η^2-Pyrrole Complexes as Synthons to Alkaloid Derivatives

L. Mark Hodges, Javier Gonzalez, Jason I. Koontz, William H. Myers,† and W. D. Harman*,[1]

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, and Department of Chemistry, University of Richmond, Richmond, Virginia 23173

Received April 9, 1993

Summary: η^2-Pyrrole complexes, readily generated from the corresponding pyrrole and $Os(NH_3)_5(OTf)_3$, are combined with Michael acceptors under appropriate conditions to yield selectively α- or β-substituted 1*H*-pyrroles or 7-azabicyclo[2.2.1]heptanes.

Pyrroles represent an important class of synthons for alkaloids, providing up to four activated carbons in a heterocyclic ring. However, the pronounced tendency of pyrroles to undergo electrophilic attack at the α position often preempts reactivity at the biologically more significant β positions, and its tendency to rearomatize or polymerize in the presence of electrophiles limits the scope of useful addition reactions.[2] Recently, we reported that η^2-coordination of pyrrole by pentaammmineosmium(II) dearomatizes the heterocyclic ligand and profoundly enhances its reactivity toward both β-electrophilic addition[3a,b] and 1,3-dipolar cycloaddition.[3c] Of equal significance, the π-donating metal system greatly stabilizes the resulting 2*H*- and 3*H*-pyrrolium species allowing for their facile manipulation. Whereas our initial investigation focused on the fundamental organometallic transformations of these complexes, in this report we explore the potential utility of this *dearomatization* methodology in the context of organic synthesis. Through osmium coordination, Michael acceptors as mild as acrylonitrile or methyl acrylate can be *selectively* added at the α-carbon, the β-carbon, or across the two α carbons to form, after further transformations, substituted pyrrolizinones, 1*H*-pyrroles, or 7-azanorbornenes, respectively.[4]

Pyrrole complexes of the form $[Os(NH_3)_5(4,5\text{-}\eta^2\text{-L})](OTf)_2$, (L = pyrrole (**I-1**), *N*-methylpyrrole (**I-2**), 2,5-dimethylpyrrole (**I-3**), 3-methylpyrrole (**I-4**); OTf^- = $CF_3SO_3^-$) are readily generated in good yield (85–95%) from the Mg° reduction of $Os(NH_3)_5(OTf)_3$ in the presence of an excess of the pyrrole in either *N*,*N*-dimethylacetamide (DMAc) or a cosolvent mixture of DMAc and 1,2-dimethoxyethane (DME).[3] Two modes of addition are possible with electron-deficient olefins and an η^2-pyrrole complex depending on the site of metal coordination. In the dominant isomer of the pyrrole complex, the metal binds across C(4) and C(5).[5] Here, the uncoordinated portion of the ligand resembles an enamine, and consequently this isomer undergoes electrophilic addition at the β-carbon C(3).[3a,6] For example, 1 equiv of methyl vinyl ketone (MVK) reacts at 20 °C with the *N*-methylpyrrole complex (**I-2**) in methanol to give the β-alkylated pyrrole complex (**III-2c**); subsequent heating (80 °C, CH_3CN, 1 h) yields the decomplexed β-substituted pyrrole, (**IV-2c**) (>80% overall) completely free of any α addition products (Figure 1). When the *N*-methylpyrrole complex (**I-2**) is combined with 1 equiv of methyl acrylate or acrylonitrile in the presence of *tert*-butyldimethylsilyl triflate (TBSOTf), the corresponding 3*H*-pyrrolium adduct (**II-2a** or **II-2d**) is generated after hydrolysis.[7,8] The π-basic metal is stabilized by the resulting azadiene π acid, and consequently this 3*H*-pyrrolium species resists decomplexation in the absence of a moderate base. Heating (80 °C) in the presence of an amine induces rearomatization and decomplexation to form the β-substituted pyrrole (**IV-2a** or **IV-2d**), in reasonable yield and free of α-alkylated products.[9] A similar reaction sequence may be carried out with 2,5-dimethylpyrrole complex (**I-3**) and methyl acrylate (overall yield of **IV-3a** >85% from **I-3**). *Even in the case of the β-methyl pyrrole (i.e., I-4), alkylation can be achieved exclusively at C(3)* by prior complexation to osmium, generating a β,β-disubstituted 3*H*-pyrrolium complex (**II-4a**) directly from a β-alkylated pyrrole.[10] The parent pyrrole complex also reacts with Michael acceptors at C(3) to form β-alkylated pyrroles, but uncharacterized organometallic side reactions have resulted in poor overall yields (Table I).[11] In contrast, reactions of *uncomplexed* pyrroles with these Michael acceptors generally lead to mixtures of products. For example, the reaction of uncomplexed *N*-methylpyrrole with 1 equiv of methyl acrylate and TBSOTf (in CH_3CN) yields a complex mixture of polyalkylated products and the unreacted pyrrole. The analogous reaction with uncomplexed 2,5-dimethylpyrrole gives a 1:2:1 ratio of the unreacted pyrrole, **IV-3a**, and the 2,5-dimethyl-β,β'-dialkylated product.[12]

† University of Richmond.

(1) Camille and Henry Dreyfus Teacher–Scholar 1992–1997; NSF Young Investigator 1993–1998.

(2) Jones, R. A. In *The Chemistry of Heterocyclic Compounds, Pyrroles*; Wiley & Sons: New York, 1990; Vol. 48.

(3) (a) Myers, W. H.; Koontz, J. I.; Harman, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 5684. (b) Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 6682. (c) Cordone, R.; Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111*, 5969.

(4) For compound identification, **I-V** refer to the class of product (Figures 1 and 2), 1-4 refer to the pyrrole of origin (pyrrole (1), *N*-methyl- (2), 2,5-dimethyl- (3), and 3-methylpyrrole (4)), and **a-e** refer to the olefin of origin (where **a** = methyl acrylate; **b** = dimethyl fumarate; **c** = methyl vinyl ketone; **d** = acrylonitrile; **e** = methyl 3-(3-pyridyl)acrylate.)

(5) Here, the carbons to which the osmium are coordinated are numbered C(4)–C(5) in order to use conventional numbering in the pyrrole nomenclature.

(6) Examples of electrophiles which readily undergo β-electrophilic addition with Os(II)–pyrrole complexes include alkyl triflates, nitrilium salts, anhydrides, aldehydes, ketones, and Michael acceptors. Hodges, L. M.; Myers, W. H.; Koontz, J. I.; Harman, W. D. Manuscript in preparation.

(7) NMR data for **II-2a**: ^1H NMR (300 MHz, acetone-d_6) δ 9.08 (s, 1H), 6.73 (d, J = 3.6 Hz, 1H), 5.14 (br s, 3H), 5.04 (d, J = 3.9 Hz, 1H), 4.06 (s, 3H), 3.91 (br s, 12H), 3.65 (s, 3H), 3.28 (s, 1H), 2.71 (dd, 2H), 2.38 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 174.66 (CH), 173.25 (CO), 74.40 (CH), 53.43 (CH), 51.45 (CH_3), 48.53 (CH), 41.87 (CH_3), 30.83 (CH_2), 24.93 (CH_2).

(8) Compound **II-2a** may be reduced with $NaBH_4$ to give the corresponding 2-pyrroline complex.

(9) ^1H NMR data for **IV-2a**: (300 MHz, CD_3CN) δ 6.47 (t, J = 2.1 Hz, 1H), 6.39 (br s, 1H), 5.85 (t, J = 2.1 Hz, 1H), 3.59 (s, 3H, OCH_3), 3.62 (s, 3H, NCH_3), 2.66 (dd, J = 7.8, 7.2 Hz, 2H), 2.48 (dd, J = 7.8, 7.2 Hz, 2H, CH_2).

(10) Irradiation of the *cis*-ammine gives a 4.5% NOE enhancement of the C(3)-methyl, consistent with *anti*-addition to the pyrrole ring. Decomplexation of the intact 3*H*-pyrrolium ligand has not been achieved.

(11) A paramagnetic Os(III) compound is formed along with the Michael adduct complex. Subsequent removal of the intact ligand has been further hampered by retroaddition.

(12) The characterization of (3,4-bis[2-(carbomethoxy)ethyl]-2,5-dimethylpyrrole) is described in the supplementary material.

0022-3263/93/1958-4788$04.00/0

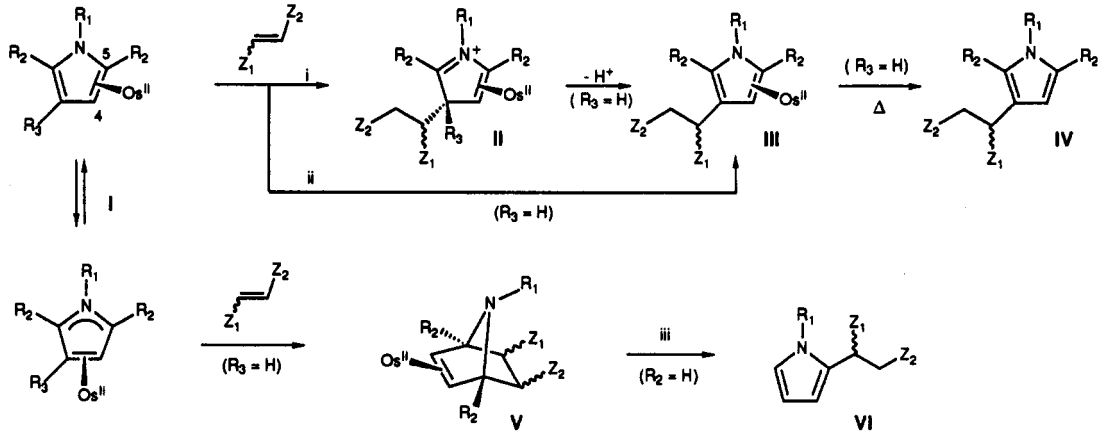

Figure 1. General scheme for Michael addition at C(3) and 1,3-dipolar cycloaddition across C(2) and C(5) for η^2-pyrrole complexes ($Os^{II} = [Os(NH_3)_5]^{2+}$): (i) (1) TBSOTf, MeCN, 5 min; (2) H_2O; (ii) MeOH, 1 h; (iii) TBSOTf, MeCN, 5 min; (2) H_2O; (3) Proton Sponge, 80 °C.

Table I. Compound Key and Yield Data for Reactions of Figure 1.

complex (% yield)	R_1	R_2	R_3	Z_1	Z_2	organic product (% yield)
II-1a (40)	H	H	H	H	CO_2Me	**IV-1a** (8)
II-2a (97)	Me	H	H	H	CO_2Me	**IV-2a** (75)
II-3a (93)	H	Me	H	H	CO_2Me	**IV-3a** (>90)
II-4a (50	H	H	Me	H	CO_2Me	
II-2d (50)	Me	H	H	H	CN	**IV-2d** (40)
III-2c (93)	Me	H	H	H	COMe	**IV-2c** (>90)
V-3a (97)	H	Me	H	H	CO_2Me	*a*
V-3e (93)	H	Me	H	3-py	CO_2Me	
V-2a (70)	Me	H	H	H	CO_2Me	**VI-2a** (50)
V-1b (78)	H	H	H	CO_2Me	CO_2Me	
V-3d (79)	H	Me	H	H	CN	

[a] See Figure 2 for examples of decomplexation.

In dynamic equilibrium with the 4,5-η^2-pyrrole complex is a minor isomer in which the metal binds across C(3) and C(4) of the pyrrole ligand. Although the population of this species is low enough as to be unobservable by ^1H NMR,[13] the uncoordinated fragment of the 3,4-η^2 form resembles an azomethine ylide and as such is significantly more reactive than the 4,5-η^2 species toward certain electrophiles.[3] The presence of methyl groups either at the α-carbons or at nitrogen destabilizes the 4,5-η^2 tautomer and correspondingly increases the effective concentration of the azomethine ylide tautomer. Thus, when the 2,5-dimethylpyrrole complex (**I-3**) is allowed to stand with methyl acrylate in the absence of a Lewis acid, a dipolar cycloaddition occurs generating the 7-azabicyclo-[2.2.1]heptene complex, **V-3a** (95% yield, 85–90% de) (Figure 1, Table I).[14,15] Here, the metal serves not only to activate pyrrole toward formation of an *exo*-cycloaddition product[16] but also to stabilize the 5-carbomethoxy-7-azabicyclo[2.2.1]hept-2-ene ligand which otherwise would spontaneously undergo cycloreversion under ambient conditions.[17] For the 2,5-dimethylpyrrole complex **I-3**, the scope of dipolarophiles includes acrylonitrile along with maleate esters and imides. Also included are β-(3-pyridyl)acrylates, for which the resulting products contain the carbon skeleton of the potent nonopioid analgesic epibatidine.[18] The *N*-methylpyrrole complex (**I-2**) also reacts with dipolarophiles as mild as methyl acrylate to give analagous cycloadducts (e.g., **V-2a**; Table I). For the parent pyrrole complex (**I-1**), ligand substitution preempts cycloaddition with methyl acrylate but cycloaddition is observed with more electron-deficient olefins such as dimethyl fumarate (**V-1b**) or N-methylmaleimide.[3a]

The 7-azanorbornene ligands can be removed from the metal intact, provided that the ligand nitrogen is protonated *prior* to removal of the ligand. For example, treatment of the acrylate adduct **V-3a** with acid (3 equiv of HOTf levelled in CH_3CN) followed by $Ce(NH_4)_2(NO_3)_6$ (1 equiv) generates a metastable triflate salt which may be hydrogenated *in situ* to yield, upon workup, the *exo*-2-carbomethoxy-7-azanorbornane **VII** (44% overall yield from **I-3**; Figure 2).[19] Alternatively, in order to stabilize the 7-azabicycloheptene ring system, the ester linkage of cycloadduct **V-3a** may be reduced with Li(9-BBN-H) prior to decomplexation of the metal. Subsequent treatment of the resulting alcohol complex (**VIII**) with $Ce(NH_4)_2(NO_3)_6$ (1 equiv) yields the 7-azanorbornene nucleus **IX** in 34% overall isolated yield from **I-3**.[20] Conventional syntheses involving [2 + 4] cycloadditions of pyrroles with alkenes have been limited by the thermodynamic instability of the 7-azanorbornene cycloadducts under the reaction conditions used.[21,22] 7-Azanorbornadienes are more stable and may be accessed when reactive acetylenic

(13) Even for the 2,5-dimethylpyrrole complex the ratio of 4,5-η^2 to 3,4-η^2 isomers is >100:1; see ref 3.

(14) NMR data for **V-3a**: ^1H NMR (300 MHz, CD_3CN) δ 3.97 (br s, 3H, *trans*-NH_3), 3.65 (s, 3H, CH_3O), 3.34 (br s, 12H, *cis*-NH_3), 3.17 (d, J = 6.3 Hz, 1H, H2 or H3), 3.13 (d, J = 6.3 Hz, 1H, H3 or H2), 2.77 (dd, J = 8.1, 4.2 Hz, 1H, H5), 2.14 (br s, 1H, NH), 2.05 (dd, J = 11.6, 8.1 Hz, 1H, $H6_{endo}$), 1.63 (dd J = 11.6, 4.2 Hz, $H6_{exo}$), 1.39 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3CN) δ 176.4 (CO), 75.7 (C), 71.0 (C), 59.1 (CH), 58.0 (CH), 55.3 (CH), 51.6 (OCH_3), 47.1 (CH_2), 18.3 (CH_3), 15.9 (CH_3).

(15) *N*-Benzoylpyrrole failed to react with ethyl acrylate even under high-pressure (>1 GPa) conditions: Drew, M. G. B.; George, A. V.; Isaacs, N. S.; Rzepa, H. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1277.

(16) Stereochemical assignments for cycloadduct complexes V are consistent with NOE and/or X-ray structure data. See supplementary material and ref 17.

(17) Gonzalez, J.; Hodges, L. M.; Koontz, J. I.; Myers, W. H.; Neely, L.; Sabat, M.; Harman, W. D. Manuscript in preparation.

(18) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W.; *J. Am. Chem. Soc.* **1992**, *114*, 3475.

(19) NMR data for **VII**: ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H, CH_3O), 2.63 (dd, J = 8.1, 5.1 Hz, 1H, H2), 2.49 (br s, 1H, NH), 1.82 (dd, J = 12.2, 8.1 Hz, 1H, $H3_{endo}$), 1.75–1.2 (m, overlap, 5H), 1.32 (s, CH_3), 1.2 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5 (CO), 67.7, 63.4, 53.0, 51.3, 44.0, 38.3, 36.7, 20.5, 18.3.

(20) NMR data for **IX**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (d, J = 5.3 Hz, 1H), 6.09 (d, J = 5.3 Hz, 1H), 3.99 (dd, J = 10.3, 2.1 Hz, 1H), 3.67 (dd, J = 10.3, 2.1, 1H), 3.6–2.8 v br, ~2H, OH and NH), 1.4–1.8 (m, 3H), 1.48 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2 (CH), 141.5 (CH), 69.9 (C), 67.0 (C), 61.5 (CH_2), 41.7 (CH), 37.0 (CH_2), 18.9 (CH_3), 15.7 (CH_3).

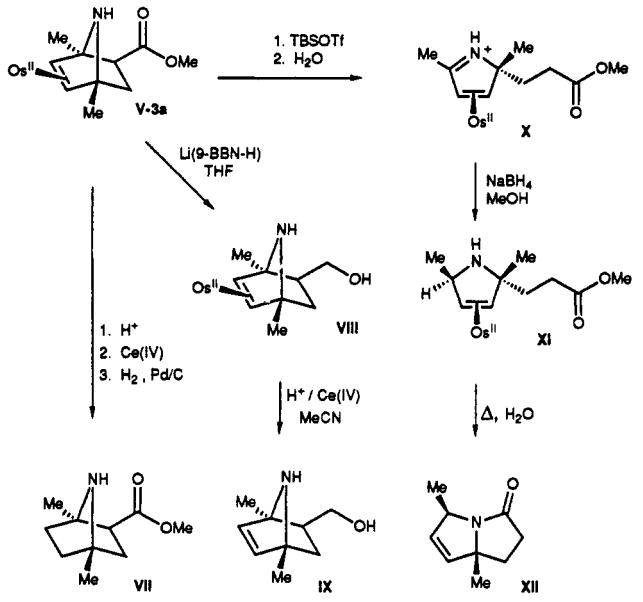

Figure 2. Synthesis of various bicyclic heterocycles from the azobicyclo[2.2.1]heptene complex (**V-3a**). $Os^{II} = [Os(NH_3)_5]^{2+}$.

dienophiles are used,[21] but in this approach the stereochemistry of substituents is not set in the ring-forming step. Since some of the osmium-promoted dipolar cycloadditions described here occur with high stereoselectivity, the methodology may be used in the stereospecific synthesis of substituted 7-azanorbornanes or 7-azanorbornenes.[23]

Cycloadduct complexes such as **V-3a** may also be used as intermediates in the synthesis of the pyrrolizidine ring system originating from net electrophilic addition at C(2). Treatment of the acrylate cycloadduct complex **V-3a** with TBSOTf (1 equiv, CH_3CN, 20 °C) results in a clean retro-Mannich reaction in which the complex **X** is produced, after hydrolysis, in 98% yield (Figure 2).[24] This metal-stabilized 2*H*-pyrrolium ligand may then be reduced stereoselectively to the corresponding 3-pyrroline complex, **XI**, through the use of a hydride reagent (e.g., $NaBH_4$; de >90%). NOE studies are consistent[25] with both cycloaddition and hydride addition occurring from the face of the ring *anti* to the metal moiety.[26] Thus, hydride is added stereoselectively to the more congested face of the ligand. Heating the 3-pyrroline complex (**XI**) effects decomplexation, and subsequent aqueous workup induces ring closure to the γ-lactam to give a single diastereomer of the pyrrolizidine nucleus **XII** (overall isolated yield from **I-3**: 65%).[27,28] Here, the unnatural angular substituent at C(8) is conveniently established from α-substitution of the pyrrole precursor.[29]

Finally, cycloadducts generated from pyrrole complexes lacking substituents at the α-position can be used to generate α-substituted 1*H*-pyrroles. For example, treatment of the acrylate-derived cycloadduct **V-2a** with TBSOTf effects a retro-Mannich ring opening to the 2*H*-pyrrolium complex, which upon heating (80 °C) with base forms the corresponding α-substituted pyrrole (**VI-2a**) in 45–50% yield (Figure 1).[30]

Although transition metal complexes of unsaturated hydrocarbons have been widely investigated for their applications to organic synthesis, remarkably little has been reported on the synthetic potential of heterocyclic complexes.[31] Several η^5-pyrrole and pyrrolyl complexes are known,[32] but pentaammineosmium(II) is the only metal center reported to form dihapto-coordinate complexes with pyrroles. The high degree of substrate activation, intermediate stabilization, and regio- and stereocontrol demonstrated in these examples make *dearomatization* agents such as $[Os(NH_3)_5]^{2+}$ exciting new tools for the synthesis of organic molecules.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (PRF no. 26027-AC), the Camille and Henry Dreyfus Foundation, and the National Science Foundation (CHE-9212008) for their generous support of this work.

Supplementary Material Available: Experimental details for the synthesis and characterization of compounds I–XII (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) For reviews on 7-azanorbornanes and Diels–Alder reactions of pyrroles, see: Kricka, L. J.; Vernon, J. M. *Adv. Heterocycl. Chem.* **1974**, *16*, 87. Jones, R. A. In *The Chemistry of Heterocyclic Compounds, Pyrroles*; Wiley & Sons: New York, 1990; Vol. 48. Bird, C. W.; Cheeseman, G. W. H. *Comprehensive Heterocyclic Chemistry*; Pergamon: London 1984; Vol. 4, p 261.

(22) High-pressure conditions have been used to promote this reaction, but the scope appears to be limited to highly reactive dienophiles (e.g., maleimides and maleic anhydride) and acylated pyrroles (ref 15). Even in an intramolecular example, long reaction times (2–3 weeks) were required at the low temperatures necessary for a favorable equilibrium constant. Jung, M. E.; Rohloff, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 630.

(23) A synthesis of the epibatidine ring system is described in ref 17. Since the cycloadditions often result in *exo* selectivity for the carboxylate group, the use of (*E*)- or (*Z*)-β-pyridyl acrylates yields the corresponding cycloadducts bearing *endo* or *exo* pyridyl substituents, respectively.

(24) NMR data for **X**: ^1H NMR (300 MHz, acetone-d_6) δ 11.5 (br s, 1H), 5.73 (d, J = 4.8 Hz, 1H), 5.44 (d, J = 4.8 Hz, 1H), 5.24 (bs, 3H), 4.15 (bs, 12H), 3.63 (s, 3H), 2.57 (s, 3H), 2.48 (m, 4H), 1.48 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6) δ 200.72 (C), 172.94 (CO), 75.67 (C), 61.65 (CH), 51.86 (CH), 51.49 (OCH_3), 36.39 (CH_2), 28.99 (CH_2), 18.82 (CH_3), 18.67 (CH_3).

(25) Irradiation of the *cis*-ammine peak results in a 5.8% enhancement of *both* methyl resonances.

(26) The feature of stereoselective addition to the ring face opposite the metal has been observed previously with electrophilic addition reactions of η^2-arene complexes of pentaammineosmium(II). Kopach, M. E.; Gonzalez, J.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 8972. Gonzalez, J.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.*, accepted for publication.

(27) Formation of the γ-lactam appears to be promoted by water. This effect has been observed in the ammonolysis of esters. Gordon, M.; Miller J. G.; Day, A. R. *J. Am. Chem. Soc.* **1949**, *71*, 1245.

(28) NMR data for **XII**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dd, J = 6.6, 1.8 Hz, 1H), 5.71 (dd, J = 6.6, 1.8 Hz, 1H), 4.62 (qdd, J = 6.6, 1.8, 1.8 Hz, 1H), 2.81 (m, 1H), 2.29 (m, 1H), 2.04 (m, 2H), 1.36 (s, 3H), 1.24 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.92 (CO), 134.53 (CH), 131.71 (CH), 73.45 (C), 57.38 (CH), 35.87 (CH_2), 33.15 (CH_2), 27.71 (CH_2), 21.50 (CH_3).

(29) The regiochemistry of cycloaddition reactions involving unsymmetric pyrroles with unsymmetric dipolarophiles is under current investigation.

(30) ^1H NMR data for **VI-2a**: (300 MHz, CD_3CN) δ 6.51 (d, 1H), 5.89 (t, J = 3.0 Hz, 1H), 5.76 (br s, 1H), 3.61 (s, 3H, OCH_3), 3.50 (s, 3H, NCH_3), 2.81 (dd, J = 7.8, 7.2 Hz, 2H), 2.59 (dd, J = 7.8, 7.2 Hz, 2H).

(31) Hansson, S.; Miller, J. F.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 9660 and references cited therein.

(32) (a) Felkin, H.; Zakrzewski, J. *J. Am. Chem. Soc.* **1985**, *107*, 3374. (b) Chase, K. J.; Grimes, R. N. *Organometallics* **1989**, *8*, 2492 and references cited therein.