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Ultrasound assisted synthesis of aryl nitriles from aldehydes

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Abstract: A series of structurally diverse aryl/heteroaryl nitriles has been synthesized by ultrasound assisted reaction of aldehydes and hydroxyl amine hydrochloride in dimethyl sulphoxide. Despite of using any acid, base or metal catalyst, the corresponding nitriles are obtained in good to excellent yields with high purity. The methodology presented here is applicable for aromatic or heteroaromatic aldehyde possessing electron donating or electron withdrawing substituents.

Keywords: Aryl aldehydes, Aryl/heteroaryl nitrile, Hydroxyl amine, Mild conditions, Ultrasound.

Introduction

Organonitriles are important key components of many natural products as well as pharmaceuticals, material sciences, agriculture and dyes [1-6]. It has been used as precursors for the synthesis of amides, amines, caroboxylic acids, esters, aldehydes and numerous heterocyclic compounds [7-12]. The cyno compounds such as Vildagliptin (**1**), has anti-hypertensive properties[13], Anastrozole (**2**), Letrozole (**3**), Fadrozole (**4**) are nonsteroidal aromatase inhibitors [14-16], Cyamemazine (**5**), acts as antipsychotic agent[17] and Citalopram (**6**) has antidepressant properties [18] (Figure **1**).

Now a day, nitrile chemistry has been well explored and numerous efforts have been devoted for the synthesis of these compounds. Among the methods available, dehydration of aldoxime was found to be the most acceptable transformation because the methods available for the synthesis of nitrile from alkyl or aryl halide involve use of hazardous metal cyanides. Consequently, the direct synthesis of nitrile from aldehyde without isolation of intermediate aldoxime in presence of dehydrating agents was the most fascinating method over other reported methods [19-32]. The dehydrating agents used so far for the synthesis of nitriles including *N*-methyl-2-pyrrolidinone [23], $MeSO_2Cl$/alumina [19], silica chloride [21], sodium iodide [22], dichlorophosphate-DBU [24], propyl phosphonic anhydride (T3P) [25], $CuCl_2$/NaOMe/O_2 [26], KF/Al_2O_3[27], I_2[28], NBS [29] graphite/$MeSO_2Cl$ [30], choline chloride-urea [31] and transition metal catalysts [32]. However, these reported methods suffer from some disadvantages as requirement of drastic reaction conditions [19,22,23,30], limited substrate scope [33], use of expensive and hazardous metallic reagents [34-39]. In addition, some of these methods are not suitable for thermally unstable and enolizable aliphatic aldehydes [24]. Hence, there is still need to develop more efficient and direct methodology for the synthesis of nitrile from aldehyde.

During the past few decades, attention being focused on the development of ultrasound assisted reactions [40]. The application of 'cavitations' as energy source allows organic reactions faster with more selectivity and excellent product yields in shorter reaction time and [41-46]. The utility and applicability of ultrasound

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promoted reactions have been well documented in literature [47-50].

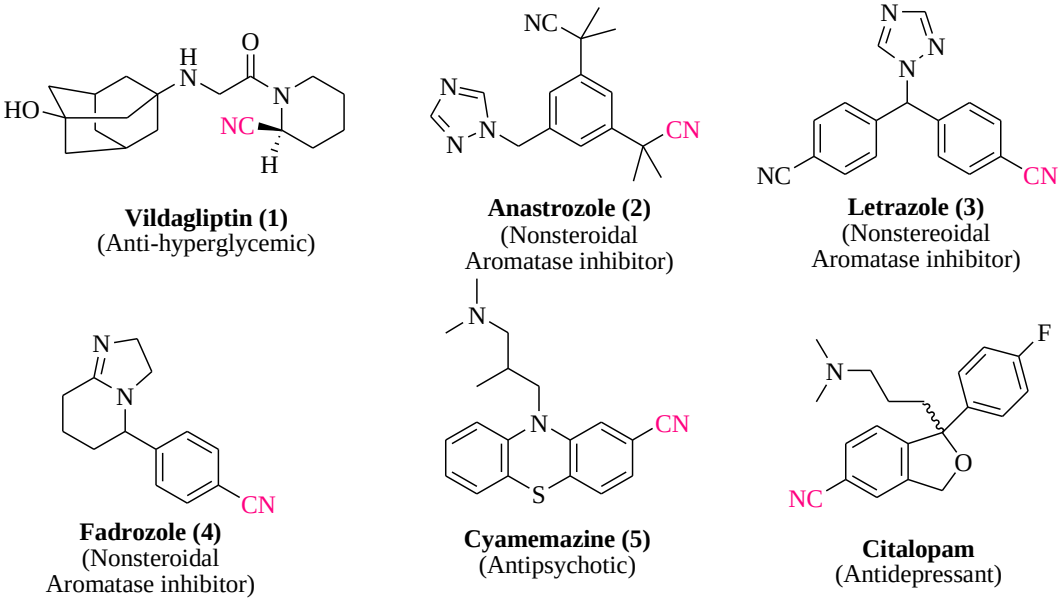
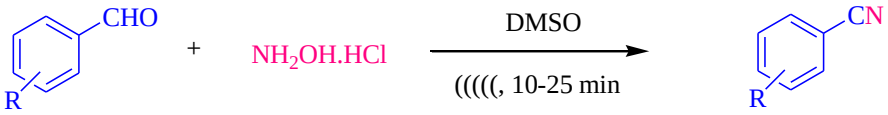


Figure 1: Some bioactive cyno compounds.

In previous work reported by Augustine J.K. *et al* [51], the synthesis of structurally diverse nitriles has been conducted from aldehyde and hydroxyl amine hydrochloride by activation of dimethyl sulphoxide at 90 ^{o}C temperature. In this context, we have decided to explore the ultrasound for the direct synthesis of nitrile from aldehyde and hydroxyl amine hydrochloride in DMSO at ambient temperature. Previously, it has been observed that combination of DMSO with electrophilic species formed the activated DMSO which has been utilized for oxidation of alcohol to corresponding carbonyl compounds [51-57]. In continuation to our ongoing research on the development of novel synthetic methodologies using green chemistry techniques [58-64], herein, we have described the ultrasound promoted efficient, cost effective and transition metal free synthesis of nitrile directly from aldehyde (Scheme **1**).



1 **2** **3(a-n)**

3a: R = H
3b: R = 4-OMe
3c: R = 4-Me
3d: R = 3-Cl
3e: R = 4-Cl
3f: 4-Pyridyl
3g: 2-Thiophene
3h: R = 4-Br
3i: Cinnamoyl
3j: R = 4-NO_2
3k: R = 2-OH
3l: R = 4-OH
3m: R = 2-NO_2
3n: 2-Naphthyl
3o:2-(3-trifluromethyl)pyridine
3p: 2-(4-bromo)thiophene

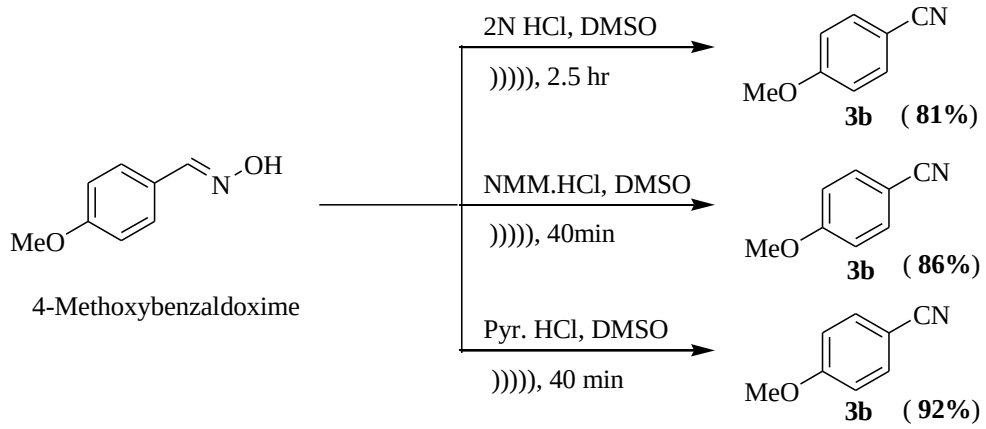
Scheme 1: Ultrasound assisted synthesis aryl nitriles under mild conditions.

Results and discussion

For the optimization of reaction, we have conducted the reaction of benzaldehyde (2 mmol), hydroxyl amine hydrochloride (2.5 mmol) in different solvents such as methanol, dichloromethane, acetonitrile, tetrahydrofuran, *N*,*N*-dimethyl formamide and dimethyl sulphoxide under ultrasonic conditions (Table **1**). It was found that when reaction was conducted in methanol, the corresponding aldoxime (**3aa**) was obtained in 61 % yield (Entry 1, Table **1**). Further, reaction progress was not observed when reaction was

conducted in DCM and DMF. Less than 20% of benzaldoxime (**3aa**) was isolated when reaction was conducted in MeCN and THF as solvents (Entry 3 and 4, Table **1**). Then same reaction was conducted the same reaction in DMSO, benzonitrile (**3a**) was obtained in 98% yield under ultrasonic conditions after 10 mins (Entry 6, Table **1**). Encouraged these results, we have decided to study effect of ultrasound on the formation of nitriles. Therefore, the reaction of benzaldehyde and hydroxyl amine in DMSO was conducted at room temperature in absence of ultrasound but unfortunately formation of nitrile did not observed even after long term stirring (8 hr).

Moreover, as studied by Augustine *et al* [25] and as per results obtained in our study, the role of HCl in dehydration step is limited because when reaction of 4-methoxybenaldoxime was carried out in the presence of HCl, the desired 4-methoxybenzonitrile (**3a**) was obtained in 81% yield under ultrasonic conditions after 2.5hrs (Scheme **2**). When same reaction was conducted under ultrasound in the presence of *N*-methylmorpholine hydrochloride and pyridinium hydrochloride the corresponding 4-methoxybenzonitrile was obtained in 86% and 92 % yield after 40 min under sonication **(**Scheme **2**).



Scheme 2: Practical evaluation of reactivity of DMSO and HCl.

The plausible mechanism for the synthesis of aryl and hetero aryl nitrile involves activation of DMSO by ultrasound. The reaction of DMSO and HCl yield oxysulfonium salt '**B**' which on further reaction with aldoxime '**A**' to produced intermediate '**C**' by electrophilic addition.[16] The intermediate '**C**' on subsequent elimination afforded nitrile product (Figure **2**).

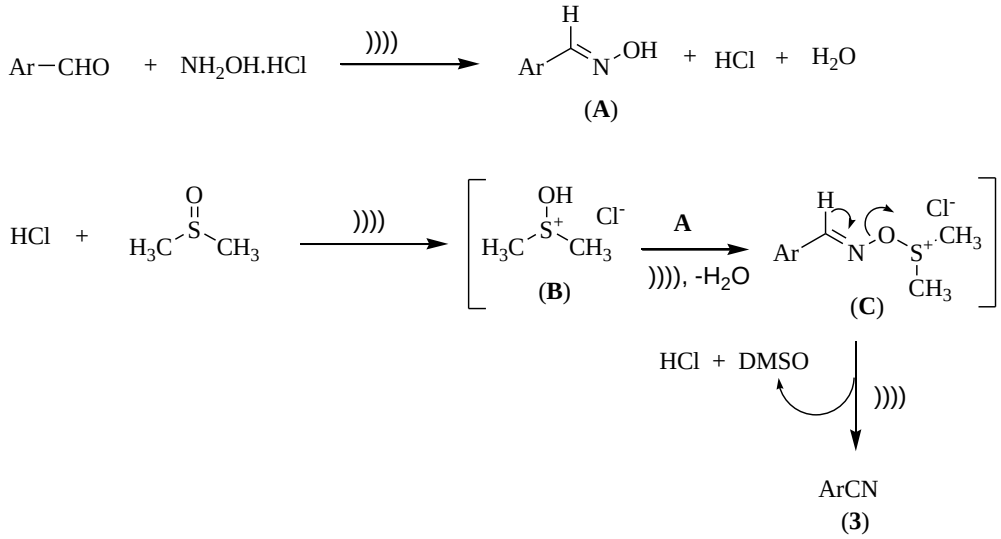
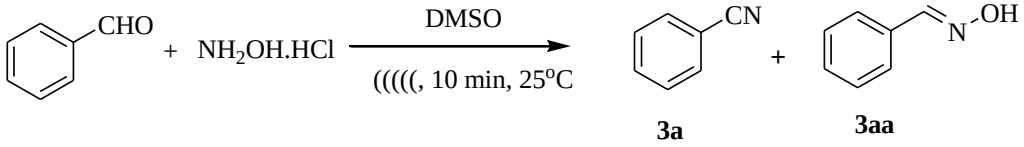


Figure 2: Plausible mechanism of ultrasound assisted synthesis of nitriles from aldehyde.

Table 1: Optimization of reaction conditions for the synthesis of '**3a**'

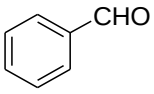
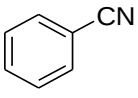
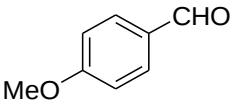
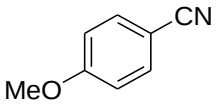
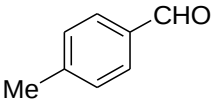
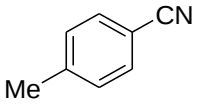
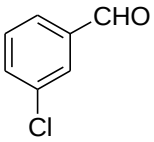
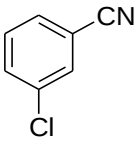
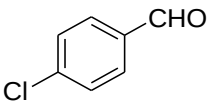
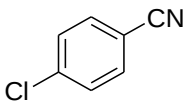


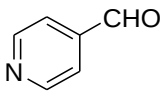
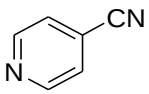
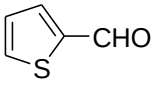
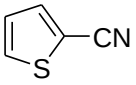
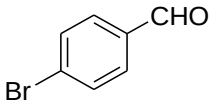
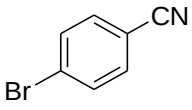
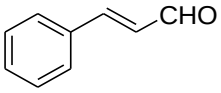
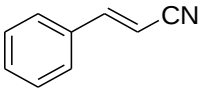
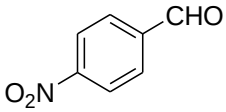
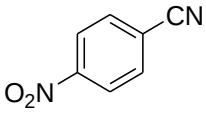
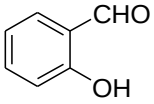
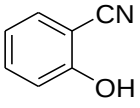
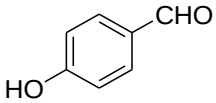
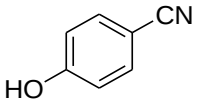
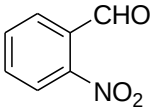
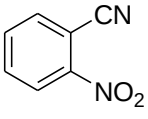
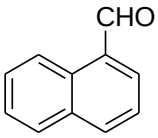
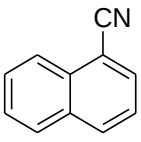
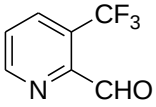
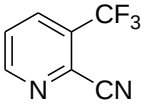
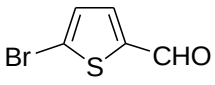
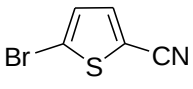
3a **3aa**

Entry	Solvent	Time (min)	Yield of Benzonitrile (3a) (%)[a]	Yield of benzaldoxime (3aa) (%)
1.	MeOH	120	0	61
2.	CH_2Cl_2	120	0	0[b]
3.	MeCN	150	0	Negligible[c]
4.	THF	120	0	<20[c]
5.	DMF	120	0	0[b]
6.	DMSO	10	98	0[b]
7.	DMSO	8 hr	0	0[c, d]

[a]Isolated yield of the product.
[b]Starting material is isolated.
[c]Slow reaction progress.
[d]Reaction is carried out at ambient temperature in absence of ultrasound.

Table 2: Ultrasound assisted synthesis of nitrile from aldehyde under mild conditions.

Entry	Substrate	Product	Reaction Time (min,)	Yield (%)[a,b]
1.		 **3a**	10	98[31]
2.		 **3b**	10	96[30]
3.		 **3c**	15	90[30]
4.		 **3d**	10	95[31]
5.		 **3e**	20	97[31]

6.		 **3f**	20	94[31]
7.		 **3g**	15	>99[30]
8.		 **3h**	20	98[24]
9.		 **3i**	20	92[21]
10.		 **3j**	25	99[23]
11.		 **3k**	20	92[30]
12.		 **3l**	25	89[30]
13.		 **3m**	15	96[30]
14.		 **3n**	20	98[30]
15.		 **3o**	20	86
16.		 **3p**	10	91

[a]Isolated yields of the product.
[b] Products were confirmed by comparing physical constants and spectral analysis such as IR, ^{1}H-NMR and Mass spectral data with reported in literature.

Experimental

Apparatus and analysis:

All of synthesized compounds are known compounds and identified by comparison of their physical and spectral data with previous reports.

Melting points were recorded in open capillary using paraffin bath and are uncorrected. Progress of the reaction was studied using thin layer chromatography(TLC) technique using petroleum ether:ethyl acetate (4:0.5) solvent system. IR spectra were recorded using KBr disc. 1H NMR spectras were recorded 400 MHz instrument using CDCl3 solvent.

General Procedure for the synthesis of nitriles:

A mixture of aldehyde (2 mmol), hydroxylamine hydrochloride (2.5 mmol) in DMSO (3 mL) was placed in ultrasonic bath. After completion of reaction (as indicated by TLC), reaction mixture was poured in ice water (10 mL) and subsequently extracted in ethyl acetate (2x5mL). Organic layer was dried over anhydrous sodium sulphate and filtered. Solvent was removed under reduced pressure to afford nitriles in excellent yields. Further confirmation of product done by comparing physical constants reported in literature previously and spectral data.

Spectral data of representative compounds:

*4-Methoxybenzonitrile (**3b**):* Mp=58-60 ^{o}C; IR (KBr) (υ_{max}, cm^{-1}), 3066, 2245; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.3(2H, d, *J*=9.1Hz, Ar-H), 6.6 (2H, d, *J*=9.1Hz, Ar-H), 3.7 (s, 3H).

*4-Chlorobenzonitrile (**3e**):* Mp= 92-94 ^{o}C; IR (KBr) (υ_{max},, cm^{-1}), 3061, 2242; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)=7.4(2H, d, *J*=8.3Hz, Ar-H), 7.3 (2H, d, *J*=8.3Hz, Ar-H).

*4-Nitrobenzonitrile (**3j**):* Mp= 144-145 ^{o}C; IR (KBr) (υ_{max},, cm^{-1}), 3070, 2236; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)=8.3(2H, d, *J*=8.0Hz, Ar-H), 7.9(2H, d, *J*=8.0Hz, Ar-H).

*3-(Trifluoromethyl)pyridine-2-carbonitrile (**3o**):* Bp= 240-242 ^{o}C; IR (KBr) (υ_{max},, cm^{-1}), 3068, 2242; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)=: 7.67-7.70(1H, m, Ar-H), 8.11 (1H, d, Ar-H), 8.90 (1H, d, Ar-H).

*5-Bromothiophene-2-carbonitrile (**3p**):* Bp=224-226 ^{o}C; IR (KBr) (υ_{max},, cm^{-1}), 3073, 2252; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)= 7.4(1H, d, Ar-H), 7.8 (1H, d, Ar-H).

Conclusion

In conclusion, the direct synthesis of aryl or heteroaryl nitrile was conducted by ultrasound assisted reaction of aldehyde and hydroxyl amine hydrochloride in DMSO under mild conditions. The corresponding nitrile derivatives are obtained in good to excellent yield avoiding the use of acid, base and metal catalyst. A convenient, practicability and cost effectiveness are the most accepting features of present method. Hence, the methodology presented here was found to be new addition for the development of 'Green Chemistry'.

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