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Short Report

Palladium/Heteropoly Acid Catalyzed Oxidative Coupling of 2-Methoxy-1,4-benzoquinone with Arenes

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O acoplamento oxidativo entre a 2-metoxi-1,4-benzoquinona e metoxiarenos em ácido acético resulta na formação de metoxiaril-1,4-benzoquinonas. Esta reação é efetivamente catalisada pelo sistema redox $Pd(OAc)_2$/heteropoliácido ($H_9PMo_6V_6O_{40}$) e envolve dioxigênio como oxidante final.

Oxidative coupling of 2-methoxy-1,4-benzoquinone and arenes in acetic acid gives methoxyaryl-substituted 1,4-benzoquinones. The reaction is effectively catalyzed by a $Pd(OAc)_2$/heteropoly acid ($H_9PMo_6V_6O_{40}$) redox system with dioxygen as the final oxidant.

Keywords: oxidative coupling, arenes, quinones, catalysis, palladium/heteropoly acid

Introduction

Naturally occurring compounds containing a quinone group are involved in various bioenergetic processes as important electron-transport agents. These compounds have also attracted considerable attention because of their biological activity and chemotherapeutic value.[1] Various quinones containing oxygenated aromatic rings have been reported to present biological activities.[2] Accordingly, in order to discover new medicinal materials, it is important to develop simple but powerful methods for the synthesis of such compounds, in particular, methoxyaryl-substituted benzoquinones.

Most of the synthetic routes to substituted quinones are based on the elaboration of the preexisting aromatic or heteroaromatic core. The methods for the preparation of aryl-1,4-benzoquinones were limited mainly to the reactions of 1,4-benzoquinones with aryldiazonium salts.[3] The direct synthesis of aryl-1,4-benzoquinones by oxidative coupling of 1,4-benzoquinone with arenes, such as benzene, 2,5-dimethylbenzene and 2,5-dichlorobenzene, in acetic acid under reflux with *stoichiometric* amounts of palladium acetate was described by Itahara.[4] Recently, we have extended this *non-catalytic* methodology to the preparation of various methoxyaryl-1,4-benzoquinone, using wood tar constituents as a starting material.[5]

Palladium assisted oxidative reactions may be converted into catalytic processes by the introduction of suitable reoxidants to recycle reduced palladium species. Itahara[6] reported the palladium catalyzed oxidative coupling of 1,4-naphtoquinone with benzene and 2,5-dimethylbenzene using *stoichiometric* amounts of reoxidants such as peroxodisulfates, $FeCl_3$, $KMnO_4$, $K_2Cr_2O_7$ and $Cu(OAc)_2$. However, he failed to realize, under similar conditions, the oxidative coupling of 1,4-benzoquinone with arenes other than benzene.[6] We tried to apply the methods described by Itahara to prepare methoxyaryl-1,4-benzoquinones. However, we obtained a complex mixture of unidentified compounds and starting material, with not even trace amounts of quinone-benzene coupling products (2-methoxy-1,4-benzoquinone: 1 mmol, $Pd(OAc)_2$: 0.05 mmol, reoxidant $Na_2S_2O_8$ or $FeCl_3$: 1 mmol, benzene: 25 mL, acetic acid: 25 mL, reflux temperature, 25 h, in air).

Efforts are being made to develop a *catalytic* method for the synthesis of methoxyaryl-substituted 1,4-benzoquinones via oxidative coupling of 2-methoxy-1,4-benzoquinone and methoxyarenes using *dioxygen* as a final oxidant. We now wish to report the oxidative coupling of 2-methoxy-1,4-benzoquinone and methoxyarenes by dioxygen in the presence of palladium/heteropoly acid catalytic system (Scheme 1). Keggin-type mixed-addenda heteropoly acids

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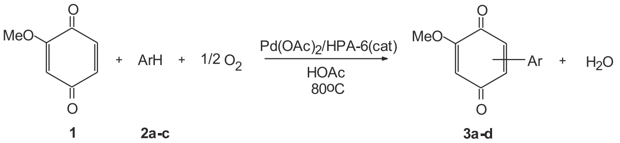
$H_{3+n}[PMo_{12-n}V_nO_{40}]$ (HPA-n) are strong oxidants soluble in water and oxygenated organic solvents, which act reversibly under mild conditions, *i.e.*, their reduced forms are easily recycled by dioxygen. These remarkable compounds are valuable reoxidants for the Pd(0)/Pd(II) redox couple in aerobic liquid-phase oxidation processes, such as olefin oxidations and oxidative coupling of arenes.[7-10]



a: Ar = 5-phenyl
b: Ar = 2,5-dimethoxyphenyl
c,d: Ar = 3-acetoxy-4-methoxyphenyl

Experimental

The uncorrected melting points were determined on a Mettler FP800 apparatus. Column chromatography was performed with flash-grade silica gel E. Merck 230-400 mesh. IR spectra were obtained on a Perkin-Shimadzu IR-408 instrument. ^{1}H and ^{13}C NMR spectra were recorded on an Avance-Bruker DRX-200 or Avance-Bruker DRX-400 instrument ($CDCl_3$, tetramethylsilane). The assignment of hydrogen and carbon resonances was realized with the help of COSY (^{1}H, ^{1}H), HMQC (^{1}H, ^{13}C), DEPT NMR and NOESY experiments. Mass spectra were obtained on a Hewlett-Packard MSD 5890/Series II instrument operating at 70 eV.

Reagents and materials

The heteropoly acid $H_9[PMo_6V_6O_{40}]$ (HPA-6) was synthesized by the reaction of Na_2MoO_4, $NaVO_3$ and H_3PO_4 in aqueous sulfuric acid solution according to the literature.[11] 1-Acetoxy-2-methoxybenzene was prepared by the reaction of 2-methoxyphenol with acetyl anhydride and pyridine.[12] 2-Methoxy-1,4-benzoquinone was prepared by the oxidation of freshly distilled 2-methoxyphenol according to the method of Teuber.[13]

General procedure

The reactions were carried out in a stirred glass reactor connected to a gas burette and followed by measuring a dioxygen uptake. In a typical run the mixture of 2-methoxy-1,4-benzoquinone (1 mmol), arene (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), HPA-6 (0.25 mmol) and acetic acid (15 mL) in a dioxygen atmosphere (1MPa) was magnetically stirred at the indicated temperature until the dioxygen uptake decreased significantly. After cooling to room temperature, the reaction solution was filtered and poured into a saturated aqueous solution of NaCl. The products were extracted with chloroform (3x50 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuum. The residue (crude product) was analyzed by ^{1}H NMR spectroscopy. The substrate conversion, product distribution and yield were determined based on the integration of the signals from the corresponding olefinic protons (*i.e.* from the unconverted quinone and from the products). The products were isolated by flash chromatography (silica, hexane/chloroform) as pure compounds **3a** and **3b** and the isomeric mixture of **3c** and **3d** (**3c/3d** @ 60/40) and identified by IR, ^{1}H and ^{13}C NMR spectroscopy.

2-Methoxy-5-phenyl-1,4-benzoquinone (3a): crystalline orange solid, m.p.187.6-188.9^{o}C (Lit[14]: 187^{o}C); IR (KBr) ν_{max}/cm^{-1}: 1670, 1640, 1620, 1580, 1440; ^{1}H NMR (400 MHz) δ: 3.87 (s, 3H, OC*H*$_3$), 6.04 (s, 1H, C*H*=C), 6.81 (s, 1H, C*H*=C), 7.4-7.5 (m, 5H, Ar-*H*); ^{13}C NMR (100 MHz) δ: 56.38, 108.05, 128.51, 129.56, 130.24, 130.92, 134.30, 146.54, 158.67, 182.21, 186.67; MS m/z (rel.int.): 214 (M$^+$, 100), 213 (60), 186 (55), 171 (35), 155 (13), 128 (20), 102 (25), 84 (9), 69 (60); Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.70; found C, 72.87; H, 4.67.

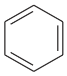
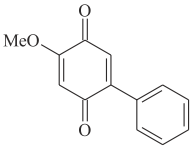
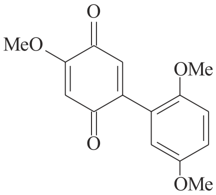
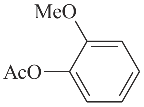
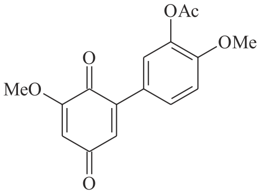
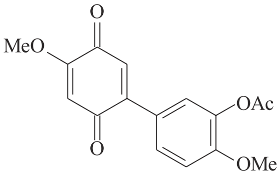
2-(2', 5'-Dimethoxyphenyl)-5-methoxy-1,4-benzoquinone (3b): crystalline red solid, m.p.: 130.3-131.4^{o}C (Lit[15] 132-134^{o}C); IR (KBr) ν_{max}/cm^{-1}: 1680, 1650, 1600, 1550, 1460; ^{1}H NMR (200 MHz) δ: 3.73 (s, 3H, OC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 6.03 (s, 1H, C*H*=C), 6.72 (dd, *J* 2.7 and 0.5 Hz, 1H, Ar-*H*), 6.76 (s, 1H, C*H*=C), 6.90-6.95 (m, 2H, Ar-*H*);^{13}C NMR (50 MHz) δ: 55.83, 56.2, 56.37, 108.03, 112.58, 116.02, 116.35, 123.25, 132.62, 146.25, 151.50, 153.30, 158.50, 182.30, 186.80; MS m/z (rel.int.): 274 (M$^+$, 100), 259 (22), 243 (65), 231 (28), 215 (33), 201 (12), 203 (10),175 (87), 147 (27), 119 (15); Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14; found: C, 65.65; H, 5.12.

2-(3'-Acetoxy-4'-methoxyphenyl)-6-methoxy-1,4-benzoquinone (3c) and 2-(3'-acetoxy-4'-methoxyphenyl) -5-methoxy-1,4-benzoquinone (3d): (orange oil) IR (film) ν_{max}/cm^{-1}: 3000, 1780, 1670, 1640, 1580, 1500, 1480, 1450, 1350, 1200, 1000; ^{1}H NMR (400 MHz): δ 2.36 (s, 6H, 2 x COC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.88 (s, 6H, 2 x OC*H*$_3$), 5.96 (d, *J* 2.3 Hz, 1H, C*H*=C), 6.00 (s, 1H, C*H*=C), 6.75 (d, *J* 2.3 Hz, 1H, C*H*=C), 6.79 (s, 1H, C*H*=C), 7.02 (d, *J* 8.6 Hz, 2H, 2 x Ar-*H*), 7.29 (d, *J* 2.3 Hz, 2H, 2 x Ar-*H*), 7.40-7.50 (m, 2H, Ar-*H*); ^{13}C NMR (100 MHz) δ: 20.63, 56.05, 56.35, 56.49, 107.23, 112.22, 112.26, 123.84, 124.39, 124.92, 125.24, 128.16, 128.63, 129.74, 132.30, 139.68, 142.66, 144.77, 152.84, 153.06, 158.76, 168.71, 181.14, 182.05, 187.09, 187.11; MS m/z (rel.int.): 302 (M^+, 22), 260 (100), 245 (6), 229 (75), 217 (9), 201 (7), 189 (5), 173 (3), 161 (9), 133 (5).

Results and Discussion

All arenes studied rapidly reacted with 2-methoxy-1,4-benzoquinone and dioxygen under the conditions used resulting in the formation of corresponding methoxyaryl-substituted 1,4-benzoquinones (Table 1). Within 4 hours ca. 80% quinone conversions are achieved with 70-75% selectivity for the specific coupling product. Dioxygen uptake corresponds to the amounts of quinone reacted and in all the runs presented in Table 1, their molar ratio is close to stoichiometric one (O_2/quinone=1/2). After this, the gas uptake decreases markedly indicating that the rate of arene-arene homocoupling, if any, is rather low. No products of the oxidative arene-arene coupling have been detected in significant amounts. The main advantage of the developed method compared to the previously reported one[5] is the use of palladium acetate in *catalytic* amounts. The reoxidant, *i.e.*, heteropoly acid, is also used in *catalytic* amounts and only dioxygen is consumed as the final oxidant. In addition, lower temperatures (80 °C vs. reflux temperature) and shorter reaction times (4 h vs. 18-36 h) can be used, along with the possibility to monitor the substrate conversion during the reaction by measuring the dioxygen uptake.

Table 1. Palladium/HPA-6 catalyzed oxidative coupling of 2-methoxy-1,4-benzoquinone with arenes by dioxygen. [a]

Run	Arene	Conversion[b] (%)	Dioxygen/quinone[c] (mol/mol)	Products (Selectivity [b], %)	TON[d]	Yield[e] (%)
1[f]	 **2a**	80	0.59	 **3a** (75)	12	60
2	 **2b**	82	0.50	 **3b** (67)	11	55
3	 **2c**	76	0.62	 **3c** (70)	15[g]	75[g]
				 **3d** (28)		

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[a] All reactions were performed under the following conditions, unless otherwise indicated: 2-methoxy-1,4-benzoquinone (1 mmol), arene (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), HPA-6 (0.25 mmol), HOAc (15 mL), O_2 (1MPa), 80^0C, 4 h. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Molar ratio between consumed dioxygen and reacted quinone. [d] Turnover numbers. [e] ^{1}H NMR yield based on reacted quinone. [f] 25 mL of benzene. [g] For the mixture **3c**/**3d**

The substituents of the arene strongly influence the regioseletivity of quinone-arene oxidative coupling. In all cases coupling occurs at the C-5 or C-6 positions of quinone (*meta* or *para* position with respect to the methoxy group), possibly due to the steric hindrance of the quinone methoxy group. Benzene and 1,4-dimethoxybenzene give mainly 5-arene-substituted quinone (75 and 67%, respectively; Table 1, runs 1 and 2), while 1-acetoxy-2-methoxybenzene results in 6-arene-substituted quinone (70%, run 3). Oxidative coupling of 2-methoxy-1,4-benzoquinone with asymmetrically substituted arene, *i.e,* 1-acetoxy-2-methoxybenzene, occurs at the *para* position with respect to the arene methoxy group (products **3c** and **3d**).

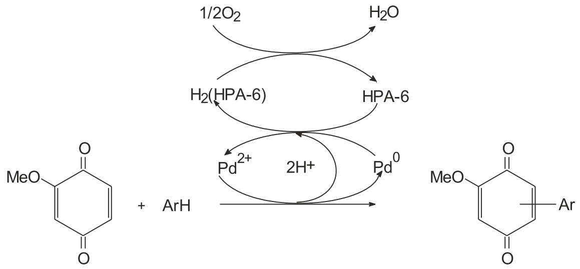
The results presented in Table 1 have been obtained at the temperature of 80 °C, which has been found to be optimum. The temperature effect on the quinone conversion and product yield at the oxidative coupling of 2-methoxy-1,4-benzoquinone and benzene is illustrated by the data summarized in Table 2. The selectivity for the formation of coupling product **3a** and quinone conversion decreases markedly with lowering the reaction temperature. Conversions of 41 and 29% are observed for 4 h at 65 and 45 °C, respectively (Table 2, runs 3 and 4), while 80% at 80 °C (Table 2, run 2). In addition to the expected reaction deceleration, both the selectivity for **3a**, and, consequently, the yield based on quinone drop dramatically (yield of 60% at 80 °C vs. 7% at 45 °C). Interestingly, at reflux temperature (ca.120 °C), quinone is consumed at a much lower rate and a dark oil is obtained as a crude product, with only trace amounts of product **3a** being detected after 4 h of reaction. Thus, the degradation of the catalytic system seems to take place at high temperatures.

Table 2. The effect of temperature on the palladium/HPA-6 catalyzed oxidative coupling of 2-methoxy-1,4-benzoquinone (**2a**) with benzene resulting in 5-phenyl-2-methoxy-1,4-benzoquinone (**3a**) [a]

Run	Temperature (°C)	Conversion[b] (%)	Selectivity[b] for **3a** (%)	TON[c]	Yield[d] (%)
1	reflux	25	15	0.8	4
2	80	80	75	12	60
3	65	41	43	3.6	18
4	45	29	25	1.4	7

[a] All reactions were performed under the following conditions: 2-methoxy-1,4-benzoquinone (1 mmol), $Pd(OAc)_2$ (0.05 mmol), HPA-6 (0.25 mmol), benzene (25 mL), HOAc (15 mL), O_2 (1MPa), 4 h. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Turnover numbers. [d] ^{1}H NMR yield based on reacted quinone.

As mentioned above, in the oxidative coupling of 2-methoxy-1,4-benzoquinone with arenes at 80 °C, dioxygen is consumed in stoichiometric amounts based on the reacted quinone. Therefore, under these conditions, the effective reoxidation of both the reduced palladium species and the blue-colored reduced forms of HPA-6 ("blue") occurs in solution, which remains brown-colored during the reaction. The catalytic cycle of the oxidative quinone-arene coupling catalyzed by the two-component $Pd(OAc)_2$/HPA-6 system is presented in Scheme 2. Palladium can be recycled either by HPA-6, as shown in Scheme 2, or, alternatively, by quinone itself, with the hydroquinone formed being reoxidized by HPA-6. Dioxygen oxidizes the HPA-6 blue $[H_2(HPA\text{-}6)]$, thus acting as the final oxidant. For all arenes studied the turnover numbers of 11-15 have been achieved (Table 1). It is worthwhile noting that the direct reaction of dioxygen with both Pd metal and hydroquinones is kinetically unfavorable.[16]



Conclusions

A novel *catalytic* method for the synthesis of methoxyaryl-substituted 1,4-benzoquinones via palladium/heteropoly acid catalyzed oxidative coupling of 2-methoxy-1,4-benzoquinone and arenes using dioxygen, which is the most abundant and cheapest oxidant, has been developed. We are presently developing the process showing higher turnover numbers and trying to extend the scope of this highly convenient method.

Acknowledgments

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