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Intermolecular 1,3-Dipolar Cycloadditions of Münchnones with Acetylenic Dipolarophiles: Sorting out the Regioselectivity

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Abstract: A series of 1,3-dipolar cycloadditions of münchnones with acetylenic dipolarophiles was studied, wherein factors related to regioselectivity were investigated. The results from münchnones with electronically divergent thioaryl substituents compared with others bearing alkyl substituents suggest that an unsymmetrical transition state structure, rather than FMO perturbation, plays a significant role in regioselection. If eclipsing interactions preclude a highly unsymmetrical transition state, however, then minimizing steric interactions becomes important. A pair of complementarily substituted münchnones, differing only in the position of isotopic labels, establishes an inherently symmetrical electronic nature of the mesoionic heterocycle.

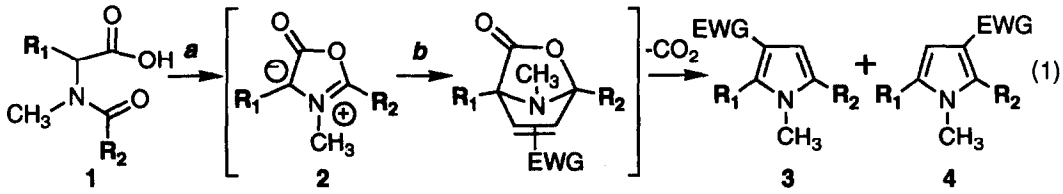
INTRODUCTION

Some 1,3-dipolar cycloaddition reactions have limited synthetic utility because of their unpredictable and/or low regioselectivities. The many productive applications of this cycloaddition chemistry continue to spur interest in (a), defining the contributing factors that influence the distribution of products[1] and (b), creating regiochemical and stereochemical control elements that can increase the predictability and selectivity of the reactions.[2] Historically, outside of intermolecular complexation (such as hydrogen bonding), or intramolecular tethering of the reacting partners, the regioselectivities observed in 1,3-dipolar cycloaddition reactions have been rationalized by FMO interactions.[3] In the past few years, the role of non-covalent interactions has been included in these analyses. Huisgen has summarized these effects as they pertain to some experimental observations.[4] Sustmann has explicitly incorporated a partitioned contribution from covalent and non-covalent interactions into a computational model.[5] Improving models for analyzing transition state structures, especially in conjunction with experimental observations, may create ways to evaluate the balance of many contributing factors for a given cycloaddition reaction. This is important for reactions where

asynchronous bond formations and high dipolar character conflict with the usual assumptions about transition state structure.[6]

The 1,3-dipolar cycloaddition reactions of mesoionic compounds have eluded an even loosely unified theory to account for observed regioselectivities.[7] As part of an investigation into methods that may be used to control the cycloaddition regioselectivity of these compounds, we have re-examined factors to which the observed regioselectivities have been attributed. We have prepared a set of molecules where we have attempted to isolate the electronic distributing (FMO) and non-covalent effects of substituents. We have found evidence that the degree of symmetry in the transition state structure may be highly related to the steric interactions between dipole/dipolarophile substituents, and plays a more significant role in regioselection than FMO effects. The results from a set of compounds with isotopically labeled substituents provides the most direct evidence to date that there is no inherent electronic bias contributed by the mesoionic heterocycle.

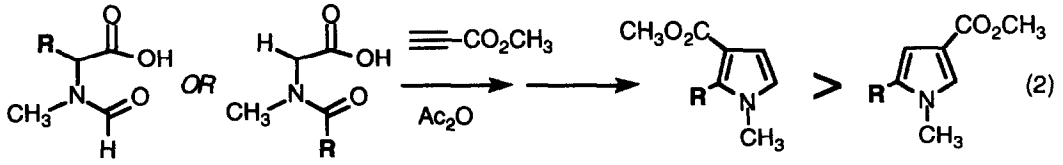
Because of the ready availability and variety of substituted amino acid precursors, we selected the mesoionic 1,3-oxazolium-5-olates (münchnones) **2** (eq. 1) to further study the factors influencing the regioselectivity of cycloaddition reactions with acetylenic dipolarophiles. Generally, münchnones are not isolated, but are generated *in situ* by the cyclodehydration of secondary N-acylamino acids **1** in the presence of a dipolarophile. The cycloaddition reactions with acetylenic dipolarophiles efficiently give pyrroles **3** and **4** after a decarboxylative cycloreversion, which also occurs under the reaction conditions.



(1)

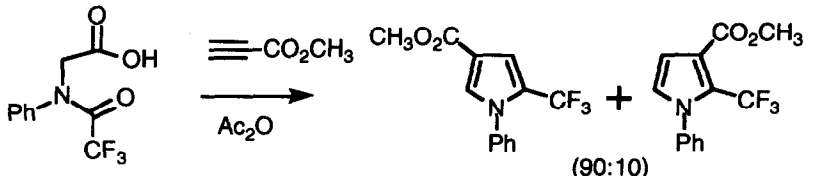
a) Ac_2O; *b*) ≡–EWG (EWG = electron-withdrawing group)

Huisgen,[8] Padwa,[9] and others[10] have studied münchnone cycloaddition reactions in some detail. Mechanistic experiments performed with münchnones imply that the observed product distributions are the result of kinetic control.[11] Many of these investigations have concluded that the substituents on the mesoionic heterocycle are the dominant influence on the FMO electronic distribution, and therefore the regioselectivity. On the other hand, results consistent with the apparent electronic effect of the heterocycle itself are also known.[8c, 12] The reaction of an unsymmetrically substituted monocyclic münchnone with methyl propiolate is the archetypical example of a cycloaddition that gives rise to a mixture of pyrrole regioisomers. In the case where one of the substituents is a hydrogen atom, there is a very consistent trend to produce the 3-pyrrolecarboxylate isomer (eq. 2) as the major product.[13] The product distribution of regioisomers is



(2)

generally in about a 3-to-4:1 ratio favoring this isomer, regardless of the original position of the hydrogen atom substituent (R_1 or R_2 in **1**, see eq. 2). There are a few examples that are noteworthy exceptions to this generalization. First, the hydrogen/trifluoromethyl-substituted münchnone gives the opposite sense of regioselectivity (eq. 3).[8] Second, polycyclic münchnones derived, for example, from N-acylproline and N-acyl(homoproline) give the bicyclic products shown in eq. 4 with very high regioselectivity.[14] Even here, however, a substituent with a strong charge stabilizing effect counteracts this generalization.[15] There are many examples of 1,3-dipolar cycloadditions that are consistent with the formation of the more crowded adduct as the major isomer, as in eq. 2: the addition of some non-stabilized azomethine ylids[16] to methyl propiolate, the analogous carbonyl ylids,[17] isomünchnones,[18] and azomethine imines.[19]



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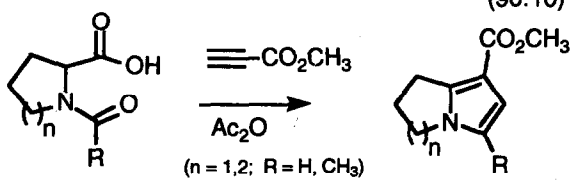
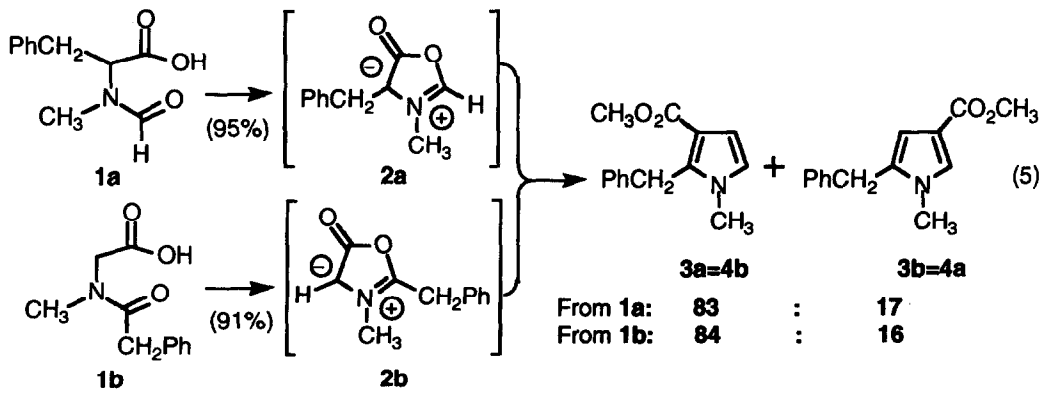


(4)

RESULTS AND DISCUSSION

Electronic Effect of Munchnone Substituents. Arylthio groups have been used in conjunction with alkoxy and acyloxy groups as regiocontrol elements for Diels-Alder cycloaddition reactions.[20a,b] More recently, they have been used in a similar fashion in palladium catalyzed cycloadditions involving substituted trimethylenemethane units.[20c] Testing such substituents seemed especially attractive in the 1,3-dipole question, where FMO electronic effects had generally received strong attribution. As reference compounds, we

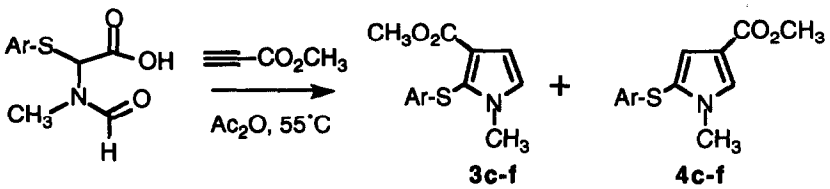


(5)

prepared the two N-acylamino acids **1a-b**[21] (eq. 5) that yield a pair of regioisomeric münchnones **2a-b** under the cyclodehydration reaction conditions. The same regioisomeric distributions of pyrroles, (**3a=4b**):(**3b=4a**), were observed. This result is consistent with those observed for the other reported cases of regioisomeric münchnone pairs (see **Table VI**).

The series of N-acyl-α-(arylthio)amino acids **1c-f** was prepared by the amidoalkylation[22] reaction of arylthiols with N-formyl-N-methyl-α-hydroxyglycine. The ratios of regioisomeric pyrroles resulting from the cycloaddition of the derived münchnone with methyl propiolate were determined.[23] These results are summarized in **Table I**. As noted earlier, the major regioisomer in each case is the 2-substituted pyrrole-3-carboxylate. There are two interesting features in this series of experiments that contrast with the typical behavior observed in Diels-Alder reactions.[24] First, the electronically divergent series of arylthio substituents in **1c-f**, which demonstrated successful regiocontrol as part of Diels-Alder dienes, do not dramatically affect the regioselectivities observed in the münchnone cycloadditions. Second, the regioselectivities of the arylthio-substituted münchnone reactions, taken together, are the same as both of the benzyl-substituted münchnones derived from **1a** and **1b**.

TABLE I. Cycloaddition Reactions of Arylthio-substituted Munchnones

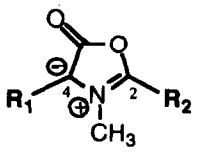


	3c-f		4c-f
1c: Ar = p-CH_3OPh-	**80**	:	**20**
1d: Ar = Ph-	**82**	:	**18**
1e: Ar = m-CF_3Ph-	**84**	:	**16**
1f: Ar = p-NO_2Ph-	**84**	:	**16**

The MNDO-derived coefficients and charges do not help to clarify this picture. A $HOMO_{dipole}$ control assumption is commonly used for cycloaddition reactions with electron-poor dipolarophiles.[25] The reactivity profile of münchnones with various dipolarophiles is consistent with Sustmann's Type I classification[25c] ($HOMO_{dipole}$- $LUMO_{dipolarophile}$ control). The results from MNDO calculations[26] on the münchnones **2a-f** imply that the regiochemistry should be dominated by the higher coefficient (*c*) and charge density (*q*) on the carbonyl substituted C-4 terminus. This is only consistent with the results from example **2b**, where the non-hydrogen substituent is at C-2. A number of different interaction energy terms have been used to qualitatively correlate regioselectivity differences.[3b] The ΔE_{ct} (charge transfer interaction) and ΔE_{el} (electrostatic interaction) have both been used with MINDO-derived data for münchnone systems.[9] The Type II behavior of two energetically comparable FMO interactions has also been suggested,[27] particularly in evaluating the ΔE_{ct} ratio as an index for regiochemical prediction. The MNDO-derived FMO data and the ΔE_{ct} ratios for compounds **1a-f** are given in **Tables II** and **III**, respectively. The similarity of the ΔE_{ct} ratios is comforting from the perspective that the observed regioselectivities were roughly the same for all six cases. However,the ΔE_{ct} values are all just slightly greater than unity, which predicts only a small regioselectivity in favor of the

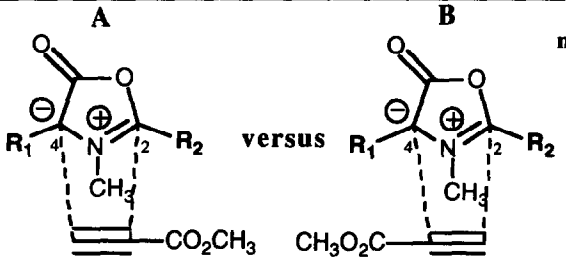
same orientation predicted by the $HOMO_{dipole}$ control assumption, which is not observed except for **2b**. Values of 1.25 and 2.37 were calculated in the cases of a münchnone and a sydnone, respectively, when modeling reactions that gave 75:25 regioisomeric ratios.[9] The relatively narrow HOMO/LUMO gaps calculated for all six of these dipoles lie within the HOMO/LUMO gap calculated for the dipolarophile. Both of the FMO interactions taken together (Type II assumption, as used in the ΔE_{ct} calculation) must result in no significant regioselection based on substituent perturbation. The previously cited trifluoromethyl/hydrogen-substituted münchnone (eq. 3) stands as the single example that contradicts this generalization. In this case, the electronic perturbation due to the C-2 trifluoromethyl substituent might be strong enough to close one of the FMO gaps into dominance.

TABLE II. MNDO Values for Munchnones 2a-f



R_1	R_2	HOMO	c_2	c_4	q_2	q_4	LUMO	c_2	c_4
2a: $PhCH_2$-	-H	-8.01 eV	0.48	-0.71	0.11	-0.30	-0.38 eV	0.68	0.38
2b: H-	-CH_2Ph	-7.89 eV	0.44	-0.64	0.12	-0.31	-0.33 eV	0.54	0.33
2c: p-CH_3OPhS -	-H	-8.42 eV	0.40	-0.68	0.17	-0.48	-0.68 eV	0.71	0.34
2d: PhS -	-H	-8.37 eV	0.41	-0.69	0.17	-0.48	-0.64 eV	0.71	0.34
2e: m-CF_3PhS -	-H	-8.58 eV	0.39	-0.69	0.18	-0.49	-0.82 eV	0.69	0.32
2f: p-NO_2PhS -	-H	-8.79 eV	0.41	-0.73	0.19	-0.50	-0.99 eV	0.72	0.32

TABLE III. ΔE_{ct} Ratios for 2a-f Cycloadditions with Methyl Propiolate



munchnone	$\Delta E_{ctA}/\Delta E_{ctB}$
2a	1.09
2b	1.09
2c	1.11
2d	1.11
2e	1.12
2f	1.12

The results from the regioisomeric pairs of münchnones (such as **2a** and **2b**) are the most convincing evidence favoring substituent control in the regioselectivity of the cycloaddition reactions. The nature of the substituent effect is an open question, however. Furthermore, there are cases where analogous pairs of münchnones give products which reflect a complete insensitivity to the placement of exocyclic substituents.[8c,12] Given the general lack of sensitivity to electronic perturbation observed with the arylthio substituents, both within the series and relative to the benzyl-substituted compounds, it is tempting to view these münchnones as a class of sterically similar compounds. The contrathermodynamic selection of the more

crowded pyrrole isomer might allow an insight into the transition state structure of the kinetically controlled cycloaddition reactions. We propose that an unsymmetrical transition state is favored in the case where one of the münchnone's dipolar termini bears a hydrogen atom. This transition state has advanced bond formation between the hydrogen-substituted terminus of the dipole and the sterically less demanding ß-carbon of methyl propiolate, which represents a high Michael-like character in the initial bond-forming process (**Fig. 1**).[28] Such a criterion may be especially significant for acetylenic dipolarophiles because the münchnone's substituents are expected to eclipse those of the dipolarophile during the cycloaddition reaction.

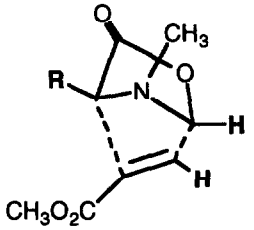
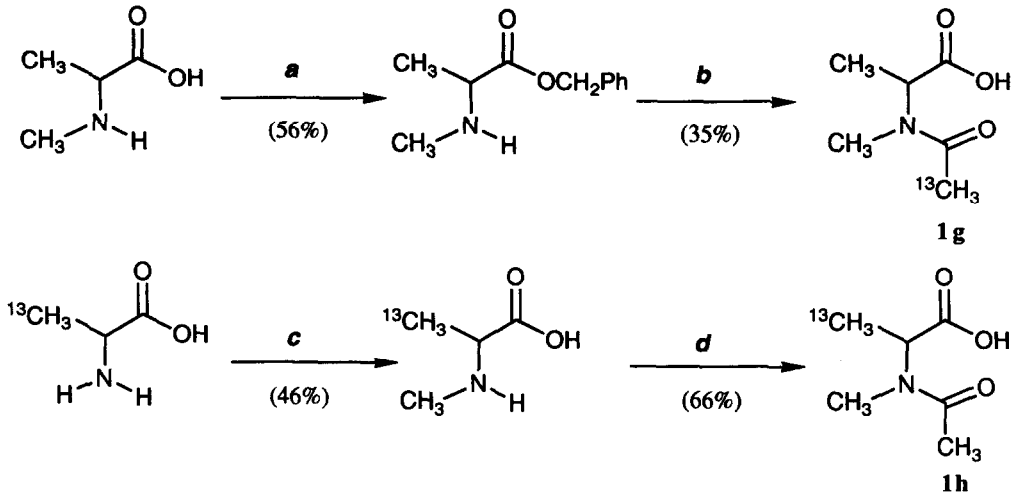


Figure 1. Proposed Unsymmetrical Transition State Structure for R/H-Substituted Münchnone Cycloaddition

The Nature of the Mesoionic Heterocycle. The inherent bias of the mesoionic heterocycle has never been unequivocably established for any substituent. The inference from regioisomeric münchnone pairs such as **2a** and **2b** is that there is an insignificant regiochemical contribution due to the unsymmetrical nature of the oxazolium ring, and that selectivity is dominated by a substituent effect. Padwa[16] has reported the single example which is a direct comparison between an identically substituted münchnone (a stabilized azomethine ylid) with respect to its non-stabilized azomethine ylid counterpart. In this case, the regioselectivities observed with methyl propiolate were the same, implying no additional effect due to the mesoionic ring. Unfortunately, there are a limited number of examples of münchnone cycloadditions with unsymmetrical dipolarophiles where the electronic effects of the different substituents $\mathbf{R_1}$ and $\mathbf{R_2}$ (in **2**) are predicted to be equal. In the handful of cases where both $\mathbf{R_1}$ and $\mathbf{R_2}$ are alkyl groups, regioselectivities ranging from high to none have been reported.[29] In the case of identical substituents $\mathbf{R_1}$=$\mathbf{R_2}$, the regiochemical information with respect to the original heterocycle is lost since decarboxylation from both of the non-isolable[30] bicyclic intermediates gives the same pyrrole isomer (**3=4**).

We have prepared a pair of regioisomeric dipoles that differ only by the position of isotopic labels in order to establish the inherent electronic bias of the münchnone heterocycle. The synthesis of two ^{13}C-labeled N-acylamino acid[31] münchnone precursors **1g** and **1h** is outlined in the **Scheme**.[32] Under the standard cycloaddition conditions, these precursors generate a pair of münchnones differentiated only by the position of the isotopically enriched methyl group (**2g**: $\mathbf{R_1}$ = $^{12}CH_3$, $\mathbf{R_2}$ = $^{13}CH_3$ and *vice versa*, **2h**).

Methyl propiolate was once again used as the dipolarophile in the cycloadditions reactions. The $\mathbf{R_1}$= $\mathbf{R_2}$= $^{12}CH_3$ pyrrole, **3i=4i**, derived from N-acetyl-N-methylalanine,[33] served as the spectroscopic reference compound. In both cases, isomeric ratios could be easily determined by ^1H- and ^{13}C-NMR analyses of the crude reaction mixtures.[34] The results of the cycloaddition experiments are summarized in **Table IV**. The slight regioselectivity observed from both of the ^{13}C-labeled isomers suggests that only a small inherent bias,

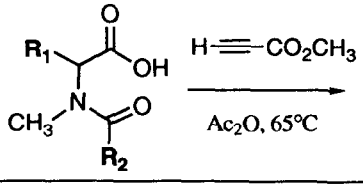


a) 1) $PhCH_2OH$ / $SOCl_2$/ 100°C/ 5hr; 2) Et_3N / EtOAc; *b)* 1)$^{13}CH_3CO_2H$/ DCC/ CH_2Cl_2, 2) H_2 / 5% Pd-C/ AcOH / EtOAc; *c)* 1) $PhCH_2OCOCl$, 2) 9 CH_3I / NaH / THF, 3) H_2 / 10% Pd-C/ CH_3OH / AcOH; *d)* Ac_2O/ NaOH / H_2O

Scheme. Synthesis of Isotopically Labelled Amido Acids

at best, can be attributed to the mesoionic heterocycle. This observed bias is consistent with all of the previously calculated ΔE_{ct} ratios for **2a-f**, as well as the $HOMO_{dipole}$-control assumption, in which the carbonyl-substituted terminus of the münchnone is predicted to be more electron-rich, thereby showing a regioselectivity in favor of the electron-deficient ß-carbon of methyl propiolate. The ΔE_{ct} ratio calculated for **2i** (the symmetrical R_1=R_2=$^{12}CH_3$ münchnone) is 1.08. While the quantitative significance of this number is difficult to ascribe, the index is consistent with the observed low regioselectivity. We conclude that the ΔE_{ct}

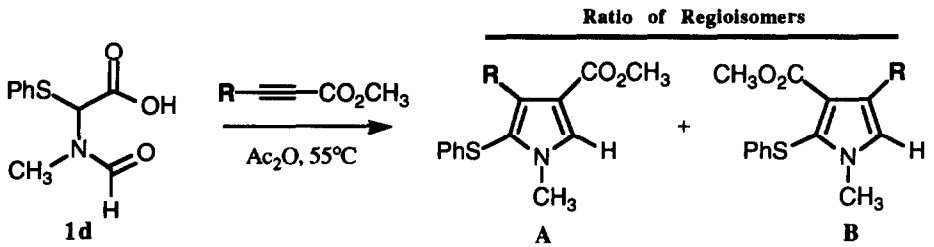
Table IV. Cycloaddition Reactions of Isotopically Labelled Munchnones

Precursor	Pyrrole Isomer Ratio		
			
1g R_1= CH_3, R_2=$^{13}CH_3$	**55**	**3g:4g**	**45**
1h R_1=$^{13}CH_3$, R_2= CH_3	**53**	**3h:4h**	**47**
1i R_1= CH_3, R_2= CH_3		**3i=4i**	

ratios for all of these examples might indeed reflect an authentic lack of FMO bias in the regioselectivity question for mesoionic compounds. This picture could indicate that most substituents simply do not possess enough perturbing effect to overcome either the Type II behavior and/or the electron-delocalization effect of the mesoionic heterocycle. The contribution that the unsymmetrical transition state model plays may also be limited to cases where at least one of the substituent groups is a hydrogen atom and the cycloaddition is irreversible, so that the various bond formations are differentiated enough to favor one of the pathways.

The Role of Non-Covalent Interactions. Two series of cycloadditions were performed in order to examine how important eclipsing interactions and transition state symmetry might be in determining regioselectivity. In the first, the structure of the dipolarophile was varied by changing the nature of the group attached to the ß-carbon of the acetylenic ester. The phenylthio/hydrogen-substituted münchnone precursor **1d** was heated with methyl 2-butynoate and methyl phenylpropiolate under the same conditions as with methyl propiolate. The results are presented in **Table V**. There is a remarkable difference between the product distribution observed from the cycloaddition with methyl propiolate (entry **1**) and that of methyl 2-butynoate (entry **2**) in spite of the fact that the individual FMO characteristics for these two dipolarophiles are quite similar. Further modification by exchanging the ß-methyl group for a ß-phenyl group as in methyl phenylpropiolate[35] (entry **3**) leads to the cycloadduct **A** with no evidence of the other regioisomer detectable by either spectroscopic or analytical HPLC methods. In these three cases, as is indeed true for all of the others reported so far, an unsymmetrical transition state where advanced bond formation favors the joining of the two least encumbered reacting termini can be used to predict the major regioisomer. The trend in A-values[36] for the substituents on the dipolarophile is consistent with the trend in **Table V** [Ph (2.9) > CH_3 (1.71) > CO_2CH_3 (1.27-1.31) > H].

TABLE V. Cycloaddition of 1d-derived Münchnone with Acetylenic Dipolarophiles

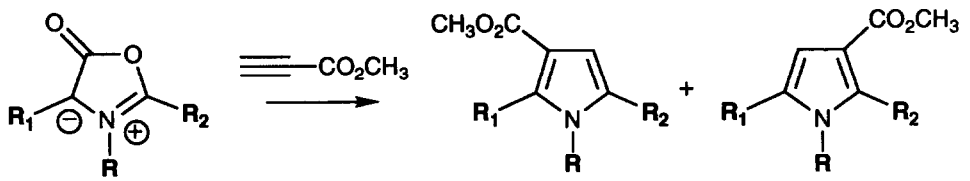


1d **A** **B**

		Ratio of Regioisomers		
entry **1**	**R** = H	18	:	82
entry **2**	**R** = CH_3	75	:	25
entry **3**	**R** = Ph	100	:	0

In the second series of cycloaddition reactions, the regioselectivities exhibited by a series of alkyl/alkyl substituted münchnones were compared to some alkyl/hydrogen compounds. The results of these cycloaddition reactions with methyl propiolate are presented in **Table VI** (entries **1-6**),[37] along with four pertinent examples from earlier work in this report (entries **7, 8, 18, 19**) and from the literature, including aryl/hydrogen and aryl/alkyl substituted münchnones (entries **9-17**).[9, 10a] In those cases where one of the

Table VI. Summary of Unsymmetrical Munchnone Cycloadditions with Methyl Propiolate



entry	R_1	R_2	R	isomer ratio	
1	$(CH_3)_2CH$-	H-	CH_3-	57	43
2	H-	$(CH_3)_2CH$-	CH_3-	25	75
3	CH_3-	$(CH_3)_2CH$-	CH_3-	67	33
4	$(CH_3)_2CH$-	CH_3-	CH_3-	23	77
5	CH_3-	CH_3CH_2 -	CH_3-	55	45
6	$(CH_3)_3C$-	H-	CH_3-	67	33
7	$PhCH_2$-	H-	CH_3-	83	17
8	H-	$PhCH_2$-	CH_3-	16	84
9[10a]	CH_3-	H-	CH_3CH_2 -	84	16
10[9,10a]	H-	CH_3-	CH_3CH_2-,Ph -	25	75
11[9]	H-	CF_3-	Ph -	90	10
12[10a]	Ph-	H-	CH_3CH_2 -	86	14
13[10a]	H-	Ph-	CH_3CH_2 -	25	75
14[10a]	CH_3-	Ph-	CH_3CH_2 -	57	43
15[10a]	Ph-	CH_3-	CH_3CH_2 -	38	62
16[9]	Ph-	CH_3-	CH_3CH_2 -	55	45
17[9]	$PhCH_2$-	CH_3-	CH_3CH_2 -	45	55
18	CH_3-	$^{13}CH_3$-	CH_3-	55	45
19	$^{13}CH_3$-	CH_3-	CH_3-	53	47

münchnone substituents is a hydrogen atom, there is a consistent trend to produce the 3-pyrrolecarboxylate isomer as the major product. This is true for the hydrogen/alkyl pairs (entries **1**, **2**, **6**, **7**, **8**, **9**, **10**), hydrogen/thioaryl pairs (see **Table I**), and hydrogen/aryl pairs (entries **12** and **13**). As mentioned before, the hydrogen/trifluoromethyl methyl example (entry **11**) stands as the lone exception. In the examples of alkyl/alkyl pairs (entries **3**, **4**, **5**, **17-19**), an opposite sort of selectivity is observed. Using the methyl/methyl case (entries **18-19**) as the starting point, the methyl/ethyl pair (entry **5**) and the methyl/isopropyl pair (entries **3** and **4**) show a consistent trend to form the *less crowded* isomer as the major product to an increasing extent. Here, where one of the münchnone substituents is not a hydrogen atom, we propose that a more synchronous set of bond formations is required relative to the hydrogen/alkyl compounds (see **Figure 1**). Without a dominant FMO interaction to guide the regioselectivity, the favored transition state is simply the one that has the lower set of non-covalent interactions when considering both pairs of termini combining in a symmetrical fashion. The number of aryl/alkyl examples is too limited to make a generalization (entries **14**, **15**, and **16**), and there is some inconsistency in those reported regioisomeric ratios (entries **15** and **16**).

We have not included any further discussion thus far about münchnones that are part of bicyclic ring systems, which exhibit completely regioselective cycloaddition reactions with methyl propiolate (see eq. 4). The cycloaddition reactions with the münchnones[14] derived from N-formylproline and N-formyl(homoproline) can be viewed as hydrogen/alkyl cases where the alkyl substituent is intramolecularly tethered back to the central nitrogen atom (eq. 4.). The regioselectivities with methyl propiolate cycloadditions completely favor the isomer where the two hydrogen atom termini end up bonded in the pyrrole ring of the product. In the N-acetylproline and N-acetyl(homoproline) experiments reported by the same authors, which may be viewed as alkyl/alkyl cases where one of the chains is tethered back, the selectively is complete, and in the same sense as the N-formyl derivatives. We consider these examples (especially the latter, when compared with the alkyl/alkyl examples in **Table VI**) to strongly support the view of an asynchronous transition state, where the comparative ease of an initial bond formation differentiates between the two modes of cycloaddition. In these cases, the relative flexibility of the non-tethered terminus allows for a greater degree of bonding in a transition state with a highly Michael-like character. We have investigated this tethering of substituents with regard to the regioselectivity question and have observed a clear and consistent trend favoring highly regioselective cycloadditions.[38]

Computational Transition State Search. We have also performed a computational search for the transition state structures arising from the two possible cycloaddition orientations for one of our münchnones **2b** with methyl propiolate. Transition state geometries (**Figure 2**) were located with the SADDLE option using the MNDO Hamiltonian parameters of MOPAC (Version 6.0), and refined by Baker's method.[39] Both of the transition states were characterized by one negative force constant and gradient values of 1.9 (formation

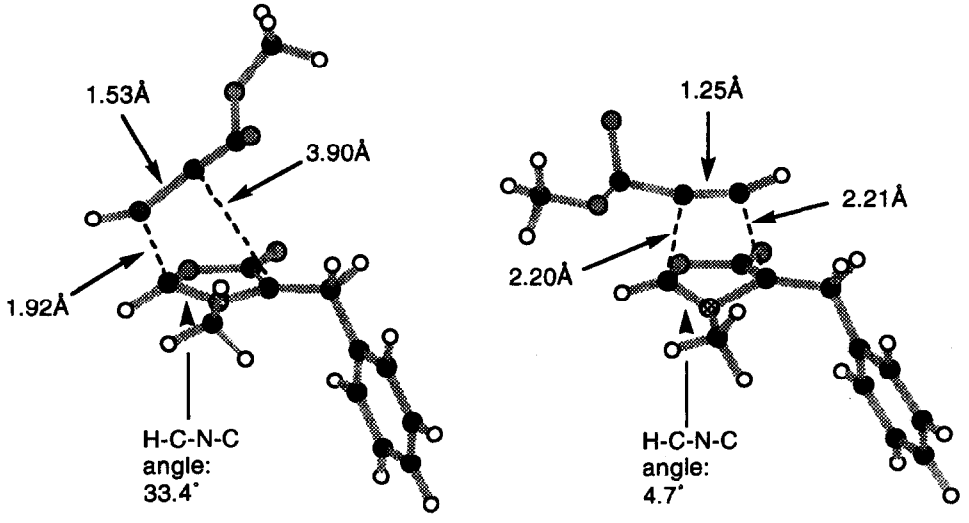


Figure 2. Calculated Transition State Structures for Münchnone 2b plus Methyl Propiolate Intermediates leading to 3b and 4b.

of major isomer **4b**) and 14.8 (formation of minor isomer **3b**). The results from these calculations are consistent with the picture we predicted from the experimental work. In the case of the orientation leading to the observed major product **4b**, a highly asynchronous cycloaddition with a Michael-like character results. In this case, the 'nucleophilic' terminus of the münchnone is the one with the hydrogen substituent. In the case of the orientation leading to the observed minor product **3b**, a more synchronous cycloaddition reminiscent of the prediction for the alkyl/alkyl cases results. This transition state is also calculated to have a higher energy than the one depicted for the major regioisomer. Supporting evidence for an unsymmetrical transition state structure can be found in the theoretical analysis of Quast's stepwise azide reaction,[6] where the calculated bond distances (3.11Å and 1.97Å) are comparable to ours. In related work,[38] we have proposed that a transition state with a high Michael-like character is also required to explain the regioselectivity derived from a set of polycyclic compounds.

CONCLUSION

No single criterion can successfully be used to correlate the experimental observations regarding the regioselectivity in münchnone cycloaddition reactions. As others in this area have concluded, both the steric and electronic properties of the münchnone substituents must be considered. However, the FMO contribution appears to be minimally responsible in the cases investigated here. These examples also suggest the importance of considering the molecular flexibility towards a favorable, unsymmetrical transition state. As Houk has stated, the lack of information directly related to the 1,3-dipolar cycloaddition transition state is an enormous hindrance to a more complete understanding of the process.[40]

By creating a better model for correlating the factors responsible for the regioselectivity, the construction of more predictable regiocontrol elements is possible. Additional investigations along these lines are currently in progress, and they will reported in due course.

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EXPERIMENTAL

General Methods. Unless otherwise specified, all reactions were carried out in flame-dried glassware under a positive atmosphere of dry nitrogen. Toluene and acetonitrile were distilled from CaH_2 prior to use. Acetic anhydride was distilled from CaC_2 prior to use. N,N-Dimethyl formamide was distilled from BaO prior to use. THF was freshly distilled from sodium/benzophenone. Proton and carbon nuclear magnetic resonance spectra (^1H- and ^{13}C-NMR) were recorded on a Bruker AM 300, Bruker AM 360 or on a Varian 200 MHz spectrometer. Infrared spectroscopy was performed on a Nicolet 5DX Spectrometer. Mass Spectroscopy was obtained using 70 eV electron impact ionization or chemical ionization (CI) and quadrapole moment detection. Ultraviolet spectroscopy was performed on a Cary 17 instrument.

Starting Materials. Methyl propiolate, methyl 2-butynoate, dimethyl acetylenedicarboxylate and methyl phenylpropiolate were obtained commercially and distilled before use. Thiophenols were distilled from calcium hydride. Glyoxylic acid and amino acids were obtained commercially (Aldrich Chemical Company). Amidoalkylation reactions were performed as described by Zoller.[22]

N-Formyl-N-methylphenylalanine (1a): Compound **1a** was prepared by the method of Quitt[21a] to give 83% of a white solid, mp. 180°C (lit. 181-2°C). IR (KBr): 3300, 3070, 1735, 1650, 1250, 1055, 1040, 770, 690 cm^{-1}; ^{1}H-NMR (DMSO-d_6, as rotamers) : δ1.95, 2.00 (3H, s), 2.19, 2.28 (2H, s), 2.60 (2H, m), 4.10, 4.50 (1H, dd, J=8, 4 Hz), 6.80 (10H, bs), 7.16, 7.30 (1H, s); MS (m/e, %): 207 (0.6), 192 (3), 179 (19), 156 (57), 148 (63); exact mass calculated for $C_{11}H_{13}NO_3$: 207.0892; found: 207.0894.

N-Methyl-N-(phenylacetyl)glycine (1b)[21b]: To a stirred, room temperature solution of N-methylglycine (4.5 g, 51 mmol) in chloroform (50 mL) and tetrahydrofuran (10 mL) was added trimethylchlorosilane (5.53 g, 6.5 mL, 51 mmol) The resulting solution was stirred for 3 hr at 65°C, then cooled to -10°C. To this cooled solution was added phenylacetyl chloride (7.87 g, 51 mmol) followed by dropwise addition of triethylamine (10.3 g, 14.2 mL, 0.102 mol). Stirring was continued at -10°C for 30 min, after which time the mixture was poured into a separatory funnel containing 10 mL of 10% aqueous hydrochloric acid. The organic layer was washed with 3 x 10 mL of 10% aqueous hydrochloric acid, 1 x 10 mL of water, separated and dried ($MgSO_4$). Evaporation of the solvents yielded 8.0 g (76%) of **1b** as a waxy solid. Recrystallization (ethanol/water) gave 7.5 g (70%) of clear needles, mp. 150-1°C. IR (KBr): 3200, 3010, 1610, 1450, 1420, 1205 $cm.^{-1}$; ^{1}H-NMR ($CDCl_3$, as rotamers) δ2.95, 3.0 (3H, s), 3.64, 3.76 (2H, s), 3.96, 4.10 (2H s), 7.24 (5H, m); MS (m/e, %): 207 (1) 192 (30) 175 (20) 163 (45) 146 (20), 128 (50), 97 (90); exact mass calculated for $C_{11}H_{13}NO_3$: 207.0892; found: 207.0889.

α-Hydroxy-N-formyl-N-methylglycine (1j): A solution of glyoxylic acid monohydrate (3.32 g, 36 mmol) and N-methyl formamide (2.13 g, 35 mmol) was refluxed for 24 h in 70 mL of acetone. After cooling the mixture to room temperature, the solvent was evaporated to yield 4.7 g (97%) of the title compound as a waxy solid. While the product was generally used directly in the amidoalkylation reactions, a sample was recrystallized from chloroform/dioxane to give white needles, mp. 101-3°C. IR (KBr) 3330, 1730, 1610 cm^{-1}; ^{1}H-NMR (DMSO-d_6, as rotamers): δ2.68, 2.88 (3H, s) 5.52, 5.92 (1H, s), 8.08, 8.22 (1H, s), 8.7 (2H, bs); MS (m/e, %) 133 (2), 132 (1), 118 (3), 115 (29), 112 (10), 105 (19), 98 (21), 89 (79); exact mass calculated for $C_4H_7NO_4$: 133.0373; found: 133.0372.

General Procedure for Amidoalkylations A: To a stirred, 0°C 1 M suspension of α-hydroxy-N-acyl-N-alkylglycine in glacial acetic acid was added 4 equivalents of the thiol to be amidoalkylated. To this stirred suspension was added, dropwise, concentrated sulfuric acid (1 mL for every 10 mL of suspension). The resulting mixture was generally homogeneous within 12 h after stirring at room temperature. After an additional 1.5 days, the reaction mixture was poured into 70 g of ice. The organic products were extracted with 4 x 20 mL of ethyl acetate. The organic solution was then washed with 2 x 50 mL of water, followed by extraction with 5 x 30 mL of 5% aqueous sodium bicarbonate. The combined aqueous extracts were washed with 3 x 30 mL of ether, acidified with concentrated hydrochloric acid, and extracted with 4 x 20 mL of ethyl acetate. The organic extracts were combined, dried ($MgSO_4$) and evaporated to yield the amidoalkylated products as white solids; recrystallization could be effected with chloroform/ether or ethyl acetate/hexane mixtures, although the products were generally of sufficient purity to utilize directly.

General Procedure for Amidoalkylations B: To a stirred, 0.3 M solution of the appropriate glycine derivative in 1,2-dichloroethane was added 1 equivalent of the thiol to be amidoalkylated, followed by 50-100 mg of β-naphthalenesulfonic acid. The resulting solution was heated at 90°C for 48 hr. After cooling to room temperature, the reaction mixture was washed with 3 x 25 mL of water, dried ($MgSO_4$) and evaporated to yield off-white to yellow solids which could be purified as described in **Procedure A**.

α-(4'-Methoxyphenylthio)-N-formyl-N-methylglycine (1c): Compound **1c** was prepared from **1j** (3.3 g, 24 mmol) and 4'-methoxythiophenol (12.0 g, 97 mmol) via general procedure A for the amidoalkylation of thiols as a white solid (3.6 g, 62%), mp 137-9°C. IR (KBr): 3220, 1720, 1630, 1300, 1170, 1050 cm^{-1}; ^{1}H-NMR (DMSO-d_6, as rotamers): δ2.76 (3H, s), 3.76 (3H, s), 6.0, 6.28, (1H, s), 6.9 (2H, d, J=8 Hz), 7.20 (2H, d, J=8 Hz), 7.6, 7.96 (1H, s); MS (m/e, %): 255 (3), 227 (9), 211 (17), 181 (37), 157 (45), 148 (36), 139 (56), 136 (55), 116 (81), 98 (15); exact mass calculated for $C_{11}H_{13}NO_4S$: 255.0562; found: 255.0562.

α-Phenylthio-N-formyl-N-methylglycine (1d): Compound **1d** was prepared from **1j** (717 mg, 5.38 mmol) and thiophenol (2.4 g, 21.6 mmol) via general procedure A for the amidoalkylation of thiols as white crystals (0.93 g, 72%), mp. 212°C. IR (KBr): 3300, 1710, 1620, 1520, 1440, 1330, 1110, 750, 690 cm^{-1}; ^{1}H-NMR (DMSO-d_6, as rotamers): δ2.70, 2.96 (3H, s), 6.24, 6.50 (1H, s), 7.40 (5H, bm), 7.76, 8.04 (1H, s); MS (m/e, %): 225 (0.5), 223 (0.1), 197 (30), 196 (35), 185 (40), 181 (56), 157 (16), 116 (63), 110 (83); exact mass calculated for $C_{10}H_{11}NO_3S$: 225.0457; found: 225.0452.

α-(3'-Trifluoromethylphenylthio)-N-formyl-N-methylglycine (1e): Compound **1e** was prepared from **1j** (1.2 g, 9.2 mmol) and 3'-trifluoromethylthiophenol (1.8 g, 10.1 mmol) via general procedure B for the amidoalkylation of thiols. The initial viscous oil (98%) crystallized upon standing to give 1.2 g (85%, after washing with cold ether) of an off-white solid, mp 170-3°C. IR ($CDCl_3$): 3100, 1730, 1685, 1330, 1170, 1150, 1065, 1045 $cm.^{-1}$; ^{1}H-NMR ($CDCl_3$, as rotamers): δ2.88, 3.02 (3H, s), 5.65, 6.64 (1H, s), 7.70 (4H, bm), 7.88, 8.0 (1H, s); MS (m/e, %) 293 (0.1), 286 (0.5), 275 (15), 249 (35), 235 (19), 198 (57) 113 (68); exact mass calculated for $C_{11}H_{10}F_3NO_3S$: 293.0331; found: 293.0332.

α-(4-Nitrophenylthio)-N-formyl-N-methylglycine (1f): Compound **1f** was prepared from **1j** (2.35 g, 17 mmol) and 4'-nitrothiophenol (2.74 g, 18 mmol) via general procedure B for the amidoalkylation of thiols as a pale yellow solid (4.4 g, 92%) mp 64-6°C. IR ($CDCl_3$) : 3100, 1730, 1535, 1330, 1150, 1060 $cm.^{-1}$; ^{1}H-NMR (DMSO-d_6, as rotamers): δ 2.78, 2.98 (3H, s), 5.98, 6.00 (1H, s), 6.45, 6.74 (1H, s), 7.6 (2H, m), 8.1 (2H, m); MS (m/e, %): 270 (1), 181 (0.1), 169 (0.4), 155 (100), 125 (31), 109 (49), 69 (46); exact mass calculated for $C_{10}H_{10}N_2O_5S$: 270.0303; found: 270.0306.

General Procedure for Cycloaddition reactions with acetylenic dipolarophiles. All of the cycloaddition reactions of precursors **1a-i** with methyl propiolate, methyl 2-butynoate or methyl phenylpropiolate were performed as follows: To a 0.5 M mixture of amidoacid (3-10 mmol scale) in acetic anhydride was added a 5 molar excess of the dipolarophile. The resulting suspension was heated to 55°; solution generally occurred within 5 to 10 minutes. After stirring for 24 h at 55°C, solvents and excess dipolarophile were removed via distillation at reduced pressure (0.01-0.1 mm Hg). The material thereby obtained was directly subjected to analytical HPLC and NMR analyses.[23] The pyrrole regioisomers were generally inseparable by preparative thin layer chromatographic techniques. Yields of pyrrole products were consistently good to excellent on all reaction scales.

Methyl 2-benzyl-1-methyl-3- and 4-pyrrolecarboxylate (3a=4b and 4a=3b).
A. Reaction of **1a** (153 mg, 0.74 mmol) with methyl propiolate (280 mg, 3.3 mmol) under cycloaddition conditions gave 173 mg (95%) of a 5.0:1 mixture of **3a:4a**. Chromatographic (preparative TLC plate; 1:1 ether; hexane/1% AcOH; 3 elutions) separation yielded the two isomers (**3a**, R_f = 0.25; **4a**, R_f =0.29) as clear oils.

3a: IR ($CDCl_3$) : 1700, 1500, 1440, 1260, 1140 cm^{-1}; ^{1}H-NMR (3-isomer, $CDCl_3$): δ3.24 (3H, s), 3.68 (3H, s), 4.32, (2H, s), 6.26 (1H, bd, J=2 Hz), 6.5 (1H, bd, J=2 Hz), 7.05 (5H, m); MS (m/e, %) : 229 (1), 214 (13) 206 (10), 198 (15); exact mass calculated for $C_{14}H_{15}NO_2$: 229.1099; found: 229.1100.

4a: IR ($CDCl_3$): 1705, 1500, 1400, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ3.68 (3H, s), 3.96 (3H, s), 4.04 (2H, s), 6.42 (1H, bs), 7.2 (6H, bm); MS (m/e, %): 229 (0.5), 219 (19), 206 (10), 205 (8), 198 (23), 168 (35); exact mass calculated for $C_{14}H_{15}NO_2$: 229.1099; found: 229.1099.

B. Reaction of **1b** (248 mg, 1.2 mmol) with methyl propiolate (450 mg, 5.3 mmol) under cycloaddition conditions gave 268 mg (91%) of a 4.8:1 mixture of **4b:3b** which were separable and spectroscopically identical to those from part A.

Methyl 2-(4'-methoxyphenylthio)-1-methyl-3- and 4-pyrrolecarboxylate (3c and 4c): Reaction of **1c** (461 mg, 1.9 mmol) with methyl propiolate (730 mg, 8.7 mmol) under cycloaddition conditions gave 520 mg (91%) of **3c** and **4c**, partially separable (preparative TLC; 1:3 EtOAc: hexane; 3 elutions; (**3c**, R_f = 0.32; **4c**, R_f = 0.35) as clear oils.

3c: IR ($CDCl_3$): 2970, 2920, 1705, 1600, 1500, 1250, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ3.59 (3H, s), 3.72 (3H, s), 3.79 (3H, s), 6.67 (1H, d, J=3.2 Hz), 6.75 (1H, d, J=3.2 Hz), 7.1 (2H, m), 7.3 (2H, m); MS (3-isomer, m/e, %): 277 (4), 262 (25), 246 (29), 231 (30), 195 (16); exact mass calculated for $C_{14}H_{15}NO_3S$: 277.0769; found: 277.0772.

4c: IR ($CDCl_3$): 2970, 2920, 1705, 1495, 1250, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ3.59 (3H, s), 3.75 (3H, s), 3.8 (3H, s), 7.05 (2H, m) 7.07 (lH, d, J=2 Hz), 7.11 (2H, m), 7.42 (1H, d, J=2 Hz); MS (m/e, %): 227 (0.3), 262 (19), 246 (30), 230 (18), 195 (20), 168 (39); exact mass calculated for $C_{14}H_{15}NO_3S$: 277.0769; found: 277.0761.

Methyl 1-methyl-1-phenylthio-3- and 4-pyrrolecarboxylate (3d and 4d): Reaction of **1d** (320 mg, 1.4 mmol) with methyl propiolate (540 mg, 6.4 mmol) under cycloaddition conditions gave 350 mg (93%) of the **3d** and **4d** as a viscous oil. IR ($CDCl_3$) : 1700, 1490, 1240 cm^{-1}; ^{1}H-NMR (3*-+ 4-isomer, $CDCl_3$): δ3.55* (3H, s), 3.75* (3H, s), 6.72* (1H, d, J=2.5 Hz), 6.8* (1H d, J=2.5 Hz), 7.0-7.1* (6H, m); 3.51 (3H, s), 3.78 (3H, s), 7.0-7.1 (6H, m), 7.47 (1H, bs); MS (m/e, %): 247 (3), 232 (19), 216 (8), 201 (45), 192 (20), 169 (35), 135 (20); exact mass calculated for $C_{13}H_{13}NO_2S$: 247.0664; found: 247.0666.

Methyl 1-methyl-1-(3-trifluoromethylphenylthio)-3- and 4-pyrrolecarboxylate (3e and 4e): Reaction of **1d** (229 mg, 0.78 mmol) with methyl propiolate (260 mg, 3.12 mmol) under cycloaddition conditions gave 594 mg (94%) of **3e** and **4e** as inseparable oils. IR ($CDCl_3$): 2970, 1700, 1485, 1320, 1250, 1170, 1140 cm^{-1}; ^{1}H-NMR (3*- + 4-isomer, $CDCl_3$): δ3.62* (3H, s), 3.77* (3H, s), 6.77* (1H, d, J=2.3), 6.88* (1H, s, J=2.3 Hz), 7.1-7.3* (3H, m); 3.57 (3H, s), 3.82 (3H, s), 7.04 (1H, bs), 7.1-7.3 (3H, m) 7.53 (1H, bs); MS (m/e, %): 315 (3), 300 (15), 284 (30), 282 (25), 194 (30), 175 (40), 165 (25), 116 (18); exact mass calculated for $C_{14}H_{12}F_3NO_2S$: 315.0586; found: 315.0554.

Methyl 1-methyl-2-(4'-nitrophenylthio)-3- and 4-pyrrolecarboxylate (3f and 4f): Reaction of **1d** (340 mg, 1.2 mmol) with methyl propiolate (200 mg, 2.4 mmol) under cycloaddition conditions gave 325 mg (93%) of **3f** and **4f** as inseparable oils. IR ($CDCl_3$): 2970, 1700, 1570, 1515, 1470, 1340, 1240 cm^{-1}; ^{1}H-NMR (3*-+ 4-isomer, $CDCl_3$): δ3.66* (s, 3H),3.77* (s, 3H), 6.8* (d, J=3 Hz, 1H), 6.94* (d, J=3 Hz, 1H), 7.07* (2H, d, J=9.5 Hz), 8.09* (2H d, J=9.5 Hz); 3.6 (3H, s), 3.83 (3H, s), 7.07 (2H, d, J=9.5 Hz), 7.58 (1H, bs), 8.1 (3H, m); MS (m/e, %) : 292 (2), 277 (10), 261 (18), 233 (30), 138 (49); exact mass calculated for $C_{13}H_{12}N_2O_4S$: 292.0515; found: 292.0486.

N-Methylalanine, benzyl ester, hydrochloride salt (1ga): Compound **1ga** was prepared by a modification of the procedure of Patel and Price.[41] To a stirred, 0° C mixture of N-methylalanine (2.88 g, 28 mmol) in benzyl alcohol (50 mL) was added, dropwise, thionyl chloride (12 mL, 19.87 g, 167 mmol). The solution was stirred for 7 h at 95°- 100° C. After cooling the solution to room temperature, ether was added to the solution until turbidity appeared. The mixture was refrigerated for 30 minutes and then filtered to give 4.78 g (88%) of the crude product as a fine white solid, m.p. 140°- 150° C. The crude product (4.66 g) was dissolved in 50 mL of water. Solid sodium carbonate was added until pH 9. The aqueous mixture was extracted with ether (3 x 30 mL) and the combined organic layers dried ($MgSO_4$). After filtration and dilution with ether to a volume of 150 mL, the solution was saturated with HCl gas and refrigerated for 30 minutes.

Filtration gave 2.59 g (56%) of **1ga** as white solid, m.p. 162°-165°C. IR (KBr): 3475, 2875, 2710, 1740, 1250, 1210, 760, 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ1.60 (3H, d, J=7 Hz), 2.65 (3H, bs), 3.85 (1H, bs), 5.20 (2H, m), 7.30 (5H, s), 9.70 (1H, bs), 10.30 (1H, bs); MS (m/e, %): 194 (s), 91 (12), 58 (100), 36 (15); exact mass calculated for $C_{11}H_{16}NO_2$: 194.1181; found: 194.1170.

N-Acetyl-N-methylalanine, benzyl ester (1gb): Compound **1gb** was prepared by a modification of the procedure of Bonner and McNamee.[42] To a mixture of **1ga** (0.733 g, 3.20 mmol) in ethyl acetate (25 mL) was added triethylamine (1.30 mL, 9.29 mmol). The organic layer was extracted with saturated, aqueous sodium chloride (3 x 25 mL), and dried (Na_2SO_4). The solution was filtered and solvents removed *in vacuo* to give the **1gb** as a light yellow oil. A small amount of methylene chloride (ca. 5 mL) was immediately added to the product. The methylene chloride solution was drawn into a syringe and equally distributed (by volume) into two flasks, one for the ^{12}C-acetylation control reaction and one for the ^{13}C-acetylation reaction (.309 g, 1.60 mmol of amino ester per reaction) used to prepare **1gc**.

N-2-^{13}C-Acetyl-N-methylalanine, benzyl ester (1gc): To a stirred solution of dicyclohexylcarbodiimide (0.463 g, 12.25 mmol) in methylene chloride (12 mL) was added, dropwise, a solution of acetic acid (acetic-2-^{13}C acid, 0.092 g, 1.53 mmol) in methylene chloride (2 mL) over 15 minutes. Dicyclohexylurea formed as a white precipitate within 5 minutes after the beginning of the addition. After the mixture was stirred for 1.5 h, a 15 mL portion of pentane was added The mixture was cooled to 0° C and filtered. The filtrate was immediately added to the previously-prepared solution of **1gb** that had been reserved for ^{13}C-acetylation. Dicyclohexylurea again precipitated within 15 minutes after mixing. The mixture was stirred for 24 h, after which a 10 mL portion of pentane was added. The mixture was cooled to 0° C and filtered. Evaporation of the solvents gave 0.497 (138%) of a light yellow oil. The crude product was dissolved in 1-2 mL ethyl acetate, run through a filter pipet (silica gel) to remove a small amount of insoluble impurities, and then flash chromatographed (2:1 ethyl acetate:hexane; R_f = 0.33). Compound **1gc** (0.301g, 61%) was obtained as an opaque white oil. IR (neat): 3470, 2940, 1745, 1660, 1405, 1325, 1215, 1100, 740, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, major and minor* rotamer ratio ca. 4:1): δ1.35, 1.40* (3H; d, J = 7Hz; d*, J = 7Hz), 2.05 (3H, d, J = 130 Hz), 2.75*, 2.90 (3H, s), 5.10 (2H, m), 4.45*, 5.25 (1H; q, J = 7Hz; q*, J = 7Hz), 7.30 (5H, m); MS (m/e, %): 236 (18), 192 (1), 145 (8), 101 (41), 91 (13), 58 (100); exact mass calculated for $C_{12}{}^{13}CH_{17}NO_3$: 236.1242; found: 236.1237.

N-2-^{13}C-Acetyl-N-methylalanine (1g): To a solution of **1gb** (0.157 g, 0.662 mmol) in ethyl acetate (20 mL) was added 3-4 drops of glacial acetic acid and 5% palladium on carbon (ca. 4 mg). The mixture was stirred in a hydrogen atmosphere at a positive pressure for 16h, and then filtered through celite. Evaporation of the solvents gave 0.098 g (101%) of **1g** as a white solid, m.p. 100-5°C. IR (KBr): 3440 (br), 2980 (br), 2580 (br), 1735, 1610, 1425, 1270, 1220, 1110, 1040, 815 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, major and minor* rotamer ratio ca. 4:1): δ1.35,1.45* (3H; d, J=7 Hz; d*, J=7 Hz), 2.10 (3H, d, J=135 Hz), 2.95*, 2.80 (3H; s*; s), 4.50*, 5.15 (1H; q*, J=7 Hz; q, J=7 Hz); MS (m/e, %): 146 (6), 102 (12), 101 (30), 58 (100), 56 (14), 44 (24), 42 (13); exact mass calculated for $C_5{}^{13}CH_{11}NO_3$: 146.0772; found: 146.0764.

Methyl 1,2,5-^{13}C-trimethylpyrrole-3-carboxylate (3g) and Methyl 1,2-^{13}C,5-trimethylpyrrole-3-carboxylate (4g): To a stirred solution of **1g** (0.105 g, 0.724 mmol) in acetic anhydride (1.38 mL) was added methyl propiolate (0.232 g, 2.76 mmol). The solution was stirred at 55-65°C for 2.5h. Evaporation of the solvents and excess dipolarophile yielded 103 mg (85%) of the crude product as a beige solid. Flash chromatography (2:1 hexane:ethyl acetate; R_f = 0.42) gave 14 mg (17%) of a white solid, m.p. 115-116.5°C. The isomers are not chromatographically separable. IR (KBr): 3130, 2950, 1690, 1535, 1230, 1190, 1075 cm^{-1}; the **3g:4g*** isomer ratio were determined from both ^{1}H- and ^{13}C-nmr integration as 55:45*; ^{1}H-NMR ($CDCl_3$): δ 2.18 (3H; d, J=135Hz; s*), 2.50 (3H; s; d*, J=135Hz), 3.39 (3H, s), 3.78 (3H, s), 6.23 (1H, s); ^{13}C-NMR ($CDCl_3$): (excitation time: 0.004s; relaxation time: 6 sec) δ 11.4*, 12.3 (for enriched methyl groups); MS (m/e, %): 168 (69), 153 (71), 137 (100), 109 (26), 108 (30), 93 (41), 68 (36), 58 (56), 57 (28), 56 (35), 53 (9), 42 (37); calculated exact mass for $C_8{}^{13}CH_{13}NO_2$: 168.0980, found: 168.0976.

N-Benzyloxycarbonyl-2-^{13}C-alanine (1ha): To a solution of 2-^{13}C-alanine (0.300g, 3.33 mmol) in 4M NaOH (0.850 mL) was added, in five portions of 0.160 mL each, a total of 0.800 mL benzyl chloroformate (0.850g, 5.00 mmol) over a period of 1 hr. The reaction mixture was kept at 0°C throughout the addition period. An additional 0.200 mL portion of benzyl chloroformate was added at the end of the addition period, and the mixture was stirred at room temperature for 35 minutes. The pH of the aqueous mixture was adjusted to 10.0 with 2N NaOH, and the mixture was washed once with ether to remove unreacted benzyl chloroformate. The aqueous layer was then acidified to pH < 2.0 with 3M HCl. The turbid solution was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and solvents were removed *in vacuo*. The oily residue was crystallized from ethyl acetate/hexanes, to give 0.570g (76.0%) of **1ha** as a colorless solid, m.p. 87-89°C. IR (KBr): 3332 (vs), 3300-2500 (b), 1692 (vs), 1534 (s), 1292 (s), 1253 (s), 1072 (s), 1026 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ7.32 (5H, s), 5.20 (2H, bs), 4.43 (1H, q, J = 7.0 Hz), 1.49 (3H, dd, J = 130.0 Hz, 7.0 Hz); MS (m/e, %): 224 (10), 135 (10), 108 (90), 91 (100); calculated exact mass for $C_{10}{}^{13}CH_{13}NO_4$: 224.0878, found: 224.0871.

N-Methyl-N-benzyloxycarbonyl-2-^{13}C-alanine (1hb): Compound **1hb** was prepared according to the general procedure of McDermott and Benoiton.[43] Thus, to a stirred 0°C solution of **1ha** (0.490g, 2.19 mmol) in THF (7 mL) was added iodomethane (1.20 mL, 19.3 mmol). Sodium hydride (0.450g, 50% dispersion in mineral oil, 9.38 mmol, rinsed with dry pentane) was added slowly to the mixture. The mixture was stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate (6 mL), and water (10 mL) was added to consume any remaining sodium hydride. The organic layer was separated, and the aqueous layer was extracted once with ether (10 mL) to remove any remaining iodomethane. The ether layer was separated and washed with saturated aqueous sodium bicarbonate. The combine aqueous layers were acidified to pH < 2.0 with 3.0M HCl. The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed once with 10 mL of 5% aqueous sodium thiosulfate and twice with 10 mL of water. The organic layer was then dried ($MgSO_4$) and filtered. Solvents were removed under reduced pressure giving the crude product as a colorless oil (0.507g, 98%). The crude material was used in the subsequent hydrogenolysis step without further purification. IR (neat): 3611 - 2400 (b), 1742 (vs), 1704 (vs), 1680 (vs), 1455 (s), 1405 (s), 1320 (s), 1162 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ7.33 (bs, 5H), 5.16 (s, 2H), 4.93, 4.75 (rotamer*, 40%) (m, m*; 1H), 3.02 (bs, 3H), 1.48 (dd, J=128.9, 6.8 Hz, 3H); MS (m/e, %): 238 (1), 193 (10), 149 (15), 122 (3), 108 (12), 103 (18), 91 (100), 77 (3), 65 (7), 59 (4), 51 (2), 42 (4); exact mass calculated for $C_{11}{}^{13}CH_{15}NO_4$: 238.1035; found: 238.1033.

N-Methyl-2-^{13}C-alanine (1hc): To a solution of **1hb** (0.500g, 2.10 mmol) in methanol (10 mL) was added glacial acetic acid (1.0 mL) and 10% palladium on activated carbon (0.080g). The mixture was stirred 9 hr at room temperature under a positive atmosphere of hydrogen gas. The mixture was filtered, and the solids were rinsed with methanol. Methanol and acetic acid were removed *in vacuo*. The oily residue was crystallized from methanol/acetic acid/acetone, to give 0.132g (61%) of a colorless solid. IR (KBr): 3500-2400 (b), 1584 (vs), 1394 (s), 1351 (s) cm^{-1}; ^{1}H-NMR (D_2O, 360 MHz): δ3.48 (q, J=7 Hz, 1H), 2.55 (s, 3H), 1.35 (dd, J = 129, 7 Hz, 3H); MS (m/e, %): 104 (3), 87 (3), 59 (100), 57 (17), 45 (12), 42 (15); exact mass calculated for $C_3{}^{13}CH_9NO_2$: 104.0667; found: 104.0670.

N-Acetyl-N-methyl-2-^{13}C-alanine (1h): To a stirred, room temperature solution of **1hc** (0.102g, 0.961 mmol) in 2M NaOH (1.3 mL) was added acetic anhydride (0.292g, 0.270 mL, 2.86 mmol). The mixture stirred at room temperature for 2.25 hours. After cooling the solution to 0°C, the pH was adjusted to < 2 with 3M HCl. The solution was extracted ethyl acetate (3x15mL), and the combined organic layers were dried ($MgSO_4$) and filtered. Solvents were removed under reduced pressure, and the oily residue solidified on standing. The solid material was recrystallized from ethyl acetate/hexanes, giving **1h** (0.048g, 33.5%) as a colorless solid, m.p. 92-94 °C. IR (KBr): 3400-2500 (b), 1730 (vs), 1602 (vs), 1214 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 360 MHz, as rotamers, major:minor* ca. 6:1): δ5.14, 4.53* (q, J=7 Hz; q*, J=7 Hz; 1H), 2.96, 2.80* (s; s*; 3H), 2.18 (s, 3H), 1.43, 1.51* (dd, J=130, 7 Hz; dd*, J=130, 7 Hz; 3H); MS (m/e, %): 146 (7), 101 (43), 88 (4), 86 (0.3), 59 (100), 57 (15), 45 (6), 43 (29); exact mass calculated for $C_5{}^{13}CH_{11}NO_3$: 146.0772; found: 146.0771.

Methyl 1,2-^{13}C,5-trimethylpyrrole-3-carboxylate (3h) and methyl 1,2,5-^{13}C-trimethylpyrrole-3-carboxylate (4h): To a stirred, room temperature solution of **1h** (0.043g, 0.30 mmol) in acetic anhydride (0.41 mL) was added methyl propiolate (0.074 mL, 0.070g, 0.831 mmol). The mixture was heated to 65°C for 3 hr. Solvents and unreacted dipolarophile were removed *in vacuo*, to give the crude mixture of **3h** and **4h** as a colorless solid (0.040g, 80%). m.p. 115-117°C. IR (KBr): 3448 (bs), 1686 (vs), 1638 (s), 1560 (s), 1534 (m), 1226 (s), 1069 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): **3h, 4h***: δ6.23 (s, 1H), 3.78 (s, 3H), 3.39 (s, 3H), 2.50 (d, J=126 Hz; s*; 3H), 2.18 (s; d*, J=126 Hz; 3H), relative isomer ratio **3h:4h*** = 47:53; ^{13}C-NMR ($CDCl_3$): (excitation time: 0.004s; relaxation time: 6 sec): δ11.4, 12.3* (for enriched methyl groups), relative isomer ratio **3h:4h** = 47:53; MS (m/e): 168 (100), 153 (61), 137 (72), 123 (1), 108 (17), 93 (2), 80 (2), 68 (18), 57 (16), 52 (5), 42 (21); calculated exact mass for $C_8{}^{13}CH_{13}NO_2$: 168.0980;found: 168.0976.

N-Acetyl-N-methylalanine (1i): To a solution of N-methylalanine (1.51g, 14.5 mmol) in 2M NaOH (8.7 mL) was added acetic anhydride (4.16 mL, 4.49 g, 44.0 mmol). The mixture was stirred at 50°C for 1.5 hr, after which time TLC showed no remaining N-methylalanine (60:40 CH_3CN/NH_4OAc, Ninhydrin, R_f=0.50). The mixture was cooled on an ice bath and acidified to pH < 2 with 6N H_2SO_4. The aqueous solution was extracted ethyl acetate (3x15mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The oily residue was dried *in vacuo*, giving a colorless solid. The solid was recrystallized from ethyl acetate/hexanes giving 1.27g (66%) of **1i** as a colorless solid, m.p. 97-99°C. IR (KBr): 3600 - 2200 (b), 1731 (vs), 1600 (vs), 1416 (s), 1214 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ5.15 (q, J = 7.6 Hz, 1H), 2.93 (s, 3H), 2.09 (s, 3H), 1.30 (d, J = 7.6 Hz, 3H); MS (m/e, %): 145 (8), 100 (44), 88 (0.2), 86 (1), 58 (100), 56 (21), 43 (29); calculated exact mass for $C_6H_{11}NO_3$: 145.0739; found: 145.0745.

Methyl 1,2,5-trimethylpyrrole-3-carboxylate. (3i=4i): To a stirred, room temperature suspension of **1i** (0.050g, 0.345 mmol) in acetic anhydride (0.48 mL, 5.0 mmol) was added methyl propiolate (0.086 mL, 0.0813g, 0.967 mmol). The mixture was stirred at 65°C for 2.5 hr. Solvents and excess dipolarophile were removed *in vacuo* to give the crude product as a brown solid. The material was purified by flash chromatography (5:1 hexane/ethyl acetate eluent, R_f = 0.30), to give 0.033g (62%) of **3i=4i** as a colorless solid, m.p. 117-118°C. IR (KBr): 2900 (m), 1689 (vs), 1533 (s), 1439 (s), 1226 (vs), 1191 (s), 1070 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ6.23 (s, 1H), 3.78 (s, 3H), 3.39 (s, 3H), 2.50 (s, 3H), 2.18 (s, 3H). MS (m/e, %): 167 (100), 152 (63), 136 (73), 107 (17), 92 (2), 79 (2), 67 (25), 56 (30), 52 (5), 42 (20); calculated exact mass for $C_9H_{13}NO_2$: 167.0946; found: 167.0939.

Methyl 1,4- and 1,3-dimethyl-2-phenylthio-3- and 4-pyrrolecarboxylate (Table IV, entry 2): Reaction of **1d** (345 mg, 1.5 mmol) with methyl 2-butynoate (150 mg, 1.5 mmol) under the cycloaddition conditions gave 360 mg (90%) of the title compounds as inseparable oils. IR ($CDCl_3$): 1700, 1425, 1250, 1075 cm^{-1}; ^{1}H-NMR (3*-+4-isomer, $CDCl_3$) : δ2.27* (3H, s), 3.53* (3H, s), 3.76* (3H, s), 6.62* (1H, bs), 6.99-7.08* (5H, m); 2.38 (3H, s), 3.54 (3H, s), 3.8 (3H, s), 6.9-7.2 (5H, m), 7.47 (lH, s); MS (m/e, %) : 261 (1), 246 (12), 230 (20), 203 (15), 152 (32); calculated exact mass for $C_{14}H_{15}NO_2S$: 261.0820; found: 261.0836.

Methyl 1-methyl-3-phenyl-2-phenylthio-4-pyrrolecarboxylate (Table IV, entry 3): Reaction of **1d** (297 mg, 1.3 mmol) with methyl phenylpropiolate (0.21 g, 1.3 mmol) under the cycloaddition conditions gave 400 mg (94%) of a single regioisomer. The product was chromatographed (preparative TLC; 1:3 EtOAc:hexane) to give 340 mg (80%) of the title compound, mp. 163-6°C; IR ($CDCl_3$): 2965, 1705, 1520, 1440, 1270, 1190, 1135 cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ3.47 (3H, s), 3.65 (3H, s), 6.87-7.27 (10H, m), 7.53 (1H, s); MS (m/e, %) : 323 (5), 308 (20), 292 (13), 277 (18), 214 (39), 199 (67), 184 (75); calculated exact mass for $C_{19}H_{17}NO_2S$: 323.0976; found: 323.0981.

N-Formyl-N-methylvaline (Table VI, entry 1): To a stirred, 0°C solution of N-methylvaline (0.090g, 0.689 mmol) in 88% aqueous formic acid (0.770 mL) was added, dropwise, acetic anhydride (0.447 mL, 0.482g, 4.72 mmol). The solution was stirred at room temperature for 3 hr. The mixture was dried *in vacuo* 9 hours to give the title compound as a clear, colorless oil (0.097g, 88%). The material was sufficiently pure for characterization and was used without further purification. IR (neat): 2800-3500 (b), 1732 (vs), 1637 (vs), 1471 (s), 1391 (vs), 1276 (s), 1255 (s), 1250 (s), 1210 (vs), 1067 (s) cm^{-1}.; ^{1}H-NMR ($CDCl_3$, 360 MHz, as rotamers in a ca. 3:2* ratio): δ8.11*, 8.10 (s*; s; 1H), 4.60*, 3.61 ppm (d*, J=7 Hz; d, J=7 Hz; 1H), 3.05*, 2.90 (s, 3H), 2.30 (bm, 1H), 1.09 (m, 3H), 0.90 (m, 3H); MS (m/e, %): 159 (8), 114 (96), 99 (42), 88 (41), 86 (53), 70 (27), 60 (33), 55 (39), 42 (100), 39 (32); calculated exact mass for $C_7H_{13}NO_3$: 159.0895; found: 159.0890.

Methyl 2-isopropyl-1-methylpyrrole-3-carboxylate (A) and Methyl 5-isopropyl-1-methylpyrrole-3-carboxylate (B) (Table VI, entry 1): To a stirred suspension of N-formyl-N-methylvaline (0.072g, 0.453 mmol) in dry acetic anhydride (0.770 mL, 0.831g, 8.15 mmol) was added methyl propiolate (0.200 mL, 0.190g, 2.26 mmol). The mixture was stirred for 2.5 hr at 65°C, after which point TLC indicated complete reaction (2:1 hexanes/ethyl acetate, R_f A/B = 0.70). Solvents and unreacted dipolarophile were removed *in vacuo*, to give the crude products as a tan oil (0.046g, 56%). Ratio of regioisomers determined from crude and chromatographed reaction mixture, **A:B** = 57:43. The mixture was purified using column chromatography (silica gel, 2:1 hexanes/ethyl acetate, R_f = 0.70). IR (neat): 2964 (vs), 1713 (vs), 1701 (vs), 1524 (s), 1507 (s), 1467 (s), 1457 (s), 1441 (s), 1250 (vs), 1200 (vs), 1173 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): **A**: δ6.48 (d, J=3 Hz, 1H), 6.38 (d, J=3 Hz, 1H), 3.87 (q, J=7 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 1.38)d, J=7 Hz, 6H). **B**: δ7.18 (m, 1H), 6.31 (m, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 2.86 (q, J=7 Hz, 1H), 1.22 (d, J=7 Hz, 6H); MS (m/e, %): 181 (47), 166 (100), 150 (28), 134 (44), 122 (11), 107 (31), 92 (5), 77 (10), 65 (11), 59 (5), 51 (8), 42 (20), 39 (19); calculated exact mass for $C_{10}H_{15}NO_2$: 181.1102; found: 181.1103.

N-Isobutyryl-N-methylglycine (Table VI, entry 2): To a stirred, 0°C solution of N-methylglycine (0.891g, 10.0 mmol) in 2M NaOH (5.00 mL) was added, simultaneously, in five equal portions over 30 minutes, isobutyric anhydride (1.70 mL, 1.62 g, 10.26 mmol) and diisopropylethylamine (1.79 mL, 1.33 g, 10.26 mmol). The solution was warmed to 40°C for 3 hr. The mixture was then cooled on an ice bath, and the pH was brought to < 2.0 with 6N H_2SO_4. The aqueous solution was extracted ethyl acetate (3x15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The oily residue was dried *in vacuo*, and excess isobutyric acid was removed by azeotropic distillation *in vacuo* with toluene. The solid residue was recrystallized from hot ethyl acetate/hexanes, giving the product as a colorless solid (1.29g, 81%). m.p. 108 - 109°C. IR (KBr): 3000-2800 (b), 1758 (vs), 1736 (vs), 1609 (vs), 1500 (vs), 1425 (vs), 1408 (vs), 1211 (vs), 1092 (vs) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, as rotamers in a ca. 3:2* ratio): δ9.10 (b, 1H), 4.14, 4.10* (s; s*; 2H), 3.13, 2.98* (s; s*; 3H), 2.87, 2.65* (q, J=7.6 Hz; q*, J=7.6 Hz; 1H), 1.18, 1.15* (d, J = 7.6 Hz; d*, J=7.6 Hz; 6H); MS (m/e, %): 159 (15), 115 (46), 100 (10), 88 (34), 71 (51), 58 (6), 55 (11), 44 (100); calculated exact mass for $C_7H_{13}NO_3$: 159.0895; found: 159.0903.

Methyl 5-isopropyl-1-methylpyrrole-3-carboxylate (A) and Methyl 2-isopropyl-1-methylpyrrole-3-carboxylate (B) (Table VI, entry 2): To a stirred, room temperature solution of N-isobutyryl-N-methylglycine (0.200g, 1.26 mmol) in dry acetic anhydride (2.13 mL, 2.30g, 22.6 mmol) was added methyl propiolate (0.560 mL, 0.529g, 6.29 mmole). The mixture was stirred for 2.5 hr at 60°C. TLC indicated a complete reaction after 2 hours (2:1 hexanes/ethyl acetate, R_f **A/B** = 0.90). Solvents and excess dipolarophile were removed *in vacuo*, to give the crude products as a tan oil (0.210g, 92%). Ratio of regioisomers determined from crude and chromatographed reaction mixture, **A:B** = 75:25. A portion of the crude material was purified by column chromatography (2:1 hexanes/ethyl acetate , Rf = 0.90), to give a light yellow oil. IR (neat): 2969 (vs), 1731 (vs), 1703 (vs), 1648 (vs), 1250 (s), 1202 (s), 1188 (s), 1174 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): **A**: δ6.48 (d, J=3 Hz, 1H), 6.38 (d, J=3 Hz, 1H), 3.87 (q, J=7 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 1.38 (d, J=7 Hz, 6H); **B**: δ7.18 (m, 1H), 6.31 (m, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 2.86 (q, J=7 Hz, 1H), 1.22 (d, J=7 Hz, 6H); MS (m/e, %): 181 (47), 166 (100), 150 (28), 134 (44), 122 (11), 107 (31), 92 (5), 77 (10), 65 (11), 59 (5), 51 (8), 42 (20), 39 (19); calculated exact mass for $C_{10}H_{15}NO_2$: 181.1102; found: 181.1107.

N-Isobutyryl-N-methylalanine (Table VI, entry 3): To a stirred, 0°C solution of N-methylalanine (0.500g, 4.80 mmol) in 2M NaOH (2.40 mL) was added, simultaneously, in five equal portions spaced 6 minutes apart, diisopropylethylamine (0.637 g, 0.860 mL, 4.93 mmol) and isobutyric anhydride (0.780g, 0.818 mL, 4.93 mmol). The solution was heated to 40°C for 3.5 hr. The mixture was cooled to 0°C, and acidified to pH < 2.0 with 6N H_2SO_4. The aqueous mixture was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The oily residue was dried *in vacuo*, and isobutyric acid was removed by azeotropic distillation *in vacuo* with toluene. The residue was crystallized from toluene/hexanes as a light yellow solid and then recrystallized from ethyl acetate/hexanes as a colorless solid (0.137g, 17%), m.p. 84-86°C. IR (KBr): 2975 (vs), 2941 (vs), 2882 (s), 1734 (vs), 1608 (vs), 1602 (vs), 1486 (s), 1419 (s), 1307 (s), 1205 (vs), 1180 (s), 1098 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 360 MHz, as rotamers in a ca. 6:1* ratio): δ5.17, 4.60* (q, J=7.3 Hz; q*, J=7.3 Hz; 1H), 3.00, 2.82* (s;s*; 3H), 2.83 (m, 1H), 1.50*, 1.48 (d*, J = 7.3 Hz; d, J = 7.3; 3H), 1.13 (d, J = 7 Hz, 6H); MS (m/e, %): 173 (3), 129 (20), 114 (7), 102 (18), 86 (6), 71 (15), 58 (100), 43 (53); calculated exact mass for $C_8H_{15}NO_3$: 173.1052; found: 173.1051.

Methyl 5-isopropyl-1,2-dimethylpyrrole-3-carboxylate (A) and methyl 2-isopropyl-1,5-dimethylpyrrole-3-carboxylate (B) (Table VI, entry 3): To a suspension of N-isobutyryl-N-methylalanine (0.050g, 0.29 mmol) in acetic anhydride (0.490 mL, 5.20 mmol) was added methyl propiolate (0.122g, 1.45 mmol). The mixture was stirred at 65°C for 2.5 hr. Solvents and unreacted dipolarophile were removed *in vacuo* to give 0.050g (88%).of the products as a light yellow oil sufficiently pure for characterization. Ratio of regioisomers determined from the reaction mixture, **A:B** = 67:33. IR (neat): 2964 (vs), 1700 (vs), 1527 (vs), 1460 (s), 1438 (s), 1222 (vs), 1185 (s), 1062 (s), 775 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): **A**: δ6.25 (d, J = 1.0 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 2.85 (m, 1H), 2.51 (s, 3H), 1.21 (d, J = 7.27 Hz, 6H); **B**: δ6.21 (bq, J = 1 Hz, 1H), 3.94 (m, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 2.15 (bs, 3H), 1.40 (d, J = 7.27 Hz, 6H); MS (m/e, %): 195 (48), 180 (100), 164 (16), 148 (15), 136 (3), 121 (10), 84 (1), 58 (10), 42 (10); calculated exact mass for $C_{11}H_{17}NO_2$: 195.1259; found: 195.1260.

Methyl 5-isopropyl-1,2-dimethylpyrrole-3-carboxylate (A) and methyl 2-isopropyl-1,5-dimethylpyrrole-3-carboxylate (B) (Table VI, entry 4): To a solution of N-methyl-N-acetylvaline (0.100g, 0.578 mmol) in dry acetic anhydride (1.00 mL, 1.08 g, 10.4 mmol) was added methyl propiolate (0.257 mL, 0.243g, 2.88 mmol). The mixture was stirred at 60°C for 2.5 hr. Solvents and unreacted dipolarophile were removed *in vacuo* to give the crude products as a red oil. Ratio of regioisomers determined from the crude and chromatographed reaction mixture, **A:B** = 77:23. The crude product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate, Rf **A/B** = 0.65), to give the 0.095g (84%) of the products as a light yellow oil. IR (neat): 2965 (vs), 1702 (vs), 1694 (vs), 1527 (vs), 1460 (vs), 1438 (s), 1414 (s), 1230 (vs), 1198 (s), 1185 (vs), 1171 (vs), 1061 (s), 774 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): **A**: δ6.25 (d, J = 1.0 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 2.85 (m, 1H), 2.51 (s, 3H), 1.21 (d, J = 7.27 Hz, 6H); **B**: δ6.21 (bq, J = 1 Hz, 1H), 3.94 (m, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 2.15 (bs, 3H), 1.40 (d, J = 7.27 Hz, 6H); MS (m/e, %): 195 (46), 180 (100), 164 (16), 148 (22), 136 (3), 121 (9), 84 (6), 56 (8), 49 (12), 42 (11); calculated exact mass for $C_{11}H_{17}NO_2$: 195.1259; found: 195.1257.

N-Propanoyl-N-methylalanine (Table VI, entry 5): To a stirred, room temperature solution of N-methylalanine (0.350g, 3.40 mmol) in 2M NaOH (5.0 mL) was added propanoic anhydride (1.106g, 1.10 mL, 8.50 mmol). The mixture was stirred for 3 hr at room temperature. The solution was cooled to 0°C and acidified to pH < 2.0 with 6N H_2SO_4. The aqueous layer was extracted with ethyl acetate (3x15 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residual oil crystallized from hot ethyl acetate/petroluem ether as a colorless solid (0.270g, 50%), m.p. 80-82°C. IR (KBr): 3500-2100 (b), 1750 (vs), 1620 (vs), 1430 (s), 1210 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 360 MHz): 5.17 (q, J=6.7 Hz, 1H), 2.93 (s, 3H), 2.38 (q, J=6.9 Hz, 2H), 1.42 (d, J = 6.7 Hz, 3H), 1.21 (t, J = 6.9 Hz, 3H); MS (m/e, %): 159 (4), 115 (17), 114 (23), 102 (9), 87 (4), 58 (100), 42 (17); calculated exact mass for $C_7H_{13}NO_3$: 159.0895; found: 159.0885.

Methyl 2-ethyl-1,5-dimethylpyrrole-3-carboxylate (A) and methyl 5-ethyl-1,2-dimethylpyrrole-3-carboxylate (B) (Table VI, entry 5): To a stirred, room temperature solution of N-propanonyl-N-methylalanine (0.122g, 0.772 mmol) in dry acetic anhydride (1.38 mL) was added methyl propiolate (0.232g, 2.76 mmol, 0.246 mL). The mixture was stirred for 2.5 hr at 65°C. The mixture was cooled to room temperature,. Solvents and unreacted dipolarophile were removed *in vacuo* , to give the crude product as a red oil (83 mg, 64%). Ratio of regioisomers determined from the crude and chromatographed reaction mixture, **A:B** = 45:55. The crude product was purified by column chromatography (silica gel, 2:1 hexanes/ethyl acetate, Rf **A/B** = 0.75) to give a colorless oil. IR (neat): 2950 (vs), 1750 (vs), 1700 (vs), 1650 (vs), 1575 (s), 1530 (vs), 1450 (vs), 1410 (vs), 1360 (vs), 1225 (vs), 1180 (vs), 1075 (vs), 1010 (vs), 775 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): **A**: δ6.25 (bs, 1H), 3.77 (s, 3H), 3.42 (s, 3H), 2.98 (q, J=7 Hz, 2H), 2.19 (s, 3H), 1.25 (t, J=7 Hz, 3H). **B**: δ6.26 s (1H), 3.78 (s, 3H), 3.40 (s, 3H), 2.51 (q, J=7 Hz, 2H), 2.50 (s, 3H), 1.15 (t, J=7 Hz, 3H); MS (m/e, %): 181 (50), 166 (100), 122 (16), 150 (31), 134 (18), 107 (15), 92 (4), 77 (6); calculated exact mass for $C_{10}H_{15}NO_2$: 181.1102; found: 181.1108.

N-Formyl-N-methyl-3-methylvaline. (Table VI, entry 6)
To a stirred, 0°C solution of N-methyl-3-methylvaline[44] (0.100 g, 0.689 mmol) in 88% aqueous formic acid (0.770 mL) was added, dropwise, acetic anhydride (0.447 mL, 0.482 g, 4.72 mmol). The mixture was stirred at room temperature for an additional 3 hr. Removal of solvents *in vacuo* gave the title compound as a clear oil (0.110 g, 92%). IR (neat): 3319 (m), 2971 (s), 3600-2200 (b), 1722 (s), 1631 (vs), 1376 (m), 1235 (s), 1075 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 360 MHz, as a mixture of rotamers in a ca. 2:1* ratio): δ8.11, 7.98* (s; s*; 1H), 4.89*, 3.82 (s*;s; 1H), 3.12*, 2.97 (s*; s; 3H), 1.08, 1.06* (s; s*; 9H); MS (m/e,%): (CI, NH_4^+): M^+ 174 (40) 117 (48), 99 (100), 85 (15), 71 (19), 57 (95), 41 (69); calculated exact mass for $C_8H_{15}NO_3H^+$: 174.1130; found: 174.1134.

Methyl 2-t-butyl-1-methylpyrrole-3-carboxylate (A) and methyl 5-t-butyl-1-methylpyrrole-3-carboxylate (B) (Table VI, entry 6): To a stirred solution of 0.100 g (0.578 mmol) of N-formyl-N-methyl-3-methylvaline in acetic anhydride (1 mL) was added methyl propiolate (0.173 g, 0.183 mL, 2.06 mmol). The solution was stirred at 65°C for 2.5 hr. Evaporation of the solvents *in vacuo* gave the products as a red oil (60 mg, 53%) which was chromatographed (silica gel, 5:1 hexane/ethyl acetate, Rf.**A/B** = 0.50). The **A:B** regioisomeric ratio, as determined from the crude and chromatographed reaction mixture, was 77:33. IR (neat): 2962 (vs), 1711 (vs), 1475 (m), 1440 (m), 1365 (m), 1255 (s), 1220 (vs), 1204 (vs), 1158 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): **A**: 7.08 (d, J=2.0 Hz, 1H), 6.27 (d, J=2.0 Hz, 1H), 3.69 s (3H), 3.69 s (3H), 1.43 (s, 9H); **B**: 6.28 (d, J=3.15 Hz, 1H), 6.26 (d, J=3.15 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 1.26 s (9H); MS (m/e, %): 195 (40), 180 (100), 164 (19), 148 (82), 121 (14), 106 (6), 77 (8), 61 (16), 42 (22); calculated exact mass for $C_{11}H_{17}NO_2$: 195.1259; found: 195.1256.

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30. For a notable exception, see reference 10c.

31. Our initial experiments to prepare the $\mathbf{R_1/R_2}$ = H/D and $\mathbf{R_1/R_2}$ = CH_3/CD_3 series of compounds were unsuccessful due to H/D exchange reactions under any cycloaddition conditions.
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35. The cycloaddition reactions of an intriguing bicyclic mesoionic compound with methyl propiolate and methyl phenylpropiolate have been reported: see reference 1b. The pyrroles observed from reactions with both of these two dipolarophiles show the opposite type of substitution pattern as that found in *entries* **2** and **3** of **Table V**. This is proposed to be due to a reversable cycloaddition reaction of this particular masked azomethine ylid that can achieve a thermodynamic distribution of the intermediate structures leading to the observed products. Methyl phenylpropiolate was also the dipolarophile used with a pair of regioisomeric münchnones that gave completely regioselctive formation of pyrroles that were insensitive to a set of aryl substituents (see ref. 10f).
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