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PHOTOCYCLOADDITION OF 6-CHLORO-1,3-DIMETHYLURACIL TO ALKENES: SYNTHESIS OF 1,2-DIHYDROCYCLOBUTA[d]PYRIMIDINE-4,6(3H,5H)-DIONES[1]

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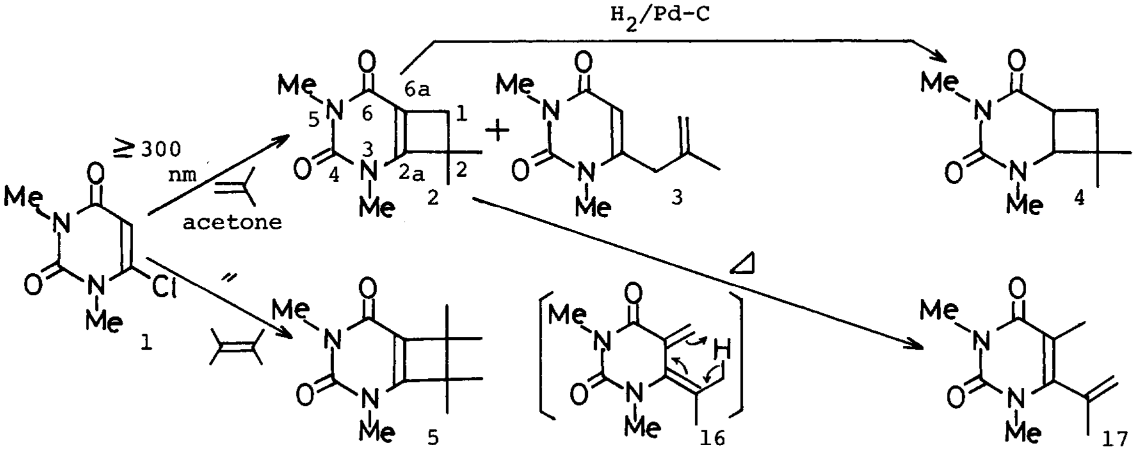
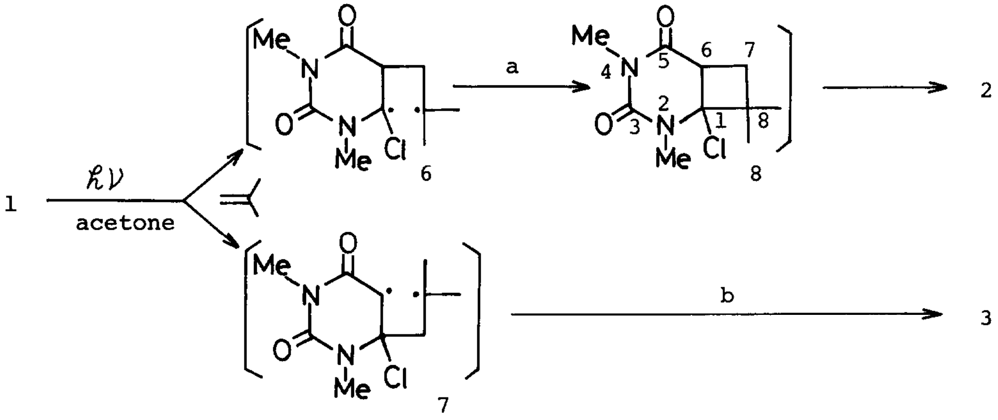
Summary: The acetone-sensitized photocycloaddition of 6-chloro-1,3-dimethyluracil to alkenes affords directly 1,2-dihydrocyclobuta[d]pyrimidine-4,6(3H,5H)-diones *via* 1-chloro-2,4-dimethyl-2,4-diazabicyclo[4.2.0]octa-3,5-diones.

While photochemical cycloaddition reactions of uracil derivatives to simple alkenes have been extensively investigated, the lack of regioselectivity detracts from its general utility in the modification of uracil derivatives.[2] In connection with synthetic studies of cyclobutane-fused heteroaromatics,[3] we found the powerful influence of a chloro-substituent in controlling regioselectivity. In addition, a facile elimination of HCl from the initially formed 2+2 cycloadducts to give the corresponding cyclobutenes has been uncovered. This fact amplifies the utility of 6-chlorouracils as photochemical synthons for the so-far unknown 1,2-dihydrocyclobuta[d]pyrimidine-4,6-diones, which like benzocyclobutenes[4] would offer a rational method for the construction of a carbocyclic ring fused to uracil ring system.

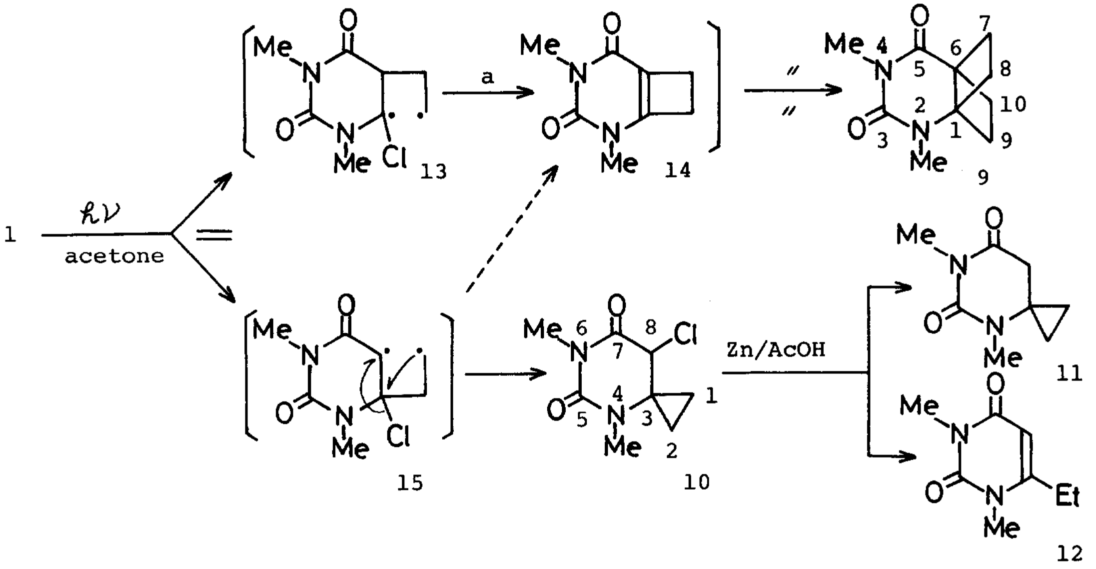
A solution of 6-chloro-1,3-dimethyluracil (1) in acetone in the presence of a large excess of isobutene[5] was irradiated at ≥300 nm (Toshiba 400P high-pressure mercury lamp, Pyrex filter) until disappearance of the starting material. Evaporation of the solvent followed by silica gel chromatography gave 2,2,3,5-tetramethyl-1,2-dihydrocyclobuta[d]pyrimidine-4,6(3H,5H)-dione[6] [2: mp 52-54°C, δ; 1.44 (6H, s), 2.60 (2H, s), 3.21 (3H, s), 3.25 (3H, s), λ_{max} nm (log ε): 208 (4.04), 269 (3.95)] in 59% yield, together with 9% of 6-(2-methylprop-2-enyl)-1,3-dimethyluracil[7] [3: δ; 1.81 (3H, s), 3.11 (2H, s), 3.2-3.3[7] (6H), 4.71 and 4.97 (each 1H, bs, exocyclic methylene), 5.56 (1H, s)]. Catalytic hydrogenation of 2 over palladium-charcoal furnished 2,4,8,8-tetramethyl-2,4-diazabicyclo[4.2.0]octa-3,5-dione[2] (4: mp 98-98.5°C) in a quantitative yield. Similarly, by the cycloaddition of 1 to tetramethylethylene, 1,1,2,2,3,5-hexamethyl-1,2-dihydrocyclobuta[d]pyrimidine-4,6(3H,5H)-dione [5: mp 151-153°C, δ; 1.30 (6H, s), 1.32 (6H, s), 3.21 (3H, s), 3.24 (3H, s), λ_{max} nm (log ε): 208 (4.08), 269 3.95)] was obtained in 99% yield.





The direct formation of the cyclobutane-fused uracils (2 and 5) is rationally explained by assuming a primarily formed 1-chloro-2,4-diazabicyclo[4.2.0]octa-3,5-dione species (*e.g.*, 8) as a key intermediate. Thus, photoaddition of 1 to isobutene affords at first 1-chloro-2,4,8,8-tetramethyl-2,4-diazabicyclo[4.2.0]-octa-3,5-dione (8), which spontaneously eliminates HCl to furnish the cyclobutene derivatives (2). It should be noted that cycloaddition of 1 to isobutene proceeded in a regioselective manner to give 8,8-dimethyl derivative (2) in predominance, showing the pronounced stability of the biradical (6) over the other one (7) or the enhanced rate of path *a* over path *b*. Such a regioselectivity has not been observed for uracil, thymine, and 6-methyluracil (or their N,N-dimethyl derivatives) and, upon cycloaddition to isobutene, both regioisomers are formed in nearly comparable yields.[2,8]

Photocycloaddition of 1 to ethylene was obviously related to the above reactions, but resulted in the formation of the more complicated products. Thus, irradiation of 1 in acetone under bubbling of ethylene afforded two products (9 and



10) in each 26% yield. The structure of 9 (mp 87-89.5°C) was deduced to be 2,4-dimethyl-2,4-diazatricyclo[4.2.2.0]deca-3,5-dione from its NMR spectrum, δ: 2.1-2.9 (8H, m), 2.73 (3H, s), 3.16 (3H, s). The other product (10: mp 96.5-98°C) was assigned as 8-chloro-4,6-dimethyl-4,6-diazaspiro[2.5]octa-5,7-dione by the following data. Reduction of 10 by zinc in aq. AcOH (reflux, 1 hr) afforded the dechlorination product [11: mp 73-75°C, δ: 0.55-1.25 (4H, a typical A_2B_2 pattern), 2.53 (2H, s), 2.80 (3H, s), 3.16 (3H, s)] in 51% yield, together with 26% of 1,3-dimethyl-6-ethyluracil [12: δ: 1.23 (3H, t, J=7.0 Hz), 2.48 (2H, q, J=7.0 Hz), 3.29 (3H, s), 3.36 (3H, s), 5.56 (1H, s), λ_{max} nm: 207, 266]. The formation of 12 clearly indicates that the cyclopropane ring is attached to the C-6 position of the uracil ring in the product (10). Here again, the result can be rationalized by assuming biradical intermediates (13 and 15). Direct ring closure of the biradical (13) followed by subsequent elimination of HCl furnish the cyclobutene (14), which may further add to ethylene to give the propellane (9). The other biradical intermediate (15) can undergo a 1,2-chlorine shift with concomitant cyclopropane formation to furnish the cyclopropane (10). No formation of cyclopropane derivative from 7 indicates that such a path is prohibited to occur by steric hindrance due to the presence of two extra methyl groups in it, and a possible path (b) from 7 to the ene product (3) may be inefficient as compared to its reversion to 1 and isobutene.

Finally, a facile conversion of 2 to 6-isopropenyl-5-methyl-1,3-dimethyluracil [17: mp 59.5-61°C, δ: 1.88 (3H, s), 1.94 (3H, bs), 3.29 (3H, s), 3.32 (3H, s), 5.0 (1H, bs), 5.39 (1H, bs), λ_{max} nm (log ε): 209 (4.01), 272 (3.96)] by refluxing in o-dichlorobenzene is worthy to comment. Since this conversion obviously proceeds via the corresponding uracil-5,6-quinodimethane (16) as the intermediate, trapping of such intermediates with olefin would give rise 5,6,7,8-tetrahydroquinazoline-2,4-diones.[4]

The present work provides a useful synthetic method for appending a cyclobutane ring on the C-5 and -6 positions of the uracil nucleus. Furthermore, the powerful effect of a chlorine atom at the 6-position of the uracil ring on the regioselectivity in the cycloaddition to isobutene coupled with the unique facile elimination of HCl from the adducts may suggest further utility of β-chloro-α,β-unsaturated enone in the 2+2 photocycloaddition reactions. We are continuing to explore the scope and mechanistic details of this novel photoreaction.

REFERENCES AND NOTES

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2. A. J. Wexler, J. A. Hyatt, P. W. Raynolds, C. Cottrell, and J. S. Swenton, J. Amer. Chem. Soc., 100, 512 (1978) and references cited therein.
3. We have already shown that intermolecular 2+2 cycloaddition of heteroaromatic enone compounds having an alkoxy function at the β-position with olefin can be effected photochemically and the resultant adducts can be transformed to cyclobutane-fused heteroaromatics by elimination of the alcohol. For the syntheses of cyclobutane-fused 2-quinolone,[a] 2-pyridone,[b] and coumarin,[c] see: a) C. Kaneko and T. Naito, Chem. Pharm. Bull., 27, 2254 (1979); b) H. Fujii, K. Shiba, and C. Kaneko, JCS Chem. Comm., 1980, 537; c) T. Naito, N. Nakayama, and C. Kaneko, Chem. Lett., 1981, 423.
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5. Cycloaddition of 1 to alkenes can be carried out using 5-10 mM solution of 1 in acetone in the presence of 50-100 mol equivalent of alkenes.
6. Satisfactory analyses were obtained for all crystalline compounds. All new compounds were supported by the presence of molecular ion in the mass spectra and by other spectral data (IR, UV, and NMR). Unless otherwise noted, NMR spectra (60 MHz) were recorded in $CDCl_3$, UV in MeOH, and IR in KBr pellet.
7. This compound (3) could not be obtained in pure state due to the presence of minor contaminators. The NMR data are those of major signals and the signal at δ 5.56 indicated it to be the 6-alkyluracil. For example, the olefinic proton signal appears at δ 5.52 for 6-methyl- and at δ 6.89 for 5-methyl-1,3-dimethyluracil.
8. Uracils having 5-F, and 5-CF_3,[a] or 6-CN group[b] are known to give almost selectively the photoadducts expected from the head-to-tail biradicals (e.g., 6). a) A. Wexler and J. S. Swenton, J. Amer. Chem. Soc., 98, 1602 (1976); b) I. Saito, K. Shimozono, and T. Matsuura, ibid., 102, 3948 (1980).

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