Efficient Synthesis of Pyrroles from Chemoselective Addition of Primary Amines to 1,6-Dioxo-2,4-dienes

Chi Wi Ong,* Chong Meng Chen, Long Hu Wang, and Jiing Jyh Jan

Department of Chemistry, National Sun Yat Sen University, Kaohsiung, Taiwan

Po Chuen Shieh

Department of Pharmacy, Ta Jen Pharmaceutical Junior College, Ping Tung, Taiwan

Received August 4, 1998

Introduction

Pyrroles are widespread in nature. The classical methods for pyrrole ring synthesis include (i) the Hantzsch synthesis,[1] (ii) the Paal Knorr synthesis,[2] (iii) the Knorr synthesis,[3] and (iv) cycloaddition reactions such as those of nitrile ylides with alkynes.[4] Several new variations in the formation of pyrrole rings have also been reported such as the reaction of dichloroazodienes with electron-rich olefins,[5] the rhodium-catalyzed reaction of α-diazo ketoacyl amides,[6] the reaction of chromium carbene complexes with 1-azadienes,[7] and the McMurry intramolecular type II alkylidenation of acylamidocarbonyl.[8] Gilchrist[9] has recently reviewed several new combinatorial methods for the preparation of pyrroles.

In our previous paper,[10] we reported that furans can be easily obtained from the acid-catalyzed intramolecular cyclization of 1,6-dioxo-2,4-dienes. As part of our long-standing interest in the chemistry of 1,6-dioxo-2,4-dienes, we have investigated their reaction with primary amines in the hope of constructing pyrroles to illustrate their versatility as synthetic intermediates.

Results and Discussion

At the onset of this work, we were uncertain as to the outcome of primary amine addition to the 1,6-dioxo-2,4-diene system. The 1,6-dioxo-2,4-diene has six reaction sites available for addition with a primary amine, the two carbonyls and the α, *β*, *γ*, and *δ* positions of the carbon−carbon double bonds. The products that can be obtained from these reaction sites are shown in Scheme 1. (1) Reaction at the C-1 carbonyl with a primary amine would give rise to an imine. The geometric constraint of the (*E*,*E*)-diene excludes further reaction until isomerization to the (*E*,*Z*)-diene, which can then undergo an intramolecular Michael cyclization onto the *γ*-position followed by aromatization to give pyrrole **2**. (2) Michael addition of the primary amine at the α-position of the diene followed by an intramolecular cyclization with the carbonyl would give a six-membered ring hemiaminal **3**, which eliminates water to give dihydropyridine. (3) Michael addition at the *β*-carbon atom of the diene followed by isomerization to the *Z*-olefin, condensation with the carbonyl, and dehydration in this case would give pyrrole **4**. In the case of symmetric 1,6-dioxo-2,4-diene, pyrroles **2** and **4** are the same compound. Interestingly, in the case of asymmetric 1,6-dioxo-2,4-diene, whereby the number of reactive sites is doubled, reaction at the C-1 and *γ*-positions would give rise to the same pyrrole, **2**, whereas reaction at the C-6 and *β*- positions would give the same pyrrole, **4**. Thus, irrespective of the increasing number of reaction sites, only two types of pyrrole, **2** and **4**, can be formed from these reactions. Our first task was to determine whether chemoselectivity exists in the reaction with primary amines.

For simplicity, the initial study was carried out using the symmetric 2,6-dioxo-octa-3,5-diene **1a** obtained from the reaction of methylfuran with 1-diazoacetone.[10] Treatment of **1a** with glycine ethyl ester in ethanol was found to give 2-(2-oxopropyl)-5-methyl-(pyrrol-1-ly)acetic acid ethyl ester **5** in a good yield. Pyrrole **5** arises irrespective of reaction at either the C-1 and C-6 carbonyls or the *β* (*γ*) double bonds with the primary amino group of glycine ethyl ester, as shown in Scheme 1. The (pyrrol-1-ly)acetic acid ethyl ester derivatives have been prepared previously by the reaction of 1,4-dichloro-1,4-dimethoxybutane[11] or 4-oxopentanal[12] with glycine ethyl ester. The product derived from the addition of primary amine at the α (*δ*) double bond to give six-membered ring heterocycle **3** or dihydropyridine was not observed, which excluded this pathway. This result can be explained by the fact that the initial intermolecular addition reaction of amine to all the reaction sites and the further intramolecular cyclization reactions are reversible; in contrast, the aromatization step to pyrrole is irreversible.

The use of an appropriate asymmetric 1,6-dioxo-2,4-diene might enable us to distinguish whether the initial reaction occurs at the carbonyls or the double bonds during pyrrole formation. Most important, the compound must possess two differentiable carbonyl groups to probe the chemoselectivity of the reaction. With this intention, 1-phenyl-1,6-dioxo-hepta-2,4-diene **1b** and 1-ethoxy-1,6-dioxo-hepta-2,4-diene **1c** were synthesized from the reaction of methylfuran with α-diazoacetophenone and ethyl diazoacetate, respectively. In the case of **1b** (Scheme 1, R_1 = Me, R_2 = Ph), the C-1 carbonyl and the *β*-double bond are the more reactive sites, and reaction of primary amine unselectively at both positions will lead to the formation of pyrroles **2** and **4**, respectively. Reaction of **1b** with glycine ethyl ester was found to proceed chemoselectively at the C-1 carbonyl to give pyrrole **6** (Table 1). Structural evidence for **6** can be gleaned from the IR

(1) Beelen van, D. C.; Wolters, J.; Gen van der, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 437.
(2) Jones, R. A.; Been, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, 1977; Chapter 3.
(3) Kleinspehn, G. G. *J. Am. Chem. Soc.* **1955**, *77*, 1546.
(4) Huisgen, R.; Stangl, H.; Sturm, H. J.; Wagenhofer, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 50.
(5) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *Tetrahedron Lett.* **1996**, *37*, 1351.
(6) Padwa, A.; Deen, D. C.; Hertzog, D. C.; Wadler, W. R.; Zhi, L. *Tetrahedron* **1992**, *48*, 7565.
(7) Danks, T. N.; Velo-Rego, D. *Tetrahedron Lett.* **1994**, *35*, 9443.
(8) Furstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442.
(9) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615.
(10) Ong, C. W.; Chen, C. M.; Juang, S. S. *J. Org. Chem.* **1995**, *60*, 3135.
(11) Chan, T. H.; Lee, S. D. *J. Org. Chem.* **1983**, *48*, 3059.
(12) Salomon, R. G.; Miller, D. B.; Zagorski, M. G.; Coughlin, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 6049.

10.1021/jo981566x CCC: $15.00
Published on Web 11/03/1998

Scheme 1. Potential Reaction Sites and Product Formation from the Reaction of 1,6-Dioxo-2,4-diene with Primary Amines

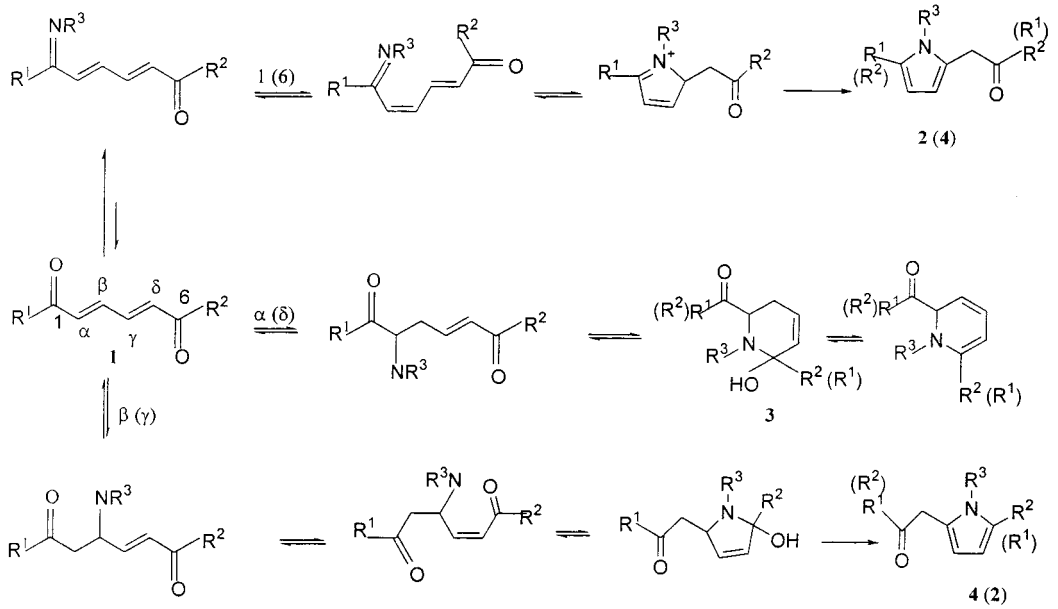


Table 1. Synthesis of Pyrrole Derivatives from 1 (R_1 = Me)

Entry	Dienedione	Primary Amine	Product (yield)
1	**1a**, R_2=-CH_3	NH_2CH_2COOEt	**5** (70)
2	**1b**, R_2=-Ph		**6** (95)
3	**1c**, R_2=-OEt		**7** (90)
4	**1b**	NH_2	**8** (45)
5	**1b**	NH_2	**9** (75)
6	**1b**	NH_2NH_2	**10** (70)
7	**1b**	NH_2OH	**11** (45)
8	**1b**	H_2N	**12** (65)
9	**1a**, R_2=-CH_3	NH_2, CH_3, MeOOC, H	**15** (25)
10	**1b**, R_2=-Ph		**16** (45)
11	**1c**	NH_3	**17** (42%)

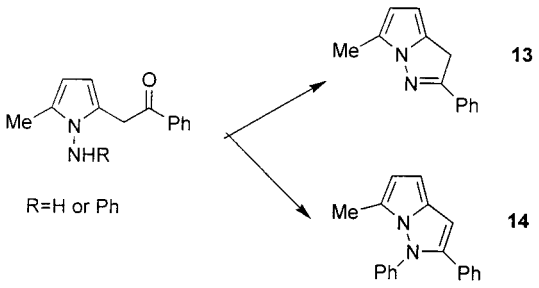
absorption at 1681 cm^{-1}, indicating a conjugated ketone to phenyl. The product from addition to the β-double bond was not formed. Similarly, reaction of **1c** (Scheme 1, R_1 = Me, R_2 = OMe) with glycine took place chemoselectively at the C-1 carbonyl to give pyrrole **7**. On the basis of these findings, we propose that the $\alpha,\beta,\gamma,\delta$-dienone preferentially undergoes a chemoselective 1,2-addition at the more reactive carbonyl with primary amines, followed by an intramolecular cyclization and aromatization to give a pyrrole. This is because addition at the carbonyl of the $\alpha,\beta,\gamma,\delta$-dienone has the least deconjugation effect with the formation of an imine, whereas addition at any position of the double bond destroys the continuity of the conjugate system. The $\alpha,\beta,\gamma,\delta$-dienone thus behaves differently from a simple α,β-enone, which preferentially undergoes 1,4-addition at the carbon double bond with primary amines.

The 1-phenyl-1,6-dioxo-hepta-2,4-diene **1b** was found to be the more stable of these compounds. It was thus chosen to react with a wide array of primary amines to probe the generality of this methodology for the synthesis of *N*-2,5-trisubstituted pyrroles. Compound **1b** reacts with aniline to give *N*-phenylpyrrole **8** (Table 1, entry 4), which could be of importance in the design of potential antagonist for the interaction of HIV surface protein with cellular receptor CD4.[13] Reaction of benzylamine with **1b** gave *N*-benzylpyrrole **9**, an important intermediate whereby the benzyl group might be selectively deprotected. Hydrazine and hydroxylamine react with the carbonyl group to give hydrazone and oxime intermediates, which undergo intramolecular Michael cyclizaztion to give *N*-amino- and *N*-hydroxypyrrole **10** and **11**, respectively. The reaction of **1b** with hexylamine also proceeded chemoselectively to give *N*-alkyl pyrrole **12**. Table 1 summarizes these results. All reactions were found to proceed chemoselectively to give only a single product.

The amino pyrrole **10** derived from the reaction with hydrazine (Table 1, entry 6) was found to undergo an acid-catalyzed intramolecular condensation with the carbonyl present to give the 3H-pyrrolo[1,2-b]pyrazole ring system **13** in a good yield (Scheme 2). This isomeric structure for compound **13** was confirmed from its ^1H NMR spectra showing a singlet for the methylene protons at δ3.35. When **1b** was reacted with phenylhydrazine, the *N*-aminophenylpyrrole was not isolated, but instead,

(13) Javest, R. L.; Marshall, J. E. *J. Heterocycl. Chem.* **1992**, *29*, 1401.

Scheme 2. Acid-Catalyzed Formation of 3-H-Pyrrolo[1,2-b]pyrazole



it underwent a second condensation as above to give compound **14**. In this case, only one isomer can be formed.

We also investigated the reaction of dienones **1a** and **1b** with a chiral amino acid, (−)alanine, and these gave rise to pyrrole derivatives **15** and **16**, respectively (Table 1, entries 9 and 10). Although the synthesis was ultimately successful, the pyrrole was formed only after a prolonged reaction time and in a low yield. It is not clear what untoward interaction during the reaction might be responsible for this phenomenon, which must await further experimentation.

The reaction of 1,6-dioxo-2,4-diene with ammonia would give rise to N-unsubstituted pyrrole. The ethyl-2-methylpyrrole-5-acetate, **17**, has been obtained by the reaction of 2-methylpyrrole with diazoacetic acid ethyl ester.[14] We prepared the pyrrole **17** from the reaction of **1c** with liquid ammonia in tetrahydrofuran. The use of saturated aqueous ammonia water was unsuccessful.

Conclusion

In conclusion, we have developed a new synthetic method for the efficient preparation of N-substituted 2,5-disubstituted pyrrole from 1,6-dioxo-2,4-diene via a chemoselective addition of a primary amine to the carbonyl followed by an intramolecular Michael addition and aromatization. Furthermore, this methodology can be extended to the synthesis of the 3H-pyrrolo[1,2-b]-pyrazole ring system.

Experimental Section

Melting points reported were uncorrected. ^{1}H NMR spectra were recorded on a 200 MHz spectrometer in $CDCl_3$ and infrared spectra in $CHCl_3$. HRMS and elemental analysis were obtained from the instrumentation laboratory of the NSC, Taiwan. Diazald was purchased from Aldrich. Compound **1b** was synthesized in our previous report,[10] and **1a**,**c** were synthesized accordingly.

2,7-Dioxo-octa-3,5-diene 1a. This was prepared from 1-diazoacetone and 2-methylfuran in 70% yield as a brown oil. ^{1}H NMR δ 8.22 (dd, J = 11.3, 11.1 Hz, 1H), 6.52 (t, J = 11.3 Hz, 1H), 6.37 (dd, J = 11.3, 11.1 Hz, 1H), 6.29 (d, J = 11.1 Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H). MS m/z 138. Anal. Calcd for $C_8H_{10}O_2$: C, 69.53; H, 7.30. Found: C, 69.23; H, 7.59.

1-Ethoxy-1,6-dioxo-hepta-2,4-diene 1c. This was prepared from ethyl diazoacetate and methyl furan in 75% yield as a dark-brown oil. ^{1}H NMR δ 8.27 (dd, J = 11.4, 11.3 Hz, 1H), 6.47 (t, J = 11.4 Hz, 1H), 6.32 (dd, J = 11.3, 11.2 Hz, 1H), 6.14 (d, J = 11.2 Hz, 1H), 4.24 (q, 2H), 2.29 (s, 3H), 1.31 (t, 3H). MS m/z 168. Anal. Calcd for $C_9H_{12}O_2$: C, 64.26; H, 7.20. Found: C, 64.06; H, 7.15.

General Procedure: Reaction of Primary Amines with 1a−c. The primary amine (1.1 mmol) was dissolved in ethanol. In the case of primary amine hydrochloride salt, it was first neutralized using an equivalent amount of sodium carbonate in ethanol prior to further reaction. To this stirred solution was added the respective 1,6-dioxo-2,4-diene (1 mmol, dissolved in ethanol), and the mixture was left to react overnight at room temperature. The reaction mixture was concentrated under reduced pressure and extracted with chloroform. The crude product obtained was purified by chromatography to afford pure compound.

2-(2-Oxo-propyl)-5-methyl-(pyrrol-1-ly)acetic Acid Ethyl Ester 5. Reaction of **1a** with glycine ethyl ester hydrochloride gave **5** in 70% yield after chromatography (SiO_2, EtOAc/hexane, 1:5) as a yellowish oil. ^{1}H NMR δ 5.98 (d, J = 3.2 Hz, 1H), 5.88 (d, J = 3.20 Hz, 1H), 4.49 (s, 2H), 4.21 (q, 2H), 3.58 (s, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 1.26 (t, 3H). MS m/z 223. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.56; H, 7.67; N, 6.27. Found: C, 64.61; H, 7.79; N, 6.25.

2-(2-Oxo-phenylethyl)-5-methyl-(pyrrol-1-ly)acetic Acid Ethyl Ester 6. Reaction of **1b** with glycine ethyl ester hydrochloride gave **6** in 95% yield (SiO_2, EtOAc/hexane, 1:5) as a yellow solid. mp 82−83 °C. ^{1}H NMR δ 8.02 (2H), 7.55 (1H), 7.45 (2H), 5.95 (d, J = 3.3 Hz, 1H), 5.86 (d, J = 3.3 Hz, 1H), 4.61 (s, 2H), 4.21 (s, 2H), 4.20 (q, 2H), 2.17 (s, 3H), 1.25 (t, 3H). MS m/z 285. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.53; H, 6.74; N, 4.93.

2-(2-Carboethxoxyethyl)-5-methyl-(pyrrol-1-ly)acetic Acid Ethyl Ester 7. Reaction of **1c** with glycine ethyl ester hydrochloride gave **7** in 90% yield (SiO_2, EtOAc/hexane, 1:5) as a yellow oil. ^{1}H NMR δ 5.98 (d, J = 3.5 Hz, 1H), 5.86 (d, J = 3.5 Hz, 1H), 4.61 (s, 2H), 4.12 (m, 4H), 3.56 (s, 2H), 2.16 (s, 3H), 1.27 (m, 6H). MS m/z 253. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.73; H, 7.49; N, 5.60.

2-Methyl-5-(2-oxo-phenylethyl)-l-phenylpyrrole 8. Reaction of **1b** with aniline gave **8** in 45% yield (SiO_2, EtOAc/hexane, 1:10) as a yellowish-orange solid. mp 46−47 °C. ^{1}H NMR δ 7.77 (2H), 7.40 (6H), 7.21 (2H), 6.03 (d, J = 3.4 Hz, 1H), 5.98 (d, J = 3.4 Hz, 1H), 4.03 (s, 2H), 2.03 (s, 3H). MS m/z 275. Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.59; H, 6.03; N, 5.00.

1-Benzyl-2-methyl-5-(2-oxo-phenylethyl)pyrrole 9. Reaction of **1b** with benzylamine gave **8** in 75% yield (SiO_2, EtOAc/hexane, 3:10) as a yellow solid. mp 75−76 °C. ^{1}H NMR δ 7.88 (2H), 7.52 (1H), 7.39 (2H), 7.24 (3H), 6.85 (2H), 5.97 (d, J = 3.5 Hz, 1H), 5.91 (d, J = 3.5 Hz, 1H), 5.08 (s, 2H), 4.10 (s, 2H), 2.19 (s, 3H). MS m/z 289. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.07; H, 6.65; N, 5.01.

1-Amino-2-methyl-5-(2-oxo-phenylethyl)pyrrole 10. Reaction of **1b** with hydrazine gave **10** in 70% yield (SiO_2, EtOAc/hexane, 1:4) as a light-brown solid. mp 88−89 °C. ^{1}H NMR δ 8.02 (2H), 7.55 (1H), 7.44 (2H), 5.83 (d, J = 3.7 Hz, 1H), 5.75 (d, J = 3.7 Hz, 1H), 4.37 (brs, 2H), 4.28 (s, 2H), 2.21 (s, 3H). MS m/z 214. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.54; H, 6.31; N, 12.89.

1-Hydroxy-2-methyl-5(2-oxo-phenylethyl)pyrrole 11. Reaction of **1b** with hydroxylamine gave **11** in 45% yield (SiO_2, EtOAc/hexane, 1:5) as a light-yellow solid. mp 82−83 °C. ^{1}H NMR δ 8.48 (brs, 1H), 8.02 (2H), 7.62 (1H), 7.49 (2H), 5.74 (d, J = 3.9 Hz, 1H), 5.66 (d, J = 3.9 Hz, 1H), 4.34 (s, 2H), 2.26 (s, 3H). MS m/z 215. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.55; H, 6.09; N, 6.51.

***N*-Hexyl-2-methyl-5-(2-oxo-phenylethyl)pyrrole 12.** Reaction of **1b** with hexylamine gave **12** in 65% yield (SiO_2, EtOAc/hexane, 1:10) as a yellow oil. ^{1}H NMR δ 8.01 (2H), 7.43 (3H), 5.87 (d, J = 3.2 Hz, 1H), 5.81 (d, J = 3.2 Hz, 1H), 4.21 (s, 2H), 3.75 (t, 2H), 2.21 (s, 3H), 1.58 (m, 8H), 0.87 (t, 3H). MS m/z 283. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.33; H, 8.77; N, 4.78.

1-Phenyl-6-methyl-3-H-pyrrolo[1,2-b]pyrazole 13. Reaction of **10** with a catalytic amount of *p*-TsOH in refluxing toluene overnight gave **13** in 82% yield (SiO_2, EtOAc/hexane, 2:5) as a slight yellowish solid. mp 91−92 °C. ^{1}H NMR δ 7.83 (2H), 7.39 (2H), 7.29 (1H), 6.51 (d, J = 3.5 Hz, 1H), 5.61(d, J = 3.5 Hz, 1H), 3.35 (br s, 2H), 2.39 (s, 3H). MS m/z 196. Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.31; H, 6.04; N, 14.13.

1,2-Diphenyl-6-methylpyrrolo[1,2-b]pyrazole 14. Reaction of **1b** with phenylhydrazine directly gave **14** in 75% yield

(14) Clemo, G. R.; Metcalfe, T. P. *J. Chem. Soc.* **1936**, 606.

(SiO_2, EtOAc/hexane, 1:4) as a yellow solid. mp 92−93 °C. ^{1}H NMR δ 7.92 (2H), 7.54 (1H), 7.41 (2H), 7.17 (2H), 6.95 (s, 1H), 6.84 (1H), 6.41 (2H), 5.97 (d, J = 3.6 Hz, 1H), 5.87 (d, J = 3.6 Hz, 1H), 2.13 (s, 3H). MS m/z 272. Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.56; H, 6.01; N, 10.14

2-[2-(2-Oxo-propyl)-5-methyl-(pyrrol-1-ly)]propionic Acid Methyl Ester 15. Reaction of **1a** with L-alanine methyl ester gave **15** in 25% yield (SiO_2, EtOAc/hexane, 1:5) as a light-yellow oil. ^{1}H NMR δ 5.95(d, J = 3.5 Hz, 1H), 5.89 (d, J = 3.5 Hz, 1H), 4.73 (q, 1H), 4.13 (s, 2H), 3.74 (s, 3H), 3.65 (s, 3H), 2.17 (s, 3H), 1. 65 (d, 3H). MS m/z 223. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.56; H, 7.67; N, 6.27. Found: C, 64.45; H, 6.58; N, 6.17.

2-[2-(2-Oxo-phenylethyl)-5-methyl-(pyrrol-1-ly)]propionic Acid Methyl Ester 16. Reaction of **1b** with alanine methyl ester gave **16** in 45% yield (SiO_2, EtOAc/hexane, 1:5) as a light-yellow oil. ^{1}H NMR δ 8.02 (2H), 7.52 (1H), 7.45 (2H), 5.92 (d, J = 3.3 Hz, 1H), 5.85 (d, J = 3.3 Hz, 1H), 4.97 (q, 1H), 4.25 (s, 2H), 3.70 (s, 3H), 2.17 (s, 3H), 1.65 (d, 3H). MS m/z 285. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.80; H, 6.98; N, 4.81.

Ethyl-2-methylpyrrole-5-acetate 17.[12] Compound **1c** (168 mg, 1 mM) was dissolved in THF (5 mL) and condensed ammonia using a cold trap and was added, and the mixture was stirred for 8 h, after which the ammonia was left to evaporate. The reaction mixture was concentrated under reduced pressure and extracted with dichloromethane. Purification on preparative plate chromatography gave 40 mg of pure **17** as a yellow oil together with 75 mg of unreacted starting material. The yield based on recovered stating material was 42%. ^{1}H NMR δ 8.40 (br, 1H), 5.86 (s, 1H), 5.77 (s, 1H), 4.17 (q, 2H), 3.60 (s, 2H), 2.24 (s, 3H), 1.26 (t, 3H). Anal. Calcd For $C_9H_{13}NO_2$: C, 64.65; H, 7.84. Found: C, 64.79; H, 7.82.

Acknowledgment. We thank the National Science Council of Taiwan for financial support.

JO981566X