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Orginal Research Article

One-pot route to nitriles from aldehyde and hydroxylamine hydrochloride on silica-gel

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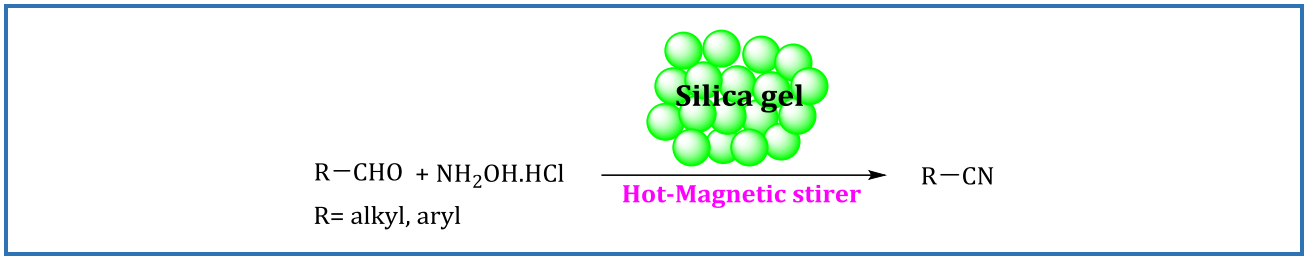
ABSTRACT

A green and facile methodology for the synthesis of nitrile has been established from the corresponding aldehydes and hydroxylamine hydrochloride on silica-gel in hot condition. The protocol is equally effective for aliphatic as well as aromatic aldehydes, and has wide range of functional group tolerance. In addition, this methodology is solvent-free, inexpensive, environmental friendly and involves simple work-up process.

Graphical Abstract



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Introduction

Nitriles are the important intermediate for synthesis of the pharmaceuticals, dyes, pesticides, pigments, and polymers [1]. Nitriles also undergo functional group transformation, leading to different types of compounds including acids [2], amides [3], amines [4], aldehydes [5], esters [6], amidines [7], and ketones [8]. Nitriles have been widely used for producing the nitrogen heterocycles such as tetrazole [9], pyrrolidines [10], thiadiazoles [11] imidazoles [12], oxazoles [13], and thiazoles [14]. Traditional methods used to synthesize the nitriles are including sandmeyer reaction [15], kolbe nitrile synthesis [16], and ammoxidation of aldehydes [17] hydrocyanation of alkene [18]. There are many catalytic systems which take part in transformation of the nitriles from different functional group, such as from alcohol [19], aldoxime [20, 21], amines [22], azides [23], amides [24], and carbonyls [25].

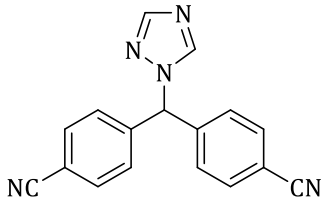
Alkene, benzyl or allylhalide and methyl arenes by oxidative rearrangement also yield nitriles. One of the general traditional method for the nitrile synthesis is the nucleophilic substitution of alkyl halide by metal cyanides. However, this method is not attractive due to its toxicity and difficult work-up process. Besides, all the methods mentioned so far involves increase in one carbon atom of the parent compound [26–28]. Therefore, transformation of the aldehyde and hydroxylamine hydrochloride into nitrile is an alternative attractive methodology since there is no increase in carbon atom. A great number of processes used for synthesis of the nitriles from aldehyde, such as $FeCl_3/NH_2OH$,HCl [29], anhyd $Na_2SO_4/NaHCO_3$ with NH_2OH,HCl under MW irradiation [30], NH_2OH, $HCl/dryAl_2O_3/MeSO_2Cl$ [31], NH_2OH,$HCl/anhyd.Na_2SO_4$ [32], triethylamine sulfurdioxide [33], montmorillonite KSF [34], formamide [35], and acetohydroxamic acid/$Bi(OTf)_3$catalyst [36]. Although a huge synthetic methodology have been reported, the use of expensive catalyst, long reaction time, different oxidants, toxic metal salts, and tedious work-up process makes the existing methodologies avoidable under the aspect of the green chemistry. Since nitrile acts as important bioactive material [37] (Scheme 1) and synthon for designing bioactive molecule, a straight forward, less expensive and environmentally benign methodology needs to be developed.

Recently, solvent-free synthesis has received much attention from the chemists as this technique is an environmentally benign process. In continuation of our present interest in the development of the solvent-free synthesis [38], herein we report a new synthetic methodology for the synthesis of nitriles catalyzed by silica-gel under solvent-free condition.

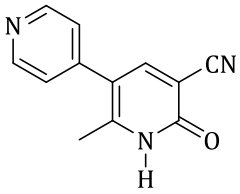
Silica-gel has been effectively used in organic synthesis not only as a simple medium but also as a mild acid catalyst or as an accelerator. It is easily separable from the product due to its insolubility in the organic solvents. Silica-gel supports catalysts such as SiO_2/BF_3, $SiO_2/NaHSO_4$, $SiO_2/FeCl_3$, and SiO_2/H_2SO_4 [39] have also been used in various types of the organic transformations. With this

background of the silica-gel and in connection with our present interest, we envisioned that the silica-gel itself could serve as an eco-friendly, easily available, high functional group tolerance, and cheap alternative catalyst for synthesis of the nitriles from aldehyde through the metal-free, solvent-free condition in one-pot protocol (Scheme 2).

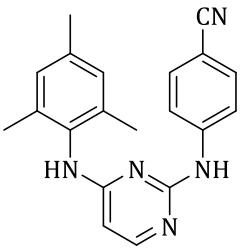
Scheme 1. Bio-active nitrile derivatives



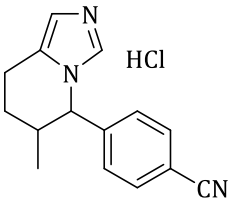
Letrozole



Milrinone

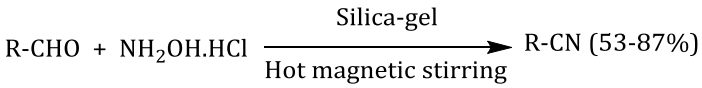


Dapivirine



Fadrozole monohydrochloride

Scheme 2. Synthesis of nitriles from aldehydes and hydroxylaminehydrochloride on silica-gel



Experimental

General procedure for the synthesis of nitrile

Aldehydes (1 mmol) and hydroxylamine hydrochloride (1.2 mmol) were mixed with silica-gel (60-120 mesh, 1 g) in motor and pestle. The mixture was grinded thoroughly. Then themixture was poured into a round bottom flask (50 mL) and stirred with a magnetic stirrer at 100 °C for 3–8 h (As shown Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3×15 mL) and washed several times with water. The combined reaction mixture was dried over the anhydrous Na_2SO_4, then the solution was concentrated and purified by column chromatography on silica-gel (60-120 mesh using petroleum

ether/ethylacetate as eluent to yield pure nitrile. The desired isolated products were characterized by the IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Results and discussion

In this study, we used vanillin as a model compound for the expected transformation. The model reaction is consisting of vanillin (1 mmol), hydroxylamine hydrochloride (1 mmol) and silica-gel (1 g) on magnetic stirring at room temperature gave no reaction. As the reaction temperature increased, the nitrile (58%) was formed in 3 h along with a trace amount of aldoxime at 70 °C (Table 1, entry 2). Then, we used 1.5 mmol hydroxyl amine hydrochloride and got 63% nitrile at 70 °C in 3 h (Table 1, entry 3). Finally, the reaction was optimized as hydroxylamine hydrochloride (1.2 mmol), vanillin (1 mmol), and silica-gel (1 g), and the reaction mixture was kept on hot magnetic stirrer for four hours at 83 °C and got 85% nitrile (Table 2, entry 3).

Table 1. Optimization of temperature[a]

Entry	Time (h)	Temperature (°C)	Hydroxylamine (mmol)	Yield (%)[b]
1	8	r.t.	1	Nill
2	3	70	1	58
3	3	70	1.5	63
4	4	83	1.2	87[c]
5	5	100	1.2	86
6	6	110	2	83

[a] Reaction of vanillin (1 mmol), silica-gel (1 g) on magnetic stirrer in different time and temperature

[b] Isolated yield

[c] Optimized reaction condition

Table 2. Optimization of catalyst[a]

Entry	Silica-gel (g)	Yield (%)[b]
1	Nill	Oxime
2	0.5	53
3	1	85[c]
4	1.5	84
5	2	75

[a] Reaction of vanillin (1 mmol), Hydroxylamine hydrochloride (1.2 mmol), silica-gel in different amount

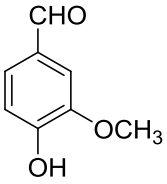
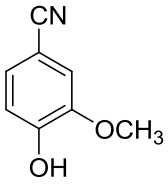
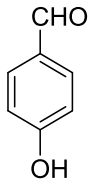
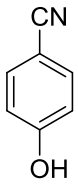
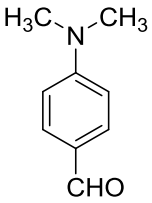
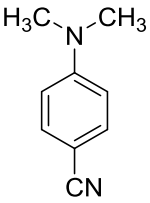
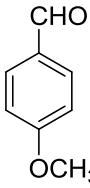
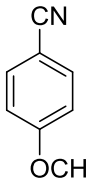
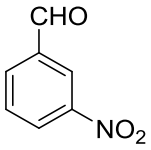
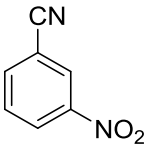
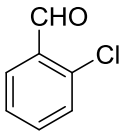
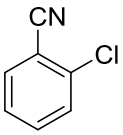
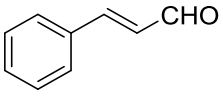
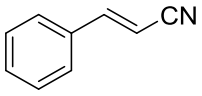
[b] Isolated yield

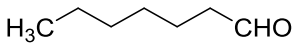
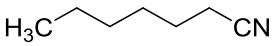
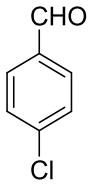
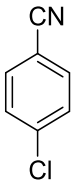
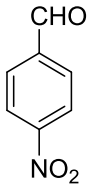
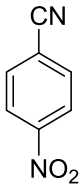
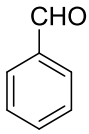
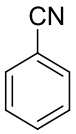
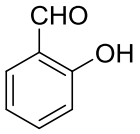
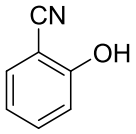
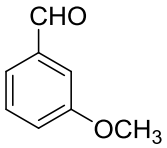
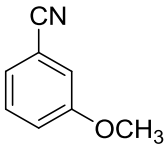
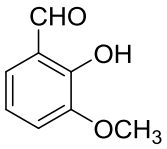
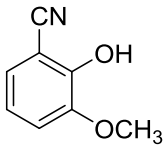
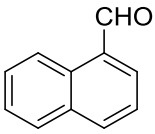
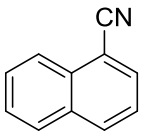
[c] Optimized reaction condition

We applied this optimized methodology to various aldehydes and obtained nitriles in 53 to 87% yields (Table 3). As seen in Table3, the aldehydes with electron-donating groups such as –OH, –OMe, and $-NMe_2$ produced higher yields; however, the aldehydes with electron-withdrawing groups require higher temperature and produce lower yields.

Plausible mechanism for synthesis of the nitrile from aldehyde and hydroxylamine hydrochloride on silica-gel (Scheme 3).

Table 3. Synthesis of nitrile from aldehyde on silica-gel

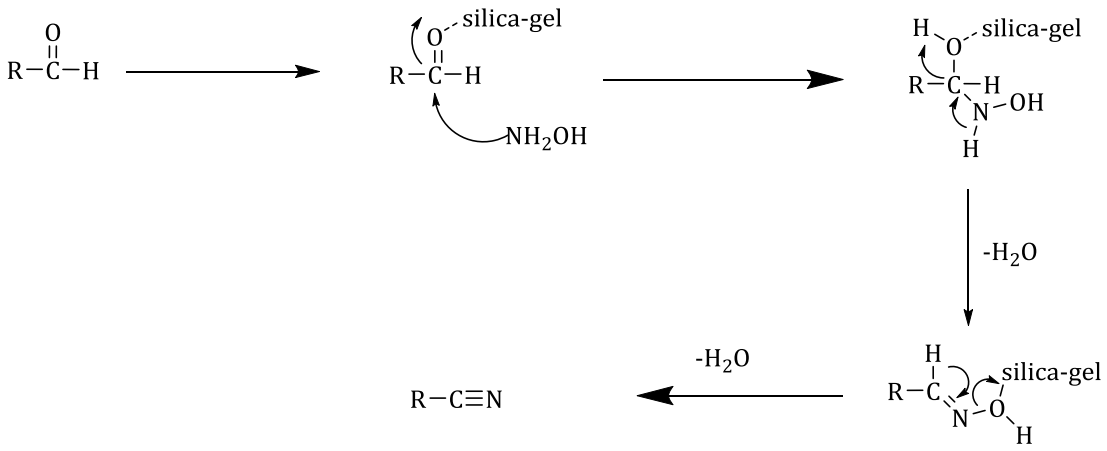
Entry	Aldehydes	Time (h)	Temperature (°C)	Product	Yield (%)[a]
1		4	83		87
2		4.5	110		81
3		5.5	110		82
4		5.5	83		59
5		5.5	130		54
6		5.5	105		69
7		6	130		56

8		5	130		53
9		5.5	110		62
10		5	130		64
11		4.5	100		73
12		4.5	110		82
13		4	100		89
14		4.5	100		87
15		5	110		79

[a] Isolated yield

Conclusion

We have explored a very facile one-pot transformation of nitrile from aldehyde, hydroxylamine hydrochloride, and silica-gel. The main advantage of this protocol is that, the other groups present in the aldehydes remain unaffected and both aliphatic and aromatic aldehydes are subject to this transformation. Also, this technique is in expensive solvent-free, environmental friendly, and simple work-up process.



Scheme 3. Plausible mechanistic pathway

Acknowledgment

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Disclosure statement

No potential conflict of interest was reported by the authors.

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