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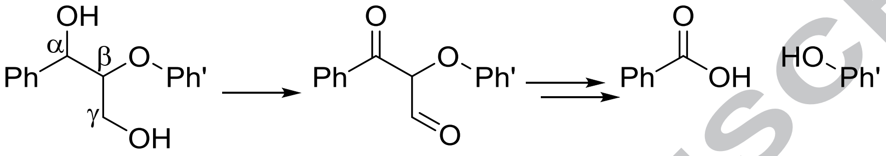

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Investigate cleavage of β-O-4 linkage in lignin model compounds by aerobic oxidation of Cα and Cγ hydroxyl groups

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ABSTRACT

The selective cleavage of common linkages in lignin polymers is a promising approach to generate valuable aromatic hydrocarbons. Herein, we found that on oxidation of Cα and Cγ hydroxyl groups in β-O-4 lignin model compounds with TEMPO catalyst resulted in the formation of 1,3-dicarbonyl TEMPO adduct. These oxidized products readily underwent fragmentation at Cα-Cβ bond in the presence of a catalytic amount of acid to generate corresponding carboxylic acid and phenol monomers.

1. Introduction

Lignin is a highly cross-linked aromatic polymer biosynthesized from three common monolignol monomers: p-coumaryl alcohol, coniferly alcohol, and sinapyl alcohol.[1] It is an indispensable component of the plant cell wall that protects the plant from biodegradation, provides mechanical support, and transports liquid in plant stem.[2] The rich aromatic structure of the lignin has potential to produce valuable bulk chemicals and bio-based fuel additives as well as has substantial prospect for application in polymer resin systems, such as polyurethane and epoxy.[3-6] At present, lignin has limited high-valued commercial applications, and hence, every year million tons of lignin generated as a waste stream from the pulp and paper industries are largely burned as a low-grade fuel.[7] The lignin depolymerization processes have several practical difficulties because of lignin's complex rigid structure. Therefore, many researchers took a simpler approach using lignin model compounds with similar linkages and functional groups to native lignin polymer in their studies.[8-11] Conducting oxidation study using synthetically pure lignin model compounds have several advantages over the native lignin polymers. The selectivity of the reaction can be properly addressed because it is possible to separate oxidized products and characterize them using conventional analytical techniques. And, insights gained from studying model compounds will greatly benefit our understanding of natural lignin depolymerization process as a whole.

In recent years, many researchers have reported catalytic aerobic oxidation of electronically active benzylic hydroxyl in lignin model compounds. The benzylic ketone products are quite stable and do not readily undergo fragmentation reaction. Therefore, many researchers adopt a two-step process for selective cleavage of β-O-4 linkage in dimer model compounds.[12-14] Stephenson and co-workers utilized a photochemical process in their study, which consisted of chemoselective oxidation of benzylic hydroxyl group in the first step followed by a catalytic reductive cleavage of the C-O bond in the second step.[15] Likewise, Moody *et al.* reported photochemical catalytic oxidative cleavage of lignin model compounds using hydroquinone and copper nanoparticles.[16] Westwood *et al.* reported oxidative cleavage of Cβ-O linkage in β-O-4 model compounds by Zinc and NH_4Cl treatment.[17] Meier and group studied selective aerobic oxidation of hydroxyl groups using TEMPO/$NaNO_2$ and DDQ/$NaNO_2$ oxidation process, and further cleavage of the Cα-Cβ linkages by Baeyer-Villiger oxidation.[14] Loh and co-workers studied selective oxidation of benzylic alcohol and cleavage of β-O-4 linkage by amide bond formation.[18] However, most of these methods demanded an additional step, the usage of stoichiometric amounts of reagents (non-catalytic), transition metal catalysts, and energy intensive reaction conditions. Other challenges involved the limited selectivity of the oxidation process and also the fragmented phenolic compounds further underwent in-situ polymerization. As a result, development of a more selective depolymerization process is still an ongoing research focus worldwide.

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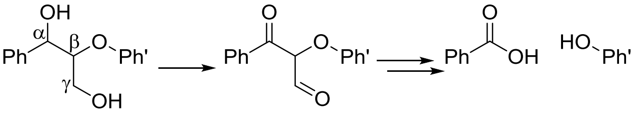
Alternatively, the selective aerobic oxidation of Cγ primary alcohol using TEMPO/Cu system, in combination with suitable ligand has been reported by Stahl *et al.* and also by Baker and group.[19,12,20] Their study on lignin model compounds demonstrated that selective oxidation of primary alcohols facilitated cleavage of Cα-Cβ via retro-aldol reactions. However, the yield of the oxidized product was low since catalytic oxidation of primary alcohol groups in model compounds was more challenging. None of the previous groups has attempted to oxidize both primary and benzylic hydroxyl groups of the lignin model compounds with an excess amounts oxidants in the system.



Scheme 1. Oxidative fragmentation pathway for β-O-4 dimeric lignin model compounds

Therefore, in this work, we aim to study the fragmentation pattern (as shown in Scheme 1) upon oxidation of both Cα benzylic and Cγ primary hydroxyl groups in lignin model compounds. We believe that catalytic aerobic oxidation of Cα and Cγ alcohol groups in model compounds will provide important insight for depolymerizing natural lignin polymer targeting value-added applications.

We first prepared monomeric and β-O-4 dimeric lignin model compounds, and then opted for selective cleavage of Cα-Cβ bond facilitated by aerobic oxidation of hydroxyl groups. In order to address the selectivity of the oxidation process, dimer model compounds with benzylic hydroxyl groups having different steric surroundings were synthesized. The chemoselective oxidation of primary alcohol in both monomer and dimer lignin model compounds by TEMPO/CuCl/bpy/NMI system was carried out and compared. In addition, the oxidation of benzylic and primary alcohol in model compounds to corresponding 1,3-dicarbonyl adducts was performed by two different pathways. In the first pathway, step-wise selective oxidation of benzylic hydroxyl groups and primary alcohol using TEMPO/$NaNO_2$ and TEMPO/Cu process was studied. And then in the second pathway, a single-step oxidation was studied using a surplus amount of TEMPO catalyst and oxidant. Lastly, we report a novel approach to cleave Cα-Cβ bond in lignin model compounds to produce carboxylic acids and phenol monomers. Although past literature has found that natural lignin could be oxidatively degraded into methoxybenzoic acids and phenols, their degradation pathway and mechanism were not studied and were unclear.[21,22] Herein, we present our findings on how the lignin polymer undergoes oxidative fragmentation. We believe that in depth knowledge of the fragmentation pattern can help develop a better method for lignin depolymerization.

2. Results and Discussion

The most abundant β-O-4 linkage in lignin polymer has characteristic benzylic and primary aliphatic alcohol groups.[23,7] Lately, various methods for selectively oxidation of electronically active benzylic hydroxyl groups have been reported in literature, however effective method for selective oxidation of primary alcohols in lignin model compounds still needs improvements. The aerobic oxidation of primary alcohols in lignin is an important step towards depolymerization of the lignin polymer. In 1984, Semmelhack *et al.* reported the catalytic mixture of TEMPO and CuCl for aerobic oxidation of benzylic alcohol. However, for oxidation of non-benzylic alcohol, a stoichiometric amount of reagent was used.[24] Over the last two decades, considerable progresses have been made to develop an effective catalytic process for the oxidation of a wide range of primary alcohols. In our study, chemoselectivity oxidation of monomeric and dimeric lignin model compounds was compared by treating 20 mol % TEMPO, CuCl, bpy each and 40 mol % of NMI in MeCN, under an air atmosphere.[12,19] The percentage of recovery and yields of the products formed are listed in Table 1 and Scheme 2. In this method, bpy ligand enhanced the solubility of copper catalyst, and NMI increased the rate of reaction. Under these conditions, 2-phenoxyethylbenzene (Table 1, entry i) being a non-hydroxylated simple model compound and 2-phenoxy-1-phenylethan-1-ol (Table 1, entry ii) compound with neither γ carbon nor hydroxyl group did not react since most of the starting material was recovered.

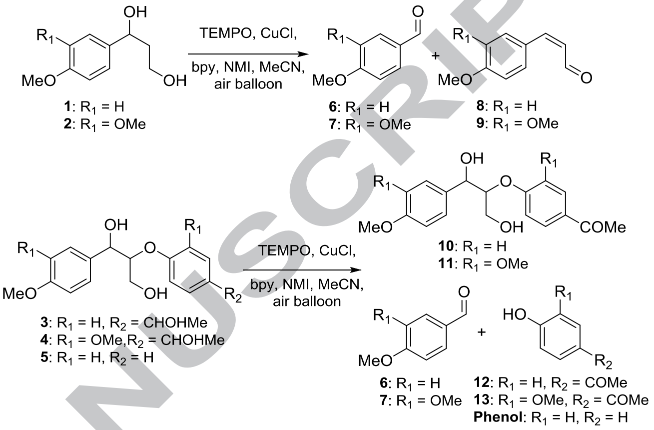
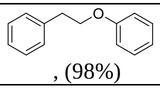
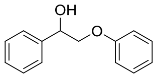
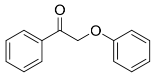


Table 1. Oxidation of lignin model compounds with

Scheme 2. TEMPO/CuCl chemoselective oxidation of **1** – **5**

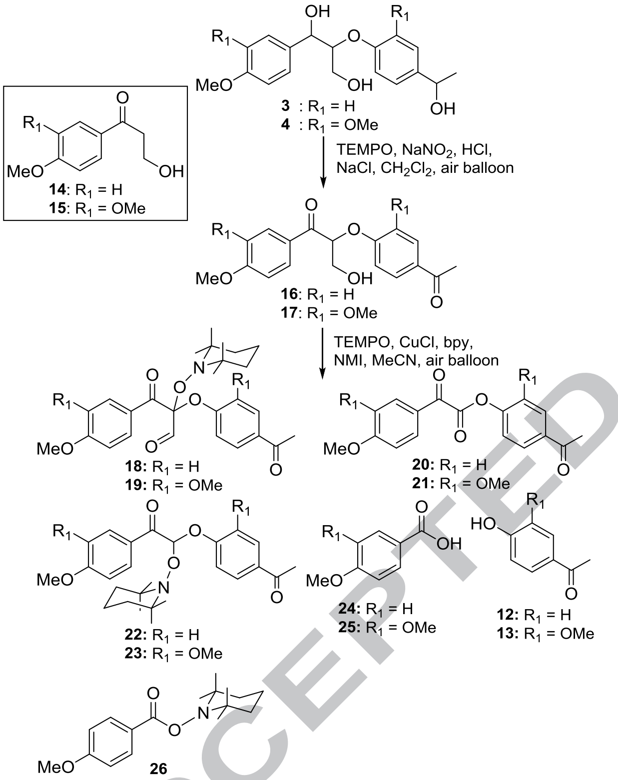
TEMPO/CuCl[a, b]

Entry	Substrate, (% recovery)[a]	Products, (% yield)[b]		
i.	 , (98%)			
ii.	 , (95%)	 , (2%)		
iii.	1	6, (34%)	8, (39%)	
iv.	2	7, (35%)	9, (38%)	
v.	3, (51%)	10, (31%)	6, (10%)	12, (7%)
vi.	4, (43%)	11, (35%)	7, (12%)	13, (9%)
vii.	5, (77%)	6, (13%)	Phenol, (6%)	

[a] Reaction were carried out for 20 h under air atmosphere at room temp using 0.2eq of TEMPO, CuCl, bpy and 0.4eq of NMI. [b] Purified and isolated products yield and recovery.

In monomeric model compounds, primary alcohol oxidized product appeared to undergo retro-aldol reaction as well as *in situ* dehydration of benzylic alcohol to produce corresponding benzylic aldehydes and enal.[12] The oxidative cleavage reaction was not observed in 2-phenoxy-1-phenylethan-1-ol as γ carbon and hydroxyl group were not present. We observed that primary alcohol oxidation yield in the dimer model compound was relatively low compared to monomeric model compounds, as less than 13% retro-aldol products were produced. It appeared that dimer compounds underwent Cα-Cβ cleavage to form benzyl aldehyde and substituted 2-phenoxyacetaldehyde intermediate which further underwent fragmentation to yield phenol and water soluble acetaldehyde.[15] The water soluble acetaldehyde would account for the loss of two carbons in Scheme 2. Furthermore, in the dimer model compounds **3** – **4,** less sterically hindered secondary hydroxyl groups also underwent oxidation to produce **10** – **11** (Table 1, entry v and vi). These findings are in agreement with previously published results.[12] We believe that catalytic TEMPO/CuCl conditions were inadequate in oxidation of primary alcohol in dimer model compounds because of steric constraints around a reactive site. These oxidation conditions were further used to accomplish oxidation reaction in Scheme 3.

As lignin being a multifunctional complex polymer, predominantly selective oxidation of primary hydroxyl groups has several practical difficulties. We, therefore, carried out an investigation to study the fragmentation pattern of β-O-4 model lignin compounds by oxidation of both types of hydroxyl groups. In stepwise oxidation study, benzylic hydroxyl groups was initially oxidized followed by the primary alcohols groups. The benzylic hydroxyl groups in **3** – **4** were selectively oxidized using a catalytic TEMPO and $NaNO_2$ system at ambient temperature under air atmosphere to form **16** – **17** with ~90% yields. Later, the primary alcohol groups in product **16** – **17** were further oxidized by the TEMPO/CuCl system as shown in Scheme 3 (Table 2, entry i and ii)



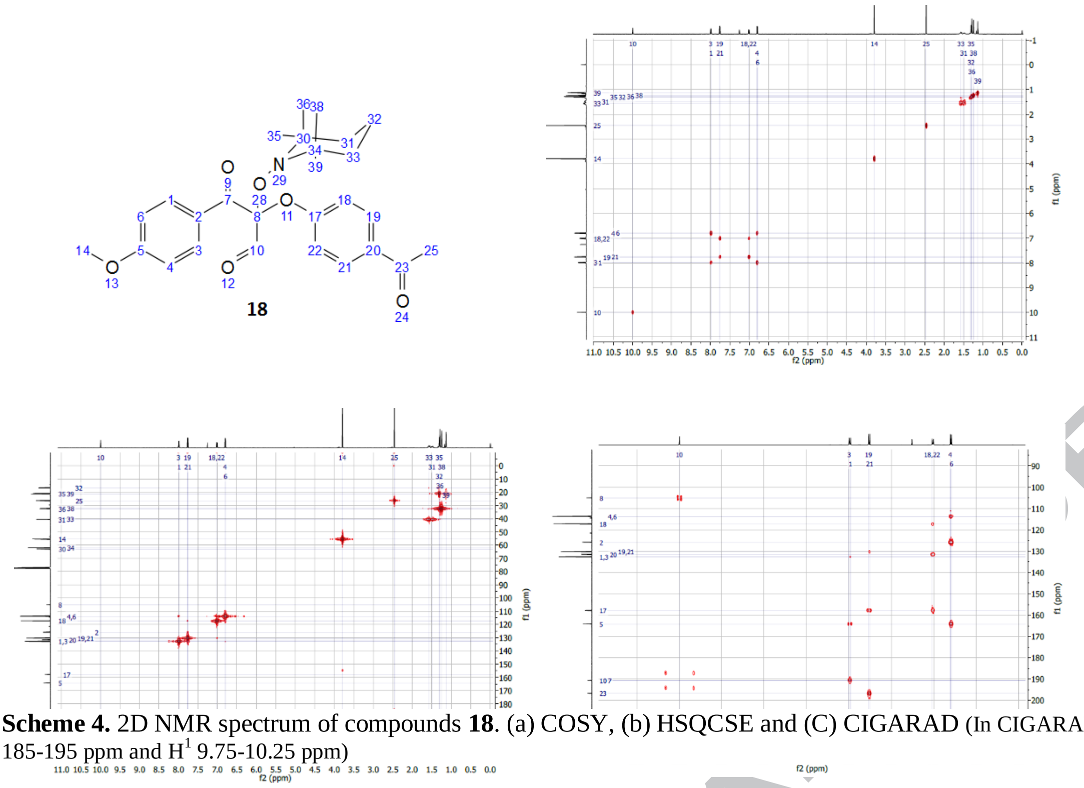
Scheme 3. Stepwise oxidation of benzylic and primary alcohol in **3 – 4**

We observed that under these conditions, the 1,3-diketone oxidized products rapidly underwent the addition reaction to produce alkoxyl amine **18** – **19** (Table 2, entry i and ii). Similarly, **16** – **17** also underwent minor dehydration reaction.[25,14] On the other hand, when compound **3** – **4** was oxidized using an excess amount of TEMPO catalyst and oxidant, the hydroxyl groups of the model compounds were oxidized to yield 1,3-dicarbonyl-TEMPO adduct **18** – **19** as the major products.[26,13] The detailed characterization of the compounds were done by 2D NMR: COSY, HSQC and CIGARAD, as shown in Scheme 4. The product **18** was relatively labile, and thus easily underwent in-situ Cα-Cβ bond cleavage to produce compounds **24** and **12**. The phenol **12** was only 10 % in yield, as under these conditions it might endure oxidative polymerization.[27] The exact mechanism is still unclear; however, the formation of carboxylic acid suggested retro-Claisen reaction might be one of the intermediate steps that facilitated cleavage of Cα-Cβ linkage.[28,29] This protocol provided a simple and effective one-pot strategy for depolymerization of lignin model compounds. Also under these acidic reaction conditions, products **18** – **19** reacted to form a series of products ranging from **20** to **26**, these results were in agreement with some previously report studies.[30,31] Although, we were unable to isolate fragmented products derived from **19**. When model compounds **14**– **15** were oxidized under conditions B, a minor amount of unidentified dimers were isolated.

Table 2. Oxidation of **16 – 17**, and **3 – 4.**

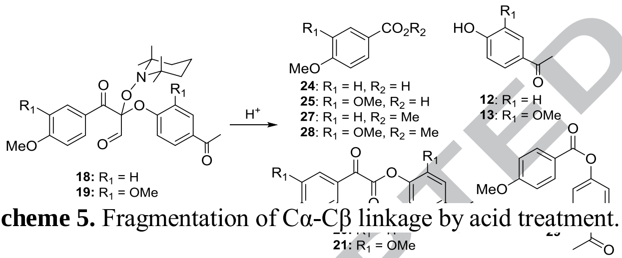
Entry	Subs, (%recovery)	Products, (%yield)[c]					
i.	16, (84%)[a]	18, (10%)					
ii.	17, (83%)[a]	19, (13%)					
iii.	3[b]	18, (37%)	20, (10%)	22, (2%)	12, (10%)	24, (39%)	26, (7%)
iv.	4[b]	19, (56%)		21, (23%)		23, (19%)	

[a] Conditions A: Reaction were carried out for 20 h under air atmosphere at room temp using 0.2eq of TEMPO, CuCl, bpy and 0.4eq of NMI. [b] Conditions B: Reaction were carried out for 14 h under air atmosphere at room temp using 5eq of TEMPO, 5eq $NaNO_2$ and 10eq HCl. [c] Purified and isolated products yield and recovery.



Scheme 4. 2D NMR spectrum of compounds **18**. (a) COSY, (b) HSQCSE and (C) CIGARAD (In CIGARAD artifact noise between C[13] 185-195 ppm and H[1] 9.75-10.25 ppm)

Table 3. Oxidation of **3** and **4** with TEMPO/NaNO$_2$.[b]



Scheme 5. Fragmentation of Cα-Cβ linkage by acid treatment.

Entry	Substrate	Products, (% yields)		
i.	18^{a,b}	24, (79%)	12, (78%)	20, (9%)
ii.	19^{a,b}	25, (55%)	13, (53%)	21, (40%)
iii.	18^{c,d}	27, (64%)	12, (73%)	29, (14%)
iv.	19^{c,d}	28, (80%)	13, (83%)	21, (5%)

[a] Yield determined is based on the integration ratio of crude ^{1}H NMR spectra. [b] Substrate, 1eq of 36% HCl and CH$_2$Cl$_2$ was stirred at 25ºC for 14 h. [c] Purified and isolated products yield. [d] Substrate, 0.1eq of conc H$_2$SO$_4$ and MeOH was reflux for 1 h.

In the final step, the cleavage of Cα-Cβ linkage was successfully carried out by two different methods. In the first method, the substrate was stirred at room temperature in 1eq HCl and CH$_2$Cl$_2$, whereas in the second method, substrate was refluxed in methanol for 1h in the presence of a catalytic amount of H$_2$SO$_4$ to give corresponding methoxyester and phenol. The formation of methoxyester products **27** – **28** suggested the possibility of a retro-Claisen reaction (Scheme 5, Table 3, entry iii and iv),[28,29] however precise mechanism is under further investigation. The generation of product **29** revealed that fragmented phenol **12** also promoted cleavage of compound **18**.

In conclusion, oxidation of sterically hindered primary alcohol groups in dimer lignin model compounds under TEMPO/CuCl conditions had a lower conversion compared to monomeric compounds. We have demonstrated that 1,3-dicarbonyl-TEMPO adduct substructure produced by oxidation of alcohols in β-O-4 lignin model compounds could easily undergo Cα-Cβ bond fragmentation in the presence of a catalytic amount of acid. We have identified an important oxidation step that promotes the fragmentation of the linkages in the lignin polymer. Further research will focus on depolymerization of lignin polymers to produce valuable aromatic hydrocarbons.

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Highlights

- Selective cleavage of β-O-4 linkages in lignin model compounds.
- Aerobic oxidation of lignin model compounds.
- Fragmentation of 1,3-dicarbonyl-TEMPO adduct in the presence of a catalytic amount of acid.