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Efficient Transformation of Aldoximes to Nitriles Using 2-Chloro-1-methylpyridinium Iodide Under Mild Conditions

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ABSTRACT

Various (aliphatic, aromatic, and heterocyclic aromatic) types of aldoximes were converted into the corresponding nitriles in good to excellent yields using 2-chloro-1-methylpyridinium iodide (CMPI) as a dehydrating agent under mild conditions.

Key Words: Dehydration; Aldoxime; Nitrile; Primary amide; 2-Chloro-1-methylpyridinium iodide.

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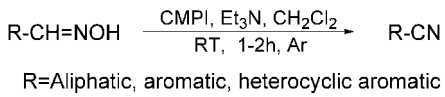
INTRODUCTION

Nitriles are important intermediates in organic synthesis,[1] especially in the synthesis of various heterocyclic compounds and biologically important molecules.[2] While a wide variety of synthetic approaches to nitriles from diverse chemical sources have been developed,[1a,3] nitrile synthesis from aldoxime using various dehydrating agents has been one of the classical routes. Numerous reagents, e.g., Burgess reagent,[4a] PPh_3/CCl_4,[4b] alkyl cyanoformates,[4c] AlI_3,[4d] dichlorocarbene/reverse micelle,[4e] di-2-pyridyl sulfite,[4f] $InCl_3$,[4g] $TiCl_3(OTf)$,[4h] cytochrome p450,[4i] $[RuCl_2(p\text{-cymene})]_2$,[4j] etc. have been developed. Many reagents, however, may have some limitations such as low yields, use of strong acids/or bases or oxidants, harsh reaction conditions, use of expensive or less readily available reagents, tedious workup procedure, or limited substrate scope. Therefore there is still a need to develop mild and general dehydrating reagent for this transformation.

2-Chloro-1-methylpyridinium iodide (CMPI) was initially introduced as an efficient condensing reagent for the synthesis of carboxylic esters,[5] and has extensively been studied as a powerful reagent for many useful transformations. However, to the best of our knowledge, CMPI has not been previously utilized for the synthesis of nitriles from aldoximes. We herein wish to report the first application of CMPI to the effective generation of nitriles from aldoximes under mild conditions (Sch. 1).

Various aldoximes were tested following the protocol described in Sch. 1, and the results were summarized in Table 1. To obtain the basic information regarding the optimum reaction conditions, anthracene oxime **1a** reacted first with CMPI (1.1 equiv) in CH_2Cl_2 for ca. 10 min, then with Et_3N (2.2 equiv) at room temperature under Ar. As the reaction proceeded, the color of the reaction mixture was gradually changed from yellow to reddish brown and the reaction was confirmed to be complete in 2 hr by TLC-analysis without any significant side reactions. Upon completion of reaction, the reaction mixture was quenched with aqueous HCl (5%) to remove the by-product (1-methyl-2-pyridone), and the crude product obtained was subjected to flash column chromatography on SiO_2 to provide the pure nitrile **2a** in 94% yield (entry 1). Attempts to utilize $(i\text{-Pr})_2NEt$ as base or THF as reaction medium were found to be equally effective, however, with less amount of CMPI or



Scheme 1.

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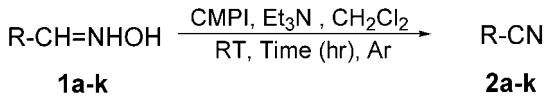
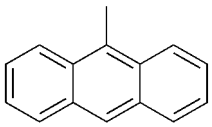
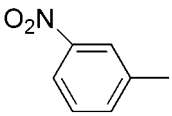
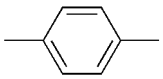
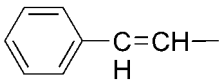
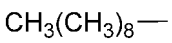
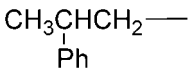
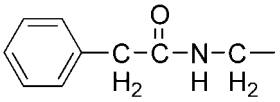
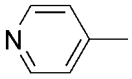
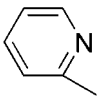
Table 1. Results of attempted reaction of aldoximes with CMPI



1a-k **2a-k**

Entry	R =		CMPI (equiv)	Et_3N (equiv)	Time (hr)	Yield (%)[a]
1		(**1a**)[b]	1.10	2.20	2.0	94
2		(**1b**)[c]	1.05	2.10	1.0	91
3		(**1c**)[c]	2.20	4.40	2.0	92[d]
4		(**1d**)[e]	1.05	2.10	1.5	88
5		(**1e**)[c]	1.10	2.20	2.0	81
6		(**1f**)[f]	1.10	2.20	2.0	93
7		(**1g**)[c]	1.00	2.00	1.0	91
8		(**1h**)[g]	1.05	2.10	1.0	86[h]
9		(**1i**)[g]	1.05	2.10	1.0	88[h]

(*continued*)

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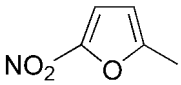
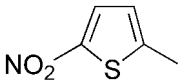
Table 1. Continued.

Entry	R =		CMPI (equiv)	Et_3N (equiv)	Time (hr)	Yield (%)[a]
10		(**1j**)[c]	1.00	2.00	1.5	90
11		(**1k**)[c]	1.00	2.00	1.5	90

[a]Isolated yields by flash column chromatography (SiO_2).
[b]Mixture (ca. 7 : 93) of *E*- and *Z*-isomer.
[c]Predominantly *E*-isomer.
[d]CH_3CN was used as solvent.
[e]Mixture (ca. 60 : 40) of *E*- and *Z*-isomer.
[f]Mixture (ca. 55 : 45) of *E*- and *Z*-isomer.
[g]Predominantly *Z*-isomer.
[h]Saturated brine instead of HCl (5%) was used for the quenching step.

base the reaction was confirmed to be incomplete. Other aromatic aldoximes (**1b**, **1c**) have shown the similar reactivity with CMPI under the similar conditions to afford the corresponding nitriles in excellent yields (entries 2 and 3).

With promising results in hand, we next tested other types of aldoximes to examine the generality of this reaction. Several aliphatic (entries 4–7) and heterocyclic aromatic (entries 8–11) aldoximes were found to exhibit the same reaction patterns under the similar reaction conditions, and the desired nitriles were obtained in 81–93% yields, respectively.

It has been known that many dehydrating reagents reported to be efficient for the generation of nitriles from aldoximes are also able to transform primary amides to nitriles.[4a,b,f] Therefore, it is highly desirable to check whether CMPI could react with primary amides or not. CMPI was turned out to be inactive at all with both aliphatic and aromatic primary amides under the similar reaction conditions,[a] which renders another advantage of CMPI as a selective dehydrating agent.

In summary, we have found that CMPI is a mild and practical reagent for the effective conversion of aldoximes into nitriles. Considering commercial

[a]When primary amide such as *m*-nitrobenzamide or 5-phenylvalerylamide was reacted with CMPI (1.05 equiv) and Et_3N (2.10 equiv) in CH_2Cl_2 at rt for 4 hr under Ar, no reaction occurred.

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availability and cheap cost of CMPI, mild reaction conditions, good to excellent yields, wide scope of applicability, and furthermore excellent selectivity differentiating primary amide from aldoxime, this dehydration protocol should be the method of choice in the synthesis of nitriles from various aldoximes.

EXPERIMENTAL

All reactions were carried out in oven-dried glassware under an argon atmosphere. Melting points were taken on an electrothermal melting-point apparatus and were not corrected. IR-spectra were obtained on a Jasco FT-IR/410 using KBr or as CH_2Cl_2 solution. ^{1}H-NMR (400 MHz) spectra were obtained in $CDCl_3$ on Jeol JNM-EX400 FT NMR spectrometer, and chemical shifts (δ) were reported in ppm downfield from tetramethylsilane. Flash column chromatography was carried out on silica gel (Merck, 230–400 mesh) and solvents were reported as V/V ratio mixtures. CH_2Cl_2 was distilled from calcium hydride. 2-Chloro-1-methylpyridinium iodide was purchased from Aldrich Chemical Co. and used directly without further purification. The aldoximes were purchased from Aldrich Chem. Co., or synthesized from their corresponding aldehydes according to the literature procedures.[7] All other chemicals were purchased from commercial sources and used as received unless otherwise stated.

General Procedure for the Dehydration of Aldoxime to Nitrile

To a solution of anthracene oxime **1a** (127.0 mg, 0.574 mmol) in CH_2Cl_2 (10 mL) was added CMPI (161.0 mg, 1.10 equiv) in one portion and the resulting mixture was stirred vigorously for ca. 10 min at room temperature under Ar. Et_3N (176.0 μL, 2.20 mmol) was then added by syringe and stirring was continued for an additional 2 hr. During this time, the color of the reaction mixture was changed slowly from yellow to reddish brown. The reaction was quenched with aqueous HCl (5%, 10 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2), and the combined organic layers were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash column chromatography on SiO_2 (hexane/CH_2Cl_2, 2/1) provided **2a** (119.0 mg, 94%) as a yellow solid: mp 172–174°C (lit.[8a] 173–174°C); R_f 0.53 (hexane/EtOAc, 3/1); IR (KBr) 2213 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 7.59 (t, 2H, $J = 7.6$ Hz), 7.72 (t, 2H, $J = 7.6$ Hz), 8.08 (d, 2H, $J = 7.9$ Hz), 8.42 (d, 2H, $J = 8.5$ Hz), 8.67 (s, 1H).

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2b. Yield 91%; an off-while solid; mp 115–116°C (lit.[8b]114–115°C); R_f 0.43 (hexane/EtOAc, 1/2), IR (KBr) 2237 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 7.75 (t, 1H, $J = 7.9$ Hz), 8.01 (d, 1H, $J = 7.9$ Hz), 8.49 (d, 1H, $J = 7.9$ Hz), 8.55 (bs, 1H).

2c. Yield 92%; an off-while solid; mp 223–225°C (lit.[8c] 222°C); R_f 0.40 (hexane/EtOAc, 2/1), IR (KBr) 2232 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 7.80 (s, 4H).

2d. Yield 88%; yellow liquid;[8d] R_f 0.48 (hexane/EtOAc, 3/1), IR (CH_2Cl_2) 2220 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 5.88 (d, 1H, $J = 16.6$ Hz), 7.38–7.46 (m, 6H).

2e. Yield 81%; colorless liquid;[8e] R_f 0.58 (hexane/EtOAc, 6/1), IR (CH_2Cl_2) 2248 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 0.88 (t, 3H, $J = 6.6$ Hz), 1.28–1.29 (m, 10H), 1.41–1.46 (m, 2H), 1.58–1.69 (m, 2H), 2.34 (t, 2H, $J = 7.1$ Hz).

2f. Yield 93%; colorless liquid;[4a] R_f 0.59 (hexane/CH_2Cl_2, 1/3), IR (CH_2Cl_2) 2249 cm^{-1}(CN); ^{1}H-NMR ($CDCl_3$), δ 1.43 (d, 3H, $J = 6.8$ Hz), 2.52 (dd, 1H, $J_1 = 16.7$ Hz, $J_2 = 7.6$ Hz), 2.59 (dd, 1H, $J_1 = 16.7$ Hz, $J_2 = 6.8$ Hz), 3.11–3.16 (m, 1H), 7.20–7.25 (m, 3H), 7.32–7.35 (m, 2H).

2g. Yield 91%; an off-while solid; mp 88–90°C (lit.[8f] 91°C); R_f 0.51 (hexane/EtOAc, 1/2); IR (KBr) 2245 cm^{-1}(CN); ^{1}H-NMR ($CDCl_3$), δ 3.63 (s, 2H), 4.10 (d, 2H, $J = 5.9$ Hz), 5.96 (br s, 1H), 7.24–7.26 (m, 2H), 7.31–7.40 (m, 3H).

2h. Yield 86%; an off-while solid; mp 78–79°C (lit.[8g] 79°C); R_f 0.50 (hexane/EtOAc, 1/1), IR (KBr) 2242 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 7.55 (d, 2H, $J = 5.6$ Hz), 8.83 (d, 2H, $J = 5.6$ Hz).

2i. Yield 88%; yellow liquid;[8h] R_f 0.47 (hexane/EtOAc, 2/1), IR (KBr) 2242 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 7.64 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.7$ Hz), 7.72 (d, 1H, $J = 7.8$ Hz), 7.88 (td, 1H, $J_1 = 7.8$ Hz, $J_2 = 2.0$ Hz), 8.74 (d, 1H, $J = 4.7$ Hz).

2j. Yield 90%; yellow solid; mp 60–62°C (lit.[8i] 59–62°C); R_f 0.44 (hexane/EtOAc, 2/1); IR (KBr) 2240 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 7.28 (d, 1H, $J = 3.9$ Hz), 7.37 (d, 1H, $J = 3.9$ Hz).

2k. Yield 91%; yellow solid; mp 45–46°C (lit.[8j] 45°C); R_f 0.42 (hexane/EtOAc, 4/1); IR (KBr) 2224 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$), δ 7.58 (d, 1H, $J = 4.4$ Hz), 7.90 (s, 1H, $J = 4.4$ Hz).

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