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Structural rearrangement cascade initiated by irradiation of but-3-enyl orotates

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ABSTRACT

Upon irradiation at λ = 254 nm in acetonitrile solution, the title compounds formed 8-(2-formyloxyethyl)-substituted 2,4-diazabicyclo[4.2.0]oct-1(8)-en-3,5-diones, which underwent thermal cyclobutene ring opening to 6-substituted pyrimidine-2,4-diones. The reaction cascade results in an unprecedented formal 1,5-shift of the substituent at the pyrimidine-2,4-dione core. It was shown that the reaction is likely to proceed via the [2 + 2] photocycloaddition products of the orotates, which could be intercepted in good yields (85% and 98%) upon irradiation at λ = 300 nm. At shorter wavelength a cleavage of the bond between the lactone carbonyl carbon atom and the α-carbon atom is induced, which leads – as shown by deuterium labelling experiments – by intramolecular hydrogen abstraction to the above-mentioned cyclobutenes.

1. Introduction

Ever since its discovery [1], the [2 + 2] photocycloaddition reaction has been performed with cyclic α,β-unsaturated ketones (enones) as prototypical substrates [2]. In addition, α,β-unsaturated carbonyl compounds such as lactones and lactams can be utilized in [2 + 2] photocycloaddition chemistry although they normally require shorter excitation wavelengths than enones [3]. A benefit of the latter substrate class is the fact that the lactone or lactam bond is readily amenable to substitution reactions by a given nucleophile (Nu). After intra- or intermolecular [2 + 2] photocycloaddition, the resulting cyclobutanes exhibit – upon appropriate substitution – at least two exit vectors, i.e., a modified carboxyl group (—CONu) and a hydroxy (—OH, for a lactone) or amino (—NHR, for a lactam) group. In recent years, several new scaffolds have been photochemically generated, that feature a cyclobutane as a core structural element [4,5]. Compounds of this type allow for a broad variety of substituents to be used as decoration elements in the context of lead structure optimization [6]. Along these lines, we became interested in the synthesis of orotic acid esters (orotates) and their intramolecular [2 + 2] photocycloaddition. The pyrimidine-2,4(1*H*,3*H*)-dione skeleton of this acid is best known for its occurrence in the pyrimidine bases uracil and thymine, the photochemistry of which has been extensively explored [7]. The [2 + 2] photocycloaddition of orotic acid has received lesser attention. The group of Aitken has studied the reaction of orotic acid with ethylene upon irradiation at λ > 280 nm (pyrex filter) [8]. They found the desired cyclobutanes to be accompanied by the respective photodimerization products. Photodimerization [9] prevailed for free orotic acid, while the methyl and hexyl orotates delivered upon irradiation in a solvent mixture of acetone/water the [2 + 2] photocycloaddition product in yields of 47% and 52%. In the present study, we have now prepared the respective but-3-enyl derivatives **1** of orotic acid (Fig. 1) and its *N,N*-dimethyl derivative and attempted the first intramolecular [2 + 2] photocycloaddition of orotates. Much to our surprise, preliminary experiments performed at λ = 254 nm in acetonitrile solution delivered cyclobutenes *rac*-**2**. Upon warming to 50 °C, a smooth cyclobutene ring opening was observed.

In this short note we give full experimental details on the photochemical reactions, which we have performed. We discuss the mechanistic reaction course of these transformations and provide via deuterium labeling studies evidence for a photochemical α-cleavage of an intermediately formed δ-lactone and subsequent intramolecular hydrogen abstraction.

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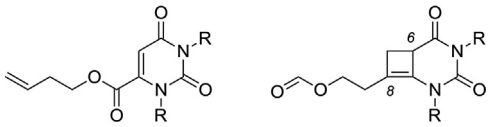

1a R = H *rac*-**2a**
1b R = CH_3 *rac*-**2b**

Fig. 1. Structure of but-3-enyl orotates **1** and of products *rac*-**2** obtained upon irradiation at λ = 254 nm.

2. Materials and methods

2.1. General methods

All reactions, sensitive to air or moisture, were carried out in flame-dried glassware under an argon atmosphere using standard Schlenk techniques. Thin layer chromatography (TLC) was performed on silica coated glass plates (*Merck* silica 60 F_{254}). Compounds were detected by UV (λ = 254 nm) and/or $KMnO_4$ solution (potassium permanganate solution). Technical solvents (*n*-pentane, ethyl acetate, diethyl ether, dichloromethane, methanol) for preparative column chromatography were purified by distillation prior to use. All other chemicals were either commercially available or prepared according to the literature. Nuclear magnetic resonance-spectra (NMR) were recorded at 300 K. ^{1}H NMR spectra were calibrated to the residual solvent signal, ^{13}C NMR spectra to the ^{13}C–D signal [$CDCl_3$ $\delta(^1H)$ = 7.26 ppm, $\delta(^{13}C)$ = 77.16 ppm; DMSO-d_6 $\delta(^1H)$ = 2.50 ppm, $\delta(^{13}C)$ = 39.5 ppm; CD_3CN $\delta(^1H)$ = 1.94 ppm, $\delta(^{13}C)$ = 1.32 ppm]. Apparent multiplets which occur as a result of accidental equality of coupling constants to those of magnetically nonequivalent protons are marked as virtual (*virt.*). Analytical gaschromatography was performed at a HP 6890 Series GC, MS data on a Finnigan MAT 8200 (EI). HRMS data were recorded by electron ionization (EI) on a Finnigan MAT 8200 (EI) or electron spray ionization (ESI) on a *Finnigan* LCQ classic. Infrared spectra (IR) were measured on a Jasco IR-4100 (ATR) spectrometer. The signal intensity is assigned using the following abbreviations: s (strong), m (medium), w (weak). UV–vis spectra were obtained on a PerkinElmer Lambda 35 UV–vis spectrometer.

2.2. Preparation of orotates

2.2.1. But-3-enyl orotate (1a)

To a solution of orotic acid (2.34 g, 15.0 mmol, 1.00 equiv.) in 20 mL of DMF were added 3-buten-1-ol (1.29 mL, 1.08 g, 15.0 mmol, 1.00 equiv.) and DMAP (91.6 mg, 750 μmol, 0.05 equiv.). After EDC (2.88 g, 15.0 mmol, 1.00 equiv.) was added, the mixture was stirred for 16 h at room temperature. The suspension was quenched by addition of 20 mL of water. The layers were separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined, washed with sat. NaCl solution (15 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the volatile components were evaporated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate/*n*-pentane = 9/1) to give the product (1.16 g, 5.52 mmol, 37%) as colorless crystals. TLC (ethyl acetate/*n*-pentane = 9/1): R_f = 0.50 [UV, $KMnO_4$]; mp 197 °C; IR (ATR): $\tilde{\upsilon}$ (cm^{-1}) = 3112 (w) (υ N—H), 3010 (w) (υ C—H), 1736 (m) (υ C=O), 1700 (s) (υ C=O), 1670 (s) (υ C=C), 1633 (s) (υ C=O), 1498 (s) (δ N—H), 1421 (s); ^{1}H-NMR (DMSO-d_6, 300 K, 500 MHz): δ (ppm) = 2.45 (*virt.*qt, $^3J \approx {}^3J$ = 6.6 Hz, $^4J \approx$ 1.4 Hz, 2H, H-2'), 4.30 (t, ^3J = 6.6 Hz, 2H, H-1'), 5.08 (*virt.* dq, ^3J = 10.2 Hz, $^2J \approx {}^4J$ = 1.2 Hz, 1H, H_{trans}-4'), 5.15 (*virt.* dq, ^3J = 17.1 Hz, $^2J \approx {}^4J$ = 1.7 Hz, 1H, H_{cis}-4'), 5.84 (ddt, ^3J = 17.1, 10.2, 6.6 Hz, 1H, H-3'), 6.02 (s, 1H, H-5), 11.18 (s, 1H, N—H), 11.41 (s, 1H, N—H); ^{13}C NMR (DMSO-d_6, 300 K, 126 MHz): δ (ppm) = 32.2 (t, C-2'), 65.4 (t, C-1'), 103.6 (d, C-5), 117.6 (t, C-4'), 134.3 (d, C-3'), 141.5 (s, C-4), 150.9 (s, C-2), 160.2 (s, C-7), 163.8 (s, C-6); MS (EI): *m/z*(%) = 210 (7) $[M]^+$, 139 (14) $[M\text{-}C_4H_7O]^+$, 73 (100) $[C_3H_5O_2]^+$, 54 (51) $[C_4H_6]^+$, 44 (82) $[C_2H_4O]^+$; HRMS (ESI): $[M+H]^+$ calcd.: 211.0713, found: 211.0713.

2.2.2. But-3-enyl-N,N-dimethylorotate (1b)

The reaction was performed in analogy to the preparation of compound **1a**. *N,N*-dimethylorotic acid (276 mg, 1.50 mmol, 1.00 equiv.) was used as starting material, dissolved in 10 ml DMF and 3-buten-1-ol (129 μL, 108 mg, 1.50 mmol, 1.00 equiv.), DMAP (18.3 mg, 150 μmol, 0.10 equiv.) and EDC (288 mg, 1.50 mmol, 1.00 equiv.) were added. The suspension was quenched with 10 mL of water. The layers were separated and the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The organic layers were combined, washed with sat. NaCl solution (15 mL) and dried over Na_2SO_4. The drying agent was removed by filtration and the volatile components were evaporated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate/*n*-pentane = 1/1) to give the product (157 mg, 659 μmol, 44%) as a colorless oil. TLC (ethyl acetate/*n*-pentane = 1/1): R_f = 0.53 [UV, $KMnO_4$]; IR (ATR): $\tilde{\upsilon}$(cm^{-1}) = 3080 (w) (υ=CH_2), 2960 (w) (υ C—H), 1737 (m) (υ C=O), 1708 (m) (υ C=O), 1660 (s) (υ C=C), 1251 (m), 757 (m); ^{1}H-NMR (DMSO-d_6, 300 K, 300 MHz): δ (ppm) = 2.50–2.43 (m, 2H, H-2'), 3.17 (s, 3H, N^1—CH_3), 3.34 (s, 3H, N^3—CH_3), 4.36 (t, ^3J = 6.6 Hz, 2H, H-1'), 5.10 (ddt, ^2J = 2.0 Hz, ^3J = 10.2 Hz, ^4J = 1.2 Hz, 1H, H_{trans}-4'), 5.16 (*virt.* dq, ^3J = 17.2 Hz, $^2J \approx {}^4J$ = 1.6 Hz, 1H, H_{cis}-4'), 5.84 (ddt, ^3J = 17.2, 10.2, 6.6 Hz, 1H, H-3'), 6.08 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6, 300 K, 126 MHz): δ (ppm) = 27.8 (q, N^1—C), 32.3 (t, C-2'), 33.8 (q, N^3—C), 65.5 (t, C-1'), 102.9 (d, C-5), 117.6 (t, C-4'), 134.3 (d, C-3'), 144.1 (s, C-4), 151.5 (s, C-2), 161.3 (s, C-7), 161.5 (s, C-6); MS (EI): *m/z*(%) = 238 (4) $[M]^+$, 179 (8) $[M\text{-}C_3H_5]^+$, 82 (100) $[C_5H_6O]^+$, 55 (32) $[C_4H_7]^+$; HRMS (ESI): $[M+H]^+$ calcd.: 239.1026, found: 239.1025.

2.3. Photochemical reactions

General procedure. A 15 mL quartz tube with a rubber seal was charged with the orotates and acetonitrile under argon, and the solution was degassed by purging with argon in an ultrasonicating bath for 10 min. The reaction mixture was irradiated at r.t. (λ = 254 nm or λ = 300 nm [10]). The solvent was removed under reduced pressure. The remaining residue was directly subjected to purification by column chromatography to yield the photoreaction products.

2.3.1. 8-(2-Formyloxyethyl)-2,4-diazabicyclo[4.2.0]oct-1(8)-en-3,5-dione (rac- 2a)

According to the general procedure, a solution of but-3-enyl orotate (**1a**) (84.0 mg, 400 μmol) in 80 mL acetonitrile (distributed in eight quartz phototubes of 10 mL each) was irradiated at λ = 254 nm for one hour. After column chromatography (dichloromethane/methanol = 9/1), product *rac*-**2a** (13.0 mg, 61.9 μmol, 16%) was obtained as a yellow solid. TLC (dichloromethane/methanol = 9/1): R_f = 0.40 [$KMnO_4$]; mp 125 °C; IR (ATR): $\tilde{\upsilon}$(cm^{-1}) = 3057 (w) (υ N—H), 2850 (w) (υ C—H), 1692 (s) (υ C=O), 1198 (s) (υ C—O), 743 (s); ^{1}H-NMR (CD_3CN, 300 K, 500 MHz): δ (ppm) = 2.46–2.35 (m, 1H, H-1'), 2.49–2.55 (m, 1H, H-7), 2.60 (dd, ^2J = 11.9 Hz, ^3J = 4.5 Hz, 1H, H-7), 3.38 (*virt.*dquint, ^3J = 4.5 Hz, $^3J \approx {}^5J$ = 2.0 Hz, 1H, H-6), 4.22 (td, ^3J = 6.6 Hz, ^4J = 2.5 Hz, 2H, H-2'), 7.86 (br s, 1H, N—H), 8.00 (br s, 1H, N—H), 8.06 (s, 1H, CHO); ^{13}C NMR (CD_3CN, 300 K, 126 MHz): δ (ppm) = 28.0 (t, C-1'), 31.2 (t, C-7), 39.5 (d, C-6), 62.1 (t, C-2'), 119.8 (s, C-8), 153.7 (s, C-3), 162.3 (d, CHO), 170.4 (s, C-5);