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Electrochemistry in Media of Intermediate Acidity

Part VI.[1] Coupling Reactions of Simple Aryl Ethers

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The anodic oxidation of anisole and several substituted anisoles as well as diphenyl ether in media containing trifluoroacetic acid is accompanied by the formation of the corresponding biphenyl and the cation radical of the biphenyl. Conditions for optimum yield of coupled products were examined. The solvent system of choice consists of dichloromethane-trifluoroacetic acid (2:1). The limiting factor for the yield of coupled products is the concentration of product in the anolyte. Up to concentrations of about 1 mM, both yield and current efficiency is very high. The reactions were found to be highly specific with only *para* coupling observed.

The low yields observed during oxidative coupling of simple aryl ethers [2] is readily understood when one considers the relative ease of oxidation of the substrate and the dimeric product. The increased conjugation in the biaryl in addition to the strong electron releasing tendency of the ether group renders the biaryl product much more easily oxidized than the simple aryl ether. The initial oxidation product of an aryl ether by electron transfer is the corresponding cation radical. In addition to dimerisation, the cation radical is highly susceptible to electrophilic reactions with even trace quantities of nucleophiles present in the medium, thus further lowering the yields of desired products. Furthermore, the *ortho-para* directing ether linkage contributes to the complexity of the reaction by favoring the production of isomeric mixtures.

The most successful coupling reactions of the simplest aryl ether, anisole, which have previously been reported involve the action of benzoyl peroxide and aluminium chloride on anisole in nitrobenzene [3] giving 4,4′-dimethoxybiphenyl in 23 % yield and the lead(IV) tetraacetate-boron trifluoride etherate oxidation of anisole in dichloromethane [4] which resulted in the formation of all three possible biphenyls with 4,4′-dimethoxybiphenyl predominating (30 % yield).

It is apparent from the discussion above that what is necessary for a successful biaryl synthesis from simple aromatic ethers is that (a) a medium be employed in which the isomer distribution favors the desired product and (b) in which the initial intermediate is restricted to dimerisation and (c) in which the coupled product is stabilised toward further oxidation and other reactions. Here, we report the results of a study of the coupling of simple aryl ethers in media containing trifluoroacetic acid (TFA). The study was restricted to anisole, diphenyl ether, and simple substituted anisoles since more complex ethers such as the trimethoxybenzenes [2,5,6] or alkoxynaphthalenes [2,7,8] are readily coupled in high yield using conventional techniques.

RESULTS

Voltammetry of anisoles in CH_2Cl_2-TFA (2:1). In general, anisole and substituted anisoles are considerably more difficult to oxidize than the corresponding biphenyls. The latter fact gives rise to a characteristic voltammetric behaviour for this series of compounds which is illustrated by the voltammograms in Fig. 1. For example, anisole is oxidized in CH_2Cl_2-TFA (2:1) with an oxidation peak potential (O_1) equal to +1.55 V (Fig. 1a). On the cathodic

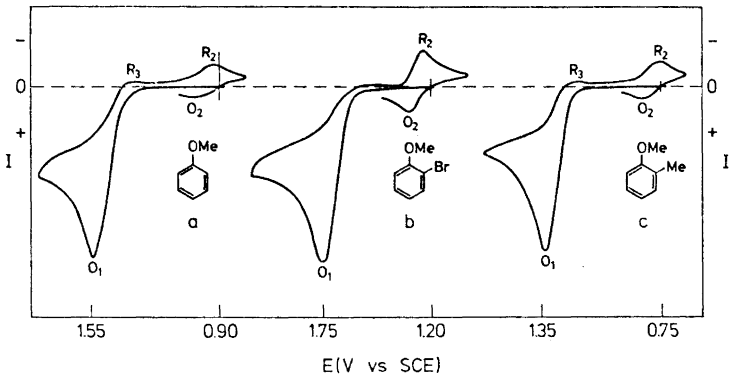


Fig. 1. Cyclic voltammetry for the anodic coupling of anisoles in CH_2Cl_2 – TFA (2:1) containing n-Bu_4NBF_4 (0.2 M). (a) Anisole, (b) 2-bromoanisole, (c) 2-methylanisole. Voltage sweep rate = 156 mV/sec.

going sweep, a very small reduction peak (R_3) is first seen and then more cathodic a larger reduction peak (R_2) appears with a corresponding oxidation peak (O_2) being observed on the second anodic sweep. The redox couple, $R_2 - O_2$, was found to be due to the oxidation-reduction of 4,4′-dimethoxybiphenyl and the corresponding cation radical by comparison with the authentic compound. Furthermore, the small reduction peak, R_3, was found to appear at the same potential as the reduction peak for the dication of 4,4′-dimethoxybiphenyl. This behaviour appears to be general for compounds having a free position *para* to a methoxy group. Two other typical examples are illustrated

by the voltammograms for 2-bromoanisole (Fig. 1b) which exhibits an initial oxidation peak (O_1) at +1.76 V. In the case of 2-methylanisole in the same solvent system, the oxidation of the substrate occurs with a peak potential of +1.33 V (Fig. 1c). Both the latter voltammograms have the characteristic reversible couple, $R_2 - O_2$, as seen in the case of anisole. In addition to the above examples, a similar behaviour was observed for the following compounds: 2,6-dimethylanisole, 2,3,5,6-tetramethylanisole, diphenylether, and 4-methoxybiphenyl. Compounds substituted in the position *para* to methoxy such as 4-methylanisole failed to give voltammograms showing the reversible couple, $R_2 - O_2$, due to the corresponding dimeric product.

Exhaustive electrolysis of 1.0 mM solutions of all the compounds listed above in CH_2Cl_2-TFA (2:1) using constant current coulometric techniques,[9] resulted in coulometric n values ranging from 1.5 to 1.7. The theoretical n value for oxidation of an anisole to the cation radical of the corresponding biaryl is equal to 1.5. Yields of the dimers could be determined readily by a comparison of the voltammetry of the resulting coulometric solution with that of solutions of known concentrations of the dimers. Yields of 90 – 100 % were observed.

The effect of solvent composition on the yield of coupling products. Anisole was selected as the model compound for the study of the conditions to give optimum yields of coupling products. Previous results had shown that significant yields of coupling products from simple aryl ethers could not be attained by anodic oxidation in acetonitrile.[10] However, it had not been established whether or not dichloromethane, which has been found to be a suitable medium for the coupling of aromatic hydrocarbons,[11] could also be of utility in the coupling of aryl ethers. Thus, the anodic oxidation of anisole (1.0 mM) in dichloromethane containing n-Bu_4NBF_4 (0.2 M) was carried out until 1.5 F/mol had been passed. Only traces of the desired product, 4,4′-dimethoxybiphenyl, could be detected. Thus, TFA is a necessary and essential part of the CH_2Cl_2-TFA solvent mixtures if coupling of aryl ethers is to be observed. The data in Table 1 indicate how the yield of 4,4′-dimethoxybiphenyl from the anodic oxidation of anisole varies with solvent composition during preparative scale (2 mmol) electrolysis. Table 2 gives data for the yield of product and current efficiency during electrolysis under coulometric conditions as a func-

Table 1. Effect of solvent composition on the yield of 4,4′-dimethoxybiphenyl. 3.0 F/mol passed at 20°. Supporting electrolyte = n-Bu_4NBF_4 (0.1 M).

TFA (ml)	Dichloromethane (ml)	% Yield
0	100	4
10	90	22
17	83	30
25	75	58
33	67	63
50	50	61
100	0	57

tion of the current passed. The data in Table 1 indicate that the preferred medium for the preparation of 4,4′-dimethoxybiphenyl by anodic oxidation of anisole contains about 66 % by volume of dichloromethane. Going to solutions containing higher percentage of TFA resulted in a slight lowering of the yield. Increasing the proportion of dichloromethane to 75 % resulted in a lowering of the yield and still higher proportions caused the yield of product to decrease drastically. The data in Table 2 show the same trend regarding the

Table 2. Yield and current efficiency for formation of 4,4′-dimethoxybiphenyl during oxidation of anisole.[a]

Faraday ($\times 10^4$)[b]	TFA		CH_2Cl_2–TFA (2:1)		CH_2Cl_2–TFA (5:1)	
	Yield[c] %	Current[d] Efficiency	Yield[c] %	Current[d] Efficiency	Yield[c] %	Current[d] Efficiency
1	90	103	100	100	96	58
2	81	94	99	91	59	60
3	77	78	85	89	48	61
4	69	80	80	79	41	57
5	62	78	74	76	40	50
6	57	76	65	73	36	53
7	53	74	60	70	33	52
8	47	72	54	68	29	49

[a] Substrate (0.4 mmol) dissolved in solvent containing n-Bu_4NBF^4 (0.2 mM). [b] Constant current electrolysis at 25 mA for 6.44 min = 10^{-4} Faraday. [c] Based on anisole consumed. [d] Expressed in % based on 1.5 F/mol anisole = 100 %.

solvent composition. Best results were obtained with a CH_2Cl_2-TFA ratio of 2:1. The *data* clearly show that both yield and current efficiency is high at low conversion but falls off drastically with increasing degree of conversion. The latter effect is even more clear from the graphs of Fig. 2. When the solvent

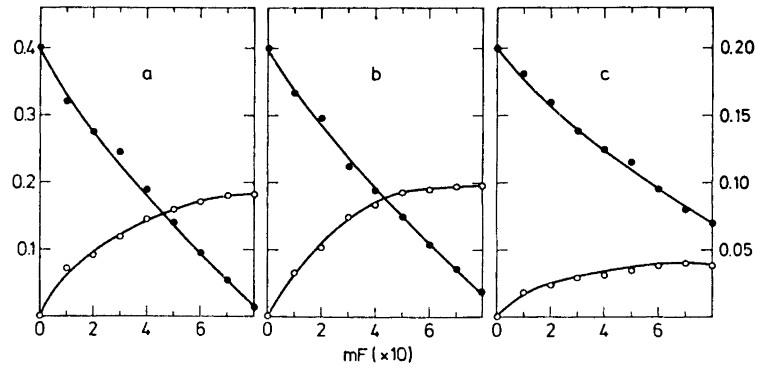


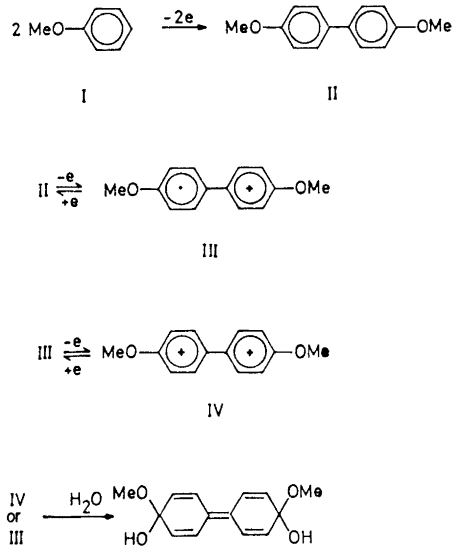
Fig. 2. Consumption of anisole and formation or 4,4′-dimethoxybiphenyl as a function of number of Faraday passed. ● Anisole, ○ 4,4′-dimethoxybiphenyl. Solvent: (a) TFA, (b) CH_2Cl_2–TFA (2:1), (c) CH_2Cl_2–TFA (5:1). Left hand scale refers to mmol anisole and right hands scale refers to mmol 4,4′-dimethoxybiphenyl.

was TFA the amount of product rose rather sharply and then leveled off at about 0.09 mmol (maximum possible = 0.2 mmol). The same general trend is seen with CH_2Cl_2-TFA (2:1) as solvent (Fig. 2b) with the maximum being approached after the consumption of 0.5 mF and then remaining level at about 0.1 although the anisole continued to be consumed. A much lower level of product (0.04 mmol) was attained in CH_2Cl_2-TFA (5:1). It is also seen that the comsumption of anisole was less efficient in the latter case (Fig. 2c). In order to determine whether the level to which the amount of product reached was determined by an optimum concentration of product or by the amount of substrate oxidized, an experiment identical to that giving the data for Fig. 2b was carried out with one major change, *i.e.* the amount of anisole used was increased by a factor of 10 (4.0 mmol). The results were nearly the same as those in Fig. 2b with amount of product formed leveling off at about 0.11 mmol.

Several experiments were carried out at different temperatures ranging from $-20°$ to $+30°$. No significant change in the yield of product was observed upon changing the temperature.

DISCUSSION

Clearly, an important factor contributing to the complexity of aryl ether and phenol oxidation is that the coupled products are invariably more easily oxidized than the substrates. This fact is demonstrated by the cyclic voltammograms (Fig. 1) for anisoles in CH_2Cl_2-TFA (2:1). The three examples shown: anisole, 2-bromoanisole, and 2-methylanisole, are all oxidized about 600 mV more anodic than their corresponding dimers. Thus, at the potential necessary for anisole oxidation to occur, all the reactions in Scheme 1 take



Scheme 1.

place. The cation radical (III) and the dication (IV) are both reactive species and react with any nucleophiles present. An expected reaction, when water is present, is the formation of cyclohexadienones [12] of type V which would undergo loss of methanol to give the quinone. Reactions of this type have been observed previously during oxidation of methoxybenzenes in both aqueous [13] and non-aqueous [14] systems. Water is nearly always present in solvents used for electrolytic reactions and has been implicated in reactions of a variety of aromatic cation radicals in "dry" acetonitrile.[15–20] Other possible reactions such as polymerisation are also likely when cation radical concentrations become high.

The success of coupling reactions of simple aryl ethers in media containing trifluoroacetic acid must be attributed to the stabilizing influence of TFA on the cation radicals and dications of the dimers. The stabilishing influence of TFA on aromatic cation radicals as well as the deactivation of water as a nucleophile toward aromatic cation radicals has recently been described.[21] While the potential for oxidation of the anisole is sufficient to oxidize the biaryl to the dication, it is not necessary for the dication to be stable for long times in the medium since it behaves as a potent oxidant, most likely oxidizing both the substrate and the biaryl in homogeneous electron transfer reactions. The dications of several biaryls are sufficiently stable in media containing TFA to show reversible behavior for the cation radical-dication couple.[22]

As indicated by the data in both Tables 1 and 2, best results were obtained using a mixed solvent and the optimum ratio of CH_2Cl_2-TFA appears to be about 2:1. The latter is of practical importance since our reason for going to the mixed solvent system was to use the inexpensive dichloromethane as a diluent for the more expensive TFA.

The data in Table 2 and Fig. 2 indicate that the formation of biaryls is a very efficient, high yield process until a certain concentration of the product is achieved after which the concentration of product remains nearly the same while the substrate is continuing to be consumed. This is also seen from the coulometric experiments where nearly quantitative yields of the dimers were obtained during oxidation of 1.0 mM solutions of the substrates. When the solvent was CH_2Cl_2-TFA (2:1), the yield was essentially quantitative up until about 0.2 mF had been consumed. The concentration of dimer at that point (Fig. 2) was equal to about 1.0 mM. Thus if one were to oxidize an aryl ether which was sufficiently valuable to warrant use of dilute solutions to achieve the maximum yield, our data suggest that a 2 mM solution of the ether should be exhaustively oxidized, following the reaction by voltammetry to determine the stopping point. In this manner it should be possible to obtain nearly 400 mg of product (for a substrate of molecular weight 200) per liter of solution oxidized.

EXPERIMENTAL

TFA was reagent grade and used without further purification. Dichloromethane was passed through a column of neutral alumina before use. The aryl ethers were either reagent grade or prepared from the corresponding phenols by standard procedures. The apparatus used for voltammetry and coulometry has been described.[23]

General procedure for yield and current efficiency experiments (Table 2). Anisole (0.4 mmol) was dissolved in the solvent (50 ml) containing n-Bu_4NBF_4 (0.2 M) and placed

in the cell which consisted of a 100 ml beaker equipped with magnetic stirring and a platinum gauze electrode which fit snugly into the beaker. Solvent containing electrolyte was placed in a tube, the bottom of which was a sintered glass disk (G–4). The tube was supported in the electrolytic solution with the liquid levels adjusted to be the same in both solutions. The tube served as the cathode compartment and was equipped with a platinum gauze electrode. The peak voltammogram of the anolyte was recorded at a Beckman platinum button electrode. The reference electrode was an aqueous saturated calomel electrode and was placed in the cathodic compartment while the large platinum gauze served as the counter electrode. Constant current electrolysis was carried out for 6.45 min at 25.0 mA which corresponds to 0.1 mF. The peak voltammogram, showing a peak for anisole as well as for 4,4'-dimethoxybiphenyl was recorded. The concentration of 4,4'-dimethoxybiphenyl was determined by comparison of the peak current with that obtained from a voltammogram of a solution of known concentration of the compound in the solvent system. The above procedure was repeated at 0.1 mF intervals until a total of 0.8 mF had been consumed.

General procedure for preparative scale oxidations (Table 1). Anisole (2.0 mmol) was dissolved in the solvent (100 ml) containing n-Bu_4NBF_4 (0.1 M) and placed in a two compartment water jacketed cell. The compartments were separated by a sintered glass disk (G–4). The anode was a platinum sheet (area = 75 cm^2) and the cathode was a coiled platinum wire. Electrolysis was conducted at constant current (200 mA) under an atmosphere of nitrogen * until 3 F/mol had been passed. The anolyte was stirred magnetically and kept at 8° by external cooling. After treatment of the anolyte with zinc dust to reduce any of the product present as an oxidized form, the solution was filtered and evaporated to dryness *in vacuo* at 40°. The residue was treated with dry ether to precipitate the supporting electrolyte. After evaporation of the ether, the yield was determined from the NMR spectrum and the peak voltammogram of the crude product. Further purification was carried out either by vacuum sublimation or preparative thin layer chromatography.

2,2',3,3',5,5',6,6'-Octamethyl-4,4'-dimethoxybiphenyl was prepared as described above. Yield 53 %, m.p. 131 – 131.5°, NMR ($CDCl_3$); 1.73 (s, 12 H), 2.22 (s, 12 H) and 3.77 (s, 6 H). (Found C 81.3; H 9.0. Calc. for $C_{22}H_{30}O_2$: C 81.0; H 9.2).

4,4'''-Dimethoxyquaterphenyl was obtained in 48 % yield as described above. M.p. 336 – 339° (lit.[24] 336 – 339°).

3,3'-Dibromo-4,4'-dimethoxybiphenyl was obtained in 43 % yield in the manner described above. M.p. 167 – 168° (lit.[25] 167°).

4,4'-Diphenoxybiphenyl was prepared in 56 % yield as described above. M.p. 155 – 157° (lit.[26] 150 – 151°).

3,3'-Dimethyl-4,4'-dimethoxybiphenyl was obtained in 42 % yield by the standard procedure. M.p. 155 – 156° (lit.[27] 154.5°).

3,4,3',4'-Tetramethoxy-2,2'-dimethylbiphenyl was obtained in 86 % yield as described above. M.p. 115 – 116° (lit.[28] 115 – 116°).

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