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SYNTHESIS OF 5-STYRYL DERIVATIVES OF URACIL NUCLEOSIDES AND NUCLEOTIDES.[1]

Christopher F. Bigge, Panos Kalaritis and Mathias P. Mertes*
Department of Medicinal Chemistry, University of Kansas
Lawrence, Kansas 66045

Summary: Uracil nucleosides and nucleotides undergo a palladium catalyzed coupling reaction with styrenes to yield the respective 5-substituted derivatives.

Synthetic routes to C-5 substituted nucleosides and nucleotides have been limited to tedious primary methods of pyrimidine ring construction followed by condensation of the appropriate halosugar and finally phosphorylation at the primary sugar hydroxyl group to give the nucleotide Alternatively, manipulation of 5-substituted pyrimidine nucleosides or nucleotides requires attention to the appropriate protecting groups. Bergstrom and Ruth[2,3] have reported a palladium catalyzed coupling reaction useful for the preparation of substituted nucleosides. In a route leading to affinity labels for thymidylate synthetase we have found that 5-styryl derivatives of 2'-deoxyuridine can be conveniently prepared in reasonably good yield from the corresponding mercuri-nucleoside and styrene or nitrostyrenes. In addition we found that under the appropriate conditions the reaction was successful in the direct synthesis of 5-substituted uracil nucleotides.

m-Nitrostyrene and 5-chloromercuri-2'-deoxyuridine gave a 45% isolated yield of trans-5-(3-nitrostyryl)-2'-deoxyuridine (Table 1). The use of the acetoxymercuri-nucleoside[4] substantially improved the yield. On the other hand, use of the methanol soluble trifluoroacetoxy-mercuri-nucleoside, prepared from a tetrahydrofuran solution of the nucleoside and an equivalent of mercuric trifluoroacetate, did not offer any yield advantage.

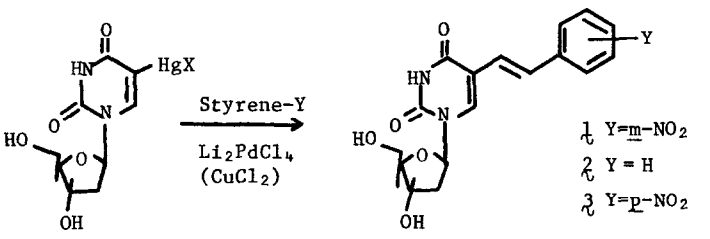
It has been shown that the palladium coupling reactions can be made catalytic with respect to Pd by reoxidizing with cupric chloride.[5] In our studies a two-fold excess of cupric chloride was effective in the synthesis of 1 and 2.

Although it is not reflected in Table 1, the crude yields of 2 were significantly higher than those of 1, but recrystallization did not give a comparable return. The electronic nature of the various styrenes appears to affect the outcome of the reaction as can be seen by the low yields of the p-nitro derivative, 3.

m-Nitrostyrene is electron withdrawing only through inductive effects, whereas p-nitrostyrene is electron withdrawing through resonance effects as well, which suggests that the electron density of the olefin is important in the reaction with the organo-palladium intermediate. However, electronic effects cannot fully account for the lower yield of the p-nitro derivative

since Heck and Nolley found the yield of 4-nitrostilbene exceeded that of stilbene in a palladium catalyzed coupling reaction of iodobenzene with styrene and it's p-nitro derivative.[6] Comparing styrene and the m- or p-nitro derivatives it is unlikely that steric effects play a role in the low yield of the para derivative. Considering the low recovery of starting nucleoside in all of these reactions it would appear that the low yield of compound 3 could be due to an unfavorable balance of side reactions by the palladium nucleoside complex and a lower reactivity for p-nitrostyrene.

Table 1 - Synthesis of 5-Styryl Derivatives of 2'-Deoxyuridine[a]



Compound	Y	X	Li_2PdCl_4[b]	$CuCl_2$	Recrystallized Yield[c]
1	m-NO_2	Cl^-	1.1 mmole	0 mmole	45%
		CH_3COO^-	1.1	0	61%
		CF_3COO^-	1.1	0	47%
		Cl^-	0.1	4	43%
2[d]	H	Cl^-	1.1	0	55%
		CH_3COO^-	1.1	0	50%
		Cl^-	0.1	4	47%
3	p-NO_2	CH_3COO^-	1.1	0	8%

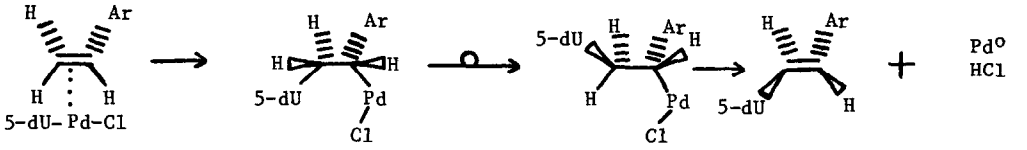
a. The 5-acetoxy- or chloromercurinucleoside (1 mmole) (D.E. Bergstrom and J.L. Ruth, J. Carbohydrates·Nucleosides·Nucleotides, 4, 257 (1977) was suspended in a methanol solution of 3 mmoles of the styrene derivative and 4 mmoles of cupric chloride if indicated. Li_2PdCl_4 (0.1 M MeOH solution) was added to give 1.1 mmoles or 0.1 mmole if cupric chloride was present. After stirring at 25° (X = acetate or trifluoroacetate) or heating to 50° (X=chloride) for several hours the solution was saturated with H_2S, filtered, and the filtrate resolved on silica gel. The product fractions were evaporated and the residue recrystallized. ^{1}H-NMR was the most distinguishing physical characteristic for proving the structures. The ^{1}H-NMR for 1-3 are as follows: 1), trans-5-(3-nitrostyryl)-2'-deoxyuridine ($(CD_3)_2SO$)-δ8.44(s,1,C-6), 8.2-7.5(m,4,aromatic), 7.63(d,1,J = 16Hz,vinyl), 7.10(d,1,J = 16Hz,vinyl); 2), trans-5-styryl-2'-deoxyuridine (CD_3COOD) - 8.2(s,1,C-6), 7.63-6.92(m,5,aromatic), 7.45(d,1,J = 16.5 Hz,vinyl) 6.85(d,1,J = 16.5Hz,vinyl); 3) trans-5-(4-nitrostyryl)-2'-deoxyuridine ($(CD_3)_2SO$) - 8.33(s,1, C-6), 8.23(d,2,J = 9Hz,aromatic), 7.74(d,2,J = 9Hz,aromatic), 7.60(d,1,J = 16Hz,vinyl), 7.13(d, 1,J = 16Hz,vinyl). Each NMR also showed the characteristic 2'-deoxyribosyl peaks. The coupling constant of the vinylic protons in each case indicate that all products are exclusively trans. All compounds were within experimental limits on CHN analysis (±0.4%).

b. A methanol solution was prepared by dissolving $PdCl_2$ (10 mmoles) in 100 mL of methanol containing 20 mmoles of LiCl.

c. Calculated from 2'-deoxyuridine.

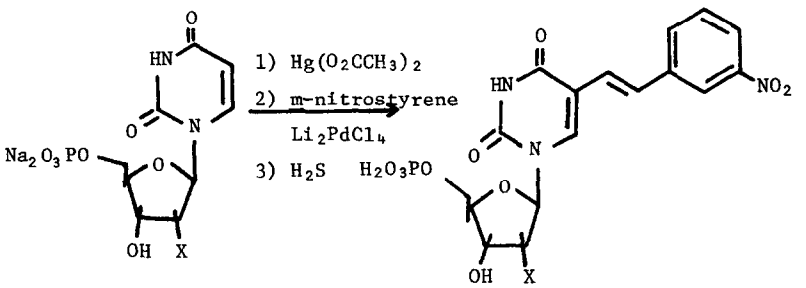
d. The synthesis of this compound recently has been reported, D.E. Bergstrom and M.K. Ogawa, J. Amer. Chem. Soc., 100, 8106 (1978).

Scheme 1



The reaction is believed to proceed via cis addition of the organopalladium compound to the olefin, followed by a cis elimination of hydridopalladium chloride. The less hindered intermediate gives the trans-stereochemistry as shown in Scheme 1.

Since the acetoxymercuri-derivative of the nucleoside gave a better yield than the mercuri-chloride derivative the former was employed in the synthesis of nucleotides. Both uridine 5'-phosphate and 2'-deoxyuridine 5'-phosphate gave the corresponding 5-m-nitrostyryl derivatives via palladium catalyzed coupling of the water soluble acetoxymercuri-nucleotides with m-nitrostyrene. The nucleotide reaction proceeded faster and gave higher yields of the products 6 and 7 than was obtained with the corresponding nucleoside.



4 X = OH
5 X = H

6 X = OH
7 X = H

For the synthesis of 6, 5-acetoxymercuriuridine 5'-phosphate was prepared by adding 2.8 mmoles of mercuric acetate to a water solution (50 ml) of 2.7 mmoles of the disodium salt of uridine 5'-phosphate and the solution maintained at 50° overnight. To this solution at 50° was added a methanol solution (10 ml) containing 10.9 mmoles of m-nitrostyrene; water was added to the suspension until the solution was slightly cloudy. A methanol solution (19.3 ml) containing 3.7 mmoles of Li_2PdCl_4 was added and the solution stirred vigorously at 50° for thirty minutes. After cooling to 25°, hydrogen sulfide gas was bubbled through the stirred solution until a black precipitate formed. The suspension was filtered (Celite), the filtrate concentrated and the crystalline product collected. A 75% yield of 6 was isolated after recrystallization from tetrahydrofuran-ether, m.p. 162-166°d. NMR (D_2O with sodium acetate added to solution) δ8.3-7.6 (m,5,Arom and C-6), 7.5 (d,1,J = 16H,vinyl), 7.2 (d,1,J = 16Hz,vinyl). The elemental analysis for the monohydrate of the phosphate 6 was within ±0.5% of theoretical.

The same procedure was used in the preparation of 5-(3-nitrostyryl)-2'-deoxyuridine 5'-phosphate (7) in 69% yield starting with 1.26 mmoles of the disodium salt of 2'-deoxyuridine 5'-phosphate (5), m.p. 156-160° (soften) 225-230°d: NMR of 7 (D_2O with sodium acetate added to solution)

δ8.0-7.4 (m,5,Arom and C-6) 7.76(d,1,J = 16Hz,vinyl) 7.03 (d,1,J = 16Hz,vinyl). The remainder of the NMR spectra for 6 and 7 was consistent with the expected chemical shifts for the sugar protons.

REFERENCES AND NOTES

1. This work was supported by a grant (CA7522) from the National Cancer Institute, National Institutes of Health.

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