Tetrahedron Letters,Vol.25,No.27,pp 2901-2904,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

REGIOSPECIFIC OXIDATION BY DDQ OF UNHINDERED ALKYL GROUPS IN STERICALLY HINDERED AROMATIC AMINES

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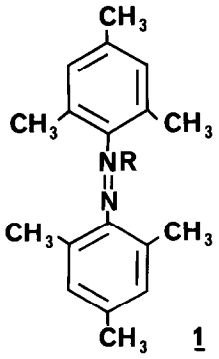
Summary : DDQ oxidises an unhindered activated alkyl group to a carbonyl or a hydroxymethyl group depending on the nature of the substitution, in a sterically hindered aromatic amine.

The oxidation of the sterically hindered aromatic amine mesidine (3) has been reported using enzymatic[1], electrochemical[2] and chemical[3,4] reactions. In these reactions the nitrogen of the molecule is involved in the oxidation, and not the alkyl group. The products obtained in case of mesidine were either the azo (R=:)/azoxy (R=O) compounds 1, or the anils 2a and 2b, the latter bearing a migrated alkyl group.



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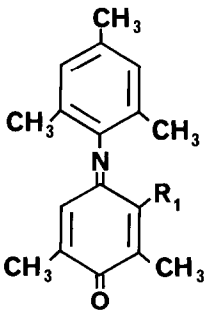


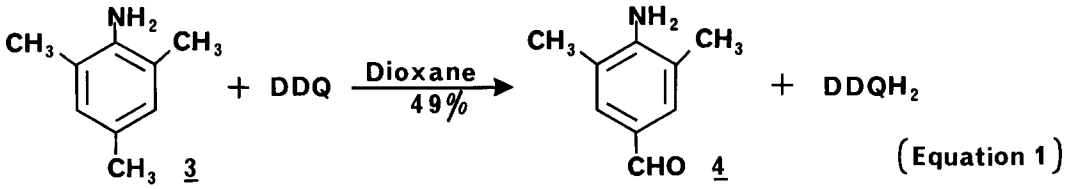
2a: $R_1 = H$
2b: $R_1 = CH_2OCH_3$

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and related high potential oxidants interact with aliphatic amino groups and doubts have been raised about the nature of reaction with aromatic amines[5].

To our knowledge there is no report on the oxidation of an unhindered alkyl group by DDQ in a sterically hindered aromatic amine.

When mesidine (3) was treated with DDQ in dioxane, the 4-methyl group was regiospecifically oxidised to the corresponding aldehyde 4 (Equation I).

Though an earlier report[6] had mentioned this compound as unstable, it was isolated as a crystalline solid. We have found that the compound is stable in the pure state and can be stored for a long period of time.



(Equation 1)

Similarily, 2-chloro-4-methylaniline (3b) and 2-bromo-4-methylaniline (3c) were successfully oxidised in good yields to the corresponding aldehydes 4b and 4c respectively. 2,6-Dimethyl-4-propylaniline (3d), however, on DDQ oxidation was converted into the expected 2,6-dimethyl-4-propionyl aniline (4d) in poor yield (15%). The poor yield might be due to a further dehydrogenation of the $-CO-CH_2CH_3$ group thereby generating the very active species $-CO-CH=CH_2$, although this is only speculation, since we do not have evidence on this matter.

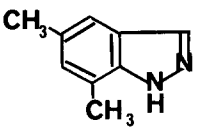
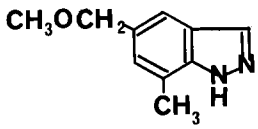
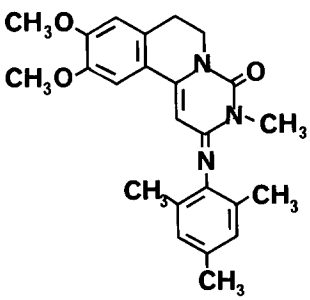
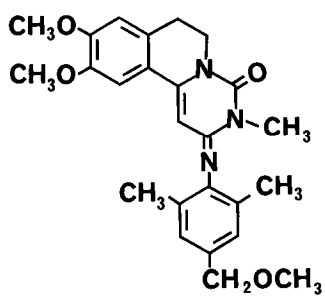
In more complex molecules, where the aromatic amino function is incorporated into a heterocyclic skeleton such as 6,7-dimethyl benzo(1,2-c)imidazole (3e), DDQ oxidation did not lead to the aldehyde. A complex was formed which did not break after water treatment as it was the case with the anilines mentioned above. A new method to break the complex had to be developed. Refluxing with anhydrous $ZnCl_2$ and methanol gave the corresponding methoxy methyl compound 4e.

An interesting application of this reaction was demonstrated in the preparation of an intermediate of one of the major metabolites of the antihypertensive Trequinsin (3f)[10,a,b]. Oxidation gave the DDQ complex, which was cleaved on treatment with $ZnCl_2$-methanol to give the 4'-methoxymethyl compound 4f Table I (details of this study on Trequinsin metabolites will be published elsewhere). It should be noted that in the above reaction the dihydroisoquinoline part of the molecule was left intact.

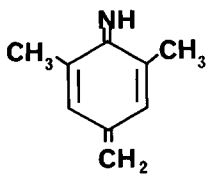
Steric hindrance has certainly a major role to play in the success of this reaction. An earlier observation that the amino group is not a favourable substituent in DDQ oxidations[5], still holds good, as long as it is not crowded by other groups. Less hindered anilines are not suitable for the oxidation. p-Toluidine failed to give any p-aminobenzaldehyde and 2,4-dimethylaniline (3a) gave only 10% of the aldehyde 4a. A considerable increase in the yield was observed when the substituent in ortho position to the amine was more bulky such as in compounds 3b and 3c.

By analogy with previous DDQ oxidation studies on mesitol[8] and on other alkyl phenolic compounds[9] we could confirm that the amino group acts as an activator for the alkyl group in para-position. N-Acetylmesidine or N-

Table I

Starting material		Final Product		Yield%[11]	m.p.°C
2,4-$(CH_3)_2C_6H_3NH_2$	3a	2-CH_3-4-CHO,$C_6H_3NH_2$	4a	10	98-100[7]
2-Cl-4-$CH_3C_6H_3NH_2$	3b	2-Cl-4-CHO,$C_6H_3NH_2$	4b	46	104-105
2-Br-4-$CH_3C_6H_3NH_2$	3c	2-Br-4-CHO,$C_6H_3NH_2$	4c	64	109-110
2,6-$(CH_3)_2$-4-n-Pr$C_6H_2NH_2$	3d	2,6-$(CH_3)_2$-4-COC_2H_5,$C_6H_2NH_2$	4d	15	81-82
	3e		4e	10	112-114
	3f		4f	45	160-162

mesitylphthalimide when subjected to DDQ oxidation, did not react indicating the importance of the basic amino functionality. The intense colour changes at the start of the reaction in case of mesidine and others, suggest a charge transfer complex formation for the oxidation of mesidine to 4. Abstraction of a hydride ion at the activated para-benzylic carbon as a possible first step could ultimately result in the formation either of an iminoquinone methide intermediate (5) or of a benzylic ether intermediate (6a), which then could lead through 6b or 6c respectively to 4, by mechanisms analogous to those proposed for DDQ oxidation of alkyl phenolic compounds[8,9].



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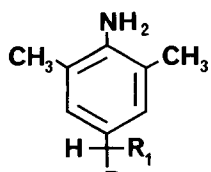

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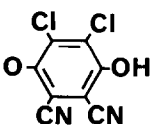
6a: R_1=H, R_2= 

6b: R_1=R_2=OH

6c: R_1=R_2= 

Typical Procedure

Mesidine (15.0 g; 0.111 mole) was dissolved in 1,4-dioxane (300 ml) and DDQ (15.0 g; 0.225 mole) was added. A green coloured complex was generated which changed its colour to dark brown, within five minutes of stirring. Stirring was further continued for 6 hrs and the excess 1,4-dioxane was distilled off under reduced pressure. The residue was treated with dilute sodium hydroxide and extracted with ethyl acetate and then worked up in the usual manner. Final purification by column chromatography on silica gel, using benzene as eluent, gave, firstly, the starting amine (5.7 g, 38%). As the main fraction 2,6-dimethyl-4-formylaniline (8.1 g, 49%) was isolated, m.p. 78-80°C; IR(KBr) in cm^{-1} 3550, 3450, 2950, 1675; ^{1}H-NMR ($CDCl_3$) δ 2.27 (6H, s, 2,6-CH_3), 4.33 (2H, br hump, NH_2), 7.4 (2H, s, 3,5-Ar-H), 9.73 (1H, s, CHO).

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11. All the compounds showed correct spectral, and microanalytical data and no attempt has been made to optimise the yield.

(Received in UK 1 May 1984)