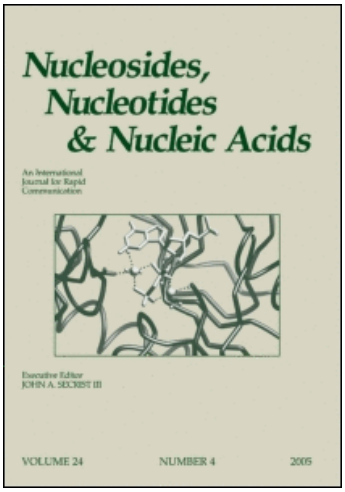

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Facile Synthesis of 5-Fluorocytidine

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FACILE SYNTHESIS OF 5-FLUOROCYTIDINE

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ABSTRACT

A facile synthesis of 5-fluorocytidine, an important intermediate of various biological interests, is described in 2 steps from commercially available 5-fluorocytosine and 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose.

5-Fluorocytidine (5-FCyd) is a biologically active compound which has fungistatic properties[1]. 5-FCyd is also found in RNA of cells[2] which are grown in the presence of 5-FU (5-fluorouracil), an important chemotherapeutic agent. The homopolynucleotide of 5-FCyd, poly(5-fluorocytidylic acid), forms a complex with poly(I). This polynucleotide duplex is a good interferon inducer[3]. In addition to the general utility of pyrimidine nucleoside analogs as antiviral and antitumor agents[4], we are interested in large scale synthesis of 5-fluorocytidine, in order to convert it to various phosphorylated forms for enzymatic studies.

5-FCyd is not commercially available. The procedure reported by Robins et al.[5] for its synthesis includes direct fluorination of cytidine with trifluoromethyl hypofluorite. This fluorinating agent is toxic and its large scale use can be hazardous. The isolation of 5-FCyd using this procedure in our laboratory has always required preparative column or plate chromatography. Saneyoshi et al.[6] reported the synthesis of various 5-fluoropyrimidine nucleosides by modification of the stannic chloride catalyzed glycosylation method first introduced by Niedballa and Vorbrüggen[7]. This modified procedure is a definite improvement over the use of toxic hypofluorite used to synthesize 5-FCyd[5]. However, this procedure[6] involves several steps both for synthesis and isolation of pure 5-FCyd.

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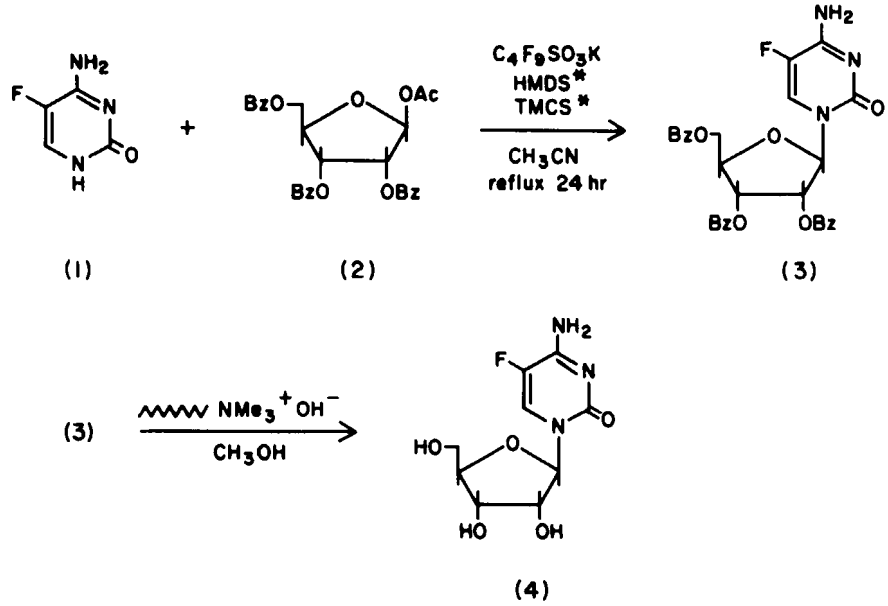
We wish to report in this communication the synthesis of 5-FCyd from inexpensive, commercially available 5-fluorocytosine (1) and 1-O-acetyl-2,3,5-tri-O-benzoyl- β-D-ribofuranose (2) by the Vorbrüggen single-pot method[8], without a chromatographic purification step. This procedure does not require prior synthesis of N_4-acetyl-5-fluorocytosine from 5-fluorocytosine nor isolation of the silylated derivative of 5-fluorocytosine before coupling with the blocked carbohydrate, as described previously[6].

The sugar-protected nucleoside (3) was synthesized by adding silylating agent (HMDS; 1.5 ml, 7 mmol) and TMCS (5.92 ml, 31 mmole) to an anhydrous suspension of (1) (1.3 g, ∿10 mmol), (2) (5.04 g, 10 mmol) and the



(1) (2) (3)

(4)

* See reference 10

catalyst, potassium nonaflate (8.12 g, 24 mmol) in acetonitrile under dry nitrogen atmosphere. The reaction mixture is refluxed for 24 hours, and is followed by silica gel TLC (methanol: chloroform, 20:80; R_f (3) 0.56). After workup (3) is deblocked directly. In the reported procedure[6], (3) was isolated by silica gel column chromatography as a syrup which could not be crystallized from several solvents.

The final step in nucleoside synthesis is the removal of the protecting groups. The Vorbrüggen procedure routinely treats the benzyolated nucleoside with excess methanolic ammonia for 1-3 days. This procedure failed to completely debenzoylate (3), even after 72 hours of similar treatment.

On the other hand, when the crude product, following routine workup from the condensation step, is stirred in methanol at room temperature with Amberlyst A-26 (OH^-) resin[7], deblocking is complete overnight (using 1 gm moist resin per gm blocked nucleoside). After workup the crude product crystallizes from water-methanol (55% yield from 5-fluorocytosine). TLC indicates the mother liquor still contains some (4). This deblocking procedure is quite simple; crystalline product (4) was obtained without the need of charcoal treatment and ion-exchange chromatography[6]. The crystalline product co-migrates with an authentic sample on cellulose TLC (n-butanol/H_2O saturated; R_f(4) 0.25). The UV spectrum and m.p. of (4) are are in agreement with literature values[3].

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10. Abbreviations: HMDS, hexamethyldisilazane; TMCS, trimethylchlorosilane.