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Azide- or Fluorine-Containing 2' & 3'-Azolyluridines by Regioselective Opening of 1-(2',3'-Anhydro-ß-D-lyxofuranosyl)uracils

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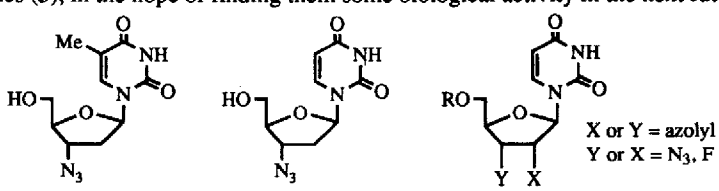
Abstract: *Azide- or fluorine-containing imidazol-1-yl, pyrazol-1-yl, and 1,2,4-triazol-1-yl 2',3'-dideoxyuridines have been synthesised from uridine in 5-6 steps, via «2',3'-β-epoxy» derivatives. Regioselective oxirane-ring openings have been accomplished by appropriate choice of the reaction conditions.*

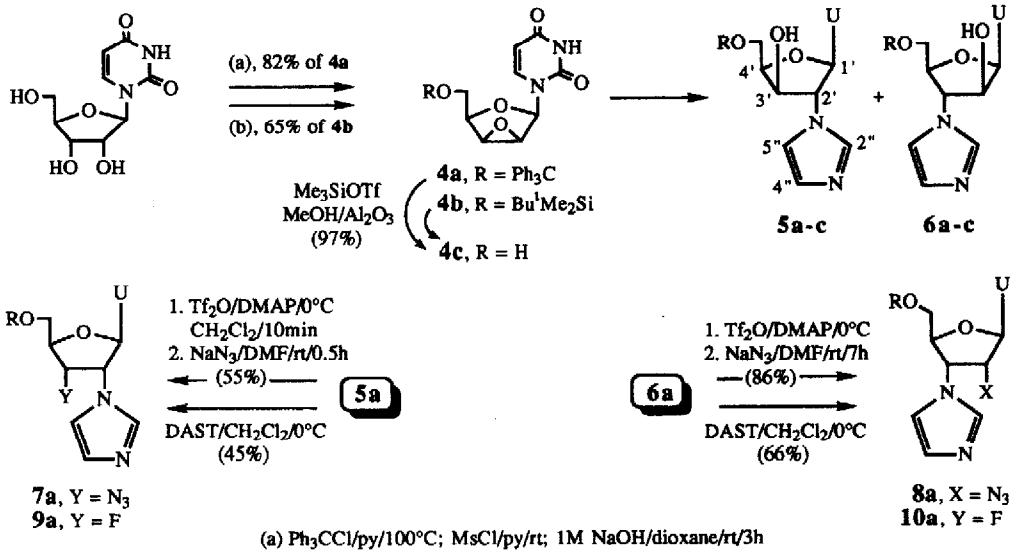
The fight against human immunodeficiency viruses (HIV), mainly based so far on the oral administration to AIDS patients of large doses of 3'-azido-3'-deoxythymidine (AZT, **1**), is demanding more active and less toxic drugs;[1] recent clinical studies have shown that other deoxynucleosides such as 3'-azido-2',3'-dideoxyuridine (AZDU, **2**) and 2',3'-dideoxyinosine (DDI) may replace AZT in the next future.[2,3] In this connection, we reasoned that azolyl substituents could be appropriate bioisosters of a freely rotating non-linear[4] azide group. Several groups[5] chose the [3+2]-cycloaddition between the azide group of AZT and triple bonds to prepare 3'-(1,2,3-triazol-1-yl) derivatives. Very recently, when the present work was in course,[5d] other interesting routes to azolyl derivatives of 3'-deoxythymidine were described. Unfortunately, all these compounds showed no inhibitory activity against HIV-1 and other viruses.[5,6] We report here the syntheses of a parallel series, the hitherto unknown azide- or fluorine-containing imidazol-1-yl-, pyrazol-1-yl-, and 1,2,4-triazol-1-yl-2',3'-dideoxyuridines (**3**), in the hope of finding them some biological activity in the next future.



1 **2** **3**

Readily prepared 1-(2',3'-anhydro-ß-D-lyxofuranosyl)uracils (epoxides **4a** and **4b**)[7] were treated with an excess of either imidazole or imidazolate under a variety of conditions, including a fusion reaction. To our surprise, since it is known that nucleophiles like Br^-, I^-, N_3^-, and SCN^- cleave the 2',3'-ß-epoxy rings by attack at C-3',[8] mixtures of 2'-imidazol-1-yl (*xylo*, **5a-b**) and 3'-imidazol-1-yl (*arabino*, **6a-b**) derivatives in similar amounts were obtained; their separation by flash chromatography (FC) or preparative TLC appeared to be really difficult. Nevertheless, acetylation (Ac_2O/py/rt, 90-95%) of the mixtures **5a+6a** and **5b+6b** allowed us to distinguish readily which is which (acetylation causes the expected downfield shift of ca. 1 ppm for the adjacent methine proton) and to separate both pairs by FC. After deacetylation (NH_3/MeOH/rt/3h, 95-97%), **5a** and **6a**[9] were submitted to standard azido-dehydroxylation and fluoro-dehydroxylation procedures to afford **7a**, **8a**, **9a**, and **10a**.[10] Deprotection by standard methods or with Me_3SiOTf[11] gave the desired **7c-10c**.

Controlling at will the regioselectivity of the attack of azoles and/or azolate anions on epoxides **4** *seemed us essential for the future utility of this synthetic approach.* On the basis that the electron-withdrawing



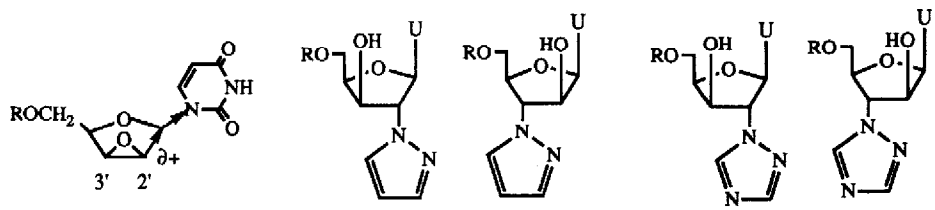
(a) Ph_3CCl/py/100°C; MsCl/py/rt; 1M NaOH/dioxane/rt/3h

(b) Bu^tMe_2SiCl/py/rt; MsCl/py/rt; K^+phthalimide$^-$/DMF/H_2O/rt; 1M NaOH/EtOH/rt/15min

character of the uracil moiety may be higher than that of most $ROCH_2$ groups (see **11**),[12] we thought that those conditions favouring S_N2-like transition states could give rise to a preferent attack at C-2' whereas those favouring S_N1-like ones could afford mainly the C-3'-substituted product, as known,[8] provided that steric hinderance on both sides was similar. We also speculated about the conformational equilibrium around the N-C1' bond, governed probably by the solvent polarity, and its possible relevance.[13]

In practice, we have investigated the effect of medium polarity, temperature, substituent R, counterion nature (Li^+, Na^+, K^+, and Bu_4N^+), presence of either $LiClO_4$ or Ti^{IV}, use of 1-(trimethylsilyl)azoles and TiX_4, as well as timing of the reagent addition, on the regioselectivity of the reaction of **4** with imidazole, pyrazole, and 1,2,4-triazole. After ca. sixty experiments, we have found optimum conditions to obtain one or another regioisomer as the major product, which was isolated now much more readily from the reaction mixture. In this way, besides the imidazolyl derivatives already mentioned, pyrazolyl derivatives **12** and **13** and 1,2,4-triazol-1-yl derivatives **14** and **15**[14] have been obtained in a pure condition.

In the following Table we have summarised the better results as far as 2'-azolyl vs. 3'-azolyl ratios are concerned. It is seen that the ***attack at C-3' is favoured: (i) in DMSO but also to some extent in DMF;***[15] ***(ii) when the substrate is the unsubstituted compound (4c); and (iii) when azoles, rather than azolate anions, are used.*** Regarding this last statement we should point out that, since the pyrazole and triazole molecules appeared to be unable to cleave the epoxide ring only by heating, the reactions were performed in the presence of Lewis acids: the most significant effect was observed in the pyrazole case, with $Ti(OPr^i)_4$.[16]



11 **12a-c** **13a-c** **14a-c** **15a-c**

Table. Selected Conditions for the Reaction of Epoxydes **4a-c** with Azoles and with Azolate Anions[a]

	reagents (no. equiv.)	reaction conditions	yield[b] 2'	yield[b] 3'	regioselectivity (2' to 3')[c]
4a[d]	imidazole (3), NaH (2)	DMSO, 100 °C, 30 min	20%	64%	1 : 3
4a	imidazole (3), NaH (2)	DMF, 110 °C, 30 min	25%	55%	1 : 2
4c	imidazole (3), NaH (3)	DMF, 130 °C, 30 min	15%	62%	1 : 4
4c	imidazole (3)	DMF, 120 °C, 24 h	10%	73%	1 : 7
4a	imidazole (3), KH (2)	toluene, 18-crown-6 (0.2), 100 °C, 2.5 h	50%	24%	2 : 1
4a	imidazole (1.5), KH (1.2)	toluene, 18-crown-6 (0.2), 110 °C, 18 h	56%	21%	2.5 : 1
4a	pyrazole (3), NaH (2)	DMSO, rt, 44 h (or 100 °C, 30 min)	24%	60%	1 : 2.5
4c	pyrazole (10), $Ti(OPr^i)_4$ (2.5)	dioxane, 110 °C, 72 h	10%	62%	1 : 6
4a	pyrazole (3), KH (2)	*o*-$C_6H_4Cl_2$, 18-crown-6 (0.2), 100°C, 2h	70%	12%	7 : 1
4a	pyrazole (3), NaH (2)	pyridine, 100 °C, 2 h	75%	5%	13 : 1
4a	1,2,4-triazole (3), NaH (2)	DMSO, 100 °C, 3 h	20%	65%[e]	1 : 3
4c	1,2,4-triazole(10), $Ti(OPr^i)_4$(2.5)	dioxane, 110 °C, 72 h	*f*	*f*	1 : 3
4a	1,2,4-triazole (3), NaH (2)	pyridine, 100 °C, 4 h	65%	12%	5 : 1

[a] General procedure.- To a stirred solution or suspension of the azole (0.6 mmol) and base (0.4 mmol) in the solvent indicated (4 ml), 0.2 mmol of solid **4a-c** was added. The flask was inmmersed in a silicone bath preheated at the temp. pointed out, and the reaction was monitored by TLC or HPLC. Evaporation of the solvent in vacuo after neutralisation afforded the crude mixtures, which were separated by FC (CH_2Cl_2-MeOH). [b] Isolated yields (not optimised) of the products of attack at 2' (**5**, **12**, and **14**, respectively) and 3' (**6**, **13**, and **15**, respectively); according to TLC and HPLC the conversions are quantitative in most cases. [c] **5**:**6** ratio (imidazole), **12**:**13** ratio (pyrazole), and **14**:**15** ratio (triazole), as determined by HPLC and/or ^1H NMR of the crude mixtures. [d] **4b** gave percentages of regioisomers similar to **4a** in trial experiments. [e] Only traces of 1,2,4-triazol-4-yl derivatives have been detected (more polar spots on TLC and triazole protons at δ 8.54). [f] Not isolated.

On the other hand, the ***attack at C-2' is relatively favoured: (i) in the pyrazole case*** (its anion appears to behave as a stronger nucleophile than the imidazolate ion, in spite of their similar basicity, which is likely due to an α-effect); ***(ii) in apolar or slightly polar solvents like toluene, o-dichlorobenzene or pyridine***[15b] (in the first two cases, a crown ether is necessary to solubilise the potassium azolates).[17]

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9. **5a**: mp 210-211 °C (EtOH); ^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.47 (dd, *J*=11 Hz, *J*=3 Hz, H-5'a), 3.74 (dd, *J*=11 Hz, *J*=6 Hz, H-5'b), 4.37 (br s, H-3'), 4.50 (m, H-4'), 4.79 (br s, H-2'), 5.48 (d, *J*=8 Hz, H-5), 6,13 (d, *J*=2 Hz, H-1'), 6.98 & 7.06 (H-4"&H-5"), 7.2-7.6 (m, Ph_3C), 7.64 (s, H-2"), 7.64 (d, *J*=8 Hz, H-6); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 62.2 (C-5'), 68.8 (C-2'), 74.1 (C-3'), 83.4 (C-4'), 87.2 ($Ph_3\underline{C}$), 89.5 (C-1'), 101.4 (C-5), 117.3 (C-5"), 127.1, 127.8 & 128.5 (*p,o,m*), 128. (C-4"), 136.2 (C-2"), 140.1 (C-6), 143.2 (C_{ipso}), 150.5 (C-2), 164.1 (C-4).
6a: mp 150-152 °C (CH_2Cl_2-EtOH); ^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.16 (dd, *J*=10 Hz, *J*=2 Hz, H-5'a), 3.62 (dd, *J*=10 Hz, *J*=2 Hz, H-5'b), 4.17 (m, H-4'), 4.80 (m, H-2'&H-3'), 5.49 (d, *J*=8 Hz, H-5), 6.33 (d, *J*=5 Hz, H-1'), 6.96 (br s, H-4' &H-5"), 7.2-7.4 (m, Ph_3C), 7.63 (s, H-2"), 8.02 (d, *J*=8 Hz, H-6); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 60.5 (C-3' or C-5'), 61.7 (C-5' or C-3'), 74.9 (C-2'), 78.9 (C-4'), 83.9 (C-1'), 87.3 (Ph_3C), 101.5 (C-5), 117.5 (C-5"), 127.4, 128.0 & 128.4 (*p,o,m*), 129.0 (C-4"), 136.3 (C-2"), 141.7 (C-6), 142.9 (C_{ipso}), 151.1 (C-2), 164.3 (C-4).
10. Summary of relevant spectral data (in $CDCl_3$, *J* values in Hz): **7a**; ^{1}H NMR δ 4.30 (dd, *J*=6.0, 4.8, H-3'), 5.11 (t, *J*=6.2, H-2'), 6.42 (d, *J*=6.3, H-1'), 5.44 (d, *J*=8.1, H-5), 7.69 (d, *J*=8.1, H-6), 7.09 & 7.16 (H-5"&H-4"), 7.72 (H-2"); ^{13}C NMR δ 62.1 & 62.2 (C-2'&C-3'), 85.9 (C-1'), 103.4 (C-5), 138.7 (C-6), 118.6 (C-5"), 130.1 (C-4"), 137.3 (C-2"). **8a**; ^{1}H NMR δ 4.57 (br d, J=5.5, H-2'), 5.14 (dd, *J*=10.3, 5.5, H-3'), 5.91 (br s, H-1'), 5.45 (d, *J*=8.1, H-5), 7.97 (d, *J*=8.1, H-6), 7.04 & 7.13 (H-5"&H-4"), 7.69 (H-2"); ^{13}C NMR δ 55.5 (C-2'), 67.0 (C-3'), 89.6 (C-1'), 102.4 (C-5), 139.3 (C-6), 118.7 (C-5"), 129.5 (C-4"), 137.2 (C-2"). **9a**; ^{1}H NMR δ 4.95-5.28 (m, H-2'&H-3'), 6.67 (d, *J*=9.2, H-1'), 5.43 (d, *J*=8.2, H-5), 7.54 (d, *J*=8.2, H-6), 7.12 (H-4"&H-5"), 7.66 (H-2"); ^{13}C NMR δ 61.1 (J_{CF}=16.6, C-2'), 92.3 (J_{CF}=188.0, C-3'), 84.2 (C-1'), 104.0 (C-5), 138.4 (C-6), 119.3 (C-5"), 130.0 (C-4"), 137.4 (C-2"). **10a**; ^{1}H NMR δ 5.2-5.5 (m, H-2'&H-3'), 5.94 (d, J_{HF}=19.7, H-1'), 5.50 (d, *J*=8.1, H-5), 7.84 (d, *J*=8.1, H-6), 6.97 & 7.08 (H-5"&H-4"), 7.65 (H-2"); ^{13}C NMR δ 55.9 (J_{CF}=16.9, C-3'), 90.5 (d, J_{CF}=36.1, C-1'), 93.5 (d, J_{CF}=188.4, C-2'), 102.8 (C-5), 140.7 (C-6), 119.3 (C-5"), 129.3 (C-4"), 137.4 (C-2").
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12. Control of the medium basicity could be important as well, in order to avoid deprotonation of the uracil NH (pKa in water = 9.5; cf. ref. 3b) which might modify the relative electron-withdrawing character of the uracil moiety; however, *N*-methyluridine and imidazolate gave, either in polar or apolar solvents, ca. 1:1 mixtures of regioisomers.
13. If, in hydrophobic solvents, the 2-CO group "looked" at inside, the attack at C-2' could be relatively favoured (on the basis of electronic considerations concerning the transition state).
14. Sodium and lithium tetrazolate also reacted with **4**, to afford mixtures of four compds, the 3'-substituted products always predominating over the 2'-substituted ones. For example, in DMF at 110 °C for 6 h, **4a** and sodium tetrazolate gave 9% of 2'-(1"-tetrazolyl), 11% of 2'-(2"-tetrazolyl), 23% of 3'-(1"-tetrazolyl), and 44% of 3'-(2"-tetrazolyl) derivatives.
15. (a) Other solvents studied, apart from those appearing in the Table, were CH_3CN, HMPA, DMSO-H_2O, and EtOH. Other bases employed were BuLi and $Bu_4N^+OH^-$. The effects of the concentration, slow addition, and temperature were not significant, in general. Substituents at C-5' like PhCO and Bu^tCO did not survive under the reaction conditions. (b) Other solvents such as benzene and CCl_4 gave similar results to those obtained in toluene.
16. In the imidazole case, with $Ti(OPr^i)_4$, the epoxide opening did not occur; coordination of imidazole with Ti^{IV} turned out to be too strong. Use of $TiCl_4$ or $TiCl_4/Ti(OPr^i)_4$ mixtures as Lewis acids gives chloro rather than azolyl derivatives.
17. Samples of the compounds reported here are offered to public labs interested in the screening of their antiviral activity.

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