

## Fe(HSO<sub>4</sub>)<sub>3</sub>-Catalyzed Direct Conversion of Aldehydes into Nitriles Using Hydroxylamine Hydrochloride

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Due to the importance and various applications of nitriles, especially in medicinal productions, a new method for conversion of aldehydes to nitriles has been presented. Several nitrile-containing aromatic compounds were synthesized through the treatment of various aldehydes and hydroxylamine hydrochloride as nucleophile in the presence of ferric hydrogen sulfate as a heterogeneous, efficient, and recyclable catalyst in DMF in good to excellent yields.

**Keywords:** Hydroxylamine hydrochloride, Ferric hydrogen sulfate, Nitriles, Aldehydes

### INTRODUCTION

Nitriles are key constituents in a variety of biologically active compounds like natural products [1,2]. They are also important synthetic intermediates for pharmaceuticals, pesticides and dyes [3]. Numerous methods to synthesize nitriles have been documented in the literature, such as Sandmeyer reaction [4], ammoxidation of aldehydes [5], Kolbe nitrile synthesis [6], hydrocyanation of alkenes [7], Rosenmund-von Braun reaction [8], metal-catalyzed cyanation of aryl halides, the nucleophilic substitution of alkyl halides with cyanides, oxidation of amines [9,10], and dehydration of amides and aldoximes [11-13]. Among these plethora of available methods to prepare nitriles, the simple and straightforward routes are those based on the dehydration of aldoximes, formed *in situ* by condensation of aldehydes and hydroxylamine hydrochloride due to the availability of starting materials and the avoidance of very toxic cyanide ion. A number of metal catalysts, such as nickel catalysts [14,15], metal triflates [16,17], [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> [18], [(EtCN)<sub>2</sub>PtCl<sub>4</sub>] [19], copper salts [20,21], zinc salts [22,23], Pd(OAc)<sub>2</sub> [24], [(Ipr)AuCl]/AgBF<sub>4</sub> [25], iron porphyrin [26] and tungsten-tin mixed hydroxide [27], have been reported. In addition, supported catalysts [28],

and ionic liquids [29,30] were employed in the conversion of aldoximes into nitriles.

In recent years, ferric hydrogen sulfate (FHS) has emerged as a promising solid acid catalyst for acid catalyzed reactions, such as Schmidt reaction [31], functional group protections [32-35] and Friedel-Crafts acylation [33-35].

With these backgrounds and as a part of our ongoing study on a milder reaction condition coupled with the use of environment-friendly, cost efficient and high functional group tolerance [36,37], we have chosen FHS as an efficient catalyst for the one step conversion of aldehydes into nitriles (Scheme 1).

### EXPERIMENTAL

#### General Procedure for the Conversion of Aldehydes to Nitriles

To the mixture of an appropriate aldehyde (1 mmol), DMF (5 ml) and hydroxylamine hydrochloride (1.2 mmol, 0.09 g), FHS (1.5 mol%, 0.52 g) was added and heated at 120 °C according to the times mentioned in Table 2. After the completion of the reaction monitored by TLC using *n*-hexane: EtOAc (9:1), the catalyst was centrifuged off and the solvent was evaporated under the reduced pressure. To the resulting oily liquid, CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added, and the

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**Table 1.** The Data for the Oxidation of 4-Chlorobenzaldehyde to 4-Chlorobenzonitrile<sup>a</sup>

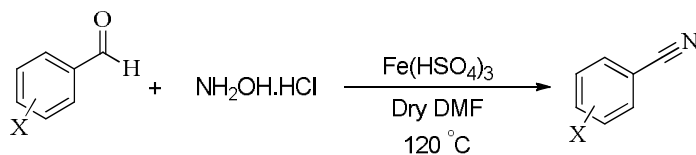
Entry	Solvent	FHS (mol%)	Time (h)	Temperature (°C)	Conversion (%)
1	THF	3	12	rf <sup>b</sup>	Trace
2	Toluene	3	12	rf	40
3	CH <sub>3</sub> CN	3	12	rf	50
4	MeOH	3	12	rf	Trace
5	EtOH	3	12	rf	Trace
6	H <sub>2</sub> O	3	12	rf	Trace
7	AcOH	3	12	rf	50
8	DMF	3	12	rf	95
9	DMF	0	12	120	Trace
10	DMF	30	12	120	95
11	DMF	20	11	120	95
12	DMF	10	24	120	95
13	DMF	5	12	120	95
14	DMF	3	12	120	95
15	DMF	1.5	12	120	95
16	DMF	0.75	15	120	65
18	DMF	1.5	24	25	10
19	DMF	1.5	12	50	15
20	DMF	1.5	12	100	80
21	DMF	1.5	3	120	95

<sup>a</sup>All reactions were carried out with 1 mmol of 4-chlorobenzaldehyde and 1.2 mmol of hydroxylamine hydrochloride in 5 ml of solvent. <sup>b</sup>rf= reflux.

organic phase was consecutively washed with aqueous 10% NaOH solution (10 ml), aqueous 10% NaHSO<sub>3</sub> (10 ml) and distilled water (10 ml) to remove impurities and unreacted aldehydes. Eventually, the organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated under the reduced pressure to afford the pure products.

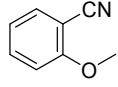
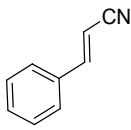
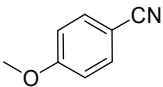
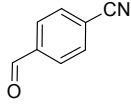
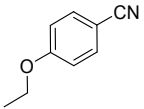
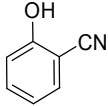
## RESULTS AND DISCUSSION

In an endeavor to start the present investigation, 4-chlorobenzaldehyde was chosen as a model compound. The results of optimization reactions were summarized in Table 1.

**Table 2.** Substrates Tested in Conversion of Aldehydes into Nitriles with Hydroxylamine Hydrochloride in the Presence of FHS

Entry	Product	Time (h)	Yield (%) <sup>a</sup>	Entry	Product	Time (h)	Yield (%) <sup>a</sup>
1		1	90	15		2	90
2		1.2	80	16		2	85
3		0.5	95	17		3	75
4		1.5	80	18		2.5	80
5		0.5	90	19		2	85
6		2	85	20		2	90
7		1	95	21		1.5	80
8		0.5	95	22		2	90
9		2.5	80	23		1	80
10		2	85	24		0.5	65

Table 2. Continued

11		2.5	70	25		3.5	90
12		1.5	90	26		4	90
13		1.5	90	27	n-C <sub>6</sub> H <sub>11</sub> -CN	1	Trace
14		1.5	85	28	n-C <sub>8</sub> H <sub>15</sub> -CN	1	Trace

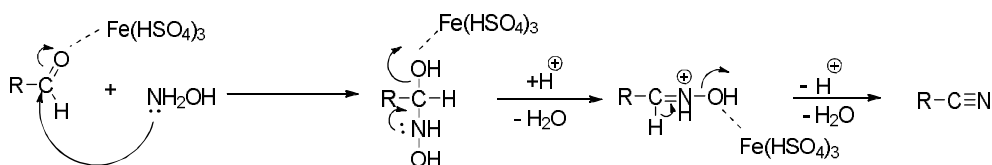
<sup>a</sup>Isolated yields.

Fig. 1. The proposed mechanism for the conversion of aldehydes into nitriles.

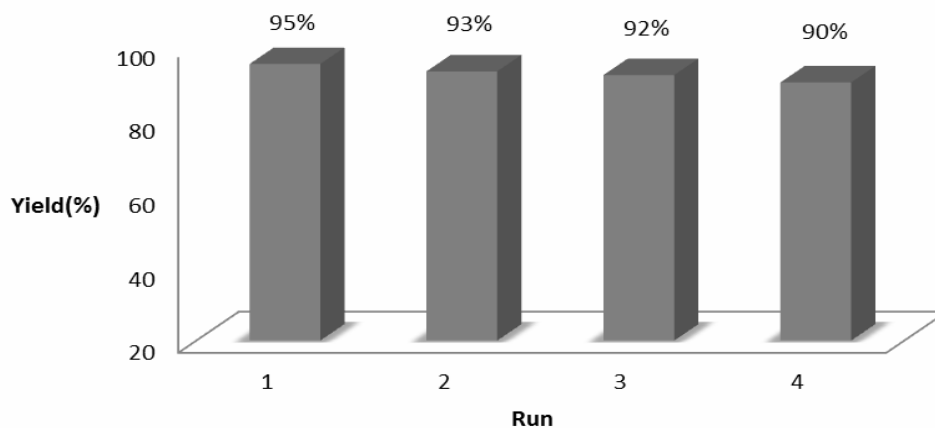
The conversion of 4-chlorobenzaldehyde into 4-chlorobenzonitrile catalyzed by FHS in the presence of hydroxylamine hydrochloride was screened in several solvents and DMF was found to be the best solvent among the other ones. (Table 1, entry 1-8)

To show the catalytic role of FHS, the model reaction was performed in the absence of catalyst so that the conversion was not completed even after 12 h. Therefore, the model reaction was performed in different molar ratios of the catalyst and 1.5 mol% of the catalyst was selected as the optimum mole ratio of the catalyst, allowing the complete conversion of 4-chlorobenzaldehyde into the corresponding nitrile. (Table 1, entry 9-15)

Temperature variations also affected the yields (Table 1, entries 18-21). When the reaction was carried out at room temperature, 50 and 100 °C, the yields were too low and longer reaction time was needed.

To explore the scope and substrate limitations of the reaction, the applicability of this method for the synthesis of a wide variety of diverse nitriles are demonstrated in Table 2. The reactions were carried out by mixing the various substituted aldehydes with hydroxylamine hydrochloride in the presence of FHS in DMF at 120 °C until TLC showed complete disappearance of the mentioned aldehyde and appearance of the corresponding nitrile. Generally, excellent preparation of nitriles with different aryl groups were obtained under the optimized reaction conditions, including those bearing electron-withdrawing or electron-donating groups and the corresponding products were obtained in appropriate reaction times with excellent yields in most cases.

The transformation of aromatic aldehydes containing functional groups Cl and Br were completed within 0.5-2 h and the corresponding nitriles were isolated in relatively



**Fig. 2.** Recycling of FHS in the conversion of aldehydes into nitriles.

**Table 3.** Comparison of this Study with some other Reported Conversions in Literatures

Entry	Reagent	Catalyst	Temperature (°C)	Time (h)	Yield (%)	Ref.
1	NaN <sub>3</sub> (1.5 eq)	Triflic acid (3 eq.)	rt	2 min	39-96	[38]
2	Acetohydroxamic acid	Bi(OTf) <sub>3</sub> (5 mol%)	Reflux	14-24	88-97	[39]
3	NH <sub>2</sub> OH.HCl, MsCl <sup>a</sup>	Dry chitosan supported [BMIm]FeCl <sub>4</sub> <sup>b</sup> (15 mg)	70	1-2	90-97	[40]
4	NH <sub>2</sub> OH.HCl	FHS (1.5 mol%)	120	0.5-2	80-95	- <sup>c</sup>

<sup>a</sup>Mesyl chloride. <sup>b</sup>Butyl methyl imidazolium tetrachloro ferrate. <sup>c</sup>This work.

high yields (Table 2, entries 2-6). 4-Me- and 3-Me-benzaldehyde were also successfully converted under the optimized reaction conditions in good yields after 2-2.5 h (Table 2, entries 9,10). The conversion of aromatic aldehydes containing electron-donating groups OMe, and OEt were also performed in good to excellent yields (Table 2, entries 11-13). However, these reactions require more reaction time than the conversion of aldehydes bearing electron-withdrawing groups like NO<sub>2</sub> and substrates containing heterocyclic aromatic compounds. (Table 2, entry 7, 8, 23, 24). The reaction is chemoselective and the other functional group like double bond and hydroxyl group are not affected under these reaction conditions. (Table 2, entries 14-16, 18, 25). The aliphatic aldehydes were also

converted in these conditions. (Table 2, entries 27, 28).

The plausible mechanism of the transformation of aldehydes into nitriles with NH<sub>2</sub>OH.HCl in the presence of FHS as catalyst are depicted in Fig. 1. In the first step, FHS may complex with the carbonyl oxygen atom of aldehyde, thus activating it for the nucleophilic attack of hydroxylamine and resulting in the formation of a tetrahedral intermediate in which the dehydration may take place to produce the corresponding oxime. The acidic catalyst is expected to promote the next dehydration to complete the formation of nitriles.

Due to the need to obtain catalysts for green processes, the use of recycled catalysts is required for reducing the catalytic cost. The reusability of the FHS was also examined

under the optimized reaction conditions with 4-chlorobenzaldehyde as the model reaction. For each of the repeated reactions, the catalyst was recovered, washed with CH<sub>2</sub>Cl<sub>2</sub> and EtOH, successively and dried before being used for the next conversion. It is important to note that the catalyst was reused four times with a little loss of activity and selectivity as shown in Fig. 2.

A literature survey was also performed to compare this method with some previously reported ones. As shown in Table 3, the FHS is moderately an efficient catalyst for this selective transformation.

## CONCLUSIONS

In summary, we have developed a simple one-pot, chemoselective and highly efficient route for the transformation of aldehydes into the corresponding nitriles using hydroxylamine hydrochloride in the presence of catalytic amount of FHS. Furthermore, the protocol offers several advantages including excellent yield, cost efficient, environmentally benign, high functional group tolerance and simple work-up process.

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