Characterization of a Stable Carboxylic Acid Intermediate from 1,3-Dipolar Cycloaddition of a Munchnone with 1,2-Dicyanocyclobutene†

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Reaction of **1** and **2** in acetic anhydride at 110 °C produced intermediate **6**, which captured the exo stereochemistry of the unseen primary cycloadduct, **5**. Thermolysis of **6** at a much higher temperature readily gave the expected dihydroazepine **4**. The stereochemistry of **6** was unambiguously established by the single-crystal X-ray analysis of methyl ester **8**, formed by treating **6** with diazomethane under mild conditions. The isolation of **6** suggests that elimination of carbon dioxide from such primary cycloadducts need not be a concerted process.

Oxazolium 5-oxides, or munchnones, are a class of mesoionic heterocycles that have been employed in a variety of 1,3-dipolar cycloadditions with alkenes and alkynes.[4] In intermolecular reactions, primary cycloadducts have generally not been isolated and identified because carbon dioxide is readily eliminated to yield more highly unsaturated products. Unfortunately, with an alkene dipolarophile this results in a loss of information pertinent to cycloaddition stereochemistry.

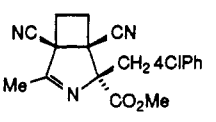
Padwa and co-workers have isolated and characterized several primary adducts from intramolecular cycloadditions to terminal alkenes.[5] In this type of reaction, expulsion of carbon dioxide is presumably impeded by the severe structural constraints in the intermediate polycycle. By the same token, the exo stereochemistry of the substituent derived from the alkene reflects a steric situation imposed by the unimolecular transition state, rather than a free combination of reactant molecules. Some intermolecular reactions of various mesoionic heterocycles with alkenes have occasionally led to isolable intermediates with established stereochemistry.[4] We report herein the characterization of a carboxylic acid intermediate from intermolecular cycloaddition of a munchnone with a substituted alkene, which indicates very high exo stereoselectivity for the primary cycloaddition process.

Results and Discussion

1,2-Dicyanocyclobutene (**1**) is reported to react with various munchnones, generated in situ, to give 4,5-dihydroazepine derivatives.[6] Pursuing this chemistry further, we had the opportunity to use chlorophenylalanine **2** as a reaction partner with **1**. In heating **1**, **2**, and acetic anhydride (5.5 h at 110 °C), we expected to generate munchnone **3**, which would then combine with **1** to give target dihydroazepine **4** via a transient bicyclic intermediate, such as **5**. During the course of the reaction, a solid material surprisingly separated from the solution. This substance, isolated in 50% yield, was not the anticipated dihydroazepine **4**, but thermolysis of it in refluxing decalin for 30 min did produce **4** in 70% yield. Analytical data established imino acid structure **6** for this intermediate, rather than that of a primary cycloadduct. Nevertheless, intermediate **6** still managed to capture the essential stereochemistry of the cycloaddition step.

HPLC analysis of the total crude product from the reaction of **1** and **2** revealed the presence of just two compounds, 80% of **6** and 18% of **4**. Thus, the cycloaddition step appears to be highly stereoselective for the exo dicyano species, **5**, which then proceeds to acid **6** presumably via zwitterion **7** (Scheme I). Obviously, the isolation of **6** indicates that extrusion of carbon dioxide from the primary cycloadduct is not a concerted process.

Acid **6** in methanol was esterified with ethereal diazomethane to give **8**,[7] which was subjected to a single-crystal X-ray analysis. This provided structural confirmation



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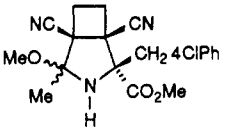

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and, importantly, the stereochemical assignment for **6**. An ORTEP representation of the molecular structure is presented in Figure 1. Details of the X-ray analysis are given in the Experimental Section and in the supplementary material.[8] One noteworthy feature of the X-ray structure is the spatial proximity of the 5-cyano group to the plane of the 4-chlorophenyl group, 3.5–3.6 Å, suggesting a charge-transfer interaction in the solid state. The dihedral angles at the ring junction are 18° for CH_2–C–C–CH_2 in the cyclobutane ring, 20° for NC–C–C–CN, and ca. 10° for C2–C1–C5–C4. The value for the NC–C–C–CN

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(7) When this reaction was performed with methanol that had been pretreated with potassium carbonate for 30 min, the product was a mixture of **8** and both diastereomers of **9** (mass spectrum, ^1H NMR, TLC), the latter resulting from addition of MeOH across the imine double bond.

(8) See paragraph at the end of this paper regarding supplementary material.

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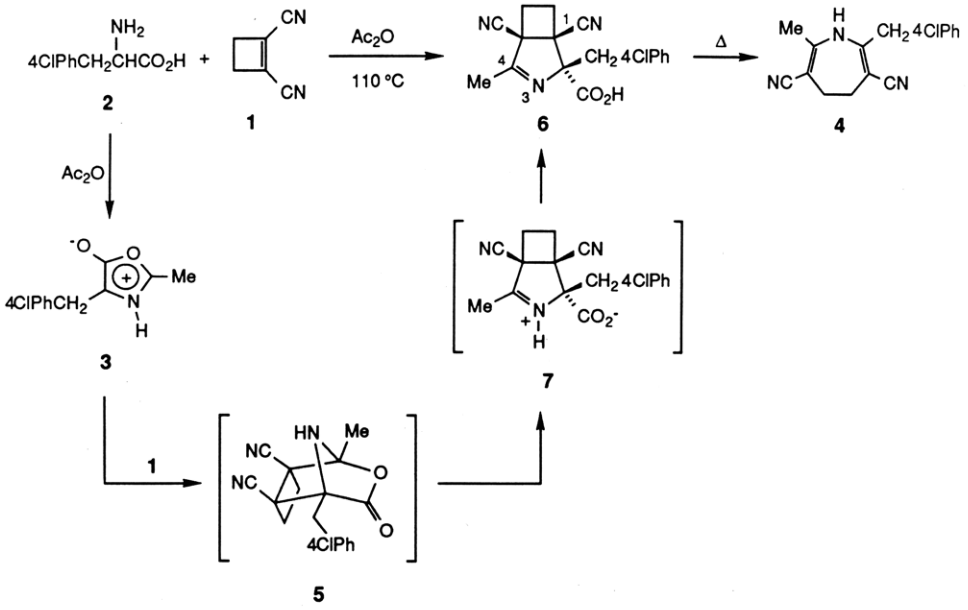
Scheme I[a]



[a] 4ClPh = 4-chlorophenyl.

Figure 1. ORTEP diagram of the molecular structure of 8.

dihedral angle is reflective of the adjacency of the 5-cyano group and the benzene plane. No evidence for charge-transfer interactions was found in solution. This may be appreciated by the absence of dramatic changes in the UV spectra (MeOH) for *p*-chlorophenylalanine, acid **6**, and ester **8**: λ_{max} (ϵ) 219 (8260), 221 (14 170), 220 (10 590) nm.

The stereochemistry of **6** establishes an exo stereochemistry for the unseen primary cycloadduct, as represented in **5**. Although exo stereochemistry was also observed in the examples reported by Padwa et al.,[5] it was necessarily imposed by a tether connecting the nitrogen substituent to the alkene, whereas our example involves interactions between freely associating components. The stereochemistry of cycloaddition reactions involving different types of mesoionic heterocycles with alkenes has varied widely.[4] The current endo positioning of the ethano bridge seems to be the more sterically encumbered one. Thus, electronic effects favoring exo orientation of the π-deficient cyano groups, in specific HOMO–LUMO[5b,9] interactions, may play a dominant role.

In an attempt to rationalize the stereochemical result, we carried out molecular orbital calculations on the reactants by using the MNDO,[10a] AM1,[10b] and π-VESCF[10c] methods. An inspection of the pertinent orbital coefficients for the HOMO of munchnone **3** and the LUMO of **1** revealed that the secondary orbital interactions are too complex for simple FMO theory to provide information on the stereochemical course of this cycloaddition. A more detailed theoretical analysis of this and other munchnone cycloadditions will be the subject of a future study. From such an analysis, we should also be able to gain insight into the transition state for the elimination of carbon dioxide from the primary cycloadduct. Although this step may be regarded as a concerted process,[4] extrapolation of our observation to other cases unavoidably draws this idea into question.[11]

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer at 60 MHz, and ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer at 20 MHz. Chemical shifts are reported in parts per million downfield of Me_4Si (internal reference). Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E instrument at 70 eV.

2-[(4-Chlorophenyl)methyl]-1,5-dicyano-4-methyl-3-azabicyclo[3.2.0]hept-3-ene-2-carboxylic Acid (6) and 2-[(4-Chlorophenyl)methyl]-7-methyl-4,5-dihydro-1*H*-azepine-3,6-dicarbonitrile (4). A mixture of D,L-3-(4-chlorophenyl)alanine (**2**, 9.57 g, 0.048 mol), 1,2-dicyanocyclobutene[12] (**1**, 5.00 g, 0.048 mol), and 35 mL of acetic anhydride was heated at 110 °C for 5.5 h. A solid precipitated during this process. After cooling, the reaction mixture was diluted with 40 mL of methylene chloride and filtered. The solid was rinsed with methylene chloride and dried in vacuo to give a white powder (7.84 g, 50%), mp (205 °C, shrinking and sintering) 212.5–213 °C dec. A 5.00-g sample of **6** was recrystallized from methanol to afford 3.15 g of colorless crystals, mp (207.5 °C) 213.5–215 °C dec: IR (KBr) ν_{max} 3150–2300 (very br, COOH), 2270 (CN), 1720 (CO), 1690 (sh), 1630, 1500, 1420, 1395, 1245, 1140, 1100, 1080, 1000, 822, 718, 705 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 221 (14 170), 201 (13 710) nm; ^{1}H NMR (Me_2SO-d_6) δ 2.0–3.5 (complex m, 9 H, s for Me at δ 2.09), 6.0 (br s, 1 H, COOH), 7.1–7.25 (m, 4 H, aromatic); MS (EI) m/z 327 ($M^{\cdot+}$); ^{13}C NMR (Me_2SO-d_6) δ 15.3, 26.7, 27.4, 41.9, 48.0, 54.0, 87.0, 114.2 (CN), 117.9 (CN), 128.1, 132.4, 132.7, 132.9, 167.4, 169.9.

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Anal. ($C_{17}H_{14}ClN_3O_2$) C, H, Cl, N.

Acid **6** dissolved in 5% aqueous sodium carbonate, as the sodium salt. The free acid was regenerated by acidification with 5% HCl; it was identical with the original substance.

The filtrate from above was concentrated in vacuo to a brown oil, which was partitioned between methylene chloride and 5% aqueous sodium bicarbonate. The organic solution was dried (Na_2SO_4) and concentrated to a brown gum, which was chromatographed on a column of silica gel to give 1.5 g of tan oil. Addition of ether supplied colorless crystals of **4** (0.90 g, 7%). This sample of **4** was combined with a 0.92-g sample from the thermal decarboxylation of **6** (see below) and recrystallized from ether to furnish 1.47 g of TLC-homogeneous, colorless crystals, mp 102-103.5 °C: IR (KBr) ν_{max} 3350 (NH), 3280, 3175, 3085, 2205 (CN), 1740, 1440, 1312, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3 H, Me), 2.60 (s, 4 H), 3.73 (s, 2 H, CH_2), 6.18 (s, 1 H, NH), 7.05-7.35 (m, 4 H, aromatic); MS (EI) m/z 283 ($M^{\bullet+}$). Anal. ($C_{16}H_{14}ClN_3$) C, H, Cl, N.

Thermal Decarboxylation of 6 to 4. Acid **6** (1.51 g, 0.0046 mol) and 10 mL of decalin were heated at reflux with stirring under argon until the evolution of carbon dioxide ceased (ca. 40 min). After cooling, the decalin was decanted from the brown residue, which was rinsed twice with hexane and then dissolved in ether. Partial concentration gave 0.92 g (70%) of colorless, TLC-homogeneous crystals. Characterization was conducted on a combination of this material and another sample (see above).

Formation of Methyl Ester 8. Excess ethereal diazomethane was added to a methanol solution of **6** (0.50 g, 1.5 mmol) in 125 mL of methanol at 0 °C. Acetic acid was used to destroy the excess diazomethane. Removal of the solvent gave a green oil, which was dissolved in methylene chloride. The solution was washed with aqueous sodium bicarbonate, washed with water, dried (Na_2SO_4), and concentrated to an orange oil (0.40 g), which crystallized. Recrystallization from ether afforded 0.22 g (43%) of TLC-homogeneous, pale orange crystals, mp 181-182.5 °C: IR (KBr) ν_{max} 2250 (CN), 1740 (CO), 1430, 1245, 1225, 1075 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 220 (10590), 200 (10420) nm; ^1H NMR ($CDCl_3$) δ 2.0-2.9 (complex m, 9 H, s for Me at δ 2.20), 3.24 (AB q, 2 H), 3.77 (s, 3 H, OMe), 7.1-7.3 (m, 4 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 15.5, 27.3, 28.1, 42.5, 48.5, 53.1, 54.8, 88.0, 113.3, 117.0, 128.8, 130.8, 132.7, 134.1, 168.5, 169.3; MS (EI) m/z 341 ($M^{\bullet+}$). Anal. ($C_{18}H_{16}ClN_3O_2$) C, H, Cl, N. Another slow recrystallization provided the batch of crystals from which one was selected for X-ray analysis.

X-ray Crystal Structure Analysis of 8. Crystals of $C_{18}H_{16}ClN_3O_2$ are triclinic (space group $P\bar{1}$) with a = 11.438 (3) Å, b = 12.108 (5) Å, c = 6.895 (1) Å, α = 104.39 (2)°, β = 106.26 (2)°, γ = 95.19 (3)°, and D_{calcd} = 1.30 g cm^{-3} for Z = 2. The intensity data were collected from a small single crystal (0.10 × 0.12 × 0.16 mm^3) on a Syntex $P2_1$ diffractometer with the θ-2θ scan mode and a scan speed of 2.0 deg min^{-1}. Data were collected with Mo Kα (λ = 0.71069 Å) radiation (graphite monochromator) to a scattering angle of 2θ = 45° for a total of 1113 intensities greater than $2.5\sigma(I)$ from 2276 reflections scanned. The structure was solved by a multiple solution procedure[13] and was refined by full-matrix least-squares methods. No absorption corrections were made (μ = 2.3 cm^{-1}). The chlorine atom was refined with anisotropic thermal parameters, and all other non-hydrogen atoms were refined isotropically. The hydrogen atoms were included in the structure factor calculation with fixed distances of 1.0 Å and idealized locations. Final discrepancy factors were R = 0.088 and R_w = 0.098. The final difference map had no peaks greater than 0.6 e A^{-3}.

Supplementary Material Available: Tables containing bond lengths, bond angles, fractional atomic coordinates, and thermal parameters for the X-ray analysis of **8**, molecular structure of **8** showing the atom-numbering scheme, and AM1 heats of formation, geometries, frontier orbital coefficients, and charge distributions for **1** and **3** (7 pages). Ordering information is given on any current masthead page.

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Mechanism of an Acid Chloride-Imine Reaction by Low-Temperature FT-IR: β-Lactam Formation Occurs Exclusively through a Ketene Intermediate

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The reaction of acid chloride **8** with imine **9** in the presence of a base to form 2-azetidinones **10** and **11** was examined by low-temperature FT-IR spectroscopy. The rate constants for formation of the ketene **12** from the acid chloride and base and for subsequent reaction of this ketene with the imine were measured. From the kinetic data we conclude that the azetidinone products arise completely from the ketene intermediate and not via direct acylation of the imine with the acid chloride.

The reaction of an imine and an acid chloride in the presence of an amine base has been used extensively in the preparation of β-lactams.[1] Two mechanistic pathways (Scheme I) by which acid chlorides **1** and imines **3** combine to form β-lactams have been proposed: (1) prior formation of ketene **2** by reaction of acid chloride with base and subsequent cycloaddition with imine (the Staudinger reaction), perhaps via zwitterionic intermediate **4**[2] (Scheme I); (2) direct acylation of the imine with the acid chloride, giving *N*-acyliminium chloride **6**, which may be in equilibrium with chloro amide **7**.[3] Reaction of **6** or **7** with base then gives β-lactam **5**.[3]

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