Syntheses of Various 5-(Bromoaryl)-substituted Uracils

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The Suzuki Pd(0)-catalyzed coupling between arylboronic acids and aryl bromides or iodides in weakly alkaline medium, previously further developed by us, has been used for regioselective preparation of 5-(2'-bromo-5'-furyl)-, 5-(2'-bromo-4'-furyl)-, 5-(2'-bromo-5'-thienyl)-, 5-(2'-bromo-4'-thienyl)-, 5-(4'-bromo-2'-thiazolyl)-, 5-(3'-bromophenyl)-, 5-(6'-bromo-2'-pyridyl)- and 5-(4'-bromo-2'-pyrimidyl)-substituted 2,4-di-*t*-butoxypyrimidines. In the coupling between 2,4-di-*t*-butoxy-5-pyrimidineboronic acid and the nine different aryl dibromides that were tried as coupling partners, only the 2,4- and 2,5-dibromothiazoles did not give satisfactory yields, 15% and 0%, respectively. The other seven aryl dibromides gave the desired 5-(bromoaryl)-2,4-di-*t*-butoxypyrimidines in 58-89% yield. Attempts to synthesise 2,4-di-*t*-butoxy-5-(2'-bromo-4'-thienyl)pyrimidine from 2-bromo-4-iodothiophene failed. Dealkylation of the 5-(bromoaryl)-2,4-di-*t*-butoxypyrimidines in 2.5 *M* hydrochloric acid gave the corresponding 5-(bromoaryl)uracils in almost quantitative yields.

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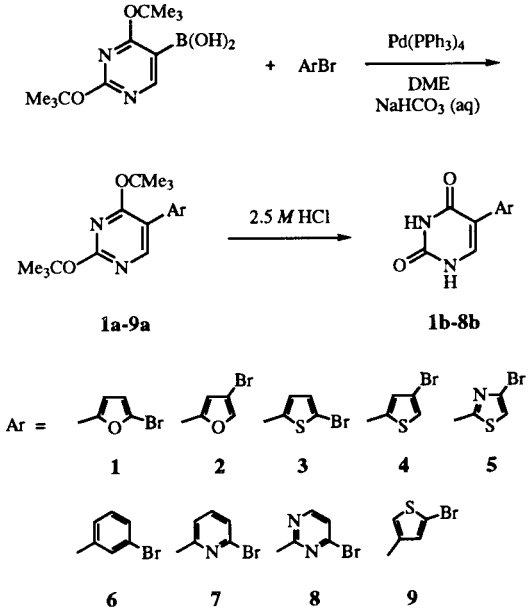
Introduction.

In connection with work on potential antiviral compounds, we have previously prepared various 5-substituted uracils [1]. These have been coupled with 2'-deoxyribose in order to investigate the antiviral activity of 5-substituted 2'-deoxyuridines [2]. Previous results indicate that uridines substituted with a 3'-bromoaryl in the 5-position of the uracil ring are biologically active [3,4]. These results made it interesting to prepare various 5-(bromoaryl)-substituted uracils since these are easily converted to their corresponding nucleosides [2,5]. A ring closure reaction between 3',5'-di-*O*-*p*-toluoyl-5-ethynyl-2'-deoxyuridine dibromoformaldoxime has been reported to give 5-(3'-bromo-5'-isoxazolyl)-2"-deoxyuridine [6], but this procedure is of rather limited use. Several Pd-catalyzed coupling reactions have been evaluated by us for the syntheses of 5-substituted uracils [1], and one approach to obtain the desired 5-(bromoaryl)uracils would be to prepare the trimethylstannyl aryl bromides and react these with 5-bromo-2,4-di(trimethylsilyloxy)pyrimidine. This strategy was abandoned since the relatively long reaction time, about 20 hours [1], probably would give a high yield of polymerized byproducts derived from self coupling of the trimethylstannyl aryl bromides. Another possible way would be to prepare the corresponding 5-aryl-2,4-di-*t*-butoxypyrimidines or 5-aryluracils followed by bromination of the aryl unit. This has been carried out with 5-(2"-furyl)-2'-deoxyuridine and 5-(2"-thienyl)-2'-deoxyuridine [7] as well as with 5-(2"-thienyl)arabinofuranosyluracil [8], but the major drawback with this method is the regioselectivity of the bromination. Compounds **2a** or **b**, **4a** or **b** and **6a** or **b** (Scheme 1) would not be possible to prepare with this method, and attempts to synthesize compound **5a** or **b** (Scheme 1) would probably have resulted in a mixture of the 4- and 5-brominated products.

Scheme 1



With these considerations in mind, it was decided to try the Suzuki Pd(0)-catalyzed coupling between 2,4-di-*t*-butoxy-5-pyrimidineboronic acid and the appropriate aryl dibromide in weakly alkaline medium [1]. This method is widely used for the preparation of unsymmetrical biaryls [9-14]. Modifications of this procedure involve the use of fluoride-mediation [15], palladium(II)acetate catalysis in aqueous ethanol [16] and palladium(II)acetate catalysis in water [17]. By using bromo-iodo aryls instead of dibromo aryls, it is possible to obtain a more selective coupling since the iodo group is more reactive than a bromo in this palladium catalyzed reaction. We decided to try to couple 2,4-di-*t*-butoxy-5-pyrimidineboronic acid with 2-bromo-4-iodothiophene in an attempt to obtain 2,4-di-*t*-butoxy-5-(2'-bromo-4'-thienyl)pyrimidine **9a** in a reasonable yield.

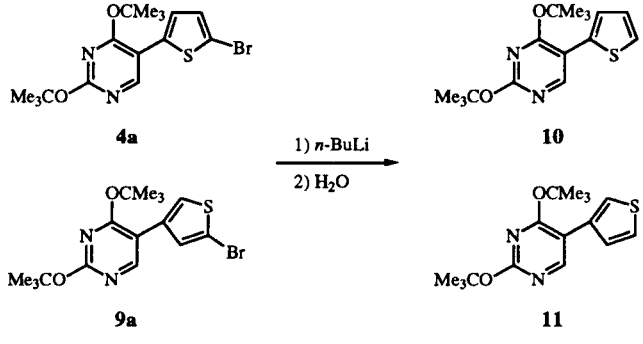
This would be the main product if the iodo group at the less reactive 4-position of thiophene could enhance the reactivity of this position, compared to the more reactive 2-position having the bromo group.

Results.

The palladium(0) catalyzed couplings gave predictable regioselectivity and acceptable yields of the desired products. Using 1.1 (unsymmetrical aryl dibromides) or 1.5 (symmetrical aryl dibromides) equivalents of the aryl dibromide, only traces of products that had coupled at the less reactive position of the aryl dibromide, as well as dicoupled products, could be detected. These byproducts were easily separated by chromatography using silica gel 60 and heptane:ethyl acetate as eluent, except for compound **5a** that had to be further purified using hplc. The attempted coupling between 2,4-di-*t*-butoxy-5-pyrimidineboronic acid and 2-bromo-4-iodothiophene resulted in a complex mixture of products. The desired product **9a** was isolated in 3% yield together with low yields of various other compounds (Scheme 3).

In order to confirm the regioselectivity of the reaction, the 5-thienyl-containing byproduct **9a** (Scheme 1) was isolated from the synthesis of **4a**. Debromination of **4a** and **9a** gave compounds **10** and **11**, respectively (Scheme 2) and the nmr data for these compounds (Table 3 and 4) confirms the regiochemistry by showing the expected

Scheme 2



Scheme 3

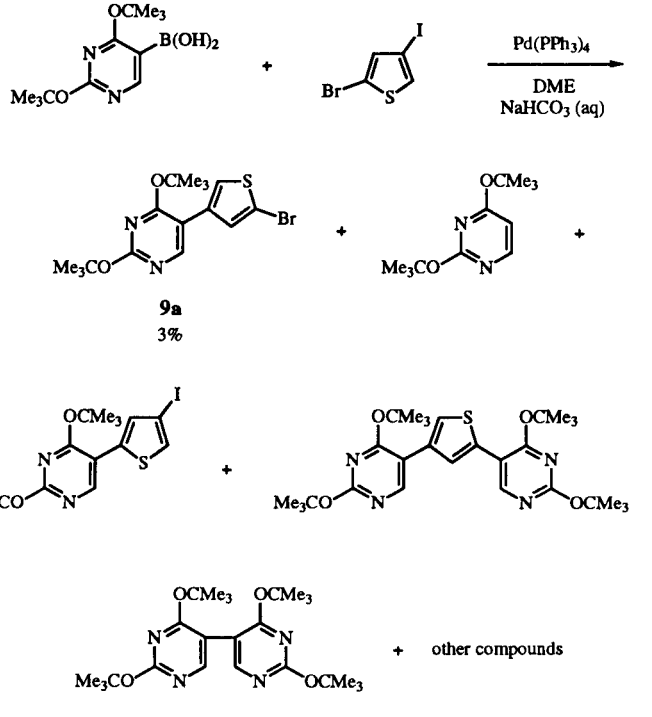


Table 1

Elemental Analyses for some 5-Substituted Pyrimidines

	Compound	Found % C	Found % H	Calcd. % C	Calcd. % H
1a	$C_{16}H_{21}BrN_2O_3$	51.99	5.81	52.05	5.73
2a	$C_{16}H_{21}BrN_2O_3$	51.94	5.80	52.05	5.73
3a	$C_{16}H_{21}BrN_2O_2S$	49.95	5.52	49.88	5.49
4a	$C_{16}H_{21}BrN_2O_2S$	49.82	5.71	49.88	5.49
5a	$C_{15}H_{20}BrN_3O_2S$	46.77	5.26	46.64	5.22
6a	$C_{18}H_{23}BrN_2O_2$	57.26	6.14	57.00	6.11
7a	$C_{17}H_{22}BrN_3O_2$	53.74	5.90	53.69	5.83
8a	$C_{16}H_{21}BrN_4O_2$	50.33	5.82	50.40	5.55

Table 2

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

Compound	Yield (%)	mp (°C)	Calcd. MW	Found MW
1a	58	97-99	368.1/370.1	368/370
2a	86	86-88	368.1/370.1	368/370
3a	62	82-85	384.1/386.0	384/386
4a	76	74-77	384.1/386.0	384/386
5a	15	112-114	385.0/387.0	385/387
6a	89	91-94	378.1/380.1	378/380
7a	68	139-141	379.1/381.1	379/381
8a	58	132-134	380.1/382.1	380/382

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	8.63	—	6.68 [a]	6.36	—	—
2a	8.64	—	7.42 [b]	—	6.76	—
3a	8.46	—	7.12 [b]	7.01	—	—
4a	8.47	—	7.28 [b]	—	7.18	—
5a	9.20	—	—	—	7.20	—
6a	8.21	7.67	—	7.44	7.26	7.41 [b]
7a	8.87	—	7.34 [a]	7.52	7.83	—
8a	9.14	—	—	—	7.93	8.48
9a	8.57	—	7.44	—	7.33	—
10	8.52	—	7.40	7.07	7.30	—
11	8.41	7.58	—	7.40	7.34	—

[a] No NOE was observed between H-6 and H-3'. [b] Was confirmed by NOE experiment.

Table 4

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

Compound	2'-4'	2'-5'	2'-6'	3'-4'	3'-5'	4'-5'	4'-6'	5'-6'
1a	—	—	—	3.4	—	—	—	—
2a	—	—	—	—	0.8	—	—	—
3a	—	—	—	4.0	—	—	—	—
4a	—	—	—	—	1.4	—	—	—
6a	1.8	—	1.8	—	—	7.8	1.1	7.8
7a	—	—	—	7.7	1.0	7.7	—	—
8a	—	—	—	—	—	—	—	5.4
9a	—	—	—	—	1.7	—	—	—
10	—	—	—	3.7	1.1	5.2	—	—
11	1.4	3.1	—	—	—	5.1	—	—

coupling constants for the thiophene substituent.

Compounds **1a-8a** were dealkylated in almost quantitative yields by the action of 2.5 *M* hydrochloric acid [1].

The aryl dibromides 2,5-dibromofuran [18], 2,4-dibromofuran [19], 2,5-dibromothiophene, 2,4-dibromothiophene [20], 2,5-dibromothiazole [21] and 2,4-dibromothiazole [22] were prepared according to literature. Attempts to prepare 2,4-dibromopyrimidine according to Gronowitz *et al.* [23] failed, but a modification of the procedure that was used for the synthesis of 2,4-dibromothiazole [22] gave 2,4-dibromopyrimidine in 22% yield.

2-bromo-4-iodothiophene was prepared according to Gronowitz *et al.* [24] but with the use of 1,2-dibromotetrachloroethane as brominating agent in order to obtain a more selective bromination.

5-Bromouracil was transformed to 2,4-di-*t*-butoxypyrimidineboronic acid [23,25-27]. The boronic acid was then reacted with 1.1 or 1.5 equivalents (see above) of aryl dibromide with Pd(0)$(PPh_3)_4$-catalyst in a dimethoxy ethane:1 *M* sodium bicarbonate solution 1:1, giving compound **1a-4a** and **6a-8a** (Scheme 1) in 58-89% yield after column chromatography and compound **5a** (Scheme 1) in 15% yield after column chromatography and further purification by hplc. Using the same approach, 2,5-dibromothiazole did only give polymerized products that were not characterized. The problems using dibromothiazoles were not unexpected since we have had difficulties using 2,5-dibromothiazole in Pd(0)-catalyzed cross-coupling with aryl boronic acids before [28].

Table 5

Elemental Analyses for some 5-Substituted Uracils

	Compound	Found % C	Found % H	Calcd. % C	Calcd. % H
1b	$C_8H_5BrN_2O_3$	37.26	1.97	37.38	1.96
2b	$C_8H_5BrN_2O_3$	37.26	1.96	37.38	1.96
3b	$C_8H_5BrN_2O_2S$	35.09	1.91	35.18	1.85
4b	$C_8H_5BrN_2O_2S$	35.26	1.94	35.18	1.85
5b	$C_7H_4BrN_3O_2S$	30.55	1.52	30.67	1.47
6b	$C_{10}H_7BrN_2O_2$	45.08	2.67	44.97	2.64
7b	$C_9H_6BrN_3O_2$	40.28	2.31	40.33	2.26
8b	$C_8H_5BrN_4O_2$	35.50	2.28	35.71	1.87

Table 6

Melting Points and Molecular Weight Data for some 5-Substituted Uracils

Compound	mp (°C)	Calcd. MW	Found MW
1b	>350 [a]	255.9/257.9	256/258
2b	>350 [a]	255.9/257.9	256/258
3b	>350	271.9/273.9	272/274
4b	>350	271.9/273.9	272/274
5b	>350	272.9/274.9	273/275
6b	335-337	266.0/268.0	266/268
7b	342-345 [a]	267.0/269.0	267/269
8b	>350 [a]	268.0/270.0	268/270

[a] With decomposition.

Table 7

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

Compound	N1-H	N3-H	H-6	H-2'	H-3'	H-4'	H-5'	H-6'
1b	11.44	11.29	7.70	—	6.81	6.60	—	—
2b	11.47	11.33	7.77	—	7.89	—	6.88	—
3b	11.54	11.40	8.10	—	7.33	7.13	—	—
4b	[a]	[a]	8.15	—	7.53	—	7.51	—
5b	11.78	11.78	8.30	—	—	—	7.70	—
6b	11.32	11.26	7.75	7.80	—	7.56	7.32	7.47
7b	11.47	11.43	8.15	—	7.46	7.72	8.26	—
8b	11.83	11.61	8.44	—	—	—	8.37	8.61

[a] Was not observed.

Table 8

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

Compound	1-6	2'-4'	2'-6'	3'-4'	3'-5'	4'-5'	4'-6'	5'-6'
1b	—	—	—	3.4	—	—	—	—
2b	—	—	—	—	0.8	—	—	—
3b	—	—	—	4.1	—	—	—	—
4b	—	—	—	—	1.5	—	—	—
6b	—	1.3	1.0	—	—	7.9	2.0	7.9
7b	6.2	—	—	7.9	0.8	7.8	—	—
8b	6.5	—	—	—	—	—	—	5.3

The regiochemistry of compounds **10** and **11** (Scheme 2) was confirmed by their ^{1}H nmr coupling constants (Table 4). Compound **10** shows characteristic coupling constants between H3' and H4' and between H4' and H5', 3.7 and 5.2 Hz, respectively. The regiochemistry of compound **11** is given by the coupling constants between H2' and H5' and between H4' and H5', 3.1 and 5.1 Hz, respectively [29].

The 5-substituted 2,4-di-*t*-butoxypyrimidines **1a-8a** were converted to their corresponding uracils **1b-8b** (Scheme 1) in almost quantitative yields by stirring at room temperature with a 1:1 mixture of 5 *M* hydrochloric acid and methanol [1]. Compounds **1b-8b** precipi-

tated and were obtained pure after washing with methanol and water.

EXPERIMENTAL

Melting points were recorded on a Lietz Wetzlar Microscope Heating Stage 350 Melting Point Apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Varian XL-200 or XL-300 spectrometer. The mass spectra were recorded on a JEOL-SX 102 spectrometer.

2,4-Dibromopyrimidine.

The procedure of Reynaud *et al.* [22] was followed but with a different workup. A 1 l one-necked flask equipped with a magnetic stirrer and a condenser with nitrogen inlet was charged with 250 g (810 mmoles) of phosphorus oxy bromide and 22.4 g (200 mmoles) of uracil. The two solids were mixed by shaking the flask and the temperature was raised to 120°. The stirring was started and after 12 hours at 120° the reaction mixture was cooled to 0°. Ice (500 g) was carefully added and the resulting mixture was poured onto another 1000 g of ice. The aqueous phase was extracted five times with 250 ml of ether. The organic phase was dried over magnesium sulphate, filtered and evaporated *in vacuo*. The residue was destilled under reduced pressure yielding 10.4 g (22%) of the title compound. Boiling point, melting point and ^{1}H nmr were identical to the ones reported in the literature [23].

2-Bromo-4-iodothiophene.

To 33.6 g (0.100 mole) of 2,4-diiodothiophene [30] dissolved in 100 ml of ether cooled to -70° was added 120 ml of 0.90 *M* (0.108 mole) butyllithium in cyclohexane:ether 1:1 at such a rate that the temperature never exceeded -70°. After stirring for an additional 20 minutes, 35.2 g (0.108 mole) of 1,2-dibromotetrachloroethane dissolved in 100 ml of ether was added dropwise so that the temperature never exceeded -70°. After pouring the reaction mixture into 300 ml of ice water, the ether phase was separated and the aqueous phase extracted with three 100 ml portions of ether. The combined ether phase was washed with 100 ml of 1 *M* sodium thiosulphate solution, 100 ml of 1 *M* sodium hydroxide solution, and 100 ml of water. After drying over magnesium sulphate, the ether was evaporated *in vacuo* and the crude product destilled at reduced pressure yielding 10.5 g (36%) of 2-bromo-4-iodothiophene, bp 113-116°/12 mm Hg (lit 36%, bp 106-108°/10 mm Hg [24]). The product was further purified by column chromatography using silica gel 60 and heptane as eluent.

General Procedure for the Palladium(0)-catalyzed Coupling Reaction Between 2,4-Di-*t*-butoxy-5-pyrimidineboronic Acid and Aryl Dibromides.

The procedure follows the one presented by Peters *et al.* [1] but with the aryl dihalide in excess. A 250 ml three-necked flask equipped with condenser, magnetic stirrer and nitrogen inlet was charged with 26 (unsymmetrical aryl dibromides) or 36 (symmetrical aryl dibromides) mmoles of the aryl dibromide, 0.75 mmole of tetrakis(triphenylphosphine)palladium(0) [31] and 80 ml of dimethoxyethane. After stirring for 10 minutes 24 mmoles of 2,4-di-*t*-butoxy-5-pyrimidineboronic acid was added, immediately followed by 60 ml of 1 *M* sodium bicarbonate solution. The reaction mixture was refluxed for 1 hour (compounds **1a-4a**, **6a**, **7a**), 2 hours (compound **8a**) or 4 hours (compound **5a**) with vigorous stirring. After cooling to room temperature, the organic phase was separated. The aqueous phase was extracted with three 50 ml portions of ether and the combined organic phase was washed with water and saturated sodium chloride solution. After drying over magnesium sulphate the organic solvents were evaporated *in vacuo*. The residue was flash chromatographed using silica gel 60 and heptane:ethyl acetate 19:1 (compounds **1a-6a**) or 18:2 (compounds **7a** and **8a**) as eluent. Compound **5a** was further purified by hplc using an RP-C_{18} Dynamax 250 x 20 mm column and acetonitrile:water 9:1 as eluent. Elemental analyses for compounds **1a-8a** are given in Table 1, yield, melting point and molecular weight data in Table 2 and ^{1}H nmr data in Tables 3 and 4.

Debromination of 2,4-Di-*t*-butoxy-5-(bromothienyl)pyrimidines **4a** and **9a** (Scheme 2).

A 25 ml one-necked flask equipped with nitrogen inlet was charged with 350 mg (0.91 mmole) of 2,4-di-*t*-butoxy-5-(bromothienyl)pyrimidine **4a** or **9a** dissolved in 10 ml of dry tetrahydrofuran. The reaction mixture was cooled to -78° and 0.8 ml of 1.47 *N* butyllithium was added with a syringe. The reaction mixture was allowed to stand at -78° with stirring for 3 hours after which it was poured into 10 ml of ice water. The organic phase was separated and the aqueous phase extracted with three 10 ml portions of ether. The combined organic phase was dried over magnesium sulphate, filtered and evaporated *in vacuo*. The crude product was flash chromatographed using silica gel 60 and heptane:ethyl acetate 9:1 as eluent. The ^{1}H nmr data for compounds **9a**, **10** and **11** are given in Tables 3 and 4.

The dealkylation of compounds **1a-8a** was performed as described by Peters *et al.* [1]. Elemental analyses for compounds **1b-8b** are given in Table 5, melting point and molecular weight data in Table 6 and ^{1}H nmr data in Tables 7 and 8.

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