Photochemical behaviour of 5-formyl and 5-acetyl uracils in the presence of ethene

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Elisabeth Pereira [a], Sophie Faure [a], David J. Aitken [a,b,*]

[a] *Laboratoire de Synthèse et Etude de Systèmes d'Intérêt Biologique, SEESIB (UMR 6504—CNRS), Département de Chimie, Université Blaise Pascal—Clermont-Ferrand II, 24 Avenue des Landais, 63177 Aubière cedex, France*

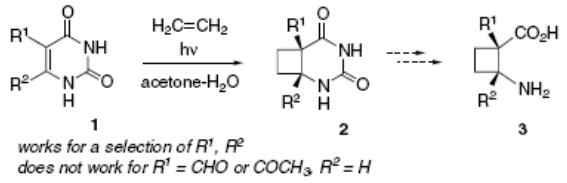
[b] *Laboratoire de Synthèse Organique et Méthodologie, ICMMO (UMR 8182—CNRS), Université Paris-Sud 11, Bât. 420, 15 rue Georges Clemenceau, 91405 Orsay cedex, France*

Abstract

Atypically for uracils, 5-formyl and 5-acetyl uracils react photochemically with excess ethene to produce non-acylated cyclobutane adducts whose formation can be explained by a novel, tandem [2+2] cycloaddition/Norrish-I α-cleavage process.

We recently showed that a [2+2] photocycloaddition reaction between ethene and substituted uracils **1** served as a general route for the preparation of cyclobutane β-amino acids **3**, after appropriate transformation of the initially-formed photoadducts **2** (Scheme 1).[1] The photocycloaddition reaction was successful for a variety of 5- (and some 6-) substituted uracils, but curiously 5-formyl and 5-acetyl uracils (5-Fo-U and 5-Ac-U, respectively) did not furnish the expected adducts **2**.

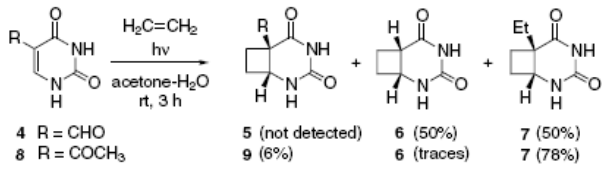
5-Acyl uracils are of particular biological importance. Some are constituents of therapeutically promising molecular structures,[2] and others have been incorporated into RNA sequences, which serve as high-affinity ligands for specific protein targets.[3] More significantly, 5-Fo-U is formed from thymine when DNA is oxidatively damaged, and this transformation frequently provokes replication miscoding, leading to diverse pathologies.[4] Indeed, some biological repair mechanisms specifically target 5-Fo-U.[5] Furthermore, ultraviolet sunlight induces various types of DNA damage, including thymine–thymine photodimer formation.[6] In the above context, the photochemical reactivity of 5-formyl (and other 5-acyl) uracils appears worthy of investigation; we therefore decided to examine further the behaviour of 5-Fo-U and 5-Ac-U in the conditions used in Scheme 1.



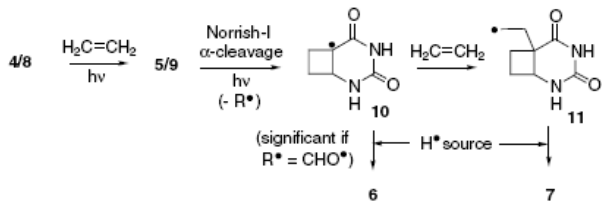
Scheme 1.

Irradiation of an acetone–H_2O solution of 5-Fo-U (**4**) at rt for 3 h followed by standard work-up[1a,7] produced a clean product mixture, which consisted of roughly equal amounts of two inseparable cyclobutane adducts: the known[1b] *unsubstituted* compound **6** and its previously unknown *ethyl* derivative **7** (Scheme 2). The structure of the latter was deduced from its NMR spectral data within the product mixture, and confirmed by comparison with an authentic sample, prepared in 94% yield from 5-ethyl uracil according to the general procedure.[7,8] None of the anticipated formyl cyclobutane **5** was detected. Under the same

* Corresponding author. Tel.: +33 (1)69153238; fax: +33 (1)69156278.
E-mail address: David.Aitken@u-psud.fr (D. J. Aitken).



Scheme 2.



Scheme 3.

conditions, 5-Ac-U (**8**) gave a clean product mixture comprised of **7** as the major component, traces of **6**, and a small amount of the acetyl cyclobutane adduct **9**.

The unexpected formation of compounds **6** and **7** can be explained by the following tandem photochemical process (Scheme 3): the [2+2] photocycloaddition of the uracil with ethene proceeds rapidly to give the acyl cyclobutane (**5** or **9**), which evolves via Norrish-I α-cleavage, giving radical **10**. Reaction of this species with a second molecule of ethene gives ethyl radical **11**, which picks up a hydrogen atom from a nearby donor to provide **7**. The photodecarbonylation of aldehydes with direct return of hydrogen from the formyl radical after α-cleavage is a known process,[9] and probably contributes to the significant formation of **6** from **4**.

An important feature of this proposed sequence is the transient formation of the anticipated [2+2] adduct. Since this intermediate was detected in the case of 5-Ac-U (**8**), the reaction was repeated to follow the evolution of all four components in the mixture. The course of the reaction was followed by the removal of small samples, which were analysed by ^{1}H NMR spectroscopy. Results are shown in Figure 1. Upon irradiation, the concentration of substrate **8** dropped rapidly as the [2+2] photocycloaddition reaction progressed, giving an efficient build-up of **9**, which reached a maximum after about 20 min. Thereafter, the proportion of **9** dropped off continuously as **7** appeared and accumulated steadily, becoming the main component at the end of the 3 h period. The amount of **6** present was low at all times, and only became detectable towards the end of the reaction time. The kinetics profile is consistent with the sequence of events proposed in Scheme 3.

These observations suggested that it should be possible to obtain acetyl cyclobutane **9** in high yield if the reaction mixture was irradiated for only 20 min. Indeed, this turned out to be the case: **9** was thus obtained in 84% yield after simple purification by column chromatography.[10]

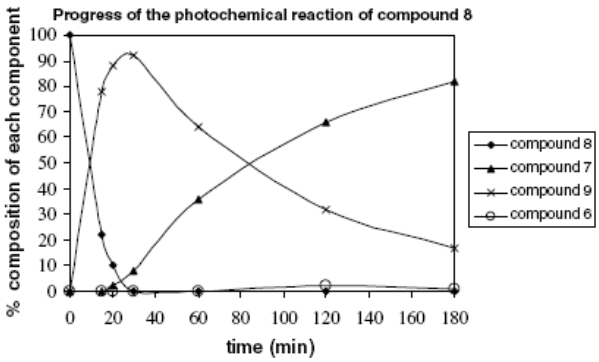


Fig. 1.

In conclusion, this short study reveals the atypical tandem photochemical reactivity of 5-acyl uracils in the presence of ethene. Although we found no evidence for uracil photodimer formation in the present reactions, Norrish-I processes may yet turn out to have some significance in the evolution of photooxidatively damaged DNA in which 5-Fo-U has been formed from thymine.

References and notes

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7. 5-Substituted uracil (0.25 g) was dissolved in a 1:1 acetone–H_2O mixture (160 mL) in a cylindrical water-cooled reactor. The solution was degassed with argon for 30 min, then saturated with ethene for 30 min. With continued ethene bubbling, the stirred mixture was irradiated at rt for 3 h with a 400 W medium-pressure Hg lamp fitted with a Pyrex filter (thickness 5 mm). The solution was then evaporated and the residual solid was washed with cyclohexane then a small amount of acetone.
8. *Compound* **7**: 6-ethyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione; mp 243–247 °C (subl); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (t, $J = 7.6$ Hz, 3H, CH_3), 1.62 (m, 1H, CH_2 ethyl), 1.77 (m, 3H, H7/H8/CH_2 ethyl), 1.98 (m, 1H, H7), 2.11 (m, 1H, H8), 3.63 (m, 1H, H1), 7.74 (s, 1H, H4), 10.08 (s, 1H, H2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 8.5 (CH_3), 26.7 (C7), 27.4 (C8), 30.1 (CH_2), 47.7 (C6), 49.2 (C1), 152.4 (C3), 175.7 (C5); ESI-HRMS: m/z $[M+H]^+$ calcd for $C_8H_{13}N_2O_2$: 169.0977; found: 169.0992.

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10. *Compound* **9**: 6-acetyl-2,4-diazabicyclo[4.2.0]octane-3,5-dione; mp 224–227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 3H, CH_3), 1.89 (m, 1H, H7), 2.07 (m, 2H, H7/H8), 2.33 (m, 1H, H8), 4.04 (m, 1H, H1), 8.03 (d, $J = 4.4$ Hz, 1H, H4), 10.53 (s, 1H, H2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2 (C7), 26.1 (CH_3), 26.9 (C8), 47.6 (C1), 58.2 (C6), 151.1 (C3), 169.9 (C5), 202.0 (CO); ESI-HRMS: m/z $[M+H]^+$ calcd for $C_8H_{11}N_2O_3$: 183.0770; found: 183.0772.