

Microwave Assisted, Solvent Free One Pot Synthesis of Nitriles from Aryl Aldehydes on Melamin Formaldehyde as Solid Support

Rezaei, Ramin^{*,a} Mohammadi, Mohammad Kazem^b Rastin, Neda^a

^a Department of Chemistry, Islamic Azad University, Firoozabad Branch, 74715, Iran

^b Faculty of Science, Islamic Azad University, Ahwaz Branch, 61349-68875, Iran

Various aryl aldehydes underwent prompt one pot conversion into the corresponding nitriles in high yields by reacting with hydroxylamine hydrochloride supported on melamine formaldehyde under microwave irradiation in the presence of ammonium acetate as catalyst.

Keywords aryl aldehydes, nitriles, microwave irradiation, melamine formaldehyde

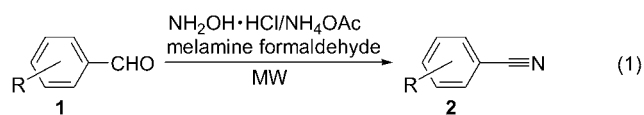
Introduction

The conversion of aldehydes into the corresponding nitriles is a synthetically useful transformation. Nitriles are required to construct a variety of biologically active compounds.¹ Nitriles are very useful starting materials for the synthesis of various bioactive molecules.² The versatile nitriles are used for the preparation of thiazoles, 2-oxazolines, tetrazoles, imidazoles, triazoles and benzamides possessing a broad spectrum of biological activities.³ The conversion of nitriles into amides, amines, ketones, carboxylic acids and esters are of considerable interests.⁴ They are used for the preparation of tetrazole derivatives as antipicornavirus agents⁴ and as carboxylic acid bioisosteres (particularly in the preparation of commercially important angiotensin receptor ligands, losartan and valsartan),⁵ thiazole analogues as inhibitors of superoxide⁶ and 1,2-diarylimidazoles as anti-inflammatory drugs.⁷

The conversion of nitriles into amides, amines, ketones, carboxylic acids and esters are of considerable interests.⁸ In the majority of cases, the aldoxime is prepared first and then dehydrated using a wide variety of reagents such as chloramine/base,⁹ *O,N*-bis-(trifluoroacetyl)-hydroxylamine or trifluoroacetoxyhydroxamic acid,¹⁰ triethylamine/dialkyl hydrogen phosphinates,¹¹ *p*-chlorophenyl chlorothionoformate/pyridine,¹² nitromethane/pyridine hydrochloride,¹³ TiCl₄/pyridine,¹⁴ triethylamine/phosphonitrilic chloride,¹⁵ 1,1'-dicarbonylbisimidazole.¹⁶

Conventional methods for the dehydration of aldoximes include the use of reagent systems on solid supports such as alumina/methanesulfonyl chloride,¹⁷ graphite/methanesulfonyl chloride,¹⁸ aluminium chloride/potassium iodide,¹⁹ NaI/MeCN,²⁰ alumina/PCl₅,²¹ and [RuCl₂(*p*-cymene)]₂/molecular sieves.²²

However, most of these reported methods are associated with significant drawbacks such as low yields, long reaction time, toxic and non-available reagents and harsh reaction conditions. Recently we have developed a more advantageous method for the one-pot conversion of aldehydes into nitriles by treatment with hydroxylamine hydrochloride under solvent free and microwave irradiation conditions using melamine formaldehyde resin as catalyst [Eq. (1), Table 1].



Results and discussion

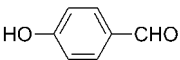
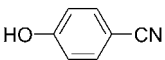
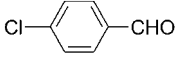
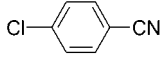
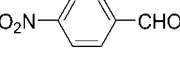
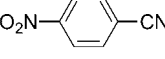
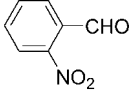
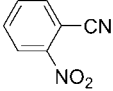
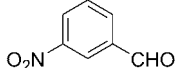
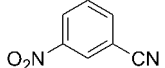
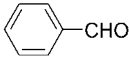
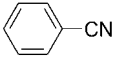
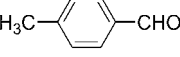
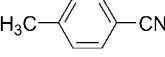
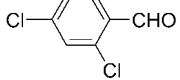
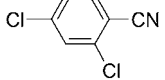
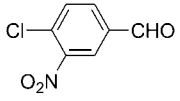
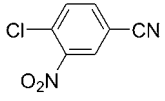
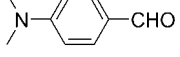
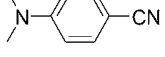
As shown in the Table 1, the reaction could be easily applied to structurally diverse aldehydes to give the corresponding nitriles in excellent yields. This protocol was compatible with reactive benzaldehydes containing different electron-withdrawing and electron-donating substituents. The variation of electron-donating and withdrawing substituents to the aromatic rings have no significant effect on the reaction rates and yields. The present method probably proceed via initial formation of *O*-acetylaldoxime intermediates, formed *in situ* by the reaction of aldoxime intermediates with acetic anhydride, followed by its decomposition under microwave irradiation conditions.

In these reactions, arylaldehydes bearing both electron-donating and electron-withdrawing substituents, are rapidly converted into nitriles in good yields (58%–83%) with melamine formaldehyde supported hydroxylamine hydrochloride coupled with MW irradiation under solvent free condition.

* E-mail: mohammadi@iauahvaz.ac.ir

Received November 13, 2009; revised January 11, 2010; accepted March 16, 2010.

Table 1 One pot microwave-assisted conversion of aryl aldehyde into corresponding nitriles using $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{NH}_4\text{OH}/\text{melamine}$ formaldehyde system

Entry	Substrate	Time/min	Yield/%	m.p./°C	b.p./°C	Product
1		6	58	112		
2		5	62	90–91		
3		5	75	148		
4		5	83	109		
5		7	72	117		
6		2	67		189–190	
7		3	72		216–218	
8		3	78	58–60		
9		3	81	98–101		
10		7	48	73–75		

The procedure in its entirety involves admixing aldehydes with melamine formaldehyde supported hydroxylamine hydrochloride and subjecting the solid reaction mixture to microwave irradiation in an unmodified laboratory MW oven at its full power (900 W) for 2–7 min. A variety of aldehydes undergo facile conversion in the presence of hydroxylamine hydrochloride “doped” melamin formaldehyde to afford high yield of nitriles within a short time of irradiation [Eq. (1)].

In the case of aliphatic aldehydes, however, only poor yields of nitriles (10%–15%) are obtained with complex by-product formation that was not included in Table 1. It was showed from Table 1 that withdrawing groups such as Cl and NO_2 decrease the time of the reaction probably due to increase of the positive property of carbonyl group, but it was not case sensitive for yield of products. As a model compound, we examined the reaction of benzaldehyde with various bases such as $\text{NH}_4^+\text{OAc}^-$, KF, KSF, NaHCO_3 and NaHSO_4 (Table 2). Best results are obtained with $\text{NH}_4^+\text{OAc}^-$, in the case of reaction time and yield of the reactions.

Table 2 Conversion of benzaldehyde to benzonitrile in the presence of various bases

Entry	Base	Reaction time/min	Yield/%
1	$\text{NH}_4^+\text{OAc}^-$	6	58
2	KF	6	28
3	KSF	5	35
4	NaHCO_3	3	43
5	NaHSO_4	2	52

Selected data for compounds (2a–2j)

p-Hydroxybenzaldehyde (2a) m.p. 112–114 °C (Lit.²³ 112 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 9.21 (br.s, $J=3$ Hz, 1H, OH), 7.47 (d, $J=8.0$ Hz, 2H, Ar-H), 7.14 (d, $J=8.10$ Hz, 2H, Ar-H); IR (KBr) ν : 3031, 2232 cm^{-1} .

p-Chlorobenzonitrile (2b) m.p. 91–93 °C (Lit.²⁴ 95–96 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 7.37 (d, $J=8.4$ Hz, 2H, H-Ar), 7.47 (d, $J=8.4$ Hz, 2H, H-Ar); IR (KBr) ν : 3065, 2215 cm^{-1} .

p-Nitrobenzonitrile (2c) m.p. 146–149 °C (Lit.²³ 147 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 8.37 (d, $J=8.0$ Hz, 2H, H-Ar), 7.92 (d, $J=8.0$ Hz, 2H, H-Ar); IR (KBr)

ν : 3094, 2230 cm^{-1} .

***o*-nitrobenzoyl nitrile (2d)** m.p. 109–110 °C (13) (Lit.²⁵ 109 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 8.40 (d, $J=8.25$ Hz, 1H, ArH), 7.85 (dd, $J=8.0$ Hz, 1H, ArH), 7.82 (dd, $J=7.85$ Hz, 1H, ArH), 7.79 (dd, $J=8.10$ Hz, 1H, ArH); IR (KBr) ν : 3120, 2909, 2261 cm^{-1} .

***m*-Nitrobenzoyl nitrile (2e)** m.p. 115–117 °C (Lit.²⁶ 115 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 8.46 (s, 1H, H-Ar), 7.90 (d, $J=9.0$ Hz, 1H, H-Ar), 7.70 (dd, $J=8.35$, 7.12 Hz, 1H, H-Ar); IR (KBr) ν : 3036, 2238 cm^{-1} .

benzoyl nitrile (2f) b.p. 189–190 °C (Lit.²³ 190 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 7.55–7.61 (m, 5H, H-Ar); IR (liq) ν : 3031, 2232 cm^{-1} .

***p*-Tolunitrile (2g)** b.p. 216–218 °C (Lit.²³ 218 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 7.23 (d, $J=7.4$ Hz, 2H, H-Ar), 7.47 (d, $J=7.4$ Hz, 2H, H-Ar); IR (KBr) ν : 3039, 2229 cm^{-1} .

2,4-dichlorobenzoyl nitrile (2h) m.p. 58–60 °C (Lit.²³ 61 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 7.54 (s, $J=8.0$ Hz, 1H, H-Ar), 7.42 (d, $J=7.95$ Hz, 1H, H-Ar), 7.46 (d, $J=8.0$ Hz, 1H, H-Ar); IR (KBr) ν : 3076, 2234 cm^{-1} .

4-Chloro-3-nitrobenzoyl nitrile (2i) m.p. 98–101 °C (Lit.²³ 103 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 8.45 (s, $J=8.0$ Hz, 1H, H-Ar), 7.87 (d, $J=8.23$ Hz, 1H, H-Ar), 7.81 (d, $J=8.15$ Hz, 1H, H-Ar); IR (KBr) ν : 3076, 2234 cm^{-1} .

***p*-Dimethylaminobenzoyl nitrile (2j)** m.p. 69–71 °C (Lit.²⁷ 75–77 °C); ^1H NMR (CDCl_3 , 300 MHz) δ : 3.02 (s, 6H, Me), 6.63 (d, $J=8.2$ Hz, 2H, H-Ar), 7.43 (d, $J=8.2$ Hz, 2H, H-Ar); IR (KBr) ν : 2909, 2261 cm^{-1} .

Conclusion

It can be concluded that melamin formaldehyde/hydroxylamine hydrochloride/ammonium acetate support, can be used as an efficient, excellent, readily available, and cheap catalyst in conversion of aldehydes to nitriles under microwave irradiation. Furthermore, the reaction is a green process and the catalyst is recyclable for several uses. The advantages of the present method in terms of facile manipulation, fast reaction rates, and formation of cleaner products under neat reaction conditions should make this protocol as a valuable alternative to the existing methods.

Materials and method

Benzaldehyde derivatives, NH_2OH , HCl , $\text{NH}_4^+\text{OAc}^-$, melamin formaldehyde (Merck) were used without further purification. Silica gel Aldrich, 150 mesh (Aldrich) and TLC plates (Merck) were used. Solvents were purified by standard methods. Infrared spectra were recorded as KBr disks on a Shimadzu model 420 spectrophotometer. The UV/Vis measurements were made on a Uvicon model 922 spectrometer. ^1H and ^{13}C NMR were carried out on a Bruker AVANCE DRX 300 spectrometer. All the chemical shifts are quoted in δ using the high-frequency positive

convention; the ^1H and ^{13}C NMR spectra were referenced to external SiMe_4 . Experiments were carried out in closed vessel multi mode Microsynth Milstone laboratory microwave oven (not domestic oven) using a 900 W Westpointe microwave operating at 3.67 GHz with an internal volume of 0.9 m^3 . All experiments had good reproducibility by repeating the experiments in same conditions.

Experimental

Benzaldehyde (2 mmol), hydroxylamine hydrochloride (4 mL), ammonium acetate (1 mL) and melamin formaldehyde (2 g) were mixed thoroughly with mechanical mixer. This mixture was then irradiated in microwave oven (800 W). The progress of the reaction was monitored with period of 30 s by TLC ($\text{EtOAc}/\text{CHCl}_3$). On the completion of the reaction (monitored by TLC), CHCl_3 was added priority (10 mL \times 3). The formaldehyde was removed by simple filtration and the organic layer was separated. The solvent was removed by a rotary evaporator and the resulting precipitate was washed with CHCl_3 (10 mL \times 2). The residue was then recrystallized with ethanol and dried in electrical oven to give benzoyl nitrile in good to high yields (Table 1). For other benzaldehyde derivatives, procedure was the same as benzaldehyde.

Acknowledgment

We gratefully thank the chemical research center of Islamic Azad University, Firoozabad Branch for their financial support of this work.

References

- Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117.
- (a) Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A.; Tarrant, M. E.; Torley, I. W.; Wrenn, S. *J. Med. Chem.* **1990**, *33*, 1230.
(b) Judkins, B. D.; Allen, D. G.; Cook, T. A.; Evans, B.; Sardharwala, T. E. *Synth. Commun.* **1996**, *26*, 4351.
(c) Fang, C. B.; Hu, H. Z. *Chin. J. Med. Chem.* **1997**, *12*, 134.
- (a) Cohen, M. A.; Sawden, J.; Turner, N. J. *Tetrahedron Lett.* **1990**, *31*, 7223.
(b) Crossby, J.; Moiller, J.; Parratt, J. S.; Turner, N. J. *J. Chem. Soc., Perkin Trans 1* **1994**, 1679.
(c) Lou, F. T.; Jeevanandam, A. *Tetrahedron Lett.* **1998**, *39*, 9455.
- Diana, G. D.; Cutcliffe, D.; Volkots, D. L.; Mallamo, J. P.; Bailey, T. R.; Vescio, N.; Oglesby, R. C.; Nitz, T. J.; Wetzel, J.; Girandu, V.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1993**, *36*, 3240.
- Fabiani, M. E. *Drug News Perspect* **1999**, *12*, 207.
- Chihiro, M.; Nagamoto, H.; Takemura, I.; Kitano, K.; Komatsu, H.; Sekiguchi, K.; Tabusa, F.; Mori, T.; Tominnaga, M.; Yabuuchi, Y. *J. Med. Chem.* **1995**, *38*, 353.

- 7 Khanna, I. K.; Weier, R. M.; Yu, Y.; Xu, X. D.; Koszyk, F. J.; Callins, P. W.; Koboldt, C. M.; Veenhuizen, A. W.; Perkins, W. E.; Casler, J. J.; Masferrer, J. L.; Zhung, Y. Y.; Gregory, S. A.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1634.
- 8 (a) Cohen, M. A.; Sawden, J.; Turner, N. J. *Tetrahedron Lett.* **1990**, *31*, 7223.
(b) Crosby, J.; Moiller, J.; Parratt, J. S.; Turner, N. J. *J. Chem. Soc., Perkin Trans 1* **1994**, 1679.
(c) Lou, F. T.; Jeevanandam, A. *Tetrahedron Lett.* **1998**, *39*, 9455.
- 9 Mowry, D. T. *Chem. Rev.* **1948**, *42*, 250.
- 10 Pomeroy, J. H.; Craig, C. A. *J. Am. Chem. Soc.* **1959**, *81*, 6340.
- 11 Foley, P. J. *J. Org. Chem.* **1969**, *34*, 2805.
- 12 Clive, D. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1014.
- 13 Dauzonne, D.; Demerseman, P.; Royer, R. *Synthesis* **1981**, 739.
- 14 Karmarkar, S. N.; Kelkar, S. L.; Wadia, M. S. *Synthesis* **1985**, 510.
- 15 Villemain, D.; Lalaoui, M.; Ben Album, A. *Chem. Ind.* **1991**, 176.
- 16 Delgado, F.; Cano, A. C.; Garcia, O.; Alvarado, J.; Velasco, L.; Alvarez, C.; Rudler, H. *Synth. Commun.* **1992**, *22*, 2125.
- 17 Sharghi, H.; Sarvari, M. H. *Tetrahedron* **2002**, *58*, 10323.
- 18 Sharghi, H.; Sarvari, M. H. *Synthesis* **2003**, 243.
- 19 Boruah, M.; Konwar, D. *J. Org. Chem.* **2002**, *67*, 7138.
- 20 Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* **2003**, 1841.
- 21 Niknam, K.; Karami, B.; Kiasat, A. R. *Bull. Korean Chem. Soc.* **2005**, *26*, 975.
- 22 Yang, A. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209.
- 23 Sampath, K. H. M.; Subba-reddy, B. V.; Tirupathi, R. P.; Yadav, J. S. *Synthesis* **1999**, 586.
- 24 Gallo, G. G.; Sensi, P. *Ann. Chim. (Rome)* **1956**, *46*, 816.
- 25 Juncai, F.; Bin, L.; Yang, L.; Changchuan, L. *Synth. Commun.* **1996**, *26*, 4545.
- 26 (a) Nitin, D. A.; Dinesh, S. B.; Krishnacharya, G. A. *Tetrahedron Lett.* **2007**, *48*, 3651.
(b) Beck, G. *Justus Liebigs Ann. Chem.* **1968**, *716*, 47.

(E0911122 Ding, W.; Zheng, G.)