Electrophilic Aromatic Substitution by Positive Iodine Species. Iodination of Deactivated Aromatic Compounds

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The anodic oxidation of iodine in trifluoroacetic acid containing solvents produces a highly reactive positive iodine species which selectively iodinates even the most highly deactivated monosubstituted benzenes such as nitrobenzene and benzotrifluoride in high yield. The reactivity of the positive iodine species was found to be markedly dependent upon the nature of the solvent. In solvent containing 10 % trifluoroacetic acid, the yield of 3-iodonitrobenzene increased from 0 to 47 to 78 % in the series; series; acetonitrile, dichloromethane and 1,2-dichloroethane. In the latter solvent the yield of 3-iodonitrobenzene increased from 47 to 78 % upon increasing the trifluoroacetic acid concentration from 1 to 10 %. The mechanism of the reaction involves the direct attack of the positive iodine species on the aromatic compound.

Recent work by Miller and coworkers[1,2] has demonstrated that molecular iodine can be electro-oxidized in either dichloromethane or acetonitrile to an electrophilic positive iodine species. Solutions obtained after electrolysis have been used to iodinate alkenes[3] and certain aromatic compounds in high yield.[1,2] A limitation of the method is that the iodinating reagent is not reactive to deactivated aromatic compounds. We have recently found that when molecular iodine is oxidized in solvents containing trifluoroacetic acid (TFA) a highly electrophilic reagent is produced which rapidly attacks strongly deactivated compounds such as nitrobenzene and benzonitrile producing the corresponding aryl iodide in high yield.

RESULTS

The iodinations were performed in a divided cell using a platinum anode in a solvent mixture consisting of TFA (10 %) and either dichloromethane or 1,2-dichloroethane. A few drops of TFA anhydride were also added to ensure anhydrous conditions. Constant current electrolysis of iodine in the presence of the various substrates gave the results shown in Table 1. The iodinations were found to be very rapid, even for nitrobenzene so that the solutions could be worked up immediately after the termination of the electrolyses. In contrast to the findings of Miller and coworkers[1] for iodinations performed in acetonitrile, we observe that the reagent generated in our system is rather unstable so that addition of the aromatic substrates to a pre-electrolyzed iodine solution results in substantially reduced yields.

Benzene was cleanly monoiodinated when stoichiometric quantities of benzene (4 mmol) and iodine (2 mmol) were electrolyzed (Table 1). The use of half the amount of benzene resulted in a 77 % conversion to 1,4-diiodobenzene. Benzaldehyde ($\sigma_m = 0.36$) reacts solely at the *meta* position. In fact, a preparative scale electrolysis, using 5 g of iodine, was used to prepare an authentic specimen of 3-iodobenzaldehyde when alternative multistep chemical methods gave unexpectedly low yields.* Rather surprisingly, acetophenone ($\sigma_m = 0.376$) did not undergo iodination under the reaction condi-

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* For example, reduction of the acid chloride of 3-iodobenzoic acid by LiAlH(O-t-Bu)$_3$ gave 10 % of aldehyde. Similarly, reduction of 3-nitrobenzaldehyde by SnCl$_2$/HCl gave very poor yields of the amino compound for use in a subsequent diazonium reaction.

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Table 1. Iodination of aromatic compounds.[a]

Substrate	σ_m	Product	Yield/%	Material balance/%
Benzene	—	Iodobenzene	79	—
Iodobenzene	0.352	1,4-Diiodobenzene	77	95
Benzaldehyde	0.36	3-Iodobenzaldehyde	74	100
Acetophenone	0.376	No reaction	—	100
Benzotrifluoride	0.43	3-Iodobenzotrifluoride	97	—
Benzonitrile	0.56	3-Iodobenzonitrile	40	74
Nitrobenzene	0.71	3-Iodonitrobenzene	78	94
4-Chloronitrobenzene	—	3-Iodo-4-chloro-1-nitrobenzene	56	100

[a] Oxidation of 2 mmol I_2; *ca.* 4 mmol substrate; 1,2-dichloroethane -10 % TFA -0.2 M TBAF; 2.5 F mol^{-1} I_2.

tions and was recovered unchanged at the end of the electrolysis. An explanation of this apparent inertness will be discussed later, but it appears that the carbonyl oxygen is protonated in the acidic solvent thereby strongly deactivating the aromatic ring toward electrophilic substitution. Support for this is shown in Fig. 1, where it can be seen that the carbonyl stretching band of acetophenone in 1,2-dichloroethane (Fig. 1a) completely disappears on addition of TFA (to 10 %, Fig. 1b). The rise in absorption towards 1750 cm^{-1} is due to TFA. In contrast to acetophenone, benzotrifluoride was iodinated almost quantitatively while nitrobenzene yielded 78 % of 3-iodonitrobenzene. Benzonitrile, which has a σ_m value (0.56) midway between benzotrifluoride and nitrobenzene, reacted only to
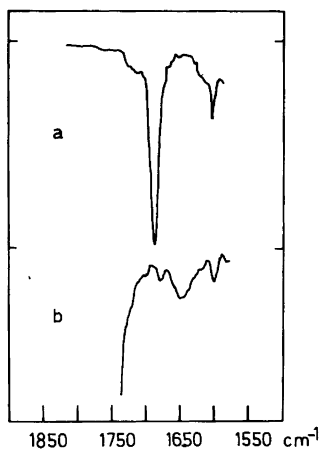
the extent of 40 %. The material balance for this reaction was 74 % showing that side reactions occurred, although no specific products were detected by gas liquid chromatography.

The possibility of iodinating aromatics having two deactivating groups was briefly investigated. 4-Chloronitrobenzene was cleanly iodinated to 3-iodo-4-chloronitrobenzene but both 3-nitrobenzaldehyde and 1,3-dinitrobenzene failed to react. The latter result is not surprising, but it is felt that 3-nitrobenzaldehyde might be iodinated if forcing conditions such as heating the anolyte during the electrolysis were employed. This was not pursued in that modification of the cell design would have been necessary.

Although cyclic voltammetric oxidation of iodine in the solvent system gave a number of poorly resolved peaks, second harmonic *ac* voltammetry
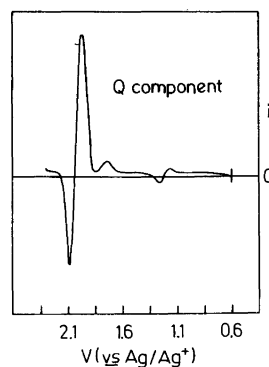

Fig. 1. The infrared spectrum of acetophenone in 1,2-dichloroethane (a) and with 10 % added TFA (b).

Fig. 2. Second harmonic *ac* voltammogram of iodine in 1,2-dichloroethane – TFA (10 %) at a platinum electrode. *ac* frequency = 9 Hz and amplitude = 10 mV. *dc* voltage sweep rate = 50 mV s^{-1}.

Table 2. Yield of 3-iodonitrobenzene *vs.* charge passed [a].

Charge/F mol^{-1}	Yield/%
2.0	60
2.5	78
3.0	76

[a] Oxidation of 2 mmol I_2; *ca.* 4 mmol $PhNO_2$; 1,2-dichloroethane $-$ 10 % TFA $-$ 0.2 M TBAF.

Table 3. Yield of 3-iodonitrobenzene *vs.* solvent composition [a].

Solvent	Yield/%
1,2-Dichloroethane $-$ 10 % TFA	78
Dichloromethane $-$ 10 % TFA	47
Dichloromethane	0
Acetonitrile $-$ 10 % TFA	0

[a] Oxidation of 2 mmol I_2; *ca.* 4 mmol $PhNO_2$; 2.5 F mol^{-1} I_2.

Table 4. Yield of 3-iodonitrobenzene *vs.* TFA content s [a].

TFA/%	Yield/%
0	0
1	47
5	57
10	78
20	65

[a] Oxididation of 2 mmol I_2; *ca.* 4 mmol $PhNO_2$; 1,2-dichloroethane $-$ 0.2 M TBAF (40 ml) $-$ 2.5 F (mol $I_2)^{-1}$.

showed a distinct wave at about 2.0 V *vs.* Ag/Ag$^+$ (Fig. 2). The electrode process at this potential was found to be irreversible due to rapid follow-up reactions of the initially formed intermediate.

The direct determination of coulometric *n* values proved unsuccessful, so an indirect method was adopted which involved the observation of the yield of 3-iodonitrobenzene as a function of the quantity of charge passed. The maximum yield of 3-iodonitrobenzene was obtained after the consumption of about 2.5 F mol^{-1} of iodine (Table 2) which agrees with the *n* value measured for the oxidation of iodine in acetonitrile.[1]

Tables 3 and 4 show the significant effects that solvent composition has on the product yields, again taking nitrobenzene as the model substrate. Despite having similar physical properties, 1,2-dichloroethane and dichloromethane differ appreciably as solvents for the reaction with the use of the former being accompanied by much better yields of product. With compounds with substituents having lower σ_m values (<0.5) or with benzene, the product yields in the two solvents are similar. The effect of the concentration of TFA in 1,2-dichloroethane on product yields is emphasized in Table 4. The yield of 3-iodonitrobenzene rises from zero in the absence of TFA to 78 % with 10 % acid. The latter corresponds to a molar ratio of acid/iodine equal to 26. The use of higher concentrations of TFA appears unnecessary and lowers the solubility of iodine in the electrolyte. Iodination of nitrobenzene failed in acetonitrile/TFA.
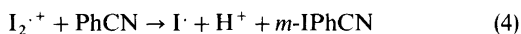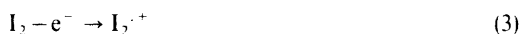
DISCUSSION

The sequence of reactions involved in the electro-iodination reaction is that shown in eqns. (1) and (2). Although experimental *n* values for step (1) indicate 2.5 F mol^{-1}, it is most likely that the non-integral value is due in part to side reactions.

$$I_2 - 2e^- \xrightarrow{\text{TFA}} 2I^+/\text{TFA} \qquad (1)$$

$$I^+/\text{TFA} + \text{Ar-H} \longrightarrow \text{Ar-I} + H^+ + \text{TFA} \qquad (2)$$

An alternative mechanism involving the anodic oxidation of the aromatic compound followed by reaction between the cation radical and iodine can be ruled out from the following two facts. Firstly, substitution takes place, albeit in lower yield, if the aromatic substrate is added to a pre-electrolyzed iodine solution and secondly, recent work[4,5] has shown that nucleophilic attack on an aromatic cation radical having an electron withdrawing substituent leads to *ortho* and *para* as well as *meta* substitution. For example, anodic trifluoro-acetoxylation of benzonitrile[4] results in an *o:m:p* ratio of products of 45:30:25 very close to the 42:30:28 ratio predicted from consideration of charge density at the various positions of the cation radical. We only observe *meta* iodination of benzonitrile.

The structure of the iodinating agent is unknown. An obvious candidate is iodine trifluoroacetate.

However, this compound is known and has been used in benzene solutions for the iodination of aromatic compounds.[6] The species that we are dealing with is obviously much more reactive, iodination of benzene taking place instantaneously upon mixing with the electrophilic reagent. Another attractive possibility is the iodine cation radical, $I_2^{\cdot+}$ which has been characterized as the product of anodic oxidation of iodine in fluorosulfonic acid.[7] However, the involvement of the latter intermediate is unlikely since its formation is a one electron oxidation of iodine and the stoichiometry of the iodinations requires the consumption of at least $2 \, F \, mol^{-1}$. However, with the evidence available at this time, we cannot rule out the cation radical as the iodinating agent in an ECE mechanism when the oxidation is carried out in the presence of an aromatic compound as in eqns. (3)−(5) with benzonitrile as the substrate.

$$I_2 - e^- \rightarrow I_2^{\cdot+} \tag{3}$$

$$I_2^{\cdot+} + PhCN \rightarrow I^{\cdot} + H^+ + m\text{-}IPhCN \tag{4}$$

$$I^{\cdot} - e^- \rightarrow I^+ \tag{5}$$

Since the visible absorption spectrum of $I_2^{\cdot+}$ has been obtained previously[7] mechanistic studies using spectroelectrochemistry should be possible. Further work is planned to attempt to characterize the nature of the intermediate and the mechanistic details of this reaction.
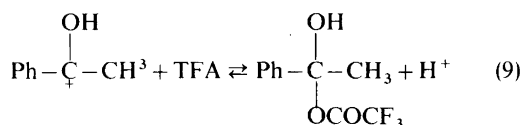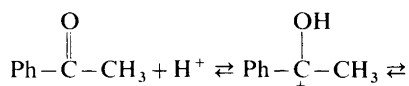
It is of interest to note that the yield of 3-iodobenzonitrile and the material balance resulting from iodination of benzonitrile are exceptionally low. This may be due to competition between attack of the iodinating species 'I$^+$' on the ring and attack on the nitrile group as shown below. The latter pathway is analogous to the scheme proposed for

$$Ph\text{-}CH + `I^+ ` \rightarrow m\text{-}IPhCN + H^+ \tag{6}$$

$$Ph\text{-}CN + `I^+ ` \rightarrow Ph\text{-}\overset{+}{C} = N - I \tag{7}$$
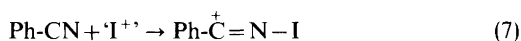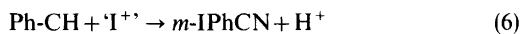
the oxidation of iodine in acetonitrile.[1]

Another apparent anomaly is the failure of acetophenone to undergo iodination under conditions where the more strongly deactivated substrates react readily. As mentioned earlier, the IR carbonyl absorption band of benzophenone in 1,2-dichloroethane disappears upon the addition of

TFA to the solution. The substrate can be recovered quantitatively after neutralization of the acid. A possible explanation of these facts is the reversible addition of TFA to the carbonyl group as illustrated in eqns. (8) and (9).* Carbonyl frequency shifts[8] have been used extensively to determine the relative

$$\underset{\displaystyle O}{Ph - \overset{\overset{\displaystyle O}{\|}}{C} - CH_3} + H^+ \rightleftharpoons \underset{\displaystyle +}{Ph - \overset{\overset{\displaystyle OH}{|}}{C} - CH_3} \rightleftharpoons$$

$$Ph - \overset{\overset{\displaystyle OH}{|}}{C} = CH_2 + H^+ \tag{8}$$

$$Ph - \overset{\overset{\displaystyle OH}{|}}{\underset{+}{C}} - CH^3 + TFA \rightleftharpoons Ph - \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle OCOCF_3}{|}}{C}} - CH_3 + H^+ \tag{9}$$

basicities of carbonyl compounds, *e.g.* Denisov[9] has measured the frequency shifts of several aliphatic ketones in carbon tetrachloride-TFA solutions. These shifts (up to *ca.* $25 \, cm^{-1}$) were then related to the strength of the hydrogen bond between the acid and the carbonyl compound. The fact that we did not observe a frequency shift but rather the disappearance of the carbonyl band in the simulated electrolyte solutions strongly suggests the almost complete shift of the equilibria shown above to the right.

In conclusion, the results outlined above represent a useful extension of electrochemical iodination to deactivated aromatic compounds, thus broadening the scope of electrolytic halogenation and making this method an attractive alternative to conventional chemical procedures.

EXPERIMENTAL

All the oxidations were performed in cylindrical cells having two compartments. The cell used for analytical work had a working capacity of 40 ml while the preparative scale cell could contain up to 200 ml of anolyte. In both cases the concentric cathode compartment was separated from the anode by a grade 4 glass frit. A cylindrical Pt gauze

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* As pointed out by a referee, this explanation is not very convincing since it is not obvious that the monoacylated ketal should be inactive toward the iodinating agent.

(48 cm^2) was used as the working electrode. All the electrolyses were carried out at a constant current of 150 mA from a conventional 40V Ce power supply. The cell temperatures were not controlled and usually rose to *ca.* 30 °C in the course of the experiments.

The solvents, 1,2-dichloroethane (Koch-Light, *puriss* grade) and dichloromethane (Fluka, *puriss* grade), were used as received. Tetrabutylammonium tetrafluoroborate, prepared by mixing aqueous solutions of the hydrogen sulfate and fluoroboric acid, was used as the supporting electrolyte. The trifluoroacetic acid was *purum* grade from Fluka.

Product identification was achieved by comparison with authentic samples (mostly prepared by standard literature procedures) using IR, NMR and GLC retention time information. Once the identity of the products had been established, yield data was obtained by GLC analysis (Perkin Elmer 3029B) of the anolytes using the method of internal standards. The separations were conducted on a 180 cm × 3 mm column of 5 % OV101 on 80 – 100 mesh chromosorb temperature programmed between 100 and 200 °C. The yields quoted in Table 1 are the average of at least three experiments. Where possible, material balances were also calculated both as a check on products not detected by GLC and on the overall accuracy of the method. The two examples given below are representative of the procedures used for carrying out a preparative and an analytical scale electrolysis.

3-Iodobenzaldehyde. Iodine (5 g, 0.02 mol) and benzaldehyde (4.24 g, 0.04 mol) were weighed into the anode compartment of the preparative cell followed by 200 ml of the electrolyte solution (1,2-dichloroethane – 10 % TFA – 0.2 M TBAF). The anolyte was stirred for a few minutes to dissolve the iodine and then electrolysed for 9 h at 150 mA (2.5 F mol^{-1} I$_2$) under a nitrogen atmosphere. The solvent was removed under reduced pressure and diethyl ether (150 ml) added to the residue to precipitate the supporting electrolyte. The ether solution was then washed with saturated sodium bicarbonate (2 × 30 ml) and sodium thiosulfate solutions (50 ml) before drying over anhydrous magnesium sulfate. The solution was filtered and evaporated to give a pale pink semi-solid residue (9 g) containing both the product and starting material. Separation of the product was achieved by column chromatography (silica gel 60; CCl$_4$ – 40 % CH$_2$Cl$_2$). 3-Iodobenzaldehyde was eluted first and evaporation of the solvent afforded colourless plates (6.4 g, 60 %) m.p. 55 – 57 °C, lit. 57 °C.[11]

Analytical scale iodinations. In these experiments 0.5 g (2 mmol) of iodine were used together with a known excess (usually 10 – 20 %) of the aromatic substrate. The electrolysis conditions were the same as those employed for the preparative experi-

ment. A simplified work-up procedure was used which omitted the washing steps. Instead, a known amount of an internal standard (*e.g.* 1-chlorooctane) was added to the ether solution and the mixture analysed by GLC. Measurement of the relative areas of the product and internal standard peaks together with the previously determined response factors enabled the yields and material balance for each electrolysis to be determined. The results are presented in Tables 1 – 4.

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