An efficient and solvent-free one-pot synthesis of nitriles from aldehydes

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Aldehydes are converted into corresponding nitriles in high yields by a one-pot solvent-free reaction with hydroxylamine hydrochloride in the presence of catalytic amount of pyridine under microwave irradiation. The reactions go to completion within one minute. The process is green, efficient and inexpensive.

Keywords: Aldehydes, hydroxylamine hydrochloride, pyridine, nitriles, microwave

The development of simple, efficient and environmentally benign chemical processes for the synthesis of widely used organic compounds from readily available reagents is one of the challenges for chemists in organic synthesis\(^{10}\). Nitriles are of particular interest in preparative organic chemistry due to their rich chemistry\(^{11}\). Nitriles are useful precursors for the synthesis of amines, carboxylic acids, amides, ketones, and heterocyclic compounds such as thiazoles, oxazoles, and 2-oxazolines\(^{12-14}\). It has also been well documented that the cyano group itself is present in HIV protease inhibitors, 5-lipoxygenase inhibitors, and many other bio-active molecules\(^{15,16}\). Nitriles are usually prepared by nucleophilic substitution with the cyanide anion or by generating the cyano group from aldehyde-\(N,N\)-dimethylhydrazones via oxidation, rearrangement, or elimination\(^{17}\).

The conversion of aldehydes into nitriles is a useful transformation\(^5\) and a topic of current interest. As a result, a number of reagents have emerged for this purpose including use of triethylaminesulfuryl dioxide\(^{18}\), montmorillonite\(^1\), formamide/pyridine\(^2\), and sulphonyl chloride fluorides\(^3\). However, these methods suffer from disadvantages such as, preparation of triethylaminesulfuryl dioxide and sulphonyl chloride fluoride is tedious and possible at \(-70^{\circ}\)C, dehydration of aldoximes with KSF, zeolite\(^4\), and environat EPZG\(^1\) requires high temperature or long reaction duration for completion of the reaction.

On the other hand, pyridine has invoked enormous interest as a catalyst to construct carbon-carbon or carbon-heteroatom bonds. Its cost, ease of handling, good reactivity, and excellent solubility in water and organic solvents makes it an attractive catalyst to carry out various organic reactions. Saednya, in the year 1982 (Ref. 10b) showed that nitriles could be obtained by a one-pot reaction of aldehydes with hydroxylamine hydrochloride in the presence of pyridine. However, the reaction is carried out in toluene as a solvent, works at reflux temperature, requires equimolar amounts of pyridine and goes to completion in 3 to 5 hr.

In continuation with the work on the development of novel methods and novel catalysts for the functional group inter-conversions\(^{11}\), it was decided to use pyridine for the conversion of aldehydes into nitriles by a one-pot solvent-free reaction of aldehydes, hydroxylamine hydrochloride under microwave irradiation Scheme I. Catalytic amount of pyridine has been found to have a remarkable activity on the conversion of various aryl and heterocyclic aldehydes into nitriles in high yields within 1 min, without any of the environmental disadvantages of using toxic solvents.

In a typical experiment, aldehyde, hydroxylamine hydrochloride and pyridine (catalytic) were mixed thoroughly. The mixture was irradiated in a domestic microwave oven at 320 W for the appropriate time (Table I). The products were analyzed by IR spectral analysis, and by direct comparison with authentic samples.

Experimental Section

Aldehydes, hydroxylamine hydrochloride, pyridine and other chemicals were commercial. All solvents were distilled before use and all the reactions were carried out using a conventional (unmodified) household microwave oven (LG, 230 V, \(-50\) Hz).

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\text{RCHO} \quad \text{NH}_2\text{OH.HCl} / \text{Pyridine} \quad \text{MW} / 320 \text{ W / Solvent free} \quad \text{RCN}
\]

Scheme I
Reactions were monitored on TLC by comparison with the authentic samples. The IR spectra of the products were recorded on a Shimadzu FT-IR-8400s spectrophotometer. Yields refer to the isolated yields of the products.

**General procedure for the preparation of nitriles from aldehydes**

Aldehyde (1 mmole), NH₂OH·HCl (0.08 g, 1.2 mmole), pyridine (0.04 g, 0.5 mmole), were thoroughly mixed. The resulting mixture was transferred to a 10 mL beaker and irradiated in a domestic microwave oven at 320 W for the appropriate time (Table I). At the end of irradiation, the mixture was cooled to RT and extracted with dichloromethane (5 mL). The organic layer was separated and dried over fused calcium chloride and the solvent was removed under vacuum. The crude product was subjected to silica gel chromatography (short column-15 cm × 1.2 cm) using 2.5% EtOAc in light petroleum as eluent to get the pure nitrile.

**Conclusion**

In conclusion, an efficient, solvent-free and facile one-pot synthesis of nitriles from aldehydes and hydroxylamine hydrochloride in the presence of
catalytic amounts of pyridine under microwave irradiation has been presented. The method is simple, and requires less than one minute for completion making the method environmentally friendly, and it is felt that it is a valuable addition/alternative to the existing methods.

References