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Highly Efficient Microwave-assisted One-Pot Synthesis of Aromatic Nitriles from Aromatic Aldehydes

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Abstract—A highly efficient and environmentally benign protocol is described for the microwave-assisted one-pot synthesis of aromatic nitriles from aromatic aldehydes by the reaction with hydroxylamine hydrochloride in DMSO, which involves the intermediate formation of aldoximes and subsequent dehydration. The developed synthetic methodology can be readily accomplished with various aldehydes containing both electron-donor and electron-acceptor groups, providing excellent yields of the target products in shorter reaction times (1–2 min) compared to previously reported methodologies.

Keywords: microwave irradiation, aryl nitriles, green protocol, DMSO

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INTRODUCTION

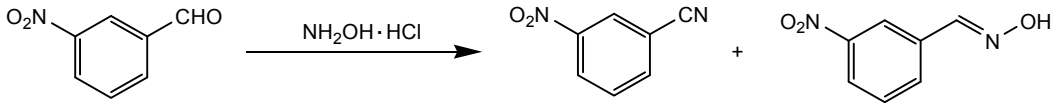
Nitriles are widely used key intermediates in many organic transformations. Due to the versatility of this functional group, it has been used as a synthon for preparing various functional derivatives, such as amines, carboxylic acids, amides, aldehydes, etc. The use of nitriles as key starting materials in the synthesis of such pharmaceutically important heterocyclic compounds as triazoles, oxazoles, imidazoles, and others has also been reported [1, 9]. Furthermore, the pharmacophore moieties of some important drug molecules, for example, Letrozole (aromatase inhibitor), Zaleplon, Vildagliptin, and Rilipivirine (anti-HIV), Neratinib (anticancer), and Escitalopram (antidepressant) contains nitrile as one of the functional groups [14]. The synthesis of aromatic nitriles is a well-documented topic [3–8]. One of the common nitrile synthesis by transition metal−mediated cyanation makes use of toxic reagents (NaCN, KCN, CuCN, etc.) and leads to a build-up of the skeleton by one carbon atom. An attractive alternative synthetic approach to nitriles involves either dehydration of aldoximes or conversion of aldehydes using hydroxylamine hydrochloride [8–16]. However; many of the reported protocols are not fully satisfactory and feature some shortcomings, specifically, the use of toxic reagents, prolonged reaction time, low isolated yields, and tedious workups. Searching for an efficient and economical method for the synthesis of nitriles starting from aromatic aldehydes, we initially screened various conventional methods but often ended with low selectivities and yields. Therefore, to obtain sufficiently clean and pure products in good yields remained as a challenge for us.

Recently, microwave-assisted organic transformations have gained considerable attention. Microwave heating is a greener and an alternative approach compared to conventional heating. Among the reported microwave-assisted syntheses of aromatic nitriles one employs iodine and aqueous ammonia [2], while the other involves aminosulfonic acid and alumina [5]. Both of these methods suffer from either formation of an explosive intermediate ($NI_3 \cdot NH_3$) or use of toxic reagents and additives. In the pursuit of a better synthetic approach, we have developed simple, rapid, and efficient one-pot green protocol for the synthesis of aromatic nitriles by the reaction of aromatic aldehydes with hydroxylamine hydrochloride in DMSO under microwave irradiation.

RESULTS AND DISCUSSION

Initially, we selected 3-nitrobenzaldehyde **1b** as the starting compound to optimize the reaction conditions

Table 1. Optimization of reaction conditions



1b **2b** **3b**

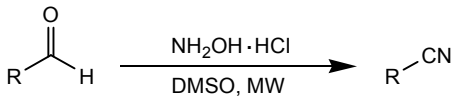
Entry no.	Solvent	Co-oxidant	Temperature	Time	Yield, %[a]	
					Nitrile **2**	Oxime **3**
1	DMSO	I_2	RT	4 h	ND	90%
2	DMSO	I_2	90–100°C	6 h	92%	–
3	DMSO	I_2	MW (180W)	60 s	94%	ND[b]
4	DMSO	–	RT	4 h	ND	50%
5	DMSO	–	90–100°C	6 h	94%	–
6	DMSO	–	MW (180W)	60 sec	98%	ND[c]
7	DMF	I_2	MW (180W)	80 sec	Trace	80%
8	DMF	–	MW (180W)	80 sec	Trace	85%

[a] Isolated yield.
[b] Not detected.

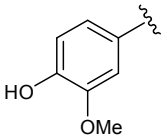
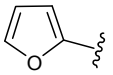
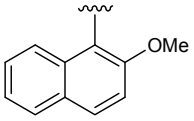
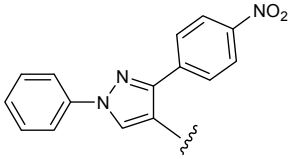
(Table 1). We started with the previously reported [6] DMSO–I_2 reaction system. The reaction with hydroxylamine hydrochloride in the presence of DMSO–I_2 gave 3-nitrobenzaldoxime (**3b**) after stirring for 4 h at room temperature (Table 1, entry 1), while under conventional heating [16] at 100°C (Table 1, entry 2) the target 3-nitrobenzonitrile **2b** was detected in the reaction mixture only after 6 h (TLC). To our surprise, microwave irradiation at 180 W (with 15-s intervals) led to the formation of nitrile **2b** in an excellent yield (94%) in as short as 60 s. Inspired by these first results we investigated the necessity of molecular iodine for this transformation. Surprisingly, we found that even in absence of I_2 (Table 1, entry 6) 3-nitrobenzonitrile was obtained in quantitative yield and superior in color. To obtain evidence for the necessity of DMSO for this transformation, we carried out the reaction in the high- boiling aprotic polar solvent DMF (Table 1, entries 7 and 8). The subsequent FTIR analysis revealed formation of aldoxime **3b** and only traces of nitrile **2b**. This result confirmed the importance of DMSO for the conversion of aldehydes to nitriles. Thus, we found that the best conditions for the one-pot conversion of aromatic aldehydes to nitriles were microwave irradiation at 180 W in a DMSO solvent. Further on we checked whether the developed methodology works with aromatic aldehydes containing electron-donor and electron-acceptor substituents. Commercially available aldehydes with various functional groups, such as OH, OMe, NO_2, and Cl, in the *ortho*-, *meta*-, and *para*-positions, converted into corresponding nitriles in good yields (Table 2). 2-Methoxynaphthalene-1-carbonitrile **2k** was obtained in excellent yield (94%) starting with 2-methoxynaphthalene-1-carbaldehyde successfully prepared from 2-methoxynaphthalene by the Vilsmeier–Haack reaction. The methodology was extended to heterocyclic aldehydes. Furfural gave 2-furonitrile **2j** in 68% yield and 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1l** prepared by a known procedure [23] was converted into 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile **2l** in 90% yield. We found that all the aldehydes irrespective of whether they contain electron-donor or electron-acceptor substituents convert into the corresponding nitriles in good- to-excellent yields (Table 2).

The plausible reaction mechanism is shown below (Scheme 1). Aldehyde **1** reacts with hydroxylamine hydrochloride forms aldoxime **3** and HCl. The released acid protonates DMSO to generate a hydroxy-sulfonium salt (activated DMSO), whose reaction with aldoxime **3** to form intermediate **4** and subsequent

Table 2. Substrate and product scope for the synthesis of aromatic nitriles[a]



1a–1l **2a–2l**

Aldehyde no.	Nitrile no.	R	Time, s	Yield, %[b]
1a	**2a**	C_6H_5	75	86
1b	**2b**	3-$NO_2C_6H_4$	60	98
1c	**2c**	2-$NO_2C_6H_4$	90	85
1d	**2d**	4-$NO_2C_6H_4$	90	90
1e	**2e**	4-Cl C_6H_4	75	90[c]
1f	**2f**	4-Br C_6H_4	105	95
1g	**2g**	2-OH C_6H_4	90	92
1h	**2h**	4-OMeC_6H_4	75	92
1i	**2i**		75	84
1j	**2j**		75	68
1k	**2k**		90	94
1l	**2l**		75	90

[a] Reaction conditions: aldehyde (1.0 equiv.), hydroxylamine hydrochloride (1.1 equiv), DMSO, 180 W.
[b] Isolated yield.
[c] Yield after recrystallization.

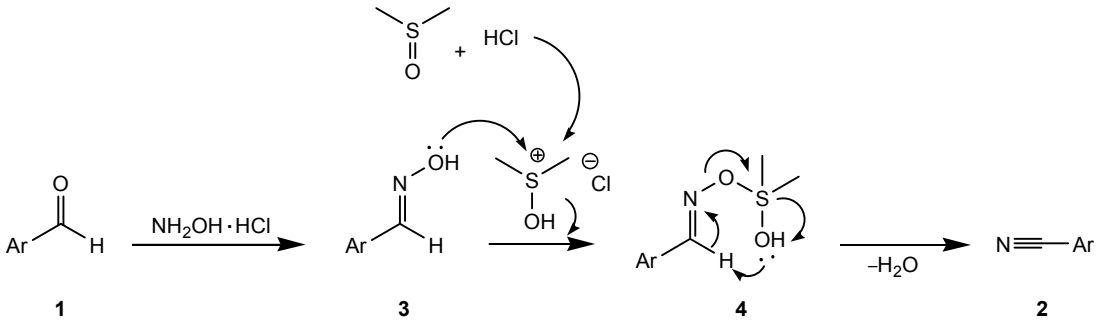
dehydration of the latter under microwave irradiation affords nitrile **2**.

In this study, FTIR spectroscopy played an important role both in characterization of the intermediate products and in efficient optimization of the reaction conditions. The FTIR spectrum of 3-nitrobenzonitrile **2b** displays a sharp band at 2233 cm^{-1}, which is a characteristic band of the C≡N group. Intermediate 3-nitroaldoxime **3b** gives a broad band at 3300 cm^{-1} assignable to the oxime OH group. The incomplete conversion is confirmed by the observation in the spectrum of both the nitrile and oxime absorption bands.

CONCLUSIONS

In conclusion, we have successfully developed a one-pot, highly efficient and green protocol for the synthesis of aromatic nitriles starting from commercially available aldehydes. This synthetic technique makes use of an inexpensive solvent DMSO and is cost effective, metal free, additive free, operationally simple, and clean. Due to mild reaction conditions and shorter reaction time, this method works with many functional groups and provides high yields of the target products.

Scheme 1.



EXPERIMENTAL

The IR spectra were measured on a Shimadzu IRAffinty-1S FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were taken on a Bruker Avance II 400 MHz Spectrometer at 400 MHz at SAFE, Punjab University, Chandigarh, India. The reactions were performed in a Samsung CE104VD microwave oven.

Synthesis of nitriles 2 (*general procedure*). Hydroxylamine hydrochloride, 0.55 g (0.72 mmol) was added to a solution of 0.5 g (0.66 mmol) aldehyde **1** in 3 mL of DMSO. The reaction mixture was subjected to microwave irradiation at 180 W (with 15-s intervals) for 60–120 s. Reaction progress was monored by TLC on aluminum coated silica gel (ethyl acetate:hexane, 1 : 4). After the reaction had been complete, the reaction mixture was cooled to room temperature and poured on crushed ice, the reaction product was extracted in ethyl acetate, the extract was dried over Na_2SO_4 and concentrated in a vacuum, and the residue was recrystallized.

Benzonitrile (2a). Yield 90%, colorless oil, bp 188–190°C (193°C [5]). IR spectrum, ν, cm^{-1}: 2227 s (CN), 1662–1504 s (CH_{arom}), 1305 m (C–OH).

3-Nitrobenzonitrile (2b). Yield 0.460 g (95%), white solid, mp 114–116°C (117–118°C [5]). IR spectrum, ν, cm^{-1}: 3080 m (CH_{arom}), 2235 s (CN), 1703–1614 m (C=N), 1529–1350 s (NO_2).

2-Nitrobenzonitrile (2c). Yield 98%, white solid, mp 112°C (108–109°C [5]). IR spectrum, ν, cm^{-1}: 3080 m (CH_{arom}), 2228 s (CN), 1705–1616 m (C=N), 1539–1340 s (NO_2).

4-Nitrobenzonitrile (2d). Yield (98%), white solid, mp 144–146°C (146–148°C [5]). IR spectrum, ν, cm^{-1}: 3080 m (CH_{arom}), 2235 s (CN), 1703–1614 m (C=N), 1535–1340 s (NO_2).

4-Chlorobenzonitrile (2e). Yield (98%), white solid, mp 92–94°C (93–94°C [6]). IR spectrum, ν, cm^{-1}: 2223 s (CN), 1594–1483 s (CH_{arom}), 825 m (C–Cl).

4-Bromobenzonitrile (2f). Yield (90%), white solid, mp 110–112°C (109–112°C [5]). IR spectrum, ν, cm^{-1}: 3080 w (CH_{arom}), 2235 s (CN), 1703–1614 m (C=N).

2-Hydroxybenzonitrile (2g). Yield (90%), brown oil, bp 96–98°C (96–98°C [6]). IR spectrum, ν, cm^{-1}: 3267 br (OH), 2227 s (CN), 1662–1504 s (CH_{arom}), 1305 m (C–OH), 761 s (1,2-disubstituted benzene).

4-Methoxybenzonitrile (2h). Yield (90%), white solid, mp 54–56°C (58–68°C [6]). IR spectrum, ν, cm^{-1}: 3080 w (CH_{arom}), 2235 s (CN), 1703–1614 m (C=N).

4-Hydroxy-3-methoxybenzonitrile (2i). Yield (98%), yellow oil, bp 84–86°C (84–86°C [22]). IR spectrum, ν, cm^{-1}: 3379 br (OH), 2223 s (CN), 1592–1516 m (CH_{arom}), 1288 m (C–O).

Furan-2-carbonitrile (**2j**). Yield (68%), brown oil, bp 144–146°C (146–147°C). IR spectrum, ν, cm^{-1}: 2227 s (CN), 1662–1504 s (CH_{arom}), 1305 m (C–OH).

2-Methoxynaphthalene-1-carbonitrile (2k). Yield (90%), white solid, mp 92–94°C. IR spectrum, ν, cm^{-1}: 3080 m (CH_{arom}), 2235 s (CN), 1703–1614 m (C=N). ^{1}H NMR spectrum (400MHz, $CDCl_3$), δ, ppm: 7.98–8.00 d (1H, H_{arom}, *J* 8.0 Hz), 7.92–7.94 d (1H, H_{arom}, *J* 8.0 Hz), 7.73–7.75 d (1H, H_{arom}, *J* 8.0 Hz), 7.54–7.58 d.d (1H, H_{arom}, *J* 12.0 Hz), 7.36–7.40 d.d (1H, H_{arom}, *J* 12.0 Hz), 7.16–7.18 d (1H, H_{arom}, *J* 8.0 Hz), 3.99 s (3H, OCH_3). ^{13}C NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 161.5 (Ar<u>C</u>-OCH_3), 135.3 (Ar<u>C</u>H), 133.4 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 125.0 (Ar<u>C</u>H), 123.8 (Ar<u>C</u>H), 115.8 (CN), 111.9 (Ar<u>C</u>H), 94.9 (Ar<u>C</u>–CN), 56.5 (ArC–O<u>C</u>H_3).

3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2l). Yield 0.460 g (95%), white solid, mp 162–164°C. IR spectrum, ν, cm^{-1}: 3080 m (CH_{arom}), 2235 s (CN), 1703–1614 m (C=N), 1529–1350 s (NO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.49 s (1H, H_{arom}), 8.42–8.40 d (2H, H_{arom}, *J* 8.0 Hz), 8.25–8.23 d (2H, H_{arom}, *J* 8.0 Hz), 7.96–7.94 d (2H, H_{arom}, *J* 8.0 Hz), 7.57–7.61 d.d (1H, H_{arom}, *J* 8.0 Hz),7.44–7.48 d.d (1H, H_{arom}, *J* 8.0 Hz). ^{13}C NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 150.3 (Ar<u>C</u>NO_2), 147.7 (Ar<u>C</u>), 138.1 (Ar<u>C</u>), 136.7 (Ar<u>C</u>), 136.1 (Ar<u>C</u>), 129.6 (Ar<u>C</u>), 128.2 (Ar<u>C</u>), 127.3 (Ar<u>C</u>), 124.2 (Ar<u>C</u>), 119.3 (Ar<u>C</u>H), 113.7 (CN), 91.4 (Ar<u>C</u>–CN), 79.1 (Ar<u>C</u>H), 79.0 (Ar<u>C</u>H), 78.8 (Ar<u>C</u>H), 78.5 (Ar<u>C</u>H) [24].

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Batool, A. and Soodabeh, R, *J. Braz. Chem. Soc*., 2012, vol. 23, p. 2197.
2. Bhattacharyya, N.K., Jha, S., Bhutia, T.Y., and Adhikary, G., *Int. J. Chem. App.*, 2012, vol. 4, p. 295.
3. Shie, J. and Fang, J., *J. Org. Chem*., 2017, vol. 72, p. 3141.
4. Yan, G., Zhang, Y., and Wang, J., *Adv. Synth. Catal.*, 2017, vol. 359, p. 4068.
5. Juncai, F., Bin, L., Yang, L., and Li, C., *Synth. Commun*., 1996, vol. 26, p. 4545.
6. Gaikwad, D.D., Renukdas, S.V., Kendre, B.V., Shisodia, S.U., Borade, R.M., Shinde, P.S., Chaudhary, S.S., and Pawar, R.M., *Synth. Commun*., 2007, vol. 37, p. 257.
7. Patil, D.D., Wadhava, G.C., and Deshmukh, A.K., *Asian J. Chem*., vol. 2012, vol. 24, p. 1401.
8. Soltani, R.M.N., Nezhad, K., Somayeh, A.B., Zohreh, A., and Marzieh, B., *Synth. Commun*., 2010, vol. 40, p. 2429.
9. Sribalan, R., Sangili, A., Banuppriya, G., and Padmini, V., *New J. Chem*., 2017, vol. 41, p. 3414.
10. Singh, M.K. and Lakshman, M.K., *J. Org. Chem*., 2017, vol. 74, p. 3079.
11. Jagadeesh, R.V., Junge, H., and Beller, M., *Nat.Commun*., 2014, vol. 5, p. 4123.
12. Fong, C. and Li, M., *RSC Adv*., 2017, vol. 7, p. 1484.
13. Aspinall, H.C., Beckingham, O., Farrar, M.D., Greeves, N., and Thomas, C.D., *Tetrahedron Lett*., 2011, vol. 52, p. 5120.
14. Ghosh, P. and Subba, R., *Tetrahedron Lett*., 2013, vol. 54, p. 4885.
15. Chill, S.T. and Mebane, R.C., *Synth. Commun*., 2009, vol. 39, p. 3601.
16. Augustine, J.K., Bombrun, A., and Atta, R.N., *Synlett*, 2011, p. 2223.
17. Patil, U.B., Shendage, S.S., and Nagarkar, J.M., *Synthesis*, 2013, vol. 45, p. 3295.
18. Wu, Q., Luo, Y., Lei, A., and You, J., *J. Am. Chem. Soc*, 2016, vol. 138, p. 2885.
19. Hyodo, K., Kitagawa, S., Yamazaki, M., and Uchida, K., *Chem. Asian J*., 2016, vol. 11, p, 1348.
20. Kim, J.N., Chung, K.H., and Ryu, E.K., *Synth. Commun*., 1990, vol. 20, p. 2785.
21. Sarvari, M.H., *Synthesis*, 2005, p. 787.
22. Sosnovsky, G., Krogh J.A., and Umhoefer S.G.A., *Synthesis*, 1979, p. 722.
23. Baluja, S. and Chanda, S., *Rev. Colomb. Cienc. Quím. Farm*., 2016, vol. 45, p. 201.
24. Ramadan, E., Sharshira, E., El Sokkary, R., and Morsy, N., *Z. Naturforsch. B*, 2018, vol. 73, p. 389. doi 10.1515/znb-2018-0009