An Efficient and Improved Method for the Preparation of Nitriles from Primary Amides and Aldoximes†

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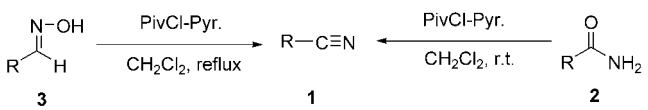
Abstract: The pivaloyl chloride-pyridine system has been utilized as a novel and efficient reagent for the preparation of nitriles from primary amides and aldoximes. The reaction proceeds smoothly under mild reaction conditions and the products are obtained in excellent yields. This method is applicable to a wide range of substrates including aromatic, heterocyclic and aliphatic species. The dehydration takes place at room temperature in the case of primary amides and dichloromethane at reflux temperature is required for rapid conversion in the case of aldoximes.

Keywords: aldoximes; dehydration; nitriles; pivaloyl chloride-pyridine reagent; primary amides

Owing to the increasing demand for generic procedures in solution-phase chemistry and the broad range of commercial importance of nitriles, it has become desirable to devise an improved protocol for the dehydration of primary amides and aldoximes. Although this reaction has found endless applications in synthetic organic chemistry over the years, most procedures involve the use of stoichiometric or excess amounts of highly reactive reagents or harsh conditions and hence suffer from a lack of selectivity and generality.

The most commonly desired conditions should be milder, involve easier to handle reagents, and offer a better scope for functional group compatibility. Numerous examples can be found in the literature demonstrating the enormous changes in this methodology. Due to the remarkable synthetic properties of the nitrile group as an intermediate for the preparation of carboxylic acids, aldehydes, amides, amines and ketones, have undergone long-standing studies of their utilization in organic synthesis[1] and continue to receive attention from the chemists round the globe in search of new methodology. In recent years, the potential utility of nitriles was also demonstrated in the synthesis of thiazoles, 2-oxazolines, tetrazoles, imidazoles, triazoles and benzamidines possessing a broad spectrum of biological activities.[2] Several methods are available in the literature to prepare nitriles starting from aldehydes,[3] aldoximes,[4] primary amides,[5] primary amines[6] and also by nucleophilic substitution[7] with the cyano group. However, many of these methods are deficient in some respect or other. Some are expensive, require vigorous reaction conditions, others involve hazardous[8] (selenium dioxide) and corrosive[9] (formic acid) reagents, the work-up is tedious or perhaps, more importantly, the method is not generally applicable to alkyl, aryl and heterocyclic compounds. Hence, there is considerable interest in finding convenient, less toxic, more affordable, universally applicable reagents with potential selectivity towards other protecting groups.



Scheme 1.

Trimethylacetyl chloride (pivaloyl chloride) is a reagent for the selective protection of less hindered primary alcohols and also is able to activate heteroaromatic amines towards ring lithiation.[10] It has not been used for the synthesis of nitriles from aldoximes and primary amides so far. As part of our ongoing program on the synthesis and development of new methodologies in organic synthesis,[11] we report here an efficient protocol for the chemoselective transformation of primary amides and aldoximes into nitriles using pivaloyl chloride and pyridine in dichloromethane at room temperature to 50 °C that furnishes the products in excellent yields. Accordingly, treatment of 3,4,5-trimethoxybenzaldoxime (Table 1, entry 1) with pivaloyl chloride and pyridine afforded the corresponding 3,4,5-trimethoxybenzonitrile in 95% yield.

The dehydration is very clean and completed with in 3.0 h in dichloromethane at reflux temperature. In a similar manner various aliphatic and aromatic aldoximes underwent dehydration with pivaloyl chloride and pyridine to give the corresponding nitriles in high yield. The α,β-unsaturated oxime (entry 2) also smoothly converted to corresponding nitrile in 76% yield and the com-

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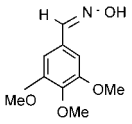
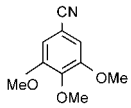
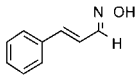
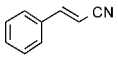
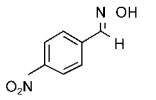
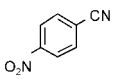
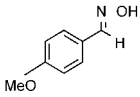
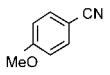
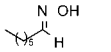
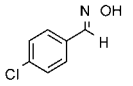
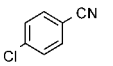
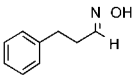
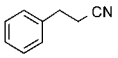
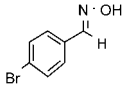
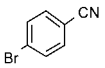
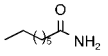
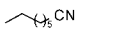
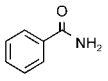
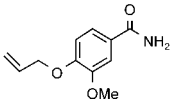
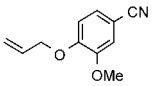
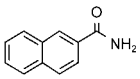
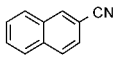
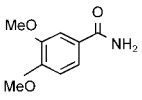
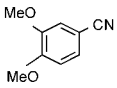
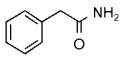
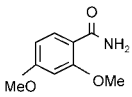
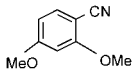
Table 1. Conversion of aldoximes to nitriles.

Entry	Substrate	Product[a]	Time [h]	Yield[b] [%]
1			3.0	95
2			5.0	76
3			5.0	88
4			4.0	85
5			5.5	78
6			4.0	88
7			5.0	78
8			4.0	82

[a] All products were characterised by comparison of their mp, IR and ^{1}H NMR data with those of the authentic samples.
[b] Yields of isolated products.

Table 2. Conversion of primary amides to nitriles.

Entry	Substrate	Product[a]	Time [h]	Yield[b] [%]
9			3.5	82
10			6.0	75
11			4.0	87
12			4.0	83
13			5.0	81
14			4.5	84
15			5.5	79
16			4.5	82

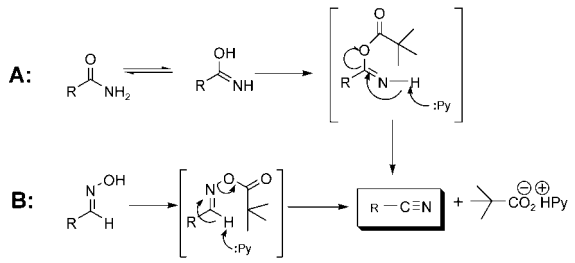
[a] All the products were characterised by comparison of their m.p. IR and ^{1}H NMR spectra with those of the authentic samples
[b] Yields of isolated products.

pounds having halogen substituents (entries 6 and 8) were converted to the corresponding nitriles in excellent yields. In all the cases reactions were completed 3 to 5.5 h and the yields were 76 to 95%.

In the same way, the treatment of benzamide (Table 2, entry 11) with pivaloyl chloride and pyridine, afforded the corresponding benzonitrile in 87% yield. The dehydration is very clean and completed within 4 h at room temperature. In a similar manner various aromatic, heteroaromatic and aliphatic primary amides underwent dehydration with pivaloly chloride and pyridine to give the corresponding nitriles in very good yields. The dehydration reaction with the heterocyclic system of 2-ethyl-4-pyridinamide (entry 9) proceeded smoothly, without forming any side products, within 3.5 h at room temperature in 82% yield, whereas, the aliphatic amide (entry 10) required a little more time and the yield was also somewhat lower (75%) but the substrate allyloxy and methoxy (entry 12) groups also undergone dehydration in excellent yield. In all cases the reaction proceeded smoothly at room temperature. The results are summarized in the Tables 1 and 2, respectively.

Compared to the other classical amide to nitrile methods, one advantageous feature of the present protocol is demonstrated with various different functional groups such as methoxy, allyloxy, halogens, and nitro; also aliphatic and heterocylic substrates participated in this reaction, affording excellent yields and high purities. Furthermore, in the case of 4-nitrobenzaldoxime (entry 3) the dehydration takes place with in 5 h, the yield is 88% and in the same way, 4-methoxybenzaldoxime (entry 4) yields the corresponding 4-methoxybenzonitrile in 85%. From this observation, it appears that electron-withdrawing or electron-donating groups do not affect significantly the rate of reaction.

Among the bases investigated for this conversion, pyridine was found to be more effective than triethylamine in terms of conversion and reaction time. Primary amides were converted at room temperature, but aldoximes require reflux temperature because the intermedi-



Scheme 2.

ate of pathway **B** is relatively stable. The formation of nitriles from aldoximes and primary amides can be explained by the mechanism shown in Scheme 2.

In summary, we have demonstrated an efficient method for the conversion of primary amides and aldoximes to nitriles. The mild method offers several advantages over existing methods in terms of enhanced reaction rates, high yields, easily handled reagent system, ambient temperature, cleaner products and wide applicability for heterocyclic, aromatic as well as aliphatic compounds.

Experimental Section

General

Melting points are uncorrected. TLC was performed using precoated silica gel 60 F_{254} (0.25 mm) glass plates. Chromatography was performed using silica gel (60–120 mesh). IR spectra were recorded neat and in KBr on a refractive spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz. Chemical shifts are given in ppm with respect to internal TMS, and J values are quoted in Hz. Mass spectra were recorded 70 eV.

General Procedure for Dehydration of Aldoximes

To a stirred mixture of the aldoxime (5 mmol) and pivaloyl chloride (5.5 mmol) in dichloromethane (10 mL) was added pyridine (6 mmol) slowly and the reaction mixture was heated at reflux for the specified time (Table 1). Then, the reaction mixture was diluted with dichloromethane and washed with water (3×25 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield the crude product, which was purified by chromatography, eluting with a 9:1 hexane-ethyl acetate mixture.

General Procedure for Dehydration of Amides

To a stirred mixture of the primary amide (5 mmol) and pivaloyl chloride (5.5 mmol) in dichloromethane (10 mL) was added pyridine (6 mmol) at room temperature and stirring was continued for 3–6 h. After complete conversion as indicated by TLC, the reaction mixture was diluted with dichloromethane and washed with water (3×25 mL). The organic layer was dried over Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography, using 60–120 mesh silica gel and eluting with a 9:1 hexane-ethyl acetate.

3,4,5-Trimethoxybenzonitrile (entry 1):[4g] Light coloured solid, mp 92–94 °C; IR (KBr): ν = 3068, 2934, 2823, 2238, 1605, 1550, 1456, 1130, 876 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3H), 3.90 (s, 6H), 6.90 (s, 2H); EIMS: *m/z* (%) = 193 (M^+, 100), 178, (62), 150 (46), 132 (24), 106 (12), 74 (27), 49 (19).

Cinnamonitrile (entry 2):[3e] Colourless liquid; IR (neat): ν = 3085, 2963, 2846, 2235, 1606, 1588, 1434, 1269, 1035, 864, 766 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 5.83 (d, 1H, J = 17.5 Hz), 5.91 (d, 1H, J = 17.5 Hz), 7.32–7.63 (m, 5H); EIMS: *m/z* (%) = 129 (M^+, 18), 103 (34), 77 (100), 51 (43).

4-Nitrobenzonitrile (entry 3):[3e] Colourless solid, mp 147–149 °C; IR (KBr): ν = 3092, 2964, 2846, 2234, 1593, 1542, 1400, 1336, 1084, 782 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.37 (d, 2H, J = 8.5 Hz), 7.89 (d, 2H, J = 8.5 Hz): EIMS: *m/z* (%) = 148 (M^+, 69), 102 (100) 75 (32), 48 (23).

4-Methoxybenzonitrile (entry 4):[3e] Colourless solid; mp 56–57 °C, IR (KBr): ν = 3089, 2967, 2834, 2218, 1596, 1422, 1306, 1285, 974 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.66 (d, 2H, J = 8.5 Hz), 6.97 (d, 2H, J = 8.5 Hz), 3.87 (S, 3H); EIMS: *m/z* (%) = 133 (M^+, 100), 102 (42), 75 (26), 50 (18).

Octanenitrile (entry 5):[5c] Syrup; IR (KBr): ν = 2233, 1452, 1366, 1238, 1059, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.36 (t, J = 7.0 Hz, 2H), 1.76–1.57 (2H, m,), 1.43–1.12 (8H, m) 0.94 (t, 3H, J = 7.0 Hz); EIMS: *m/z* (%) = 125 (M^+, 25), 79 (6), 51 (4).

4-Chlorobenzonitrile (entry 6):[4g] Solid; mp 92–93 °C; IR (KBr): ν = 3093, 2964, 2839, 2235, 1632, 1560, 1465, 1305, 1056, 865, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.56 (d, 2H, J = 6.0, Hz), 7.62 (d, 2H, J = 6.0 Hz); EIMS: *m/z* (%) = 139 (M^+ + 2, 81), 137 (100), 102 (32), 77 (21) 51 (28).

Phenylpropionitrile (entry 7):[4f] Liquid; IR (neat): ν = 3096, 2974, 2832, 2230, 1588, 1493, 1336, 1184, 1053, 935, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.13 (br s, 5H), 2.85 (t, 2H, J = 7.5 Hz), 2.53 (t, 2H, J = 7.5 Hz); EIMS: *m/z* (%) = 131 (M^+, 11), 105 (62), 77 (100), 51 (32).

4-Bromobenzonitrile (entry 8):[4g] Colourless solid, mp 110–112 °C, IR (KBr): n = 3100–2850, 2240, 1590, 1450, 1260, 1040, 830, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.60 (dd, 4H, J = 4.0 Hz, J = 1.5 Hz); EIMS: *m/z* (%) = 182 (M^+, 17), 102 (48), 76 (100), 50 (29).

2-Ethyl-4-cyanopyridine (entry 9):[5a] Liquid: IR (neat): ν = 3096, 2968, 2837, 2234, 1608, 1559, 1405, 1400,1126, 1034, 868, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 3H, J = 8.5 Hz), 2.90 (q, 2H, J = 8.5 Hz), 7.30 (s, 1H), 7.65 (d, 1H, J = 6.0 Hz), 8.66 (d, 1H, J = 6.0 Hz); EIMS: *m/z* (%) = 132 (M^+, 24), 106 (59), 80 (19), 66 (100), 41 (32).

Benzonitrile (entry 11):[4f] Liquid; IR (neat): ν = 3069, 2934, 2860, 2238, 1610, 1585, 1430, 1286, 1065, 976, 834, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.62–7,80 (m, 3H), 7.40–7.50 (d, 2H, J = 8.5 Hz, 2H); EIMS: *m/z* (%) = 103 (M^+, 36), 77 (100), 51 (48).

3-Methoxy-4-allyloxybenzonitrile (entry 12):[5a] Solid; mp 59–60 °C; IR (KBr): ν = 3069, 2938, 2842, 2239, 1608, 1552, 1461, 1220, 864, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 3.88 (s, 3H), 4.65 (dd, J = 5.4, 1.2 Hz, 2H), 5.33 (m, 1H), 5.42 (m, 1H,), 6.05 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.3 (dd, J = 8.4, 2.0 Hz, 1H); EIMS; *m/z* (%) = 189 (M^+, 28), 148 (43), 133 (69), 117 (83), 91 (10), 75 (29), 49 (11).

Naphthalene-2-carbonitrile (entry 13):[3e] Solid; mp 66–68 °C, IR (KBr): ν = 3086, 2961, 2842, 2230, 1604, 1558, 1383, 1027, 834 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.26 (s, 1H) 7.9 (m, 3H), 7.64 (m, 3H); EIMS: *m/z* (%) = 153 (M^+, 41), 127 (69), 101 (22), 76 (100), 53 (32).

3,4-Dimethoxybenzonitrile (entry 14):[3g] Colourless solid; mp 66–68 °C; IR (KBr): n = 3092, 2968, 2835, 2238, 1596, 1437, 1254, 987, 673 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.8 (s, 3H), 3.9 (s, 3H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.1 (s,1H), 7.25 (d, *J* = 8.0 Hz, 1H); EIMS; *m/z* (%) = 163 (M^+, 46), 101 (100), 75 (38), 49 (23).

Phenylacetonitrile (entry 15):[4c] Liquid; IR (neat): ν = 3089, 2958, 2839, 2225, 1600, 1558, 1436, 1265, 968 cm^{-1}; ^1H NMR ($CDCl_3$): d = 7.35 (brs, 5H) 3.74 (s, 2H); EIMS: *m/z* (%) = 117 (M^+, 34), 91 (27), 77 (100), 51 (49).

2,4-Dimethoxybenzonitrile (entry 16):[5a] Colourless solid; mp 93–94 °C, IR (KBr): ν = 3098, 2956, 2832, 2238, 1596, 1468, 1310, 1266, 1049, 834, 675 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.42 (d, 1H, *J* = 8.5 Hz), 6.40–6.50 (m, 2H), 3.92 (s,3H), 3.80 (s,3H); EIMS: *m/z* (%) = 163 (M^+, 40), 133 (100), 107 (52), 76 (34), 43 (25).

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References and Notes

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