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PALLADIUM (II) ASSISTED PREPARATION OF METHOXYARYLBENZOQUINONES

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ABSTRACT: The reaction of 2-methoxy-1,4-benzoquinone with methoxyphenolic derivative compounds obtained from wood tar constituents, assisted by palladium (II) acetate in acetic acid, allowed the preparation of five novel methoxyaryl-substituted 1,4-benzoquinones, as well as four structural isomer mixtures.

In Brazil, forest biomass from reforestation with plants chiefly of the *Eucalyptus* genus has always been a prominent energetic source mainly for paper and cellulose industries and charcoal steel mills. Chromatographic analysis of *Eucalyptus* tar recovered by some steel mills during charcoal production shows that it is mainly constituted of 2,6-dimethoxyphenol, 2-methoxyphenol and their

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4-alkyl derivatives[1], which makes wood tar a valuable source for the production of 1,4-benzoquinones with good yield.

There are a number of quinone in nature which play important roles in several metabolic sequences and show biologic activity[2,3]. Due to wide biological activity of this class of compounds, medicinal agents based on the quinone structure have been developed[4]. Accordingly, it is important to uncover simple yet powerful methods for the synthesis of substituted quinones for the development of new medicinal agents.

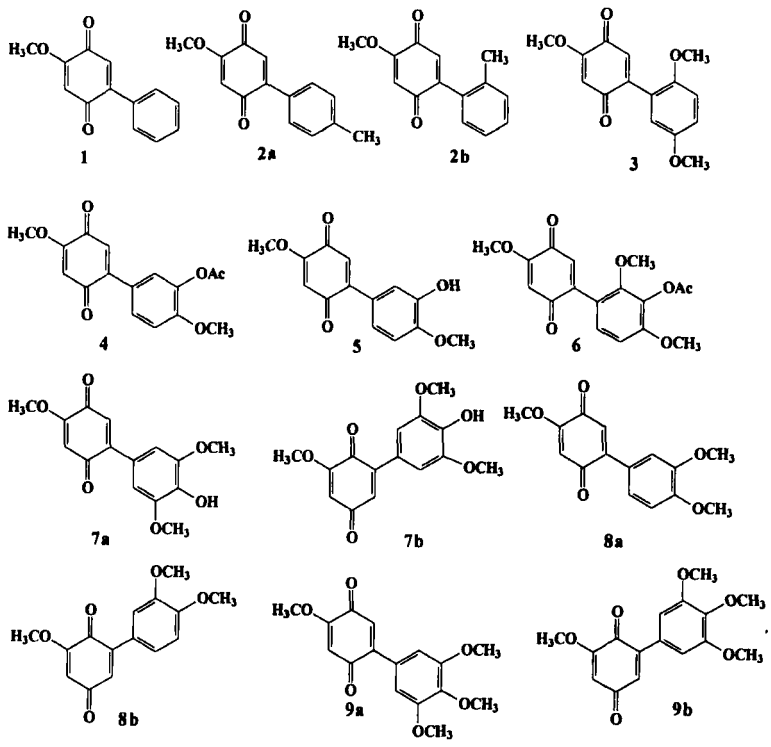
Most of synthetic methods for prepared quinones have relied the elaboration of a preexisting aromatic or heteroaromatic core. However, a few methods are related to the direct synthesis of methoxyarylbenzoquinones. Aryl-substituted quinones have been synthesized by the reaction of quinones with aryldiazonium salts[5]. Another method, reported by Itahara, consists in oxidative coupling of 1,4-benzoquinone with arene in the presence of palladium[6].

Despite the large number of substances containing oxygenated aromatic rings with biological activity in nature[7], there are few methods to prepare methoxyarylbenzoquinone derivatives. Higuchi reported selective quinone formation from the oxidation of tetramethoxybiphenyls with the Ru(por)-2,6-disubstituted pyridine N-oxide system in the presence of acid[8].

This paper describes the utilization of methoxyphenolic derivative compounds in oxidative coupling reactions in the presence of palladium (II) acetate in acetic acid as a direct method to prepare methoxyarylbenzoquinones.

In order to do this, some wood tar constituents were converted into methoxyphenolic derivatives. Thus, 2-methoxyphenol was transformed into its acetylated derivative, while 2,6-dimethoxyphenol was converted into methylated and acetylated derivatives.

2-Methoxybenzoquinone was submitted to the reaction with methoxyarenes, using the Itahara protocol[6], leading to formation of thirteen methoxyarylbenzoquinone (**1, 2a, 2b, 3, 4, 5, 6, 7a, 7b, 8a, 8b, 9a** and **9b**). These results are summarized in Table 1.



In this reaction, as palladium (II) complexes are electrophilic, they tend to react with electron-rich organic compounds, particularly olefins and arenes[9], as a consequence, the 1,4-benzoquinone reacts with arene[9].

The crude oxidative coupling products were purified by flash chromatography, affording pure compounds and structural isomeric mixtures. The several products formed by the coupling of 2-methoxybenzoquinone and methoxyphenolic derivative compounds show that the substituent groups influence both the coupling reactivity and orientation. Conversion yield and product ratio of the mixtures obtained could be accurately determined by integration of the corresponding olefin hydrogens by ^{1}H NMR analys.

2-Methoxy-1,4-benzoquinone reacts with symmetric compounds like benzene, 1,4-dimethoxybenzene and 1-acetyl-2,6-dimethoxybenzene yielding

Table I: Reaction of 2-methoxybenzoquinone with methoxyarenes

Arenes	Reaction time, h	Conv [a], %	Products (yield [b, c])%
Benzene (15 mL)	18	83	**1** (84,50)
Toluene (15 mL)	18	86	**2a** and **2b** (69,28[d])
1,4-Dimethoxybenzene (1.2 mmol)	18	86	**3** (87, 34)
1-Acetoxy-2-methoxybenzene (1.2 mmol)	18	87	**4** (60,13)
1-Acetoxy-2-methoxybenzene (1.2 mmol)	36	92	**5** (57,15)
2-Acetoxy-1,3-dimethoxybenzene (1.2 mmol)	18	71	**6** (47, 12)
2-Acetoxy-1,3-dimethoxybenzene (1.2 mmol)	36	100	**7a** and **7b** (#, 6[d])
1,2,3-trimethoxybenzene (1.2 mmol)	18	86	**8a** and **8b** (#,16[d]) **9a** and **9b** (#,13[d])

[a] Conversion of quinone based on analyses of crude products by ^{1}H NMR (200 MHz). [b] Yields based on quinone consumed. [c] Isolated. [d] Isolated as mixture, # could not be determined.

oxidative coupling products **1**, **3** and **6** with good conversion, in 18 hours of reaction. To improve the yied of product **6**, the reaction time was increased to 36 hours. This procedure led to the total conversion of quinone into coupling products. The purification of these products by flash chromatography yielded the coupling product mixture **7a** and **7b**, as result of the two possible coupling position of the quinonoid nucleus, as predicted by the Itahara protocol for 1,4-benzoquinone[6]. The structures proposed for these compounds were confirmed by ^{1}H and ^{13}C NMR. The increase in reaction time lead to a total conversion of quinone into coupling products despite the lower selectivity.

This quinone was submitted to oxidative coupling with acetoxy-2-methoxybenzene for 36 hours to verify the behavior of the acetoxymethoxyarenes in the coupling with methoxybenzoquinone. Flash chromatography purification allowed isolation of the desacetylated derivative **5**. A small increase in the conversion ratio of the quinone into coupling products also occurred.

The coupling of 1,2,3-trimethoxybenzene with quinone gives mixtures **8a**, **8b** and **9a**, **9b**. Compound ratios were determined by integration of hydrogen olefins and methoxy hydrogens. Compounds **8a** and **8b** have two methoxy groups. This fact suggests that coupling takes place at an *ortho* position and the coupling product undergoes demethoxylation.

However, compounds **9a** and **9b** result from *para* coupling of the 1,2,3-trimethoxybenzene with the quinone. The effects of group orientation also stand out in the toluene coupling.

These results show that the quinone is highly reactive in oxidative coupling in the presence of palladium II acetate. The substituents in the arene influence orientation and reactivity of this oxidative coupling. It was possible to prepare five pure substances and four mixtures of structural isomers even though the separation method used greatly reduced the isolated yields.

EXPERIMENTAL:

All melting points were performed in Metter FP800 apparatus and are uncorrected. Thin-layer chromatography was made with E. Merck silica gel 60F-254 glass-backed 0.25-mm thick plates and visualized in saturated iodine chamber. Column chromatography was performanced with flash-grade silica gel E. Merck 230-400 mesh. Dimethyl sulfate, benzene, toluene and acetic acid were purified according to literature procedures[10]. All other reagents and solvents were reagent-grade quality and used as received from the supplier. IR spectra were performed on a Perkin-Shimadzu IR-408 instrument. ^{1}HNMR and ^{13}C NMR spectra were recorded on a Avance-Bruker-DRX200 or Avance-Bruker-DRX400 instrument. NMR samples were dissolved into $CHCl_3$-d unless otherwise

specified, and chemical shifts are reported in δ scale relative to tetramethylsilane as internal standard.

2-Methoxy-1,4-benzoquinone: Freshly distillated 2-methoxyphenol was oxidized according to the method of Teuber[11].

1-Acetoxy-2-methoxybenzene and 1-acetoxy-2,6-dimethoxybenzene: These acetyl derivatives were prepared by reaction of the corresponding phenolic substance with acetyl anhydride and pyridine[12].

1,2,3-Trimethoxybenzene: This methylated derivative was prepared by methylation of 2,6-dimethoxyphenol with dimethyl sulfate in a NaOH (10%) solution[13].

General procedure for oxidative coupling: A solution of 2-methoxybenzoquinone (1 mmol) and palladium acetate (1 mmol) in 25 mL acetic acid containing arene was heated at reflux temperature under nitrogen (Table 1). The reaction was cooled, filtrated, and poured into saturated NaCl solution. The resulting mixture was extracted with chloroform (3 X 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuum. The residue was purified by flash chromatography, and elution with hexane/chloroform 8:2 gave methoxyarylbenzoquinones.

5-Phenyl-2-methoxy-1,4-benzoquinone, 1: crystalline orange solid, m.p.187.6-188.9°C (Lit[14]: 187°C). IR (KBr):1670, 1640, 1620, 1580, 1440. ^{1}H NMR (400 MHz) δ: 3.87 (3H, s, OCH_3), 6.04 (1H,s, CH=C), 6.81 (1H,s, CH=C), 7.4-7.5 (5H, m, 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,%): 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.

5-(4'-Methylphenyl)-2-methoxy-1,4-benzoquinone, 2a and 5-(2'-methylphenyl)-2-methoxy-1,4-benzoquinone, 2b: yellow solid, m.p.:183.2-186.8

°C. IR (KBr): 1680, 1640, 1600, 1580, 1430. ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ: 2.36 (3H,s, CH_3-Ar), 2.79 (3H,s, CH_3-Ar), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.10 (1H, s, CH=C), 6.11 (1H, s, CH=C), 6.76 (1H,s , CH=C), 6.77 (1H,s , CH=C), 7.25 (2H, d, J=8.2 Hz, 2 x Ar-H), 7.26-7.35 (4H, m, Ar-H), 7.44 (2H, dd, J=8.2 and J=1.9 Hz, Ar-H). ^{13}C NMR (100 MHz) δ: 21.40, 21.43, 56.34, 108.03, 126.67, 128.39, 129.27, 129.88, 129.50, 130.11, 130.20, 130.80, 130.94, 130.98, 132.70, 138.18, 146.46, 146.74, 158.62, 182.22 , 186.74, 186.86. MS (m/z,%): 228 (M^+, 100), 213 (84), 185 (72), 157 (12), 129 (36).

5-(2', 5'-Dimethoxyphenyl)-2-methoxy-1,4-benzoquinone, 3: crystalline red solid, m.p.: 130.3-131.4°C (Lit[8] 132-134°C). IR (KBr): 1680, 1650, 1600, 1550, 1460. ^{1}H NMR (200 MHz) δ: 3.73 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.03 (1H,s, CH=C), 6.72 (1H, dd, J=2.7 and J=0.5 Hz, Ar-H), 6.76 (1H, s, CH=C), 6.90-6.95 (2H, m, 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,%): 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 .

5-(3'-Acetoxy-4'-methoxyphenyl)-2-methoxy-1,4-benzoquinone, 4: orange solid, m.p.: 191.8–192.1°C. IR(KBr): 2950, 1780, 1680, 1640, 1600, 1460, 1310, 1290, 1180, 1110, 1010, 900, 800. ^{1}H NMR (400 MHz): 2.33 (3H, s, $OCOCH_3$), 3.87 (3, s, OCH_3), 3.88 (3H, s, OCH_3), 6.01 (1H, s, CH=C), 6.77 (1H, s, CH=C), 7.02 (1H, d, J =8.6 Hz, Ar-H), 7.29 (1H, d, J=2.3 Hz, Ar-H), 7.45 (1H, dd, J=8.6 and J= 2.3 Hz, Ar-H). ^{13}C NMR (100 MHz) δ: 20.63, 56.04, 56.35, 107.98, 112.31, 124.38, 125.23, 128.63, 129.73, 139.67, 144.70, 153.05, 158.65, 168.81, 182.04, 186.72. MS (m/z,%): 302 (M^+,12), 260 (100), 245 (6), 229 (75), 217 (9), 201 (7), 189 (5), 173 (3), 161 (9), 133 (5). Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.51; H 4.65 .

5-(3'-Hydroxy-4'-methoxyphenyl)–2–methoxy-1,4-benzoquinone, 5: red solid, m.p.: 157.8-159.3°C. IR (KBr): 3500, 2900, 1670, 1650, 1610, 1550, 1450, 1360, 1250, 1200, 1980, 1120, 1050, 900, 880, 770. ^{1}H NMR (400 MHz) δ: 3.86 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.64 (1H, s, OH), 6.03 (1H, s, CH=C), 6.77 (1H, s, CH=C), 6.90 (1H, d, J =8.4 Hz), 7.06 (1H, dd, J=8.4 and J=2.2 Hz, Ar-H), 7.11 (1H, d, J=2.2 Hz, Ar-H).

^{13}C NMR (100 MHz) δ: 56.32, 56.41, 108.03, 110.46, 115.65, 122.46, 125.98, 129.70, 145.60, 145.83, 148.54, 158.63, 182.18, 186.92. MS (%): 260 ($M^{+\cdot}$,55), 229 (10), 201 (10), 173 (15), 69 (100). Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.67. Found: C, 64.42; H, 4.67 .

5-(3'-Acetoxy-2',4'-dimethoxyphenyl)-2-methoxy-1,4-benzoquinone, 6: orange solid. m.p.:180.8-182.5 °C. IR (KBr): 2900, 1740, 1670, 1640, 1600, 1500, 1450, 1400, 1350, 1310, 1200, 1140, 1090, 1000, 830. ^1H NMR (400 MHz) δ: 2.39 (3H,s, $COCH_3$), 3.73 (3H, s, OCH_3), 3.89 (6H, s, OCH_3), 6.02 (1H, s, CH=C), 6.75 (1H, d, J=8.6 Hz, Ar-H), 6.79 (1H, s, CH=C), 7.04 (1H, d, J=8.6 Hz, Ar-H). ^{13}C NMR (100 MHz) δ: 19.50, 55.24, 60.36, 105.96, 118.87, 127.13, 131.22, 132.07, 144.07, 150.40, 153.01, 157.56, 167.26, 181.09, 185.09. MS (%): 323 [$M^{+\cdot}$] (19), 290 (100), 275 (34), 259 (34), 247 (10), 229 (19), 219 (9). Anal. Calcd. for $C_{17}H_{16}O_7$: C, 63.58; H, 4.67. Found: C, 63.54 ; H 4.69.

5-(3',5'-Dimethoxy-4'-hydroxyphenyl)-2-methoxy-1,4-benzoquinone,7a and 6-(3',5'-dimethoxy-4'-hydroxyphenyl)-2-methoxy-1,4-benzoquinone,7b: brown solid, m.p:. 158-162°C. IR (KBr): 3500, 3000, 1660, 1640, 1600, 1500, 1450, 1410, 1350, 1300, 1200, 1020, 1100, 850, 750. ^1H NMR (400 MHz) δ: 3.87 (6H, s, 2 x OCH_3), 3.91 (6H, s, 2 x OCH_3), 3.94 (6H, s, 2 x OCH_3), 5.76 (1H, s, OH), 5.97 (1H, s, OH), 5,98 (1H, d, J=2.2 Hz, CH=C), 6.03 (1H, s, CH=C), 6.76 (1H, d, J=2.2 Hz, CH=C), 6.80 (1H,s, CH=C), 7.78 (2H, s, 2 x Ar-H),7.79 (2H, s, 2 x Ar-H). ^{13}C NMR (100 MHz) δ: 56.37, 56.44, 56.47, 106.36, 106.90, 107.13, 108.04, 123.40, 123.80, 129.55, 131.97, 137.03, 137.37, 143.72, 145.94, 147.32, 158.66, 158.81, 181.52, 182.12, 187.04, 187.26 . MS (m/z,%): 290 ($M^{+\cdot}$,10), 259 (10), 228 (20), 213 (20), 185 (40), 141 (30), 69 (100).

5-(3',4'-Dimehtoxyphenyl)-2-methoxy-1,4-benzoquinone, 8a and 6-(3',4'-dimethoxybenzene)-2-methoxy-1,4-benzoquinone, 8b. Orange oil. IR (film): 2900, 1680, 1650, 1600, 1510, 1480, 1420, 1300, 1250, 1210, 1100, 1000, 900, 800. ^1H NMR (200 MHz) δ: 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.87 (6H, s, 2 x OCH_3), 3.90 (6H, s, 2 x OCH_3), 5.98 (1H, d, J=2.5 Hz, CH=C), 6.03 (1H, s, CH=C), 6.67 (1H, d, J=2.5 Hz, CH=C), 6.68 (2H, d, J=8.6 Hz, 2 x Ar-H), 6.73 (1H, s, CH=C), 6.90 (2H, dd, J= 8.6 and J=1.9 Hz, Ar-H), 6.66 (2H, d, J=1.9 Hz, 2 x Ar-H). ^{13}C NMR (50 MHz) δ:

56.03, 56.20, 60.11, 60.62, 60.67, 61.03, 106.96, 107.20, 107.84, 119.81, 120.03, 124.65, 125.06, 131.83, 134.30, 142.01, 144.03, 146.11, 151.66, 151.98, 158.49, 159.03, 181.03, 182.16, 186.22, 187.34. MS (%): 274 ($M^{+\cdot}$, 100), 243 (20), 228 (19), 200 (65).

2-Methoxy-5-(3',4',5'-trimethoxyphenyl)-1,4-benzoquinone, 9a and 2-methoxy-6-(3',4',5'-trimethoxyphenyl)-1,4-benzoquinone, 9b. Brown-reddish solid, m.p.:154.3-156.2°C. IR (KBr): 2900, 1660, 1640, 1610, 1600, 1500, 1450, 1400, 1360, 1250, 1210, 1140, 1000, 850. ^{1}H NMR (200 MHz) δ: 3.88 (6H, s, 2 x OCH_3), 3.89 (6H, s, 2 x OCH_3), 3.90 (6H, s, 2 x OCH_3), 3.91 (6H, s , 2 x OCH_3), 5.99 (1H, d, J= 2.4 Hz, CH=C), 6.03 (1H, s, CH=C), 6.72 (2H, s, 2 x Ar-H), 6.73 (2H, s, 2 x Ar-H), 6.78 (1H, d, J=2.4 Hz, CH=C), 6.79 (1H, s, CH=C). ^{13}C NMR (50 MHz) δ: 56.21, 56.24, 56.35, 56.51, 60.91, 106.56, 107.05, 107.09, 108.02, 127.57, 127.93, 130.36, 132.77, 139.93, 140.19, 143.79, 146.03, 153.11, 153.14, 158.61, 158.78, 181.25, 182.07, 186.75, 187.11. MS (%): 304 (M^{+}, 100), 289 (21), 273 (21), 261 (7), 254 (10), 233 (5), 205 (9), 175 (3).

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