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# A Practical Photochemical Synthesis of 6-AZA-1, 10-Phenanthroic Anhydride

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### A PRACTICAL PHOTOCHEMICAL SYNTHESIS OF 6-AZA-1,10-PHENANTHROIC ANHYDRIDE

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**Abstract:** A high yield synthesis of 6-aza-1,10-phenanthroic anhydride has been developed. The key step is a volume-efficient photochemical cyclization of azastilbene **5** to the photochemically stable dihydroazaphenanthrene **9**.

DMP 315, 1, is an unsymmetrical bis-imide antitumor agent which shows activity against human solid tumor xenographs.<sup>1</sup> We recently required hundreds of grams of a key intermediate, 6-aza-1,10-phenanthroic anhydride, 2. Although the synthesis of 2 has been reported,<sup>2</sup> we found portions of the route to be impractical for scale-up. The synthesis employed the Stobbe condensation of dimethyl homophthalate  $3^{3,4}$  with pyridine 4-carboxaldehyde 4 to give the azastilbene half acid ester 5. Dilute (0.0026 molar) photolysis in ethanol / iodine gave the half acid

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ester 6 which was not isolated but saponified to the diacid 7. This material, which is amorphous and difficult to purify, was subsequently converted to 2 (of variable purity) by treatment with acetic anhydride.



Our scalable process (Scheme 1) begins with an improved preparation of 5. Dimethyl homophthalate<sup>5,6</sup> was readily converted to 5 utilizing sodium methoxide in methanol instead of sodium hydride in THF. After neutralization with aqueous hydrochloric acid, the highly crystalline product was isolated in 90 to 97 % yield.

The photochemical cyclization of stilbenes or azastilbenes must generally be run under high dilution (typically  $10^{-3}$  to  $10^{-5}$  M) to minimize the formation of dimers and polymeric species.<sup>7</sup> Under photolytic conditions, the cis/trans stilbenes and dihydrophenanthrene intermediates equilibrate, with the equilibrium favoring the stilbenes unless there are strong electron withdrawing groups on the olefin portion or the dihydrophenanthrene is oxidized to the phenanthrene.<sup>8,9</sup> An additional difficulty with azastilbenes is that the preferred oxidant, iodine, tends to form insoluble charge transfer complexes, giving a mixture which greatly decreases the light absortion and reaction rate.<sup>10</sup>

Although 5 has low solubility in practically all solvents, its hydrochloride, sodium, or potassium salts are very soluble in methanol (as is iodine). Under these conditions, the photocyclization of 5 to 6 could be run at a relatively high



Scheme 1

concentration (0.06 - 0.12 molar) and a moderate rate (24 - 48 hours). The sodium salt method was abandoned because of significant transesterification to **8**, an intermediate which was found to be difficult to cyclize to anhydride **2**. Under acidic conditions; however, the amine hydroiodide salts gave a brown precipitate

which again decreased light absorption and the reaction rate. Our solution was to start with the hydrochloride salt of **5** and periodically add sodium hydroxide to titrate the hydrogen iodide which was formed as the reaction proceeded. Excess iodine was destroyed with metabisulfite, the pH was adjusted and the half acid ester **6** was isolated in 70 to 80 % yields. This material, which contained about 5 % of the transesterified isomer **8**, was converted to anhydride **2** simply by heating in an appropriate solvent. Although little cyclization occured in refluxing dioxane, the material slowly cyclized then crystallized from hot acetic acid. In DMSO cyclization occured rapidly at 80 °C and the product crystallized pure in 75 - 85 % yields.

Although this process was used to prepare 300 g product, we were dissatisfied with the heterogeneity and still rather slow reaction rate. We tried a few other oxidants for this process including bromine, air, and periodic acid, but all were inferior to iodine. Instead we isolated the dihydroazphenanthrene 9 as a major by-product. Remarkably, when re-exposed to photolysis in the absence of oxidant, it did not revert to the azastilbene.<sup>11</sup> The photocyclization and oxidation steps were then decoupled, allowing the photocyclization to be run at a higher concentration and faster reaction rate. We increased the concentration of 5 to 0.34 molar and completed the photocyclization to 9 in four hours with minimal by-product formation. A number of oxidants readily converted 9 to 6, including ferric chloride, manganese dioxide, iodosobenzene diacetate and iodine. In all cases, the reactions proceeded best in refluxing acetic acid or hot DMSO and under these conditions 6 was not isolated but directly converted to anhydride 2. The best method used iodine in DMSO employing sodium acetate to neutralize the liberated hydrogen iodide to give 2 in 86 % yield. This route, based on isolation of the dihydroazaphenanthrene gives an overall yield from homophthalic acid of 62 %. The scope of the photochemical preparation of other substituted dihydro 6azaphenanthrenes is under investigation and will be reported in due course.

#### **EXPERIMENTAL SECTION**

General Methods. Melting points are uncorrected. All reactions were run under nitrogen and all reagents were reagent grade. NMR spectra were obtained on a Varian Unity 300 MHz spectrometer. High resolution mass spectra were collected on a VG 70-VSE mass spectrometer.

Methyl  $\alpha$ -[(4-pyridyl)methylene]-(2-carboxyphenyl)acetate, 5. Dimethyl homophthalate (936 g, 4.50 mol) and 4-pyridinecarboxaldehyde (531 g, 4.95 mol) were dissolved in methanol (6.8 L) and cooled to 0 - 10 °C. Sodium methoxide (25 wt % in methanol, 1360 mL, 5.95 mol) was added keeping the temperature below 10 °C. The solution was allowed to stir at ambient temperature overnight then the reaction mass was diluted with 6.8 L water and neutralized to pH 5 with 6 N aqueous hydrochloric acid. The resulting slurry was cooled to 5 °C and the product filtered, washed with water and dried to a constant weight to give 1228 g (96 %) as an off-white solid: mp 165-167 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  8.46 (2H, d, *J* = 7.5 Hz), 8.14 (1H, m), 7.72 (1H, s), 7.60 (2H, m), 7.15 (1H, m), 7.00 (2H, d, *J* = 7.5 Hz), 3.73 (3H, s). HRMS (M + H<sup>+</sup>) Calcd for C16H13NO4: 284.0923. Found: 284.0919.

6-Azaphenanthrene-10-carbomethoxy-1-carboxylic acid, 7. Methyl  $\alpha$ -[(4-pyridyl)methylene]-(2-carboxyphenyl)acetate (215 g, 760 mmol) was dissolved in methanol (11.0 L) containing 64 mL 36 % aqueous hydrochloric acid (768 mmol) in a 15 L photoreactor containing two 500 watt mercury lamps (254 nm). Iodine (205 g, 807 mmol) was added then the mixture stirred vigorously and photolyzed for 34 hours. At four to six hour intervals, the photolysis was briefly interrupted and the liberated hydrogen iodide titrated with 10 N sodium hydroxide. A solution of sodium metabisulfite (30 g) in 300 mL water was added and the solution stirred for 15 minutes. Acetic acid (200 mL, 3.5 mol) was added and the resulting slurry stirred at 20 - 25 °C for two hours. The product was isolated by vacuum filtration, washed with 300 mL 80/20 methanol/water, reslurried with 4 L water, refiltered and dried *in vacuo* at 50 - 60 °C to give 159 g (74 %) as an off-white solid: mp 303-305 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  10.35 (1H, s), 9.40 (1H, d, J = 8 Hz), 8.93 (1H, d, J = 7.5 Hz), 8.46 (1H, s), 8.20 (2H, d, J = 7.5 Hz), 7.98 (t, 1H, J = 8 Hz), 3.92 (3H, s); HRMS (M + H<sup>+</sup>) calcd for C<sub>16</sub>H<sub>11</sub>NO4: 282.0766. Found: 282.0754.

#### 6-Aza-1,10-phenanthroic anhydride, 2. Method A. 6-

Azaphenanthrene-10-carbomethoxy-1-carboxylic acid (398 g, 1.42 mol) and DMSO (3.0 L) were combined and heated to 85 - 90 °C for 15 minutes, cooled to room temperature, held two hours and filtered. The solids were reslurried at room temperature with 3 L methyl ethyl ketone, refiltered, washed twice with 200 mL portions of methyl ethyl ketone and dried *in vacuo* at 70 - 80 °C to give 286 g (81 %) as an off-white solid: mp 310-312 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  10.35 (1H, s), 9.50 (1H, d, *J* = 8 Hz), 9.05 (1H, s), 8.92 (1H, d, *J* = 7 Hz), 8.58 (2H, d, *J* = 7 Hz), 8.30 (2H, d, *J* = 7 Hz), 8.10 (1H, t, *J* = 8 Hz); HRMS Calcd for C15H7NO3: 249.0426. Found: 249.0415.

6-Aza-9,10-dihydrophenanthrene-10-carbomethoxy-1carboxylic acid, 8. Methyl  $\alpha$ -[(4-pyridyl)methylene]-(2-carboxyphenyl)acetate (23 g, 81 mmol) was dissolved in 230 mL methanol containing 6.5 mL (78 mmol) 36 % hydrochloric acid. The solution was photolyzed in a 500 watt Hanovia reactor for four hours. Sodium hydroxide (2.5 N, 32 mL, 80 mmol) was added and the resulting mixture stirred one hour in an ice bath. The product was isolated by vacuum filtration, washed with water and dried *in vacuo* at 60 °C to give 15.1 g (75 %) of the product as a light tan solid: mp 232-234 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.15 (1H, s), 8.56 (1H, d, J = 7 Hz), 8.30 (1H, d, J = 8 Hz), 8.00 (1H, d, J = 8Hz), 7.63 (1H, t, J = 8 Hz), 7.44 (1H, d, J = 7 Hz), 5.10 (1H, d, J = 7.5 Hz), 3.38 (1H, d, J = 14 Hz), 3.20 (1H, ABq, J = 14, 7 Hz); HRMS (M + H<sup>+</sup>) Calcd for C<sub>16</sub>H<sub>13</sub>NO<sub>4</sub>: 284.0923. Found: 284.0925.

6-Aza-1,10-phenanthroic anhydride, 2. Method B. 6-Aza-9,10dihydrophenanthrene-10-carbomethoxy-1-carboxylic acid (2.83 g, 10 mmol), iodine (2.54 g, 10 mmol) and sodium acetate (1.64 g, 20 mmol) were dissolved in DMSO (30 mL) and heated to 100 °C. After two hours, the resulting slurry was cooled to room temperature and the product isolated by vacuum filtration, washed twice with 10 mL portions of methyl ethyl ketone and dried to a constant weight to give 2.15 g (86 %) as an off-white solid. The physical properties were identical with product produced by method A.

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