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Alcohol oxidation and aldol condensation during base-catalyzed reaction of primary alcohols with 1-chloroanthraquinone

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Abstract

When chloroanthraquinone is treated with primary alcohols under basic conditions, the notoriously low yields observed for substitution result in part from oxidation of the alcohol followed by aldol condensation.

Anthraquinone is an intriguing but complex organic residue.[1] Its three fused rings make it a potential building block in supramolecular chemistry that has a planar span, between the 2- and 6-positions, of >10 Å.[2] It has two carbonyl groups directly opposite each other and it is reducible by one- or two-electron transfer to the radical anion or to the dianion, respectively. The anthraquinone residue has been incorporated into crown ethers,[3] podands,[4] cryptands,[5] cyclodextrins,[6] fluorescent sensors[7] and molecular (cyclophane) receptors,[8] and even into an 'organic superstructure'.[9] Some of this work has recently been reviewed.[10] Furthermore, certain anthraquinones occur in nature and the proteins involved in their synthesis from polyketides are under study.[11]

A limitation in the approach to these novel and interesting molecules has been the lack of appropriate synthetic methodology. Of course, important synthetic methods have been developed in connection with tetracycline[12] syntheses, but much of this elegant work deals with ring construction[13] rather than skeletal modification.

Attempts to prepare relatively simple anthraquinone-substituted podands and lariat ethers met with substantial difficulties. Simple alkylation reactions of 1-hydroxyanthraquinone proved not to be easy and nucleophilic aromatic substitution reactions of electron-deficient chloroanthraquinone were poor yielding or afforded only intractable mixtures of product and by-products, although substitution by methoxide ion was reported to be successful.[14] The application of phase

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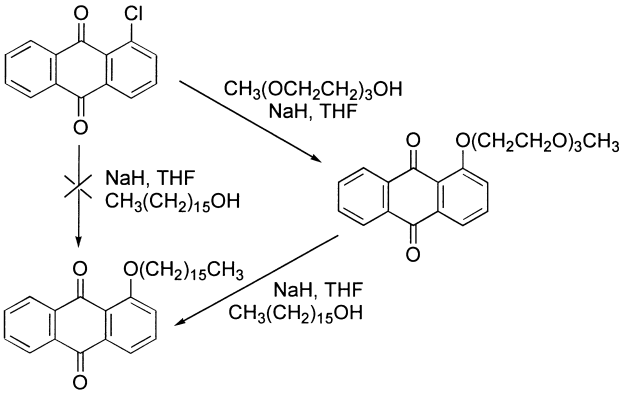
transfer catalysis also proved useful.[15] In the pragmatic sense, we solved the general problem of synthetic access by development of a podand-catalyzed substitution reaction (see Scheme 1). This approach permitted the syntheses of a variety of 1-alkoxyanthraquinones.[16] It was thought that the podands were serving both as nucleophiles and as leaving groups, enhancing nucleophilic aromatic substitution. Additional study showed[17] that certain alkynes could function as catalysts for the same reaction that was effected by podands. Enhancement of leaving group ability (podand relative to chloride) could not account for this catalytic efficacy and the mode of action of alkynes in this process remains obscure.

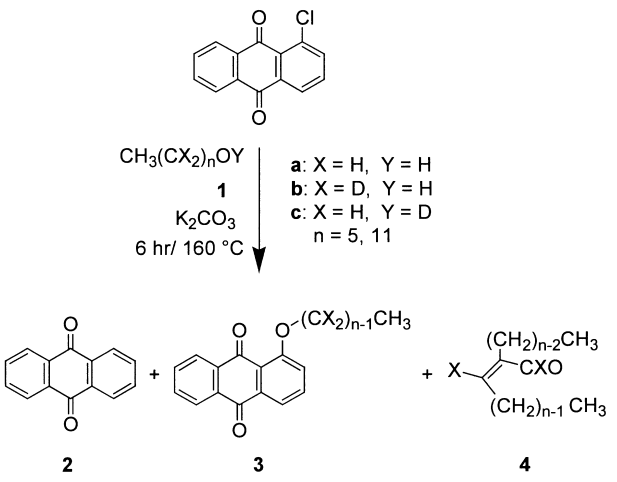


Scheme 1.

Recent work related to our own efforts[18] has demonstrated that modest yields and dehalogenation can occur with 1,8-dichloroanthraquinone as well as with 1-chloroanthraquinone. We now present evidence that suggests the intervention of a more complex mechanism than we at first envisioned. This process involves redox chemistry, by which the alkanols are converted into aldehydes. Once formed, the aldehydes self-condense under the basic reaction conditions to afford aldol products.

When 1-chloroanthraquinone (5 mmol) was heated for 6 h with 1-hexanol (solvent, 50 ml) at 160°C in the presence of K_2CO_3 (4 equiv.), three major products were isolated. 1-Hexyloxyanthraquinone (**3a**, $n=5$), the expected substitution product, was isolated in 10% yield. The major product of the reaction is anthraquinone (**2a**, $n=5$, 45%). Habata and co-workers[18] have postulated that dehalogenation in their NaH/alcohol/dichloroanthraquinone systems occurs by direct hydride substitution. The base used in the present studies is K_2CO_3 and there is no obvious source of hydride. A third product, shown in Scheme 2 as compound **4a**, was isolated in 26% yield. The latter is the product of aldol condensation of hexanal followed by dehydration. Compound **4a** ($n=5$) is an aldehyde and its 2,4-dinitrophenylhydrazone derivative was found to melt at 130–132°C.[19] For comparison, when *n*-dodecanol (50 ml) was heated with K_2CO_3 (4 equiv.) at 160°C in the absence of 1-chloroanthraquinone, no aldol product was detected by TLC. When anthraquinone rather than 1-chloroanthraquinone was present or when no K_2CO_3 was used, no ether or other product was isolated. Thus, base, 1-chloroanthraquinone and alcohol are all required for the aldol product to be isolated.

It seemed surprising that the aldehyde chemistry is so prominent and there is no evidence for the corresponding carboxylic acid. The reaction mixture is basic and the product is isolated by short path (Kugelrohr) distillation followed by isolation of the aldol condensation products as



Scheme 2.

their 2,4-dinitrophenylhydrazone derivatives. The alcohols studied here were used in part because their condensation products have already been fully characterized. Any carboxylic acid remaining after the reaction would be present as its potassium salt. This would probably precipitate, would certainly not distill, and does not move on the TLC plates used in this study. Its presence would therefore be undetected.

A series of experiments was conducted in an effort to gain additional insight into this process. It was decided to use *n*-dodecanol as the nucleophile and as the solvent. Two variants were prepared: $CH_3(CH_2)_{11}OD$ and $CH_3(CH_2)_{10}CD_2OH$. The former was prepared by titration of *n*-dodecanol with 1 equiv. of *n*-butyllithium in hexanes followed by careful quenching with D_2O. The latter was prepared by $LiAlD_4$ reduction of methyl dodecanoate. When 1-chloroanthraquinone (5 mmol) was treated with K_2CO_3 (20 mmol) in *n*-dodecanol (6 h, 160°C), compounds **2a** ($n = 11$, 39%), **3a** (9%) and **4a** (42%) were obtained. When the corresponding reaction was done using $CH_3(CH_2)_{11}OD$, similar yields of identical products were obtained. Thus, no deuterium incorporation was observed in either case. In contrast, when $CH_3(CH_2)_{10}CD_2OH$ was used as solvent, compound **4b** was obtained (β-double bond and aldehyde hydrogen atoms both deuterated). As expected, NMR analysis showed that anthraquinyl ether **3b** was deuterated at the methylene group adjacent to oxygen. In both cases, deuterium substitution was determined by ^1H NMR analysis. The presence of deuterium was confirmed by mass spectrometric analyses. In no case was 1-deuterioanthraquinone detected either by NMR or mass spectrometry.

It seems reasonable to assume that the poor yields in alkanol substitutions are due to competing oxidation and condensation. We previously reported that phenols give much higher yields in the substitution reaction than do aliphatic alcohols. No obvious mechanism exists for the formation of an aldehyde from phenol. It was also found that podands, even short-chained ones, substituted 1-chloroanthraquinone in much better yield than do alkanols. Likewise, alkynols, but not alkenols, gave good yields of substitution products (corresponding to **1**). In the former case, reaction was best when the triple bond was closest to the hydroxyl group. Yields declined more or less monotonically as the triple bond was moved down the carbon chain.

We demonstrate in the present study that substitution reactions in 1-chloranthraquinone derivatives may lead to oxidation of alkanol nucleophiles by a previously unknown mechanism

that involves hydride transfer. The generality of the oxidation is demonstrated for several simple alkanols and the mechanism is considered in light of observations presented in other work, which comport with the postulates presented here.

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