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.

(13) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr. Sect. A* **1971**, *A27*, 368.

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]

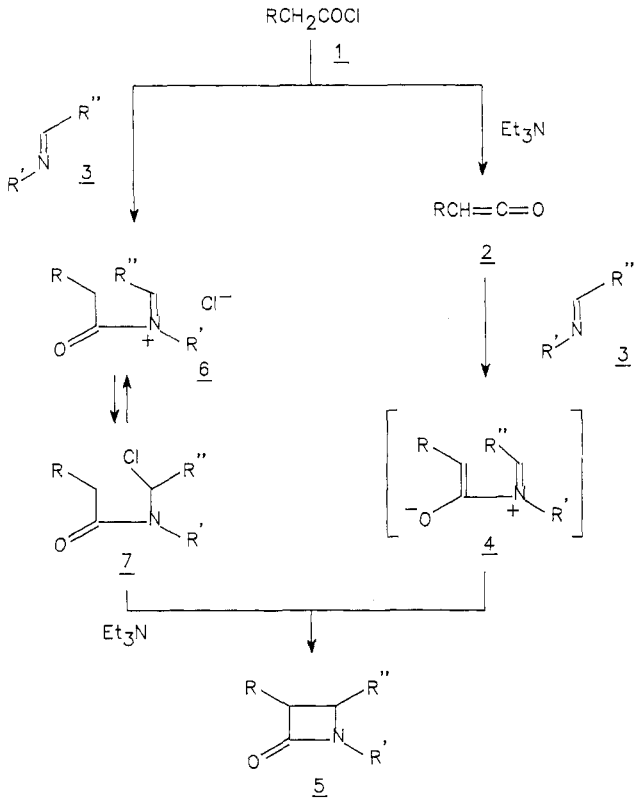
(1) (a) Sandhn, J. S.; Sain, B. *Heterocycles* **1987**, *26*, 777. (b) Gouindachaii, T. R.; Chinnasamy, P.; Rajeswari, R.; Chandrasekaran, S.; Premila, M. S.; Nakaraja, S.; Nagarajan, K.; Pai, B. R. *Heterocycles* **1984**, *22*, 585. (c) Mukarjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731. (d) Isaacs, N. S. *Chem. Soc. Rev.* **1976**, *4*, 181.

(2) Moore, H. W.; Hernandez, L.; Chambers, R. *J. Am. Chem. Soc.* **1978**, *100*, 2245.

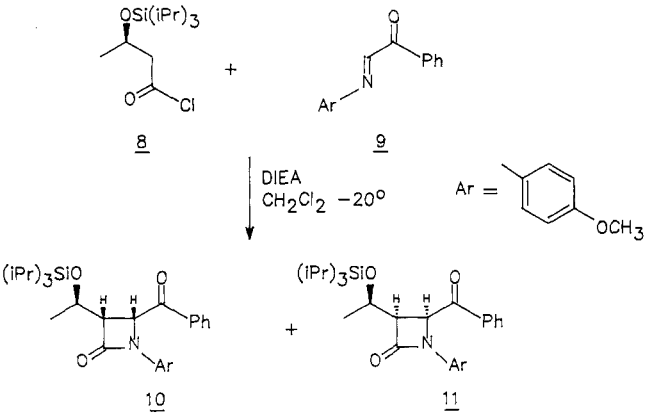
(3) (a) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, *245*. (b) Bohme, H.; Ebel, S.; Hartke, K. *Chem. Ber.* **1965**, *98*, 1463. (c) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167.

0022-3263/89/1954-3792$01.50/0

Scheme I



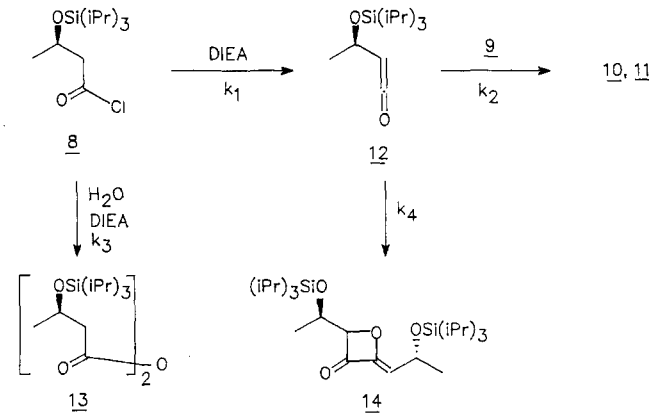
Scheme II



Several examples have been reported where variable ratios of cis and trans isomers of β-lactams were formed, depending on the order of addition of reactants.[4] This was rationalized in terms of a change from one to the other of the above mechanisms. Thus, the stereochemical outcome of the acid chloride–imine reaction may depend on which mechanistic pathway obtains under a given set of conditions.

We are interested in the reaction of imine **9** and acid chloride **8** as a potential diastereoselective route to carbapenem antibiotics[5] (Scheme II). Of particular interest is the stereochemical control that the stereogenic center of acid chloride **8** exerts on the newly developed stereogenic centers at C-3 and C-4 of the 2-azetidinone ring. The degree and sense of this stereocontrol need not be the same

Scheme III



for the two mechanisms shown in Scheme I (deprotonation of **6** need not give the same intermediate **4** as reaction of **2** with **3** especially regarding the enolate and imine geometries). The reaction of **8** and **9** in the presence of diisopropylethylamine (DIEA) in methylene chloride gave cis β-lactams **10** and **11** in a 1:4 ratio.[5] Thus, although we observed exclusive formation of cis β-lactams, we felt an understanding of the mechanism by which they combine might provide some insight into obtaining optimum stereocontrol.

The mechanisms shown in Scheme I are readily distinguishable kinetically since in the first the rate of disappearance of the acid chloride is a function of diisopropylethylamine (DIEA) concentration and in the second that rate is a function of imine concentration.

Previously, it had been observed that treatment of **8** with DIEA in an FT-IR cell gave a compound exhibiting a strong band at 2120 cm^{-1}, which was assigned to ketene **12** (Scheme III).[6] Since the carbonyl bands of the acid chloride (1800 cm^{-1}) and the β-lactams (1750 cm^{-1}) were well resolved, it occurred to us that IR spectroscopy could provide a valuable analytical tool for monitoring the progress of this reaction.

Solutions of imine, DIEA, and acid chloride in CH_2Cl_2 were prepared in volumetric flasks at −78 °C and then were transferred to a jacketed IR flow cell maintained at −22 °C; spectra were then obtained at specified time intervals. In addition to the major products **10** and **11**, small amounts of anhydride **13** and another byproduct, tentatively assigned as ketene-dimer **14** (based only on the position of its carbonyl band at 1860 cm^{-1}), were also detected. Concentrations of reactants and products were determined by integration of their carbonyl absorbances. The amide carbonyl absorbances of β-lactams **10** and **11** were indistinguishable and integrations thereof were taken as a measure of total β-lactam concentration. Standard calibration curves for concentrations of acid chloride, imine, β-lactams (1:1 mixture[7]), and anhydride **13** vs integrated carbonyl absorbances were linear over the range 0.05 M to 0.5 M. The molar absorptivity[8] of the ketene was estimated by using a dilute solution of acid chloride (0.005 M) and DIEA (2.5 M), assuming that acid chloride con-

(4) (a) Bose, A. K.; Chang, Y. H.; Manhas, M. S. *Tetrahedron Lett.* **1972**, 4091. (b) Oshiro, Y.; Komatsu, M.; Uesaka, M.; Agawa, T. *Heterocycles* **1984**, *22*, 549. (c) Doyle, T. W.; Belleau, B.; Luh, B.-Y.; Ferrari, C. F.; Cunningham, M. P. *Can. J. Chem.* **1977**, *55*, 468.

(5) Tschaen, D. M.; Fuentes, L. M.; Lynch, J. E.; Laswell, W. L.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 2779.

(6) Riseman, S. R.; Fuentes, L. M. Unpublished observation.

(7) Recrystallization of the crude azetidinone mixture from hexane/ethyl acetate gave a compound containing equimolar amounts of **10** and **11**. The assumption that this 1:1 compound has the same molar adsorptivity as the 1:4 mixture produced in the reaction is supported by the fact that the sum of the concentrations (as determined from the calibration curves) of products and starting material remains constant throughout the reaction.

(8) The actual value measured was the product of molar absorptivity and cell path length (ϵB); the path length was not independently determined for the reflectance cell.

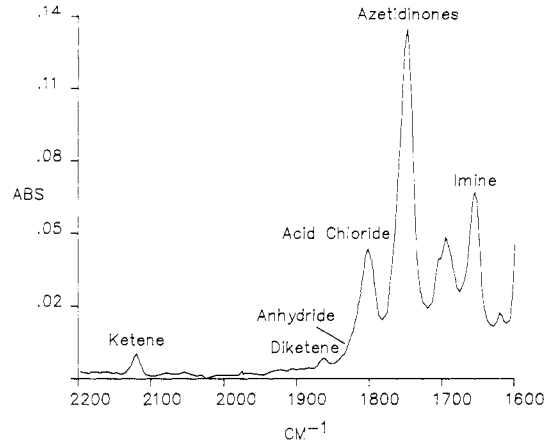


Figure 1.

sumed and ketene generated were equivalent. This assumption was supported by the lack of any other carbonyl bands in the spectrum. Optimum fit values of rate constants and the concentration of adventitious water were calculated by simplex calculations.[9] Each simplex optimization was started with a reasonable guess set of parameter values; simultaneous differential rate equations based on the reactions shown in Scheme III were integrated numerically, giving calculated values of concentrations of each species 8–14 at a given time. Fit was measured by the sum of squares of the differences of calculated concentrations and experimental data. Parameters were then adjusted by using a simplex algorithm, and the cycle was repeated until optimum values corresponding to minimum sum of squares were obtained.

The rates of reaction of 0.4 M acid chloride in the presence of 0.5, 1.5, and 5.0 equiv of DIEA and 1.1 equiv of imine were measured. A typical spectrum taken at approximately $t_{1/2}$ for reaction in the presence of 5 equiv of DIEA is shown in Figure 1. The kinetic profiles of reactions at the three levels of DIEA were qualitatively similar. There was a rapid rise in ketene concentration, followed by a period of several hours when ketene concentration remained at a steady state, followed ultimately by a slow decline. The experimental and calculated concentrations vs time for a representative experiment are shown in Figure 2. A comparison of the rate of consumption of acid chloride for each of the three charges of DIEA is consistent with a reaction first order in DIEA and acid chloride. The computer-generated curves based on the mechanism shown in Scheme III are consistent with the experimental data.[11]

In the presence of a large excess of DIEA (5 equiv), the rate of disappearance of acid chloride followed pseudo-first-order kinetics with computer-optimized values k_1 = 0.094 h^{-1} M^{-1} and k_2 = 12 h^{-1} M^{-1}. With 0.5 and 1.5 equiv

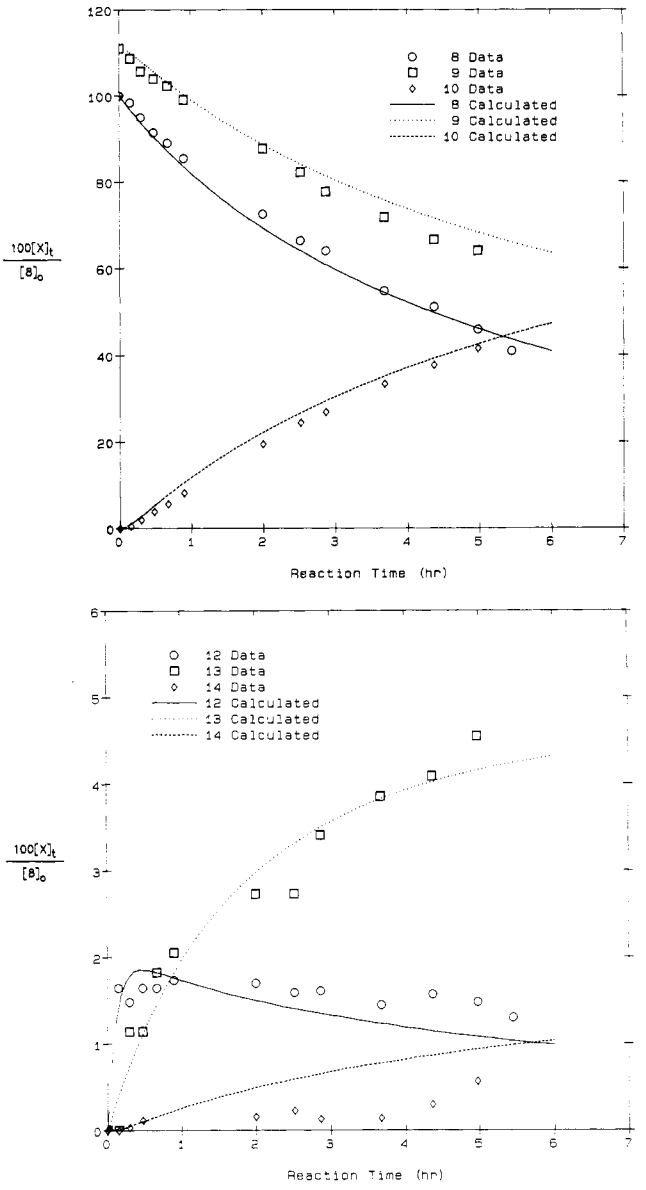
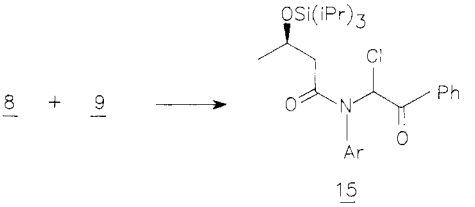


Figure 2.

Scheme IV



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of DIEA, significantly higher values of k_1 = 0.22 h^{-1} M^{-1} and k_2 = 16 h^{-1} M^{-1} were found.[10] We attribute the changes in the values of these rate constants to a change in solvent polarity since with 5 equiv of DIEA the reaction solution was 43% DIEA by volume. In further support of the mechanism in Scheme III, the rate of reaction of acid chloride with 1.5 equiv of DIEA was independent of the concentration of imine; thus, the same value of k_1 was found with 0.0 or 1.0 equiv of imine.

Only in the absence of DIEA does acid chloride **8** react with imine **9**, giving chloro amide **15** (Scheme IV). Duran and Ghosez have reported a similar observation.[3a] Chloro amide **15** did not react with DIEA to give β-lactams **10** or **11** under a variety of conditions and exhibited unusual stability in that it was isolated by silica gel chromatogra-

(9) Nelder, J. A.; Mead, R. *Comput. J.* **1965**, *7*, 308.

(10) We do not consider the values for k_3 and k_4 to be significant due to the low concentrations of the species involved.

(11) Other mechanisms involving first-order reaction of the acid chloride with DIEA can be written that are also consistent with these kinetic measurements, for example, acylation of DIEA to give the quaternary ammonium chloride. It appears that ketenes have been formed from such salts in some cases;[12] however, a mechanism involving deprotonation of this salt by a second molecule of DIEA is second order in DIEA and is not consistent with our observations. Although the acylammonium salt could be an alternative intermediate in azetidinone formation (independent of the ketene pathway), we see no evidence of its formation. Furthermore, substitution of triethylamine for DIEA in reactions of **8** and **9** did result in exclusive formation of the acylammonium salt from which no azetidinone was formed, even on warming to room temperature.

(12) (a) Hoye, T.; Magee, A. S.; Trumper, W. S. *Synth. Commun.* **1982**, *12*, 183. (b) Payne, G. B. *J. Org. Chem.* **1966**, *31*, 718.

phy. No trace of **15** was detected either by ^1H NMR or HPLC in reactions of **8** and **9** in the presence of DIEA. We also observed that even small amounts of DIEA (0.1 equiv) completely inhibited formation of **15** until such time as DIEA was consumed in the formation of **10** and **11**, and only then did formation of **15** become the major pathway for reaction of **8** with **9**. This result is not understood at this time but suggests that formation of **15** may be an acid-catalyzed process.

We conclude that formation of β-lactams **10** and **11** proceeds entirely through ketene intermediate **12** and that low temperature FT-IR spectroscopy provides a uniquely powerful method for the analysis of this reaction since it allows simultaneous quantitation of all reactants and products as well as the ketene intermediate.

Experimental Section

General. Unless otherwise noted materials were obtained from commercial suppliers and used without purification. Methylene chloride was dried over 3-Å molecular sieves, and diisopropylethylamine was distilled and stored over 3-Å sieves. NMR spectra were recorded on a Bruker AM-300 spectrometer (^1H 300 MHz, ^{13}C 75.5 MHz) in $CDCl_3$ solution; microanalyses were performed by Mrs. Jane E. Perkins, Analytical Research, Merck Sharp & Dohme Research Laboratories. IR spectra were recorded on Perkin-Elmer 281B or Nicolet 7199 spectrometers.

(3*R*)-(−)-3-[[Tris(1-methylethyl)silyl]oxy]butanoyl Chloride (8). 2,6-Lutidine (30.5 mL, 261 mmol) was added to methyl 3(*R*)-hydroxybutanoate (18.0 mL, 163 mmol) in CH_2Cl_2 (325 mL) at 0 °C followed by the dropwise addition of tris(1-methylethyl)silyl trifluoromethanesulfonate (50.00 g, 163 mmol) over 30 min with temperature increase to 6 °C. The resulting mixture was warmed to room temperature and aged 3 h. The mixture was washed with 2 N HCl (2 × 100 mL) and H_2O (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield 116.20 g (100%) of methyl 3(*R*)-[[tris(1-methylethyl)silyl]oxy]butanoate (**16**) as a faint yellow oil. ^1H NMR: δ 4.32–4.43 (sext, 1 H, J = 6.3 Hz), 3.63 (s, 3 H), 2.53 (dd, 1 H, J = 6.4, 14.6 Hz), 2.38 (dd, 1 H, J = 6.4, 14.6 Hz), 1.22 (d, 3 H, J = 6.0 Hz), 1.03 (s, 21 H). ^{13}C NMR: δ 172.0, 65.9, 51.4, 44.9, 24.1, 18.0, 12.4. Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.25; H, 11.04. Found: C, 61.00; H, 11.19. $[\alpha]^{25}_D$ −19.07° (*c* 10.12, $CHCl_3$). IR ($CDCl_3$) cm^{-1}: 1735.

Lithium hydroxide solution (1.03 M, 14.0 mL, 14.4 mmol) was added to **16** (2.64 g, 9.63 mmol) in THF (14.0 mL) at room temperature and the solution was stirred for 40 h. After removal of THF under reduced pressure the residue was acidified with 1 N HCl to pH 3.5, extracted with CH_2Cl_2 (3 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield 2.47 g (98.3%) of 3(*R*)-[[tris(1-methylethyl)silyl]oxy]butanoic acid (**17**) as a clear colorless oil. ^1H NMR: δ 9.95 (br, 1 H), 4.34–4.44 (sext, 1 H, J = 6 Hz), 2.48–2.61 (m, 2 H), 1.29 (d, 3 H, J = 6 Hz), 1.07 (m, 21 H). ^{13}C NMR: δ 177.5, 65.7, 44.7, 23.8, 18.0, 12.3. Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.93; H, 10.86. Found: C, 60.02; H, 11.10. $[\alpha]^{25}_D$ +5.06° (*c* 0.998, $CHCl_3$). IR ($CDCl_3$) cm^{-1}: 1750, 1710.

Oxalyl chloride (1.09 mL, 12.5 mmol) was added to **17** (2.17 g, 8.32 mmol) in CH_2Cl_2 (12.5 mL) at room temperature and the solution was stirred 2.5 h. The reaction mixture was concentrated under reduced pressure and distilled (Kugelrohr) (92–94 °C at 0.65 mmHg) to yield 2.06 g of **8** (88.7% yield) as a clear colorless oil. ^1H NMR: δ 4.42–4.52 (sext, 1 H, J = 6.1 Hz), 3.08 (dd, 1 H, J = 6.4, 15.6 Hz), 2.94 (dd, 1 H, J = 5.8, 15.6 Hz), 1.28 (d, 3 H, J = 6.2 Hz), 1.07 (m, 21 H). ^{13}C NMR: δ 171.4, 65.5, 56.9, 23.7, 18.1, 18.0, 12.4. Anal. Calcd for $C_{13}H_{27}O_2SiCl$: C, 55.97; H, 9.78. Found: C, 55.81; H, 9.84. $[\alpha]^{25}_D$ −12.6° (*c* 5.06, $CHCl_3$). IR ($CDCl_3$) cm^{-1}: 1800.

3(*R*)-[[Tris(1-methylethyl)silyl]oxy]butanoic Anhydride (13). Triethylamine (400 mg, 3.95 mmol) and then *p*-toluenesulfonyl chloride (352 mg, 1.85 mmol) were added to 3(*R*)-[[tris(1-methylethyl)silyl]oxy]butanoic acid (949 mg, 3.64 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min, diluted with hexanes (5 mL), and washed with water (5 mL). The solution was dried (Na_2SO_4) and concentrated to a colorless oil (872 mg, 1.73 mmol, 95%). ^1H NMR: δ 4.41 (sext, J = 7 Hz, 1 H), 2.62 (ABX, J = 16, 7 Hz, 2 H); 1.30 (d, J = 7 Hz, 3 H), 1.05 (m, 21 H). ^{13}C NMR: δ 167.0, 65.3, 45.8, 23.9, 18.1, 18.0, 12.4. Anal. Calcd for $C_{26}H_{54}O_5Si_2$: C, 62.10; H, 10.82. Found: C, 61.58; H, 10.73. IR ($CDCl_3$) cm^{-1}: 1820, 1750.

***N*-(1-Chloro-2-oxo-2-phenylethyl)-*N*-(4-methoxyphenyl)-3-[[tris(1-methylethyl)silyl]oxy]butanamide (15).** The acid chloride **8** (504 mg, 1.80 mmol) was added to imine **9** (425 mg, 1.79 mmol) in dry CH_2Cl_2 (4.9 mL) at −20 °C under N_2. The solution was allowed to stand at −20 °C for 16 h, warmed to 20 °C, concentrated, and chromatographed on silica gel (5:1 hexane/ethyl acetate), giving the chloro amide **15** as a yellow oil 354 mg (38%). NMR shows the presence of two isomeric compounds, both showing hindered rotation about the nitrogen–4-methoxyphenyl bond. We were unable to determine whether these isomers are diastereomers or conformers resulting from hindered rotation about the amide nitrogen carbon bond. ^1H NMR: δ 0.98 (m, 21 H), 1.11 (d, J = 6.8 Hz, 1.5 H) and 1.13 (d, J = 6.8 Hz, 1.5 H), 2.10 (m, 1 H), 2.35 (m, 1 H), 3.76 (s, 3 H), 4.39 (m, 1 H), 6.77 (br, 4 H, resolved into 8 separate signals at −40 °C), 7.47 (m, 2 H), 7.62 (m, 1 H), 7.89 (m, 2 H), 8.10 (s, 0.5 H), 8.16 (s, 0.5 H). ^{13}C NMR: 188.0, 187.9, 171.7, 160.0, 134.1, 134.0, 130.4, 129.3, 129.2, 129.0, 128.9, 128.6, 121.4, 114.5, 71.6, 71.3, 66.2, 65.8, 55.3, 44.5, 44.2, 23.9, 23.8, 18.04, 18.01, 17.98, 12.25. Anal. Calcd for $C_{28}H_{40}ClNO_4Si$: C, 64.94; H, 7.78; N, 2.70; Cl, 6.85. Found: C, 64.95; H, 7.70; N, 2.44; Cl, 6.80. IR ($CDCl_3$) cm^{-1}: 1712, 1616.

(3*S*,4*R*)-4-Benzoyl-3(*R*)-[1-[[tris(1-methylethyl)silyl]oxy]ethyl]azetidin-2-one (10) and (3*R*,4*S*)-4-Benzoyl-3-(*R*)-[1-[[tris(1-methylethyl)silyl]oxy]ethyl]azetidin-2-one (11). Diisopropylethylamine (349 mg, 2.70 mmol) was added to imine **9** (427 mg, 1.78 mmol) in dry CH_2Cl_2. The solution was cooled to −20 °C under N_2 and acid chloride **8** (500 mg, 1.79 mmol) was added. The solution was kept at −20 °C for 16 h and then warmed to 20 °C, diluted with hexanes (10 mL), washed with 2 N HCl (5 mL) and then water (2 × 5 mL), and dried (Na_2SO_4). Concentration gave a solid mass, which was dissolved in a minimum amount of CH_2Cl_2 and chromatographed on silica gel with 5:1 hexane/ethyl acetate, giving β-lactams **10** (154 mg 0.30 mmol, 17%) and **11** (611 mg, 1.18 mmol, 66%).

β-Lactam **10**. ^1H NMR: δ 8.09 (dd, 2 H, J = 0.6, 7.9 Hz), 7.63–7.68 (m, 1 H), 7.50–7.55 (m, 2 H), 7.14–7.19 (m, 2 H), 6.77–6.83 (m, 2 H), 5.63 (d, 1 H, J = 5.9 Hz), 4.30–4.39 (m, 1 H), 3.74–3.78 (m, 1 H), 3.75 (s, 3 H), 1.37 (d, 3 H, J = 6.3 Hz), 0.81–0.90 (m, 18 H), 0.58–0.71 (m, 3 H). ^{13}C NMR: δ 193.4, 163.5, 156.2, 135.9, 134.1, 131.0, 128.8, 128.8, 118.2, 114.4, 65.3, 63.0, 56.3, 55.5, 22.4, 18.2, 17.9, 13.0. IR (CH_2Cl_2): 1750, 1690 cm^{-1}. Anal. Calcd for $C_{28}H_{39}NO_4Si$: C, 69.80; H, 8.18; N, 2.91. Found: C, 69.67; H, 8.25; N, 2.86. $[\alpha]^{25}_D$ +39.64° (*c* = 3.91, $CHCl_3$).

β-Lactam **11**. ^1H NMR: δ 7.98 (d, 2 H, J = 7.33 Hz), 7.61 (dd, 1 H, J = 7.3, 7.3 Hz), 7.49 (dd, 2 H, J = 7.4, 7.8 Hz), 7.20–7.23 (m, 2 H), 6.76–6.80 (m, 2 H), 5.36 (d, 1 H, J = 6.4 Hz), 4.27–4.30 (m, 1 H), 3.85–3.89 (m, 1 H), 3.71 (s, 3 H), 1.33 (d, 3 H, J = 6.4 Hz), 0.89 (s, 21 H). ^{13}C NMR: δ 192.4, 163.6, 156.0, 135.1, 134.0, 131.5, 128.9, 128.6, 118.5, 114.2, 65.8, 62.1, 58.3, 55.4, 21.9, 18.1, 18.0, 13.0. IR ($CDCl_3$): 1750, 1690 cm^{-1}. Anal. Calcd for $C_{28}H_{39}NO_4Si$: C, 69.80; H, 8.18; N, 2.91. Found: C, 70.09; H, 8.26; N, 2.87. $[\alpha]^{25}_D$ −141.48° (*c* = 5.40, $CHCl_3$).

Kinetic Runs. Diisopropylethylamine, imine, and acid chloride were added to a graduated centrifuge tube fitted with a gas-tight septum and containing the appropriate amount of CH_2Cl_2 at −78 °C to give a solution concentration of acid chloride and imine of 0.4 M. Acid chloride was in all cases added last to minimize the reaction time while the solution was at −78 °C. The mixture was then quickly transferred, via cannula (maintained at −78 °C), to a "circle" cell (Spectra Tech) fitted with a GE internal reflectance element and variable temperature jacket which was mounted in the sample chamber of a Nicolet 7199 spectrometer. The cell temperature was maintained at −22 °C with ethanol in the cell jacket circulated from a thermostated reservoir and chilled using a Neslab "Cryocool 100" immersion cooler (the change in volume of the solution on warming from −78 °C to −22 °C was estimated at 6% by comparing the weight of CH_2Cl_2 contained in a 10-mL volumetric at the two temperatures). Data acquisition began when the solution was visible in the exit port of the cell. Three hundred scans at 2 cm^{-1} resolution were co-added for each spectrum. This corresponded to a spectral acquisition time of 3.5 min. Spectra were then collected periodically while the reaction proceeded in the cell. Carbonyl bands were integraged electronically from base

line to valley point or valley point to valley point as appropriate. Error in integrations was estimated at ±6% by standard deviations obtained while generating calibration curves.

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Supplementary Material Available: Plots of kinetic data for runs with 0.5 and 5 equiv of DIEA, plot of acid chloride concentration vs time with 5 equiv of DIEA with and without imine present, and ^{13}C NMR spectrum of **13** (6 pages). Ordering information is given on any current masthead page.

Halogenated Adamantanes: Intermolecular Interactions in the Solid State. X-ray Crystal Structures of Difluorodiiodo-, Trifluoroiodo-, and Tetraiodoadamantane

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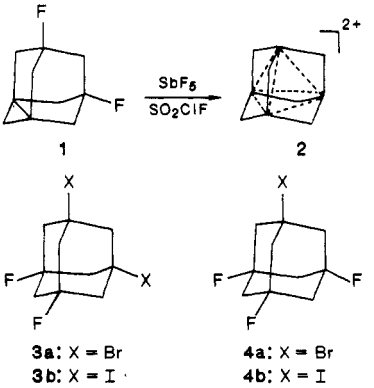
Partial halogen exchange can be achieved selectively from tetraiodoadamantane by using mercuric fluoride. Difluorodiiodo- or trifluoroiodoadamantane are formed in good yields depending on the conditions employed. The X-ray structures of these compounds illustrate the role of anisotropic intermolecular halogen–halogen interactions in the formation of ordered crystalline phases. Tetraiodoadamantane forms a "super-diamond" lattice with tetragonal symmetry, which has only been precedented in Ermer's recent crystal structure of adamantanetetracarboxylic acid.

Whereas all bridgehead-substituted tetrahaloadamantanes AdX_4 (X = F, Cl, Br, I) are well known,[1] those with mixed halogen subsituents are not. Selective halogenation or partial halogen exchange presents considerable difficulties since in most cases product mixtures are obtained. We were interested in the synthesis of 1,3-didehydro-5,7-difluoroadamantane **1** as a precursor for the nonclassical 1,3-didehydro-5,7-adamantanediyl dication **2**.[2] A number of 1,3-didehydroadamantanes have been synthesized by Pincock and co-workers[3] by bridgehead halogen elimination reactions. Hence, the possible precursors to **1**, difluorodibromo(iodo)adamantane **3** and monofluorotribromo(iodo)adamantane **4**, were prepared from tetrabromoadamantane **5** and tetraiodoadamantane **6**, respectively. X-ray crystallography showed **3b**, **4b**, and **6** to have special solid-state properties. Intermolecular halogen–halogen interactions permit these derivatives to crystallize in an orderly manner.

Results and Discussion

Synthesis of Haloadamantanes. When reacted with silver(I) fluoride in cyclohexane or methylcyclohexane, tetrabromoadamantane **5** as well as tetraiodoadamantane **6** gave product mixtures, AdX_nF_m (n, m = 0...4, $n + m$ = 4, X = Br, I), which could be separated by preparative HPLC.[4] However, not only are the yields of the desired compounds, **3** and **4**, unsatisfactory, but also the chromatographic separations are tedious and time consuming. Hence, considerable effort was expended in finding conditions for more selective halogen exchange.

While tetrabromoadamantane **5** did not react with mercuric fluoride in refluxing chloroform, tetraiodoadamantane **6** gave either **3b** or **4b**, depending on the conditions. The latter reacts smoothly with butyllithium in ether/pentane to give **1**, which in turn could be converted to the three-dimensional aromatic didehydroadamantanediyl dication **2**.[2]



Structures of Haloadamantanes. Tetraiodoadamantane 6. Many symmetrically substituted adamantanes do not form crystals suitable for X-ray structural determination due to the formation of plastic crystalline phases.[1,5] In contrast, the structures of **3b**, **4b**, and **6** could be solved by X-ray diffraction and exhibit interesting solid-state features. Intermolecular I···F and I···I interactions have an ordering influence on the molecules within the crystal lattice and thus help to determine long-range

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