SHORT PAPER

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Efficient synthesis of 4,4-dimethyl-1,9,10(1*H*)-anthracenetrione†

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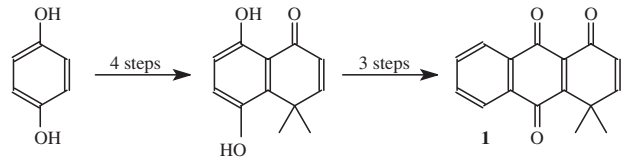
A concise route to the title compound was achieved via annulation of 4,4-dimethylcyclohexenone with 3-cyanophthalide, followed by oxidation with DDQ.

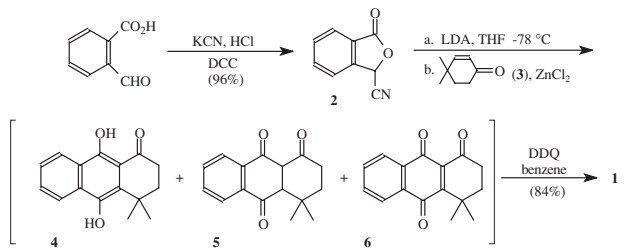
Keywords: annulation, anthracenetrione, 3-cyanophthalide, DDQ oxidation

Chagas' disease or American trypanosomiasis, a devastating protozoan infection caused by *Trypanosoma cruzi*, affects *ca.* 24 million people in the Americas with a mortality rate greater than 50,000 per year In Latin America it is a major cause of heart disease. Nifurtimox and benznidazole, two nitroheterocyclic drugs, are currently used to treat the acute phase of the disease. Both compounds, however, require high dosage levels over long time periods which result in irreversible organ damage. There are no effective therapeutic agents for the chronic phase of the disease.[1–4]

A decade ago the synthesis of 4,4-dimethyl-1,9,10(1*H*)-anthracenetrione (**1**) and its potent lytic activity *in vitro* against *T. cruzi* were reported.[5] The preparative route involved seven linear steps (eight steps overall), starting from hydroquinone.[5–8] Continued interest in this ring system has recently led to a series of derivatives.[9] Our interest in developing efficient annulation strategies for total synthesis[10] led us to consider alternate routes to **1** and herein we report a facile preparation of **1** in three steps with an overall yield of 80% (Scheme 1).



Equation 1



Scheme 1

Annulations with **2** are well-documented.[11] In the early phases of our study of the reaction of **2** with **3** in the absence of a catalyst, a side product with mass[5] was detected by GC–MS. On the assumption that this compound was 3-cyano-4,4-dimethylcyclohexanone (**7**), formed by conjugate addition to **3** of cyanide ion eliminated in the annulation process, we employed $ZnCl_2$. Lewis acids, in general, can assist Michael additions and this Lewis acid, in particular, served also to suppress totally the formation of **7**. We believe this is the first report of $ZnCl_2$ serving a dual role in such annulations. GC-MS analysis of the crude product mixture showed only three peaks: two peaks with *m*/*z* 256 (84% **4** and 4% **5**) and one peak with *m*/*z* 254 (12%), assumed to be 2,3-dihydro-4,4-dimethyl-1,9,10(1*H*)-anthracenetrione (**6**). The final step involved oxidation of **4**–**6** with excess DDQ which afforded **1** (84%) in two steps from **2**. Compound **4** from the annulation step was isolated, characterised, and independently converted to **1** in the same manner. The assignment of structure **5** to the minor annulation product is consistent with analogous tautomers observed in similar systems.[5,9,12] The presence of **6**, resulting from oxidation of **4** and/or **5**, reflects the facile air oxidation reported for comparable compounds.[13]

Experimental

GC-MS analyses were performed on a Hewlett Packard 6890 gas chromatograph with a (5%)diphenyl-(95%)dimethyl-polysiloxane crosslinked column (30 m × 0.25 mm with 0.25 μm film) and a HP 5973 mass selective detector (EI, 70 eV). NMR spectra were recorded in $CDCl_3$ on a Varian GEM-300 spectrometer with chemical shifts reported in parts per million (δ) relative to tetramethylsilane for ^1H and relative to the centre line of the 77.0 ppm triplet of chloroform-*d* for ^{13}C; *J* values are given in Hz. IR spectra were recorded as films on NaCl plates with a Perkin Elmer Paragon 500 FT-IR spectrophotometer; absorbance frequencies are reported in reciprocal centimeters (cm^{-1}) and intensities are designated as (s)=strong, (m)=medium, (w)=weak. Melting points (uncorrected) were determined on a modified Hershberg apparatus with matched Anschutz thermometers. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, TN, USA. Solvents were purified by the method of Grubbs *et. al.*[14] All chemicals used in this study were commercially available.

3-Cyanophthalide (**2**): Compound **2** was prepared by a modification of the literature method[15] in 96% yield and recrystallized from AcOEt: m.p. 120–121 °C (lit[15] 120–121 °C).

4,4-Dimethyl-1,9,10(1H)-anthracenetrione (**1**): A 2.5M solution of *n*-butyllithium in hexanes (0.20 ml, 0.50 mmol) was added via a syringe to a stirred solution of diisopropylamine (0.081 ml, 0.57 mmol) in THF (3 ml) at 0 °C under argon. After 30 min at 0 °C the reaction solution was cooled to –78 °C and a solution of **2** (72.3 mg, 0.454 mmol) in THF (1 ml) was added via syringe. After stirring for 30 min, a solution of **3** (0.0718 ml, 0.545 mmol) in 0.5M $ZnCl_2$ in THF (0.60 ml, 0.30 mmol) was added similarly and the orange solution was stirred at **–78** °C for 30 min and then at room temperature for 3 h. The dark green solution was diluted with H_2O, acidified with 1M HCl and extracted with benzene. The combined extract was washed with H_2O, dried, concentrated to 5 ml, treated with DDQ (619 mg, 2.73 mmol) and stirred at reflux for 24 h. The reaction mixture was diluted with CH_2Cl_2, filtered, washed with saturated aqueous $NaHCO_3$, then water, dried, and evaporated to dryness at reduced pressure to give a residual dark red solid (107 mg) which by GC–MS analysis was 90% **1** (96 mg, 84%) and 10% **4.** The crude product was flash chromatographed on silica gel and eluded with Et_2O-pet. ether (1:1 v/v) to give **1**: m.p. 158.5–160 °C (95% EtOH) (lit [6] 156–158 °C); spectroscopic data corresponded to literature values.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

3,4-Dihydro-9,10-dihydroxy-4,4-dimethyl-1(2H)-anthracenone (**4**): In the same manner as above **2** (0.23 mmol) was condensed with **3** (0.27 mmol). The dark green solution was diluted with H_2O, acidified with 1M HCl and extracted with CH_2Cl_2. The combined extract was washed with H_2O, dried, and evaporated *in vacuo* to give a residual yellow solid (44 mg, 76%) which by GC–MS analysis consisted of **4** (84%), **5** (5%), and **6** (12%). The solid was recrystallised from CH_2Cl_2-pet. ether to give **4**: m.p. 152.5–153.5 ˚C; IR (film) 3335(m), 2944(w), 1604(s), 1587(w), 1464(w), 1376(s), 1285(m), 1262(m), 1222(m), 1084(w) cm^{-1}; ^1H NMR (300 MHz) δ 14.46 (s, 1H), 8.42 (d, *J*=8.3 Hz, 1H), 7.94 (d, *J*=8.2 Hz, 1H), 7.66 (t, *J*=8.3 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 1H), 4.91 (s, 1H), 2.75 (t, *J*=6.7 Hz, 2H), 1.98 (t, *J*=6.9 Hz, 2H) 1.61 (s, 6H); ^{13}C NMR (75 MHz) δ 205.1, 158.7, 139.8, 130.9, 130.3, 126.7, 125.6, 124.8, 124.3, 120.0, 110.1, 38.6, 34.9, 33.9, 27.8; MS *m*/*z* 256 (M^+, 100), 241 (71), 223 (31). Anal. calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.76; H, 6.41.

A mixture of **4** (23 mg, 0.090 mmol) and DDQ (123 mg, 0.540 mmol) in toluene (2 ml) under argon was stirred at reflux for 10 h, diluted with CH_2Cl_2 and worked up as above to give a dark red solid (22 mg, 97%) which by GC–MS analysis was exclusively **1**: m.p. 157.5–158.5 ˚C (95% EtOH).

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