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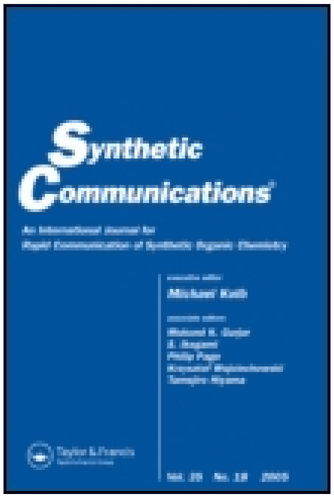

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NICKEL/ZINC-MEDIATED SYNTHESIS OF AROMATIC NITRILES FROM AROMATIC OXIME ETHERS

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ABSTRACT

Treatment of *o*-alkoxybenzaldoxime ethers **3** with an equimolar amount of $NiCl_2$ and 3 equimolar amounts of Zn gave *o*-alkoxybenzonitriles **4** in good yields. It is suggested that the reaction proceed via coordination of the ether oxygen atom of alkyl ether moiety to low-valent metal species.

Key Words: Aromatic oxime ether; Aromatic nitriles; Nickel/zinc reagent

Nitriles are the useful synthetic intermediates applicable to transformation to various organic compounds such as amines, ketones, and heterocycles. In general, nitriles have been synthesized via substitution reaction of alkyl halides with metal cyanide,[1] reaction of diazonium salts with copper cyanide,[2] and dehydration of primary amides or aldoximes.

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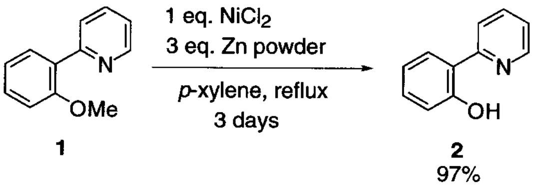
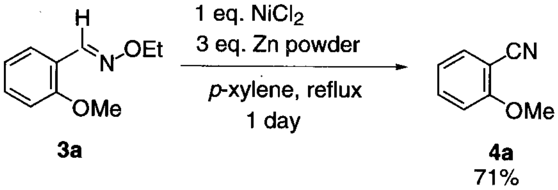
However, metal cyanide has high toxicity and is troublesome to be handled. Dehydration of primary amides or aldoxime generally requires acidic dehydrating reagent such as P_2O_5[3] or $SOCl_2$.[4] Basic reagents such as *n*-BuLi are also available for the synthesis of nitriles from aldoximes or aldoxime ethers.[5] A few papers have been reported on synthesis of nitriles from aldoximes using DCC or 1,1′-carbonyldiimidazole under neutral conditions.[6] Previously, we reported $NiCl_2$/Zn-mediated alkyl carbon–oxygen bond cleavage of alkyl aryl ethers (Scheme 1).[7] This reaction proceeds by coordination of nitrogen atom on the pyridine ring to low-valent nickel species. The results prompted us to extend the reaction to other conversions. We planned the synthesis of nitriles utilizing activation of aldoxime derivatives by low-valent metal species.



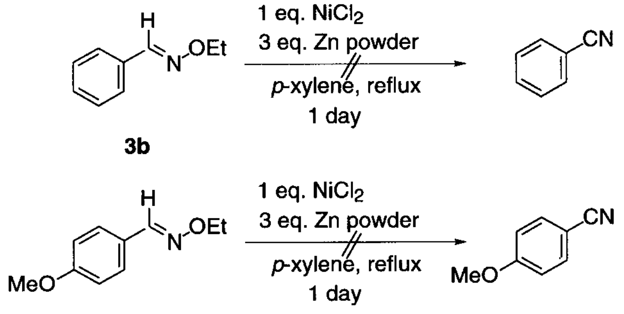
Scheme 1. Reaction of 2-(2′-pyridyl)anisole (**1**) with Ni/Zn reagent.



Scheme 2. Reaction of ethyl (*E*)-*o*-anisaldehyde *O*-ethyloxime (**3a**) with Ni/Zn reagent.

Herein we would like to report that a mixture of $NiCl_2$ and Zn is a useful reagent for the conversion of aldoxime ethers to the corresponding nitriles on condition that a coordination site is located at a suitable position in the aldoxime ether molecules (Scheme 2).

When (*E*)-*o*-methoxybenzaldehyde *O*-ethyloxime (**3a**) was treated with an equimolar amount of $NiCl_2$ and 3 equimolar amounts of zinc powder in *p*-xylene under reflux, *o*-methoxybenzonitrile (**4a**) was obtained in a 71% yield. To estimate the feasibility for this transformation, we attempted the reaction of benzaldoxime ethyl ether (**3b**) with $NiCl_2$/Zn reagent. However, only recovery of the starting material was confirmed.



3b

3c

Scheme 3. Reaction of benzaldoxime ethyl ether derivatives with Ni/Zn reagent.

This fact means the methoxy group would promote this transformation. Then, we next attempted the reaction of aldoxime ether **3c** with methoxy group at *p*-position. However, the transformation did not proceed and the starting material was recovered. On the basis of these results, we were convinced that the reaction proceeds by the assist of the coordination of the oxygen atom on aryl methyl ether moiety to low-valent metal species (Scheme 3).

Then we examined the effects of the kind of metal reagents and reaction conditions. Table 1 shows the results.

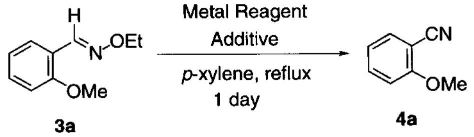
When the reaction was carried out in the presence of $NiCl_2$/Zn, Ni(acac)$_2$/Zn, or Ni(cod)$_2$, the desired product was obtained in moderated yields (Runs 1–3). However, the yield was lowered when the reaction was undertaken in the presence of an equimolar amount of PPh_3 (Run 4). Addition of an extra ligand was proved to interfere with the reaction. These results demonstrate that low-valent metal species takes part in the reaction.

The reaction of aldoxime ether **3a** with $FeCl_3$/Zn system gave no nitrile compound. Instead, only *o*-anisaldehyde was obtained which was probably produced via hydrolysis of aldoxime ether **3a**. Accordingly, it has become apparent that $NiCl_2$/Zn, Ni(acac)$_2$/Zn, or Ni(cod)$_2$ is suitable for this transformation.

The reaction of aldoxime ether **3a** with $FeCl_3$/Zn system gave no nitrile compound. Instead, only *o*-anisaldehyde was obtained which was probably produced via hydrolysis of aldoxime ether **3a**. Accordingly, it has become apparent that $NiCl_2$/Zn, Ni(acac)$_2$/Zn, or Ni(cod)$_2$ is suitable for this transformation.

Then we examined the effect on the substituents (R^1, R^2) on the two kinds of ether bonds in the reaction with $NiCl_2$/Zn. The results are shown in Table 2. In the reaction of aldoxime ethers **3a,d,e**, the desired product was obtained in moderated yields (Runs 1–3). However, when

Table 1. Reaction of Aromatic Aldoxime Ether **3a**



Run	Metal Reagents	Additive	Yield (%)
1	$NiCl_2/Zn$	none	71
2	$Ni(acac)_2/Zn$	none	72
3	$Ni(cod)_2$	none	55
4	$NiCl_2/Zn$	PPh_3[a]	43
5	$FeCl_3/Zn$	none	0[b]

Reaction conditions: substrate, 0.3 mmol; nickel or iron reagent, 0.3 mmol; Zn, 0.9 mmol (except for Run 3); *p*-xylene, 1 mL.

[a] PPh_3 (0.3 mmol) was added.

[b] *o*-Anisaldehyde was obtained in a ca. 40% yield.

isopropyl ether **3f** was employed for this reaction, the yield was greatly lowered (Run 4). It is due to the difficulty of coordination or interaction of the sterically hindered oxygen atom to the metal center.

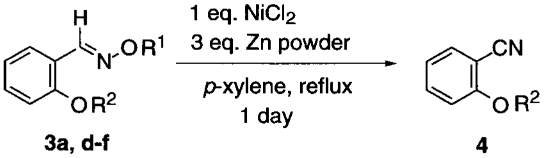
This result demonstrates that the coordination or the related interaction of the oxygen atom of the aryl methyl ether moiety is essential for this reaction. There are two plausible pathways; one is oxidative addition of nickel(0) reagent generated in situ to nitrogen–oxygen bond followed by β-elimination to produce nitriles and H–Ni–OR. In this pathway, however, the nitrogen–oxygen bond and aryl alkyl ether oxygen atom are suspected to be too apart to coordinate to one metal center at the same time. The other pathway is as follows: (1) coordination of aryl alkyl ether oxygen atom to low-valent metal species, (2) its oxidative addition to imino carbon–hydrogen bond situated in the neighborhood of the coordination site, and (3) β-elimination to produce nitriles and H–Ni–OR. At present, however, we have not made the reaction mechanism clear yet.

In conclusion, we realized the effective conversion of alkyl aromatic aldoxime ethers, which have a coordination site on the benzene ring, to aromatic nitriles in the presence of Ni/Zn reagent.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-A500 (^{1}H; 500 MHz, ^{13}C; 125 MHz) spectrometer or a JEOL FX-200 (^{1}H;

Table 2. Reaction of Aromatic Aldoxime Ethers **3**



Run	Substrate	R^1	R^2	Yield (%)
1	**3a**	Et	Me	71
2	**3d**	Me	Me	43
3	**3e**	Et	Et	68
4	**3f**	Et	*i*-Pr	20

Reaction conditions: substrate, 0.3 mmol; nickel chloride, 0.3 mmol; Zn, 0.9 mmol; *p*-xylene, 1 mL.

200 MHz) spectrometer using Me_4Si (^1H, δ 0.00) and $CDCl_3$ (^{13}C, δ 77.0) as internal standards. IR spectra were recorded on a JEOL FTIR-5300 spectrometer. Aldoxime ethers **3** were prepared according to a conventional procedure. $Ni(acac)_2$ and $FeCl_3$ were dried at 150°C under reduced pressure before use. $Ni(cod)_2$ was purchased and used without any purification. $NiCl_2$ was dried at 150°C in vacuo for 3 h and immediately used for the reaction. *p*-Xylene was distilled from CaH_2 just before use. Zinc powder was activated according to the following method. Acetic acid (200 mL) was added to zinc powder (40 g), and the mixture was stirred overnight. After acetic acid was removed by decantation, the residual mixture was washed with ether for three times, and dried under reduced pressure.[8]

(*E*)-*o*-Anisaldehyde *O*-ethyloxime (3a) IR (neat) 2976, 2839, 1607, 1489, 1464, 1439, 1252, 1055, 1028 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.32 (3H, t, $J = 6.7$ Hz), 3.83 (3H, s), 4.22 (2H, q, $J = 6.7$ Hz), 6.88 (1H, d, $J = 7.5$ Hz), 6.94 (1H, t, $J = 7.5$ Hz), 7.31 (1H, t, $J = 7.5$ Hz), 7.79 (1H, d, $J = 7.5$ Hz), 8.48 (1H, s) ppm; ^{13}C NMR δ ($CDCl_3$) 14.6, 55.5, 69.6, 111.0, 120.7, 121.0, 126.3, 130.9, 144.5, 157.5 ppm. Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.00%; H, 7.32%; N, 7.82%. Found: C, 67.22%; H, 7.60%; N, 7.57%.

(*E*)-*o*-Anisaldehyde *O*-methyloxime (3d)[5] IR (neat) 2937, 1607, 1489, 1466, 1254, 1055, 754 cm^{-1}; ^1H NMR δ ($CDCl_3$) 3.84 (3H, s), 3.97 (3H, s), 6.88 (1H, d, $J = 7.6$ Hz), 6.95 (1H, t, $J = 7.6$ Hz), 7.34 (1H, dt, $J = 2.0$, 7.6 Hz), 7.78 (1H, dd, $J = 2.0$, 7.6 Hz), 8.46 (1H, s) ppm; ^{13}C NMR δ ($CDCl_3$) 61.8, 62.4, 110.0, 120.7, 120.8, 126.4, 131.1, 144.8, 157.5 ppm. Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.42%; H, 6.71%; N, 8.48%. Found: C, 65.29%; H, 6.59%; N, 8.28%.

(*E*)-*o*-Ethoxybenzaldehyde *O*-ethyloxime (3e) IR (neat) 2980, 2934, 1607, 1489, 1454, 1250, 1053 cm^{-1}; ^{1}H NMR δ (CDCl$_3$) 1.34 (3H, t, $J = 7.0$ Hz), 1.42 (3H, t, $J = 7.0$ Hz), 4.05 (2H, q, $J = 7.0$ Hz), 4.23 (2H, q, $J = 7.0$ Hz), 6.93 (1H, d, $J = 7.2$ Hz), 6.99 (1H, t, $J = 7.2$ Hz), 7.37 (1H, dt, $J = 2.0$, 7.2 Hz), 7.86 (1H, dd, $J = 2.0$, 7.2 Hz), 8.48 (1H, s) ppm; ^{13}C NMR δ (CDCl$_3$) 14.6, 14.8, 63.9, 69.6, 112.0, 120.6, 121.0, 126.2, 130.7, 144.6, 156.9 ppm. Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.35%; H, 7.83%; N, 7.25%. Found: C, 68.65%; H, 7.89%; N, 7.17%.

(*E*)-*o*-Isopropoxybenzaldehyde *O*-ethyloxime (3f): IR (neat) 2978, 2932, 1607, 1485, 1246, 1055 cm^{-1}; ^{1}H NMR δ (CDCl$_3$) 1.32–1.34 (9H, m), 4.22 (2H, q, $J = 7.0$ Hz), 4.56 (1H, sept, $J = 6.0$ Hz), 6.88 (1H, d, $J = 7.5$ Hz), 6.91 (1H, t, $J = 7.5$ Hz), 7.29 (1H, dt, $J = 1.5$, 7.5 Hz), 7.80 (1H, dd, $J = 1.5$, 7.5 Hz), 8.48 (1H, s) ppm; ^{13}C NMR δ (CDCl$_3$) 14.6, 22.0, 69.6, 70.7, 113.8, 120.6, 122.0, 126.3, 130.7, 144.8, 155.9 ppm. Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.52%; H, 8.27%; N, 6.76%. Found: C, 69.63%; H, 8.40%; N, 6.47%.

Typical reaction procedure: reaction of (*E*)-*o*-Anisaldehyde *O*-ethyloxime (3a) with Ni/Zn reagent: A mixture of nickel(II) chloride (39 mg, 0.30 mmol), zinc powder (59 mg, 0.90 mmol), and (*E*)-*o*-anisaldehyde *O*-ethyloxime (**3a**) (56 mg, 0.30 mmol) was stirred in *p*-xylene (1 mL) under reflux for 1 day under nitrogen atmosphere. The resulting solution was quenched by addition of water (20 mL). The aqueous solution thus obtained was extracted with ethyl acetate (15 mL) for three times. The combined extracts were washed with brine and dried over with MgSO$_4$ overnight. After removal of solvents, the residue was separated by preparative TLC (Wakogel B-5F) with *n*-hexane/ethyl acetate (9 : 1) to give *o*-methoxybenzonitrile **(4a)** (28 mg) in a 71% yield.

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