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CERIUM(IV) INDUCED HYDROXYLATION OF C-ALKYLATED HYDROCARBONS AND PHENOLS

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Abstract: Hydroxylation of C-alkylated phenols has been achieved by employing cerium (IV) ammonium nitrate and hydrogen peroxide in acetic acid medium. The yield of hydroxylation products increases markedly when 3×10^{-3} M solution of sodium dodecyl sulphate is added to the oxidation system. The plausible mechanism of the reaction seems to involve free radical intermediates and is influenced by hydrophobic environment. The findings are also of significance from the view point of oxidative coupling of phenols.

There have been only a few reports of direct hydroxylation of aromatic species by an electrophilic process initiated by metal ions[1]. The yields in such reactions are generally poor partly because the hydroxyl group activates the benzene ring and makes it further prone to oxidation to quinones. Amongst various reagents tried for conversion of benzene derivatives to phenols and oxidative coupling, the most important ones are based on Milas and Fenton's reagents; i.e., H_2O_2 in $HF\text{-}BF_3$[2,3]; $H_2O_2\text{-}AlCl_3$[4] or in some cases with H_2O_2 and CO_2 under reduced pressure[5,6]. Though cerium (IV) salts are potent one electron transfer agents and are capable of producing hydroxyl radicals from hydrogen peroxide, under predetermined reaction conditions, there seems to be no report in literature on their use for hydroxylation. In this paper, we report an efficient one pot hydroxylation procedure involving the use of cerium(IV) in conjunction with hydrogen peroxide and sodium dodecyl sulphate to give phenols in moderate to good yields.

We have determined that the substrates (1-5) when treated with cerium(IV) ammonium nitrate and hydrogen peroxide in acetic acid medium and in the presence of an added sodium dodecyl sulphate yielded the corresponding hydroxy derivatives in 30%-70% (Table: 1). In some cases (e.g., 2, 6-dimethylphenol), the alkyl groups also get oxidized and decarboxylated on prolonged reaction. When the reaction was repeated in the absence of hydrogen peroxide or of acetic acid or of Ce(IV) reagent, hydroxy products or their derivatives were not obtained as revealed by TLC with authentic samples. The reaction rates were practically unaffected by addition of ammonium nitrate (5-20 mM) and were inhibited by free radical quenchers like 2,6-ditertiary-butylphenol. The product ratio remained unchanged in the presence of singlet oxygen quenchers like diazabicyclo (2,2,4)-octane (DABCO)[7,8].

Hydroxylation of the substrate 1-5 can be explained by three pathways A-C as depicted in scheme-1. In pathway A, a transient complex between the electron rich substrates 1-5 and cerium(IV) leads to a single electron transfer to yield a radical cation[9] which can solvolyze to the products in the presence of H_2O_2. Since the solvent was acetic acid and no products corresponding to the acetoxyl participation were detected in the reaction mixture, this pathway seems to

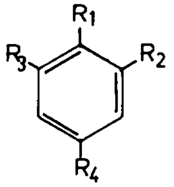
Table 1: Products Obtained from Ce(IV)/AcOH/H_2O_2 Reaction on substrates.

Substrates	Product Obtained					
	Hydroxylated products	Yield[a] (%)	Melting[b] point (°C)	Nitro or Coupling products	Yield[a] (%)	Melting[b] point (°C)
1	6	30	--	7	37	35
2	8	22	169	9	30	112
				10	15	113
3	11	30	126	12[c]	20	154
				13[c]	15	176
4	14	30	64	16	12	33
	15	22	105			
5	8	60	169	17[c]	12	173

a: Yields are based on isolated products, are unoptimized and confirmed by NMR of product mixture which showed them to be roughly 5% higher than the isolated yields.

b: All the melting points were taken in open capillaries and are uncorrected.

c: New compounds.



1 $R_1=CH_3$, $R_2=R_3=R_4=H$

2 $R_1=OH$, $R_2=R_3=R_4=H$

3 $R_1=OH$, $R_2=CH_3$, $R_3=R_4=H$

4 $R_1=OH$, $R_2=R_3=H$, $R_4=CH_3$

5 $R_1=OH$, $R_2=R_3=CH_3$, $R_4=H$

6 $R_1=OH$, $R_2=R_3=H$, $R_4=CH_3$

7 $R_1=CHO$, $R_2=R_3=R_4=H$

8 $R_1=R_4=OH$, $R_2=R_3=H$

9 $R_1=OH$, $R_2=R_3=H$, $R_4=NO_2$

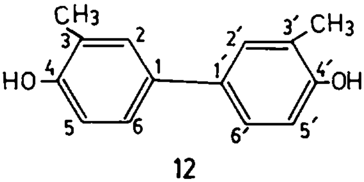
10 $R_1=OH$, $R_2=R_4=NO_2$, $R_3=H$

11 $R_1=R_4=OH$, $R_2=CH_3$, $R_3=H$

14 $R_1=R_2=OH$, $R_3=H$, $R_4=CH_3$

15 $R_1=CH_3$, $R_2=R_4=OH$, $R_3=H$

16 $R_1=OH$, $R_2=NO_2$, $R_3=H$, $R_4=CH_3$



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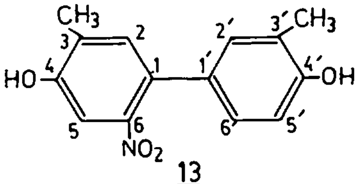

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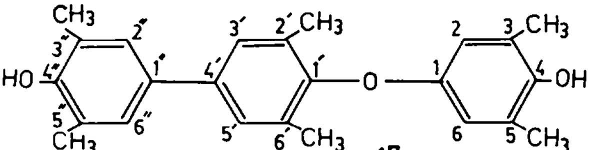

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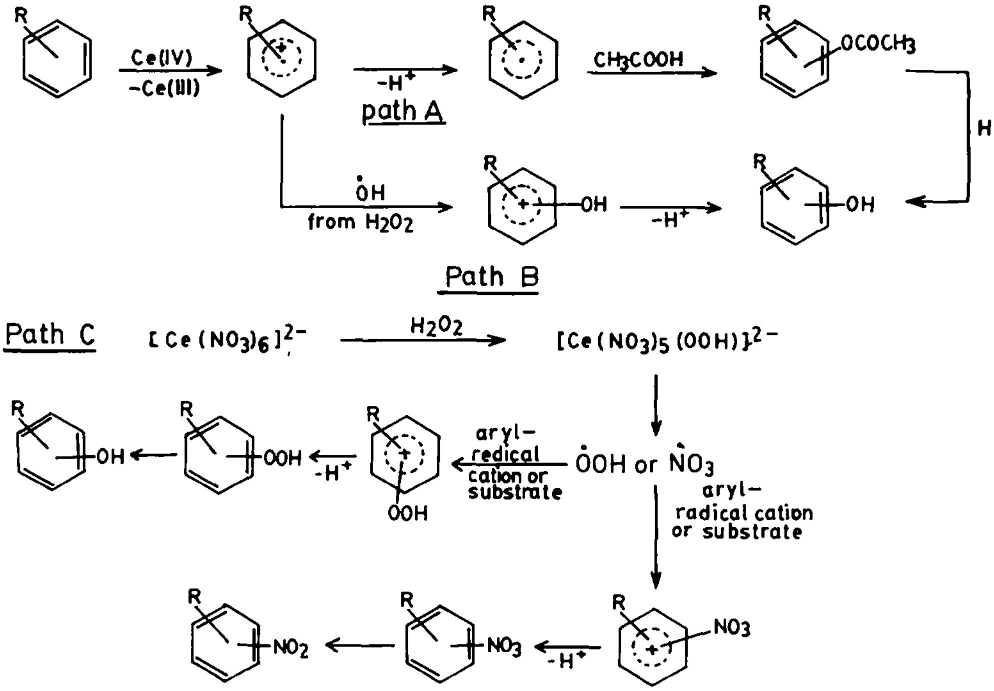
be less likely. In the pathway B, direct hydroxylation of the radical cation or the substrate itself by $\dot{O}H$ or OH^- followed by loss of a proton or a hydrogen radical is envisaged but this does not appear to govern the reaction because the hydroxyl ions if at all formed from the peroxide would get neutralized by the acidic solvent. The formation of the hydroxyl radical is also energetically less favoured because generally it requires a reducing agent to generate free radicals from H_2O_2 (cf. Fenton's reagent) whereas cerium(IV) is a powerful oxident.



SCHEME-1: Mechanistic pathways for the formation of hydroxylation & nitro products

The alternative pathway C involves the formation of peroxocerate complex which in principle can transfer the hydroperoxide species to either the aromatic substrate directly or via radical cation intermediate as postulated earlier[10,11]. The resultant unstable aryl hydroperoxide can then yield the hydroxylation products as has been observed in related parallel singlet oxygen reactions[12] and old sample of cerium dioxide and hydrogen peroxide[13]. The formation of peroxocerate complex is substantiated by the recent isolation of ceric trihydroxy hydroperoxide [Ce(OH)$_3$OOH] [14,15]. The possibility of formation of singlet oxygen by the reaction of cerium(IV) and hydrogen peroxide[13] can also be discounted as the reaction was insensitive to singlet oxygen quencher like DABCO[7,8] and hence the formation of distinct aryl hydroperoxides seems to be less likely. The hydroperoxy radical/nitrate redical can remain in the coordination sphere of Ce(IV) or in the solvent cage. Such an inference is based upon the following observations: (a) Simultaneous formation of nitro substituted phenols and oxidatively coupled products in the reaction (b) radical sensitivity of the reaction (c) capacity of cerium(IV) to expand its coordination sphere[16] (d) positional selectivity in cerium(IV) induced reactions with several aromatic hydrocarbons as observed by us earlier[17] and (e) the known unstable nature of aryl nitrates which usually decompose into nitro compounds[18].

Concomitant formation of aryl nitro, oxidatively coupled products and hydroxy compounds on the reaction indicates that both the nitrate and peroxy/hydroxy radicals held in the solvent cage are competing with each other and therefore, can be made to react selectively. To test this, the reaction was repeated in the micellar environment introduced into the reaction media by addition of surfactant molecules because it has been observed earlier that hydroperoxide redical can be stabilized in the presence of anionic sodium dodecyl sulphate (SDS) micelles[19,20]. As expected, the yield of hydroxy products were enhanced in the presence of micellar aggregates formed by SDS. Further, it has been observed that the yield of hydroxylation products is dependent upon the concentration of SDS and maximum yield of hydroxy product (in the case of 2,6-dimethylphenol) was obtained when the surfactant concentration in the medium was between 2-4 x 10^{-3} ML^{-1}. Since this is the usual concentration range in which sodium dodecyl sulphate forms micellar aggregates, micellar stablization of the hydroperoxide radicals can be inferred. This was further confirmed by the observation that the yield of hydroxy products dropped markedly at higher concentration of SDS; remained practically constant when SDS concentration was between 4 x 10^{-3} ML^{-1} and 6 x 10^{-3} ML^{-1} after which the concentration of hydroxylation products rapidly decrease in a linear fashion (Curve A, Fig.1). On the otherhand, the effect of cationic surfactants such as cetyl trimethyl ammonium bromide (CTAB) was observed to lead to larger concentration of coupling products. These micellar effects are analogous to the ones already observed in the case of regioselective chlorination of phenols by hypochlorite in chloroperoxidase mimetic reaction[19].

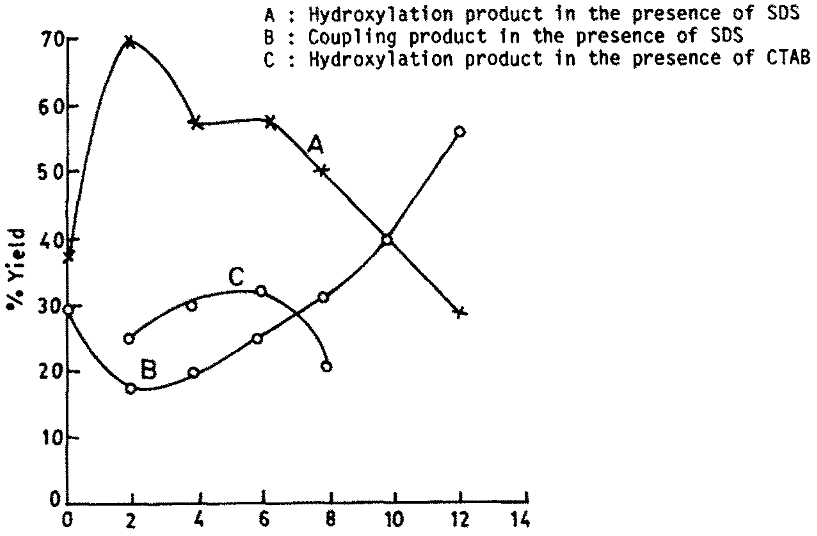


FIG.1.Concentration of surfactant (x10^{-3})

Though we have not investigated the observed dealkylation completely, it appears that the simultaneous oxidation of the alkyl groups to the corresponding carboxylic acid or aldehyde followed by decarboxylation or decarbonylation is operating through a mechanism recently proposed by Baciocchi et al.[9,11]. The formation of the hydroxy derivatives in these reactions is very significant because these compounds under conditions of the experiment should be expected to get further oxidized to quinones as reported by earlier workers[21-23] and therefore indicate the complexity of the mechanistic aspects of the reaction which is a subject of further investigation.

EXPERIMENTAL

Melting points were determined in open capillaries on an electric melting point apparatus (Adair Dutt) and are uncorrected. IR spectra were recorded in KBr on a SP-1200 Grating IR spectrophotometer and 5-DX-Nicolet FT IR spectrophotometer. ^1H NMR spectra were recorded on

Nicolet-99.95 Mz Jeol-FT NMR spectrometer using TMS as the internal standard and values reported are in δ scale and mass spectra on an IMS-D 300 Jeol mass spectrometer at 70 eV. UV spectra were recorded on 330 Hitachi spectrophotometer. The time allowed for completion of the reaction and purity of the prepared compounds were controlled by means of TLC performed on silica gel (BDH, Bombay) plates using iodine for visualizing the spots. Organic solvents used were freshly distilled and usually dried over anhydrous $MgSO_4$ before use. Petroleum ether solvent refers to the one with the boiling range of 60-80°C.

GENERAL REACTION PROCEDURE

To a solution of compound (10 m mol) in acetic acid (20 ml) was added a solution of cerium(IV) ammonium nitrate (BDH, 10 m mol) in 5-6 lots followed by dropwise addition of H_2O_2 (30%, 10 m mol). A distinct colour change was observed and the progress of reaction was monitored by TLC. The reaction mixture was kept at room temperature for 48 h and then poured into crushed ice (100 g) and extracted with chloroform (3 x 50 ml) and ethyl acetate (3 x 50 ml). The combined organic extracts were dried and concentrated under reduced pressure. The crude combined mass was subjected to column chromatography over silica gel (50 g) using petroleum ether, benzene, chloroform, ethylacetate and methanol as the eluting solvents and the products were isolated pure by recrystallization before subjecting them to analysis.

GENERAL PROCEDURE FOR REACTION IN PRESENCE OF SURFACTANTS

To a solution of compound (10 m mol) in acetic acid (15 ml) was added a solution of the surfactant (x 10^{-1} - 10^{-5} ML^{-1}) followed by solution of cerium(IV) ammonium nitrate (10 m mol) in 5-6 lots. H_2O_2 (30%, 10 ml) was added to the reaction mixture drop-wise and the contents stirred for 3 h. The work up procedure adopted was the same as given above. Quantitative experiments to determine the yield were carried out by UV absorption analysis at 295 nm against a standard calibration curve at this wavelength.

REACTION PRODUCTS FROM TOLUENE (1)

The reaction after work up gave a complicated mixture which could be resolved into two compounds both of which were liquids.

4-Methylphenol 6 (30%), mp. 35°C (lit. mp. 36°C)[24], gave positive ferric reaction for phenols. IR(KBr): ν_{max}: 3300 (-OH) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 12.21 (2, 1H, Ar-OH), 2.32 (2, 3H, Ar-CH_3), 6.61 (q, 2H, H-3 and H-5), 7.21 (q, 2H, H-2 and H-6). Benzoate mp. 70°C (lit. mp 71°C)[24].

Benzaldehyde 7 (37%), gave bitter almond smell; IR (KBr): ν_{max}: 1715 (Ar-CHO), ^1H NMR ($CDCl_3$, δ): 12.57 (s, 1H, CHO), 7.25 (m, 5H, Ar-H).

REACTION PRODUCTS FROM PHENOL (2)

Hydroquinone 8 (22%), crystallized from chloroform-ethylacetate (1:2) as white needles, mp.159°C (lit mp. 162°C)[24] and gave transient blue colour with aq. $FeCl_3$. IR (KBr): ν_{Max}: 3350 (-OH) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 12.92 (s, 2H, OH),7.21(m,4H,Ar-H). Diacetate mp. 119°C (lit mp. 121°C)[24].

4-Nitrophenol 9 (30%), recrystallized from petroleum ether as light yellow needles, mp. 112°C (lit mp. 113°C)[25], gave a positive ferric chloride reaction for phenol and a positive Lassaigne's test for nitrogen, IR (KBr): ν_{max}: 3350 (OH), 1560 and 1360 (-NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, δ):

12.10 (s, 1H, Ar-OH), 7.92 (m, 4H, Ar-H). Acetate mp. 80^oC (lit mp. 81^oC)[25].

2,4-Dinitrophenol 10 (15%), recrystallized from petroleum ether-benzene (4:1) as pale yellow needles, mp. 113^oC (lit. mp. 112^oC)[25] and gave positive $FeCl_3$ test for phenol and a positive Lassaigne's test for nitrogen. IR (KBr): ν_{max}: 3350 (-OH), 1530 and 1360 ($-NO_2$) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 11.84 (s, 1H, Ar-OH), 8.21 (d, 1H, H-3), 7.74 (q, 1H, H-5) and 7.58 (s, 1H, H-6). Acetate mp. 70^oC (lit. mp. 72^oC)[25].

REACTION PRODUCTS FROM 2- METHYLPHENOL (3)

3-Methyl-1, 4-benzenediol 11 (30%), crystallized from petroleum ether-benzene (10:1), mp. $126\text{-}7^oC$ (lit. mp. 127^oC)[25] and gave a positive ferric reaction. IR (KBr): ν_{max}: 3350 (-OH) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 12.21 (s, 2H, Ar-OH), 7.21 (m, 3H, Ar-H), 2.12 (s, 3H, $Ar\text{-}CH_3$).

3,3'-Dimethyl -4,4' -dihydroxybiphenyl 12 (20%), crystallized from petroleum ether-benzene (1:4) as yellow granules, mp. $154\text{-}156^oC$, gave a positive ferric chloride reaction for phenol. IR (KBr): ν_{max}: 3330 (OH) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.31 (s, 6H, $Ar\text{-}CH_3$), 6.81-7.32 (m. 6H, Ar-H), 12.72 (s, 2H, Ar-OH), m/z (% abundance); 214 (55.7), 197 (33.0), 180 (56.0), 165 (29.0), 107 (100), 90 (55.0), 77 (33.8), Anal. calcd. for $C_{14}H_{14}O_2$ (Found: C, 78.0; H, 6.42 requires: C, 78.50 and H, 6.54%).

6-Nitro-4,4'-dihydroxy-3,3'-dimethylpiphenyl 13 (15%), Crystallized from petroleum ether-chloroform (1:1) as red needles, mp. 176^oC and gave a positive $FeCl_3$ test for phenol and Lassaigne's test for nitrogen. IR (KBr): ν_{max}: 3335 (-OH),1535 and 1325 ($-NO_2$) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.35 (s, 6H, $Ar\text{-}CH_3$), 7.32 (s, 1H, H-6), 7.92 (s, 1H, H-3) 12.52 (s, 1H, Ar-OH), 10.73 (s, 1H, Ar-OH), 7.02-7.53 (m, 3H, Ar-H). M/z (% abundance): 259 (85.0), 242 (42.3), 225 (25.6), 210 (64.0), 152 (100), 135 (73.3), 120 (29.7), 107 (60.3). Anal. calcd. for $C_{14}H_{13}NO_4$ (Found: C, 64.75; H, 5.05; N, 5.32 require : C, 64.86; H, 5.01 and N, 5.41%).

REACTION PRODUCTS FROM 4- METHYLPHENOL (4)

2-Nitro-4-methylphenol 16 (12%), crystallized from petroleum ether as light yellow granules, mp. 32^oC (lit. mp. 33^oC)[25] and gave $FeCl_3$ test of phenol. IR (KBr): ν_{max}: 3380 (-OH), 1580 and 1345 ($-NO_2$) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 12.36 (s, 1H, Ar-OH), 2.12 (s, 3H, CH_3), 7.42-7.92 (m, 3H, Ar-H). Benzoate mp. 98^oC (lit. mp. 100^oC)[25].

4-Methyl-1,2-benzenediol, 14 (30%), crystallized from a mixture of petroleum ether-benzene (2:1) as white needles, mp. 64^oC (lit. mp. 65^oC)[25] and gave $FeCl_3$ test of phenol. IR (KBr): ν_{max}: 3340 (-OH) cm^{-1}. ^1H NMR ($CDCl_3$, δ); 12.26 (bs, 2H, Ar-OH), 2.10 (s, 3H, CH_3), 6.82-7.25 (m, 3H, Ar-H).

4-Methyl-1,3-benzenediol, 15 (22%), crystallized from petroleum ether-benzene (1:1) as white needles. mp. 105^oC (lit. mp. 105^oC)[25], gave $FeCl_3$ reaction test for phenol. IR (KBr): ν_{max}:3330 (-OH) cm^{-1}. ^1H NMR ($CDCl_3$; δ): 12.06 (bs, 2H, Ar-OH), 2.06 (s, 3H, CH_3), 6.92-7.21 (m, 3H. Ar-H).

REACTION PRODUCTS FROM 2,6-DIMETHYLPHENOL (5)

Hydroquinone 8 (60%), crystallized from chloroform-methanol (9:2) as white needles, mp. 159°C (other data observed were the same as given under reaction products from phenol).

2',6',3",5"-Tetramethyl-4"-hydroxybiphenyl-3,5-dimethyl-4-hydroxyphenylether 17 (12%), crystallized from chloroform as brown needles, mp. 173°C and gave a positive $FeCl_3$ test for phenols, IR (KBr): ν_{max}: 3350 (-OH), 1320 (-O-) cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.12 (s, 18H, Ar-CH_3), 12.96 (s, 2H, Ar-OH), 6.32-7.24 (m, 6H, Ar-H). M/z (% abundance): 362 (29.2), 242 (92.2), 240 (97.2), 225 (12.5), 211 (14.6), 195 (9.7), 148 (21.9), 121 (100), 120 (68.2) 107 (70.7). Anal. Calcd. for $C_{24}H_{26}O_3$ (Found: C, 79.21; H, 7.18 requires: C, 79.55 and H, 7.18%).

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