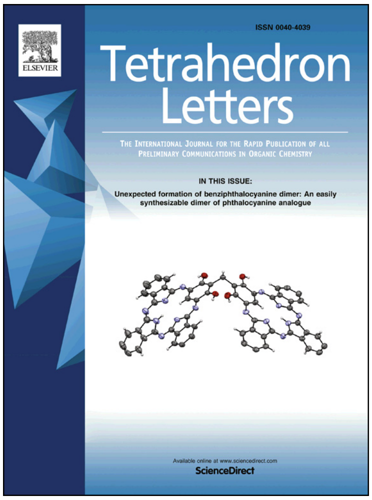

"Catalyst-free, efficient and one pot protocol for synthesis of nitriles from aldehydes using glycerol as green solvent"

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Graphical Abstract

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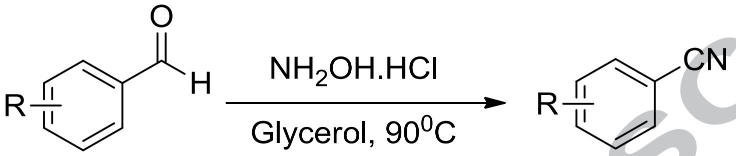

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"Catalyst-free, efficient and one pot protocol for synthesis of nitriles from aldehydes using glycerol as green solvent"

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ARTICLE INFO

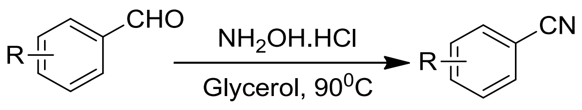
ABSTRACT

We described herein the novel, efficient and one-pot catalyst free protocol for the synthesis of nitriles from aldehydes by using hydroxyl amine hydrochlorides in glycerol as a green solvent. This protocol was efficiently used for transformation of aromatic aldehydes bearing electron-withdrawing and electron-donating groups into a aryl nitriles in good to excellent yields. The methodology offers a very simple, efficient and environmentally benign procedure.

Keywords:
Glycerol
aldehydes
Nitriles

Nitriles are versatile synthetic precursors for the preparation of agricultural chemicals, polymers, pigments, dyes and pharmaceuticals.[1] In addition, they are used for preparation of amines, amidines, amides, aldehydes and carboxylic acid and nitrogen containing heterocyclic systems.[2] More-over, the cyano group itself is present in biologically active compound, such as Letrazole (used in the treatment of breast cancer), Periciazine (an antipsychotic drug), Citalopram (an antidepressant drug), HIV protease inhibitors, and 5-lipoxygenase inhibitors.[3] Numerous methods are reported in the literature for the synthesis of aryl nitriles using various reagents. Sandmeyer and Rosenmund -von Braun reactions are classic methods for the synthesis of aryl nitriles, but both methods require stoichiometric amounts of Copper(I)cyanide reagents and prefunctionlized starting materials.[4] The well developed transition-metal catalysed cyanation of aryl halides[5] and C-H cyanation reactions[6] also used for synthesis of aryl nitriles. Metal cyanide has been commonly used in direct cyanation reactions, such as KCN, NaCN, CuCN, AgCN, and TMSCN. The ammoxidation of toluene derivatives is an industrial scale method for nitrile synthesis.[7] The ammoxidation is applicable only to a limited number of substituted toluene derivatives and it is also requires high temperature and high pressure besides the use of excess ammonia restricts its application. Many methods have been reported that aldehydes can be directly converted into nitriles without isolation of aldoxime intermediates upon the one-pot treatment with hydroxylamine in the presence of various dehydrating reagents.[8] The main disadvantages of these methods are limited scope of substrates, corrosive, toxic, expensive, or commercial unavailable reagents, no reusability of reagents, drastic reaction conditions, tedious workup, and unsatisfactory yields. Therefore, new methods for this transformation are still desirable.

In this context, the development of protocols using recyclable and environmentally friendly solvent has gained much interest recently because of the extensive uses of solvents in almost all of the chemical industries, and of the predicted disappearance of fossil oil.[9] It has also observed that the catalysts employed are not always ecofriendly and because of this, serious environmental pollution often results. Therefore, the design of catalyst-free reactions is a crucial goal for chemist. In this regard, the use of glycerol as a promoting medium for organic reaction was recently demostrated.[10] Glycerol due to its unique combination of physical and chemical properties such as polarity, low toxicity, no flammability, high boiling point, biodegradability, and easy availability from renewable feed stocks prompted us to extend its use as green solvent in organic synthesis.[11] In this sense, we describe here the catalyst-free, efficient, one-pot green protocol for synthesis of nitriles from aldehydes using glycerol as green solvents (Scheme 1).

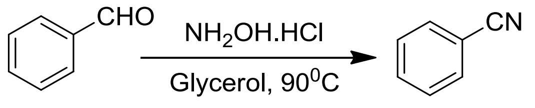


1a-1q **2a-2q**

Scheme 1. General scheme of reaction

In order to investigate the scope and limitations of catalyst-free green protocol, we have chosen benzaldehyde as our model compound for the desired transformations. Initially, we reacted benzaldehyde **1a** (1.0 mmol) with a hydroxylamine hydrochloride (1.0 mmol) using glycerol (5 mL) as solvent at different temperatures to optimize the reaction conditions to access benzonitrile **2a** (Table 1). When reaction was performed at room temperature, product **2a** was not formed, the benzaldehyde remains unreacted. To our satisfaction, by increasing the temperature, the reaction proceeds smoothly, and at 90^0C benzonitrile **2a** was obtained in 90% yield (Table 1, entry 3). It is observed that an optimum yield of nitrile was obtained in glycerol at 90^OC (Table 1, entry 3). No there is no significant improvement in reaction time and yield of product was observed above that temperature (Table 1, entry 6), so 90^OC was chosen as the reaction temperature. It is also important to mention that when the reaction was performed without glycerol no product was obtained (Table 1, entry 4). When we performed the reaction using other alcoholic solvents such as ethanol, methanol, no product **2a** was obtained (Table 1, entry 5). In an optimized reaction[12], benzaldehyde **1a** (1.0 mmol) and hydroxylamine hydrochloride (1.0 mmol) was dissolved in glycerol (5 ml) and stir at 90^0C for 7.5 hours to obtained benzonitrile **2a** in 96% yield (Table1, entry 3).

Table 1
Reaction conditions optimization[a]



1a **2a**

Entry	Temperature (°C)	Time (h)	Yield **2a**[b] (%)
1	rt	24	-
2	60	12	43
3	90	7.0	90
4	90	24	-
5	90	24	-
6	120	7.0	90

[a] Reactions are performed using benzaldehyde 1a (1.0 mmol), hydroxylamine hydrochloride (1.0 mmol) in glycerol (5 mL).
[b] Yields are given for isolated product.
[c] Reaction performed without glycerol.
[d] Reaction performed in ethanol, methanol.

With the optimized reaction conditions in hand, the scope and limitations of functionalized aldehydes were studied, as shown Table 2. Generally, substrate bearing electron-donating groups as well as 1-formyl naphthalenes provided the nitriles product in good to excellent yields **(Table 2, entry 2b-2h).** However, for the substrates possessing electron-withdrawing groups, moderate yields were obtained **(Table 2, entry 2i-2o).** Next, the scope of heteroaromatic substrate was investigated and they are also suitable for reaction and did not show any remarkable difference in the yields **(Table 2, entry 2p-2q)**. However, aliphatic aldehydes were unable to provide the desired product in acceptable yield.

After reaction optimization, a study regarding the use of glycerol was performed. After the completion of reactions, the reaction mixture was diluted and extracted with mixture of hexane/ethyl aceate (95:5) (5 x 5). The upper phase was dried and the solvent evaporated. The glycerol phase was dried under vacuum and directly reused. Glycerol maintained its good level of efficiency even after being reused three times. The product 2a was obtained in 89%, 89% and 88% yields after the successive cycles.

Table 2
Synthesis of organic nitriles 2a-2q using glycerol as solvent[a]

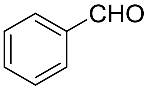
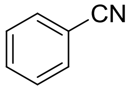
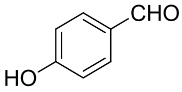
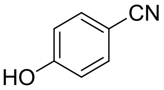
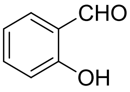
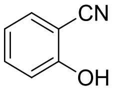
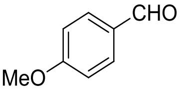
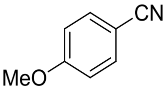
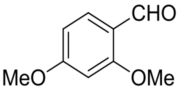
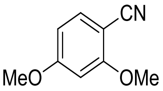
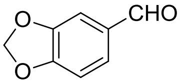
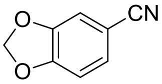
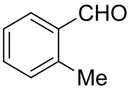
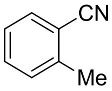
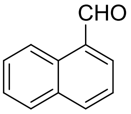
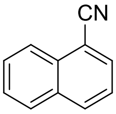
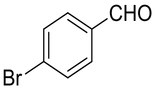
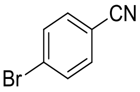
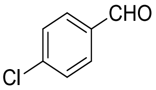
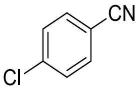
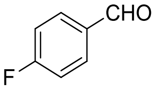
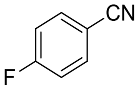
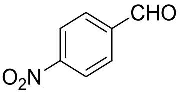
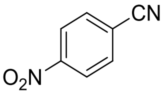
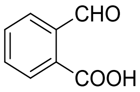
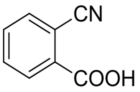
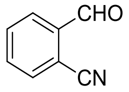
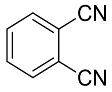
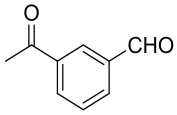
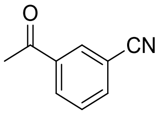
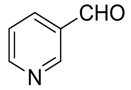
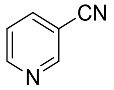
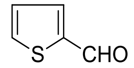
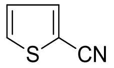
Entry	**Aldehyde (1)**	**Time (h)**	**Product (2)**	**Yield[b] (%)**
1	 **1a**	7.0	 **2a**	90%
2	 **1b**	7.0	 **2b**	91%
3	 **1c**	7.0	 **2c**	90%
4	 **1d**	6.5	 **2d**	92%
5	 **1e**	6.5	 **2e**	93%
6	 **1f**	6.5	 **2f**	93%
7	 **1g**	7.0	 **2g**	89%
8	 **1h**	7.0	 **2h**	86%
9	 **1i**	8.5	 **2i**	85%
10	 **1j**	8.5	 **2j**	85%
11	 **1k**	9.0	 **2k**	83%
12	 **1l**	9.5	 **2l**	81%
13	 **1m**	9.5	 **2m**	80%

Table 2 (continued)

14	 **1n**	9.5	 **2n**	83%
15	 **1o**	8.0	 **2o**	83%
16	 1p	7.0	 **2p**	86%
17	 **1q**	7.0	 **2q**	86%

[a] Reactions are performed using aryl aldehydes **1a-1q** (1.0 mmol), hydroxylamine hydrochloride (1.0 mmol) in glycerol (5 mL).

[b] Yields are given for isolated product.

The role of glycerol in this one pot protocol was established by the fact that in the absence of glycerol the formation of nitrile does not take place. Obviously, glycerol is an essential component of reaction. In addition, we performed the reaction using other alcoholic solvents such as ethanol, methanol, no product was obtained. The role of glycerol in this reaction is obscure at this stage. We suggest that hydrogen of hydroxyl group of glycerol through the formation of hydrogen bonding activated the aldehyde carbonyl to form the aldoxime associated with HCl in glycerol. After that the glycerol and HCl in glycerol help for dehydration of aldoxime formed to afford the desired nitrile at 90^{O}C. It is very well known that it has three hydroxyl groups which may provide hydrogen bonding to the Cl$^-$ counter anion and helps acid in dehydration of aldoxime.

In conclusion, we have developed here a green and catalyst-free protocol for the synthesis of nitriles from aldehydes by using glycerol as green solvent. Excellent yield, catalyst-free, cost efficient, environmentally benign, and simple work-up procedures are the advantages of this protocol.

Acknowledgments

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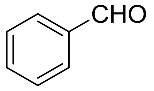
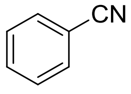
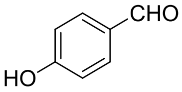
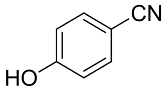
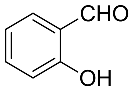
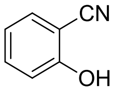
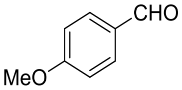
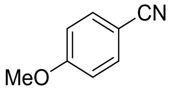
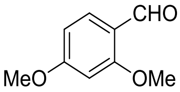
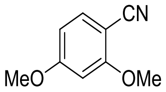
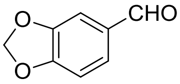
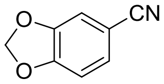
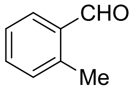
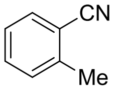
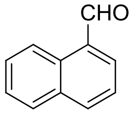
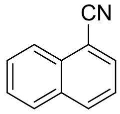
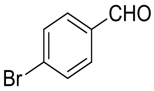
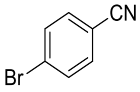
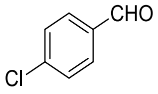
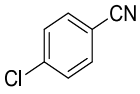
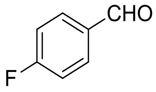
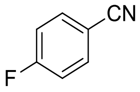
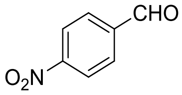
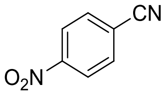
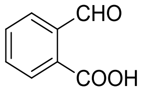
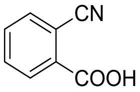
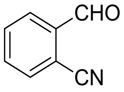
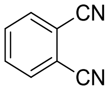
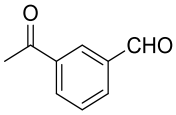
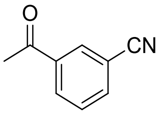
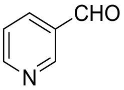
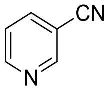
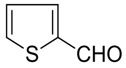
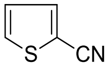
11. (a) Nelson, W. M. *In green Solvents for Chemistry: Perspectives and practice;* Oxford University Press: Oxford, 2003; (b) Pagliarao, M; Rossi, M. *In future of Glycerol: New Usages for a Versatile Raw Materia*l; Clark, J. H., Kraus, G. A., Eds.; RSC Green Chemistry Series: Cambridge, 2008.
12. ***General procedure for synthesis of nitriles:*** To a round bottom flask aldehydes (1a-1q) (1.0 mmol) and hydroxylamine hydrochloride (1.0 mmol) was added in glycerol (5 ml). The reaction mixture was allowed to stir at 90^{0}C for the time indicated in table 2. After the completion of reaction, the reaction mixture was washed with a mixture of hexane/Ethyl acetate (95:5) (3 x 3 mL) and the organic phase were separated from glycerol, dried with $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent. All the compounds were characterized by comparison with mp and ^{1}H NMR, ^{13}C NMR spectra with literature. Selected spectral data for: Benzonitrile (2a): Colorless Oil; b.p 191-192^{o}C; FT-IR (υ, cm^{-1}): 3097, 3050, 2231, 1502, 1401, 1276, 1198, 844; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ 7.65 (s, 3H), 7.45 (s, 2H); ^{13}C NMR (100 MHz,

CDCl$_3$, ppm): δ 132.6, 132.0, 129.0, 118.6, 112.5. GC-MS *m/z* (% relative intensity): 103 (M$^+$, 100), 76 (40), 50 (11).

Table 2
Synthesis of organic nitriles 2a-2q using glycerol as solvent[a]

Entry	Aldehyde (1)	Time (h)	Product (2)	Yield[b] (%)
1	 **1a**	7.0	 **2a**	90%
2	 **1b**	7.0	 **2b**	91%
3	 **1c**	7.0	 **2c**	90%
4	 **1d**	6.5	 **2d**	92%
5	 **1e**	6.5	 **2e**	93%
6	 **1f**	6.5	 **2f**	93%
7	 **1g**	7.0	 **2g**	89%
8	 **1h**	7.0	 **2h**	86%
9	 **1i**	8.5	 **2** **i**	85%
10	 **1j**	8.5	 **2j**	85%
11	 **1k**	9.0	 **2k**	83%
12	 **1l**	9.5	 **2l**	81%
13	 **1m**	9.5	 **2m**	80%
14	 **1n**	9.5	 **2n**	83%
15	 **1o**	8.0	 **2o**	83%
16	 **1p**	7.0	 **2p**	86%
17	 **1q**	7.0	 **2q**	86%

[a] Reactions are performed using aryl aldehydes **1a-1q** (1.0 mmol), hydroxylamine hydrochloride (1.0 mmol) in glycerol (5 mL).

[b] Yields are given for isolated product.

Research Highlights

- Catalyst-free protocol for the synthesis of nitriles in glycerol as green solvent.
- Methods is suitable for aromatic aldehyde and heteroaromatic aldehydes
- Excellent yield, cost-efficient and environmentally benign are advantages of protocol.

Graphical Abstract

Catalyst-free, efficient and one pot protocol for synthesis of nitriles from aldehydes using glycerol as green solvent

Ajit P Ingale, Shripad M Patil and Sandeep V Shinde

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