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NICKEL/ZINC-MEDIATED ALKYL CARBON-OXYGEN BOND CLEAVAGE OF ALKYL ARYL ETHERS

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ABSTRACT

Alkyl carbon-oxygen bonds of alkyl aryl ethers bearing suitable coordination sites were efficiently cleaved by treatment with nickel(II) chloride and zinc in *p*-xylene under neutral conditions.

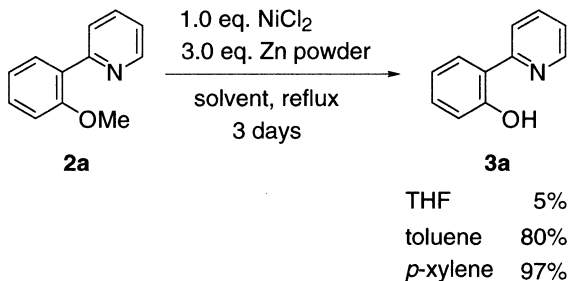
There are many reagents^{1,2} for cleavage of sp^3 carbon-oxygen bond in alkyl ethers, such as $HBr/AcOH$ ³ and BBr_3 .^{4,5} However, almost all of these reagents are rather violent, so the application to alkyl aryl ethers having other functionalities is often troublesome. The development of milder reagents for this purpose is considered to be helpful for the syntheses of organic materials and natural products.⁶ Herein, we report that a mixture of $NiCl_2$ and Zn is a useful reagent for the cleavage of alkyl aryl ethers where a coordination site is located at a suitable position.

To estimate the feasibility for carbon-oxygen bond cleavage by the oxidative addition to low-valent transition metals, we attempted the reaction of anisole or 2-methoxynaphthalene with palladium(0) or nickel(0)

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reagent. However, only recovery of the starting materials was confirmed in these reactions. Then, we planned to cleave alkyl aryl ether by the assist of a coordination site to low-valent metals in the same molecule, which might enable metal reagents to approach to the carbon-oxygen bond like *ortho*-palladation of aromatic compounds.⁷⁻¹⁰ At first, we chose anisole derivative **2a**, which has a 2-pyridyl group at *o*-position to methoxy group.¹¹

When substrate **2a** was treated with 1.0 equiv. of NiCl₂ and 3.0 equiv. of zinc powder in THF under reflux, the sp³ carbon-oxygen bond cleavage of alkyl aryl ethers proceeded to give phenol derivative **3a** in 5% yield. The conversion of this dealkylation raised when solvents with high boiling points were used. Aromatic solvents were found to be suitable for this reaction. Particularly when *p*-xylene was used as the solvent, cleavage proceeded to give phenol derivative **3a** under reflux in an almost quantitative yield.



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

Next, we investigated the effect on the alkyl substituents under the optimized conditions for the reaction in *p*-xylene. The results are shown in Table 1. The reactions of aryl ethyl ether **2b** and aryl isopropyl ether **2c** proceeded as well to give the dealkylated product **3a** in good yields (Runs 2 and 3). However, when phenyl ether **2d** was allowed to react under the same conditions, no reaction proceeded only to recover substrate **2d** (Run 4). It is found that application of this method is limited to the cleavage of the sp³ carbon-oxygen bond in alkyl aryl ethers.

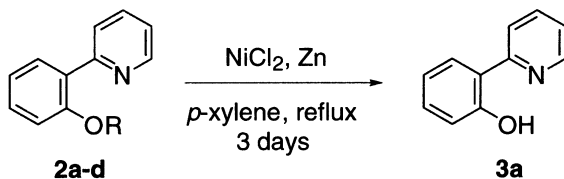


Table 1. Cleavage of Alkyl Aryl Ethers

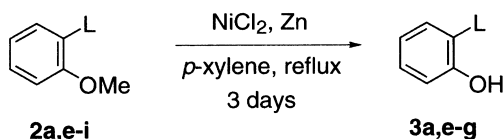
Run	Substrate	R	Yield (%)
1	2a	CH ₃	97
2	2b	C ₂ H ₅	68
3	2c	<i>i</i> -C ₃ H ₇	71
4	2d	C ₆ H ₅	0 ^a

Reaction conditions: Substrate, 0.3 mmol; NiCl₂, 0.3 mmol; Zn, 0.9 mmol; *p*-xylene, 1 mL, reflux, 3 days.

^aSubstrate was recovered.

Furthermore, we studied the effect of the structure and the property of the coordination site in the substrates. Instead of 2-pyridyl group, we employed substrates **2e–g**, having a nitrogen atom as the coordination site at *o*-position to methoxy group. The results of the reaction are shown in Table 2. Substrate **2e**, which has an *N*-methylimidazolyl group, gave the corresponding product (**3e**) in a moderate yield (Run 2). A small decrease of the yield is considered to be due to the delicate difference of the coordination directions of the metal to the nitrogen atom. Similarly, substrate **2f**, having an imino group, produced dealkylated product **3f** in a moderate yield (Run 3). The small decrease of the yield is thought to be caused by the steric hinderance of the phenyl group bonded to the nitrogen atom. The reaction of substrate **2g**, having an *N,N*-diethylaminomethyl group where the coordination site was connected to the aryl part through the sp³ carbon, gave product **3g** in a 51% yield (Run 4). The moderate yield is supposed to be due to the steric hinderance of ethyl groups bonded to the nitrogen atom, and also attributed to the free rotation of benzylic carbon-nitrogen σ bond. When substrates with carbonyl parts as the coordination sites were allowed to react, no reaction proceeded (Runs 5 and 6).

Considering these results, substrate **2a**, which has 2-pyridyl group at *o*-position to methoxy group, is most suitable to the cleavage of alkyl aryl ethers.



To examine toleration of other functionalities, we next carried out the reaction of substrate **2j** which has a methoxy and an ethoxycarbonyl group

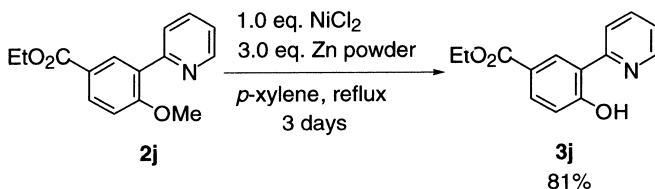
Table 2. Reaction of Anisole Derivatives with Coordination Sites

Run	Substrate	L	Yield (%)
1	2a	2-C ₅ H ₄ N	97
2	2e	1-Methyl-2-imidazolyl	68
3	2f	CH=NC ₆ H ₅	71
4	2g	CH ₂ NEt ₂	51
5	2h	CO ₂ Et	0 ^a
6	2i	CONEt ₂	0 ^a

Reaction conditions: Substrate, 0.3 mmol; NiCl₂, 0.3 mmol; Zn, 0.9 mmol; *p*-xylene, 1 mL, reflux, 3 days.

^aSubstrate was recovered.

at *o*- and *m*-positions to 2-pyridyl group, respectively. As a result, the reaction proceeded to produce only dealkylated product **3j** in a good yield. Only the sp³ carbon-oxygen bond was cleaved and the ester part tolerated. In this way, this reaction takes place under mild conditions, and only the neighboring ether bond to the coordination site can be cleaved.

**Scheme 2.** Chemoselective ether cleavage.

In conclusion, the Ni/Zn-mediated dealkylation of alkyl aryl ethers occurs in existence of a nitrogen coordination site in the same molecule. Particularly, when 2-pyridyl group locates at the *o*-position to alkoxy group on the substrate, reaction proceeds most efficiently. This reaction occurs without cleavage of coexisting ester parts.

EXPERIMENTAL

¹H and ¹³C NMR spectra were recorded on a JEOL JNM-A500 (¹H; 500 MHz, ¹³C; 125 MHz) spectrometer or a JEOL FX-200 (¹H; 200 MHz) spectrometer using Me₄Si (¹H, δ 0.00) and CDCl₃ (¹³C, δ 77.0) as internal standards. IR spectra were recorded on a JEOL FTIR-5300 spectrometer.

Synthesis of 2-(2'-pyridyl)anisole (**2a**)^{11,12}

A hexane solution of *n*-butyllithium (11 mL, 1.5 M, 16.5 mmol) was added dropwise to a freshly distilled THF solution (23 mL) of 2-bromoanisole (**1**) (2.81 g, 15 mmol) at -78°C under nitrogen atmosphere. After stirring for 0.5 h, a THF solution (45 mL) of anhydrous zinc chloride (6.33 g, 46.5 mmol) was added, resulting in the formation of heavy white precipitates. The mixture was gradually warmed to room temperature over 0.5 h, then treated with tetrakis (triphenylphosphine)palladium (0.87 g, 0.75 mmol), followed by the addition of 2-bromopyridine (3.08 mg, 18 mmol). The reaction mixture was heated under reflux for 1.5 h. Cool water was added and the mixture was extracted with dichloromethane (50 mL) three times. The combined extracts were washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by chromatography on silica gel (Merck Silica gel 60, 0.063–0.200 mm) with *n*-hexane/ethyl acetate (3:1) to give 2-(2'-pyridyl)anisole (4.38 g, 8.7 mmol, 58%) as a yellow oil: IR (KBr) 3055, 3005, 2835, 1601, 1583, 1494, 1259, 1242, 754 cm^{-1} ; ^1H NMR δ (CDCl_3) 4.07 (3H, s), 6.97 (1H, d, $J=8.0$ Hz), 7.07 (1H, t, $J=7.2$ Hz), 7.17 (1H, t, $J=7.2$ Hz), 7.66 (1H, t, $J=8.0$ Hz), 7.76 (1H, dd, $J=2.0, 8.0$ Hz), 7.79 (1H, d, $J=8.0$ Hz), 8.68 (1H, d, $J=4.8$ Hz) ppm; ^{13}C NMR δ (CDCl_3) 55.4, 111.2, 120.1, 125.0, 129.0, 131.0, 135.5, 149.2, 156.0, 156.8 ppm.

Typical Reaction Procedure: Reaction of 2-(2'-Pyridyl)anisole (**2a**) with Ni/Zn Reagent

A mixture of nickel(II) chloride¹³ (39 mg, 0.30 mmol), zinc powder¹⁴ (59 mg, 0.90 mmol), and 2-(2'-pyridyl)anisole (**2a**) (56 mg, 0.30 mmol) was stirred in *p*-xylene (1 mL) under reflux for 3 days under nitrogen atmosphere. The resulting solution was quenched by the addition of water (20 mL). The aqueous solution thus obtained was extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over with MgSO_4 . After removal of solvents, the residue was purified by preparative TLC (Wakogel B-5F) with *n*-hexane/ethyl acetate (3:1) to give 2-(2'-pyridyl)phenol (**3a**) (47 mg, 0.29 mmol) in 97% yield.

2-(2'-Pyridyl)phenol (**3a**)¹²

IR (KBr) 3055, 2569, 1593, 1562, 1502, 1269, 754 cm^{-1} ; ^1H NMR δ (CDCl_3) 4.47 (1H, br), 7.93 (1H, t, $J=8.6$ Hz), 7.07 (1H, d, $J=9.4$ Hz), 7.20–7.40 (2H, m), 7.70–7.90 (3H, m), 8.50 (1H, d, $J=5.0$ Hz) ppm;

^{13}C NMR δ (CDCl_3) 118.2, 118.5, 118.5, 118.7, 121.2, 125.9, 131.2, 137.5, 145.4, 157.4 ppm.

2-(1-Methyl-2-imidazolyl)phenol (**3e**)¹⁵

IR (KBr) 2924, 2364, 1608, 1469, 1377, 1292, 1145, 750 cm^{-1} ;
 ^1H NMR δ (CDCl_3) 3.90 (3H, s), 6.84–6.89 (2H, m), 7.08–7.13 (2H, m), 7.24 (1H, s), 7.55 (1H, dd, $J=1.0$, 8.0 Hz) ppm; ^{13}C NMR δ (CDCl_3) 36.3, 113.8, 117.7, 118.3, 122.6, 125.3, 125.4, 130.0, 145.6, 157.8 ppm.

(2-Hydroxybenzylidene)aniline (**3f**)¹⁶

IR (KBr) 3055, 2883, 1616, 1589, 1572, 1483, 1400, 1277, 756 cm^{-1} ;
 ^1H NMR δ (CDCl_3) 6.97 (1H, t, $J=8.3$ Hz), 7.01 (1H, t, $J=8.3$ Hz), 7.20–7.50 (4H, m), 8.60 (1H, s), 13.30 (1H, s) ppm; ^{13}C NMR δ (CDCl_3) 117.2, 119.0, 119.2, 121.1, 126.9, 132.2, 133.1, 148.5, 161.1, 162.6 ppm.

Ethyl 4-hydroxy-3-(2'-pyridyl)benzoate (**3j**)

IR (KBr) 3003, 2986, 2912, 1707, 1597, 1496, 1284, 765 cm^{-1} ;
 ^1H NMR δ (CDCl_3) 1.40 (3H, t, $J=6.7$ Hz), 4.37 (2H, q, $J=6.7$ Hz), 5.11 (1H, br), 7.02 (1H, d, $J=8.6$ Hz), 7.27 (1H, t, $J=6.0$ Hz), 7.86 (1H, dd, $J=2.2$, 8.0 Hz), 7.97 (1H, dd, $J=2.2$, 8.6 Hz), 8.02 (1H, d, $J=8.0$ Hz), 8.48 (1H, d, $J=6.0$ Hz), 8.54 (1H, d, $J=2.2$ Hz) ppm; ^{13}C NMR δ (CDCl_3) 14.3, 60.6, 118.0, 118.3, 119.1, 120.7, 121.9, 128.3, 132.5, 137.9, 145.4, 156.8, 164.1, 166.2 ppm.

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