Synthesis of Various 5-Substituted Uracils

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Several Pd-catalyzed coupling reactions have been evaluated for the synthesis of 5-substituted uracils. A convenient reaction, further developed by us, is the Suzuki Pd(0)-catalyzed coupling between arylboronic acids and aryl bromides or iodides in weakly alkaline medium. However, all attempts to use 5-bromo- or 5-iodouracil as the aryl halide failed. On the other hand, couplings between 2,4-di-*t*-butoxy-5-bromopyrimidine and various arylboronic acids were successful. In cases when the arylboronic acids were not available, it was better to reverse the coupling functionalities and use 2,4-di-*t*-butoxy-5-pyrimidineboronic acid and arylbromides. A large number of 5-aryluracils were prepared in this way. They were obtained in almost quantitative yields by dealkylation of the 5-aryl-2,4-di-*t*-butoxypyrimidines. However, a great drawback of these procedures is the highly allergenic properties of 2,4-dichloro-5-bromopyrimidine, which is an intermediate in the synthesis of 2,4-di-*t*-butoxy-5-bromopyrimidine and 2,4-di-*t*-butoxy-5-pyrimidineboronic acid. In order to avoid this intermediate the coupling between 5-bromo-2,4-ditrimethylsilyloxypyrimidine and arylboronic acids were attempted but failed. Also attemptes to prepare 2,4-di-trimethylsilyloxy-5-pyrimidineboronic acid failed due to migration of a silyl group to the 5-position upon halogen-metal exchange. We therefore turned to the use of tin derivatives instead of boronic acids in the coupling reaction, which can be carried out under neutral conditions. Thus 5-(1-methyl-2-pyrrolyl)uracil, which could not be prepared from 2-bromo-1-methylpyrrole and 2,4-di-*t*-butoxy-5-pyrimidineboronic acid was obtained through the Pd(0)-catalyzed coupling of 1-methyl-2-trimethylstannylpyrrole and 2,4-di-*t*-butoxy-5-bromopyrimidine followed by dealkylation. However, the great advantage with the tin derivatives was that 5-bromo-2,4-ditrimethylsilyloxypyrimidine could be used in the coupling with aryltin derivatives giving 5-aryluracils in reasonable yields. We also tried to use unprotected 5-halouracils in the coupling reactions. We were unsuccessful with the 5-bromo derivative. However, with 5-iodouracil coupling was achieved in some cases.

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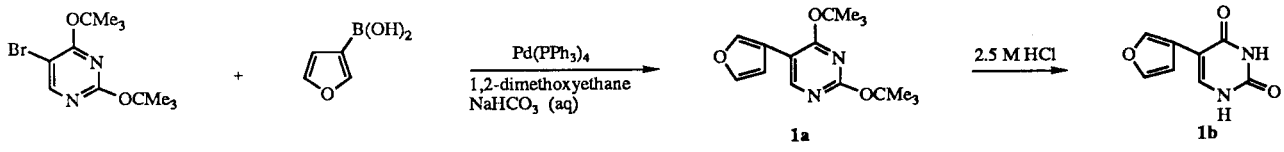
Introduction.

In connection with work on potential antiviral compounds, we wished to prepare substituted uracils with various heterocyclic rings such as pyridine, thiazole, furan, alkylthiophene, thienothiophene and 1-methylpyrrole, as well as with acyclic groups, such as 3-propynyl, *trans*-propenyl, and methylselenomethyl connected to the 5-position. These compounds are easily converted to the corresponding nucleosides [1]. Most methods for the preparation of 5-substituted uracils are based on palladium-catalyzed C–C bond formation at the 5-position of uracil or of pyrimidine derivatives. Ring-closure reactions giving 5-substituted uracils were previously regarded as less useful due to low yields [2]. 2-Thienylzinc chloride has been coupled with 5-bromo-2,4-ditrimethylsilyloxypyrimidine using nickel(0)tetra(triphenyl)phosphine as catalyst [3]. After hydrolysis, 5-(2′-thienyl)uracil was obtained in 35% yield. However, this reaction could not be generalized [2]. 5-Hydroxyuracil has been reacted with stable Wittig reagents to yield the corresponding 5-alkyluracil [4]. Reaction of 5-chloromercuriuracil nucleosides with olefins in the presence of Li_2PdCl_4 gave the corresponding 5-alkyluracil nucleosides [5]. Coupling of terminal alkynes with protected 5-iodouracil nucleosides using $PdCl_2(PPh_3)_2$ and copper(I) iodide as catalyst has been described [6]. Cross coupling of 5-hydroxyuracil triflates with alkenes and alkynes in the presence of palladium catalyst and triphenylphosphine gave 5-vinyluracils and 5-alkynyluracils in good yields [7]. By using one equivalent of palladium acetate, the hydrogen in the 5-position of uracil derivatives was replaced by a vinylic side chain [8]. Vinylation in the 4-position of pyrimidine has been obtained in a palladium-catalyzed coupling reaction between organotin reagents, alkenes and 4-iodopyrimidines [9]. 2′-Deoxyuridines substituted at C-5 by a heterocycle or a carbocycle were obtained by palladium catalyzed-reactions of organozinc reagents [10].

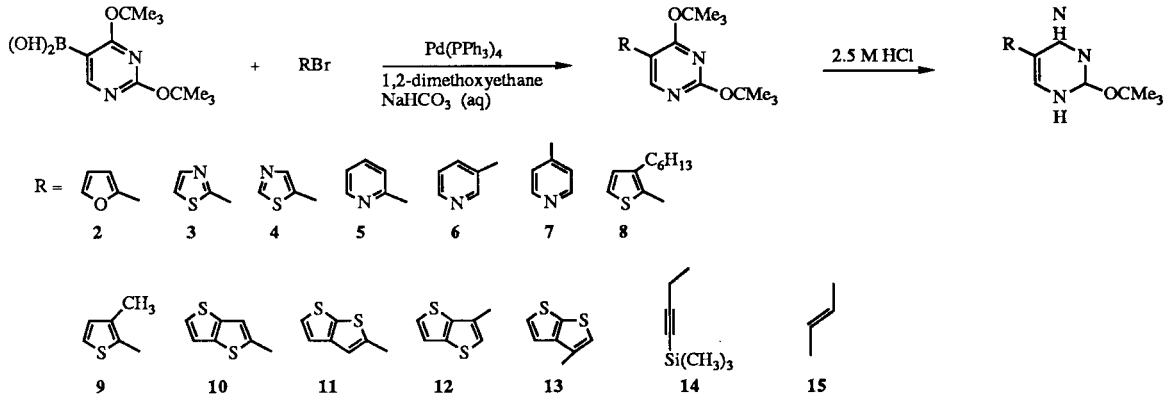
Results.

One direct approach to obtain 5-substituted uracil derivatives would be the Pd(0)-catalyzed couping reaction between 5-bromo- or 5-iodouracil, which are easily available, and the appropriate boronic acids [11-17]. However, neither 5-bromouracil nor 5-iodouracil gave the desired coupling under the normal conditions with aqueous sodium bicarbonate as base and 1,2-dimethoxyethane as solvent, or under anhydrous conditions with triethylamine and dimethylformamide [18]. The presence of base is essential in the coupling reaction of boronic acids [19]. 5-Bromouracil was therefore transformed to 5-bromo-2,4-dichloropyrimidine through reaction with phosphorus oxychloride [20]. Great care has to be exercised in the synthesis and handling of 5-bromo-2,4-dichloropyrimidine, since it is higly allergenic. Upon treatment with sodium *t*-butoxide, this compound gave 5-bromo-2,4-di-*t*-butoxypyrimi-

Scheme 1



Scheme 2



dine [21], which previously has been shown to undergo a Pd(0)-catalyzed coupling reaction with 2- and 3-thiopheneboronic acid and 2- and 3-selenopheneboronic acid [2]. This reaction was now used for the synthesis of 5-(3′-furyl)-2,4-di-*t*-butoxypyrimidine, **1a**, from 3-furanboronic acid [22] (Scheme 1).

The success of this approach is of course dependent on the availability of the boronic acids, and the stability of the carbon-boron bond towards hydrolysis under the weakly alkaline conditions used in the reaction. As we were not successful in our attempts to prepare 2-furan- and 2-thiazoleboronic acid, we changed the reaction partners and prepared 2,4-di-*t*-butoxy-5-pyrimidineboronic acid [2], which then under Pd(0)-catalysis was coupled with 2-bromofuran [23,24], 2-bromothiazole [25], 5-bromothiazole [26], 2-, 3- and 5-bromopyrimidine, 2-bromo-3-*n*-hexylthiophene [27] and 2-bromo-3-methylthiophene [28]. Halides of π-electron deficient heterocycles are very reactive in the coupling reaction and compounds **2a-9a** (Scheme 2) were obtained in 50-70% yields, after purification by column chromatography.

Using the same approach as above the four isomeric thiophtenes were introduced in the 5-position of 2,4-di-*t*-butoxypyrimidine giving compounds **10a-13a** (Scheme 2).

The precursor of 2- and 3-bromothieno[3,2-*b*]thiophene, thieno[3,2-*b*]thiophene, was synthesised by two different routes: rearrangement and ring closure of (2-thienylthio)-acetic acid to 2*H*,3*H*-thieno[3,2-*b*]thiophen-3-one [29], which was reduced to thieno[3,2-*b*]thiophene [30]; or formylation of methyl (3-thienylthio)acetate [31] to methyl (2-formyl-3-thienylthio)acetate [32], which was ring-closed to thieno[3,2-*b*]thiophene-2-carboxylic acid [33], and finally decarboxylated to give thieno[3,2-*b*]thiophene. Unfortunately, the first route was of almost no preparative value, since the yield was low, but the second route gave a good yield. Thieno[3,2-*b*]thiophene was brominated to 2-bromothieno[3,2-*b*]thiophene [34] with *N*-bromosuccinimide (NBS).

2-Bromothieno[2,3-*b*]thiophene was synthesized by protection of 3-thiophenealdehyde with ethylene glycol, giving 2-(3-thienyl)-1,3-dioxolane [35], which was converted to 2-thieno[2,3-*b*]thiophenecarboxylic acid and decarboxylated to thieno[2,3-*b*]thiophene [36], which was then brominated with NBS [34]. 3-Bromothieno[3,2-*b*]thiophene was obtained by bromination of thieno[3,2-*b*]thiophene in carbon disulfide to give 2,3,5-tribromothieno[3,2-*b*]thiophene, which was reduced with zinc in acetic acid in a procedure modified from that given in ref [34] (*cf.* Experimental). 3-Bromothieno[2,3-*b*]thiophene was similarly prepared [34].

All of the above-mentioned 5-substituted 2,4-di-*t*-butoxypyrimidines, were converted to the corresponding uracils, in almost quantitative yields, by stirring at room temperature with a 1:1 mixture of methanol and 5 *M* hydrochloric acid. In the case of 5-(3′-furyl)uracil (**1b**), 5-(2′-furyl)uracil (**2b**), 5-(3-hexyl-2′-thienyl)uracil (**8b**), 5-(3-methyl-2′-thienyl)uracil (**9b**), 5-(2′-thieno[3,2-*b*]thienyl)uracil (**10b**), 5-(2′-thieno[2,3-*b*]thienyl)uracil (**11b**), 5-(3′-thieno-[3,2-*b*]thienyl)uracil (**12b**), and 5-(3′-thieno[2,3-*b*]thienyl)uracil (**13b**),

the compounds precipitated and were obtained pure after washing with methanol and water. Regarding the basic 5-(2′-thiazolyl)uracil (**3b**), 5-(5′-thiazolyl)uracil (**4b**), 5-(2′-pyridyl)uracil (**5b**), 5-(3′-pyridyl)uracil (**6b**), and 5-(4′-pyridyl)uracil (**7b**), the hydrochlorides precipitated out, giving broad ^{1}H nmr signals at 8.3, 4.8, 3.8, 3.8 and 3.4 ppm. All attempts to obtain the free bases in pure form failed, due to the high solubility of uracils in aqueous alkaline solutions. However, by recrystallization from methanol the hydrochlorides could be purified, except for **3b**, which crystallized as the free base, probably due to its low basicity.

Attempts were made to react 5-lithio-2,4-di-*t*-butoxypyrimidine with 3-bromo-1-trimethylsilylpropyne in order to prepare 5-(3′-propynyl)uracil (**14c**). However, according to ^{1}H nmr analysis no trace of the expected compound, 5-(1′-trimethylsilyl-3′-propynyl)-2,4-di-*t*-butoxypyrimidine (**14a**) was present in the product. Therefore, **14a** was prepared in the Pd(0)-catalyzed coupling reaction between 3-bromo-1-trimethylsilylpropyne and 2,4-di-*t*-butoxy-5-pyrimidineboronic acid (Scheme 2).

3-Bromo-1-trimethylsilylpropyne was prepared from 2-propyn-1-ol by reaction with 2.8 equivalents of ethylmagnesium bromide followed by chlorotrimethylsilane, giving 3-trimethylsilyl-2-propyn-1-ol upon work up [37]. This compound was brominated with phosphorus tribromide in pyridine to yield 3-bromo-1-trimethylsilylpropyne [38], which should be handled very carefully because of its irritant effect on the respiratory system. Treatment of **14a** with methanol/5 *M* hydrochloric acid 1:1, gave 5-(1-trimethylsilyl-3′-propynyl)uracil (**14b**). The trimethylsilyl group was, as expected, stable to acid hydrolysis. The challenge of this synthesis was to remove the trimethylsilyl group without destroying the uracil ring. The uracil ring has been shown to be stable in alkaline solutions such as 0.4 *M* potassium hydroxide [39]. Alkaline cleavage of phenylethynylsilanes has been shown to occur under mild conditions, such as 0.3 *M* sodium hydroxide in methanol/water, 7:1, [40]. By refluxing **14b** one hour under these conditions, it was successfully converted to 5-(3′-propynyl)uracil (**14c**). The reaction mixture was neutralized by acid before evaporation of the methanol, whereupon a crystalline product was obained.

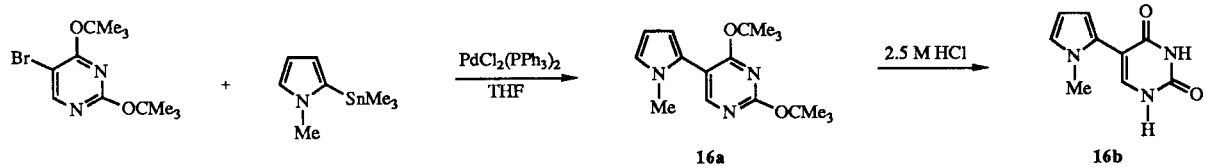
In order to obtain 5-*trans*-propenyluracil (**15b**), 5-lithio-2,4-di-*t*-butoxypyrimidine was reacted with propionaldehyde followed by elimination. However, we were not successful: the main component in the product was 2,4-di-*t*-butoxypyrimidine according to ^{1}H nmr analysis. Another route was to react to 70:30 mixture of *cis-trans*-bromopropene with 2,4-di-*t*-butoxy-5-pyrimidineboronic acid using $Pd(PPh_3)_4$ as the catalyst. We found that *trans*-bromopropene was more reactive than *cis*-bromopropene. When 3 equivalents of the 70:30, *cis-trans* mixture was used the reversed *cis-trans* composition of the product was obtained. When the experiment was repeated by using 3 equivalents of a 5:95 *cis-trans* mixture, obtained by reflux of the 70:30 *cis-trans*-bromopropane with butanolic sodium hydroxide for 40 hours [41], only 5-*trans*-propenyluracil was obtained according to the ^{1}H spectrum of the product. Attempts have also been made to prepare 5-(1′-methyl-2′-pyrrolyl)uracil (**16b**), using the Pd(0)-catalyzed coupling approach with 2-bromo-1-methylpyrrole [42] and 2,4-di-*t*-butoxy-5-pyrimidineboronic acid as coupling partners. However, these attempts failed, probably because of the instability of the halide, when it was refluxed in a solvent system of 1,2-dimethoxyethane and a weakly alkaline water phase. When the temperature was lowered to 40°, the same negative result was obtained.

Upon changing the strategy, using tin compounds instead of boronic acids and $PdCl_2(PPh_3)_2$ as catalyst, 5-(1′-methyl-2′-pyrrolyl)-2,4-di-*t*-butoxypyrimidine (**16a**), was obtained in the reaction between 1-methyl-2-trimethylstannylpyrrole and 5-bromo-2,4-di-*t*-butoxypyrimidine in anhydrous tetrahydrofuran (Scheme 3). After column chromatography and treatment with methanol/5 *M* hydrochloric acid, 1:1, **16b** was obtained as a crystalline precipitate.

5-Methylselenomethyluracil (**17**) was prepared from 5-chloromethyluracil [43] and lithium methylselenolate, which was obtained by adding methyllithium to a suspension of gray selenium in anhydrous tetrahydrofuran [44]. The preparation was a modification of the reaction of aryl halides with lithium methylselenoate described in ref [45] (*cf.* Experimental). The impurities found seemed to be the result of a Wurtz-related coupling of two 5-chloromethyluracil molecules, according to ^{1}H nmr and mass spectroscopic analysis. These impurities could be removed by column chromatography with ethyl acetate as eluent, followed by recrystallization from water.

Another approach to 5-substituted uracils would be to couple 5-bromo or 5-iodouracil directly with various tin compounds. By using dimethylformamide as solvent and $PdCl_2(PPh_3)_2$ as catalyst in the reaction with reactive tin

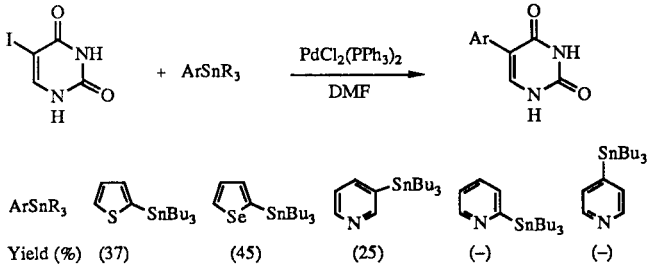
Scheme 3



16a 16b

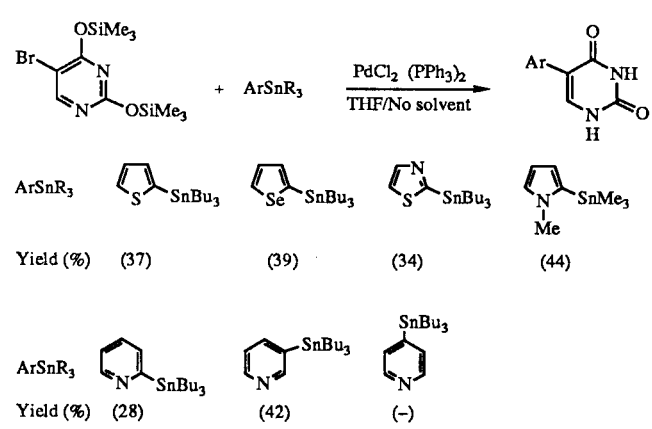
compounds such as 2-tributylstannylthiophene, 2-tributylstannylselenophene [46] and the less reactive 3-tributylstannylpyridine [47], 5-iodouracil gave the two known compounds, 5-(2′-thienyl)- and 5-(2′-selenyl)uracil [2] and 5-(3′-pyridyl)uracil (**19**), the free base of the previously mentioned hydrochloride **6b** (procedure D Scheme 4). However, the electron-deficient compounds 2- and 4-tributylstannylpyridine did not undergo this coupling reaction. It was also found that 5-bromouracil did not react with any of the tin compounds under the conditions given in Scheme 4.

Scheme 4



A more general route to 5-substituted uracils was found by silylating 5-bromouracil with 1,1,1,3,3,3-hexamethyldizilazan (HMDS) to give 5-bromo-2,4-ditrimethylsilyloxypyrimidine [48]. This compound was successfully coupled with 2-tributylstannylthiophene, 2-tributylstannylselenophene 2-tributylstannylthiazole, and 1-methyl-2-trimethylstannylpyrrole, using tetrahydrofuran as solvent and $PdCl_2(PPh_3)_2$ as catalyst. The resulting coupling products, upon aqueous hydrolysis gave the two previously known compounds 5-(2′-thienyl)- and 5-(2′-selenyl)uracil [2], and the above described 5-(2′-thiazoyl)- and 5-(1′-methyl-2′-pyrrolyl)uracils **3b** and **16b** in moderate yields (Scheme 5). Attempts to couple 2- and 3-tributylstannylpyridine in a similar way using dry tetrahydrofuran as solvent were not successful, but if the reactions were performed with the liquid reactants in the absence of solvent at 80°, 5-(2′-pyridyl)- and 5-(3′-pyridyl)uracils **18** and **19** could be isolated in moderate yields, after aqueous hydrolysis, (procedure C, Scheme 5). Repeated attempts were made to react 4-tributylstannylpyridine in the same way, but only tarry mixtures were obtained. When **18** and **19** were prepared according to procedure A, they were isolated as hydrochlorides **5b** and **6b**. To confirm the structures of **18** and **19**, they were converted to the corresponding hydrochlorides **5b** and **6b** by treatment with hydrochloric acid in methanol.

Scheme 5



EXPERIMENTAL

Melting points are uncorrected. The ^1H nmr spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a Finnigan 4021 and a JOEL JMS-SX 102 spectrometer. Analyses (glc) were carried out on a Varian 3700 gas chromatograph using a Dexil 300, 3% column.

General Procedure for the Palladium(0)-catalysed Coupling Reaction Between Halides and Boronic Acids (Procedure A).

A 250 ml flask equipped with condenser, magnetic stirrer and nitrogen inlet was charged with 24 mmoles of the halo compound, 0.75 mmole of tetrakis(triphenylphosphine)palladium(0) and 80 ml of ethylene glycol dimethyl ether. After stirring for 10 minutes 27 mmoles of the boronic acid was added, immediately followed by 60 ml of 1 *M* sodium bicarbonate solution. The reaction mixture was refluxed for 4 hours with vigorous stirring under nitrogen. After cooling to room temperature, the organic solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with three 50 ml portions of ether. The combined ethereal phases were washed with water, and with saturated sodium chloride solution, and dried over magnesium sulfate. The ether was evaporated and the residue was flash chromatographed [49] using Silica gel 60 as the solid phase and heptane/ethyl acetate, 19:1, and 4:1 for compounds **5-7**, as eluent. Elemental analyses for compounds **1a-13a** are given in Table 1, yields, melting points and molecular weight data in Table 2 and ^1H nmr data in Tables 3 and 4.

Table 1

Elemental Analyses for some 5-Substituted Pyrimidines

Compound	Found %C	%H	%N	Calcd. %C	%H	%N
1a $C_{16}H_{22}N_2O_3$	65.6 [a]	7,68	9.64	66.2	7.64	9.65
2a $C_{16}H_{22}N_2O_3$	66.5	7.74	9.61	66.2	7.64	9.65
3a $C_{15}H_{21}N_3O_2S$	59.0	7.05	13.7	58.6	6.88	13.7
4a $C_{15}H_{21}N_3O_2S$	58.6	6.94	13.6	58.6	6.88	13.7
5a $C_{17}H_{23}N_3O_2$	67.6	7.70	14.1	67.8	7.69	13.9
6a $C_{17}H_{23}N_3O_2$	67.8	7.68	13.8	67.8	7.69	13.9
7a $C_{17}H_{23}N_3O_2$	67.5	7.62	13.9	67.8	7.69	13.9
8a $C_{22}H_{34}N_2O_2S$	67.9	8.7	7.3	67.7	8.8	7.2
9a $C_{17}H_{24}N_2O_2S$	63.9	7.62	8.87	63.7	7.55	8.74
10a $C_{18}H_{22}N_2O_2S_2$	59.6	6.13	7.51	59.6	6.12	7.72
11a $C_{18}H_{22}N_2O_2S_2$	59.6	6.09	7.73	59.6	6.12	7.72
12a $C_{18}H_{22}N_2O_2S_2$	59.6	6.19	7.76	59.6	6.12	7.72
13a $C_{18}H_{22}N_2O_2S_2$	59.6	6.12	7.72	59.6	6.12	7.72
14a $C_{18}H_{30}N_2O_2Si$	64.8	9.04	8.35	64.6	9.04	8.37
15a $C_{15}H_{24}N_2O_2$	67.8	9.08	12.1 [b]	68.2	9.15	12.1 [b]
16a $C_{17}H_{25}N_3O_2$	67.0	8.37	13.7	67.3	8.30	13.8

[a] A more satisfactory C analysis could not be obtained. [b] % Oxygen.

Table 2

Yields, Melting Points and Molecular Weight Data for some 5-Substituted Pyrmidines

Compound	Yield (%)	mp (° C)	Calcd MW	Found MW
1a	59	[a]	290.1632	290.1633
2a	49	87-88	290.2	290
3a	49	102-103	307.1	308
4a	62	68-69	307.1	307
5a	60	128-129	301.2	301
6a	69	88-89	301.2	303
7a	70	92-93	301.2	303
8a	61	[a]	390.2	391
9a	62	74-75	320.2	320
10a	57	108-110	362.1	362
11a	60	108-110	362.1	362
12a	55	105-107	362.1	362
13a	40	88-90	362.1	362
14a	72	[a]	334.2	[b]
15a	32	[a]	264.2	264
16a	39	113-114	303.2	303

[a] Liquid compounds. [b] Unstable compound.

Table 3

^{1}H NMR Chemical Shifts (ppm) for some 5-Substituted Pyrimidines in Deuteriochloroform

Compound	H 6	H 2'	H 3'	H 4'	H 5'	H 6'
1a	8.36	7.88	–	6.72	7.77	–
2a	8.68	–	6.75	6.46	7.43	–
3a	9.22	–	–	7.85	7.34	–
4a	8.49	8.76	–	8.17	–	–
5a	8.85	–	7.84	7.69	7.19	8.65
6a	8.22	8.73	–	7.80	7.32	8.53
7a	8.28	8.60	7.45	–	7.45	8.60
8a	8.13	–	–	6.94	7.26	–
9a	8.17	–	–	6.90	7.25	–
10a	8.52	–	7.57	–	7.35	7.25
11a	8.52	–	7.51	7.21	7.32	–
12a	8.57	7.62	–	–	7.41	7.27
13a	8.40	7.41	–	7.23	7.36	–
16a	8.12	–	6.09	6.18	6.72	–

General Procedure for the Preparation of 5-Substituted Uracils from 5-Substituted 2,4-Di-*t*-butoxypyrimidines (Procedure B).

A 100 ml flask was charged with 5 mmoles of the 2,4-di-*t*-butoxy-5-substituted pyrimidine dissolved in 25 ml of methanol and 25 ml of 5 *M* hydrochloric acid and the mixture was stirred for 30 minutes. The precipitated crystals were collected by filtration, washed with methanol and water, and dried. The yields obtained were almost quantitative. Elemental analyses for compounds **1b-13b** are given in Table 5, their melting points and molecular weight data in Table 6, and ^{1}H nmr data in Tables 7 and 8.

Table 5

Elemental Analyses for some 5-Substituted Uracils

Compound	Found %C	%H	%N	Calcd. %C	%H	%N
1b $C_8H_6N_2O_3$	54.1	3.34	15.5	53.9	3.39	15.7
2b $C_8H_6N_2O_3$	54.2	3.42	15.6	53.9	3.39	15.7
3b $C_7H_5N_3O_2S$	42.5 [a]	2.46	21.1	43.1	2.58	21.5
4b $C_7H_6ClN_3O_2S$	35.3 [a]	2.54	18.3	36.3	2.61	18.1
5b $C_9H_8ClN_3O_2$	47.8	3.58	18.4	47.9	3.57	18.2
6b $C_9H_8ClN_3O_2$	47.9	3.58	18.6	47.9	3.57	18.2
7b $C_9H_8ClN_3O_2$	47.8	3.60	18.6	47.9	3.57	18.2
8b $C_{14}H_{18}N_2O_2S$	60.4	6.46	10.1	60.4	6.52	10.1
9b $C_9H_8N_2O_2S$	51.8	3.65	13.5	51.9	3.87	13.4
10b $C_{10}H_6N_2O_2S_2$	48.0	2.44	11.3	48.0	2.42	11.2
11b $C_{10}H_6N_2O_2S_2$	48.0	2.46	11.2	48.0	2.42	11.2
12b $C_{10}H_6N_2O_2S_2$	47.8	2.36	11.2	48.0	2.42	11.2
13b $C_{10}H_6N_2O_2S_2$	48.0	2.44	11.1	48.0	2.42	11.2
14b $C_{10}H_{14}N_2O_2Si$	54.1	6.26	12.6	54.0	6.35	12.6
14c $C_7H_6N_2O_2$	56.0	4.01	18.6	56.0	4.03	18.7
15b $C_7H_8N_2O_2$	55.1	5.18	18.2	55.3	5.23	18.4
16b $C_9H_9N_3O_2$	56.0	4.70	22.0	56.5	4.74	22.0
17 $C_6H_8N_2O_2Se$	34.3	3.49	13.8 [a]	32.9	3.68	12.8

[a] A more satisfactory analysis could not be obtained.

Table 4

^{1}H NMR Coupling Constants (Hz) for some 5-Substituted Pyrimidines

Compounds	2'-3'	2'-4'	2'-5'	3'-4'	3'-5'	3'-6'	4'-5'	4'-6'	5'-6'
1a	–	0.8	1.6	–	–	–	1.9	–	–
2a	–	–	–	3.3	0.7	–	1.7	–	–
3a	–	–	–	–	–	–	3.4	–	–
4a	–	0.7	–	–	–	–	–	–	–
5a	–	–	–	7.7	1.2	1.1	9.2	1.9	5.4
6a	–	2.4	0.9	–	–	–	9.2	1.7	4.9
7a	4.5	–	–	–	1.5	–	–	–	4.5
8a	–	–	–	–	–	–	5.2	–	–
9a	–	–	–	–	–	–	5.1	–	–
10a	–	–	–	–	–	0.7	–	–	5.2
11a	–	–	–	–	–	–	5.3	–	–
12a	–	–	1.6	–	–	–	–	–	5.3
13a	–	–	1.2	–	–	–	5.2	–	–
16a	–	–	–	3.5	1.8	–	2.7	–	–

Table 6
Melting Points and Molecular weight Data for some 5-substituted Uracils

Compound	mp (° C)	Calcd. MW	Found MW
1b	320-324 [a]	178.0	178
2b	270-274	178.0	178
3b	285-289	195.0103	195.0101
4b (HCl)	350-354 [a]	195.0103 [b]	195.0099
5b (HCl)	266-270	189.1 [b]	189
6b (HCl)	310-314	189.1 [b]	189
7b (HCl)	280-284	189.1 [b]	189
8b	190-192	278.1	278
9b	248-250	208.0	208
10b	>360 [a]	250.0	250
11b	335-339 [a]	250.0	250
12b	328-332 [a]	250.0	250
13b	335-339 [a]	250.0	250
14b	242-244	222.1	222
14c	256-260	150.0	150
15b	232-236	152.1	152
16b	244-248	191.1	191
17	239-241	219.9752	219.9753
18	285-289	189.1	189
19	264-268	189.1	189

[a] With decomposition. [b] Calculated values without hydrocholoride.

$PdCl_2(PPh_3)_2$-Catalysed Coupling Reaction of 5-Bromo-2,4-ditrimethylsilyloxypyrimidine with Tin Compounds in THF (Procedure C).

A 10 ml flask equipped with condenser, magnetic stirrer and nitrogen inlet was charged with 0.50 g (1.49 mmoles) of 5-bromo-2,4-ditrimethylsilyloxypyrimidine, 1.64 mmoles of the trialkylstannylaryl compound, 52 mg (0.075 mmole) of $PdCl_2(PPh_3)_2$ and 5 ml of anhydrous THF. The reaction mixture was refluxed for 20 hours whereupon it was hydrolysed by stirring with 5 ml water for 1 hour. The precipitated product was filtered off and washed with diethyl ether. Finally the product was recrystallized from 95% ethanol. No coupling product was obtained under these conditions when the aryl group was pyridine. However, when the reaction was performed in a pressure bottle without solvent, the result improved. Upon work up 5 ml of THF was added. Compounds and yields are given in Scheme 5.

$PdCl_2(PPh_3)_2$-Catalysed Coupling Reaction of 5-Iodouracil with Tin Compounds in DMF (Procedure D).

A pressure bottle with magnetic stirrer was charged with 50 mg (0.210 mmole) of 5-iodouracil, 0.252 mmole of the aromatic tin compound, 7.4 mg (0.010 mmole) of $PdCl_2(PPh_3)_2$ and 1.0 ml of anhydrous DMF. The mixture was stirred at reflux for 20 hours. After evaporation of the solvent, THF was added and the work up procedure was performed as above. Compounds and yields are given in Scheme 4.

3-Bromothieno[3,2-*b*]thiophene.

A mixture of 30.4 g (0.081 mole) 2,3,5-tribromothieno[3,2-*b*]-thiophene, 31.6 g (0.484 mole) of zinc dust and 600 ml of glacial acetic acid was refluxed for 5 hours. The reaction mixture was cooled to room temperature, the zinc dust was filtered off and replaced by 10.4 g (0.161 mole) of fresh zinc dust, followed by 5 hours reflux. After the work up procedure [34] 6.6 g (0.030 mole) of 3-bromothieno[3,2-*b*]thiophene (85%), 2,6-dibromothieno-[3,2-*b*]thiophene (10%) and thienothiophene (5%) was obtained according to glc analysis.

2-Tributylstannylthiazole.

To a stirred solution of 7.4 g (0.05 mole) of 2-bromothiazole in 50 ml of dry ether at −70° under nitrogen, 35 ml (0.055 mole) of butyllithium (1.42 *M*) was added dropwise at such a rate that the temperature did not exceed −70°. The solution was stirred for 30 minutes at −70° whereupon 14.7 g (0.05 mole) of tributylstannyl chloride dissolved in 20 ml of dry ether was added. The solution was stirred for 4 hours at the same temperature, and then allowed to reach room temperature. Water was added to the mixture, the organic phase was separated and the aqueous phase was extracted with three 30 ml portions of ether. The combined ethereal phases were dried over magnesium sulfate. After evaporation, followed by distillation under reduced pressure, 8.3 g (49%) of the title compound was obtained, bp 122°/0.7 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.54 (d, 1H), 8.17 (d, 1H) ppm.

Anal. Calcd. for $C_{15}H_{29}NSSn$: C, 48.2; H, 7.81. Found: C, 48.4; H, 7.88.

Table 7
^{1}H NMR Chemical Shifts (ppm) for some 5-Substituted Uracils om DMSO-d_6

Compound	N1-H	N3-H	H-6	H-2'	H-3'	H-4'	H-5'	H-6'
1b	11.29	11.17	7.81	8.18	–	6.93	7.64	–
2b	11.40	11.20	7.71	–	6.83	6.51	7.62	–
3b	11.85	11.78	8.55	–	–	7.92	7.71	–
4b	11.56	11.61	8.22	9.11	–	8.39	–	–
5b	11.90	11.74	8.49	–	8.67	8.20	7.58	8.33
6b	11.69	11.58	8.13	9.12	–	8.70	7.98	8.76
7b	12.00	11.66	8.43	8.77	8.37	–	8.37	8.77
8b	11.10	11.29	7.45	–	–	6.96	7.42	–
9b	11.13	11.31	7.52	–	–	6.91	7.70	–
10b	11.38	11.49	8.03	–	7.81	–	7.58	7.39
11b	11.36	11.50	8.05	–	7.69	7.27	7.58	–
12b	11.21	11.42	7.75	8.02	–	–	7.71	7.46
13b	11.27	11.32	7.70	7.73	–	7.27	7.62	–
16b	11.05	11.23	7.37	–	5.95	5.95	6.76	–
18	11.27	11.36	8.25	—	8.23	7.77	7.25	8.53
19	11.32	11.32	7.80	8.72	–	7.95	7.38	8.45

Table 8

^{1}H NMR Coupling Constants (Hz) for some 5-Substituted Uracils In DMSO-d_6

Compound	2'-4'	2'-5'	3'-4'	3'-5'	3'-6'	4'-5'	4'-6'	5'-6'	1-6
1b	0.8	1.6	–	–	–	1.8	–	–	5.6
2b	–	–	3.5	0.9	–	1.8	–	–	6.1
3b	–	–	–	–	–	3.4	–	–	5.7
4b	0.8	–	–	–	–	–	–	–	6.2
5b	–	–	7.4	1.2	–	9.7	–	7.0	5.4
6b	2.1	–	–	–	–	8.8	1.2	5.6	5.8
7b [a]	–	–	–	–	–	–	–	5.3	5.4
8b	–	–	–	–	–	5.2	–	–	–
9b	–	–	–	–	–	5.1	–	–	–
10b	–	–	–	–	0.7	–	–	5.2	–
11b	–	–	–	–	–	5.1	–	–	–
12b	–	1.6	–	–	–	–	–	5.3	–
13b	–	1.2	–	–	–	5.2	–	–	–
16b	–	–	[b]	[b]	–	2.3	–	–	5.2
18	–	–	9.9	1.1	–	7.7	1.9	5.2	–
19	2.3	0.8	–	–	–	9.2	1.6	4.8	–

[a] J(2'-3') = J(5'-6'). [b] Could not be evaluated due to overlapping signals, see Table 7.

4-Tributylstannylpyridine.

To a stirred solution of 20.0 g (0.13 mole) of 4-bromopyridine in 200 ml of dry ether at −70° under nitrogen, 68 ml (0.14 mole) of butyllithium (2.06 *M*) was added dropwise at such a rate that the temperature did not exceed −70°. The solution was stirred for 30 minutes at −70° whereupon 41.2 g (0.13 mole) of tributylstannyl chloride dissolved in 60 ml of dry ether was added. After stirring at −70° for 4 hours, the work up was performed as described above, giving 21.5 g, (46%), bp 146-148°/1.1 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.36 (dd, 2H), 8.47 (dd, 2H) ppm.

Anal. Calcd. for $C_{17}H_{31}NSn$: C, 55.5; H, 8.5. Found: C, 54.6; H, 8.8.

2-Tributylstannylpyridine.

To a stirred solution of 20.0 g (0.13 mole) of 2-bromopyridine in 200 ml of dry ether at −70° under nitrogen, 68 ml (0.14 mole) of butyllithium (2.06 *M*) was added dropwise at such a rate that the temperature did not exceed −70°. The solution was stirred for 30 minutes at −70° whereupon 41.2 g (0.13 mole) of tributylstannyl chloride dissolved in 60 ml of dry ether was added. After stirring at −70° for 4 hours, the work up was performed as described above, giving 24.6 g (53%), lit [50], 48%, bp 130-132°/0.8 mm Hg, lit 116-120°/0.20 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.11 (m, 1H), 7.40 (m, 1H), 7.48 (m, 1H), 8.73 (m, 1H) ppm.

2-Tributylstannylthiophene.

To a solution of 5.0 g (0.06 mole) thiophene, 8.6 g (0.07 mole) of dry TMEDA and 100 ml of dry ether under nitrogen, 46 ml of (1.42 *M*) butyllithium was added at such a rate that moderate reflux was maintained. When the addition was complete, the mixture was refluxed for one hour and then cooled to −70° whereupon 19.4 g (0.06 mole) of trimethylstannyl chloride dissolved in 30 ml of dry ether was added at such a rate that the temperature did not exceed −70°. After stirring the reaction mixture at −70° for four hours, the same work up procedure was performed as described above. 10.2 g (46%) of the title compound was obtained, lit [51], 72%, bp 148°/2 mm Hg, lit 150°/1 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.83 (dd, 1H), 7.28 (dd, 1H) and 7.20 (dd, 1H) ppm.

1-Methyl-2-trimethylstannylpyrrole.

To a solution of 8.1 g (0.10 mole) of 1-methylpyrrole, 14.5 g (0.125 mole) of dry TMEDA and 100 ml of dry ether under a nitrogen atmosphere 73 ml of (1.50 *M*) butyllithium was added at such a rate that moderate reflux was maintained. After complete addition, the mixture was refluxed for one hour. The solution was cooled to −70° and 20.0 g (0.10 mole) trimethylstannyl chloride dissolved in 30 ml of dry THF was added at such a rate that the temperature did not exceed −70°. When the addition was complete, the mixture was stirred for four hours at the same temperature, whereupon it was allowed to reach room temperature. After hydrolysis, extraction, drying and vacuum distillation, 11.4 g (47%) was obtained. bp 95°, 15 mm Hg; ^{1}H nmr (deuteriochloroform) δ 6.90 (dd, 1H), 6.33 (dd, 1H), 6.27 (dd, 1H), 3.75 (s, 3H) ppm ([52], no data presented).

5-(3'-1-Propynyl)uracil, **14c**.

A two necked flask, equipped with condenser, magnetic stirrer and nitrogen inlet, was charged with 5.0 g (0.03 mole) of 3-bromo-1-trimethylsilylpropyne, 0.87 g (0.75 mmole) of tetrakis(triphenylphosphine)palladium(0), and 100 ml of ethylene glycol dimethyl ether. After stirring for 10 minutes, 7.7 g (0.03 mole) of 2,4-di-*t*-butoxy-5-pyrimidineboronic acid was added, immediately followed by 75 ml of 1 *M* sodium bicarbonate solution. The reaction mixture was refluxed under nitrogen for four hours with vigorous stirring. After cooling to room temperature, the organic solvent was evaporated under reduced pressure, and the residue was diluted with water and extracted with three 40 ml portions of ether. The combined ethereal phases were washed with water and dried over magnesium sulfate. The ether was evaporated and the residue was purified by flash column chromatography [49] using Silica gel 60 as solid phase and pentane/ether as eluent. 5-(3'-1-trimethylsilylpropynyl)-2,4-di-*t*-butoxypyrimidine (**14a**), 2.8 g (32%) was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 8.21 (H-6, s, 1H) and 3.33 (H-1', s, 2H) ppm. Elemental analyses are given in Table 1 with melting points and molecular weight data given in Table 2. Compound **14a** (2.6 g) was converted to the corresponding uracil by stirring with 30 ml of methanol and 30 ml of methanol and 30 ml of 5 *M* hydrochloric acid for 30 minutes. The precipitated crystals were collected by filtration, washed with methanol and water and dried, which yielded 1.35 g (78%) of 5-(3'-1-trimethylsilylpropynyl)uracil, (**14b**); ^{1}H nmr (DMSO-d_6): δ 11.18 (NH-1, d, 1H), 10.73 (NH-3, s, 1H), 7.28 (H-6, d, 1H), (H-1', s, 2H) ppm. Elemental analyses are given in Table 5 with melting points and molecular weight data given in Table 6. Compound **14b** (1.0 g) was desilylated by refluxing in a mixture of 125 ml methanol and 20 ml 2 *M* sodium hydroxide for 2 hours; 20 ml of 5 *M* hydrochloric acid was slowly added at 0° to the stirred mixture, and the methanol was evaporated. The precipitated crystals were collected by filtration, and yielded 0.45 g, (67%) of 5-(3'-propynyl)uracil (**14c**). The 3-step synthesis above was repeated on a slightly larger scale with similar results giving yields of 30, 73 and 66%. Compound **14c** was recrystallized from water after first trying methanol as solvent; ^{1}H nmr (DMSO-d_6): δ 11.18 (NH-1, d, 1H), 10.81 (NH-3, s, 1H), 7.32 (H-6, d, 1-H), 3.10 (1-H', dd, 2H) and 3.03 (H-1', t, 1H) ppm; J (NH-1-H-6) = 4.8; J

(H-1'-H-3') = 2.6; J (H-6-H-1') = 1.2 Hz. Elemental analyses are given in Table 5 with molecular weight data and melting points given in Table 6.

trans-Propenyluracil (**15b**).

5-*trans*-Propenyl-2,4-di-*t*-butoxypyrimidine (**15a**) was prepared in 72% yield according to general procedure A with the exception that 3 equivalents of the halo compound, *trans*-bromopropene was used instead of the normal 1 equivalent. Elemental analyses are given in Table 1 and molecular weight data in Table 2. Compound **15a** was hydrolysed to **15b** in an almost quantitative yield, according to general procedure B; ^{1}H nmr (DMSO-d_6): δ 11.07 (NH-3, s, 1H), 10.89 (NH-1, d, 1H), 7.43 (H-6, d, 1H), 6.39 (H-2', dd, 1H), 6.03 (H-1', dd, 1H) and 1.74 (H-3', dd, 3H) ppm; J (NH-1-H-6) = 5.6; J (H-1'-H-2') = 15.8; J (H-1'-H-3') = 1.6; J (H-2'-H-3') = 6.6 Hz. Elemental analyses are given in Table 5 with melting points and molecular weight data given in Table 6.

5[2'-(1-Methylpyrrolyl)]uracil (**16b**).

A 250 ml flask equipped with condenser, magnetic stirrer and nitrogen inlet was charged with 9.0 g (0.03 mole) of 5-bromo-2,4-di-*t*-butoxypyrimidine, 1.05 g (1.50 mmoles) of $PdCl_2(Ph_3)_2$ and 8.0 g (0.03 mole) of 1-methyl-2-trimethylstannylpyrrole in 80 ml dry THF. The mixture was refluxed for 20 hours. After cooling, the reaction mixture was diluted with 200 ml of ether and washed twice with 50 ml of water. After drying with magnesium sulfate and evaporating the solvent the residue was purified by flash column chromatography [49] on Silica gel 60 as solid phase and pentane/ether, 9:1, as eluent. As an intermediate 3.5 g (39%) of 5-(1'-methyl-2'-pyrrolyl)-2,4-di-*t*-butoxypyrimidine (**16a**) was obtained which was converted to the corresponding uracil **16b** by stirring in 40 ml of methanol and 40 ml of 5 *M* hydrochloric acid for 30 minutes. The precipitated crystals were collected by filtration, washed with methanol and water and dried. Elemental analyses are given in Table 1 and 5, melting points and molecular weight data in Tables 2 and 6, and ^{1}H nmr data in Tables 3, 4, 7 and 8.

5-Methylselenomethyluracil (**17**).

A stirred suspension of 22.7 mmoles (1.60 *M*) of lithium methylselenolate [36] in 50 ml of anhydrous THF was prepared. The suspension was stirred and cooled to −5° and a solution of 5-chloromethyluracil [43] dissolved in 50 ml of anhydrous DMF was added at such a rate that the temperature did not exceed −5°. After complete addition and stirring at room temperature for one hour the mixture was refluxed for two hours and the solvents were evaporated. The residue was treated with a mixture of 30 ml of methanol and 30 ml of 5 *M* hydrochloric acid and the precipitated crystals were collected by filtration and washed with 10 ml of methanol and 10 ml of water. After drying 2.0 g (44%) of the title compound with mp 239-241° was obtained. Even after purification by flash column chromatography on Silca gel 60 and ethyl acetate as eluent followed by recrystallization from water, a correct element analysis could not be obtained, see Table 5; ^{1}H nmr (DMSO-d_6): δ 11.12 (NH-3, s, 1H), 10.76 (NH-1, d, 1H), 7.39 (H-6, d, 1H), 3.33 (CH_2, s, 2H), 1.92 (CH_3, s, 3H) ppm; J (NH-1-H-6) = 5.5 Hz. Melting points and molecular weight data are given in Table 6.

Hydrochloride of 5-(2'-Pyridyl)uracil (**18**).

This compound was prepared according to general procedure D and was obtained in a yield of 28%. Melting points and molecular weight data are given in Table 6 and ^{1}H nmr data are given in Tables 7 and 8. Ten mg of **18** was stirred with a mixture of 1 ml of methanol and 1 ml of 5 *M* hydrochloric acid for 20 hours followed by filtration and recrystallization from 95% ethanol. The ir spectrum of the resulting hydrochloride was identical to that of **5b**.

Hydrochloride of 5-(3'-Pyridyl)uracil (**19**).

This compound was prepared according to general procedures C and D, and was obtained in yields of 42% and 25%, respectively. Melting points and molecular weight data are given in Table 6. The ^{1}H nmr data are given in Tables 7 and 8. Ten mg of **19** was converted to the corresponding hydrochloride as described above. The ir spectrum of the hydrochloride was identical to that of **6b**.

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