SHORT PAPER

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Formamide assisted one-pot conversion of aromatic aldehydes into the corresponding nitriles[†]

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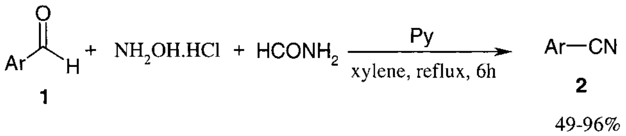
A single step conversion of aromatic aldehydes **(1)** into the corresponding nitriles **(2)** has been achieved in high yields using stoichiometric amounts of hydroxylamine hydrochloride, pyridine and formamide in refluxing xylene.

Nitriles are of particular interest in preparative organic chemistry due to their conversion into carboxylic acids, aldehydes, amides, amines and ketones.[1] They are usually prepared by nucleophilic substitution[2a] with CN^- or by regenerating CN group *via* oxidation,[2b] rearrangement[2c] or elimination. The direct preparation of nitriles from aldehydes is generally achieved by the dehydration of the corresponding aldoximes using classical reagents[3] or other new reagents.[4] Several procedures for the direct conversion of aldehydes into nitriles without isolation of nitrogen-containing intermediates are also reported.[5] However, these procedures are deficient in some respects. For example, the preparation of $Et_3N\text{-}SO_2$ and sulfuryl chloride is inconvenient (–70°C),[6] dehydration with KSF, zeolite and envirocat requires high temperature (350°C).[7] Further, the reagents like phosgene, diphosgene and triphosgene are hazardous to handle. Therefore, there is still a need for convenient and generally applicable method for this conversion. We wish to report here that aromatic aldehydes can be transformed into their corresponding nitriles in a single step using stoichiometric amounts of hydroxylamine hydrochloride, pyridine and formamide in refluxing xylene (Scheme I).



Scheme 1

The results indicate that this methodology gives good yields of aryl nitriles with aromatic aldehydes when reacted with a mixture of hydroxylamine hydrochloride, formamide and pyridine at reflux temperature in xylene (Table 1). However, the reaction failed to proceed in the case of many aliphatic aldehydes such as isobutryaldehyde, *tert*-butyraldehyde, cyclohexylcarboxaldehyde, *n*-hexanal *etc.*, although their corresponding oximes could be isolated in high yields. Further, it was interesting to note that various aryl aldoximes also underwent dehydration to give the corresponding nitriles when reacted with formamide (1 equiv.) in xylene at reflux temperature.

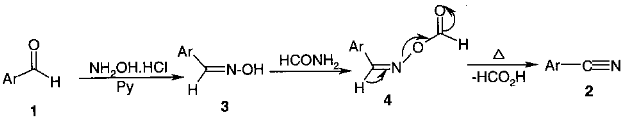
Among the various solvents studied, xylene is the choice, as best results were obtained. Also when these reactions were conducted in $CHCl_3$ and MeOH, the conversion was only marginal even after 15h. In the absence of formamide, no nitrile could be formed either from aldehydes or from aldoximes. We also found that 1 equiv. of formamide is needed to achieve the excellent yield of nitrile from aldehyde.

Table 1 Formamide assisted direct conversion of aryl aldehydes into aryl nitriles

Structure no.	R	t/h	Yield[a, b] (%)	b.pt / m.pt. (°C)[c]
1	Ph	6	50	60°/6 mm (191°)
2	4–Me	6	51	75°/6 mm (217.6°)
3	4–OMe	5	96	58 (57–59)
4	2–OH	5	60	95–97 (98)
5	4–OH	5	65	112–114 (113)
6	2–Cl	6	70	42–44 (43)
7	3–OMe–4–OH	6	51	83–85 (85–87)
8	3, 4–$(OMe)_2$	6	75	67–69 (68–70)
9	3, 4, 5–$(OMe)_3$	6	65	142–144 (143–145)
10	4–NMe_2	5	80	71–73 (73–75)
11	3–NO_2	5	61	117–118 (117–118)
12	3–NO_2–4–Me	5	87	107–109 (109)
13	4–NO_2	5	76	148–150 (149)
14	1–Naphthyl	5	70	34–35 (36–38)
15	2–Cl–3–quinolinyl	6	49	183–185

[a] : Isolated yield after chromatographic purification; [b] : All the product characterized by b.pt m.pt., CH analysis, IR and NMR spectroscopy;[8] [c] : Number in parenthesis refers to literature b.p./ m.p.[8]

Mechanistically, the first step involves the formation of aldoxime **3** followed by its reaction with formamide to generate aldoxime formate **4**, the key intermediate. The aldoxime formate **4** subsequently undergoes elimination thermally to produce the nitriles **2** with the liberation of formic acid. For aliphatic case, the formation of aldoxime formate from their corresponding oximes is not favoured possibly due to less acidic nature of the OH proton compared to the aromatic aldoximes.



Scheme 2 Possible mechanistic pathway

In conclusion, we have developed a new reagent system ($NH_2OH.HCl\text{–}Py\text{–}HCONH_2$) which can directly convert aromatic aldehydes into the corresponding nitriles in high yields.

Experimental

A mixture of anisaldehyde (5 mmol, 0.680g), hydroxylamine hydrochloride (5 mmol, 0.345g)), pyridine (5 mmol, 0.395 g) and formamide (5 mmol, 0.225g) in xylene (10 ml) was subjected to reflux for 5-6 h. The progress of the reaction was monitored by TLC (20% ethyl acetate in pet ether). After the reaction was complete, xylene was distilled under reduced pressure. Water (20 ml) was added to the reaction mixture followed by the neutralization of pyridine with 2N HCl. It was then extracted with EtOAc (3 × 20 ml) washed with brine and dried

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

over anhyd. Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (5% EtOAc in pet ether). 4-Methoxybenzonitrile: Yield 96%; m. p.t. 58 ºC; ^{1}H NMR ($CDCl_3$): δ 3.8 (s, 3H), 6.95 (2H, d, J=8 Hz), 7.6 (2H, d, J=8 Hz); IR (Nujol) ν/cm^{-1} 840, 950, 1250, 1440, 1590, 600, 2200, 2900; Found: C, 72. 09; H, 5.25; N, 10.53%. C_8H_7NO requires C, 72.16; H, 5.29; N, 10.52%.

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Spectral Data

2-Chlorobenzonitrile
mpt: 42-44 ^{O}C; IR: (Nujol, cm^{-1}): 2200, 1570, 1430, 1360, 1165, 1040; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.7 (1H, d, J= Hz), 7.5-7.6 (2H, m), 7.3-7.4 (1H, m); Anal. Calcd for C_7H_4NCl: C, 61.09, H, 2.92, N, 10.18, Cl, 25.78. Found: C, 61.11; H, 2.89, N, 10.12, Cl, 25.76%.

2-Cl, 3-Quinolinecarbonitrile
mpt: 183-185 °C; IR: (Nujol, cm^{-1}): 2180, 1580, 1430, 1360, 960; ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO d6): δ 8.1-8.4 (1H, m), 7.5-7.6 (1H, m), 7.2-7.5 (2H, m), 7.0-7.2 (1H, m); Anal. Calcd for $C_{10}H_5N_2Cl$: C, 63.66, H, 2.67, N, 14.86, Cl, 18.80. Found: C, 63.63; H, 2.60, N, 14.79, Cl, 18.77%.

References

1 (a). K. Friedrich, K. Wallensfels, In *The Chemistry of Cyano Group*; Z. Rappoport, Ed.; Wiley-Interscience: New York, 1970. (b). D. T. Mowry, *Chem. Rev.* 1948, **42**, 250.
2 (a). A. J. Fatiadi, *The Chemistry of triple-bonded functional group* Part 2, Ed by S. Patai and Z. Rappoport, John Wiley and sons, New York, 1983, pp. 1057. (b). T. E. Stevens, *J. Org. Chem.* 1961, 26, 2531. (c). J. Pakusch and C. Ruchardt, *Chem. Ber*. 1991, **124**, 971.
3 I. T. Harrison, S. Harrison, In *Compendium of Organic Synthetic Methods*, Interscience Publishers, New York, 1971, vol. I, pp. 457–458, 1972, vol. II, 185-192.
4 (a). G. A. Olah, S. C. Narang, A. Garcia-Luna, *Synthesis*, 1980, 659. (b). A. Saednya, *Synthesis*, 1983, 748. (c). A. Kamal, M. Arifuddin and N. Venugopal Rao, *Synth. Commun.* 1998, **28**, 4507. (d). G. Sabitha and M. Syamala, *Synth. Commun*. 1998, **28**, 4577.
5 H. M. Sampath Kumar, B. V. Subba Reddy, P. Tirupathi Reddy, J. S. Yadhav, *Synthesis*, 1999, 586 and references cited therein.
6 G. A. Olah, Y. D. Yankar, *Synthesis*, 1978, 702.
7 M. Narayana Rao, P. Kumar, K. Garyali, *Org. Prep. Proc. Int.* 1989, **21**, 230
8 Chapman and Hall, 6th Ed., *Dictionary of Organic Compounds*, 1996; C. J. Pouchert, *The Aldrich Library of NMR Spectra* Ed. II Vol. 2, 1983; C. J. Pouchert, J. Behuke, *The Aldrich Library of NMR Spectra* Ed. I Vol. 3, 1993.