Thermal Cyclization of 2-Acyl-1-azido-3-phenalenones to Phenaleno[1,2-*c*]isoxazol-7-ones [1]

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1-Azido-3-phenalenones **5** with acyl substituents in position 2, obtained by acylation and azidation of 1-hydroxy-3-phenalenones **1**, cyclized by thermolysis to give phenaleno[1,2-*c*]isoxazol-7-ones **9**. The thermolysis conditions were studied by differential scanning calorimetry.

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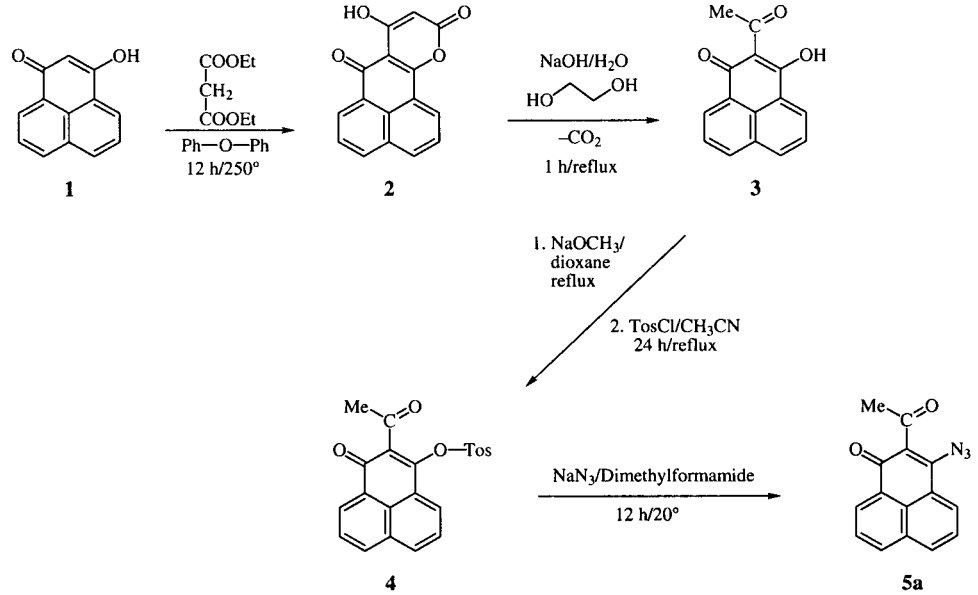
Investigation of thermolysis reactions of azidoarenes [2] with *ortho*-acyl substituents are known to give isoxazoles, a class of compounds which shows interesting biological properties, *e.g.* antiinflammatory [3], antibacterial [4] or cytostatic [5] activity. Our investigations in the synthesis of oxazoles from *ortho*-acylazides showed that the reactions took place within a large temperature range [6]. Thermic reactions of this type were studied with good results by differential scanning calorimetry, a method which provided us with important reaction data [7]. In this paper we want to report the synthesis of a new ring system, 7*H*-phenaleno[1,2-*c*]isoxazole, starting from 1-azido-3-phenalenones with acylsubstituents at position 2.

Our synthesis path started from 1-hydroxy-3-phenalenone (**1**) which was prepared as described in reference [8]. Attempts to obtain 2-acetyl-1-azido-3-phenalenone (**3**) in a one step reaction by reaction with acetyl chloride or acetic anhydride in the presence of acid catalysts failed. Thus, we used a two step reaction involving as the first reaction step a cyclocondensation with diethyl malonate to give the fused hydroxypyrandione **2**, which gave upon basic ring opening followed by spontaneous decarboxylation 2-acetyl-1-hydroxy-3-phenalenone (**3**) according to the method which we have developed for 3-acyl-4-hydroxyquinolones [9]. As the next step towards the 2-acetyl-1-azido-3-phenalenone **5a** the synthesis of a reactive intermediate such as the 2-acetyl-1-chloro-3-phenalenone was intended. However, efforts to convert the hydroxyphenalenone **3** to the corresponding chloro derivative failed, probably because of strong hydrogen bondings between the acetyl and the hydroxy group, which prevented chlorination. Also the addition of strong bases in order to destroy the hydrogen bondings was not successful. So we decided to carry out the reaction *via* the tosyloxy phenalenone **4**. The first attempts to react **3** with toluenesulfonyl chloride directly in pyridine as a base failed. Thus we converted **3** with sodium methoxide to the corresponding sodium salt and reacted this salt with toluenesulfonyl chloride to 2-acetyl-1-tosyloxy-3-phenalenone (**4**). Reaction of the tosylate **4** with sodium azide at 60° afforded 2-acetyl-1-azido-3-phenalenone (**5a**) in good yields.

Scheme 1

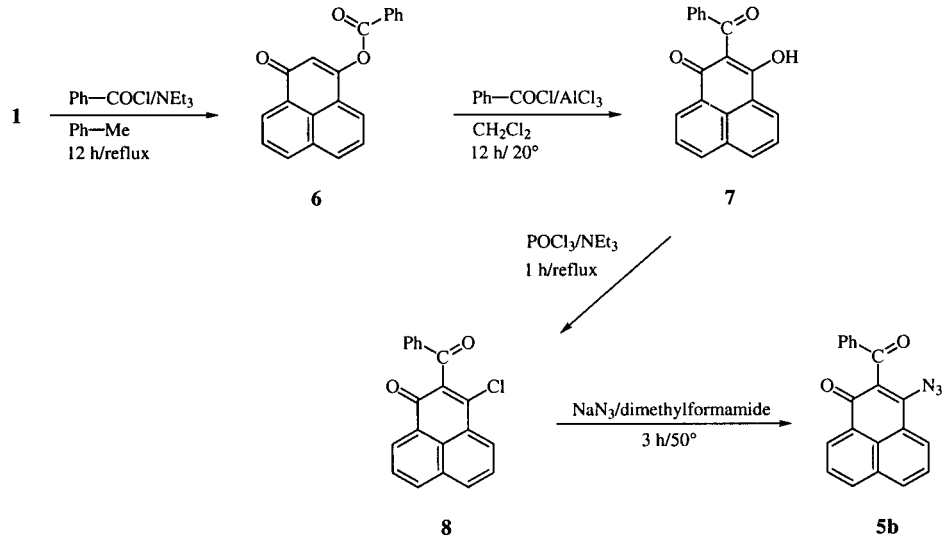


1 **2** **3** **4** **5a**

The synthesis of 2-benzoyl-1-hydroxy-3-phenalenone (**7**) again could not be accomplished by a one step reaction by direct benzoylation of the 1-hydroxy-phenalenone **1** with acid catalysts. So **1** was allowed to react with benzoyl chloride in the presence of triethylamine as a base to give as the first step 3-benzoyloxy-1-phenalenone (**6**). However, efforts to convert the 1-benzoate **6** to the 2-benzoyl derivative **7** by a Fries rearrangement or by rearrangement with potassium cyanide, as decribed recently [10] failed.

Whereas the 1-hydroxy-phenalenone **1** did not react in a direct Friedel-Crafts acylation because of its insolubility, we succeeded in a Friedel-Crafts acylation of the benzoate **6** with benzoyl chloride and aluminium chloride. During the work up the benzoyloxy group was cleaved and we obtained in moderate yields the 2-benzoyl derivative **7**. Chlorination of **7** with phosphoryl chloride and triethylamine as base led in excellent yields to 2-benzoyl-1-chloro-3-phenalenone (**8**), which was converted in turn to 1-azido-2-benzoyl-3-phenalenone (**5b**).

Scheme 2

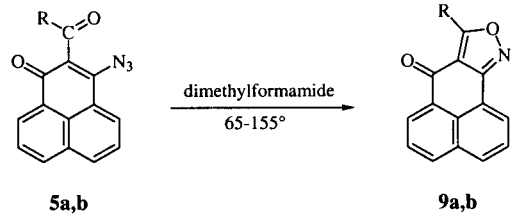


As mentioned in the introduction, *ortho*-acyl azides of type **5** cyclize easily by photolysis or thermolysis to give mainly isoxazoles [2,6]. This cyclization is reported to run *via* an electrocyclic process and not *via* the formation of nitrenes [2,11]. To obtain data for the thermolytic decomposition we studied the thermic behaviour by means of differential scanning calorimetry.

The calorimetric diagrams of the acetyl azide **5a** (Figure 1) showed a broad exothermic peak starting at about 100° with a peak maximum at about 122° which gave us the information for the best conditions for the cyclization reaction. This peak was followed only by an endothermic melting area at about 175° (which derived from the isoxazole **9a** having a mp of 184-187° in pure form), but not by any exothermic decomposition reaction. However, when we thermolyzed **5a** in dimethylformamide at about 100° in a preparative scale, we found that many side products were formed which made the isolation of a pure product difficult. Only when we lowered the temperature to 65°, we obtained after 5-6 hours reaction time in good yields 8-methyl-phenaleno[1,2-*c*]isoxazol-7-one (**9a**). Thus the broad exothermic reaction area seems to contain a consecutive decomposition reaction (probably the shoulder at about 125°), which can only be avoided by lower temperatures, but with the drawback of long reaction times.

The calorimetric diagrams of the benzoyl azide **5b** (Figure 2) showed an exothermic reaction with a sharp peak at about 160° and exothermic decomposition reactions beyond 310°. These results prompted us to thermolyze the azide **5b** in refluxing dimethylformamide at 155° and we obtained after 60 minutes reaction time in about 50% yield 8-phenylphenaleno[1,2-*c*]isoxazol-7-one (**9b**) without any difficulties.

Scheme 3



5a,b **9a,b**

5, 9 R
a Me
b Ph

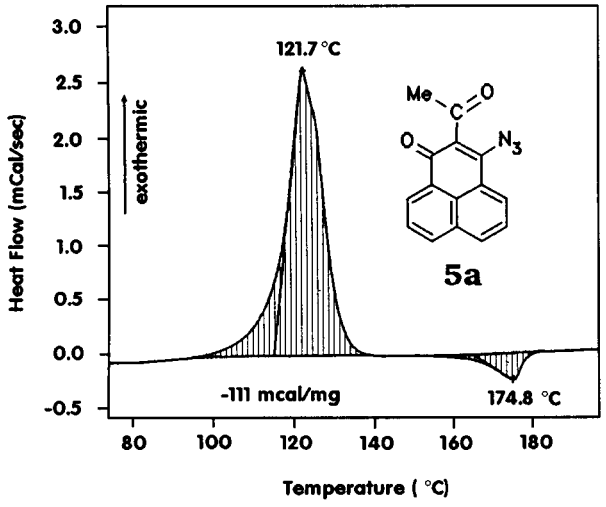


Figure 1. Differential scanning calorimetry diagram of **5a**.

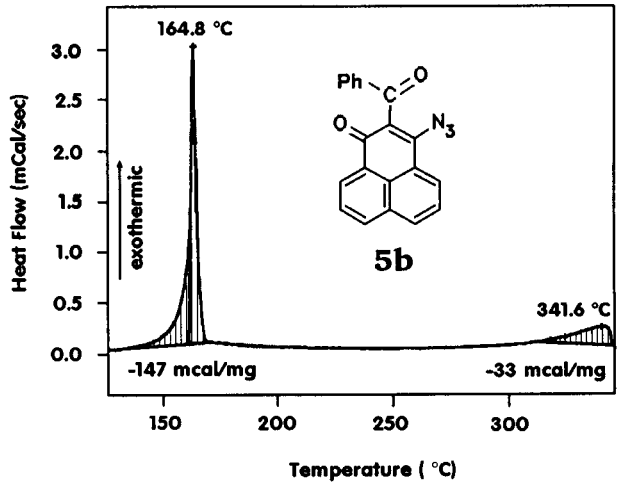


Figure 2. Differential scanning calorimetry diagram of **5b**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Model MFB-595 in open capillary tubes. Calorimetric data were obtained on a Rheometric Scientific DSC-Plus instrument with the differential scanning calorimetry software V5.42. The differential scanning calorimetry plots were recorded between 25-500°, with a heating rate of 2-10°/minute, and 1.5-3 mg compound in sealed aluminium crucibles (11 bar). Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer or a Galaxy Series FTIR 7000 in potassium bromide pellets. The ^{1}H nmr spectra were recorded on a Varian Gemini 200 (200 MHz) or a Bruker AM 360 instrument (360 MHz). The solvent for nmr spectra was deuteriodimethyl sulfoxide. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. Elemental analyses were performed on a Fisons elemental analyzer, Model EA 1108 and are within ±0.4 of the theoretical percentages. All reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel F-254 (Merck) plates using uv light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

1-Hydroxyphenalen-3-one (**1**).

Compound **1** was prepared as described in reference [8].

8-Hydroxyphenaleno[1,2-*b*]pyran-7,10-dione (**2**).

A mixture of the hydroxyphenalenone **1** (10.0 g, 51 mmoles), diethyl malonate (7.78 ml, 51 mmoles) and diphenylether (15 ml) was heated under reflux until the eliberation of ethanol had stopped (about 12 hours). Then the reaction mixture was cooled to 100°, and dioxane (20 ml) was added. After cooling to room temperature the precipitate was filtered by suction and washed with dioxane and diethylether. The yield was 10.4 g (77%), brown prisms, mp 270.6-271.7° (xylene); ir: 1735 s, 1660 s, 1605 w, 1570 s cm^{-1}; ^{1}H nmr: δ 5.63 (s, H at C-10), 7.80-7.99 (m, 2 Ar-H at C-3 and C-6), 8.46-8.61 (m, 4 Ar-H at C-2, C-4, C-5 and C-7), 12.95 (s, OH).

Anal. Calcd. for $C_{16}H_8O_4$: C, 72.73; H, 3.05. Found: C, 74.55; H, 3.52. (Despite several purifications no analytical pure sample could be obtained because of the ease of decomposition to **3**).

2-Acetyl-1-hydroxyphenalen-3-one (**3**).

A solution of sodium hydroxide (8 g) in water (9 ml) was added to a suspension of the pyran **2** (10.48 g, 40 mmoles) in 1,2-ethanediole (90 ml) and the mixture heated under reflux for 1 hour. Then the reaction mixture was poured into ice/water (300 ml) and acidified with 12 *M* hydrochloric acid. The formed precipitate was filtered by suction, washed with water and dried. The yield was 2.8 g (30%), yellow prisms, mp 174.2-176.3° (ethanol/water); ir: 1640 s, 1580 s cm^{-1}; ^{1}H nmr: δ 2.70 (s, CH_3), 7.70-7.85 (m, 2 Ar-H at C-5 and C-8), 8.30-8.49 (m, 3 Ar-H at C-4, C-6, C-7 and C-9).

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.50; H, 4.46.

2-Acetyl-1-(4-toluenesulfonyloxy)phenalen-3-one (**4**).

1) Preparation of the Sodium Salt of **4**.

A solution of **4** (12.0 g, 50.4 mmoles) in boiling dry dioxane (180 ml) was added to sodium methoxide (from 1.44 g of sodium and 40 ml of methanol). Then the mixture was allowed to stand at 4° for 12 hours to finish the precipitation of the sodium salt; the salt was filtered by suction. The yield was 7.14 g (54%) **4**-sodium salt as a colorless powder.

2) Tosylation.

A mixture of **4**-sodium salt (6.11 g, 23.4 mmoles) and 4-toluenesulfonyl chloride (5.25 g, 27.5 mmoles) in dry acetonitrile (50 ml) was heated under reflux with vigorous stirring for 24 hours. After cooling the reaction mixture was poured into ice/water (700 ml), the resulting precipitate allowed to stand for 2 hours, filtered by suction and dried *in vacuo* at room temperature. The yield was 5.11 g (55%), yellow crystals, mp 127-129.9° (ethanol); ir: 1690 m, 1640 s, 1580 s cm^{-1}; ^{1}H nmr: δ 0.75 (s, acetyl-CH_3), 2.50 (s, tosyl-CH_3), 7.72-8.05 (m, 4 Ar-H), 8.50-8.65 (m, 6 Ar-H).

Anal. Calcd. for $C_{22}H_{16}O_5S$: C, 67.34; H, 4.11; S, 8.17. Found: C, 66.98; H, 4.31; S, 7.92.

2-Acetyl-1-azidophenalen-3-one (**5a**).

A mixture of the tosylate **4** (3.0 g, 7.6 mmoles) in dimethylformamide (75 ml) and sodium azide (1.5 g, 23 mmoles) was stirred at room temperature for 12 hours. Then the mixture was poured into ice/water (250 ml) and after standing for 1 hour filtered by suction, recrystallized from acetone/water and dried *in vacuo* at room temperature. The yield was 1.25 g (62%), yellow powder, mp 115-116° dec (acetone/water); calorimetric data for thermolysis: cyclization starting at about 115°, maximum 121°, ΔH -111 mcal/mg, mp onset 164.6°, maximum 174.8°; ir: 2140 s (N_3), 1680 s, 1635 s, 1615 m, 1575 s cm^{-1}.

Anal. Calcd. for $C_{15}H_9N_3O_2$: C, 68.44; H, 3.45; N, 15.96. Found: C, 70.71; H, 4.40; N, 11.41. (Because of the ease of decomposition to **9a** no exact analytical data could be obtained.)

1-Azido-2-benzoylphenalen-3-one (**5b**).

A mixture of the chloro compound **8** (1.34 g, 4.2 mmoles) in dimethylformamide (50 ml) and sodium azide (1.21 g, 18.6 mmoles) was stirred at 50-60° for 3 hours and then worked up as described for **5a**. The yield was 1.2 g (88%), yellow powder, mp 159-161° dec (acetone/water); calorimetric data for thermolysis: cyclization starting at about 160°, maximum 164.8°, ΔH -147 mcal/mg, decomposition starting at about 315°, maximum 41.6°, ΔH -33 mcal/mg; ir: 2140 s (N_3), 1670 s, 1630 s, 1615 m, 1605 m, 1580 s cm^{-1}.

Anal. Calcd. for $C_{20}H_{11}N_3O_2$: C, 73.84; H, 3.41; N, 12.92. Found: C, 74.73; H, 3.56; N, 12.48. (Because of the ease of decomposition to **9b** no exact analytical data could be obtained.)

1-Benzoyloxyphenalen-3-one (**6**).

A mixture of the hydroxyphenalenone **1** (7.84 g, 40 mmoles), benzoyl chloride (5.6 ml, 48 mmoles) and triethylamine (5.6 ml, 40 mmoles) in dry toluene (200 ml) was heated under reflux for 12 hours. After cooling, dichloromethane (500 ml) was added, the organic layer extracted with 6 *M* hydrochloric acid (500 ml), then washed with water and dried with anhydrous sodium sulfate. The organic layer was taken to dryness *in vacuo* and the residue dissolved in acetone and precipitated with water. The yield was 6.14 g (51%), yellowish prisms, mp 136.3-140° (acetone/water); ir: 1725 s, 1640 s, 1590 s cm^{-1}.

Anal. Calcd. for $C_{20}H_{12}O_3$: C, 79.99; H, 4.03. Found: C, 79.80; H, 4.34.

2-Benzoyl-1-hydroxyphenalen-3-one (**7**).

Benzoyl chloride (4.04 ml, 35 mmoles) was added slowly to an ice cold mixture of anhydrous aluminium chloride (17.75 g, 0.13 mole) in dry dichloromethane (50 ml). Then a solution of the benzoate **6** (10.0 g, 33 mmoles) in dry dichloromethane (120 ml) was added slowly while the temperature was kept at 20°. The mixture was stirred for 12 hours at room temperature, then poured onto ice (100 g) and hydrolyzed by addition of concentrated hydrochloric acid (50 ml). The solution was brought to *p*H = 10 with 2 *M* sodium hydroxide solution and the organic layer separated. The aqueous layer was extracted with dichloromethane (100 ml) and then acidified with 12 *M* hydrochloric acid. The precipitate was washed with water and dried. The yield was 1.64 g (16%), yellow prisms, mp 198.5-202° (ethanol); ir: 1645 s, 1590 s cm^{-1}; ^1H nmr: δ 6.15 (s, OH), 7.52-7.89 (m, 5 phenyl-H), 7.79-7.89 (m, 2 Ar-H at C-4 and C-9), 8.30-8.47 (m, 4 Ar-H at C-5, C-6, C-7 and C-8).

Anal. Calcd. for $C_{20}H_{12}O_3$: C, 79.99; H, 4.03. Found: C, 79.61; H, 4.21.

2-Benzoyl-1-chlorophenalen-3-one (**8**).

A suspension of the 2-benzoyl-1-hydroxyphenalenone **7** (4.0 g, 13 mmoles) in phosphoryl chloride (40 ml) and triethylamine (1.92 ml, 14 mmoles) was heated under reflux for 1 hour. After cooling the mixture was poured into ice/water (300 ml) and after 2-3 hours the precipitate filtered by suction. The yield was 4.0 g (94%), yellow prisms, mp 229.1-229.8° (ethanol); ir: 1670 s, 1630 s, 1615 w, 1580 s cm^{-1}.

Anal. Calcd. for $C_{20}H_{11}ClO_2$: C, 75.36; H, 3.48; Cl, 11.12. Found: C, 75.11; H, 3.69; Cl, 11.31.

8-Methylphenaleno[1,2-*c*]isoxazol-7-one (**9a**).

A solution of the 2-acetyl-1-azidophenalenone **5a** (0.5 g, 1.9 mmoles) in dimethylformamide (30 ml) was stirred at 65° for 5-6 hours. After cooling the reaction mixture was diluted with ice/water (100 ml), taken to dryness *in vacuo* and the residue triturated with water. The yield was 0.27 g (60%), yellow prisms, mp 184-187° (cyclohexane); ir: 1665 s, 1630 sh, 1610 s cm^{-1}. ^1H nmr: δ 2.90 (s, CH_3), 7.80-8.55 (m, 6 Ar-H).

Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found: C, 76.46; H, 3.94; N, 5.86.

8-Phenylphenaleno[1,2-*c*]isoxazol-7-one (**9b**).

A solution of **5b** (1.0 g, 3.1 mmoles) in dimethylformamide (30 ml) was heated under reflux for 1 hour, then diluted with water (200 ml) and after standing 1 hour at room temperature filtered by suction. The yield was 0.45 g (49%), orange prisms, mp 219-221° (cyclohexane); ir: 1660 w, 1630 s, 1610 m, 1580 s cm^{-1}; ^1H nmr: δ 7.82-9.15 (m, 11 Ar-H).

Anal. Calcd. for $C_{20}H_{11}NO_2$: C, 80.80; H, 3.73; N, 4.71. Found: C, 80.63; H, 3.88; N, 4.63.

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