Synthesis of Various 5-Arylsubstituted Cytosines

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Some Pd-catalyzed coupling reactions have been evaluated for the synthesis of 5-substituted cytosines. A large number of 5-arylcytosines were prepared in good yields by using 2,4-*O*,*N*-bis-trimethylsilyl-5-iodocytosine with various aryl tin compounds. The use of trimethylsilyl groups proved to be essential for the reaction, attempted coupling of 5-iodocytosine and 2-trimethylstannylthiazole was not successful. One convenient alternative, which unfortunately was not successful, would have been to reverse the coupling functionalities and couple commercial arylhalides with 5-trimethylstannyl- or 5-tributylstannyl-derivatives or the corresponding 2,4-*O*,*N*-bis-trialkylsilylcytosines.

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Introduction.

In connection with previous investigations of substances with antiviral effects, we have synthesized 5-aryl substituted uracils and nucleosides derived from them. In our first attempts we used the cross-coupling between trimethylsilyl protected 5-bromouracil and 2-thienylzinc chloride, using nickel(0)tetra(triphenyl)phosphine as the catalyst. The reaction could however, not be generalized [1].

A more successful route is, the tetrakis(triphenylphosphine-palladium(0) catalyzed cross-coupling between heteroaromatic boronic acids and 5-bromo-2,4-di-*t*-butoxypyrimidine. In this type of reaction the functionality of the coupling partners can be reversed [1,2] in cases where the carbon boron bond in the boronic acids is too labile. The coupling partners can also be changed to 5-iodouracil or 5-bromo-2,4-di(trimethylsilyloxy)pyrimidine and various heteroaryl tin compounds [2]. Palladium catalyzed cross-coupling reactions have also been used in the preparation of 5-aryl and 5-heteroaryl substituted 2′-deoxyuridines using arylzinc compounds [3]. C_5 Heteroaryl pyrimidine nucleosides can be obtained photochemically [4].

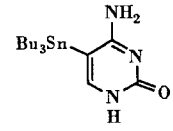
We have now prepared a series of 5-heteroaryl substituted cytosines. There are several routes for the preparation of substituted cytosines. One is the preparation *via* 2-mercapto-4-aminopyrimidines [5]. 5-Phenylcytosine has been obtained in a ring closure reaction between 2-phenyl-3-methoxypropenenitrile and urea [6]. In an other cyclization reaction 5-(phenylsulphonyl)pyrimidines were obtained starting with 3-[(aminocarbonyl)amino]propenenitriles [7]. Uridine can be converted into cytidine by first silylating with hexamethyldisilazane and then heating with ammonia in an autoclave [8].

In 1981 Sung showed that in aqueous ammonia 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-3,5-di-*O*-acetyl-2-deoxyribofuranosyl)primidin-2(1*H*)-one, prepared from thymidine, gave 5-methyl-2′-deoxycytidine [9]. Since then there have been many variations and applications of this method [10-14]. However, when we tried this transformation on 5-heteroaryl substituted uracils or the corresponding 2′-deoxyuridines, no positive results were obtained. One possible reason for this may be steric hindrance from the heterocycle [15,16]. Recently, De Clercq *et al.* showed that the procedure of Sung has to be modified, when the substituent in the 5-position is in conjugation with the heterocyclic ring [17]. We have used Pd(0) catalyzed cross-coupling reactions between 2,4-*O*,*N*-bis-trimethylsilyl-5-iodocytosine and arylstannanes to achieve the same goal.

Results.

5-Tributylstannylcytosine (**1**) was prepared in 27% yield by dilithiation of 2,4-*O*,*N*-bis-trimethylsilyl-5-iodocytosine (**2**) [18], followed by treatment with tributylstannyl chloride. Fortunately, no migration of any of the silyl groups to the 5-position was observed, which was the case when 5-bromo-di(trimethylsilyloxy)pyrimidine underwent halogen metal exchange [1,19]. However, when attempts were made to prepare 5-trimethylstannylcytosine in the same way by using trimethylstannyl chloride as electrophile, we obtained a 1:2 mixture of cytosine and 5-trimethylsilylcytosine (according to ^{1}H nmr, previously reported [16] and mass spectral analysis). By recrystallisation of this mixture pure 5-trimethylsilylcytosine could be obtained (melting point 240-244°, literature value 240° dec [16]), indicating a migration of the trimethylsilyl group to the 5-position. When 5-bromo 2,4-*O*,*N*-bis-trimethylsilylcytosine was used as starting material, no migration was observed, in agreement with earlier observations [20]. Unfortunately no reaction with trimethylstannyl chloride took place and the desired 5-trimethylstannylcytosine could not be obtained.

Scheme 1



1

2

Several routes were studied for the palladium catalyzed coupling reaction. The reaction between **1** and 2-bromo-

thiophene using di(triphenylphosphine)palladium (II) dichloride as the catalyst and dimethylformamide as the solvent led to destannylation both at 100° and room temperature. This was also the case, when 2,4-*O*,*N*-bis-trimethylsilyl-5-tributylstannylcytosine (silylated in the same way as **2**) was used as starting material.

Another possible approach is the reaction between 5-cytosineboronic acid and various bromoaryls. However, neither the boronic acid nor 2-thiazoleboronic acid from a previous work [21] could be obtained.

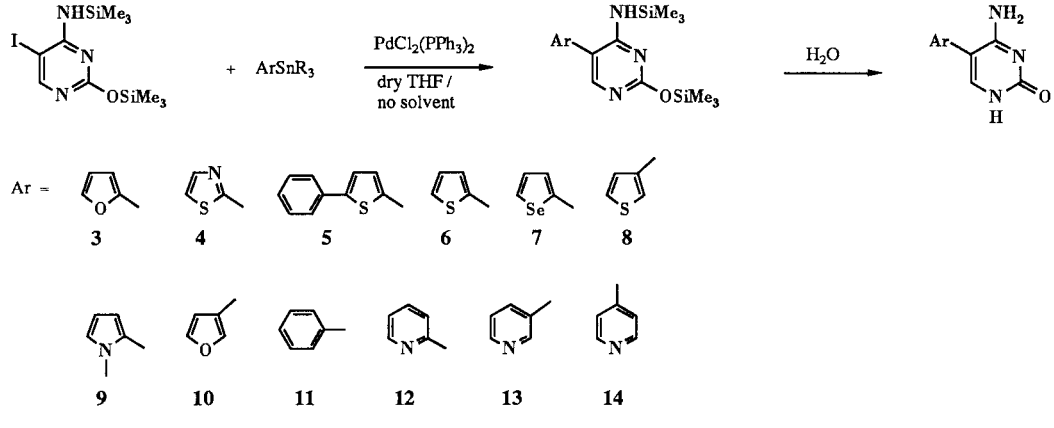
Alternatively the functionalities of the coupling partners could be reversed. Reacting 5-iodocytosine [18] with 2-trimethylstannylthiazole [22] in dimethylformamide as the solvent and di(triphenylphosphine)palladium (II) dichloride as the catalyst at 100° gave upon work up only 5-iodocytosine. When the temperature was increased to 115°, a tarry product was obtained. This behaviour is in contrast to that of 5-iodouracil, which was successfully coupled with various heteroaryl tin compounds [2]. This indicates that the halogen carrying carbon in 5-iodouracil is more positive than that in silylated 5-iodocytosine, and consequently the oxidative addition of palladium is favoured in 5-iodouracil. This is analogous to the reactivity observed in the coupling reaction between arylboronic acids and various halides [2,21,23,24].

The most successful conditions for the preparation of the desired compounds were coupling of the 2,4-*O*,*N*-bis-silylated 5-iodocytosine (**2**) with various aryl tin compounds using tetrahydrofuran as the solvent and di(triphenylphosphine)palladium (II) dichloride as the catalyst. After aqueous hydrolysis the 5-arylcytosines given in Scheme 2 were obtained: 2′-furyl- **3**, 2′-thiazoyl- **4**, 5-phenyl-2′-thienyl- **5**, 2′-thienyl- **6**, 2′-selenienyl- **7**, 3′-thienyl- **8**, 1-methyl-2′-pyrrolyl- **9**, 3′-furyl- **10**, phenyl- **11**, 2′-pyridyl- **12**, 3′-pyridyl- **13** and 4′-pyridyl- **14**. Due to the low reactivity of the tributylstannylpyridines, the preparation of **12-14** was performed without solvent.

In order to estimate the reaction time for the different reactions preliminary small scale experiments were performed. The results and those of the larger scale experiments are given in Table 1, which also gives yields and melting points of the compounds obtained. From the small scale experiments, it can be concluded that the reactivity of the arylstannyl compounds decreases in the following order 2-tributyl-stannylfuran [25], 2-trimethylstannylthiazole [22], 2-phenyl-5-tributylstannylthiophene, 2-tributylstannylthiophene [2], 2-tributylstannylselenophene [21], 3-tributylstannylthiophene [21], 2-tributylstannyl-1-methylpyrrole [26], 3-trimethylstannylfuran [25], trimethylstannylbenzene [27], 2-, 3- and 4-tributylstannylpyridine [2,28]. It seems as the reactivity is optimal when electron rich aryls are used, **3-10**. However, they do not follow exactly the same order as that expected for normal electrophilic aromatic substitution reactions. 2-Trimethylstannylthiazole was more reactive than expected. This is also the case for the pyridines were 2-tributylstannylpyridine is more reactive than 3-tributylstannylpyridine. This may be due to the fact that the nitrogen in the 2-substituted derivatives plays a coordinative role in the reaction, which has been observed in the Heck reaction of 2-vinylpyridine [29]. The best yields in the preparation of **12-14** were obtained when the reaction was carried out at 100° without solvent for 72 hours (Table 1). When the temperature was increased decomposition took place.

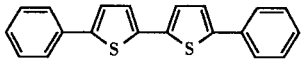
Self-coupling of the tributylstannyl compounds is a competing reaction. However, the symmetrical compounds obtained are much more soluble than the desired 5-arylcytosines and therefore easily separated in the work up procedure, with the exception of 5,5′-diphenyl-2,2′-bithienyl (**15**). The separation of **5** and **15** was achieved by bis-silylation of **5** and filtration of **15**, followed by recrystallisation from ethanol (cf. experimental part). The amount of **15** compared to **5** could not be determined by ^{1}H nmr as the

Scheme 2



signals due to the two compounds were overlapping. In an experiment when **2** was excluded **15** was obtained in 2.5% yield. The yield was also low when compound **15** was prepared through an Ullman coupling in order to study its nematicidal activity [30].

Scheme 3



15

5-Phenylcytosine (**11**) has previously been prepared in 47% and in 48% yields [5,6].

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H 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. The glc analyses were carried out on a Varian 3700 gas chromatograph using a Dexil 300, 3% column.

Example 1: Preparation of 5-(2'-Thienyl)cytosine (**6**) (for compounds **3**, **4**, **5**, **7**, **8**, **9**, **10**, **11** see Table 1).

A flask, equipped with condenser, magnetic stirrer was charged with 8.00 g (21.0 mmoles) of **2**, 0.73 g (1.04 mmoles) of di(triphenylphosphine)palladium (II) dichloride, 15.6 g (41.8 mmoles) of 2-tributylstannylthiophene (2 equivalents) and 70 ml of dry THF. The reaction mixture was refluxed for 72 hours with vigorous stirring under nitrogen. After cooling to room temperature, 70 ml of water was added, followed by stirring for one hour, compound **9** was stirred for 12 hours. The precipitated crystals were collected by filtration and washed with 100 ml of diethyl ether. The crude product was dissolved in boiling ethanol which was allowed to evaporate until a small quantity of the product (<1%) precipitated, it was then separated together with the palladium traces by warm filtration, followed by crystallisation. Yields and melting points are given in Table 1, Molecular weight data and elemental analyses are given in Table 2, and ^{1}H nmr data in Tables 3 and 4.

Example 2: Preparation of 5-(2'-Pyridyl)cytosine (**12**) (for Compounds **13** and **14** see Table 1).

A pressure bottle with a magnetic stirrer was charged with 8.00 g (21.0 mmoles) of **2**, 0.73 g (1.04 mmoles) of di(triphenylphosphine)palladium (II) dichloride, 11.6 g (31.4 mmoles) of 2-tributylstannylpyridine (1.5 equivalents). The reaction mixture was stirred at 100° for 72 hours. After cooling to room temperature a mixture of 70 ml THF and 70 ml of water was added, followed by stirring for one hour. The workup procedure was performed as described above. Yields and melting points are given in Table 1, Molecular weight data and elemental analyses are given in Table 2, and ^{1}H nmr data in Tables 3 and 4.

Table 1

Reaction Times, Equivalents of Tin Compound, Product-ratio (equivalents determined by ^{1}H nmr), Volume of Solvent, Yields, and Melting Points for some 5-Arylcytosines

Compound	RT/h	Equivalent $ArSnR_3$	Ratio product: halide	Scale/ mmoles	ml THF	Yield % after recrystallization	Mp/°C
3	40	1.2	100:0	20.9	70	57	264-266
	15	1.2	97:3	2.6	10	–	–
4	40	1.2	100:0	20.9	70	82	325-327
	15	1.2	95:5	2.6	10	–	–
5	40	1.3	100:0	20.9	50	82	270-272
	15	1.2	72:28	2.6	10	–	–
6	72	2.0	100:0	20.9	70	77	280-282
	15	1.2	38:62	1.3	5	–	–
7	72	2.0	100:0	20.9	70	57	302-304
	15	1.2	34:66	1.3	5	–	–
8	72	2.0	100:0	20.9	70	57	286-288
	15	1.2	22:78	2.6	10	–	–
9	72	2.0	100:0	20.9	100	44	272-274
	15	1.2	18:82	2.6	10	–	–
10	72	2.0	100:0	20.9	70	47	318-322
	15	1.2	18:82	1.3	5	–	–
11	72	2.0	100:0	10.4	40	62	330-334
	15	1.2	10:90	2.6	10	–	–
12 [a]	72	1.5	100:0	20.9	[b]	60	308-312
	15	1.2	4:96	2.6	10	–	–
13 [c]	72	2.0	100:0	20.9	[b]	45	312-316
	15	1.2	0:100	2.6	10	–	–
	15	1.5	33:67	2.6	[b]	–	–
14 [c]	72	2.0	100:0	20.9	[b]	34	326-330
	15	1.2	0:100	2.6	10	–	–

[a] Mp = 308-310° for the corresponding hydrochloride. [b] No solvent, 100°. [c] Mp **13** = 336-340° and mp **14** = 354-358° for the corresponding oxalic acids.

Table 2

Molecular Weight Data and Elemental Analyses for some 5-Arylcytosines

Compound	Formula	Calcd. MW	%C	%H	%N	Found MW	%C	%H	%N
3	$C_8H_7N_3O_2$	177.0539	54.2	3.98	23.7	177.0543	53.9	4.0	23.8
4	$C_7H_6N_4OS$	194.0262	43.3	3.11	28.8	194.0263	42.9	3.1	29.0
5	$C_{14}H_{11}N_3OS$	269.0624	62.4	4.12	15.6	269.0625	62.6	4.3	14.6
6	$C_8H_7N_3OS$	193.0311	49.7	3.65	21.7	193.0316	49.2	3.5	21.3
7	$C_8H_7N_3OSe$	240.9754	40.0	2.94	17.5	240.9758	39.8	2.9	17.5
8	$C_8H_7N_3OS$	193.0311	49.7	3.65	21.7	193.0310	49.1	3.4	21.4
9	$C_9H_{10}N_4O$	190.1	56.8	5.30	29.5	190	56.5	5.4	29.4
10	$C_8H_7N_3O_2$	177.1	54.2	3.98	23.7	177	54.3	4.1	23.9
11	$C_{10}H_9N_3O$	187.0747	[a]	[a]	[a]	187.0741	[a]	[a]	[a]
12	$C_9H_8N_4O$ [b]	188.0699	48.1	4.04	24.9	188.0699	47.3	4.3	25.3
13	$C_9H_8N_4O$ [c]	188.0699	47.5	3.62	20.1	188.0698	46.7	3.5	20.5
14	$C_9H_8N_4O$ [c]	188.0699	47.5	3.62	20.1	188.0694	47.4	3.6	20.6

[a] Previously prepared [5,6]. [b] Elemental analysis for the hydrochloride, $C_9H_9ClN_4O$. [c] Elemental analysis for the oxalic acid salts, $C_{11}H_{10}N_4O_5$. A more satisfactory C analysis for compounds **6**, **8**, **12** and **13**and a more satisfactory N analysis for compounds **5** and **14** could not be obtained.

Table 3

^{1}HNMR Chemical Shifts (ppm) for some 5-Arylcytosines in DMSO-d_6

Compound	H6	H2'	H3'	H4'	H5'	H6'
3	7.69	–	6.62	6.54	7.68	–
4	8.16	–	–	7.81	7.66	–
5 [a]	7.52	–	7.11	7.51	–	–
6	7.43	–	7.11	7.12	7.62	–
7	7.42	–	7.24	7.31	8.18	–
8	7.40	7.51	–	7.16	7.63	–
9	7.29	–	5.99	6.04	6.83	–
10	7.43	7.82	–	6.66	7.73	–
11	7.30	7.33	7.44	7.35	7.44	7.33
12	8.19	–	7.82	8.54	7.28	9.26
13	7.40	8.51	–	7.73	7.42	8.53
14	7.50	8.56	7.36	–	7.36	8,56

[a] Phenyl protons are not given.

Table 4

^{1}H NMR Coupling Constants (Hz) for some 5-Arylcytosines in DMSO-d_6

Compound	2'-3'	2'-4'	2'-5'	3'-4'	3'-5'	4'-5'	5'-6'
3	–	–	–	3.4	0.7	1.9	–
4	–	–	–	–	–	3.4	–
5	–	–	–	3.7	–	–	–
6	–	–	–	3.7	1.4	4.6	–
7	–	–	–	3.7	1.0	5.6	–
8	–	1.3	2.9	–	–	4.9	–
9	–	–	–	3.5	1.9	2.6	–
10	–	0.9	1.5	–	–	1.8	–
11	7.4	–	–	7.0	–	7.0	7.4
12 [a]	–	–	–	4	–	7	5 [b]
13 [a]	–	2	–	–	–	8	5
14 [a]	5	–	–	–	1	–	5

[a] Due to limited solubility only approximative values are given. [b] Position 6' is unresolved, J(5'-6') is only based on the resolution found for 5'.

5-Tributylstannylcytosine (**1**).

To a stirred solution of 8.00 g (21.0 mmoles) 2,4-*O*,*N*-bis-trimethylsilyl-5-iodocytosine (**2**) in 100 ml of anhydrous ether at -70° under nitrogen, was added 21 ml (44.0 mmoles) of butyllithium dropwise at such a rate that the temperature did not exceed -70°. The solution was stirred for 30 minutes at -70°, whereupon 6.8 g (0.0209 mole) of tributylstannyl chloride dissolved in 20 ml dry ether was added. After stirring at -70° for 4 hours, the solution was allowed to reach room temperature. Water (100 ml) was added. After stirring for one hour, the precipitated crystals were filtered off and washed with 20 ml water and 20 ml ether, yield 2.3 g (27%), dec 185°; ^{1}H-nmr (deuteriochloroform): δ 7.32 (s, 1H) ppm; hrms calcd: (M + H) 402.1567. Found: (M + H) 402.1574.

Anal. Calcd. for $C_{16}H_{31}N_3OSn$: C, 48.0; H, 7.81; N, 10.5. Found: C, 47.5; H, 7.8; N, 10.6.

2-Phenylthiophene.

A 1 ℓ flask, equipped with a condenser, magnetic stirrer and nitrogen inlet was charged with 15.0 g (95.6 mmoles) of bromobenzene, 3.31 g (2.87 mmoles) of tetrakis(triphenylphosphine)-palladium(0) and 320 ml of ethylene glycol dimethyl ether. After stirring for 10 minutes, 13.4 g (105 mmoles) of 2-thiopheneboronic acid was added, immediately followed by 240 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 and the residue was diluted with water and extracted with three 200 ml portions of ether. The combined ethereal phases were washed with water, with saturated sodium chloride solution and dried over magnesium sulfate. The ether was evaporated, followed by distillation under reduced pressure, yield 8.9 g (58%), mp 39-40°, bp 72-74°/0.5 mm Hg (lit [31] mp 42-43°).

2-Phenyl-5-tributylstannylthiophene.

To a stirred solution of 8.0 g (0.050 mole) of 2-phenylthiophene in 200 ml of dry ether under nitrogen, 35 ml (0.055 mole) of butyllithium was added dropwise at such a rate that moderate reflux was maintained. The solution was refluxed for 30 minutes, followed by cooling to -70° whereupon 16.3 g (0.050 mole) of tributylstannyl chloride dissolved in 30 ml of dry ether were added at such a rate that the temperature did not exceed -70°. 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 200 ml of aqueous phase was extracted with three 50 ml portions of ether. The combined ethereal phases were dried over magnesium sulfate and the ether was evaporated followed by distillation under reduced pressure, yield 16.6 g (74%), bp 183-186°/0.30 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.44 (d, 1H), δ 7.15 (d, 1H) ppm.

Anal. Calcd. for $C_{22}H_{34}SSn$: C, 58.8; H, 7.63; S, 7.14. Found: C, 58.8; H, 7.56; S, 6.98.

Trimethylstannylbenzene.

To a stirred solution of 10.0 g (0.064 mole) of bromobenzene in 100 ml of dry ether under nitrogen, 47 ml (0.070 mole) of butyllithium was added dropwise at such a rate that moderate reflux was maintained. The solution was refluxed for 30 minutes, followed by cooling to -70° whereupon 12.7 g (0.064 mole) of trimethylstannyl chloride dissolved in 30 ml of dry THF was added at such a rate that the temperature did not exceed 70°. 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 200 ml of aqueous phase was extracted with three 50 ml portions of ether. The combined ethereal phases were dried over magnesium sulfate and the ether was evaporated, followed by distillation under reduced pressure, yield 8.4 g (55%), lit [27] 45-50%, bp 76-78°/13 mm Hg, (lit 88.5°/16 mm Hg).

5,5'-Diphenyl-2-2'-bithienyl (**15**).

A 25 ml flask, equipped with condenser and magnetic stirrer was charged with 0.80 g (1.78 mmoles) of 2-phenyl-5-tributylstannylthiophene, 62 mg (0.089 mmole) di(triphenylphosphine)palladium (II) dichloride and 5 ml of dry THF. The reaction mixture was refluxed for 15 hours with vigorous stirring under nitrogen. After cooling to room temperature, the THF was evaporated and the crude reaction mixture was separated chromatographically on silica gel 60 using 1:9 followed by 2:1 ethyl acetate:heptane as the eluent, yield 7 mg (2.5%), (lit [30] 19%), mp 235°, (lit 237°); ms Calcd: 318.1. Found: 318.

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