Simple Method for the Synthesis of 5-Substituted 2′,5′-Anhydro-2′,5′-dideoxy-1-β-D-arabinofuranosyluracils

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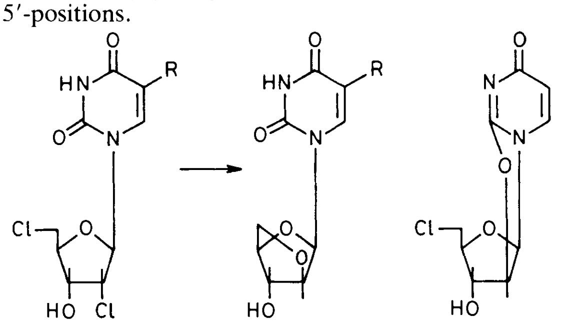
Reaction of 5-substituted 2′,5′-dichloro-2′,5′-dideoxyuridines (**1**) with methanolic sodium hydroxide under reflux afforded the corresponding 5-substituted 2′,5′-anhydro-2′,5′-dideoxy-1-β-D-arabinofuranosyluracils (**2**) in high yields.

The direct synthesis of 5-substituted 2′,5′-dihalogeno-2′,5′-dideoxyuridines from uridine derivatives by use of the Vilsmeier reagent has recently been reported.[1] These 2′,5′-dihalogeno-nucleosides are versatile intermediates for the preparation of biologically interesting 2′ and/or 5′-deoxyuridines.[2] 2′,5′-Anhydropyrimidine nucleosides have been synthesized by several procedures from, *e.g.*, 5′-halogeno (or methylsulphonyl)-5′-deoxy-1-β-D-arabinofuranosyluracil (or cytosine) or from 2,2′-anhydro-5′-chloro-5′-deoxy-1-β-D-arabinofuranosyluracil (**3**), but most of these syntheses involve tedious steps.[3,4] During our investigation on the reactivities of 2′,5′-dihalogenouridines, we have found a practical and convenient method for the synthesis of 5-substituted 2′,5′-anhydro-2′,5′-dideoxy-1-β-D-arabinofuranosyluracils (**2**) in high yields.

Treatment of 2′,5′-dichloro-2′,5′-dideoxyuridine (**1a**) with methanolic sodium hydroxide (5 equiv.) under reflux for 3 h afforded 2′,5′-anhydro-2′,5′-dideoxy-1-β-D-arabinofuranosyluracil (**2a**) in 85% yield as the sole product. The 2′,5′-anhydrouridine (**2a**) was identical in every respect with an authentic sample prepared by the reaction of the 2,2′-anhydrouridine (**3**) with aqueous sodium hydroxide.[4]

A plausible mechanism for the formation of the 2′,5′-anhydrouridine (**2a**) from the 2′,5′-dichlorouridine (**1a**) is as follows: (i) anhydro bond formation between the 2- and 2′-positions; (ii) cleavage of the 2,2′-anhydro bond by the attack of OH⁻; (iii) anhydro bond formation between the 2′- and 5′-positions.



(**1**) (**2**) (**3**)

	R	M.p.[a] (t/°C)	% Yield
		Compound (2)	
a;	H	277[b]	85
b;	F	298	83
c;	Br	270	85
d;	Me	277	93

[a] Decomp. [b] Lit.,[4] 249—256 °C.

Analogous treatment of the 5-substituted 2′,5′-dichloro-2′,5′-dideoxyuridines (**1b**), (**1c**), and (**1d**) with aqueous sodium hydroxide in methanol similarly gave compounds (**2b**), (**2c**), and (**2d**).†

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† All new compounds gave satisfactory elemental analyses and exhibited spectra completely in accord with their assigned structures.

References

1 K. Hirota, Y. Kitade, F. Iwami, S. Senda, and Y. Maki, *Synthesis*, 1983, 121.
2 H. Hřebabecký and J. Beránek, *Collect. Czech. Chem. Commun.*, 1978, **43**, 3268; *Nucleic Acids Res.*, 1978, **5**, 1029.
3 I. L. Doerr, J. F. Codington, and J. J. Fox, *J. Org. Chem.*, 1965, **30**, 467; K. Kikugawa and M. Ichino, *ibid.*, 1972, **37**, 284.
4 H. Hřebabecký, J. Brokeš, and J. Beránek, *Collect. Czech. Chem. Commun.*, 1982, **47**, 2961.