Electrochemically Induced Radical Cyclization Reactions

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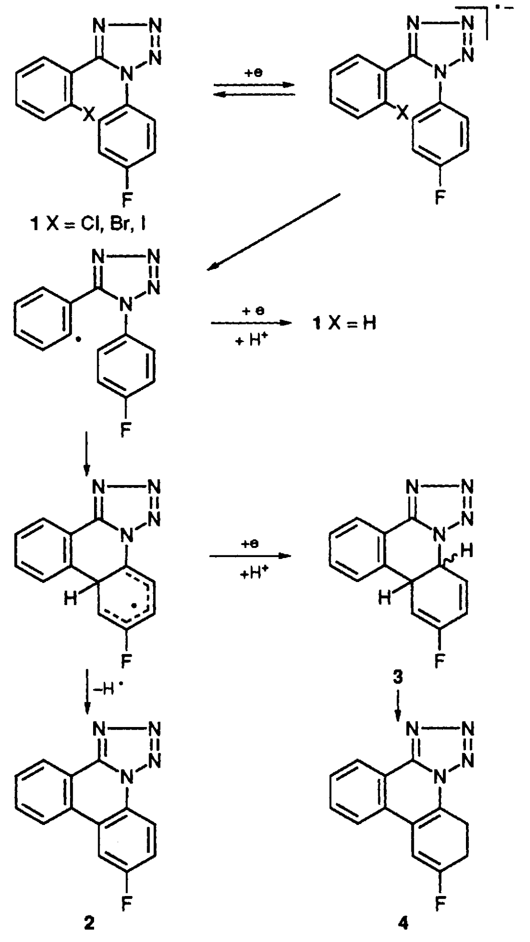
A new route has been devised for intramolecular aryl radical cyclization reactions involving the electrochemical reduction of an *ortho*-halogenophenyl compound in acetonitrile at a mild steel cathode.

Carbon σ-radicals are well known to react with alkenes and arenes forming a new carbon–carbon bond.[1] One route for the generation of the initial radical is by electrochemical reduction of halogenoarenes. Here the halogenoarene accepts an electron from the cathode to give the radical anion which undergoes carbon–halogen bond cleavage to leave an aryl σ-radical and halide ion.[2] The rates of carbon–halogen bond cleavage in the radical anions vary widely with the structure of the substrate.[3] For a specific cyclization process, carbon–halogen bond cleavage must be faster than any other reaction of the radical anion such as protonation. However, if cleavage is very fast, the σ-radical is generated within the electrical double layer and undergoes further reduction at the cathode.[4] This second process leads to replacement of the halogen substituent by hydrogen and competes with the cyclization step.

For a range of ring systems with adjacent phenyl and 2-halogenophenyl substituents, electrochemical reduction has been shown to afford good yields of a product where a new carbon–carbon bond has been formed between these two substituents.[5,6] An essential structural requirement for this carbon–carbon bond formation is that the reacting groups must be held close to each other so that other modes of decomposition of the phenyl σ-radical do not interfere.

Electrochemical reduction of the tetrazoles **1** at a mercury cathode has been shown to yield **1**, X = H, **2**, **3** and **4** by the mechanism indicated (Scheme 1).[6] The individual products have been isolated and their spectral characteristics determined.[6] These substrates with a fluorine substituent are convenient for the investigation of alternative experimental procedures because the products are easily identified and quantified through the ^{19}F NMR spectrum. The carbon–fluorine bond is not cleaved under the reaction conditions.

For the preparation on any appreciable scale of condensed ring systems by this electrochemical process, it is necessary to investigate other materials for replacement of mercury as cathode. We have examined the reduction of **1** in acetonitrile solution at a number of metal cathodes. Cathode materials were chosen with appreciable overvoltage for the hydrogen evolution reaction which is likely to be the most important competing process. Cadmium, zinc and mild carbon-steel (commercial material with 0.1–0.35% carbon) were used and the yields of product obtained are given in Table 1. A platinum anode was used in the first experiments with a divided cell.



Scheme 1

Table 1 Electrochemical reduction of substrates **1**[a]

Substrate **1**, X	Cathode material	Cathode potential *E*/V *vs.* SCE	Faradaic yield[b]	% of total products[c]			
				2	**4**	**3**	**1**, X = H
Cl	Hg pool	−1.86		63	22	5	10
Br	″	−1.84		50	9	2	39
I	″	−1.66		66	0	3	31
Cl	Cd	−2.20	72	79	4	12	2
Br	″	−2.15	69	82	3	8	6
I	″	−2.10	65	69	1	9	21
Cl	Zn	−2.35	69	87	3	10	0
Br	″	−2.24	66	80	4	13	3
I	″	−2.08	66	75	2	6	17
Cl	Mild steel	−2.20	72	81	4	15	1
Br	″	−2.05	68	91	1	6	2
I	″	−1.95	64	85	0	0	15

[a] Substrate **1** (50 mg) in acetonitrile (25 ml) containing 0.1 mol l^{-1} Et_4NBF_4, carried to *ca.* 90% conversion in 10–15 min. The anode is platinum in acetonitrile, 0.1 mol l^{-1} Et_4NClO_4, divided cell. [b] At *ca.* 90% conversion. Faradaic yield = moles substrate consumed × F × 100/coulombs passed. [c] Determined from ^{19}F NMR spectrum.

Table 2 Electrochemical reduction of substrates **1** at a mild steel cathode

Substrate **1**, X	Type of cell	Cathode potential/ E/V *vs.* SCE	Faradaic yield[b]	% of total products[c]			
				2	**4**	**3**	**1**, X = H
Cl	Divided	−2.20	68	90	2	7	1
Br	"	−2.08	67	97	0	1	2
I	"	−2.00	62	74	0	0	26
Cl	Undivided	−2.20	41	72	11	7	10
Br	"	−2.15	40	65	14	7	14
I	"	−2.10	41	67	8	5	20

[a] Substrate **1** (50 mg) in acetonitrile (25 ml) containing 0.1 mol l^{-1} Et_4NBF_4 carried to *ca.* 60–90% conversion at a mild steel cathode with a magnesium anode. [b,c] see Table 1.

Experiments were conducted using a potentiostat to maintain a pre-set cathode potential *vs.* a saturated calomel reference electrode. Significantly higher cathode potentials were required at cadmium, zinc or mild steel relative to mercury in order to give approximately the same overall current density for the reaction.

All three solid metal cathodes gave better yields of cyclization product than the mercury pool cathode. A possible explanation is that the electron transfer rate for a given potential at these surfaces is slower than at mercury, so that further reduction of the σ-radical competes less with the cyclization step. Reactions at all three solid metal cathodes gives the cyclization product in excellent chemical and Faradaic yields. The tetrazole **1**, X = I gave the lowest yield of cyclization products because carbon–iodine bond fragmentation is fast and generates the σ-radical close to the electrode surface where it can undergo further reduction and protonation to yield **1**, X = H.

This is the first time a mild steel cathode has been used in the cyclization reaction. The process should be a valuable addition to synthetic organic chemistry. It can be used with a large range of substrates and is capable of large-scale operation.

In any electrochemical cell we have to consider the reactions at both cathode and anode. Replacement of platinum as anode with a sacrificial material offers possibilities for further improvements in the cyclization process. We have used magnesium where the anode reaction is oxidation of the metal to magnesium ions. The yields of products obtained in reduction of substrates **1** in acetonitrile at a mild steel cathode and magnesium anode are given in Table 2. Good Faradaic and chemical yields of cyclization products were obtained in a divided cell.

From the viewpoint of simplicity in the design of a reaction vessel, the ideal situation is to carry out this reaction at a steel cathode with a magnesium anode in an undivided cell. When the cyclization process was carried out under these conditions, the anode reaction remained formation of magnesium ions and no new products were encountered from oxidation of the substrate which is now exposed to the anode. Product yields are given in Table 2. The Faradaic yield of cyclised material was depressed in relation to that obtained in a divided cell and the competing cathode reaction is likely to be hydrogen evolution.

We have compared the efficiency of this electrochemical cyclization reaction with that of the related chemical process in which aryl σ-radicals are generated from the substrates **1** by the action of tributyltin hydride and a free radical initiator.[7] The chemical step gives good yields of product only with aryl iodide. The bromo and chloro substrates reacted slowly, if at all. Tin byproducts from these reactions present a considerable environmental hazard.

We believe that the electrochemical process which is applicable to chloroaryl substrates and which can be carried out at a mild steel cathode should be considered very strongly as a more environmentally friendly alternative for this and related cyclization steps.

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