PALLADIUM CATALYZED COUPLING REACTION FOR THE SYNTHESIS OF C-5 ARYL AND HETEROARYL SUBSTITUTED 2'-DEOXYCYTIDINE

Mohamed E. HASSAN

Chemistry Department, Faculty of Science, The African University Aswan, Egypt

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Cytosine nucleosides substituted at C-5 with differently substituted aryls and heteroaryls have been prepared via a palladium catalyzed reaction utilizing 5-chloromercuri or acetoxymercuri nucleosides and haloarenes or heteroarenes.

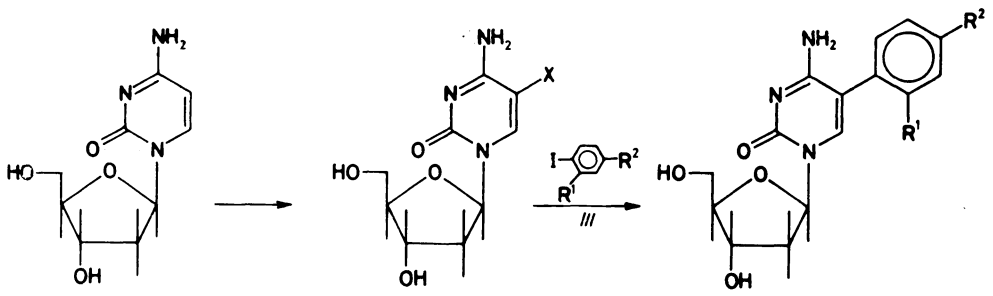
Cytosine nucleosides substituted at 5-position share the chemotherapeutic activity with their deaminated counterparts. Some of them are potential inhibitors of thymidylate synthetase and therefore they might be clinically important as viral inhibitors and antitumor agents[1]. Modified cytosine nucleosides are known to be considerably less toxic to the uninfected host cells in comparison with the modified uracil nucleosides[2].

We have been interested in the development of facile and direct routes for the synthesis of C-5 substituted cytosine derivatives[3]. The direct synthesis of 5-aryluracil nucleosides has been reported by two routes[4,5]. Coupling reactions employing palladium(II) most likely proceed via a mechanism employing palladium(0) (ref.[4]), or by photochemical route which proceed through an initial reactive species from either 5-iodonucleoside or haloaromatic derivatives[5]. In a recent report we extended the photochemical approach to the synthesis of 5-arylcytidine nucleosides[3]; in this paper we wish to report our exploitation of the palladium catalyzed coupling route for the synthesis of these 5-arylcytosine nucleoside derivatives.

Palladium – catalyzed coupling reactions are remarkably tolerant of a wide variety of functional groups[6]. Plevyak and Heck[7] noted that amino, formyl and carboxyl substituents do not affect yields in this reaction. It has been also found that the exocyclic amino group of cytidine does not appear to inhibit its palladium catalyzed allylation reaction[8].

5-Phenyl-2'-deoxycytidine (*IVa*) was prepared by stirring one equivalent of lithium tetrachloropalladate with 5-(chloromercuri)-2'-deoxycytidine (*IIa*) for 1 h followed by iodobenzene (*IIIa*) and continuous stirring for 72 h at room temperature (see Scheme 1). Higher reaction temperature did not facilitate the reaction; stirring at

reflux gave much lower yield (6% compared to 22% in the first case). However, an improved yield (29%), together with more convenient procedure that obviated isolation of the potentially toxic mercurinucleoside intermediate *IIa*, was observed when the nucleoside *I* was converted to the acetoxymercuri derivative *IIb* (ref.[9]) and treated with iodobenzene and lithium tetrachloropalladate in one-pot. The use of catalytic amount (0·1 eq.) of palladium(II) in the presence of excess oxidizing agent like cupric



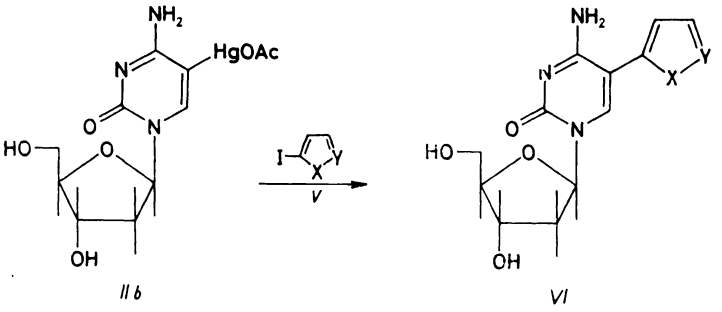
I *IIa*, R = HgCl *IIb*, R = HgOAc *IV*

In formulae *III* and *IV*: *a*, R^1, R^2 = H *b*, R^1, R^2 = OCH_3 *c*, R^1 = H ; R^2 = OCH_3 *d*, R^1 = H ; R^2 = CH_3 *e*, R^1 = H ; R^2 = NO_2

SCHEME 1

chloride (4 eq.) afforded *IV* with insignificant yield reduction (25%). Activation of both the aromatic ring and the nucleoside moiety at carbon-5 are essential, since reactions in which benzene was used instead of iodobenzene, or in which 2'-deoxy--cytidine *I* was used instead of the mercuri derivative *II* failed to give adduct formation.

The presence of two methoxy groups at the aromatic ring increased the yield. Therefore, 5-(2,5-dimethoxyphenyl)-2'-deoxycytidine (*IVb*) was obtained in 43% yield upon treatment of *IIb* with 2-chloro-1,4-dimethoxybenzene (*IIIb*) under the above conditions. 5-(4-Anisyl), 5-(4-tolyl) and 5-(3-nitrophenyl)-2'-deoxy-cytidine (*IVc*–*IVe*) were also prepared under similar conditions from the reaction of *IIb* with *IIIc*, *IIId* and *IIIe* respectively. Surprisingly, the presence of electron releasing or electron withdrawing substituents did not seem to have much effect on the reaction yield in these cases. The reaction was also exploited for the synthesis of 5-heteroaryl nucleosides. 5-(2-Thienyl) and 5-(3-thienyl)-2'-deoxycytidines (*VIa*, *VIb*) were obtained upon treatment of *IIb* with 2-iodothiophen (*Va*) or 3-iodothiophen (*Vb*), respectively. 5-(2-Furyl) and 5-(1-methylpyrrol-2-yl)-2'-deoxycytidines (*VIc*, *VId*) were also obtained under similar conditions (Scheme 2).



IIb *VI*

In formulae *V* and *VI*: *a*, X = S ; Y = CH *b*, X = CH ; Y = S *c*, X = O ; Y = CH
d, X = NCH_3 ; Y = CH

SCHEME 1

EXPERIMENTAL

Melting points were taken on a Fisher–Johns melting apparatus and are uncorrected. IR spectra were measured with a Unicam S.P. 2006, and UV Spectra with a Perkin–Elmer 554 recording spectrophotometer. Mass spectra were obtained on a Varian CH5 mass spectrometer. C,H,N analysis were performed by Cairo University Microanalytical center. HPLC was performed with Partisil PXS 10/25 ODS-II. A solution of 0·1M lithium tetrachloropalladate was prepared by stirring palladium chloride (1·77 g, 10 mmol) and lithium chloride (0·85 g, 20 mmol) in 100 ml of anhydrous methanol at room temperature.

5-Phenyl-2'-deoxycytidine (*IVa*)

A: A suspension of 5-chloromercuri-2'-deoxycytidine (ref.[8]) (1·22 g, 2·55 mmol) and lithium-tetrachloropalladate (28 ml of 0·1 mol l^{-1}, 2·6 mmol) in 30 ml of methanol was stirred at room temperature for 1 h. Iodobenzene (3·6 ml, 3·2 mmol) was added and the reaction mixture stirred for 72 h. Treatment with H_2O and filtration through Celite were followed by neutralization with saturated $NaHCO_3$ solution. Chromatography on a column of 50 g of silica gel using 0—15% methanol in chloroform as eluent gave *IVa* (0·17 g, 22%) of white crystals. M.p. 183°C (ethanol); mass spectrum (*m/z*, %): 303 (7, M^+), 187 (100· 5-phenyl cytosine), 144 (12), 143 (21), 117 (38). For $C_{15}H_{17}N_3O_4$ (303·4) calculated: 59·40% C, 5·61% H, 13·86% N; found 58·96% C, 5·32% H, 13·29% N. UV (MeOH): λ_{max} 280, λ_{min} 250.

B: A solution of 2'-deoxycytidine. HCl (0·67 g, 2·55 mmol) in H_2O (10 ml) was treated with mercuric acetate (0·89 g, 2·7 mmol) and heated at 60°C for 5 h. After evaporation in vacuo, the resulting white solid was suspended in 20 ml methanol and stirred with iodobenzene (3·6 ml, 3·2 mmol) and lithiumtetrachloropalladate (28 ml, 2·8 mmol). Workup was identical with method *A* and gave *IVa* (0·22 g, 29%) after recrystallization.

C: The same procedure described in method *B* with the exception that a catalytic amount of lithium tetrachloropalladate (56 mg, 0·25 mmol) was used together with cupric chloride (1·35 g, 10 mmol) afforded *IVa* in 24·6% yield.

5-(2,5-Dimethoxyphenyl)-2′-deoxycytidine (*IVb*)

A solution of lithium tetrachloropalladate (11 ml, 1·1 mmol) was added to a stirred suspension of 5-chloromercuri-2′-deoxycytidine (0·48 g, 1 mmol) in 10 ml methanol. 2-Chloro-1,4-dimethoxybenzene was added after 1 h and stirring was continued for another 72 h. quenched by saturation with hydrogen sulfide gas, filtration and chromatography (silica gel 25 g, 0·15% MeOH–$CHCl_3$) afforded *IVb* (0·16 g, 43%). Mass spectrum (*m/z*, %): 363 (28, M^+), 274 (9), 247 (100, base), 232 (30), 231 (28), 205 (15). For $C_{17}H_{21}N_3O_6$ (363·5) calculated: 56·20% C, 5·79% H, 11·57% N; found: 55·28% C, 5·28% H, 11·16% N. UV (MeOH) λ_{max} 269, λ_{min} 245.

5-(4-Anisyl)-2′-deoxycytidine (*IVc*)

A solution of 2′-deoxycytidine.HCl (0·26 g 1 mmol) and mercuric acetate (0·32 g, 1 mmol) in 10 ml of water was heated with stirring at 60°C for 5 h. Solvent was removed under vacuo and the white solid residue was suspended in 10 ml methanol and stirred with 4-iodoanisole (0·34 g, 1·5 mmol) and lithium tetrachloropalladate (11 ml, 1·1 mmol) for 72 h. Workup was identical as above and gave *IVc* (0·066 g, 20%). Mass spectrum, (*m/z*, %): 333 (32, M^+) 329 (10), 302 (6), 294 (40), 216 (base), 195 (17), 117 (100, deoxyribose). For $C_{16}H_{19}N_3O_5$ (333·4) calculated: 57·66% C, 5·70% H, 12·61% N; found: 57·82% C, 5·94% H, 12·18% N. UV (MeOH) λ_{max} 279 λ_{min} 248.

5-(4-Tolyl)-2′-deoxycytidine (*IVd*)

5-Chloromercuri-2′-deoxycytidine (0·48 g, 1 mmol) was treated with lithium tetrachloropalladate (11 ml, 1·1 mmol) according to method *A* above. 4-Iodotoluene was added and the reaction mixture stirred for 72 h. Workup as above gave *IVb* (57 mg, 18%) Mass spectrum (*m/z*), %: 317 (21, M^+), 302 (12), 200 (base), 196 (15), 195 (26), 117 (100). For $C_{16}H_{19}N_3O_4$ (317·5) calculated: 60·56% C, 5·99% H, 13·25% N; found: 60·83% C, 6·21% H, 21·87% N. UV (MeOH) λ_{max} 265, λ_{min} 236.

5-(3-Nitrophenyl)-2′-deoxycytidine (*IVe*)

A solution of 1-iodo-3-nitrobenzene (250 mg, 1 mmol) and lithium tetrachloropalladate (11 ml, 1·1 mmol) in 20 ml methanol was stirred for 1 h. 5-(Chloromercuri-2′-deoxycytidine (462 mg, 1 mmol) was added and the reaction mixture was refluxed for 72 h, cooled, saturated with hydrogen sulfide, and filtered through Celite. Workup as above gave *IVe* (56 mg, 16%). Mass spectrum (*m/z*, %): 348 (3·2 M^+), 232 (100, base), 188 (40), 117 (45, deoxyribose). For $C_{16}H_{19}$. $.N_4O_6$ (348·5) calculated: 51·72% C, 4·60% H, 16·09% N; found: 51·96% C, 4·92% H, 16·32% N. UV (MeOH) λ_{max} 272, λ_{min} 245.

5-(2-Thienyl)-2′-deoxycytidine (*VIa*) and 5-(3-Thienyl)-2′-deoxycytidine (*VIb*)

A solution of 2-iodothiophene (0·3 g, 1·5 mmol) and lithium tetrachloropalladate (11 ml, 1·1 mmol) in 20 ml methanol was stirred for 1 h. A separate solution of 2′-deoxycytidine. HCl (0·26 g, 1 mmol) in 10 ml H_2O was treated with mercuric acetate (0·32 g, 1 mmol) and heated at 60°C for 5 h. After the removal of water and acetic acid under vacuo, the resulting white solid was suspended in 10 ml methanol and was added to the first solution and mixture was stirred for 72 h. Workup as above afforded *VIa* (45 mg, 14·5%). Mass spectrum (*m/z*, %): 309 (26, M^+), 193 (100, heterocyclic base), 158 (12), 117 (68, deoxyribose). For $C_{13}H_{15}N_3O_4S$ (309·3) cal-

culated: 50·49% C, 4·85% H, 13·59% N, 10·35% S; found: 50·32% C, 5·41% H, 13·32% N, 10·59% S. UV (MeOH) λ_{max} 274, λ_{min} 256.

Conditions identical with those described above except the use of 3-iodothiophene (0·3 g, 1·5 mmol) afforded *VIb* (37 mg, 12%). Mass spectrum (*m/z*, %): 309·3 (18, M^+), 193 (100, base), 159 (20), 158, 117 (72, deoxyribose). For $C_{13}H_{15}N_3O_4S$ (309·3) calculated: 50·49% C, 4·85% H, 13·59% N, 10·35% S; found: 50·92% C, 5·21% H, 13·21% N, 10·68% S. UV (MeOH) λ_{max} 270 λ_{min} 254.

5-(2-Furyl)-2′-deoxycytidine (*VIc*)

2-Iodofuran (0·29 g, 1·5 mmol) and lithium tetrachloropalladate (11 ml, 1·1 mmol) were stirred in 20 ml methanol for 1 h. Then mixture was treated with a suspention of 5-acetoxymercuri-2′-deoxycytidine (1 mmol) in methanol prepared as described above and stirred for 72 h. Workup as above afforded *VIc* (41 mg, 14%). Mass spectrum (*m/z*, %): 293 (6, M^+), 225 (32), 177 (40, base), 176 (50), 117 (100, deoxyribose). For $C_{13}H_{15}N_3O_5$ (293·3): calculated: 53·24% C, 5·12% H, 14·33% N; found: 53·49% C, 5·66% H, 14·00% N. UV (MeOH) λ_{max} 268, λ_{min} 236.

5-(1-Methylpyrrol-2-yl)-2′-deoxycytidine (*VIb*)

A solution of 2-iodo-1-methylpyrrol (0·3 g, 1·5 mmol) and lithium tetrachloropalladate (11 mol. $.l^{-1}$, 1·1 mmol) in 20 ml methanol was stirred for 1 h. A suspension of 5-acetoxymercuri-2′-deoxycytidine (1 mmol) in methanol was added and refluxed for 72 h. Workup as above gave *VIb* (34 mg, 11%). Mass spectrum (*m/z*, %): 306 (10, M^+), 291 (32), 225 (28), 189 (100, base), 177 (70, deoxyribose). For $C_{14}H_{18}N_4O_4$ (306·4) calculated: 54·90% C, 5·88% H, 18·30% N; found: 54·52% C, 5·64% H, 18·78% N. UV (MeOH) λ_{max} 277, λ_{min} 258.

REFERENCES

1. Lee L. S., Cheng Y. C.: Biochemistry *15*, 3686 (1976).
2. Declercq E., Torrence P. F.: J. Carbohydr. Nucleosides Nucleotides *5*, 187 (1978).
3. Hassan M. E.: Nucleosides Nucleotides, in press.
4. Bigge C. F., Mertes M. P.: J. Org. Chem. *46*, 1994 (1981).
5. Saito I., Ito S., Shimmura T., Matsuura T.: Tetrahedron Lett. *1980*, 2813.
6. Heck R. F.: Acc. Chem. Res. *12*, 146, (1979).
7. Plevyak J. E., Heck R. F.: J. Org. Chem. *43*, 2454, (1978).
8. Ruth J. L., Berstrom D. E.: J. Org. Chem. *43*, 2870 (1978).
9. Dale R. M. K., Martin E., Livingston D. C., Ward D. C.: Biochemistry *14*, 2447 (1975).