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THERMAL AND PHOTOCHEMICAL REARRANGEMENTS OF 4-BENZYL-THIOPYRIMIDIN-2-ONES

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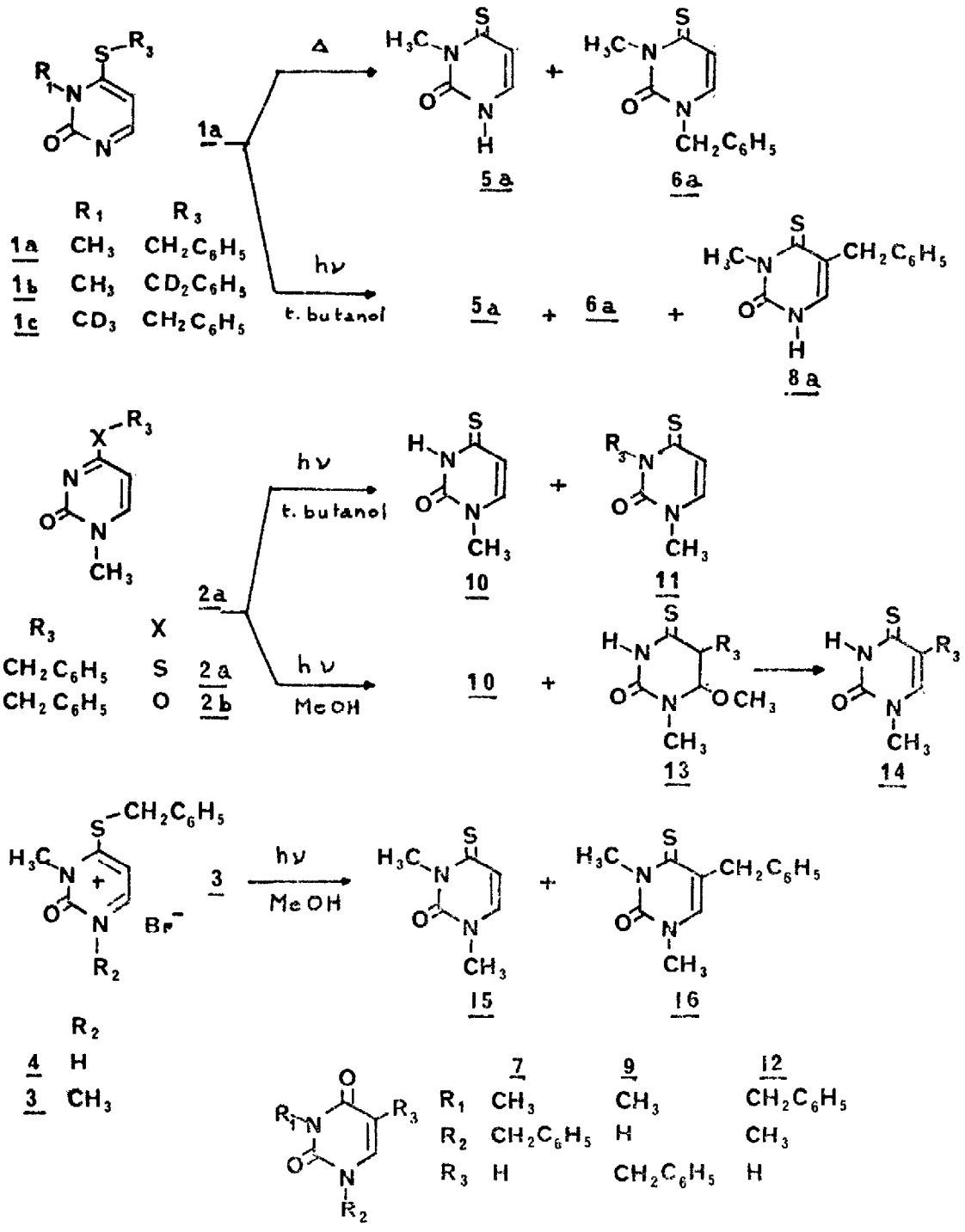
Recently some unusually facile Claisen rearrangement reactions[1] involving heterocyclics related to nucleic acid constituents have been reported. These reactions of potential synthetic value deal with allyl derivatives of substituted pyrimidines (5-hydroxyuracil[2] and 4-thiouracil[3]) and of purine (guanine[4]). The mechanism of the rearrangement of the latter has been studied in details[4].

We have now investigated the reactivity of the three new 4-thiouracil derivatives 1a, 2a and 3 which represent another type of 1,5-diene system. In contrast to their S-allyl analogs[3] none of these sulfides undergo the thio-Claisen rearrangement. However, we have found that 1a, 2a and 3 are readily rearranged in presence of light to their N- or C-benzyl isomers. Compound 1a can be also thermally transformed to its N-benzyl isomer. In this case we have established that the thermal conversion occurs through a non electrocyclic intermolecular pathway while the light induced lateral rearrangement is intramolecular.

Compound 1a (mp 130-131°) was prepared by sodium carbonate treatment of an acetone solution of the salt 4 which results from interaction of 3-methyl 4-thiouracil 5a and benzyl bromide in acetonitrile. When sulfide 1a was heated at 160° in the absence of solvent it was rearranged to an isomer 6a (mp 89-90° ; 90 %), identical to the thiation product of 1-benzyl 3-methyluracil 7[5].

In order to establish the mechanism of this rearrangement reaction we used doubly deuterated starting material. For this purpose compounds 1b and 1c were prepared by reacting benzyl-α,α-d_2 bromide[6] with 3-methyl-4-thiouracil 5a and benzyl bromide with 3-methyl-d_3-methyl-4-thiouracil 5b respectively. The mass spectrum of the product isolated after thermal rearrangement of a 1:1 mixture of deuterated derivatives 1b and 1c exhibited four molecular ion peaks (equal intensity) at m/e 232, 234, 235 and 237. This unambiguously demonstrates that the process leading from 1a to 6a is intermolecular.

Since UV light excitation of compound 1a was expected to result in the homolysis of the benzylic C-S bond it was of interest to devise appropriate reactionsconditions to induce the benzyl radical migration towards the pyrimidine moiety. Irradiation[7] of 1a in t-butanol until


1a
Δ
hν
t. butanol
5a
6a
8a
1a CH3 CH2C6H5
1b CH3 CD2C6H5
1c CD3 CH2C6H5
2a
2b
hν
MeOH
10
11
13
14
3
15
16
4 H
3 CH3
7
9
12
R1 CH3 CH3 CH2C6H5
R2 CH2C6H5 H CH3
R3 H CH2C6H5 H

complete disappearance of the starting material resulted in the formation of three products. Two of these, found identical to the 4-thiouracil derivatives 5a and 6a, have been obtained in 30 % and 10 % yield respectively. The third photoproduct (Yield 45 %), an isomer of compound 1a ($M^{\cdot +}$ at m/e 232), has the characteristic UV absorption of a 4-thiouracil derivative (λ_{max} 328 nm, ϵ 1.4 x 10^4). Its NMR spectrum displays an olefinic proton singlet at 6.7 ppm in addition to the C-benzyl and N-methyl proton signals. On the basis of these findings structure 8a (mp 163-164°) was attributed to this new substituted 4-thiouracil. Confirmation of this assignment was achieved by replacing the sulfur at C-4 by an oxygen leading to 9 (mp 162-163°), the NMR spectrum of which displayed the olefinic proton signal at 6.8 ppm, a typical position for a uracil H-6 proton.

To ascertain the mechanistic pathway we have irradiated a 1:1 mixture of deuterated derivatives 1b and 1c. We have obtained deuterated photoproducts 6 and 8 whose mass spectra display minor peaks at m/e 232 and 237 while the molecular ion peaks of the main constituents are found at m/e 234 and 235. This finding demonstrates that each deuterated photoproduct 6 and 8 consists mainly (over 95 %) of 1:1 mixture of 6b + 6c and 8b + 8c respectively. It therefore follows that the photoprocess leading to compounds 6 and 8 is intramolecular. Presumably, recombination of the fission products occurs within the solvent cage.

4-Benzythio-1-methyl pyrimidin-2-one 2a (mp 150-151°), a new compound, prepared by interaction of 1-methyl-4-thiouracil 10 with benzyl bromide in acetonitrile in the presence of sodium carbonate, is thermally stable. However, when irradiated[7] in t-butanol it disappears rapidly yielding 1-methyl-4-thiouracil 10 (20 % yield) and a compound 11 (mp 110-111°, 70 %) identical to the thiation product of 3-benzyl-1-methyluracil 12[5]. When compound 2a was irradiated[7] in methanol the two main photoproducts were 1-methyl-4-thiouracil 10 (Yield 45 %) and a compound (oil, 40 %) which has been assigned structure 13 on the basis of analytical and spectral data (UV : λ_{max} 285 nm ; NMR : H_6 δ 4.1 ppm, broad singlet ; N-CH_3 and O-CH_3 δ 3.1 and 3.2 ppm). When heated in refluxing toluene, compound 13 loses methanol (this elimination is accelerated in presence of traces of HCl) to give 5-benzyl 1-methyl 4-thiouracil 14 (mp 168-170°) whose structure was evident from the UV (λ_{max} 342 nm, ϵ 1.5 10^4) and the NMR spectra (H_6 δ 6.6 ppm). Formation of compound 13 suggests that in this reaction 1, 4-methanol addition to the excited pyrimidine might trigger the benzyl migration to C-5. It is noteworthy that in contrast to uracil[9], 4-thiouracil[10] does not add hydroxylic solvents like water or methanol[11].

We have also investigated the photochemistry of the thermally unstable salt 3 which is produced by interacting benzyl bromide with 1, 3-dimethyl-4-thiouracil 15. Irradiation of a methanolic solution of salt 3 yielded the rearranged 5-benzyl-1, 3-dimethyl 4-thiouracil 16 (mp 109-110° ; 10 %) along with 15.

These new photochemical rearrangement reactions in mercaptopyrimidine series could be applied to the synthesis of biologically important 5-substituted pyrimidines[13] and to the functionalization of related heterocyclics[14].

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