

Highly Efficient and Catalytic
Conversion of Aldoximes to Nitriles

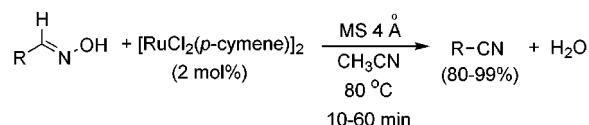
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ABSTRACT



Catalytic dehydration of aldoximes can be performed highly efficiently with a catalyst system of $[\text{RuCl}_2(\text{p-cymene})]_2$ /molecular sieves under essentially neutral and mild conditions, and various types of cyano compounds are produced in good to excellent yields.

Nitrile is a key constituent in numerous natural products, and it also serves as an important synthetic intermediate for pharmaceuticals, agricultural chemicals, dyes, and material sciences.¹ One of the most general methods for synthesis of alkylnitriles is a direct nucleophilic substitution of alkyl halides with inorganic cyanides although the reaction is frequently accompanied by elimination of hydrogen halides especially with bulky alkyl halides.² α,β -Unsaturated nitriles can be prepared via a Wittig reaction of the corresponding aldehyde with cyanoalkyl phosphonate. However, it frequently results in an unbiased mixture of *E*- and *Z*-isomeric nitriles.³ Nitrile synthesis by means of dehydration of amides or aldoximes with an appropriate nonmetal dehydrating agent would be an alternative method.⁴ However, it suffers from some disadvantages such as inconvenient preparation of the reagents, limited substrate scope, or incompatibility of sensitive groups to the reaction conditions. Recently, there

have been several reports describing dehydration methods of aldoximes with the use of stoichiometric amounts of certain main or transition metal complexes.⁵ Despite the recent progress, there is still a strong need for a *preparative method of highly efficient and catalytic conversion of aldoximes to nitriles*.⁶ In continuation of our studies directed toward the development of metal-catalyzed efficient reactions,⁷ described herein is a realization of this goal with a Ru catalyst.

Conversion of 4-bromobenzaldoxime to 4-bromobenzonitrile was first examined as a test reaction under various conditions (Table 1). Whereas no conversion of the oxime to cyano was observed in the absence of catalyst, some Rh or Ru complexes exhibited noticeable catalytic activities on the transformation. While Rh complexes displayed moderate to low reactivity, use of certain Ru catalysts led to higher conversion and better selectivity in general. For example, addition of $\text{Ru}_3(\text{CO})_{12}$ catalyst provided good conversion albeit with modest selectivity for the formation of nitrile

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Table 1. Catalytic Conversion of *p*-Bromobenzaldoxime to *p*-Bromobenzonitrile^a

$(4\text{-Br})\text{C}_6\text{H}_4\text{N}^{\text{OH}} + \text{cat} \xrightarrow[80\text{ }^{\circ}\text{C}]{\text{CH}_3\text{CN}} (4\text{-Br})\text{C}_6\text{H}_4\text{CN}$ (3 mol%)			
entry	catalyst	time	convn (yield, %) ^b
1		8 h	<5
2	RhCl ₃ /3H ₂ O	2 h	11 (<5)
3	RhCl(PPh ₃) ₃	2 h	21 (15)
4	[Rh(OAc) ₂] ₂	2 h	66 (23)
5	Ru ₃ (CO) ₁₂	2 h	82 (55)
6	RuCl ₂ (PPh ₃) ₃	2 h	21 (15)
7	RuH ₂ (PPh ₃) ₄	2 h	30 (21)
8	[RuCl ₂ (benzene)] ₂	2 h	77 (70)
9	[RuCl ₂ (<i>p</i> -cymene)] ₂	2 h	95 (91)
10 ^c	[RuCl ₂ (<i>p</i> -cymene)] ₂	5 min	>99 (95)

^a Concentration of these test reactions was 0.1 M to aldoxime in all cases.

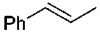

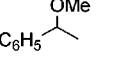
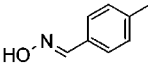
^b Conversion was calculated by ¹H NMR integration using an internal standard (anisole); yields refer to isolated yields after chromatography. ^c The reaction was carried out in the presence of molecular sieves (4 Å, 2 weight equiv to aldoxime).

(entry 5). One of other side products from the reaction was identified as 4-bromobenzamide (15% yield).⁸ Although ruthenium complexes ligated with phosphines resulted in low conversion (entries 6 and 7), dimeric Ru–arene complexes afforded significantly improved conversion and selectivity for the formation of nitrile. Among those examined, a *p*-cymene ruthenium complex, [RuCl₂(*p*-cymene)]₂ (**1**), displayed slightly higher catalytic activity compared to the corresponding benzene complex (entries 8 and 9).⁹ Whereas no conversion was observed by the action of molecular sieves alone (10 weight equiv to oxime) without metal catalysts even after 24 h under reflux, we found that the reaction rate and selectivity could be significantly increased when the reaction was carried out in the presence of molecular sieves (4 Å, 2 weight equiv to oxime). The reaction was complete within 5 min in the presence of molecular sieves while it took more than 3 h to achieve a full conversion in the absence of molecular sieves (compare entries 9 and 10). Among several solvents tested, acetonitrile was the medium of choice with respect to both conversion and selectivity in the dehydration reaction. Very low conversion (<10%) was observed in toluene, benzene, or THF under otherwise identical conditions. In DMF, however, a complete conversion could be attained after 2 h at temperatures above 130 °C. The reaction rate was slowed at lower temperatures, and low conversion was observed at room temperature in acetonitrile (<10%, 24 h).

High efficiency of the catalyst system of [RuCl₂(*p*-cymene)]₂/molecular sieves for the dehydration was main-

tained to the same extent with structurally diverse aldoximes (Table 2).¹⁰ The reaction was complete in less than 1 h for

Table 2. Catalytic Conversion of Various Aldoximes to Nitriles Using [RuCl₂(*p*-cymene)]₂ (**1**) as a Catalyst^a

$\text{R}-\text{N}^{\text{OH}} + \text{1} \xrightarrow[80\text{ }^{\circ}\text{C}]{\text{MS 4 \AA, CH}_3\text{CN}} \text{R}-\text{CN}$ (2 mol%)			
entry	R	time (min)	yield (%) ^b
1	C ₆ H ₅	10	94
2	4-Br-C ₆ H ₄	10	92
3	4-MeO-C ₆ H ₄	15	99
4	4-O ₂ N-C ₆ H ₄	30	87
5	2,6-(Cl) ₂ -C ₆ H ₃	15	80
6	4-OH-C ₆ H ₄	30	99
7	4-TBSOCH ₂ -C ₆ H ₄	10	99
8		10	92
9	3-Pyridyl	60	88
10	2-Thienyl	10	95
11	2-Furanyl	10	81
12	Cyclohexyl	10	90
13		15	99
14 ^c		60	80
15		15	80 ^d

^a All reactions were carried out in the presence of 2 weight equiv of 4 Å molecular sieves to aldoximes. ^b Isolated yields after column chromatography on silica gel. ^c Aldoxime of inseparable mixture of two isomers (*anti/syn* = 1:0.4 at 25 °C) was used. ^d Yield of 1,4-dicyanobenzene.

all substrates tested with the use of 2 mol % of the ruthenium catalyst in the presence of molecular sieves, and the corresponding nitriles were isolated in good to excellent yields.¹¹ Electronic variation on the aromatic substituents did not diminish the efficiency and selectivity (entries 2–4). Good yield was also obtained from the reaction of a sterically congested oxime (entry 5). It is noteworthy that protection of a hydroxyl group on substrates is not necessary as

(8) Reverse transformation of nitriles to aldoximes was not observed under the employed conditions and the formation of amide can be rationalized by assuming hydrolysis of the formed nitrile by water, which is generated during the course of aldoxime dehydration.

(9) When the reaction was carried out in CD₃CN, formation of an equivalent amount of water was detected on ¹H NMR.

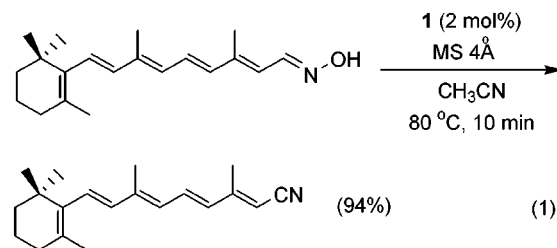
(10) Aldoximes were readily prepared in quantitative yields by reaction of the corresponding aldehydes with H₂NOH·HCl (in pyridine/EtOH, 1:1).

(11) **Representative experimental procedure:** To a solution of benzaldehyde oxime (242.3 mg, 2.0 mmol) in acetonitrile (2 mL) were added [RuCl₂(*p*-cymene)]₂ (24.5 mg, 0.04 mmol) and molecular sieves (4 Å, dried under reduced pressure at 110 °C for 5 h, 480 mg). The reaction mixture was stirred for 10 min at 80 °C. After removal of solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel to afford benzonitrile (193 mg, 94%).

demonstrated by the reaction of 4-hydroxybenzaloxime (entry 6). A silyloxy group was tolerated under the reaction conditions (entry 7). *trans*-Cinnamaloxime was also conveniently converted to the corresponding nitrile with stereochemical retention of the double bond (entry 8). Various heteroatoms turned out to be compatible with the employed reaction conditions (entries 9–11). For example, 3-pyridinealoxime was smoothly dehydrated with the catalyst system to give 3-cyanopyridine in 88% yield. It should be noted that the same reaction proceeded much slowly when $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was employed as a catalyst, and the dehydrated product could be isolated in only 39% yield (55% conversion) after 8 h in CH_3CN (80 °C) with the copper acetate hydrate (2 mol %)/molecular sieves. The same trend was also observed with other substrates examined. For example, while complete conversion of 4-hydroxybenzaloxime to the corresponding cyano compound was achieved in 30 min with the Ru-catalyst system (entry 6), it took 3 h to afford the full conversion (90% isolated yield of nitrile) with copper acetate hydrate (2 mol %)/molecular sieves under otherwise identical conditions.¹² Due to the fact that the copper complex has been known as one of the most efficient catalysts for dehydration of aldoximes,^{6a} this result amply illustrates advantageous aspects of the present catalytic system over the previously reported dehydration systems^{2–6} for the preparation of nitriles. Not only were aromatic aldoximes efficiently converted to aromatic cyano compounds but aliphatic aldoximes could also be employed as a good substrate with similar selectivity to afford the corresponding aliphatic nitriles (entries 12–14).¹³ A substrate bearing bis-aldoxime was uneventfully dehydrated to give 1,4-dicyanobenzene in good yield (entry 15).

Synthetic utility of the present method was demonstrated in the preparation of a multiply conjugated nitrile, which

has been used as a useful intermediate in organic synthesis (eq 1).¹⁴ *all-trans*-Retinaldoxime was readily converted to



its corresponding nitrile¹⁵ in high yield with 2 mol % of $[\text{RuCl}_2(p\text{-cymene})]_2$. No isomerization of the double bonds was detected in the reaction. Applicability of the present protocol to a larger scale process was next tried. Dehydration of 4-chlorobenzaloxime (15.6 g, 0.1 mol) was complete in 10 min by the action of ruthenium catalyst **1** (0.5 mol %) in the presence of molecular sieves in CH_3CN (1.5 M, 80 °C), and analytically pure 4-chlorobenzonitrile was isolated in high yield (12.2 g, 89%).

In conclusion, we have shown here several noteworthy features of a new catalyst system for the dehydration of aldoximes. The reaction proceeds under essentially neutral conditions, and the present method is mild and simple to conduct. This protocol can be readily applied to large scale processes with high efficiency and selectivity, making it an economical and an environmentally benign process for the preparation of nitriles.

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Supporting Information Available: Spectroscopic data of all new compounds obtained in this study. This material is available free of charge via Internet at <http://pubs.acs.org>.

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(12) A rate difference was also observed with the aliphatic aldoximes tested. For example, it took less than 15 min to achieve complete conversion of 10-undecynaloxime (entry 13) with the presently employed Ru catalyst; reaction of the same substrate was slower with the $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2 mol %)/molecular sieves system (4 h, 95% conversion and 90% isolated yield) under otherwise identical conditions.

(13) Although 2-methoxy-2-phenylacetaldoxime was used as an inseparable mixture of two isomers (entry 14), there were no any detectable differences on the dehydration reaction rates between the two isomers.

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