On the Problem of Regioselectivity in the 1,3-Dipolar Cycloaddition Reaction of Munchnones and Sydnones with Acetylenic Dipolarophiles

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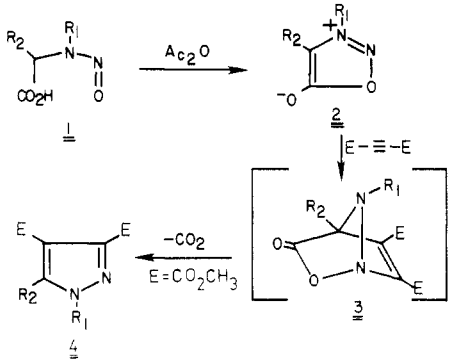
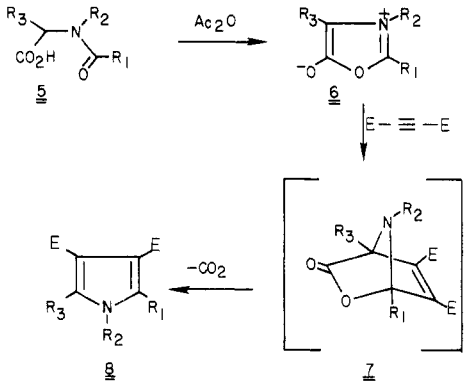
The 1,3-dipolar cycloaddition reaction of several unsymmetrically substituted munchnones and sydnones with methyl propiolate has been examined. The initially formed cycloadducts readily extrude carbon dioxide to produce five-membered heteroaromatic ring compounds. The reaction of sydnones with methyl propiolate produced a mixture of regioisomeric pyrazoles. The analogous [3 + 2] cycloaddition reaction of munchnones with methyl propiolate proceeds with formation of mixtures of both possible regioisomeric pyrroles. The structural assignment of the isolated adducts is based on spectroscopic data. The distribution of products depends on the nature and location of the substituent groups present on the heterocyclic ring. The observed regioselectivity is discussed on the basis of MO-perturbation theory.

During the last decade a new impulse has been given to research in the field of heterocyclic chemistry when it was found that various mesoionic compounds undergo 1,3-dipolar cycloaddition with different dipolarophiles.[1-19] Of the known mesoionic heterocycles, the structure, physical properties, and reactions of sydnones have drawn the closest scrutiny.[20] These mesoionic compounds can be readily prepared by cyclodehydration of *N*-nitroso-α-alkyl amino acids (**1**) with reagents such as acetic anhydride. The resulting compounds contain a mesoionic aromatic system (**2**) which can only be depicted with polar resonance structures.[21] Sydnones undergo smooth cycloaddition with acetylenes to give pyrazoles (**4**) in high yield.[22-24] The reaction involves a 1,3-dipolar cycloaddition of the sydnones, behaving like a cyclic azomethine imine, to the corresponding acetylene followed by carbon dioxide evolution and aromatization.



Huisgen and co-workers have also described the cycloaddition behavior of the "munchnones", unstable mesoionic Δ^2-oxazolium 5-oxides of type **6** with azomethine ylide structures.[25-29] Their reactions closely parallel those of the related sydnones. The reaction of munchnones with acetylenic dipolarophiles constitutes a pyrrole synthesis of broad scope.[30-36] 1,3-Dipolar cycloaddition of acetylene to the Δ^2-oxazolium 5-oxide (**6**) followed by cycloreversion of carbon dioxide from the initially formed adduct **7** gives pyrrole derivatives **8** in good yield.



Apart from the obvious synthetic value associated with the 1,3-dipolar cycloaddition reaction of mesoionic com-

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(21) W. Baker and W. D. Ollis, *Q. Rev., Chem. Soc.*, **11**, 15 (1957).
(22) R. Huisgen, *Bull. Soc. Chim. Fr.*, 3431 (1965).
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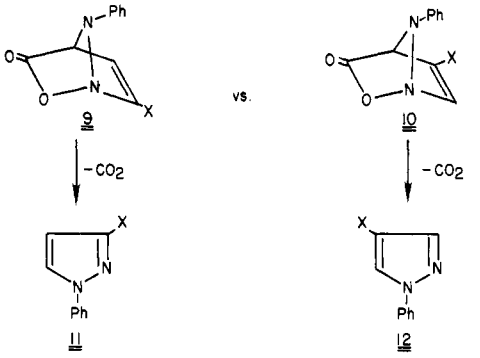
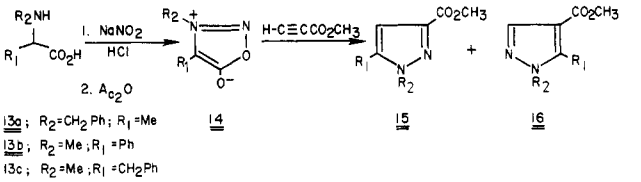
pounds, there has been considerable interest in the reaction mechanism and regioselectivity of the cycloaddition. The mechanism that has emerged from Huisgen's group is that of a single-step, four-center, "no-mechanism" cycloaddition, in which the two new bonds are both partially formed in the transition state, although not necessarily to the same extent.[1-3] An alternative mechanism that has been proposed is a two-step process involving a spin-paired diradical intermediate.[37] In order to predict regioselectivity, it becomes necessary to determine the relative magnitudes of the coefficients in the HOMO and LUMO of the 1,3-dipole and dipolarophile. According to simple FMO theory, bond formation is dictated primarily by the charge transfer interaction energy determined by overlap of the HOMO(dipole)–LUMO(olefin) and the LUMO-(dipole)–HOMO(olefin) with the appropriate symmetry.[38,39] Which of these interactions will dominate is sometimes determined by the relative energy differences of either pair of orbitals. The regioselectivity is then the result of best orbital overlap, i.e., the atoms with the largest orbital coefficients combine preferentially.

When sydnones are used as 1,3-dipoles, the dipole LUMO and dipolarophile HOMO interaction has been suggested to be the controlling term.[38,40] Calculations by Houk indicate that the terminal coefficients of the azomethine imine system are almost identical in the LUMO.[38,40] Thus, although LUMO control of reactivity will obtain, a decrease in regioselectivity of sydnone cycloaddition with respect to that observed with simpler azomethine imines is expected. In fact, sydnones do undergo regioselective reactions, but the degree of regioselectivity appears to be smaller than is observed with simpler azomethine imines.[40] For example, *N*-phenylsydnone is known to react with all three classes of dipolarophiles to give predominantly the products resulting from intermediate adduct **9**.[41] Methyl propiolate gives a 4:1 mixture of adducts arising from **9** and the other regioisomer **10**, respectively.[41]

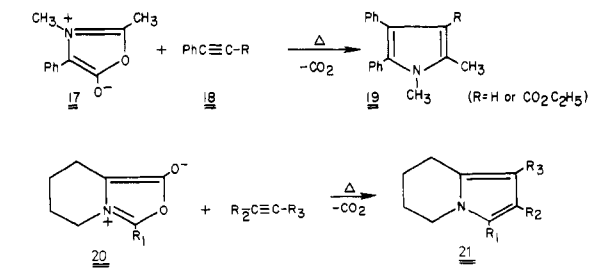
We have encountered similar results in our investigation with sydnones **14a–c**. The conversion of the three amino acids **13a–c** to a mixture of regioisomeric carbomethoxypyrazoles was accomplished by treating the acid with methyl propiolate in acetic anhydride at 100–120 °C. No



attempt was made to isolate the intermediate sydnones **14a–c**. The progress of the reaction was monitored by carbon dioxide evolution. Workup procedures consist of addition of water, extraction with ether, and silica gel chromatographic separation of the mixture of regioisomers. Identification of each isomer was made on the basis of its characteristic NMR spectrum. Particular attention was given to the chemical shift of the pyrazole proton. The ring proton in the 3-carbomethoxy-substituted isomer appeared 1.2–1.3 ppm upfield relative to the 4-carbomethoxy-substituted isomer. In all cases, a mixture of two regioisomeric cycloadducts was obtained. The major product (i.e., **15**) always corresponded to the 3-carbomethoxy-substituted isomer (**15**/**16** ~ 3:1).



The 1,3-cycloaddition of Δ^2-oxazolium 5-oxides (munchnones) with dipolarophiles has frequently been utilized in the synthesis of a variety of heterocyclic systems.[25-29] The reaction pathway involves a cycloaddition to an azomethine ylide to give a N-bridged intermediate that loses carbon dioxide and forms a heterocycle. Houk[39] has suggested that unsymmetrically substituted azomethine ylides such as munchnones will react readily with both electron-deficient and electron-rich dipolarophiles due to the narrow frontier orbital separation (i.e., Sustmann[42] type II classification). The regiochemistry of the cycloaddition should be controlled by asymmetry in the dipole frontier orbitals caused by the substituent groups. When electron-deficient dipolarophiles such as unsymmetrically substituted acetylenes are used, the cycloaddition reaction of a number of munchnones has been reported to produce a single cycloadduct. Two typical examples are outlined below.[25,34,35]



During the course of a study dealing with the 1,3-dipolar cycloaddition behavior of mesoionic compounds,[43] we in-

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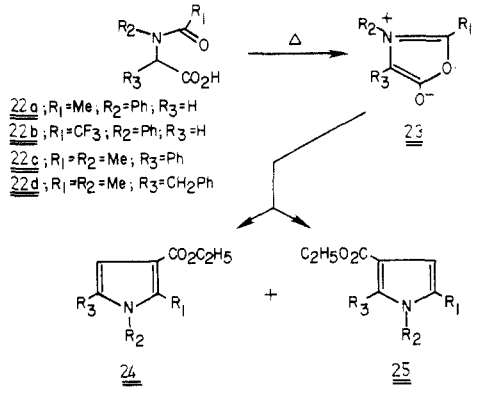
(42) R. Sustmann, *Tetrahedron Lett.*, 2721 (1971); *Pure Appl. Chem.*, **40**, 569 (1974); J. Geittner, R. Huisgen, and R. Sustmann, *Tetraedron Lett.*, 881 (1977).

Table I

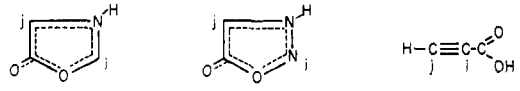
parameter	value for compd 26	27	28
$E_h(\pi)$	−7.794	−8.490	−11.233
$E_l(\pi^*)$	0.960	1.176	0.345
$E_l(\sigma^*)$	1.614	2.153	0.882
q_i	+0.298	−0.164	+0.073
q_i	−0.458	−0.018	−0.393
$C_{lh}(\pi)$	0.419	0.656	0.657
$C_{jh}(\pi)$	0.737	0.645	0.587
$C_{il}(\pi^*)$	0.738	0.369	0.434
$C_{jl}(\pi^*)$	0.260	0.555	0.563
$C_{il}(\sigma^*)$	0.060	0.159	0.079
$C_{jl}(\sigma^*)$	0.393	0.229	0.170

vestigated the cycloaddition of several unsymmetrically substituted munchnones and have found that the reaction leads to a mixture of regioisomeric cycloadducts. This stands in marked contrast to the situation encountered with the munchnones outlined above. Munchnones **23a–c** were obtained by treating the appropriate α-amino acid with acetic anhydride at 100–130 °C. No attempt was



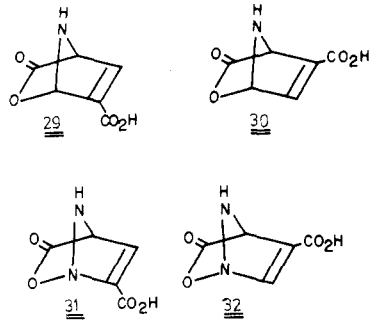
made to isolate the intermediate munchnones, since Huisgen has shown the Δ^2-oxazolium 5-oxide system to be extremely reactive.[24-29] In all four cases studied, a mixture of two regioisomeric pyrroles was obtained. NMR spectroscopy allows unambiguous distinction of the regioisomers and the determination of their relative amounts in the crude reaction mixture. Cycloaddition of munchnone **23a** with ethyl propiolate produced a 3:1 mixture of pyrroles **24** and **25**. Replacement of the methyl group (i.e., R_1) with a trifluoromethyl substituent resulted in a pronounced change in the distribution of the pyrroles. Thus, the reaction of *N*-phenylglycine with trifluoroacetic anhydride in the presence of ethyl propiolate at 130 °C furnished a 1:9 mixture of pyrroles **24** and **25**, respectively. Once again, no attempt was made to isolate the intermediate munchnone **23b**. It should be noted that the reaction of munchnones **23c** and **23d** with ethyl propiolate was nonregiospecific, giving rise to a 1:1 mixture of pyrroles **24** and **25**. These results clearly establish that the regioselectivity associated with the cycloaddition of munchnones is markedly dependent on the nature of the substituent groups attached to the heterocyclic ring.

In an attempt to rationalize the regiochemical results encountered with both the munchnone and sydnone systems, we decided to evaluate the relative influence of charge and orbital interaction between these mesoionic dipoles and propiolic acid. A fully geometry-energy optimized MINDO[44] calculation on **26**, **27**, and **28** gave the values shown in Table I where the subscripts h and l refer to the highest occupied and lowest unoccupied orbitals of energy, E (in eV) and subscripts i, j to the orbitals on the indicated atomic center with total charge density, q, and coefficients, c. The interaction energy between two



25 27 28

reactants, A and B, at some distance R may be assumed to be the sum of terms representing the covalent or intermolecular charge transfer energy, ΔE_{ct}; the van der Waals or ionic (ion pairs without any charge transfer) energy, ΔE_i; and solvation energy which is neglected here.[45] This interaction energy is expressed in first and second order by Rayleigh–Schrodinger perturbation treatment given the zeroth order energies and associated wave functions. The usual assumptions of separability of the interacting electronic systems, zero overlap between reactants, and neglect of multicenter integrals allow convenient estimates to be made of the relative interaction energy difference between two cycloaddition partners at the two points of union leading to two possible regioisomeric products. Only frontier (HOMO, LUMO) orbitals are considered, and the perturbation of one reactant upon the other is assumed to be small. The latter requires analysis to be carried out at the very beginning of the reaction coordinate and the difference developed between two regioisomeric interactions is carried to the two possible transition states allowing an energy of activation differentiation between the two possible cycloaddition pathways.[46] At large distance the various interaction terms are very small and may cancel or add, but a relative comparison of the same term for the two regioisomeric arrangements of atoms may be meaningful. Since different terms have different distance dependence, relative weighting of the various energy contributions is not possible unless an origin of a reaction coordinate can be defined. With these assumptions and constraints in mind, the following frontier orbital analysis is presented for the concerted cycloaddition of unsubstituted munchnones and sydnones with propiolic acid leading to the intermediates **29–32**.



The charge transfer interaction energy for a four-center cycloaddition reaction from second-order theory has the form

$$\Delta E_{ct} = 2\beta^2[(C_{ih}^A C_{il}^B + C_{jh}^A C_{jl}^B)^2/E_h^A - E_l^B + (C_{il}^A C_{ih}^B + C_{jl}^A C_{jh}^B)^2/E_h^B - E_l^A] \quad (1)$$

where β is the resonance integral developed between the

(43) For an earlier study, see A. Padwa, H. L. Gingrich, and R. Lim, *Tetrahedron Lett.*, 3419 (1980).
(44) R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, **97**, 1285, 1294, 1302 (1975).
(45) For an excellent discussion of the definition and interplay between these energies, see G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968).
(46) W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972).

Table II

term	ratio (26 → 29)/(26 → 30)	ratio (27 → 31)/(27 → 32)
ΔE_{ct}	2.37	1.25
$\Delta E_{pol}(\pi^*)$	1.21	1.48
$\Delta E_{pol}(\sigma^*)$	1.68	1.43

atomic frontier orbitals at the points of union and assumed here to be the same for all four centers at any given distance. Evaluation of only part of this term ("LUMO or HOMO control") had led to a simplification[38,42] which is not justified. The suggestion that the dipole π^*- and dipolarophile π-orbital interaction is the controlling term for sydnone cycloadditions is an example, for here its value is somewhat less than the other possible frontier orbital interaction. As an index of the energy difference between the two regioisomeric transition states the ratio of the interaction energy for **26** → **29** vs. **26** → **30** and **27** → **31** vs. **27** → **32** seems appropriate. The ΔE_{ct} ratio is shown in Table II and indicates munchnones should demonstrate greater regioselectivity than sydnones although it is difficult on this level of approximation to ascribe an observed ratio of cycloadducts to the magnitude of this ratio. In the present study both sydnones and munchnones having the same substitution pattern give the same ratio of products although the index in both cases correctly predicts the major isomer. The clear exception is the regiochemistry of the trifluoromethyl derivative **23b**. Attachment of such a strong electron-withdrawing group to position i of a munchnone should increase the magnitude of C_{ih} at the expense of C_{jh} in the π orbital and reduce the ΔE_{ct} ratio. It should be noted (Table I) that the propiolic acid dipolarophile has only one π orbital of the proper symmetry for a concerted cycloaddition and has nearly equal HOMO coefficients so any regioselection must result from the π^*-orbital frontier interaction.

Although ΔE_{ct} is a popular index[38] for regiochemical predictions and has enjoyed considerable success, it should best apply to nonpolar reactions. In the present case mesoionic compounds having high local charge densities give rise to a complex inhomogeneous electric field in the vicinity of the approaching dipolarophile, and van der Waals energy considerations[47] may be important and provide some insight into the regiochemistry of the cycloadditions. The ΔE_{ct} contribution is related to the overlap (neglected in the above analysis) of the atomic orbitals at the union sites and thus depends exponentially on the distance R and may be considered to be a short-range interaction. In first order van der Waals energies are inversely dependent upon R and therefore extend to long range for highly charged atoms.[48] The ΔE_i interaction can be decomposed into three terms; the electrostatic (ΔE_{el}), polarization (ΔE_{pol}), and dispersion energies. The first-order electrostatic contribution for a cycloaddition may be expressed as

$$\Delta E_{el} = (-q_i^A q_i^B - q_j^A q_j^B)\Gamma/\epsilon \qquad (2)$$

where Γ is the couloumb repulsion integral at some distance and ϵ the local dielectric constant and the assumption is made here of an electrostatic point-charge approximation and neglect of cross terms involving $q_i^A q_j^B$. The ΔE_{el} difference for **26** → **29** and **26** → **30** is $0.133\Gamma/\epsilon$. With this index munchnones should be more regiospecific than sydnones and the preference for the formation of **29** and **31** is clear in both cases. A substituent at the ith position of munchnones such as trifluoromethyl should reduce the charge density at the expense of the jth site and decrease the regiospecificity.

The second-order contributions to ΔE_i consists of polarization involving the excited states of one cycloaddend and dispersion when both cycloaddends are monoexcited. We will neglect this latter term and consider only polarization due to the first monoexcited π^* and σ^* configurations by the expression:

$$\Delta E_{pol} = \frac{2(C_{ih}^A C_{il}^A q_i^B + C_{jl}^A C_{jh}^A q_j^B)^2\alpha^2}{E_h^A - E_l^A} + \frac{2(C_{il}^B C_{ih}^B q_i^A + C_{jl}^B C_{jh}^B q_j^A)^2\alpha^2}{E_h^B - E_l^B} \qquad (3)$$

where α is the electric field interaction integral and the assumptions governing eq 1 are used. The consideration is made that the point charge on one cycloaddend position only results in second-order mixing of π with π^* or π with σ^* (the integral $\langle\pi|\alpha|\pi^*\rangle$ and $\langle\pi|\alpha|\sigma^*\rangle \neq 0$) in the other reaction partner, i.e., the electric fields are homogeneous and separable at the sites of union. The calculated values are shown in Table II, and in each case the leading contribution is from polarization of the dieneophile by the 1,3-dipolarophile with the π^* contributions greater than σ^*. Interestingly, here sydnones are predicted to be more regiospecific than munchnones. If the cycloaddition employed dieneophiles with more conjugating substituents such as phenylacetylene, where excited states lie lower in energy, this index could indicate decreased regiospecificity or a reversal of the regiochemistry of the reaction observed in the present study. No estimates can be made of the influence of ΔE_{ct} vs. ΔE_{pol} without definition of the reaction coordinate position at which regiochemistry finally observed in the product is controlled and even then the relative magnitude of the various indices would require a more careful analysis. A complete self-consistent calculation to minimize the charge densities at some distance along the reaction coordinate would include all of the above effects; however, given the SCF parameters for each partner in the cycloaddition, the foregoing simplified analysis does seem to fit the experimental observation. In conclusion, the regiochemistry exhibited in the cycloaddition of sydnones and munchnones with ethyl propiolate is sensitive to substitution and has its basis in all possible frontier interactions.

Experimental Section[49]

Methyl 5-Methyl-1-(phenylmethyl)-1*H*-pyrazole-3-carboxylate (15a) and Methyl 5-Methyl-1-(phenylmethyl)-1*H*-pyrazole-4-carboxylate (16a). A mixture of *N*-(phenylmethyl)-DL-alanine ethyl ester[50] (20.7 g, 100 mmol), sodium hydroxide (6.00 g, 150 mmol), and water (50 mL) was heated at reflux with stirring for 45 min. Upon cooling, the reaction mixture was diluted with water (50 mL), extracted with ether (100 mL), and adjusted to a pH of ca. 3 with 10% hydrochloric acid. A

(47) J. Bertran, E. Silla, and J. I. Fernandez-Alonso, *Tetrahedron*, **31**, 1093 (1975). H. Fujimoto and R. Hoffman, *J. Phys. Chem.*, **78**, 1874 (1974), and references therein.

(48) W. Kutzelnigg, *Angew. Chem., Int. Ed. Engl.*, **12**, 546 (1973).

(49) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. NMR spectra were obtained on a Varian T-60 spectrometer. Microanalyses were performed at FMC Corporation, Princeton, NJ. Preparative chromatographies were performed on EM silica gel 60 (70–230 mesh), E. Merck Co., or by medium-pressure liquid chromatography, using a Jobin-Yvon Chromatospec.

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solution of sodium nitrite (7.59 g, 110 mmol) in water (25 mL) was then added dropwise with stirring to the above aqueous reaction mixture at 0 °C. Upon completion of this addition, the reaction mixture was allowed to stir at 0 °C for an additional 2 h. The reaction mixture was then acidified to a pH of ca. 1 with 10% hydrochloric acid and extracted with methylene chloride (2 × 100 mL). The combined methylene chloride extracts were in turn washed with water (100 mL). The dried (sodium sulfate) methylene chloride layer was then evaporated at reduced pressure (at ambient temperature) to give the crude *N*-nitroso amino acid. A solution of the crude *N*-nitroso amino acid and methyl propiolate (12.6 g, 150 mmol) in acetic anhydride (100 mL) was heated with stirring at 100 °C (sand bath temperature) for 16 h and at 130 °C for an additional 24 h. Upon cooling, the reaction mixture was poured into water (500 mL) to hydrolyze the excess acetic anhydride. After being stirred for 30 min, the acidic aqueous reaction mixture was extracted with ether (2 × 250 mL). The combined ethereal extracts were in turn washed successively with water (3 × 300 mL), saturated aqueous sodium bicarbonate (300 mL), and water (300 mL). The dried (magnesium sulfate) ethereal layer was then evaporated at reduced pressure to give a brown oil (18.5 g). The NMR spectrum of this oil indicated a ratio of ca. 80:20 of the 3-carboxylate to the 4-carboxylate. This oil was chromatographed over a column of silica gel eluting with 5:95 acetone/hexane. The first eluted component was methyl 5-methyl-1-(phenylmethyl)-1*H*-pyrazole-4-carboxylate (**16a**), which was obtained as a pale yellow oil (3.74 g, 16%). Crystallization from ether/petroleum ether (bp 35–60 °C) afforded colorless crystals (3.22 g, 14%): mp 40–41 °C; IR (KBr) 1705, 1560, 1250, 1205, 1190, 1080 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 2.48 (s, 3 H), 3.82 (s, 3 H), 5.30 (s, 2 H), 6.87–7.47 (m, 5 H), 7.90 (s, 1 H).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.57; H, 5.95; N, 12.01.

The second eluted component was methyl 5-methyl-1-(phenylmethyl)-1*H*-pyrazole-3-carboxylate (**15a**), which was also obtained as a pale yellow oil (13.2 g, 57%). Crystallization from ether/petroleum ether (bp 35–60 °C) afforded colorless crystals (11.1 g, 48%): mp 49–50.5 °C; IR (KBr) 1720, 1455, 1225, 725 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 2.17 (s, 3 H), 3.91 (s, 3 H), 5.37 (s, 2 H), 6.60 (s, 1 H), 6.92–7.45 (m, 5 H).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.92; H, 5.93; N, 12.33.

Methyl 1-Methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (15b) and Methyl 1-Methyl-5-phenyl-1*H*-pyrazole-4-carboxylate (16b). A solution of 5.69 g of sodium nitrite in 20 mL of water was added dropwise to a stirred suspension of the hydrochloride salt of *N*-methyl-2-phenyl-DL-glycine[51] (15.1 g, 75.0 mmol) in water (60 mL) at 0 °C. Upon completion of this addition, the reaction mixture was allowed to stir at 0 °C for an additional 2 h. The reaction mixture was then extracted with methylene chloride (2 × 100 mL). The combined methylene chloride extracts were in turn washed with water (100 mL). The dried (sodium sulfate) methylene chloride layer was then evaporated at reduced pressure (at ambient temperature) to give the crude *N*-nitroso amino acid. A solution of the crude *N*-nitroso amino acid and methyl propiolate (9.46 g, 113 mmol) in acetic anhydride (75 mL) was heated with stirring at 130 °C (sand bath temperature) for 25 h. Upon cooling, the reaction mixture was poured into water (400 mL) to hydrolyze the excess acetic anhydride. After being stirred for 30 min, the acidic aqueous reaction mixture was extracted with ether (2 × 250 mL). The combined ethereal extracts were in turn washed successively with water (3 × 300 mL), saturated aqueous sodium bicarbonate (300 mL), and water (300 mL). The dried (magnesium sulfate) ethereal layer was then evaporated at reduced pressure to give a brown oil (13.2 g). The NMR spectrum of this oil indicated a ratio of ca. 67:33 of the 3-carboxylate to the 4-carboxylate. This oil was chromatographed over a column of silica gel, eluting with 10:90 acetone/hexane. The first eluted component was methyl 1-methyl-5-phenyl-1*H*-pyrazole-4-carboxylate (**16b**), which was obtained as a yellow solid (3.06 g, 19%). Recrystallization from methylene chloride/hexane afforded colorless crystals (2.72 g, 17%): mp 107–108 °C; IR (KBr) 1715, 1505, 1440, 1295, 1205, 810, 700 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 3.72 (s, 3 H), 3.77 (s, 3 H), 7.32–7.62 (m, 5 H), 7.98 (s, 1 H).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.39; H, 5.38; N, 12.96.

The second eluted component was methyl 1-methyl-5-phenyl-1*H*-pyrazole-3-carboxylate (**15b**), which was also obtained as a yellow solid (5.37 g, 33%). Recrystallization from methylene chloride/hexane afforded colorless crystals (4.11 g, 25%): mp 70.5–72 °C; IR (KBr) 1725, 1203, 1220, 780 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 3.97 (s, 6 H), 6.83 (s, 1 H), 7.43 (s, 5 H).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.91; H, 5.74; N, 12.75.

Methyl 1-Methyl-5-(phenylmethyl)-1*H*-pyrazole-3-carboxylate (15c) and Methyl 1-Methyl-5-(phenylmethyl)-1*H*-pyrazole-4-carboxylate (16c). Concentrated aqueous hydrochloric acid (3.5 mL) was added dropwise to a stirred mixture of *N*-methyl-DL-phenylalanine[52] (6.27 g, 35.0 mmol) and sodium nitrite (2.66 g, 38.5 mmol) in methylene chloride (100 mL) and water (100 mL) at 0 °C. Upon completion of this addition, the reaction mixture was allowed to stir at 0 °C for an additional 2 h. The layers were then separated, and the methylene chloride layer was washed with water (100 mL). The dried (sodium sulfate) methylene chloride layer was then evaporated at reduced pressure (at ambient temperature) to give the crude *N*-nitroso amino acid. A soultion of the crude *N*-nitroso amino acid and methyl propiolate (4.41 g, 52.5 mmol) in acetic anhydride (35 mL) was heated with stirring at 120 °C (sand bath temperature) for 24 h. Upon cooling, the reaction mixture was poured into water (175 mL) to hydrolyze the excess acetic anhydride. After being stirred for 30 min, the acidic aqueous reaction mixture was extracted with ether (2 × 100 mL). The combined ethereal extracts were in turn washed successively with water (3 × 100 mL), saturated aqueous sodium bicarbonate (100 mL), and water (100 mL). The dried (magnesium sulfate) ethereal layer was then evaporated at reduced pressure to give a brown oil (4.65 g). The NMR spectrum of this oil indicated a ratio of ca. 78:22 of the 3-carboxylate to the 4-carboxylate. This oil was chromatographed over a column of silica gel, eluting with 5:95 acetone/hexane. The first eluted component was methyl 1-methyl-5-(phenylmethyl)-1*H*-pyrazole-4-carboxylate (**16c**), which was obtained as a pale yellow oil (0.80 g, 10%). Crystallization from methylene chloride/hexane afforded colorless crystals (0.64 g, 8%): mp 99–100.5 °C; IR (liquid film) 1700, 1555, 1440, 1250, 1140 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 3.65 (s, 3 H), 3.78 (s, 3 H), 4.40 (s, 2 H), 6.81–7.33 (m, 5 H), 7.82 (s, 1 H).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81, H, 6.13; N, 12.16. Found: C, 67.80; H, 6.22; N, 12.03.

The second eluted component was methyl 1-methyl-5-(phenylmethyl)-1*H*-pyrazole-3-carboxylate (**15c**), which was obtained as a pale yellow oil (2.92 g, 36%): IR (liquid film) 1720, 1480, 1460, 1385, 1225, 1020, 785 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 3.79 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 2 H), 6.57 (s, 1 H), 6.93–7.43 (m, 5 H).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81, H, 6.13; N, 12.16. Found: C, 67.44; H, 5.63; N, 12.74.

Ethyl 2-Methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (24a) and Ethyl 5-Methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (25a). A mixture of *N*-acetyl-*N*-phenylglycine[53] (19.3 g, 100 mmol), ethyl propiolate (14.7 g, 150 mmol), and acetic anhydride (100 mL) was heated with stirring at 115 °C (sand bath temperature) for 3 h. Upon cooling, the reaction mixture was poured into water (500 mL) to hydrolyze the excess acetic anhydride. After being stirred for 30 min, the acidic aqueous reaction mixture was extracted with ether (2 × 250 mL). The combined ethereal extracts were in turn washed successively with water (3 × 300 mL), saturated aqueous sodium bicarbonate (300 mL), and water (300 mL). The dried (magnesium sulfate) ethereal layer was then evaporated at reduced pressure to give a brown oil (13.5 g). The NMR spectrum of this oil indicated a ratio of ca. 75:25 of the 2-methyl isomer to the 5-methyl isomer. This oil was chromatographed over a column of silica gel eluting with 3:97 acetone/hexane. The first eluted component was ethyl 2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (**24a**), which was obtained as a light yellow oil (7.41 g, 32%): IR (liquid film) 1695, 1595, 1500, 1260, 1190,

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(53) C. Paal and G. Otten, *Chem. Ber.*, **23**, 2587 (1890).

1105, 1055, 920, 770, 695 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.35 (t, J = 7 Hz, 3 H), 2.45 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 6.63 (s, 2 H), 7.03–7.63 (m, 5 H).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.12. Found: C, 73.11; H, 6.56; N, 5.83.

The second eluted component was ethyl 5-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (**25a**), which was also obtained as a yellow oil (2.09 g, 9%): IR (liquid film) 1705, 1595, 1520, 1500, 1255, 1185, 1100, 755, 695 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.33 (t, J = 7 Hz, 3 H), 2.16 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 6.40–6.57 (br s, 1 H), 7.13–7.67 (m, 6 H).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.12. Found: C, 73.46; H, 6.58; N, 6.30.

Ethyl 1-Phenyl-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (24b) and Ethyl 1-Phenyl-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (25b). Trifluoroacetic anhydride (18.5 g, 12.4 mL, 88.0 mmol) was added dropwise to a stirred suspension of *N*-phenylglycine[54] (6.05 g, 40.0 mmol) and ethyl propiolate (5.89 g, 60.0 mmol) in toluene (80 mL) at 0 °C under a nitrogen atmosphere. Upon completion of this addition, the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was then heated with stirring to 130 °C (sand bath temperature) over a period of 3 h and maintained at 130 °C for an additional 3 h. Upon cooling, the reaction mixture was diluted with ether (80 mL) and washed successively with water (3 × 100 mL), saturated aqueous sodium bicarbonate (2 × 100 mL), and water (100 mL). The dried (magnesium sulfate) organic layer was then evaporated at reduced pressure to give a brown oil (7.63 g). The NMR spectrum of this oil indicated a ratio of ca. 10:90 of the 2-trifluoromethyl isomer to the 5-trifluoromethyl isomer. This oil was chromatographed over a column of silica gel eluting with 5:95 acetone/hexane to afford the unseparated isomer mixture as a light yellow oil (6.60 g, 58%): IR (liquid film) 1715, 1570, 1510, 1270, 1230, 1115 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.35 (t, J = 7 Hz, 3 H), 4.33 (q, J = 7 Hz, 2 H), 6.77 (s, 0.2 H, H_4 and H_5 of the 2-trifluoromethyl isomer), 7.25 (br s, 0.9 H, H_4 of the 5-trifluoromethyl isomer), 7.32–7.67 (m, 5.9 H, ArH and H_2 of the 5-trifluoromethyl isomer).

Anal. Calcd for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.95. Found: C, 59.33; H, 4.32; N, 4.80.

Ethyl 1,2-Dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylate (24c) and Ethyl 1,5-Dimethyl-2-phenyl-1*H*-pyrrole-3-carboxylate (25c). A mixture of *N*-acetyl-*N*-methyl-2-phenylglycine[25] (6.0 g, 29 mmol), ethyl propiolate (4.8 g, 49 mmol), and acetic anhydride (40 mL) was heated at 45–50 °C (sand bath temperature) with stirring for 3 h. Upon cooling, 50 mL of water was added to hydrolyze the excess acetic anhydride. After being stirred for 0.5 h, the reaction mixture was poured into an additional 50 mL of water and extracted with ether (2 × 50 mL). The organic phase was washed successively with water (3 × 50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (50 mL). The dried (potassium carbonate) ethereal layer was evaporated in vacuo to give 4.2 g of crude product. The NMR spectrum indicated a ratio of ca. 55:45 of the 5-methyl isomer to the 2-methyl isomer. The isomers were separated by medium-pressure chromatography, eluting with 95:5 hexane/acetone. The first eluted compound was ethyl 1,2-dimethyl-5-phenyl-1*H*-pyrrole-3-carboxylate (**24c**; 0.90 g, 13%), which was obtained as a crystalline solid (mp 83–85 °C): IR (KBr) 1695, 1525, 1490, 1260, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, J = 7 Hz, 3 H), 2.23 (br s, 3 H), 3.23 (s, 3 H), 4.03 (q, J = 7 Hz, 2 H), 6.33 (br s, 1 H), 7.23 (s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.14; H, 7.30; N, 5.67.

The second eluted component was ethyl 1,5-dimethyl-2-phenyl-1*H*-pyrrole-3-carboxylate (**25c**; 1.10 g, 16%), which was also a crystalline solid (64–66 °C): IR (KBr) 1700, 1520, 1490, 1255, 1200 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 2.60 (s, 3 H), 3.47 (s, 3 H), 4.27 (q, J = 7 Hz, 2 H), 6.50 (s, 1 H), 7.30 (s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.01; H, 6.94; N, 5.65.

Methyl 1,2-Dimethyl-5-(phenylmethyl)-1*H*-pyrrole-3-carboxylate (24d) and Methyl 1,5-Dimethyl-2-(phenylmethyl)-1*H*-pyrrole-3-carboxylate (25d). A mixture of *N*-acetyl-*N*-methylphenylalanine[55] (1.8 g, 8.1 mmol), methyl propiolate (1.9 g, 22 mmol), and acetic anhydride (20 mL) was heated at 80 °C for 24 h. Upon cooling, 25 mL of water was added to hydrolyze the excess acetic anhydride. After being stirred for 0.5 h, the reaction mixture was poured into an additional 25 mL of water and extracted with ether (2 × 50 mL). The organic phase was washed successively with water (2 × 50 mL), saturated aqueous sodium bicarbonate solution (50 mL), and brine (50 mL). The dried (potassium carbonate) ethereal layer was evaporated in vacuo to yield 1.8 g of crude product. The NMR spectrum of the oil indicated a ratio of ca. 55:45 of the 5-methyl isomer to the 2-methyl isomer. This oil was chromatographed on 75 g of silica gel, eluting with 95:5 hexane/acetone, to afford 1.35 g (69%) of the unseparated isomer mixture: IR (neat) 1690, 1520, 1430, 1230 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (br s, 0.55 × 3 H), 2.47 (s, 0.45 × 3 H), 3.23 (s, 3 H), 3.77 (s, 3 H), 3.87 (br s, 0.45 × 2 H), 4.40 (br s, 0.55 × 2 H), 6.27 (m, 1 H), 7.1 (m, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 73.65; H, 7.18; N, 5.83.

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Registry No. 13a ethyl ester, 64892-53-1; **13b**, 54422-64-9; **13c**, 2566-35-0; **14a**, 80326-66-5; **14b**, 35431-71-1; **14c**, 80326-67-6; **15a**, 80326-68-7; **15b**, 10250-65-4; **15c**, 80326-69-8; **16a**, 80326-70-1; **16b**, 80326-71-2; **16c**, 80326-72-3; **22a**, 579-98-6; **22c**, 2392-54-3; **22d**, 55260-07-6; **24a**, 80326-73-4; **24b**, 80326-74-5; **24c**, 3652-47-9; **24d** methyl ester, 80326-75-6; **25a**, 80326-76-7; **25b**, 80326-77-8; **25c**, 80326-78-9; **25d** methyl ester, 80326-79-0; **26**, 497-24-5; **27**, 534-24-7; **28**, 471-25-0; methyl propiolate, 922-67-8; ethyl propiolate, 623-47-2; *N*-phenylglycine, 103-01-5.

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(55) F. C. Uhle and L. S. Harris, *J. Am. Chem. Soc.*, 78, 381 (1956).