Efficient and Rapid One-pot Conversions of Aldehydes into Nitriles and Ketones into Amides Using Silica Chloride under Microwave Irradiation[1]

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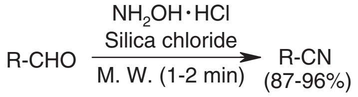
Under solvent free conditions, several aldehydes and ketones were efficiently and rapidly converted into the corresponding nitriles and amides respectively by treatment with hydroxylamine hydrochloride under microwave irradiation using silica chloride as catalyst. The yields of the products were very high and the time required for their preparation was very short compared to conventional heating experiments.

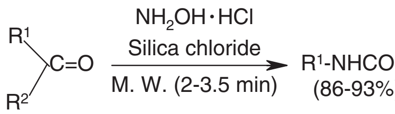
The transformations of aldehydes to nitriles,[2] and ketones to amides[3] are highly useful for the synthesis of bioactive as well as commercially important compounds. Nitriles are employed for the preparations of *anti*-picornavirous and *anti*-inflammatory drugs[2a,b] and angiotension receptor ligands like losartan and valsartan.[2c] Amides are also used in medicine as febrifuge[4] and the cyclic derivatives for the preparation of industrially useful polymeric compounds like Nylon 6.[3b] Nitriles can be converted into amines, amides, ketones, acids and esters while amides into nitriles, acids, esters, and amines.[4,5] These conversions are of considerable importance in synthetic organic chemistry. Nitriles and amides can be prepared from the corresponding aldehydes and ketones respectively. The aldehydes can be converted[6] into aldoximes which undergo dehydration to form nitriles. The ketones, on the other hand, can be converted[7] into ketoximes which under Beckmann rearrangement can produce amides. A limited numbers of microwave assisted rapid one-pot conversions of aldehydes into nitriles, and ketones into amides are also known but most of these methods are associated with certain drawbacks. As for example, for conversion of aldehydes into nitriles under microwave irradiation reagents like corrosive formic acid[8] (which may affect the sensitive aldehydes)[9] oxidant potassium peroxymonosulfate[10] (which may oxidise the functional groups)[11] and hygroscopic ammonium acetate[12] (which may itself decompose under microwaves) have been used. Mexican Bentonite[13] which was applied for microwave assisted conversion of ketones into amides afforded very low yields of the products while hydroxylamine-*o*-sulfonic acid[14] required tedious work up procedure. Silica-supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$)[15] and HY-Zeolite[16] have also recently been employed for both the conversions of aldehydes into nitriles, and ketones into amides under microwave irradiation. However, the first catalyst should be freshly prepared at the time of its use and properly activated keeping in oven to make the conversions efficient while the second catalyst is not a common desk reagent in the laboratory of organic chemist. An another microwave assisted method[17] for direct conversion of aldehydes into nitriles used *N*-methyl pyrrolidone as a solvent without any catalyst but benzaldehye itself did not give high yield (65%) of benzonitrile. Thus there is a need to develop improved methods for rapid one-pot conversions of aldehydes into nitriles and ketones into amides using easily available catalysts. Here we describe our recent work on such conversions in the presence of silica chloride (silica gel treated[18] with thionyl chloride) under microwave irradiation.

In continuation of our research[19] on eco-friendly reactions we have observed that aldehydes and ketones can rapidly be converted into nitriles and amides respectively by treatment with hydroxylamine hydrochloride under microwave irradiation in the presence of silica chloride as catalyst.

Various aldehydes were readily converted into the corresponding nitriles (Table 1), and ketones into amides (Table 2). Cyclohexanone was transformed to the industrially important compound, caprolactam (Table 2, Entry 8). The structures of all the products were established from their analytical and spectral data. The products were formed in very high yields within a very short period of time. The experimental procedure is very simple and the conversions occurred under solvent free conditions.[20] The catalyst, silica chloride, can easily be prepared[18] from the readily available inexpensive reagents, thionyl chloride and silica gel (100-200 mesh). As it is a heterogenous catalyst it can easily be removed by filtration from the reaction mixture.



$$\text{R-CHO} \xrightarrow[\text{M. W. (1-2 min)}]{\text{NH}_2\text{OH}\cdot\text{HCl} \atop \text{Silica chloride}} \underset{(87\text{-}96\%)}{\text{R-CN}}$$



The mechanism of the formation of nitriles from aldehydes may be proposed as follows. The reaction between aldehydes and hydroxylamine hydrochloride produced first the corresponding aldoximes which then underwent dehydration to afford the nitriles. Similarly, for the conversion of ketones into amides the former first reacted with hydroxylamine hydrochloride to form ketoximes which subsequently under Beckmann rearrangement yielded the amides.

In conclusion, we have developed a novel, simple and efficient method for one-pot conversions of aldehydes into nitriles, and ketones into amides using inexpensive silica chloride as catalyst under microwave irradiation. The yields of the products are very high and the time required for their preparation is very short. The process is environmentally benign.

Table 1. Conversion of Aldehydes (R-CHO) into Nitriles (R-CN)

Entry	R	M.W.	Conventional	Isolated Yield/%	
		Time/min	Time/h	M.W.	Conventional
1.	C_6H_5	1	8	92	72
2.	4-(OH)C_6H_4	1.5	9	94	73
3.	4-(NO_2)C_6H_4	1.5	9	91	70
4.	3-(MeO)C_6H_4	1	8	94	76
5.	3-(MeO), 4-(OH)C_6H_3	1.5	8.5	96	78
6.	3,4-$(MeO)_2C_6H_3$	1	7	95	72
7.	3,4-$(CH_2O_2)C_6H_3$	1	8	92	73
8.	3,4,5-$(MeO)_3C_6H_2$	1	7.5	94	78
9.	2,4,6-$(MeO)_3C_6H_2$	1	7.5	93	76
10.	$C_6H_5CH{=}CH$	2	8.5	90	68
11.	C_7H_{15}	2	7	87	64
12.	C_9H_{19}	2	8	89	67

Table 2. Conversion of Ketones (R^1COR^2) into Amides (R^1NHCOR^2)

Entry	R^1	R^2	M.W.	Conventional	Isolated Yield/%	
			Time/min	Time/h	M.W.	Conventional
1.	C_6H_5	CH_3	3	9.5	90	63
2.	C_6H_5	C_6H_5	3	10	93	67
3.	4-(Cl)C_6H_4	CH_3	3	10.5	89	62
4.	4-(Br)C_6H_4	CH_3	3	11	86	64
5.	4-(MeO)C_6H_4	CH_3	2	10	93	66
6.	4-(Me)C_6H_4	CH_3	2	10.5	91	60
7.	4-(OH)C_6H_4	CH_3	3.5	11	92	59
8.	$-(CH_2)_5-$		2.5	9	91	62

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References and Notes

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20 a) **Typical procedure for conversion of aldehydes into nitriles**: i) **Microwave irradiation**: 3,4-Dimethoxybenzaldehyde (166 mg, 1 mmol) and $NH_2OH{\cdot}HCl$ (91 mg, 1.3 mmol) were mixed thoroughly with silica chloride (100 mg). The mixture was taken in a test tube, kept in an alumina bath inside a microwave oven (BPL, BMO, 700 T, 466 watt) and irradiated for 1 min at 105 °C maintaining 70% efficiency of the oven. The mixture was removed from the oven, cooled, shaken with EtOAc (10 mL) and filtered. The filtrate was concentrated and purified by column chromatography over silica gel using hexane–EtOAc (1:1) as eluent to produce 3,4-dimethoxybenzonitrile (155 mg, 95%), mp 63-65 °C, IR: ν_{max} (KBr) 2931, 2223, 2026 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.25 (1H, dd, $J = 9.0$, 1.5 Hz, H-6), 7.06 (1H, d, $J = 1.6$ Hz, H-2), 6.87 (1H, d, $J = 9.0$ Hz, H-5), 3.93, 3.89 (3H each, s, 2x-OMe); MS: m/z 163 (M^+), 148, 120, 102. ii) **Conventional method**: 3,4-Dimethoxybenzaldehyde (166 mg, 1 mmol) and $NH_2OH{\cdot}HCl$ (91 mg, 1.3 mmol) were taken in acetonitrile (15 mL). Silica chloride (100 mg) was added. The mixture was refluxed under N_2 atmosphere for 7 h. After filtration the filtrate was purified by column chromatography over silica gel using hexane–EtOAc (1:1) as eluent to give 3,4-dimethoxybenzonitrile. (117 mg, 72%). b) **Typical procedure for conversion of ketones into amides**: i) **Microwave irradiation**: 4-Hydroxyacetophenone (136 mg, 1 mmol) and $NH_2OH{\cdot}HCl$ (104 mg, 1.5 mmol) were mixed with silica chloride (100 mg). The mixture was taken in a test tube, placed in an alumina bath inside the microwave oven and irradiated for 3.5 min at 160 °C maintaining 70% efficiency of the oven. The mixture was cooled and shaken with EtOAc (10 mL). After filtration the filtrate was concentrated and the residue was purified by column chromatography over silica gel using hexane-EtOAc (1:1) as eluent to afford 4-hydroxyacetanilide (139 mg, 92%), m.p. 167-168 °C, IR: ν_{max} (KBr) 3325, 1655, 1600, 1562 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6): δ 7.34 (2H, d, $J = 8.0$ Hz, H-2, H-6), 6.62 (2H, d, $J = 8.0$ Hz, H-3, H-5), 2.03 (3H, s, -Me); MS: m/z 151 (M^+), 136, 108. ii) **Conventional method**: 4-Hydroxyacetophenone (136 mg, 1 mmol) and $NH_2OH{\cdot}HCl$ (104 mg, 1.5 mmol) were taken in acetonitrile (15 mL). Silica chloride (100 mg) was added. The mixture was refluxed under N_2 atmosphere for 11 h. After filtration the filtrate was purified by column chromatography over silica gel using hexane–EtOAc (1:1) as eluent to give 4-hydroxyacetanilide (89 mg, 59%).