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A direct route to isoflavan quinones. The synthesis of colutequinones A and B

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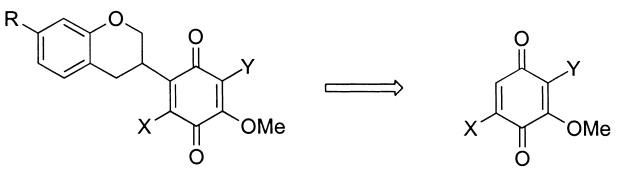
Abstract—The first syntheses of colutequinone A and colutequinone B were achieved. Radical generation via phenyliodoso diacetate was superior to radical generation via ammonium persulfate.

Colutequinone A (**1**),[1] colutequinone B (**2**)[2] and claussequinone (**3**)[3] are members of a growing family of isoflavan quinones. Colutequinone B exhibits antifungal activity in vitro. Claussequinone exhibits potent activity against bloodstream forms of *Trypanosoma cruzi* (Chagas' disease).[4] It also exhibits anti-inflammatory activity, antifertility activity and is a feeding deterrent for the grass grub *Costelytra zealandica*.[5–8] Claussequinone has been synthesized by Farkas and coworkers using thallium trinitrate in the key step.[9] As part of a program to develop environmentally benign radical reactions,[10,11] we report the first syntheses of **1** and **2** from quinones **4** and **5** (Scheme 1).



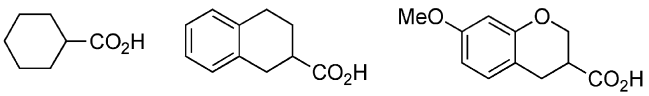
1: R,Y = OMe, X = H
2: R,X = OMe, Y = H
3: R = OH, X,Y = H

4: X = OMe, Y = H
5: X = H, Y = OMe

Scheme 1.

The additions of radicals derived from the decarboxylation of carboxylic acids to quinones have been reported by Barton,[12] Torssell,[13] Schaefer,[14] and Theodorakis.[15] Using the persulfate method of radical generation, Torssell[13] converted carboxylic acids into alkoxymethyl-, benzyl- and phenoxymethyl radicals, which reacted with naphthoquinones in good to excellent yields. He also generated alkoxycarbonyl radicals from monoesters of oxalic acid.[16]

We compared two methods for radical generation from carboxylic acids: (1) the method using ammonium persulfate in combination with a catalytic amount of a silver salt and (2) the method using phenyliodoso diacetate. We evaluated acids **6**, **7**, and **8**. Cyclohexanecarboxylic acid (**6**) and 1,2,3,4-tetrahydro-2-naphthoic acid (**7**) are commercially available. Acid **8** was synthesized from 4-methoxysalicylaldehyde by reaction with *tert*-butyl acrylate according to the method of Satoh[17] to produce an unsaturated ester followed by hydrolysis (CF_3CO_2H) and reduction (H_2, 10% Pd/C).



6 **7** **8**

The reaction of acid **6** with benzoquinone using ammonium persulfate with a catalytic amount of silver nitrate in acetonitrile:water at 70°C afforded cyclohexylbenzoquinone[18] in 91% isolated yield (Scheme 2). Similarly, the reaction of **7** with benzoquinone generated quinone **9** in 55% isolated yield (Scheme 3). The reaction with phenyliodoso diacetate also produced cyclohexylbenzoquinone in 55% yield (at 20% conversion relative to the quinone) and **9** in 45% yield (at 30% conversion relative to the quinone).

Surprisingly, the reaction of **8** with benzoquinone, **4** or **5** using the standard persulfate conditions did not afford *any* desired product, but returned unreacted benzoquinone and most of the carboxylic acid. Increasing the amount of persulfate had no effect. Even when we employed a stoichiometric amount of silver salt, no alkylated quinone was isolated. The rationale for this unusual result with acids bearing electron-rich aromatic rings is not clear, particularly given Torssell's successful result with phenoxyacetic acid.

Keywords: quinones; persulfate; phenyliodoso diacetate.
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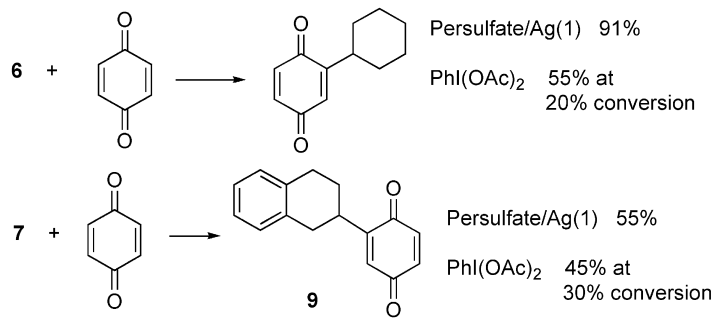
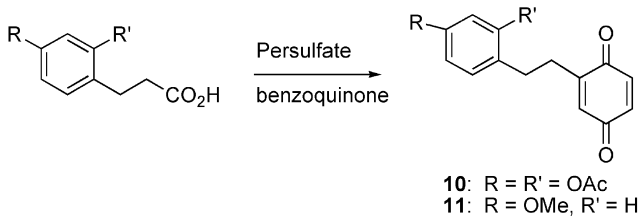
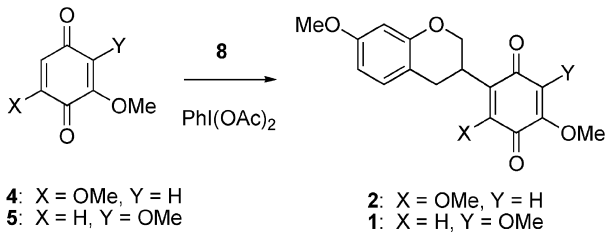


Scheme 2.



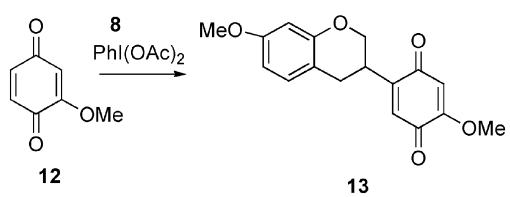
Scheme 3.

In view of these results, we examined two phenylpropionic acids. The reaction of 2,4-diacetoxyphenylpropionic acid (prepared by acetylation of commercially available 2,4-dihydroxyphenylpropionic acid) with persulfate and a catalytic amount of silver salt afforded a 28% isolated yield of quinone **10**. In contrast, the reaction of 4-methoxyphenylpropionic acid (commercially available) did not produce the desired quinone **11**. These results further show the incompatibility of electric rich aromatic rings with the persulfate conditions (Scheme 4).



Scheme 4.

The reaction of acid **8** with commercially available 2,6-dimethoxybenzoquinone **4** and phenyliodoso diacetate[19] afforded a 92% isolated yield (at 24% conversion) of colutequinone B (**2**). Similarly, the reaction of **5** with **8** produced colutequinone A (**1**) in 87% yield (at 11% conversion) (Scheme 5).



Scheme 5.

The reaction of methoxybenzoquinone **12** with acid **8** presented a question of regiocontrol in the radical addition. The reaction of **8** with quinone **12** produced quinone **13**, the major product, in 84% yield (at 9% conversion). Its proton and carbon NMR are identical to an authentic sample.[10] Bieber has shown that radicals add regioselectively to methoxybenzoquinone.[20]

In summary, the reaction of chroman carboxylic acids with benzoquinones provides a direct entry to biologically active quinones. Using the phenyliodoso diacetate method, the chemistry is flexible with regard to substitution pattern on both the quinone and the carboxylic acid.

1. Experimental

1.1. General experimental for radical formation using phenyliodoso diacetate

To a mixture of quinone (1 equiv.) and acid (3 equiv.) in benzene (5 mL/mmol of quinone) was added phenyliodoso diacetate (1 equiv.). The reaction mixture was heated to reflux for 36 h under an argon atmosphere. The mixture was cooled to rt, diluted with ethyl acetate, and washed with $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by either silica gel chromatography or prep tlc (hexanes:ethyl acetate) to give the product.

1.1.1. Colutequinone A (1). Purified using 4:1 hexanes: ethyl acetate. 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, d, J=8.4 Hz), 6.48 (1H, dd, J=8.7, 2.7 Hz), 6.37 (1H, d, J=2.7 Hz), 6.37 (1H, s), 4.25 (1H, dd, J=10.8, 3.0 Hz), 4.06 (1H, dd, J=10.8, 6.0 Hz), 4.02 (3H, s), 4.01 (3H, s), 3.76 (3H, s), 3.50–3.40 (1H, m), 3.05 (1H, dd, J=16.2, 6.0 Hz), 2.71 (1H, dd, J=15.9, 6.3 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 184.3, 183.7, 159.6, 154.9, 146.8, 145.3, 144.9, 131.2, 130.3, 112.2, 108.3, 101.8, 68.4, 61.6, 61.5, 55.6, 31.0, 29.1; HRMS m/z for $C_{18}H_{18}O_6$ calcd 330.1103, found 330.1109.

TLC (2:1 hexanes:ethyl acetate), R_f=0.20.

1.1.2. Colutequinone B (2). Purified using 3:1 hexanes: ethyl acetate. 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.92 (1H, d, J=8.4 Hz), 6.47 (1H, dd, J=8.1, 2.4 Hz), 6.41 (1H, d, J=2.7 Hz), 5.86 (1H, s), 4.44 (1H, dd, J=10.8, 10.2 Hz), 4.13 (1H, ddd, J=10.2, 3.3, 3.0 Hz), 3.97 (3H, s), 3.81 (3H, s), 3.77 (3H, s), 3.70–3.55 (1H, m), 3.13 (1H, dd, J=15.0, 12.0 Hz), 2.66 (1H, ddd, J=15.0, 5.1, 2.1 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 186.9, 178.4, 159.3, 157.4, 155.9, 155.3, 131.6, 130.2, 114.1, 107.7, 107.6, 101.8, 67.9, 61.6, 56.7,

55.6, 31.4, 29.4; HRMS *m/z* for $C_{18}H_{18}O_6$ calcd 330.1103, found 330.1109.

TLC (2:1 hexanes:ethyl acetate), R_f=0.30.

1.1.3. 2-(1,2,3,4-Tetrahydronaphth-2-yl)benzoquinone (9). Purified using 5:1 hexanes:ethyl acetate. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.20–7.02 (4H, m), 6.80 (1H, d, *J*=9.9 Hz), 6.74 (1H, dd, *J*=9.9, 2.1 Hz), 6.58 (1H, dd, *J*=2.4, 1.2 Hz), 3.26–3.13 (1H, m), 3.07–2.84 (3H, m), 2.70 (1H, dd, *J*=15.9, 11.1 Hz), 2.10–1.97 (1H, m), 1.82–1.65 (1H, m); 75 MHz ^{13}C NMR ($CDCl_3$) δ 188.1, 187.2, 153.0, 137.3, 136.3, 135.8, 135.3, 131.4, 129.2, 129.16, 126.3, 126.1, 35.1, 33.3, 29.1, 28.3; HRMS *m/z* for $C_{16}H_{14}O_2$ calcd 238.0994, found 238.0996.

TLC (5:1 hexanes:ethyl acetate), R_f=0.37.

1.1.4. O-Methyl claussequinone (13). The yield was 84 % based on the recovered methoxybenzoquinone) was purified by prep tlc (3:1 hexanes:ethyl acetate). NMR ($CDCl_3$ 300 MHz) δ 6.95 (1H, d, *J*=8.4 Hz), 6.48 (1H, dd, *J*=8.4, 2.4 Hz), 6.48 (1H, d, *J*=1.2 Hz), 6.37 (1H, d, *J*=2.7 Hz), 5.968 (1H, s), 4.26 (1H, ddd, *J*=11.1, 3.3, 1.2 Hz), 4.07 (1H, ddd, *J*=10.8, 6.0, 1.2 Hz), 3.82 (3H, s), 3.76 (3H, s), 3.46 (1H, m), 3.06 (1H, dd, *J*=16.5, 6.3 Hz), 2.73 (1H, dd, *J*=15.9, 6.3 Hz). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 29.1, 31.1, 55.5, 56.5, 68.5, 101.8, 108.1, 108.3, 112.3, 130.3, 131.1, 149.5, 154.9, 158.7, 159.6, 182.3, 186.9. HRMS: *m/z* for $C_{17}H_{16}O_5$ calcd 300.0998, found 300.1002.

TLC (2:1 hexanes:ethyl acetate), R_f=0.50.

1.2. General experimental for radical formation using persulfate

To a mixture of 1,4-benzoquinone (1 equiv.) and carboxylic acid (1.5 equiv.) in CH_3CN (2 mL/mmol of quinone)/H_2O (2 mL/mmol of quinone) were added $AgNO_3$ (0.2 equiv.) and $(NH_4)_2S_2O_8$ (1.5 equiv.) at rt. After being heated at 70°C for 5 h, the mixture was cooled to rt. The solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with H_2O and $NaHCO_3$, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by sgc (hexanes:ethyl acetate) to give the product.

1.2.1. 2-(2,4-Diacetoxyphenyl)ethylbenzoquinone (10). Purified using 3:1 hexanes:ethyl acetate. 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.22 (1H, d, *J*=8.4 Hz), 6.95 (1H, dd, *J*=8.4, 2.4 Hz), 6.87 (1H, d, *J*=2.4 Hz), 6.76 (1H, d, *J*=9.9 Hz), 6.71 (1H, dd, *J*=10.2, 2.1 Hz), 6.51–6.46 (1H, m), 2.80–2.60 (4H, m), 2.35 (3H, s), 2.27 (3H, s); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.7, 187.5, 169.3, 169.25, 149.8, 149.3, 148.2, 137.0, 136.7, 133.4, 130.6, 129.9, 119.6, 116.5, 30.6, 29.0, 21.3, 21.1; HRMS *m/z* for $C_{18}H_{16}O_6$ calcd 328.0947, found 328.0954.

TLC (2:1 hexanes:ethyl acetate), R_f=0.40.

Acknowledgements

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