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A NOVEL DEGRADATIVE STRATEGY FOR THE SYNTHESIS OF p-QUINONES.

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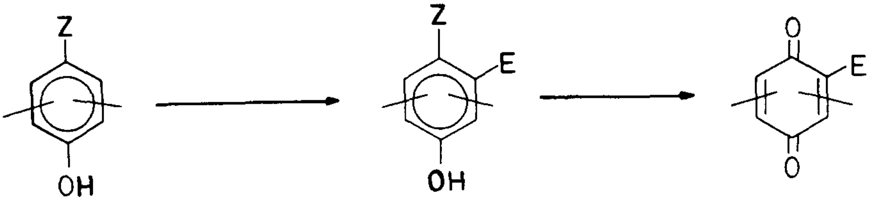
Abstract: p-Hydroxybenzylalcohols undergo Fremy's salt promoted degradative oxidation to give the corresponding p-benzoquinones. A novel strategy for the synthesis of p-benzoquinones based on the regioselective metalation of 2-methoxy-4-methoxymethyl phenols is presented.

For our ongoing research program aimed towards the synthesis of some naturally occurring quinones[1], we needed a new series of p-quinone precursors that could be alkylated or functionalized in a predictable regioselective manner. In particular we thought it would be highly desirable to develop a class of quinone synthons[2] possessing a structural unit which, as depicted in scheme 1, could serve as a handle to carry out regioselective operations based on a metalation/alkylation protocol.



Scheme 1

For such a strategy to be of general validity, two main achievements should be accomplished. First, the Z group must be capable of directing lithiating agents[3] to available ortho sites, and, last but not least, the Z group (or an easily available derivative thereof) should undergo degradative oxidation.

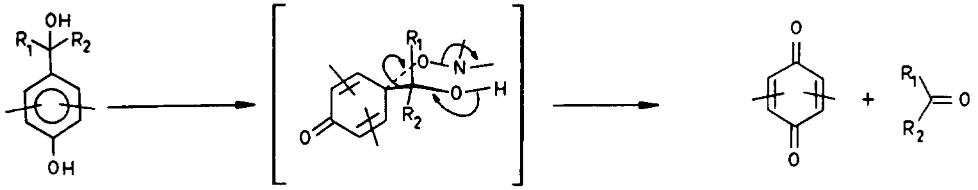
The purpose of this letter is to report our preliminary results which illustrate the usefulness of this approach for the synthesis of quinones.

Besides the well-known oxidative demethylations of hydroquinone mono or dimethylethers[4], we have found in the literature only a few scattered reports on successful degradative oxidations of p-substituted phenols or phenolethers[5]. In this context, the observations of Adler et al.[6] concerning the Fremy's salt[7] oxidation of several lignin models seemed to be of particular interest for our plans. These authors reported late in 1961 that some p-hydroxybenzylalcohols (2 examples examined) underwent Fremy's salt (F.S.) promoted degradative oxidation thus leading to the corresponding p-benzoquinones.

We decided to examine first the full scope and limitations of the above degradative oxidation on a wide variety of p-hydroxybenzylalcohols as a consequence of our reliability on the well-known capacity of benzylalcohols[8] (or easily available precursors or derivatives) to facilitate ortho lithiation.

As expected, these substrates, routinely prepared from commercial starting materials, were found to undergo F.S. degradative oxidation thus leading to the corresponding p-benzoquinones in good yields (Table I).

From a mechanistic point of view, our observations , together with the generally accepted pathway for the F.S. oxidation of phenols[9], suggest a three step pathway[10] involving fragmentation of the cyclohexadienone intermediate 2 as shown in scheme 2. Additional support for this mechanistic reasoning was found during oxidation of 1h and 1i, which afforded benzaldehyde (82%) and benzophenone (90%) respectively.



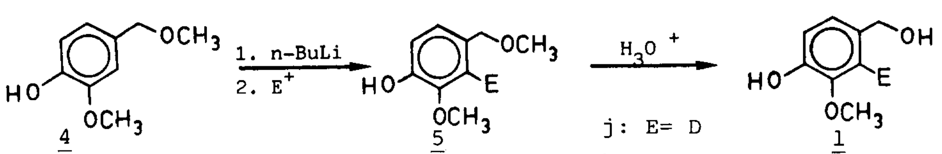
1 2 Scheme 2 3

With these encouraging results in hand we focussed our efforts towards finding the appropriate conditions for the desired regioselective metalation and subsequent trapping with electrophiles.

Firstly we attempted the direct metalation of vanillyl alcohol (THF,1.5 eq. n-Buli,0º r.t., 4h) followed by treatment with MeI. Not unexpectedly the starting material was recovered unchanged in 90%.

In spite of the fact that benzylethers are generally considered unsuitable[11] for facilitating regioselective metalation, we felt it might be worthwhile to carry out the metalation/alkylation sequence on these type of substrates.

To our delight, treatment of the easily available 4 with n-BuLi, as above, followed by treatment with D_2O, MeI or $BrCH_2CH=C(CH_3)_2$, gave the desired 5j, 5k and 5l in surprisingly high yields[12]: 88, 82 and 72% respectively[13] . The subsequent hydrolysis carried out under carefully controlled conditions (HCl. $THF.H_2O$, pH=1.5, 72h, r.t.) provided 1j, 1k, and 1l in only acceptable isolated yields (40-60% scheme 3). These compounds on final treatment with F.S., yielded p-benzoquinones[13] 3j, 3k[14] and 3l in the reported yields (Table I).



4 5 1

j: E= D

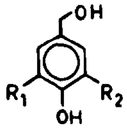
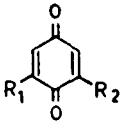
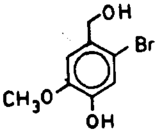
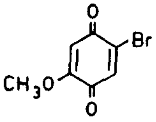
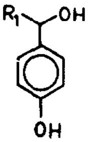
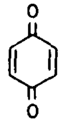
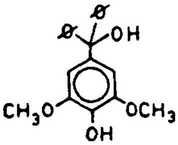
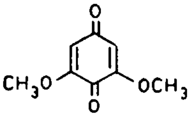
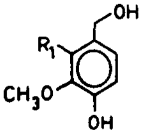
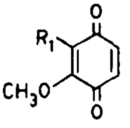
k: E= Me

l: E= $CH_2CH=CH_2$

Scheme 3

The remarkable[11] ortho metalation of 2-methoxy-4-methoxymethyl phenol 4 may be understood as a consequence of the cooperative coordination of the lithium atom by the methoxy groups adjacent to it, although the importance of other stabilizing factors[15] have not yet been evaluated. In accordance with

Table I. Fremy's salt degradative oxidation of p-hydroxybenzyl alcohols.[a]

Substrate		(Mmol)	time (h)	yield (%)	Product[13]	mp. or bp.(°C)
	1a, $R_1=R_2=H$	(1.6)	15	57	 3a-3e	
	1b, $R_1=OMe; R_2=H$	(1.3)	1	83		3b:138-9;lit^{13}:140
	1c, $R_1=OMe; R_2=Br$	(0.9)	1	82		3c:162-3;lit^{13}:161-2
	1d, $R_1=R_2=OMe$	(1.1)	1	87		
	1e, $R_1=R_2=Br$	(0.5)	3	80		3e:128-30;lit^{13}:130-1
	1f	(0.9)	1	84	 3f	3f:192-4;lit^{13}:190-1
	1g, $R_1=CH_3$	(1.2)	1	77	 3a	3a:115-6;lit^{13}:115-6
	1h, $R_1=C_6H_5$	(1.0)	1	70		
	1i	(0.6)	1	88	 3d	3d:250-2;lit^{13}:249
	1j, $R_1=D$	(0.4)	1	90	 3j-3l	3j:135-7
	1k, $R_1=CH_3$	(0.6)	1	89		3k:90-5/0.06mmHg[b]; lit^{14}:55-60/0.04mmHg
	1l, $R_1=CH_2CH=C(CH_3)_2$	(0.3)	4	63		3l:80-5/0.09mmHg[b]

a) General procedure: A chloroform (or ether) solution of phenol 1 was treated with a PO_4HNa_2-PO_4H_2Na buffered solution (pH=6) of Fremy's salt (3 molar excess) with stirring for the required period of time. Work-up involved separation of the organic phase, and final evaporation of the extracts followed by crystallization when apropriate.

b) Bulb to bulb distillation.

this we have observed that guaiacol[16] and 4-methoxymethyl phenol itself were recovered unchanged when independently submitted to the above metalation/alkylation protocol, thus confirming that both methoxy groups are necessary for the success of the metalation.

In summary, p-hydroxybenzylalcohols should be considered valuable p-quinone synthons. Furthermore, the strategic use of the alcohol functionality for the regioselective introduction of electrophiles, although limited in scope, appears to be a novel and useful appoach for the synthesis of p-quinones.

Our recent observations on the F.S. degradative oxidation of p-hydroxybenzaldehydes, naphthaldehydes and benzoic acids[17], clearly suggests that several reasonable alternatives to overcome the above limitation are at hand. Further work is in progress.

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