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Regioselective oxidation of 3-monosubstituted juglone derivatives

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Abstract

Derivatives of 3-substituted juglones with either electron-withdrawing or -donating substituents are regioselectively oxidized to *o*- or *p*-naphthoquinones using salcomine/air or [bis(trifluoroacetoxy)iodo]benzene, respectively. The structure of the oxidation products was confirmed by chemical transformations. A correlation between chemical shift of the single quinoid proton and the quinone structure was established.

Keywords: juglone derivatives; oxidation; salcomine; [bis(trifluoroacetoxy)iodo]benzene; naphthoquinones.

Derivatives of both *o*- and *p*-naphthoquinones, as well as their corresponding 1,2- and 1,4-dihydroxynaphthalenes, have a wide spectrum of applications in biology,[1] pharmacology[2] and material science,[3] in addition to their use in the chemical and pharmaceutical industry. Furthermore, they are also key intermediates for the synthesis of several biologically active natural products[4] and industrially useful compounds, such as perylenequinones[5] and anthracyclines.[6] The most direct synthetic approach is considered to be the regioselective oxidation of the parent juglone derivative.[7] However, this type of reaction is most suitable for heavily substituted naphthols, where only one position is accessible for oxidation.[8] Otherwise, low regioselectivity and/or marginal chemical yields are obtained.[9] Given that the spectroscopic properties of isomeric naphthoquinones is almost identical, it is often difficult to assign a structure for the product quinone. We would like to report two methods for the regioselective oxidation of monosubstituted juglones concurrently clarifying some contradictory literature reports.[10a]

In order to have reference compounds of indisputable structures, we initially synthesized some *p*-quinone derivatives via the well established and widely applied Hauser's approach (Scheme 1).[11] Thus, protected dihydro-*p*-naphthoquinones **3a** and **3b** were synthesized according to our previous work[12] and converted to *p*-quinone **5** after reduction, deprotection and air-oxidation. Subsequently, key intermediate **8** was prepared by a Stobbe type condensation[13] of substrates **6** and **7**, followed by deacetylation

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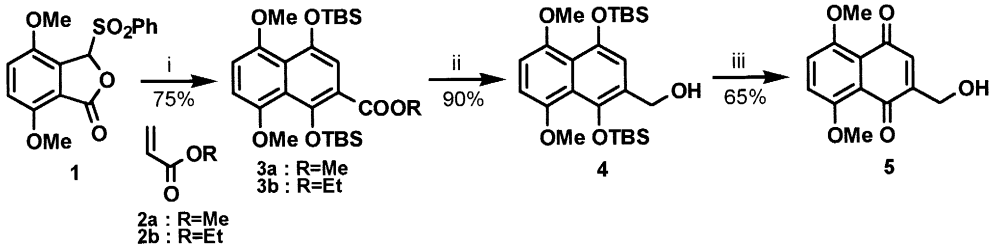
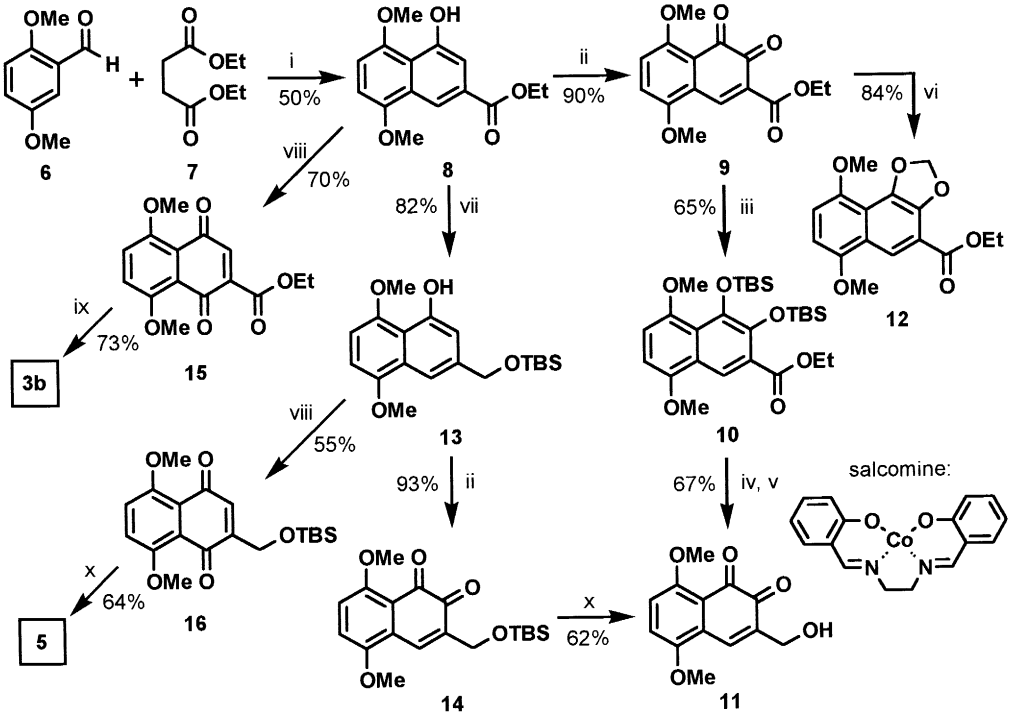


Scheme 1. Preparation of reference *p*-quinone derivatives. Reagents and conditions: (i) LDA, THF, −78°C then **2a** or **2b**; TBSCl, imidazole, DMF; (ii) DIBAL-H, CH_2Cl_2, −78°C; (iii) TBAF, THF, 0°C, air oxidation

(Scheme 2). The chemical shifts of the quinoid protons of all new compounds are shown in Table 1. Oxidation of naphthol **8** in the presence of catalytic amount of bis(salicylidene)ethylenediiminocobalt(II) (salcomine),[14] almost exclusively afforded a naphthoquinone which was anticipated to have structure **15** according to the literature.[10a,b] However, the chemical shift of the single quinoid proton of this product did not agree with the corresponding values of our reference *p*-quinoid isomers. To confirm its structure (whether it was **9** or **15**), further transformation to one of the reference compounds was considered. Therefore, it was subjected to a sequence of reactions in order to be converted either into compound **5** or compound **11**. Since the quinone alcohol so formed (see sequences **9** to **11**), showed a different colour and



Scheme 2. Oxidation of juglone derivatives. Reagents and conditions: (i) NaH, toluene, EtOH (cat.), 40°C; Ac_2O, AcONa, reflux; HCl conc., EtOH, reflux; (ii) Salcomine (cat.), CH_3CN, air, rt, 24 h; (iii) $Na_2S_2O_4$, $CHCl_3/H_2O$; TBSCl, imidazole, DMAP, DMF, 65°C; (iv) DIBAL-H, CH_2Cl_2, −78°C; (v) TBAF, THF, 0°C, air oxidation; (vi) $Na_2S_2O_4$, $CHCl_3/H_2O$; CH_2Br_2, Cs_2CO_3, DMF, 100°C; (vii) DIBAL-H, CH_2Cl_2, −78°C; TBSCl, imidazole, DMF; (viii) $(CF_3CO_2)_2IC_6H_5$, CH_3CN/H_2O 2:1, 0°C; (ix) $Na_2S_2O_4$, $CHCl_3/H_2O$; TBSCl, imidazole, DMF; (x) TBAF, THF, 0°C. LDA: lithium diisopropylamine; TBSCl: *tert*-butyldimethylsilyl chloride; DIBAL-H: diisobutylaluminum hydride; TBAF: tetrabutylammonium fluoride; DMAP: 4-dimethylaminopyridine

^{1}H NMR spectrum than *p*-naphthoquinone **5**, structure **11** is most likely.[15] Following this assumption, dithionite reduction of compound **9** and subsequent treatment with methylene dibromide under alkaline conditions[16] furnished **12** as a single product (supported by all spectroscopic evidence). It was now apparent that the electron deficient naphthol **8** afforded *o*-quinone **9** exclusively under salcomine/air oxidation, in contrast to the reported results.[10,17] Salcomine-catalyzed oxidation on a more electron-rich naphthol, such as substrate **13**, deprived of a directing group like the carboxylate, was also studied. Once again, oxidation under the same conditions followed by deprotection of the benzylic alcohol, yielded intermediate **11** without any trace of **5**. The same products (**9** and **11**) were also formed using Fremy's salt on substrates **8** and **13**, respectively, although in relatively lower yields. Moreover, diphenylselenic anhydride,[18] a known reagent for the regioselective *o*-oxidation of naphthols, afforded the *o*-isomers as well.

Table 1
^{1}H NMR chemical shifts of H^2 and H^4 protons (in ppm) of the naphthols and quinones synthesized

Compound	H^2	H^4
3a	7.18	–
3b	7.18	–
4	6.94	–
5	6.82	–
8	7.50	8.47
9	–	8.66
10	–	8.25
11	–	7.96
12	–	8.45
13	6.96	7.68
14	–	7.98
15	7.01	–
16	6.82	–

To achieve the synthesis of the desired *p*-isomer, a number of oxidants were employed, such as $Pb(OAc)_4$, CrO_3 and CAN. Most of them gave poor yields and mixture of products with the *o*-derivatives always predominating. On the contrary, hypervalent iodine reagents[19] were found to be suitable for the desired transformation. Thus, both naphthols **8** and **13** after treatment with [bis(trifluoroacetoxy)iodo]benzene, afforded *p*-quinones **15** and **16**, respectively, in satisfactory yields. Their structure was firmly established by converting them into reference compounds **3b** and **5**.

Regarding structure elucidation of the isomeric quinones by ^{1}H NMR, it is evident that the chemical shift of the quinoid proton is around 7.0 ppm for all *p*-naphthoquinones, while the corresponding proton of the *o*-isomers, resonates at significantly lower field (around 8.0 ppm, Table 1).

In conclusion, we have further distinguished routes towards the regioselective transformation of 3-substituted juglone derivatives to *o*- or *p*-naphthoquinones in synthetically useful ways. In addition, the use of the chemical shift of the single quinoid proton as indicative evidence for the assignment of the isomeric quinone, was shown to be an effective and conclusive tool.

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15. All new compounds were characterized by ^{1}H NMR and HRMS or MS. Data for a representative pair of *o*–*p* quinones is given. ^{1}H NMR (300 MHz, $CDCl_3$) Compound **9**: δ 8.66 (s, 1H), 7.19 (AB q, J=9.49 Hz, $\Delta\nu$=9.65 Hz, 2H), 4.36 (q, J=7.0 7 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 1.37 (t, 3H); m.p.=172–174°C; Compound **15**: δ 7.07 (AB q, J=9.12 Hz, $\Delta\nu$=42.90 Hz, 2H), 7.01 (s, 1H), 4.36 (q, J=7.07 Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 1.37 (t, 3H); m.p.=130–132°C.
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