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A facile and efficient method for synthesis nitriles under visible light conditions

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Abstract: In this work, a heterogeneous, stable and inexpensive catalyst of iron (III) fluoride (FeF_3) under visible light conditions is used to catalyze the two component reaction of aldehyde and hydroxyl amine hydrochloride for the synthesis of nitriles in high yields (82-98 %) over a short reaction time (10-55) minutes. Utilization of visible light for this reaction can generate a highly green protocol in the terms of easy experimental workup, excellent yields, short reaction times and minimum pollution of the environment. It facilitates recovery and reusability of the catalyst by simple filtration and recycled up to four consecutive runs without losing the activity of the catalyst.

Keywords: Hydroxyl amine hydrochloride, Iron (III) fluoride, Nitrile compounds, Visible light.

Introduction

Due to the huge applications of nitrile compounds, the chemistry of organic cyano compounds has been developed very rapidly [1].The process the synthesis of nitriles is one of the most important reactions in organic transformation and in synthesis of heterocyclic compounds, an extensive utilization of these compounds have a broad spectrum of biological activates such as oxazoles [2], tetrazoles [3], thiazoles[4], and benzamidines[5]. Furthermore, nitrile compounds are considered synthetic intermediates because of their being easily converted into pharmaceuticals, dyes, agricultural, and fine chemicals [6-8]. The tradional method for the synthesis of nitrile compounds is the nucleophilic substitution reaction of alkyl halides with metal cyanides.

However, this method is considered unsafe because of the increase of the toxicity of metal cyanides which are used as reagents in this method. Consequently, many researchers focused on the synthesis of nitriles as they proposed other various methods as the nitriles prepared from aldoxime that can be dehydrated with various reagents [9]. One of the most important methods for the synthesis of nitriles was by the reaction of aldehyde with hydroxyl amine hydrochloride in the presence of different reagents such as pyridine[10], sodium sulphate and sodium bicarbonate[11], iodine[12], ionic liquids[13], formamide [14], $FeCl_3$[15], Al_2O_3/PCl_5[16], dry or wet alumnia[17],IBX in aqueous ammonia[18], sodium dichloroiodate[19], peroxymonosulfate on alumina [20], and so more. Although, previous methods have their own advantages, they still suffer from some limitations such as using harmful reagents, cost catalysts, tedious work-up procedure, hard reaction conditions and low yields of product. Consequently,

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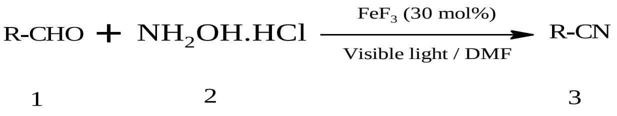
*Corresponding author. Tel: +917276481456, E-mail: bushrasaleh46@gmail.com there is a dire need for developing a protocol using rapidly available and green method and catalysts that leads to obtain high yields of nitriles compounds.

Recently, the utilization of heterogeneous catalyst has received considerable attention owing to their operational features such as insolubility in organic solvent as well as in water. They can be easily recovered from reaction media and produce the smallest amount of hazard to environment [21-23]. Iron (III) Fluoride is considered as one of heterogeneous catalysts and it has gained more importance in organic syntheses over its companion reagents such as $FeCl_3$, $FeBr_3$, and FeI_3 because of its exacting characteristics as stability in water and air utilized as a catalyst for carrying out various organic syntheses as bisindolyl methanes, addition process of cyanotrimethylsilane to aldehyde, cross-coupling reactions, and sulenylation and selenation reactions [24-29].

Herein, we report an efficient method for the synthesis of nitriles **(3)** directly from aldehyde by one pot reaction aldehyde**(1)**, hydroxyl amine hydrochloride **(2)** and using FeF_3 as catalyst in the presence of visible light irradiation emitted from tungsten lamp as shown in the scheme **1**.



$$\underset{1}{\text{R-CHO}} + \underset{2}{NH_2OH.HCl} \xrightarrow[\text{Visible light / DMF}]{FeF_3\ (30\ mol\%)} \underset{3}{\text{R-CN}}$$

Scheme 1: Photochemical synthesis of nitriles **4a-s.**

Results and discussion

As part of our continued interest in the development of new methodologies for the synthesis of organic compounds that possess a biological activity by using visible light conditions, we reported an efficient and easy method for the synthesis of nitrile compounds by one-pot two component reaction of aromatic aldehyde and hydroxylamine hydrochloride in the presence of FeF_3 as a catalyst dissolved in DMF as a solvent, and the reaction mixture was irradiated using visible light irradiation emitted from 200W tungsten lamp. For studying the optimize of the reaction conditions, the reaction of vanillin (1mmol), hydroxylamine hydrochloride (1.2 mmol) was chosen as the typical model of this reaction.

First of all, to study the effect of the catalyst on the synthesis of nitriles, the reaction was carried out in the absence of FeF_3. After 6 hours, the product was formed but could not be detected (Table **1**, entry **1**). However, when various amounts of FeF_3 (5, 10, 15, 20, 30 and 50) were added to the mixture of reaction, it was found the yield and the speed of reaction increased when the amount of catalyst was increased. For instance, 5 mol% of catalyst increased the yield to 35 % but in 280 mins. So the best yield (95%) was obtained by the use of 30 mol% of FeF_3 (high yield of product at very short time (10 min) (Table **1**, entry **5**). Here, it is worth noting that the same yield of 95% was obtained in 15 min when the amount of the catalyst was 50 mol % of FeF_3 . This means that the reaction was not significantly improved when the amount of the catalyst was above 30 % (Table **1**, entry **6**).

After that, the role that the solvent played in synthesis of nitriles was investigated. The reaction was tested with several solvents (water, ethanol, acetonitrile, DMF, and THF). In each case, the reactants were mixed together with 30 mol% of FeF_3 in 5 ml of each solvent. It was observed that the reaction ran rapidly in the case of DMF as a solvent and furnished excellent yield of 95% obtained in 10 min as the shortest period of time (Table **2**, entry **4**) in comparison with other solvents (Table **2**, entries **1**, **2**, **3** and **5**).

After evaluating the substituted extend of the reaction with different aromatic aldehydes having electron withdrawing group such as halide and nitro groups or electron donating groups as hydroxyl or alkoxy groups, it was found that all the tested substituted underwent the electrophilic substitution reaction to the synthesis of nitriles in short time with good to excellent yields. All results are presented in the Table (3).

Moreover, in order to show the advantages of Iron (III) fluoride under visible light conditions used in the present work in comparison with other catalysts reported in the literatures, (benzaldehyde (1mmol), hydroxylamine hydrochloride (1.2 mmol), were dissolved in 5ml of DMF using FeF_3 as a catalyst was also carried out with different catalysts as iodine at room temperature,[12][bmim][OTf],[13] and Al_2O_3/PCl_5 [17]under heat conditions. After comparing the catalyst Iron (III) fluoride with these catalysts, it was found that FeF_3 under visible light conditions was the best catalyst for the synthesis of benzonitrile with respect to the reaction time and the product yield (Table **4**, entry **6**).

Finally, to demonstrate the reusability of catalyst in the synthesis of nitrile compounds, the reaction was performed with using the same reactants; benzaldehyde, hydroxylamine hydrochloride, and using FeF_3 as a catalyst. After four successive runs, the results indicated that the recovered FeF_3 could be reused and recycled many times successfully without losing its activity in spite of losing its weight due to mechanical loss from cycle to cycle. All the results are shown in Table **5.**

Table 1: Screened various amounts of catalyst for synthesis of 3-Methoxy4-hydroxy-benzonitrile [a]

Entry	FeF_3 mol %	Time (min)	Yield (%)[b]
1	No catalyst	360	15
2	5	280	35
3	10	100	48
4	20	60	79
5	**30**	**10**	**95**
6	50	15	95

[a] Condition of reaction : vanillin (1mmol), hydroxylamine hydrochloride(1.2 mmol), Solvent: DMF (5ml), [b] yield of product

Table 2: Effect of different solvents on synthesis of 3-Methoxy4-hydroxy-benzonitrile

Entry	Solvent (5ml)	Time (min)	Yield(%)[a]
1	Water	240	55
2	Ethanol	180	78
3	Acetonitrile	40	85
4	**DMF**	**10**	**95**
5	THF	60	70

[a]Yield of product

Table 3: Conversion of aldehydes into nitriles using FeF_3 induced by visible light conditions

Entry	Aldehyde	Product	Time(min)	Yield (%)[a]
1	C_6H_5	**3a**	20	98
2	2-$NO_2C_6H_4$	**3b**	35	82
3	3-$NO_2C_6H_4$	**3c**	40	89
4	4-$NO_2C_6H_4$	**3d**	25	87
5	2-$CH_3OC_6H_4$	**3e**	15	90
6	3-$CH_3OC_6H_4$	**3f**	40	88
7	4-$CH_3OC_6H_4$	**3g**	55	85

8	2-OH-4$CH_3OC_6H_3$	**3h**	10	95
9	2-$ClC_6H_5C_6H_4$	**3i**	30	82
10	3-$ClC_6H_5C_6H_4$	**3j**	45	87
11	4-$ClC_6H_5C_6H_4$	**3k**	35	90
12	4-$BrC_6H_5C_6H_4$	**3l**	55	80
13	4-FC_6H_4	**3m**	20	88
14	4-OHC_6H_4	**3n**	25	92
15	2,4-$(CH_3O)_2C_6H_3$	**3o**	15	85
16	3,4-$(CH_3O)_2C_6H_3$	**3p**	35	93
17	4-N $(CH_3)_2C_6H_3$	**3q**	25	88
18	3-CH_3O4-OHC_6H_3	**3r**	20	85
19	3,4- $(CH_3)_2C_6H_3$	**3s**	45	90

[a] Yield of Product

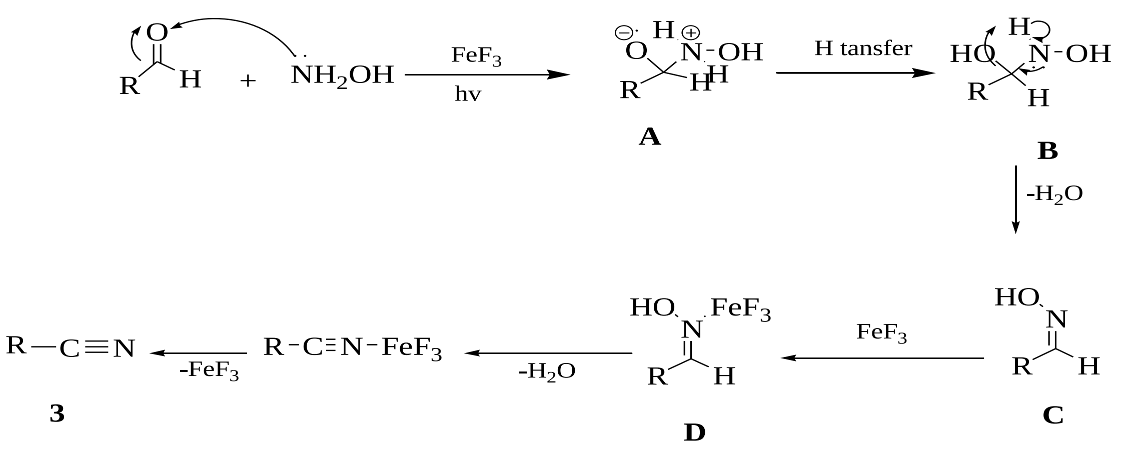
Table 4: Comparing different conditions for synthesis of Benzonitrile

Entry	Catalyst	Condition of Reaction	Time (min)	Yield (%)	Ref
1	I_2 /NH_3	R.T	75	82	(12)
2	[bmim][OTf],	Neat /120 °C	60	97	(13)
3	Al_2O_3/PCl_5	Neat /120 °C	80	908	(17)
4	FeF_3	R.T	250	40	present work
5	FeF_3	Neat /120 °C	90	75	present work
6	FeF_3	**Visible light**	**20**	**98**	**present work**

Table 5: Evaluation reusability of FeF_3 for synthesis Benzonitrile

Entry	Time of cycle	Isolated yield (%)
1	1st	98
2	2nd	94
3	3rd	92
4	4th	90

To speculate the plausible mechanistic pathway for the photochemical synthesis of nitriles, the reaction might plausibly be initiated by the transfer of an electron from hydroxylamine in the presence of visible light to the carbonyl group of aldehyde to produce a radical anion A followed by transform of hydrogen to give intermediate B which underwent dehydration to form an oxime C. The oxime C reacted with the catalyst FeF_3 to afford compound D which underwent dehydration to produce the product 3 as illustrated in the Scheme **2**.



Scheme 2: Plausible mechanistic pathway for the photochemical synthesis of nitriles

Experimental

Materials and methods:

All reagents and solvents were used without further purification except benzaldehyde was distillated. Melting points were measured on the programmable melting point apparatus and were uncorrected. The progress of the reaction was monitored by thin –layer chromatography (TLC) performed in the presence of petroleum ether and ethyl acetate (8:2) on silica plates. ^{1}H NMR spectra were recorded at 400 MHz using $CDCl_3$ as a solvent in the presence of TMS as an internal standard, and (IR) spectra were recorded on a Bruker equinox-55 spectrometer using KBr discs. All products were subject to short column chromatography for purification on silica gel 60-120 mesh in the presence of petroleum ether/ ethyl acetate (98:2) as eluent, and yields denote the isolated yields of the products.

General procedures for the synthesis of Nitrile compounds

(1mmol) of aromatic aldehyde, (1.2mmol) of hydroxylamine hydrochloride and (30 mol %) of FeF_3 were dissolved by DMF as a solvent which was irradiated with 200W tungsten lamp. After completing the reaction monitor by thin-layer chromatography (TLC) indicated by disappearing of the starting material, the solution was poured into 100 ml cold water and then washed with diethyl ether and washed many times by water. It was, after that, filtered to remove FeF_3, The organic mixture was dried over anhydrous Na_2SO_4 which was purified by short column chromatography on silica gel (60-120 mesh) by using petroleum ether /ethyl acetate (98:2) as eluent . All the products were characterized by IR and ^{1}HNMR.

Spectral Characterization of some Synthesized Compounds:

Benzonitrile **(3a)**: Yield: 98 %, colorless oil, Bp = 190 ^{o}C, IR (KBr) ν_{max} = 2225(C≡N str.), 1591, 1514, 1423, 1026 (C-C str.) cm^{-1}, ^{1}HNMR (400MHz, $CDCl_3$) δ= 7.68-7.79 (m, 5H) ppm.

4-Methoxybenzonitrile **(3g)**: Yield: 85 %, white solid, mp = 193 ^{o}C, IR (KBr) ν_{max} = 2227(C≡N str.), 1596, 1528, 1352, 1214 (C-C str.) cm^{-1}, ^{1}HNMR (400MHz, $CDCl_3$) δ= 3.36 (s, 3H, $-OCH_3$), 6.92 (d, 2H, *J*= 9.1 Hz, H-Ar), 7.38 (d, 2H, *J*= 9.1 Hz, H-Ar) ppm.

3, 4-Dimethoxybenzonitrile **(3p)**:

Yield: 93%, yellow solid, m.p = 63-65 ^{o}C, IR (KBr) ν_{max} = 2223 (C≡N str.), 1645, 1578, 1481, 1071(C-C str.) cm^{-1}, ^{1}HNMR ($CDCl_3$) δ =3.92 (s, 3H, $-OCH_3$), 5.90 (s, 3H, $-OCH_3$), 6.98 (m, 1H, ArH), 7.0 (m, 2H, ArH) ppm.

3-Methoxy4-hydroxy-benzonitrile **(3r)**

Yield: 85 %, White crystals, Mp =103-105 ^{o}C, IR (KBr) ν_{max} = 2224 (CN); 1578, 1481, 1405, 1071 (C-C str.) cm^{-1} , ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 3.86 (s, 3H, OCH_3), 6.88 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 8.18 (dd, *J* = 8.4 Hz, 1H) ppm.

Conclusion

We have described a facile and efficient method for the synthesis of nitrile compounds. There are several advantages associated with this newly developed procedure, including its easily experimental procedure, green conditions of reaction, use of heterogeneous, cheap, non-toxic and reusable catalyst, good to excellent yields, short reaction, high catalytic activity, recyclability and reusability of the catalyst at least four times without substantial reduction in its catalytic activity that makes it a useful process for the synthesis of nitriles.

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