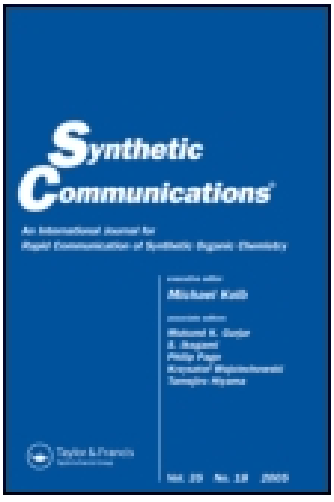

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N-Formamido-Containing Mono- and Diheterocyclic Pyrrole-and Imidazole-2-carboxylic Acids as Building Blocks for Polyamide Synthesis

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Abstract: Four *N*-formamido-containing mono-and diheterocyclic pyrrole- and imidazole-2-containing acids **1**–**4** were synthesized as intermediates for the preparation of polyamide molecules. The *N*-formamido-moiety forces the compounds to bind strongly as a stacked dimer, and in a staggered fashion, at specific sequences in the minor-groove of DNA. The acid moiety at the *C*-terminus of compounds enables these molecules to be coupled to amine-containing intermediates to form the amide linkages of the target polyamide. This convergent approach increases the synthetic diversity in polyamide chemistry by enabling one acid to be used with a variety of different *C*-terminus-functionalized intermediates.

Keywords: acid, distamycin, DNA, formamido, polyamide

INTRODUCTION

The formamido (f-) group, Fig. 1 found at the *N*-terminus of the naturally occurring polyamide distamycin, is known to contribute significantly to its binding affinity, specificity, and orientation.[1] The f-group has been shown

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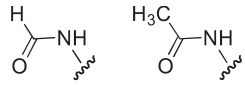


A B

Figure 1. Structure of possible *N*-terminus groups found on polyamides: (a) the formamido-group (f-) and (b) the acetyl-group (CH_3-).

to affect the stacking of two polyamide molecules in the minor groove of DNA.[2,3] When the f-group is present, the compounds tend to favor a staggered motif;[3] conversely, when the f-moiety is absent, a fully overlapped conformation is adopted by the two polyamide compounds[4] (Fig. 2).

The f-group is not found abundantly in natural molecules in comparison to other acyl groups, such as the acetyl group (Ac-) (Fig. 1), which is much more prevalent in nature.[5] DNA binding studies have been performed with compounds that replaced the f- with the Ac-, and previous results showed that this substitution had consequences on binding orientation.[6] The authors showed that when an f-group is present, the polyamide binds to the minor groove in a 5′ to 3′ orientation (*N*-terminus to *C*-terminus), but when the Ac-group is present, the polyamide binds backward, in the 3′ to 5′ direction.[6] In addition, the formamido group has been shown to have a positive effect on the binding affinity of polyamide molecules.[3,7] When directly comparing f- and nonformamido (nf-) derivatives of the same heterocyclic order, the f-containing polyamide generally binds with significantly stronger affinity than its nf- counterpart.[3]

Because the formamido group is of such scientific interest, this article describes the synthesis of four *N*-formamido heterocyclic acids (**1**–**4**, Fig. 3). These compounds contain a one- or two-heterocycle core, with the formamido group on the *N*-terminus and an acid functional group at the *C*-terminus of the molecule. The acid group is present to enable the molecule to be coupled to any amino-containing intermediate, allowing amide bonds to be formed and a range of polyamides to be produced from

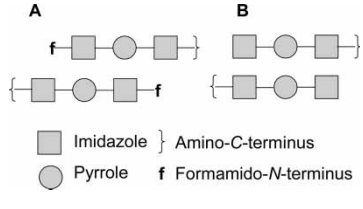


Figure 2. Two possible stacking modes found for polyamides binding to DNA in a 2:1 complex: (a) the staggered mode (observed when compounds possess the f-group) and (b) the overlapped mode (observed in compounds with no f-group).

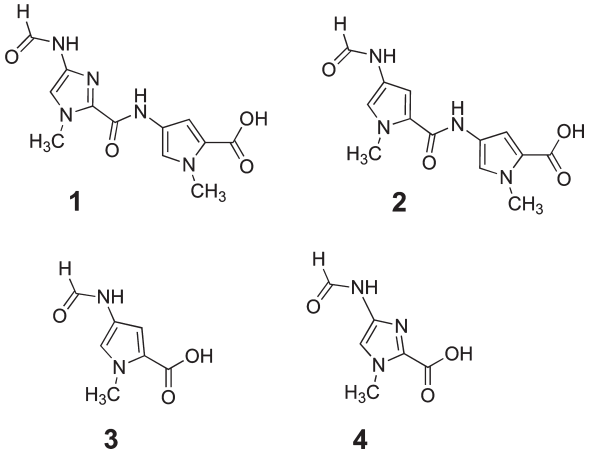
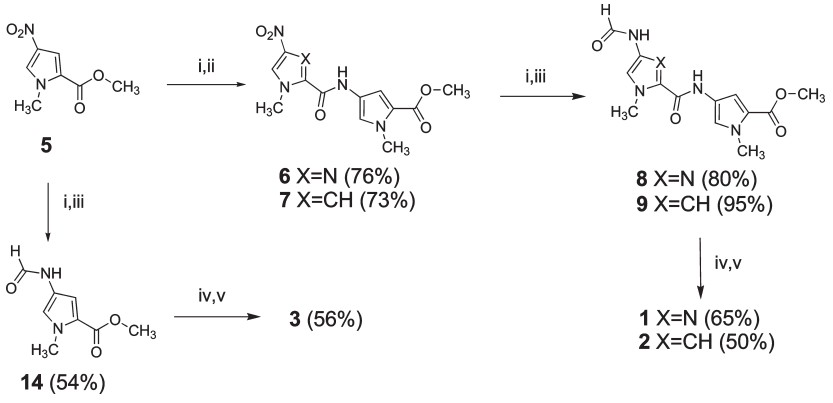


Figure 3. Structures of the four-heterocyclic formamido-acids **1**–**4**.

one batch of the acid compound.[8] This convergent synthesis increases the synthetic diversity of producing polyamide compounds.

RESULTS AND DISCUSSION

The syntheses of compounds **1**, **2**, and **3** (Fig. 1) begin with the common building block, compound **5**.[9] The synthesis of compounds **1** and **2** was achieved by reducing the nitro-group on **5** to an amine using palladium-on-carbon catalytic hydrogenation under atmospheric pressure (Scheme 1).[8] The



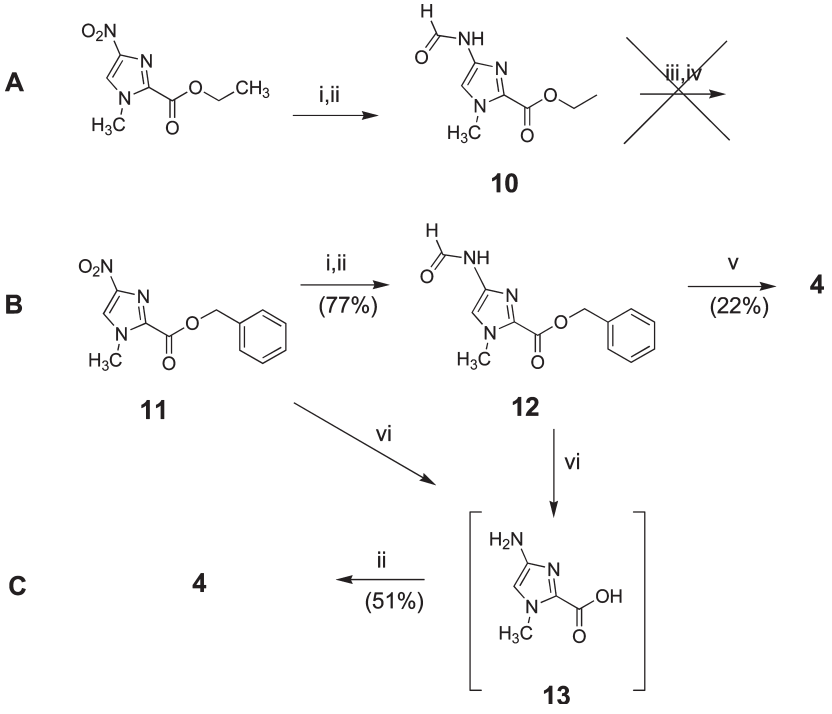
Scheme 1. (i) 10% Pd/C, cold MeOH, H_2, 24 h; (ii) 1-methyl-4-nitroimidazole-2-acid chloride, triethylamine, dry CH_2Cl_2, 0°C-rt, 24 h; (iii) formic acetic anhydride, THF, 0°C-rt; (iv) THF/MeOH, NaOH, reflux, 3–5 h; (v) 1 M HCl; (vi) 10% Pd/C, MeOH/THF, H_2, 24 h.

resulting amine was coupled directly to either 1-methyl-4-nitroimidazole-2-acid chloride or 1-methyl-4-nitropyrrole-2-acid chloride using Schotten–Bauman conditions[10] to produce amides **6** and **7** in yields of 76 and 73%, respectively. Further reduction of these nitro-groups to the amines, using the same conditions as already described,[8] followed by formylation with acetic formic anhydride (formed in situ by reaction of formic acid with acetic anhydride[3]) produced **8** and **9** in yields of 80 and 95%, respectively. The formylated compounds were hydrolyzed by refluxing in THF, MeOH, and aqueous NaOH. Acidification with aqueous HCl formed pure compounds **1** and **2** in 65 and 50% yields, respectively. The overall yields of these compounds were good (40 and 35% for **1** and **2**, respectively) considering flash-column purification was required at the first two steps. The monopyrrole compound, **3**, was performed in a similar manner (Scheme 1). Thus **5** was formylated directly (using the same nitro-to-amine reduction as previously described) to produce **1** in overall 55% yield. The lower yield could be attributed to a drop in solubility when working with the monoheterocycle compared to the diheterocyclic compounds.

Synthesis of the imidazole compound **4** was more challenging. The first attempt at producing compound **4** was unsuccessful and employed similar chemistry as described in the synthesis of compound **3**, except that ethyl 1-methyl-4-nitroimidazole-2-carboxylate was used (Scheme 2i). The formylation step to produce compound **10** was successful; however, isolating the acid product from the aqueous phase following hydrolysis of the ester was unsuccessful because it was fully water soluble. Removal of sodium chloride from the mixture was difficult.

A second, successful route employed the benzyl-protected-nitroimidazole starting material (**11**, Scheme 2ii). The first step employed a reduction and formylation (as described previously) to form compound **12** in good yield (77%). The benzyl protecting group was removed by catalytic hydrogenation using a 10% palladium-on-carbon catalyst (50 psi). The suspension was vacuum filtered over Celite®, and the residue was vigorously washed with copious amounts of *N*,*N*-dimethylformamide (DMF). Concentration of the DMF solution under vacuum gave the desired compound **4** in 22% yield. The insolubility of this product accounts for the low yield, as repeated washings were needed to extract the product from the residue.

A shorter, more efficient synthetic pathway to forming compound **4** was discovered when the aforementioned synthesis was reattempted (Scheme 2iii). In this case, $CHCl_3$ was used instead of MeOH in the catalytic hydrogenation of benzyl ester **12**. Upon workup of the reaction, it was discovered that the formamidogroup had been removed and the amine **13** had been isolated. This intermediate was treated directly with acetic formic anhydride, and during the workup the reaction was quenched with H_2O instead of MeOH to remove any *C*-terminus adducts. The target molecule **4** was obtained via filtration of the precipitate. This serendipitous finding was interesting for two reasons: (a) a step in the synthesis could potentially be eliminated, and



Scheme 2. (i) 10% Pd/C, cold MeOH, H_2, 24 h; (ii) formic acetic anhydride, THF, 0°C-RT; (iii) THF/MeOH, NaOH, reflux; (iv) 1 M HCl; (v) 10% Pd/C, MeOH/THF, H_2, 24 h; (vi) 10% Pd/C, $CHCl_3$, H_2, 24 h.

(b) the product could be obtained by filtration, rather than extraction with DMF, which was tedious to remove.

A fourth reaction was attempted to determine if compound **4** could be obtained from the shortened synthesis, mentioned previously. Compound **11** (Scheme 2ii) was reduced directly in $CHCl_3$ with 10% Pd/C to determine if the nitrogroup and the benzyl protecting group could be removed in onestep. The isolated intermediate was then treated with acetic formic anhydride, quenched with water, and filtered, and the target compound (**4**) was obtained in 51% yield. This yield represented a significant improvement over the previous method (Scheme 2ii). One step in the synthesis was eliminated, and the product was obtained directly without the need for a lengthy extraction procedure.

CONCLUSION

This article describes the synthesis of four *N*-formamido-containing mono- and diheterocyclic carboxylic acid intermediates **1**–**4** with potential

application in the field of polyamide chemistry. The syntheses described are versatile, and the products can be obtained in good yields without the need for difficult isolation or purification techniques. All compounds provided satisfactory >96% purity by 500-MHz ^{1}H NMR as well as by thin-layer chromatography (TLC) analysis. Finally, compound **4** can be obtained via a shortened route that improves on yield and ease of isolation of the compound.

EXPERIMENTAL

Compound 7

Methyl-1-methyl-4-nitropyrrole-2-carboxylate (**5**)[9] (1.51 g, 8.22 mmol) was reduced under H_2 at atmospheric pressure with 5% Pd/C (50% by weight) in cold MeOH. The reaction mixture was stirred for ~24 h, and the catalyst was removed by filtration through Celite®, washed thoroughly with MeOH, and evaporated to dryness. Residual MeOH was removed by co-evaporation with dry CH_2Cl_2 (3 × 2 mL). The resulting amine was dissolved in triethylamine (1.20 mL, 8.5 mmol) and dry CH_2Cl_2 (20 mL) and cooled to 0°C (ice/H_2O). 1-Methyl-4-nitropyrrole-2-carbonyl chloride[10] (9.04 mmol) was dissolved in CH_2Cl_2 and added dropwise to the amine solution with stirring. The reaction was stirred at Rt for ~24 h, and the solvent was removed by evaporation. The resulting yellow solid was suspended in water (10 mL), filtered, washed with hexanes (10 mL) and isopropanol (IPA) (10 mL), and dried under vacuum over P_2O_5 to yield **7** as a yellow solid (1.84 g, 73%), mp 257–261°C. Rf: 0.31 (98:2% v/v $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1H, *J* 1.5 Hz); 7.53 (s, br, 1H); 7.38 (d, 1H, *J* 1.5 Hz); 7.17 (d, 1H, *J* 1.5 Hz); 6.79 (d, 1H, *J* 1.5 Hz); 4.03 (s, 3H); 3.93 (s, 3H), 3.83 (s, 3H); IR (neat) 2947, 2906, 2841, 1694, 1667, 1652, 1645, 1574, 1568, 1558, 1538, 1505, 1447, 1393, 1317, 1250, 1108, 750 cm^{-1}; MS (direct probe) *m*/*z* (rel. intensity) 306 ([M] 80%), 153 (100%).

Compound 2

Compound **7** (104 mg, 0.34 mmol) was reduced for ~18 h in the presence of H_2 using 5% Pd/C (50% by weight) in MeOH. The amine was isolated as described for compound **7**. Acetic anhydride (4 mL) was cooled to 0°C (ice/H_2O) with stirring, and formic acid (2 mL) was added dropwise. The solution was heated to 50°C for ~20 min and then cooled to 0°C. *N*,*N*-dimethylaminopyridine (DMAP) (10 mg, 0.082 mmol) were dissolved in dry THF (30 mL), and the formic acetic anhydride was added dropwise at 0°C (ice/$H_2$0 bath).

The reaction was stirred at 0°C for a further ~4 h and was then quenched by the dropwise addition of MeOH (50 mL). The reaction stirred for ~1 h at

this temperature. The solvent was removed, and the resulting orange oil was dissolved in $CHCl_3$ (50 mL) and water (50 mL). The pH of the aqueous layer was adjusted using aq. NaOH (1 M, pH ~11), and the aqueous layer was back-extracted with $CHCl_3$ (×3). The organic layers were combined and dried (Na_2SO_4). Following evaporation, the crude orange product was purified via silica gel (70–230 mesh) column chromatography (100:0–90:10% v/v, $CHCl_3$/MeOH) to yield **9** as an orange solid (98.2 mg, 95%): Rf: 0.14 (98:2% v/v, $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 8.29 (s, 1H); 7.41 (d, 1H, *J* 1.5 Hz); 7.11 (d, 1H, *J* 1.5 Hz); 6.74 (d, 1H, *J* 1.5 Hz); 6.66 (d, 1H, *J* 1.5 Hz); 3.94 (s, 3H); 3.92 (s, 3H), 3.82 (s, 3H). Compound **9** (330 mg, 1.08 mmol) was suspended in aq. NaOH (0.22 M) and refluxed for ~1 h. The solid was then dissolved with MeOH to make an orange solution, which was cooled to 0°C, and cold 1 M HCl was added dropwise. A precipitate formed, which was filtered, washed with H_2O, and dried over P_2O_5 under vacuum to yield an orange solid (155.1 mg, 50%), mp 154–160°C. ^{1}H NMR (CD_3OD) δ 8.21 (s, 1H); 7.34 (d, 1H, *J* 1.5 Hz); 7.19 (d, 1H, *J* 1.5 Hz); 6.94 (d, 1H, *J* 1.5 Hz); 6.85 (d, 1H, *J* 1.5 Hz); 3.90 (s, 3H); 3.89 (s, 3H); IR (neat) 3288 (br), 3134, 2958, 1646, 1576, 1436, 1265 cm^{-1}; MS (ES+) *m*/*z* (rel. intensity) 145 (40%), 291 ([M + H] 100%), 305 (50%), 305 (50%), 313 (20%), 397 (20%).

Compound 14

Compound **5**[9] (200 mg, 1.09 mmol) was dissolved in chilled MeOH (10 mL) and reduced in the presence of H_2 using 5% Pd/C (120 mg, 50% by weight) at rt for ~18 h. The amine was isolated using the same procedure as described for compound **7**. Acetic anhydride (6.7 mL) was stirred at 0°C (ice/H_2O), and formic acid (3.3 mL) was added dropwise. The reaction was stirred at 50°C for ~15 min and then stored at 0°C (ice/H_2O). THF (10 mL) was added to the amine, and the mixture was cooled to 0°C (ice/H_2O) with stirring. The formic acetic anhydride mixture was added dropwise to the amine solution and stirred overnight while warming to rt. The reaction was cooled to 0°C (ice/H_2O) and quenched with MeOH (10 mL), followed by removal of the solvent. The obtained product was dissolved in CH_2Cl_2 and washed with H_2O (2 × 15 mL), followed by back-extraction with CH_2Cl_2 (2 × 10 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness to yield compound **14** as a yellow solid (106 mg, 54%), mp dec. 250°C. Rf 0.9 (70:30%v/v $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 1H); 7.375 (d, 1H, *J* 1.5 Hz); 7.14 (s, 1H); 6.70 (d, 1H, *J* 3 Hz); 5.26 (s, 3H); 3.94 (s, 3H); IR (neat) 3299, 3150, 3122, 2921, 2858, 1690, 1586, 1457, 1410, 1457, 1385, 1354, 1293, 1277, 1222, 1134, 1096 cm^{-1}; MS (direct probe) *m*/*z* (rel. intensity) 182 ([M] 100%), 153 (35%).

Compound 3[8]

Compound **14** (1.1 g, 6.04 mmol) was dissolved in dry THF (17 mL) and MeOH (17 mL). The mixture was stirred under reflux for ~2.5 h following the addition of aq. NaOH (2 M, 4.5 mL). The solvents were removed, and CH_2Cl_2 (3 mL) was added. The solution was stirred for 15 min. The organic solvent was removed, and the aqueous layer was cooled to 0°C (ice/H_2O) and acidified by the dropwise addition of aq. HCl (1 M). Ice chips were added to facilitate the precipitation of the product. Filtration afforded a solid that was dried under vacuum for ~2 h to yield compound **3** as an orange solid (573 mg, 56%), mp dec. 200°C. ^{1}H NMR (DMSO-d_6) δ 9.98 (s, 1H); 8.08 (s, 1H); 7.92 (s, 1H); 7.21 (d, 1H, *J* 1 Hz); 6.641 (d, 1H, *J* 1 Hz); 3.79 (s, 3H); IR (neat) 3309 (br), 2961, 2890, 1713, 1635, 1457, 1442, 1368, 1345, 1322, 1191, 1121, 1066, 1037, 966 cm^{-1}; MS (direct probe) m/z (rel. intensity) 168 ([M] 100%), 139 (35%); HRMS for $C_7H_8N_2O_3$ calcd. 168.0535, obsvd. 168.0532.

Compound 6

Compound **5** (247 mg, 1.34 mmol) was dissolved in MeOH (10 mL) and reduced in the presence of H_2 using Pd/C (5%, 124 mg) at rt for ~4 h. The amine was isolated as described for compound **7**. 1-Methyl-4-nitroimidazole carbonyl chloride[10] (1.60 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a mixture of the isolated amine in THF (15 mL) and triethylamine (0.188 mL = 136.5 mg, 1.35 mmol) at 0°C (ice/H_2O) with stirring. The reaction was allowed to stir at rt for ~18 h. The compound was isolated in a similar manner as compound **7**. The crude product was dried under vacuum to yield compound **6** as a yellow residue (313 mg, 76%): Rf: 0.41 (98:2% v/v $CHCl_3$/MeOH) ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H); 7.83 (s, 1H); 7.39 (d, 1H, *J* 1.5 Hz); 7.38 (d, 1H, *J* 2 Hz); 4.21 (s, 3H); 3.93 (s, 3H), 3.83 (s, 3H); IR (neat) 2955, 2918, 2849, 1705, 1652, 1557, 1463, 1455, 1309 cm^{-1}; MS (ES+) m/z (rel. intensity) 308 ([M + H] 20%), 242 (25%), 226 (30%), 152 (45%).

Compound 8

Compound **7** (1.83 g, 5.9 mmol) was dissolved in cold MeOH (10 mL) and THF (5 mL) and reduced in the presence of H_2 using Pd/C (5%, 0.60 g) at rt for ~4 h. The amine was isolated as described for compound **7**. Acetic anhydride (15 mL) was stirred at 0°C (ice/H_2O), and formic acid (7.5 mL) was added dropwise. The mixture was heated at 50°C with stirring for ~20 min followed by cooling to 0°C (ice/H_2O). The resulting formic acetic anhydride was added dropwise to a solution of the amine in THF (15 mL)

and DMAP (20 mg), followed by stirring for ~4 h. The reaction was quenched by the addition of MeOH (10 mL), followed by stirring for 15 min. The solvent was removed, followed by addition of H_2O (10 mL) and aqueous NaOH (1 M, pH~11). The aqueous layer was washed with $CHCl_3$ (3 × 15 mL), and then the organic layer was dried (Na_2SO_4) and evaporated to dryness to yield compound **8** as a yellow solid (1.46 g, 80%), mp 215–219°C. Rf 0.3 (95:5% v/v $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1H); 8.26 (s, 1H); 7.64 (s, 1H); 7.39 (s, 1H); 7.38 (d, 1H, *J* 2 Hz); 6.81 (d, 1H, *J* 1.5 Hz); 4.02 (s, 3H); 3.88 (s, 3H); 3.78 (s, 3H); IR (neat) 2950, 2913, 2844, 1694, 1652, 1567, 1557, 1471, 1447, 1259, 1199, 1120, 1098, 1062 cm^{-1}; MS (direct probe) m/z (rel. intensity) 305 ([M] 100%).

Compound 1

Compound **8** (293 mg, 0.961 mmol) was stirred in aq. NaOH (0.5 mL, 2 M) and H_2O (4.3 mL) at reflux for ~1 h. An additional aliquot of NaOH solution (0.1 mL) was added, and the reaction was stirred at reflux for an additional 30 min. The orange reaction mixture was cooled to 0°C (ice/H_2O), and aq. HCl (1 M) was added until a solid precipitated. The solid was filtered, washed with H_2O, and dried under vacuum over P_2O_5 to produce the product **1** as a yellow/brown solid (181 mg, 65%), mp 188–194°C. ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H); 7.44 (d, 1H, *J* 2 Hz); 7.25 (s, 1H); 6.85 (d, 1H, *J* 2 Hz); 4.05 (s, 3H); 3.89 (s, 3H); MS (ES+) m/z (rel. intensity) (292 [M + H] 100%).

Compound 11

1-Methyl-4-nitroimidazole carbonyl chloride[10] (8.89 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and added dropwise to a cooled solution (ice/H_2O) of benzyl alcohol (2.0 mL ≡ 2.09 g, 19.33 mmol) and triethylamine (1.5 mL ≡ 1.09 g, 10.78 mmol) in CH_2Cl_2 (20 mL). Following the complete addition, the reaction was stirred at rt for 12–18 h. The crude material was isolated in a similar manner as described for compound **14**, except the reaction was not quenched with MeOH. The organic layers were combined and dried (Na_2SO_4), evaporated to dryness, and residual benzyl alcohol removed via Kügelrohr distillation (5 mmHg, 100°C). The obtained white solid was purified by precipitation using petroleum ether 60:80 and diethyl ether to yield a cream/white powder (2.22 g, 96%), mp 168.4–170.2°C. Rf 0.42 (98:2% v/v $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H); 7.38 (m, 5H); 5.42 (s, 2H); 4.10 (s, 3H); IR (neat) 1726, 1542, 1496, 1382, 1311, 1261, 1122 cm^{-1}; MS (direct probe) m/z (rel. intensity) 261 ([M] 10%), 244 (20%), 155 (35%), 127 (100%), 91 (75%).

Compound 12

Compound **11** (2.43 g, 0.0093 mol) and Pt/O_2 (1.22 g) were dissolved in MeOH (15 ml) and THF (15 mL). The solution was placed under H_2 at 55 lbs. of pressure. Upon complete reduction, the Pt/O_2 was filtered off through Celite®. The filtrate was concentrated to dryness, and the amine was coevaporated three times with dry CH_2Cl_2 (5 ml each). Acetic anhydride (15 mL) was added to formic acid (7.5 mL) dropwise while stirring at 0°C. Upon complete addition, the mixture was heated to 50°C, stirred at reflux for ~20 min, and then cooled to 0°C. The amine was redissolved in dry CH_2Cl_2 (30 mL), and the formic acetic anhydride was added dropwise at 5°C. The reaction mixture was brought to rt and left stirring overnight. The reaction was quenched with MeOH (20 mL), and concentrated to dryness. Water was then added to the reaction mixture (and made alkaline with aq. NaOH), and the aqueous layer was then extracted three times with $CHCl_3$ (50 ml each) and once with ethyl acetate (30 mL). The organic layers were combined and dried ($NaSO_4$) and then concentrated to dryness. The product was then purified by column chromatography (80:20% v/v $CHCl_3$/MeOH) to yield compound **12** as a pale yellow solid (1.86 g, 77%), mp 172–176°C. Rf 0.26 (95:5% v/v $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H); 8.33 (s, 1H); 7.53 (s, 1H); 7.39–7.32 (m, 5H); 5.39 (s, 2H); 3.99 (s, 3H); IR (neat) 3210, 3161, 2919, 1714, 1686, 1436, 1269, 1210, 1118, 1060, 1012 cm^{-1}; MS (direct probe) m/z (rel. intensity) 259 ([M] 30%), 125 (70%), 91 (100%).

Method 1, Compound 4[8]

Compound **12** (1.86 g, 0.0072 mol) and 10% Pd/C (0.186 g) were dissolved in MeOH (15 mL) and THF (15 mL) and reduced in the presence of H_2 at atmospheric pressure with stirring for ~18 h. The amine was filtered, and compound **4** was extracted from the Pd/C catalyst DMF (3 × 5 mL each). The DMF was removed via Kügelrohr distillation (60°C, 0.005 atm) and was washed with acetone (2 × 10 mL) to yield compound **4** as a grey powder (0.27 g, 22%).

Method 2, Compound 4[8]

Compound **11** (1.01 g, 3.85 mmol) was dissolved in $CHCl_3$ (10 mL) and reduced for ~18 h in the presence of H_2 using Pd/C (10%, 0.2 g, 50 psi). The amine was isolated as described for compound **7**. Acetic anhydride (7 mL) was stirred at 0°C (ice/H_2O), and formic acid (3.5 mL) was added. The reaction was heated at 50°C for ~20 min and then stored at 0°C (ice/H_2O) until required. The reduced compound was dissolved in dry THF (30 mL) and cooled to 0°C (ice/H_2O), and the formic acetic anhydride

mixture was added dropwise and stirred overnight while warming to rt. The reaction was cooled to 0°C (ice/H_2O) and quenched with H_2O/ice (20 mL) followed by removal of the solvent by evaporation. The suspension was filtered, washed with H_2O, and dried under vacuum (5 mmHg and 100°C) to yield compound **4** a grey solid (331 mg, 51%), mp dec. 200°C. ^{1}H NMR (DMSO-d_6) δ 10.6 (s, 1H); 8.19 (s, 1H); 7.49 (s, 1H); 3.89 (s, 3H); IR (neat) 3298 (br), 2962, 2888, 1706, 1622, 1569, 1476, 1383, 1368, 1278, 1191, 1121, 1064, 1037, 966, 926 cm^{-1}; MS (ES-) m/z (rel. intensity) 168 ([M-H] 100%), 124 (100%), 97 (60%). HRMS for $C_6H_7N_3O_3$ calcd. 168.0409, obsvd. 168.0412.

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