PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF ORGANOSTANNANES WITH NUCLEOSIDE HALIDES

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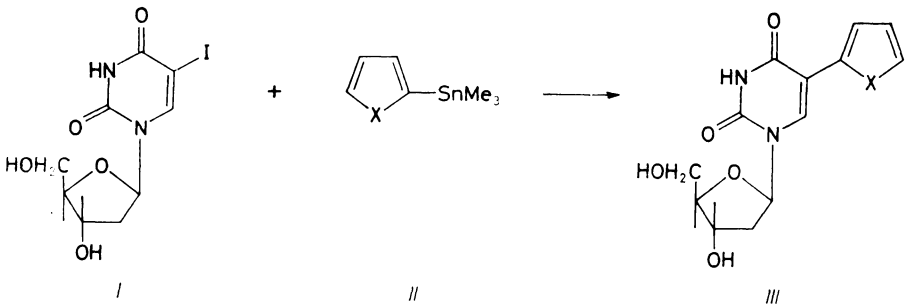
A general reaction is described for the synthesis of C-5 substituted nucleosides through the coupling of organostannanes with nucleoside–palladium intermediate derived in situ from 5-iodouridine (or 5-iodo-2′-deoxyuridine) and $[PdCl_2(PPh_3)_2]$. The reaction was used for the synthesis of C-5 aryl, heteroaryl, vinyl, allyl and alkyl substituted nucleosides.

Several C-5 modified nucleosides and nucleotides have found significant applications as antiviral and antitumor agents[1,2]. However, synthetic methodology for linking the side chain at C-5 position of pyrimidine nucleosides is very limited[3–5]. The palladium-mediated olefination reaction of 5-mercurated nucleosides is remarkably tolerant of the wide variety of functional groups present in the nucleosides and represents a useful synthetic procedure which allows for ready access to these compounds. However, the reaction with simple monosubstituted alkenes generally led to complicated product mixture. The reaction of mercurated nucleosides with allylic halides is limited by the problems of allylic halide synthesis and purification[6], while other allylic derivatives afford poor yields and/or additional side products. Saturated alkyl halides, on the other hand, undergo a facile β-hydride elimination in preference to insertion[7].

A promising new palladium-catalyzed unsymmetrical biaryl synthesis was recently described[8] which involves the cross-coupling of trialkylstannanes with aryl halides. However, the exploatation of this approach for the synthesis of 5-heteroaryl and/or 5-alkyl nucleosides has still to be explored.

Unlike aryl Grignard and aryl zinc reagents, aryl and heteroaryl stannanes are insensitive to moisture and are quite stable. They are readily generated in excellent yields by quenching the lithio anion of the aryl or heteroaryl with trialkyl chlorostannane according to known procedures[8–10]. Thus, 5-iodo-2′-deoxyuridine (*I*) when allowed to react with the aryl and heteroaryl stannanes *IIa*–*IId* using bis(triphenylphosphine)palladium(II) dichloride $[PdCl_2(PPh_3)_2]$ as a catalyst in refluxed tetrahydrofuran under nitrogen, affords 5-phenyl, 5-thienyl-, 5-furyl, and 5-(N-methylpyrrol-2-yl)-2′-deoxyuridines *IIIa*–*IIId*, respectively (Scheme 1). The products were identified by NMR and mass spectroscopy and compared to known

standards[11,12] by HPLC. In most cases the yield so obtained was superior to that obtained from the photochemical synthesis of these derivatives[12] (Table I).



I *II* *III*

In formulae *II* and *III*: *a*, X = —CH=CH—; *b*, X = S; *c*, X = O; *d*, X = NCH_3

SCHEME 1

We have also explored the possibility of extending this reaction to the synthesis of 5-alkyl-2′-deoxyuridine derivatives. Therefore, treatment of 5-iodo-2′-deoxyuridine (*I*) with vinyl- (*IVa*), allyl- (*IVb*) or (2-methyl-1-propenyl)tributylstannane (*IVc*) in refluxed tetrahydrofuran in presence of $[PdCl_2(PPh_3)_2]$ afforded 5-(2--ethenyl)-2′-deoxyuridine (*Va*), 5-(2-propen-1-yl)-2′-deoxyuridine (*Vb*) and 5-(2-

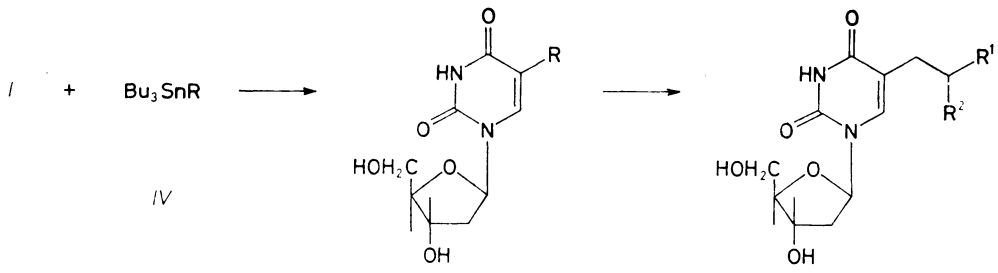
TABLE I

Palladium-catalyzed coupling of nucleosides with organostannanes

Stannane[a]	Product[a]	Yield, %[b]	Structure determination[c]
IIa	*IIIa*	72	ref.[11]
IIb	*IIIb*	69	ref.[12]
IIc	*IIIc*	64	ref.[12]
IId	*IIId*	60	ref.[12]
IVa	*Va*	47	ref.[4]
IVb	*Vb* → *VIb*	55	refs[13]
IVc	*Vc* → *VIc*	57	*d*
IVd	*Vd*	42	*d*

[a] For designation see Schemes 1 and 2. [b] Determined using HPLC and standard solutions. [c] The structure of the product confirmed by NMR, mass spectra and by HPLC comparison with the standards prepared according to the references cited. [d] For NMR and mass spectra see Experimental.

-methyl-1-propenyl)-2′-deoxyuridine (*Vc*), respectively (Scheme 2). These compounds were identified by NMR, mass spectroscopy and compared to known standards. Moreover, the reaction product in each case was subjected to catalytic hydrogenation (Scheme 2) to afford the following 5-alkyldeoxyuridines: 5-ethyl- (ref.[2]), 5-propyl- (ref.[13]), and 5-(2-methylpropyl) derivatives *VIa*–*VId*. The simple alkyl derivative *Vd* was also available by the direct coupling of *I* with tetrabutylstannane *IVd*.



In formulae *IV* and *V*: *a*, R = $CH{=}CH_2$; *b*, R = $CH_2CH{=}CH_2$; *c*, R = $CH{=}C(CH_3)_2$; *d*, R = $(CH_2)_3CH_3$

SCHEME 2

Summarizing, this novel catalytic procedure proved to be a general and efficient one-step synthesis of versatile 5-substituted nucleosides.

EXPERIMENTAL

IR spectra were measured with a Unicam S.P. 2006, and UV spectra with a Perkin–Elmer 554 recording spectrophotometer. ^{1}H NMR spectra were obtained on a Varian 56/69 A and mass spectra on a Varian CH5 mass spectrometer. Unless indicated, C, H, N-analyses were ±0·4% of the calculated values, and were performed at the Microanalytical Centre, Cairo University. HPLC was performed using Partisile PXS 10/25 ODS-II, and preparative Partisile M9-10/50 ODS-2 columns.

Coupling reaction. 5-Iodo-2′-deoxyuridine *I* (1·0 g, 2·82 mmol) in dry tetrahydrofuran (50 ml) was treated with $[PdCl_2(PPh_3)_2]$ (0·34 g, 0·05 mmol) and trialkystannyl derivative (3·5 mmol) and refluxed under nitrogen for 24 h. The black reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (50 ml), and filtered through Celite. The filtrate was washed with 10% ammonium hydroxide solution and with water and then dried ($MgSO_4$). The resulting solution was concentrated in vacuo and resolved on silica gel, using 10% MeOH–$CHCl_3$ solution as an eluent. After the structure had been established, additional studies for characterization and yield determination utilizing HPLC and standard solutions were performed.

Hydrogenation procedure. The nucleosides *Va*—*Vc* (0·1 mmol) were dissolved in methanol (100 ml), treated with 50 mg of 10% Pd/C and stirred under 24 psi of hydrogen for 10 h. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed on silicagel, using 10% methanol in chloroform as an eluent to give hydrogenated products *VIa*—*VIc*, respectively. The product was subjected to HPLC characterization against the standards.

Spectral characterization of some products. a) 5-(2-Methyl-1-propenyl)2′-deoxyuridine *Vc*. ^{1}H NMR (D_2O), δ 1·83 s, 6 H (2 × CH_3); 3·95 m, 2 H; 4·20 m, 2 H; 4·25 m, 1 H; 6·4 s, 1 H (olefinic proton); 6·52 d, 1 H (anomeric proton, J = 4·3 Hz); 7·68 s, 1 H (C-6). Mass spectrum m/z (%) 282 (10, M^+), 167 (36, heterocyclic base + 2 H), 166 (32, base + 1), 165 (62, base), 117 (76, deoxyribose). For $C_{13}H_{18}N_2O_5$ (282·3) calculated: 55·32% C, 6·38% H, 9·93% N; found: 55·73% C, 6·42% H, 9·59% N. *b)* 5-(2-Methyl-1-propyl)2′-deoxyuridine *VIc*, ^{1}H NMR (D_2O), δ 0·93 and 1·26 bm, 7 H (CH_3—CH—CH_3); 2·43 m, 2 H (CH_3—CH_2—CH_3); 3·95 m, 2 H (CH_2OH); 4·28 m, 3 H (3 ribose protons); 6·10 m, 1 H (anomeric proton); 7·78 s, 1 H (C-6). Mass spectrum m/z (%) 284 (12, M^+), 168 (46, heterocyclic base + H), 167 (78, base), 133 (100, deoxyribosyl). *c)* 5-(1-Butyl)-2′-deoxyuridine *Vd*. ^{1}H NMR (D_2O), δ 1·2 d, 6 H (2 × CH_3); 1·67, 1 H (Me—CH—Me); 2·3 t, 2 H; 3·91 m, 2 H; 4·32 m, 3 H; 6·1 m, 1 H (anomeric); 7·70 s, 1 H (C-6). For $C_{13}H_{20}N_2O_5$ (284·3) calculated: 54·93% C, 7·04% H, 9·86% N, found: 55·18% C, 7·21% H, 9·63% N. *d)* 5-(2-Thienyl)2′-deoxyuridine *IIIb*. For $C_{13}H_{14}N_2O_5S$ (310·2) calculated: 50·32% C, 4·52% H, 9·03% N, 10·33% S; found: 50·63% C, 4·86% H, 8·84% N, 10·17% S. *e)* 5-(2-Furyl)2′-deoxyuridine *IIIc*. For $C_{13}H_{14}N_2O_6$ (294·2) calculated: 53·06% C, 4·76% H, 9·52% N; found 53·23% C, 4·88% H, 9·61% N. *f)* 5-(1-Methylpyrrol-2-yl)2′-deoxyuridine *IIId*. For $C_{14}H_{17}N_3O_5$ (307·3) calculated: 54·72% C, 5·54% H, 13·68% N; found: 54·68% C, 5·32% H, 13·79% N. *g)* S-Ethenyl-2′-deoxyuridine *Va*. For $C_{11}H_{14}N_2O_5$ (254·3) calculated: 51·97% C, 5·51% H, 11·02% N; found: 51·76% C, 5·20% H, 10·88% N. *h)* 5-Allyl-2′-deoxyuridine *Vb*. For $C_{12}H_{16}N_2O_5$ (268·3) calculated: 53·73% C, 5·97% H, 10·44% N; found: 53·96% C, 6·02% H, 10·28% N. *i)* 5-Propyl-2′-deoxyuridine *VIb*. For $C_{12}H_{18}N_2O_5$ (270·3) calculated: 53·33% C, 6·67% H, 10·37% N; found: 53·09% C, 6·28% H, 10·52% N.

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