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PHOTOCHEMISTRY OF 6-HALO- AND 5,6-DIHALOURACILS. A SIMPLE SYNTHESIS OF FLUORESCENT URACIL DERIVATIVES[1]

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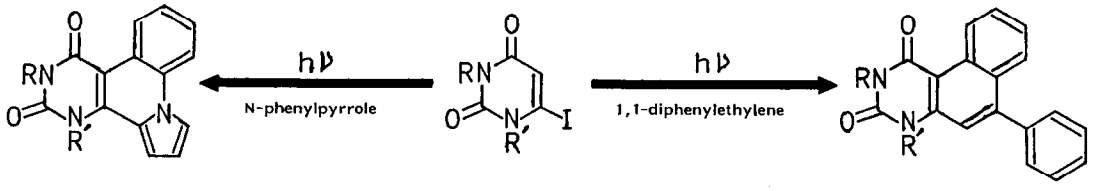
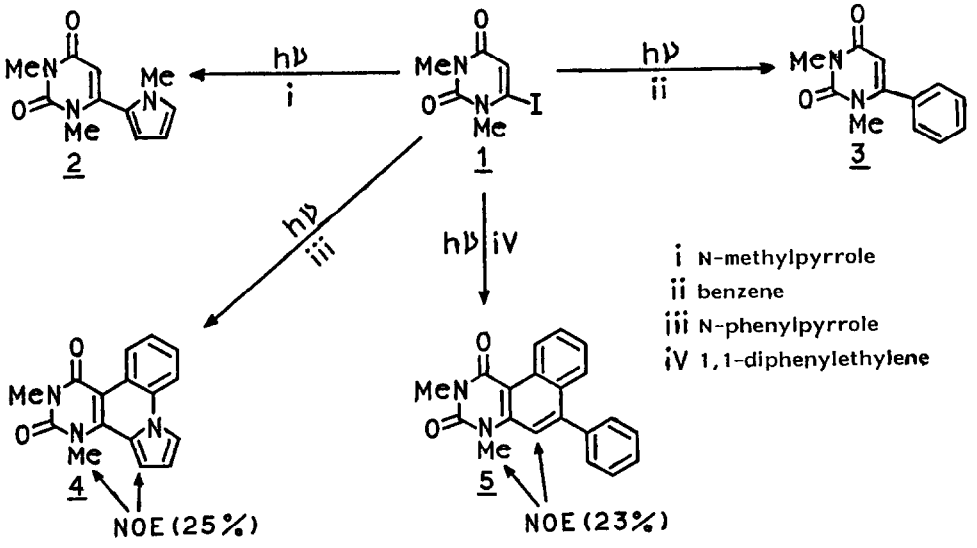
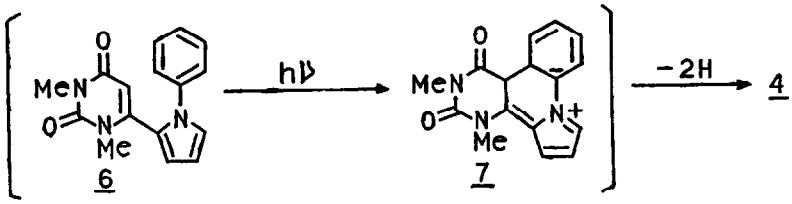
Summary: 6-Iodo- and 5,6-dihalouracil derivatives undergo remarkably efficient photocoupling reactions leading to strongly fluorescent heterocycles in the presence of suitable radical acceptors.

Pyrimidine base analogues of high photochemical reactivity are an intriguing class of compounds for modification of nucleic acids and their monomeric units.[2,3] Uracil derivatives that can produce strongly fluorescent chromophores upon UV irradiation are of particular importance for investigating the structure and function of nucleic acids in macromolecular complexes.[2,4] Such a photoreaction leading to fluorescent heterocycles would also be of a considerable synthetic utility. In this context photochemistry of 5-halouracils has been extensively studied[5,6] and was used for investigating structures of macromolecular complexes as a cross-linking reagent.[7] In a continuation of our studies on the photochemistry of nucleic acid bases, we now report that 6-iodo- and 5,6-dihalouracil derivatives undergo remarkably efficient photocoupling reactions leading to strongly fluorescent products in the presence of radical acceptors such as benzene, N-substituted pyrroles and 1,1-diphenylethylene as typically exemplified below.

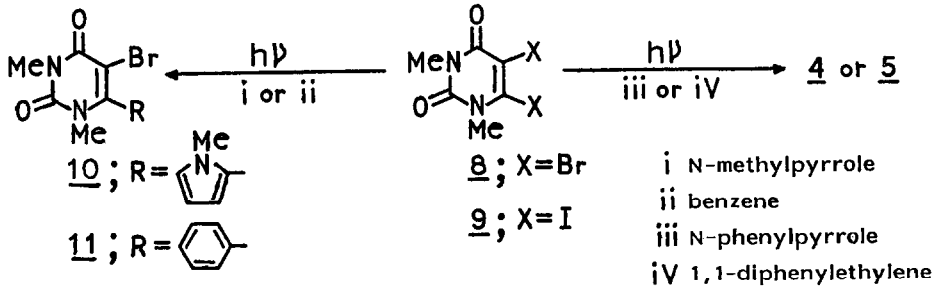


6-Iodo- (1) and 5,6-diiodo-1,3-dimethyluracil (9)[8] are readily available from the corresponding 6-lithiated uracil by quenching with iodine.[9,10] 5,6-Dibromo-1,3-dimethyluracil (8) was prepared as described earlier.[10] Irradiation of 1 (0.38 mmol) in benzene (200 mL) with a 400 W high-pressure Hg lamp (Pyrex filter) at ambient temperature produced 3 (89%) as a single product, whereas 2 (79%) was obtained regiospecifically in irradiation of 1 with N-methylpyrrole (10 eq) in acetonitrile. However, irradiation of 1 (0.38 mmol) in the presence N-phenylpyrrole (10 eq) in acetonitrile (50 mL) under the conditions produced a strongly fluorescent product 4 (57%). The structure of 4 was confirmed by its spectral data[11] including NOE measurement of the 400 MHz ^{1}H NMR spectrum. The formation of 4 would be explained by the attack of the 6-uracilyl radical formed by homolysis of 1 to the α-position of N-phenylpyrrole giving 6 which then undergoes further photocyclization to 4 probably via 7.[12] Similarly, irradiation of 1 with 1,1-diphenylethylene (10 eq) in acetonitrile under the conditions gave the fluorescent product 5[11] (58%) whose structure was again confirmed by ^{1}H NMR NOE technique. These results demonstrate the synthetic usefulness of the photochemistry of 6-iodouracil as a route to a variety of C-6 substituted and C-5, C-6 fused uracil derivatives which are not readily accessible by other routes.[13]





A similar photoaddition has been observed with 5,6-dihalo-1,3-dimethyluracils (8, 9). Irradiation of 8 with N-phenylpyrrole (10 eq) and 1,1-diphenylethylene (10 eq) in acetonitrile gave 4 (46%) and 5 (27%), respectively. Photoreaction of 8 with N-methylpyrrole gave exclusively 10[11] (85%). There was no indication for the formation of the regioisomers. These results indicate that the C-6 uracilyl radical is preferentially formed by photolysis of 5,6-dibromo-1,3-dimethyluracil (8). In fact, irradiation of 8 in benzene for 6 h afforded 5-bromo-6-phenyluracil derivative 11 (45%) as a major product together with a small amount of 12 (less than 5%), although prolonged irradiation (24 h) increased the yield of 12 up to 15%. Such C-6 substituted 5-halouracils are useful intermediates for further manipulation. Strongly fluorescent uracil 12[8] (30%) was more easily prepared by irradiation of 5,6-diiodouracil 9 in benzene.



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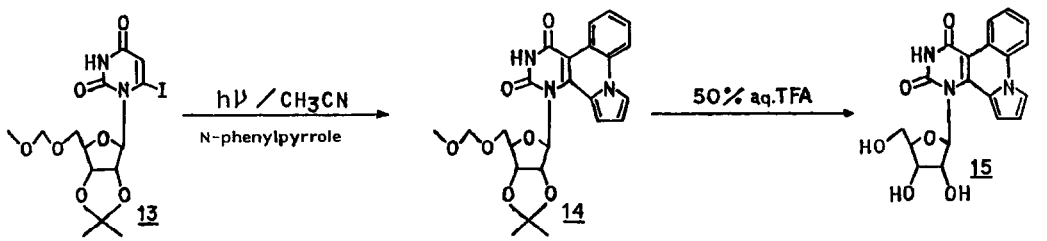
Finally, we note the application of this photoreaction to the synthesis of a fluorescent nucleoside as illustrated below. 6-Iodouridine 13 prepared by trapping of the protected



6-lithiated uridine (LDA/THF/-78 °C) with ICl was converted to 14 (27%) by irradiation with N-phenylpyrrole. Deprotection gave the fluorescent nucleoside 15[11] (70%).

References and Notes

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11. 4: mp 255-258 °C; ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3 H), 3.97 (s, 3 H), 6.68-6.83 (m, 1 H), 7.11-7.50 (m, 3 H), 7.58-7.73 (m, 1 H), 7.81-8.00 (m, 1 H), 9.33-9,68 (m, 1 H); λ_{max} (EtOH) 355 nm (ε 15000), 274 (16300), 266 (36200); fluorescence emission λ_{max} (CH_3CN) 420 nm; 5: mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 3 H), 3.70 (s, 3 H), 7.00-7.80 (m, 9 H). 9.68 (d, J = 8 Hz, 1 H); UV (EtOH) λ_{max} 361 nm (ε 4310), 347 (4580), 314 (7510), 258 (27600); fluorescence emission λ_{max}(CH_3CN) 435 nm; 10: mp 126 °C; ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3 H), 3.42 (s, 3 H), 3.50 (s, 3 H), 6.10-6.30 (m, 2 H), 6.70-6.80 (m, 1 H); UV λ_{max}(CH_3CN) 288 nm (ε 6600), 220 (10600); 15: mp 230-240 (dec); ^{1}H NMR (CD_3OD) δ 2.20-2.45 (m, 2 H), 3.51-3.75 (m. 1 H), 3.80-4.15 (m, 2 H), 6.31 (brs, 1 H), 6.96-7.01 (m, 1 H), 7.45-7.51 (m, 1 H), 7.57-7.64 (m, 1 H), 7.71-7.76 (m, 1 H), 8.12-8.20 (m, 1 H), 8.35-8.40 (m, 1 H), 9.50-9.55 (m, 1 H), UV λ_{max} (CH_3OH) 380 nm (ε 4470), 365 (4470), 268 (10900), 253 (7020); fluorescence emission λ_{max} (CH_3OH) 430 nm.
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