A Direct Synthesis of 5-Fluorocytosine and Its Nucleosides Using Trifluoromethyl Hypofluorite

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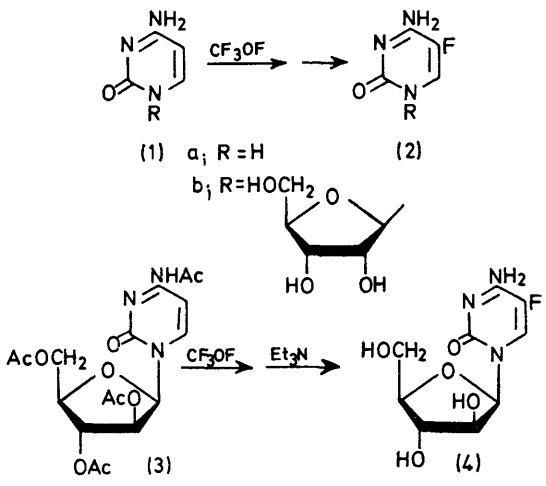
Summary Reaction of the cytosine ring system with trifluoromethyl hypofluorite followed by decomposition of the resulting adduct gives the first direct synthesis of 5-fluorocytosine and selected 5-fluorocytosine nucleosides in good yields.

PREVIOUS methods[1] for preparation of 5-fluorocytosines and their nucleosides depended on *de novo* construction of the 5-fluoropyrimidine ring beginning ultimately[1a,b] with the highly toxic ethyl fluoroacetate. The resulting 5-fluorouracil was then transformed *via* thiation–amination [1d,h,j,k] or chlorination–amination [1b,g,k] into the corresponding 5-fluorocytosine. In the case of nucleosides, a carbohydrate–base coupling [1c,e,f,i] was required before transformation to the 5-fluorocytosine nucleoside.

We have found a direct route[2] applicable to uracil bases and acylated nucleosides and now report the direct fluorination of cytosine (**1a**), cytidine (**1b**) and tetra-acetylarabin-

osylcytosine (**3**) by means of trifluoromethyl hypofluorite[3] as fluorinating agent.



To a vigorously stirred solution of cytosine (**1a**) in methanol at −78° was added a solution of trifluoromethyl hypofluorite in trichlorofluoromethane. After *ca.* 5 min the mixture was worked-up and the resulting solid was dissolved in methanol and treated with 10% triethylamine in 50% aqueous methanol. 5-Fluorocytosine[1b],† (**2a**) was obtained in 85% yield, m.p. 300—302° (decomp.).

Analogous treatment of cytidine (**1b**) and decomposition of the adduct with ethanolic hydrogen chloride gave 5-fluorocytidine[1d] (**2b**) (55%) isolated as the hydrochloride, m.p. 174—176° (decomp.).

A similar reaction between trifluoromethyl hypofluorite and 4-acetamido-1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-2-pyrimidinone[4] (**3**) in chloroform followed by decomposition by triethylamine of the adduct with concomitant deblocking gave 1-β-D-arabinofuranosyl-5-fluorocytosine[1h,i] (**4**) (83%), as the hydrochloride, m.p. 178—180°.

Thus a ready direct route to 5-fluorocytosine (**2a**) and 5-fluorocytidine (**2b**) as well as the currently interesting antineoplastic and antiviral agent 5-fluorocytosine arabinoside[1h,5] (**4**) is now available. The application of this procedure to other base and nucleoside systems is in progress.

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† Correct analyses were obtained for all new compounds.

[1] (*a*) C. Heidelberger, *Progr. Nucleic Acid Res. Mol. Biol.*, 1965, **4**, 4; (*b*) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, 1957, **79**, 4559; (*c*) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *ibid.*, 1959, **81**, 4112; (*d*) I. Wempen, R. Duschinsky, L. Kaplan, and J. J. Fox, *ibid.*, 1961, **83**, 4755; (*e*) M. Prystaš and F. Šorm, *Coll. Czech. Chem. Comm.*, 1964, **29**, 2956; (*f*) M. Prystaš and F. Šorm, *ibid.*, 1965, **30**, 1900; (*g*) G. J. Durr, *J. Medicin. Chem.*, 1965, **8**, 253; (*h*) J. J. Fox, N. Miller, and I. Wempen, *ibid.*, 1966, **9**, 101; (*i*) F. Keller, J. E. Bunker, and A. R. Tyrrill, *ibid.*, 1967, **10**, 979; (*j*) I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, *ibid.*, 1968, **11**, 144; (*k*) K. Undheim and M. Gacek, *Acta Chem. Scand.*, 1969, **23**, 294.

[2] M. J. Robins and S. R. Naik, *J. Amer. Chem. Soc.*, 1971, **93**, 5277.

[3] K. B. Kellogg and G. H. Cady, *J. Amer. Chem. Soc.*, 1948, **70**, 3986; J. A. C. Allison and G. H. Cady, *ibid.*, 1959, **81**, 1089; D. H. R. Barton, *Pure Appl. Chem.*, 1970, **21**, 285.

[4] A. P. Martinez, W. W. Lee, and L. Goodman, *J. Medicin. Chem.*, 1966, **9**, 268.

[5] H. N. Prince, E. Grunberg, M. Buck, and R. Cleeland, *Proc. Soc. Exp. Biol. Med.*, 1969, **130**, 1080.