REGIOCHEMICAL STUDY IN THE DIELS-ALDER REACTION OF 2-AZAANTHRAQUINON-3-ONES

Boufelja Bouammali, Félix Pautet, and Houda Fillion*
Laboratoire de Chimie Organique, Institut des Sciences Pharmaceutiques et Biologiques, 8 avenue Rockefeller, 69008 Lyon, France

Abstract-The regiochemistry of the Diels-Alder reaction between 2-aza-1,3-butadienes (1) and naphthoquinones (2) (R = OH or OAc) is investigated.

Several examples of [4+2] cycloadditions of 2-aza-1,3-butadienes have been described. More recently, 1-alkoxy-3-(t-butyldimethylsilyl)oxy-2-aza-1,3-butadienes (1), readily available from N-acylimidates were reported to react with activated nitriles. In order to get some polysubstituted 2-azaanthraquinon-3-ones, we have carried out their synthesis through a Diels-Alder reaction of 2-azadienes (1) and naphthoquinones (2) (R = OH, OAc) and investigated their regiochemistry:

So, azadienes (1) reacted with 5-hydroxy- or 5-acetoxy naphthoquinone to yield cycloadducts which, after aromatization and desilylation, gave a mixture of the substituted 2-azaanthraquinon-3-ones (3) and (4) or (5) and (6) (Table 1).
Table 1. Synthesis of 2-Azaanthraquinon-3-ones

<table>
<thead>
<tr>
<th>Azadiene</th>
<th>Naphthoquinone (2)</th>
<th>Time (a) (h)</th>
<th>Products</th>
<th>Yield [%]</th>
<th>Ratio of regioisomers 2,8:2,5(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R₃ = OH</td>
<td>2.5</td>
<td>3a + 4a</td>
<td>77</td>
<td>84:16</td>
</tr>
<tr>
<td>1b</td>
<td>R₃ = OH</td>
<td>4</td>
<td>3b + 4b</td>
<td>64</td>
<td>91:9</td>
</tr>
<tr>
<td>1c</td>
<td>R₃ = OH</td>
<td>4</td>
<td>3c + 4c</td>
<td>43</td>
<td>82:18</td>
</tr>
<tr>
<td>1d</td>
<td>R₃ = OH</td>
<td>2.5</td>
<td>3d + 4d</td>
<td>38</td>
<td>78:22</td>
</tr>
<tr>
<td>1a</td>
<td>R₃ = OAc</td>
<td>4.5</td>
<td>5a + 6a</td>
<td>36</td>
<td>37:63</td>
</tr>
<tr>
<td>1b</td>
<td>R₃ = OAc</td>
<td>8</td>
<td>5b + 6b</td>
<td>32</td>
<td>30:70</td>
</tr>
<tr>
<td>1c</td>
<td>R₃ = OAc</td>
<td>5</td>
<td>5c + 6c</td>
<td>29</td>
<td>43:57</td>
</tr>
<tr>
<td>1d</td>
<td>R₃ = OAc</td>
<td>6.5</td>
<td>5d + 6d</td>
<td>20</td>
<td>54:46</td>
</tr>
</tbody>
</table>

(a) The reactions were followed by tlc.
(b) The ratio of regioisomers was evaluated from the ¹H-nmr spectra of the crude mixture (see Table 2). The same ratio was generally observed in the isolated pure material excepted in the case of 5c + 6c where the yellow precipitate was constituted by the pure regioisomer (6c).

It is apparent from Table 1 that the cycloadditions are more regioselective with juglone (2) (R = OH) than with acetyljuglone. Moreover, azadiene (1b) gives a best regioselectivity with the two naphthoquinones. The structures of compounds (3) are in good agreement with the known directing effect of the 5-hydroxy group in juglone in analogous Diels-Alder reactions. The poor regioselectivity and the generally opposite regiochemistry observed with acetyljuglone are also in accord with the literature.

Identification of the regioisomeric 2-azaanthraquinon-3-ones was established from their ¹H-nmr 300 MHz spectra (Table 2). Thus, in the 8-hydroxylated derivatives (3), the peri-OH signals are more deshielded than those of the 5-hydroxylated 4. Furthermore, in compounds (3), the R₁ substituent (H or Me) is shifted to the lower fields while in 4, R₂ (H or Me) is deshielded.

Assignment of the structure of the acetates (5) and (6) was made after their hydrolysis (5 % aqueous NaOH) and comparison of the ¹H-nmr spectral data of the hydrolysed products with those of compounds (3) and (4) prepared directly from juglone. We have also observed that the R₁
substituent \((H\ or\ Me)\) was more deshielded after deacetylation of 5 than \(R_2\) \((H\ or\ Me)\), while the reverse was obtained with the regioisomeric acetates (6).

Table 2. \(^1\)H-Nmr Spectral Data of 2-Azaanthraquinon-3-ones
(300 MHz, DMSO-d\(_6\), \(\delta\) ppm)

<table>
<thead>
<tr>
<th>NH</th>
<th>OH</th>
<th>R(_1)(H or Me)</th>
<th>R(_2)(H or Me)</th>
<th>OCOCH(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-OH</td>
<td>5-OH</td>
<td>2,8- 2,5-</td>
<td>2,8- 2,5-</td>
<td>2,8- 2,5-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regioisomers</td>
<td>regioisomers</td>
<td>regioisomers</td>
</tr>
</tbody>
</table>

3a + 4a 12.84 12.84 12.25 8.47 8.37 6.90 6.97
5a + 6a 12.85 8.39 8.33 6.82 6.87 2.39 2.37
3b + 4b 12.82 13.11 12.10 2.76 2.74 6.81 6.91
5b + 6b 12.70 2.67 2.75 6.79 6.74 2.36 2.39
3c + 4c 12.78 12.77 12.45 8.32 8.24 2.46 2.53
5c + 6c 12.67 8.16 8.22 2.47 2.49 2.36 2.38
3d + 4d 12.74 13.08 12.35 2.74 2.70 2.42 2.45
5d + 6d 12.59 2.61 2.70 2.39 2.36 2.35 2.29

EXPERIMENTAL PART

Melting points were taken in capillary tube using a Büchi 510 apparatus and are corrected. Ir spectra were performed on a Perkin-Elmer 1310 spectrophotometer. \(^1\)H-Nmr spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-24B or at 300 MHz on a Bruker AM 300 spectrometer. Mass spectra were performed by direct ionisation (EI at 70 eV) on an AEI MS 902 apparatus. Elemental analysis were made at the Centre de Microanalyse du CNRS at Solaise. Azadienes (1a, 1b, and 1c) were prepared according to Ph. Bayard procedure. These azadienes are stable at \(-25^\circ\)C during two or three weeks, but they decompose quickly at room temperature.

SYNTHESIS OF ETHYL (N-PROPIONYL)ACETIMIDATE

Triethylamine (15 ml) was added to a stirred solution of ethyl acetimidate hydrochloride (6 g, 0.049 mol) in dry dichloromethane (65 ml) at \(-30^\circ\)C. Then 4.3 ml (0.049 mmol) of freshly distilled propionyl chloride were
quickly added. Petroleum ether (120 ml) was added to the reaction mixture and the cooling bath was removed. The solid was filtered off and the filtrate was concentrated in vacuo. The residue was again dissolved in petroleum ether (60 ml) and any insoluble material was removed by filtration. The solution was concentrated and the residue was distilled through a 10 cm Vigreux column. Yield: 5.7 g (83%). bp27mmHg 78-79°C. Ir (film): 1690, 1660 cm⁻¹. ¹H-Nmr (CDCl₃, 60 MHz): δ 3.90 (2H, q, J = 6.5 Hz); 2.15 (2H, q, J = 7.0 Hz); 1.80 (3H, s); 1.12 (3H, t, J = 6.5 Hz); 0.92 (3H, t, J = 7.0 Hz). Anal. Calcd for C₇H₁₃N0₂: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.52; H, 8.78; N, 9.47.

SYNTHESIS OF 3-AZA-4-((t-BUTYLDIMETHYLSILYL)OXY-2-ETHOXY-2,4-HEXADIENE (1d)
A mixture of ethyl (propionyl)acetimidate (3 g, 21 mmol) and anhydrous triethylamine (3.2 ml) in dry ether (15 ml) was treated with t-butyldimethylsilyl triflate (5.76 g, 21.8 mmol) diluted in ether (6ml). Two phases were obtained. The upper ethereal phase was removed and the lower phase was washed twice with dry ether (2.10 ml). The combined ethereal fractions were concentrated in vacuo and distilled through a 10 cm Vigreux column. Yield: 3.8 g (70%). bp0.5mmHg 76-77°C. Ir (film): 1690, 1660 cm⁻¹. ¹H-Nmr (CDCl₃, 60 MHz): δ 3.90 (2H, q, J = 6.5 Hz); 3.60 (1H, q, J = 6.5 Hz); 1.80 (3H, s); 1.40 (3H, d, J = 6.5 Hz); 1.10 (3H, t, J = 6.5 Hz); 0.78 (9H, s); -0.02 (6H,s).

SYNTHESIS OF 2-AZAANTHRAQUINON-3-ONES. GENERAL PROCEDURE
A solution of 2-aza-1,3-diene (1) (2.52 mmol) and naphthoquinone (2) (1.68 mmol) in chloroform (5 ml) was stirred and heated under nitrogen at 70°C for a variable time (see Table 1). Then, an aqueous solution of 40% hydrofluoric acid (0.27 ml) was added at room temperature and the mixture was stirred for 2 h. After evaporation of the solvent, the residue was heated in acetone (10 ml) under reflux for 2 h. The precipitate was constituted by a mixture of the regioisomers (3) and (4) or (5) and (6). It was isolated by filtration and recrystallized from acetone.

2-Aza-8- and 2-aza-5-hydroxy-9,10-anthraquinon-3-ones, (3a) and (4a)
mp > 300°C (acetone). Ir (KBr): 3220-3120, 1725, 1680, 1640 cm⁻¹. ¹H-Nmr (DMSO-d₆, 300 MHz): 3a: δ 12.84 (2H, s, OH and NH); 8.47 (1H, s, H-1); 7.83 (1H, H-6, dd, J = 7.5 and 8.0 Hz); 7.75 (1H, H-5, d, J = 8.0 Hz); 7.39 (1H, H-7, d, J = 7.5 Hz); 6.97 (1H, s, H-4). 4a: δ 12.84 (1H, s, NH);
12.25 (1H, s, OH); 8.37 (1H, s, H-1); 7.83 (1H, H-7, dd, J = 7.5 and 8.0 Hz); 7.75 (1H, H-8, d, J = 8.0 Hz); 7.38 (1H, H-6, d, J = 7.5 Hz); 6.90 (1H, s, H-4). Anal. Calcd for C_{13}H_{7}N_{04}, 0.66 H_{2}O: C, 61.66; H, 3.05; N, 5.53. Found: C, 61.61; H, 2.84; N, 5.59. Hrms Calcd for C_{13}H_{7}N_{04}: M^+ 241.0375. Found: 241.0361.

2-Aza-8- and 2-aza-5-hydroxy-1-methyl-9,10-anthraquinon-3-ones, (3b) and (4b)

mp > 300°C (acetone). Ir (KBr): 3600-3400, 1670, 1635 cm\(^{-1}\). \(^{1}\)H-Nmr (DMSO-d\(_6\), 300 MHz): 3b: \(\delta\) 13.11 (1H, s, OH); 12.82 (1H, s, NH); 7.73 (1H, H-5, d, J = 7.0 Hz); 7.62 (1H, H-6, d, J = 8.2 Hz); 7.33 (1H, H-7, d, J = 8.2 Hz); 6.81 (1H, s, H-4); 2.76 (3H, s, CH\(_3\)-1). 4b: \(\delta\) 12.10 (H, s, OH); 12.10 (1H, s, NH); 7.73 (1H, H-7, dd, J = 7.0 and 8.8 Hz); 7.62 (1H, H-8, d, J = 7.0 Hz); 7.33 (1H, H-6, d, J = 8.8 Hz); 6.88 (1H, s, H-4); 2.76 (3H, s, CH\(_3\)-1). Anal. Calcd for C\(_{14}\)H\(_9\)N\(_0\)O\(_5\), 0.5 H\(_2\)O: C, 63.64; H, 3.43; N, 5.30. Found: C, 63.59; H, 3.43; N, 5.14. Hrms Calcd for C\(_{14}\)H\(_9\)N\(_0\)O\(_5\): M^+ 255.0532. Found: 255.0527.

2-Aza-8- and 2-aza-5-hydroxy-4-methyl-9,10-anthraquinon-3-ones, (3c) and (4c)

mp > 300°C (acetone). Ir (KBr): 3600-3270, 1700, 1640 cm\(^{-1}\). \(^{1}\)H-Nmr (DMSO-d\(_6\), 300 MHz): 3c: \(\delta\) 12.78 (1H, s, NH); 12.77 (1H, s, OH); 8.31 (1H, s, H-1); 7.77 (1H, H-6, dd, J = 7.7 and 8.2 Hz); 7.65 (1H, H-5, d, J = 7.4 Hz); 7.33 (1H, H-7, d, J = 8.2 Hz); 2.46 (3H, s, CH\(_3\)-4). 4c: \(\delta\) 12.78 (1H, s, NH); 12.45 (1H, s, OH); 8.24 (1H, s, H-1); 7.77 (1H, H-7, dd, J = 7.7 and 8.2 Hz); 7.62 (1H, H-8, d, J = 8.2 Hz); 7.23 (1H, H-6, d, J = 8.1 Hz); 2.53 (3H, s, CH\(_3\)-4). Anal. Calcd for C\(_{14}\)H\(_9\)N\(_0\)O\(_4\), 0.5 H\(_2\)O: C, 63.68; H, 3.81; N, 5.30. Found: C, 63.46; H, 3.55; N, 5.28. Hrms Calcd for C\(_{14}\)H\(_9\)N\(_0\)O\(_4\): M^+ 255.0531. Found: 255.0538.

2-Aza-8- and 2-aza-5-hydroxy-1,4-dimethyl-9,10-anthraquinon-3-ones, (3d) and (4d)

mp > 300°C (acetone). Ir (KBr): 3600-3300, 1690, 1632 cm\(^{-1}\). \(^{1}\)H-Nmr (DMSO-d\(_6\), 300 MHz): 3d: \(\delta\) 13.08 (1H, s, OH); 12.74 (1H, s, NH); 7.72 (1H, H-6, dd, J = 7.8 and 7.8 Hz); 7.59 (1H, H-5, d, J = 7.8 Hz); 7.31 (1H, H-7, d, J = 7.8 Hz); 2.74 (3H, s, CH\(_3\)-1), 2.42 (3H, s, CH\(_3\)-4). 4d: \(\delta\) 12.74 (1H, s, NH); 12.35 (1H, s, OH); 7.72 (1H, H-7, dd, J = 7.8 and 7.8 Hz); 7.59 (1H, H-8, d, J = 7.8 Hz); 7.31 (1H, H-6, d, J = 7.8 Hz); 2.74 (3H, s, CH\(_3\)-1);

8-Acetoxy- and 5-acetoxy-2-aza-9,10-anthraquinon-3-ones, (5a) and (6a) mp 250-253°C decomp. (acetone). IR (KBr): 1765, 1690, 1640 cm⁻¹. ¹H-Nmr (DMSO-d₆, 300 MHz): 5a: δ 12.85 (1H, s, NH); 8.39 (1H, H-1); 8.18 (1H, H-5, d, J = 7.4 Hz); 7.98 (1H, H-6, dd, J = 7.3 and 7.4 Hz); 7.62 (1H, H-7, d, J = 7.4 Hz); 6.82 (1H, s, H-4); 2.39 (3H, s, COCH₃). 6a: δ 12.85 (1, s, NH); 8.32 (1H, s, H-1); 8.16 (1H, H-8, d, J = 7.2 Hz); 7.93 (1H, H-7, dd, J = 7.2 and 7.4 Hz); 7.64 (1H, H-6, d, J = 7.4 Hz); 6.87 (1H, s, H-4); 2.37 (3H, s, COCH₃). Anal. Calcd for C₁₅H₁₁NΟ₅: C, 63.61; H, 3.20; N, 4.95. Found: C, 63.75; H, 3.39; N, 4.67. Hrms Calcd for C₁₅H₁₁NΟ₅: M⁺ 283.0481. Found: 283.0476.

8-Acetoxy- and 5-acetoxy-2-aza-1-methyl-9,10-anthraquinon-3-ones, (5b) and (6b) mp > 270-280°C decomp. (acetone). IR (KBr): 1772, 1675, 1660 cm⁻¹. ¹H-Nmr (DMSO-d₆, 300 MHz): 5b: δ 12.70 (1H, s, NH); 8.13 (1H, H-5, d, J = 7.4 Hz); 7.90 (1H, H-6, dd, J = 7.4 and 8.0 Hz); 7.60 (1H, H-7, d, J = 8.0 Hz); 6.79 (1H, H-8, d, J = 7.2 Hz); 7.93 (1H, H-7, dd, J = 7.2 and 7.4 Hz); 7.64 (1H, H-6, d, J = 7.4 Hz); 6.87 (1H, s, H-4); 2.37 (3H, s, COCH₃). 6b: δ 12.70 (1H, s, NH); 8.08 (1H, H-8, d, J = 7.4 Hz); 7.95 (1H, H-7, dd, J = 7.4 and 8.0 Hz); 7.57 (1H, H-6, d, J = 8.0 Hz); 6.74 (1H, s, H-4); 2.75 (3H, s, CH₃-1); 2.38 (3H, s, COCH₃). Anal. Calcd for C₁₆H₁₁NΟ₅: C, 64.00; H, 3.69; N, 4.64. Found: C, 63.98; H, 3.55; N, 4.59. Hrms Calcd for C₁₆H₁₁NΟ₅: M⁺ 297.0637. Found: 297.0628.

8-Acetoxy- and 5-acetoxy-2-aza-4-methyl-9,10-anthraquinon-3-ones, (5c) and (6c) mp 265-271°C decomp. (acetone). IR (KBr): 1767, 1675, 1646 cm⁻¹. ¹H-Nmr (DMSO-d₆, 300 MHz): 5c: δ 12.67 (1H, s, NH); 8.16 (1H, s, H-1); 8.11 (1H, H-5, d, J = 7.1 Hz); 7.90 (1H, H-7, dd, J = 7.1 and 8.0 Hz); 7.59 (1H, H-6, d, J = 8.0 Hz); 2.47 (3H, s, CH₃-4); 2.36 (3H, s, COCH₃). 6c: δ 12.67 (1H, s, NH); 8.22 (1H, s, H-1); 8.09 (1H, H-8, d, J = 7.1 Hz); 7.93 (1H, H-7, dd, J = 7.1 and 8.1 Hz); 7.59 (1H, H-6, d, J = 8.1 Hz); 2.49 (3H, s, CH₃-4); 2.38 (3H, s, COCH₃). Anal. Calcd for C₁₆H₁₁NΟ₅: C, 64.69; H, 3.73; N, 4.71. Found: C, 64.60; H, 3.84; N, 4.67. Hrms Calcd for C₁₆H₁₁NΟ₅: M⁺ 297.0637. Found: 297.0639.
8-Acetoxy- and 5-acetoxy-2-aza-1,4-dimethyl-9,10-anthraquinon-3-ones, \( (5d) \) and \( (6d) \)

mp 250-253°C decomp. (acetone). \( \text{Ir(KBr)}: \) 1768, 1650, 1641 cm\(^{-1}\). \( ^{1} \text{H-Nmr} \)

(DMSO-\( \text{d}_6 \), 300 MHz): \( 5d: \) \( \delta \) 12.59 (1H, s, NH); 8.00 (1H, H-5, dd, \( J = 1.1 \) and 7.8 Hz); 7.84 (1H, H-6, dd, \( J = 7.8 \) and 8.0 Hz); 7.56 (1H, H-7, dd, \( J = 1.1 \) and 8.0 Hz); 2.61 (3H, s, CH\(_3\)-1); 2.39 (3H, s, CH\(_3\)-4); 2.35 (3H, s, COCH\(_3\)). \( 6d: \) \( \delta \) 12.59 (1H, s, NH); 8.01 (1H, H-8, dd, \( J = 1.1 \) and 7.8 Hz); 7.84 (1H, H-7, dd, \( J = 7.8 \) and 8.0 Hz); 7.53 (1H, H-6, dd, \( J = 1.1 \) and 8.0 Hz); 2.70 (3H, s, CH\(_3\)-1); 2.36 (3H, s, CH\(_3\)-4); 2.29 (3H, s, COCH\(_3\)). \text{Anal. Calcd for} \ C_{17}H_{13}NO_{5}, 0.25 H\(_2\)O: C, 64.66; H, 4.23; N, 4.43 Found: C, 64.66; H, 4.35; N, 4.69. \text{Hrns Calcd for} \ C_{17}H_{13}NO_{5}: M^+ 311.0794. Found: 311.0795.

ACKNOWLEDGEMENTS

The authors thank the University Claude Bernard for its financial support on a high field nmr program.

REFERENCES AND NOTES

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A mixture of the regioisomeric acetates (5d) and (6d) (0.06 g, 0.19 mmol) was stirred at room temperature for 2 h with 5 ml of an aqueous solution of 5% sodium hydroxide. Then, the hydroxylated derivatives (3d) and (4d) were precipitated by addition of an aqueous solution of 5% hydrochloric acid.

Received, 10th December, 1990