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Catalytic oxidation of catechins to *p*-benzoquinones with hydrogen peroxide/methyltrioxorhenium

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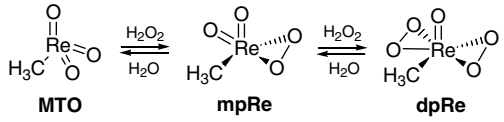
Abstract—New *p*-benzoquinones were obtained by oxidation of catechin and epicatechin derivatives with the hydrogen peroxide/methyltrioxorhenium catalytic system. Reactions were carried out both in homogeneous and heterogeneous conditions and proceeded with high conversion and moderate yields. Polymer-supported methyltrioxorhenium systems were used as heterogeneous catalysts. After the first oxidation, the catalytic systems can be recovered and reused for five consecutive times without loss of stability and efficiency.

p-Benzoquinones are bioactive natural compounds showing antimicrobial, antifungal, antibacterial, antiviral and anticancer activities.[1] Furthermore, they are useful chemicals in organic synthesis.[2] Generally, they are prepared by stoichiometric or catalytic oxidations of inexpensive phenol and methoxybenzene derivatives.[3] When hydrogen peroxide (H_2O_2) is used as the oxygen atom donor, its activation is required. Among the catalysts useful for this purpose, methyltrioxorhenium (CH_3ReO_3, MTO) has been largely used in the last few years being commercially available, stable in air and efficient in many organic solvents.[4] Hydrogen peroxide was converted into the mono(peroxo) **mpRe** and bis(peroxo)rhenium complexes **dpRe**, the active catalytic species in the oxidations (Scheme 1).[5] A probable mechanism of the reaction, via an arene oxide as intermediate, was postulated to explain the conversion of simple phenols and methoxybenzenes into the corresponding *p*-benzoquinones.[6]

It is well known that methyltrioxorhenium can be bonded to polymers bearing oxygen and nitrogen atoms



Scheme 1. Activation of hydrogen peroxide by CH_3ReO_3 (MTO).

to obtain heterogeneous catalyst. Among the commercial available supports, non-toxic and cheap polyvinylpyridines (PVP) were described (Fig. 1).[7] PVP-2%/MTO and PVP-25%/MTO catalytic system were prepared supporting MTO on poly(4-vinylpyridine) 2% or 25% cross-linked with divinylbenzene; PVPN-2%/MTO on poly(4-vinylpyridine-*N*-oxide) 2% cross-linked with divinylbenzene previously obtained by oxidation of the PVP-2% with an excess of 3-chloroperbenzoic acid.[8] All catalytic systems were characterized by a loading factor that expresses the mmol of MTO for gram of support.

Catechins (flavan-3-ols) constitute a large class of phenolic compounds ubiquitous in plants and widely found in fruits, vegetables and beverages.[9] In particular, they are one of the major quality factors in grapes and then in the resulting wine.[10] During its elaboration, large quantities of these compounds remain in the grapes

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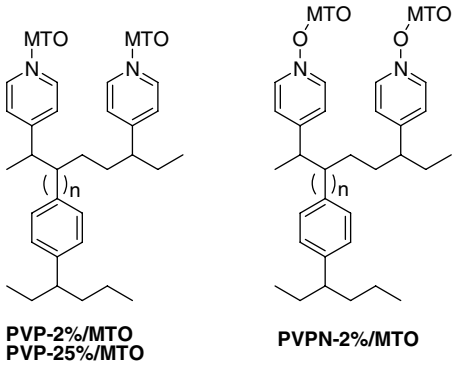
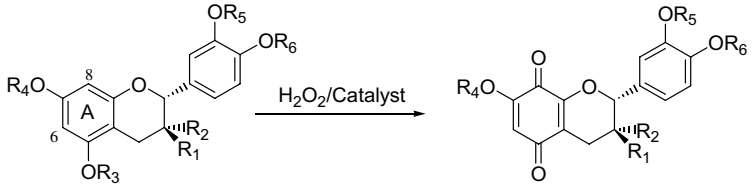


Figure 1. Polymer-supported methyltrioxorhenium catalysts.

pomace consisting of skins, seeds and stems.[11] Recently, these winery by-products have attracted great attention in nutrition, health and medicine areas.[12]

Continuing our studies on the environmentally friendly oxidative conversion of flavonoids into bioactive compounds and on the chemical valorization of molecules present into renewable sources as the agroindustrial wastes,[13] we report here the first catalytic oxidation of the catechins derivatives to new A-ring *p*-benzoquinones with the catalytic system H_2O_2/CH_3ReO_3 in homogeneous and heterogeneous conditions (Scheme 2). First, we tried the oxidation on the non-methylated (−)-epicatechin **1** and (+)-catechin **2**. When we added these substrates to the yellow solution of H_2O_2/MTO in ethanol, a purple-violet colour appeared. Similarly, as reported for the simple catechol,[14] this colour can be attributed to the condensation reaction between the MTO and the *ortho*-hydroxyl group of the B ring of catechins; the following oxidative opening of this complex afforded a complex and useless mixture of polar compounds.[15] Therefore, we performed the oxidation reaction on the methylated (−)-epicatechin 5,7,3′,4′-tetramethyl ether **3** and on the (+)-catechin 5,7,3′,4′-tetramethyl ether **5** in different experimental conditions. As reported in Table 1, our best results were obtained in acetic acid, in terms of conversion, reaction time and yield. In fact, using ethanol or dichloromethane as solvents, the oxidation



1: R_1=R_3=R_4=R_5=R_6=H; R_2=OH; **2**: R_1=OH; R_2=R_3=R_4=R_5=R_6=H
3: R_1=H; R_2=OH; R_3=R_4=R_5=R_6=CH_3;**4**: R_1=H; R_2=OH; R_4=R_5=R_6=CH_3
5: R_1=OH; R_2=H; R_3=R_4=R_5=R_6=CH_3; **6**: R_1=OH; R_2=H; R_4=R_5=R_6=CH_3
7: R_1=H; R_2=OAc; R_3=R_4=R_5=R_6=CH_3; **8**: R_1=H; R_2=OAc; R_4=R_5=R_6=CH_3
9: R_1=OAc; R_2=H; R_3=R_4=R_5=R_6=CH_3; **10**: R_1=OAc; R_2=H; R_4=R_5=R_6=CH_3

Scheme 2. Oxidation of catechin derivatives **3**, **5**, **7**, **9** to *p*-benzoquinones **4**, **6**, **8**, **10** with H_2O_2/MTO catalytic system.

Table 1. Experimental data of the oxidations of catechins derivatives **3**, **5**, **7** and **9**

Entry	Substrate	Product	Catalyst[a]	H_2O_2[b] (equiv)	Solvent	*T* (°C)	Time (h)	Conversion (%)	Yield[c] (%)
1	**3**	**4**	MTO	8	EtOH	70	24	65	21 (33)
2	**3**	**4**	MTO	8	CH_2Cl_2	25	24	98	24
3	**3**	**4**	MTO	2	AcOH	25	0.5	98	42
4	**3**	**4**	PVP-2%/MTO	6	AcOH	50	6	98	26
5	**3**	**4**	PVPN-2%/MTO	6	AcOH	50	8	98	27
6	**3**	**4**	PVP-25%/MTO	10	AcOH	50	6	98	38
7	**5**	**6**	MTO	8	EtOH	70	24	92	16 (17)
8	**5**	**6**	MTO	10	CH_2Cl_2	25	48	98	23
9	**5**	**6**	MTO	2	AcOH	25	2	98	38
10	**5**	**6**	PVP-2%/MTO	6	AcOH	50	24	79	25 (32)
11	**5**	**6**	PVPN-2%/MTO	10	AcOH	50	24	98	23
12	**5**	**6**	PVP-25%/MTO	6	AcOH	50	24	98	36
13	**7**	**8**	MTO	2	AcOH	25	4	98	44
14	**7**	**8**	PVP-2%/MTO	6	AcOH	50	24	98	28
15	**7**	**8**	PVP-25%/MTO	6	AcOH	50	24	98	38
16	**9**	**10**	MTO	2	AcOH	25	4	98	42
17	**9**	**10**	PVP-2%/MTO	6	AcOH	50	24	98	26
18	**9**	**10**	PVP-25%/MTO	6	AcOH	50	24	98	35

[a] MTO (5 mol %); loading factor of PVP-2%/MTO, PVPN-2%/MTO and PVP-25%/MTO: 1.0.
[b] H_2O_2 (50% aqueous solution).
[c] In brackets calculated yields on converted substrate were reported.

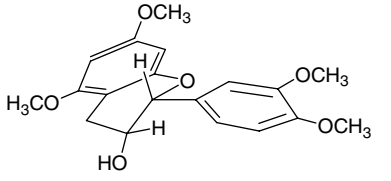
proceeded sluggish (compare entries 1, 2 with entry 3 and entries 7, 8 with entry 9). In the absence of the catalyst, less of 5% conversion of substrate took place in identical conditions. In all cases, the oxidation reactions proceed with high regioselectivity at C-8 position, the C-6 being unaffected. The disappearance of the two doublet at 6.08 and 6.16 ppm in the proton NMR of **3**, given to C-8 and C-6 positions and the appearance of a singlet at 5.85 ppm in the ^{1}H NMR spectrum of product **4** and of two signals at 175.6 and 186.5 ppm in its ^{13}C NMR spectrum,[16] confirmed the presence of a quinone moiety in the A ring of **4**. Specifically, the *p*-benzoquinonic structure was fully assigned with HMQC, HMBC and NOESY spectroscopy.[17] Similar spectroscopic data were obtained for the quinone **6**.[18]

Successively, we performed the oxidations of **3** and **5** in heterogeneous conditions using the PVP-2%/MTO, PVPN-2%/MTO and PVP-25%/MTO catalysts. Under the reported experimental conditions, both catalysts were effective in the oxidation of **3** and **5** to the corresponding quinones **4** and **6**. Better results were obtained using the PVP-25%/MTO, evidencing the influence of the morphologic properties of the polymeric support on the efficiency of the catalyst (compare entries 4, 5 with entry 6 and entries 10, 11 with entry 12). This catalyst was then recovered by filtration, washed with ethyl acetate and reused in successive oxidations under identical conditions. Table 2 shows its efficiency to perform five recycling experiments with similar conversion, yield and selectivity.

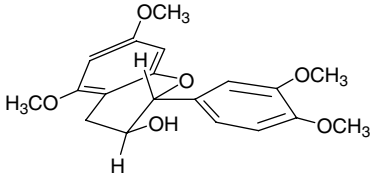
Table 2. Yields (%) of the quinones **4** and **6** using the recycled PVP-25%/MTO for the oxidation of the (−)-epicatechin 5,7,3′,4′-tetramethyl ether **3** and the (+)-catechin 5,7,3′,4′-tetramethyl ether **5** with hydrogen peroxide

Substrate	Run 1	Run 2	Run 3	Run 4	Run 5
3	38	35	36	34	33
5	36	36	34	35	32

Reactions were performed in acetic acid, at 50 °C, with H_2O_2 (50% water solution). Conversions are quantitative.



(-)-Epicatechin-5,7,3',4'-tetramethyl ether **3**



(+)-Catechin-5,7,3',4'-tetramethyl ether **5**

Figure 2. Stable conformations of **3** and **5**.[19]

Noteworthy, in all the reported experiments the epicatechin tetramethyl ether **3** reacted faster than the catechin tetramethyl ether **5**, especially in heterogeneous catalytic conditions (Table 1, compare entries 4, 5, 6 with 10, 11, 12). This higher reaction rate of **3** can be reasonably ascribed to a more efficient coordination of the bulky rhenium–polyvinylpyridine complex with the C-3 OH group oriented in the more accessible α-axial orientation (Fig. 2).[19] In fact, when we performed the same reaction with the C-3 acetate **7** of the (−)-epicatechin 5,7,3′,4′-tetramethyl ether **3**, the reactivity significantly slow down, the reaction time became similar to the catechin derivative **9** (Table 1, entries 14, 15, 17 and 18).

The oxidation of catechins is an important route to new potential bioactive molecules and chemical intermediates for the synthesis of polyphenolic compounds.[20] To the best of our knowledge, we described the first catalytic benign methodology to obtain new A-ring *p*-benzoquinones. Work is in progress in our laboratory to test their potential biological activities.

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16. *p*-Benzoquinone **4**: yellow solid. Mp 198–200 °C. ^{1}H NMR δ_H ($CDCl_3$, 200 MHz): 2.61–2.87 (2H, m, H-4α,4β); 3.78 (3H, s, OCH_3); 3.86 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 4.21–4.23 (1H, m, H-3), 4.96–4.99 (1H, m, H-2); 5.85 (1H, s, H-6); 6.85–7.00 (3H, m, H-2′,5′,6′); δ_C ($CDCl_3$, 200 MHz): 26.7 (C-4); 55.9 (OCH_3); 56.0 (OCH_3); 56.3 (OCH_3), 65.2 (C-3), 79.7 (C-2), 106.9 (C-6), 109.3 (C-2′), 111.3 (C-5′), 116.4 (C-7), 118.5 (C-6′), 128.4 (C-1′), 149.2 (C-3′), 149.3 (C-4′), 151.3 (C-10), 157.0 (C-9); 175.6 (C-8), 186.5 (C-5).
17. For example, no cross peaks between vinylic proton at 5.85 ppm and the aromatic protons in the C ring were observed in different NOESY experiments, performed with mixing time ranging from 400 to 1200 ms, suggesting an interprotonic distance greater than 5 Å, clearly in agreement with the *p*-benzoquinonic structure respect to the *o*-quinonic.
18. *p*-Benzoquinone **6**: yellow solid. Mp 211–212 °C. ^{1}H NMR δ_H ($CDCl_3$, 200 MHz): 2.48 (1H, dd, J = 18.4 and 8.2 Hz, H-4α); 2.89 (1H, dd, J = 18.5 and 5.4 Hz, H-4β); 3.79 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 3.86 (3H, s, OCH_3); 4.01–4.12 (1H, m, H-3), 4.75 (1H, d, J = 7.7 Hz, H-2); 5.84 (1H, s, H-6); 6.84–6.94 (3H, m, H-2′,5′,6′); δ_C ($CDCl_3$, 200 MHz): 29.3 (C-4); 55.9 (OCH_3); 56.0 (OCH_3); 56.4 (OCH_3); 66.7 (C-3); 82.8 (C-2); 107.0 (C-6); 109.9 (C-2′); 111.3 (C-5′); 117.3 (C-7); 119.8 (C-6′); 128.4 (C-1′); 149.4 (C-3′); 149.5 (C-4′); 151.4 (C-10); 157.2 (C-9); 175.8 (C-8); 185.9 (C-5).
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