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Microencapsulated methylrhenium trioxide (MTO)/H_2O_2 systems for the oxidation of cardanol derivatives*

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Abstract: A convenient and efficient application of microencapsulated/methylrhenium trioxide (MTO) and MTO/pyridine systems for the selective oxidation of cardanol derivatives is reported. Environmentally friendly and low-cost H_2O_2 was used as the oxygen atom donor. The catalysts were stable systems for at least five recycling experiments. In the oxidation of C2 alkyl-substituted cardanol derivatives, high conversion and yields of the corresponding *para*-benzoquinones were obtained. By contrast, in the absence of the C2 substituent, an unprecedented oxidative degradation to di-γ-lactone derivative was observed.

INTRODUCTION

Cardanol, a mixture of 3-*n*-pentadecylphenol, 3-(*n*-pentadeca-8-enyl)phenol, 3-(*n*-pentadeca-8,11-dienyl)phenol, and 3-(*n*-pentadeca-8,11,14-trienyl)phenol, is the main component of the roasted "cashew nut shell liquid" (CNSL) obtained as side-product from the mechanical processing (hot bath process) of the cashew nut of *Anacardium occidentale* L [1,2]. As worldwide cashew nut production is nearly 1 200 000 tons per year, CNSL represents a widely available and renewable source for the preparation of fine chemicals, additives, resins, polymers, and rubbers [3,4]. Cardanol derivatives show antibacterial, antifungal, antioxidant, and antitumor activities [5], without any appreciable mutagenic, carcinogenic, and cocarcinogenic activities [6]. Until now, few data are available in the literature on the biological activities of products of oxidative metabolism of cardanol derivatives (e.g., the corresponding quinone and hydroquinone or cathecol derivatives) [7], probably because of the lack of selective and efficient synthetic procedures [8]. Recently, we have reported the application of manganese and iron tetraphenylporphyrins {Mn or Fe[(Cl_{16})TDMPP]Cl} and methylrhenium trioxide (MTO) as homogeneous catalysts for the efficient synthesis of *ortho*- and *para*-benzoquinones of cardanol derivatives [9,10]. A fine-tuned substituent effect on the regioselectivity of the oxidation (*ortho*- vs. *para*-benzoquinones) was observed depending on the steric hindrance and position of the substituents on the aromatic ring and on the catalyst structure and nature of the oxidant. Noteworthy, benzoquinones of cardanol derivatives showed potent cytotoxic effects on fibroblast cell lines (3T3, NSO, and PHA cells) [10], while the corresponding hydroquinone and cathecol derivatives have low toxicity and antioxidant activity higher than commercial products, such as 2,6-di-*tert*-butyl-4-phenol (BHT), and 2,6-di-*tert*-

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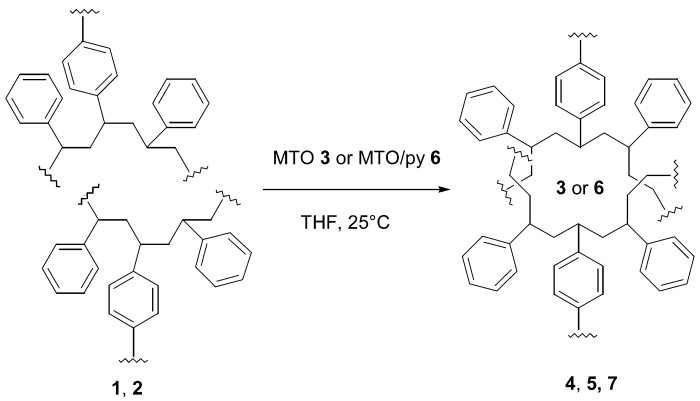
butyl-4-methoxyphenol (DBHA) [11]. In an effort to develop more versatile heterogeneous rhenium compounds by heterogenation of MTO on easily available polymeric support, we have synthesized novel poly(4-vinylpyridine)/MTO (PVM) and polystirene/MTO (PSM) catalysts applying the ligand-accelerated catalysis (LAC) concept [12]. These systems showed high catalytic activity and selectivity in hydrogen peroxide (H_2O_2) oxidation of alkenes [13] and phenols [14]. Higher conversions and yields of quinones were obtained with PVM catalysts with respect to MTO in homogeneous phase, probably because of a support-mediated molecular recognition process based on hydrogen-bonding interactions between the pyridinyl moiety and the phenolic group [15]. We report here that polymer-supported rhenium compounds, obtained by microencapsulation of MTO and MTO/pyridine complex with polystirene (PSM catalysts), are efficient and selective catalysts for the oxidation of cardanol derivatives with H_2O_2 as environment-friendly primary oxidant. PSM catalysts show a different selectivity for the oxidation of 3-*n*-pentadecylphenol (hydrogenated cardanol [16]) with respect to PVM catalysts.

RESULTS AND DISCUSSION

Preparation of PSM catalysts was successfully performed by the general procedure for the formation of microcapsules, using polystirene **1** (PS) or polystirene 2 % cross-linked with divinilbenzene **2** (PS2) as polymeric supports [13,17]. Compounds **1** or **2** were suspended at room temperature in tetrahydrofuran (THF) in the presence of the appropriate amount of powdered MTO **3**. Grumes were found in suspension in the mixture, and hexane was added to harden the capsule walls. Polystirene/MTO **4** (PSM) and polystirene cross-linked/MTO **5** (PS2M) catalysts were obtained by filtration of the reaction mixture and used without further purification (Scheme 1). PSM catalysts were prepared with a loading factor (that is mmol of MTO for 1 g of support) equal to 1.



1, **4**: polystirene. **2**, **5, 7**: polystirene 2 % cross-linked with divinylbenzene.

Scheme 1

Lewis base adducts of MTO, of general formula MTO/L*n* (where L = nitrogen or oxygen ligand, n = 1 or 2), prepared by reaction with pyridine, [18] pyridine derivatives [19], quinuclidine [20], aniline, toluidine, and pyrazole [21], reduce the Brønsted and Lewis acidity of MTO and may tune its reactivity in oxidative transformations [22]. On the basis of these data, MTO/pyridine complex **6** (Mpy) was prepared using a small excess of pyridine (1.5 mmol) as ligand for the rhenium atom and microencapsulated with PS2 to give PS2Mpy **7** (Scheme 1). A scanning electron microscopy (SEM) photograph showing the morphology of the surface of particles of **7** is reported in Fig. 1. Compound **7** is composed by regular spherical microcapsules, with an average value of diameter of the order of 50 μm.

The oxidation of cardanol derivatives with PSM systems **4**, **5**, and **7** were investigated using 3-*n*-pentadecylphenol (**8**) [16], 2-*tert*-butyl-5-*n*-pentadecylphenol (**9**) [23], and 2-*tert*-amyl-5-*n*-pen-

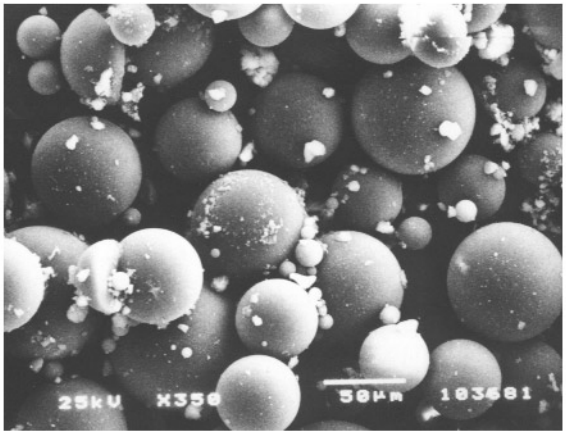
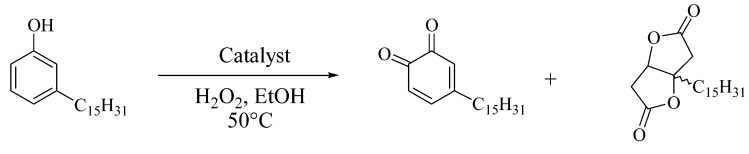


Fig. 1 SEM micrograph of PS2Mpy **7**.

tadecylphenol (**10**) [23], as representative CNSL phenolic models. As a general procedure, the cardanol derivative (1 mmol) to be oxidized was added to a suspension of the catalyst in ethanol (EtOH, 5 ml) at 50 °C under nitrogen atmosphere. The oxidations with homogeneous MTO (**3**), and Mpy (**6**) [24], were also performed as references under similar experimental conditions. In the absence of MTO less than 2 % conversion of substrates took place under otherwise identical conditions. The oxidation of **8** using the **3**/H_2O_2 system gave the corresponding 4-*n*-pentadecyl-1,2-benzoquinone **11** in low conversion and yield as the only recovered product (Scheme 2, Table 1, entry 1). When the oxidation was performed in the presence of **4**, 2-*n*-pentadecyl-tetrahydro-1*H*,4*H*-furo[3,4-c]furan-1,4-dione **12**, was recovered as the main reaction product in the presence of low amount of **11** (Table 1, entry 2). Similar results were obtained in the oxidation of **8** with the **5**/H_2O_2 system, in which case highest conversion of substrate and yield of **12** were recovered (Table 1, entry 3).



8 **11** **12**

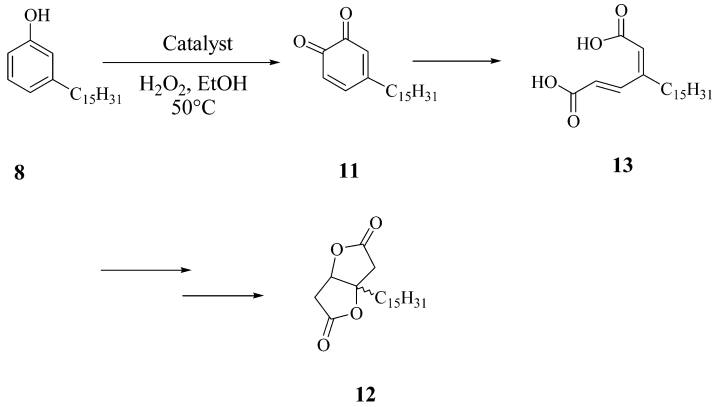
Scheme 2

Table 1 PSM-catalyzed oxidation of 3-*n*-pentadecylphenol **8**[a].

Entry	Catalyst	Conversion (%)	Product(s)	Yield(s)[b] (%)
1	**3**	37	**11**	30
2	**4**	55	**11(12)**	25(46)
3	**5**	62	**11(12)**	20(59)
4	**6**	50	**11(12)**	9(67)
5	**7**	91	**11(12)**	10(72)

[a]All the reactions were performed in ethanol (5 mL) at 50 °C, with H_2O_2 (50 % aqueous solution), using a value of the catalyst loading factor of 1.0.
[b]Refers to isolated materials. Yields normalized to 100 % conversion.

Di-γ-lactones similar to **12** exhibit a wide range of biological activities, such as allergenic, antitumor, antimitotic, antimicrobial, and antiviral properties [25]. To the best of our knowledge, this is the first report in the literature dealing with the one-pot synthesis of di-γ-lactone derivative by oxidative degradation of cardanol derivatives. Even if we have not studied in detail the mechanism of the reaction, it is reasonable to hypothesize that **12** may be formed by oxidative ring-opening of the *ortho*-quinone **11** to give the muconic acid derivative **13**, followed by a tandem intramolecular Michael addition (Scheme 3). It is reasonable to assume that in this case PSM systems react as bi-functional catalysts. This hypothesis is in part confirmed by GC-MS analysis of traces of the trimethylsilyl derivative of **13** after treatment of the reaction mixture with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and pyridine. Moreover, the oxidation of **11** performed under similar experimental conditions gave **12** in high yield (>95 % yield). An enhancement of the conversion of **8** and yield of **12** were successively obtained with the **7**/H_2O_2 system (Table 1, entry 5). In this case, **7** showed a reactivity higher than the reference catalyst **6**, probably because of the well-known low stability of this complex in homogeneous phase [26]. By contrast, according to our previous data about the epoxidation of alkenes [13], Table 2 shows that PSM catalysts **4** and **5** are stable enough to perform at least five recycling experiments with similar conversion and selectivity. On the other hand, a slow decrease of conversion was observed with **7**.



8 **11** **13**

12

Scheme 3

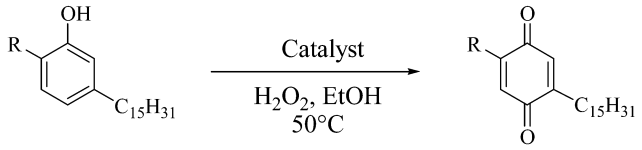
Table 2 Stability of PSM catalysts in the oxidation of 3-*n*-pentadecylphenol **8**[a].

Catalyst	Conversion (%)				
	Run no. 1	Run no. 2	Run no. 3	Run no. 4	Run no. 5
4	55 (46)[b]	56 (44)	53 (47)	50 (48)	51 (44)
5	62 (59)	60 (63)	61 (58)	61 (57)	60 (59)
7	91 (72)	87 (73)	88 (70)	85 (69)	80 (70)

[a]The reactions were performed in ethanol (5 mL) at 50 °C with H_2O_2 (50 % aqueous solution) using a value of the catalyst loading factor of 1.0.
[b]Values of the di-γ-lactone yields are given in parentheses and are normalized to 100 % of conversion.

With the more electron-rich derivatives **9** and **10**, highest conversion of substrate and yield of benzoquinone were observed (Scheme 4).

Thus, while MTO showed a low reactivity in the oxidation of **9** (Table 3, entry 1), 48–69 % conversion of substrate, and 79–81 % yield of 2-*tert*-butyl-5-*n*-pentadecyl-1,4-benzoquinone **14** were obtained with **4** and **5** as catalysts, respectively (Table 3, entries 2 and 3). As we have previously reported



9, **10** **14**, **15**

8, **14**: R= *tert*-butyl. **9**, **15**: R=*tert*-amyl

Scheme 4

Table 3 PSM-catalyzed oxidation of 2-substituted-5-*n*-pentadecylphenol **9** and **10**[a].

Entry	Catalyst	Conversion (%)	Product(s)	Yield(s)[b] (%)
1	**3**	37	**14**	18
2	**4**	48	**14**	79
3	**5**	69	**14**	81
4	**7**	85	**14**	87
5	**4**	51	**15**	87
6	**5**	75	**15**	91
7	**7**	83	**15**	90

[a]All the reactions were performed in ethanol (5 mL) at 50 °C, with H_2O_2 (50 % aqueous solution), using a value of the catalyst loading factor of 1.0.
[b]Refers to isolated materials. Yields normalized to 100 % conversion.

[10], the presence of the bulky alkyl substituent in the C2 position of the phenolic ring shifts the reactivity of the oxidation toward the formation of the *para*-benzoquinone. Better results were obtained with **7**, in which case 85 % conversion of substrate and 87 % yield of **14** were obtained (Table 3, entry 4). It is interesting to note that in the oxidation of C2 substituted cardanols we do not have evidence for the formation of di-γ-lactone derivatives or of other possible over-oxidation product.

Similar results were obtained in the oxidation of **10**, the 2-*tert*-amyl-5-*n*-pentadecyl-1,4-benzoquinone **15** being obtained as the only recovered product (Scheme 4). Also, in this case, **7** was the most efficient catalyst (Table 3, entry 7), while **4** showed a yield of **10** similar to **5** (Table 3, entries 5 and 6).

CONCLUSIONS

Microencapsulated rhenium compounds **4**, **5**, and **7** (PSM systems) are efficient and selective catalysts for the oxidation of cardanol derivatives with environmentally friendly H_2O_2 as oxygen atom donor. The reactivity of these systems, under relatively mild experimental conditions, may be attributed to the retained reactivity of the monoperoxo metal [$MTO(O)_2(O_2)$] and a bisperoxo metal [$MTO(O)(O_2)_2$] intermediates [27] even in the presence of the polymeric support. Catalysts **4** and **5** are stable systems for at least five recycling experiments. Catalyst **7** shows a slight decrease of conversion of substrate in the fifth recycling step. Independently for the system used for the oxidation, PSM catalysts are more efficient than MTO in homogeneous phase. In the oxidation of hydrogenated cardanol **8**, PSM/H_2O_2 systems show a different selectivity with respect to previously described 4-polyvinylpyridine (PVP)/H_2O_2 systems [13], affording the di-γ-lactone derivative **12** as the main reaction product. On the other hand, PSM/H_2O_2 and PVP/H_2O_2 systems show a similar reactivity in the oxidation of C2 substituted cardanol derivatives **9** and **10**, in which case the corresponding *para*-benzoquinones were obtained as the only recovered products. Moreover, PS2Mpy **7** is the best catalyst system, giving the di-γ-lactone derivative **12** and the *para*-benzoquinones **14** and **15** in highest conversion and yield.

EXPERIMENTAL

Descriptions of analytical instruments and ^{1}H NMR, and IR spectrometers have been previously published [28]. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. Microanalyses were performed with a C. Erba 1106 analyzer. Chromatographic purifications were performed on columns packed with Merck silica gel, 230–400 mesh, for flash technique. Thin-layer chromatography (TLC) was carried out using Merck Kiesegel 60 F254 plates. All reagents and solvents were of highest grade commercially available and used purified or freshly distilled as required by literature procedures. BSTFA was purchased from Sigma.

Starting materials

3-*n*-Pentadecylphenol **8**, 2-*tert*-butyl-5-*n*-pentadecylphenol **9**, 2-*tert*-amyl-5-*n*-pentadecylphenol **10** have been prepared by procedures reported in the literature [16,23].

Preparation of microencapsulated/MTO catalysts (PSM)

PSM catalysts were prepared as previously reported [13]. PS or PS2 600 mg was suspended in 5.0 ml of THF at 25 °C, and 77 mg of MTO (0.3 mmol) as a solid core was added to this solution. In the preparation of PS2Mpy, a small excess of pyridine (1.5 mmol) was also added to the reaction mixture. The suspension was stirred for 1 h at this temperature and then slowly cooled to 0 °C. Coocervates were found to envelop the solid core dispersed in the medium, and 5.0 ml of hexane were added to harden the capsule walls. The mixture was stirred for 1 h at 25 °C. The solvent was removed by filtration, and the residue was washed five times with 20 ml of ethyl acetate each time and finally dried under high vacuum. In each case, MTO had completely bound to polymer as confirmed by spectroscopic analysis of the residue obtained by evaporation of the organic layers.

General procedure for the oxidation of cardanol derivatives

To a solution of the specific cardanol derivative (1.0 mmol) and PSM catalyst (146 mg) in ethanol (5 ml) was added 50 % hydrogen peroxide (2.0–3.0 mmol). The reaction mixture was stirred at 50 °C under a nitrogen gas atmosphere. The reaction was monitored by TLC. The suspension was filtered and the recovered catalyst washed three times with 10 ml of ethyl acetate each time. After drying under high vacuum, the catalyst was used for further reaction. The filtrate was treated with a little MnO_2 and after filtration dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The products were obtained by chromatographic purification from acceptable to good yields and identified by spectroscopic analyses, mass spectroscopy, and comparison with authentic samples. 4-*n*-Pentadecyl-1,2-benzoquinone **11**, 2-*tert*-butyl-5-*n*-pentadecyl-1,4-benzoquinone **14**, and 2-*tert*-amyl-5-*n*-pentadecyl-1,4-benzoquinone **15** gave spectroscopic data consistent with the literature [10,14].

2-*n*-Pentadecyl-tetrahydro-1*H*,4*H*-furo[3,4-c]furan-1,4-dione 12. Oil (Found: C, 71.60; H, 10.29; $C_{21}H_{36}O_4$ requires C, 71.55; H, 10.29 %); ν_{max}/cm^{-1} (KBr) 1775, 2850; $\delta_H(CDCl_3)$ 4.56 (1H, m, CH), 3.50 (4H, m, CH_2), 1.81 (2H, m, CH_2), 1.25 (26H, m, CH_2), 0.95 (3H, m, CH_3). $\delta_C(CDCl_3)$ 176.72 (q), 169.47 (q), 61.68 (s), 61.50 (s), 35.13 (t), 34.74 (q), 29.69 (s), 29.46 (s), 29.37 (s), 29.28 (s), 29.10 (s), 28.94 (s), 27.66 (s), 27.0 (s), 25.70 (s), 24.70 (s), 14.10 (p); mass-to-charge ratio (*m/z*) (EI) 352 (M^+).

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