



The Application of Vinylogous Iminium Salts and Related Synthons to the Regiocontrolled Preparation of 2,3- and 2,5-Disubstituted Pyrroles

John T. Gupton*

Department of Chemistry, University of North Carolina at Asheville
Asheville, North Carolina 28804

**Scott A. Petrich, Lana L. Smith, Marc A. Bruce, Phong Vu,
Karen X. Du and Eric E. Dueno**

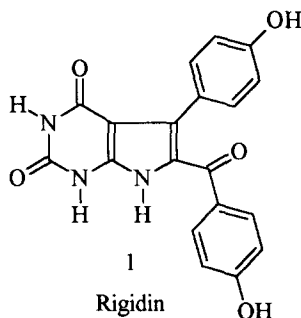
Department of Chemistry, University of Central Florida, Orlando, Florida 32816

Claude R. Jones and James A. Sikorski*

Monsanto Corporate Research, 700 Chesterfield Parkway North,
St. Louis, Missouri 63198

Abstract: The reaction of 1-substituted vinamidinium salts with sarcosine ethyl ester produced 2,3-disubstituted pyrroles; a similar reaction with glycine ethyl ester gave 2,5-disubstituted pyrroles. Reactions of related three-carbon synthons with sarcosine and glycine were studied under basic, neutral and acidic conditions which demonstrated the utility of these derivatives for the regiocontrolled preparation of disubstituted pyrroles. Copyright © 1996 Elsevier Science Ltd

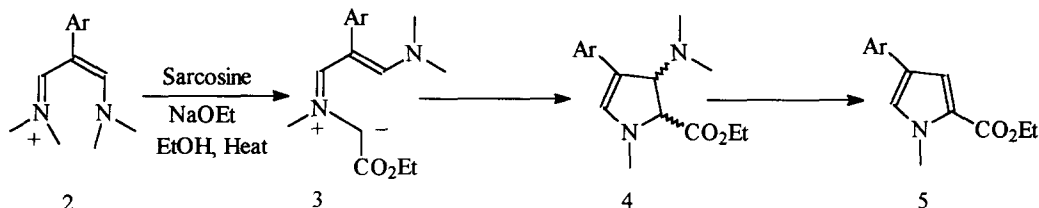
Since many pyrrole containing compounds have demonstrated interesting biological activity in recent years (e.g. Rigidin (**1**)¹), there has been a significant interest in the efficient preparation of such molecules².



Ideally in such systems the most efficient syntheses will require full control of regiochemistry. For example in the case of Rigidin, there is a 2-phenacyl-3-phenyl arrangement for the eastern portion of the molecule. Edstrom^{1a} and Sakamoto^{1b} have both synthesized Rigidin by first constructing the uracil portion of the molecule and subsequently building the pyrrole, aryl and aroyl groups at a later stage.

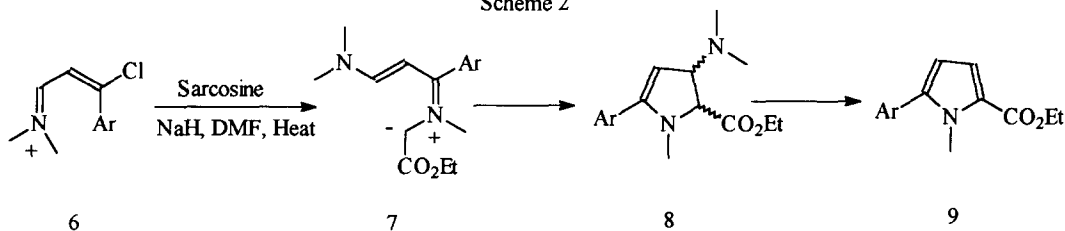
Because of our interest in developing iminium salt based methodology which could be used for the preparation of pyrrole containing natural products, we now report the use of such systems for the regiocontrolled synthesis of 2,3- and 2,5-disubstituted pyrroles. We have recently reported³ the regiocontrolled synthesis of 4-aryl-2-carbethoxy-N-substitutedpyrroles (**5**) from the reaction of 2-arylvinamidinium salts (**2**) with glycine derivatives (Scheme 1).

Scheme 1



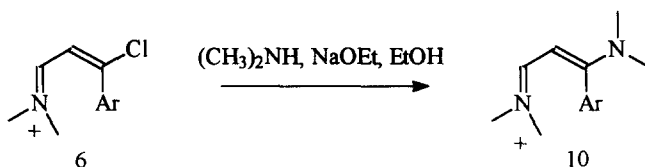
We have also reported⁴ the synthesis of a series of 5-aryl-2-carbethoxy-N-substituted pyrroles (**9**) from the reaction of 3-aryl-3-chloropropeniminium salts⁵ (**6**) with N-substituted glycine derivatives (Scheme 2). The proposed mechanism delineated in Scheme 2 involves a nucleophilic attack of the amino group at the more electrophilic site of **6** which is the carbon bearing the chlorine. After elimination of chloride, anion-mediated cyclization followed by elimination of dimethylamine would yield **9**. This reaction worked equally well with glycine ethyl ester and sarcosine ethyl ester. The use of this vinylogous iminium salt based methodology has consequently provided two of the possible three isomeric disubstituted pyrrole systems.

Scheme 2



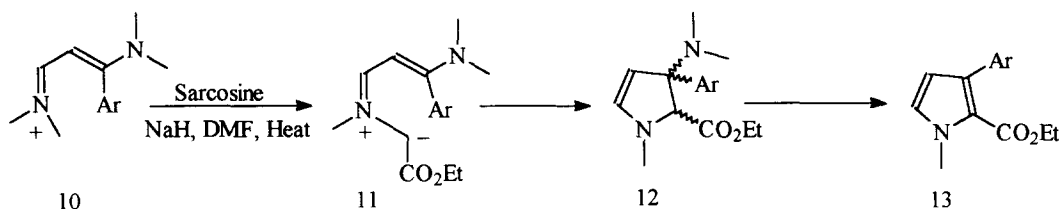
If unsymmetrical vinamidinium salts (**10**) were used instead of **6**, a different regiochemical control may be involved and the 2,3-disubstituted pyrrole may result. These unsymmetrical vinamidinium salts are easily prepared in one step from the corresponding chloropropeniminium salts⁵ (Scheme 3).

Scheme 3



For the 2,3-disubstituted pyrrole to be formed requires that nucleophilic attack of the amino group of sarcosine ethyl ester on **10** would result in an amine-exchange reaction at the least sterically hindered position. Anion-mediated cyclization and elimination of dimethylamine from **12** would lead to the 2,3-disubstituted pyrrole **13**.

Scheme 4



When the reaction of sarcosine ethyl ester and **10** was performed in the presence of sodium hydride and DMF, good yields of **13** were obtained. The aromatic substituents were represented by a variety of groups such as phenyl, 4-chlorophenyl, 4-bromophenyl, 4-methoxyphenyl, 4-nitrophenyl and 4-methylphenyl and are listed in Table 1.

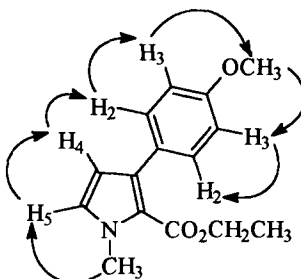
Table 1. Preparation of 2,3-Disubstituted Pyrrole Analogs

Compound	Ar	% Yield (Isolated)
13a	4-MeOPh	71%
13b	4-MePh	63%
13c	Ph	40%
13d	4-ClPh	79%
13e	4-NO ₂ Ph	52%
13f	4-BrPh	32%

The assignment of the 2,3-disubstitution pattern for these pyrroles was determined in part by comparison of coupling constants of the pyrrole hydrogens⁶. The coupling constant for pyrrole hydrogens at the 4 and 5 positions (2,3-isomer) is in the range of 2.5 Hz whereas the coupling constant for the 3 and 4 positions (2,5-isomer) is in the range of 3.5 Hz. The experimental coupling constant for the pyrrole series represented by **13a-13f** is approximately 2.5 Hz. In addition, a NOESY NMR experiment was run on **13a** and the results (Table 2) are fully consistent with the assigned 2,3-disubstitution pattern. The NOESY cross peak pattern observed for **13a**

is clearly different from that observed for the 2,5-disubstituted pyrrole isomer⁴.

Table 2. NOESY Correlation for a 2,3-Disubstituted Pyrrole

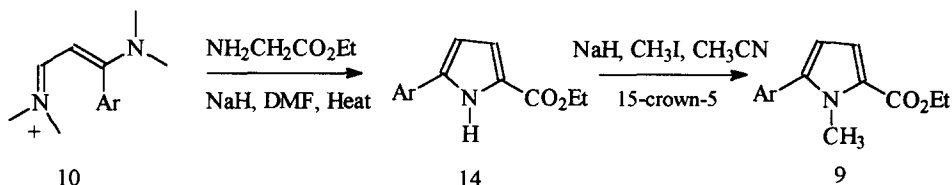


	ppm	OCH ₃ 3.75	H ₃ 6.88	H ₂ 7.25	H ₄ 6.10	H ₅ 7.07	NCH ₃ 3.84
OCH ₃	3.75	---	XXX	---	---	---	---
H ₃	6.88	XXX	---	XXX	---	---	---
H ₂	7.25	---	XXX	---	XXX	---	---
H ₄	6.10	---	---	XXX	---	XXX	---
H ₅	7.07	---	---	---	XXX	---	XXX
NCH ₃	3.84	---	---	---	---	XXX	---

Note: XXX = NOESY cross peak

When glycine ethyl ester was treated with **10**, the expected 2,3-disubstituted pyrrole (**13**) was not the resulting product but the 2,5-disubstituted pyrrole (**14**) was obtained instead (Scheme 5).

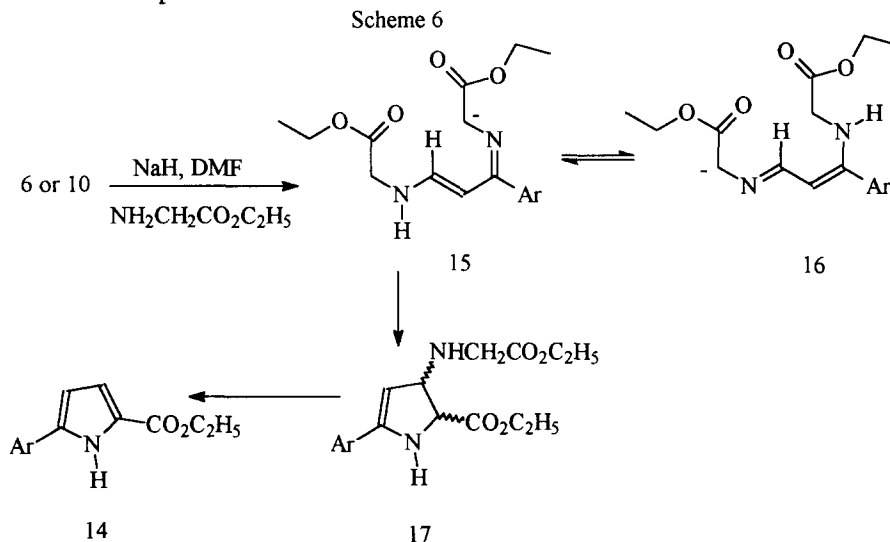
Scheme 5



The regiochemical assignment was determined in part by coupling constants of the pyrrole hydrogens.⁶ The experimental coupling constant (H_3-H_4) of 4.0 Hz was consistent with the 2,5-substitution pattern. In addition we also alkylated the nitrogen of the pyrrole to obtain the corresponding N-methylated pyrrole (**9**) (Scheme 5). The ¹H NMR and tlc of these pyrroles

were identical to the ^1H NMR and tlc of the pyrroles obtained in the reaction of **6** with sarcosine ethyl ester.⁴

Since the reaction of chloropropeniminium salts (**6**) and unsymmetrical vinamidinium salts (**10**) with glycine ethyl ester result in the same substitution pattern, the same intermediate may be involved in both reactions. It has already been proposed that a 2 to 1 adduct may be involved in the reaction of chloropropeniminium salts (**6**)⁴ with primary amines. If that is the case, the starting material could be either **6** or **10** which would react with glycine ethyl ester to form an imino enamine (**15** or **16**) (Scheme 6). Anion-mediated cyclization would most likely occur at the least sterically hindered position of the appropriate intermediate (**15**) followed by elimination of glycine ethyl ester from **17** to form the 2,5-disubstituted pyrrole (**14**). It appears from our previous studies that primary amines tend to form bis-adducts with vinylogous iminium salts and that secondary amines tend to form mono-adducts. This is presumably due to the ability of the bis-adducts to form highly stabilized, intramolecularly hydrogen bonded species.



Since the reaction with glycine ethyl ester gave interesting results, a broader study of related three-carbon synthons was performed in order to understand the role of steric vs. electronic factors in these reactions. The synthons that were studied included the vinylogous amide (**18**), chloropropeniminium salt (**6a**), vinamidinium salt (**10a**), β -chloroenal (**19**), and vinylogous formamide (**20**). Scheme 7 shows how these synthons were made and their relationship with one another. These synthons were treated with sarcosine ethyl ester and glycine ethyl ester under basic (NaH , DMF)

reflux), neutral (DMF reflux), and acidic (HOAc reflux) conditions. Table 3 summarizes the results for the reaction with sarcosine ethyl ester and Table 4 summarizes the results for the reaction with glycine ethyl ester.

Table 3. Reactions of Three Carbon Synthons with Sarcosine Ethyl Ester

Substrate	Product (%Yield Crude)		
	NaH/DMF	DMF	HOAc
6a	9a (100%)	9a (100%)	NP
10a	13a (71%)	NR	NP
18	NR	NP	NP
19	9a (85%)	9a (85%)	NP
20	13a (21%)	NP	NP

All products were analyzed by ^1H NMR and TLC and compared with authentic samples of 9a and 13a.

NP= No identifiable pyrrole products formed

NR= No reaction

Table 4. Reactions of Three Carbon Synthons with Glycine Ethyl Ester

Substrate	Product (%Yield Crude)		
	NaH/DMF	DMF	HOAc
6a	14a (100%)	NP	NP
10a	14a (76%)	NR	NP
18	NR	NP	NP
19	14a (60%)	14a (98%)	NP
20	NR	NP	NP

All products were analyzed by ^1H NMR and TLC and compared with authentic samples of 14a.

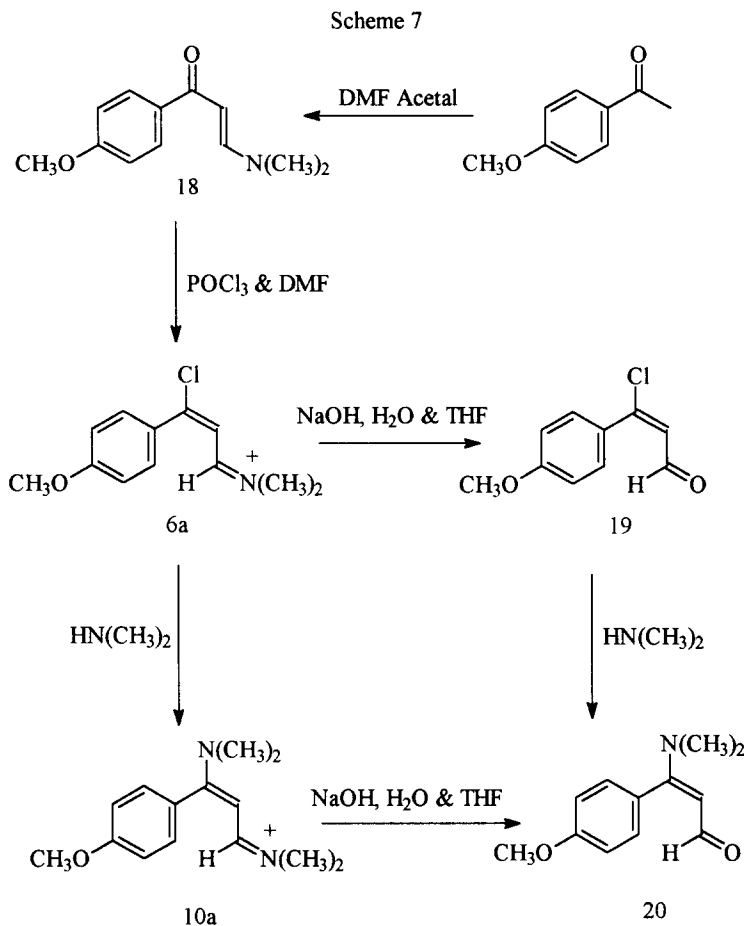
NP= No identifiable pyrrole products formed

NR= No reaction

The reactions of sarcosine (N-methylglycine ethyl ester) with the various three carbon synthons depicted in Table 3 indicate that all of the substrates with the exception of the vinylogous amide (**18**) can be converted to disubstituted pyrroles. The chloropropeniminium salt (**6a**) and the β -chloroal (**19**) react to give the 2,5-disubstituted pyrrole whereas the vinamidinium salt (**10a**) and the vinylogous formamide (**20**) produce the 2,3-disubstituted pyrrole under these conditions. It is also clear that the chloropropeniminium salt, the vinamidinium salt and the β -chloroal are very good substrates for preparing the appropriate disubstituted pyrrole

and that in most cases either basic or neutral reaction conditions are successful for such transformations.

Analogous reactions of glycine ethyl ester with the various three carbon synthons to form 2,5-disubstituted pyrroles as depicted in Table 4 suggest trends similar to those observed for the sarcosine reactions. The single exception was the vinylogous formamide (20) which formed no pyrrole under the various reaction conditions examined.



In summary, we have synthesized a series of 2,3-disubstituted pyrroles from the reaction of 1-aryl-vinamidinium salts with sarcosine ethyl ester. The corresponding reaction with glycine ethyl ester resulted in 2,5-disubstituted pyrroles. A study of related three-carbon synthons revealed the best substrates and conditions for pyrrole formation. This methodology provides a clean and efficient regiocontrolled synthesis of 2,3-disubstituted pyrroles which may possess interesting biological properties

and also complements our previous work on the syntheses of 2,4- and 2,5-disubstituted pyrroles. This methodology, therefore, may provide a new approach to the preparation of more complex, pyrrole containing substances (e.g. Rigidin, 1).

Experimental Section⁷

The following procedures are typical of the experimental conditions used for the reaction of vinylogous iminium salts and three-carbon synthons with α -amino acid esters. The vinylogous iminium salts were prepared by standard methods.⁵ All pyrrole products were purified by radial chromatography and gave a single spot upon TLC analysis on silica gel 7GF with an ethyl acetate/hexane mixture used as the eluent.

2-Carbethoxy-3-(4-methoxyphenyl)-1-methylpyrrole (13a). A dry 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer and was placed under a nitrogen atmosphere. Into the flask was placed 1.192 g (29.8 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed with 30 mL of hexane and the hexane was removed via cannula. Dry DMF (30 mL) was added to the flask. Sarcosine ethyl ester HCl (2.288 g, 14.9 mmoles) was carefully added followed by 2.0 g (5.96 mmol) of **10a**. The mixture was stirred for 1 h at room temperature followed by refluxing for 20 h. The solvent was removed in vacuo. The residue was partitioned three times between water and chloroform, the combined chloroform layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was dissolved in 50 mL of a 70% hexane and 30% ethyl acetate mixture and filtered through a 2.0 g plug of 200 mesh silica gel. The silica gel was washed with the mixture of hexane and ethyl acetate, and the solvent was removed in vacuo (1.10g, 71% yield). For an analytically pure sample, the residue was applied to a 1mm plate of silica gel 60, which was mounted on a radial chromatotron. The sample was eluted with a 70:30 mixture of hexane:ethyl acetate, and 1.08 g (64% yield) of a light yellow oil was obtained which had the following physical properties: bp 95 °C at 0.05 Torr; ¹H NMR (CDCl₃) δ 1.13 (t, J = 7 Hz, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 4.15 (q, J = 7 Hz, 2H), 6.13 (d, J = 2.5 Hz, 1H), 6.77 (d, J = 2.5 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H); ¹³C NMR (CDCl₃) δ 16.2, 39.7, 57.3, 61.8, 112.1, 114.9, 120.7, 130.2, 131.3, 132.7, 135.7, 160.5, and 163.8; IR (neat) 1692 cm⁻¹; HRMS for C₁₅H₁₇NO₃, calcd 259.1208, found 259.1209.

2-Carbethoxy-3-(4-methylphenyl)-1-methylpyrrole (13b). This material was prepared in a manner identical to the previous procedure. A 63% yield of a yellow oil was obtained which had the following physical properties: bp 86 °C at 0.10 Torr; ¹H NMR (CDCl₃) δ 1.12 (t, J = 7 Hz, 3H), 2.38 (s, 3H),

3.93 (s, 3H), 4.15 (q, $J = 7$ Hz, 2H), 6.14 (d, $J = 2.5$ Hz, 1H), 6.77 (d, $J = 2.5$ Hz, 1H), 7.14 (d, $J = 8$ Hz, 2H), 7.29 (d, $J = 8$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 16.0, 23.2, 39.7, 61.8, 112.2, 121.0, 130.1, 131.5, 135.9, 136.0, 138.1, 163.9; IR (neat) 1693 cm^{-1} ; HRMS for $\text{C}_{15}\text{H}_{17}\text{NO}_2$, calcd 243.1259, found 243.1264.

2-Carbethoxy-3-phenyl-1-methylpyrrole (13c). This material was prepared in a manner identical to the previous procedure. A 40% yield of a yellow oil was obtained which had the following physical properties: bp 86°C at 0.05 Torr; ^1H NMR (CDCl_3) δ 1.08 (t, $J = 7$ Hz, 3H), 3.95 (s, 3H), 4.14 (q, $J = 7$ Hz, 2H), 6.17 (d, $J = 2.5$ Hz, 1H), 6.78 (d, $J = 2.5$ Hz, 1H), 7.35 (m, 5H); ^{13}C NMR (CDCl_3) δ 15.9, 39.6, 61.8, 112.2, 121.1, 128.6, 129.4, 130.2, 131.7, 135.7, 139.0, 163.8; IR (neat) 1695 cm^{-1} ; MS m/e 229 (M^+); anal. calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_2 \cdot 10\% \text{H}_2\text{O}$: C, 72.77; H, 6.63; N, 6.06; found: C, 72.70; H, 6.57; N, 6.11.

2-Carbethoxy-3-(4-chlorophenyl)-1-methylpyrrole (13d). This material was prepared in a manner identical to the previous procedure. A 79% yield of a yellow oil was obtained which had the following physical properties: bp 86°C at 0.20 Torr; ^1H NMR (CDCl_3) δ 1.13 (t, $J = 7$ Hz, 3H), 3.94 (s, 3H), 4.16 (q, $J = 7$ Hz, 2H), 6.13 (d, $J = 2.5$ Hz, 1H), 6.78 (d, $J = 2.5$ Hz, 1H), 7.33 (s, 4H); ^{13}C NMR (CDCl_3) δ 15.8, 39.7, 61.9, 112.1, 121.1, 129.6, 130.3, 133.0, 134.4, 134.6, 137.4, 163.6; IR (neat) 1695 cm^{-1} ; HRMS for $\text{C}_{14}\text{H}_{14}\text{ClNO}_2$ calcd 263.0713, found 263.0714.

2-Carbethoxy-3-(4-nitrophenyl)-1-methylpyrrole (13e). This material was prepared in a manner identical to the previous procedure. A 52% yield of a yellow solid was obtained which had the following physical properties: mp $100\text{--}102^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.11 (t, $J = 7$ Hz, 3H), 3.96 (s, 3H), 4.17 (q, $J = 7$ Hz, 2H), 6.19 (d, $J = 2.6$ Hz, 1H), 6.83 (d, $J = 2.6$ Hz, 1H), 7.54 (d, $J = 7$ Hz, 2H), 8.20 (d, $J = 7$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 16.0, 39.8, 62.2, 112.2, 121.4, 124.7, 130.6, 132.4, 133.3, 146.0, 148.4, 163.2; IR (CHCl_3) 1693 cm^{-1} ; MS m/e 274 (M^+); anal. calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C, 61.30; H, 5.15; N, 10.22; found: C, 61.35; H, 5.44; N, 10.21.

2-Carbethoxy-3-(4-bromophenyl)-1-methylpyrrole (13f). This material was prepared in a manner identical to the previous procedure. A 32% yield of a yellow oil was obtained which had the following physical properties: bp 91°C at 0.90 Torr; ^1H NMR (CDCl_3) δ 1.12 (t, $J = 7$ Hz, 3H), 3.93 (s, 3H), 4.15 (q, $J = 7$ Hz, 2H), 6.12 (d, $J = 2.6$ Hz, 1H), 6.78 (d, $J = 2.7$ Hz, 1H), 7.27 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 16.0, 39.8, 61.9, 112.1, 121.1, 122.6, 130.3, 132.5, 133.3, 134.6, 137.9, 163.6; IR (neat) 1698 cm^{-1} ; MS m/e 307 (M^+); anal. calcd for $\text{C}_{14}\text{H}_{14}\text{BrNO}_2$: C, 54.56; H, 4.59; N, 4.55. found: C, 54.40; H, 4.45; N, 4.44.

2-Carbethoxy-5-(4-methoxyphenyl)pyrrole (14a). A dry 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer and was placed under a nitrogen atmosphere. Into the flask was placed 1.058 g (26.5 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed with 30 mL of hexane and the hexane was removed via cannula. To the flask was carefully added 30 mL of dry DMF, glycine ethyl ester HCl (1.846 g, 13.2 mmol) and 2.00 g (5.29 mmol) of **10a**. The resulting mixture was refluxed for 20 h, and the solvent was removed in vacuo. The residue was partitioned three times between water and chloroform, the combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and the solvent removed. The residue was dissolved in a mixture of 70% hexane and 30% ethyl acetate and filtered through a 2.0-g plug of 200-mesh silica gel. The silica gel was washed with additional solvent and the solvent was removed in vacuo to give 0.59 g (46% yield) of a light brown solid. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-methylphenyl)pyrrole (14b). This material was prepared by the above procedure except the reaction mixture was allowed to stir at room temperature for one hour before refluxing. A brown solid was obtained in 95% yield. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-chlorophenyl)pyrrole (14c). This material was prepared by the above procedure except the reaction mixture was allowed to stir at room temperature for one hour before refluxing. A light brown solid was obtained in 28% yield. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-phenylpyrrole (14d). This material was prepared by the above procedure and a light brown solid was obtained in 93% yield. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-nitrophenyl)pyrrole (14e). This material was prepared by the above procedure except the reaction mixture was allowed to stir at room temperature for one hour before refluxing. A light brown solid was obtained in 56% yield. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-bromophenyl)pyrrole (14f). This material was prepared by the above procedure except the reaction mixture was allowed to stir at room temperature for one hour before refluxing. A tan solid was obtained in 53% yield. An analytically pure sample was obtained by radial chromatography using a 70:30 mixture of hexane: ethyl acetate. A light yellow solid was

obtained which had the following physical properties: mp 170–172 °C; ^1H NMR (CDCl_3) δ 1.37 (t, J = 7.1 Hz, 3H), 4.34 (q, J = 7.1 Hz, 2H), 6.53 (t, J = 3.7 Hz, 1H), 6.96 (t, J = 3.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H); ^{13}C NMR (CDCl_3) δ 16.5, 62.6, 110.3, 118.8, 123.5, 125.8, 128.3, 132.3, 134.1, 137.6, 163.3; IR (CCl_4) 1697 cm^{-1} ; HRMS for $\text{C}_{13}\text{H}_{12}\text{BrNO}_2$ calcd. 293.0051, found 293.0057.

2-Carbethoxy-5-(4-methoxyphenyl)-1-methylpyrrole (9a). A 100-mL, three-neck, round-bottom flask was equipped with a magnetic stirrer and was placed under a nitrogen atmosphere. Into the flask was placed 0.024 g (0.61 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed with hexane and the hexane was removed via cannula. Acetonitrile (30 mL) was added along with 0.010 g of 15-crown-5 as a catalyst. 2-Carbethoxy-5-(4-methoxyphenyl)pyrrole (**14a**) (0.050 g, 0.204 mmol) and iodomethane (0.202 g, 1.43 mmol) were added and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was partitioned between water and chloroform. The combined chloroform extracts were dried, filtered and concentrated in vacuo to yield 100% of a yellow solid. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-methylphenyl)-1-methylpyrrole (9b). This material was prepared in 100% yield by the above procedure. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-chlorophenyl)-1-methylpyrrole (9c). This material was prepared in 100% yield by the above procedure. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-phenyl-1-methylpyrrole (9d). This material was prepared in 100% yield by the above procedure. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-nitrophenyl)-1-methylpyrrole (9e). This material was prepared in 100% yield by the above procedure. The product was characterized by ^1H NMR and tlc and was identical to an authentic sample⁴.

2-Carbethoxy-5-(4-bromophenyl)-1-methylpyrrole (9f). This material was prepared in 100% yield by the above procedure. The ^1H NMR and tlc of the residue was identical to those of the compound prepared below. This material was also prepared from **10f** and sarcosine ethyl ester HCl by the following procedure. A dry 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer and was placed under a nitrogen atmosphere. Into the flask was placed 0.48 g (12.0 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed with hexane and the hexane was removed via cannula. To the flask was

successively added, 30 mL dry DMF, sarcosine ethyl ester HCl (1.10 g, 7.2 mmol), and 2.0 g (4.8 mmol) of **10f**. The reaction mixture was stirred for one hour at room temperature followed by refluxing for 2 h. The solvent was removed in vacuo and the residue was partitioned between water and chloroform. The combined chloroform layers were dried and concentrated. For an analytically pure sample the residue was applied to a 1-mm plate of silica gel 60, which was mounted on a radial chromatotron. The sample was eluted with a 70:30 mixture of hexane: ethyl acetate and 0.30 g (20% yield) of a white solid was obtained after solvent removal. The compound had the following physical properties: mp 50-52 °C; ^1H NMR (CDCl_3) δ 1.34 (t, J = 7.1 Hz, 3H), 3.84 (s, 3H), 4.27 (q, J = 7.1 Hz, 2H), 6.16 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H); ^{13}C NMR (CDCl_3) δ 16.5, 38.5, 61.9, 111.2, 119.6, 124.3, 126.1, 132.8, 133.0, 133.7, 142.2 and 163.4; IR (neat) 1705 cm^{-1} ; HRMS for $\text{C}_{14}\text{H}_{14}\text{BrNO}_2$ calcd 307.0208, found 307.0208.

1-(4-Methoxyphenyl)-3-(dimethylamino)-2-propenone (18). A dry, 150-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer. Into the flask was placed 20 mL of DMF, 5.0 g (33.3 mmol) of 4'-methoxyacetophenone and 15.87 g (133.0 mmol) of the dimethylacetal of DMF. The resulting solution was heated at reflux for 8 h. The DMF and the unreacted DMF acetal were removed in vacuo leaving 5.0 g (74% yield) of a yellow solid when cooled to room temperature. This material had the following properties: mp 95-96 °C; ^1H NMR (CDCl_3) δ 3.00 (broad s, 6H), 3.80 (s, 3H), 5.67 (d, J = 12.3 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 12.3 Hz, 1H) and 7.87 (d, J = 8.8 Hz, 2H); ^{13}C NMR (CDCl_3) δ 39.3, 46.5, 57.3, 93.6, 115.3, 131.4, 135.1, 155.8, 163.7 and 189.3; IR (KBr pellet) 3006, 2911, 2837, 1636 and 1363 cm^{-1} ; HRMS for $\text{C}_{12}\text{H}_{15}\text{NO}_2$ calcd 205.1103, found 205.1101.

3-Chloro-3-(4-methoxyphenyl)-2-propenal (19). A 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer. Into the flask was placed 2.0 g (5.4 mmol) of **6a** and 30 mL of 50:50 water:THF. The mixture was heated at 65-70 °C for 4 h. After the THF was removed in vacuo, the solution was extracted three times with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate and filtered. The chloroform was removed in vacuo leaving 0.8 g (76% yield) of a brown solid which had the following properties: mp 58-60 °C; ^1H NMR (CDCl_3) δ 3.87 (s, 3H), 6.62 (d, J = 7.0 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H) and 10.18 (d, J = 7.0 Hz, 1H); ^{13}C NMR (CDCl_3) δ 57.6, 116.3, 124.5, 129.6, 131.0, 154.2, 164.7 and 193.7; IR

(KBr pellet) 3423, 1664, 1398, 1273 and 1022 cm^{-1} ; HRMS for $\text{C}_{10}\text{H}_9\text{O}_2\text{Cl}$ calcd. 196.0291, found 196.0285.

3-(4-Methoxyphenyl)-3-(dimethylamino)-2-propenal (20). A 150-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer. Into the flask was placed 4.0 g (10.6 mmol) of **10a**, 6.72 g (63.4 mmol) of sodium carbonate, and 70 mL of 50:50 water:THF. The mixture was heated at reflux for 24 h. After the THF was removed in vacuo, the water phase was extracted three times with chloroform. The combined chloroform extracts were concentrated in vacuo and distilled at 160–172 $^{\circ}\text{C}$ (25–28 Torr). The distillate was then purified by radial chromatography using a gradient elution of hexane and ethyl acetate. A 30% yield of a light brown oil was obtained which had the following properties: bp 162 $^{\circ}\text{C}$ at 25 Torr; ^1H NMR (CDCl_3) δ 2.76 (broad s, 3H), 2.99 (broad s, 3H), 3.82 (s, 3H), 5.35 (d, J = 8.5 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H) and 8.64 (d, J = 8.5 Hz, 1H); ^{13}C NMR (CDCl_3) δ 57.4, 79.3, 105.6, 115.8, 128.0, 132.7, 162.4, 170.6 and 193.1; IR (CHCl_3) 3417 (broad), 2937, 2838, 1609, 1386, 1251 and 1027 cm^{-1} ; HRMS for $\text{C}_{12}\text{H}_{15}\text{NO}_2$ calcd 205.1103, found 205.1098.

Reactions Performed under Basic Conditions. A dry, 100-mL, three-neck, round-bottom flask was equipped with a reflux condenser and magnetic stirrer, and placed under a nitrogen atmosphere. Into the flask was placed a 60% mineral oil dispersion of sodium hydride (0.098 g, 2.44 mmol). The dispersion was washed twice with dry hexane and the hexane was removed via cannula. To the flask was successively added 30 mL of dry DMF, sarcosine ethyl ester hydrochloride (0.187 g, 1.22 mmol), and β -chloroal (19a) (0.1 g, 0.51 mmol). The resulting mixture was stirred for 1 h at room temperature followed by refluxing overnight. The solvent was removed in vacuo and the residue was partitioned between water and chloroform. The combined chloroform extracts were dried and concentrated leaving 0.11 g (84% yield) of **9a**. This material was characterized by ^1H NMR and tlc and compared with those of an authentic sample⁴.

Reactions Performed under Neutral Conditions. Into a 50-mL flask were placed 25 mL of dry DMF, sarcosine ethyl ester (0.187 g, 1.22 mmol), and β -chloroal (19) (0.1 g, 0.51 mmol). The flask was equipped with a reflux condenser and magnetic stirrer. The resulting mixture was stirred for one hour at room temperature, followed by refluxing overnight. The solvent was removed in vacuo and the residue was partitioned between water and chloroform. The combined chloroform extracts were dried and concentrated leaving 0.12 g (90% yield) of **9a**. This material was characterized by ^1H NMR and tlc and compared with those of an authentic sample⁴.

Reactions Performed under Acidic Conditions. Into a 50-mL flask were placed 25 ml of acetic acid, sarcosine ethyl ester (0.187 g, 1.22 mmol), and β -chloroenal (**19**) (0.1 g, 0.51 mmol). The flask was equipped with a reflux condenser and magnetic stirrer. The resulting mixture was stirred for 1 h at room temperature, followed by refluxing overnight. Water was added to the reaction mixture and partitioned with chloroform. The combined chloroform extracts were washed with saturated bicarbonate, dried, and concentrated. The ^1H NMR and tlc of the crude material showed that no pyrrole was produced or starting material recovered.

Acknowledgements. We thank the National Science Foundation for an equipment grant (CHE-8068881) which was made for the purchase of high field NMR equipment. Acknowledgement is also made to the National Institutes of Health (grant no. 1R15GM46078-01A1), Monsanto Company, and CIBA-GEIGY Corporation for support of this research. We gratefully acknowledge the Camille and Henry Dreyfus Foundation for a Scholar/Fellow Award to John T. Gupton. In addition, we would also like to thank the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln (supported by NSF grant # DIR9017262) for providing mass spectral analysis on the compounds reported in this paper.

References

- 1.a. E. D. Edstrom and Y. Wei, *J. Org. Chem.*, 1993, **58**, 403; b. T. Sakamoto, Y. Kondo, S. Sato and H. Yamanaka, *Tetrahedron Lett.*, 1994, **35**, 2919.
2. For some recent pyrrole syntheses see a; W. W. Wilkerson, W. Galbraith, K. Gans-Brangs, M. Grubb, W. E. Hewes, B. Jaffee, J. P. Kenney, J. Kerr and N. Wong, *J. Med. Chem.*, 1994, **37**, 988; b; A. Padwa and Norman, B. H. Norman, *J. Org. Chem.*, 1990, **55**, 4801.
3. J. T. Gupton, D. A. Krolikowski, R. H. Yu, J. A. Sikorski and S. W. Riesinger, *J. Org. Chem.*, 1990, **55**, 4735.
4. J. T. Gupton, D. A. Krolikowski, R. H. Yu and P. Vu, J. A. Sikorski, M. L. Dahl and C. R. Jones, *J. Org. Chem.*, 1992, **57**, 5480.
5. J. Liebscher and H. Hartman, *Synthesis*, 1979, 241.
6. E. Pretsch, T. Clerc, J. Seibl and W. Simon, *Spectral Data for Structure Determination of Organic Compounds*, Springer-Verlag, 1989, H265.
7. IR spectra were recorded on a Perkin-Elmer 1600 FTIR and NMR spectra were obtained with a Varian Gemini 200 spectrometer. All melting points and boiling points are uncorrected.