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• SPECIAL ISSUE • C–H bond activation

CsOH catalyzed aerobic oxidative synthesis of *p*-quinols from multi-alkyl phenols under mild conditions

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p-Quinols are ubiquitous structural motifs of various natural products and pharmaceutical compounds, and versatile building blocks in synthetic chemistry. The reported methods for the synthesis of *p*-quinol require stoichiometric amounts of oxidants. Molecular oxygen is considered as an ideal oxidant due to its natural, inexpensive, and environmentally friendly characteristics. During the ongoing research of C–H bond hydroxylation, we found that multi-alkyl phenols could react with molecular oxygen under mild conditions. Herein, we describe an efficient oxidative de-aromatization of multi-alkyl phenols to *p*-quinols. 1 atm of molecular oxygen was used as the oxidant. Many multi-alkyl phenols could react smoothly at room temperature. Isotopic labeling experiment was also performed, and the result proved that the oxygen atom in the produced hydroxyl group is from molecular oxygen.

***p*-quinol, molecular oxygen, de-aromatization, carbanion, cesium hydroxide**

1 Introduction

p-Quinol moiety (4-hydroxy-2,5-cyclohexadienone) is a structural component of a great number of natural products such as Teteapetalone [1], Manumycin A [2], Frondosin C [3], and Elisabethol [4] (Figure 1), as well as being useful synthetic intermediates in organic synthesis [5–8], and present in various novel therapeutic agents [9–12]. In this context, the development of efficient procedures for synthesis of *p*-quinols is of great importance [13,14]. A frequently used method for the preparation of *p*-quinols is oxidative de-aromatization of 4-substituted phenols [15–35]. Among those reported methods, stoichiometric amounts of oxidants, such as [(diacetoxy)iodo]benzene (PIDA) [15], [bis(trifluoroacetoxy)iodo]benzene (PIFA) [16–19], thallium(III) nitrate trihydrate ($Tl(NO_3)_3 \cdot 3H_2O$, TTN) [20], 3-chloroperbenzoic acid (*m*-CPBA) [21,22], perchloric acid ($HClO_4$) [23], periodic acid (H_5IO_6) [24], hydrogen peroxide (H_2O_2)

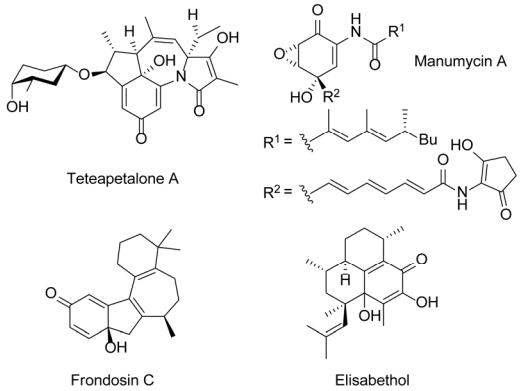

Figure 1 Natural products with *p*-quinol fragment.

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[25,26], oxone (potassium peroxymonosulfate) [27–29], etc. [30–35] were employed. Molecular oxygen is natural, inexpensive and as a reagent, produces no environmentally harmful byproduct and is thus considered as an ideal oxidant [36–39]. With the increasing demand for sustainable synthesis, the direct oxidation by using dioxygen as oxidant is highly desirable [40–45].

We recently reported a $Cs_2CO_3/P(OEt)_3/O_2$ system for the direct α-hydroxylation of carbonyl compounds through the cleavage of C–H bond for the synthesis of tertiary α-hydroxycarbonyls [46]. On the basis of this work, we apply this system to the oxidative de-aromatization of multi-alkyl phenols to *p*-quinols. Herein, we report a base catalyzed synthesis of *p*-quinols with dioxygen as the oxidant under mild conditions.

2 Experimental

2.1 General information

CsOH was purchased from Alfa Aesar Chemical Company and used as received. $P(OEt)_3$ was purchased from Beijing Ouhe Company (China). DMSO and other solvents were purchased from Beijing Chemical Works and purified under standard conditions. Other commercially available compounds were purchased from Sigma-Aldrich, Alfa-Aesar and Acros (USA) and used as received. Reactions were performed in a schlenk tube under standard conditions. Analysis of crude reaction mixture was done on an Agilent 7890 GC System with an Agilent 5975 Mass Selective Detector (USA). Products were purified by flash chromatography or by preparative thin-layer chromatography on silica gel. ^{1}H NMR spectra were recorded on a Bruker AVIII-400 spectrometers (Germany). Chemical shifts (in ppm) were were calibrated with $CDCl_3$ (tetramethylsilane, δ=0 ppm). ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ=77.00 ppm). Mass spectra were recorded using a PE SCLEX QSTAR spectrometer (Thermo Finnigan, USA). High resolution mass spectra were obtained with a Bruker APEX IV Fourier transform ion cyclotron resonance mass spectrometer (USA) using electrospray ionisation (ESI).

2.2 General procedure for aerobic oxidative synthesis of *p*-quinols from multi-alkyl phenols

CsOH (7.5 mg, 0.05 mmol), $P(OEt)_3$ (167 mg, 1.0 mmol), **3** (0.5 mmol) were added to a 25 mL Schlenk tube with a magnetic bar under O_2. DMSO (2.0 mL) was added and then the mixture was stirred at room temperature (25 °C) under O_2 (1 atm) for 12 h. The solution was then diluted with ethyl acetate (10 mL), washed with brine (3 mL), extracted with ethyl acetate (3×5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel to get the desired product **4**.

2.3 Characterizations of products

4a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 2 H), 2.43 (brs, 1 H), 1.85 (s, 6 H), 1.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 147.4, 133.24, 133.21, 67.0, 26.9, 15.7 ppm.

4b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (s, 2 H), 1.84 (brs, 1 H), 1.41 (s, 3 H), 1.21 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 145.3, 143.1, 67.3, 34.5, 29.3, 27.9 ppm.

4c: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (s, 2 H), 1.80 (s, 1 H), 1.23 (s, 18 H), 0.97 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 147.3, 141.0, 73.8, 39.8, 34.8, 29.4, 25.4 ppm.

4d: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (s, 2 H), 1.97 (brs, 1 H), 1.75 (q, J=7.6 Hz, 2 H), 1.22 (s, 18 H), 0.73 (t, J=7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 147.0, 141.9, 70.7, 34.6, 33.6, 29.4, 8.2 ppm.

4e: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (d, J=3.2 Hz, 1 H), 6.59 (s, 1 H), 2.42 (brs, 1 H), 1.84 (s, 3 H), 1.42 (s, 3 H), 1.21 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 145.5, 145.4, 143.7, 134.5, 67.1, 34.2, 29.1, 27.4, 16.0 ppm.

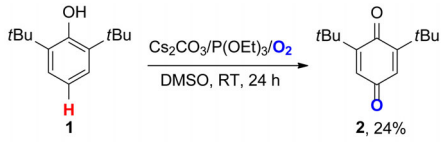
4f: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (s, 2 H), 2.18 (brs, 1 H), 1.68–1.55 (m, 2 H), 1.14 (s, 18 H), 0.83–0.75 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.5, 147.3, 146.9, 141.6, 140.9, 72.4, 44.6, 34.7, 34.6, 29.44, 29.41, 23.7, 13.4, 12.5 ppm.

4g: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (s, 2 H), 2.87 (brs, 1 H), 2.10 (s, 6 H), 1.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.8, 163.5, 125.6, 71.4, 25.8, 18.1 ppm.

4h: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (s, 2 H), 2.76 (t, J=8.4 Hz, 2 H), 2.28 (t, J=8.4 Hz, 2 H), 1.23 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.5, 175.7, 147.7, 137.1, 79.8, 34.8, 33.2, 29.2, 28.5 ppm.

3 Results and discussion

Our original intention is the direct hydroxylation of electron rich arenes with O_2 as the oxidant through the cleavage of C–H bond. Direct transformation of C–H bonds into desired functionalities could improve the atom economy and more importantly the step-economy of organic synthesis [47,48]. Over the past decade, C–H bond functionalization has become one of the most exciting and rapidly developing fields of organic chemistry [49–55]. Initially, we conducted an experiment of electron rich substrate 2,6-di-*tert*-butylphenol **1** under our precious conditions. However, the expected aromatic C–H bond hydroxylation product was not found. Interestingly, the corresponding *p*-quinone **2**, which is the over-oxidation product of *p*-quinol, was obtained although in low yield (Eq. (1)):



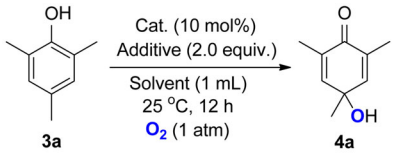
(1)

This positive outcome indicated that the electron rich phenol could react with O_2 under mild conditions. Base on this result and our precious hydroxylation reaction [46], which was proposed to proceed carbanion intermediate generated by Cs_2CO_3, we envisioned that the *p*-substituted electron rich phenols could be easily converted to phenoxide anion with an appropriate base, and then the anion could be transferred to C-4 position, generating a carbanion. If the reaction is conducted under O_2, the carbanion could react with O_2 in the way as our previous work, and a hydroxyl group could be obtained at C-4. This one-pot method, if successful, could offer a new approach to the highly valuable *p*-quinols.

Consequently, 2,4,6-trimethylphenol (**3a**) was used as a model substrate for evaluating the feasibility of the hypothesis. To our delight, when **3a** was treated with Cs_2CO_3 (10 mol%) under a dioxygen atmosphere (1 atm) in DMSO at room temperature for 12 h, this reaction produced 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (**4a**) in 15% yield (Table 1, Entry 1). However, other weak bases, such as Na_2CO_3, K_2CO_3, Li_2CO_3, and $NaHCO_3$ failed to give the product (Table 1, Entries 2–5). Further screening of the cesium bases indicated that CsF, CsOAc, $CsNO_3$ were less efficient than Cs_2CO_3 (Table 1, Entries 6–8). Similar results were obtained when NaOH and KOH was employed (Table 1, Entries 9, 10). CsOH gave the highest yield among the bases examined (Table 1, Entry 11). Gratifyingly, the efficiency was significantly improved by the addition of $P(OEt)_3$ as the reductant and **4a** could be isolated in 99% yield (Table 1, Entry 12). Slightly lower yield was observed when $P(OEt)_3$ was replaced by PPh_3 (Table 1, Entry 13). However, the reaction did not proceed in the presence of $Na_2S_2O_3$ and NaI (Table 1, Entries 14, 15). Several solvents were also tested, and found that polar solvent (DMF, DMAc, NMP) gave the good yields although lower than DMSO, whereas non-polar solvent (toluene, DCE, CH_3CN, THF) failed to give the desired product (Table 1, Entries 16–22). A lower yield was obtained when O_2 was replaced with air (Table 1, Entry 23). Finally, the reaction could not work in the absence of a catalyst (Table 1, Entry 24).

Next, the scope of this base catalyzed oxidative de-aromatization of multi-alkyl phenols with molecular oxygen was examined under the optimized reaction conditions (Table 2). The reactions proceeded smoothly, and the corresponding *p*-quinols were formed in moderate to excellent yields. It is noteworthy that product **4a**, obtained in 99% yield, is the precursor of vitamin E [56,57]. The oxidation of 2,6-di-*tert*-butyl-4-methylphenol afforded the product **4b** in quantity yield. Substrate bearing a sterically hindered *t*Bu group at *para* position was also tested, and the desired

Table1 Screening on different parameters [a)]

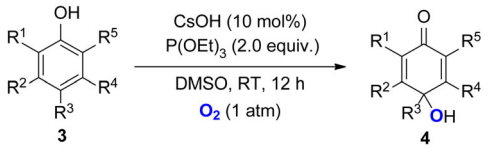


Entry	Cat.	Additive	Solvent	Yield [b)]
1	Cs_2CO_3	–	DMSO	15%
2	Na_2CO_3	–	DMSO	trace
3	K_2CO_3	–	DMSO	trace
4	Li_2CO_3	–	DMSO	trace
5	$NaHCO_3$	–	DMSO	trace
6	CsF	–	DMSO	8%
7	CsOAc	–	DMSO	7%
8	$CsNO_3$	–	DMSO	trace
9	NaOH	–	DMSO	18%
10	KOH	–	DMSO	20%
11	CsOH	–	DMSO	37%
12	CsOH	$P(OEt)_3$	DMSO	99%
13	CsOH	PPh_3	DMSO	90%
14	CsOH	$Na_2S_2O_3$	DMSO	trace
15	CsOH	NaI	DMSO	trace
16	CsOH	$P(OEt)_3$	DMF	94%
17	CsOH	$P(OEt)_3$	DMAc	93%
18	CsOH	$P(OEt)_3$	NMP	86%
19	CsOH	$P(OEt)_3$	toluene	N.R. [c)]
20	CsOH	$P(OEt)_3$	DCE	N.R.
21	CsOH	$P(OEt)_3$	CH_3CN	N.R.
22	CsOH	$P(OEt)_3$	THF	N.R.
23 [d)]	CsOH	$P(OEt)_3$	DMSO	41%
24	–	$P(OEt)_3$	DMSO	N.R.

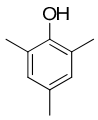
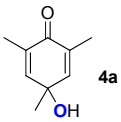
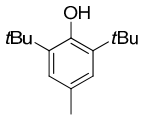
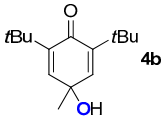
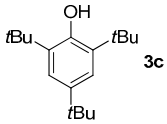
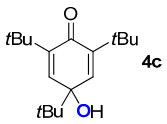
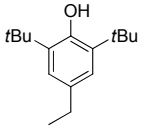
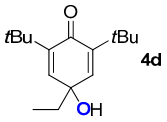
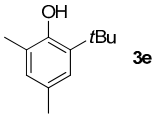
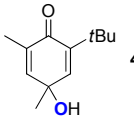
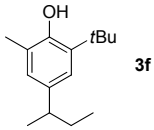
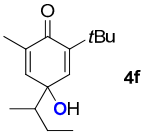
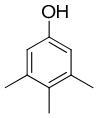
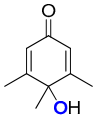
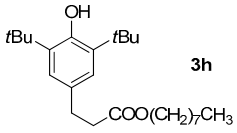
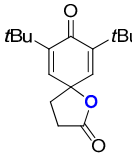
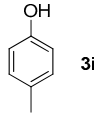
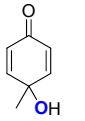
a) Reaction conditions: **3a** (0.5 mmol), catalyst (0.05 mmol), additive (1.0 mmol), solvent (1 mL), stirred at RT (25 °C) under O_2 (1 atm) for 12 h; b) isolated yield; c); N.R.means no reaction; d) the reaction was carried out under air (1 atm).

product **4c** could be still isolated in excellent yield. Ethyl group substituted also produced the target product **4d** in 96% yield. 2-*tert*-Butyl-4,6-dimethylphenol gave the corresponding product **4e** in good yield. Notably, different substituted at 2,4,6-position, the reaction selectively afforded the corresponding *p*-quinol **4f**. 3,4,5-Trimethylsubstituted phenol could also perform in this transformation, leading to the corresponding oxidative hydroxylation product **4g** in moderate yield. Interestingly, when the *para*-substituent contains an ester group, the reaction afforded lactone product **4h**, which was generated by the intramolecular transesterification of the ester group with the produced hydroxyl group. Unfortunately, *p*-cresol did not proceed under the optimized conditions. The yield of **4i** was still very low (<10%) even if the reaction temperature was raised to 60 °C.

Table 2 Substrate scope of aerobic oxidative synthesis of *p*-quinols [a)]



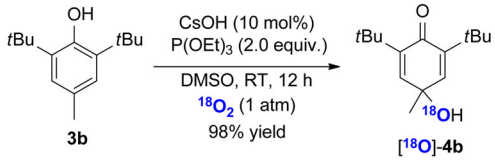
3 4

Entry	Substrate	Product	Yield [b)]
1	 **3a**	 **4a**	99%
2	 **3b**	 **4b**	99%
3	 **3c**	 **4c**	93%
4	 **3d**	 **4d**	96%
5	 **3e**	 **4e**	71%
6	 **3f**	 **4f**	90%
7	 **3g**	 **4g**	51%
8	 **3h**	 **4h**	86%
9	 **3i**	 **4i**	trace

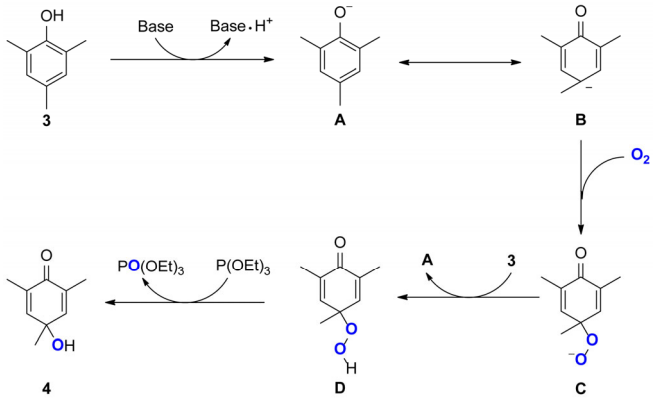
a) Reaction conditions: **3** (0.5 mmol), CsOH (0.05 mmol), $P(OEt)_3$ (1.0 mmol), DMSO (1 mL), stirred at RT (25 °C) under O_2 (1 atm) for 12 h; b) isolated yield.

The multi-alkyl group was essential to the success of this transformation.

To illustrate the original of oxygen atom of the hydroxyl group in products, the ^{18}O-labeling experiment was conducted. The analysis of the product by HRMS indicated that the oxygen atom in the hydroxy group was from molecular oxygen (Eq. (2)):



(2)



Scheme 1 A plausible mechanism for the oxidative de-aromatization of multi-alkyl phenols with dioxygen.

On the basis of our previous work, a possible mechanism is shown in Scheme 1. Firstly, the substrate multi-alkyl phenols **3** could undergo a deprotonation process by the base catalyst to produce the corresponding phenoxide anion **A** with its resonance structure carbanion **B**. Subsequently, carbanion **B** is trapped by O_2 to afford superoxide anion **C**, which could abstract a proton from multi-alkyl phenols **1** to form superoxide **D** and regenerate phenoxide anion **A** to complete the catalytic cycle. Finally, superoxide **D** undergoes reduction by $P(OEt)_3$ to produce the *p*-quinol product **4**.

4 Conclusions

In conclusion, we have demonstrated a base initiated oxidative de-aromatization of multi-alkyl phenols to *p*-quinols. 1 atm of molecular oxygen was employed as the oxidant. The reaction could proceed well at room temperature. Several *p*-quinols were obtained in moderate to excellent yield. The ^{18}O-labeling result indicated that the oxygen atom of hydroxy group in product was originated from molecular oxygen. This reaction was proposed to proceed through phenoxide anion and carbanion intermediates.

Supporting information

The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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