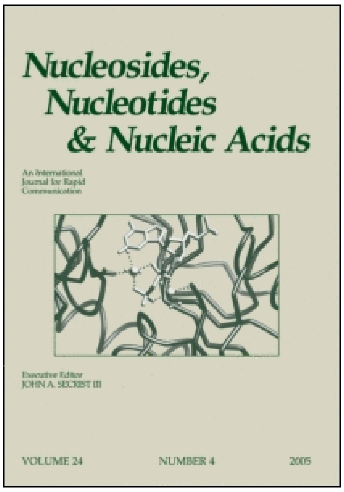


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Aromatic Photosubstitution Reactions for the Synthesis of 5-Aryl-2'-Deoxyuridines

Laman Al-razzak[a]; Mohamed E. Hassan[a]; Mathias P. Mertes[a]
[a] Department of Medicinal Chemistry, School of Pharmacy, University of Kansas Lawrence, Kansas

To cite this Article Al-razzak, Laman , Hassan, Mohamed E. and Mertes, Mathias P.(1983) 'Aromatic Photosubstitution Reactions for the Synthesis of 5-Aryl-2'-Deoxyuridines', Nucleosides, Nucleotides and Nucleic Acids, 2: 3, 243 — 248
To link to this Article: DOI: 10.1080/07328318308078858
URL: http://dx.doi.org/10.1080/07328318308078858

NUCLEOSIDES & NUCLEOTIDES, 2(3), 243-248 (1983)

AROMATIC PHOTOSUBSTITUTION REACTIONS FOR THE SYNTHESIS OF 5-ARYL-2'-DEOXYURIDINES

Laman Al-Razzak, Mohamed E. Hassan and
Mathias P. Mertes*

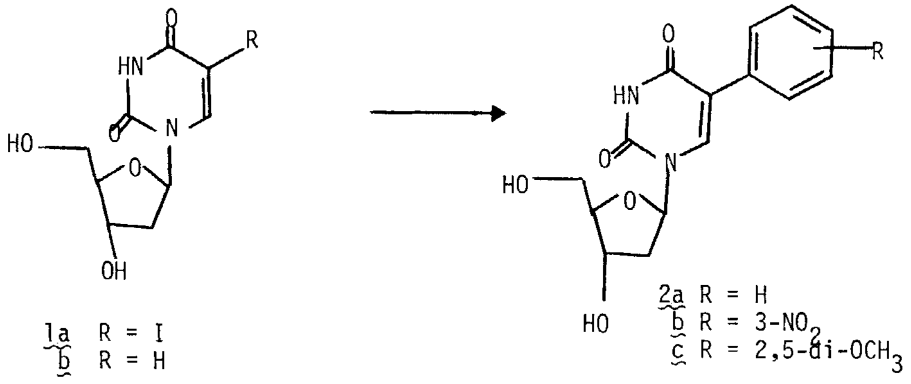
Department of Medicinal Chemistry, School of
Pharmacy, University of Kansas
Lawrence, Kansas 66045

Abstract: The title compounds can be prepared by ultraviolet irradiation of solutions of 5-iodo-2'-deoxyuridine and aromatic compounds or 2'-deoxyuridine and haloaromatic derivatives.

The photochemistry of nucleic acid bases has centered chiefly on the mutational effects of the dimer coupling reactions and the products formed from coupling with amino acids[1] with particular emphasis on the reactions with cysteine,[2] lysine[3] and tryptophane.[4] Extensive mechanism studies have revealed that halopyrimidines proceed via an electron transfer mechanism[3,5] to give the tryptophane adduct[3] or the photoreduction product.[5]

The application of photochemical methods for the practical synthesis of 5-substituted pyrimidines has been found to be a useful entry into unusual adducts.[6] Our interest in this area has been the development of facile routes for the synthesis of aromatic derivatives of pyrimidine nucleosides and nucleotides. The direct synthesis of 5-aryl substituted pyrimidine nucleosides and nucleotides has been reported by two routes.[7] Coupling reactions employing palladium (II) most likely proceed via a mechanism employing palladium (0).[8] Examination of the photochemical route to these derivatives has shown that generation of the initial reactive species from either 5-iodo-

0732-8311/83/0203-0243$3.50/0



1a R = I
b R = H

2a R = H
b R = 3-NO_2
c R = 2,5-di-OCH_3

2'-deoxyuridine (1a) or 5-haloaromatic derivatives is a useful synthetic procedure which allows for ready access to potential antiviral or anticancer agents.[10] Furthermore it has been found that the preparation of the silyl derivatives is not necessary since these reactions can be run in protic solvents.

Irradiation of the trimethylsilyl derivative of 5-iodo-2'-deoxyuridine (1) with aromatic compounds afforded up to 48% yields of the coupled products (TABLE I). It was found the wavelength of irradiation (254 or 300 nm) was not critical since the iodonucleoside absorbed in both regions. However, there appeared to be fewer side reactions using light of 300 nm; consequently product purification was easier. Formation of the trimethylsilyl derivative was required for complete solubility when benzene was used as the solvent and reactant. However, 5-iodo-2'-deoxyuridine (1a) was soluble in a water acetonitrile mixture; the use of this solvent gave slightly lower yields. When nitrobenzene was the substrate in the photosubstitution reaction using compound 1a it was found that the major aryl substituted nucleoside was the meta derivative 2b (7%). Increased yields in these reactions were noted using dilute solutions and the high intensity light source (compare ref. 7).

Since photolysis of bromobenzene in benzene afforded 40% of biphenyl[9] this sequence of reactions was examined for regioselective substitution on the nucleophilic 5-

TABLE I. Photosubstitution Reaction Conditions[a]

Reactants		Solvent	Wavelength (nm)	Yield
5-Iodo-2' deoxyuridine	Benzene	Benzene[b]	254	48%
5-Iodo-2'-deoxyuridine	1,4-Dimethoxybenzene	Acetonitrile[b,c]	254	34%
		Water-acetonitrile[d] (1:3)	254	29%
5-Iodo-2'-deoxyuridine	Nitrobenzene	Acetonitrile[b]	254	7% (meta product)
Iodobenzene	2'-Deoxyuridine	Water-acetonitrile (1:9)	254	10%[e]
2-Chloro-1,4 dimethoxybenzene	2'-Deoxyuridine	Acetonitrile[b]	254	20%[e]
		Water-acetonitrile (1:10)	254	12%[e]
3-Iodonitrobenzene	2'-Deoxyuridine	Acetonitrile[b,f]	254-300	17%
		Water-acetonitrile (2:98)	254	8%

[a] Reactions normally were run for 48 hours.

[b] The nucleoside was converted to the soluble trimethylsilyl derivative.

[c] The reaction was run for 30 hours.

[d] The reaction was run for 40 hours.

[e] Yield was determined by HPLC

[f] The reaction was run for 36 hours.

carbon of uracil nucleosides. Iodobenzene upon photolysis in the presence of 2'-deoxyuridine (1b) gave a 10% yield of the 5-phenyl derivative 2a. Under the same conditions (water: acetonitrile) 3-iodonitrobenzene gave 8% of the 3-nitrophenyl nucleoside 2b. Somewhat improved yields by this sequence were observed using the non-aqueous reaction conditions which required conversion of 2'-deoxyuridine (1a) to the soluble trimethylsilyl derivative.

Experimental:

The compounds prepared in this work were identified by mass and ultraviolet spectroscopy and compared to known standards[7] by HPLC on Partisil PXS 10/25 ODS-II using methanol-water as the solvent. Yields were determined by isolation of the product; after the structure was established additional studies utilized HPLC and standard solutions for yield determination. Rayonet Models RRR 100 and RPR 208 reactors was used; the 254 and 300 nm source lamps and quartz reactions tubes were products of Southern New England Ultraviolet Co.

5-(2,5-Dimethoxyphenyl)-2'-deoxyuridine (**2c**).

Method A: A solution of 5-iodo-2'-deoxyuridine (2.6 g, 7.4 mmol) and hexamethyldisilazine (1.3 g, 8 mmol) in 10 mL of dry pyridine was stirred overnight at 25° in an argon atmosphere. After removal of the pyridine *in vacuo* the residue was dissolved in 100 mL of anhydrous acetonitrile, 1,4-dimethoxybenzene (6.1 g, 44.3 nmol) was added and the solution was deoxygenated by bubbling dry argon gas through the solution. Irradiation at 254 nm for 30 hrs was done at the reactor chamber temperature (40°). This was followed by the addition of 10 mL of a 0.1 N hydrochloric acid in 50% methanol-water. This mixture was stirred for 3 hours at 25° to assure deprotection. After evaporation *in vacuo* the residue was resolved on silica gel using 7% ethanol in chloroform to give 890 mg of the product 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine (**2c**, 34% yield).

Method B: Using the above procedure a solution of 5-iodo-2'-deoxyuridine (**1a**, 1 g, 2.8 mmol) and 1,4-dimethoxybenzene (3.1 g, 22.4 mmol) in 500 mL of 25% water in acetonitrile was irradiated at 254 nm for 40 hr. The brown mixture was evaporated *in vacuo*, the residue extracted with hexane (4 X 15 ml), and the hexane insoluble fraction resolved on silica gel using 10% ethanol in chloroform; the product **2c** (306 mg) was isolated in 29% yield.

Method C: Using the same procedure described in Method A 100 mg of 2'-deoxyuridine (**1b**, 0.4 mmol) and 450 mg of hexamethyldisilazine (2.8 mmol) in 2 mL of pyridine was stirred overnight. The residue after evaporation *in vacuo* was dissolved in 30 mL of acetonitrile containing 6.4 g of 2-chloro-1,4-dimethoxybenzene (37 mmol) and irradiated for 48 hr at 254 nm. The product **2c**, identified by HPLC fractionation and the ultraviolet spectrum, was formed in 20% yield.

Method D: Following the procedure described in Method B 100 mg of deoxyuridine (**1b**, 0.4 mL) and 6.4 g, of 2-chloro-1,4-dimethoxybenzene (37 mmol) in 31 mL of 3% water in acetonitrile was irradiated for 48 hr. The yield of **3c** as determined by HPLC was 12%.

Acknowledgement: This work was supported by a research grant (CA 7522) from the National Cancer Institute of the National Institutes of Health.

REFERENCES

1. Wang, S. Y. *Photochemistry and Photobiology of Nucleic Acids*, Academic Press, New York, N. Y. 1976.
2. Williams, G. J. B.; Varghese, A. J.; Berman, H. M. *J. Am. Chem. Soc.* 1977, **99**, 3150-3154.
3. Saito, I.; Sugiyama, H.; Ito, S.; Furukawa, N.; Matsuura, T. *J. Am. Chem. Soc.* 1981, **103**, 1598-1600.
4. Ito, S.; Saito, I.; Matsuura, T. *J. Am. Chem. Soc.* 1980, **102**, 7535-7541.
5. Swanson, B. J.; Kutzer, J. C.; Koch, T. H. *J. Am. Chem. Soc.* 1981, **103**, 1274-1276.
6. a) Swenton, J. S.; Fritzen, E. L.; Shih, C. *J. Org. Chem.* 1980, **45**, 4462-4471; b) Shetlar, M. D. *J. Chem. Soc. Chem. Communic.* 1975, 653-654; c) Allen, D. W.; Buckland, D. J.; Hutley, B. G.; Oades, A. C.; Turner, J. B. *J. Chem. Soc., Perkin I*, 1977, 621-624; d) Youssefyeh, R. D.; Lichtenberg, L. *ibid*, 1974, 2649-2654; Saito, I.; Ito, S.; Shinmura, T.; Matsuura, T. *Tetrahedron Lett.* 1980, **21**, 2813-2816.
7. Bigge, C. F.; Mertes, M. P. *J. Org. Chem*, 1981, **46**, 1994-1997.

8. Chang, G.; Mertes, M. P. unpublished results.

9. Matsuura, T.; Omura, K. Bull. Chem. Soc. Jpn., 1966, **39**, 944-947.

10. DeClercq, E.; Balzarini, J.; Descamps, J.; Bigge, C. F.; Chang, C. T.-C.; Kalaritis, P.; Mertes, M. P. Biochem. Pharmacol. 1981, **30**, 495-502.

Received December 30, 1982