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In-cell Indirect Electrochemical Halogenation of Pyrimidine Bases and their Nucleosides to 5-Haloderivatives

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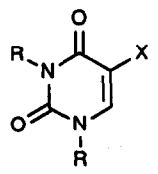
Abstract: Reaction of anodically generated "halonium" species (LiX or Bu_4NX, $LiClO_4$, MeCN, Pt/Pt; I_2, $LiClO_4$, MeCN) with pyrimidine bases and their nucleosides leads to 5-halo compounds in good yields.

In connection with our own interest in the synthetic application of anodically-generated electrophilic species, we recently examined the electrochemical preparation of haloderivatives of some pharmacologically relevant molecules, *e.g.*, ergolines and tryptophan-related compounds.[1]

Although many reports concerning halogenation of nucleic acid bases and their ribonucleosides have been published, we desired to utilize a procedure for the large scale preparation of halogenated analogs, which would avoid the use of large amounts of harmful and/or expensive reagents.[2] The 5-halopyrimidine nucleosides have been shown to exhibit remarkable chemotherapeutic, biochemical, and biophysical properties. In particular, a number of 5-substituted uracil derivatives, especially 2'-deoxyuridines, have been investigated extensively for the experimental and clinical treatment of neoplastic diseases. The selective modification of uracil nucleus (starting from the 5-halo compounds) has been a challenge in the quest for the development of new medicinal agents for the treatment of viral infections such as herpes and AIDS.[3] Furthermore, several natural and synthetic cytosine nucleoside analogues have potent antiviral activity and among them 1-(2-fluoro-2-deoxy-β-D-arabino furanosyl)-5-iodo cytosine deserves special mention.[4]

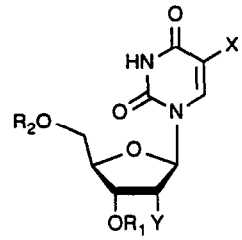
We report in this Letter that regioselective halogenation (chlorination, bromination and iodination) of various pyrimidine bases and nucleosides can be carried out anodically at a Pt electrode in MeCN at r.t, under a constant electrode potential (1.40 V, 1.20V and 1.90V *vs.* SCE, respectively) in the presence of lithium or tetra-*n*-butylammonium halide as electroactive electrolyte and $LiClO_4$ as supporting electrolyte (method A). Alternatively, anodic oxidation of I_2 in MeCN/$LiClO_4$ at 1.90V [*vs.* $Ag/Ag^+(0.1M)$][5], followed by addition of pyrimidine derivative to the anolyte

yielded the corresponding 5-iodo compounds in higher yields (method B)[1b]. The current-potential curves of pyrimidine bases in the presence of halide ions suggest that the anodic halogenation is initiated by one-electron transfer from X^- and the subsequent attack to "X^+" (indirect mechanism)[6] takes place by C(5) of pyrimidine, *i.e.*, the site with the highest single coefficient in the HOMO.[7]



1 R,X:H

2 R:H,X:Me



3 R_1, R_2:H; Y:OH

4 R_1, R_2:H; Y:H

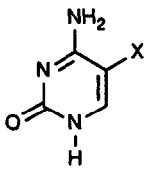
5 R_1, R_2:Ac; Y:OAc

6 R_1, R_2:Ac; Y:H

7 R_1, Y:$OCMe_2$; R_2:H

8 R_1, R_2:TBDMS; Y:OTBDMS

a X: Cl, **b** X: Br, **c** X: I



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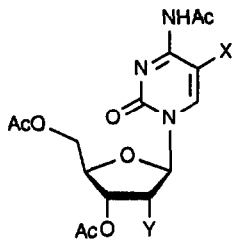

10 Y:OAc

11 Y:H

To assess the scope of the reaction, a variety of structurally different compounds (1-11) was examined. In most cases, the corresponding 5-halo derivatives were the only detected compounds (TLC) and the isolated yields ranged from 63% for **10c** (method A) to 93% for **5c**.[8] As a limitation of the procedure, the selective halogenation of uridine **3** in MeCN was hampered by its poor solubility, whereas, any attempts to carry out it in MeOH or AcOH failed to give a complex mixture of products. Acid-sensitive compounds such as ketal **7** or silyl ether **8** were not stable under electrochemical conditions, however, undesired side-reactions could be suppressed by adding solid $NaHCO_3$ in order to keep the solution neutral.

Chlorination and bromination . A general procedure of bromination is exemplified by the preparation of 5-bromo-2',3'-*O*-isopropylideneuridine **7b**. In the anode chamber of a three-compartment cell, equipped with Pt sheets (4x4 cm) as electrodes and SCE reference, a suspension of powdered $NaHCO_3$ (500 mg) in 0.5 M $LiClO_4$in MeCN (150 mL) containing **7** (850 mg, 3.0 mmol) and LiBr (540 mg, 6.3 mmol) was introduced. In the cathode compartment was placed a 0.5 M $LiClO_4$ in MeCN (150 mL). The anolyte was blanketed with nitrogen, magnetically stirred at r.t. and electrolyzed at + 1.2V(SCE).

The maintenance of substantial current (0.15–0.30 A) was obtained by potentiostatic pulse technique using a potentiostat and applying a square wave generator to the working electrode so that every 20 s the electrode spent 1 s to 0.0 V. When 2.2 F/mol had passed,TLC (CH_2Cl_2–MeOH, 25:1) indicated complete reaction and the formation of a faster moving component. The electrolysis was halted and the anolyte was filtered and evaporated to dryness. The syrupy residue was taken up in H_2O (150 mL) and extracted with $CHCl_3$ (3x100 mL). Silica gel filtration of the evaporated organic dried layer yielded 5-bromo-2',3'-*O*-isopropylideneuridine **7b**[8] (965 mg,89%), Rf 0.19; ^1H NMR (DMSO-d_6, 300 MHz) 1.28 (3 H, s, Me_{exo}), 1.48 (3 H, s, Me_{endo}), 3.60 (2 H, m, $H_{5'}$), 4.11 (1 H, m, $H_{4'}$), 4.77 (1 H, dd, J=6.8,3.5; $H_{3'}$), 4.91 (1 H, dd, J=6.8,2.5; $H_{2'}$), 5.21 (1 H, t J=5.2; OH), 5.83 (1 H, d, J=2.5; $H_{1'}$), 8.34 (1 H, s, H_6), 9.5 (1 H, br s, NH); ^{13}C NMR (DMSO-d_6) 26.1 (Me), 27.9 (Me), 62.0 (C-5'), 81.1 (C-3'), 84.6 (C-2'), 87.8 (C-4'), 92.3 (C-1'), 96.7 (C-5), 113.78 (s, O-C-O), 142.2 (C-6), 152.1 (C-2), 161.0 (C-4).

Iodination (method A). In iodination it was especially advantageous to introduce in the electrolysis cell an ion-exchange membrane as diaphragm to avoid electrical migration out of the working electrode compartment of the electrogenerated species and its subsequent reduction. Thus, iodination (method A) of 1,3-dimethyluracil 2 was carried out in a divided cell (H-cell): the anolyte was made up of 2 (300 mg, 2.41 mmol), tetra-*n*-butylammonium iodide (1.860 g, 5.06 mmol) in 0.5 M $LiClO_4$ in MeCN (125 mL). The catholyte (125 mL) was an acetonitrile solution of $LiClO_4$(0.5 M). The electrolysis was carried out at 1.90 V *vs* SCE until 2.2 F per mol of 2 had passed through the electrolyte. Work-up as described above, and purification by flash chromatography (hexane–EtOAc 2:1) gave 2c (490 mg, 81% yield), R_f 0.27; ^1H NMR (DMSO-d_6) 3.22 & 3.31 (2 x Me, s), 8.25 (1 H, s, H_6); ^{13}C NMR (DMSO-d_6) 28.7 (Me), 36.4 (Me), 66.2 (C-5), 148.9 (C-6), 151.1 (C-2), 160.2 (C-4).

Iodination (method B). Iodination according to the method B was carried out as follows: in the anode chamber of a three-compartment cell with Pt electrodes and Ag/Ag^+ (0.1 M) reference, was introduced iodine (300 mg, 1.18 mmol) in 0.5 M $LiClO_4$ in MeCN (125 mL). In the cathode compartment was introduced a 0.5 M $LiClO_4$. The solution is magnetically stirred at room temperature and electrolysed at 1.90 V *vs*. Ag/Ag^+. After transfer of 2.1 F per mol of iodine a slightly cloudy pale-yellow solution was obtained. 3',5'-di-*O*-acetyl-2'-deoxyuridine 6 (625 mg, 2.0 mmol) was added to the stirred anolyte solution. The solution colour remained yellow and after 45 min at room temperature, the solvent was evaporated to dryness. Work-up as described above, and filtration on silica column ($CHCl_3$–MeOH 19:1) afforded 6c (790 mg, 90% yield), R_f 0.35;^1H NMR (DMSO-d_6) 2.06 & 2.11 (2 x Me, s), 4.17–4.19 (1 H, m, $H_{3'}$), 6.11 (1 H, t, J=7.0, $H_{1'}$), 8.04 (H_6), 11.75 (NH); ^{13}C NMR (DMSO-d_6) 19.3 ($OCO\underline{C}H_3$), 19.4 ($OCO\underline{C}H_3$), 35.5 (C-2'), 62.2 (C-5'), 68.2 (C-5), 72.6 (C-3'), 80.6 (C-4'), 83.7 (C-1'), 142.6 (C-6), 148.6 (C-2), 158.8 (C-4), 168.3 ($O\underline{C}OCH_3$)

It is clear from the above results that the electrochemical method is mild, efficient, and almost general. Both diverse silyl and ester protecting groups are retained

and undesirable side reactions completely suppressed. In conclusion, this method provides an attractive alternative approach to strategically important 5-halopyrimidines and derivatives thereof.

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6) For example, the cyclic voltammetry of Br^- in MeCN showed to major waves at +0.7 V and +1.0 V *vs.* SCE while all pyrimidine bases used in the present study showed no oxidation peak below 2.1 V (SCE). On the other hand in LiX-MeCN and Bu_4NI-MeCN system current-potential curves are not affected by the addition of the substrate. See also, Konno, A.; Fukui, K.; Fuchigami, T.; Nonaka, T. *Tetrahedron* **1991**,*47*,887; Shono, T.; Matsumura, Y.; Inoue, K. *J.Org.Chem.* **1985**,*50*,3160; Okamoto, M.; Chiba, T. *J.Org.Chem.* **1988**,*21*,780.

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8) By electrochemical halogenation of compounds 1-11 the following compounds were isolated: **1a** (77% yield), **1b** (81), **1c** (80,84[a]), **2a** (85), **2b** (93), **2c** (81,87[a]), **4a** (71), **4b** (77), **4c** (70,75[a]), **5a** (88), **5b** (91), **5c** (88,93[a]), **6a** (95), **6b** (81), **6c** (87,90[a]), **7a** (68), **7b** (89), **7c** (73,72[a]), **8a** (65), **8b** (83), **8c** (77,86[a]), **9b** (73), **10c** (63,72[a]), **11c** (83,91[a]), [a]Method B.

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