Photochemical Functionalization of 6-Azauracils to 5-Substituted-6-Azauracils

John S. Swenton (1) and Robert J. Balchunis

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

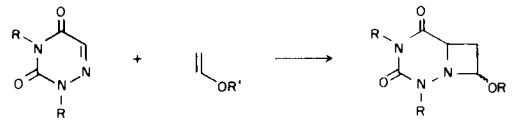
Received May 31, 1974

Photochemical cycloaddition of 6-azauracil derivatives to enol acetates yields hydrolytically labile bicyclic azetidines which decompose in good to excellent yield to 5-substituted-5,6-dihydro-6-azauracils. These compounds can in turn be oxidized by bromine to the 5-substituted-6-azauracil. This reaction sequence has also been applied to 2′,3′,5′-tri-*o*-benzoyl-6-azauridine resulting in a 60% overall yield of the functionalized nucleoside derivative. The three-step procedure reported here affords a simple method for carbon-carbon bond formation at the 5-position of 6-azauracil and may be applicable to other imines systems.

Introduction.

While the *as*-triazine ring system has been known for many years (2), the biological interest in the compounds was not aroused until the 1950's. Compounds of central interest during the intervening years were 6-azauracil (1,2,4-triazine-3,5-(2*H*,4*H*)dione) (3) and its ribosyl derivative. Thus, 6-azauracil itself exhibits anti-microbial potency in a number of systems (4) and more recently 6-azauridine has demonstrated antiviral activity (5). In spite of the potential biological interest of 5-substituted-6-azauracils, the syntheses of substituted compounds are limited to the cyclizations of semicarbazones and thiosemicarbazones of appropriate α-ketoacid derivatives (6). Furthermore, we are unaware of any method of direct functionalization of this position in the more biologically important nucleoside derivatives.

Our interest in the photochemistry of nucleic acid base systems (7) led us earlier to investigate the photoaddition reactions of 6-azauracil to various olefins (8). Thus, sensitized cycloaddition of either **1a** or **1b** to vinyl ethers or vinyl acetates produces 8-substituted-1,2,4-triazabicyclo-[4.2.0]octa-3,5-diones; the 7-substituted derivatives have not been detected in our studies. The biological interest



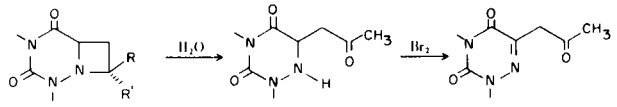
1a R = H
1b R = CH_3

2 **3**

and the lack of a general synthetic route to 5-substituted-6-azauracils coupled with the high synthetic yields observed in our photoaddition studies prompted us to explore the synthetic utility of these photo-reactions. In this work we have exploited the facile hydrolyses of the $-\overset{|}{\underset{|}{N}}-\overset{|}{\underset{|}{C}}-O\overset{O}{\overset{\|}{C}}CH_3$ linkage in the enol acetate cycloadducts to effect high yield functionalization of the 5-position of these systems. We wish to report experimental details for this convenient high yield route to functionalization of 6-azauracil, its 1,3-dimethyl derivative, and its benzoyl protected nucleoside.

Functionalizations of 6-Azauracil Derivatives.

The initial system selected for study was the epimeric cycloaddition products, **4a** and **4b**, obtained from sensitized irradiation of 1,3-dimethyl-6-azauracil and isopropenyl acetate. When the crude irradiation mixture was treated with water there was obtained an 80% yield of crystalline solid. This material showed in addition to N-H absorption in the ir (3.04 μ), two carbonyl absorptions at



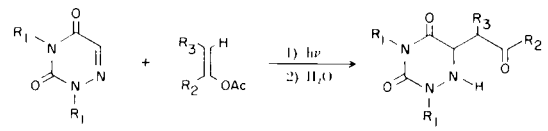
4a R = CH_3, R′ = OAc
4b R = OAc, R′ = CH_3

5 **6**

5.89 and 6.03 μ. The nmr spectrum of **5** was quite simple, showing in addition to the two *N*-methyl groups: the N-H as a singlet at 5.0 δ, the C_5 tertiary proton as a triplet (J = 5 Hz) at 3.86 δ, the methylene group as a partially obscured multiplet at 2.94 δ, and the methyl group as a singlet at 2.19 δ. Finally, oxidation of this material with bromine (9) yielded **6**, whose nmr spectrum consisted of 4 singlets at: 3.71 (2H), 3.63 (3H), 3.34 (3H), and 2.30 (3δ). Thus, the analytical and spectroscopic data, together with the facile oxidation of this compound to **6**, establishes the hydrolysis product as **5**.

To establish the generality of this process, the 6-azauracil itself was utilized for cycloaddition; additionally, the more sterically hindered cyclohexenyl acetate was utilized as the olefinic substrate. The general reaction scheme is shown below and the results are recorded in Table I. While the

SCHEME I



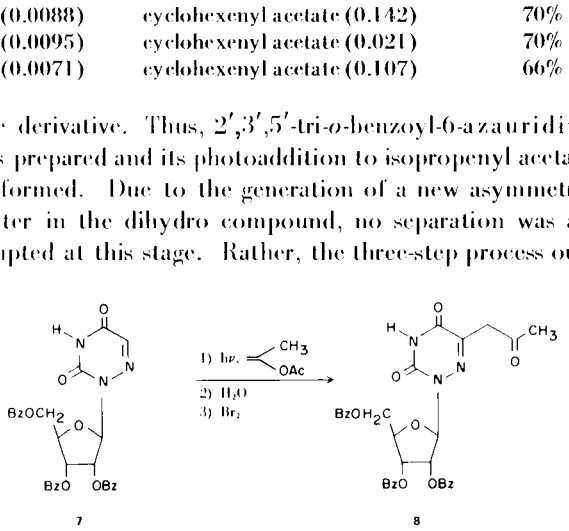
isomeric bicyclic azetidines could presumably be isolated by silica gel chromatography, synthetically this was of no advantage since the photochemical process is remarkably clean. Rather, the crude photolysis mixture was treated with water and the corresponding dihydro compounds obtained as crystalline solids. The yields reported in Table I are those obtained by direct crystallization of the reaction mixture and would undoubtedly be higher had chromatography been employed. The structure of these dihydro compounds was in each case in agreement with analytical and spectroscopic data (see Experimental). The structures were further supported by their oxidation with bromine to the corresponding 6-azauracil derivative.

Having established this method of functionalization for the nitrogen base, we examined the feasibility of extending this reaction sequence to the biologically interesting nucleoside derivative. Thus, 2′,3′,5′-tri-*o*-benzoyl-6-azauridine was prepared and its photoaddition to isopropenyl acetate performed. Due to the generation of a new asymmetric center in the dihydro compound, no separation was attempted at this stage. Rather, the three-step process outlined above was executed affording the functionalized nucleoside in 60% overall yield, demonstrating that this is a practical route to functionalizing nucleoside derivatives.

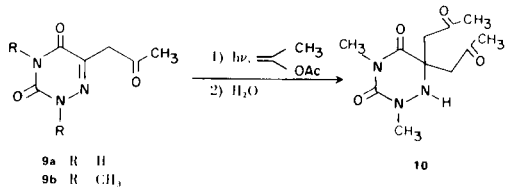
TABLE I

Acetone Sensitized Addition of 6-Azauracils to Vinyl Acetates

6-Azauracil Derivative (moles)	Olefin (moles)	Yield of Hydrolyzed Adduct
1a (0.019)	isopropenyl acetate (0.30)	83%
1b (0.0071)	isopropenyl acetate (0.018)	70%
1b (0.0142)	isopropenyl acetate (0.20)	80%
1a (0.0088)	cyclohexenyl acetate (0.142)	70%
1a (0.0095)	cyclohexenyl acetate (0.021)	70%
1b (0.0071)	cyclohexenyl acetate (0.107)	66%



Finally, it was of some interest if the 5-position of the 6-azauracil system could be functionalized a second time to afford the bis-addition product. Indeed, photoaddition of **9a** or **9b** to vinyl acetate followed by hydrolysis of the crude reaction product afforded **10a** and **10b** in yields of 84 and 75%, respectively. The structures of the products were convincingly established by spectroscopic and analytical data (see Experimental). Thus, it would appear that alkylation of substituted systems can also readily be effected using this procedure.



Discussion.

We have presently demonstrated that the photoaddition of enol acetates to the carbon-nitrogen double bond of 6-azauracil derivatives affords an exceptionally simple procedure for carbon-carbon bond formation at the 5-position. The reactions are simple, characterized by ease of operation and high yields of purified products. We are exploring extensions of this work in other imine systems and other nucleoside derivatives.

EXPERIMENTAL

General Procedures.

Melting points were taken in capillaries in a Thomas-Hoover "Unimelt" apparatus and are corrected. Ir spectra were taken in the indicated phase on either a Perkin-Elmer Model 137 or 467 spectrophotometer. Nmr spectra were recorded at 60 mHz on Varian A-60 and A-60A instruments; spectra were recorded in the indicated solvent and are reported in δ units downfield from internal TMS standard. Unless otherwise noted, irradiations were performed with Corex-filtered light from a 450-watt Hanovia medium-pressure source, in a nitrogen atmosphere. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and by Heterocyclic Chemical Co., Harrisonville, Mo., on recrystallized samples.

Dihydro-2,4-dimethyl-6-(2-oxopropyl)-1,2,4-triazine-3,5-(2*H*,4*H*)-dione.

A solution of 2.0 g. (0.0142 mole) of **1b**, 20.0 g. (0.20 mole) of isopropenyl acetate, and 20 ml. of acetone in 200 ml. of acetonitrile was irradiated for 4 hours. At this time vpc analysis (5′ x 1/8″, 5% SE-30 at 140°) indicated nearly complete consumption of the starting material and formation of a product of greater retention time. The solvent was removed *in vacuo* yielding a clear yellow oil. To this material 50 ml. of water was immediately added and the mixture was heated for a few minutes to approximately 70°,

then stirred at room temperature for 2 hours. This aqueous phase was extracted with methylene chloride (5 x 50 ml.), and the dried extract evaporated to yield a yellow oil which crystallized on cooling. Recrystallization from ethanol/hexane gave an 80% yield (based on **1b**) of white crystals (a 2.6 molar excess of isopropenyl acetate afforded a 70% yield of material); m.p. 90-92°; ir (potassium bromide): 3.04(w) 5.89(s), 6.03(s), envelope of absorptions 6.9-7.9(m), 8.55(m), 8.99(s), 9.7(m), 13.31(m) μ; nmr (deuteriochloroform): 5.00 (s, 1H), 3.84 (t, 1H, J = 5 Hz), 3.20 (s, 3H), 3.12 (s, 3H), 2.90 (m, partially obscured, 2H), and 2.19 (s, 3H) δ.

Anal. Calcd. for C, 48.3; H, 6.57; N, 21.1. Found: C, 48.4; H, 6.63; N, 20.9.

Dihydro-2,4-dimethyl-6-(2-oxocyclohexyl)-1,2,4-triazine-3,5(2*H*,4*H*)dione.

One g. (0.007t mole) of **1b**, 15 ml. of cyclohexenyl acetate and 20 ml. of acetone were dissolved in 75 ml. of acetonitrile. The solution was irradiated 1 hour, at which time tlc analysis (silica gel eluted with ether/hexane) indicated consumption of **1b**. The solvent was removed *in vacuo* at 80-85°. To the resulting residue, 20 ml. of water was added with a few drops of glacial acetic acid and the mixture was stirred at room temperature for 1 hour. The solvent was again removed *in vacuo* with heating and the residue was dried at room temperature at ~0.55 mm. On addition of ether and chilling, the oil crystallized to yield 1.132 g. (66%) of product, m.p. 112-114°; ir (potassium bromide): 3.07(w), 5.84(m), 5.91(m), 6.02(s), 6.98(m), 7.61(m), 9.01(br, m), and 13.41 (m) μ.

Anal. Calcd. for: C, 55.3; H, 7.12; N, 17.6. Found: C, 55.12; H, 7.05; N, 17.56.

Dihydro-6-(2-oxopropyl)-1,2,4-triazine-3,5-(2*H*,4*H*)dione.

Two g. (0.0195 mole) of **1a** was dissolved in 200 ml. of 70% acetone/water with 30 ml. of isopropenyl acetate. This solution was irradiated for 2.5 hours and the solvent removed by heating *in vacuo*. Evaporation of the solvent yielded 2.5 g. (85%) of white solid which was recrystallized from ethanol/water, m.p. 191-193°; ir (potassium bromide): 3.01(br, s), 5.86-6.05(br, s), 6.85(s), 7.43(s), 7.90(s), 8.04(s), 8.49(s), 12.19(br, m), and 13.38(br, m); nmr (DMSO-d_6): 10.20 (s, 1H), 8.79 (s, 1H), 5.40 (d, J = 11 Hz, 1H), multiplet extending from 3.95 to 3.56 (1H), multiplet extending from 2.75 to 2.62 (2H), and 2.14 (s, 3H) δ.

Anal. Calcd. for: C, 42.1; H, 5.30; N, 24.5; Found: C, 42.42; H, 5.58; N, 24.23.

Dihydro-6-(2-oxocyclohexyl)-1,2,4-triazine-3,5-(2*H*,4*H*)dione.

One g. (8.8 mmoles) of **1a** and 3 g. of cyclohexenyl acetate were dissolved in ~80% acetone/water. The solution was irradiated for 1 hour, after which time the solvent was removed *in vacuo* at 80-85° to yield 1.28 g. (69%) of white crystals. The crystals were collected, washed with ether and dried at room temperature at 0.15 mm, m.p. 224-226°; ir (potassium bromide): 3.06(m), 3.17(m), 5.90(s), 7.05(m), 7.55(m), 8.08(m), 12.15(br, m), and 13.18(m) μ.

Anal. Calcd. for: C, 51.2; H, 6.16; N, 19.9. Found: C, 50.99; H, 6.22; N, 19.79.

2,4-Dimethyl-6-(2-oxopropyl)-1,2,4-triazine-3,5-(2*H*,4*H*)dione.

To 500 mg. (0.0024 mole) of the dihydro compound in 15 ml. of water was added with stirring, 400 mg. (0.0025 mole) of bromine in 15 ml. of water. The reaction was complete in approximately two minutes (bromine color dissipated) and the mixture was extracted (3 x 30 ml.) with chloroform. The extract was dried and evaporated *in vacuo* to yield a crystalline product which was recrystallized from ethanol/hexane to yield 375 mg. (75%) of white needles, m.p. 102-103°; ir (potassium bromide): 5.92(m), 6.13(s), 6.90(m), 7.63(m), 8.64(m), 9.54(m), 13.28(m), and 13.46(m) μ; nmr (deuteriochloroform): 3.71 (s, 2H), 3.63 (s, 3H), 3.34 (s, 3H), and 2.30 (s, 3H) δ.

Anal. Calcd. for: C, 48.6; H, 5.63; N, 21.3. Found: C, 48.6; H, 5.86; N, 21.03.

2,4-Dimethyl-6-(2-oxocyclohexyl)-1,2,4-triazine-3,5-(2*H*,4*H*)dione.

The dihydro compound (239 mg., 0.001 mole) was added to 10 ml. of water with enough ethanol to dissolve the solid. To the ethanolic-water solution was added 160 mg. (0.001 mole) of bromine. The color was instantaneously dissipated and the volume of solvent was then reduced *in vacuo* with heating. Chilling the solution produced 170 mg. (71%) of white crystals, m.p. 128.5-130°; ir (potassium bromide): 5.88(s), 6.05(s), 6.94(m), 7.46(m), 7.56(m), 8.91(m), 10.20(m), 13.44(m), and 13.92(m) μ; nmr (deuteriochloroform): 3.58 (s, 3H), 3.30 (s, 3H), 2.17 to 1.50 (broad envelope, 9H) δ.

Anal. Calcd. for: C, 55.7; H, 6.34; H, 17.7. Found: C, 55.52; H, 6.36; N, 17.64.

6-(2-Oxopropyl)-1,2,4-triazine-3,5-(2*H*,4*H*)dione.

To 1.5 g. (0.0088 mole) of the dihydro compound in 75 ml. of water was added 1.4 g. (0.088 mole) of bromine. The mixture was stirred at room temperature until the bromine color was completely dispersed. At this time the volume of the solvent was reduced by heating *in vacuo* and the solution was cooled to -10°. There was obtained 1.08 g. (72%) of white needles, m.p. 174-176° (from ether/ethanol); ir (potassium bromide): 3.05(s), 5.85(br, s), envelope of absorption 6.99 to 7.56(m), 8.56(m), 11.55(br, m), and 13.60(br, s) μ; nmr (DMSO-d_6): 3.68 (s, 2H), and 2.20 (s, 3H) δ.

Anal. Calcd. for: C, 42.6; H, 4.14; N, 24.8. Found: C, 42.7; H, 4.22; N, 24.79.

6-(2-Oxocyclohexyl)-1,3,4-triazine-3,5-(2*H*,4*H*)dione.

Two hundred mg. (0.95 mmole) of the dihydro compound was dissolved in a mixture of ethanol water. To the solution was added 152 mg. of bromine (0.9 mmole). The reaction was instantaneous and the solvent was removed *in vacuo* to afford 170 mg. (85%) of white crystals, m.p. 239-240°; ir (potassium bromide): 3.0(m), 3.20(m), 5.85(s), 7.01(m), 7.66(m), 8.90(m), and 13.64(m) μ.

Anal. Calcd. for: C, 51.6; H, 5.26; N, 20.1. Found: C, 51.49; H, 5.24; N, 19.92.

Functionalization of 2′,3′,5′-Tri-*o*-benzoyl-6-azauridine (10).

In a mixture of 130 ml. of acetonitrile, 10 ml. of acetone and 10 ml. of isopropenyl acetate was dissolved in 1.0 g. of **7**. The solution was irradiated 1.3 hours, after which time the solvent was removed *in vacuo* at ~ 50°. Thirty ml. of methanol was then added with 3 ml. of water and the solution was allowed to stir to ambient temperature for 23 hours. Additional methanol was added and the solution filtered through Celite. After filtration, water was added until the clear colorless solution became almost cloudy. Bromine was then added dropwise until a yellow color persisted. After stirring at room temperature for 1.0 hour, the volume of the solution was reduced *in vacuo* at ~40°. The mixture thus obtained was extracted with dichloromethane and dried over calcium sulfate. The clear, colorless solution was evaporated *in vacuo* to yield a light yellow oil which was chromatographed on silica gel, 620 ml. of 20% ether/perroleum-ether, nil; 700 ml. 50% ether/petroleum-ether, nil; 750 ml. of ether (100%) ~870 mg. oil; 225 ml. of ether, nil. The oil thus obtained crystallized on standing. The crystals were thoroughly washed with ether to yield 660 mg.

(60%) of **8**, m.p. 147-148°; ir (potassium bromide): 3.09(w), 5.87 (br, s), 6.93(m), 7.94(br, s), 8.98(br, s), and 14.10(br, s) μ; nmr (deuteriochloroform, 60 mHz): 8.00 and 7.43 (m, 15H), 6.61 (d, J = 3.5 Hz, 1H), 6.09 (m, 2H), 4.71 (m, 3H), 3.52 (s, 2H), and 2.19 (s, 3H).

Anal. Calcd. for: C, 62.6; H, 4.33; N, 6.85. Found: C, 62.53; H, 4.39; N, 6.83.

Dihydro-2,4-dimethyl-6,6-di(2-oxopropyl)-1,2,4-triazine-3,5-(2*H*, 4*H*)dione.

In a solution of 7 ml. of isopropenyl acetate, 10 ml. of acetone and 75 ml. of acetonitrile was dissolved 290 mg. (0.00147 mole) of **9b**. The solution was irradiated for 3 hours, after which time the solvent was evaporated *in vacuo* at 60°. The resulting yellow oil was hydrolyzed by the addition of 20 ml. of water and a few drops of acetic acid. After stirring at room temperature for 4 hours, the solution was extracted with methylene chloride (4 x 25 ml.), dried and evaporated. The yellow oil which resulted crystallized upon addition of ether/ethanol to afford 250 mg. (75%) of **10a**, m.p. 96-98°; ir (potassium bromide): 3.01(w), 5.89(s), 5.99(s), structured envelope 6.89 to 7.91, 8.69(m), 8.99(m), 9.60(m), and 13.31(m) μ; nmr (deuteriochloroform): 3.13 (s, 6H), AB quartet centered at 2.92 (4H, J = 16 Hz), and 2.18 (s, 6H) δ.

Anal. Calcd. for: C, 51.7; H, 6.66; N, 16.5. Found: C, 51.74; H, 6.65; N, 16.44.

Dihydro-6,6-di(2-oxopropyl)-1,2,4-triazine-3,5-(2*H*,4*H*)dione.

Three hundred mg. of **9a** (0.00177 mole) was dissolved in 90 ml. of 70% acetone/water, with 7 ml. of isopropenyl acetate. The solution was irradiated for 1 hour, after which time the solvent was removed *in vacuo* at ~80°. There was obtained 340 mg. (84%) of white crystals. Recrystallization was carried out in ethanol/water to yield pure **11**, m.p. 204-206°; ir (potassium bromide): 5.86 to 6.04(br), 7.33(m), 7.94(m), 8.42(m), 13.20(m), and 13.68(br, m) μ; nmr (DMSO-d_6): 10.31 (s, 1H), 8.86 (s, 1H), 5.57 (s, 1H), AB quartet centered at 2.79 (J = 16 Hz, 4H), and 2.12 (s, 6H) δ.

Anal. Calcd. for: C, 47.6; H, 5.73; N, 18.5. Found: C, 47.51; H, 5.70; N, 18.53.

REFERENCES

(1) Alfred P. Sloan Fellow, 1971-1973, Camille and Henry Dreyfus Teacher-Scholar, 1972-1977.

(2) S. Thiele and J. Bailey, *Ann. Chem.*, **303**, 75 (1898).

(3) As is customary for compounds of biological interest, the relationship between these compounds and the uracil ring system will be stressed. Thus, the compounds in the text will be referred to as 6-azauracil derivatives while the 1,2,4-triazine nomenclature will be utilized in the experimental section.

(4) J. Skoda, *Progress in Nucleic Acid Research*, Vol. 2, 197 (1963).

(5a) B. Rada, *Ann. N.Y. Acad. Sci.*, **173**, 176 (1970); (b) J. Elis and H. Raskova, *Europ. J. Clin. Pharmacol.*, **4**, 77 (1972).

(6a) For a review see J. Gut, *Adv. in Heterocyclic Chemistry*, **1**, 189 (1963); (b) M. Bobek, J. Farkas, and J. Gut, *Collect. Czech. Chem. Commun.*, **32**, 1295 (1967) and references cited therein.

(7a) J. A. Hyatt and J. S. Swenton, *J. Am. Chem. Soc.*, **94**, 7605 (1972); (b) J. S. Swenton, J. A. Hyatt, J. M. Lisy, and J. Clardy, *ibid.*, **96**, 4885 (1974).

(8a) J. A. Hyatt and J. S. Swenton, *J. Chem. Soc. Chem. Commun.*, 1144, (1972); (b) J. S. Swenton and J. A. Hyatt, *J. Am. Chem. Soc.*, **96**, 4879 (1974); (c) J. S. Swenton and R. Balchunis, *J. Heterocyclic Chem.*, 453, (1974).

(9) G. Grundmann, H. Schroeder, and R. Rätz, *J. Org. Chem.*, 23, 1522 (1958).

(10) U. Niedballa and Helmut Vorbrüggen, *Agnew. Chem. Intern. Edit. Engl.*, 9, 461 (1970).