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The Application of Disubstituted Vinylogous Iminium Salts and Related Synthons to the Regiocontrolled Preparation of Unsymmetrical 2,3,4-Trisubstituted Pyrroles[1]

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Abstract: *Reactions of 2,3-disubstituted chloropropeniminium salts and related synthons with ethyl glycinate, ethyl N-methylglycinate, and ethyl N-benzylglycinate have been studied under acidic, basic and neutral conditions. Such reactions have resulted in efficient and selective methodology for the synthesis of unsymmetrical 2,3,4-trisubstituted pyrrole systems.*

Over the last several years a significant part of our research efforts have been directed at developing regiochemically controlled syntheses of substituted pyrroles which rely on the condensation of vinylogous iminium salts or their derivatives with α-aminocarbonyl compounds. To this end, we have reported[2,3,4] successful syntheses of 2,3-, 2,4- and 2,5-disubstituted pyrroles. This interest has come from the reports of pyrrole containing substances[5,6,7] which have been isolated from a variety of marine organisms. Compounds 1-4 illustrate some examples of these interesting structural types.

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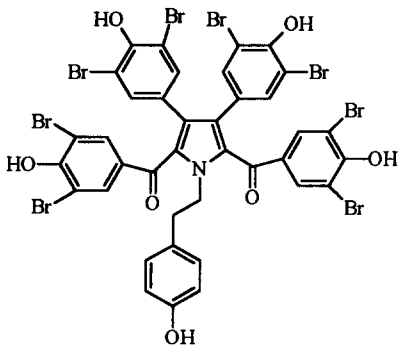
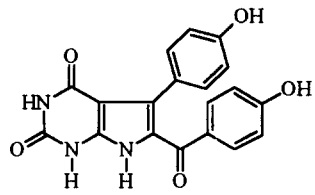


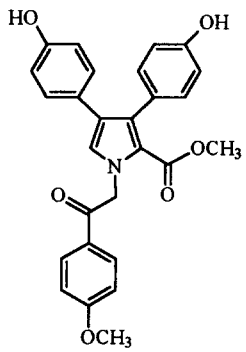
Polycitone A

1



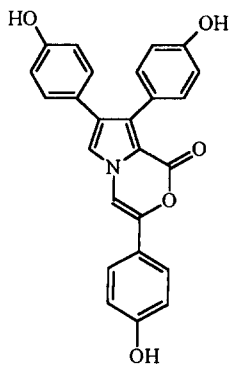
Rigidin

2



Lamellarin O

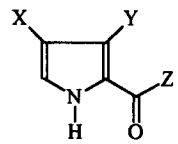
3



Lukianol A

4

All of these natural products could be synthesized from a trisubstituted pyrrole of the following generalized structure:

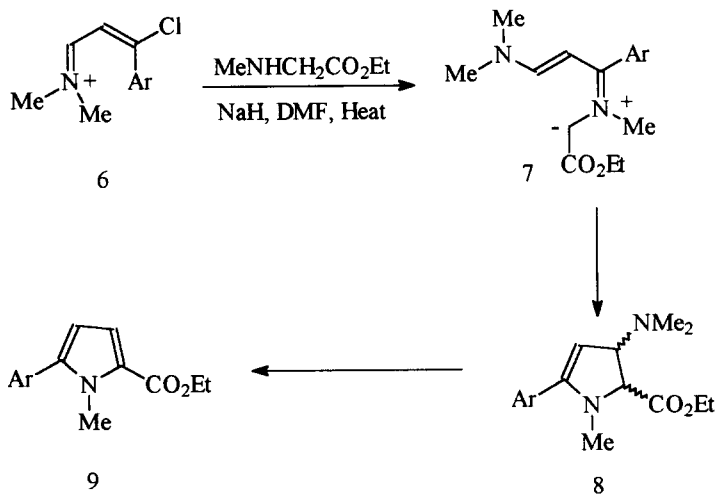


5

If this regioisomer (2,3,4-trisubstituted) can be efficiently and selectively obtained, subsequent substitution at C-5 and nitrogen could be accomplished in a straight forward manner by electrophilic and nucleophilic substitution conditions respectively. Modern synthetic methods have been lacking for the construction of unsymmetrical trisubstituted pyrroles and herein we present a versatile and efficient method for the preparation of intermediates such as (5) from simple acyclic precursors. Some of our previous work in this area involved the condensation of esters of glycine or ethyl N-methylglycinate with 3-aryl-3-chloropropeniminium salts to give 2,5-disubstituted pyrrole systems (Scheme 1). Since chloropropeniminium salts are one of the important

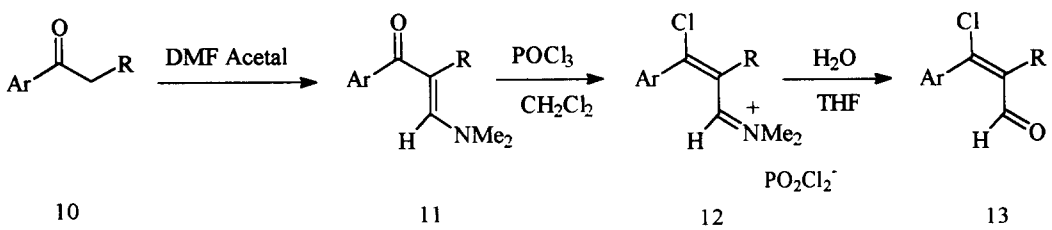
building blocks for such pyrrole forming reactions, the preparation of disubstituted salts **(12)** is required to extend this chemistry to the synthesis of trisubstituted pyrroles. Scheme 2 represents the established method for preparing such compounds[8] as well as related analogs.

Scheme 1



Where Ar = aromatic group

Scheme 2



Scheme 2 allows for the preparation of a vinylogous amide **(11)** and a β-chloroenal **(13)** which are also potential building blocks for pyrrole synthesis. With this in mind, a number of vinylogous amides were prepared by condensing the appropriate ketones with N,N-dimethylformamide dimethylacetal (Table 1). All of these reactions proceeded in a relatively clean manner to give the respective vinylogous amide.

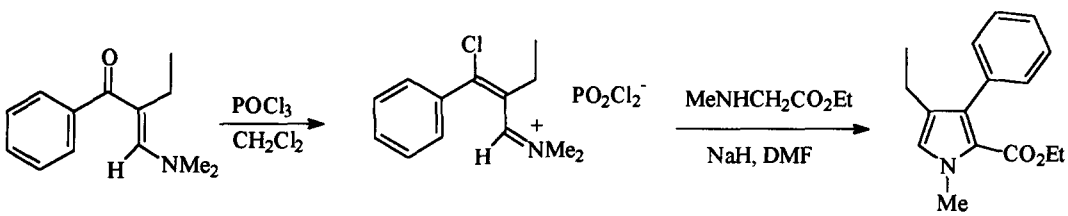
Compound **11a** (ethyl analog) was chosen as our model compound for subsequent exploratory studies and was converted to the chloropropeniminium salt by reaction with phosphorous oxychloride in methylene chloride. This iminium salt was not a well defined solid and was usually generated and used immediately without further purification. In addition, treatment of this iminium salt with water/THF afforded the corresponding β-chloroeneal in 84%

yield. When this crude iminium salt product was condensed with ethyl N-methylglycinate in the presence of sodium hydride and DMF, a 60% yield of a trisubstituted pyrrole (Scheme 3) was obtained after radial chromatography.

Table 1. Preparation of Vinylogous Amide Analogs

Compound	Ar	R	% Yield
11a	Ph	Et	88
11b	Ph	Me	98
11c	Ph	n-Pr	41
11d	Ph	n-Bu	43
11e	Ph	Ph	94
11f	4-MeOPh	Me	96

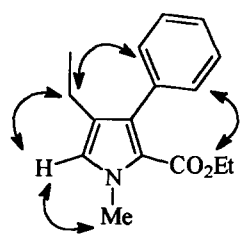
Scheme 3



11a 12a 14a

Previous work on the monosubstituted system (Scheme 1) demonstrated that the 2,5-disubstituted pyrrole isomer was preferred for such systems and this would suggest that the 2,4,5-trisubstituted pyrrole isomer was the expected product for the more highly substituted system. A NOESY NMR experiment was run on the purified pyrrole product (**14a**) and the results clearly indicated that the 2,3,4-trisubstituted pyrrole isomer is favored exclusively over the 2,4,5-isomer.

NOESY NMR Correlation of Trisubstituted Pyrrole 14a

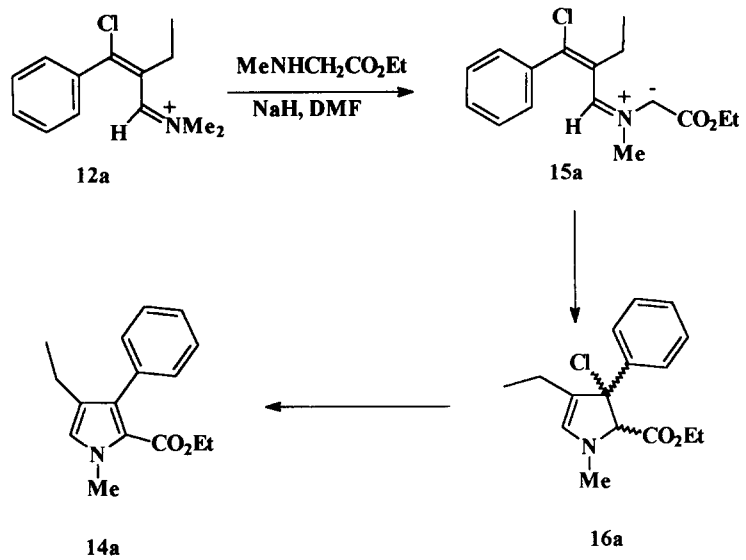


14a

Close inspection of chloropropeniminium salt **12a** suggests that the chlorovinyl carbon is flanked by two groups and is probably too sterically hindered for nucleophilic addition of the

amino acid ester. As observed previously for monosubstituted unsymmetrical vinamidinium salts, reaction of the amino acid ester at the least sterically hindered site ultimately leads to the observed 2,3,4-trisubstituted pyrrole product in good yield (Scheme 4).

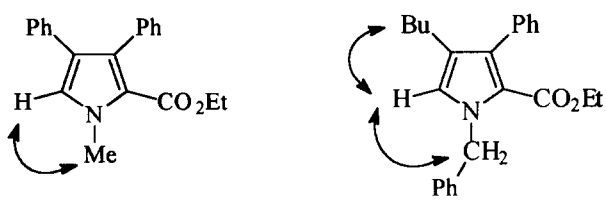
Scheme 4



12a 15a 16a 14a

Since our initial trials with our model vinylogous iminium salt and ethyl N-methylglycinate had demonstrated the feasibility for 2,3,4-trisubstituted pyrrole synthesis, we decided to evaluate additional analogs in order to determine the scope and limitation of such condensation reactions. The resulting new, highly functionalized pyrroles are given in Table 2. Several of the purified pyrrole analogs were also subjected to NOEDIF NMR analysis and the results from these experiments were consistent with the 2,3,4-trisubstitution pattern.

NOEDIF NMR Correlation for Trisubstituted Pyrrole 14b and 14i

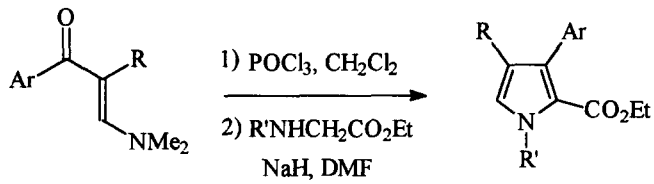


14b 14i

The NMR results clearly indicate that the 2,3,4-trisubstituted pyrrole isomer is consistently favored in these pyrrole forming condensation reactions. In addition, the pyrrole derived from the ethyl

glycinate condensation product (**14f**) was alkylated with iodomethane and benzyl chloride in separate experiments and the resulting pyrrole products were identical to compounds **14a** and **14i** respectively (Scheme 6). These experiments further establish the individual and relative regiochemistry of the pyrrole condensation products.

Scheme 5

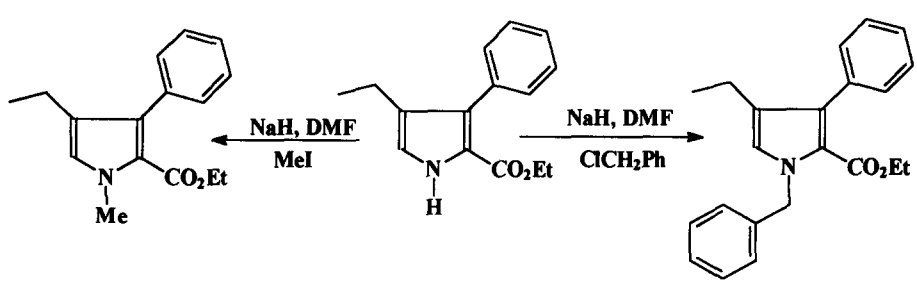


11 14

Table 2. Preparation of 2,3,4-Trisubstituted Pyrrole Analogs

Compound	R	Ar	R'	% Yield (Isolated)
14a	Et	Ph	Me	60
14b	Ph	Ph	Me	60
14c	Me	Ph	Me	68
14d	n-Pr	Ph	Me	69
14e	n-Bu	Ph	Me	55
14f	Et	Ph	H	11
14g	n-Bu	Ph	H	25
14h	Ph	Ph	H	17
14i	Et	Ph	CH_2Ph	50
14j	n-Bu	Ph	CH_2Ph	46
14k	Ph	Ph	CH_2Ph	22

Scheme 6



14a **14f** **14i**

The results from the analog study also reveal that a variety of substituents on the chloropropeniminium salt are compatable with the pyrrole forming reaction and N-substitution on the amino acid ester is also favorable. However, ethyl glycinate itself was a poor partner in the condensation reaction for the conditions specified. In order to improve the generality of this transformation and to better understand the process, we decided to examine all three synthetic building blocks (vinylogous amide, chloropropeniminium salt and β-chloroenal) under a variety of different reaction conditions (acidic, neutral and basic). The three carbon synthons bearing the phenyl and ethyl groups were again chosen as model compunds for this study. Additionally, ethyl N-methylglycinate, ethyl glycinate and ethyl N-benzylglycinate were also evaluated as possible condensing agents under the various reaction conditions specified. The following tables summarize these trials.

Table 3. Reactions of Various 3-Carbon Synthons with Glycine Derivatives Under Acidic, Neutral and Basic Conditions

Amino Acid Ethyl Ester	Substrate	Pyrrole Product	% Yield[a] HOAc	% Yield[a] DMF	% Yield[a] NaH,DMF
N-Methylglycine	11a	14a	68[c]	19	NPF
N-Methylglycine	12a[b]	14a	NPF	22[c]	60[c]
N-Methylglycine	13a	14a	NPF	77[c]	30
Glycine	11a	14f	NPF	NPF	8
Glycine	12a[b]	14f	NPF	12	11[c]
Glycine	13a	14f	NPF	44[c]	27[c]
N-Benzylglycine	11a	14i	55[c]	NPF	NPF
N-Benzylglycine	12a[b]	14i	NPF	26	50[c]
N-Benzylglycine	13a	14I	NPF	75[c]	NPF

[a]Determined by GC analysis and proton NMR unless otherwise specified.
[b]Starting material prepared by reaction of 11a with $POCl_3$.
[c]Isolated yield.
NPF = no pyrrole formed

From Table 3 it can be seen that the N-methylpyrrole (**14a**) is obtained from all three synthons (**11a**, **12a** and **13a**) and ethyl N-methylglycinate in good yield and under a variety of different reaction conditions. It appears, however, that the chloropropeniminium salt (**12a**) reacts best under basic conditions, the vinylogous amide reacts successfully under acidic conditions and the β-chloroenal (**13a**) reacts favorably under neutral conditions. The same conclusions can also be drawn for the various reactions evaluated for ethyl N-benzylglycinate. Since both amino acid esters are N-substituted, it is not surprising that they behave similarly. The vinylogous amide (**11a**) probably undergoes an acid catalyzed amine exchange reaction with ethyl N-methylglycinate prior to acid catalyzed cyclization and the presence of an acidic medium would likely facilitate these

processes. The chloropropeniminium salt (**12a**) requires base for the condensation sequence with ethyl N-methylglycinate and this may be related to the need for deprotonation in the cyclization step. The β-chloroenal (**13a**) may well be base unstable and could be sufficiently reactive to condense with ethyl N-methylglycinate in the absence of any strongly basic species. The N-unsubstituted pyrrole formation did not take place in a similar fashion and the best conditions involved using the β-chloroenal (**13a**) as the substrate under neutral conditions. The unique behavior for ethyl glycinate condensation reactions may relate to earlier observations[4] that ethyl glycinate acts somewhat different than N-substituted amino acid esters.

In conclusion, we have demonstrated that disubstituted vinylogous iminium salt derivatives (vinylogous amide, chloropropeniminium salt and β-chloroenal) can serve as successful and efficient precursors to trisubstituted pyrrole systems and that the 2,3,4-trisubstitution pattern is the preferred regiochemistry. These results now establish the opportunity to employ such chemistry for the construction of a variety of important pyrrole containing marine natural products.

Experimental Section

The following procedures are typical of the experimental conditions used for the reaction of vinylogous iminium salts and other three-carbon synthons with α-amino acid esters. The vinylogous iminium salts and β-chloroenals were prepared by standard methods.[8] All purified compounds gave a single spot upon TLC analysis on silica gel 7GF with an ethyl acetate/hexane mixture (30:70 respectively) used as the eluent. Distillations were carried out on an Aldrich kugelrohr apparatus at reduced pressure. Chromatographic separations were carried out on a Harrison Chromatotron using silica gel plates of 2mm thickness with a fluorescent backing or by standard column chromatography techniques. IR spectra were recorded on a Perkin-Elmer 1600 FTIR and NMR spectra were obtained with a Varian Gemini 200 spectrometer. All samples gave ^{13}C NMR spectra consistent with a sample purity in excess of 95%. All melting points and boiling points are uncorrected. High resolution mass spectra were obtained by the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln

2-Ethyl-3-(dimethylamino)-1-phenylprop-2-enone (11a): A 100 mL round-bottom flask was equipped with a magnetic stirrer and condenser. Into the flask were placed 4.0 g (27 mmol) of butyrophenone, 13.0 g (108 mmol) of *N,N*-dimethylformamide dimethyl acetal, and 30 mL of DMF. The resulting mixture was heated at reflux for 2 hours. The solvent was removed in vacuo leaving 4.7 g (88% yield) of a viscous yellow liquid. An analytically pure sample can be obtained through a bulb-to-bulb distillation. The pure compound exhibited the following properties: bp 125 °C at 0.6 torr; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3H), 2.57 (q, J = 7.3 Hz, 2H), 2.95 (s, 6H), 6.75 (s, 1H), and 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.2, 17.6, 43.4, 113.4, 128.3, 128.8, 129.4, 142.9, 156.4, and 197.4; FTIR (neat) 1629 cm^{-1}; HRMS calcd for $C_{13}H_{17}NO$ 203.1310 found 203.1312.

2-Methyl-3-(dimethylamino)-1-phenylprop-2-enone (11b): This compound was prepared in 98% yield in manner similar to vinylogous amide **(11a)**. The pure compound exhibited the following properties: bp 107-110 °C at 0.2 torr; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 2.98 (s, 6H), 6.82 (s, 1H), and 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.2, 43.5, 106.5, 128.3, 128.7, 129.4, 142.7, 157.2, and 197.6; FTIR (neat) 1631 cm^{-1}; HRMS calcd for $C_{12}H_{15}NO$ 189.1154 found 189.1154.

3-(Dimethylamino)-1-phenyl-2-propylprop-2-enone (11c): This compound was prepared in 41% yield in a manner similar to vinylogous amide **(11a)**. The pure compound exhibited the following properties: bp 108-110 °C at 0.3 torr; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.46 (sextet, J = 7.4 Hz, 2H), 2.54 (t, J = 7.4 Hz, 2H), 2.97 (s, 6H), 6.77 (s, 1H), and 7.25-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 24.8, 26.4, 43.4, 112.3, 128.3, 128.8, 129.4, 142.9, 156.4, and 197.7; FTIR (neat) 1628 cm^{-1}; HRMS calcd for $C_{14}H_{19}NO$ 217.1467 found 217.1463.

2-Butyl-3-(dimethylamino)-1-phenylprop-2-enone (11d): This compound was prepared in 43% yield in a manner similar to vinlyogous amide **(11a)**. The pure compound exhibited the following properties: bp 150 °C at 1.3 torr; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.25-1.55 (m, 4H), 2.55 (t, J = 6.9 Hz, 2H), 2.96 (s, 6H), 6.77 (s, 1H), and 7.25-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 23.1, 24.2, 34.0, 43.4, 112.2, 128.2, 128.8, 129.4, 142.8, 156.5, and 197.6; FTIR (neat) 1629 cm^{-1}; HRMS calcd for $C_{15}H_{21}NO$ 231.1623 found 231.1618.

3-(Dimethylamino)-1,2-diphenylprop-2-enone (11e): This compound was prepared in 94% yield in a manner similar to vinylogous amide **(11a)** with the exception that an analytically pure sample was obtained by recrystallization from an 80:20 mixture of hexane and ethyl acetate. The pure compound exhibited the following properties: mp 126-128 °C; ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 6H), 7.10-7.30 (m, 8H), 7.32 (s, 1H), and 7.35-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 43.8, 112.3, 126.8, 128.1, 129.2, 129.7, 132.6, 137.8, 142.5, 154.6, and 195.5; FTIR (KBr pellet) 1618 cm^{-1}; HRMS calcd for $C_{17}H_{17}NO$ 251.1310 found 251.1318.

1-(4-Methoxyphenyl)-2-methyl-3-(dimethylamino)prop-2-enone (11f): This compound was prepared in 96% yield in manner similar to vinylogous amide **(11a)**. The pure compound exhibited the following properties: mp 86-87 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.02 (s, 6H), 3.18 (s, 3H), 6.84 (d, J = 8.7 Hz, 2H), 6.88 (s, 1H), and 7.39 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.5, 43.4, 55.6, 106.4, 113.5, 130.8, 135.0, 156.5, 161.1, and 197.0; FTIR (neat) 1630 cm^{-1}; HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259 found 219.1257.

Preparation of N,N-Dimethyl-2-ethyl-3-phenyl-3-chloropropeniminium salt (12a): A 50 mL round-bottom flask was equipped with a condenser and stir bar and into the flask was placed 1.0 g (4.9 mmol) of vinylogous amide **(11a)**, 20 mL of methylene chloride, and 0.75 g (4.9 mmol) of phosphorous oxychloride. The mixture was heated at reflux for 2 hours. The solvent was removed in vacuo and the resulting oil was used in subsequent experiments without purification.

Preparation of 2-Carbethoxy-4-ethyl-1-methyl-3-phenylpyrrole (14a) Under Basic Conditions: The chloropropeniminium salt (**11a**, 4.9 mmol) from the previous reaction was dissolved in 10 mL of DMF and the resulting solution was placed in an addition funnel. A 100 mL round-bottom flask was equipped with a stir bar and condenser into the flask was placed 0.80 g (20 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed with 50 mL of hexane, and the hexane was removed via cannula. Into the flask were added 50 mL of DMF, 1.13 g (7.4 mmol) of ethyl N-methylglycinate hydrochloride, and the previously prepared chloropropeniminium salt/DMF solution. The mixture was heated at reflux for 18 hours and cooled to room temperature. The solvent was removed in vacuo and the residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated. The crude product was passed through a short plug of silica gel and purified by radial chromatography using a gradient elution of hexane and ethyl acetate. A viscous amber liquid (0.76 g, 60% yield) was obtained. The pure compound exhibited the following properties: bp 85 °C at 0.5 torr; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.6 Hz, 3H), 2.33 (q, J = 7.6 Hz, 2H), 3.92 (s, 3H), 4.03 (q, J = 7.2 Hz, 2H), 6.64 (s, 1H), and 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.8, 15.3, 18.4, 37.3, 59.6, 120.1, 125.6, 126.6, 126.8, 127.8, 130.7, 132.9, 137.2, and 162.4; FTIR (neat) 1694 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_2$ 257.1416 found 257.1414.

2-Carbethoxy-1-methyl-3,4-diphenylpyrrole (14b): This compound was prepared in 60% yield in a manner similar to pyrrole (**14a**). The pure compound exhibited the following properties: mp 84-86 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.1 Hz, 3H), 4.00 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 6.96 (s, 1H), and 7.05-7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 13.8, 37.8, 60.0, 121.2, 124.5, 126.3, 127.0, 127.4, 127.9, 128.6, 131.2, 131.5, 135.1, 136.6, and 162.5; FTIR (neat) 1690 cm^{-1}; HRMS calcd for $C_{20}H_{19}NO_2$ 305.1416 found 305.1419.

2-Carbethoxy-1,4-dimethyl-3-phenylpyrrole (14c): This compound was prepared in 68% yield in a manner similar to pyrrole (**14a**). The pure compound exhibited the following properties: bp 95-96 °C at 0.4 torr; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 1.88 (s, 3H), 3.87 (s, 3H), 4.00 (q, J = 7.2 Hz, 2H), 6.60 (s, 1H), and 7.15-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.8, 37.3, 59.7, 118.3, 119.9, 126.8, 127.7, 127.8, 130.7, 133.4, 136.9, and 162.3; FTIR (neat) 1694 cm^{-1}; HRMS calcd for $C_{15}H_{17}NO_2$ 243.1259 found 243.1266.

2-Carbethoxy-1-methyl-3-phenyl-4-propylpyrrole (14d): This compound was prepared in 69% yield in a manner similar to pyrrole (**14a**). The pure compound exhibited the following properties: bp 110-115 °C at 0.5 torr; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H), 1.39 (sextet, J= 7.3 Hz, 2H), 2.23 (t, J = 7.3 Hz, 2H), 3.89 (s, 3H), 3.98 (q, J = 7.1 Hz, 2H), 6.60 (s, 1H), and 7.15-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.1, 24.0, 27.2, 37.4, 59.6, 120.0, 123.8, 126.7, 127.1, 127.8, 130.7, 133.1, 137.1, and 162.4; FTIR (neat) 1695 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO_2$ 271.1572 found 271.1581.

4-Butyl-2-carbethoxy-1-methyl-3-phenylpyrrole (14e): This compound was prepared in 55% yield in a manner similar to pyrrole **(14a)**. The pure compound exhibited the following properties: bp 110 °C at 1.1 torr; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 1.10-1.45 (m, 4H), 2.25 (t, J = 7.2 Hz, 2H), 3.88 (s, 3H), 3.98 (q, J = 7.2 Hz, 2H), 6.60 (s, 1H), and 7.15-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 22.9, 25.0, 33.4, 37.7, 59.8, 119.8, 123.9, 126.7, 127.0, 127.8, 130.7, 133.1, 137.1, and 162.3; FTIR (neat) 1694 cm^{-1}; HRMS calcd for $C_{18}H_{23}NO_2$ 285.1729 found 285.1732.

2-Carbethoxy-4-ethyl-3-phenylpyrrole (14f): This compound was prepared in 11% yield in a manner similar to pyrrole **(14a)** with the exception that ethyl glycinate hydrochloride was used as one of the starting materials. The pure compound exhibited the following properties: mp 76-78 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (m, 6H), 2.38 (q, J = 7.2 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 6.78 (d, J = 2.9 Hz, 1H), 7.32 (m, 5H), and 9.16 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 15.2, 18.7, 60.3, 119.5, 119.8, 127.2, 128.0, 128.1, 130.8, 131.0, 135.5, and 161.9; FTIR (KBr pellet) 3308, 1668 cm^{-1}; HRMS calcd for $C_{15}H_{17}NO_2$ 243.1259 found 243.1264.

4-Butyl-2-carbethoxy-3-phenylpyrrole (14g): This compound was prepared in 25% yield in a manner similar to pyrrole **(14f)**. The pure compound exhibited the following properties: bp 130-131 °C at 1.3 torr; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H), 1.15-1.50 (m, 4H), 2.35 (t, J = 7.2 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 6.76 (d, J = 3.0 Hz, 1H), 7.31 (m, 5H), and 9.04 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.6, 22.9, 25.2, 33.2, 60.4, 119.4, 120.1, 126.5, 127.1, 127.9, 130.8, 131.2, 135.5, and 161.7; FTIR (neat) 3310, 1670 cm^{-1}; HRMS calcd for $C_{17}H_{21}NO_2$ 271.1572 found 271.1574.

2-Carbethoxy-3,4-diphenylpyrrole (14h)[9]: This compound was prepared in 17% yield in a manner similar to pyrrole **(14f)**. The pure compound exhibited the following properties: mp 118-119 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 4.16 (q, J = 7.1 Hz, 2H), 7.05-7.30 (m, 11H), and 9.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.1, 62.3, 122.1, 122.3, 128.0, 128.7, 128.8, 129.5, 130.2, 130.3, 131.3, 132.8, 136.4, 136.5, and 163.3; FTIR (KBr pellet) 3302, 1670 cm^{-1}; HRMS calcd for $C_{19}H_{17}NO_2$ 291.1259 found 291.1271.

1-Benzyl-2-carbethoxy-4-ethyl-3-phenylpyrrole (14i): This compound was prepared in 50% yield in a manner similar to pyrrole **(14a)** with the exception that ethyl *N*-benzyl glycinate hydrochloride was used as one of the starting materials. The pure compound exhibited the following properties: bp 165-166 °C at 0.7 torr; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H), 2.28 (q, J = 7.2 Hz, 2H), 3.90 (q, J = 7.2 Hz, 2H), 5.50 (s, 2H), 6.68 (s, 1H), and 7.10-7.50 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.5, 18.9, 52.8, 60.0, 119.7, 126.0, 126.2, 126.8, 127.4, 127.8, 127.9, 129.1, 130.6, 133.3, 137.0, 139.2, and 162.1; FTIR (neat) 1693 cm^{-1}; HRMS calcd for $C_{22}H_{23}NO_2$ 333.1729 found 333.1729.

1-Benzyl-4-butyl-2-carbethoxy-3-phenylpyrrole (14j): This compound was prepared in 46% yield in a manner similar to pyrrole **(14i)**. The pure compound exhibited the following properties: bp 180-181 °C at 0.7 torr; ^{1}H NMR ($CDCl_3$) δ 0.75 (m, 6H), 1.10-1.50 (m, 4H), 2.30 (t, J = 7.5 Hz, 2H), 3.94 (q, J = 7.2 Hz, 2H), 5.55 (s, 2H), 6.72 (s, 1H), and 7.10-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.4, 22.9, 25.1, 33.2, 52.8, 59.9, 119.6, 124.6, 126.4, 126.8, 127.4, 127.7, 127.8, 129.2, 130.6, 133.6, 137.0, 139.2, and 162.1; FTIR (neat) 1693 cm^{-1}; HRMS calcd for $C_{24}H_{27}NO_2$ 361.2042 found 361.2037.

1-Benzyl-2-carbethoxy-3,4-diphenylpyrrole (14k): This compound was prepared in 22% yield in a manner similar to pyrrole **(14i)**. The pure compound exhibited the following properties: mp 116-118 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 3.97 (q, J = 7.2 Hz, 2H), 5.60 (s, 2H), and 7.00-7.40 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 14.1, 53.2, 60.3, 121.0, 125.1, 126.4, 126.8, 127.1, 127.7, 128.0, 128.1, 128.6, 129.2, 131.2, 132.0, 135.0, 136.5, 138.6, and 162.2; FTIR (KBr pellet) 1701 cm^{-1}; HRMS calcd for $C_{26}H_{23}NO_2$ 381.1729 found 381.1744.

3-Chloro-2-ethyl-3-phenylprop-2-enal (13a): Into a 250-mL round bottomed flask was placed 2-ethyl-3-phenyl-3-chloropropeniminium salt **(33a)** (6.25 g, 17.5 mmol), water (50 mL) and THF (50 mL). The flask was equipped with a reflux condenser and a magnetic stirrer. The reaction mixture was allowed to reflux overnight. The THF was removed *in vacuo*, and the aqueous phase was washed with chloroform. The combined chloroform layers were dried over anhydrous magnesium sulfate, filtered and concentrated, giving 100 % crude product which was a mixture of two isomers. The crude material was dissolved in ethyl acetate and placed on the top of a short plug of silica gel. The silica gel was washed with a mixture of 70:30 hexane:ethyl acetate, and the solvent was removed *in vacuo*. An analytical sample was obtained by radial chromatography using an 80:20 mixture of hexane:ethyl acetate as eluant. After removal of solvent, an 84 % yield of a light yellow oil (the major isomer) was obtained which exhibited the following properties: bp: 51-52 °C at 0.5 torr; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.5 Hz, 3 H), 2.61 (q, J = 7.5 Hz, 2 H), 7.35-7.50 (m, 5 H) and 9.44 (s, 1 H); IR (CCl_4) 3064 and 1680 cm^{-1}; HRMS (EI) for $C_{11}H_{11}OCl$ calcd. 194.0498, found 194.0493.

Methylation of 2-Carbethoxy-4-ethyl-3-phenylpyrrole (14f): A 100 mL three-neck round-bottom flask was equipped with a magnetic stirrer and placed under a nitrogen atmosphere. Into the flask was placed 0.09 g (2.3 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed several times with hexane and the hexane was removed via cannula. Into the flask was consecutively added 20 mL of DMF, 0.05 g (0.2 mmol) of pyrrole **(14f)**, and 0.41 g (2.9 mmol) of iodomethane. The solution was allowed to stir overnight at room temperature. The solvent was removed in vacuo and the residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated to yield a quantitative amount of pyrrole **(14a)**. The tlc and proton NMR of the product were identical to an authentic sample.

Benzylation of 2-Carbethoxy-4-ethyl-3-phenylpyrrole (14f): A 100 mL three-neck round-bottom flask was equipped with a magnetic stirrer and placed under nitrogen. Into the flask was placed 0.13 g (3.3 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed several times with hexane and the hexane was removed via cannula. Into the flask was consecutively added 20 mL of DMF, 0.10 g (0.4 mmol) of pyrrole **(14f)**, and 0.06 g (0.4 mmol) of benzylchloride. The solution was allowed to stir overnight at room temperature. The solvent was removed in vacuo and the residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated leaving 0.1 g of crude product. An analytical sample was obtained by radial chromatography using a hexane/ethyl acetate mixture as eluant. The purified material was identical by tlc and ^{1}H NMR to an authentic sample of the N-benzylated pyrrole **(14i)**.

Preparation of 2-Carbethoxy-4-ethyl-1-benzyl-3-phenylpyrrole (14i) Under Acidic Conditions: Into a 100 mL, round bottom flask was placed ethyl N-benzylglycinate (1.43 g, 7.40 mmol), 2-ethyl-3-(dimethylamino)-1-phenylprop-2-enone **(11a)** (1.00 g, 4.90 mmol) and glacial acetic acid (50 mL). The flask was equipped with a magnetic stirrer and a reflux condenser and the resulting mixture stirred and refluxed for 24 hours. After cooling , the reaction mixture was diluted with water and extracted with chloroform (3 x 100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was passed through a short plug of silica gel and purified by radial chromatography (2 mm silica gel plate) using a 95:5 mixture of hexane:ethyl acetate as the eluant. The resulting amber liquid (0.897 g, 54.9% yield) was identical to an authentic sample of **14i** by tlc and ^{1}H NMR comparison.

Preparation of 2-Carbethoxy-4-ethyl-1-benzyl-3-phenylpyrrole (14i) Under Neutral Conditions: Into a 100 mL , round bottom flask were placed ethyl N-benzylglycinate (1.14 g, 5.88 mmol), 3-chloro-2-ethyl-3-phenylpropenal **(12a)** (1.03 g, 5.28 mmol) and anhydrous DMF (25 mL). The flask was equipped with with a magnetic stirrer and a reflux condenser and the resulting reaction mixture was refluxed and stirred for 18 hours. After cooling to room temperature, the solvent was removed in vacuo and the residue was taken up in chloroform and passed through a short plug of silica gel. The resulting material was then subjected to column chromatography on silica gel using 95:5 hexane:ethyl acetate as the eluant. The purified product amounted to 1.32 g (75% yield) and was identical to an authentic sample of **14i** by tlc and ^{1}H NMR comparison.

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