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Oxidations Of Substituted Phenols With Hypervalent Iodine : Applications To The Phthalide Annulation Route To Anthraquinones

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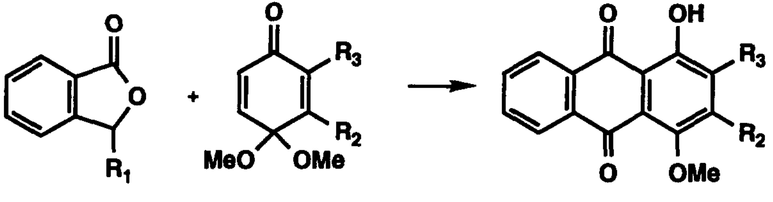
Abstract: Substituted phenols are oxidized by phenyliodonium diacetate in methanol to yield either cyclohexa-2,4-dienones or the isomeric 2,5-dienones depending upon the structure of the phenol. Annulation of these oxidation products with the anion of 3-cyanophthalide affords access to a range of anthraquinones not previously accessible by this route.

The annulation of *p*-quinone monoacetals (3) with anions of 3-phenylsulfonylphthalide[1] (1) or 3-cyanophthalide[2] (2) (Scheme 1) has for the past decade been crucial to the synthesis of a wide variety of anthraquinones[3] and related natural products including the anthracyclines[4]. Indeed, the mild conditions and regiochemical integrity of this process has made it the reaction of choice when assembling anthraquinones containing the 1,4-dioxygenated pattern *e.g.* (4). The acceptance of this reaction has been further enhanced by the ready availability of a wide variety of *p*-quinone monoacetals either by electrochemical or chemical oxidation of 1,4-dioxygenated aromatic molecules[5].



(1) $R_1 = PhSO_2$
(2) $R_1 = CN$

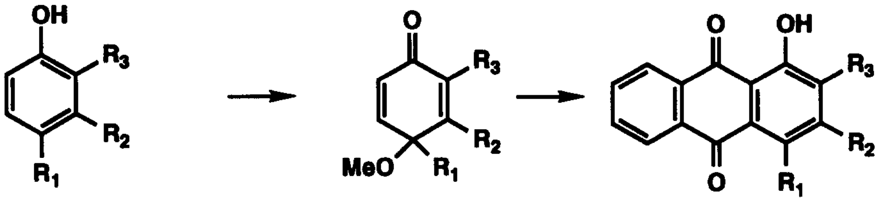
(3)

(4)

Scheme 1

Although recent applications of hypervalent iodine based oxidants have also focussed upon the conversion of 4-alkoxyphenols to *p*-quinone monoacetals[6], isolated cases of 4-alkylphenols being oxidized have been reported[7]. However no comment has been made on the reactivity or synthetic utility of products of the latter reaction.

We now wish to report that the 4-alkylphenols (5a-c) and the 4-arylphenol (5d) are readily converted to dienones (6a-d) upon oxidation with one equivalent of phenyliodonium diacetate (PIDA) in methanol at ambient temperature. The resulting products of these oxidations are stable enough to permit isolation[8] and may be annulated efficiently with the anion of 3-cyanophthalide, (-78°C in THF), to yield the respective anthraquinones (7a-d)[9,10] in high yield (Scheme 2).



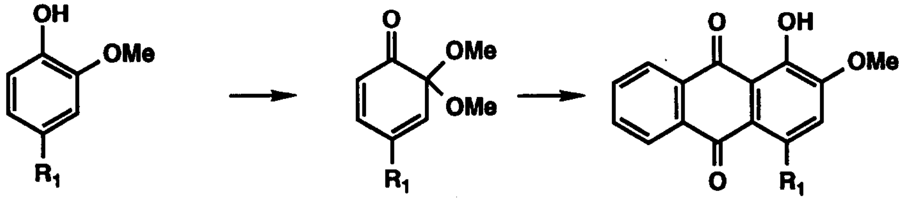
(5) (6) (7)

a) R_1 = Me R_2 = H R_3 = H
b) R_1 = Me R_2 = Me R_3 = H
c) R_1 = Me R_2 = H R_3 = Me
d) R_1 = Ph R_2 = H R_3 = H
e) R_1 = *t*-Bu R_2 = H R_3 = H

Scheme 2

Furthermore, oxidation of eugenol (8a) and creosol (8b) with one equivalent of PIDA affords the *o*-quinone monoacetals (9a) and (9b) respectively. Whilst these compounds self dimerise[5b] on standing at ambient temperature they can nevertheless be rapidly isolated and immediately annulated to afford anthraquinones (10a) and (10b) respectively (Scheme 3) in high yield.

This is the first report of such *o*-quinone acetals undergoing annulation and presumably involves 1,4-elimination of methanol from the intermediate (11) (Scheme 4). In general, *o*-quinone monoacetals have attracted little attention as synthetic intermediates due to their propensity towards self dimerisation[13]. In the present context the use of these compounds is facilitated by a combination of the rapid oxidation and work up coupled with an inert reaction by-product, iodobenzene, which can be carried through the annulation sequence[8].

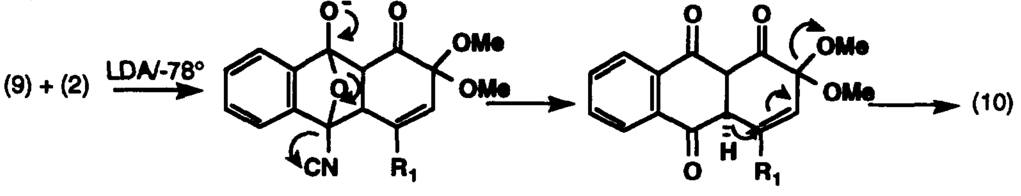


(8) (9) (10)

a) R_1 = allyl b) R_1 = Me c) R_1 = *t*-Bu

Scheme 3

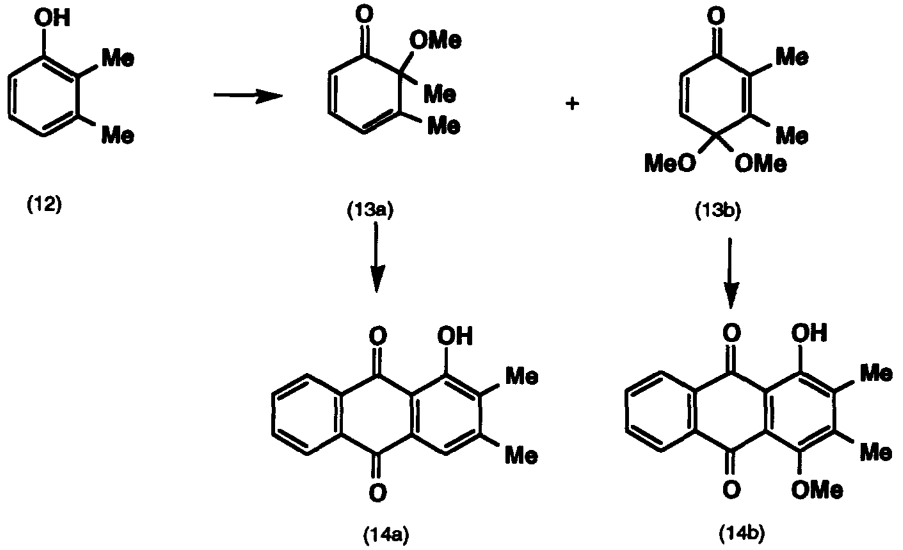
With 1.5 equivalents of PIDA oxidation of 4-*t*-butylphenol (8c) occurs both ortho and para to the hydroxyl group to afford (9c) and (6e) in 43% and 55% yield respectively. The *o*-quinone acetal (9c) presumably arises *via* the intermediacy of (8c), which is more susceptible to oxidation than the starting phenol (6e). Whilst (9c) annulates efficiently with the cyanophthalide anion (2), surprisingly, (6e) fails to yield any detectable trace of an anthraquinone. This latter outcome is one of the rare exceptions to the otherwise general annulation reaction. A mixture of dienones is also obtained upon oxidation of 2,4-dimethylphenol (5c), this time the product being a 3:1 mixture of (6c) and its isomeric 2,4-dienone[15]. This mixture, which is not readily separated, affords a single product (7c) upon annulation to the anthraquinone. This product can clearly arise from either of the isomeric dienones.



(11)

Scheme 4

2,3-Dimethylphenol (12) oxidises with two equivalents of PIDA to afford a 1:4 mixture of dienones (13a) and (13b), which upon annulation afford the corresponding anthraquinones (14a) and (14b) (Scheme 5). The monohydroxyanthraquinone (14a) is the first example of such a structure being obtained by the phthalide anion route, and points to the utility of 2,4-dienones for the synthesis of other natural products. Work currently underway in our laboratories is addressing this issue.



Scheme 5

The financial support of the Australian Research Council is gratefully acknowledged

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8. The reaction mixture was diluted with water, extracted with chloroform and the extract dried over $MgSO_4$. The products were used without further purification in the subsequent annulation reactions. Only in the cases of (6d), (6e) and (9c) were the oxidation products purified by chromatography.

9. All crystalline compounds gave satisfactory nmr, ir and mass spectra as well as combustion analyses. Non-crystalline dienones were identified by nmr prior to annulation.

10. **%Yield of anthraquinone based on phenol, m.p. °C / lit.m.p.°C** : (7a), 86/169-70/17171-2[11a]; (7b), 96/168-9/168-9[11b]; (7c), 82/180-81/173-5[11c]; (10a), 92/144-5; (10b),79/212-213/212.5[11d]; (13a), 23/220-221.5; (13b), 48/159-60 :
    %Yield of anthraquinone based on purified dienone, m.p. °C : (7d), 88/206-7; (10c), 84/160-163.

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12. That addition occurs β to the carbonyl is evident from the ^{1}H-nmr spectrum of the product which shows a resonance (δ 13 ppm) indicative of a single hydrogen bonded phenolic proton.

13. 6,6-Diacetoxycyclohexa-2,4-dienones are reportedly more stable than the corresponding dimethyl acetals[5b], and one case of a mixed acetoxy methoxy derivative has appeared in the literature recently[14].

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15. The assignment of the cyclohexa-2,4-dienone structure as opposed to the alternate cyclohexa-2,5-dienone was based on the characteristic ^{1}H nmr shift of the proton β to the carbonyl. In the case of 2,4-dienones, this resonance occurs close to δ 6.0 ppm, whereas in the isomeric structure it occurs at a lower field closer to δ 6.4 ppm.

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