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PHOTOOXIDATIVE SET INITIATED N-DEMETHYLATION OF N,N'-DIMETHYLANILINES : MIMICKING THE CYTOCHROME P-450 TYPE OXYGENATIONS

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ABSTRACT: Photoinduced single electron transfer initiated selective N-demethylation of N,N'-dialkyl anilines in alkaline methanol is reported.

Oxidative N-dealkylation of tertiary amines has attracted much attention due to its relevance to enzymatic[1] and as model for cytochrome P-450 specific reactions[2]. Several model reactions using ironporphyrins in the presence of various alternative sources of oxygen including iodosobenzene and hydroperoxides have also been reported[3,4]. It is now believed that the oxidative dealkylation of tertiary amines by cytochrome P-450 dependent monooxygenases is initiated by one electron transfer from the amine to the active oxidants[2]. Subsequent steps of proton loss and hydroxylation leads to the unstable intermediate α-hydroxylamine[5] and finally to secondary amine and aldehyde. However, model studies have indicated two different mechanisms for dealkylation, depending very much on the nature of oxidants[3d,f] and catalyst[6]. For instance, the oxidation of N,N-dimethylaniline with iodosobenzene catalysed by [Fe(tpp)cl] proceeds via initial one-electron oxidation, whereas with t-butyl hydroperoxide, hydrogen abstraction of the amine by the oxidant is the predominant reaction[3d,f].

Following these premises and enormous synthetic importance of N-demethylation we felt it necessary to investigate oxidation behaviour of tertiary alkylamines in concert with our ongoing interest in photoinduced SET initiated oxidative reactions of amino compounds[7], where we noticed a novel cytochromeP-450 type oxidation of tertiary amines upon irradiation in the presence of dicyanonaphthalene (DCN) as electron acceptor in methanolic potassium hydroxide.

Photolysis ($>$280 nm) of N,N'-dimethylaniline ($1,2\times10^{-2}$M) in methanol containing 0.25 M potassium hydroxide in the presence of DCN (light absorbing species, 5×10^{-4} M) under nitrogen atmosphere[8] for 10h gave N-methyl aniline (5) as major product (90%). However, careful analysis of the reaction mixture by capillary column (methyl silicone 50 mts) Gc mass spectra showed the formation of 6 (5%) and 7 (2%) as other products. DCN was recovered almost quantitatively after the reaction as noticed earlier[7].

Mechanistically, the reaction may be envisioned by considering one electron transfer from amine 1 to $^1DCN^*$ resulting in amine radical cation 2. The electron transfer process in this case has been supported from the large negative value for free energy change (ΔG_{et} = 24.6 K.cal mole)[9,10] estimated by the Weller equation[11] and diffusion controlled fluorescence quenching of DCN by 1. Proton loss from the α-carbon of 2 gives iminium cation 3 which is reasonable to presume will produce methyl phenylaminomethyl methyl ether 4 by nucleophilic trapping with methanol (Scheme 1). However, under our present experimental conditions, formation of 4 could not be established although a photoreaction carried out in methanol (wihtout alkali) showed the formation of 4. This led us to doubt the stability of 4 in alkaline methanol. Independent study carried out with an authentic sample of 4 synthesised by the literature procedure[12],

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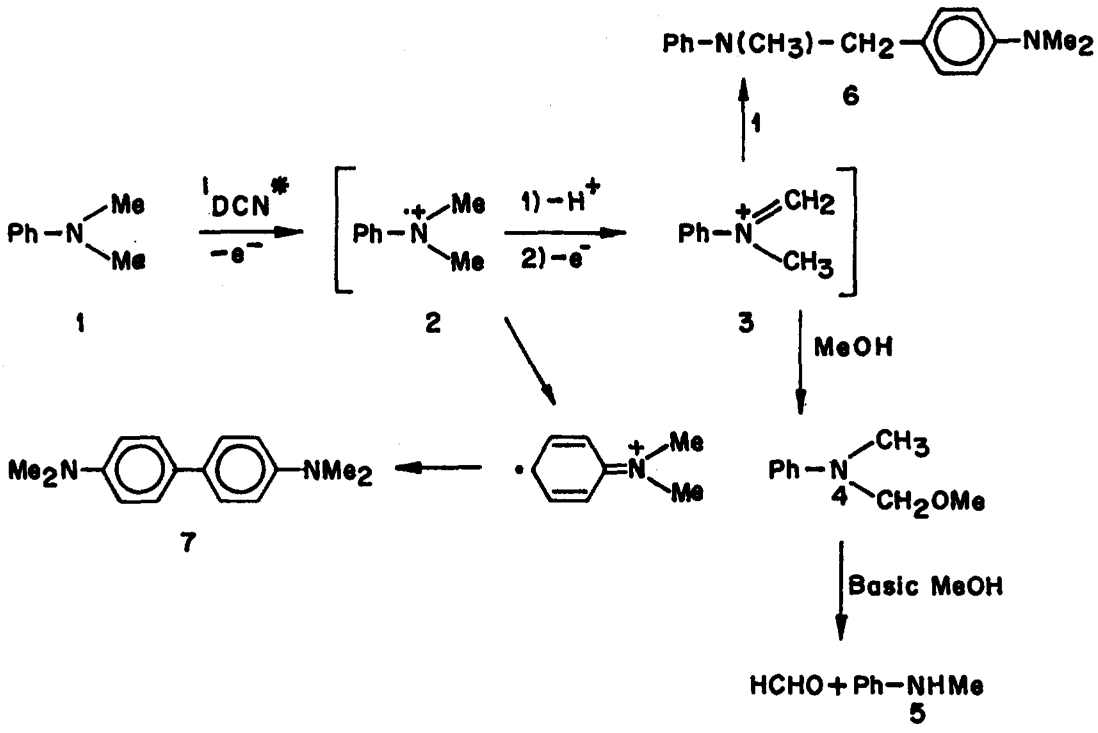
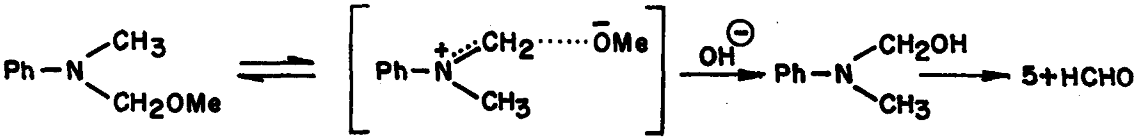
revealed that 4 is unstable to methanolic potassium hydroxide solution and instantaneously gives 5 at room temperature in quantitative yield. It has been to our utmost surprise to note that Shono et al[13] have reported the isolation of 4 on a preparative scale by anodic oxidation of 1 in alkaline methanol where a similar mechanism seems to be operative. The exact mechanism for the transformation of 4 to 5 in alkaline methanol is not very clear but may be postulated as shown below (Scheme II) which is supported by literature precedence made in early thirties[12] in the hydrolysis of aminomethyl ethers[14]. The oxidation of 1 to 5 via SET initiation and the mechanism discussed above resembles with the cytochrome P-450 type oxygenations[2,5].



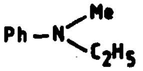
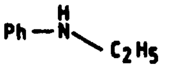
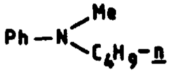
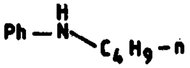
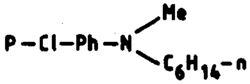
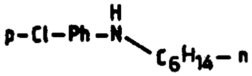
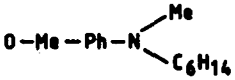
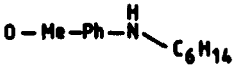
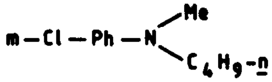
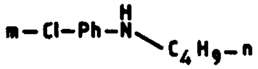
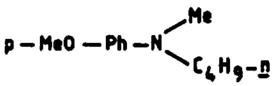
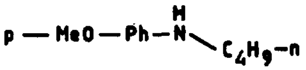
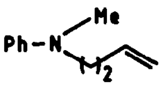
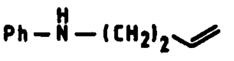
SCHEME I



SCHEME II

As a result of these studies it was thought worth while to examine the scope of N-demethylation of tertiary methylamines by the present photoinduced SET initiated oxidation which represent the first synthetically versatile method for the N-demethylation of tertiary methylamines, although a few catalytic[3,6b] and stoichiometric reactions[15] have been reported. The representative results of the N-demethylation are listed in Table 1.

Table 1: Selective N-Demethylation of tertiary Amines

Entry	Substrate[a]	Product[b]	Irrd[n] time (h)	Yield[c]
1	 $Ph-N<^{Me}_{C_2H_5}$	 $Ph-\overset{H}{N}-C_2H_5$	12	80
2	 $Ph-N<^{Me}_{C_4H_9-n}$	 $Ph-\overset{H}{N}-C_4H_9-n$	12	82
3	 $p-Cl-Ph-N<^{Me}_{C_6H_{14}-n}$	 $p-Cl-Ph-\overset{H}{N}-C_6H_{14}-n$	11	85
4	 $O-Me-Ph-N<^{Me}_{C_6H_{14}}$	 $O-Me-Ph-\overset{H}{N}-C_6H_{14}$	10	80
5	 $m-Cl-Ph-N<^{Me}_{C_4H_9-n}$	 $m-Cl-Ph-\overset{H}{N}-C_4H_9-n$	12	78
6	 $p-MeO-Ph-N<^{Me}_{C_4H_9-n}$	 $p-MeO-Ph-\overset{H}{N}-C_4H_9-n$	10	80
7	 $Ph-N<^{Me}_{(CH_2)CH=CH_2}$	 $Ph-\overset{H}{N}-(CH_2)_2CH=CH_2$	12	75

a) Irradiation was conducted in methanol containing 0.25M NaOH. b) Satisfactory IR and NMR spectral data were obtained. c) Isolated yields but not optimised.

As evident from the examples listed in Table1, the methyl groups are removed chemoselectively over other alkyl groups in the dealkylation of tertiary amines. It appears that the more acidic hydrogen atom of the N-methyl group is dissociated as a proton in this oxidation. These tendencies also resemble those of the other cytochromeP-450 type oxygenation. Further study is in progress.

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8. Presence or absence of inert atmosphere seem to have very little effect on the reaction.

9. Oxidation potential of 1 (1.01 ev) has been taken from Hall, L.R., Iwamoto, R.T. and Hanzlik, R.P., **J.Org.Chem., 54**, 2446 (1989).

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14. a) We have observed that hydrolysis of 4 to 5 is dependent on alkali concentration. 70% conversion was noticed even at very low concentration (.025 M) of potassium hydroxide in 10 min. in methanol at room temperature. b) During our photochemical experiments we did not try to detect the formation of formaldehyde.

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