Short communication

Study of the nitroxyl radical catalyst in aerobic oxidative cleavage and functionalization of lignin model compounds

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A B S T R A C T

The selective aerobic oxidation of hydroxyl groups, α-oxyamination of benzylic ketones, and selective cleavage of $C\alpha$-$C\beta$ linkages in lignin model compounds were studied using nitroxyl radical catalysts and sodium nitrite. The less hindered nitroxyl radical catalysts (ABNO, 1-Me-AZADO) were found to be more reactive in comparison to TEMPO. We identified a novel method to convert α,γ-dihydroxyl β-O-4 lignin model compounds directly into corresponding α-oxyaminated products and 1,2-keto esters. A new pathway for cleavage of $C\alpha$-$C\beta$ linkage in β-O-4 link p-hydroxyphenyl (H-units) model compounds to produce useful aromatic monomers has also been demonstrated.

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1. Introduction

Lignin is an intrinsic component of plant cell walls, which serves as the protective barrier against biodegradation [1] There are many ongoing research efforts to utilize lignin polymers as alternatives to petroleum-derived compounds for various valued-added applications, such as polyurethane foams, adhesives [2], fire retardants [3], and epoxy resins [4]. Generally, for fundamental studies related to lignin modification and degradation, lignin model compounds with similar but simpler structures to native lignin polymers are first probed by targeting specific functional groups and linkages [5]. The structure of β-O-4 dimer model compound illustrated in Scheme 1, **I**, has a benzylic hydroxyl group at the $C\alpha$ and a primary hydroxyl group at $C\gamma$ position.

Using TEMPO catalyst for selective aerobic oxidation of electronically activated benzylic hydroxyl groups (hydroxyl group at $C\alpha$ position) in β-O-4 dimer lignin model compounds has been extensively studied by many researchers previously [6–9]. The resulting benzylic ketone product, Scheme 1, **II**, has distinctive structural features which can be chemically modified to proliferate cleavage of C-C linkage in β-O-4 link model compounds. Or it can be further functionalized for broader applications. In an effort to fragment the key linkages, Meier et al. recently investigated cleavage of $C\alpha$-$C\beta$ linkage in β-O-4 model compounds **II** by Baeyer-Villiger oxidation using formic acid and hydrogen peroxide [6]. Stahl, S

reported effective approach for depolymerization of **II** by formic acid and sodium formate treatment [7].

On the other hand, efforts have been made to promote functionalization of lignin to enhance its usability in a wide range of applications [10]. In that respect, Loh, T. and group reported transformation of **II** to α-keto amide derivatives and phenols via Cu-catalyst and secondary amines [11]. Plietker and coworkers described a new approach for selective cleavage of $C\beta$-O linkage and sequential alkylation of the corresponding acetophenone derivative using primary alcohols [12].

On a particular note, TEMPO has been the most studied catalyst as compared to other stable nitroxyl radicals. That is largely due to the fact that TEMPO is inexpensive, commercially available, and relatively safe. Meanwhile, the new generation of nitroxyl radical with less steric hindrance around the stable nitroxy radical active site is more effective as catalysts for oxidation of a wide range of alcohol groups. However, no reported study has explored the ability of ABNO (9-azabicyclo[3.3.1]nonane N-oxyl) and 1-Me-AZADO (1-Methyl-2-azaadamantane-N-oxyl) catalysts (Scheme 2) for oxidation of benzylic and electronically inactive primary alcohol groups in β-O-4 model compounds. In this work, capability of different nitroxyl catalysts to perform oxidation of hydroxyl groups and functionalization of lignin model compounds were studied. Herein, we report our finding of a novel method using nitroxyl radical catalyst/$NaNO_2$/HCl to convert β-O-4 model compounds into α-aminooxyketones and α-ketoesters. These transformations convert

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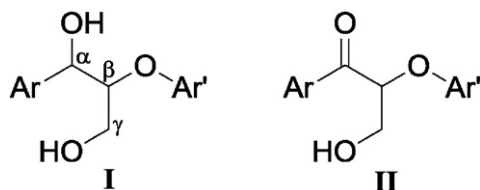
Scheme 1. Schematic representation of the β-O-4 dimer model compound (**I**) and benzylic hydroxyl group oxidized model compound (**II**).

lignin model compounds into interesting compounds with a wide applicability for developing novel materials and chemical precursors. (See Scheme 3.)

2. Results and discussion

The lignin model compounds, **1–6**, were synthesized according to a procedure reported in literature [6,13,14]. The β-O-4 linkages have characteristic benzylic alcohol (Cα) and electronically less active primary alcohol (Cγ) groups. 1,3-dicarbonyl compounds generated by oxidation of 1,3-diol have a unique reactivity and have been used as an intermediate for synthesis of wide range of organic compounds. Oxidation of both the hydroxyl groups of the β-O-4 linkage of lignin is an interesting approach to transform lignin into valuable intermediates. The oxidation of hydroxyl groups and chemical modification of lignin model compounds have been studied using different oxidation reagent. The initial study done using conventional oxidants, like 2-Iodoxybenzoic acid (IBX) [15], Dess-Martin periodinane [16], and Swern oxidation [17] system, was ineffective in oxidizing primary alcohol in dimer lignin compounds. Therefore, a new class of sterically less hindered nitroxyl radical catalysts (ABNO, 1-Me-AZADO) was considered for further lignin oxidation study.

In order to identify the ABNO catalyst efficiency for oxidation of the alcohol groups we screened several potential co-catalysts that could assist the oxidation process. We first examined the nitroxyl radicals/sodium hypochlorite (NaOCl) oxidation process developed by Iwabuchi Y; however, in that process benzylic ketone products underwent α-chlorination and then formed complex mixtures [18]. The oxidation study using NaNO₂ co-catalyst in AcOH transformed lignin model compound **5** into an unresolved complex mixture. (Table 1, entry i) [19]. The reaction utilizing FeCl₃/NaNO₂ and Fe(NO₃)₃·8H₂O co-catalysts exhibited a good selectivity for oxidation of benzylic hydroxyl groups, as **7** and **8** were the only products formed. The reaction using Fe(NO₃)₃·8H₂O co-catalyst exhibited slightly better conversions, and the results also suggested that sterically less hindered benzylic alcohol had a higher reactivity [20,21]. Furthermore, when the reaction was performed at 50 °C, oxidation rate was certainly enhanced but product **8** underwent additional reaction to form **9** (Table 1, entry iv) [22]. The rate of reaction by incorporating NaNO₂/HNO₃ oxidation system was quite slow [19]. Under aerobic oxidation system NaNO₂/HCl/NaCl, **8** was the major product, which then underwent in situ reaction to form interesting organic compounds **10** (α-aminooxyketone), **11** (α-ketoesters) and products **12–13** resulted from fragmentation of Cα-Cβ linkage [23]. The efficiency of these oxidation conditions was again studied by performing the reaction at 50 °C, it was found that the oxidation rate was fairly low (Table 1, entry vii). The yield of these interesting
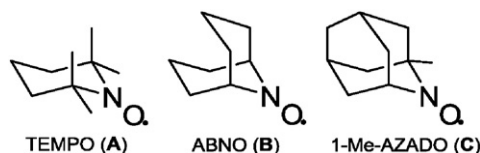
Scheme 2. Structures of nitroxyl radical catalysts.
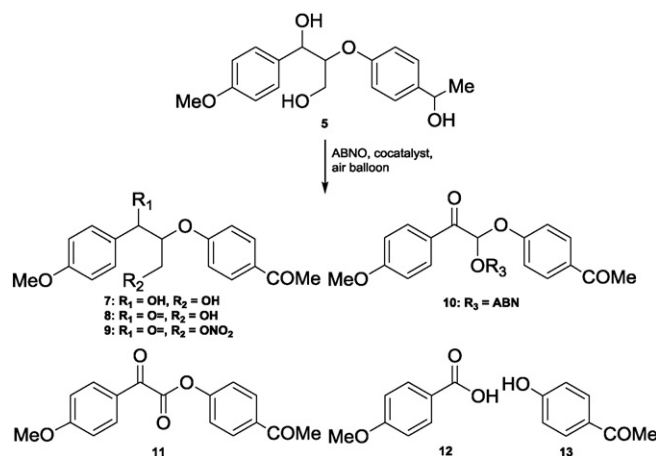
Scheme 3. Oxidation of **5** by ABNO and co-catalyst.

molecules encourages the usage of these conditions to perform additional oxidation studies on different lignin model compounds with TEMPO, ABNO and 1-Me-AZADO catalysts.

The alkoxyamines belong to a vital class of bioactive organic compounds, they are widely used as precursors to produce flame retardants and rheology modifiers. Due to their characteristic weak N-O bond, alkoxyamines can also be used as the initiators for well-ordered radical polymerization [24,25]. The development of efficient methods to generate alkoxyamines has been an attractive research topic. Recently, oxyamination of enolizable ketones like 1,3-dicarbonyl, 2-phenoxy-1-phenylethanone, silyl enol ether and enamines has been reported in literature using N-oxoammonium salts [26–30]. Song, R and group reported α-oxyamination of 2-phenoxy-1-phenylethanone using copper/iron catalyst and TEMPO [28]. Jiao et al. showed a rapid and effective method for α-aminoxylation of 1,3-dione using TEMPO and Cerium Ammonium Nitrate (CAN) catalyst [27]. Sibi, M and co-workers have reported an excellent enantioselective method for α-aminoxylation of aldehyde via enamines intermediate with the help of stoichiometric proportion of ferrocenium tetrafluoroborate [29]. Herein, we demonstrated the ability of ABNO and 1-Me-AZADO over TEMPO towards direct transformation of 1,3-diol model compounds to α-aminooxyketones and α-ketoesters.

The schematic representation of reactions between nitroxyl radical catalyst and model lignin compounds (**1–6**) under optimized conditions is illustrated in Scheme 4, and the yield of the products is summarized in Table 2 [6,23]. After systematic oxidation studies of the lignin model compounds, each product was carefully separated by column chromatography and structural characterization was carried out by NMR and HR-MS analysis. It was found that compound **1** did not react under these conditions since the starting material was mostly recovered after 14 h. After monitoring progression of the oxidation reaction by thin-layer chromatography (TLC), it was observed that ABNO and 1-Me-AZADO exhibited higher efficiencies than TEMPO as oxidation of benzylic hydroxyl group occurred much quicker. The oxidation of **3** and **4** by all three catalysts resulted in formation of 75–83% corresponding benzylic ketones **15** and **16**. The selective oxidation of primary alcohol in **3–4**, and dehydration of resulting products yielded minor amounts of compounds **17–18**. Surprisingly, α-oxyamination products, **19–21**, were also observed (Table 2. entry vi, vii and xi) and the yield of the products did not vary even when the reaction was carried out for 72 h. We believe that sterically less hindered nitroxyl radical catalysts (ABNO, 1-Me-AZADO) have accessible reactive sites to react with the intermediate enol. Nevertheless, similar α-oxyamination of **2** was not observed. The monomeric 1,3-dicarbonly products resulting from oxidation of primary alcohol or its fragmented product were not isolated. However, it was possible that such type of reaction did not occur or reactive products formed further reacted to produce unidentified mixture.