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A Direct Synthesis of *O*-Methyl Claussequinone

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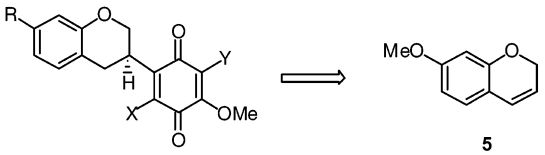
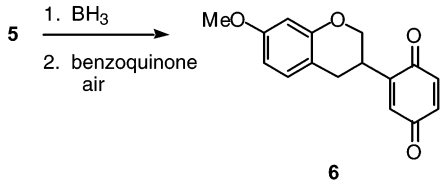
Abstract: The reaction of a chromene with BH_3 followed by treatment with benzoquinone and air is the key step in a direct entry to *O*-methyl claussequinone.

Colutequinone A (**1**),[1] colutequinone B (**2**),[2] and claussequinone (**3**)[3] are members of a growing family of isoflavan quinones. Claussequinone exhibits potent activity against bloodstream forms of *Trypanosoma cruzi* (Chagas' disease).[4] It also exhibits antiinflammatory activity and antifertility activity and is a feeding deterrent for the grass grub *Costelytra zealandica*.[5,6] Claussequinone has been synthesized by Farkas and co-workers using thallium trinitrate in the key step.[7] As part of a program to develop environmentally benign radical reactions,[8] we report a direct synthesis of **4**, the *O*-methyl analogue of **3**.



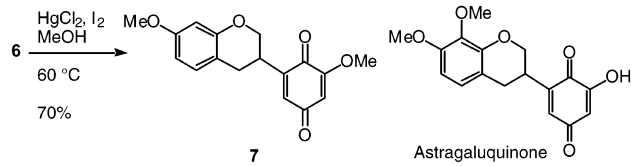
1: R,Y = OMe, X = H
2: R,X = OMe, Y = H
3: R = OH, X,Y = H
4: R = OMe, X,Y = H

Our synthetic route began with chromene **5**, which was readily prepared in two steps from 3-methoxyphenol and the diethyl acetal of 3-chloropropanal.[9] The reaction of chromene **5** with BH_3 followed by benzoquinone and air led to quinone **6**[10] in 37% yield.[11] Resubmission of the recovered starting materials to the same reaction conditions increased the yield to 65%. In view of this promising result, we reacted the borane with methoxybenzoquinone with the intent of producing **4** in one step. Surprisingly, the desired adduct was not formed. The major product was the chromanol derived from oxidation of the borane with oxygen. This result was surprising in light of a recent report of the successful regioselective addition of alkyl radicals to methoxybenzoquinone.[12]



6

The regioselective addition of alcohols to benzoquinones has little precedent. We recently used a Lewis acid catalyst for the regioselective addition of methanol to a phenanthrene quinone.[13] Using these conditions with **6**, we obtained quinone **7** in 70% yield. The NMR spectrum shows differences from the reported spectrum for **3**. In **7**, the proton at C-5 of the quinone (ortho to the methoxyl group) has a chemical shift of 5.89 with a coupling constant of 2.4 Hz. The corresponding hydrogen in astragaluquinone (shown below) has a chemical shift of about 6.25 with a coupling constant of 2.5 Hz.[14]



The reaction of **6** with thiophenol and PTSA in methanol at 25 °C followed by oxidation with silver oxide produced adducts **8** and **9** in a 5:1 ratio in 93% yield. Although no precedent was found for the directed addition of thiophenol to substituted benzoquinones, the regiochemistry of thiophenol addition is in accord with our observation for the acid-catalyzed addition of methanol to quinones. Oxidation of **8** with *m*-CPBA in chloroform at 0 °C afforded a sulfoxide that was treated with methanol at reflux to afford compound **4** in 70% yield. Its proton and carbon NMR were consistent with the structure of **4**. Presumably, this transformation occurs by way of methanol addition to the activated benzoquinone followed by sulfoxide elimination. Compound **9**, the minor product of thiol addition, was treated with sodium methoxide to afford **4** in 63% yield.

In summary, the reaction of chromene **5** with BH_3 and benzoquinone followed by subsequent elaboration provides a direct entry to benzoquinones with useful biological activity. Convenient procedures for the regiospecific

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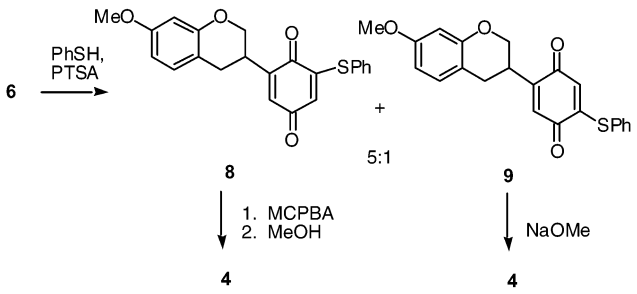

addition of thiophenol and methanol to substituted benzoquinones have been developed. These procedures will be useful for the synthesis of quinone natural products.

Experimental Section

(3,4-Dihydro-7-methoxybenzopyran-3-yl)-1,4-benzoquinone (6). To a solution of 3-chromene (800 mg, 4.94 mmol) in THF (4 mL) was added 1 M BH_3·THF (1.65 mL, 1.65 mmol) at 0 °C. After the mixture was stirred at rt for 5 h, H_2O (89 μL, 4.94 mmol) was added at 0 °C. Then benzoquinone (178 mg, 1.65 mmol) was added at rt in one portion. After the mixture was stirred at rt for 2 h, the mixture was evaporated in vacuo. The residue was purified by SGC (H/EA = 7:1) to give compound **6** (165 mg, 37%): 300 MHz NMR ($CDCl_3$) δ 6.95 (1H, d, J = 8.4 Hz), 6.81 (1H, d, J = 10.2 Hz), 6.73 (1H, dd, J = 10.2, 2.1 Hz), 6.55 (1H, dd, J = 2.1, 1.2 Hz), 6.49 (1H, dd, J = 8.4, 2.7 Hz), 6.38 (1H, d, J = 2.7 Hz), 4.27 (1H, dd, J = 10.8, 3.0 Hz), 4.07 (1H, dd, J = 10.8, 6.6 Hz), 3.76 (3H, s,), 3.43 (1H, m), 3.06 (1H, dd, J = 15.9, 5.7 Hz), 2.75 (1H, dd, J = 15.9, 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.6, 186.9, 159.6, 154.9, 148.6, 137.1, 136.5, 133.0, 130.3, 112.2, 108.3, 101.8, 68.3, 55.6, 31.2, 29.0; HRMS m/z for $C_{16}H_{14}O_4$ calcd 270.0892, measured 270.0895; mp 120−123 °C (lit.[10] mp 125 °C); TLC (3:1 H/EA) R_f = 0.25.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-methoxy-1,4-benzoquinone (7). To a solution of **6** (34 mg, 0.126 mmol) in MeOH (3 mL) were added $HgCl_2$ (34 mg, 0.126 mmol) and I_2 (3 mg, 0.013 mmol) at rt. After being stirred at 60 °C for 3 h, the reaction mixture was evaporated in vacuo. The resulting residue was diluted with ethyl acetate and washed with brine. The aqueous layer was extracted with ethyl acetate one more time. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by SGC (H/EA = 2:1) to give compound **7** (26.5 mg, 70%): 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, d, J = 8.4 Hz), 6.48 (1H, dd, J = 8.4, 2.4 Hz), 6.47 (1H, d, J = 1.2 Hz), 6.37 (1H, d, J = 2.4 Hz), 5.89 (1H, d, J = 2.4 Hz), 4.27 (1H, ddd, J = 10.8, 2.7, 0.9 Hz), 4.06 (1H, ddd, J = 10.5, 6.3, 1.2 Hz), 3.83 (3H, s), 3.75 (3H, s), 3.45 (1H, m), 3.04 (1H, dd, J = 15.9, 5.7 Hz), 2.74 (1H, dd, J = 15.6, 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 187.3, 181.6, 159.6, 159.0, 154.8, 146.5, 133.6, 130.3, 112.2, 108.3, 107.5, 101.8, 68.3, 56.6, 55.5, 31.1, 29.1; HRMS m/z for $C_{17}H_{16}O_5$ calcd 300.0998, measured 300.1004; TLC (3:1 H/EA) R_f = 0.21.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-6-phenylthio-1,4-benzoquinone (8) and 2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5-phenylthio-1,4-benzoquinone (9). To a mixture of **6** (83 mg, 0.307 mmol) and PhSH (35 μL, 0.338 mmol) in MeOH (10 mL) was added PTSA·H_2O (117 mg, 0.614 mmol) at rt. After being stirred at rt for 7 h, the reaction mixture was evaporated in vacuo. The resulting residue was diluted with CH_2Cl_2 and washed with brine. The aqueous layer was extracted with CH_2Cl_2 once more. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by SGC (H/EA = 3:1) to afford a regioisomeric mixture of quinols (108.8 mg, 93%). The mixture of quinols (108.8 mg, 0.286 mmol) was dissolved in benzene (10 mL). Then, Na_2SO_4 (81 mg, 0.572 mmol) and Ag_2O (133 mg, 0.572 mmol) were added at rt. After being stirred at rt for 4 h, the mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was evaporated and purified by SGC (H/EA = 10:1) to give minor product **9** and major product **8** (total 108 mg, 100%).

8: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.49 (5H, br s), 6.95 (1H,d, J = 8.4 Hz), 6.48 (1H, dd, J = 8.4, 2.4 Hz), 6.44 (1H, m), 6.37 (1H, d, J = 2.7 Hz), 5.84 (1H, d, J = 2.4 Hz), 4.28 (1H, dd, J = 10.5, 2.4 Hz), 4.09 (1H, dd, J = 10.8, 6.3 Hz), 3.75 (3H, s), 3.46 (1H, m), 3.07 (1H, dd, J = 16.2, 6.0 Hz), 2.75 (1H, dd, J = 16.2, 6.6 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 184.6, 183.9, 159.6, 155.0, 154.9, 148.0, 135.9, 133.9, 130.8, 130.6, 130.4, 127.4, 126.1, 112.2, 108.3, 101.8, 68.3, 55.5, 31.4, 29.1;. HRMS m/z for $C_{22}H_{18}O_4S$ calcd 378.0926, measured 378.0931; TLC (3:1 H/EA) R_f = 0.36.

9: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.50 (5H, br s), 6.94 (1H, d, J = 8.4 Hz), 6.74 (1H, d, J = 1.2 Hz), 6.48 (1H, dd, J = 8.4, 2.4 Hz), 6.37 (1H, d, J = 2.4 Hz), 5.89 (1H, s), 4.23 (1H, ddd, J = 10.8,3.0, 0.9 Hz), 4.04 (1H, ddd, J = 10.8, 6.0, 0.9 Hz), 3.76 (3 H, s), 3.39 (1H, m), 3.02 (1H, dd, J = 15.9, 5.7 Hz), 2.72 (1H, dd, J = 16.2, 6.9 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 184.3, 183.9, 159.6, 154.9, 154.6, 149.7, 135.9, 132.4, 130.8, 130.6, 130.3, 127.2, 126.3, 112.2, 108.3, 101.8, 68.4, 55.6, 31.2, 29.1; HRMS m/z for $C_{22}H_{18}O_4S$ calcd 378.0926, measured 378.0931; TLC (3:1 H/EA) R_f = 0.42.

2-(3,4-Dihydro-7-methoxybenzopyran-3-yl)-5-methoxy-1,4-benzoquinone (4). To a solution of **8** (35 mg, 0.093 mmol) in $CHCl_3$ (3 mL) was added 77% *m*-CPBA (23 mg, 0.102 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 one more time. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by SGC (H/EA = 3:1) to give sulfoxide (35 mg, 96% yield).

The sulfoxide (35 mg, 0.089 mmol) was dissolved in MeOH (3 mL). The solution was heated to reflux overnight. The solvent was evaporated, and the residue was purified by SGC (H/EA = 3:1) to afford compound **4** (18.7 mg, 70% yield): 300 MHz NMR ($CDCl_3$) 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), 5.97 (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); 75 MHz ^{13}C NMR ($CDCl_3$) δ 186.9, 182.3, 159.6, 158.7, 154.9, 149.5, 131.1, 130.3, 112.3, 108.3, 108.1, 101.8, 68.5, 56.5, 55.5, 31.1, 29.1; HRMS m/z for $C_{17}H_{16}O_5$ calcd 300.0998, measured 300.1002; TLC (2:1 H/EA) R_f = 0.36.

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Supporting Information Available: Proton NMR spectra for compounds **4**, **6**, **7**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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