



**ONE POT SYNTHESIS OF NITRILES FROM ALDEHYDES AND  
HYDROXYLAMINE HYDROCHLORIDE USING CALCIUM CHLORIDE IN DMF  
SOLVENT UNDER REFLUX CONDITION**

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**Abstract:** A rapid and facile one pot synthesis of nitrile has been carried out in high yields from the corresponding aldehydes and hydroxylamine hydrochloride in the presence of anhydrous calcium chloride and DMF Under reflux condition.

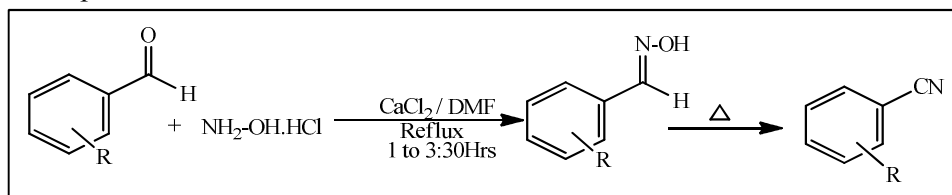
**Key words:** Nitriles, aldehyde, hydroxylamine hydrochloride, anhydrous calcium chloride.

**Introduction**

Nitriles(R-CN) are very useful starting materials for the synthesis of various bioactive molecules<sup>I</sup>. The versatile nitriles are used for the preparation of thiazole, 2-oxazolines, tetrazoles and triazoles, imidazoles, benzamidines possessing a broad spectrum of biological activities<sup>II</sup>. Nitriles are widely used for transformation into amides, amines, ester and carboxylic acids<sup>III</sup>. Hence they have been used as intermediates for the synthesis of fine chemicals such as, agricultural chemicals, dyes and medicines<sup>IV</sup>. One of the most general methods for the synthesis of nitriles is the nucleophilic substitution reaction of alkyl halides with metal cyanides. The method is, however inconvenient because of high toxicity of metal cyanides and troublesome handling. They are also usually prepared by regenerating CN group via oxidation<sup>V</sup>, rearrangement<sup>VI</sup> or elimination. Consequently, other method such as, dehydration of primary amides<sup>VII</sup> or aldoximes have attracted attention. It is known that dehydration of aldoximes into nitriles can be achieved by using a variety of reagents or new other reagents like, triethylamine/sulphur dioxide<sup>VIII</sup>, zeolites<sup>IX</sup>, sulfur chloride<sup>X</sup>, trichloroisocyanuric acid<sup>XI</sup>, dicyclohexylcarbodiimide<sup>XII</sup>, phosphonitric chloride<sup>XIII</sup>, chlorosulfonylisocyanate, triphenylphosphine Burgess reagent<sup>XIV</sup>, and also include the use of expensive (2,4-dinitrophenyl hydroxylamine)<sup>XV</sup>, (hydroxylamine-*o*-sulphonic acid)<sup>XVI</sup>, selenium dioxide<sup>XVII</sup>, etc. but many of these suffer from limitations such as, high toxicity, vigorous reaction conditions, unsatisfactory yields, tedious work up and use of large excess of reagents. We have recently reported a rapid synthesis of nitriles in high yields from aldoximes using silica gel<sup>XVIIIa</sup> and one pot synthesis of nitriles from aldehyde and hydroxylamine hydrochloride using silica gel, Mont K-10 and KSF catalyst in dry media under microwave irradiation<sup>XVIIIb</sup>. Some rapid procedures for one pot synthesis of nitriles have been described using formic acid<sup>XIX</sup> and potassium peroxy monosulfate<sup>XX</sup> but whereas

the first method suffers from undesirable action of formic acid that can affect acid-sensitive aldehydes, the second suffers from the rapid undesirable oxidation of some functional groups. So, there exists a need for developing and facile methods for one pot synthesis of nitriles.

We report herein one pot transformation of aldehydes into nitriles by their treatment with hydroxylamine hydrochloride using anhydrous calcium chloride and DMF under reflux condition which we thought would catalyze both oxime formation and then consequent nitrile formation step.



**Scheme-1**

There has been growing interest over the past few years to carry out organic reactions, over homogeneous catalysts, because of simple set ups and workup, lesser chemical degradation, higher product purity and chemical yield. Investigations were initiated with 4-Hydroxy benzaldehyde being chosen as a model compound. It was reflux with hydroxylamine hydrochloride in presence of anhydrous calcium chloride and DMF.

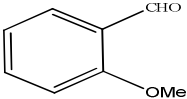
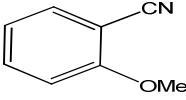
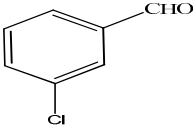
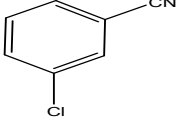
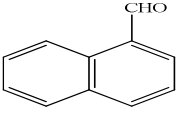
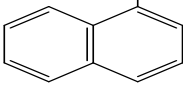
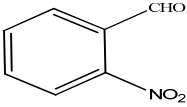
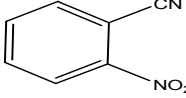
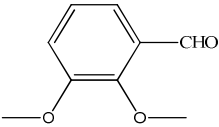
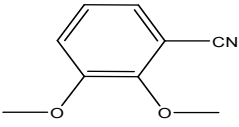
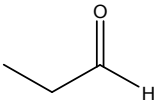
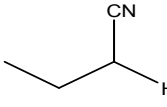
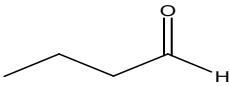
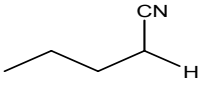
### Result and discussion

As can be seen, the nitriles were formed in high yields of 85-95% yield within 1hrs -3.3hrs. Hence, all the subsequent reactions were carried out under this reaction conditions a variety of substituted aromatic aldehydes (1-8) and aliphatic aldehydes (9-10) including. The reactions were monitored by TLC. The product yields and reaction times are collected and presented in Table-1. All the products are known compounds and were identified on the basis of their spectroscopic analysis and by direct comparisons of their M.P with those of authentic samples<sup>XXI</sup>. The products were obtained in more than 90% purity as determined by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, Mass analysis and were further purified by column chromatography.

As we have observed, the nitriles were formed in high yield of 85-95% within 1hrs-3.3 hrs. It should note that the nitriles were formed with 1-2% yield under identical reaction conditions in the absence of catalyst there by confirming the role of the catalyst in the reaction.

**Table1: One pot synthesis of nitriles from aldehydes and hydroxylamine Hydrochloride using anhydrous Calcium chloride in DMF at reflux condition.**

Entry	Aldehyde	Nitrile	Time in hr.	Isolated yield (%)
1			1Hrs30 min	90%
2			2Hrs.20 min	86%
3			2 Hrs 30 min	95%

4			2Hrs 45min	90%
5			2Hrs 20 min	93%
6			1Hrs 30 min	88%
7			1Hrs.20 min	86%
8			3Hrs.20 min	92%
9			2Hrs.45min	93%
10			2Hrs.30 min	95%

### Conclusion:

In summary, we have demonstrated the use of inexpensive, easy to handle anhydrous calcium chloride catalyst in rapid one pot synthesis of nitriles from aldehydes and hydroxylamine hydrochloride in high yields.

### Experimental section

Melting points were determined in open capillaries.  $^1\text{H}$  NMR spectra was recorded at 400 MHz (Bruker Avance) Cryo-magnet Spectrometer in  $\text{CDCl}_3$  or DMSO Solvent using TMS as an internal standard. The  $^{13}\text{C}$  NMR Spectra were recorded at 100 MHz in  $\text{CDCl}_3$  using TMS as an internal standard. IR spectra was recorded on a FT infra-Red Spectrophotometer Model RZX Perkin Elmer. The products were confirmed by the comparison of their Mass Spectra, IR,  $^1\text{NMR}$ ,  $^{13}\text{C}$  NMR. TLC was carried out on Silica gel G plates with benzene/ethyl acetate (4:1) system. The products were purified by column chromatography on silica gel (100-200).

### General procedure

4-Hydroxybenzaldehyde (1mmol), hydroxylamine hydrochloride (1.2mmol) mixed with calcium chloride (1mmol) and taken in 25ml Round bottom flask and 5ml DMF was added. Whole mixture was reflux for 1-3.3 Hrs. After completion of reaction, the mixture was poured in water (5 ml) and extracted with ethyl acetate (5mL $\times$ 3) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Evaporated ethyl acetate layers to give residue which was purified by column chromatography using benzene/ethyl acetate (4:1) as, eluent to afford the desired nitrile.

### Spectral Analysis:

**(1) Benzonitrile. Colorless liquid; bp : 186-190 °C (lit.-188-191).**

IR (KBr Pellets  $\text{cm}^{-1}$ ): 3065 (C-H Str. aromatic), 2229 (CN-triple bond), 1597, 1491, 1446 (C=C, str. aromatic hydrogen), 800-650 (5 adj. Hydrogen), 689, 737 (C=C-H, opp. bending).  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 400 MHz):  $\square$  7.68-7.65 (m, 2H, Ar-H), 7.62 (t, 1H, Ar-H), 7.47 (t, 2H, Ar-H).  $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ , 100 MHz): 132.74, 132.16, 129.10, 118.83, 122.45. Mass (EI) – (m/z) - 103 (100), 76, 50.

**(2) 4-Hydroxybenzonitrile –Off White solid, m.p.-107- 111°C (lit.- 109-112)**

IR (KBr Pellets  $\text{cm}^{-1}$ ): 3288 (OH str.), 2233 (CN-Triple bond), 2810, 2668 (C-H str.), 1659, 1609, 1510 (C=C str., Ar-H), 1284, 1225, 1167 (C-O str. C=C-O bond), 838, 701 (C=C-H, Opp. bending).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\square$  7.46 (d, 2H, Ar-H), 6.85 (d, 2H, Ar-H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz): 161.44, 133.64, 119.20, 116.18, 101.15. Mass (EI) – (m/z) - 119 (100), 91, 64, 44.

**(3) 4-Methylbenzonitrile – Colorless liquid, b.p.-215-218°C (lit.-217-220).**

IR (KBr Pellets  $\text{cm}^{-1}$ ): 3039, 2825 (C-H str.), 2228 (CN-Triple bond), 1587, 1450, 1430 (C=C, str, aromatic), 803 690 (C=C-H, opp. bending).  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 400 MHz):  $\square$  7.55 (d, 2H, Ar-H), 7.30 (d, 2H, Ar-H), 2.44 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz): 143.74, 132.02, 129.96, 119.16, 109.28, 21.82. Mass (EI) - (m/z) - 117 (100), 116, 90, 63.

**(4) Butyronitrile –Colorless liquid, b.p. – 113-116 °C (lit. - 115-117)**

IR (KBr Pellets  $\text{cm}^{-1}$ ): 2973, 2941, 2881 (str. C-H saturated), 2249 (CN-Triple bond), 1464, 1427, 1385 (CH<sub>2</sub>, CH<sub>3</sub> bending);  $^1\text{H}$ NMR – ( $\text{CDCl}_3$ , 400 MHz):  $\square$  0.62 (t, 3H, aliphatic-H), 1.22 (m, 2H, aliphatic-H), 1.90 (t, 2H, aliphatic-H);  $^{13}\text{C}$ NMR – ( $\text{CDCl}_3$ , 400 MHz): 118.96, 18.38, 18, 12.28. Mass (EI) - (m/z) - 44 (100), 68, 54, 39, 29, 28.

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