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# Fremy's Salt Promoted Oxidative Degradation of p-Hydroxybenzylamines and p-Hydroxybenzamides. A Novel Approach to p-Quinones

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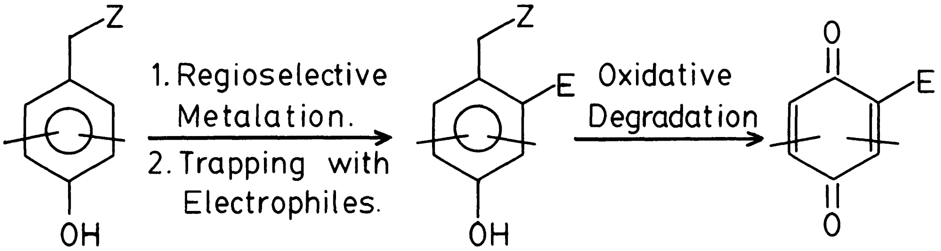
p-Hydroxybenzylamines and primary p-hydroxybenzamides undergo oxidative degradation by the action of Fremy's salt, thus providing p-benzoquinones in good yields.

Our recent involvement in the synthesis of naturally occurring quinonoid compounds[1] has led us to search for new synthons for the widespread quinone functionality.[2]

According to our planned strategy for the synthesis of elaborated quinones we hoped to find a p-quinone synthon characterized by a structural unit which, as illustrated in Scheme 1, could be used to advantage for the introduction of additional functionality via regioselective metalation.[3] Eventually oxidative degradation of the elaborated phenol should allow for the removal of the above structural accesory thus yielding functionalized p-benzoquinones.



Scheme 1.

Partial success along these lines has been disclosed in a recent communication[4] in which p-hydroxybenzylalcohols were shown to be oxidatively degraded to the corresponding p-quinones by the action of Fremy's salt (F.S.).[5] Unfortunately yields decreased considerably when the reaction was scaled up (2 g). Furthermore regioselective metalation and subsequent trapping with electrophiles was attained on the easily available p-hydroxybenzylmethyl ethers. The scope of this regioselective operation appeared improvable *a priori* if a better directing group, yet removable by oxidation, could be found.

The recognized ability of the amino and amido groupings of benzylamines and benzamides to direct metalating agents towards available ortho sites,[3] has led us now to study the F.S. promoted degradation of the titled phenolic substrates.[6] At the outset we worried, however, by the reported negative results on the oxidative degradation of p-hydroxybenzylmethyl ethers which apparently indicated that tertiary amines and amides would not be oxidized.4)

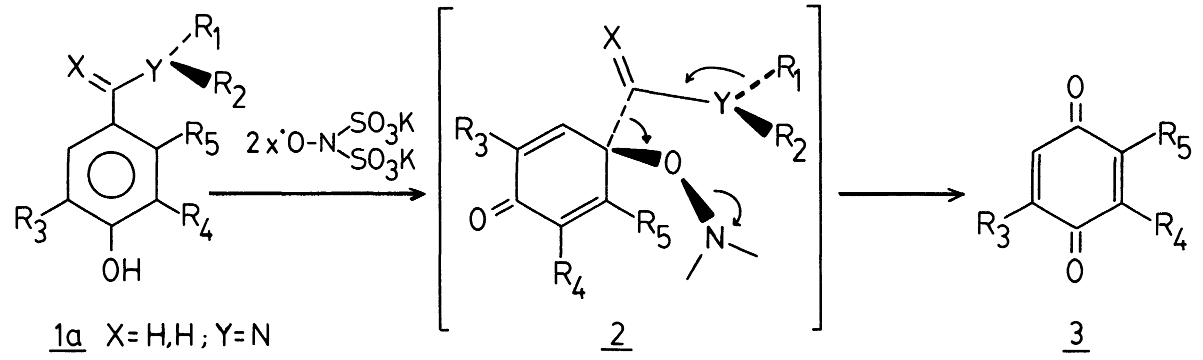
Fortunately, as shown in Table 1, not only the easily available primary and secondary p-hydroxybenzylamines, but also the tertiary ones 1a,7) were found to be efficiently converted into the corresponding p-quinones 3 7) by the action of Fremy's salt. Most important, no decrease in yield when working in medium scale (2 g) quantities has been noticed.

Table 1. Oxidative degradation a) of p-hydroxybenzylamines 1a, 1b, and p-hydroxybenzamides 1c

| Entry | Phenol | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | 1,4-Benzoquinone | % Yieldb) | Mp or Bpc) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1a | H | H | H | OMe | H | 3 | 87 | 138-9 °C12) |
| 2 | 1a | H | H | OMe | OMe | H | 3 | 95 | 250-2 °C13) |
| 3 | 1a | H | nBu | H | OMe | H | 3 | 88 | 138-9 °C12) |
| 4 | 1a | H | nBu | OMe | OMe | H | 3 | 98 | 250-2 °C13) |
| 5 | 1a | Me | Me | H | OMe | H | 3 | 80 | 138-9 °C12) |
| 6 | 1a | Me | Me | H | OMe | D | 3 | 71 | 80-5 °C/0.09 mmHg4) |
| 7 | 1a | Me | Me | OMe | OMe | H | 3 | 98 | 250-2 °C13) |
| 8 | 1a | Me | Me | OMe | OMe | D | 3 | 90 | 254-5 °C |
| 9 | 1a | Me | Me | Me | OMe | H | 3 | 95 | 148-9 °C14) |
| 10 | 1a | Me | Me | H | OMe | SMe | 3 | 65 | 80-3 °C/0.005 mmHg |
| 11 | 1a | H | COMe | OMe | OMe | H | 3 | 35 | 250-2 °C13) |
| 12 | 1b | H | H | H | OMe | H | 3 | 73 | 138-9 °C12) |
| 13 | 1c | H | H | H | H | H | 3 | 23 | 115-6 °C15) |
| 14 | 1c | H | H | OMe | OMe | H | 3 | 84 | 250-2 °C13) |
| 15 | 1c | H | nBu | OMe | OMe | H | -------- | | |
| 16 | 1c | Et | Et | OMe | OMe | H | -------- | | |

a) General Procedure: To a stirred chloroform solution of the phenolic substrate 1a, 1b, or 1c, a 3 molar excess of Fremy's salt dissolved in $PO_4HNa_2$-$PO_4H_2Na$ solution (pH=6) was added. Stirring was continued until disappearance of starting material. Extractive workup yielded a yellow-orange residue which was cristallized from an appropriate solvent. b) Yields are of isolated products. c) Bulb to bulb distillation.

From a mechanistic point of view this result taken together with that of the easy degradation of p-hydroxybenzylalcohols,5) and the fact that p-hydroxybenzylmethyl ethers are not degraded by F.S.,8) clearly shows that the driving force for fragmentation of the key intermediate 2 (Scheme 2) may be provided either by the presence of a loosely held electron pair on heteroatom Y (nitrogen but not oxygen) or by a labile Y-H bond (OH or NH).



1a X=H,H; Y=N
1b X=H,Me; Y=N
1c X=O; Y=N

Scheme 2.

Further evidence which confirms the above mechanistic reasoning came from the study of the action of F.S. on p-hydroxybenzamides 1c. Thus, on the one hand, primary benzamides did undergo degradation, although, as expected from their redox potentials,[9] this took place at a significantly lower rate than that of benzylamines or benzylalcohols. On the other hand, neither secondary nor tertiary p-hydroxybenzamides underwent analogous degradation to p-quinones. Obviously there is no driving force for fragmentation of the cyclohexadienone intermediate 2 in the case of tertiary benzamides. Furthermore, the non degradability of the secondary benzamides appears to be due to the stereoelectronics of the fragmentation step which, being a double β elimination process, requires an antiperiplanar relationship between intervening bonds. Thus, in stricking contrast with primary benzamides, the secondary ones (obtained as the more stable Z isomer),[10] due to the rotational barrier for conversion into the required E isomer,[11] cannot reach the necessary stereochemical arrangement for fragmentation (2c, $R_1$=H, $R_2$= alkyl, Scheme 2).

Final proof for the above hypothesis was found during oxidation of N-acetyl syringylamine (entry 11, Table 1) which yielded the expected 2,6-dimethoxy-1,4-benzoquinone on treatment with Fremy's salt. In this case the required conformation for fragmentation is easily attained due to free rotation around the $CH_2$-N bond.

Most interesting, initial metalation experiments (3 equiv. nBuLi, THF, rt, 4 h) carried out on phenolic substrates (1a, $R_1$=$R_2$=Me, $R_3$=H or OMe, $R_4$=OMe, $R_5$=H) indicate that, as expected, electrophiles ($D_2O$, MeSSMe) can be introduced regioselectively in a very efficient one-pot operation (80-85% yield).[7] Subsequent treatment with F.S. yielded the expected p-benzoquinones 3[7] (entries 6, 8, and 10).

In summary, a new interesting series of p-benzoquinone synthons with improved properties is now available. Further work is in progress.

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