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A New Convenient Synthesis of 5-Aryl Uracils Using SRN1 Aromatic Nucleophilic Substitution

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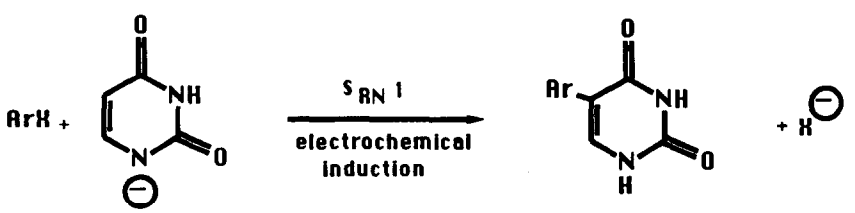
Abstract: Direct and indirect electrochemical reduction of aryl halides in the presence of the uracil anion in dimethylsulfoxide yields the corrsponding 5-aryl uracils by an $S_{RN}1$ mechanism.

Nucleophilic aromatic substitution catalyzed by electron injection (electrochemical, photochemical, solvated electrons, redox reagents), *i.e.*, reactions occurring by an $S_{RN}1$ mechanism[1], have been shown to occur with a large variety of nucleophiles and leaving groups[2]. Recently we have shown that pyrimidine anions could be good nucleophiles in the context of an $S_{RN}1$ mechanism with perfluoroalkyl iodides as substrates[3]. Introduction of alkyl[4a], alkenes, alkynes[4b,c,d], perfluoroalkyl[4e,f] and aryl[4g] substituents into pyrimidines, appears to be a valuable goal in view of the applications of the resulting species as potential antiviral agents. Pyrimidines modified at the 5-position have been previously prepared by a number of routes. Most methods for the preparation of 5-substituted pyrimidines are based on palladium-catalyzed C-C bond formation at the 5-position of uracil or of pyrimidine derivatives[5]. Photochemically induced coupling of the 5-iodo pyrimidines or of the nucleoside derivative has been also described[6]. However many of these routes are specific to the particular type of group which has to be transferred to the 5-position of the pyrimidine ring. In addition, most of these procedures require the preparation of specific reagents such as 5-hydroxyuracil triflates[5a], arylboronic acids[5b], aryltrimethylstannanes[5c] and 5-halogenomercuriuracil[4a,c] in the presence of a palladium catalyst. New and mild methods for the synthesis of 5-substituted pyrimidines and especially 5-aryl or heteroaryl pyrimidines would therefore be worth designing. We describe, in the following, as new examples of electrochemically induced $S_{RN}1$ processes involving aryl halides, the reaction of 4-bromobenzophenone, 4-chlorobenzonitrile, 1-iodo-4-nitro benzene and 1-iodo-2-trifluoromethyl benzene with the uracil anion:



The occurence of the reaction may be attested by cyclic voltammetry: since in the electrocatalytic process no electrons are consumed, the height of the cyclic voltammetric peak of the substrate should decrease upon the addition of the nucleophile[2a,d]. This is indeed what was observed in the case of 4-bromobenzophenone and the uracil anion (figure 1b). However, such a decrease could be only observed with large excesses of nucleophile,

demonstrating that the reaction between the nucleophile and the aryl radical is slow. Some hydrogenolysis product (benzophenone) also appears as demonstrated by the appearance of a wave at - 2.0 V vs SCE. Upon repetitive potential scanning the first wave of the substrate decreases to zero (figure 1c) and a new reversible wave, located at - 1.90V vs SCE (peak potential at 0.2V/s) appears that corresponds to the reduction of the anion of the substituted product as checked with an authentic sample (figure 1d).

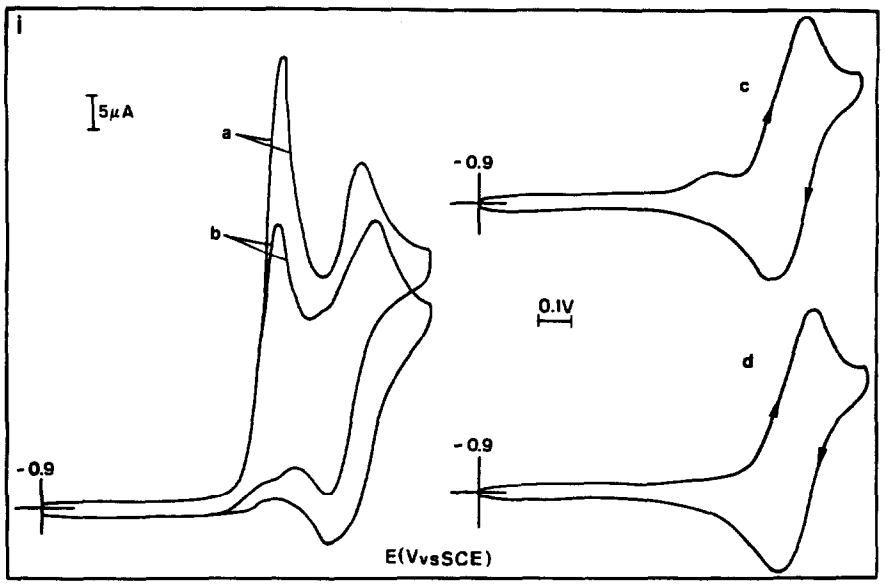


Figure 1. Cyclic voltammetry of 4-bromobenzophenone in DMSO + 0.1M NEt_4BF_4 at 25°C and reaction products (a): 4-bromobenzophenone (2.56 mM) alone (b): after the addition of 100.1 mM of the uracil anion (c): steady-state voltammogram after 10 cycles (d): cyclic voltammetry of the 5-(benzophenone)-uracil (2.56 mM) in DMSO + 0.1M NEt_4BF_4 + 4.0 mM of NMe_4OH at 25°C.

Except for the trifluoromethyl derivative, all the substituted products gave a single reversible wave in basic dimethylsulfoxide at potentials more negative than the first reduction wave of the substrate. This wave corresponds to the reduction of the substituted anion into a stable radical dianion.

Preparative-scale electrolyses (as reported in the table below) lead to the substituted products[7]. The consumption of electrons is always lower than the 2F/mole required for the reduction of the aromatic halide. Besides some unreacted starting material some hydrogenolysis product resulting from hydrogen atom transfer to the aryl radical or through further reduction and protonation is obtained[2]. These side reactions are responsible for the observed consumption of electricity. The rather low yield obtained in the reaction of the 1-iodo-2-trifluoromethyl benzene with the uracil anion. This may be related to the unstability of the trifluoromethyl group in basic dimethylsulfoxide as already observed for the reactions with enolates as nucleophiles[8]. The yields are roughly of the same order as those obtained in the case of the reaction of the uracil anion with perfluoroalkyl iodides. We note, that the substitution always take place at the carbon C-5 leading to C-arylated uracils; similar

behaviour was observed with perfluoroalkyl iodides[3], with the substitution of aryl halides with pyrrole anions[9a] and with phenolates[9a].

Preparative-Scale Electrolyses[a]

Substrate	Uracil anion[b]	Substituted product	Yield[c](%)	F/mole[d]
4-bromo benzophenone C=3.87x10^{-2}M E=-1.70Vvs SCE	C= 0.25M	5-(benzophenone)-uracil Ep= -1.90Vvs SCE[e]	55	1.0
4-chloro benzonitrile C=7.27x10^{-2}M E=-2.2Vvs SCE	C= 0.25M	5-(p-cyanophenyl)-uracil Ep= -2.35V vs SCE[e]	50	1.0
1-iodo-4-nitro benzene C=4.0x10^{-2}M E=-1.0Vvs SCE	C= 0.25M	5-(p-nitrophenyl)-uracil Ep= -1.45V vs SCE[e,f]	55	0.8
1-iodo-2-trifluoromethyl benzene[g] C=3.67x10^{-2}M E=-1.75Vvs SCE	C= 0.25M	5-(o-trifluoromethyl)-uracil Ep= -2.25V vs SCE[h]	30	1.2

(a): In DMSO + 0.1M NEt_4BF_4 (b): Tetramethylammonium salt (c): Isolated yield (d): Faradays per mole of starting ArX (e): Peak potential at 0.2V/s, C= 1 mM + 1.5 mM of NMe_4OH. $5H_2O$, in DMSO + 0.1M NEt_4BF_4, glassy carbon electrode (f): This compound also give a second reduction wave at a potential close to - 2.0 V vs SCE (g): Phtalonitrile (1.20 x10^{-2}M) was used as mediator. (h): C= 1 mM, in neutral DMSO + 0.1M NEt_4BF_4.

These results provide another example of the possibility to induce electrochemically $S_{RN}1$ reactions involving aryl halides, leading to interesting pyrimidines. Despite of moderate yields, this mild and quick method, offers the advantage of preparing in one step, useful synthons for the synthesis of nucleosides. Pyrimidines nucleosides substituted at the 5-position represent an important class of biologically active compounds and some of the 5-aryl derivatives have been shown to possess potential antiviral activity against the Human Immunodefenciency Virus (HIV)[4g]. We are now extending the reaction to other aryl and heteroaryl halides and to different types of pyrimidines including purines anions as nucleophiles.

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7. A typical procedure for the electrolysis of 4-bromobenzophenone in the presence of the uracil anion is as follows: a 125-mL glassy-carbon (Carbon-Lorraine V25) crucible was used as the cathode with a platinum electrode as the anode separated from the catholyte with a glass fritt of porosity 4. Into 100 mL of DMSO containing 4.6g (25 mmol) of the tetramethylammonium salt of uracil, were added 2.17g (10 mmol) of NEt_4BF_4 and then 1.0g (3. 87 mmol) of 4-bromobenzophenone. The potential was set at the first reduction wave of the substrate. When 90% of the substrate has reacted (as checked by cyclic voltammetry), the solution was cooled and neutralized with 100 ml of HCl 2N; the resulting precipitate was filtered, carefully washed with water (4x50 mL) and triturated with hot Et_2O to yield 0.56g (1.92 mmol, 55%) of the chromatographically pure compound (TLC). ***5-(benzophenone)-uracil***: Yellowish powder, m.p>260°C; TLC ($CHCl_3$-MeOH, 75-25): R_F= 0.50; ^1H NMR (DMSO-d_6): δ_H= 7.6-7.8 (H-aromatic, 10H, multiplet), 7. 96 (H-6, 1H, doublet), 11.4 (NH-1, 1H, singulet); Mass (CI/NH_3): m/e= 293 ($M+H^+$), 310 ($M+NH_4^+$); UV (MeOH) λ_{max} 258 and 300nm; Analysis: Calcd. C 69.86, H 4.11, N 9.59. Found. C 67. 10, H 4.16, N 9.69.

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