Hydroxylation and Amidation of Aromatic Carbonyl Compounds

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Summary *Ortho-para*-Hydroxylation and acetamidation of aromatic carbonyl compounds has been accomplished anodically.

FEW synthetic methods exist for the direct introduction of hydroxy- or amino-groups on to an aromatic ring. We report here an electrochemical technique for such transformations at ambient temperature in good yield at the *ortho*- and *para*-positions of aromatic carbonyl compounds. The positional selectivity is of particular interest because electrophilic substitution reactions on (**1**) produce mainly *meta*-substituted products.

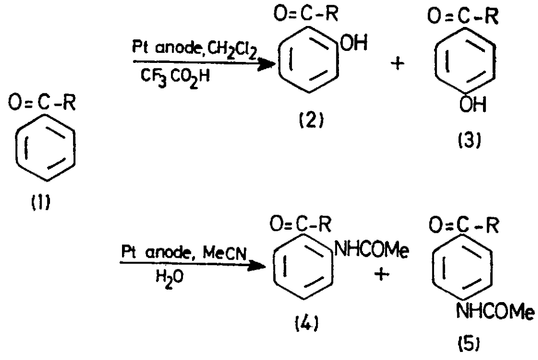
Hydroxylation was accomplished by oxidation at platinum in 2 : 1 CH_2Cl_2–CF_3CO_2H containing 0·1 M-Et_4NBF_4 (see Table 1). The background current was *ca.* 10% of the initial current with added substrate. The anodic products of oxidation at controlled potential in a divided cell were isolated by washing the mixture with water and evaporation. The products were isolated and identified spectroscopically. The major product in each case resulted from hydroxylation (Table 1).

Table 1. Hydroxylation products from (**1**)[a].

R	E/V[b]	n[c]/ (F/mol)	Products (% yield)[d]
Me	2·4	2·1	(**2**)(61)[e]
		2·5	(**2**)(85)
		3·0	(**2**)(79)
		2·0[f]	(**2**)(60)
OEt	2·3	2·0	(**2**)(43), (**3**)(19)
OH	2·3	2·0	(**2**)(55), (**3**)(20)

[a] Solvent CH_2Cl_2–CF_3CO_2H (2 : 1), 0·1 M Et_4NBF_4. [b] Controlled potential *vs.* Ag/0·1M $AgNO_3$. [c] Coulometry during oxidation. [d] Yields based on amounts of carbonyl compound which had reacted. Conversions were from 60 to 80%. [e] *p*-Hydroxyacetophenone was not detected by g.l.c., but could be present in <5% yield. [f] Oxidation in a beaker.

Acetamidation was accomplished by controlled potential oxidation at platinum in MeCN with 0·1 M-Et_4NBF_4 using a divided cell. In some cases, *e.g.* benzoic acid, the potential was pulsed to 0 V for 1 s every 20 s. Work-up involved concentration of the anolyte and addition of $CHCl_3$ and water. Product isolation from the chloroform solution showed that the specificity of the reaction was similar to that found for hydroxylation (Table 2).



Systematic attempts to maximize yields have not been undertaken. Initial results suggest, however, that somewhat more than the theoretical value of 2 F/mol is required. Although a divided cell was used for this exploratory study we have demonstrated that acetophenone can be converted into *o*-hydroxyacetophenone in 60% yield using a beaker. Poor yields of substitution products were obtained with chlorobenzene, benzamide, and benzaldehyde. The latter produced mainly benzoic acid and substituted benzoic acids in either medium.

Table 2. Acetamidation products from (**1**)[a]

R	E/V[b]	n[c] / (F/mol)	Products (% yield)[d]
Me	2·4	3·0	(**4**)(70), (**5**)(24)
Pr^n	2·4	3·0	(**4**)(52), (**5**)(23)
OEt	2·3	2·0	(**4**)(18), (**5**)(14)
OH	2·3	2·0	(**4**)(54), (**5**)(11)[e]

[a] MeCN, $LiClO_4$. [b] Controlled potential *vs.* Ag/0·1M $AgNO_3$. [c] Coulometry during oxidation. [d] Yields based on amount of (**1**) consumed which was 70—80% of that initially added. [e] Based on conversion into the ethyl ester.

Aromatic anodic acetamidation is an unusual reaction even though many aromatic compounds have been oxidized in MeCN. It was successful for anthracene,[1] only under stringently dry conditions. Aromatic mono-hydroxylations are also not generally successful.[2] We believe, however, that this hydroxylation involves initial trifluoroacetoxylation. It would then be closely analogous to ring acetoxylations performed in acetic acid–acetate media,[3] even though such acetoxylations are generally impossible for aromatic carbonyl compounds.

Initial studies indicate that the mechanism of acetamidation and hydroxylation is similar to that proposed for acetoxylation involving direct oxidation of the aromatic, nucleophilic attack by trifluoroacetic acid on an oxidized intermediate and finally proton loss. Overall it is a two-electron mechanism.

In the case of hydroxylation the trifluoroacetate product, ArO_2CCF_3, should be stable in the anolyte, but will be hydrolysed by work-up with aqueous $NaHCO_3$. It is presumably important that the easily oxidized phenol is not present in the anolyte.

Whether the oxidized intermediate can be classified as having a π-vacancy or a vacancy in a non-bonding oxygen orbital[4] will be discussed elsewhere. It is, however, clear that a π-cation radical intermediate could account for the above observations.

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