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An Efficient Synthesis of 2-Nitropyrrole-3,4-dicarboxamide

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Abstract

The synthesis of N-1-substituted 2-nitropyrrole-3,4-dicarboxamides (**4-5**, **7-9**) was accomplished from diethyl 2-nitropyrrole-3,4-dicarboxylate (**2**). 2-nitropyrrole-3,4-dicarboxamide (**1**) was prepared by deprotection of 2-nitro-1-[2-(2-pyridyl)ethyl]pyrrole-3,4-dicarboxamide (**9**). Compound **9** was obtained by two different methods.

Introduction

The pyrrole ring system is perhaps the most studied of the 5-membered compounds containing a single heteroatom in the ring. In fact, pyrroles have been used extensively as synthetic precursors to obtain other heterocyclic ring systems, e.g. the 1-substituted 2-aminopyrrole-3-carboxamides have found use as synthetic precursors for acyclic nucleoside analogs of the pyrrolo[2,3-*d*]pyrimidine ring system.[1] We have recently initiated studies designed to convert 1-glycosyl 2-aminopyrrole-3-carboxamides into novel and previously unreported 7-substituted pyrrolo[2,3-*d*][1,2,3]triazines. While direct alkylations of 5-methylthio-2-aminopyrrole-3,4-dicarboxamide has been reported,[1] the yields for these

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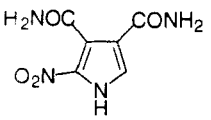
alkylations tend to be very low. In addition, we have found that the alkylation of either 2-aminopyrrole-3,4-dicarboxamide or its 5-methylthio derivative was unsuccessful when arylmethyl halides or glycosyl halides were used as the alkylating agent. Therefore, we chose to explore an alternative strategy for the preparation of these N-1 substituted pyrroles. Our strategy involved 'masking' the exocyclic 2-amino group as a 2-nitro-group, which allowed us to take advantage of the electron withdrawing effect of the 2-nitro group to facilitate N-1 alkylation.



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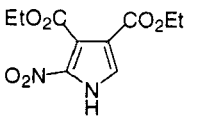

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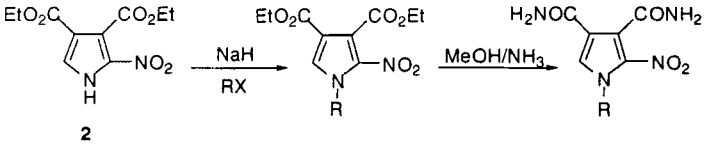
Figure 1

The electron withdrawing effect of the 2-nitro group should also facilitate diamide formation which, after removal of the N-1 substituent, would give 2-nitropyrrole-3,4,-dicarboxamide (**1**) which could then be used to prepare our 1-glycosyl 2-aminopyrrole-3-carboxamides. Therefore, we required an efficient procedure for the synthesis of compound **1** which was amenable to scale-up.

Results and Discussion

Our initial studies were directed at the preparation of 2-nitropyrrole-3,4-dicarboxamide (**1**) directly from the readily available diethyl 2-nitropyrrole-3,4-dicarboxylate (**2**)[2-8]. When compound **2** was treated with a variety of ammonia-based reagents (i.e. NH_3 (l), NH_3/MeOH, methylamine, $LiNH_2$, $NaNH_2$, $Ti(NH_3)_4$, or NH_3/base) either starting material was recovered or decomposition occurred. We attributed these failures to an abstraction of the N-1

Table 1



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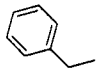
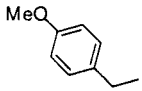
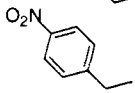
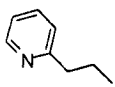
R	Compound (Yield)	Compound (Yield)
	**3** (86 %)	**4** (83 %)
	not isolated	**5** (76 %)
	**6** (71 %)	decomposition
	not isolated	**7** (51 %)
	not isolated	**8** (53 %)
	not isolated	**9** (69 %)

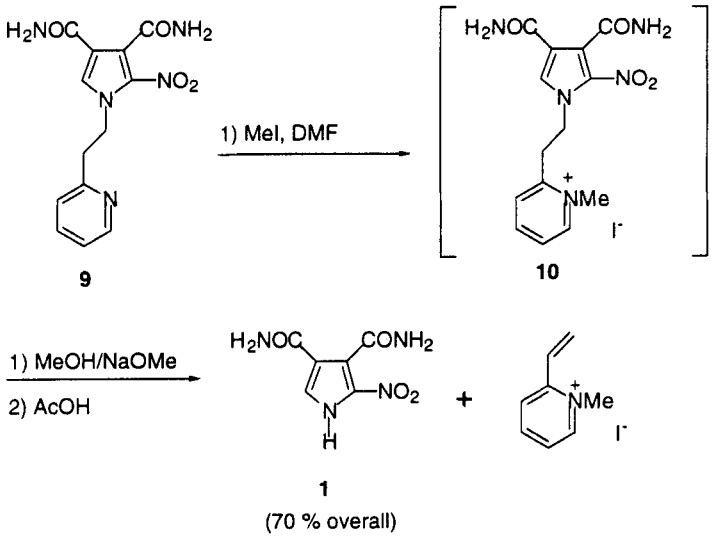
proton. Therefore, we initiated studies on the alkylation of the N-1 position of compound **2**, followed by treatment with methanolic ammonia for the preparation of N^1-alkyl and N^1-arylalkylsubstituted 2-nitropyrrole-3,4-dicarboxamide derivatives. A removal of the alkyl- or arylalkylsubstituent would then provide the 2-nitropyrrole **1**.

Diethyl 1-benzyl-2-nitropyrrole-3,4-dicarboxylate (**3**) was prepared by alkylation of the sodium salt of pyrrole **2** with benzyl bromide (**Table 1**). The pyrrole diester **3** was then treated with methanolic ammonia at 90°C for 2-3 days to

obtain 1-benzyl-2-nitropyrrole-3,4-dicarboxamide (**4**) in good yield. Subsequently, it was found that purification of the diester intermediate was unnecessary. A two-step alkylation/ammonolysis procedure was used to give good yields of analytically pure **4-5** and **7-8** (**Table 1**). The ammonolysis step failed in the case of the nitrobenzyl pyrrole **6** when decomposition occurred.

Studies were then initiated to establish conditions for a facile removal of the N^1-substituent from one of these derivatives to give 2-nitropyrrole-3,4-dicarboxamide (**1**) in a high yield. Treatment of 1-benzylpyrroles, containing only one electron withdrawing substituent, with trifluoroacetic acid/ sulfuric acid had been previously shown to result in the migration of the benzyl or *p*-methoxybenzyl moiety to the pyrrole 2-position.[9] However, treatment of either the benzylpyrrole **4** or the *p*-methoxybenzyl pyrrole **5** under these same conditions only resulted in the recovery of starting material, which would suggest that the electron withdrawing substituents render our pyrrole much less reactive. Attempts to remove the *p*-methoxybenzyl group from pyrrole **5** using a CAN oxidation[10] reaction were unsuccessful and only starting material was recovered. Moreover, attempted isomerization of the double bond of pyrrole **7** with potassium *tert*-butoxide in DMSO, or with Rh (III) only resulted in decomposition.[11] Alternatively, several attempts at acid hydrolysis of dioxolane **8** using aqueous HCl were unsuccessful.

This prompted us to investigate the use of a protecting group, the 2-(2-pyridyl)ethyl (PE) group, initially reported by Katritzky.[12] The reported procedure for the preparation of PE-protected pyrroles used an excess of the sodium salt of pyrrole and 2-vinylpyridine. We opted to develop a synthesis that involved the treatment of the sodium salt of the pyrrole diester **2** with an excess of 2-(2-pyridyl)ethyl chloride, thereby eliminating the need for excess pyrrole. Therefore, carrying out the alkylation in acetonitrile at reflux temperature for 9 days followed

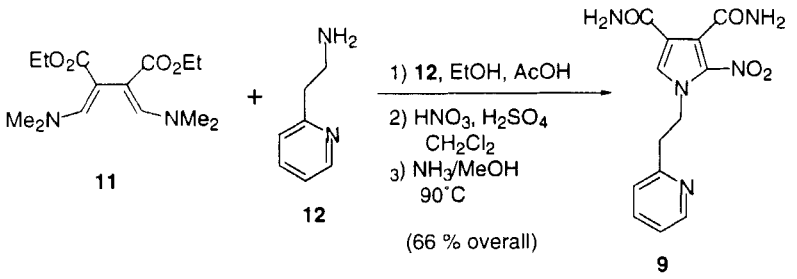


Scheme 1

by treatment with methanolic ammonia at 90°C for 64 hours gave a 69 % yield of 2-nitro-1-[2-(2-pyridyl)ethyl]pyrrole-3,4-dicarboxamide (**9**).

Deprotection of the PE-protected pyrrole **9** was accomplished by a modification of the reported[12] procedure (**Scheme 1**). Treatment of **9** with 20 equivalents of methyl iodide produced the intermediate pyridinium salt **10**. Heating this crude salt with 3 equivalents of sodium methoxide for 1 hour in methanol at reflux temperature, followed by neutralization with AcOH, gave the N^1-unsubstituted pyrrole **1** in a 70 % yield. Compound **1** obtained by this procedure contained very small amounts of impurities as determined by ^{13}C NMR and combustion analysis. Compound **1** was sufficiently pure to be used in subsequent reactions, even with minor impurities.

However, an alternative procedure for the preparation of the PE-protected pyrrole **9** was desired because of the long reaction time, the excess 2-(2-



Scheme 2

pyridyl)ethyl chloride required for the alkylation of the sodium salt of pyrrole **2**, and the difficulty in obtaining reproducible results during scale-up.

Therefore, diethyl bis[(dimethylamino)methylene]succinate (**11**)[13] was condensed with 1.2 equivalents of 2-(2-pyridyl)ethyl amine (**12**) to give diethyl 1-[2-(2-pyridyl)ethyl]pyrrole-3,4-dicarboxylate in a quantitative yield. After a subsequent nitration and ammonolysis, the PE-protected pyrrole **9** was obtained in a 66% overall yield (**Scheme 2**). We have found this procedure to be quite amenable to scale-up and have successfully prepared this compound on >50 g scale.

In conclusion, we have developed an efficient synthesis of 2-nitropyrrole-3,4-dicarboxamide (**1**) which is amenable to the preparation of large quantities of this pyrrole. We are currently using pyrrole **1** in the synthesis of novel pyrrolo[2,3-*d*][1,2,3]triazine nucleosides and other structurally related heterocycles.

Experimental

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Silica gel, SilicAR 40-63 microns 230-400 mesh (Mallinckrodt) was

used for chromatography. Flash column chromatography refers to the chromatography technique described by Still (*J. Org. Chem.* **1978**, *43*, 2923-2925). (X% EtOAc/Hex, Y cm × Z cm) means: the solvent system that is used as the eluent, the diameter of the column (Y) and the height of silica gel (Z). Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). Thin-layer chromatography (TLC) was performed on prescored SilicAR 7GF plates (Analtech, Newark, DE). Compounds were visualized by illuminating with UV light (254 nm) or by spraying with 10% methanolic sulfuric acid followed by charring on a hot plate. Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature not exceeding 50 °C, unless specified otherwise. The ^{1}H (300 or 500 MHz) ^{13}C (75 or 90) NMR spectra were recorded on Bruker instruments. The chemical shifts are expressed in parts per millions relative to the standard chemical shift of the solvent for DMSO-d_6; 2.50 ppm (^{1}H NMR), 39.50 ppm (^{13}C NMR), and relative to tetramethylsilane as an internal standard for $CDCl_3$ (^{1}H NMR), and relative to the standard chemical shift of the solvent for ^{13}C NMR (77.0 ppm). Mass spectroscopy and elemental analyses were performed by the University of Michigan Chemistry Department or by MHW Laboratories, Phoenix, AZ.

Diethyl 1-Benzyl-2-nitropyrrole-3,4-dicarboxylate (3). A suspension of DMSO (20 mL) and KOH (powdered, 499 mg, 8.9 mmoles) was stirred for 75 minutes under argon, at which time a clear solution was observed. Diethyl 2-nitropyrrole-3,4-dicarboxylate[2] (**2**, 1.5 g, 5.9 mmole) was added to the solution in one portion, followed by the dropwise addition of benzyl bromide (1.06 mL, 8.9 mmoles) over a 5 minute period. After 2.5 hours, the reaction mixture was poured onto H_2O (150 mL), extracted with EtOAc (2 x 75 mL), dried ($MgSO_4$), and

filtered. The filtrate was evaporated under reduced pressure, hexanes (20 mL) was added to the oil and the resulting precipitate was collected by filtration. Drying this solid under reduced pressure at 50°C for 24 hours gave a quantitative yield of **3** as a yellow powder. Recrystallization of this powder from methanol and drying under reduced pressure at 78°C for 48 hours yielded 1.21 g (61 %) of a white solid. An additional 505 mg (25 %) of **3** was obtained from the mother liquor for a total yield of 1.72 g (86 %). mp 118-119 °C; R_f = 0.45 (30% EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.22 (s, 1 H, ArH), 7.4-7.2 (m, 5 H, Ph), 5.64 (q, 2 H, CH_2), 4.24 (q, 2 H, CH_2), 1.27 (t, 3 H, CH_3), 1.25 (t, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.3, 161.0, 135.9, 132.9, 132.7, 128.8, 128.0, 126.8, 121.3, 112.3, 61.7, 60.7, 53.3, 14.0, 13.7; *Anal.* Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.83; H, 5.16; N, 8.02.

1-Benzyl-2-nitropyrrole-3,4-dicarboxamide (4). Diethyl 1-benzyl-2-nitropyrrole-3,4-dicarboxylate (**3**, 1.05 g, 3.03 mmoles) in methanolic ammonia (40 mL, sat. at 0°C) was heated in a sealed vial at 80 °C for 45 hours. The reaction was then cooled to -15°C and the precipitate was collected by filtration, washed with methanol (20 mL), and dried under reduced pressure at 78°C for 2 days to give 726 mg (83 %) of **4** as white crystals: mp >295°C (decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.03 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.90 (s, 1 H, ArH), 7.68 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.4-7.2 (m, 7H, Ph, 2-$CONH_2$, collapses to 5H upon addition of D_2O), 5.56 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.8, 162.8, 136.3, 133.1, 130.6, 128.8, 127.9, 126.9, 123.3, 117.1, 53.0; *Anal.* Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44. Found: C, 54.11; H, 4.33; N, 19.39.

1-*p*-Methoxybenzyl-2-nitropyrrole-3,4-dicarboxamide (5). NaH (60 % dispersion in mineral oil, 191 mg, 4.78 mmoles) was slowly added to a stirred solution of diethyl 2-nitropyrrole-3,4-dicarboxylate[2] (**2**, 1.02 g, 3.98 mmoles) and THF (20 mL), and the reaction was stirred at room temperature under argon. After stirring for 20 minutes, *p*-methoxybenzyl chloride (0.65 mL, 4.78 mmoles) was added dropwise followed by the addition of a catalytic amount of tetrabutylammonium iodide. The reaction was heated at reflux temperature for 16 hours, and the THF was then removed under reduced pressure to yield a yellow oil, $R_f = 0.89$ (30% EtOAc/hexanes). This oil was transferred to a pressure vial with the aid of a minimal amount of hot methanol. After cooling the vial to room temperature, methanolic ammonia (20 mL saturated at 0°C) was added and the vial was then sealed and heated at 85-90°C with vigorous stirring. After 45 hours, the vial was cooled to 0°C in an ice bath, the precipitate was collected by filtration and washed with cold methanol (15 mL). Drying this solid under reduced pressure at 78°C for 48 hours yielded 970 mg (76 %) of **5** as a white solid: mp >285°C (decomp); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.01 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.86 (s, 1 H, ArH), 7.67 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.40 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.34 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.16 (d, 2 H, J = 8.3 Hz, Ph), 6.92 (d, 2 H, J = 8.3 Hz, Ph), 5.49 (s, s H, CH_2), 3.73 (s, 3 H, OCH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.9, 162.8, 159.0, 133.0, 130.3, 128.9, 127.9, 123.3, 117.0, 114.1, 55.1, 52.5; *Anal.* Calcd for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.60. Found: C, 53.02; H, 4.58; N, 17.47.

Diethyl 2-Nitro-1-(*p*-nitrobenzyl)pyrrole-3,4-dicarboxylate (6). NaH (60 % dispersion in mineral oil, 44 mg, 1.1 mmoles) was slowly added to a stirred

solution of diethyl 2-nitropyrrole-3,4-dicarboxylate[2] (**2**, 256 mg, 1.0 mmoles) and THF (5 mL), and the reaction was stirred at room temperature under argon. After stirring for 20 minutes, *p*-nitrobenzyl chloride (238 mg, 1.1 mmoles) was added in one portion, followed by the addition of a catalytic amount of tetrabutylammonium iodide. The reaction was heated at reflux temperature for 3 hours, and then filtered through a 5 cm plug of silica gel. The plug was washed with EtOAc (25 mL) and the solvent and washings were evaporated to dryness under reduced pressure. The solid was recrystallized from EtOAc/hexanes and dried under reduced pressure at 78°C for 24 hours to give 277 mg (71 %) of pure **6**: mp 136-137°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H, ArH), 8.24 (m, 2H, Ph), 7.42 (m, 2H, Ph), 5.78 (s, 2H, CH_2Ph), 4.33 (q, 2H, J = 7.1 Hz), 4.25 (q, 2H, J = 7.1 Hz), 1.31-1.24 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.3, 160.9, 147.0, 143.7, 133.1, 132.9, 127.8, 124.0, 121.3, 112.6, 61.8, 60.8, 52.9, 14.0, 13.8; *Anal.* Calcd for $C_{17}H_{17}N_3O_8$: C, 52.18; H, 4.38; N, 10.74. Found: C, 52.16; H, 4.49; N, 10.66.

2-Nitro-1-(3-propenyl)pyrrole-3,4-dicarboxamide (7). Compound **7** was prepared in a 51% yield from diethyl 2-nitropyrrole-3,4-dicarboxylate[2] (**2**, 769 mg, 3.0 mmoles), NaH (60 % dispersion in mineral oil, 132 mg, 3.3 mmoles), and allylbromide (0.29 mL, 3.3 mmoles) in THF (10 mL) followed by treatment with methanolic ammonia (20 mL saturated at 0°C) as described for compound **5.** An analytical sample was prepared by recrystallizing 171 mg of **7** from 40 mL of methanol in a pressure tube (90-100°C) and drying under reduced pressure at 78°C for 36 hours to give 169 mg (99 % recovery) of **7** as white crystals: mp 275-277°C (decomp.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.00 (bs, 1 H, $CONH_2$, D_2O

exchangeable), 7.74 (s, 1 H, ArH), 7.67 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.39 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.33 (bs, 1 H, $CONH_2$, D_2O exchangeable), 6.01 (m, 1H, H-2'), 5.22 (d, 1H, J = 11 Hz., H-3b'), 5.03 (d, 1H, J = 18 Hz., H-3a'), 4.97 (d, 2H, J = 5 Hz., H-1'); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.9, 162.8, 133.3, 133.2, 129.9, 123.0, 117.7, 117.0, 52.1; *Anal.* Calcd for $C_9H_{10}N_4O_4$: C, 45.38; H, 4.23; N, 23.52. Found: C, 45.68; H, 4.32; N, 23.17.

1-[2-(1,3-Dioxolan-2-yl)ethyl]pyrrole-3,4-dicarboxamide (8). Compound **8** was prepared in a 53% yield (616 mg) from diethyl 2-nitropyrrole-3,4-dicarboxylate[2] (**2**, 1.0 g, 3.9 mmoles), NaH (60 % dispersion in mineral oil, 188 mg, 4.7 mmoles), and 1,3-dioxolan-2-yl chloride (0.7 mL, 5.4 mmoles) in acetonitrile (35 mL) followed by treatment with methanolic ammonia (20 mL saturated at 0°C) as described for compound **5**: mp >228°C; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.94 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.81 (s, 1 H, ArH), 7.62 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.47 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.30 (bs, 1 H, $CONH_2$, D_2O exchangeable), 4.84 (t, 1H, J = 3.9 Hz., H-3'), 4.40 (t, 2H, J = 6.9 Hz., H-1'), 3.8 (m, 4H, CH_2CH_2), 2.07 (m, 2H, H-2'); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.0, 162.9, 133.4, 130.3, 123.4, 116.8, 101.3, 64.5, 45.7, 34.0; *Anal.* Calcd for $C_{11}H_{14}N_4O_6$: C, 44.30; H, 4.73; N, 18.78. Found: C, 44.40; H, 4.69; N, 18.66.

2-Nitro-1-[2-(2-pyridyl)ethyl]pyrrole-3,4-dicarboxamide (9).

Method A. Compound **9** was prepared in a 69% yield (816 mg) by heating diethyl 2-nitropyrrole-3,4-dicarboxylate[2] (**2**, 1.0 g, 3.9 mmoles), NaH (60 %

dispersion in mineral oil, 188 mg, 4.7 mmoles), and 2-(2-pyridyl)ethyl chloride[16] (0.7 mL, 5.4 mmoles) in acetonitrile (35 mL) at reflux temperature for 9 days, followed by treatment with methanolic ammonia (20 mL saturated at 0°C) as described for compound **5**: mp >205°C (decomp.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.51 (d, 2H, J = 3.5 Hz.), 7.97 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.72 (t, 1H, J = 7.7 Hz.), 7.66 (bs, 1 H, $CONH_2$, D_2O exchangeable), 7.62 (s, 1H, ArH), 7.27 (m, 4H, collapses to [m, 2H] upon addition of D_2O), 4.72 (t, 2H, J = 7.0 Hz., CH_2CH_2), 3.23 (t, 2H, J = 7.0 Hz., CH_2CH_2); ^{13}C NMR (DMSO-d_6; 75 MHz) δ 165.0, 162.7, 157.1, 149.2, 136.8, 133.3, 130.1, 123.5, 122.9, 122.0, 116.7, 49.4, 38.0; *Anal.* Calcd for $C_{13}H_{13}N_5O_4$: C, 51.49; H, 4.32; N, 23.09. Found: C, 51.62; H, 4.41; N, 23.03.

Method B. A stirred solution of diethyl bis[(dimethylamino)methylene]succinate[17] (**11**, 10 g, 35 mmoles), 2-(2-pyridyl)ethylamine[18] (**12**, 5.4 g, 42 mmoles), and glacial acetic acid (21 mL) in absolute ethanol (175 mL) was heated at reflux temperature for 24 hours. The ethanol was then evaporated under reduced pressure, H_2O (100 mL) was added and the pH was adjusted to 9 with NH_4OH (conc.). The aqueous layer was extracted with EtOAc (2 x 125 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a yellow oil (quant.). This oil was dissolved in CH_2Cl_2 (50 mL) and cooled to 0°C in a 1 L 3-neck round bottom flask. Sulfuric acid (conc., 35 mL) was added very slowly with rapid stirring. (note: when a precipitate forms and the reaction becomes difficult to stir, increase the rate of addition.) Fuming nitric acid (2.46 g) was then added to the biphasic solution over

a 5 min period. The reaction was then allowed to proceed at room temperature for 45 min., at which time the flask was cooled to 0°C and ice (100 cc) was added. The pH was adjusted to 9 with NH_4OH (conc.) at which time the solution turned dark red. Chloroform (200 mL) was added and the organic layer was separated and washed with water three times (100 mL, 250 mL, 250 mL) and dried over Na_2SO_4. The resultant red solution was filtered through a 1 inch plug of silica gel, and eluted with $CHCl_3$ to give a slightly yellow solution. Evaporation of the solution under reduced pressure followed by the sequential addition of Et_2O (200 mL) and hexanes (200 mL) gave a precipitate which was collected by filtration and then dried under reduced pressure at 50°C for 12 hours. This yellow solid (11.3 g) was placed in a pressure vial with methanolic ammonia (120 mL saturated at 0°C) and heated at 90°C for 3 days. The reaction was then cooled to 0°C and the precipitate was collected by filtration. The filtrate volume was reduced by 1/2 and the resultant solid was collected as before. Repeating this reduction/collection procedure a second time and drying the combined solids under reduced pressure at 78°C for 24 hours gave 8.3 g (66 % overall) of **9**, which was identical by ^1H NMR and ^{13}C NMR to the compound obtained by Method A.

2-Nitropyrrole-3,4-dicarboxamide (1). A mixture of 2-nitro-1-[2-(2-pyridyl)ethyl]pyrrole-3,4-dicarboxamide (**9**, 1.90 g, 6.3 mmoles), methyl iodide (9.8 mL, 158 mmoles) and DMF (30 mL) was stirred at room temperature for 24 hours. The solvent was then evaporated under reduced pressure to dryness, and the resultant solid was suspended in EtOAc (100 mL). The yellow precipitate which formed was collected by filtration and washed with EtOAc (50 mL) and hexanes (50 mL). After air drying for 15 min, the solid was transferred to a 250 mL roundbottom flask and methanol (50 mL) and sodium methoxide (1.02 g, 18.9

mmoles) were added. This mixture was heated at reflux temperature for 1 hour, cooled to room temperature and quenched with 4 mL of glacial acetic acid. The solvent was reduced to approx. 10 mL under reduced pressure, and H_2O (60 mL) was added. This aqueous solution was stirred for 1 hour in an ice bath at which time a white precipitate formed. After collecting the solid by filtration and drying under reduced pressure at 50°C for 48 hours, 880 mg (70%) of **1** was obtained as a light yellow solid which was slightly impure. Recrystallization from water and drying as before gave 555 mg (63 % recovery) of **1** which was also slightly impure as determined by ^{1}H NMR and combustion analysis mp >205°C (decomp.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.50 (s, 1H, D_2O exchangeable, NH), 7.87 (s, 1H, D_2O exchangeable, $CONH_2$), 7.63 (s, 1H, D_2O exchangeable, $CONH_2$), 7.61 (s, 1H, H-5), 7.47 (s, 1H, D_2O exchangeable, $CONH_2$), 7.26 (s, 1H, D_2O exchangeable, $CONH_2$); ^{13}C NMR (DMSO-d_6; 75 MHz) δ 164.9, 163.1, 133.6, 124.9, 121.3, 119.4;); HRMS (70eV) Calcd. for $C_6H_6N_4O_4$, predicted : 199.0467, found: 199.0470. *Anal.* Calcd for $C_6H_6N_4O_4$: C, 36.37; H, 3.05; N, 28.28. Found: C, 37.30; H, 3.11; N, 28.10.

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