The molecular weight observed (MW_{obsd}) was determined by the equation:

$$MW_{obsd} = (g_{sample})(MW_{ref})(V_{ref})/(g_{ref})(V_{sample})$$

where g = mass and V = volume at equilibrium.

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Cycloadditions of (Arylalkylamino)ketenes with Cycloalkenes

William T. Brady* and Yi Qi Gu

Department of Chemistry, University of North Texas, Denton, Texas 76203

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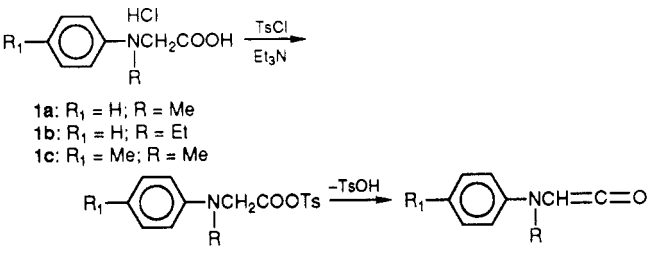
(Arylalkylamino)ketenes were prepared from the corresponding glycine derivatives and underwent in situ cycloadditions with cyclopentadiene, cycloheptene, and cyclooctene to yield only the *endo*-bicyclocyclobutanones. The cycloheptene and cyclooctene cycloaddition products underwent dehydrogenation under the reaction conditions to yield bicyclo enamines. A mechanism is proposed for this dehydrogenation involving a radical cation of the phenylalkylamine. (Phenylmethylamino)methylketene was also prepared and found to undergo an intramolecular Friedel–Crafts-type acylation to yield an indole derivative when prepared by the acetic anhydride–sodium acetate method.

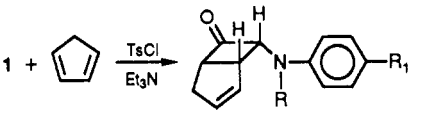
The stereospecific [2 + 2] ketene cycloaddition to alkenes is a valuable method to synthesize cyclobutanones and related compounds.[1] Ketenes bearing heteroatoms adjacent to the ketene functionality such as chlorine, oxygen, and sulfur show an increased reactivity in cycloaddition reactions and have been successfully used in many syntheses of cyclic compounds. However, there are only a few scattered reports on the chemistry of aminoketenes and these reports are limited to aminoketenes in which the nitrogen atom was substituted by an electron-withdrawing substituent such as succinoyl, maleyl, or phthaloyl groups.[2] The aminoketenes were prepared by the dehydrohalogenation of amino acid chlorides and used in the synthesis of penicillin-like β-lactams by cycloaddition with imines. The existence of aminoketenes under such conditions is questioned because of an alternative pathway to explain the formation of the β-lactams.[3] We report a one-pot preparation of (arylalkylamino)ketenes and the trapping of such ketenes with different cycloalkenes.

The starting compounds for this study are *N*-aryl-*N*-alkylglycine hydrochlorides. The use of (disubstituted-amino)ketenes is based on avoiding the possible reaction between a primary or secondary amino group with the ketene functionality. The conventional method of generating the (arylalkylamino)ketenes from the acid chlorides was unsuccessful. Therefore, *p*-toluenesulfonyl chloride was selected as the reagent for generation of the ketenes. The amino acid hydrochloride was treated with *p*-toluenesulfonyl chloride and an excess of triethylamine to form the mixed anhydride, which, based on our previous work,[4] could eliminate *p*-toluenesulfonic acid to generate the (arylalkylamino)ketene (Scheme I).

Scheme I

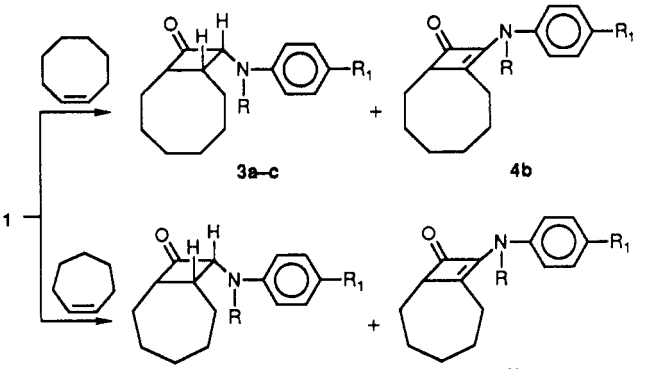


Scheme II



2a: R_1 = H; R = Me
2b: R_1 = H; R = Et
2c: R_1 = Me; R = Me

Scheme III



3a, 5a: R = Me; R_1 = H
3b, 4b, 5b, 6b: R = Et; R_1 = H
3c, 5c: R = Me; R_1 = Me

The reaction mixture of *N*-aryl-*N*-alkylglycine hydrochlorides with 1.2 to 1.5 equiv of *p*-toluenesulfonyl chloride, 5 equiv of olefin, and triethylamine in benzene is a dark red solution containing some insoluble salts (Scheme II).

(1) (a) Ghosez, L.; O'Donnell, M. J. *Pericyclic Reaction*, Volume, II; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; pp 79–140. (b) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. (c) Brady, W. T. *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Interscience Publications: New York, 1980; pp 278–308. (d) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797.

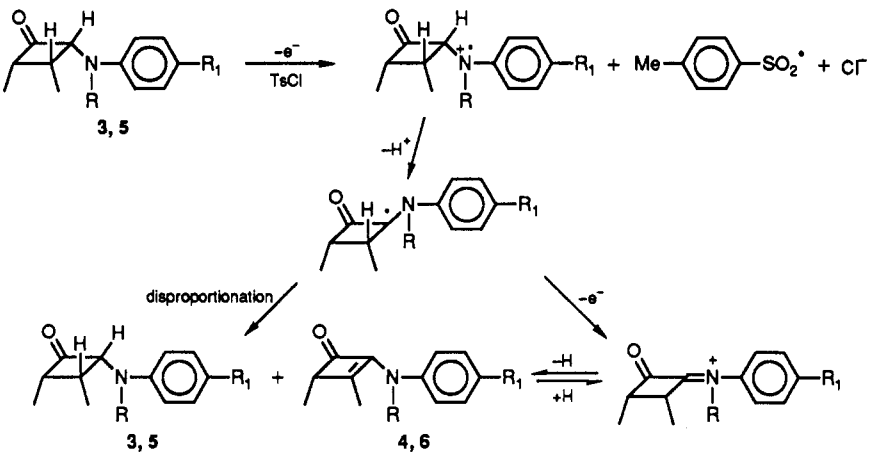
(2) Reichen, W. *Chem. Rev.* **1978**, *78*, 568.

(3) (a) Sheehan, J. C.; Ryan, J. J. *J. Am. Chem. Soc.* **1951**, *73*, 1204. (b) Doyle, T. W.; Belleau, B.; Luh, B. Y.; Ferrari, C. F.; Cunningham, M. P. *Can. J. Chem.* **1976**, *55*, 468. (c) Bose, A. K.; Spielgelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167.

(4) (a) Brady, W. T.; Marchand, A. P.; Giang, Y. F.; Wu, A. H. *Synthesis* **1987**, 395. (b) Brady, W. T.; Giang, Y. F.; Marchand, A. P.; Wu, A. H. *J. Org. Chem.* **1987**, *52*, 3457.

0022-3263/89/1954-2834$01.50/0

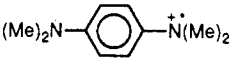
Scheme IV



The cycloadduction products were initially isolated by column chromatography and then further purified by rotary thin-layer chromatography. Cycloadditions utilizing cyclopentadiene resulted in only the isolation of the cis (endo) isomer, which was established by ^{1}H NMR analysis. The proton adjacent to the carbonyl and amino group consistently give a double doublet with a J value of 8–9 Hz and 2.7–2.9 Hz. These data are consistent with that reported in the literature for the cyclobutanone system; much larger coupling constants for vicinal ring protons in the cis isomer are observed (J_{cis} = 9–10 Hz vs J_{trans} = 5 Hz) along with relatively large cross ring proton coupling (J = 3 Hz).[5] This result is in complete accord with a concerted [2πa + 2πs] ketene cycloaddition process in which the larger group occupies the endo position.[6]

In the cycloadditions of **1b** with cyclooctene or cycloheptene, two products were obtained in each case and separated by careful chromatography. Spectral data suggested that these products were not isomers (Scheme III). Compounds **3b** and **5b** have carbonyl absorptions of 1760 cm^{-1} in the IR spectra while compounds **4b** and **6b** exhibit an absorption band at 1740 cm^{-1}. ^{1}H NMR spectra indicated that compounds **3b** and **5b** have three cyclobutanone proton signals with one signal relatively downfield (about δ 5), which is the proton α to the carbonyl and amino groups. The ^{1}H NMR spectra reveal that in compounds **4b** and **6b** there is only one cyclobutanone proton as the other two cyclobutanone proton signals have disappeared including the signal at δ 5. The ^{13}C NMR spectra reveal that **4b** and **6b** have two more sp^2-hybridized carbon atoms than do **3b** and **5b**. A carbon tetrachloride solution of **4b** or **6b** when treated with bromine in carbon tetrachloride resulted in the decolorization of the bromine color and the IR absorption of **4b** and **6b** at 1740 cm^{-1} changed to 1760 cm^{-1} after the addition of the bromine solution. These data clearly indicated that **4b** and **6b** are the dehydrogenation products of compounds **3b** and **5b**. The ^{1}H NMR data indicated that compounds **3b** and **5b** are the endo isomers. The formation of **4b** and **6b** depends on the reaction conditions and the alkyl substituent on the amino group. When R is methyl, only a trace of the dehydrogenation product was formed. The IR spectrum of the reaction mixture has a strong absorption at 1760 cm^{-1} and only a shoulder peak at 1740 cm^{-1}. However, when R is ethyl, the main product is **4b** or **6b** and the reaction mixture has a major IR absorption band at 1740 cm^{-1}. A higher reaction temperature and prolonged reflux time resulted in more dehydrogenation product. The treatment of **3b** with p-toluenesulfonyl chloride and triethylamine followed by a workup with a NaOH aqueous solution gave **4b**. These data suggest that **3b** and **5b** are the initially formed cycloadducts and **4b** and **6b** are formed from **3b** or **5b** under the reaction conditions.

We believe the presence of the arylalkylamino group in the α position of the cyclobutanone is responsible for the dehydrogenation. Horner and Nickel[7] reported that the radical cation of N,N,N,N-tetramethyl-p-phenylenediamine (11) was observed in the reaction of benzenesulfonyl



11

chloride and N,N,N,N-tetramethyl-p-phenylenediamine. Also, the anodic oxidation of tertiary amines has been intensively studied and enamines are one of the products.[8] The initial step of the anodic oxidation of tertiary amines is the formation of the radical cation of the tertiary amine. The electron-transfer redox reaction of sulfones has been well-reviewed[9] as well as the electron acceptor ability of tosyl chloride.[10] Therefore, we propose that under the reaction conditions the arylalkylamine radical cation is formed. The subsequent loss of the relatively acidic proton α to the carbonyl and the amino group and the disproportionation of the free radical will yield the enamine (dehydrogenation products) products, compounds **4b** and **6b** (Scheme IV).

No dehydrogenation product was observed in the cyclopentadiene cycloadducts. Apparently, the ring strain in the bicyclo[3.2.0]hept-2-en-6-one prevents the dehydrogenation and enamine formation.

It is interesting to note that more repulsive strain would be expected in the endo isomer of the saturated alicyclic ring as compared to the endo isomer of the cyclopentadiene adducts.[11] Dehydrogenation results in the relief of this repulsive strain as the arylalkyl amino group is moved

(5) (a) DoMinh, T.; Stransz, O. P. *J. Am. Chem. Soc.* **1970**, *92*, 1766. (b) Brailon, B. J. *Mol. Spectrosc.* **1968**, *27*, 313. (c) Sutcliffe, L. H.; Walker, S. M. *J. Phys. Chem.* **1967**, *71*, 1555.

(6) Brady, W. T.; Parry, F. H.; Roe, R.; Hoff, E. F. *Tetrahedron Lett.* **1970**, 819.

(7) Horner, L.; Nickel, H. *Ann.* **1955**, *597*, 20.

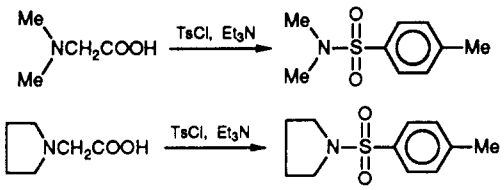
(8) (a) Chiba, T.; Tokata, Y. *J. Org. Chem.* **1977**, *42*, 2973. (b) Masui, M.; Sayo, H. *J. Chem. Soc. B* **1971**, 1593. (c) Portis, L. C.; Klug, J. T.; Mann, C. K. *J. Org. Chem.* **1974**, *39*, 3488.

(9) Chanon, M.; Samat, A. Electron Transfer Reactions of Sulfoxides and Sulfones in *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, 1988.

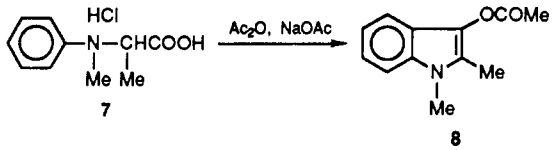
(10) (a) Kamigata, N.; Ozaki, J.; Kobayashi, M. *J. Org. Chem.* **1985**, *50*, 5045. (b) Kamigata, N.; Sawada, H.; Kobayashi, M. *J. Org. Chem.* **1983**, *48*, 3793.

(11) Rey, M.; Roberts, S. M.; Dreiding, A. S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* **1982**, *65*, 703.

Scheme V



Scheme VI



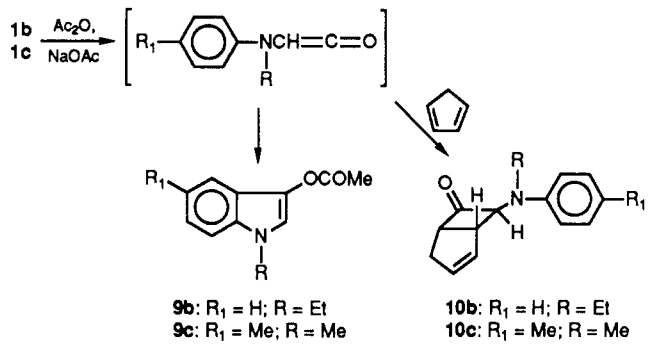
away from the alicyclic ring in compounds **4b** and **6b**. The more prevalent dehydrogenation when R is ethyl than when R is methyl could be due to this repulsive strain.

The reaction of **1** with cyclohexene and *n*-butyl vinyl ether gave a complex mixture of products. We were unable to obtain purified cycloadducts although the IR spectra of the reaction mixtures indicated that some cycloadducts were formed. Similar results have recently been reported by Motoyoshiya for the reaction of (diethylphosphoro)-ketenes with hexene and ethyl vinyl ether.[12]

Attempts to generate aminoketenes from *N*,*N*-dimethylglycine hydrochloride and (1-pyrrolidyl)propanoic acid hydrochloride by using tosyl chloride were unsuccessful. The major products were an *N*,*N*-dimethylsulfonamide and pyrrolidylsulfonamide. The increased nucleophilicity and basicity of the nitrogen in these tertiary alkylamines is probably the reason that no aminoketene cycloadducts are formed (Scheme V).

In an effort to study a ketoketene, *N*-phenyl-*N*-methylalanine hydrochloride was prepared. Employing the same reaction conditions as described above, we could not trap the elusive (phenylmethylamino)methylketene with several olefins or even using more reactive imines as trapping agents.[13] However, when this amino acid was refluxed with acetic anhydride and sodium acetate, compound **8** was formed in good yield (Scheme VI). The formation of indole derivatives by the reaction of amino acids **1a** and **1b** with acetic anhydride and sodium acetate has previously been reported.[14] We have recently demonstrated the presence of ketene intermediates in the reaction of substituted phenoxyacetic acid with acetic anhydride and sodium acetate.[15] Consequently, the formation of compounds **8** and **9** is likely via the aminoketene. The introduction of the methyl group on the aminoketene may increase the steric hindrance and retard the intermolecular cycloaddition. Formation of the (phenylmethylamino)methylketene with a subsequent intramolecular Friedel–Crafts-type acylation at the ortho position of the activated benzene ring results in the formation of the indole derivatives. The addition of cyclopentadiene to the mixture of **1b** or **1c**, acetic anhydride, and sodium acetate results in the cycloaddition products **10b** or **10c**, thus establishing the intermediacy of the aminoketene. NMR spectral analysis indicated that compounds **10b** and **10c** are the exo isomers of the compounds **2b** and **2c**

Scheme VII



(Scheme VII). We treated compound **2b** with acetic anhydride and sodium acetate; exo isomer **10b** was isolated. This experiment suggests that the endo isomers are initially formed and undergo isomerization under these reaction conditions to the exo isomers.

The yields of intermolecular cycloadducts of the aminoketenes are generally low. This could be due to the side reactions initiated by radical intermediates mentioned in Scheme IV. We did not investigate the possible side reactions at this stage.

Further studies on the chemistry and synthetic applications of aminoketenes are in progress.

Experimental Section

NMR spectra were recorded on a VXR-300 spectrometer, employing deuteriochloroform as the solvent with TMS as the internal standard. Attached Proton Test (APT) NMR experiments were performed to distinguish different carbons. The IR spectra were obtained on a Perkin-Elmer 1330 spectrometer. The MS spectra (Argon/Auto CI) were run by ICR Research Associates, Lincoln, NE. Column chromatography was performed on 100–200-mesh Florisil. Rotary preparative chromatography was performed with silica gel 60PF254 from EM Science Co. All melting points are uncorrected.

***N*-Aryl-*N*-alkylglycine Hydrochloride (1a–c).** Ethyl (phenylmethylamino)acetate, ethyl (phenylethylamino)acetate, and ethyl (*p*-tolylmethylamino)acetate were prepared by literature procedures in near quantitative yield.[13] The hydrolysis of these esters was accomplished by the following procedures. A 10-g portion of ethyl (phenylmethylamino)acetate was mixed with 150 mL of a 10% aqueous HCl solution and refluxed for 3 h. After evaporating about 100 mL of water, 150 mL of benzene was added and azeotropic distillation was performed. During the distillation, the solid *N*-phenyl-*N*-methylglycine hydrochloride precipitated. Filtration, washing with acetone, and drying resulted in 8.5 g of a white solid (**1a**), 82%, mp 217–219 °C. *N*-Phenyl-*N*-ethylglycine hydrochloride and *N*-*p*-tolyl-*N*-methylglycine hydrochloride were prepared by the same procedure in 87% and 84% yields: **1b**, mp 198–200 °C; **1c**, mp 210–211 °C.

General Procedure for Preparation and Cycloaddition of (Disubstituted-amino)ketenes. The *N*-aryl-*N*-alkylglycine hydrochlorides were stirred with 1.2–1.5 equiv of *p*-toluenesulfonyl chloride, 5 equiv of triethylamine, and 5 equiv of olefin in benzene at room temperature. The reactions were conducted under a nitrogen atmosphere and in flame-dried glassware by using a magnetic stirrer. After 3 h, cold 10% aqueous NaOH was added to the reaction mixture with stirring and stirring was continued for about 5 min at ice-bath temperature. The organic layer was separated and the aqueous layer was extracted with ether and combined with the organic layer. The combined solutions were dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent, the concentrated solution was mixed with a small amount of Florisil. The sample Florisil was subjected to column chromatography using 5% EtOAc–hexane as eluting solvent. Further purification was achieved by using rotary preparative chromatography.

***endo*-7-(Methylphenylamino)bicyclo[3.2.0]hept-2-en-6-one (2a).** From 1 g of **1a** and an excess of cyclopentadiene, 0.35 g

(12) Motoyashiya, J.; Hirata, K. *Chem. Lett.* **1988**, 211.
(13) Aminoketenes react readily with imines to give β-lactams. The results of the reaction between these aminoketenes and imines are reported in a separate paper. Brady, W. T.; Gu, Y. Q. *J. Org. Chem.*, following paper in this issue.
(14) Daisley, R. W.; Elagbar, Z. A. *Org. Prep. Proc. Int.* **1983**, *15*, 278.
(15) Brady, W. T.; Gu, Y. Q. *J. Heterocycl. Chem.* **1988**, *25*, 969.
(16) Thorpe; Wood *J. Chem. Soc.* **1913**, *103*, 1601.

of oily **2a** was obtained (33%): IR 1770, 1600, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (m, 2 H), 6.7 (m, 3 H), 5.8 (m, 1 H), 5.75 (m, 1 H), 5.05 (dd, 1 H, J = 8.1 Hz, 2.7 Hz), 3.9 (m, 1 H), 3.4 (m, 1 H), 2.85 (s, 3 H), 2.65 (m, 1 H), 2.45 (m, 1 H); ^{13}C NMR (APT) 209.6 (C), 148.3 (C), 134.4 (CH), 129.7 (CH), 129.2 (CH), 117.5 (CH), 112.4 (CH), 77.3 (CH), 54.9 (CH), 46.9 (CH), 35.5 (CH_3), 34.8 (CH_2); MS, m/e (relative intensity) 214 (M^+ + 1, 18.4), 213 (M^+, 7.3), 194 (100), 107 (21.2).

***endo*-7-(Ethylphenylamino)bicyclo[3.2.0]hept-2-en-6-one (2b).** From 2.15 g of **1b** and an excess of cyclpentadiene, 0.9 g of **2b** was obtained (39%): IR 1770, 1600, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (m, 2 H), 6.7 (m, 3 H), 5.85 (m, 1 H), 5.7 (m, 1 H), 5.05 (dd, 1 H, J = 8.4 Hz, 2.9 Hz), 3.9 (m, 1 H), 3.55 (m, 1 H), 3.4 (m, 2 H), 2.8 (m, 1 H), 2.5 (m, 1 H), 1.2 (t, 3 H); ^{13}C NMR (APT) 209.0 (C), 146.7 (C), 134.4 (CH), 129.7 (CH), 129.1 (CH), 117.1 (CH), 112.5 (CH), 76.9 (CH), 54.9 (CH), 46.6 (CH), 42.9 (CH_2), 34.9 (CH_2), 13.6 (CH_3); MS, m/e (relative intensity) 228 (M^+ + 1, 100.0), 227 (M^+, 19.9), 199 (21.9), 134 (42.7), 122 (47.0).

***endo*-7-(*p*-Tolylmethylamino)bicyclo[3.2.0]hept-2-en-6-one (2c).** From 2.15 g of **1c** and an excess of cyclopentadiene, 1 g of **2c** was obtained (44%): IR 1770, 1600, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (m, 2 H), 6.7 (m, 2 H), 5.8 (m, 1 H), 5.7 (m, 1 H), 5.2 (dd, 1 H, J = 8.1 Hz, 2.7 Hz), 4.0 (m, 1 H), 3.5 (m, 1 H), 2.9 (s, 3 H), 2.6–2.8 (m, 2 H), 2.2 (s, 3 H); ^{13}C NMR 209.0, 145.7, 133.5, 129.7, 129.0, 126.1, 112.1, 77.7, 54.1, 46.3, 35.0, 34.0, 19.4; MS, m/e (relative intensity) 228 (M^+ + 1, 100.0), 227 (M^+, 11.9), 199 (52.7), 160 (13.0).

***endo*-10-(Methylphenylamino)bicyclo[6.2.0]decan-9-one (3a).** From 1 g of **1a** and an excess of cyclooctene, 0.3 g of oily **3a** was obtained (23%): IR 1770, 1660, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 2 H), 6.8 (m, 3 H), 4.75 (dd, 1 H, J = 8.7 Hz, 2.5 Hz), 3.1 (m, 1 H), 2.9 (s, 3 H), 2.5 (m, 1 H), 2.0–1.2 (m, 12 H); ^{13}C NMR (APT) 211.0 (C), 149.1 (C), 129.2 (CH), 118.1 (CH), 113.9 (CH), 78.9 (CH), 58.0 (CH), 57.0 (CH_2), 35.4 (CH_3), 34.8 (CH), 30.6 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 26.0 (CH_2), 25.1 (CH_2); MS, m/e (relative intensity) 258 (M^+ + 1, 13.5), 257 (M^+, 2.3), 240 (9.8).

***endo*-10-(Ethylphenylamino)bicyclo[6.2.0]decan-9-one (3b) and 10-(Ethylphenylamino)bicyclo[6.2.0]dec-10-en-9-one (4b).** From 2.15 g of **1b** and an excess of cyclooctene, a trace of **3b** and 0.75 g of **4b** (28%) were obtained.

3b: IR 1765, 1595, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (m, 2 H), 6.7 (m, 3 H), 4.9 (dd, 1 H, J = 9 Hz, 3 Hz), 3.5 (m, 1 H), 3.3 (m, 1 H), 2.95 (m, 1 H), 2.75 (m, 1 H), 1.9–1.1 (m, 15 H); ^{13}C NMR (APT) 207.3 (C), 146.9 (C), 129.3 (CH), 116.7 (CH), 111.4 (CH), 73.8 (CH), 55.7 (CH), 43.1 (CH_2), 37.5 (CH), 30.4 (CH_2), 27.5 (CH_2), 25.6 (CH_2), 25.1 (CH_2), 23.9 (CH_2), 20.7 (CH_2), 13.8 (CH_3); MS, m/e (relative intensity) 271 (M^+, 2.2), 135 (10.7), 134 (100), 106 (22.9).

4b: IR, 1740, 1620, 1600, 1500 cm^{-1}; GC/MS (70 eV), m/e (relative intensity) 269 (M^+, 5.6), 212 (100), 144 (10.3), 104 (31); ^1H NMR ($CDCl_3$) δ 7.3 (m, 2 H), 6.9 (m, 3 H), 3.8 (m, 2 H), 3.3 (m, 1 H), 2.2–1.4 (m, 12 H), 1.2 (t, 3 H); ^{13}C NMR (APT) 190.1 (C), 154.6 (C), 143.8 (C), 140.6 (C), 128.9 (CH), 121.7 (CH), 119.9 (CH), 57.8 (CH), 44.3 (CH_2), 29.6 (CH_2), 28.9 (CH_2), 27.7 (CH_2), 26.2 (CH_2), 24.1 (CH_2), 23.2 (CH_2), 14.3 (CH_3).

***endo*-10-(*p*-Tolylmethylamino)bicyclo[6.2.0]decan-9-one (3c).** From 1 g of **1c** and an excess of cyclooctene, a trace of **3c** was obtained: IR 1755, 1605, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1 (d, 2 H), 6.6 (d, 2 H), 4.9 (dd, 1 H, J = 9.3 Hz, 2.4 Hz), 2.95 (s, 3 H), 2.9–2.85 (m, 2 H), 2.2 (s, 3 H), 1.2–1.9 (m, 12 H); ^{13}C NMR 208.1, 146.3, 129.7, 126.3, 111.7, 74.3, 55.6, 38.1, 35.4, 30.5, 27.6, 25.9, 25.7, 24.1, 20.7, 20.2; MS, m/e (relative intensity) 272 (M^+ + 1, 100.0), 243 (36.9), 160 (20.4), 132 (35.9).

***endo*-9-(Methylphenylamino)bicyclo[5.2.0]nonan-8-one (5a).** From 1 g of **1a** and an excess of cycloheptene, 0.3 g of **5a** was obtained (25%): IR 1765, 1600, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 2 H), 6.75 (3 H), 4.9 (dd, 1 H, J = 8.7 Hz, 2.6 Hz), 3.3–3.35 (m, 1 H), 3.1 (s, 3 H), 2.9 (m, 1 H), 2.0–1.2 (m, 10 H); ^{13}C NMR (APT) 208.5 (C), 148.3 (C), 129.2 (CH), 117.2 (CH), 111.7 (CH), 72.0 (CH), 56.7 (CH), 38.1 (CH), 35.5 (CH_3), 32.1 (CH_2), 30.3 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 25.4 (CH_2); MS, m/e (relative intensity) 244 (M^+ + 1, 100.0), 243 (M^+, 12.9), 215 (45.5), 144 (26.7).

***endo*-9-(Ethylphenylamino)bicyclo[5.2.0]nonan-8-one (5b) and 9-(Ethylphenylamino)bicyclo[5.2.0]non-9-en-8-one (6b).** From 2.15 g of **1b** and a excess of cycloheptene, a trace of **5b** and 0.85 g of **6b** (34%) were obtained.

5b: IR 1760, 1600, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 2 H), 6.75 (m, 3 H), 4.85 (dd, 1 H, J = 9 Hz, 3 Hz), 3.5–2.8 (m, 4 H), 2–1 (m, 13 H); ^{13}C NMR (APT) 208.1 (C), 147.1 (C), 129.3 (CH), 116.8 (CH), 111.7 (CH), 71.8 (CH), 56.7 (CH), 43.1 (CH_2), 37.5 (CH), 31.9 (CH_2), 26.2 (CH_2), 27.7 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 13.8 (CH_3); MS, m/e (relative intensity) 258 (M^+ + 1, 100.0), 257 (M^+, 14.4), 229 (16.5).

6b: IR 1740, 1620, 1600, 1500 cm^{-1}; GC/MS (70 eV) m/e (relative intensity) 255 (M^+, 5.5), 227 (7.0), 198 (100), 104 (16.7), 77 (32.2); ^1H NMR ($CDCl_3$) δ 7.3 (m, 2 H), 6.9 (m, 3 H), 3.8 (m, 2 H), 3.3 (m, 1 H), 2.4–1.15 (m, 13 H); ^{13}C NMR (APT) 189.0 (C), 153.1 (C), 143.4 (C), 139.3 (C), 128.8 (CH), 122.1 (CH), 120.0 (CH), 59.1 (CH), 44.3 (CH_2), 31.9 (CH_2), 31.1 (CH_2), 30.4 (CH_2), 28.9 (CH_2), 27.3 (CH_2), 14.3 (CH_3).

***endo*-9-(*p*-Tolylmethylamino)bicyclo[5.2.0]nonane (5c).** From 1 g of **1c** and an excess of cycloheptene, a trace of **5c** was obtained: IR 1760, 1610, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1 (d, 2 H), 6.7 (d, 2 H), 4.7 (dd, 1 H, J = 8 Hz, 2.7 Hz), 3.1 (m, 1 H), 2.8 (s, 3 H), 2.4 (m, 1 H), 2.2 (s, 3 H), 2–1.2 (m, 10 H); ^{13}C NMR 209.5, 146.0, 128.5, 126.6, 113.6, 74.5, 58.3, 35.2, 34.4, 32.0, 30.9, 29.0, 27.7, 25.7, 19.2; MS, m/e (relative intensity) 258 (M^+ + 1, 100.0), 257 (M^+, 14.7), 229 (58.8).

3-Acetoxy-1,2-dimethylindole (8). *N*-Phenyl-*N*-methylalanine hydrochloride (**7**) was prepared from aniline and ethyl 2-bromopropanoate, followed by methylation and hydrolysis; mp 178–180 °C. A 0.5-g portion of **7** was refluxed with 15 mL of acetic anhydride and 2 g of sodium acetate for 5 h. Usual workup and column chromatography gave 0.4 g of compound **8** (85%): IR 1745, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.1 (m, 4 H), 3.6 (s, 3 H), 2.4 (s, 3 H), 2.3 (s, 3 H); ^{13}C NMR (APT) 167.9 (C), 143.1 (C), 126.0 (C), 125.8 (C), 124.2 (CH), 120.5 (C), 119.4 (CH), 116.6 (CH), 109.0 (CH), 29.5 (CH_3), 20.6 (CH_3), 9.1 (CH_3).

3-Acetoxy-1-ethylindole (9b) and *exo*-7-(Ethylphenylamino)bicyclo[3.2.0]hept-2-en-6-one (10b). A 2.15-g portion of **1b** was refluxed with 10 mL of acetic anhydryde, 4 g of sodium acetate, and 8 g of cyclopentadiene for 3 h. The reaction mixture was poured into a cold 10% aqueous NaOH solution. The aqueous solution was extracted with ether and the ether solution was dried over anhydrous magnesium sulfate. After evaporation of the ether, the concentrated ether solution was subjected to column and rotary thin layer chromatography. A 0.3-g portion of **9b** (15%) and 0.4 g of **10b** (18%) were obtained.

9b: IR 1740, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (d, 1 H), 7.4–7.2 (m, 4 H), 4.2 (q, 2 H), 2.4 (s, 3 H), 1.4 (t, 3 H); ^{13}C NMR (APT) 168.8 (C), 132.7 (C), 129.3 (C), 122.2 (CH), 120.2 (C), 119.2 (CH), 117.6 (CH), 116.1 (CH), 109.3 (CH), 40.9 (CH_2), 20.9 (CH_3), 15.4 (CH_3); MS, m/e (relative intensity) 203 (M^+, 19.6), 161 (84.3), 146 (100).

10b: IR 1735, 1590, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 2 H), 6.8 (m, 3 H), 6.6 (m, 1 H), 3.7 (t, 1 H), 3.45 (m, 1 H), 3.35 (m, 1 H), 3.25 (m, 1 H), 3.05 (m, 1 H), 2.4 (m, 1 H), 2.2 (m, 1 H), 1.9 (t, 3 H); ^{13}C NMR 211.3, 147.8, 142.0, 133.7, 128.9, 129.1, 116.8, 60.3, 54.3, 46.2, 45.7, 44.2, 13.1; MS, m/e (relative intensity) 228 (M^+ + 1, 76.6), 227 (M^+, 12.9), 199 (53.1), 134 (100.0).

3-Acetoxy-1,5-dimethylindole (9c) and *exo*-7-(*p*-Tolylmethylamino)bicyclo[3.2.0]hept-2-en-6-one (10c). Following the same procedure as described above, 0.3 g of **9c** (15%) and 0.3 g of **10c** (13%) were obtained.

9c: IR 1740 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7 (5 H), 3.6 (s, 3 H), 2.4 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR (APT) 168.8 (C), 132.3 (C), 128.7 (C), 128.6 (C), 124.1 (CH), 120.3 (C), 118.0 (CH), 117.0 (C), 109.1 (C), 32.8 (CH_3), 21.4 (CH_3), 20.7 (CH_3); MS, m/e (relative intensity) 204 (M^+ + 1, 29.3), 203 (M^+, 15.4), 160 (100), 146 (12.8).

10c: IR 1730, 1610, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1 (d, 2 H), 6.8 (d, 2 H), 6.6 (m, 1 H), 6.3 (m, 1 H), 3.7 (d, 1 H), 3.2 (m, 1 H), 3.1 (m, 1 H), 2.9 (s, 3 H), 2.4 (m, 1 H), 2.3 (s, 3 H), 2.2 (m, 1 H); ^{13}C NMR (APT) 212.0 (C), 147.8 (C), 142.5 (CH), 133.7 (CH), 129.6 (CH), 128.3 (C), 115.4 (CH), 61.6 (CH), 54.4 (CH), 46.8 (C), 45.4 (CH_2), 37.4 (CH_3), 20.4 (CH_3); MS, m/e (relative intensity) 228 (M^+ + 1, 21.9), 227 (M^+, 3.7), 199 (8.3).

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Registry No. **1a**·HCl, 21911-75-1; **1a** (ethyl ester), 21911-74-0; **1b**·HCl, 21911-78-4; **1b** (ethyl ester), 21911-77-3; **1c**·HCl, 120547-25-3; **1c** (ethyl ester), 120547-24-2; (±)-**2a**, 120547-17-3; (±)-**2b**, 120662-11-5; (±)-**2c**, 120547-26-4; (±)-**3a**, 120547-18-4; (±)-**3b**, 120547-27-5; (±)-**3c**, 120547-28-6; (±)-**4b**, 120577-47-1; (±)-**5a**, 120547-19-5; (±)-**5b**, 120547-29-7; (±)-**5c**, 120547-30-0; (±)-**6b**, 120547-20-8; DL-**7**·HCl, 120547-21-9; **8**, 120547-22-0; **9b**, 87732-27-2; **9c**, 120547-31-1; (±)-**10b**, 120547-23-1; (±)-**10c**, 120662-12-6; TsCl, 98-59-9; $C_6H_5NH_2$, 62-53-3; (±)-$MeCHBrCO_2Et$, 41978-69-2; cyclopentadiene, 542-97-2; cyclooctene, 931-88-4; cycloheptene, 628-92-2.

Cycloadditions of (Alkylarylamino)ketenes with Imines. *cis*-3-Amino-2-azetidinones

William T. Brady* and Yi Qi Gu

Department of Chemistry, University of North Texas, Denton, Texas 76203

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The in situ cycloaddition of (alkylarylamino)ketenes with various imines to form predominately *cis*-3-amino-2-azetidinones is described. A mechanism involving a dipolar intermediate is provided whereby the structure of the intermediate is determined by both electronic and steric effects.

The discovery of β-lactam antibiotics has stimulated a lot of interest in the synthesis of β-lactams and their derivatives.[1] The synthesis of *cis*-3-amino-2-azetidinones continues to be a very active research area because of the importance of this structural unit in penicillin and related antibiotics.[2] It has been reported that reactions of azidoacetyl chloride or phthaloylglycyl chloride and imines in the presence of triethylamine form β-lactams, which may be converted to 3-amino-2-azetidinones.[3] More recently, several improved methods for the synthesis of 3-amino β-lactams have been reported by the treatment of azidoacetic acid, phthaloylglycine, or a Dane salt of glycine and an imine with a reagent for activating the carbonyl group in the presence of triethylamine.[2b,c,4] Some of these methods offer a stereocontrolled synthesis of cis 3-amino β-lactams. In the course of our work on the chemistry of ketenes, we demonstrated the intermediacy of (alkylarylamino)ketene in the reaction of *N*-alkyl-*N*-arylglycine and cycloalkenes in the presence of triethylamine. Since the cycloaddition of a ketene and an imine is one of the most important methods for the synthesis of β-lactams,[5] we investigated the reactions of (alkylarylamino)ketenes and imines and studied the stereochemistry of the resulting 3-amino β-lactams. We report here the results of this study.

An *N*-alkyl-*N*-arylglycine hydrochloride was stirred with 1 equiv of an imine, 1 equiv of *p*-toluenesulfonyl chloride, and 4–5 equiv of triethylamine in benzene at room temperature for 8–10 h. The corresponding β-lactams were obtained in moderate to good yield (Scheme I). Imines with various substituents in the benzene rings were pre-

Scheme I

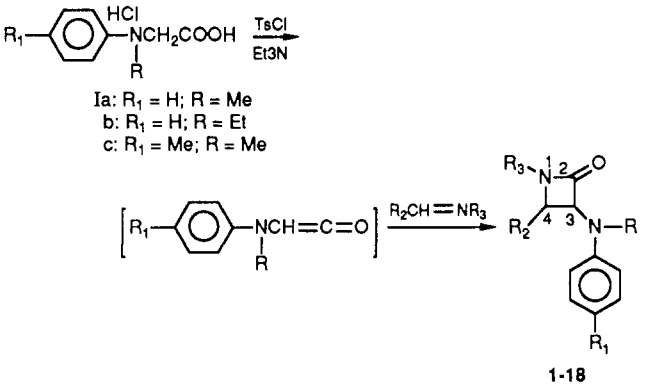
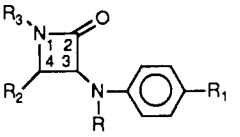


Table I. 3-(Alkylarylamino)-2-azetidinones



compd	R	R_1	R_2	R_3	isomer	yield, %
1	Me	H	C_6H_5	C_6H_5	cis	64
2	Et	H	C_6H_5	C_6H_5	cis	70
3	Me	Me	C_6H_5	C_6H_5	cis	63
4	Me	H	-CH=CHC_6H_5	C_6H_5	cis	71
5	Me	Me	-CH=CHC_6H_5	C_6H_5	cis	57
6	Et	H	*p*-ClC_6H_4	C_6H_5	cis	61
7	Me	H	*p*-Cl-C_6H_4	C_6H_5	cis	53
8	Me	H	C_6H_5	*tert*-butyl	cis	68
9	Et	H	C_6H_5	*tert*-butyl	cis	47
10	Et	H	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	cis	73
11	Me	H	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	cis	68
12	Me	H	C_6H_5	*p*-$MeOC_6H_4$	cis	70
13	Et	H	*o*-$NO_2C_6H_4$	C_6H_4	cis	68
14	Me	H	*o*-$NO_2C_6H_4$	C_6H_5	cis	62
15	Me	H	*p*-$NO_2C_6H_4$	*p*-$MeOC_6H_4$	cis	72
16a	Me	H	*o*-$MeOC_6H_4$	C_6H_5	cis	53
16b	Me	H	*o*-$MeOC_6H_4$	C_6H_5	trans	8
17a	Et	H	*o*-$MeOC_6H_4$	C_6H_5	cis	46
17b	Et	H	*o*-$MeOC_6H_4$	C_6H_5	trans	8
18a	Et	H	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$	cis	59
18b	Et	H	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$	trans	20

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