4.SiO_2$	40 °C	300	32
4	$NaHSO_4.SiO_2$	60 °C	660	82
5	None	320W	300	10

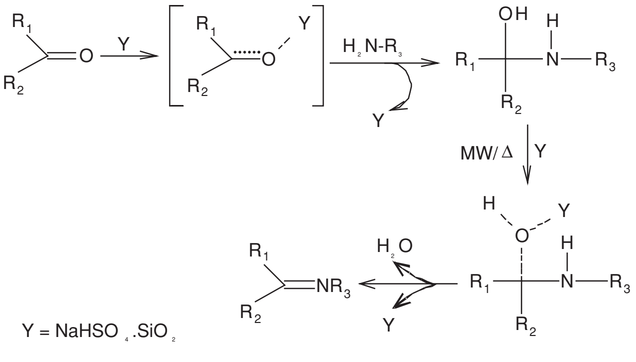
[a]Evaluated by TLC analysis.

A major role is played by $NaHSO_4.SiO_2$ catalyst, which can be reused up to 10 times by washing it with diethyl ether after each use and then activating it in an oven at 120 °C for 1 h prior to use (Fig. 1). However, there is loss of activity after six uses. This constitutes a green and efficient alternative to the use of dichloromethane or diethyl ether, which are the commonly used solvents for this reaction.

Finally, in order to check the possibility of specific non-thermal effects of microwave irradiation, reactions were carried out using a thermostated heating mantle (Δ) under similar sets of conditions of time and temperature as for the microwave-assisted method (Table 3). Significantly lower yields were obtained under conventional heating than when using the MW-assisted method under identical conditions of time and temperature. Even by extending reaction times, yields remain lower under thermal conditions when compared to MW activation. This observation clearly demonstrates that the effect of MW irradiation is not purely thermal. A possible synthetic route for the synthesis of imines is depicted in Scheme 1.

Table 3 Comparison of results under both MW and thermal conditions (power = 320 W)

Entry	Method	*T*/°C	Time/s	Yield/%
1	MW	52–54	40	99
	Δ	54	40	30
	Δ	54	480	90
11	MW	58–60	75	95
	Δ	60	75	25
	Δ	60	600	78
18	MW	58–60	90	93
	Δ	62	90	28
	Δ	62	660	80
25	MW	64–66	85	93
	Δ	66	85	30
	Δ	66	720	78
30	MW	58–60	85	96
	Δ	60	85	28
	Δ	60	360	85
33	MW	60–62	90	95
	Δ	60	90	10
	Δ	60	540	73
37	MW	58–60	260	83
	Δ	62	260	13
	Δ	62	900	63



Scheme 1

In conclusion, we have described a rapid and convenient microwave-induced solvent-free protocol for the formation of imines using non-toxic and an inexpensive $NaHSO_4.SiO_2$ catalyst. The advantages of this environmentally benign and safe protocol include a simple reaction set-up not requiring specialised equipment, high product yields, short reaction times, the elimination of solvents, and the possibility of easy recovery and reuse of the catalyst. Moreover, the use of 10 mmol of $NaHSO_4.SiO_2$ catalyst giving in quantitative formation of the corresponding imine in dry media coupled with MW irradiation is a useful alternative to organic solvents in this reaction.

Experimental

^1H NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer (400 MHz) in $CDCl_3$ using TMS as internal standard. The FT-IR spectra were recorded in NICOLET-AVATAR-360 FT-IR spectrophotometer in KBr pellets and only noteworthy absorption levels are listed. Chemical Ionisation Mass spectra were recorded on a Finnigan MAT-8230 mass spectrometer. The reactions were monitored by TLC. For the MW irradiation experiments described below a conventional (unmodified) household microwave oven equipped with a turntable was used (LG, MG-395 WA, 760W and operating at 2450 MHz).

Typical procedure for the synthesis of imine (**1**): To a mixture of benzaldehyde (1.06 g, 10 mmol) and $NaHSO_4.SiO_2$ catalyst (1.80 g, 10 mmol) in a 50 ml borosil beaker, aniline (0.93 g, 10 mmol) was added. The reaction mixture was mixed well with the help of a glass rod (15 s) and then irradiated in a microwave oven for 40 s at 320 W (monitored by TLC). The reaction mixture was cooled and extracted with Et_2O (3 × 10 ml). The catalyst was removed by filtration and reused. After drying the ether extracts over anhydrous $MgSO_4$, the combined organic phases were concentrated at reduced pressure to furnish the product (1.78g, 98%). IR: cm^{-1} (KBr) 3049, 2891, 1627, 1590. ^{1}H NMR $CDCl_3$ δ ppm: 7.92–7.20 (Ar–H), 8.45 (s, 1H). MS *m/z*: 182 $(M+H)^{+\bullet}$.

The reaction was also performed with benzaldehyde (5.30 g, 50 mmol), $NaHSO_4.SiO_2$ catalyst (9.0 g, 50 mmol) and aniline (4.65, 50 mmol) in a 50 ml borosil beaker following the same procedure. After an irradiation time of 40s, the product (8.90g, 98%) was obtained.

Spectral data (**8**)**:** IR: cm^{-1}(KBr) 3026, 2870, 2922, 1627, 1590. ^{1}H NMR $CDCl_3$ δ ppm: 7.51–6.92 (m,Ar–H), 8.28 (s,1H), 2.20 (s,3H). MS *m/z*: 196 $(M+H)^{+\bullet}$.

The structures of the products were confirmed by ^{1}H NMR, FT-IR, mass spectra and comparison with authentic samples obtained commercially or prepared by reported methods.[14,15]

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