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Palladium(0) Catalyzed Coupling Reactions in the Synthesis of 5-Arylpyrimidine Nucleosides

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Summary: The palladium(0) catalyzed coupling reaction of aryliodides and 3`,5`-di-O-acetyl-5-chloromercuri-2`-deoxyuridine (**1**) gave 5-aryl substituted 2`-deoxyuridines. Optimum yields were obtained in diglyme at 120° for 3 hours.

Synthetic approaches for the direct preparation of pyrimidine nuclosides with an aromatic substituent at carbon-5 of the pyrimidine ring are limited principally because of the reactive functional groups present in the nucleoside. Photochemical methods for the preparation of 5-phenyluridine and the 2`-deoxy analog have been described. Saito and coworkers[2] obtained the former compound by irradiation of the isopropylidene derivative of 5-iodouridine in benzene-acetonitrile. Similarly, 5-phenyl-2`-deoxyuridine and 5-(2,5-dimethoxyphenyl)-2`-deoxyuridine 5'-phosphate were prepared by photochemical coupling of the silyl derivatives of 5-iodo-2`-deoxyuridine or its 5`-phosphate with the respective aromatic compound[3]. In this earlier study on the preparation of 5-arylpyrimidine nucleosides and nucleotides, a palladium(II) catalyzed coupling reaction of iodobenzene and the chloromercuri nucleoside afforded a low yield of the desired product. Pichat and coworkers also noted low yields using palladium(II) catalyzed coupling reactions employing protected 5-iodo-2`-deoxyuridine and arylzinc reagents.[4] In view of the low yields of these reactions and the fact that the only reasonable mechanism that could be postulated employed a palladium(0) species, the reaction of chloromercuri nucleosides and iodoaryl compounds in the presence of palladium(0) is reported.

Aromatic coupling reactions other than the Ullmann reaction have been described recently that utilize nickel(0)[5] and palladium(0)[6] catalysis. Based on the proposed catalytic cycle, the reaction proceeds via an oxidative addition of the aryl halide to complexed palladium(0); the resulting arylpalladium(II) iodide complex couples with an organomagnesium, organolithium, or

organomercury compound to give biaryl products.

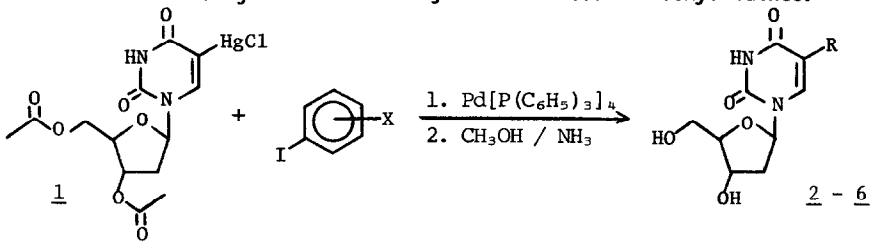
We found that the addition of a tetrahydrofuran solution of tetrakis(triphenylphosphine)palladium(0) and iodobenzene to a suspension of 5-chloromercuri-2`-deoxyuridine[7] in a variety of solvents afforded varying yields of 5-phenyl-2`-deoxyuridine (**2**). Studying the effects of a series of aprotic solvents, at various reaction times and temperatures, showed that the optimum conditions for this coupling reaction involved stirring the mixture at 120°, in diglyme for three hours, affording a 30% yield. The reaction also was shown to be catalytic in palladium(0) since the use of one-sixth of an equivalent afforded the same results.

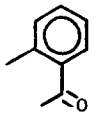
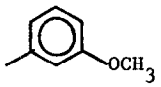
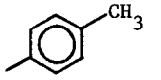
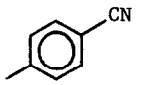
Two obvious factors that could contribute to the low yields of the reaction are the insolubility of 5-chloromercuri-2`-deoxyuridine and the oxidation of palladium(0) by mercuric ion released on product formation; mercury(0) metal was observed as a reaction product. It was apparent that exhaustion of the catalyst was not a factor since the use of one equivalent of tetrakis(triphenylphosphine)palladium(0) or the addition of a second aliquot after the reaction had run for three hours failed to increase the product yield.

In an attempt to make the chloromercuri derivative more soluble, the sugar moiety was protected with acetyl groups. Although the protected chloromercuri derivative **1** and diglyme mixture was still a suspension, after treatment with the complex formed from the aryl iodide and palladium(0), increased product yields were observed as outlined in Table I.

The principal conclusion derived from these studies is that the reaction previously reported[3] on the palladium(II) catalyzed synthesis of 5-phenyl-2`-deoxyuridine (**2**) proceeds via oxidative addition of the aryl iodide to a coordinated palladium(0) species. The subsequent coupling reaction involves transmetallation of this complex with the chloromercuri derivative to give the biaryl palladium(II) complex which collapses to give the product. It is worth noting that the reverse coupling reaction similar to those of Pichat and coworkers[4] but using palladium(0) catalyst also was attempted. A tetrahydrofuran solution of the palladium(0) catalyst and 3`,5`-di-O-trimethylsilyl-5-iodo-2`-deoxyuridine, when added to phenylmagnesium iodide in the same solvent afforded the desired product **2** in 47% yield after acid hydrolysis of the trimethylsilyl groups. The results of this study also demonstrate that the palladium catalyzed biaryl coupling reaction is a convenient method for the arylation of highly functionalized molecules such as pyrimidine nucleosides. The advantages realized over currently available photochemical alternatives[3,11] are regioselectivity in carbon-carbon bond formation and improved yields.

Table 1. Synthesis of 5-Aryl Substituted 2'-Deoxyuridines.[a,b]



Compound	R	Yield[c]	Ultraviolet Data (nm)					^{1}H-NMR[d] (PPM)
			Solvent	max	(ε)	min	(ε)	Carbon-6 H
2		58%	0.1 N HCl 0.1 N NaOH	279 268	(10,700) (8,200)	258 261	(7,900) (8,200)	8.00
3[e]		45%	0.1 N HCl 0.1 N NaOH	275 273	(10,800) (8,700)	248 256	(7,700) (7,900)	7.88
4[f]		54%	0.1 N HCl 0.1 N NaOH	281 277	(10,800) (9,900)	262 266	(8,700) (9,300)	8.04
5[g]		55%	0.1 N HCl 0.1 N NaOH	283 274[h]	(10,300) (9,700)	263	(8,000)	7.91
6[i]		55%	0.1 N HCl 0.1 N NaOH	287 289	(18,500) (16,400)	235 244	(6,600) (7,800)	8.21

[a]3',5'-Di-O-acetyl-5-chloromercuri-2'-deoxyuridine (1) was prepared by dissolving 2'-deoxyuridine (2.0 g, 8.7 mmol) in 30 ml of pyridine followed by the addition of 8 ml (85 mmol) of acetic anhydride. After stirring under an inert atmosphere at room temperature for 12 hours, the solvents were evaporated under vacuum. The remaining residue was dissolved in 20 ml of methanol and 100 ml of water. A solution (100 ml) of mercuric acetate (4.6 g, 14.4 mmol) was added, followed by stirring at 60° for 12 hours. After cooling, a 200 ml aqueous solution of sodium chloride (2.8 g, 48 mmol) was added. The reaction was filtered after 4 hours, and the precipitate was washed with 0.1 N NaCl solution, water, ethanol, and finally ether to give a 90% yield of **1**. Anal. ($C_{13}H_{15}N_2O_7HgCl$, M_r 547.3) Calcd. C, 28.53; H, 2.76; N, 5.12. Found. C, 28.90; H, 3.08; N, 5.30.

[b]The general procedure used in the preparation of the 5-aryl substituted 2'-deoxyuridines was the following which describes the preparation of **2**. A solution containing 742 mg of tetrakis-(triphenylphosphine)palladium(0) (0.64 mmol) and 270 mg of iodobenzene (1.32 mmol) in 5 ml of tetrahydrofuran was stirred at room temperature for 15 minutes. This solution was added to a suspension of 3',5'-di-O-acetyl-5-chloromercuri-2'-deoxyuridine (**1**, 0.65 mmol) in 10 ml of diglyme. The mixture was heated to 120° for 3 hours under an inert atmosphere. After cooling to 25° the black suspension was filtered using Celite. The Celite pad was washed with 20 ml of methanol and the combined organic layers were evaporated to give a viscous brown residue. After evaporation the residue was dissolved in 40 ml of methanol saturated with ammonia and this

solution was allowed to stir at 25° for 12 hours. After evaporation of the solvent, the residue was applied to a silica gel column and the mixture was resolved using 10% methanol in dichloromethane as the elution solvent to give a 58% yield of **2**. The product was recrystallized from methanol, mp 192.5-194°, lit (ref 3) 193-194.5°.

[c]These are yields of isolated products.

[d]The chemical shift of the C-6 proton of the uracil ring was determined in CD_3OD and the assignment is relative to tetramethylsilane.

[e]5-(o-Acetophenyl)-2`-deoxyuridine (**3**): mp 146-147.5°, mass spectrum m/e 346 (0.4, molecular ion), 230 (89, 5-(o-acetophenyl)uracil), 117 (40, 2`-deoxyribose). Anal. ($C_{17}H_{18}N_2O_6 \cdot H_2O$, M_r 364.4). Calcd. C, 56.04; H, 5.53; N, 7.69. Found C, 56.19; H, 5.40; N, 7.60.

[f]5-(m-Methoxyphenyl)-2`-deoxyuridine (**4**): mp 190-191°, mass spectrum m/e 334 (1.5, molecular ion), 218 (100, 5-(m-methoxyphenyl)uracil), 117 (21, 2`-deoxyribose). Anal. ($C_{16}H_{18}N_2O_6$, M_r 334.3). Calcd. C, 57.48; H, 5.43; N, 8.38. Found C, 57.60; H, 5.48; N, 8.48.

[g]5-(p-Methylphenyl)-2`-deoxyuridine (**5**): mp 197.5-198°, mass spectrum m/e 318 (1.5, molecular ion), 202 (100, 5-(p-methylphenyl)uracil), 117 (15, 2`-deoxyribose). Anal. ($C_{16}H_{18}N_2O_5$, M_r 318.3). Calcd. C, 60.37; H, 5.70; N, 8.80. Found C, 60.10; H, 5.50; N, 8.90.

[h]This is a shoulder; no minimum was observed.

[i]5-(p-Cyanophenyl)-2`-deoxyuridine (**6**): mp >300°, mass spectrum m/e 329 (5.9, molecular ion), 213 (22, 5-(p-cyanophenyl)uracil), 117 (37, 2`-deoxyribose). Anal. ($C_{16}H_{15}N_3O_5$, M_r 329.3). Calcd. C, 58.36; H, 4.59; N, 12.76. Found C, 58.49; H, 4.65; N, 12.60.

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