Spectacular Differences in the Thermal Behavior and the Aromatic Substitution Reactions of 5-Diazouracil and 5-Diazo-3-methyluracil

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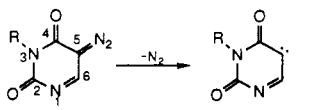
Summary: 5-Diazo-3-methyluracil reacts with varied benzenes to yield 3-methyl-5-aryluracils by apparent singlet carbene addition and homolytic rearrangement of spironorcaradiene intermediates. 5-Diazouracil, however, thermolyzes with rearrangement and loss of nitrogen to form (2,5-dioxo-3-imidazolin-4-yl)methylene, which reacts with benzene and cyclooctane to give 5-cycloheptatrienylidene-2,4-imidazolidinedione and (*E*)- and (*Z*)-5-(cyclooctylmethylene)-2,4-imidazolidinediones, respectively.

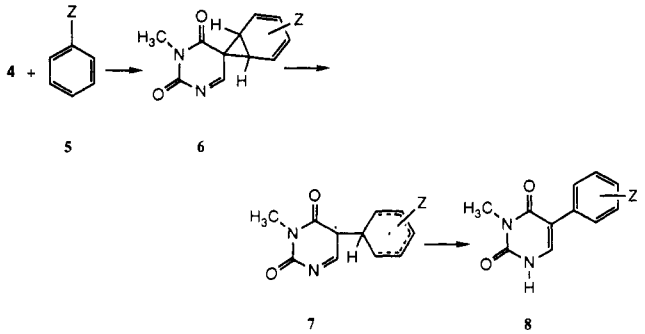
5-Diazouracil (1) has been extensively investigated for its medicinal properties.[1a] Although 1 was prepared a century ago,[1b] little is known about its carbenic chemistry.[2] A study of possible thermal conversions of 1 and 5-diazo-3-methyluracil (**3**)[3] to 5-uracilylidene (**2**)[2] and 3-methyl-5-uracilylidene (**4**), respectively, in benzenoid solvents is now reported. As will be seen, the pyrolytic behaviors of **1** and **3** are remarkably different, and much new chemistry is derivable from such systems.



1; R = H 2; R = H

3; R = CH_3 4; R = CH_3

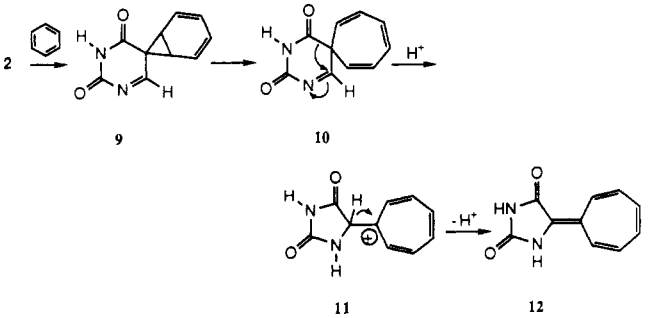
Thermolyses of **3** in varied benzenes (**5**; Z = H, OCH_3, CN, and NO_2) at 150–160 °C (6 h) result in loss of nitrogen, aromatic substitution by **4**, and hydrogen migration to give 3-methyl-5-aryluracils (**8**; Z = H, OCH_3, CN, and NO_2).[4]



5 6 7 8

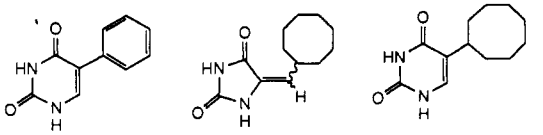
The ortho/meta/para ratios of the substituted aryluracils produced are (1) Z = OCH_3, 1/–/3; (2) Z = CN, 2/1/3; and (3) Z = NO_2, 2/1/2. The relative molar reactivities of benzenes **5** at 150–160 °C are (1) Z = OCH_3, 1.2; (2) Z = H, 1.0; (3) Z = CN, 0.51; and (4) Z = NO_2, 0.33. Thus, all the substituted benzenes undergo ortho and para rather than meta substitution and their reactivity is anisole > benzene > benzonitrile > nitrobenzene. The reactivity of **4** is as a rather indiscriminate electrophilic singlet carbene, whereas the orientation patterns for aromatic substitution are for homolytic processes.[5] Aromatic substitution by **4** thus appears to involve (1) rate-determining (low activation energy) additions of **4** to **5** to give spironorcaradienes **6** in which the structures of the transition states are close to reactants, and (2) selective homolytic collapse (product determining) of **6** to singlet diradicals **7** and hydrogen migration. The mechanistic sequence for reactions of **4** and **5** is the first of its kind for aromatic substitutions by a carbene.

Surprisingly, thermolysis of **1** in benzene at 150–160 °C yields a single capture product (42%) which NMR, mass spectral, and X-ray analyses reveal to be 5-cycloheptatrienylidene-2,4-imidazolidinedione (**12**). 5-



9 10 11 12

Phenyluracil (**13**), the product expected if **1** behaves like **3**, is not formed. Further isomerization of **12** to **13** or **13** to **12** is not observed. Since uracils are substantial acids,[6] **12** might be presumed to be formed by addition of **2** to benzene, acid-catalyzed contraction of the uracil ring in **10**, and deprotonation of **11**. Such a mechanism becomes suspect, however, upon finding that decomposition of **1** in cyclooctane at 150 °C yields a mixture of (*E*)- and (*Z*)-5-(cyclooctylmethylene)-2,4-imidazolidinediones (**14**, 62%) and no 5-cyclooctyluracil (**15**). Retrospective analysis of



13 14 15

the behavior of **1** then raises the question that **12** and **14** are formed by ring expansion of benzene and insertion into cyclooctane by an isomer of **2** such as (2,5-dioxo-3-imidazolin-4-yl)methylene (**16**) and/or its tautomers as illustrated.

(1) (a) Kolgore, W. W.; Greenberg, J. J. *J. Bacteriol.* **1971**, *81*, 258 and references therein. (b) Behrend, R.; Ernert, P. *Ann. Chem.* **1890**, *258*, 347.

(2) (a) Thermolyses of 1 in varied pyridines give 5-[3-(major) and 2-pyridyl]uracils. From the product distributions, the pyridines are presumed to add **2** as a singlet followed by heterolytic isomerization.[2b] (b) Keen, B. T.; Paudler, W. W. *J. Org. Chem.* **1975**, *40*, 3717.

(3) Thurber, T. C.; Townsend, L. B. *J. Heterocycl. Chem.* **1975**, *12*, 711.

(4) All products have proper masses, analyses, and NMR spectra and/or have physical properties comparable to literature values. (b) The NMR and the mass spectral contributions of Dr. C. E. Cottrell and C. R. Weisenberger are gratefully acknowledged. The crystallographic analysis of **12** made by Dr. J. Gallucci will be reported in detail later.

(5) (a) Sheldon, J. R.; Uzelmeier, C. W. *J. Am. Chem. Soc.* **1966**, *88*, 5222. (b) Various mechanisms of aromatic substitution by carbenes are discussed by Glinka, J.; Fiscus, D.; Rao, C. B.; Sheckter, H. *Tetrahedron Lett.* **1987**, *28*, 3221 and references 1a–o therein.

(6) Pfleiderer, W.; Deiss, H. *Isr. J. Chem.* **1968**, *6*, 603 and references therein.

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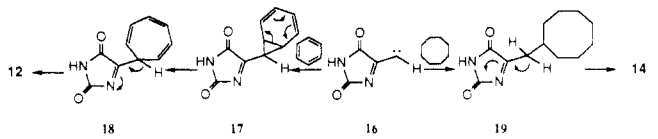
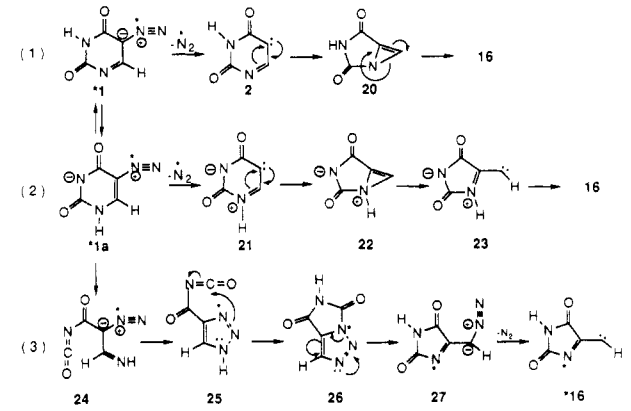


Three mechanistic routes to **16** from **1** are considered as illustrated below. Mechanism 1 involves loss of N_2 from **1** and rearrangement of carbene **2** via 1*H*-azirene **20**. This mechanism, however, fails to explain why a methyl group instead of hydrogen at N-3 changes the chemistry of **1** and **3** so spectacularly. Further, decomposition of **1** in benzene in the presence of triethylamine yields **13** instead of **12**. A more attractive possibility, mechanism 2, which is not available to **3**, results from tautomerism of **1** to **1a** and avoids **20**.[7] Expulsion of N_2 then leads to **16** via azirenium dipolar ion **22**. A much different and more complicated process, mechanism 3, is ring opening of **1a** to carbonyl isocyanate **24** which converts to 4-carbonyl-1*H*-1,2,3-triazoleisocyanate (**25**) and then to triazole **26** by cyclization and proton transfer. Collapse of **26** then gives 4-(diazomethyl)-1*H*-imidazole-2,4-dione (**27**), which loses N_2 to yield carbene **16**. An important difference in the three mechanisms is that, with *1 containing the (*) nitrogen labeled with ^{15}N, in mechanism 3 the labeled nitrogen is incorporated in carbene **16** and thus in products **12** and **14**, whereas in mechanisms 1 and 2 the products will *not* contain the isotopic nitrogen as it is lost earlier as $*N_2$.



(7) (a) 1*H*-azirenes are antiaromatic (4π electron) and usually thermally unstable. When substituted by electron-withdrawing substituents, their stabilities are increased.[7b] (b) Regitz, M.; Arnold, B.; Davidson, D.; Schubert, H.; Fusser, G. *Bull. Soc. Chim. Belg.* **1981**, *90*, 615.

Studies of the thermal reactions of *1 with benzene and cyclooctane are now summarized.

Synthesis of *1 was accomplished by: (1) nitration of uracil with 1:1 molar mixture of $H^{15}NO_3$ and fuming nitric acid in sulfuric acid at 100 °C, (2) reduction of the 5-[^{15}N]nitrouracil with ammoniacal sodium dithionite,[8a] and (3) diazotization of the resulting 5-[^{15}N]aminouracil with sodium nitrite and aqueous HCl.[8b] Mass spectral analysis (M^+ peak) reveals that the diazo group in *1 is 45 ± 2% enriched. Decompositions of the *1 in benzene and in cyclooctane at 150–160 °C yield products identical with **12** and **14**, respectively. Most importantly, the ^{15}N NMR spectrum of **12** exhibits a single resonance at 108.7 ppm, and the *E* and *Z* isomers of **14** display ^{15}N NMR peaks at 107.2 and 108.5 ppm in a 5:1 ratio. These resonances are typical of amide nitrogens[9] and indicate that the ***12** and ***14** contain ^{15}N at N-1 of their imidazolidinedione moieties. Further, mass spectral analyses of the ***12** and ***14** reveal that their ^{15}N contents are identical with that of initial *1. Formation of *12 and *14 is therefore consistent with mechanism 3 for isomerization of **1** via carbonyl isocyanates **24** and **25** to carbene ***16** and excludes any partial involvements of mechanisms 1 and 2. These labeling experiments also eliminate the possibility of formation of **12** from carbene **2** and rearrangement of spirocycloheptatriene **10**.

Investigation is being made of (1) detection and isolation of **25** and **26**,[10,11] (2) synthesis and the chemistry of **27**, and (3) the behavior of **1** and **3** in the presence of tertiary amines and various catalysts.

Acknowledgment. We thank the National Cancer Institute (Grant 5 R01 CA11185) for financial support of this research.

Supplementary Material Available: X-ray data for **12** (9 pages); structure factor listings (13 pages). Ordering information is given on any current masthead page.

(8) (a) Bogart, M. T.; Davidson, D. *J. Am. Chem. Soc.* **1933**, *55*, 1667. (b) Thurber, T. C.; Townsend, L. B. *J. Heterocycl. Chem.* **1972**, *9*, 629.

(9) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; John Wiley & Sons: New York, 1979; p 58.

(10) (a) Hydrates of 5-diazouracils having hydrogen at N-3 hydrolyze to 1,2,3-triazole-4-carboxamides when heated. Such transformations are not observed with 5-diazo-3-methyluracils.[10b,c] (b) Thurber, T. C.; Townsend, L. B. *J. Heterocycl. Chem.* **1973**, *95*, 3081. (c) Thurber, T. C.; Townsend, L. B. *J. Org. Chem.* **1976**, *41*, 1041. (d) The different behavior of the above diazouracils might have their origins in that 5-diazo-3-methyluracils can not open to carbonyl isocyanates such as **24**.

(11) 1,2,3-Triazole-4-carboxamide, as presumably derived by hydrolysis of **25** and loss of carbon dioxide, has now been found upon thermolysis and workup of **1** in benzene.

Novel Modifications of Peptides: Simple Syntheses of Difunctionalized Enamines, Enol Ethers, and Thioenol Ethers from Carboxylic Acids via Acylimidazole and Enol Phosphate Intermediates[1]

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Summary: The condensation of carboxylic acids **5** (N-protected amino acids or dipeptides) and active methylene compounds to give difunctionalized enols **6** is accomplished by the use of 1,1′-carbonyldiimidazole as an activating reagent. Enamines **7a**, enol ethers **7b**, and thioenol ethers **7c** are obtained directly from the corresponding nucleophiles and the intermediates formed from enols **6** by the action of phenyl phosphorodichloridate. The integrity of peptide chiral centers is maintained during these transformations.

(1) Presented in part at the 72nd Canadian Chemical Conference (Organic Division) Victoria, Canada, June 1989.

(2) Fellow of the NSERC-Canada, 1985–.

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