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PII: S0040-4020(18)30181-9

DOI: 10.1016/j.tet.2018.02.037

Reference: TET 29308

To appear in: *Tetrahedron*

Received Date: 7 February 2018

Revised Date: 14 February 2018

Accepted Date: 15 February 2018

Please cite this article as: Jarvis T, Saint-Louis CJ, Fisch AR, Barnes KL, Dean D, Flores LA, Hunt TF, Munro L, Simmons TJ, Catalano VJ, Zhu L, Schrock AK, Huggins MT, Pyrrole β-amides: Synthesis and characterization of a dipyrrinone carboxylic acid and an *N*-Confused fluorescent dipyrrinone, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.02.037.

Pyrrole β-amides: Synthesis and Characterization of a Dipyrrinone Carboxylic Acid and an *N*-Confused Fluorescent Dipyrrinone

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Abstract

Pyrrole β-amides are useful building blocks for the preparation of novel molecular architectures that can be used in supramolecular chemistry and sensor development. Under basic conditions, pyrrole β-amides with an α-aldehyde produce different condensation products when reacted with pyrrolinones depending on the amide substitution. Secondary amides form the expected dipyrrinones, but unexpectedly undergo a subsequent trans-amidation with the pyrrolinone nitrogen to produce an unsymmetrical imide (an *N*-confused fluorescent dipyrrinone). Under the same conditions, tertiary amides produce the expected dipyrrinone carboxylic acids, which have been shown to have strong self-association properties as determined by vapor pressure osmometry measurements, NMR studies, and X-ray crystal structure determination. Furthermore, an *N*-confused fluorescent dipyrrinone was produced from the same trans-amidation reaction during attempts to decarboxylate a dipyrrinone amide with a 9-carboxylic moiety.

Keywords: pyrrole β-amides, dipyrrinones, hydrogen bonding, trans-amidation, self-association

1. Introduction

Molecular recognition driven by hydrogen bonding[1–3] has been extensively studied over the years and is frequently found in organic and biochemistry systems with amides and carboxylic acids being among the most essential functional groups incorporated into the hydrogen bonding interactions.[4,5]

Amide-to-amide hydrogen bonding (Figure 1A) has been recognized and studied for decades with typical self-association constants, K_A, on the order of 10^2 M^{-1} in hydrogen bond-promoting solvents such as carbon tetrachloride and chloroform.[3]

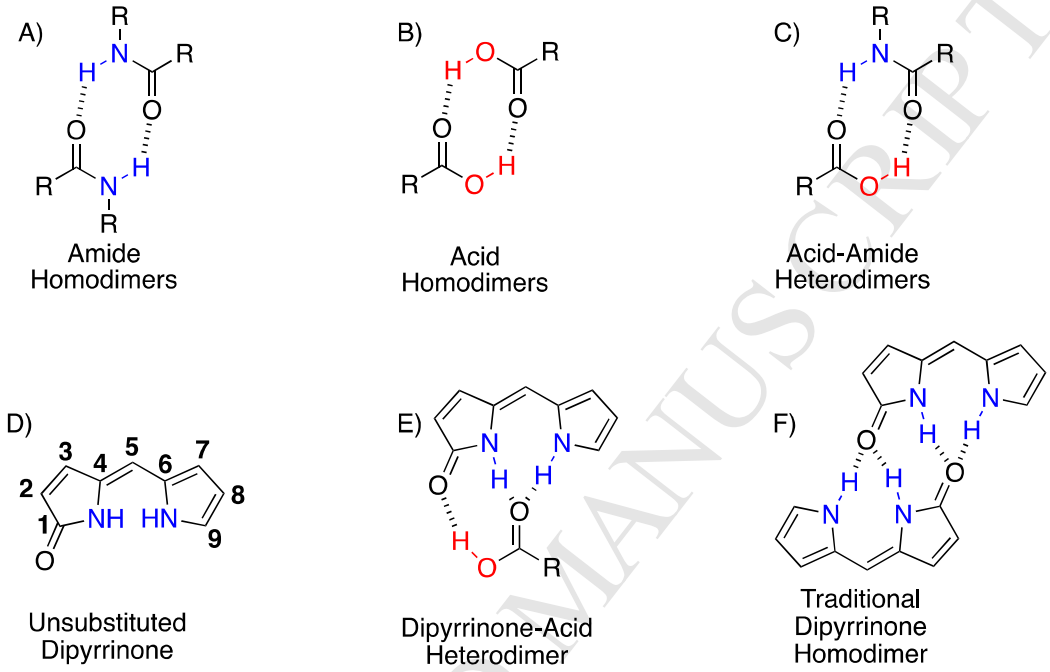


Figure 1. A) Amide-to-amide homodimer hydrogen bonds. B) Carboxylic acid to carboxylic acid homodimer hydrogen bonds. C) Amide-to-carboxylic acid heterodimer hydrogen bonds. D) Backbone of unsubstituted dipyrrinones. E) Dipyrrinones-to-carboxylic acids heterodimer hydrogen bonds. F) Dipyrrinone homodimer displaying acid-to-amide hydrogen bonding as well as a third hydrogen bond between the pyrrole NH and the acid C=O.

Carboxylic acid to carboxylic acid hydrogen bonding (Figure 1B) has also been investigated over the years.[1–4] Hydrogen bonded carboxylic acid dimers have been shown to exhibit even larger K_A's (~10^3 M^{-1}) for self-association in hydrogen bond promoting solvents.[2–4] In contrast, the mixed type, amide-to-carboxylic acid hydrogen bonding (Figure 1C) has received far less attention except in co-crystal formation,[5] and usually in connection with molecular recognition/self-assembly studies. By utilizing a combination of computational and experimental techniques, Rebek determined the order of dimerization energy to be was carboxylic homodimer > amide-carboxylic dimers

> amide homodimers. This dimerization energy order was also determined by computational methods to be the same in the gas phase, in carbon tetrachloride and in *N*,*N*-dimethylformamide solutions, as well as in molecular capsules.[6]

Dipyrrinones are well known participants in hydrogen bonding, and have been shown to be effective receptors for carboxylic acids[7–10] (Figure 1E). The hydrogen bonding pocket of the dipyrrinone unit is composed of pyrrole and lactam N–H and a lactam C=O. There are numerous examples of dipyrrinones participating in hydrogen bonding via self-association[11–14] and with other species in a host-guest type interaction, such as anions (Cl^-, HSO_4^-, etc.) and benzoic acid.[15] For self-association, the traditional hydrogen bonding motif has the two dipyrrinone units held together by a network of four intermolecular hydrogen bonds showing amide-to-amide hydrogen bonding involving the lactam rings as well as the pyrroles N–H to lactam C=O hydrogen bonding (Figure 1F).[8] When hydrogen bonding to carboxylic acids, the complex displays acid-to-amide hydrogen bonding as well as a third hydrogen bond between the pyrrole N–H and the acid C=O, Figure 1E.[7,9,16]

Interestingly, dipyrrinones have been shown to prefer the acid-to-amide hydrogen bonding interactions.[17,18] For example, dipyrrinones with a long alkyl linker between the dipyrrinone and the carboxylic acid located at the C(9) position of the dipyrrinone were found to prefer the intramolecular hydrogen bonded state with acid-to-amide hydrogen bonding over a self-associated dimer which would have displayed the amide-to-amide hydrogen bonding motif.[17] With a carboxylic acid at C(8) of the dipyrrinone, intramolecular acid-to-amide hydrogen bonding is not possible. Dipyrrinone analogs with a carboxylic acid at C(8) were found to adopt a self-associated state with the acid-to-amide hydrogen bonding pattern, again over the traditional hydrogen bonding pattern found in dipyrrinones without carboxylic acids.[19]

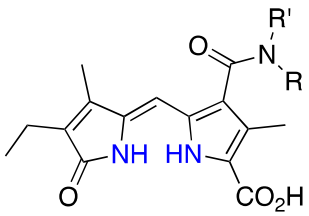


Figure 2. 7-Aminodipyrrinone Targets

In our current study, we prepared new dipyrrinone analogs to further the understanding of dipyrrinones as receptors for carboxylic acids. The target compounds contain a carboxylic acid at C(9) with no linker and an amide at C(7) (Figure 2) which should provide flexibility for adjusting solubility as well as an attachment point for incorporating the dipyrrinone moiety into larger supramolecular architectures. In the course of preparing the target compounds, we encountered unexpected reactivity in these new 7-amidodipyrrinones, which will also be discussed.

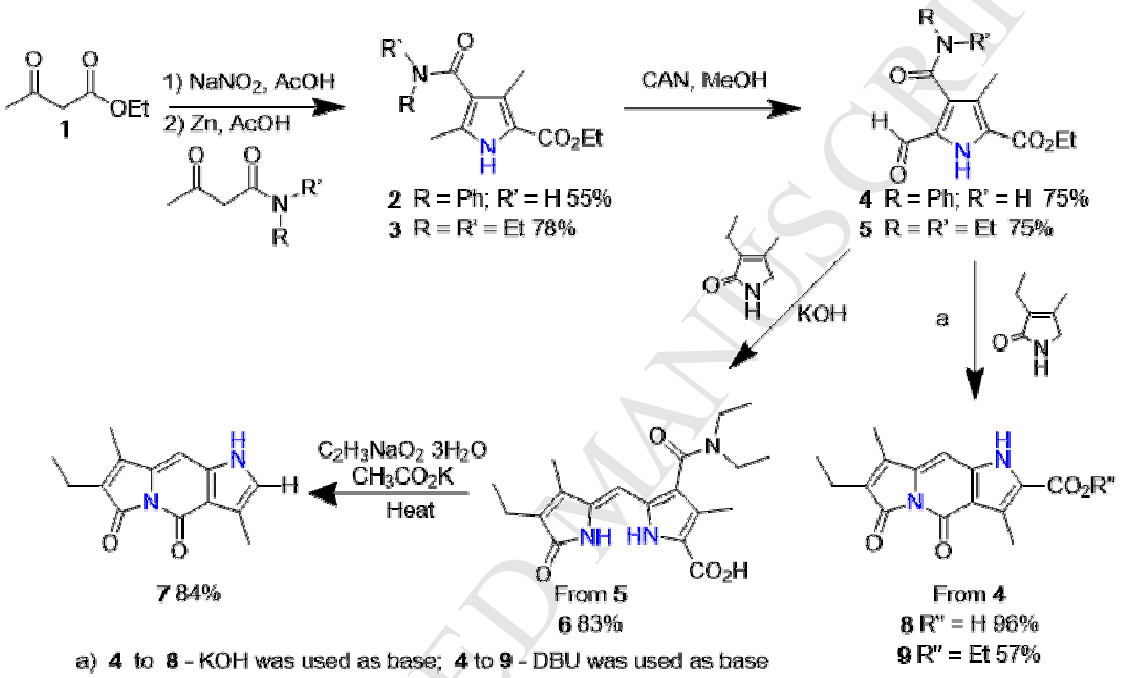
2. Results and Discussion

2a. Synthesis and Characterization

Synthesis of the target molecules began with the Knorr pyrrole preparation of the β-amide pyrrole esters **2** and **3** from their corresponding acetoacetamide derivatives and ethyl acetoacetate in reasonable yields (Scheme 1).[20,21] Ceric ammonium nitrate oxidation of the pyrrole α-methyl to the corresponding aldehyde afforded pyrroles **4** and **5** in 55–75% yield.[22] Condensation of the tertiary amide derivative **5** with 3-ethyl-4-methylpyrrolin-2-one under basic conditions, KOH, provided target **6** in 83% yield. Hydrolysis of the ester was observed under the reaction conditions producing the dipyrrinone 9-carboxylic acid derivative **6**, rather than preserving the ester of the pyrrole. Attempts to decarboxylate **6** using standard methods failed to yield the desired α-free dipyrrinone analog. Instead, the *N*-confused fluorescent dipyrrinone **7** was isolated in 84% yield. This product was formed from an intramolecular *trans*-amidation reaction involving the 7-amide substituent and the pyrrolinone N–H moieties of the dipyrrinone resulting in the imide. Similar reactions to form this ring system have been observed with 7-

ester dipyrrinone analogs, but never with amides.[23] Decarboxylation of the 9-carboxylic acid did take place, but it was not possible to determine which reaction occurred first, trans-amidation or decarboxylation.

Scheme 1. Synthesis of target 7-amidodipyrrinone **6** and *N*-confused fluorescent dipyrrinones **7**, **8**, and **9**.



Condensation of the secondary amide derivative **4** with 3-ethyl-4-methylpyrrolin-2-one under basic conditions with KOH failed to produce the desired dipyrrinone carboxylic acid targets. Interestingly, the reaction of *N*-phenyl amide **4** under the same basic conditions as **5** produced the *N*-confused fluorescent dipyrrinone carboxylic acid **8**. As observed with **6**, hydrolysis of the ester was observed to provide the carboxylic acid product **8**. The use of DBU as a non-nucleophilic base also produced the *N*-confused fluorescent dipyrrinone, but as the ester **9** rather than the carboxylic acid. Apparently, the secondary amide unit is more reactive in the trans-amidation reaction conditions than the tertiary amide. All attempts to condense the secondary amide pyrrole aldehydes with the pyrrolinone resulted in either the *N*-confused fluorescent dipyrrinone or the isolation of the starting material. Previously known *N*-confused fluorescent dipyrrinones were prepared from pyrrole aldehydes with a β-

ester moiety and were shown to be highly fluorescent with λ_{max} for emission at ~500 nm in methanol.[23] Samples **7**, **8**, and **9** are also fluorescent. The λ_{max} for emission of **9** in acetonitrile was 578 nm with a quantum yield of 0.55. The emission λ_{max} for **8** in acetonitrile was 480 nm with quantum yield of 0.15. Sample **7** has an emission λ_{max} of 500 nm in acetonitrile, but a quantum yield of only 0.05. The absorption and emission results for **7**, **8**, and **9** are summarized in the Supplemental Information.

2b. Constitutional Structure and Molecular Conformation

The constitutional structures for all of the products follow logically from the method of synthesis and were verified by a combination of two-dimensional nuclear magnetic resonance spectroscopy $^1H\{^1H\}$- NOESY, HSQC, and HMBC techniques. The ^1H-NMR spectrum of pyrrole amide **5** in $CDCl_3$ at 20 ºC was found to have broad signals for the ethyl groups of the β-amide at 3.2–3.8 ppm for the methylenes and at 1.0–1.3 ppm for the methyls (See S10). The broad resonances are due to the restricted rotation about the amide bond which resulted in the two ethyl moieties being spectroscopically different at room temperature. Upon heating the sample to 60 ºC, the amide methylene and methyl signals coalesced into one signal for the two CH_2 groups at 3.4 ppm and one signal for the two CH_3 at 1.1 ppm indicating free rotation of the ethyl moiety at the higher temperatures.

Cooling the sample to -25ºC resulted in three separate resonances for the two methylene moieties and two signals for the methyl groups (see S10). Integration of the three methylene signals indicated a 1:1:2 ratio. Additionally, the observed splitting patterns for the three methylene signals were more complicated than the expected quartets. At the lower temperature, the restricted rotation of the amide group along with the conformation adopted by the molecule resulted in diastereotopic CH_2 moieties. Such atropisomerism has been commonly observed in tertiary aromatic amides.[24] In this case, the three signals from the methylene moieties indicated two overlapping signals at 3.3 ppm with the other signals at 3.5 and 3.7 ppm. A $^1H\{^1H\}$-gCOSY spectrum measured at 5 ºC indicated that the two signals at 3.5 and 3.7 ppm corresponded to the same methylene moiety. From the variable temperature (VT) NMR data,

coalescence temperatures of 30–36 ºC were determined and an average $\Delta G^{\ddagger}$ of 18.4 kcal/mol was calculated for the rotational energies barrier (Table 1). This value was compared to the literature value of 14–18 kcal/mol and fits within the range expected for these systems.[25,26] The corresponding phenyl amide aldehyde showed similar behavior in the ^{1}H-NMR spectrum in $CDCl_3$ at 20 ºC, but no VT-NMR experiments were conducted as we expect similar results to pyrrole **5**.

Table 1. Calculated $\Delta G^{\ddagger}$ average for the rotational energies barriers for CH_2 A, CH_2 B, and CH_3 for **5** and **6**.

Compounds	**Groups**	**T_c(K)**	**δv (ppm)**	**$\Delta G^{\ddagger}$ (kcal/mol)**
5	CH_2 A	303	0.2	18.37
	CH_2 B	310	0.16	18.37
	CH_3	307	0.22	18.48
6	CH_3	330	0.09	20.46
	CH_2 A	360	0.37	21.36
	CH_2 B	360	0.14	22.03

The solution state conformation of dipyrrinone carboxylic acid **6** was studied by NOESY spectroscopy in $CDCl_3$ at room temperature, see Supporting Information. The *syn* configuration of the C(4)-C(5) alkene was confirmed by the presence of an NOE correlation between the C(5)-H and the C(3)-CH_3 as well as a correlation between the lactam and pyrrole.

The ^{1}H-NMR spectrum in $CDCl_3$ at 20 ºC of **6** showed two distinct quartets for the *N*-ethyl methylenes and two distinct triplets for the methyls, indicating strongly restricted rotation of the amide bond and no indication of the diastereotopic properties found in pyrrole amide **5 (**see S12).

At 60 ºC in $CDCl_3$, the resonances from the *N*-ethyl groups broadened substantially, however they did not coalescence, indicating a higher energy of rotation for **6** than was observed for **5**. It has

previously been shown that $(CDCl_2)_2$ and $CDCl_3$ can be used interchangeably for VT-NMR studies to study dipyrrinones.[14] Using $(CDCl_2)_2$ as the solvent, we conducted NMR studies over the temperature range of 25–100 ºC. At 100 ºC, the amide alkyl groups are fully coalesced and appear as quartet and triplet signals (See S11). The coalescence temperature for the N-ethyl groups in **6** was 83 °C with an average $\Delta G^{\ddagger}$ of 21.3 kcal/mol, significantly higher than what was measured for **5**. Thus, the dipyrrinone structure must provide additional steric interactions which hinders the rotation of the amide group. This concept will be addressed further when discussing the X-ray crystal structure of **6**.

2c. Self-Association of Dipyrrinone Carboxylic Acid 6

It has been well established that the hydrogen bonding pattern of dipyrrinones can be discerned from analysis of the N–H chemical shifts in the ^{1}H-NMR spectrum.[11,14] In $CDCl_3$, the pyrrole and lactam N-H resonances are generally located below 8.0 ppm when the dipyrrinone is not participating in hydrogen bonding or it is only weakly hydrogen bonded. In the dipyrrinone homodimer, Figure 1F, the pyrrole and lactam N–H signals appear at 10.0–10.7 ppm and 10.9–11.5 ppm, respectively. Dipyrrinones hydrogen bonded to a carboxylic acid, Figure 1E, have the pyrrole and lactam N–H signals at 8.1–9.2 ppm and 10.5–11.0 ppm, respectively. However, dipyrrinones with a carboxylic acid substituent in the 9-position have been found with lactam and pyrrole N–H signals at 11.4–12.0 ppm and 10.0–10.5 ppm, respectively. These results indicate a unique hydrogen bonding pattern for 9-carboxylic acid dipyrrinone derivatives that has yet to be fully characterized due to poor solubility in non-polar organic solvents. Dipyrrinone **6**, with its enhanced solubility in non-polar organic solvents due to the C(7)-amide moieties, provides a unique opportunity to gain a better understanding of this poorly understood aggregation state.

In $CDCl_3$ at room temperature, a NOE correlation was observed between the carboxylic acid OH and the lactam N–H in the NOESY spectrum, thus indicating their close proximity to each other. The lactam and pyrrole N–H resonances for **6** in $CDCl_3$ at room temperature were located at 11.8 and 10.2 ppm, respectively, within the range previously observed for 9-carboxylic acid dipyrrinone derivatives. The chemical shifts for the lactam and pyrrole NHs as well as the carboxylic acid OH were found to be

concentration independent over the 10 mM–0.01 mM concentration range. Based on these finding, it can be concluded that the molecule prefers a dimeric aggregation state in nonpolar solvents.

Previous NMR studies in DMSO-d_6 have shown that dipyrrinones exist as a monomer and are hydrogen bonded to the solvent.[11,14] Titration of DMSO-d_6 into a $CDCl_3$ solution of **6** at room temperature showed only minor changes in the chemical shifts of the pyrrole and lactam N–H resonances at 5% DMSO-d_6, see Supporting Information. At 10% DMSO, the lactam N–H resonance was found at ~11.1 ppm and the pyrrole N–H resonance at ~10.6 ppm. With increasing amounts of DMSO-d_6, the lactam and pyrrole N–H resonances continued their transition to the locations found in 100 % DMSO-d_6, 10.2 and 11.6 ppm, respectively. At 25% DMSO-d_6, the lactam and pyrrole N–H chemical shifts are near the locations as in pure DMSO-d_6.

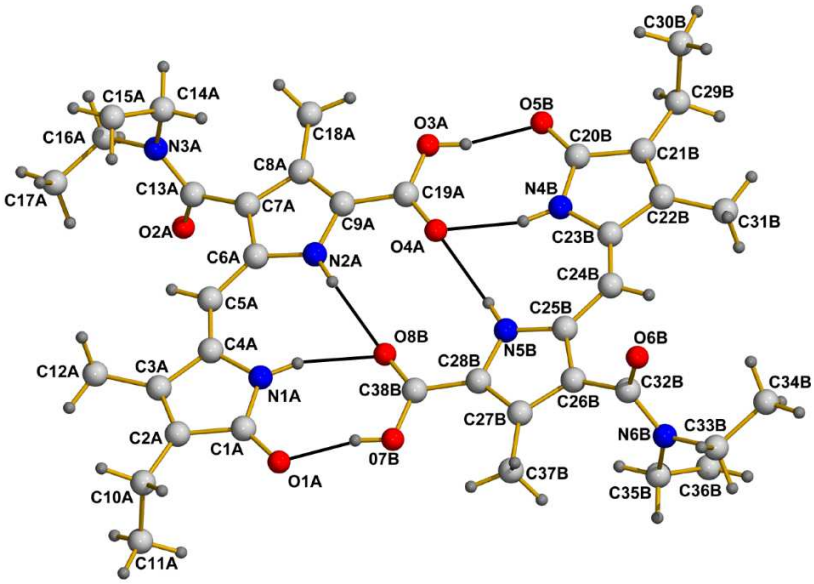
2d. Vapor Pressure Osmometry

Vapor pressure osmometry (VPO) has been found to be an effective technique to study the aggregation properties of dipyrrinones in non-polar organic solvents.[9,12,27] From such studies, the average molecular weight of the species in solution is measured providing insight into how many molecules have assembled in the aggregate. VPO measurements in chloroform at 45 °C for dipyrrinone acid **6** found a molecular weight of 740±35 g/mol which corresponds to the dimeric aggregation state (formula weight of the monomer is 359.42 g/mol). These results showing **6** exists as a dimer confirm the NMR analysis.

2e. X-Ray Crystallography

X-ray quality crystals of dipyrrinone **6** were obtained by the slow diffusion of hexanes into a 0.01 M solution of **6** in methylene chloride at room temperature. The crystallography results found that **6** adopted a dimeric structure in the solid state that has six intermolecular hydrogen bonds displaying the carboxylic acid to dipyrrinone hydrogen bonding motif (Figure 3).

A)



B)

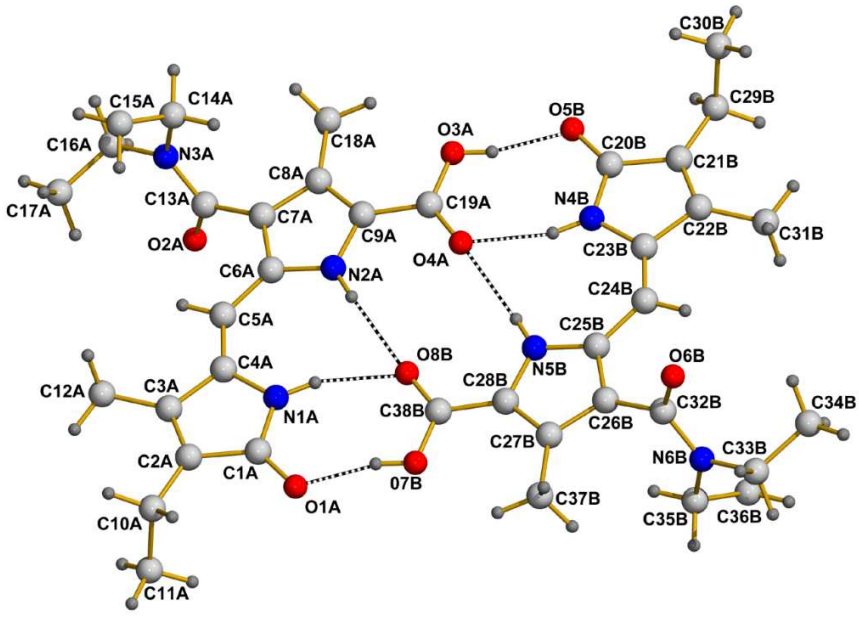


Figure 3. A) Ball and Stick representation of the X-ray structure of **6** showing the intermolecular hydrogen bond for dimeric structure A. B) Ball and Stick representation of the X-ray structure for **6** showing the intermolecular hydrogen bond for dimeric structure B. They both displayed the amide to carboxylic acid hydrogen bonding motif with a total of six intermolecular hydrogen bonds.

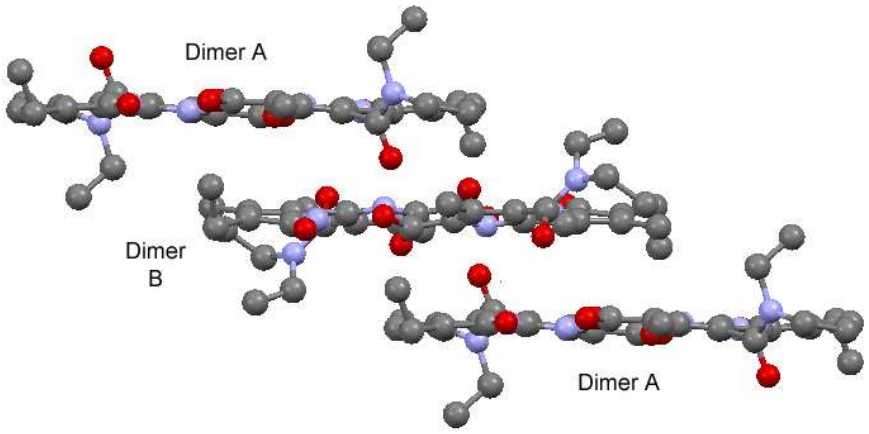


Figure 4. Ball and Stick representation of the X-ray structure of **6** showing the π-π stacking of dimers **A** and **B** and the hydrogen bonds between the amide C=O with lactam and pyrrole NH.

Interestingly, the crystal lattice of **6** contains two different dimeric structures, although the two dimer aggregates are quite similar having the same hydrogen bonding pattern (Figure 3). For dimeric structure **A**, the OH···O=C lactam and pyrrole NH···O=C distances (H···O distances) were all within the expected distances for hydrogen bonding, 1.76 and 2.14 Å, respectively (Figure 3A). The dipyrrinone backbone of **6** was found to be essentially planar in dimeric structure A with a C(4A)-C(5A)-C(6A)-N(2A) torsion angle of 3.81º (Figure 3A). In addition, the amide C=O was nearly perpendicular to the plane of the dipyrrinone with a C(6A)-C(7A)-C(13A)-O(2A) torsion angle of 67.15º which places the two ethyl substituents in two unique chemical environments and projecting towards the C(8A)-CH_3. The dimeric structure **B** found in the crystal lattice of **6** contains the same carboxylic acid to dipyrrinone hydrogen bonding motif, however the dipyrrinone backbone was found to be less planar than dimeric structure **A** with a C(4)-C(5)-C(6)-N(2) torsion angle of 20.68º. This conformation of the amide group provides a plausible explanation for the increased barrier of rotation observed in the dipyrrinone amide as compared to the pyrrole amide **5**. In pyrrole amide **5**, the two methyl groups are not impacting the rotation of the amide bond. However, the increased steric constraints associated with the C(5) moiety in the

dipyrrinone force the amide to adopt a conformation with the C=O pointing to the C(5) group and the N-R_2 moiety directed towards the C(8)-CH_3. This resulted in a lengthened pyrrole N-H···O=C dstance to 2.70 Å while the O-H···O=C and lactam N-H···O=C distances remained essentially the same 1.76 and 2.10 Å, respectively.

In the crystal lattice, dimer **B** has a dimer **A** located directly above and below as shown in Figure 4. As described above, the amide C=O in dimer **A** is nearly perpendicular to the dipyrrinone plane and has two hydrogen bonds to the lactam and pyrrole NHs in dimer **B** above or below the plane of the aggregate with lactam and pyrrole N-H···O=C distances of 2.51 ad 2.08 Å, respectively. These additional interactions are a result of crystal packing forces in the solid state and are not expected to be observed in solution.

3. Conclusions

The current study has identified a significant issue with using pyrrole amides as building blocks to prepare dipyrrinone analogs with the unexpected trans-amidation of the 7-amide dipyrrinones analogs. However, the unexpected imide formation has opened the doors to some interesting new chemistry that is currently being explored further.

Using a pyrrole amide as the key intermediate, we have prepared a 9-dipyrrinone carboxylic acid analog that is soluble in non-polar solvents. We have shown that it adopts a self-associated dimeric structure with six intermolecular hydrogen bonds in solution and solid states. The hydrogen-bonded dimers displayed an acid to amide hydrogen bonding motif. The dimeric structure appears to have a very strong self-association constant, particularly as compared to the traditional dipyrrinone self-associated dimer. Additional efforts are underway to use this new building block in self-assembly and supramolecular chemistry.

4. Experimental Section

4a. General Methods. Starting materials and solvents were purchased from commercial suppliers unless noted otherwise. ^{1}H-NMR spectra were recorded at 400 MHz, and ^{13}C spectra at 100 MHz. All chemical shifts are reported in ppm downfield from TMS (δ = 0.00 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ (δ = 77.16 ppm) for ^{13}C-NMR. Vapor pressure osmometry (VPO) measurements were performed in $CHCl_3$ at 45 °C using a concentration range of 5–36 mM with benzil used for calibration. Uv-visible and fluorescence spectra were obtained in acetonitrile.

4b. Synthesis Protocols.

Synthesis of Ethyl 4-(phenylcarbamoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (**2**). In a 250 mL round-bottom flask, ethyl acetoacetate (16.0 g, 123 mmol) was dissolved in acetic acid (40 mL). The mixture was cooled in an ice bath to 5 °C. To the mixture, $NaNO_2$ (9.75 g, 141 mmol) dissolved in 25 mL of H_2O was added to the solution dropwise over a period of 15 min. The mixture turned red-orange after the addition and was stirred vigorously overnight at room temperature.

Separately in a 500 mL round bottom flask, acetoacetanilide (23.97 g, 135 mmol) was dissolved in acetic acid (100 mL) and heated to 60 °C. Zinc powder (10.0 g) was then added followed by the slow addition of the ethyl acetoacetate and $NaNO_2$ mixture over a period of 60 min. After the slow addition of the nitrosated mixture, additional zinc powder (40.0 g) was added to the mixture in 5.0 g portions to give a total of 50.0 g, 764 mmol, zinc powder addition. Each zinc powder addition resulted in the elevation of the temperature of the mixture to 60–80 °C and the mixture was maintained at 60–80 °C for the entire zinc addition. The mixture was vigorously stirred at 60 °C for 5 h. After 5 h, the mixture was diluted by the addition of H_2O (100 mL) and stirred for 1 h at 60 °C. After 1 h, the reaction mixture was poured into a 2 L Erlenmeyer flask and diluted with 500 mL of H_2O with crushed ice to equal to 1 L total volume. The mixture was stirred vigorously for an additional 1 h. The resulting solid formed was collected by vacuum filtration, washed with cold water and air-dried. The solid product was dissolved in 500 mL of 1:1 ethyl acetate:ethanol and filtered to remove any unreacted zinc powder. The product was concentrated in vacuo and recrystallized from acetonitrile to yield the pure product (19.5 g, 68.1 mmol, 55 %). Mp

215–216 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): δ (ppm) 8.94 (s, 1H), 7.57(d, J = 7.86 Hz, 2H), 7.36 (t, J = 7.86, 2H); 7.29 (s, 1H), 7.12 (t, J = 7.25 Hz, 1H), 4.34 (q, J = 7.04 Hz, 2H), 2.60 (s, 3H), 2.52 (s, 3H), 1.38 (t, J = 7.04 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C): δ (ppm) 163.8, 138.1, 135.6, 129.1, 125.9, 124.2, 119.9, 118.7, 118.1, 60.3, 14.5, 13.4, 11.8; IR (KBr) (cm^{-1}): 747.49, 1288, 1645, 1674.7, 2934, 2978.6, 3058, 3296; MS (EI+) 148, 194, 241, 286 *m/*z; HRMS (ESI+) calcd for $C_{16}H_{18}N_2O_3$ 286.1317; found 286.1312 amu.

Synthesis of Ethyl 4-(diethylcarbamoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (**3**): Compound **3** was prepared using *N,N*-diethylacetoacetamide in place of acetoacetanilide in the procedure for **2** with no modifications. The crude product was recrystallized from methanol/water and dried to give the pure product (25.5 g, 96 mmol, 78%). Mp 128–131 °C; ^{1}H-NMR (400 MHz, $CDCl_3$, 30 °C): δ (ppm) 8.81 (s, 1H), 4.30 (q, J = 7.4 Hz, 2H), 3.48 (m, 5H), 1.37 (t, 6H), 1.16 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$, 30 °C): δ (ppm) 167.1, 161.5, 129.8, 125.7, 120.4, 117.7, 60.0, 42.8, 38.7, 14.5, 13.1, 11.9, 11.14; IR (KBr) (cm^{-1}): 1089.6, 1193.7, 1278, 1625, 1674.7, 2934, 2983.6, 3276.1; MS (EI+) 148, 194, 239, 251, 266; *m/*z; HRMS (ESI+) $C_{14}H_{22}N_2O_3$ calcd: 266.1630 amu; found: 266.1631 amu.

Synthesis of ethyl 5-formyl-3-methyl-4-(phenylcarbamoyl)-1H-pyrrole-2-carboxylate (**4**). Compound **2** (1.03 g, 3.60 mmol) was dissolved in methanol (80.0 mL). To a separate flask, ceric ammonium nitrate (8.30 g, 15.1 mmol) was dissolved in H_2O (10 mL) and then it was added slowly to the methanol mixture. The orange mixture was stirred at rt for 24 h, then it was cooled below 0°C. Water was added to the mixture to form a precipitate. The precipitate was collected via vacuum filtration and washed with cold H_2O yielding an orange compound (0.82 g, 2.70 mmol, 75%). Mp 224–227 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ (ppm); 10.04 (s 1H), 9.92 (s, 1H), 8.61 (s, 1H), 7.66 (d, J= 7.47 Hz, 2H), 7.39 (dd, J = 7.45 Hz, 2H), 7.18 (t, J = 7.47 Hz, 1H), 4.42 (q, J = 7.15 Hz, 2H), 2.68 (s, 3H), 1.42 (t, J = 7.15 Hz, 3H); ^{13}C-NMR (100 MHz, DMSO, 30 °C) δ (ppm) 181.9, 162.2, 160.7, 139.4, 131.4, 129.1, 127.8, 127.0, 124.4, 124.0, 120.0, 61.0, 14.6, 11.21; IR (KBr) (cm^{-1}): 757.4, 1094.1, 1259.1, 159.3, 1663.7, 2989.4,

3198.2, 3237.9; MS (EI+) 93, 162, 208, 238, 300 *m/z*; HRMS (ESI+) $C_{16}H_{16}N_2O_4$ calcd: 300.1110 amu; found: 300.1108 amu.

Synthesis of ethyl 4-(diethylcarbamoyl)-5-formyl-3-methyl-1H-pyrrole-2-carboxylate (**5**). In a 500 mL round bottom flask, pyrrole phenyl amide **3** (3.34 g, 12.5 mmol) was dissolved in methanol (200 mL) and water (100 mL). After stirring in an ice bath for 10 minutes, ceric ammonium nitrate (28.2 g, 51.4 mmol) was added, and the reaction mixture was stirred for an additional 30 minutes while in the ice bath. It was stirred for an additional 16 hours while allowed to slowly warm to room temperature. After 16 hours, the solution was poured over 300 mL of ice water, and allowed to stand overnight at -5 º C. The precipitate formed was filtered, washed with cold water, and dried overnight to afford the desired product (2.6 g, 9.27 mmol, 75%). Mp 121–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm) 10.27 (s, 1H), 9.94 (s, 1H), 4.41 (m, 6H), 2.61 (s, 3H), , 1.42 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm) 182.6, 163.6, 160.4, 133.3, 131.1, 123.8, 120.7, 61.3, 60.8, 14.3, 11.29; IR (KBr) (cm^{-1}): 1020, 1089, 1273, 1605, 1679, 2720, 2874, 2978, 3206, 3301; MS (EI+) 72, 162, 180, 209, 251, 280 *m/z*; HR-MS (ESI+) $C_{14}H_{20}N_2O_4$ calcd: 280.1423 amu; found: 280.1417 amu.

*Synthesis of (Z)-4-(diethylcarbamoyl)-5-((4-ethyl-3-methyl-5-oxo-1,5-dihydro-2H-pyrrol-2-ylidene)methyl)-3-methyl-1H-pyrrole-2-carboxylic acid (**6**):* In a 500 mL round bottom flask, diethyl pyrrole aldehyde **5** (2.53 g, 9.04 mmol) and 3-ethyl-4-methyl-1H-pyrrol-2-one (1.12 g, 9.04 mmol) were dissolved in 4 M KOH (100 mL) and methanol (25 mL). The reaction mixture was heated at reflux for 4 hours, then stirred overnight at room temperature. The solution was chilled in an ice bath and acidified with HCl (conc.) until red on pH paper. The resulting precipitate was collected by vacuum filtration, washed with water, and dried. The crude product was recrystallized from methylene chloride and hexanes to afford pure product (2.71g, 7.54 mmol, 83%). Mp 213–216 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): δ (ppm) 14.40 (s, 1H), 11.76 (s, 1H), 10.19 (s, 1H), 5.98 (s, 1H), 3.63 (q, J = 6.9 Hz, 2H), 3.26 (q, J = 6.9 Hz, 2H), 2.39 (q, J = 7.5 Hz, 5H), 2.08 (s, 1H), 1.29 (t, J= 7.5 Hz, 3H), 1.13 (t, J= 7.8 Hz, 3H), 1.06 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C): δ (ppm) 175.8, 166.0, 142.3, 134.7, 133.1, 127.9,

127.1, 123.4, 98.5, 43.1, 39.0, 16.7, 14.3, 13.2, 13.1, 11.5, 9.52; IR (KBr) (cm^{-1}): 1129.3, 1178.8, 1278, 1506, 1654.8, 1724.2, 2879.5, 2939, 2963.8, 3063, 3097.6, 3236.5, 3500; MS (EI+) 243, 269, 287, 315, 359 *m/z*; HRMS (ESI+) $C_{19}H_{25}N_3O_4$ calcd: 359.1845 amu; found: 359.1854 amu.

*Synthesis of 7-ethyl-3,8-dimethyl-1H-pyrrolo[3,2-f]indolizine-4,6-dione (**7**):* In a 500 mL round bottom flask, carboxylic acid dipyrrinone **6** (1.0 g, 2.79 mmol), potassium acetate (1.0 g) and sodium acetate trihydrate (1.0 g) which had been grounded finely with a mortar and pestle, were mixed. The solid mixture was heated to ~160 °C and maintained at that temperature until evolution of carbon dioxide was observed to cease. The reaction mixture was cooled to room temperature and 400 mL of water was added with vigorous stirring for one hour. The product was filtered, washed with cold acetone, and dried to give the pure product (0.377 g, 1.55 mmol, 56%). MP of 310–315 °C (dec): ^{1}H NMR (400 MHz, DMSO, 30 °C): δ (ppm) ;^{13}C NMR (100 MHz, DMSO, 30 °C): 11.48 (s, 1H), 6.86 (s, 1H), 6.64 (s, 1H), 2.31 (m, 5H), 2.13 (s, 3H), 1.06 (t, J = 8.32 Hz, 3H).δ (ppm) 168.40, 157.2, 141.9, 138.6, 136.4, 132.0, 122.2, 120.1, 115.6, 97.1, 16.5, 13.4, 11.4, 9.7; ^{1}H-NMR (400 MHz, DMSO) δ (ppm); IR (ATR or KBR) (cm^{-1}): 1657.49, 1724.41, 2874.31, 2934.39, 2960.79, 3095.95, 2321.03; MS (EI+) 99, 183, 199, 227, 242 *m/z*; HRMS (ESI+) $C_{14}H_{14}N_2O_2$ calcd: 242.1055 amu; found: 242.1056 amu.

Synthesis of 7-ethyl-3,8-dimethyl-4,6-dioxo-4,6-dihydro-1H-pyrrolo[3,2-f]indolizine-2-carboxylic acid (**8**). Compound **4** (0.30 g, 0.98 mmol) and 3-ethyl-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (0.14 g, 1.12 mmol) were dissolved in a mixture of 4M KOH (12 mL) and methanol (7 mL) resulting in a yellow mixture. The reaction mixture was heated at reflux under N_2 atmosphere for 24 h. After 24 h, the solution was cooled to rt then acidified with HCl (conc.) until red on pH paper, resulting in a yellow precipitate (0.27 g, 0.94 mmol, 96 %). Mp 345–351 °C. ^{1}H NMR (400 MHz, DMSO, 30 °C) δ (ppm) 12.33 (s, 1H), , 6.57(s, 1H), 2.59 (s, 3H), 2.31 (q, J = 7.87 Hz, 2H), 2.13 (s, 3H), 1.04 (t, J = 7.48Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 30 °C): δ (ppm) 168.2, 162.7, 157.0, 141.9, 141.2, 137.6, 133.3, 128.2, 123.7, 116.1, 96.2, 16.6, 13.4, 11.4, 9.81; IR (ATR) (cm^{-1}): 3330 (w), 3019 (w), 1732 (s), 1657 (s), 1525 (w), 1470 (m), 1292

(s), 1275 (s), 1185 (m), 1107 (m), 775 (m), 704 (m); HR-MS (ESI+) $C_{15}H_{14}N_2O_4$ calcd: 286.0954 amu; found 286.0950 amu.

*Synthesis of Ethyl 7-ethyl-4,6-dihydro-3,8-dimethyl-4,6-dioxo-1H-pyrrolo[3,2-f]indolizine-2-carboxylate (**9**):* In a 50 mL round bottom flask, compound **4** (0.56 g, 2mmol) and 3-ethyl-4-methyl-1H-pyrrol-2-one (0.275 g, 2.2 mmol) were dissolved in anhydrous ethanol (10 mL) and then DBU (1.5 mL) was added. The reaction mixture was heated at reflux for 24 hrs. After refluxing, the reaction mixture was cooled in an ice bath, then acetic acid (1.5 mL) was added followed by water (10 mL). The solution was chilled at -5 ºC overnight, and the precipitate formed was filtered, and dried to afford the desired product (0.36 g, 1.14 mmol, 57%). Mp 315–320 ºC: ^{1}H NMR (400 MHz, CDCl3, 30 °C) δ (ppm) 9.08 (s. 1H), 6.37 (s, 1H), 4.40 (q, J = 7.20 Hz, 2H), 2.76 (s, 3H), 2.45 (m, 2H), 2.15 (s, 3H), 1.43 (t, J =7. 61 Hz, 3H), 1.16 (t, J = 7.61 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C): δ (ppm) 161.7,142.2, 142.1, 140.3, 137.1, 134.9, 130.1, 122.7, 117.2, 106.2, 94.1, 61.1, 16.8, 14.4, 13.1, 11.2, 9.61; IR (ATR) (cm^{-1}): 3284 (w), 3065 (w), 2985 (w), 2870 (w), 1736 (s), 1699 (s), 1665 (w), 1453 (w), 1286 (s), 1271 (s), 1212 (m), 1106 (m), 1028 (w), 884 (w); HR-MS (EI+) $C_{17}H_{18}N_2O_4$ calcd: 314.1267 amu; found: 314.1445 amu.

5. ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website:

^{1}H NMR, ^{13}C NMR, UV-visible, and fluorescent spectra as well as X-ray data and further computational details.

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7. Notes

The authors declare no competing financial interest.

8. Acknowledgements

The authors would like to acknowledge funding from the University of West Florida Office of Undergraduate Research and the University of West Florida Office of Research and Sponsored Programs

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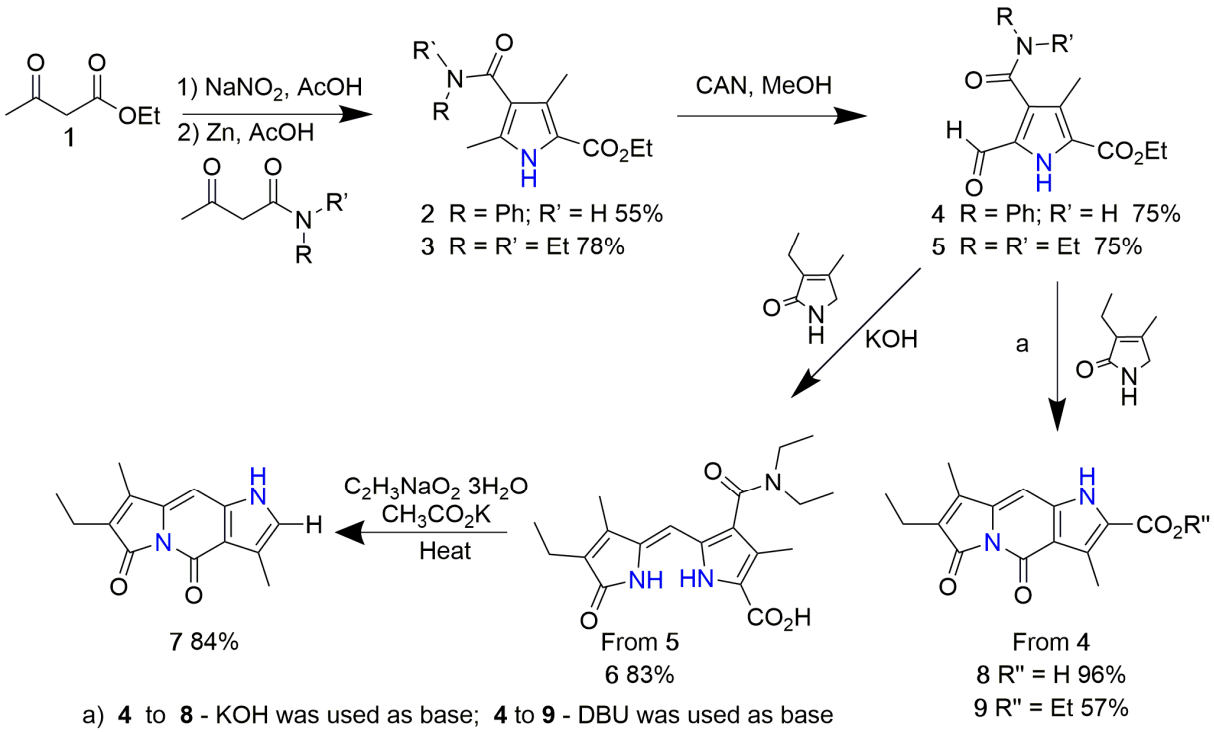

a) **4** to **8** - KOH was used as base; **4** to **9** - DBU was used as base