Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Short, Efficient Syntheses of Pyrrole α-Amides

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Version of record first published: 31 Oct 2008

To cite this article: Michael T. Huggins, Patrick S. Barber, David Florian & William Howton (2008): Short, Efficient Syntheses of Pyrrole α-Amides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:23, 4226-4239

To link to this article: http://dx.doi.org/10.1080/00397910802323130

Synthetic Communications®, 38: 4226–4239, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802323130

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Short, Efficient Syntheses of Pyrrole α-Amides

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Abstract: We report an inexpensive method for producing a diverse array of pyrrole amides on a large scale and in good yield. The synthetic sequence allows for the preparation of a number of pyrrole amide derivatives in excellent to moderate yields from commercially available compounds. The diketene adduct, in the presence of an amine nucleophile, provides an excellent method for acetoacetylation. For diversity and versatility, a second method utilizing Meldrum's acid was successfully employed for the preparation of additional acetoacetamide derivatives. Using the Knorr pyrrole synthesis, pyrrole amides were readily prepared from the oxime of the acetoacetamides.

Keywords: Diketene, Knorr pyrrole synthesis, Meldrum's acid, pyrrole amide, synthesis

INTRODUCTION

Pyrrole amides are well known for their biological activity, and many are presently either being used or pursued as herbicides,[1] cancer treatments,[2] or inhibitors of numerous enzymes.[3–5] In addition, the pyrrole amide motif has also been used by several research groups to develop receptors for anions.[6–11] In general, there have been many methods used to prepare the pyrrole amide moiety, but most have started from easily accessible pyrrole esters that can be synthesized via numerous routes.

Received May 18, 2008.
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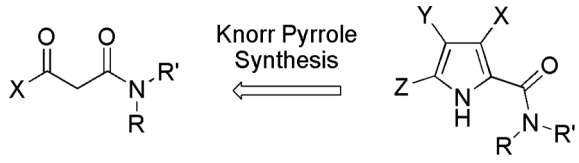


Figure 1. Target molecules.

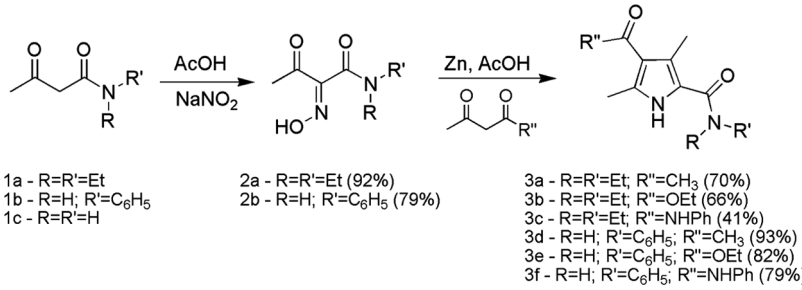
These methods are typically performed on a small scale (usually a few grams at most), often result in low yields, and can require extensive purification to obtain pure products.

We are interested in using the pyrrole amide motif for a wide range of potential applications that require the ability to control the substituents on all positions of the pyrrole. Specifically, we are interested in developing a synthetic procedure that allows for control of the substituents on the pyrrole core as well as the amide; see Fig. 1. There have been only a few reports showing the preparation of the pyrrole core with the amide group already in place.[12–15] Each used acetoacetamides under Knorr pyrrole synthesis conditions[14,16] to prepare the pyrrole α-amides. However, these reports did not explore the potential for controlling the diversity of the substituents on either the pyrrole core or the amide moiety. In the following, we report our results in developing this synthetic route to produce a wide array of pyrrole amide derivatives, which results in the ability to control the functionality on the pyrrole core.

RESULTS AND CONCLUSIONS

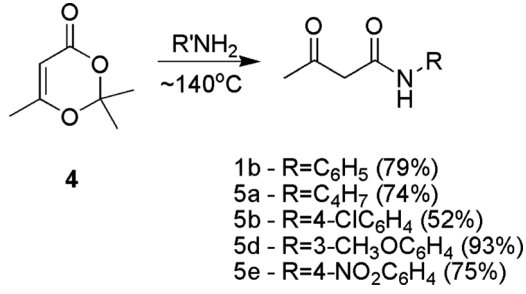
Our initial efforts used three commercially available acetoacetamide derivatives to probe the versatility of the synthetic route. Reaction of the tertiary and secondary acetoacetamides **1a** and **1b** with sodium nitrite in acetic acid gave the corresponding oximes **2a** and **2b** in high yields, 92% and 79% respectively. Unfortunately, all attempts at using the primary acetoacetamide **1c** failed to produce the desired oxime derivative. Reaction of oximes **2a** and **2b** under Knorr conditions with three different β-dicarbonyl derivatives resulted in moderate to high yields of the various pyrrole α−amide derivatives **3a–f**, see Scheme 1. Generally, the observed yields were lower when using the oxime of the tertiary amide, **2a**. The conditions for both steps of the reaction sequence are amenable to being performed on a relatively large scale (50 + g).

For this method to be truly versatile, we needed to develop a method for preparing pyrrole α-amide analogs with control of the N-alkyl



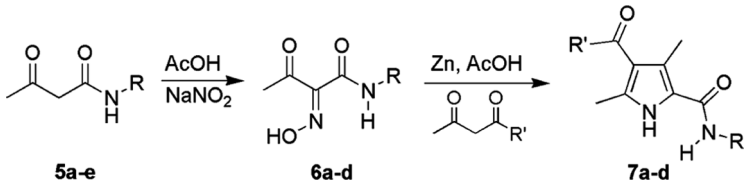
Scheme 1. Preparation of pyrrole amides from commercially available acetoacetamides.

substituents as well as substituents on the entire pyrrole core. Achieving diversity of N-alkyl substituents requires the ability to make acetoacetamides with varying N-alkyl substituents. Currently, there are several synthetic routes in the literature for preparing acetoacetamides: Meldrum's acid[17,18] or diketene[19–21] (commonly used as a diketene acetone adduct) are two of the most commonly used precursors. Reaction of the diketene adduct **4** and various primary amines[21] resulted in acceptable to excellent yields, 52–93%, of the corresponding acetoacetamide derivative (Scheme 2). For most cases, use of dry xylenes was the preferred solvent. In a few instances, use of dimethylformamide (DMF) as the solvent resulted in higher yields and easier isolation of the desired product. Most of these acetoacetamide derivatives were easily converted into their corresponding pyrrole amide derivatives **7a–d** in respectable yields (Table 1). Fortunately, it was determined that the oxime formation and Knorr pyrrole synthesis sequence can be performed in one pot, which greatly increased the overall yield. For example, the stepwise preparation of pyrrole **7a** resulted in an overall yield of 29% from the acetoacetamide,



Scheme 2. Preparation of acetoacetamide derivatives from diketene adduct.

Table 1. Synthesis of pyrrole derivatives from acetoacetamides prepared from diketene adduct **4**



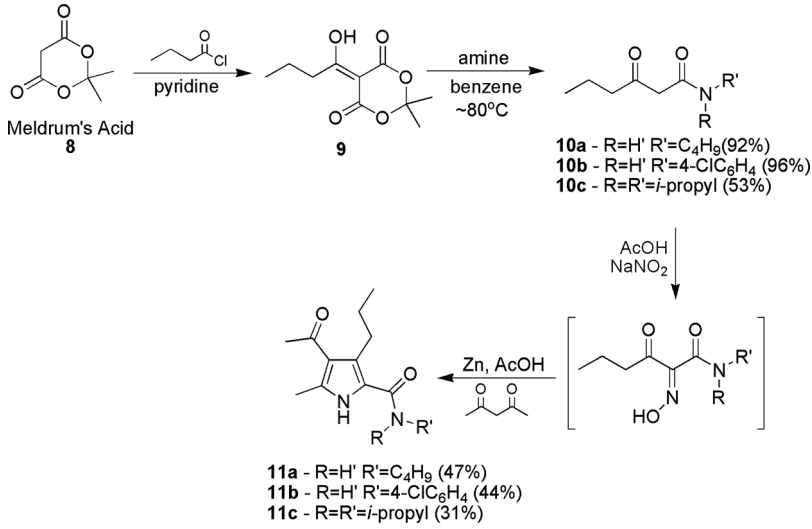
	R	R′	Yield (%)	
5a	C_4H_7	CH_3	6a 51%	7a 57%
5a	C_4H_7	CH_3	*	7a 57%
5a	C_4H_7	OEt	*	7b 58%
5b	2-pyridyl		6b 35%	**
5c	4-ClC_6H_4	OEt	6c 52%	7c 34%
5d	3-$CH_3OC_6H_4$	OEt	*	7d 56%
5e	4-$NO_2C_6H_4$		6d 75%	**

*Reaction was conducted via one-pot reaction sequence.
**Reaction failed give the desired product.

while the same compound was prepared in 57% overall yield when the crude oxime reaction mixture was used directly in the pyrrole synthesis. Isolation of the oxime intermediates typically resulted in loss of product, which was mainly responsible for the decrease in yields. With this one-pot method, care must be taken with the quantities of the sodium nitrite and β-keto derivative used in the reactions. A large excess of either material occasionally resulted in the formation of additional pyrrole products, which are difficult to separate from the desired product. This was particularly evident when using ethyl acetoacetate as the β-keto derivative.

The 4-nitrophenyl and 2-pyridyl derivatives both failed to yield the desired pyrrole amides; in both cases there were indications of these moieties being reduced under the Knorr pyrrole synthesis condition, zinc in hot acetic acid. Additionally, the 4-chlorophenyl derivative, **7c**, suffered from limited solubility, which was responsible for the low yield.

Use of the acetoacetamide derivatives prepared from diketene-acetone adduct resulted in pyrroles with methyl groups at the 3- and 5-positions. Unfortunately, this can lead to limited solubility of the desired pyrrole products, as noted in attempts to prepare the 4-chlorophenyl amide analog, **7c**. Therefore, we sought a method for preparing analogs



Scheme 3. Synthesis of pyrrole derivatives from Meldrum's acid.

that would allow changing the 3-methyl group to other alkyl and aryl substituents. Use of 4-substituted acetoacetamide derivatives provides access to modification at the 3-position of the pyrrole ring. Reaction of the Meldrum's acid, **8**, with an appropriate acid chloride[22] followed by addition of a corresponding amine allows for relatively easy preparation of the desired 4-substituted acetoacetamide derivatives. Specifically, reaction of Meldrum's acid with butanoyl chloride resulted in a 90% yield of the desired acylated Meldrum's acid product, **9** (Scheme 3). Aminolysis of **9** performed in anhydrous benzene resulted in good yields (53–96%) of the corresponding 3-oxo-hexanamide derivatives **10a–c**. Using the previously discussed Knorr pyrrole synthesis method, the corresponding pyrrole analogs **11a–c** were prepared in 31–47% yield, over two synthetic steps. In the best case (**11b**), the synthesis resulted in a 41% overall yield of the pyrrole (four total synthetic steps).

CONCLUSIONS

In this article, we present our results for the preparation of pyrrole α-amide derivatives. The synthetic routes allow for controlling the substituents on the pyrrole core as well as modification of the amide substituents. Preparation of the required acetoacetamide derivatives from either the diketene adduct or Meldrum's acid provides the flexibility in adjusting

substituents on pyrrole and amide moieties. In addition, these methods allow for the production of relatively large quantities of pyrrole α-amide derivatives in good yield and in short facile synthesis (three to four synthetic steps). The synthetic procedures used in the preparation of the pyrrole α-amides are amenable to scale-up. Successful syntheses have been carried out to produce as much as 40 g of the resulting pyrrole α-amide derivatives.

EXPERIMENTAL PROCEDURES

General Methods

Nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$, unless otherwise noted, with tetramethylsilane (TMS) as internal reference standard using a Varian 300-MHz MercuryPlus NMR. Chemical shifts are reported in δ (ppm) referenced to TMS. The reported melting points are uncorrected. Meldrum's acid was purchased from Acros and recrystallized from toluene. Xylenes and benzene were dried over phosphorus pentachloride and freshly distilled. UltraDry DMF was purchased from Acros. All other solvents and materials were purchased from common sources and used as received.

General Synthetic Procedures

Method A1: Preparation of Acetoacetamide Derivatives[21]

A solution of an amine (20 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmol) in 10 mL of dry xylenes was placed in a 50-mL Erlenmeyer flask equipped with magnetic stirring. The flask was immersed in a preheated oil bath at 150 °C and stirred vigorously for 30 min. Upon cooling to room temperature, the product precipitated. The product was collected via vacuum filtration and recrystallized in hot xylenes.

Method A2: Preparation of Acetoacetamide Derivatives

A solution of an amine (20 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmol) in 10 mL of DMF was placed in a 50-mL Erlenmeyer flask equipped with magnetic stirring. The flask was immersed in a preheated oil bath at 150 °C and stirred vigorously for 30 min. Upon cooling, the solution was poured into brine (300 mL) and extracted with methylene

chloride (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL), 10% HCl (2 × 50 mL), and saturated sodium bicarbonate (50 mL) and dried over anhydrous sodium sulfate. After decanting from the drying agent, the solvent was removed by rotary evaporation, yielding the desired product.

Method B (Preparation of Oxime Derivatives)

A solution of acetoacetamide (20 mmol) in acetic acid (50 mL) was placed in a round-bottomed flask equipped with magnetic stirring and placed in an ice water bath. An excess of sodium nitrite (~40 mmol) dissolved in a minimal amount of water was added dropwise over a 15-min period. The resulting solution was stirred for 2 h in an ice water bath followed by an additional hour of stirring at room temperature. If the product precipitated from the reaction mixture, then the product was collected via vacuum filtration. Otherwise, the resulting reaction mixture was diluted with water (200 mL) and extracted with methylene chloride (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL), 10% HCl (2 × 50 mL), and saturated sodium bicarbonate (50 mL) and dried over anhydrous sodium sulfate. After decanting, the solvent was the removed by rotary evaporation to yield the desired product. Crude products were used directly without further purification.

Method C (Pyrrole Synthesis)

A solution of oxime (20 mmol) in acetic acid (50 mL) was placed in a three-neck, round-bottom flask equipped with a condenser and magnetic stirrer. The dione (20 mmol) was added along with a slow addition of excess zinc dust (~80 mmol) to maintain a temperature of 80–85 °C. After the addition was completed, the resulting solution was heated at reflux for 2 h. The hot reaction mixture was poured into ice water (1500 mL) and allowed to crystallize overnight in the refrigerator. The solid product was collected via suction filtration and recrystallized from methanol/water to give the desired product.

Method D (One-Pot Pyrrole Synthesis)

A solution of acetoacetamide (20 mmol) in acetic acid (50 mL) was placed in a three-neck, round-bottom flask equipped with a condenser and magnetic stirrer and placed in an ice water bath. An excess of sodium

nitrite (~40 mmol) dissolved in a minimal amount of water was added dropwise over a 15-min period. The resulting solution was stirred for 2 h in an ice water bath followed by an additional hour of stirring at room temperature. The dione (20 mmol) was added all at once, followed by the slow addition of excess zinc dust (~80 mmol) such that the temperature was maintained at 80–85 °C. Upon completion of the addition, the reaction mixture was heated at reflux for 2 h. The hot solution was poured into ice water (1500 mL) and allowed to crystallize overnight in the refrigerator. The solid product was collected via suction filtration and recrystallized from methanol/water to give the desired product. Analytically pure samples were prepared either by multiple recrystallizations or radial chromatography (CH_2Cl_2/CH_3OH).

Method E (Aminolysis of Acyl Meldrum's Acid Derivative, 9)[22,23]

A solution of the corresponding amine (20 mmol) and a slight excess of freshly prepared acyl Meldrum's acid derivative[22,24] (22 mmol) in 100 mL of anhydrous benzene was heated at reflux for 4 h. The solvent was removed by rotary evaporation to yield the desired crude product. The crude product was used in the respective pyrrole synthesis without further purification.

Data

4-Acetyl-*N*,*N*-diethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxamide (**3a**)

The crude product was recrystallized from methanol and water and dried in vacuo to yield 3.3 g (70%) of pure product. It had a mp of 175–179 °C (lit.[12] = 173–174°); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.09, 13.38, 14.57, 30.75, 41.11, 120.29, 120.91, 121.83, 137.17, 165.12, 195.07 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, 6H, 7.0 Hz), 2.15 (s, 3H), 2.27 (s, 3H), 2.29 (s, 3H), 3.41 (q, 4H, 7.0 Hz), 11.00 (bs, 1H) ppm.

4-Carboethoxy-*N*,*N*-diethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxamide (**3b**)

The crude product was recrystallized from methanol and water and dried in vacuo to yield 3.5 g (66%) of pure product. It had a mp of 108–110 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.93, 13.76, 13.94, 14.69, 41.36, 59.34, 111.15, 121.81, 121.84, 138.28, 165.52, 166.2 ppm; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.17 (t, 7.0 Hz, 6 H), 1.34 (t, 7.0 Hz, 3 H), 2.25 (s, 3 H), 2.39 (s, 3 H), 3.53 (q, 7.0 Hz, 4 H), 4.26 (q, 7.0 Hz, 2 H), 10.59 (bs, 1 H) ppm; IR (KBr) 779, 1267, 1605, 1698, 2976, 3242 cm^{-1}; MS (EI+) 72, 167, 194 (base peak), 266 m/z. HR-MS (EI+) $C_{14}H_{22}N_2O_3$, calcd. 266.1630 amu; found 266.1632 amu.

N^2,N^2Diethyl-3,5-dimethyl-N^4-phenyl-1*H*-pyrrole-2,4-dicarboxamide (**3c**)

The crude product was recrystallized from water and methanol and dried in vacuo to yield 6.45 g (40.5%) of pure product. It had a mp of 149–156 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.68, 12.42, 13.49, 41.12, 116.34, 118.05, 119.96, 121.82, 123.65, 128.74, 133.05, 138.56, 165.02, 165.27 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 6H, 7.0 Hz), 2.23 (s, 6H), 3.5 (q, 4H, 7.0 Hz), 7.06 (t, 1H, 7.0 Hz), 7.28 (t, 2H, 7.5 Hz), 7.63 (d, 2H, 8.0 Hz), 7.83 (bs, 1 Hz), 10.59 (bs, 1H) ppm; IR (KBr) 759, 1441, 1598, 1638, 3249, cm^{-1}; MS (EI+) 148, 221 (base peak), 313 m/z. HR-MS (EI+) $C_{18}H_{23}N_3O_2$ calcd. 313.1790 amu; found 313.1793 amu.

4-Acetyl-3,5-dimethyl-N-phenyl-1H-pyrrole-2-carboxamide (**3d**)

The crude product was recrystallized from methanol and water and dried in vacuo to give 28.6 g (93%) of pure product. It had a mp of 235–238 °C (lit.[25] = 237–238 °C); ^{13}C NMR (75 MHz, DMSO) δ 12.54, 14.65, 31.19, 119.77, 121.93, 122.09, 123.22, 125.13, 128.72, 136.80, 139.20, 159.84, 194.41 ppm; ^{1}H NMR (300 MHz, DMSO) δ 2.38 (s, 3H), 2.49 (s, 6H), 7.07 (t, 1H, 7.0 Hz), 7.34 (t, 2H, 7.5 Hz), 7.67 (d, 2H, 7.5 Hz), 9.58 (bs, 1H), 11.68 (bs, 1H) ppm.

Ethyl 2,4-dimethyl-5-(phenylcarbamoyl)-1H-pyrrole-3-carboxylate (**3e**)

The crude product was recrystallized from methanol and water and dried in vacuo to give 11.49 g (82%) of pure product. It had a mp of 182–185 °C (lit.[25] = 178–179 °C); ^{13}C NMR (75 MHz, DMSO) δ 11.90, 13.70, 14.35, 58.84, 111.76, 119.75, 121.90, 123.18, 125.88, 128.69, 137.36, 139.18, 159.65, 164.87 ppm; ^{1}H NMR (300 MHz, DMSO) δ 1.28 (t, 3H, 7.0 Hz), 2.45 (s, 3H), 2.48 (s, 3H), 4.19 (q, 2H, 7.0 Hz), 7.06 (t, 1H, 7.5 Hz), 7.33 (t, 2H, 8.5 Hz), 7.66 (d, 2H, 8.5 Hz), 9.52 (bs, 1H), 11.71 (bs, 1H) ppm.

3,5-Dimethyl-*N*,*N*'-diphenyl-1H-pyrrole-2,4-dicarboxamide (**3f**)

The crude product was recrystallized from methanol and water and dried in vacuo to yield 12.3 g (79%). It had a mp of 236–240 °C (lit.[26] = 237–240 °C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.96, 13.01, 120.01, 120.25, 12.45, 121.59, 123.83, 123.90, 124.86, 129.31, 129.40, 132.84, 139.77, 140.11, 160.30, 164.97 ppm; ^{1}H NMR (300 MHz, DMS0-d_6) δ 2.37 (s, 3H), 2.41 (s, 3H), 7.04 (m, 2H), 7.31 (m, 4H), 7.66 (m, 4H), 9.38 (bs, 1H), 9.62 (bs, 1H), 11.45 (bs, 1H) ppm.

4-Acetyl-N-butyl-3,5-dimethyl-1H-pyrrole-2-carboxamide (**7a**)

The crude product was recrystallized from methanol and water and dried in vacuo to give 2.5 g (57%) of pure product. It had a mp of 158–161 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.83, 13.89, 15.18, 20.30, 31.44, 31.95, 39.58, 121.94, 122.30, 123.02, 136.97, 162.28, 195.73 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, 7.5 Hz), 1.40 (m, 2H), 1.60 (m, 2H), 2.43 (s, 3H), 2.54 (s, 6H), 3.54 (q, 2H, 7.0 Hz), 5.87 (t, 1H, 5.0 Hz), 10.72 (bs, 1H) ppm; IR (KBr) 1412, 162, 1639, 3241, 3272 cm^{-1}; Anal. calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N; 11.85. Found: C, 65.96; H, 8.34; N; 11.88.

Ethyl 5-(butylcarbamoyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**7b**)

The crude product was recrystallized from methanol and water and dried in vacuo to give 8.9 g (58%) of pure product. It had a mp of 145–148 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.00, 13.97, 14.12, 14.35, 20.10, 31.76, 39.35, 59.36, 117.91, 121.74, 122.47, 138.07, 162.15, 165.78 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, 7.5 Hz), 1.35 (t, 3H, 7.0 Hz), 1.39 (m, 2H), 1.59 (m, 2H), 2.50 (s, 3H), 2.55 (s, 3H), 3.45 (q, 2H, 6.5 Hz), 4.28 (q, 2H, 7.0 Hz), 5.78 (bs, 1H), 9.97 (bs, 1H) ppm; IR (KBr) 1091, 1262, 1650, 1689, 3262 cm^{-1}. Anal. calcd. for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N; 10.52. Found: C, 63.02; H, 8.11; N; 10.37.

Ethyl 5-[(4-chlorophenyl)carbamoyl]-2,4-dimethyl-1H-pyrrole-3-carboxylate (**7c**)

The crude product was recrystallized from methanol and water and dried in vacuo to give 1.23 g (34%) of pure product. It had a mp of 248–249 °C (lit.[27] = 250–251 °C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.36, 14.49, 14.59, 59.76, 113.45, 121.69, 123.81, 129.25, 129.62, 136.32, 138.93, 159.97,

165.62 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, 3H, 7.0 Hz), 2.48 (s, 3H), 2.69 (s, 3H), 4.30 (q, 2H, 7.0 Hz), 7.31 (m, 2H), 7.54 (m, 3H), 9.96 (bs, 1H) ppm.

Ethyl 5-[(3-methoxyphenyl)carbamoyl]-2,4-dimethyl-1H-pyrrole-3-carboxylate (**7d**)

The crude product was recrystallized from methanol and water and dried in vacuo to give 5.5 g (56%) of pure product. It had a mp of 140–143 °C (lit.[27] = 141–143 °C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.31, 14.35, 14.55, 55.46, 59.68, 106.47, 110.21, 112.68, 113.20, 121.90, 123.77, 129.89, 138.87, 139.10, 160.19, 160.34, 165.75 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, 7.0 Hz), 2.47 (s, 3H), 2.69 (s, 3H), 3.81 (s, 3H), 4.30 (q, 2H, 7.0 Hz), 6.69 (m, 1H), 7.06 (m, 1H), 7.32 (m, 1H), 7.59 (s, 1H), 10.31 (bs, 1H) ppm.

4-Acetyl-*N*-butyl-5-methyl-3-propyl-1*H*-pyrrole-2-carboxamide (**11a**)

The crude product was recrystallized in methanol and water and dried in vacuo to yield 1.5 g (47%). It had a mp of 85–88 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.82, 14.43, 15.32, 20.26, 24.52, 28.51, 31.34, 31.77, 39.47, 121.77, 122.89, 127.89, 136.95, 162.20, 195.33 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H, 7.0 Hz), 1.02 (t, 3H, 7.0 Hz), 1.41 (m, 4H), 1.61 (m, 4H), 2.43 (s, 3H), 2.53 (s, 3H), 2.90 (m, 2H), 3.45 (q, 2H, 7.0 Hz), 5.84 (broad triplet, 1H, 4.8 Hz), 10.06 (bs, 1H) ppm; IR (KBr) 1071, 1262, 1416, 1634, 2932, 3241 cm^{-1}; MS (EI+) 176, 192, 249, 264 (base peak) m/z. HR-MS (EI+) $C_{15}H_{24}N_2O_2$ calcd. 264.1838 amu; found 264.1833 amu.

4-Acetyl-N-(4-chlorophenyl)-5-methyl-3-propyl-1H-pyrrole-2-carboxamide (**11b**)

The crude product was recrystallized in methanol and water and dried in vacuo to yield 0.83 g (44%) of pure product. It had a mp of 155–156 °C. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.55, 15.52, 24.65, 28.55, 31.43, 121.48, 121.58, 122.83, 129.28, 129.70, 136.21, 137.77, 160.09, 195.42 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, 3H, 7.0 Hz) 1.71 (m, 2H), 2.44 (s, 3H), 2.49 (s, 3H), 3.04 (t, 2H, 8.0 Hz), 7.31 (d, 2H, 8.5 Hz), 7.50 (d, 3H, 8.5 Hz), 7.68 (bs, 1H), 10.43 (bs, 1H) ppm; IR (KBr) 826, 1065, 1337, 1490, 1626, 2950, 3245 cm^{-1}; MS (EI+) 127, 192 (base peak),

318 m/z. HR-MS (EI +) $C_{17}H_{19}N_2O_2Cl$ calcd. 318.1135 amu; found 318.1132 amu.

4-Acetyl-N,N-diisopropyl-5-methyl-3-propyl-1H-pyrrole-2-carboxamide (**11c**)

The crude product was recrystallized from methanol and water and dried in vacuo to yield 0.62 g (31%) of pure product. It had a mp of 177–179 °C. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.49, 15.19, 21.17, 24.36, 28.45, 30.99, 48.90, 120.19, 123.44, 123.87, 136.45, 166.13, 195.38 ppm; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, 7.0 Hz), 1.42 (d, 12H, 6.5 Hz), 1.49 (m, 2H), 2.31 (s, 3H), 2.37 (s, 3H), 2.63 (m, 2H) 3.87 (t, 2H, 6.0 Hz) 10.56 (bs, 1H) ppm; IR (KBr) 965, 1317, 1441, 1611, 1636, 2973, 3198 cm^{-1}. Anal. calcd. for $C_{17}H_{28}N_2O_2$: C, 69.83; H, 9.65; N; 9.58: Found: C, 69.87; H, 9.40; N; 9.45.

ACKNOWLEDGMENTS

M. T. H. thanks the American Chemical Society's Petroleum Research Fund (PRF 44304-GB4) and the University of West Florida (UWF) Research Foundation for their generous support of this work. P. S. B. was a Morelli-Quinteros Undergraduate Research Fellow. D. F. was a Project SEED summer I and II student at UWF and thanks the American Chemical Society for its support.

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