Simple Synthesis of Trifluoromethylated Pyrimidine Nucleosides

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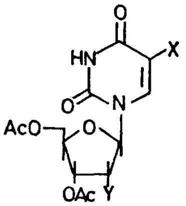
Summary Treatment of 2′,3′,5′-tri-O-acetyl-5-iodouridine and 3′,5′-di-O-acetyl-5-iododeoxyuridine with trifluoromethyl iodide and copper powder gave the corresponding 5-trifluoromethyluridine derivatives; this is the first example of direct trifluoromethylation of nucleosides.

PYRIMIDINE nucleosides containing a trifluoromethyl group at the 5-position are known to have significant biological activities,[1] and they have been synthesised by ring-closure[2] or fluorination[3] of uracil-5-carboxylic acid followed by 1-glycosidation. We now describe simple trifluoromethylation of pyrimidine nucleosides.

We have reported previously the trifluoromethylation[4] of aryl halides with trifluoromethyl iodide and copper powder. Application of this method to the 5-iodo-(**1**) and 5-iododeoxy-uridine (**2**) gave the corresponding trifluoromethyl derivatives (**3**) and (**4**). Thus, 2′,3′,5′-tri-*O*-acetyl-5-iodouridine (**1**) (1·0 g) was shaken with CF_3I (7·2 g) and copper powder (3 g) in hexamethylphosphoric triamide (20 ml) at 110 °C for 40 h in a stainless steel tube. Separation of the mixture using a silica gel column ($CHCl_3$–EtOH, 30: 1) and preparative t.l.c. (silica gel with $CHCl_3$–EtOH, 20: 1) gave the trifluoromethyluridine (**3**),† as an amorphous powder, one spot on t.l.c., 330 mg (37·5% yield); ν_{max}



(**1**) X = I, Y = OAc
(**2**) X = I, Y = H
(**3**) X = CF_3, Y = OAc
(**4**) X = CF_3, Y = H

(KBr) 1140 cm^{-1} (C-F); λ_{max} (MeOH) 258 nm (log ϵ 3·96) [258 (3·96) with acid, 260 (3·81) with alkali]; δ (^{1}H) ($CDCl_3$) 10·08 (1H, br s, NH), 8·09 (1H, s, 6-H), 6·08 (1H, d, 1′-H, *J* 5 Hz), 5·41 (2H, m, 2′- and 3′-H), 4·41 (3H, m, 4′- and 5′-H), and 2·12 (9H, s, OAc); ^{19}F-n.m.r. ($CDCl_3$; $PhCF_3$ internal standard) +0·8 (s) p.p.m.; *m/e* 378 (*M* − AcOH), 259 (sugar residue), 181 (base residue + 2H), and 69 (CF_3). Similar treatment of the 5-iododeoxyuridine (**2**) (1 g) gave the corresponding trifluoromethyl compound (**4**),† as an amorphous powder, one spot on t.l.c.; 468 mg (53·9% yield); spectral data analogous to those for (**3**).

This method shortens the route for the trifluoromethylation of pyrimidine nucleosides. Perfluoroalkylation (C_nF_{2n+1} $n \geqslant 4$) of unhalogenated pyrimidine nucleosides using perfluoroalkyl-copper was reported by Cech *et al.*[5] When this method was applied to trifluoromethylation by us, only a small amount of the trifluoromethyl compound was observed in t.l.c. They also reported that the attempted perfluoroalkylation of 5-iodouracil with perfluoroalkyl-copper gave only the reduced product, uracil. These facts show a marked difference between the reactivities of trifluoromethyl and long-chain perfluoroalkyl compounds.

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† Satisfactory elemental analyses were obtained.

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[5] D. Cech, R. Wohlfeil, and G. Atzold, *Nucleic Acids Res.*, 1975, **2**, 2183.