

Silica Chloride-Catalyzed Microwave-Assisted Efficient and Selective One-Pot Synthesis of Amides from Aldehydes

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The amide function is ubiquitous in organic and biological chemistry. Amides are used as protecting groups in organic synthesis as they offer the advantages of very good stability to a wide range of conditions. They play an important role as technical polymers, pharmaceuticals, agrochemicals, peptides and proteins. Amides are formed by the reaction of a carboxylic acid with an amine. The other alternative methods include Schotten-Baumann reaction, Beckmann rearrangement, Willgerodt reaction, Ugi reaction, Chapman rearrangement, dehydrogenative acylation. Conversion of aldoximes to amides is present in the literature.¹ We also have carried out the inter-conversion of amides to nitriles and *vice versa*.²

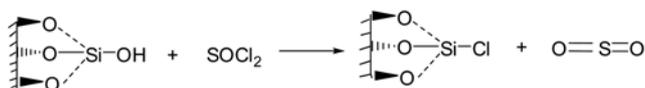
In recent years, solid-phase synthesis has become one of the most important tools in organic synthesis. Silica chloride is prepared by treating SOCl_2 with silica gel (Scheme 1). Due to its insolubility in organic solvents and the presence of labile Si-Cl bond which gives rise to Lewis acid centres, and nucleophile accepting property,³ it can be used for different purposes. $\text{SiO}_2\text{-Cl}$ catalyzed protection of carbonyl compounds^{4a} and synthesis of amidoalkyl-2-naphthols^{4b} are well known reactions. Silica chloride is also used for the preparation of other silica bonded reagents.^{4c}

The extent of chlorination of the silica surface was determined by taking 1 g $\text{SiO}_2\text{-Cl}$ in 25 mL boiled distilled water and titrated against 0.1N NaOH (9.3 mL). The amount of immobilized Cl has been found to be 0.93 milliequivalents/g SiO_2 .³

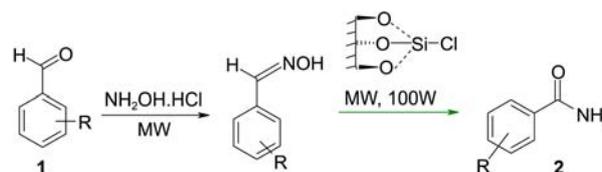
In this communication, we report an improved and simple method for the synthesis of amides by a $\text{SiO}_2\text{-Cl}$ catalyzed microwave-assisted reaction between an aromatic aldehyde and $\text{NH}_2\text{OH}\cdot\text{HCl}$ at 100 W (Scheme 2).

Experimental

$\text{SiO}_2\text{-Cl}$ was prepared by the reported method.³ Melting points were measured on a RAAGA (Indian make) apparatus. GC-Mass and IR spectra were recorded on a Shimadzu GC-MS QP 5050A and Shimadzu FT-IR-8400s instruments



Scheme 1. Preparation of Silica chloride.



Scheme 2. Synthesis of amides in the presence of $\text{SiO}_2\text{-Cl}$.

respectively. All the microwave reactions were conducted in a MILESTONE reactor at 100W.

General Procedure for the Synthesis of Amides from Aldehydes. A mixture of aromatic aldehyde (2 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (2 mmol) and $\text{SiO}_2\text{-Cl}$ (0.1 g) was taken in a Pyrex glass tube, CH_3CN (2 mL) was added, homogenized and placed in a microwave reactor at 100W for 3-4 min with 20 sec interval (Table 2). After completion of the reaction (TLC), EtOAc (5 mL) was added and the catalyst was removed by filtration, washed with warm ethanol and kept aside for reuse. The solvent was removed and the crude was subjected to silica gel column chromatography. Yields and the time taken are presented in Table 2.

Results and Discussion

Initially we found that, catalyst-free reaction did not occur when an aldehyde was treated with $\text{NH}_2\text{OH}\cdot\text{HCl}$ under microwave irradiation at 100W. Later on aromatic aldehydes were treated with $\text{NH}_2\text{OH}\cdot\text{HCl}$ in the presence of $\text{SiO}_2\text{-Cl}$ (200 mg, initially) and heated in a microwave reactor at 100W for 3-4 min (TLC). After work-up, the product was subjected to GC-Mass spectral analysis, which showed the formation of amides. Synthesis of nitriles from aldehydes in the presence of $\text{SiO}_2\text{-Cl}$ under microwave irradiation is reported by Das *et al.*⁵ When we carried out the reaction of aldehydes and $\text{NH}_2\text{OH}\cdot\text{HCl}$ at 100W in the presence of $\text{SiO}_2\text{-Cl}$, we obtained only amides. We also noticed that, amides on irradiation with $\text{SiO}_2\text{-Cl}$ at 300W in a microwave reactor give nitriles, which is in agreement with the work of Das *et al.* It is clear from this study that, nitriles are formed through amide intermediates with catalytic $\text{SiO}_2\text{-Cl}$.

We wanted to optimize the amount of silica chloride used, hence, the reaction was carried out with different amounts of the catalyst, and the best result was obtained with 100 mg

Table 1. Effect of solvents on the reaction of benzaldehyde (2 mmol) with NH₂OH·HCl (2 mmol) in the presence of SiO₂-Cl under MWI^a

Entry	Solvent	Yield (%)
a	H ₂ O	80
b	CH ₃ OH	90
c	C ₂ H ₅ OH	80
d	CH ₃ CN	90
e	DMF	80
f	THF	85
g	Ethylacetate	88
h	Diethylether	78
i	Hexane	83
j	Solvent-free	95

^aAll the reactions were conducted using 100 mg silica chloride in 2 mL solvent at 100 W for 3-4 min.

SiO₂-Cl. The reaction of benzaldehyde and NH₂OH·HCl was also carried out in different solvents and it was found that, the best yield was obtained under solvent-free condition (Table 1).

After optimizing the reaction conditions, we subsequently extended the scope of the present method to a variety of aromatic aldehydes. Aromatic aldehydes with -OMe, -OH, -Cl, -NO₂ groups gave high yields of amides. Cinnamaldehyde also gave good yield after a long time (Table 2). All the products were characterized by GC-Mass and IR spectral analysis.

To illustrate the efficacy of this expeditious microwave-

Table 2. One-pot synthesis of amides from aldehydes and NH₂OH·HCl using SiO₂-Cl in CH₃CN

Entry	R	Amide 2 ^a	Time (sec)	Yield (%) ^b	Melting Point [Lit.] (°C)
1	H	2a ⁶	220	95	128[132-133]
2	2,4-Cl ₂	2b ⁷	215	91	140[142]
3	3,4-OCH ₃	2c ⁶	235	98	66[66-68]
4	4-OCH ₃	2d ⁶	220	92	166[164-167]
5	Cinnamyl	2e ⁶	225	90	148[149-150]
6	3-NO ₂	2f ⁶	230	94	138[140]
7	2-OCH ₃	2g ⁶	230	90	124[125-126]
8	2-OH	2h ⁷	235	92	144[148-152]
9	4-Cl	2i ⁶	240	93	172[172-176]
10	4-NO ₂	2j ⁶	223	95	202[200]
11	4-OH	2k ⁶	229	95	160[160]
12	4-OH,3-OCH ₃	2l ⁷	242	89	154[153-154]

^aReferences for spectral data. ^bIsolated yield

Table 3. Quantitative analysis of recovered silica chloride

Entry	No. of times recovered silica chloride	Amount of chloride (miliquivalents)
a	1 st	0.85
b	2 nd	0.80
c	3 rd	0.74
d	4 th	0.68
e	5 th	0.61
f	6 th	0.48

assisted transformation, reaction of **1a** with NH₂OH·HCl in the presence of catalytic SiO₂-Cl under conventional heating was also carried out. The reaction did not go to completion and 55% of the oxime was formed instead of an amide even after heating at 80 °C for 3 hr.

The catalyst was recycled, and the yield was found to be 98, 97, 95, 94 and 92% respectively for 1-5 cycles, the marginal decrease of yield may be due to the depletion of the chloride from silica surface. The recovered silica chloride was also analysed by titrating with 0.1 N NaOH (Table 3).

Conclusions

In conclusion, we have demonstrated a one-pot selective conversion of aromatic aldehydes to amides with NH₂OH·HCl by catalytic SiO₂-Cl in a microwave reactor at 100W. This synthesis is suitable for e-withdrawing and e-donating aldehydes. The developed protocol has advantages of short reaction time and high yields, utilizes an efficient and recyclable heterogeneous catalyst and follows green chemistry norms.

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