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PALLADIUM-CATALYZED SYNTHESIS OF 5-HETEROARYLPYRIMIDINE NUCLEOSIDES

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A new and direct method for the facile synthesis of 5-heteroarylpyrimidine nucleosides, a potential inhibitor of thymidylate synthetase, is described. The approach is based on a palladium catalyzed reaction between haloheteroarenes and mercurated pyrimidine nucleosides.

Key words: Nucleosides, Heteroarylpyrimidines, Palladium catalysis.

Introduction

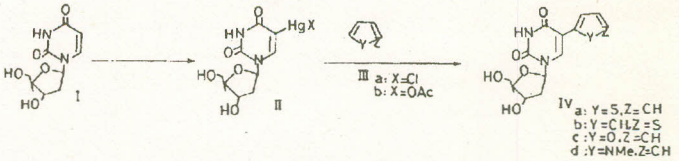
Thymidylate synthetase is the sole source of thymidine 5-phosphate the essential precursor for DNA replication [1]. Inhibition of this enzyme by 5-substituted derivatives of the substrate has afforded an opportunity to control certain cancers and infections. [2-6]. There is a great need however for new designed agents for improved therapy that are less cytotoxic to normal tissue [7,8]. We had previously described a photochemical synthesis of 5-heteroarylpyrimidine nucleosides [9-11]. Here we investigated some palladium-catalyzed approaches that would be regioselective with respect to both the heterocyclic base of the nucleoside and the heteroaryl function and would also accomodate the diverse functionality and solubility limitations of nucleosides.

Results and Discussion

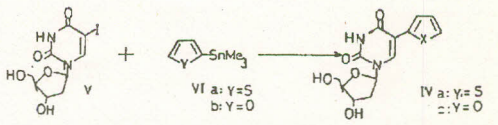
5-(2Thienyl)-2'-deoxyuridine IV a, was obtained by treating 5-(chloromercuri)-2'-deoxyuridine IIa with eguimolecular quantity of lithium tetrachloropalladate and 5 fold exces of 2-iodothiophene IIIa. After removal of the palladium and mercury salts as sulfides and purification by resolution on silica gel afforded IVa in 36% yield as determined by HPLC. An improvement in yield, together with a more convenient procedure that simplified the isolation step of the intermediate mercurinucleoside IIa was achived when the nucleoside I was converted to the acetoxymercuri derivative IIb [12]. Which was treated without isolation, with 2-iodothiophene IIIa and tetrachloropalladate in methanol to afford compound IVa in 42% yield.

5-(3-Thienyl)-2'-deoxyuridine IVb was the product obtained from the treatment of 2'-deoxyuridine with 3-bromothiophene. 5-(2-Furyl) and 5-(1-methylpyrrol-2-yl) -2'deoxyuridines IVc and IVd were also obtained under similar conditions. The structure of the products were identified by NMR and mass spectroscopy and compared to authentic standards [9] by HPLC. The mechanism for this reaction most likely proceed via a zerovalent palladium complex [13]. The use of catalytic amounts of palladium II gave lower yields.

A promising palladium-catalyzed unsymmetrical biaryl synthesis was described recently [14] which involves the cross-coupling of trialkylheteroarylstannanes with aryl halides. We attempted the exploitation of this approach for the synthesis of 5-heteroaryl nucleosides. Therefore treatment of 5-iodo-2'-deoxyuridine V in methanol with trialkylheteroarylstannes VIa,b and catalytic amount pd Cl_2 (p $Ph_3)_2$ afforded the expected products IVa,c in much lower yields. (less than 15%). Various reaction conditions are currently being investigated to control the requirements of the reaction and improving the yield.



(Scheme 1)



(Scheme 2)

Experimental

The compounds prepared in this work were identified by NMR and mass spectroscopy and compared to known standards [10] by HPLC on partisil PXS 10/25 ODS-II using methanol-water as a solvent. Yields were determined by isolation of the product; after the structure was established, additional studies utilized HPLC and standard solutions for yield determination. A (0.1 M) solution of lithium tetrachloropalladate [15] was prepared by stirring palladium chloride (1.77 gm, 10 mmol) and lithium chloride (0.85 gm, 20 mmol) in 100 ml of anhydrous methanol overnight at room temperature.

Method A. A solution of 0.1 M lithium tetrachloropalladate (11 ml) was added with stirring to a suspension

of 5-chloromercuri-2'-deoxyuridine (IIa, [16] 436 mg, 1 mmol) and haloheteroaryl compound (5 mmol) in 10 ml methanol. After refluxing for 12 hrs the mixture was saturated with H_2S gas and filtered through Celit and the filtrate evaporated. The mixture was resolved on a silica column (3x50 cm) using 10% methanol in chloroform as eluent to give IV.

Method B. A solution of 2'-deoxyuridine (I, 228 mg, 1 mmol) and mercuric acetate (319 mg, 1 mmol) in 10 ml water was heated with stirring at 60° for 5 hrs. After removal of acetic acid formed in the reaction and water in vacuo, the resulting white solid was suspended in 11 ml methanol and stirred with the haloheteroaryl compound (5 mmol) and 11 ml of 0.1 M lithium tetrachloropalladate in methanol at reflux for 12 hrs. Workup was identical with method A.

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