A short total synthesis of parvaquone

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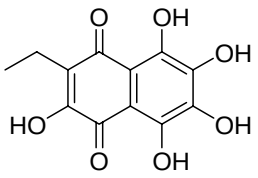
Abstract

Parvaquone **1**, a hydroxylated naphthoquinone with antiviral properties, was prepared in 26% overall yield in a straightforward manner starting from diisopropylsquarate **3**. The key features of the synthesis include addition of commercial cyclohexylmagnesium chloride to **3**, followed by acid-catalyzed rearrangement to furnish the cyclohexyl-substituted isopropylsquarate **2**. Further addition of phenyllithium to **2**, thermal cyclization and deprotection with BBr_3 gave **1**.

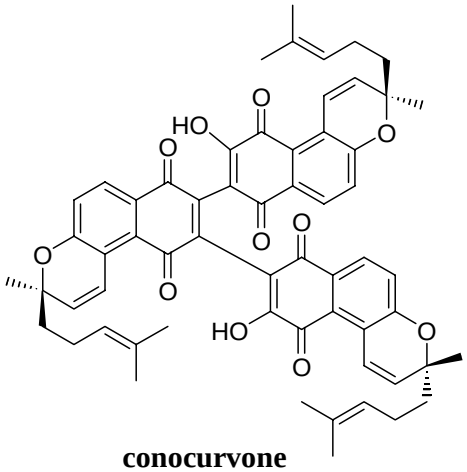
Keywords: Parvaquone, squaric acid ester

Introduction

Hydroxylated quinones often possess interesting biological activity and there is an increasing interest to develop new and efficient ways to prepare them.[1] Examples of biologically active hydroxy-substituted quinones range from those of relatively simple structure, i.e. Echinochrome A,[2] to examples of high complexity, i.e. conocurvone.[3]

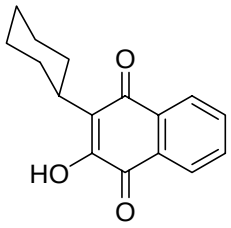


echinochrome A



conocurvone

Parvaquone **1**, is another example of a hydroxyquinone that displays interesting biological properties. It has been used against *theileria parva*, a microscopic parasite that causes East Coast Fever (theileriosis).[4] East Coast fever (ECF), a form of bovine theileriosis, is a tick-transmitted protozoal disease of cattle characterized by high fever and lymphadenopathy. The disease causes high mortalities in breeds nonindigenous to the endemic areas, and is confined to eastern, central, and parts of southern Africa.



parvaquone (1)

We wish to report the total synthesis of **1**, based on the chemistry of squaric acid esters developed by Liebeskind, Moore and others.[5]

Results and Discussion

Despite the fact that Kerr *et al*.[4] have reported an efficient chromium carbene-based synthesis of parvaquone, it was considered that a chromium-free alternative was worth pursuing. Thus, the preparation of **1** was envisioned as illustrated in **Figure 1**.

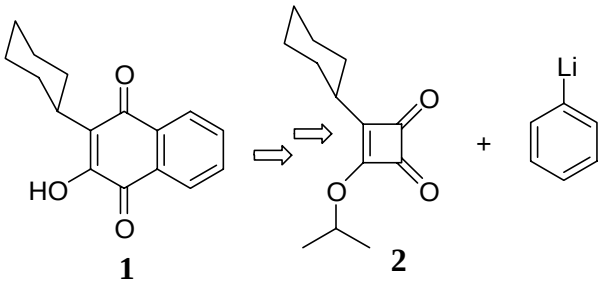
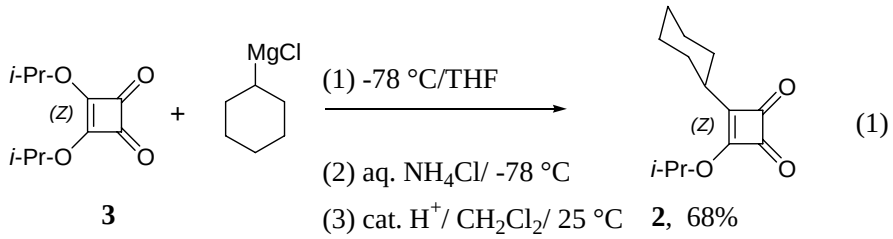


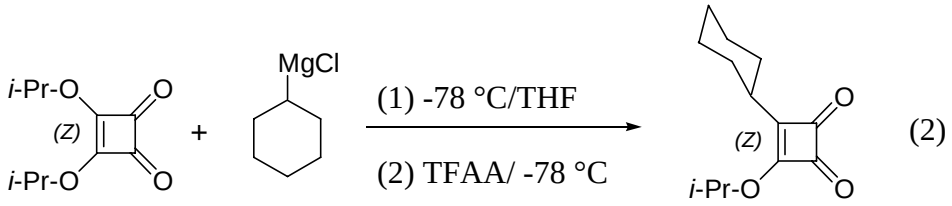
Figure 1. Retrosynthetic analysis of parvaquone.

The synthesis was begun with the addition of commercially available cyclohexylmagnesium chloride to diisopropylsquarate **3**[6] at –78 °C in THF. Quenching the reaction mixture at low temperature to give the corresponding 1,2-adduct followed by acid-catalyzed rearrangement, produced the cyclohexyl-substituted dione **2** in 68% overall yield (eq. 1).[7]



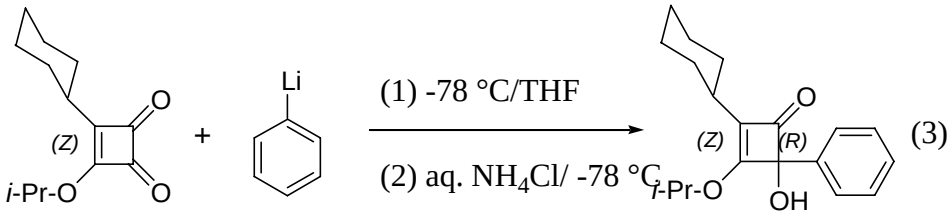
3 **2**, 68% (1)

The efficiency of the previous reaction was improved when the protocol introduced by Moore was used, i. e., low temperature trifluoroacetic anhydride (TFAA) quench of the 1,2-adduct gave **2** in 93% yield (eq. 2).[8]



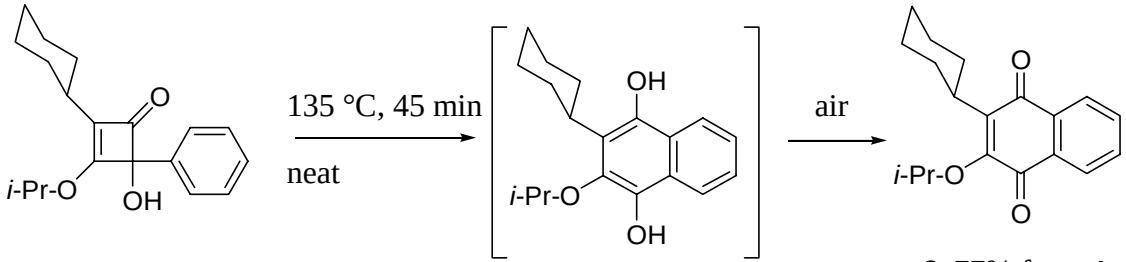
3 **2**, 93% (2)

Nucleophilic addition of phenyllithium to the more electrophilic carbonyl group of **2**, followed by aqueous quench furnished alcohol **4** in modest yield (eq.3).



2 **4**, 44% (3)

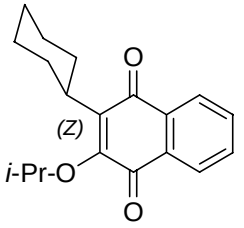
Then, thermolysis of **4** (135 °C, 45 min) generated hydroquinone **5**, which on exposure to air, immediately oxidized to naphthoquinone **6** in 78% yield (**Scheme 1**).



4 **5** **6**, 77% from **4**

Scheme 1. Synthesis of **6**.

Finally, parvaquone **1** was synthesized by treating **6** with an excess of BBr_3 to yield a yellow crystalline solid with identical spectral properties as those reported previously (eq. 4).[4]



6

(1) 2.5 eq. BBr_3/-78 °C/CH_2Cl_2

(2) H_2O, -78 °C

1, 81% (4)

In conclusion, a straightforward synthesis of parvaquone was developed with a 26% overall yield. Most of the steps in the synthetic sequence are efficient and the starting materials are either commercially available or readily prepared. Moreover, this method offers the possibility for the preparation of a host of parvaquone analogues by the addition of aryllithium derivatives with different substitution patterns.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer in deuteriochloroform ($CDCl_3$) with either tetramethylsilane (TMS) (0.0 ppm) or chloroform (7.26 ppm) as internal reference unless otherwise indicated. Data are reported in the following order: chemical shift in ppm (δ), multiplicities (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), hep (heptet), m (multiplet), exch (exchangeable), app (apparent)), coupling constants, *J*, are reported (Hz), and integration. Infrared spectra were recorded on a Perkin-Elmer FTIR 1600 series spectrophotometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium 40-67%), and w (weak 20-40%).

Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Acid-pretreated silica gel plates were used to monitor the final deprotection of **2**. Visualization was accomplished by UV-light, iodine, or *p*-anisaldehyde solution. Medium pressure liquid chromatography (MPLC) was performed as described by Baeckström *et al*.[9] using gradient solutions with the indicated solvent systems. THF was dried over sodium and stored over activated 4Å molecular sieves. All reactions were performed under a dry N_2 atmosphere in oven- and or flame-dried glassware.

Commercial chemicals. The following materials were obtained from commercial sources: $C_6H_{11}MgCl$, PhLi, TFAA, and BBr_3.

Experimental procedures

3-Cyclohexyl-4-isopropoxycyclobuten-1,2-dione (2). Cyclohexylmagnesium chloride (26 mmol of a 2M ether solution) was added via syringe to a cold (-78 °C) THF (10 mL) solution of diisopropoxysquarate **3** (4.0 g, 20.2 mmol, 1.3 equiv.). After 20 min., TFAA (3.3 mL, 20.2 mmol) was added at –78 °C via syringe, the cooling bath was removed and the mixture was allowed to reach room temperature. An aq. saturated NH_4Cl solution was added (20 mL) and then the crude material was extracted with ether (3 x 15 mL), dried over anhyd. $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a yellow oil. The product (4.2 g, 93%) was obtained as a yellow low -meting solid . TLC (silica gel, 20% ethyl acetate/hexanes R_f = 0.46); chromatographic purification (1 x 15 cm, ethyl acetate/hexanes gradient); mp 34-35 °C; IR (KBr, cm^{-1}) 2933 (s), 2854 (s), 1794 (s), 1753 (s), 1588 (s); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.41 (sept, *J* = 6.2 Hz, 1H), 2.75 (tt, *J* = 3.6, 10.8 Hz, 1H), 1.93-1.85 (m, 2H), 1.80-1.50 (m, 6H), 1.45 (d, *J* = 6.2 Hz, 6H), 1.42-1.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 197.5, 195.3, 194.8, 188.2, 79.1, 36.5, 29.0, 25.7, 25.6, 23.0. Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.15; H, 8.33.

2-Cyclohexyl-3-isopropoxy-4-hydroxy-4-phenyl-2-cyclobuten-1-one (4). Phenyllithium (3.96 mmol) was added via syringe to a cold (-78 °C) THF (10 mL) solution of dione **2** (0.8 g, 3.6 mmol). The mixture was stirred at that temperature for four hours after which, it was quenched with an aq. saturated NH_4Cl solution (15 mL). The cooling bath was removed and the mixture was allowed to reach room temperature. It was then extracted with ether (3 x 15 mL), dried (anhyd. $MgSO_4$), filtered and the solvent removed *in vacuo*. The product (0.48 g, 44%) was obtained as a white solid. TLC (silica gel, 20% ethyl acetate/hexanes R_f = 0.22); chromatographic purification (1 x 10 cm, ethyl acetate/hexanes gradient) followed by trituration with hexanes; mp 125-127 °C; IR (KBr, cm^{-1}) 3163 (m), 2980 (m), 2929 (m), 2850 (m), 1748 (s), 1607 (s); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.52-7.22 (m, 5H), 4.64 (sept, *J* = 6.2 Hz, 1H), 4.40 (bs, 1H), 2.32 (tt, *J* = 3.6, 11.1 Hz, 1H), 1.90-1.49 (m, 7H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.28 (bs, 3H), 1.03 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 190.0, 180.5, 137.5, 133.8, 128.7, 128.1, 125.7, 92.8, 78.1, 33.7, 30.5, 26.0, 23.0, 22.6. Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.61; H, 8.35.

2-Cyclohexyl-3-isopropoxy-1,4-naphthoquinone (6). Enone **4** (0.45 g, 1.5 mmol) was placed in a round-bottomed flask and purged with nitrogen. The flask was then immersed in a preheated sand-bath at 135 °C. After 45 min, total conversion to hydroquinone **5** was observed (TLC silica gel, 20% ethyl acetate/hexanes R_f = 0.59). Then, the reaction flask was cooled down to ambient temperature and ether (10 mL) was added. The crude reaction mixture was stirred open to the air during 4 h, after which all of **5** oxidized to **6**. The solvent was removed *in vacuo* to yield a yellow oil. The product (0.35 g, 78%) was obtained as a bright yellow oil. TLC (silica gel, 20% ethyl acetate/hexanes R_f = 0.75); chromatographic purification (1 x 12 cm, ethyl acetate/hexanes gradient); IR (KBr, cm^{-1}) 2926 (m), 2852 (m), 1667 (s), 1596 (m), 1573 (m); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.00–7.86 (m, 2H), 7.68-7.50 (m, 2H), 4.99 (sept, *J* = 6.2 Hz, 1H), 3.05 (tt, *J* = 3.3, 12.1 Hz, 1H), 1.99-1.20 (m, 10H), 1.28 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ

185.2, 182.4, 156.8, 140.3, 133.8, 133.1, 132.7, 131.6, 126.4, 126.0, 76.0, 36.6, 30.2, 27.1, 26.2, 23.1..

Parvaquone (1). To a cold (-78 °C) dichloromethane (8 mL) solution of naphthoquinone **6** (0.6 g, 2.0 mmol) was added dropwise a dichloromethane solution of BBr_3 (4.5 mL, 4.5 mmol, 1.0 M, 2.25 equiv). Once the addition was finished, the cooling bath was removed and the mixture was stirred for 40 min at room temperature. Then, water (15 mL) was added and the crude reaction mixture was stirred for 20 min. The organic phase was then dried (anhyd $MgSO_4$), and the solvent removed under reduced pressure. The product (0.42 g, 81%) was obtained as a yellow solid. TLC (silica gel, 20% ethyl acetate/hexanes R_f = 0.53); chromatographic purification (1 x 15 cm, ethyl acetate/hexanes gradient); mp 133-135 °C; IR (KBr, cm^{-1}) 3353 (s), 2926 (s), 1657 (s), 1385 (s); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.16–8.02 (m, 2H), 7.80-7.60 (m, 2H), 7.43 (s, 1H), 3.07 (tt, *J* = 3.5, 12.1 Hz, 1H), 2.05-1.21 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 184.8, 182.2, 153.0, 135.1, 133.4, 132.9, 129.4, 128.1, 127.1, 126.1, 35.3, 29.4, 26.9, 26.2. (Lit.[4]).

Acknowledgements

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