Short communication

Photocycloaddition of 2-Morpholinopropenenitrile to 8-Acetylquinoline

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

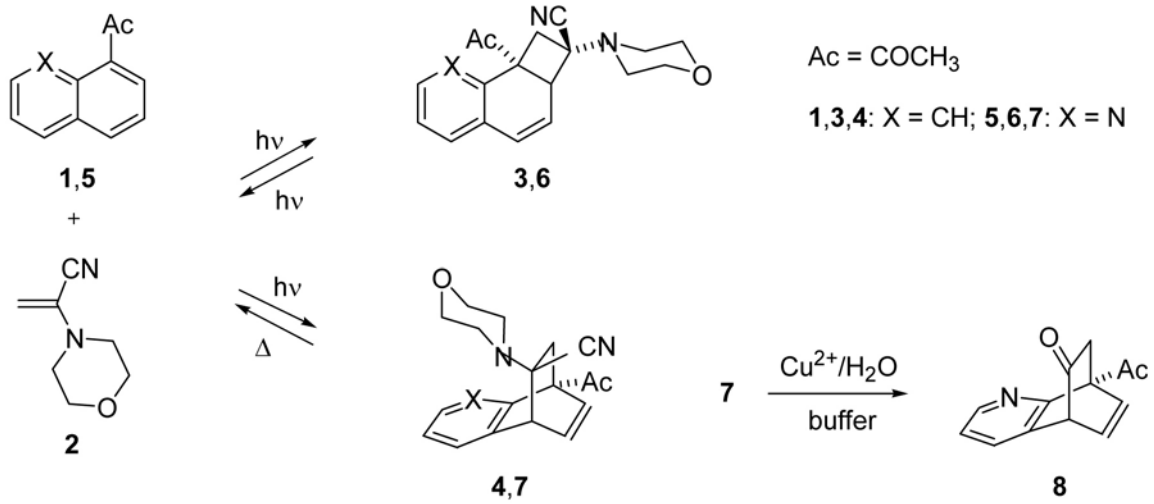
Upon broad-band UV-irradiation in benzene solution, the title compounds **2** and **5** form *rel*-(2*R*,2a*R*,8b*S*)-8b-acetyl-2-morpholino-1,2,2a,8b-tetrahydrocyclobuta[*h*]quinoline-2-carbonitrile (**6**) in a [2+2]- and *rel*-(5*R*,8*R*,10*R*)-8-acetyl-10-morpholino-5,8-ethano-5,8-dihydroquinoline-10-carbonitrile (**7**) in a [4+2]-photocycloaddition. The latter compound may be thermally cleaved into the starting materials **2** and **5** ($\Delta H^{\neq}$ = 130.5 ± 8 kJ mol^{-1} and $\Delta S^{\neq}$ = 46 ± 3 J mol^{-1} K^{-1}) and hydrolyzed to the tricyclic diketone *rel*-(5*R*,8*R*)-8-acetyl-5,8-ethano-5,5-dihydroquinolin-10-one (**8**).

Keywords: Acylquinoline photochemistry, aminonitrile hydrolysis, biradical intermediate, captodative alkene, cycloreversions, [2+2]- and [4+2]-photocycloadditions.

1. Introduction

Several light induced [2+2]-and [4+2]-cycloadditions of α-cyanoenamines to suitable ring atoms of fused aromatic hydrocarbons and carbonyl derivatives thereof have been carried out successfully,[1] especially to 1-acetonaphthone (**1**) and analogous fused carbonyl compounds.[2–4]

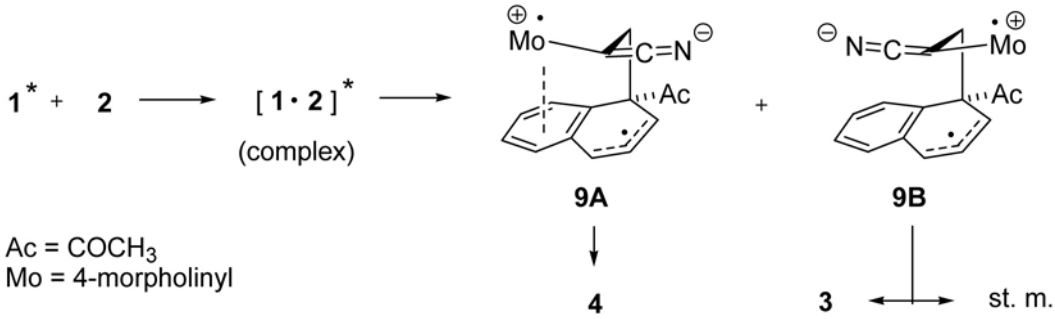
When **1** was irradiated (λ > 280 nm) in various solvents (cyclohexane, benzene, acetonitrile or methanol) in the presence of 2-morpholinopropenenitrile (**2**), a photo-Diels-Alder adduct **4** was readily formed, the structure of which was confirmed by a single crystal *X*-ray structural analysis.[2] Analogous results were obtained with 1-naphthaldehyde and 1-naphthophenone.[3] Later it was elucidated that a photoreversible [2+2]-photoaddition of **2** to the



Scheme 1

C1-C2 bond of **1** forming the tetrahydrocyclobuta[*a*]naphthalene **3** paralleled the [4+2]-photocycloaddition generating **4** (see Scheme 1). While **3** proved to be photolabile and readily underwent cleavage to the starting materials **1** and **2** upon 313 nm irradiation in solution, the [4+2]-adduct was stable under the irradiation conditions and accumulated at the expense of **3**.[4] Similar results were also obtained with methyl naphthalene-1-carboxylate in place of **1**.[5]

It had been surmised that the preferred geometry of the main product **4**, bearing the morpholino group *syn* to the unaffected benzenoid ring, was facilitated by an attractive interaction between the benzenoid ring and the partially electron-depleted donor in an intermediate captodative[6] biradical **9** assuming preferentially conformation **9A** and eventually leading to product **4**, while conformer **9B** should rather show a repulsive and thus destabilizing interaction and return to the starting materials[1] or cyclize to **3** (see Scheme 2).



Scheme 2

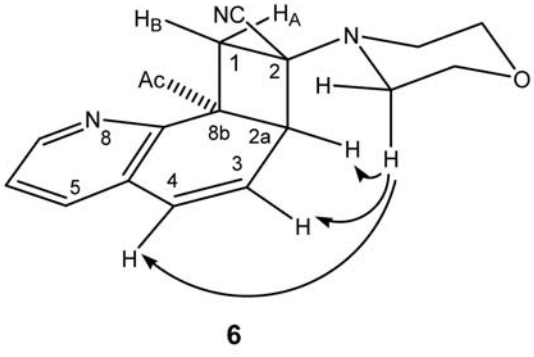
Thus, we wondered whether aza-substitution in the unaffected ring would in any way influence the efficiency of the photocycloadditions by decreasing the attractive interaction within **9A**.

2. Results and Discussion

We decided to test various 8- and 5-acylquinolines in photoreactions with **2**. Generally, with both classes of compounds, a trend to a decrease in efficiency compared to compound **1** was observed requiring longer irradiation times and leading to lower yields.[7] Among the compounds studied, 8-acetylquinoline (**5**) performed moderately well. It shows a UV absorption maximum at 280 nm in acetonitrile solution (log ε = 3.9) allowing the use of benzene as solvent (facilitating mutual complexation of both reactants prior to the first bond forming step) and the use of Duran glassware (short wavelength cut-off at 280 nm) for selective excitation.

Like for **1**, upon irradiation of **5** in the presence of **2** to 26% conversion of **5**, two products were isolated after two consecutive chromatographic operations, namely the tetrahydrocyclobuta[*h*]quinoline **6** (13%) and the 5,8-ethano-5,8-dihydroquinoline **7** (33%, yields refer to consumed starting material).

These products were characterized predominantly by ^{1}H and ^{13}C NMR spectroscopy including ^{1}H,^{1}H and ^{1}H,^{13}C correlation. The *syn* orientation of the morpholino group with respect to the heterocyclic ring in **7** and the *anti* orientation of that group with respect to the quinoline moiety in **6** were supported by comparison of the ^{1}H chemical shifts of the alicyclic part of these compounds with those for compounds **3**[4] and **4**[2], respectively, as well as for further analogous systems,[5,8,9] and by NOE intensity difference measurements. Saturation of the resonance of the axial *N*-methylene protons of **6** intensified the signals of 2a-H, 3-H, and 4-H. Irradiation into the resonance of the equatorial *N*-methylene protons increased the signal in-



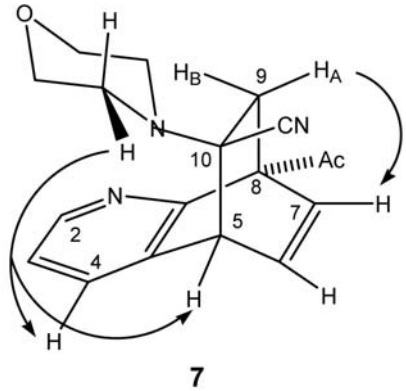


Fig. 1. Numbering and NOE interactions in compounds **6** and **7.**

tensity of 5-H and 4-H in compound **7**, and saturation of the resonance of H_A intensified the signal of 7-H in that compound (see Fig. 1 for numbering, geometries and interactions).

The mass spectra (70 eV EI mode, direct inlet system) of both **6** and **7** did not show the molecular ions due to the lability of these products. Since the UV absorption of **6** with its styrene-like chromophor is extending to longer wavelengths than that of the starting material **5**, the latter cannot (even when present in large excess) serve sufficiently as an effective screen to protect **6** from photochemical cleavage back to the starting materials, while the main product **7** is protected by **5** under the conditions of the irradiation (26% conversion of **5**) and accumulates at the expense of the initially formed **6**. Complete cleavage of isolated **6** into **2** and **5** was effected in hexadeuterobenzene using broadband UV radiation and monitored by ^{1}H NMR. There was no indication of direct conversion into the main product **7**.

It should be pointed out that [4+2]-photocycloadditions of alkenes to the quinoline skeleton have not been reported before, and such photocycloadditions to naphthalenes are rare compared to [2+2]-cycloadditions of that ring system.[10]

As typical for a photo-Diels-Alder adduct, compound **7** was thermally reverted in a unimolecular process (temperature, k, and $t_{1/2}$ given: 323 K, $1.25 \cdot 10^{-6}$ s^{-1}, 154 h; 333 K, $6.4 \cdot 10^{-6}$ s^{-1}, 30.1 h; 343 K, $2.26 \cdot 10^{-5}$ s^{-1}, 8.5 h) with $\Delta H^{\neq} = 130.5 \pm 8$ kJ mol^{-1} and a negative entropy of activation $\Delta S^{\neq} = -46 \pm 3$ J mol^{-1} K^{-1}.

The nature of the excited state of **5** responsible for the reactions cannot be stated with certainty. Attempting oxygen quenching to reveal triplet state participation turned out to be an inappropriate approach due to the sensitivity of **2** towards oxygen: *N*-cyanocarbonyl-morpholine is always formed. It was found, though, that the reaction of photoexcited **5** could be partly quenched using tetramethyldiazetine *N*,*N*-dioxide (in cyclohexane: $\lambda_{max} = 260$ nm, log $\varepsilon = 3.96$; log $\varepsilon = 2.0$ at 310 nm)[11] in concentrations between 10^{-3} to 10^{-2} mol/L. The ratio of products (**6**:**7**), however, remained constant at 1.7 over that range, indicating that probably the same excited state [$^3(\pi,\pi^*)$] was involved in the formation of both products.

Since alkenes like **2** are suitable as ketene equivalents, the bridged diketone **8** could be prepared in good yield by mild hydrolysis[12] of **7** in a buffered Cu(II) salt solution.

3. Conclusion

Substitution of C-8 of 1-acetonaphthone (**1**) by nitrogen as in 8-acetyl-quinoline (**5**) retards but does not suppress the [2+2]- and [4+2]-photocycloadditions of 2-morpholinopropene-nitrile (**2**) to the acylated ring. However, a tendency toward a higher yield of the minor product, compared to the results obtained with **1**, where only 2.6% or less of **3** had ever been isolated,[4] was observed. Thus, another example of the rare [4+2]-photocycloaddition of an alkene to a naphthalene-like system has been presented, and the product of that reaction shows normal behavior in cycloreversion.

4. Experimental Part

General: Melting points have been determined using a Reichert Thermovar hot-stage microscope. – IR spectra (from KBr disks) have been recorded on a Perkin-Elmer 283 instrument, UV spectra on a Perkin-Elmer 554 spectrophotometer. – NMR spectra: Unless stated otherwise, a Bruker WM 300 instrument (^{1}H at 300 MHz, ^{13}C at 75 MHz) has been used on solutions in $CDCl_3$ with TMS as an internal standard. The ^{13}C chemical shifts have been taken from the broadband ^{1}H decoupled spectra and assigned on the basis of DEPT and ^{13}C,^{1}H correlations. – Mass spectra: A Varian MAT 311 spectrometer equipped with digitalized data processing operating in the EI mode at 70 eV ionization energy in connection with a direct inlet system (temperature given) has been used. – Preparative layer chromatography (plc) was conducted on 20 cm tall and 48 cm wide glass plates covered with a 1 mm thick slurry applied and air dried layer of silica gel Merck PF_{254}. Sample quantities were adjusted to achieve complete separation. Zones were detected by indicator fluorescence, mechanically removed from the plates and eluted with acetone.

Starting materials: 1-(Quinolin-8-yl)ethanone (8-acetylquinoline) (5). Was prepared[13] by oxidation of 1-(quinolin-8-yl)ethanol (prepared from quinoline-8-carbaldehyde and methyl- magnesium iodide) using a finely powdered mixture of $KMnO_4$ and $CuSO_4 \cdot 5\ H_2O$ and purified by bulb-to-bulb distillation at 125 °C/0.05 mbar, m.p. 38–40 °C (ref.[14] m.p. 45 °C), yield 55%. – 80 MHz ^{1}H NMR: $\delta =$ 8.90, dd, 1H, $J = 1.9$ and 4.2 Hz, 2-H), 8.12 (dd, 1H, $J =$ 1.9 and 8.3 Hz, 4-H), 7.92–7.19 (several m, 5H), 2.37 (s, 3H, CH_3). – **2-Morpholinopropenenitrile** (**2**) was prepared according to Temin,[15] colorless to yellowish crystals, m.p. 61–62 °C, ref.[15] m.p. 62.5–63.5 °C. – UV (acetonitrile): λ_{max} (log ε) = 258 (3.83), 306 nm (2.46).

Irradiation of 5 in presence of 2: A solution of 1.01 g (5.8 mmol) of **5** and 1.73 g (12.5 mmol) of **2** in 130 mL of benzene was purged with a stream of argon 15 min prior and during the entire irradiation (10 h) with a Philips HPK 125W high pressure mercury lamp mounted in a water cooled Duran immersion well ($\lambda \geq 280$ nm). The residue after concentration was passed over a 2 cm thick layer of dry silica gel Merck PF_{254} using toluene/ethyl acetate 2:1 (v/v), concentrated and subjected to plc using the same solvent for developing. Three zones were detected: zone

1, R_f 0.54, containing 739 mg (4.3 mmol) of starting material **5** (thus 26% of **5** had been converted), zone 2, R_f 0.23 (containing 256 mg), and zone 3, R_f 0.13 (containing 127 mg). All yields reported below refer to converted starting material **5**.

***rel*-(2*R*,2a*R*,8b*S*)-8-Acetyl-2-morpholino-1,2,2a,8b-tetrahydrocyclobuta[*h*]quinoline-2-carbonitrile (6).** From zone 3, by crystallization from 2-propanol 60 mg (13%) of colorless crystals, m.p. 176–177 °C, were obtained. – IR: $\tilde{\nu}$ = 2220 (weak, CN), 1710 (C=O) cm^{-1}. –UV (acetonitrile): λ_{max} (log ε) = 272 (3.9), 320 (2.95) nm. – ^{1}H NMR: ABX [δ_A = 7.42 (5-H), δ_B = 7.18 (6-H), δ_X = 8.41 (7-H), J_{AB} = 7.7, J_{AX} = 1.7, J_{BX} = 4.9 Hz], ABX [δ_A = 6.66 (4-H), δ_B = 5.83 (3-H), δ_X = 3.44 (2a-H), J_{AB} = 9.7, J_{AX} = 1.0, J_{BX} = 5.8 Hz], 3.74–3.71 (m, 4H, CH_2–O–CH_2), AB [δ_A = 3.28 (*anti* 1-H), δ_B = 2.89 (*syn* 1-H), $|^2J_{AB}|$ = 12.2 Hz], 2.53 (m, 2H, ax. HC–N–CH), 2.05 (m, 2H, eq. HC–N–CH), 2.04 (s, 3H, CH_3). – ^{13}C NMR: δ = 204.1 (C=O), 154.2 (C8-a), 149.5 (C-7), 135.1 (C-5), 129.9 (C-6), 127.8 (C-4a), 123.4 (C-4), 123.0 (C-3), 116.3 (CN), 66.4 (H_2C–O–CH_2), 63.0 (C-2), 49.7 (C-8b), 47.5 (C-2a), 47.0 (H_2C–N–CH_2), 41.4 (C-1), 25.9 (CH_3). – MS (130 °C): *m/z* (%) = 264 (18), 239 (25) [M^+ – HCN – $COCH_3$], 181 (48), 172 (94), 171 (21) [M^+ – 2], 156 (32), 154 (47), 138 (100) [representing 2^+], 128 (30). – Anal.: Calcd for $C_{18}H_{19}N_3O_2$ (309.43): C, 69.88; H, 6.19; N, 13.58. Found: C, 69.86; H, 6.16; N, 13.50.

***rel*-(5*R*,8*R*,10*R*)-8-Acetyl-10-morpholino-5,8-dihy-dro-5,8-ethanoquinoline-10-carbonitrile (7).** From zone 2, 150 mg (32%) of colorless crystals were obtained by crystallization from 2-propanol, m.p. 153–153.5 °C. – IR: $\tilde{\nu}$ = 2220 (CN), 1710 (C=O) cm^{-1}. – UV (acetonitrile): λ_{max} = 266 nm (log ε = 3.6). – ^{1}H NMR: ABX [δ_A = 7.45 (4-H), δ_B = 7.11 (3-H), δ_X = 8.31 (2-H), J_{AB} = 7.5, J_{AX} = 1.6, J_{BX} = 5.1 Hz], ABX [δ_A = 6.98 (7-H), δ_B = 6.72 (6-H), δ_X = 4.47 (5-H), J_{AB} = 7.7, J_{AX} = 1.0, J_{BX} = 6.4 Hz], 3.60–3.44 (m, 4H, CH_2–O–CH_2), 2.73 (m, 2H, ax. CH–N–CH), 2.55 (m, 2H, eq. CH–N–CH), 2.54 (s, 3H, $COCH_3$), AB [δ_A = 2.30 (*anti* 9-H), δ_B = 2.00 (*syn* 9-H), $|^2J_{AB}|$ = 12.9 Hz]. – ^{13}C NMR: δ = 206.3 (C=O), 162.4 (C-8a), 146.2 (C-2), 137.4 (C-4), 133.3 (C-3), 132.0 (C-7), 130.6 (C-4a), 121.2 (C-6), 118.4 (CN), 66.3 (C-10 and H_2C–O–CH_2 superimposed), 60.6 (C-8), 48.7 (H_2C–N–CH_2), 44.7 (C-5), 41.3 (C-9), 29.1 (CH_3). –MS (138 °C): *m/z* (%) = 282 (15) [M^+ – HCN], 239 (29), 181 (29), 172 (80), 171 (76) [M^+ - **2**], 170 (16), 156 (81), 154 (73), 138 (100) [representing $\mathbf{2}^+$]. – Anal.: Calcd for $C_{18}H_{19}N_3O_2$ (309.43): C, 69.88; H, 6.19; N, 13.58. Found C, 69.82, H, 6.18; N, 13.51.

***rel*-(5*R*,8*R*)-8-Acetyl-5,8-dihydro-5,8-ethanoquinoline-10-one (8).** In accord with a procedure published by Büchi,[12] 91 mg (0.29 mmol) of **7** were stirred with a finely powdered mixture of 233 mg (0.52 mmol) of $CuSO_4 \cdot 5H_2O$ and 154 mg (0.48 mmol) of $Na_2HPO_4 \cdot 12H_2O$ in a mixture of 5 mL of acetone and 3 mL of water for 96 h at room temperature. The filtrate was extracted with ethyl acetate and the extract was concentrated to 62 mg of crude product, which after crystallization from hexane/ethyl acetate melted at 101–102 °C. – IR: $\tilde{\nu}$ = 1720 (10–C=O), 1705 (acetyl C=O), 1415, 1350, 700 cm^{-1}. – ^{1}H NMR: ABX [δ_A = 7.61 (4-H), δ_B = 7.15 (3-H), δ_X = 8.38 (2-H), J_{AB} = 7.5, J_{AX} = 1.6, J_{BX} = 5.1 Hz], ABX [δ_A = 7.04 (7-H), δ_B = 6.75 (6-H), δ_X = 4.49 (5-H), J_{AB} = 7.6, J_{AX} = 1.5, J_{BX} = 6.1 Hz], 2.59 (s, 3H, CH_3), AB [δ_A = 2.46 (*anti* 9-H), δ_B = 2.39 (*syn* 9-H), $|^2J_{AB}|$ = 17.6 Hz]. – ^{13}C NMR: δ = 204.8 (C=O), 202.1 (C=O), 161.9 (C-8a), 147.0 (C-2), 136.4 (C-7), 132.5 (C-4a), 130.6 (C-4), 130.0 (C-6), 121.4 (C-3), 61.5 (C-8), 58.6 (C-5), 37.1 (C-9), 28.6 (CH_3). – MS (70 °C): *m/z* (%) = 171 (14) [M^+–42], 170 (82) [M^+–43], 156 (27), 154 (15), 143 (18), 142 (100) [M^+–$COCH_3$– CO], 141 (13), 129 (10), 128 (24). – Anal.: Calcd for $C_{13}H_{11}NO_2$ (213.24): C, 73.23; H, 5.19; N, 6.56. Found C, 73.14; H, 5.24; N, 6.65.

Thermolysis of compound 7. Solutions of 25 mg of **7** in the proper amount of hexadeuterobenzene were kept in 5 mm NMR tubes at 50, 60, and 70 °C, and scanned after suitable time intervals. The relative concentrations of **7** and starting material **5** were determined by ^{1}H NMR integration. Plots of ln c(**7**) vs. time gave straight lines from which k [s^{-1}] was extracted by linear regression analysis.

5. References

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Povzetek

Fotokemijska 1-acetonaftona (**1**) in 8-acetilkinolina (**5**) na 2-morfolinopropenonitril (**2**) v benzenu je vodila [2+2]-cikloadukta, *rel*-(2*R*,2a*R*,8b*S*)-8b-acetil-2-morfolino-1,2,2a,8b-tetrahidrociklobuta-[*h*]kinolin-2-carbonitrila (**6**) in [4+2]-cikloadukta, *rel*-(5*R*,8*R*,10*R*)-8-acetil-10-morfolino-5,8-etano-5,8-dihidrokinolin-10-karbonitrila (**7**). Pod termičnimi pogoji poteče razcep cikloadukta **7** v izhodni spojini **2** in **5** ($\Delta H^{\neq} = 130.5 \pm 8$ kJ mol^{-1} and $\Delta S^{\neq} = 46 \pm 3$ J mol^{-1} K^{-1}) pod hidrolitskimi podoji pa pretvorba v triciklični diketon, *rel*-(5*R*,8*R*)-8-acetil-5,8-etano-5,5-dihidrokinolin-10-on (**8**).