Reductive Cleavage of C-O Bond in Model Compounds of Lignin

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A simple protocol for reductive cleavage of C—O bond in diaryl and aryl methyl ethers was reported, in which NaH served as a reducing agent and KO'Bu as a base and a radical initiator. The combination of NaH and KO'Bu displayed high efficiency for reductive cleavage of C—O bond in diaryl and aryl ethers (*e.g.*, dibenzofuran, diphenyl ether, anisole) without the hydrogenation of the aryl rings, in the absence of any other catalysts or ligands at 140 °C, producing corresponding arenes and phenols. It was indicated that the reaction was under a radical mechanism.

Keywords lignin, C-O bond, aryl ethers, reductive cleavage, aromatics

Introduction

As a renewable resource, biomass is of great significance for the sustainable development of human beings.^[1,2] Lignin is the second most abundant biomass in nature, and is an important natural resource of aromat-ics.^[3-5] The 4-O-5 linkage (*e.g.*, diaryl and aryl alkyl ethers) is a representative C-O linkage in lignin, and its catalytic cleavage is considered as an efficient way to depolymerize lignin for production of aromatics.^[3,4,6-11] Various metal catalysts such as Ni,^[12-15] Ru,^[16,17] Cu,^[18-21] Pd/Zn,^[22] V^[23-26] and Fe,^[27] have been reported for catalysing the cleavage of aryl C-O in lignin model compounds including diaryl ethers and aryl alkyl ethers via oxidation or hydrogenlysis. However, harsh reaction conditions including high temperature and complicated reaction systems are generally required, and the target product yields are relatively low. Recently, a transition-metal-free protocol for the efficient reductive cleavage of C-O bond in diaryl and aryl alkyl ethers was reported, in which the combination of triethylsilane with common bases (e.g., KO'Bu) formed a reductive couple that regioselectively ruptured aryl C-O bonds in aromatic ethers.^[28] However, the reaction temperature had to maintain high to 165 °C to hold a satisfactory conversion and selectivity to target products, and ortho-silvlated products could not be avoided.

Reductive cleavage of C—O bonds in lignin model compounds is an effective way to get aromatics from the lignin-derived compounds, and various reductive systems have been reported.^[27-30] For example, Wang and coworkers reported a reductive system composed of

LiAlH₄, [Fe(acac)₃] and NaO'Bu, which achieved the cleavage of the C–O bonds in aryl ethers at 140 $^{\circ}$ C, producing arenes and phenols in good yields.^[27] In our previous work, we found that the combination of LiAlH₄ and KO'Bu without any catalysts or additives was very effective for the reductive cleavage of aryl C –O bonds in phenols, solely producing arenes.^[29]

In the course of our continual investigation on cleavage of aryl C-O bond to produce aromatics from lignin model compounds, we herein report a simple protocol for reductive cleavage of C-O bond in diaryl and aryl methyl ethers, in which NaH served as a reducing agent and KO'Bu as a base and a radical initiator. It was found that the combination of NaH and KO'Bu was able to cleave the aryl C-O bond in diaryl and aryl alkyl ethers efficiently without any other catalysts or ligands, producing corresponding phenols and arenes.

Experimental

Materials

NaH (60%), KO^{*t*}Bu, anisole, dodecane, and decane were purchased from Across. Diphenyl ether and biphenyl were purchased from Alfa Aesar. 4-Bromo biphenyl, 2-ethylphenol, and 2-ethylanisole were purchased from TCI. Dibenzofuran, 2-methoxynaphthalene, 2-hydroxydiphenyl, 2-methoxybiphenyl, sodium ethoxide, sodium *tert*-butoxide, lithium *t*-butoxidediisobutyl aluminum hydride (1 mol/L solution in toluene), triethylsilane, sodium borohydride, potassium borohydride, potassium hydroxide, and 1,8-diazabicyclo[5.4.0]un-



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dec-7-ene (DBU) were purchased from J&K. Anhydrous copper iodide, pyridine-2-carboxylic acid (picolinic acid), and anhydrous K₃PO₄ were also from J&K.

Di-2-methoxyphenyl ether, di-4-*tert*-butylphenyl ether, and di-4-ethylphenylether were synthesized by ourselves based on the reported procedures.^[31] Typically, a 100 mL round bottom flask was loaded with copper(I) iodide (1 mmol), pyridine-2-carboxylic acid (2 mmol), aryl iodide (10 mmol), phenol (12 mmol), potassium phosphate (20 mmol), DMSO (30 mL) and a magnetic stir bar. The reaction flask was sealed with a septum in an argon atmosphere. After being stirred at 100 $^{\circ}$ C for 24 h, the reaction mixture was cooled down to room temperature and diluted with a saturated aqueous solution of ammonium chloride. The product was extracted with methylene chloride $(2 \times 100 \text{ mL})$, which was successively washed with a 5% aqueous solution of potassium hydroxide (100 mL), brine (100 mL) and dried over anhydrous sodium sulfate. The crude product was then purified by column chromatography.

Di-2-methoxyphenyl ether NMR data are as follows. ¹H NMR (400 MHz, CDCl₃) δ : 7.03–6.83 (m, 8H), 3.85 (s, 6H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ : 155.4 (C), 151.6 (C), 119.6 (CH), 114.7 (CH), 55.7 (CH₃).

Di-4-tert-butylphenyl ether NMR data are as follows. ¹H NMR (400 MHz, CDCl₃) δ : 7.32 (dd, J=8 Hz, 4H), 6.93 (dd, J=8 Hz, 4H), 1.31 (s, 18H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ : 155.6 (C), 146.2 (C), 126.9 (CH), 118.7 (CH), 34.7 (C), 31.9 (CH₃).

Di-4-ethylphenyl ether NMR data are as follows. ¹H NMR (400 MHz, CDCl₃) δ : 7.13 (d, J=8 Hz, 4H), 6.91 (d, J=8 Hz, 4H), 2.61 (q, J=8 Hz, 2H), 1.22 (t, J=8 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ : 155.6 (C), 138.9 (C), 129.1 (CH), 118.7 (CH), 28.3 (CH₂), 15.8 (CH₃).

General procedure for reduction of aryl ethers

The reactions were conducted in a 35 mL vial with Teflon-lined screw cap (supplied by Synthware Company) and Teflon-coated magnetic stir bar. In a glove box, the vial was loaded with corresponding substrate (1 mmol, 1 equiv.), base (2.5 equiv.) and a magnetic stirring bar, followed by syringe addition of 5 mL of decane and hydride source (2.5 equiv.). Then the vial was sealed and heated at a desired temperature (e.g., 140 $^{\circ}$ C) for a desired time. After being cooled to room temperature, the reaction mixture was carefully quenched with 5 mL of 2 mol/L aqueous HCl at 0 $^{\circ}$ C, accompanied with addition of n-dodecane (internal standard for GC analysis) to the reaction solution, and the liquid was separated. Ethyl acetate ($2 \times 3 \text{ mL}$) was used to extract the aqueous phase. The combined organic solution was subjected to GC/FID for qualitative and quantitative identification. The crude product was purified by column chromatography on silica gel (the eluent was petro to petro/ethyl acetate with a molar ratio of 15:1 or 10:1). The purified products were characterized by NMR

techniques.

Characterization

¹H NMR and ¹³C NMR spectra were recorded on a Bruker AV400 (400 MHz, 100 MHz) NMR 80 spectrometer in CDCl₃ with tetramethylsilane as an internal standard. The liquid products were analyzed by GC on an Agilent 7890B Gas Chromatography equipped with an HP-INNOWAX 19091N-133 (30 m \times 0.25 mm ID \times 0.25 µm) capillary column (Agilent) and an FID detector. The following GC temperature program was used: 50 °C hold for 2 min, ramp 20 °C/min to a final temperature of 250 °C, and hold for 8 min. The injector temperature was held at 250 °C. Nitrogen was used as a carrier gas. GC-MS analyses were performed on a Shimadzu QP-2010 gas chromatography equipped with a DB-5 30 m \times 0.25 mm \times 0.25 μ m capillary column (Agilent). The GC was directly interfaced to an Agilent 5973 mass selective detector (EI, 70 eV). The following GC temperature program was used: 50 °C hold for 2 min, ramp 20 °C/min to a final temperature of 250 °C, and hold for 20 min. Nitrogen was used as a carrier gas. The injector temperature was held constant at 250 °C.

Results and Discussion

Dibenzofuran is a model compound for the 4-O-5 linkage in lignin. The reduction of dibenzofuran was chosen as a model reaction to optimize the reaction conditions, and the results are listed in Table 1. Dibenzofuran could not be reduced by NaH in the absence of any base (Table 1, Entry 1). Excitingly, it was completely reduced to o-phenyl phenol by NaH in the presence of KO^tBu at 140 °C (Table 1, Entry 2). Compared to the reported results (Table 1, Entries 3 and 4), the combination of NaH with KO^tBu showed much higher efficiency for this reaction than that of LiAlH₄ with NaO^tBu in the presence of [Fe(acac)₃] or that of Et₃SiH/ KO^tBu as the reaction system. More importantly, no byproduct was detected, indicating obvious advantages over the combination of triethylsilane with bases.^[28] The hydrogenation of aryl ring in dibenzofuran did not occur, implying that the reductive power of NaH combined with KO^tBu was just appropriate for reductive cleavage of C-O bond in ethers. Other hydrogen donors including NaBH₄, KBH₄, diisobutyl aluminium hydride (DIBAL) and Et₃SiH were examined for this reaction in the presence of KO^tBu. It was indicated that NaBH₄, KBH₄ and DIBAL were ineffective for this reaction (Entries 5–7). Et₃SiH afforded a product yield of 82%under the same other conditions (Entry 8), however, accompanied with several byproducts, consistent with that reported previously.^[28] The bases including NaO'Bu, LiO^tBu, NaOEt, KOH and DBU instead of KO^tBu were examined in the reduction of dibenzofuran by NaH, and no reaction occurred (Table 1, Entries 9-13). These results indicated that the combination of NaH and KO^{*t*}Bu was exclusively effective for the cleavage of aryl

C-O in dibenzofuran. The temperature influence was investigated, and it was demonstrated that the product yield increased with temperature in the range of 100-140 °C (Entries, 2, 14, 15), and 140 °C was selected as the reaction temperature for the other experiments.

 Table 1
 Optimization of reductive cleavage of dibenzofuran^a

	Hydride agents base, Temp. time OH					
	1				2	
Entry	Hydride	Base	T/℃	Conv. of 1/%	Yield of 2 /%	
1	NaH	no	140	0	0	
2	NaH	KO ^t Bu	140	100	$> 99/90^{b}$	
3°	LiAlH ₄	NaO ^t Bu	140	—	80	
4 ^d	Et ₃ SiH	KO ^t Bu	165	100	85	
5	NaBH_4	KO ^t Bu	140	0	0	
6	KBH_4	KO ^t Bu	140	0	0	
7	DIBAL	KO ^t Bu	140	0	0	
8	Et ₃ SiH	KO ^t Bu	140	100	82	
9	NaH	NaO ^t Bu	140	0	0	
10	NaH	LiO ^t Bu	140	0	0	
11	NaH	NaOEt	140	0	0	
12	NaH	DBU	140	0	0	
13	NaH	KOH	140	0	0	
14^{e}	NaH	KO ^t Bu	100	51	50	
15	NaH	KO ^t Bu	120	64	63	

^{*a*} Conditions: **1** (1 mmol), NaH (2.5 mmol), KO'Bu (2.5 mmol), decane (5 mL), 24 h. ^{*b*} Yields of isolated products. ^{*c*} **1** (0.2 mmol), LiAlH₄ (0.5 mmol), [Fe(acac)₃] (0.04 mmol), toluene (1.5 mL), NaO'Bu (0.5 mmol), 140 $^{\circ}$ C, 24 h. ^{*d*} **1** (0.1 mmol), Et₃SiH (0.3 mmol), KO'Bu (0.3 mmol), mesitylene (1 mL), 20 h. ^{*e*} 48 h.

Figure 1 shows the dependence of the product yield on the reaction time. As expected, the product yields increased with reaction time, and approached 100% at 18 h. Prolonging reaction time to 24 h, the yield did not decline, suggesting that the product was tolerant to the reaction system. Notably, in the reaction process *o*-phenyl phenol was the sole product, and no byproduct was detected, suggesting the highly selective cleavage of the aryl C-O in dibenzofuran without the hydrogenation of the aryl ring. Compared to those reported previously,^[28] the reaction system in this work was simpler and more efficient, and no byproduct was yielded.

Encouraged by the above results, we extended the reaction system to diaryl and aryl alkyl ethers, and the results are listed in Table 2. It was demonstrated that the aryl C-O bond cleavage occurred without the hydrogenation of the aryl rings, producing corresponding phenols and arenes. For example, diphenyl ether was reduced to phenol and benzene in excellent yields, and 4-ethyl diphenyl ether to ethyl benzene and 2-ethyl phenol, also in high yields. The substrate bearing a

tert-butyl group in the para-position showed a low activity, however, the products were obtained in high selectivity. As for the reduction of di-2-methoxyphenyl ether that bears two OCH₃ electron-donating groups, the substrate was completely converted under the experimental conditions, but the target products were obtained in low yields, accompanied with many byproducts incluing 1-methoxy-2-phenoxybenzene, 2-(2-methoxyphenoxy)-phenol, which originated from the removal of aryl -OCH₃ and -CH₃ groups, implying that the combination of NaH and KO^tBu could cleave both the diaryl C-O and aryl alkyl C-O bonds. However, as NaH combined with KO^tBu was applied to diaryl ethers bearing electron-withdrawing groups, $-CF_3$ and $-Br_3$. the reductive cleavage of C-O bond did not occur, while debromination took place for 4-bromo-biphenyl ether, producing diphenyl ether under the experimental conditions.



Figure 1 Dependence of the residual dibenzofunan and *o*-phenyl phenol yield on reaction time.

For the reduction of aryl alkyl ethers, both the aryl C-O and alkyl C-O bonds could be cleaved by the reduction of NaH in the presence of KO'Bu, only producing corresponding phenols and arenes in different yields depending on the inherent nature of the substrates. For example, anisole was converted to benzene and phenol with the comparable yields and without any other byproducts under the experimental conditions. Similarly, 2-ethyl phenyl methoxyl ether was converted to ethylbenzene and 2-ethylphenol, with the yield of ethylbenzene much higher than that of 2-ethylphenol. This implies that the ortho-substitution of ethyl group made the aryl C-O bond easier to cleave than the alkyl C-O bond. The similar phenomenon was also observed in the reduction of 2-methoxy biphenyl, which afforded more biphenyl (83%) than biphenyl-2-ol (17%). However, the reduction of 4-methoxy biphenyl delivered contrary results, which generated more biphenyl-4-ol (78%) than biphenyl (22%), suggesting that para-substitution made alkyl C-O bond easier to cleave. Moreover, it is worth noticing that the conversions of 2-methoxy biphenyl and 4-methoxy biphenyl were much higher than those of anisole and 2-ethyl anisole, suggesting that the conjugative group linked to anisole made

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^a Condition: substrate (1 mmol), NaH (2.5 equiv.), KO'Bu (2.5 equiv.), decane (5 mL), 24 h, 140 °C; ^b Yields of isolated products.

the substrates more reactive. This was also supported by the results of the reduction of 2-methoxynaphthalene. From the above findings, it can be concluded that the combination of NaH and KO^tBu was powerful to cleave the C-O bonds in diaryl ethers and aryl alkyl ethers, producing corresponding phenols and arenes without the hydrogenation of the aryl rings.

In recent researches, some reactions mediated by KO'Bu were considered through a single-electrontransfer (SET) mechanism.^[32-34] The KO'Bu-mediated reduction of diaryl ethers and alkyl aryl ethers by NaH in this work maybe follow the similar SET mechanism as well. To verify this hypothesis, several preliminary experiments were conducted. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) (1 equiv.) as a radical scavenger was added in the reaction solution of dibenzofuran, which resulted in the total termination of the reaction. The reaction mixture was examined, and it was EPR active as shown in Figure 2. This implies that the reaction was under a SET mechanism.

Conclusions

In summary, we presented a simple and efficient catalytic system for the reductive cleavage of aryl C-Oand alkyl C-O bonds in diaryl and/or aryl alkyl ethers, producing phenols and arenes. Although the reaction mechanism needs to be further studied, the results from this work have demonstrated that the cleavage of the



Figure 2 EPR spectrum of the reaction mixture of dibenzofuran reduction by NaH/KO'Bu in decane. After the solution of dibenzofuran (1 mmol, 1 equiv.), KO'Bu (2.5 equiv.) and NaH (2.5 equiv.) in 5 mL of decane was heated for 8 h at 140 $^{\circ}$ C, the reaction mixture was centrifugated and filtered into an EPR tube. The spectrum was recorded within 15 min.

C-O bonds in aryl ethers is under a SET mechanism. This work opens a novel and simple way to produce aromatics from aryl ethers, which may have promising applications in the production of aromatics from lignin compounds.

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