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Preparation of 1,4-hydrobenzoquinones by the PCC/SiO_2-promoted double oxidation of 3-cyclohexene-1,2-diols

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The PCC/SiO_2-promoted double oxidation of 3-cyclohexene-1,2-diols, which were easily prepared by the two-step sequence of α′-hydroxylation of various conjugated cyclohexenones and the subsequent nucleophilic carbonyl addition of alkyl anions, produced diversely substituted 1,4-hydrobenzoquinones.

Quinones or hydroquinones are useful building blocks for constructing polycyclic compounds in organic synthesis.[1] Quinoids containing polyprenyl side chains such as ubiquinones, menaquinones, and plastoquinones are biologically important natural products, which show physiological and clinical activities.[2] Most of the synthetic methods for these chemically and biologically important quinones or hydroquinones are based on the oxidation of phenol or methoxybenzene derivatives,[3] which generally require strongly acidic or basic conditions.

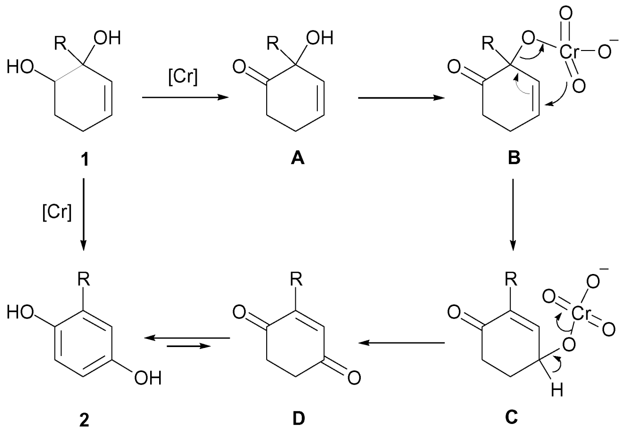
We devised a totally different synthetic approach to 1,4-hydrobenzoquinones **2** by the double oxidation of 3-cyclohexene-1,2-diols **1** (Scheme 1). While the secondary homoallylic alcohol of **1** is oxidized to the ketone of **A**, the chromate ester of the sterically congested tertiary allylic alcohol of **B** (R ≠ H) undergoes allylic migration to give the ester of the secondary allylic alcohol of **C**, which can be oxidized to the ketone of **D**. Enolization of the 1,4-diketone **D** gives rise to 1,4-hydrobenzoquinone **2**. This scenario has proven to be successful for 2-methyl-3-cyclohexene-1,2-diol (**1**) (R = Me in Scheme 1), where 2-methyl-1,4-hydrobenzoquinone (**2**) was obtained after the double oxidation with the mild Cr(VI)-based reagents in CH_2Cl_2 at RT (Table 1). An excess of oxidant (4 equiv.) was required to give the optimum yield, even though two equiv. was theoretically necessary. Silica gel supported pyridinium chlorochromate[4] (PCC) provided the best result (entry 4), which was prepared by mixing and pulverizing equal weight amounts of each material.

The scope of this synthetic method for 1,4-hydrobenzoquinones **2** depends on the availability of diversely substituted 3-cyclohexene-1,2-diols **1**. The preparation and the double oxidation of **1** was delineated in Scheme 2, and summarized in Table 2. We have reported a highly efficient synthetic method of methyl-substituted conjugated cyclohexenones by the reaction of β-ketoesters and α,β-unsaturated carbonyl compounds under *t*-BuOK–*t*-BuOH conditions.[5] We prepared 2-cyclohexen-1-ones **3** with methyl or ethyl substituents at the 2-, 4-, and 5-positions, which would constitute the three substituents (R^1, R^2, and R^3, respectively) of the 1,4-hydrobenzoquinones **2**. $Pb(OAc)_4$-mediated direct α′-acetoxylation[6] of the conjugated cyclohexenones **3** in refluxing toluene (conditions: A) produced 6-acetoxy-2-cyclohexen-1-ones **4** in reasonable yields except for *R*-(−)-carvone (**3f**), where no reaction was observed. α′-Hydroxylation of the sterically demanding *R*-(−)-carvone (**3f**) should be carried out by the peroxycarboxylic acid oxidation of the corresponding trimethylsilyl (TMS) enol ether,[7] which was prepared by the reaction with TMSCl in the presence of sodium hexamethyldisilazide (NaHMDS, conditions: B). Desilylated 6-hydroxy-2-cyclohexen-1-one **4f** was obtained in 90% yield in this case (entry 16). The fourth substituent R^4 was introduced by the nucleophilic addition of alkyl metal species to the carbonyl group of **4**. MeLi, EtMgBr, and *n*-BuLi were used to add Me, Et, and *n*-Bu groups, respectively to the six different cyclohexenones **4a**–**f** to produce eighteen different 3-cyclohexene-1,2-diols **1a**–**r** in reasonable yields.[8]

Table 1 The optimization of the double oxidation of 2-methyl-3-cyclohexene-1,2-diol (**1**) (R = Me in Scheme 1)

Entry	Oxidant/equiv.	Reaction condition	Yield **2** (%)[a]
1	PCC (2)	RT for 3 h in CH_2Cl_2	30
2	PDC (4)	RT for 1 h in CH_2Cl_2	33
3	PCC (4)	RT for 2 h in CH_2Cl_2	56
4	PCC (4)–SiO_2	RT for 1 h in CH_2Cl_2	78

[a] Isolated yield of 2-methyl-1,4-hydrobenzoquinone (**2**) after SiO_2 chromatographic separation. 1,4-Benzoquinone was also obtained during the purification process, the yield of which was about 10% of the yield **2**.



Scheme 1 A synthetic plan for 1,4-hydrobenzoquinones **2** by the double oxidation of 3-cyclohexene-1,2-diols **1** (R = alkyl).

The key double oxidation of the 3-cyclohexene-1,2-diols **1a**–**r** proceeded well under the standard conditions of 4 equiv. of silica supported PCC in CH_2Cl_2 at RT for 1 h to give rise to the diversely substituted 1,4-hydrobenzoquinones **2a**–**r** in decent yields.[9] 1,4-Hydrobenzoquinones **2** were formed exclusively under an argon atmosphere even with an excess (4 equiv.) of PCC oxidant. However, it was not possible to avoid obtaining the oxidized 1,4-benzoquinones during the purification process of SiO_2 column chromatography. The actual yield of 1,4-hydrobenzoquinones **2** must be higher by *ca.* 10% than the reported yields in Table 2.

We then studied the possibility of synthesizing 1,2-hydrobenzoquinones **5** by the PCC/SiO_2 oxidation of the 3-cyclohexene-1,2-diols **1s**, **1t**, and **1u**, which were easily prepared by hydride addition to the carbonyl groups of **4a**, **4b**, and **4f**, respectively (Scheme 3 and Table 3). We expected that the double oxidation of the secondary allylic and homoallylic

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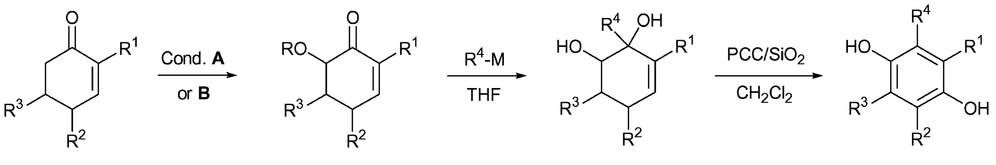
Table 2 The yields of each reaction in Scheme 2 for diverse substrates

Entry	3	R^1	R^2	R^3	Conditions^a	4	R	Yield **4** (%)^b	1	R$^{4\,c}$	Yield **1** (%)^b	2	Yield **2** (%)^{b,d}
1	**3a**	H	H	Me	A	**4a**	Ac	81	**1a**	Me	76	**2a**	71
2									**1b**	Et	55	**2b**	59
3									**1c**	Bu	52	**2c**	62
4	**3b**	H	Me	H	A	**4b**	Ac	65	**1d**	Me	80	**2d**	70
5									**1e**	Et	69	**2e**	66
6									**1f**	Bu	54	**2f**	78
7	**3c**	Me	H	H	A	**4c**	Ac	68	**1g**	Me	71	**2g**	67
8									**1h**	Et	67	**2h**	57
9									**1i**	Bu	66	**2i**	52
10	**3d**	Me	H	Me	A	**4d**	Ac	70	**1j**	Me	75	**2j**	64
11									**1k**	Et	64	**2k**	55
12									**1l**	Bu	59	**2l**	69
13	**3e**	H	Me	Et	A	**4e**	Ac	77	**1m**	Me	91	**2m**	81
14									**1n**	Et	72	**2n**	63
15									**1o**	Bu	81	**2o**	69
16	**3f**	Me	H		B	**4f**	H	90	**1p**	Me	77	**2p**	77
17									**1q**	Et	56	**2q**	67
18									**1r**	Bu	70	**2r**	60

^{a} Reaction conditions for **4**, A: **3** and $Pb(OAc)_4$ (2 equiv.) in toluene at reflux for 4 h; B: (i) **3**, TMSCl, and NaHMDS in THF at 0 °C, (ii) urea–H_2O_2 (UHP) and phthalic anhydride in MeCN at RT for 5 h. ^{b} Isolated yields after SiO_2 chromatographic separation. ^{c} An excess amount (3 equiv.) of MeLi, EtMgBr, or *n*-BuLi was used to produce 3-cyclohexene-1,2-diols **1**. ^{d} A small amount of 1,4-benzoquinone was also obtained during the purification process, which was about 10% of the yield of **2**.



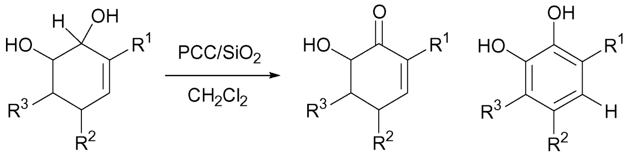
3 **4** **1** **2**

Scheme 2 Synthesis of 1,4-hydrobenzoquinones **2** from 2-cyclohexen-1-ones **3**.

Table 3 The yield **4** of the reaction in Scheme 3

Entry	1	R^1	R^2	R^3	4	Yield of **4** (%)^a
1	**1s**	H	H	Me	**4s**	78
2	**1t**	H	Me	H	**4t**	69
3	**1u**	Me	H		**4f**	83

^{a} Isolated yields after SiO_2 chromatographic separation.



1 **4** **5**

Scheme 3 The oxidation of 3-cyclohexene-1,2-diols **1s**–**u** using the standard silica supported PCC (4 equiv.) conditions at RT (see Table 3).

alcohols of **1s**–**u** would directly produce the corresponding 1,2-hydrobenzoquinones **5**. However, only the mono oxidation of the allylic alcohol of **1s**–**u** was observed to produce the 6-hydroxy-2-cyclohexen-1-ones **4s**, **4t** and **4f** in 69–83% yields. No 1,2-hydrobenzoquinone **5** was obtained under the above PCC/SiO_2 oxidation conditions.

In conclusion, we have developed a novel and efficient synthetic method for diversely alkyl-substituted 1,4-hydrobenzoquinones **2** by the mild PCC/SiO_2-promoted double oxidation of 3-cyclohexene-1,2-diols **1**, which were readily prepared from the corresponding 2-cyclohexen-1-ones **3**. This double oxidation requires the secondary allylic alcohol and a tertiary allylic alcohol in the 1,2-position to produce 1,4-hydrobenzoquinones **2** after allylic migration of the tertiary allylic alcohol and the subsequent oxidations. The 1,4-hydrobenzoquinones can be efficiently utilized in the total synthesis of various polycyclic natural products.

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8 The representative experimental procedure for **1a**: To a stirred solution of **4a** (0.26 g, 1.5 mmol) in THF at −78 °C under an argon atmosphere was added a 1.6 M solution of MeLi in ether (2.9 mL, 4.6 mmol). The mixture was stirred at that temperature for 1 h and then at

RT for 2 h. The reaction was quenched with 10% aqueous NH_4Cl solution, and extracted with ethyl acetate. The organic mixture was washed with saturated aqueous NaCl solution, dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **1a** (0.17 g, 1.2 mmol) in 76% yield. Data for **1a** (major isomer): ^{1}H NMR δ 1,09 (d, J = 6.2 Hz, 3H), 1.29 (s, 3H), 1.71 (s, 1H), 1.76–2.08 (m, 3H), 2.72 (s, 1H), 3.51 (d, J = 5.0 Hz, 1H), 5.49 (dt of A of ABq, J_{AB} = 9.8, J_d = 1.8, J_t = 0.9 Hz, 1H), 5.69 (dt of B of ABq, J_{AB} = 9.8, J_d = 1.4, J_t = 0.9 Hz, 1H) ppm; ^{13}C NMR δ 18.3, 28.4, 30.9, 31.9, 71.4, 76.9, 126.8, 131.7 ppm; IR (KBr) 3419, 1450, 1373, 1240 cm^{-1}.

9 The representative experimental procedure for **2a**: A mixture of PCC (1.20 g, 5.6 mmol) and silica gel (1.20 g, 70–230 mesh) was pulverized to give a light orange fine powder, which was added to a stirred solution of **1a** (0.17 g, 1.4 mmol) in CH_2Cl_2 at RT under an argon atmosphere. The mixture was stirred for 1 h, and the resulting mixture was filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **2a** (0.13 g, 0.98 mmol) in 71% yield. The corresponding 1,4-benzoquinone (0.01, 0.08 mmol) was also obtained in 6% yield. Data for **2a**: ^{1}H NMR δ 2.18 (d, J = 2.2 Hz, 6H), 5.44 (br s, 1H),5.47 (br s, 1H), 5.93 (br s, 2H) ppm; ^{13}C NMR δ 17.8, 128.2, 128.5, 144.1, 158.7 ppm; IR (KBr) 3450, 1377, 1235 cm^{-1}.