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Palladium catalyzed oxidation of renewable terpenes with molecular oxygen: oxidation of α -bisabolol under chloride-free nonacidic conditions

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Abstract. A novel selective palladium catalyzed oxidation of α -bisabolol by molecular oxygen under chloride-free nonacidic conditions has been developed. α -Bisabolol is a sesquiterpene alcohol available from essential oils of various plants. The reaction proceeds in aqueous methanol solutions over the Pd(OAc)₂/Cu(OAc)₂ catalytic system and gives exclusively the products resulting from the interaction of palladium with a sterically encumbered internal acyclic double bond. No concomitant oxidation of the second

double bond, the endocyclic one, occurs. Novel polyfunctionalized sesquiterpenoid compounds obtained at the oxidation of α -bisabolol are potentially interesting for cosmetic, fragrance and pharmaceutical applications.

Keywords: α -Bisabolol; Oxidation; Oxygen; Palladium; Terpenoids

Introduction

Terpenic compounds, the natural constituents of essential oils, have a variety of applications in flavor&fragrance and pharmaceutical industries.^{1,2} A sesquiterpene alcohol α -bisabolol is found in essential oils of various plants, like chamomile (*Matricaria chamomilla*), candeia (*Eremanthus erythropappus*) and sage (*Salvia runcinata*), and also produced synthetically from other terpenic compounds such as farnesol and nerolidol.³⁻⁷ Although α -bisabolol itself is an important ingredient of many cosmetic, fragrance and therapeutic products,^{3,8} the use of this compound can be significantly extended by its catalytic functionalization. It is known that natural and synthetic derivatives of α -bisabolol also show valuable therapeutic properties, such as anti-inflammatory and anti-tumor activities.^{4,9,10}

The molecule of α -bisabolol contains two olefinic bonds, both trisubstituted, which can be involved in oxidative transformations to give oxygenated bisabolane compounds. The oxidation of olefins catalyzed by palladium complexes is a powerful and well-established method in organic synthesis.^{11,12} The possibility to use molecular oxygen as a final oxidant represents the important economic and environmental advantage of the method. Auxiliary reversible co-oxidants (co-catalysts) are usually employed in these processes for the re-oxidation of reduced palladium, most commonly CuCl₂ (Wacker catalyst¹³). However,

the large amounts of chloride ions and acid required to maintain the catalytic cycle in the Wacker system often cause severe corrosion and selectivity problems. Several halide-free co-catalysts, such as heteropoly acids, nitrates, and *p*-benzoquinone (BQ), have been suggested as more benign alternatives for CuCl₂.¹⁴⁻²¹ Recent advances in the field include the use of coordinating solvents and special ligands to stabilize reduced palladium species in the solution and allow their regeneration directly by molecular oxygen. This approach was successfully applied to the palladium catalyzed oxidation of several olefins, mostly terminal olefins.²²⁻²⁸

The palladium catalyzed oxidation of terpenes with molecular oxygen has been the focus of our interest for several years.^{17-21,27,28} The use in these reactions of naturally occurring alkenolic substrates (alkenyl alcohols), such as linalool, α -terpineol, and nerolidol, allowed us to obtain a number of interesting polyfunctionalized terpenic compounds.¹⁹⁻²¹ As concern to α -bisabolol, there is very little information in the literature about its catalytic oxidation, with all the works describing the use of hydrogen peroxide or peroxy compounds as final oxidants.^{29,30}

Recently, we have started to investigate the applications of palladium catalysts for the oxidation of α -bisabolol, for the first time as far as we know.³¹ Main efforts were directed to the development of CuCl₂-free catalysts as the conventional Wacker system was found to promote a non-selective conversion. It was found that the combination of Pd(OAc)₂ with BQ effectively catalyzed the oxidation

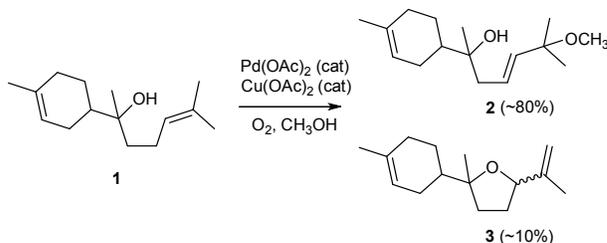
of α -bisabolol with molecular oxygen in acetic acid solutions.³¹ Both olefinic bonds of the substrate were selectively oxidized to give several new sesquiterpenoids.

In the present study, we report a novel palladium-catalyzed oxidation of α -bisabolol by molecular oxygen under nonacidic and also chloride-free conditions. The reaction resulted in poly-functionalized bisabolane derivatives potentially useful for cosmetic and pharmaceutical applications.

Results and Discussion

Representative results on the palladium catalyzed oxidation of α -bisabolol (**1**) with molecular oxygen in methanol solutions are shown in Table 1. The reaction times were selected to facilitate the comparison between the runs. Kinetic curves for some runs are given in Figure 1. The reaction readily occurred at 60 and 80 °C in the presence of the catalytic amounts of Pd(OAc)₂ and Cu(OAc)₂ (Table 1, runs 1 and 2; Figure 1). A nearly half of the substrate was converted in both runs, and then the conversion became stagnated with no palladium black formation being observed. A main reaction product, compound **2**, was detected in ca. 85% selectivity in both runs, along with compound **3** formed as a minor product in selectivity of ca. 10%. Bisabolol oxide B (identified by mass spectroscopy) was mainly responsible for the rest of the mass balance. Only very small amounts of unidentified products were observed by GC. Keeping the solution at 80 °C after the reaction stagnation resulted in a gradual decrease in the concentration of **2** (run 2).

Products **2** and **3** were isolated from the reaction solutions by column chromatography and identified by GC-MS and NMR spectroscopy. Their structures are shown in Scheme 1. Both compounds resulted from the oxidation of the acyclic olefinic bond of the α -bisabolol molecule, whereas the endocyclic double bond remained intact. Compound **3** was described for the first time in our previous work³¹ as one of the main products of the oxidation of α -bisabolol with the Pd(OAc)₂/BQ catalytic system. Allylic ether **2**, a novel compound as far as we know, was detected as two isomers **2a** and **2b** formed in approximately equal amounts and isolated as individual compounds.



Scheme 1. The products of the palladium catalyzed oxidation of α -bisabolol.

The NMR spectra of **2a** and **2b** were very similar (see Figures 2 and 3 for NMR attributions and carbon numbering). A strong NOE correlation signal between hydrogens H-10 and H-12 suggested a *trans* geometry about the acyclic C-11–C-12 double bond for both **2a** and **2b**. As natural α -(-)-bisabolol has *R* configurations at both asymmetric carbons C-4 and C-8, to explain the structural difference between **2a** and **2b** a partial inversion of the configuration at these carbons could be suggested, most probably, at carbon C-8 bound to the hydroxyl group which could be involved in the catalytic reaction. However, the elucidation of the stereochemistry of compounds **2a** and **2b** requires an additional study.

Table 1. Palladium-catalyzed oxidation of α -bisabolol (**1**) with molecular oxygen in methanol solutions^a

Run	[Cu(OAc) ₂] (M)	Added water (vol%)	<i>T</i> (h)	<i>C</i> (%)	Selectivity (%)		TOF ^b (h ⁻¹)
					2	3	
1	0.05	0	3	25	85	8	1.7
			10	40	84	10	
2 ^c	0.05	0	10	0			
3 ^c	0	0	10	0			
4 ^d	0.05	0	3	48	86	6	4.0
			10	53	70	10	
5	0.05	0.6	10	65	87	7	1.6
6	0.05	1.2	10	57	83	7	1.5
7	0.05	4.2	10	58	72	7	1.7
8	0.05	8.3	10	83	81	10	2.0
			15	96	73	9	
9 ^d	0.05	8.3	4	85	80	10	4.8
			5	87	63	10	
10 ^d	0	8.3	4	55	45	9	4.4
			7	57	48	9	
11	0.05	15	10	60	78	8	1.9
			20	91	64	7	
12	0.05	23	10	65	61	7	2.0
			20	69	59	6	
13	0.025	8.3	5	46	85	6	2.0
			15	97	76	7	
14 ^e	0.025	8.3	5	45	82	8	2.2
			15	73	80	8	
15 ^f	0.025	8.3	5	30	85	7	2.0
16 ^e	0.05	8.3	5	40	85	10	1.9
			15	59	83	10	

^a Conditions: solvent – methanol, [α -bisabolol] = 0.20 M, [Pd(OAc)₂] = 0.01 M, 60 °C, 10 atm of O₂. Conversion (*C*) and selectivity were determined by GC and calculated based on the consumed substrate. Small part of **2** (<10%) was detected in a methoxylated form (OCH₃ group at C-8).

^b Initial rate of the α -bisabolol conversion per mol of Pd (turnover frequency, TOF). ^c [Pd(OAc)₂] = 0. ^d 80 °C. ^e 5 atm. ^f [Pd(OAc)₂] = 0.007 M.

In blank reactions, with no Pd(OAc)₂ and Cu(OAc)₂ added or with Cu(OAc)₂ alone, no formation of products **2** and **3** was observed as expected (Table 1, runs 2 and 3). After the reactions in pure methanol, the formation of a water soluble

solid was noticed (probably, complexes of copper insoluble in methanol), which might be responsible for the reaction stagnation. The addition of small amounts of water allowed to keep the catalyst dissolved thus improving significantly the system performance. Although initial reaction rates (presented in Table 1 as turnover frequencies, TOF) were affected only slightly (runs 1, 5–8), neither stagnation nor solid precipitation was observed in the reactions performed in aqueous methanol solutions.

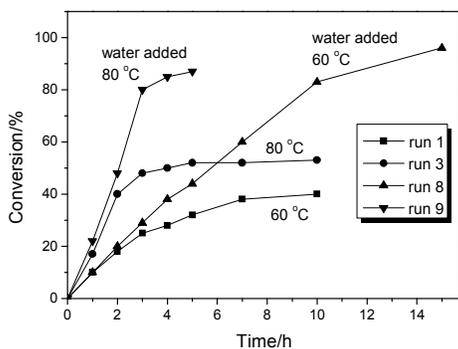


Figure 1. Palladium catalyzed oxidation of α -bisabolol with molecular oxygen in methanol solutions: effect of added water. Curves numbering corresponds to the runs in presented Table 1. Conditions: $[\alpha\text{-bisabolol}] = 0.20$ M, $[\text{Pd}(\text{OAc})_2] = 0.01$ M, $[\text{Cu}(\text{OAc})_2] = 0.05$ M, gas phase – O_2 , 10 atm. In runs 8 and 9, water was added to the reaction solutions (8.3 vol%).

The remarkable effect of water on the reaction kinetics is illustrated by Figure 1. Kinetic curves for the reactions in aqueous methanol are presented in comparison with those performed without added water (Figure 1: run 8 vs. run 1; run 9 vs. run 3). In runs 8 and 9, the selectivity for main product **2** was above 80% up to nearly 85% conversion, slightly decreasing afterwards.

Products **2** and **3** were formed from α -bisabolol in the runs presented in Table 1 with dioxygen-coupled catalytic turnover numbers, i.e., the reactions were catalytic based on both palladium and copper. The use of the $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2$ catalytic system for the aerobic oxidation of olefins in methanol solutions was described in our previous works.^{19,20} It is remarkable that the process proceeds with dioxygen-coupled turnover under chloride-free nonacidic conditions, where the re-oxidation of Pd(0) by Cu(II) is expected to be thermodynamically unfavorable. Usually, the presence of chloride ions is required in Pd/Cu systems as the chloride coordination decreases the redox potential of the $\text{Pd}^{2+}/\text{Pd}^0$ couple and increases that of the $\text{Cu}^{2+}/\text{Cu}^{1+}$ one.³²

We suppose that in our reactions zerovalent palladium, if formed, is stabilized towards aggregation by the coordination with the solvent and other species available, including the substrate. Under such conditions, the regeneration of the reduced

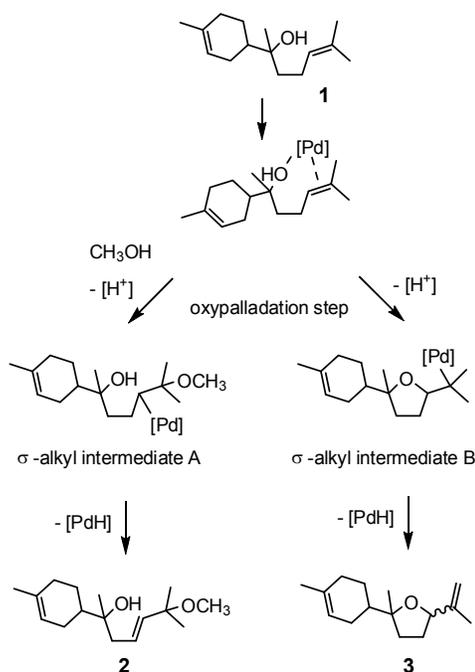
palladium could be performed directly by molecular oxygen before the formation of inactive bulk metal. Another plausible hypothesis could be the effect of the interaction of both metals with the components of the reaction solutions on their redox potentials thus enabling Cu(II) to re-oxidize Pd(0) even in the absence of chloride ions. In this context, it could also be important the possibility of the formation of bimetallic Pd-Cu complexes suggested in various olefin oxidations.³³⁻³⁵ In the absence of $\text{Cu}(\text{OAc})_2$, the reaction became stagnated after ca. 50% conversion and selectivity for product **2** decreased significantly (Table 1, cf. runs 9 and 10).

Further addition of water was not favorable for the reaction as selectivity for product **2** became lower again, especially at high conversions (Table 1, runs 11 and 12 with 15 and 23 vol% of water vs. run 8 with 8.3%).

The reaction seems to be an approximately first positive order in palladium as the initial rates calculated per mol of palladium (TOF) were similar in the runs with different $\text{Pd}(\text{OAc})_2$ concentrations (run 15 vs. run 13). On the other hand, the concentration of $\text{Cu}(\text{OAc})_2$ affected only slightly the reaction kinetics and product distribution (cf. runs 13 and 8; runs 14 and 16). The decrease in the oxygen pressure showed no appreciable effect on the initial reaction rate and selectivity (cf. runs 8 and 16; runs 13 and 14). However, in runs performed under 5 atm the substrate conversion became stagnated at 60–70%, with palladium metal being found on the walls of the autoclave. Thus, the oxygen pressure of at least 10 atm is required for the successful regeneration of palladium during the catalytic cycle.

The mechanism for the formation of products **2** and **3** is proposed in Scheme 2. The product structures imply that both compounds result from the interaction of the acyclic double bond of the substrate with palladium.

The formation of **3** involves the participation of the intramolecular hydroxyl group resulting in the molecule cyclization. As it is generally accepted that the palladium catalyzed oxidative cyclization of alkenols proceeds through the oxypalladation step,³⁶⁻⁴⁰ we suggest that products **2** and **3** are formed through the Markovnikov and anti-Markovnikov, respectively, oxypalladation of the acyclic double bond, as shown in Scheme 2. The predominant formation of product **2** implies that the Markovnikov type interaction with the palladium atom bounding to the sterically less hindered carbon atom is a much more favorable route under the conditions used. The precursor of product **2**, σ -alkyl palladium intermediate **A**, is formed due to the participation of methanol as the external nucleophile at the oxypalladation step. Alternatively, the intramolecular nucleophilic attack of the tethered hydroxyl group on the olefinic bond coordinated to palladium results in the formation of the tetrahydrofuran ring in σ -alkyl palladium intermediate **B**. Subsequent β -hydrogen elimination steps in intermediates **A** and **B** give products **2** and **3**, respectively.



Scheme 2. Proposed mechanism of the palladium oxidation of α -bisabolol.

We have previously reported that the Pd(OAc)₂/BQ catalytic system readily promotes the allylic oxidation of the endocyclic double bond in α -bisabolol and also in compound **3**.³¹ In this context, it is remarkable that no products of the endocyclic bond oxidation were detected in appreciable amounts in the Pd(OAc)₂/Cu(OAc)₂ system. The trisubstituted acyclic double bond was exclusively involved in the oxidation reaction, which gave products **2** and **3** with ca. 90% combined selectivity. These results correlate well with previously reported data on the oxidation of the related substrate, linalool, catalyzed by the Pd(OAc)₂/Cu(OAc)₂ system.¹⁹ In the linalool molecule, also only a trisubstituted internal double bond was selectively oxidized, whereas a monosubstituted terminal double bond remained intact. It should be mentioned that the Wacker-type oxidation of non-functionalized internal acyclic olefins usually is a difficult challenge due to their low reactivity. Only few successful examples of such reactions have been published so far.⁴¹ In the case of α -bisabolol and linalool, the presence of the hydroxyl group in γ -position seems to be important for the effective interaction of the acyclic sterically encumbered double bond with palladium (as shown in Scheme 2).

Conclusion

In summary, a novel palladium catalyzed selective oxidation of α -bisabolol by molecular oxygen under

chloride-free nonacidic conditions has been developed. α -Bisabolol is a sesquiterpenic alcohol available from essential oils of various plants. The reaction occurs in aqueous methanol solutions with catalytic amounts of Pd(OAc)₂ and Cu(OAc)₂ and gives exclusively the products resulting from the interaction of palladium with the sterically encumbered internal acyclic double bond of the substrate. No concomitant oxidation of the second double bond, the endocyclic one, which is expected to be more reactive in palladium catalyzed transformations, occurs. Novel poly-functionalized sesquiterpenoid compounds obtained at the oxidation of α -bisabolol are potentially interesting for pharmaceutical and fragrance industries.

Experimental Section

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Cu(OAc)₂ was dehydrated by heating. Natural α -(-)-bisabolol extracted from candeia (*Eremanthus erythropappus*) was used as the substrate (from CITROLEO Ind. Com. Oleos Essenciais). The reactions were carried out in a magnetically stirred stainless steel 100-mL autoclave and followed by gas chromatography (GC) using a sampling system. In a typical run, the solution of the substrate, palladium and copper salts, water (if any), and bornyl acetate (internal standard, 0.10 M) in methanol (total volume of 12 mL) was transferred in the reactor. The concentrations of the components are given in the Table. The autoclave was pressurized with oxygen to the indicated total pressure and placed in an oil bath. The solutions were stirred at a specified temperature for the indicated time. At appropriate intervals, aliquots were taken via a special sampling system without the depressurization of the reactor and analyzed by GC using a Shimadzu GC-2010 Plus instrument fitted with a Rtx-Wax 30 m or Rtx-5MS 30 m capillary column and a flame ionization detector. After carrying out the reaction and cooling to room temperature, the excess of oxygen was slowly vented from the reactor. A GC mass balance was based on the substrate charged using bornyl acetate as the internal standard. The difference was attributed to the formation of high-boiling products, which were not GC determinable. Initial turnover frequency, TOF, were measured up to 25–40% conversions.

The products were isolated by a column chromatography (silica gel 60) using mixtures of hexane and CH₂Cl₂ as eluents and identified by ¹H and ¹³C-NMR and GC-MS. NMR spectra were recorded in CDCl₃ using a Bruker 400 MHz spectrometer, with TMS as an internal standard (DEPT, COSY, HMQC, HMBC and NOESY experiments). Mass spectra were obtained on a Shimadzu QP2010-PLUS instrument operating at 70 eV.

Compound **2** (new compound, two isomers **2a** and **2b**): **2a**: MS (70 eV, EI): *m/z* (%): 202 (1) [*M*⁺-H₂O-CH₃OH], 139 (32), 125 (9), 121 (18), 95 (46), 82 (100), 71 (18%), 67 (32); **2b** (longer retention time than **2a**): MS (70 eV, EI): *m/z* (%): 202 (1) [*M*⁺-H₂O-CH₃OH], 125 (4), 95 (4), 73 (100), 67 (3). For NMR data of **2a** and **2b** isolated as individual compounds see Figure 2 and 3.

Compound **3** (reported for the first time in [31]): MS (70 eV, EI): *m/z* (%): 220 (1) [*M*⁺], 187 (1) [*M*⁺-H₂O-CH₃], 132 (18), 125 (100), 107 (61), 95 (14), 93 (13), 67 (18). For NMR data see [31].

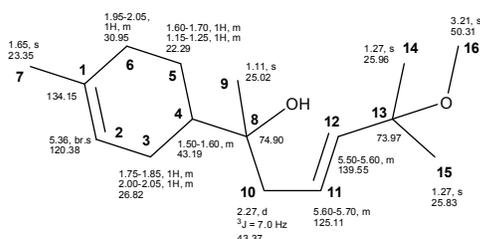


Figure 2. NMR data for product 2a

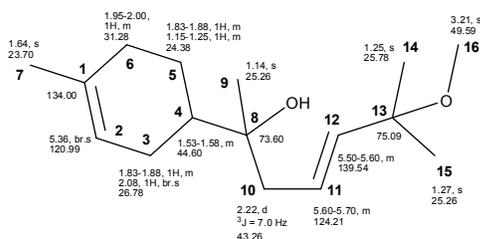


Figure 3. NMR data for product 2b

Acknowledgements

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FULL PAPER

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