Synthesis of 5-Cyclopropyluracil and 5-Cyclopropylcytosine by the Pd(0)-catalyzed Coupling Reaction

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5-Cyclopropyluracil and cyclopropylcytosine were prepared by the Pd(0)-catalyzed coupling reaction of 5-bromo-2,4-di(trimethylsilyloxy)pyrimidine and 5-bromo-2,4-*O,N*-bis-trimethylsilylcytosine with tributylstannylcyclopropane. The reactions also gave dehalogenated pyrimidine bases as by-products. Attempts to use 2,4-*O,N*-bis-trimethylsilyl-5-iodocytosine as the halide gave complete dehalogenation.

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Introduction.

The previous known method for the preparation of 5-cyclopropyluracil is both tedious and gives low yields [1], which has prompted us to develop an alternative route. The good antiviral properties of 5-cyclopropyl-β-2′-deoxyuridine [2] also made it interesting to achieve a convenient route to 5-cyclopropylcytosine, from which the corresponding nucleoside, 5-cyclopropyl-β-2′-deoxycytidine, could easily be prepared by a glycosylation reaction [3]. 5-(2,2-Dibromocyclopropyl)- and 5-(2-bromocyclopropyl)-2′-deoxyuridines have been prepared by reacting 3-*N*-3′,5′-di-*O*-tribenzoyl-2′-deoxy-5-vinyluridine with a dibromocarbene [4]. 5-Alkyluracils have previously been prepared by ring closure reactions with thiourea [5]. They have also been obtained by reacting 5-hydroxyuracil with stable Wittig reagents [6]. 5-Propyluridine was prepared by a reaction of 5-chloromercuriuridine with allyl chloride in the presence of dilithium palladium tetrachloride, followed by hydrogenation [7]. 5-Alkylcytosines have been prepared by cyclization of 2-alkyl-3-ethoxyacrylonitriles [8].

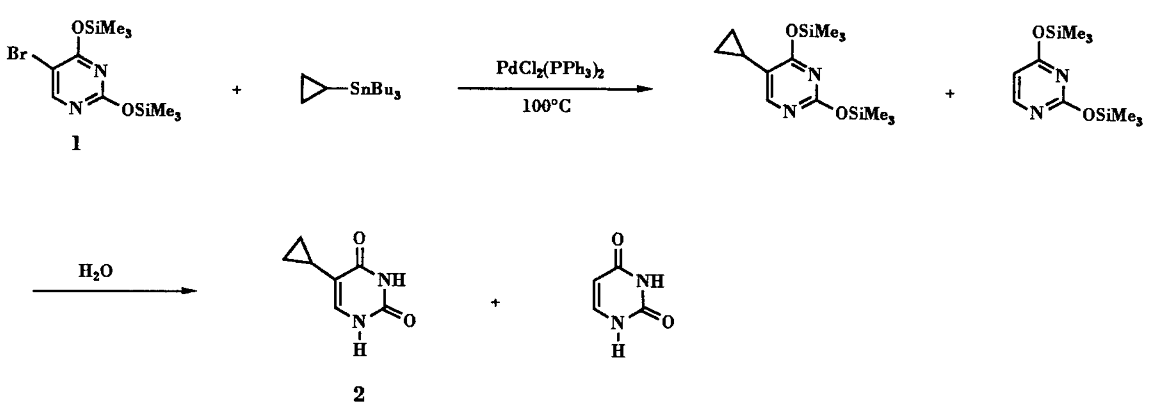
We previously prepared various 5-arylsubstituted uracils by the tetrakis(triphenylphosphine)palladium(0) catalyzed cross coupling reaction between heteroaromatic boronic acids and 5-bromo-2,4-di-*t*-butoxypyrimidine [9,10]. The reversed coupling partners could also be used in this reaction, and *trans*-bromopropene and 3-bromo-1-trimethylsilylpropyne could also be used as halides [10].

Another useful reaction that we developed was the Pd(0)-catalyzed coupling reaction of 5-iodouracil and 5-bromo-2,4-di(trimethylsilyloxy)pyrimidine with various heteroaryl tin compounds [10]. Direct C-C bond formation in the 5-position of cytosine was previously unknown until we recently showed that 2,4-*O,N*-bis-trimethylsilyl-5-iodocytosine could be coupled with various aryl tin compounds [11].

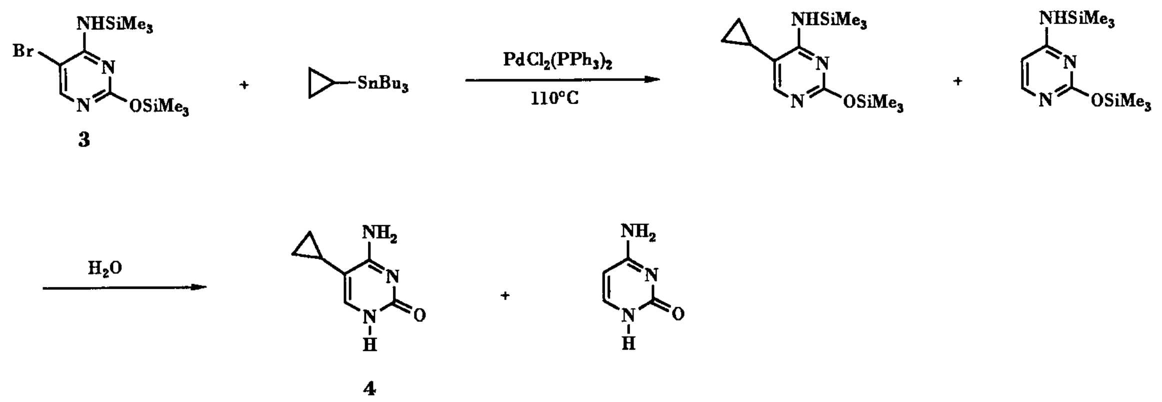
Results.

An attempt was to prepare 5-cyclopropyluracil by the Pd(0)-catalyzed reaction of cyclopropyl bromide and 2,4-di-*t*-butoxy-5-pyrimidineboronic acid using 1,2-dimethoxyethane and aqueous sodium bicarbonate solution as the solvent. We expected that the vinylic character of cyclopropyl bromide [12] would promote the reaction. However we could not obtain the desired product; according to mass spectral analysis only traces of the 5-5-dimer were formed, from a homo coupling of 2,4-di-*t*-butoxy-5-pyrimidineboronic acid. To find out whether cyclopropyl bromide could be reacted with a sterically less hindered arylboronic acid, we tried to react cyclopropyl bromide with

Scheme 1



Scheme 2



3-thiopheneboronic acid. This also resulted in dimer formation from two thiophene rings in a small quantity, using the same conditions as above. Another possible route would be to couple 5-bromo-2,4-di-*t*-butoxypyrimidine [9] or 5-bromo-2,4-di(trimethylsilyloxy)pyrimidine [13,14] with cyclopropaneboronic acid using tetrakis(triphenylphosphine)-palladium(0) as catalyst. However, cyclopropaneboronic acid could unfortunately not be prepared from cyclopropylmagnesium bromide [15] and tributylborate. We then turned to the Pd-catalyzed coupling reaction of tributylstannylcyclopropane [15] with 5-bromo-2,4-di(trimethylsilyloxy)pyrimidine (**1**) at 100° for 72 hours in the absence of solvent. This gave after hydrolysis a 2:3 mixture of 5-cyclopropyluracil (**2**) and uracil (Scheme 1). A lower temperature (85°) did not give dehalogenation nor product formation. A higher temperature (110°) gave the same product mixture as 100°.

The mixture of 5-cyclopropyluracil and uracil was recrystallized from ethanol to remove tin-containing impurities such as tributylstannyl bromide. The product mixture could be separated by repeated recrystallizations from water, which unfortunately gave a low isolated yield. A better method was separation by reversed phase hplc. Attempts to separate the mixture by the use of silica gel chromatography were not successful.

The preparation of the previously unknown 5-cyclopropylcytosine (**4**) was first attempted by the Pd-catalyzed reaction of 2,4-*O,N*-bis-trimethylsilyl-5-iodocytosine [16] with tributylstannylcyclopropane [15] in the absence of solvent at 100°. After 24 hours and hydrolysis this resulted in a mixture of mainly 5-iodocytosine and some dehalogenated cyctosine. Complete dehalogenation and no product was found after 10 days. Another more successful approach was to react 5-bromo-2,4-*O,N*-bis-trimethylsilylcytosine [16,17] (**3**) with tributylstannylcyclopropane in the absence of solvent at 110° for 72 hours (Scheme 2). This gave after hydrolysis a 4:1 mixture of 5-cyclopropylcytosine:cytosine. The mixture could be separated by silica gel chromatography after recrystallization from ethanol.

EXPERIMENTAL

5-Cyclopropyluracil (**2**).

A pressure bottle with magnetic stirrer was charged with 3.5 g (10.4 mmoles) of 5-bromo-2,4-di(trimethylsilyloxy)pyrimidine [13,14] (**1**), 6.9 g (20.9 mmoles) of tributylstannylcyclopropane [15] and 0.36 g (0.52 mmole) of di(triphenylphosphine)-palladium(II) dichloride. The reaction mixture was stirred at 100° for 72 hours. After cooling to room temperature a mixture of 40 ml of acetone and 4 ml of water was added, followed by stirring for one hour. Heptane (40 ml) was added, and the crystals were collected by filtration and washed with 20 ml of ether. The crude product was dissolved in boiling ethanol, and filtered warm. This was followed by two fractional recrystallizations. The mixture of 2:3, 5-cyclopropyluracil and uracil was separated on a reversed phase hplc Dynamax C_{18} column using 1:4 acetonitrile:water as eluent, giving 195 mg (12%) of 5-cyclopropyluracil, mp 316-320°, its ir spectrum being identical to that previously reported [1]; ^{1}H nmr: 10.99 (s, 1H), 10.68 (s, 1H), 6.99 (s, 1H), 1.53 (m, 1H), 0.66 (m, 2H), 0.48 (m, 2H) ppm; ms: Calcd. MW 152. Found: MW 152.

5-Cyclopropylcytosine (**4**).

A pressure bottle with magnetic stirrer was charged with 2.0 g (6.0 mmoles) of 5-bromo-2,4-*O,N*-bis-trimethylsilylcytosine (**3**) [16,17], 4.0 g (12.0 mmoles) of tributylstannylcyclopropane [15] and 0.21 g (0.30 mmole) of di(triphenylphosphine)-palladium(II) dichloride. The reaction mixture was stirred at 110° for 72 hours. After the same workup procedure as described above, a 4:1 mixture of 5-cyclopropylcytosine and cytosine was obtained. The mixture was separated by silica gel chromatography using 1:4 methanol:dichloromethane as eluent, giving 275 mg (30%) of 5-cyclopropylcytosine, mp 322-326°; ^{1}H nmr: 7.03 (s, 1H), 1.37 (m, 1H), 0.73 (m, 2H), 0.40 (m, 2H) ppm; ms: Calcd. for MW 151.0745. Found: MW 151.0753.

Anal. Calcd. for $C_7H_9N_3O$: C, 55.6; H, 6.0; N, 27.8. Found: C, 55.1; H, 6.3; N, 27.8.

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