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Regioselective Synthesis of 1,8-Diazaanthracene-9,10-dione by Tandem Directed *ortho*-Metallation/ Metal-Halogen Exchange.

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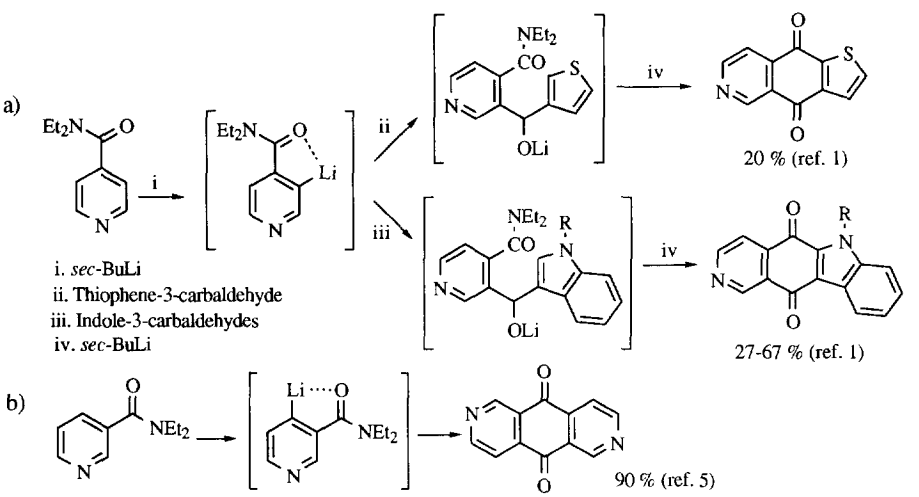
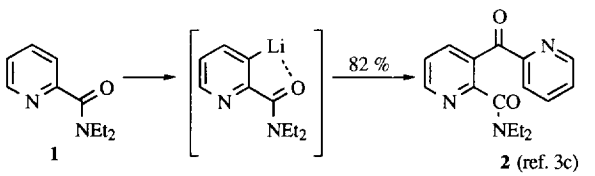
Abstract: Tandem directed *ortho*-metallation/metal-halogen exchange reactions between *N,N*-diethyl-pyridine-2-carboxamide and 2-bromopyridine-3-carbaldehyde yield 1,8-diazaanthracene-9,10-dione. This compound has been further functionalized to its *N*-oxide and the corresponding 2,9,10-trione derivative, structurally related to the antibiotic diazaquinomycin A.

Tandem tertiary aromatic amide DoM (directed *ortho*-metallation) processes using aromatic aldehydes as partners[1] have been widely used to effect one-pot regioselective synthesis of anthraquinones. Only in some instances metal-halogen exchange reactions are more convenient.[2] However, this methodology is still not free from uncertainty, and is especially difficult to apply to pyridinecarboxamides, mainly due to competing reactions such as nucleophilic addition to the azomethine bond and to self-condensation to ketoamides.[3] Consequently few syntheses of azaanthraquinones have been successfully achieved. For instance *N,N*-diethylisonicotinamide gives thiopheno-pyrido and indole-pyridobenzoquinones in moderate yields by tandem DoM with the aldehydes shown in Scheme 1a.[1]



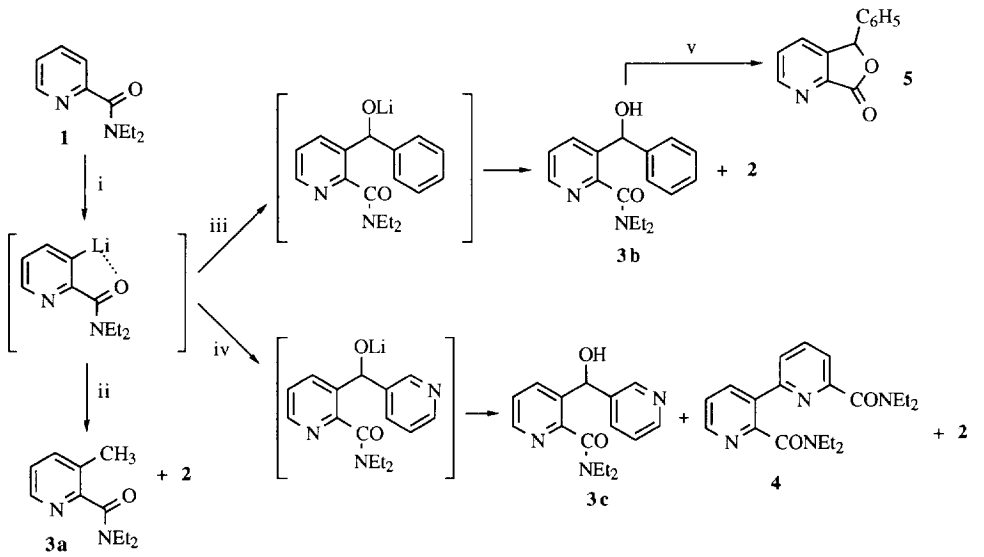
Scheme 1

In the case of *N,N*-diethylnicotinamide (Scheme 1b), 2,6-diazaanthracene-9,10-dione is obtained by DoM-dimerization.[4] However, lithiation of *N,N*-diethylpyridine-2-carboxamide (**1**) only affords ketoamide **2**[3c] (Scheme 2). Regioselectively lithiated *N,N*-diisopropylpyridine-2-carboxamide reacts with electrophiles other than the internal carbonyl group. However, the cyclization step is prevented by steric effects (iv, Scheme 1a) when aromatic aldehydes are used as partners.[1,3,5]



Scheme 2

In spite of these antecedents and as part of our current project directed to the synthesis of potencially antitumor diazaquinomycin A analogues through preformed quinones,[6] we thoroughly explored lithiation of **1**[7] searching for alternative strategies to 1,8-diazaanthracene-2,9,10-triones in which the quinone ring could be formed in a one-pot procedure. We found that *N,N*-diethylpyridine-2-carboxamide (**1**) can be synthetically useful by using *sec*-BuLi as a base and inmediately adding the electrophile. Although formation of undesired compounds such as **2** and **4**[3f] could not be avoided, the lithiated amide was stable enough to trap electrophiles, giving compounds **3a-3c** in about 50 % yield (Scheme 3). Alcohols **3b** and **3c** could not be conveniently

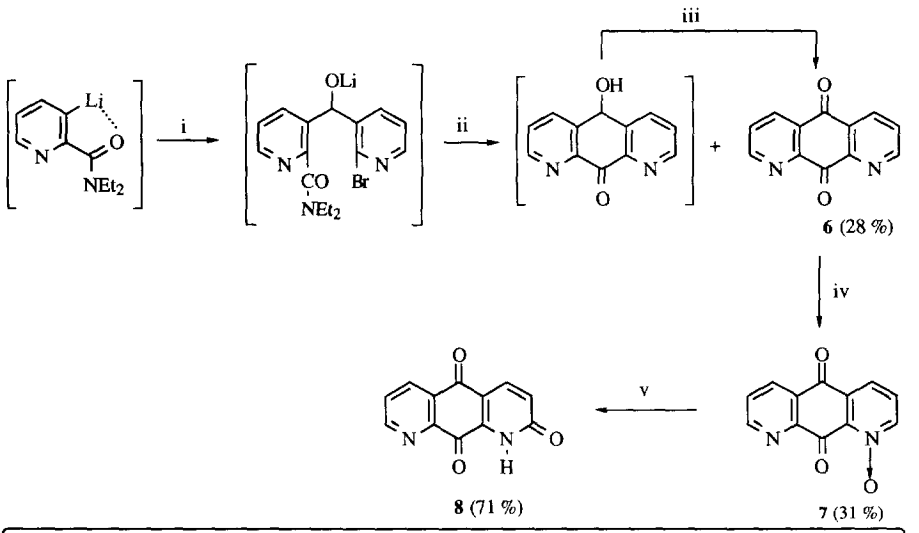


Reagents and conditions: i. *sec*-BuLi (1.1 equiv) , THF, -78 °C. ii. Methyl iodide. iii. Benzaldehyde. iv. Pyridine-3-carbaldehyde. v. SiO_2.

Scheme 3

purified due to their unstability, but the benzyl proton signal permitted the unambigous calculations of yields in the ^{1}H-NMR spectra of the crude reaction products. Flash chromatography of **3b** gave the lactone **5** among other products.

On the other hand, attempts to obtain aza- or diazaanthraquinones in one-pot reactions by further lithiation of **3b** or **3c** were unsuccessful. This failure presumably depends on the inefficiency of the benzyloxy or 3-pyridylmethyloxy substituents as metallation director groups in the second lithiation step[8] as well as the presence of competitive *ortho*-metallation sites. Therefore, it was necessary to fix the second metallation by metal-halogen exchange. By performing the reaction with 2-bromopyridine-3-carbaldehyde[9] we obtained the desired cyclized product which was *in situ* oxidized to 1,8-diazaanthracene-9,10-dione (**6**). The quinone was transformed to the *N*-oxide **7**[10] which was finally functionalized[11] to 1*H*-1,8-diazaanthracene-2,9,10-trione (**8**) (Scheme 4). This work opens a new strategy to analogues of diazaquinomycin and other natural heterocyclic quinones.



Reagents and conditions: i. 2-Bromopyridine-3-carbaldehyde, -78 °C, 1 h. ii. *sec*-BuLi (2 equiv), -78 °C to rt, overnight. iii. Air oxidation. iv. Trifluoroacetic acid, urea hydrogen peroxide adduct, rt, 24 h. v. Tosyl chloride, acetonitrile, water, 20 h.

Scheme 4

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EXPERIMENTAL

Infrared spectra were recorded on Perkin-Elmer 577 and Beckmann Acculab 4 spectrophotometers, with all compounds compressed into KBr pellets. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63

MHz for ^{13}C) and Varian VXR-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometers; $CDCl_3$ was used as solvent, and TMS was added in all cases as an internal standard. Elemental analyses of new compounds were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyser. Melting points were measured in open capillary tubes using a Büchi immersion apparatus, and are uncorrected. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh and Scharlau Ge 048). All reagents were of commercial quality (Aldrich, Fluka, Merck, SDS, Probus) and were purified following standard procedures.[12] The expression "petroleum ether" refers to the fraction boiling at 40-60 °C.

***N,N*-Diethylpyridine-2-carboxamide (1).**[7] Melting point, 28-29 °C. IR, υ_{max} (KBr): 1625 (CO) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.58 (d, 1H, *J* = 4.7 Hz, H-6); 7.78 (m, 1H, td, *J* = 7.7 and 1.6 Hz, H-4); 7.56 (d, 1H, *J* = 7.7 Hz, H-3); 7.32 (m, 1H, H-5); 3.57 and 3.37 (2 q, 4H, *J* = 7.1 Hz, CH_2-CH_3); 1.27 and 1.15 (2 t, 6H, J = 7.1 Hz, CH_2-CH_3) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 168.33 (CO); 154.92 (C-2); 148.11 (C-6); 136.63 (C-4); 123.82 and 122.63 (C-3 and C-5); 42.90 and 39.80 (CH_2-CH_3); 14.01 and 12.60 (CH_2-CH_3) ppm.

Base-catalyzed electrophilic substitution in *N,N*-diethylpyridine-2-carboxamides. General Procedure.

A magnetically stirred solution of **1** (1.0 equiv) in dry THF (30 ml) was treated under argon at -78 °C with *sec*-BuLi (1.1 equiv), maintaning the internal temperature at -78 °C. To the heterogeneous mixture was inmediately added the corresponding electrophile (1.0 equiv). The reaction mixture was allowed to stir at -78 °C for 2 h, warmed to room temperature (3 h), quenched with water (5 ml) and extracted with $CHCl_3$ (3 x 30 ml). The organic extracts were dried over sodium sulphate and concentrated *in vacuo*. The residue was purified, when possible, by column chromatography on silica gel eluting with the adequate solvent.

***N,N*-Diethyl-3-methylpyridine-2-carboxamide (3a).** Yield, 53 % after chromatography eluting with ethyl acetate-petroleum ether 3:7. Melting point, 42-44 °C. IR, υ_{max} (KBr): 1625 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.42 (dd, 1H, *J* = 4.9 and 1.7 Hz, H-6); 7.55 (dd, 1H, *J* = 7.8 and 1.7 Hz, H-4); 7.20 (dd, 1H, *J* = 7.8 and 4.9 Hz, H-5); 3.60 and 3.14 (2 q, 4H, *J* = 7.1 Hz, CH_2-CH_3); 2.33 (s, 3H, C_3-CH_3); 1.29 and 1.08 (2 t, 6H, *J* = 7.1 Hz, CH_2-CH_3) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.33 (CO); 154.55 (C-2);146.27 (C-6); 138.05 (C-4); 130.02 (C-3); 123.30 (C-5); 42.54 and 39.01 (CH_2-CH_3); 17.47 (C_3-CH_3); 13.77 and 12.69 (CH_2-CH_3) ppm. Analysis calc. for $C_{11}H_{16}N_2O$: C, 68.81; H, 8.40; N, 14.59. Found: C, 68.74; H, 8.65; N, 14.47.

***N,N*-Diethyl-3-(α-hydroxybenzyl)pyridine-2-carboxamide (3b).** Yield, 50 % (NMR). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.45 (dd, 1H, *J* = 4.96 and 1.59 Hz, H-6); 7.76 (dd, 1H, *J* = 7.94 and 1.59 Hz, H-4); 7.30 (m, 6H, C_6H_5 and H-5); 5.85 (s, 1H, CH); 5.25 (br s, 1H, OH); 3.35, 2.90 and 2.80 (3 m, 4H, CH_2-CH_3); 1.00 and 0.97 (2 t, 6H, CH_2-CH_3) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.63 (CO); 152.71 (C-2); 147.08 (C-6); 142.01 and 138.20 (C-3 and C-1'); 136.85 (C-4); 127.98, 127.10 and 126.34 (C_6H_5); 123.98 (C-5); 72.88 (CH); 43.23 and 39.40 (CH_2-CH_3); 13.26 and 12.33 (CH_2-CH_3) ppm.

***N,N*-Diethyl-3-(2'-pyridylcarbonyl)pyridine-2-carboxamide (2).**[3c] Melting point, 90-91 °C. IR, υ_{max} (KBr): 1690, 1625 (CO) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.65 (dd, 1H, *J* = 4.86 and 1.64 Hz,

H-6); 8.55 (m, 1H, H-6'); 8.19 (m, 1H, H-3'); 8.08 (dd, 1H, J = 7.7 and 1.63 Hz, H-4); 7.88 (m, 1H, H-4'); 7.44 (m, 2H, H-5 and H-5'); 3.53 and 3.25 (2 q, 4H, J = 7.06 Hz, CH_2-CH_3); 1.34 and 1.08 (2 t, 6H, J = 7.03 Hz, CH_2-CH_3) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.96 (CO); 168.40 ($CONEt_2$); 155.66 and 153.73 (C-2 and C-2'); 149.17 and 148.16 (C-6 and C-6'); 137.86 and 137.18 (C-4 and C-4'); 134.32 (C-3); 126.84 (C-3'); 123.79 and 123.68 (C-5 and C-5'); 43.33 and 39.60 (CH_2-CH_3); 13.78 and 11.65 (CH_2-CH_3). ppm.

***N,N,N',N'*-Tetraethyl-2,3'-bipyridine-2',6-dicarboxamide (4).**[3f] ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.69 (m, 1H, H-6'); 8.15 (m, 1H, H-4'); 7.99 (m, 1H, H-5); 7.86 (m, 1H, H-4); 7.41 (m, 1H, H-5'); 7.26 (m, 1H, H-3); 3.46 and 3.21 (2 m, 8H, CH_2-CH_3); 0.86 and 0.72 (2 t, 12H, CH_2-CH_3) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 168.56 and 167.21 (CO); 155.64 and 154.70 (C-2' and C-6); 148.39 (C-6'); 138.56 and 137.51 (C-4 and C-4'); 132.17; 126.91; 123.90; 122.27; 44.06, 43.61 and 39.94 (CH_2-CH_3); 14.37, 12.54, 12.02 and 11.96 (CH_2-CH_3) ppm.

5-Phenyl-1*H*-furo[3,4-b]pyridin-7-one (5). Yield, 44 % after chromatography eluting with CH_2Cl_2. Melting point, 121-123 °C. IR, υ_{max} (KBr): 1770 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.90 (dd, 1H, J = 4.5 and 1.2 Hz, H-2); 7.75 (dd, 1H, J = 8.6 and 1.2 Hz, H-4); 7.54 (dd, 1H, J = 8.1 and 4.5 Hz, H-3); 7.38 and 7.25 (2 m, 5H, C_6H_5); 6.42 (s, 1H, H-5) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.97 (CO); 152.79 (C-7a); 143.98 and 143.57 (C-1' and C-2); 135.11 (C-4); 131.60 (C-4a); 129.67 (C-3); 129.14, 127.48 and 126.85 (C_6H_5); 80.75 (C-5) ppm. Analysis calc. for $C_{13}H_9NO_2$: C, 73.93; H, 4.26; N, 6.63 . Found: C, 73.59; H, 4.51; N, 6.53 .

1,8-Diazaanthracene-9,10-dione (6).

To a magnetically stirred solution of the amide **1** (285 mg, 1.6 mmol) in anhydrous THF (30 ml) at -78 °C under argon was added *sec*-BuLi (100 mg, 1.63 mmol) by syringe injection. The heterogeneous mixture was treated inmediately with a solution of 2-bromopyridine-3-carbaldehyde[9] (300 mg, 1.6 mmol) in THF (10 ml) and, after stirring for 1 h, a further amount of *sec*-BuLi (220 mg, 3.37 mmol) was added. The reaction mixture was allowed to warm to room temperature (10-12 h) and treated with water (2 ml), and the whole system was subjected to a stream of air (1 h). Following extraction with CH_2Cl_2 (3 x 25 ml) and drying of the organic extract (Na_2SO_4), the crude product was purified by silica gel column chromatography using ethyl acetate as eluent. Yield: 93 mg, 30 %. Melting point > 300 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.17 (dd, 2H, J = 4.6 and 1.7 Hz, H-2 and H-7); 8.61 (dd, 2H, J = 8.0 and 1.7 Hz, H-4 and H-5); 7.78 (dd, 2H, J = 8.0 and 4.6 Hz, H-3 and H-6) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 184.42 (C-10); 174.91 (C-9); 150.46 (C-2 and C-7); 143.51 (C-8a and C-10a); 130.29 (C-4 and C-5); 124.69 (C-9a and C-4a); 123.08 (C-3 and C-6) ppm.

1,8-Diazaanthracene-9,10-dione-1-oxide (7)

A solution of **6** (90 mg, 0.43 mmol) and urea hydrogen peroxide adduct (82 mg, the equivalent of 0.43 mmol of H_2O_2) in trifluoroacetic acid (0.8 ml) was stirred at room temperature for 24 h with hourly additions of 40 mg of urea hydrogen peroxide adduct in the first 4 h. The reaction mixture was then basified with amonium hydroxide and extracted with $CHCl_3$ (3 x 15 ml). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with a gradient of neat ethyl acetate to ethyl acetate-ethanol (9:1). Yield 29 mg, 31%. Melting point > 300°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.19 (dd, 1H, J = 4.8 and 1.8 Hz, H-7); 8.59 (dd, 1H, J = 8.1 and 1.8 Hz, H-5); 8.58 (dd, 1H, J = 6.6 and 1.2 Hz, H-2); 8.12 (dd, 1H, J = 7.8 and 1.2 Hz, H-4); 7.76 (dd, 1H, J = 8.1 and 4.5 Hz, H-6); 7.62 (dd, 1H,

J = 7.8 and 6.6, H-3) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 180.05 (C-10); 173.24 (C-9); 156.32 (C-7); 149.00; 147.51; 147.50; 135.25; 133.62; 128.45; 127.87; 122.56 ppm.

1*H*-1,8-Diazaanthracene-2,9,10-trione (8).

To a stirred suspension of **7** (21 mg, 0.093 mmol) and tosyl chloride (12 mg, 0.062 mmol) in acetonitrile (6 ml) at 60 °C was added water (0.3 ml). The resulting solution was further stirred for 20 h at 60 °C with hourly additions of 12 mg of tosyl chloride during the first 4 h. The cooled mixture was filtered to yield 25 mg of a red solid, which was filtered and washed with methanol affording 15 mg of **8** as a yellow solid. Yield 71%. Melting point >300 °C. IR, υ_{max} (KBr): 1660, 1650, 1640 (CO) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.10 (dd, 1H, J = 4.5 and 1.8 Hz, H-7); 8.6 (dd, 1H, J = 8.1 and 1.8 Hz, H-5); 8.16 (d, 1H, J = 9.6 Hz, H-4); 7.80 (dd, 1H, J = 8.1 and 4.8 Hz, H-6); 6.97 (d, 1H, J = 9.6 Hz, H-3) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.98 and 176.20 (C-9 and C-10); 160.70 (C-2); 154.88 (C-7); 146.92; 140.90; 139.17; 135.85 and 135.31 (C-4 and C-5); 128.92 and 128.62 (C-3 and C-6); 115.95 ppm. Analysis calc. for $C_{12}H_6N_2O_3$: C, 63.72; H, 2.65; N, 12.39. Found: C, 63.81; H, 2.54; N, 12.28.

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