°C (ethanol): IR (Nujol) 1715 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR δ 0.90 (s, 3 H, CMe_2), 0.99 (s, 3 H, CMe_2), 2.33 (s, 3 H, *p*-Me), 2.39 (s, 3 H, *p*-Me), 3.26 (d, 2 H, CH_2, J = 17 Hz), 3.43 (d, 2 H, $Ph_2C{=}CCH_2$, J = 17 Hz), 3.53 (d, 2 H, $Ph_2C{=}CCH_2$, J = 17 Hz), 4.04 (d, 2 H, CH_2, J = 17 Hz), 5.89 (s, 1 H, $COCHPh_2$), 7.02–7.30 (m, 24 H, Ar H), 7.53 (d, 2 H, Ar H, J = 7 Hz), 7.77 (d, 2 H, Ar H, J = 7 Hz); mass spectrum, m/z (rel intensity) 569 (M^+ – $Ph_2C{=}C{=}O$, 2), 433 (5), 375 (4), 194 (31), 165 (60), 119 (100). Anal. Calcd for $C_{51}H_{45}N_3O_4$: C, 80.49; H, 5.93; N, 5.50. Found: C, 80.28, H, 6.07; N, 5.44.

Reaction of 1a with DCK. To a stirred solution of **1a** (342 mg, 1.5 mmol) and Et_3N (202 mg, 2.0 mmol) in dry dichloromethane (45 mL) was added dropwise a solution of dichloroacetyl chloride (266 mg, 1.8 mmol) in the same solvent (10 mL) in about 2 h. The reaction mixture was stirred at room temperature for 24 h, then a second amount of Et_3N (202 mg, 2.0 mmol) was added, followed by the dropwise addition of a solution of dichloroacetyl chloride (266 mg, 1.8 mmol) in dichloromethane (10 mL) in about 2 h. The reaction mixture was stirred for another 24 h and then was washed with water, the organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. Chromatography of the reaction mixture (silica gel, 10:1 *n*-hexane/ethyl acetate) gave the hydroxypyrazoline **5a** (250 mg, 69%), mp 158–161 °C (lit.[8] mp 158–161 °C).

Reaction of 1b with DCK. The reaction was carried out as described above to give the hydroxypyrazoline **5b** in 67% yield, mp 159–161 °C (lit.[8] mp 159–161 °C).

Reaction of 1c with DCK. The reaction was carried out as described above to give the hydroxypyrazoline **5c** in 59% yield, mp 142–144 °C (lit.[8] mp 142–144 °C).

Reaction of 1g with DCK. The reaction was carried out as described above to give the hydroxypyrazoline **5g** in 56% yield: mp 117–119 °C (ethanol); IR (Nujol) 3420 (OH), 1645 (C=O) cm^{-1}; ^1H NMR δ 1.31 (s, 3 H, CMe_2), 1.43 (s, 3 H, CMe_2), 1.76 (s, 3 H, 5-Me), 2.36 (s, 3 H, *p*-Me), 5.11 (br s, 1 H, OH), 7.16–7.41 (m, 5 H, Ar H), 7.56–7.91 (m, 4 H, Ar H); ^{13}C NMR δ 19.71 (q, J = 128 Hz, 5-Me), 21.35 (m, 4,4-Me), 21.52 (q, J = 128 Hz, *p*-Me), 53.16, 96.61, 127.59, 128.36, 128.44, 129.71, 130.25, 131.30, 131.40, 141.80, 162.06, 170.03; mass spectrum, m/z (rel intensity) 322 (M^+, 4), 119 (100).

X-ray Crystallographic Analysis of 2b. The compound **2b**, $C_{43}H_{38}N_2O_3$, M_r = 630.73, crystallizes as triclinic crystals in space group $P\bar{1}$, a = 12.072 (4), b = 11.664 (3), and c = 14.061 (4) Å, α = 112.22 (2)°, β = 76.84 (2)°, γ = 109.13 (2)°, V = 1785.5 (6) Å^3, Z = 2, D_m = 1.15 g cm^{-3}, D_c = 1.173 g cm^{-3}, μ = 0.4 cm^{-1}. Data were collected by using a crystal of ca. 0.29 × 0.32 × 0.42 mm dimensions, mounted on a Nicolet $P2_1$ diffractometer, $\omega/2\theta$ mode, Mo K$\bar{\alpha}$ Zr-filtered radiation (λ = 0.71069 Å), with scan width 1.8° (2θ) plus α_1–α_2 divergence, scan speed 2–18° 2θ°/min, $2\theta_{max}$ = 44°. Out of 3577 collected reflections 3359 were unique and 2315 were considered observed with I_0 $2.1\sigma(I_0)$. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using SHELXS-86[15] and refined by full matrix least squares using SHELX-76[16] with all non-H atoms refined anisotropically. Although most hydrogens were located from difference Fourier maps, they were all placed in calculated positions at 0.98 Å from their respective C-atoms. Methyl groups and phenyl rings (C–C = 1.4 Å) were refined as rigid groups. Final R/R_w = 0.0611/0.0565 for observed data using unit weights. $\Delta\rho_{max}/\Delta\rho_{min}$ = 0.28/–0.17 e Å^{-3}.

Acknowledgment. We are grateful to Professor P. Hofmann, Technische Universität München, for his support throughout the MNDO calculations. The financial support of the State Scholarship Foundation of the Government of Greece (to S.M.) is also gratefully acknowledged.

Registry No. **1a**, 87885-78-7; **1b**, 87885-80-1; **1c**, 98669-81-9; **1d**, 127519-02-2; **1e**, 127519-03-3; **1f**, 127519-04-4; **1f** hydroxy derivative, 127519-05-5; **1g**, 109072-63-1; **2a**, 127519-06-6; **2b**, 127519-07-7; **2c**, 127519-08-8; **2d**, 127519-09-9; **3**, 127519-10-2; **4**, 127519-11-3; **5a**, 87885-62-9; **5b**, 87885-63-0; **5c**, 87885-65-2; **5g**, 109072-62-0; α-acetylisobutyraldehyde, 1750-73-8; *p*-toluohydrazide, 3619-22-5; 3,3-dimethyl-2,4-hexanedione, 6303-70-4; benzoic hydrazide, 613-94-5; 1-benzoyl-3-ethyl-4,5-dihydro-5-hydroxy-4,4,5-trimethyl-1*H*-pyrazole, 127519-12-4; diphenylacetyl chloride, 1871-76-7; ethyl benzoate, 93-89-0; ethyl diphenylacetate, 3468-99-3; 4-methylbenzonitrile oxide, 13820-14-9; 4-methylbenzohydroxamoyl chloride, 36288-37-6; dichloroacetyl chloride, 79-36-7.

Supplementary Material Available: Tables of X-ray data for **2b** (4 pages). Ordering information is given on any current masthead page.

(15) Sheldrick, G. M. SHELXS-86 program for solution of crystal structure; Göttingen, FRG, 1986.
(16) Sheldrick, G. M. SHELX-76 program for crystal structure determination, Univ. of Cambridge, England, 1976.

Application of 2-Substituted Vinamidinium Salts to the Synthesis of 2,4-Disubstituted Pyrroles

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A variety of 2-substituted vinamidinium salts react with α-amino acid esters under basic conditions to produce 2-carbethoxy-4-substituted-pyrroles in good yield. The overall process represents a short and efficient synthesis of highly functionalized pyrroles from α-substituted acetic acid precursors. Such reactions may involve the intermediacy of azomethine ylids or "pentadienyl like" anions.

The synthesis of pyrrole derivatives[1] and related compounds has been actively pursued in recent years due in part to the pharmacological properties of certain members of this class of substances. For example pyrrolnitrin (1)[2] is a naturally occurring 4-arylpyrrole, and a number of related compounds possess antidiabetic,[3] fungicidal,[4] muscle relaxant,[5] and antibacterial[6] properties.

(1) For the synthesis of 3-substituted pyrroles, see: Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353. For the synthesis of pyrrolidine derivatives, see: Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkataramanan, M. K.; Wong, G. S. *J. Org. Chem.* **1989**, *54*, 644 and references therein.

(2) Herbert, R. B. In *The Alkaloids*; Grundon, M. F., Ed.; Chemical Society: London, 1982; Vol. 12.
(3) Holland, G. F. U.S. Patent 4,282,242, 1981; *Chem. Abstr.* **1981**, *95*, 187068e.
(4) Nippon Soda Co. Ltd. Japanese Patent 8,179,672, 1981; *Chem. Abstr.* **1981**, *95*, 187069f.

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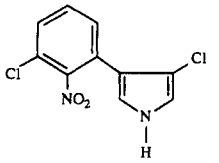


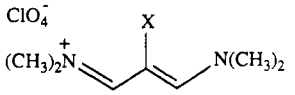
1

Some of the recent synthetic strategies that have been developed to prepare pyrroles utilize the condensation of amino acid derivatives with substances that are formally related to 1,3-dicarbonyl compounds. For example, Wilkinson[7] and co-workers have reported the condensation of an *N,N*-dibenzylglycine ethyl ester with β-keto ketals to give β-hydroxy-δ-amino-δ-carbethoxy ketals which could be deprotected and cyclized to produce 5-substituted-2-carbethoxypyrroles.

Masked 1,3-dicarbonyl compounds, such as β-alkoxyacroleins[8] or enamino ketones,[9] have also been successfully utilized to construct substituted pyrroles. In such cases the amino acid ester is initially reacted with the β-substituted α,β-unsaturated system to produce an N-substituted enamino ketone. These adducts are cyclized under either strongly basic or acidic conditions to provide the corresponding pyrroles. It is of interest to note that very few 4-arylpyrroles have been prepared by such procedures.

Padwa[10] and co-workers have developed a novel procedure for the synthesis of 3-(phenylsulfonyl)pyrroles which relies on the [4 + 1]-annulation of a 2,3-bis(phenylsulfonyl)-1,3-butadiene with a primary amine. The resulting dihydropyrrole is oxidized to the respective pyrrole with DDQ. This is a particularly important strategy since the phenylsulfonyl group allows for selective and facile metallation at the 2-position of the pyrrole and, therefore, further elaboration of the system is possible.

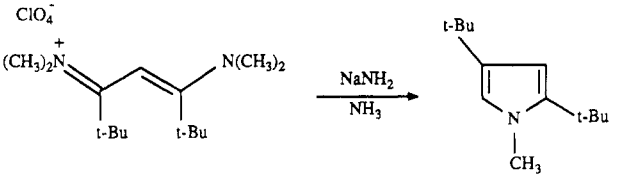
Our research group has been interested for some time in new synthetic methods that utilize vinamidinium salts[11] (**2**).



2

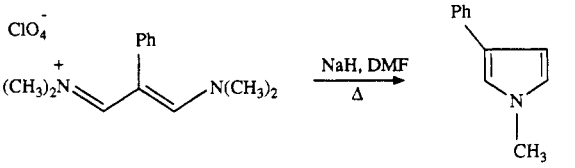
Other workers have had similar interests, and in the course of studying the reactions of a variety of vinamidinium salts with sodium amide in ammonia, Gompper[12] and co-workers reported a single example where a 2,4-di-*tert*-butylpyrrole was produced under such conditions (Scheme I). Prior to this example Arnold[13] and co-workers had described a single reaction of a 2-phenylvinamidinium salt with sodium hydride in DMF to yield *N*-methyl-3-phenylpyrrole in 32% yield (Scheme II).

Scheme I



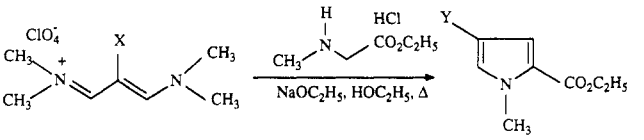
3 4 40% yield

Scheme II



5 32% yield

Table I. Reaction of 2-Substituted Vinamidinium Salts with *N*-Methylglycine Ethyl Ester

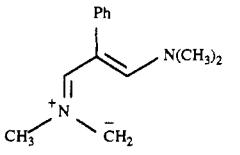


2 7

entry[a]	Y	reaction time, h	% yield	mp or bp, °C
1	4-MeOPh	20	100 (56)	106–107
2	Ph	24	87 (68)	52–53
3	4-MePh	48	100 (59)	78–79
4	3,4-$(MeO)_2$Ph	48	79 (54)	81–82
5	4-ClPh	24	100	65–67
6	4-NO_2Ph	24	100 (76)	127–130
7	4-BrPh	24	100 (78)	85–88
8	1-naphthyl	48	88 (55)	135–136[b]
9	$PhSO_2$	24	100 (91)	164–166
10	formyl	24	97 (97)	66–67

[a] In all cases but entry, 10, X is equal to Y. For entry 10, X is equal to $HC{=}N^+(CH_3)_2$ and Y is equal to formyl. In all examples studied, a single spot was obtained when the reaction products were subjected to TLC analysis on silica gel 7GF with 30% ethyl acetate and 70% hexane as the eluant. All yields in parentheses represent purified products. The difference in crude and purified product yields are primarily due to physical losses incurred during handling of the samples. [b] Boiling point at 0.8 mmHg.

Such reactions could involve the intermediacy of an azomethine ylid such as **6**, and this has been suggested by Arnold[13] to explain the formation of the pyrrole product.



6

This type of process formally represents a 1,5-electrocyclic reaction,[14] which is known to be an important principle of heterocyclic synthesis. In a somewhat analo-

(5) Hattori, K.; Hashimoto, M.; Japanese Patent 6,901,528, 1969; *Chem. Abstr.* **1969**, *70*, 87561a.
(6) Umio, S.; Kariyone, K. Japanese Patent 6,814,699, 1969; *Chem. Abstr.* **1969**, *70*, 87560z.
(7) Elder, T.; Gregory, L. C.; Orozca, A.; Pblug, J. L.; Wiens, P. S.; Wilkinson, T. J. *Synth. Commun.* **1989**, *19*, 763 and references therein.
(8) Breitmaier, E.; Walizei, G. *Synthesis* **1989**, 337 and references therein.
(9) Cohnen, E.; Dewald, R. *Synthesis* **1987**, 566.
(10) Padwa, A.; Norman, B. *Tetrahedron Lett.* **1988**, *29*, 3041.
(11) For a review of the chemistry of vinamidinium salts, see: Lloyd, D.; McNab, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 459. For recent related work by our research group, see also: Gupton, J.; Zembower, D.; Miller, J. *Synth. Commun.* **1988**, *18*, 1891. Gupton, J.; Layman, J. *J. Org. Chem.* **1987**, *52*, 3683. Gupton, J. *Aldrichimica Acta* **1986**, *19*, 43. Gupton, J.; Coury, J.; Moebus, M.; Fitzwater, S. *Synth. Commun.* **1986**, *16*, 1575. Gupton, J.; Norman, B.; Wysong, E. *Synth. Commun.* **1985**, *15*, 1305.
(12) Gompper, R.; Schneider, C. *Synthesis* **1979**, 213.
(13) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1965**, *30*, 346.
(14) Huisgen, R. *Angew Chem., Int. Ed. Engl.* **1980**, *19*, 947. Taylor, E.; Turchi, I. *Chem. Rev.* **1979**, *79*, 181.

gous process Padwa[1] and co-workers have successfully applied the use of azomethine ylids to the preparation of pyrrolidines. Therefore, in anticipation of developing a general synthetic method for the construction of substituted pyrroles from vinamidinium salts, we thought that it would be useful to attach appropriate functional groups to the carbon atom that would ultimately become part of the ylid. By doing this the resultant pyrrole would be regioselectively substituted at the 2- and 4-positions, and, if the proper groups were chosen, the formation of the ylid might be facilitated. Since an ester group could serve such a purpose, we subsequently reacted a variety of 2-substituted vinamidinium salts with *N*-methylglycine ethyl ester in ethanol that contained sodium ethoxide. These results are listed in Table I.

Results and Discussion

The conditions depicted in Table I resulted in the clean and efficient formation of a variety of 2-carbethoxy-4-substituted-pyrroles. The vinamidinium salts used in this study were prepared in a one-pot process from the appropriate substituted acetic acids[15] under Vilsmier–Haack conditions. The majority of the pyrrole products were purified with little difficulty, and in most cases no significant impurities could be detected other than some occasional unreacted starting materials. All reaction products exhibited spectral properties consistent with a 2,4-disubstituted pyrrole,[8] and since the vinamidinium salts were symmetrically substituted, other regiochemical outcomes were unlikely. Entries 9 and 10 in Table I deserve special comment since the substituent at the 4-position of the pyrrole group is a phenylsulfonyl group or a formyl group. It has already been pointed out that the phenylsulfonyl group has useful directing effects[10] regarding metalation reactions, and this would allow for further functionalization of the pyrrole at either the 3- or 5-position. This reaction utilizes a new 2-(phenylsulfonyl)vinamidinium salt, and the chemistry surrounding this substance will be reported in the near future. The 4-formyl-2-carbethoxypyrrole was prepared by the reaction of an iminovinamidinium salt (compound **2**, where X = dimethyliminium) with *N*-methylglycine ethyl ester. The vinamidinium salt used in this reaction has been previously prepared by Arnold[15] and co-workers from haloacetic acids, phosphorus oxychloride, and DMF. We have recently developed a convenient alternative preparation of this vinamidinium salt from phosphonacetic acid derivatives, and this procedure will be reported in due course. The iminium group at the 2-position of the vinamidinium salt represents a masked formyl group, and during the isolation step the aldehyde functional group is unmasked. The presence of the 4-formyl substituent in the pyrrole offers a wide variety of functional group transformations to further elaborate the side chain. The other entries in Table I represent an assortment of aryl groups which can be incorporated at the 4-position of the pyrrole in an efficient and clean fashion. This appears to be rather important in light of the previously mentioned 4-arylpyrroles which possess useful biological activity.[3-6]

It is presumed that in all of the reactions described to this point, an azomethine ylid may be formed as a transient intermediate and that this species undergoes a subsequent concerted cyclization (Scheme III). The resultant product can lose the 3-dimethylamino group by β-elimination[16] to

Scheme III

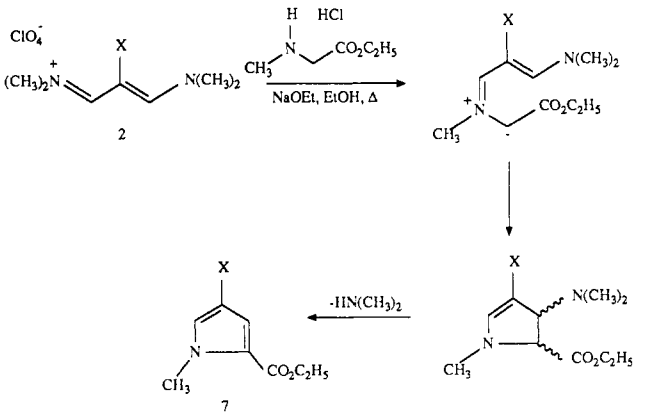
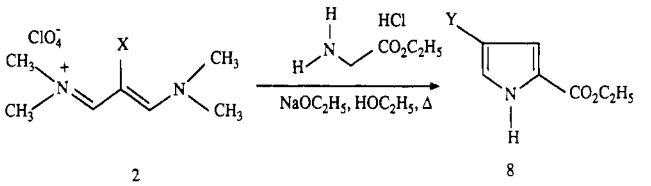


Table II. Reaction of 2-Substituted Vinamidinium Salts with Glycine Ethyl Ester



entry[a]	Y	reaction time, h	% yield	mp or bp, °C
1	4-MeOPh	20	100 (87)	132–133
2	4-BrPh	20	100 (82)	159–160
3	Ph	24	100 (82)	98–99
4	3,4-$(MeO)_2$Ph	24	100 (75)	157–158
5	4-MePh	24	100 (77)	165–166
6	4-ClPh	24	81 (81)	169–171
7	4-NO_2Ph	24	100 (87)	220–230
8	$PhSO_2$	24	100 (91)[b]	93–95
9	formyl	24	0	–
10	1-naphthyl	24	0	–

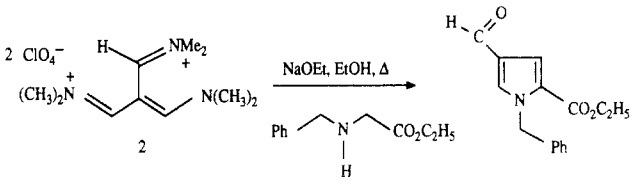
[a] In all cases but entry 9, X is equal to Y. For entry 9, X is equal to $HC{=}N^+(CH_3)_2$ and Y is equal to formyl. In all examples studied a single spot was obtained when the reaction products were subjected to TLC analysis on silica gel 7GF with 30% ethyl acetate and 70% hexane as the eluant. Entry 10 did not clearly produce any pyrrole under the specified conditions. All yields in parentheses represent purified products. The difference in crude and purified product yields are primarily due to physical losses incurred during handling of the samples. [b] This reaction was run in *N,N*-dimethylformamide instead of absolute ethanol.

yield the 2,4-disubstituted pyrrole. Since the presence of the *N*-methyl group of sarcosine provides the opportunity for an azomethine ylid to form, it seemed important to address the question of analogous reactions with glycine ethyl ester itself. Such a reaction should not involve an azomethine ylid intermediate and would therefore tend to react by a "pentadienyl like anion"[14] cyclization. The results of this study are reported in Table II. Many of the vinamidinium salts that were used as substrates for reactions described in Table I were also used in the study reported in Table II. Most of the reactions proceeded readily except in the case of the vinamidinium salts where the 2-substituent was a phenylsulfonyl group, an iminium group, or a naphthyl group. By using DMF as a solvent for the phenylsulfonyl case, a satisfactory yield of the 2-carbethoxy-4-substituted-pyrrole was obtained. Such a

(15) Jutz, C.; Kirchlechner, R.; Seidel, H. *Chem. Ber.* **1969**, *102*, 2301. Arnold, Z., *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051. Arnold, Z. *Ibid.* **1973**, *38*, 1168. Arnold, Z.; Sauliova, J.; Krchnak, V. *Ibid.* **1973**, *38*, 2633.

(16) Jutz has described in a review the concept of electrocyclic ring closure followed by an elimination step for the synthesis of aromatic and heteroaromatic systems. Jutz, C. In *Topics in Current Chemistry*; Springer-Verlag: New York, 1978; Vol. 73.

Scheme IV



modification for the other two vinamidinium salts did not appear to change the unsuccessful course of the reaction. However, since the presence of an *N*-methyl group in the α-amino acid ester component of the reaction (Table I, entry 10) resulted in a favorable outcome for the iminovinamidinium salt, we reasoned that the replacement of the *N*-methyl by an *N*-benzyl group should produce a similar result and that catalytic hydrogenolysis could possibly remove the benzyl moiety. This reaction did prove successful, albeit in a lesser yield (27%) as compared to the other analogs. The lack of reactivity of the naphthyl analogue (Table II, entry 10) with glycine ethyl ester is unclear at this point and may be due to steric factors which could affect conformational requirements of the reactions.

In conclusion, it appears that 2-substituted vinamidinium salts are efficient precursors to 2,4-disubstituted pyrroles when reacted with α-amino acid esters under basic conditions. In the case of the *N*-methylamino acid esters the reactions may involve an azomethine ylid mediated electrocyclic reaction, and in the case of glycine ethyl ester it may involve a "pentadienyl anion like" cyclization. Since vinamidinium salts are obtained in one step from α-substituted acetic acids (approximately 80% yields), the overall process constitutes a two-step convergent synthesis of highly functionalized pyrroles in overall yields of 50–80%. The presence of the 4-phenylsulfonyl and 4-formyl groups provides the opportunity for further elaboration of the pyrrole, and the 4-arylpyrroles are closely related to substances that possess important biological activity.

Experimental Section[17]

The following procedures are typical of the experimental conditions used for the reaction of vinamidinium salts with α-amino acid esters. The requisite vinamidinium salts were prepared by standard methods.[15] The preparation of the 2-(phenylsulfonyl)vinamidinium salt is described in the following section.

2-(Phenylsulfonyl)-1,1,5,5-tetramethyl-1-aza-5-azoniapentadiene Perchlorate. A 250-mL, three-necked, round-bottomed flask was equipped with a condenser, magnetic stirrer, and mineral oil bubbler. Into the flask was placed DMF (7 mL), phosphorus oxychloride (6.9 g, 0.045 mol), and (phenylsulfonyl)acetic acid (3.0 g, 0.015 mol). The resulting mixture was heated at 91 °C for 3 h, during which carbon dioxide was evolved. The reaction mixture was cooled in an ice–water bath and poured into 50 mL of ice–water that contained 3.2 g (0.026 mol) of sodium perchlorate. The mixture was cooled in an ice bath, and the resulting yellow solid (3.4 g, 62% yield) was filtered and dried under vacuum. The solid exhibited the following properties: mp 180–183 °C; ^{1}H NMR (DMSO-d_6) δ 2.98 (s, 6 H), 3.55 (s, 6 H), 7.62 (m, 3 H), 7.92 (d, J = 7.5 Hz, 2 H), and 8.45 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 42.6, 47.8, 98.9, 126.3, 129.9, 133.3, 143.9, and 162.6; IR (Nujol) 1630, 1375, 1140, and 815 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_2O_6ClS$: C, 42.56; H, 5.23; N, 7.64; S, 8.74. Found: C, 42.29; H, 4.97; N, 7.38; S, 8.76.

(17) Infrared spectra were recorded on a Perkin-Elmer Model 1420 infrared spectrophotometer as either thin films or in solution cells. NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 at 200 MHz with a Varian Gemini 200 spectrometer and tetramethylsilane as a reference. All boiling points and melting points are uncorrected, and melting points were recorded on a Fisher-Johns melting point apparatus.

Preparation of 2-Carbethoxy-4-(4-methoxyphenyl)-1-methylpyrrole. A dry 200-mL, three-necked, round-bottomed flask was equipped with a reflux condenser and magnetic stirrer and was placed under a nitrogen atmosphere. Into the flask was placed 0.233 g (0.0075 mol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed with 50 mL of dry hexane, and the hexane was removed via cannula. To the flask was added 100 mL of dry ethanol, and the mixture was allowed to react for several minutes. Sarcosine hydrochloride (0.693 g, 0.0045 mol) was added, and this was followed by the addition of 1.0 g (0.0030 mol) of the 2-(4-methoxyphenyl)vinamidinium salt. The resulting mixture was refluxed for 24 h, and the solvent was removed in vacuo. The residue was partitioned between water (60 mL) and chloroform (3 × 75 mL), and the combined chloroform extracts were dried with anhydrous magnesium sulfate. After removal of the drying agent and solvent, the residue was dissolved in 50 mL of a 70% ethyl acetate and 30% hexane mixture and filtered through a 2.0-g plug of 200-mesh silica gel. The silica gel was washed with additional ethyl acetate, and the solvent was removed in vacuo from the combined filtrates to give 0.435 g (56% yield) of a tan solid which had the following properties: mp 106–107 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 3.80 (s, 3 H), 3.95 (s, 3 H), 4.30 (q, J = 7.5 Hz, 2 H), 6.88 (d, J = 8 Hz, 2 H), 6.98 (d, J = 2.0 Hz, 1 H), 7.14 (d, J = 2.0 Hz, 1 H), and 7.40 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 37.2, 55.6, 60.2, 114.6, 114.9, 122.4, 124.2, 126.1, 126.7, 127.8, 158.7, and 161.9; IR ($CHCl_3$) 1685 cm^{-1}; mass spectrum, m/e 259 (M^+). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 54.56; H, 4.59; N, 4.55. Found: C, 54.79; H, 4.67; N, 4.26.

2-Carbethoxy-4-phenyl-1-methylpyrrole: mp 52–53 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 3 H), 3.95 (s, 3 H), 4.29 (q, J = 7.5 Hz, 2 H), 7.06 (d, J = 2 Hz, 1 H), 7.13–7.26 (m, 3 H), 7.33 (t, J = 8 Hz, 1 H), and 7.48 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 37.3, 60.3, 115.2, 123.9, 124.4, 125.6, 126.5, 126.6, 129.3, 135.0, and 161.9; IR ($CHCl_3$) 1690 cm^{-1}; mass spectrum, m/e 229 (M^+). Anal. Calcd for $C_{14}H_{15}O_2N$: C, 73.33; H, 6.61; N, 6.11. Found: C, 73.04; H, 6.87; N, 5.94.

2-Carbethoxy-4-(4-methylphenyl)-1-methylpyrrole: mp 78–79 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3 H), 2.33 (s, 3 H), 3.92 (s, 3 H), 4.28 (q, J = 7.5 Hz, 2 H), 7.02 (d, J = 2 Hz, 1 H), 7.10–7.30 (m, 3 H), and 7.37 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 21.3, 37.2, 60.2, 115.1, 123.8, 124.4, 125.5, 126.4, 129.9, 132.2, 136.2, and 161.9; IR ($CHCl_3$) 1680 cm^{-1}; mass spectrum, m/e 243 (M^+). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.06; N, 5.76. Found: C, 73.38; H, 7.08; N, 5.35.

2-Carbethoxy-4-(3,4-dimethoxyphenyl)-1-methylpyrrole: mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.30 (q, J = 7.5 Hz, 2 H), 6.84 (d, J = 8 Hz, 1 H), 6.96–7.07 (m, 2 H), 7.13 (d, J = 2 Hz, 1 H), and 7.23 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 37.2, 56.2, 56.3, 60.3, 109.1, 112.0, 115.0, 117.8, 123.7, 124.4, 126.2, 128.2, 148.1, 149.7, and 161.9; IR ($CHCl_3$) 1685 cm^{-1}; mass spectrum, m/e 289 (M^+). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.41; H, 6.63; N, 4.84. Found: C, 66.37; H, 6.58; N, 4.60.

2-Carbethoxy-4-(4-chlorophenyl)-1-methylpyrrole: mp 65–67 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.5 Hz, 3 H), 3.91 (s, 3 H), 4.28 (q, J = 7.5 Hz, 2 H), 7.02 (d, J = 2 Hz, 1 H), 7.17 (d, J = 2 Hz, 1 H), 7.28 (d, J = 8 Hz, 2 H), and 7.39 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 37.3, 60.4, 115.1, 123.2, 124.1, 126.6, 126.7, 129.3, 132.1, 133.6, and 161.8; IR ($CHCl_3$) 1685 cm^{-1}; mass spectrum, m/e 263, 265 (M^+). Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.75; H, 5.36. Found: C, 63.54; H, 5.37.

2-Carbethoxy-4-(4-nitrophenyl)-1-methylpyrrole: mp 127–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 7.5 Hz, 3 H), 3.96 (s, 3 H), 4.30 (q, J = 7.5 Hz, 2 H), 7.17 (d, J = 2 Hz, 1 H), 7.23 (d, J = 2 Hz, 1 H), 7.56 (d, J = 8 Hz, 2 H), and 8.15 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.6, 35.0, 60.5, 111.1, 112.8, 118.2, 124.4, 126.1, 130.2, 139.0, 147.6, and 161.9; IR ($CHCl_3$) 1690 cm^{-1}; mass spectrum, m/e 274 (M^+). Anal. Calcd for $C_{14}H_4N_2O_4$: C, 61.30; H, 5.15; N, 10.22. Found: C, 61.07; H, 5.20; N, 9.97.

2-Carbethoxy-4-(4-bromophenyl)-1-methylpyrrole: mp 85–88 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 3 H), 3.93 (s, 3 H), 4.28 (q, J = 7.5 Hz, 2 H), 7.02 (d, J = 2 Hz, 1 H), 7.17 (d, J = 2 Hz, 1 H), 7.33 (d, J = 8 Hz, 2 H), and 7.43 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.6, 37.2, 60.4, 115.0, 120.1, 123.2, 124.1, 126.5, 127.1, 132.3, 134.0, and 161.8; IR ($CHCl_3$) 1685 cm^{-1}; mass

spectrum, m/e 307, 309 (M^+). Anal. Calcd for $C_{14}H_{14}BrNO_2$: C, 54.56; H, 4.59; N, 4.55. Found: C, 54.79; H, 4.67; N, 4.26.

2-Carbethoxy-4-(1-naphthyl)-1-methylpyrrole: bp 135–136 °C (0.8 mmHg); ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 4.00 (s, 3 H), 4.32 (q, J = 7.5 Hz, 2 H), 7.00 (d, J = 2 Hz, 1 H), 7.20 (d, J = 2 Hz, 1 H), 7.40–7.53 (m, 4 H), 7.72–7.92 (m, 2 H), and 8.20–8.30 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.8, 37.2, 60.4, 119.1, 123.1, 123.4, 126.1, 126.3, 126.4, 126.6, 127.2, 127.6, 129.0, 129.4, 132.3, 133.8, 134.5, and 162.1; IR ($CHCl_3$) 1690 cm^{-1}; mass spectrum, m/e 279 (M^+). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.38; H, 6.15; N, 5.02. Found: C, 77.37; H, 6.04; N, 4.94.

2-Carbethoxy-4-(phenylsulfonyl)-1-methylpyrrole: mp 164–166 °C; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 3.90 (s, 3 H), 4.24 (q, J = 7.5 Hz, 2 H), 7.18 (d, J = 2 Hz, 1 H), 7.32 (d, J = 2 Hz, 1 H), 7.42–7.60 (m, 3 H), and 7.93 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.5, 37.9, 61.0, 117.3, 124.7, 125.3, 127.5, 129.7, 131.2, 133.3, 143.4, and 160.9; IR ($CHCl_3$) 1710 cm^{-1}; mass spectrum, m/e 293 (M^+). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.16; N, 4.78. Found: C, 57.46; H, 5.16; N, 4.62.

2-Carbethoxy-4-formyl-1-methylpyrrole: mp 66–67 °C; ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7.5 Hz, 3 H), 3.96 (s, 3 H), 4.30 (q, J = 7.5 Hz, 2 H), 7.32–7.38 (m, 2 H), and 9.74 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5, 38.0, 60.9, 117.9, 125.1, 125.5, 134.2, 161.5, and 185.9; IR ($CHCl_3$) 1670 and 1700 cm^{-1}; mass spectrum, m/e 181. Anal. Calcd for $C_9H_{11}NO_3$: C, 59.65; H, 6.13; N, 7.73. Found: C, 59.89; H, 6.00; N, 7.52.

2-Carbethoxy-4-(4-methoxyphenyl)pyrrole: mp 132–133 °C; ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7.5 Hz, 3 H), 3.78 (s, 3 H), 4.30 (q, J = 7.5 Hz, 2 H), 6.86 (d, J = 8 Hz, 2 H), 7.08–7.13 (m, 2 H), 7.40 (d, J = 8 Hz, 2 H), and 9.40 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 55.6, 60.8, 112.6, 114.7, 119.4, 124.0, 126.9, 127.0, 127.8, 158.8, and 161.9; IR ($CHCl_3$) 3460, 3300, and 1695 cm^{-1}; mass spectrum, m/e 245 (M^+). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.54; H, 6.18; N, 5.71. Found: C, 68.26; H, 6.20; N, 5.56.

2-Carbethoxy-4-(4-bromophenyl)pyrrole: mp 159–160 °C; ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3 H), 4.33 (q, J = 7.5 Hz, 2 H), 7.13 (m, 1 H), 7.19 (m, 1 H), 7.37 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H), and 9.40 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.6, 61.0, 112.7, 119.9, 120.3, 124.5, 126.1, 127.3, 132.3, 134.0, and 161.7; IR ($CHCl_3$) 3430, 3370, and 1690 cm^{-1}; mass spectrum, m/e 293, 295 (M^+). Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.07; H, 4.12; N, 4.76. Found: C, 52.41; H, 4.43; N, 4.43.

2-Carbethoxy-4-phenylpyrrole: mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H), 4.34 (q, J = 7.5 Hz, 2 H), 7.15–7.28 (m, 3 H), 7.34 (t, J = 8 Hz, 2 H), 7.50 (d, J = 8 Hz, 2 H), and 9.40 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 60.9, 112.9, 119.9, 124.2, 125.8, 126.8, 127.3, 129.3, 135.1, and 161.9; IR ($CHCl_3$) 3440, 3300, and 1690 cm^{-1}; mass spectrum, m/e 215 (M^+). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.10; N, 6.51. Found: C, 72.45; H, 6.39; N, 6.23.

2-Carbethoxy-4-(3,4-dimethoxyphenyl)pyrrole: mp 157–158 °C; ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3 H), 3.88 (s, 3 H), 3.92 (s, 3 H), 4.33 (q, J = 7.5 Hz, 2 H), 6.87 (d, J = 8 Hz, 1 H), 7.00–7.20 (m, 4 H), and 9.25 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 56.2, 56.3, 60.9, 109.3, 112.0, 112.7, 118.0, 119.6, 124.0, 127.2, 128.2, 148.3, 149.7, and 161.9; IR (KBr) 3280 and 1684 cm^{-1}; mass spectrum, m/e 275 (M^+). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.43; H, 6.24; N, 5.09 Found: C, 65.37; H, 6.05; N, 4.87.

2-Carbethoxy-4-(4-methylphenyl)pyrrole: mp 165–166 °C; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H), 2.35 (s, 3 H), 7.10–7.30 (m, 4 H), 7.42 (d, J = 8 Hz, 2 H), and 9.35 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 21.3, 60.9, 112.8, 119.9, 124.1, 125.7, 127.3, 130.0, 132.2, 136.5, and 162.0; IR (KBr) 3249 and 1669 cm^{-1}; mass spectrum, m/e 229 (M^+). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.33; H, 6.76; N, 6.11. Found: C, 72.42; H, 6.70; N, 5.83.

2-Carbethoxy-4-(4-chlorophenyl)pyrrole: mp 169–171 °C; ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3 H), 4.35 (q, J = 7.5 Hz, 2 H), 7.15 (broad s, 1 H), 7.20 (broad s, 1 H), 7.29 (d, J = 8 Hz, 2 H), 7.43 (d, J = 8 Hz, 2 H), and 9.55 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 61.0, 112.8, 120.1, 124.4, 126.1, 127.0, 129.4, 132.3, 133.6, and 161.9; IR (KBr) 3300 and 1693 cm^{-1}; mass spectrum, m/e 249, 251 (M^+). Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.52; H, 4.85. Found: C, 62.15; H, 4.65.

2-Carbethoxy-4-(4-nitrophenyl)pyrrole: mp 220–230 °C; ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.5 Hz, 3 H), 4.37 (q, J = 7.5 Hz, 2 H), 7.27 (m, 1 H), 7.37 (m, 1 H), 7.63 (d, J = 8 Hz, 2 H), 8.21 (d, J = 8 Hz, 2 H), and 9.40 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4, 60.0, 112.9, 123.3, 123.8, 124.2, 124.4, 125.5, 142.1, 145.2, and 160.6; IR (KBr) 3279 and 1691 cm^{-1}; mass spectrum, m/e 260 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.66; N, 10.77. Found: C, 59.53; H, 4.62; N, 10.35.

2-Carbethoxy-4-(phenylsulfonyl)pyrrole. A dry 200-mL, three-necked, round-bottomed flask was equipped with a reflux condenser and magnetic stirrer and was placed under a nitrogen atmosphere. Into the flask was placed 0.273 g (0.0114 mol) of a 60% by weight mineral oil dispersion of sodium hydride. The dispersion was washed with 5 mL of dry hexane, and the hexane was removed via cannula. To the flask were added 70 mL of dry DMF and 0.524 g (0.0114 mol) of absolute ethanol. The resulting mixture was allowed to react for several minutes, 0.572 g (0.003 95 mol) of glycine ethyl ester hydrochloride was added, and this was followed by 1.0 g (0.002 73 mol) of the (phenylsulfonyl)vinamidinium salt. This mixture was refluxed for 24 h, and the DMF was removed in vacuo. The residue was dissolved in a small amount of chloroform, filtered, and placed on a 2-mm plate of silica gel 60, which was mounted on a Harrison radial chromatotron. The residue was subjected to radial chromatography with a 60:40 mixture of ethyl acetate–hexane, and 0.69 g (91% yield) of tan solid was obtained. This material had the following physical properties: mp 93–95 °C; ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 4.32 (q, J = 7 Hz, 2 H), 7.15 (m, 1 H), 7.50 (m, 4 H), 7.95 (d, J = 7 Hz, 2 H), 9.85 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5, 61.7, 114.6, 125.5, 126.2, 127.4, 127.5, 129.7, 133.5, 143.2, and 161.2; IR (KBr) 3281 and 1687 cm^{-1}; mass spectrum, m/e 279 (M^+). Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.91; H, 4.70; N, 5.02. Found: C, 55.45; H, 4.60; N, 4.72.

***N*-Benzyl-2-carbethoxy-4-formylpyrrole.** A dry 200-mL, three-necked, round-bottomed flask was equipped with a reflux condenser and magnetic stirrer and was placed under a nitrogen atmosphere. Into the flask was placed 0.0785 g (0.003 27 mol) of a 60% by weight mineral oil dispersion of sodium hydride. The dispersion was washed with 5 mL of dry hexane, and the hexane was removed via cannula. To the flask was added 70 mL of dry ethanol, and the mixture was allowed to react for several minutes. *N*-Benzylglycine ethyl ester (0.379 g, 0.001 96 mol) was added, and this was followed by the addition of 0.5 g (0.001 31 mol) of the 2-iminovinamidinium salt.[15] The resulting mixture was refluxed for 24 h, and the solvent was removed in vacuo. The residue was dissolved in a small amount of chloroform and filtered and placed on a 2-mm plate of silica gel 60, which was mounted on a Harrison radial chromatotron. The residue was subjected to radial chromatography with a 95:5 mixture of ethyl acetate–hexane, and 0.09 g (27% yield) of an amber oil was obtained. This material had the following physical properties: bp 178 °C (0.3 mmHg); ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 4.25 (q, J = 7.5 Hz, 2 H), 5.58 (s, 2 H), 7.10–7.48 (m, 7 H), and 9.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4, 53.3, 60.9, 118.3, 125.2, 125.5, 127.9, 128.7, 129.5, 133.6, 136.9, 161.3, and 186.0; IR (thin film) 1681 and 1700 cm^{-1}; mass spectrum, m/e 257 (M^+). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.01; H, 5.89; N, 5.44. Found: C, 69.93; H, 6.05; N, 5.29.

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Registry No. **2** (X = 4-MeOPh), 7089-25-0; **2** (X = Ph), 7089-34-1; **2** (X = 4-MePh), 7089-26-1; **2** (X = 3,4-$(MeO)_2$Ph), 97176-88-0; **2** (X = 4-ClPh), 7215-49-8; **2** (4-NO_2Ph), 7099-54-9; **2** (X = 4-BrPh), 23801-14-1; **2** (X = 1-naphthyl), 23801-15-2; **2** (X = $PhSO_2$), 127572-47-8; **2** (X = $HC{=}N^+(CH_3)_2$), 2009-81-6; **7** (Y = 4-MeOPh), 127572-48-9; **7** (Y = Ph), 92802-01-2; **7** (Y = 4-MePh), 127572-49-0; **7** (Y = 3,4-$(MeO)_2$Ph), 127572-50-3; **7** (Y = 4-ClPh), 127572-51-4; **7** (Y = 4-NO_2Ph), 127572-52-5; **7** (Y =

4-BrPh), 127572-53-6; 7 (Y = 1-naphthyl), 127572-54-7; 7 (Y = $PhSO_2$), 127572-55-8; 7 (Y = formyl), 113169-27-0; 8 (Y = 4-MeOPh), 127572-56-9; 8 (Y = 4-BrPh), 127572-57-0; 8 (Y = Ph), 127572-58-1; 8 (Y = 3,4-$(MeO)_2$Ph), 127572-59-2; 8 (Y = 4-MePh), 127572-60-5; 8 (Y = 4-ClPh), 127572-61-6; 8 (Y = 4-NO_2Ph), 127572-62-7; 8 (Y = $PhSO_2$), 127572-63-8; $H_3CNHCH_2CO_2C_2H_5$·HCl, 52605-49-9; $H_2NCH_2CO_2C_2H_5$·HCl, 623-33-6; (phenylsulfonyl)acetic acid, 3959-23-7; *N*-benzyl-2-carbethoxy-4-formylpyrrole, 127572-64-9; *N*-benzylglycine ethyl ester, 6436-90-4; 2-iminovinamidinium, 127572-66-1.

Condensation of (2-Bromo-1-phenylethylidene)malononitrile with Substituted Thioureas: An Unusual Ring Size Effect

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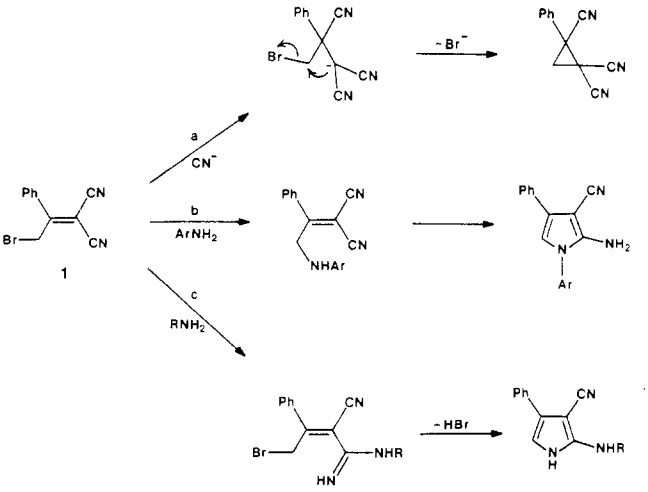
Condensations of the title electrophile with ambident S,N-nucleophiles, e.g., thiourea, *N,N'*-diphenylthiuourea, and thiosemicarbazide, proceed via initial S-alkylation followed by closure of the thiazole ring. In contrast to this, cyclic thioureas with the five-, six- and seven-membered rings afford distinct condensation products depending on the size of the ring. 2-Imidazolinethione gave 7-cyano-2,3-dihydro-5-mercapto-6-phenyl-1*H*-pyrrolo[1,2-*a*]-imidazole in low yield. 3,4,5,6-Tetrahydro-2(1*H*)-pyrimidinethione afforded [2-(1-isothiocyano-3-aminopropyl)-1-phenylethylidene]malononitrile in high yield, while 1,3,4,5,6,7-hexahydro-2*H*-1,3-diazepine-2-thione gave 7-amino-8-cyano-9-phenyl-2,3,4,5-tetrahydropyrido[1,2-*a*][1,3]diazepine in moderate yield. A common feature of these cyclizations is the primary S-nucleophilic attack, which was confirmed by isolation and characterization of the corresponding intermediates. The effects of ring size are discussed.

The reactions of (2-bromo-1-phenylethylidene)malononitrile (1)[1] with nucleophiles proceed via three main routes depending on the nature of the nucleophile.[2] With anions (RO^-, CN^-, BH_4^-) the reaction commences with addition to the double bond of 1 followed by cyclopropane ring closure (Scheme I, path a).[1a] With mildly basic amines ($ArNH_2$) S_N2 substitution of the bromine atom takes place followed by pyrrole ring closure (path b).[3] Alternatively, one of the cyano groups can be attacked by a more basic aliphatic amine (RNH_2; path c) to give rise to a differently substituted pyrrole.[3]

We have reported previously[4] that cyclic thioureas with five- and six-membered rings underwent distinct condensations with 1. Thus, 2-imidazolidinethione (2) and 1 gave the substituted pyrrolo[1,2-*a*]imidazole 3, while 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethione (4) afforded the open-ring isothiocyanate 5 (Scheme II). In contrast to 2 and 4, thiourea reacted with 1 in a usual way to afford 2-amino-4-phenylthiazole (6). We suggested a mechanistic explanation for the formation of 3 and 6 based on an initial nucleophilic displacement by the sulfur in 2 or thiourea, respectively, of the reactive allylic bromine atom in 1. On the other hand, the formation of 5 pointed to an initial nucleophilic attack by one of the nitrogen atoms in 4, followed by base-induced opening of the tetrahydropyrimidine ring.

Scheme I



The apparent dichotomy in the S- versus N-nucleophilic reactivity of 2 and 4, respectively, is remarkable indeed, as cyclic thioureas are generally regarded as archetypal S-nucleophiles.[5,6] While the different nucleophilic sites in thiourea and 4 could be explained by alkyl substituent effects that increase the nucleophilicity of the nitrogen atoms, such an explanation cannot hold for the distinct behavior of 2 and 4 in which the substitution patterns at the nitrogens are nearly identical. The unusual dichotomy

(1) *Warning!* (2-Bromo-1-phenylethylidene)malononitrile is potent allergen.

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