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A Chemoselective, One-Pot Transformation of Aldehydes to Nitriles

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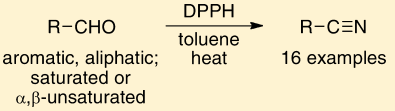
Supporting Information

ABSTRACT: This paper describes a procedure for direct conversion of aldehydes to nitriles using *O*-(diphenylphosphinyl)hydroxylamine (DPPH). Aldehydes are smoothly transformed to their corresponding nitriles by heating with DPPH in toluene. The reaction can be accomplished in the presence of alcohol, ketone, ester, or amine functionality.



The preparation of nitriles by transformation of carbon-equivalent functional groups is an important synthetic route to these versatile intermediates and valued target pharmacophores.[1] Among the most popular approaches is the oxidation-state neutral conversion of carboxylic acids to nitriles via dehydration of intermediate primary amides (Figure 1) either

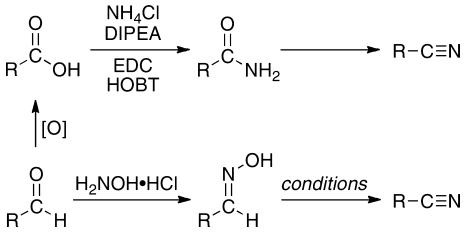


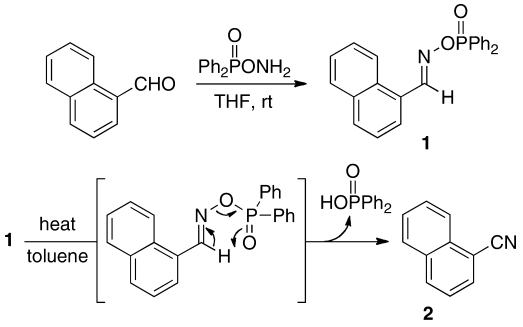
Figure 1. Common functional group interconversions to prepare nitriles.

using traditional dehydrating reagents[2] or recently developed metal-mediated procedures.[3] An efficient complement to amide dehydration is the oxidative transformation of aldehydes to nitriles. Isolation of aldoxime intermediates (Figure 1) generally is followed by activation of the oxime hydroxyl group (e.g., as a sulfonate ester derivative) and then its elimination to afford the nitrile.[4] The appeal of this approach has led to several one-pot methods for direct synthesis of nitriles from aldehydes using either hydroxylamine or ammonia in combination with a variety of activating reagents.[5]

Unfortunately, the accompanying reagents for these one-pot approaches, such as $CuCl_2/NaOMe/O_2$,[5a] $Pb(OAc)_4$,[5b] Oxone,[5e] H_2O_2,[5h] I_2,[5i] NBS,[5j] IBX,[5k] and $NaICl_2$,[5l] often are not tolerant of other functional groups or require somewhat harsh conditions to effect the transformation. Ideally, an aldehyde-selective reagent that would facilitate the conversion to the nitrile under neutral conditions would greatly expand the utility of this direct approach. We report here the use of *O*-(diphenylphosphinyl)hydroxylamine (DPPH) as such a reagent.

Our interest in aminooxy chemistry[6] led us to consider the use of DPPH ($Ph_2P(O)ONH_2$) as a possible chemoselective alternative to hydroxylamine or ammonia for introduction of nitrogen onto the carbonyl carbon of aldehydes. Since the reaction of this reagent with an aldehyde would directly form an activated oxime ester as an intermediate (e.g., **1**, Scheme 1), we reasoned that it should be possible to thermally induce an

Scheme 1



electrocyclic rearrangement resulting in the elimination of diphenylphosphinic acid. A similar mechanism involving elimination of methanesulfonic acid has been proposed for formation of nitriles from intermediate sulfonylated aldoximes.[7] Although DPPH is well appreciated as an electrophilic reagent for the amination of a variety of nucleophiles,[8] including Grignard reagents,[9] enols,[10] or for amination of tertiary amines in syntheses of aziridines from α,β-unsaturated carbonyl substrates,[11] its use as a nucleophilic counterpart, especially in chemoselective "click" transformations, has received limited attention.[12] To test the action of DPPH as a suitable reagent for oxime ester formation as well as the subsequent elimination to the nitrile, we examined the reaction between DPPH and α-naphthaldehyde (Scheme 1).

While presently not commercially available, DPPH can be readily prepared in good yield in one step from commercially available diphenylphosphinic chloride and hydroxylamine hydrochloride.[13] Reaction of DPPH with naphthaldehyde in THF gave oxime ester **1** in 79% yield. Subsequent heating in toluene revealed that the elimination of diphenylphosphinic acid from **1** required warming to above 80 °C to achieve a significant rate of formation of naphthonitrile (**2**). Of particular note is that no

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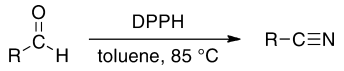
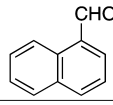
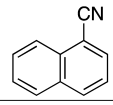
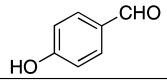
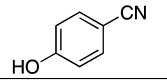
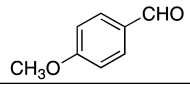
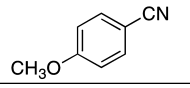
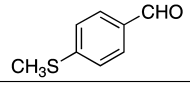
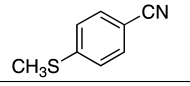
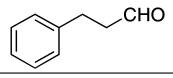
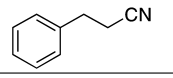
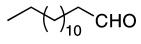
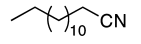
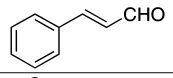
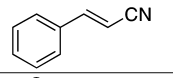
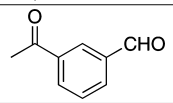
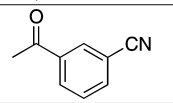
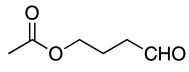
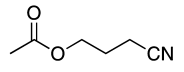
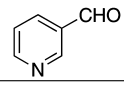
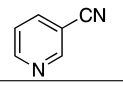
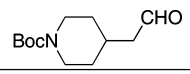
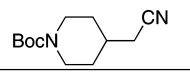
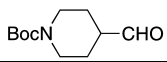
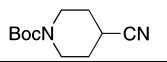
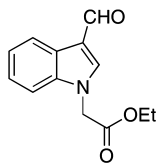
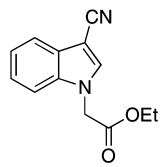
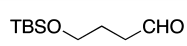
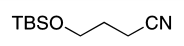
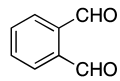
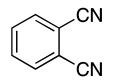
Table 1. Conversion of Aldehydes to Nitriles Using $Ph_2P(O)ONH_2$[a]



entry	starting aldehyde	method	major product	yield (%)[b]
1	Ph-CHO	A	Ph-CN	82
2		A		80
3		A B		69 78
4		A B		90 87
5		A B		37 58
6		A		80
7		A		96
8		A		81
9		A		75
10		A		85
11		A C		55 64
12		A		92
13		A		90
14		A B C		40 39 44
15		A		57
16		A		78

[a]All reactions were performed in toluene at 85 °C for 4−6 h on ≥0.5 mmol scale using 1.15 equiv of reagent (method A), 2.0 equiv of reagent at 95 °C for 12 h (method B), or 1.15 equiv of reagent and 1.1 equiv of trifluoroacetic acid at 95 °C for 12 h (method C). [b]Chromatographed (SiO_2) yield. Boc = *tert*-butyloxycarbonyl; TBS = *tert*-butyldimethylsilyl.

Lewis acid or base was required to effect the elimination, rather simple warming under catalyst- and oxidant-free conditions was sufficient to afford **2** in 88% yield.

We next examined the possibility of transforming aldehydes directly into nitriles without isolation of the oxime ester adducts. Despite the partial solubility of DPPH in toluene, we were pleased to find that its reactions with a diverse panel of aldehydes in toluene gave good yields of the corresponding nitriles on heating at 85 °C (Table 1). The conversions to the nitriles proceeded smoothly for aromatic as well as aliphatic aldehydes

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and accommodated α,β-unsaturation. Importantly, the aminooxy group of DPPH afforded a measure of chemoselectivity that enabled the selective, one-pot transformation of aldehydes to nitriles in the presence of other carbonyl groups, such as ketone, ester (including acetate), and carbamate carbonyls. While in some cases the transformation of electron-rich aldehydes required an additional equivalent of reagent for better overall conversion (entries 3 and 5), the vinylogous formamide carbonyl of entry 14 was only sluggishly transformed into the corresponding nitrile even when using excess reagent. Given that diphenylphosphinic acid (pK_a 2.32)[14] is produced during the course of the reaction, we examined the aldehyde to nitrile conversion in the presence of acid-sensitive *N*-Boc and silyl ether protection groups. Whereas the Boc group was not affected (entries 12 and 13), the TBS ether was cleaved during the reaction (entry 15). In the entry 15 example, the initially formed desilylated product, 4-hydroxybutyronitrile (isolated in 13% yield), partially cyclized under the reaction conditions to generate γ-butyrolactone (ca. 10% yield) after workup. Attempts to buffer the reaction by addition of non-nucleophilic bases (e.g., Na_2CO_3) did not prevent loss of the silyl group. Since DPPH readily reacts with amines,[8b−d,11] we noted that an acidification strategy, as in the case of 3-pyridinecarboxaldehyde (entry 11), improved the overall conversion to the nitrile, presumably by in situ pyridinium formation preventing electrophilic amination of the pyridine nitrogen. Finally, as a probe to see whether the process could be adapted to polar protic, more green solvents, we examined the reaction of 3-phenylpropionaldehyde with DPPH in water and found that heating at 95 °C for 12 h afforded the corresponding nitrile in 73% yield. In addition, heating 3-pyridinecarboxaldehyde and DPPH in acetic acid as solvent under similar conditions gave 3-pyridinecarbonitrile in 60% yield.

In conclusion, the present method is applicable for the one-pot conversion of aldehydes to nitriles in the presence of water, alcohols, and other carbonyl functionalities. DPPH is sufficiently selective in its reactions with aldehyde carbonyl groups that chemoselection is achieved on simple mixing at room temperature followed by warming to effect the transformation to the nitrile. Ease of reaction, good yields, and the absence of base or oxidant are other features of this method.

EXPERIMENTAL SECTION

Typical Procedures for One-Pot Aldehyde to Nitrile Transformation: Preparation of *trans*-Cinnamonitrile (Entry 8, Method A). To *trans*-cinnamaldehyde (0.13 g, 1.0 mmol) in toluene (5 mL) at room temperature was added DPPH (0.267 g, 1.15 mmol) in one portion. The resulting suspension was stirred at room temperature for 3 h and then gradually warmed over 45 min to 85 °C. The reaction mixture became clear as the temperature reached 80 °C. After being heated at 85 °C for 5 h, the reaction was allowed to cool to room temperature and then diluted by addition of Et_2O (20 mL) and satd aq $NaHCO_3$ to dissolve precipitated diphenylphosphinic acid. The layers were separated, and the organic layer was washed successively with saturated aq $NaHCO_3$ and brine (2 × 10 mL). The aqueous layer was extracted with EtOAc (2×). All of the organic layers were combined and then dried (Na_2SO_4). The solvents were removed by rotary evaporation, and the crude residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 2:1 v/v, R_f = 0.62) to afford *trans*-cinnamonitrile (105 mg, 81%) as a light yellow oil with spectroscopic data in agreement with published[15] values: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.38 (m, 6 H), 5.90 (d, J = 16.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 133.5, 131.2, 129.1, 127.33, 118.11, 96.3.

Preparation of 4-Hydroxybenzonitrile (Entry 3, Method B). To 4-hydroxybenzaldehyde (0.09 g, 0.78 mmol) in toluene (5 mL) at room temperature was added DPPH (0.366 g, 1.57 mmol) in one portion. The resulting suspension was stirred at room temperature for 3 h and then gradually warmed over 45 min to 95 °C. After heating at 95 °C for 12 h, the reaction was allowed to cool to room temperature and then diluted by addition of EtOAc (20 mL) and saturated aq $NaHCO_3$ to dissolve the precipitated diphenylphosphinic acid. The layers were separated, and the organic layer was washed successively with saturated aq $NaHCO_3$ and brine (2 × 10 mL). The aqueous layer was extracted with EtOAc (2×). The combined organic layer was dried (Na_2SO_4). The solvents were removed by rotary evaporation, and the crude residue was purified by column chromatography (SiO_2), eluting with hexane/ethyl acetate (2:1, v/v; R_f = 0.33) to afford 4-hydroxybenzonitrile (72 mg, 78% yield) as a yellow solid: mp 111−113 °C, having spectral characteristics in agreement with published data;[16] ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.55 (d, J = 8.4 Hz, 2 H), 6.91 (d, J = 8.4 Hz, 2 H), 5.78 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 134.3, 119.2, 116.4, 103.3.

Preparation of 3-Pyridinecarbonitrile (Entry 11, Method C). To 3-pyridinecarboxaldehyde (0.10 g, 0.93 mmol) in toluene (5 mL) at room temperature was added trifluoroacetic acid (72 μL, 1 mmol). After the mixture was stirred for 5 min, DPPH (0.250 g, 1.07 mmol) was added in one portion. The resulting suspension was stirred at room temperature for 3 h and then gradually warmed over 45 min to 95 °C. After heating at 95 °C for 12 h, the reaction was allowed to cool to room temperature and then diluted by addition of EtOAc (15 mL) and saturated aq $NaHCO_3$ to dissolve the precipitated diphenylphosphinic acid. The layers were separated, and the organic layer was washed successively with saturated aq $NaHCO_3$ and brine (2 × 10 mL). The aqueous layer was extracted with EtOAc (2×) and DCM (2×). The combined organic layer was dried (Na_2SO_4). The solvents were removed by rotary evaporation, and the crude residue was purified by column chromatography (SiO_2), eluting with CH_2Cl_2/hexane/ethyl acetate (7:2:1, v/v; R_f = 0.34) to afford 3-pyridinecarbonitrile (60 mg, 64% yield) as a white solid, mp 49.1−50.2 °C, having spectral characteristics in agreement with published data:[17] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (s, 1 H), 8.83 (d, J = 4.8 Hz, 1 H), 7.98 (d, J = 8 Hz, 1 H), 7.45 (dd, J = 4.8, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2, 152.7, 139.4, 123.7, 116.7, 110.3.

Polar Solvent Procedure: Preparation of 3-Phenylpropionitrile. To 3-phenylpropionaldehyde (0.70 g, 0.52 mmol) in water (8 mL) at room temperature was added DPPH (0.14 g, 0.60 mmol) in one portion. The resulting suspension was stirred at room temperature for 3 h and then gradually warmed over 45 min to 95 °C. After heating at 95 °C for 12 h, the reaction was cooled to room temperature and extracted with EtOAc (2 × 10 mL) and Et_2O (10 mL). The combined organic layer was washed with brine (10 mL) and then dried (Na_2SO_4). The solvents were removed by rotary evaporation, and the crude residue was purified by column chromatography (SiO_2), eluting with hexane/ethyl acetate (2:1, v/v; R_f = 0.55) to afford 3-phenylpropionitrile (50 mg, 73% yield) as a yellow oil, having spectral characteristics in agreement with published data:[18] ^{1}H NMR (400 MHz) δ 7.34 (t, J = 7.2 Hz, 2 H), 7.27 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 7.2 Hz, 3 H), 2.96 (t, J = 7.6 Hz, 2 H), 2.61 (t, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz) δ 138.2, 129.0, 128.5, 127.4, 119.3, 31.7, 19.5.

Ethyl 2-(3-cyano-1*H*-indol-1-yl)acetate (entry 14): light yellow solid; mp 96.5−98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, J = 7.6 Hz, 1 H), 7.62 (s, 1 H), 7.34−7.30 (m, 3 H), 4.87 (s, 1 H), 4.25 (q, J = 7.2 Hz, 2 H), 4.25 (q, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 135.9, 135.6, 127.8, 124.5, 122.7, 120.3, 115.6, 110.2, 87.5, 62.5, 48.3, 14.2; IR (cm^{-1}) 2223, 1740; FT-ICR-MS (ESI$^+$, m/z) calcd for $C_{13}H_{12}N_2O_2$, $[M + Na]^+$ 251.0791, found 251.0791.

1-Naphthaldehyde *O*-diphenylphosphoryl oxime (1): gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (s, 1 H), 8.34 (d, J = 8.8 Hz, 1 H), 8.00−7.95 (m, 4 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.84 (d, J = 7.6 Hz, 1 H), 7.71 (d, J = 7.2 Hz, 1 H), 7.59−7.43 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 158.0, 133.8, 132.6, 132.4, 132.3, 131.1, 130.6, 129.9, 129.8, 128.8, 128.7, 228.6, 127.8, 126.5, 126.3, 125.2, 125.0; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 35.60; FT-ICR-MS (ESI$^+$, m/z) calcd for $C_{23}H_{18}NO_2P$, $[M + Na]^+$ 394.0967, found 394.0976.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all nitrile products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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