One-Pot Oxidative Conversion of Alcohols into Nitriles by Using a TEMPO/PhI(OAc)$_2$/NH$_4$OAc System

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Dedicated to the memory of Professor Serge David

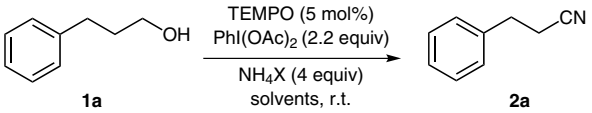
Abstract: A direct conversion of alcohols into nitriles with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), iodosobenzene diacetate, and ammonium acetate as a nitrogen source is reported. This transformation, which proceeds through an oxidation–imination–aldimine oxidation sequence in situ, has been applied to a range of aliphatic, benzylic, heteroaromatic, allylic, and propargyl alcohols. Highly chemoselective ammoxidation of primary alcohols in the presence of secondary alcohols was also achieved.

Key words: alcohols, chemoselectivity, nitriles, oxidation, TEMPO

The nitrile group plays a crucial role in organic synthesis because it can be easily transformed into a variety of important functional groups such as acids, amides, ketones, oximes, and nitrogen-containing heterocycles such as tetrazoles and oxazoles.[1] Furthermore, nitriles are versatile building blocks in the synthesis of agricultural and pharmaceutical chemicals and functional materials.[1a,2] Nitriles are also present in a number of leading pharmaceuticals.[3] Numerous methods have been developed for nitrile production. Classically, nitriles are synthesized through nucleophilic substitution of various leaving groups such as halogen, hydroxy, alkoxy, diazonium, and sulfonate functionalities, typically with toxic inorganic cyanides.[1a] Alternative procedures include the dehydration of amides[4] and aldoximes,[5] the oxidation of amines,[6] and ammoxidation of aldehydes.[7] An attractive approach to the synthesis of nitriles is the direct oxidation from alcohols, which are cheap and commercially available starting materials, and a nitrogen source. In this regard, a number of protocols have been reported that use oxidizing systems such as Ni^{2+} (cat.)/$S_2O_8^{2-}$/OH$^-$,[8a,c] MnO_2/$MgSO_4$,[8b] 1,3-diiodo-5,5-dimethylhydantoin or I_2,[8d] KI or I_2/TBHP,[6e] Ru(OH)$_x$/Al_2O_3/air,[8e,f] trichloroisocyanuric acid,[8g] $NaIO_4$/KI,[8h] H_5IO_6/KI,[8i] copper salts/TEMPO/O_2,[8j–l] I_2 or *t*-BuOCl/TEMPO,[8m] together with ammonia as a nitrogen source. Ammonium salts have been used with success as a nitrogen source in the transformation of alcohols into nitriles using oxidants such as I_2,[9a] PhI(OH)OTs/TEMPO,[6g] $CuCl_2$/air,[9b] $(Bu_4N)_2S_2O_8$/Cu(HCO$_2$)$_2$·Ni(HCO$_2$)$_2$/KOH.[8c]

In a continuation of our interest in the development of novel synthetic applications of TEMPO/co-oxidants,[10] we envisaged that TEMPO in combination with inexpensive, commercially available PhI(OAc)$_2$, which is an efficient oxidant of aldimines to nitriles,[7h] and ammonium salts could be a good alternative process for the oxidative conversion of alcohols into nitriles. For our initial optimization studies, 3-phenyl-1-propanol was chosen as a model substrate (Table 1). In a MeCN–H_2O mixture, in the presence of TEMPO (5 mol%), an excess of ammonium acetate (4 equiv), and (diacetoxyiodo)benzene (2.2 equiv), alcohol **1a** was rapidly converted at room temperature into nitrile **2a** in excellent yield (entry 1). In a biphasic system (CH_2Cl_2–H_2O, 9:1) the oxidation was slower but still gave rise to the desired compound in good yield (entry 2). Other ammonium salts were also tested and were found to be less effective than ammonium acetate (entries 3 and 4).

Table 1 Optimization of the Reaction Conditions for the Conversion of Alcohol **1a** into Nitrile **2a**



1a **2a**

Entry	Solvent	NH_4X	Time (h)	Yield (%)[a]
1	MeCN–H_2O (9:1)	NH_4OAc	0.75	89
2	CH_2Cl_2/H_2O (9:1)	NH_4OAc	2.5	90
3	MeCN–H_2O (9:1)	NH_4HCO_3	1	84
4	MeCN–H_2O (9:1)	NH_4HCO_2	24	–[b]

[a] Isolated yield.
[b] Starting material was recovered (88%).

Under the optimized reaction conditions, we examined the general applicability of this method to a range of structurally diverse primary alcohols (Table 2).[11,12] First, the reactivity was found to depend on the nature of alcohol used. In contrast to observations with the PhI(OH)OTs/TEMPO/NH_4OAc system,[6g] aliphatic alcohols reacted more readily than benzylic alcohols. Regardless of steric hindrance, aliphatic alcohols afforded the corresponding nitriles in excellent yields (entries 1–7). Substrates containing acid-sensitive protective groups such as trityl,

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t-butyldimethysilyl, Boc and acetals were well tolerated in the reaction media (entries 4–7 and 9).

In the case of optically active substrates, no racemization was observed (Table 2, entries 6 and 7). The transformation of benzyl alcohols containing electron-donating groups as well as electron-withdrawing groups proceeded efficiently to afford the corresponding nitriles in high yields (entries 8–12). It is noteworthy that 2-iodobenzyl alcohol **1k**, bearing a bulky substituent in the *ortho* position, was found to react rapidly to afford the desired 2-iodobenzonitrile **2k** in 82% yield (entry 11). Heteroaromatic alcohols **1m**–**n** were successfully oxidized in good yields but at a different rate; pyridine-3-methanol **1m** reacted much more rapidly than thiophene derivative **1n** (entries 13 and 14). Diol **1o** was converted into 1,4-benzenedicarbonitrile **2o** in excellent yield (entry 15). Ammoxidation of allylic alcohols **1p**–**r** occurred without any isomerization of the double bond (entries 16–18). Transformation of propargyl alcohol **1s** proceeded readily (30 min) to afford the corresponding nitrile **2s** in 93% yield (entry 19).

Table 2 Oxidative Conversion of Alcohols into Nitriles with TEMPO (cat.)/$PhI(OAc)_2$/NH_4OAc in MeCN–H_2O (9:1)

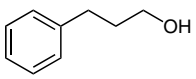
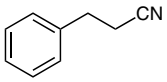
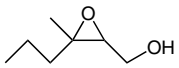
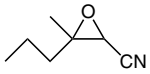
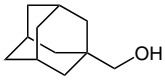
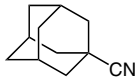
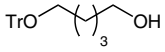
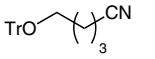
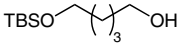
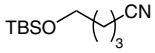
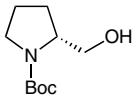
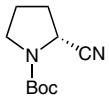
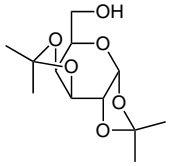
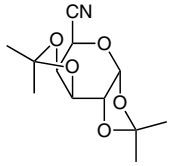
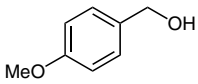
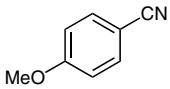
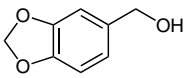
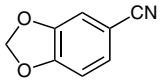
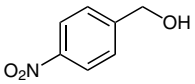
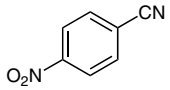
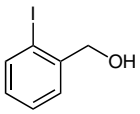
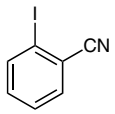
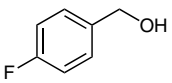
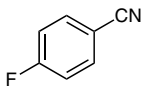
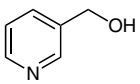
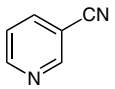
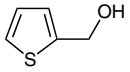
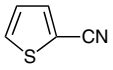
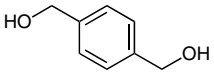
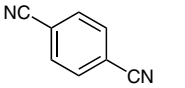
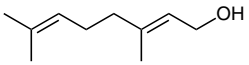
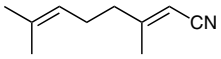
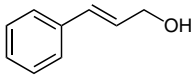
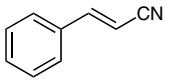
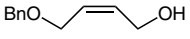
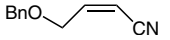
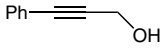
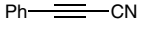
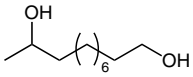
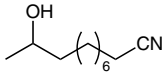
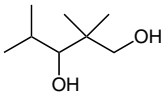
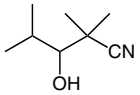
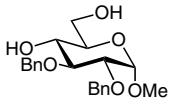
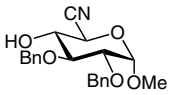
Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	**1a** 	0.75	**2a** 	89
2	**1b** 	1	**2b** 	81
3	**1c** 	2	**2c** 	88
4	**1d** 	1	**2d** 	92
5	**1e** 	0.75	**2e** 	93
6	**1f** 	1.5	**2f** 	91
7	**1g** 	0.75	**2g** 	85
8	**1h** 	8	**2h** 	85
9	**1i** 	10	**2i** 	93
10	**1j** 	10	**2j** 	90
11	**1k** 	4	**2k** 	82
12	**1l** 	5	**2l** 	87
13	**1m** 	0.75	**2m** 	80

Table 2 Oxidative Conversion of Alcohols into Nitriles with TEMPO (cat.)/PhI(OAc)$_2$/NH$_4$OAc in MeCN–H$_2$O (9:1) (continued)

Entry	Substrate	Time (h)	Product	Yield (%)[a]
14	**1n** 	9	**2n** 	84
15	**1o** 	2	**2o** 	91[b]
16	**1p** 	2	**2p** 	87
17	**1q** 	3	**2q** 	91
18	**1r** 	0.5	**2r** 	92
19	**1s** 	0.5	**2s** 	93
20	**1t** 	1	**2t** 	84[c]
21	**1u** 	8	**2u** 	87[d]
22	**1v** 	1	**2v** 	77

[a] Isolated yield.
[b] For this substrate, a mixture of PhI(OAc)$_2$ (4.4 equiv), TEMPO (0.1 equiv) and NH$_4$OAc (8 equiv) was used.
[c] Ketonitrile **2t′** was also obtained (8%).
[d] For this substrate, a mixture of PhI(OAc)$_2$ (3 equiv), TEMPO (0.1 equiv) and NH$_4$OAc (6 equiv) was used.

We then turned our attention to the ammoxidation of primary alcohols in the presence of secondary alcohols (entries 20–22). In the three cases studied, cyanoalcohols **2t**–**v** were obtained in good to excellent yields. In one case, a small amount of cyano ketone was observed (8%; entry 20).

In summary, we have reported a general, high-yielding, practical, and chemoselective protocol for the one-pot synthesis of nitriles, under mild conditions and using inexpensive commercially available starting materials and reagents: alcohols, TEMPO, PhI(OAc)$_2$, and NH$_4$OAc. Functionalized aliphatic, benzyl, allylic, and propargyl alcohols are well suited for this method. Furthermore, this procedure has advantages over a closely related method using TEMPO and Koser's reagent [PhI(OH)OTs] in that it involves an inexpensive hypervalent iodine derivative and milder reaction conditions such as room temperature reactions versus 80 °C, and no formation of strong acid by-product (*p*-TsOH).[6g]

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(11) All known compounds have physical data in accordance with those described in the literature.

(12) **Oxidative Conversion of Alcohols into Nitriles; General Procedure:** To a solution of alcohol (1 mmol) in MeCN–H_2O (9:1, 3 mL) were successively added TEMPO (7.8 mg, 5 mol%), NH_4OAc (0.308 g, 4 equiv), and $PhI(OAc)_2$ (0.708 g, 2.2 equiv). The suspension was stirred at room temperature (progress of the reaction was monitored by TLC) for the reaction time indicated in Table 2. The resultant clear two-phase reaction mixture was concentrated, diluted with H_2O and Et_2O, and the organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (PE–Et_2O or PE–CH_2Cl_2) to give **2**.

(Trityloxy)pentanenitrile (2d):
Eluent: PE–Et_2O (95:5). Yield: 92%; solid; mp 72–74 °C (hexane). ^{1}H NMR (300 MHz, C_6D_6): δ = 7.56–7.46 (m, 6 H), 7.22–7.11 (m, 6 H), 7.11–7.02 (m, 3 H), 2.92 (t, *J* = 6.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 2 H), 1.37–1.28 (m, 2 H), 1.17–1.06 (m, 2 H). ^{13}C NMR (75 MHz, C_6D_6): δ = 144.7 (3C), 129.0 (6C), 128.1 (6C), 127.3 (3C), 119.3, 86.9, 62.6, 29.0, 22.6, 16.5. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{23}NNaO$: 364.1672; found: 364.1663.

5-[(*tert*-Butyldimethylsilyl)oxy]pentanenitrile (2e):
Eluent: PE–Et_2O (9:1); Yield: 97%; liquid. ^{1}H NMR (300 MHz, C_6D_6): δ = 3.27 (t, *J* = 5.7 Hz, 2 H), 1.54 (t, *J* = 6.7 Hz, 2 H), 1.32–1.06 (m, 4 H), 0.91 (m, 9 H), –0.02 (m, 6 H). ^{13}C NMR (75 MHz, C_6D_6): δ = 119.4, 62.0, 31.6, 26.1 (3 C), 22.4, 18.4, 16.5, –5.3 (2 C). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{23}NNaOSi$: 236.1441; found: 236.1435.

(*Z*)-4-(Benzyloxy)but-2-enenitrile (2r):
Eluent: PE–Et_2O (4:1). Yield: 92%; liquid. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.22–7.02 (m, 5 H), 5.82 (dt, *J* = 11.3, 6.0 Hz, 1 H), 4.56 (dt, *J* = 11.3, 1.8 Hz, 1 H), 4.10 (s, 2 H), 3.86 (dd, *J* = 6.0, 1.8 Hz, 2 H). ^{13}C NMR (75 MHz, C_6D_6): δ = 150.2, 138.1, 128.6 (2 C), 128.0, 127.97 (2 C), 115.3, 100.3, 72.9, 68.2. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{11}NNaO$: 196.0733; found: 196.0731.

10-Hydroxyundecanenitrile (2t):
Eluent: PE–Et_2O (1:2). Yield: 84%; liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79–3.64 (m, 1 H), 2.28 (t, *J* = 7.1 Hz, 2 H), 2.11 (s, 1 H), 1.64–1.53 (m, 2 H), 1.45–1.18 (m, 12 H), 1.12 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.7, 67.7, 39.0, 29.2, 29.0, 28.44, 28.38, 25.45, 25.1, 23.2, 16.9. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{21}NNaO$: 206.1515; found: 206.1510.

10-Oxoundecanenitrile (2t′):
Eluent: PE–Et_2O (1:2). Yield 8%; liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (t, *J* = 7.4 Hz, 2 H), 2.36–2.28 (m, 2 H), 2.12 (s, 3 H), 1.73–1.12 (m, 12 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.1, 119.75, 43.6, 29.8, 29.0, 28.9, 28.5 (2 C), 25.3, 23.6, 17.05. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}NNaO$: 204.1359; found: 204.1355.

3-Hydroxy-2,2,4-trimethylpentanenitrile (2u):
Eluent: PE–Et_2O (1.5:1). Yield: 87%; oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20 (d, *J* = 3.2 Hz, 1 H), 2.44 (s, 1 H), 2.04–1.9 (m, 1 H), 1.39 (s, 3 H), 1.30 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.3, 79.9, 37.0, 29.9, 24.7, 23.7, 21.6, 15.4. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{15}NNaO$: 164.1046; found: 164.1039.

Methyl 2,3-Di-*O*-benzyl-α-D-glucopyranosiduronitrile (2v):
Eluent: PE–Et_2O (2:1). Yield: 77%; glass; $[\alpha]_D^{20}$ +76.4 (*c* 1.3, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 10 H), 4.93 (d, *J* = 11.3 Hz, 1 H), 4.79 (d, *J* = 7.7 Hz, 1 H), 4.75 (d, *J* = 7.0 Hz, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 4.60 (d, *J* = 3.3 Hz, 1 H), 4.36 (d, *J* = 9.1 Hz, 1 H), 3.74 (t, *J* = 8.6 Hz, 1 H), 3.67 (t, *J* = 8.9 Hz, 1 H), 3.48 (dd, *J* = 3.4, 9 Hz, 1 H), 3.43 (s, 3 H), 3.10 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 137.45, 128.53 (2 C), 128.50 (2 C), 128.1 (1 C), 128.03 (2 C), 127.94 (1 C), 127.91 (2 C), 116.8, 98.8, 79.7, 78.2, 75.45, 73.6, 71.35, 61.6, 56.25. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{23}NNaO_5$: 392.1468; found: 392.1457.