Synthesis of Various 5-Substituted 2'-Deoxy-3'-5'-di-*O*-Acetyluridines

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The Pd(0)-catalyzed coupling reaction of β-5-iodo-2'-deoxy-3',5'-di-*O*-acetyluridine with various heteroaryltrimethylstannyl compounds gave the corresponding β-5-heteroaryl-2'-deoxy-3',5'-di-*O*-acetyluridines in moderate yields. This direct coupling approach for nucleosides represented an interesting alternative to the 5-heteroaryl functionalization of pyrimidines followed by the Hilbert-Johnson glycosylation reaction which often yields mixtures of the α and β anomers.

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Introduction.

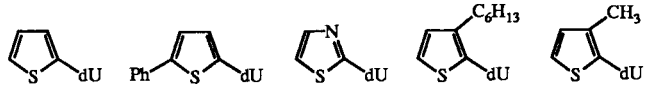
A recent poster at the 9th International Round Table, Nucleosides, Nucleotides and their Biological Application by P. Wigerinck *et al* on the synthesis of 5-(2-thienyl)-2'-deoxyuridine, has prompted us to publish related work, which was patented a few years ago [1]. In connection with work on potential antiviral compounds, we wished to prepare 5-substituted 2'-deoxy-3',5'-di-*O*-acetyluridines with various heterocyclic aryls such as thiophene, phenylthiophene, thiazole, 3-*n*-hexylthiophene and 3-methylthiophene connected to the 5-position, by a general reaction route. Various 5-heteroaryl-substituted uracils have previously been synthesized by the Pd(0)-catalyzed coupling of 5-bromo-2,4-di-*t*-butoxypyrimidine with heteroarylic boronic acids, as well as by using the reversed coupling functionalities [2,3]. Both 5-iodouracil and 5-bromo-2,4-di-(trimethylsilyloxy)pyrimidine have been coupled with various heteroaryl tin compounds [3]. 2'-Deoxyuridines substituted at C-5 by aryl or heteroaryl were previously prepared by palladium-catalyzed reactions of organozinc reagents [4]. 5-Heteroaryl-2'-deoxyuridines [5] and some 5-heteroaryl-2'-deoxyuridine-5'-phosphates [6] have been photochemically prepared. Some 5-phenyl-2'-deoxyuridines have been prepared by a palladium-catalyzed coupling reaction of 5-(chloromercuri)-2'-deoxyuridine with various iodobenzenes [7,8]. Another route to 5-phenyl- or 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine was the photochemical coupling of the pertrimethylsilylated 5-iodo-2'-deoxyuridine with benzene or 1,4-dimethoxybenzene [8]. Protected 2-iodo-6-methoxypurine has been used as a key precursor with various organostannanes to obtain functionalized nucleosides by palladium-catalyzed coupling [9]. Tin derivatives, such as 2-methylthio-5-tributylstannylpyrimidine, have been used in the Pd-catalyzed coupling reaction with β-bromostyrene and propenyl bromide to obtain the corresponding alkenylpyrimidines [10]. Uridine triflate has been coupled with organostannanes using palladium as catalyst [11]. The Pd-catalyzed coupling of 5-iodo-2'-deoxy-3'-5'-di-*O*-*p*-toluoyluridine with alkenyl stannanes gave the corresponding 5-alkenyl-2'-deoxyuridines [12]. 5-Aryluridines and 5-aryl-2'-deoxyuridines were obtained by the Pd-catalyzed coupling of 5-iodouridine and 5-iodo-2'-deoxyuridine with arylboronic acids and aryltrimethylstannanes [13].

Results and Discussion.

We prepared β-5-(2-thienyl)- (**1**), β-5-(2-phenyl-5-thienyl)- (**2**), β-5-(2-thiazoyl)- (**3**), β-5-(3-*n*-hexyl-2-thienyl)- (**4**), and β-5-(3-methyl-2-thienyl)-2'-deoxy-3',5'-di-*O*-acetyluridine (**5**) by the Pd(0)-catalyzed coupling reaction of β-5-iodo-2'-deoxy-3',5'-di-*O*-acetyluridine [14] with trimethylstannyl compounds in moderate yields, (24-56%), Scheme 1.

Scheme 1

5-aryl-2'-deoxy-3'-5'-di-*O*-acetyluridines (5-Aryl dU)



1 **2** **3** **4** **5**

2-Trimethylstannylthiophene [15] and -thiazole [16] are previously known. Compounds **4** and **5** were prepared to be lipophilic modifications of **1**; the higher lipophilicity might improve the CNS penetration [17]. All compounds were purified from the tin residues and other by-products by repeated extractions with water [18], followed by column chromatography using silica gel 60 as solid phase and 2.5 methanol:97.5 dichloromethane as eluent. However if any traces of tin remained after the work up procedure, in analogy with the case when mercury is present [19], false biological data could be a problem. Compounds **4** and **5** were obtained as mixtures with ⅓ of the reactant after the chromatographic purification. The yields of **4** and **5** were calculated from ^{1}H nmr. Further purification by hplc was performed for **4** and **5** (column: polygosil RP C18, 50*½"). The low yields of **4** (24%) and **5** (28%) were probably due

Table 1
Molecular Weight Data, Yields, Melting Points and Elemental Analyses for some 5-Aryl-2'-deoxy-3'-5'-di-*O*-acetyluridines

Compound	Found MWt (Calc. MWt)	Yield (%)	mp °C	Found C%	H%	N%	Calculated C%	H%	N%
1 – $C_{17}H_{18}N_2O_7S$	395.0921 [a] (395.0913 [a])	44	128-129	51.24 [c]	4.73	6.80	51.77	4.60	7.10
2 – $C_{23}H_{23}N_2O_7S$	471 (471.1)	56	76-77	58.10	4.60	5.90	58.9	4.90	5.90
3 – $C_{16}H_{17}N_3O_7S$	395 (395.1)	50	81-82	48.70	4.20	10.50	48.6	4.30	10.60
4 – $C_{23}H_{30}N_2O_7S$	479.1846 [a] (479.1852 [a])	24 [b]	79-80	58.50 [c]	6.30	5.70	57.7	6.30	5.80
5 – $C_{18}H_{20}N_2O_7S$	408 (408.1)	28 [b]	67-68	53.20	4.90	6.80	52.9	4.90	6.90

[a] M+H. [b] Yields are calculated from ^{1}H nmr. [c] More satisfactory analysis was not obtained after repeated attempts.

Table 2
^{1}H NMR Chemical Shifts (ppm) for some 5-Aryl-2'-deoxy-3',5'-di-*O*-acetyluridines, in DMSO-d_6 for **1-3** and in deuteriochloroform for **4-5**

Compound	Pyrimidine protons			5-Aryl protons			Sugar protons					
	NH3	H6	H3	H4	H5	H1'	H2a'	H2b'	H3	H4	H5ab'	Acetyl
1	11.79	8.03	7.47	7.08	7.50	6.20	2.38	2.61	5.20	4.23	4.31	2.08, 2.02
2 [a]	11.84	8.08	7.50	7.50	–	6.21	2.38	2.63	5.23	4.24	4.33	2.08, 2.04
3	12.02	8.67	–	7.84	7.68	6.25	2.09	2.45	5.25	4.33	4.25	2.16, 2.08
4	8.56	7.63	–	6.95	7.26	6.38	2.22	2.55	5.20	4.20	4.20	2.12, 1.82
5	8.44	7.64	–	6.90	7.25	6.38	2.26	2.53	5.23	4.31	4.31	2.20, 2.12

[a] Phenyl protons are not given.

to the steric hindrance of the 3-hexyl and 3-methyl group connected to the thiophene ring. The steric hindrance around the organostannane [11] is known to reduce the rate of the reaction. In previous work [20] we found that a trimethyltin reagent was more sterically demanding than a similar boronic acid reagent. Finally, one can conclude that the preparation was adequate for **1**, **2** and **3**, but less adequate for **4** and **5**, considering that we previously prepared the corresponding 5-substituted uracils in 77% (**1**), 49% (**3**), 61% (**4**) and 62% (**5**) yield [2,3], from which 2'-deoxynucleosides could easily be obtained [21]. A method that favored the formation of the biologically active β anomer consisted in running the reaction with cupper(I) iodide [22]. However, it should be mentioned that some α-nucleosides are known to exhibit significant antimetabolic properties [23,24,25].

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.

General Procedure for **1**, **2**, **3**, **4** and **5**.

Example: Preparation of 5-(2'-Thienyl)-2'-deoxy-3',5'-di-*O*-acetyluridine (**1**).

A flask, equipped with condenser, and magnetic stirrer was charged with 1.00 g (2.28 mmoles) of 5-iodo-2'-deoxy-3'-5'-di-*O*-acetyluridine, 80 mg (0.114 mmole) of di(triphenylphosphine)-palladium(II) dichloride, 0.68 g (2.74 mmoles) of trimethylstannylthiophene (1.2 equivalents) and 10 ml of dry THF. The reaction mixture was refluxed for 15 hours (compound **4** for 72 hours) with stirring under nitrogen. After cooling to room temperature, the THF was evaporated and 20 ml (50 ml of compound **2**) of ethyl acetate was added. The organic phase was washed with three 10 ml portions of water, and dried over magnesium sulfate. The solvent was evaporated, followed by chromatography, using 2.5:97.5, methanol:dichloromethane as eluent and silica gel 60 as solid phase. Molecular weight data, isolated yields (for **4** and **5** the yields were determined by ^{1}H nmr), melting points and elemental analyses are given in Table 1 and ^{1}H nmr data in Table 2.

2-Phenylthiophene.

A 1 l flask, equipped with condenser, magnetic stirrer and nitrogen inlet, was charged with 15.0 g (0.096 mole) of bromobenzene, 3.31 g (2.87 mmoles) of tetrakis(triphenylphosphine)palladium(0), and 320 ml of ethylene glycol dimethyl ether. After stir-

ring for 10 minutes 13.4 g (0.105 mole) of 2-thiopheneboronic acid [2] 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 and 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 [26] mp 42-43°.

2-Phenyl-5-trimethylstannylthiophene.

To a stirred solution of 8.0 g (0.050 mole) of 2-phenylthiophene in 100 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 10.0 g (0.050 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 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 10.0 g (62%), bp 137-138°/1.3 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.43 (d, 1H), 7.18 (d, 1H), 0.40 (s, 9H) ppm; ms: Found mwt. (M+H) 324.0005. Calcd. mwt. (M+H) 323.9995.

Anal. Calcd. for $C_{13}H_{16}SSn$: C, 48.3; H, 5.0. Found: C, 49.0; H, 5.0. (A more satisfactory analysis for C was unobtainable.)

3-Hexyl-2-trimethylstannylthiophene.

To a stirred solution of 8.0 g (0.032 mole) of 2-bromo-3-hexylthiophene [27] in 50 ml of dry ether under nitrogen, 24 ml (0.035 mole) of butyllithium was added dropwise at such a rate that the temperature did not exceed −70°. The solution was stirred for 30 minutes at −70°, whereupon 7.1 g (0.035 mole) of trimethylstannyl chloride dissolved in 20 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 100 ml of aqueous phase was extracted with three 50 ml portions of ether. The combined etheral phases were dried over magnesium sulfate and the ether was evaporated, followed by distillation under reduced pressure, yield 6.0 g (56%), bp 150-152°/12 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.54 (s, 1H), δ 7.11 (s, 1H), 0.91-2.66 (m, 13H), 0.39 (s, 9H) ppm.

Anal. Calcd. for $C_{13}H_{24}SSn$: C, 47.16; H, 7.31; S, 9.68. Found: C, 47.26; H, 7.55; S, 9.84.

3-Methyl-2-trimethylstannylthiophene.

To a stirred solution of 5.0 g (0.028 mole) of 2-bromo-3-methylthiophene [28] in 50 ml of dry ether at −70° under nitrogen, 15 ml (0.031 mole) of butyllithium was added dropwise at such a rate that the temperature did not exceed −70°. The solution was stirred for 30 minutes at −70°, whereupon 6.2 g (0.031 mole) of trimethylstannyl chloride dissolved in 20 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 100 ml 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 5.0 g (68%), bp 110-111°/13 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.52 (s, 1H), 7.05 (s, 1H), 1.55 (s, 3H), 0.38 (s, 9H) ppm; ms: Found mwt. (M+H) 261.9832. Calcd. mwt. (M+H) 261.9838.

Anal. Calcd. for $C_8H_{14}SSn$: C, 36.82; H, 5.41; S, 12.29. Found: C, 36.23; H, 5.34; S, 11.99. (A more satisfactory analysis for C was unobtainable.)

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