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Origins of Regioselectivity in the Reactions of α-Lactams with Nucleophiles. Two Distinct Acid-Catalyzed Pathways Involving O- and N-Protonation

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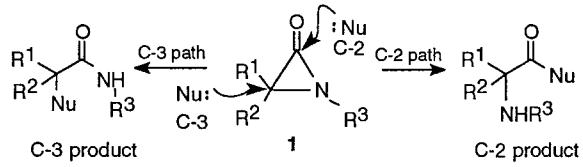
Sterically stabilized α-lactams react by two distinct acid-catalyzed pathways. Protonation on oxygen results in nucleophilic attack at the acyl carbon and gives C-2 products. Protonation on nitrogen leads to nucleophilic attack at the C-3 carbon and yields C-3 products. The mechanism thus developed is very useful for understanding the changes in rates and product distributions in the reactions of sterically stabilized α-lactams with nucleophiles. It can also be extrapolated to other α-lactams so that a more coherent picture of α-lactam reactivity can be developed.

Introduction

α-Lactams (aziridinones) **1** received a significant amount of attention in the 1960s and early 1970s because of their interesting and potentially useful reactivity. Their chemistry has been summarized in a review by Sheehan and Lengyel[1] in 1968 and in a shorter summary by L'abbé[2] in 1980. A review of the reactions of α-lactams with nucleophiles has appeared recently as well.[3] α-Lactams are reactive compounds that react with nucleophiles at room temperature to give two regioisomers. Either the nucleophile becomes attached to the acyl carbon (C-2 of the α-lactam) and a 2-amino acid derivative is formed (C-2 product) or the nucleophile becomes attached to the saturated ring carbon (C-3 of the α-lactam) and a 2-substituted secondary amide results (C-3 product) (Scheme 1).

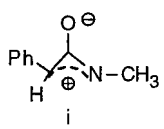
Two generalizations, which were first suggested by Sheehan[1] and reiterated by L'abbé,[2] have generally served as the starting point for most mechanistic discussions of α-lactam chemistry. Efforts to understand the factors that influence the regioselectivity of the reaction are also based on these generalizations. The first is that the nucleophile attacks the C-2 and C-3 carbons competitively.[4] For example, the groups of Quast,[5] Maran,[6] and D'Angeli[7] have used the stereospecific incorporation of nucleophiles at C-3 as evidence that simple nucleophilic attack at C-3 competes with nucleophilic addition to C-2.

SCHEME 1



The second is that good, anionic, nonprotic nucleophiles tend to attack the C-2 carbon while weaker, protic nucleophiles tend to attack the C-3 carbon. It was reported that *N-tert*-butyl-3,3-dimethylaziridinone reacts with water, methanol, *tert*-butyl alcohol, benzylamine, 2-toluenethiol, and hydrobromic acid, among others, to give C-3 products.[8] Conversely, sodium methoxide and potassium *tert*-butoxide react at the acyl carbon to give C-2 products. The same general trend was found for several other α-lactams.[9] Recently, Talaty surveyed the reactions of a large number of proton-bearing and non-proton-bearing nucleophiles with 1,3-di-*tert*-butylaziridinone and found a significant number of exceptions. In particular, amines were found give both C-2 and C-3 products depending on the nucleophilicity and the steric bulk.[10]

(1) Sheehan, J. C.; Lengyel, I. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 25.
(2) L'abbe, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 276.
(3) Hoffman, R. V. In *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-Interscience: New York, 2000; pp 137−155.
(4) In the 1968 review,[1] Sheehan was careful to include the possibility that dipolar ion i was the source of C-3 products. Stereochemical studies have largely discounted this possibility.



i

(5) (a) Quast, H.; Leybach, H. *Chem. Ber.* **1991**, *124*, 2105. (b) Quast, H.; Leybach, H.; Würthwein, E.-U. *Chem. Ber.* **1992**, *125*, 1249.
(6) Maran, F. *J. Am. Chem. Soc.* **1993**, *115*, 6557.
(7) (a) D'Angeli, F.; Marchetti, P.; Cavicchioni, G.; Maran, F.; Bertolasi, V. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1111. (b) D'Angeli, F.; Marchetti, P.; Rondanin, R.; Bertolasi, V. *J. Org. Chem.* **1996**, *61*, 1252.
(8) Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 1356.
(9) Shimazu, M.; Endo, Y.; Shudo, K. *Heterocycles* **1997**, *45*, 735.
(10) (a) Talaty, E. R.; Yusoff, M. M. *J. Chem. Soc., Chem. Commun.* **1998**, 985. See also: (b) Yusoff, M. M.; Talaty, E. R. *Tetrahedron Lett.* **1996**, *37*, 8695. (c) Talaty, E. R.; Dupuy, A. E., Jr.; Utermoehlen, *J. Chem. Soc., Chem. Commun.* **1971**, 16.

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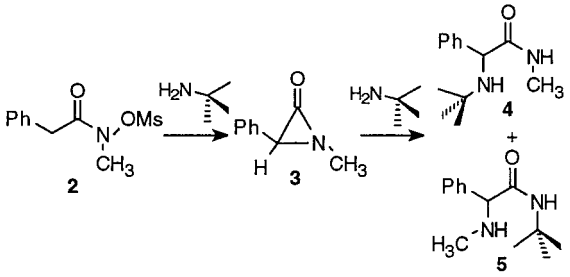
SCHEME 2

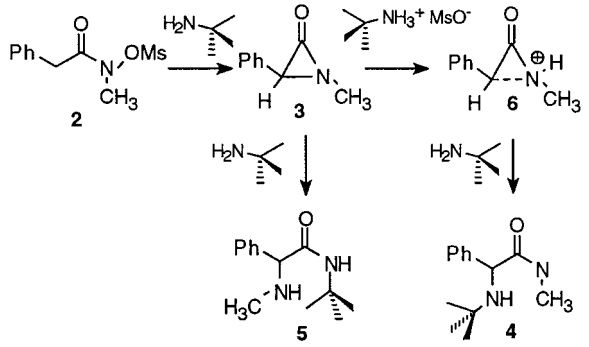


Our interest in α-lactams arose from a study of the chemistry of *N*-sulfonyloxy amides **2**. In the presence of amine bases and a variety of added nucleophiles, these compounds were found to give 2-substituted amides.[11] The first step in the process, as indicated by kinetic deuterium isotope effects and leaving group effects,[12] is a concerted 1,3-elimination to give an α-lactam **3**. The α-lactam reacts with nucleophiles to give products. Good nucleophiles attack the acyl carbon, giving C-2 products, while poor nucleophiles attack the C-3 carbon and give C-3 products. Competitive attack by the amine at either the C-2 or C-3 position was ruled out by experiments using *tert*-butylamine as the nucleophile. A mixture of products from both C-2 (**4**) and C-3 attack (**5**) was obtained (Scheme 2).[13]

Moreover, it was found that the ratio of C-2 to C-3 product is dependent on the concentration of *tert*-butylamine. Thus, there are different rate laws for the formation of the C-2 and C-3 products and the C-2 product increases in a first-order fashion with respect to *tert*-butylamine but the C-3 product does not. This finding effectively rules out the traditional mechanism invoking direct C-2 vs C-3 attack by the nucleophile (which would differ by the rate constant but not the order of the reaction). Furthermore, it suggests that there are competing pathways for the two products and that there is a second species besides **3** present in solution that leads to the C-3 product. This species was thought to be N-protonated α-lactam **6**, which is capable of reacting with even weak nucleophiles at C-3.[13] The ammonium salt produced in the formation of **3** from **2** is likely to be the proton source since it is the only known acid present in the reaction mixture. Theoretical studies indicate that N-protonation is favored slightly over O-protonation.[14] The mechanism consistent with these results is shown in Scheme 3.

Although this mechanism appears to account for the reaction of **3** with nucleophiles satisfactorily, further

SCHEME 3



insight into the process is desirable. In the first place, **3** is generated in situ from *N*-mesyloxyamide **2**. Despite the data that show that **2** undergoes a concerted 1,3-elimination to (presumably) an α-lactam, the fact that **3** cannot be isolated from reactions of **2** has led to the suggestion that some other intermediate is produced by elimination from **2**.[10a,15] This is unlikely in our opinion, but it can be addressed experimentally.

Second, the regioselectivity of nucleophilic addition to α-lactams has previously focused on the nature of the nucleophile, and little attention has been paid to the reaction environment. If protonation of the α-lactam results in C-3 attack, then the presence proton donors in the reaction mixture could play a significant role in the regioselectivity.

This study was undertaken with two goals in mind. We wished to confirm that the 1,3-elimination reaction of *N*-sulfonyloxyamides with amine bases does indeed produce α-lactams in situ, and we wished to determine if the acidity and/or protic nature of the reaction mixture influences the regioselection as suggested in Scheme 3.

Results

If the reaction of an *N*-sulfonyloxyamide with base produces an α-lactam in situ, then the chemistry of that α-lactam ought to be identical to the chemistry of the same α-lactam prepared and reacted as a pure compound (assuming that the reaction conditions are the same). Thus, *N*-sulfonyloxyamide **6** was chosen as the precursor for α-lactam generation in situ since it would produce α-lactam **7** upon reaction with base. α-Lactam **7** can also be isolated and reacted as a pure compound for comparison purposes. The regioselectivity of the reaction of pure **7** with amine nucleophiles compared with the product distribution obtained when **6** is reacted with the same amine nucleophiles could be used to confirm the identity of the intermediate as an α-lactam (Scheme 4). Moreover, the response of the regioselectivity to changes in reaction conditions would also lend mechanistic insight into the pathways leading to the C-2 and C-3 products.

N-Mesyloxyamide **6** was prepared by the literature procedure.[11e] The α-lactam **7** was prepared from *N*-*tert*-butyl-2-bromo-2-phenylacetamide **8** and potassium *tert*-butoxide in ether.[16] It was found that rigorous exclusion of moisture was necessary for success; thus, freshly dried

(11) (a) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, *60*, 7043. (b) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, *60*, 5992. (c) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1993**, *58*, 2355. (d) Hoffman, R. V.; Nayyar, N. K.; Klinekole, B. W. *J. Am. Chem. Soc.* **1992**, *114*, 6262. (e) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1992**, *57*, 5700.

(12) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Am. Chem. Soc.* **1993**, *115*, 5031.

(13) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1995**, *60*, 4121.

(14) Tantillo, D. J.; Houk, K. N.; Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 3830. The calculations were carried out on 1,3,3-trimethylazridinone, which does not have a conjugating phenyl substituent at C-3. Simple amides significantly favor O-protonation by 8−11 kcal/mol. For an excellent discussion of amide basicity, see: Greenberg, A. In T*he Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-Interscience: New York, 2000; pp 47−83.

(15) No alternatives were suggested in ref 9a, but one possibility would be dipolar ion i, which was first suggested by Sheehan.[1,4]

(16) Baumgarten, H. E.; Chaing, N.-C. R.; Elia, V. J.; Beum, P. V. *J. Org. Chem.* **1985**, *50*, 5507.

SCHEME 4

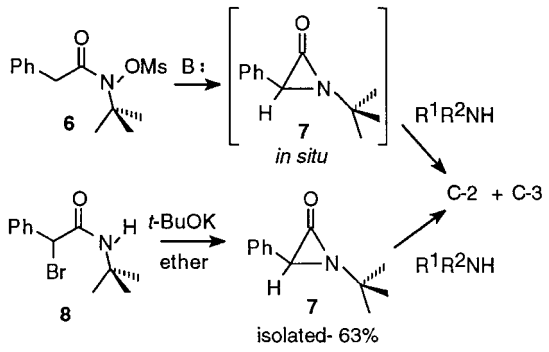
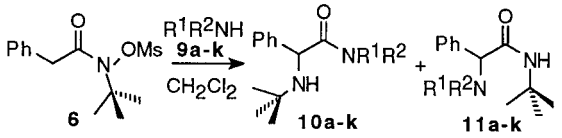


TABLE 1. Regioisomers from the Reaction of Amines with Mesyloxyamide 6



entry	amine	product ratio C-2/C-3
1	**9a**, isopropylamine	27.6
2	**9b**, pyrrolidine	21.1
3	**9c**, piperidine	7.0
4	**9d**, morpholine	6.7
5	**9e**, 1-adamantylmethylamine[a]	5.5
6	**9f**, diethylamine	0.2
7	**9g**, *tert*-amylamine	0.18
8	**9h**, diisopropylamine	0.16
9	**9i**, dicyclohexylamine	0.1
10	**9j**, 1-adamantylamine	0.08
11	**9k**, *N*-methyl-*tert*-butylamine	<0.01[b]

[a] **9e** = 1-$C_6H_{10}CH_2NH_2$. [b] Only **11k** was detected in the product.

ether and freshly sublimed potassium *tert*-butoxide were required for good results. Furthermore, the potassium *tert*-butoxide was added slowly (as an ether slurry) to the reaction mixture, the reaction was filtered and evaporated rapidly, and dry pentane was used to recrystallize the product. Given these precautions, reasonable yields of **7** can be obtained reliably.

Eleven amines **9a**−**k** were reacted with *N*-mesyloxyamide **6** to determine which (if any) gave mixtures of C-2 and C-3 products (Table 1). Generally high yields (80−90%) were obtained for regioisomeric mixtures. The individual regioisomers were separated and characterized. The C-2 products **10a**−**k** all had sharp singlets for the *N*-*tert*-butylamine group at about δ 1.1, while the C-3 products **11a**−**k** all had sharp singlets for the *N*-*tert*-butylamide group at about δ 1.3. *N*-*tert*-Butylphenylacetamide also gives an *N*-*tert*-butyl amide singlet at δ 1.3, which corroborates the assignment. These characteristic *tert*-butyl singlets were used to quantitate the C-2/C-3 ratio in the crude products. Primary and cyclic secondary amines gave mostly C-2 product (Table 1, entries 1−5), while bulkier amines gave mostly C-3 product (Table 1, entries 6−11). Diethylamine **9f** was chosen for further study since it gives C-2/C-3 mixtures, reacts at reasonable rates, and has a relatively simple NMR spectra.

Valid comparison of the reactions of *N*-mesyloxyamide **6** and α-lactam **7** with **9f** requires that the reaction conditions be the same. The reaction of **6** with an amine requires 2 equiv of the amine. One is used as a base to produce the reactive intermediate, and the second reacts as a nucleophile toward the intermediate. In addition, 1 equiv of the corresponding ammonium mesylate salt is produced during the conversion of **6** to the intermediate. Thus, for reactions of **6**, 2 equiv of the amine was used. For reactions of α-lactam **7**, 1 equiv of the amine was used and 1 equiv of the ammonium mesylate salt was added slowly to the reaction mixture to simulate the formation of the ammonium salt over the course of the reaction of **6** with the amine. The two reaction mixtures are not exactly the same since the amine concentration during the reaction of **6** is higher than for **7** (they become equal only at the end of the reaction). Moreover, the addition of the ammonium salt to **7** is somewhat faster than the rate of its formation from **6**; thus, its concentration is higher during the reactions of **7** (they become equal only at the end of the reaction). However, the reaction conditions, if not identical, are certainly comparable.

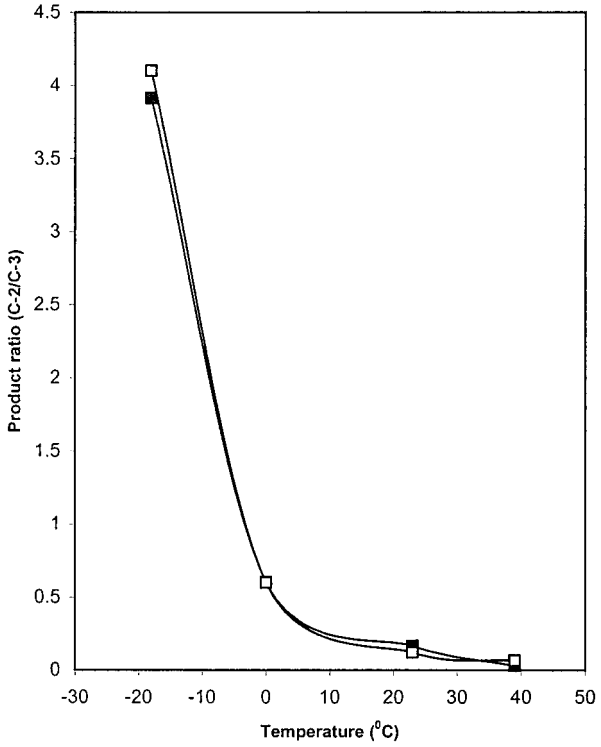


FIGURE 1. Regioselectivity in the reactions of **6** and **7** with diethylamine as a function of temperature. Open squares = **7**; filled squares = **6**.

Reactions of *N*-mesyloxyamide **6** and α-lactam with diethylamine **9f** were compared as a function of temperature, amine concentration, and ammonium salt concentration. The results are shown graphically in Figures 1−3. Reactions of **6** and **7** exhibit almost identical changes in regioselectivity as a function of temperature (Figure 1). In addition, it is seen that lower temperatures favor formation of the C-2 product while higher temperatures favor the formation of the C-3 product.

Reactions of **6** and **7** were next compared as a function of the number of diethylamine equivalents at 0 °C. To maintain similar reaction conditions, reactions of **6** contained one extra amine equivalent, and reactions of **7** had 1 equiv of diethylammonium mesylate added slowly to the reaction mixture. The results are shown in Figure

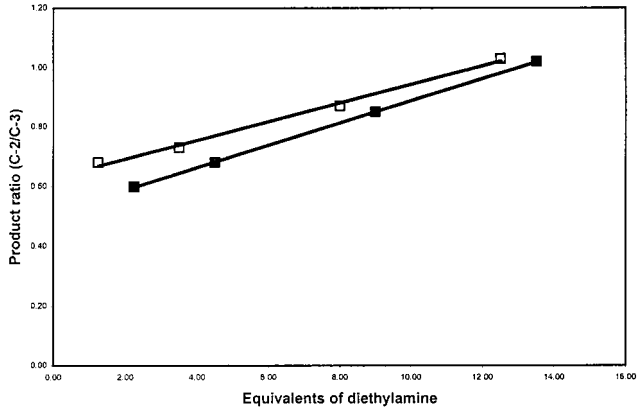


FIGURE 2. Regioselectivity in the reactions of **6** and **7** with diethylamine at 0 °C as a function of amine eqivalents. Open squares = **7**; filled squares = **6**.

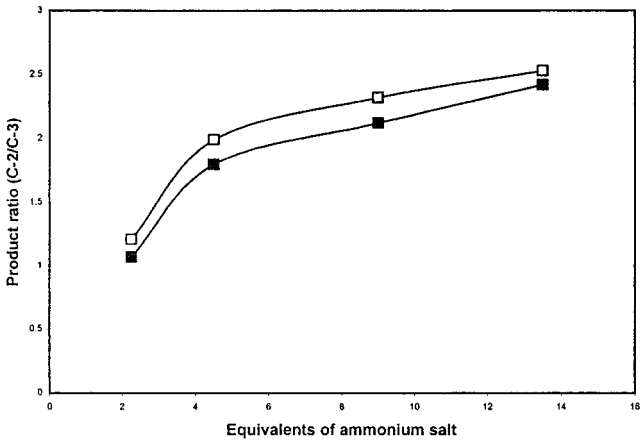


FIGURE 3. Regioselectivity in the reactions of **6** and **7** with diethylamine at 0 °C as a function of diethylammonium mesylate equivalents. Open squares = **7**; filled squares = **6**.

2. The plots in Figure 2 are offset by one amine equivalent since reactions of **6** contained one more amine equivalent at the beginning of the reaction. Moreover, **7** gave systematically higher amounts of the C-2 product, probably because the rate of salt addition to **7** (1.5 h) was faster than the rate of salt generation from **6** (3 h); thus, the salt concentration was higher in **7**. Nevertheless, the change in regiochemistry as a function of amine concentration, given by the slope of each plot, is very similar for **6** (slope = 0.037) and **7** (slope = 0.031). The data also show that increasing amine concentrations favor the C-2 product but the increase is much less than first order.

Finally, reactions of **6** and **7** were compared as a function of the ammonium mesylate salt concentration at 0 °C. It had been proposed that protonation of an α-lactam was the first step in the production of the C-3 product (Scheme 3).[13] In the experiments that led to the proposed mechanism, the only proton source in solution was the ammonium mesylate salt produced during the formation of the α-lactam from an *N*-mesyloxyamide. Thus, it was of interest to determine if an ammonium salt could actually have a significant effect on the regioselectivity. To achieve similar reaction conditions, 2.25 equiv of diethylamine was used with **6**, whereas 1.25 equiv was used with **7**. One equivalent less of diethylammonium mesylate was added initially to reactions of **6** since 1 equiv of the salt was produced over the course of the reaction. The plot for **6** in Figure 3 has been corrected for this difference by shifting the salt equivalents by one. As before, **7** gave slightly higher amounts of the C-2 product due to the higher initial salt concentration. The responses of the regiochemistry to changes in salt concentration are very similar for **6** and **7**. Figure 3 also shows that increasing the amount of ammonium salt favors the C-2 product by a significant amount.

TABLE 2. Effect of Ammonium Mesylate Salt on Reaction Time of 7 and Amines[a]

amine	reactant ratio[b]	reaction time
9f	1:1.25:0	90 min
9f	1:1.25:1	30 min
9g	1:1.25:0	6 h
9g	1:1.25:1	2.5 h

[a] Reactions were carried out in CD_2Cl_2 at room temperature. [b] Reactant ratio is **7**/amine/ammonium salt.

The data in Figures 1−3 show that the intermediate produced from **6** and α-lactam **7** show nearly identical chemical responses to changes in temperature, amine concentration, and ammonium salt concentration. Although not reported here, similar responses are observed when *tert*-amylamine is the amine reactant. Thus, it is clear that the reaction of **6** with amines does indeed produce α-lactam **7** in situ by a concerted 1,3 elimination.[12] The reason that α-lactam **7** cannot be isolated is because its rate of reaction with nucleophiles in solution is faster than its rate of formation from **6**; thus, its concentration remains low. Moreover it is reasonable to conclude that the reaction of other *N*-mesyloxyamides with bases is a general method for the generation of α-lactams in situ.

A most interesting result of these studies was the large change in regioselectivity wrought by the ammonium salt (Figure 3). This suggests that some type of acid−base interaction between the α-lactam and the ammonium ion plays an important role in the formation of at least one of the regioisomers. It was thus of interest to further characterize the effects of acids on the reactions of α-lactam **7** with nucleophiles.

The effect of the ammonium salt on the rate of reaction was studied by reacting **7** with diethylamine and *tert*-amylamine. For each amine, two reactions were run—one with 1 equiv of the corresponding ammonium mesylate salt present and one without. The reaction time was taken as the time required for the complete disappearance of the starting material by ^{1}H NMR. The results presented in Table 2 show that a single equivalent of the ammonium salt more than doubles the rate of reaction. Presumably, the ammonium ion functions as a general acid toward the α-lactam.

The effect of a specific acid on the rate of reaction was examined next using a similar approach. Two reactions were carried out using a solution of **7** in dichloromethane-d_2 containing 1.25 equiv of methanol as the nucleophile. To one reaction was added about 10 μL of methanesulfonic acid. The reaction without the added acid required 24 h for the complete disappearance of **7**, whereas the reaction to which methanesulfonic acid was added was complete in less than 15 min. Similar results were obtained using 2-propanol-d_8 as both the solvent and nucleophile. The reaction without added acid re-

TABLE 3. Effect of Specific Acid Catalysis on the Reaction Time of 7 with Weak Nucleophiles[a]

nucleophile	methanesulfonic acid (μL)	solvent	reaction time
CH_3OH[b]	0	CD_2Cl_2	24 h
CH_3OH[b]	10	CD_2Cl_2	<15 min
i-PrOH-d_8	0	*i*-PrOH-d_8	90 min
i-PrOH-d_8	10	*i*-PrOH-d_8	<15 min

[a] Reactions were carried out at room temperature. [b] 1.25 equiv of methanol was used.

TABLE 4. Effect of Solvents on the Reaction of 7 with Nucleophiles at Room Temperature

entry	nucleophile	solvent	reaction time (min)
1	MeOH-d_4	MeOH-d_4	<10
2	EtOH-d_6	EtOH-d_6	30
3	*i*-PrOH-d_8	*i*-PrOH-d_8	90
4	*t*-BuOH-d_{10}	*t*-BuOH-d_{10}	240
5	Et_2NH	CD_2Cl_2	80
6	Et_2NH	CD_3CN	80
7	Et_2NH	*i*-PrOH-d_8	<10

quired 90 min for completion, whereas addition of 10 μL of methanesulfonic acid caused complete disappearace of **7** in less than 15 min. These results, presented in Table 3, reveal that specific acid catalysis produces a dramatic rate acceleration on the reaction of **7** with weak nucleophiles.

Since acids clearly can catalyze the reaction **7** with nucleophiles, the influence of protic solvents was next considered. α-Lactam **7** was dissolved in a series of deuterated alcohols, and the reaction time was measured by NMR. The results presented in Table 4, entries 1−4, show that the rate increases several 100-fold in the order *t*-BuOH-d_{10} < *i*-PrOH-d_8 < EtOH-d_6 < MeOH-d_4. The differences between different alcohol solvents could be due to increasing acidity or increasing polarity since both properties increase in the opposite order as the reaction times. This was evaluated by using diethylamine as a nucleophile and monitoring the reaction times in deuterated dichloromethane, acetonitrile, and 2-propanol, which have dielectric constants[17] of 8.9, 36.2, and 18.3, respectively (Table 4, entries 5−7). The results show that reaction times are the same for acetonitrile and dichloromethane but much faster in 2-propanol. Thus, solvent acidity and not solvent polarity appears to play the dominant role in accelerating the reaction, and the rate increases with increasing solvent acidity. It is likely that hydrogen bonding to the α-lactam is capable of activating it toward nucleophilic attack.

Taken together, these studies demonstrate that nucleophilic attack on the α-lactam ring of **7** is very sensitive to acid catalysis (specific or general) and protic solvents (H-bonding). Thus, the α-lactam ring can be activated by partial or complete proton transfer or by hydrogen bonding. In the absence of such activation, the rate of reaction is much slower.

The above data pertain to the overall rate of reaction of **7** with nucleophiles. In order address the question of regioselectivity, it is necessary to understand how various factors affect the individual pathways that lead to the C-2 and C-3 products.[13] Thus, instead of considering the overall reaction time, it is necessary look at the individual pathways in turn.

TABLE 5. Reaction of 7 withDiethylamine in Alcohol Solvents at Room Temperature[a]

solvent	product Ratio C-2/C-3
t-BuOH	C-3 only
i-PrOH	C-3 only
EtOH	1:1.1
MeOH	6:1

[a] 1.25 equiv of diethylamine was used.

The factors known to favor the C-2 pathway can be summarized as follows. The C-2 pathway is favored by lower reaction temperatures (Figure 1). There is a slight increase in the C-2 product as the concentration of the nucleophile is increased (Figure 2). From Figure 3 and Table 2, both the overall rate of reaction and the amount of C-2 product increase in the presence of a weak acid such as the ammonium mesylate salt. This suggests that the C-2 pathway of **7** is acid catalyzed. To evaluate the effect of protic solvents on the C-2 pathway, α-lactam **7** was reacted with diethylamine in a series of alcohol solvents at room temperature (Table 5). The results show that the proportion of C-2 product is very sensitive to the acidity of the alcohol and increases markedly with an increase in solvent acidity.

The factors known to favor the C-3 pathway can be summarized as follows. The C-3 pathway is favored by higher reaction temperatures (Figure 1). In alcohol solvents where the alcohol serves as the nucleophile and only the C-3 product is formed, the rate of the C-3 reaction is increased by more acidic alcohols (Table 4, entries 1−4). The rate is also increased dramatically by specific acid catalysis (Table 3) These results show that the C-3 process is also acid catalyzed. When stronger nucleophiles are present in solution, the C-3 process is favored by protic solvents which are less acidic, e.g., *tert*-butyl alcohol (Table 5). It appears that the C-3 process is less sensitive to solvent acidity than the C-2 pathway (even though *both* are faster in more acidic solvents). As the solvent becomes more acidic going from *tert*-butyl alcohol to methanol, the rate of the C-2 reaction increases more rapidly than that of the C-3 process until in methanol it is the major pathway. In the less acidic *tert*-butyl alcohol, the C-2 process is slowed markedly and the C-3 process is dominant.

Another major factor influencing the regioselection is nucleophilicity. To clarify this dependence, α-lactam **7** was reacted with various nucleophiles in dichloromethane at room temperature and the ratio of regioisomers was measured. These reactions did not contain any added acid catalysts nor protic solvents. The results that are collected in Table 6 demonstrate several trends. Poor nucleophiles such as alcohols or mesylate ion give only C-3 product. Secondary and bulky primary amines give only C-3 attack. A less hindered primary amine such as isopropylamine gives a mixture of C-2 and C-3 products. Strong alkoxide nucleophiles give mostly C-2 product. These results reveal that the C-2 process is more dependent on nucleophilicity than is the C-3 pathway. These data parallel the results found for α-lactam **3**.[10] Whether or not the nucleophile bears a proton is ir-

(17) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; John Wiley and Sons: New York, 1972; pp 4−13.

TABLE 6. Regiochemistry of the Reaction of 7 with Various Nucleophiles[a]

nucleophile	equiv	time (h)	product ratio C-2/C-3
ROH	1.25	24	C-3 only
$CH_3SO_3^-$	1.25	24	C-3 only
Et_2NH	1.25	1.5	C-3 only
Me_2EtCNH_2	1.25	3	C-3 only
i-$PrNH_2$	1.25	1	0.79:1
CH_3O^-[b]	2.5	1	4:1
tBuO^-[b]	2.5	1	11:1

[a] Reactions were carried out in CH_2Cl_2 at room temperature. [b] Solvent was toluene.

TABLE 7. Regiochemistry of the Reaction of 7 with Amine Nucleophiles

nucleophile	reaction conditions[a]	product ratio C-2/C-3
Et_2NH	A	C-2 only
Et_2NH	B	C-3 only
tert-amylamine	A	C-2 only
tert-amylamine	B	C-3 only
t-$BuNHCH_3$	A	1/15
i-$PrNH_2$	B	1/3

[a] Key: (A) 1.25 equiv of amine, MeOH, corresponding ammonium mesylate salt, −18 °C; (B) 1.25 equiv of amine, *t*-BuOH, 38 °C.

relevant in determining the reaction outcome, it is the nucleophilicity that is the determining property.

Discussion

Evidence for the formation of α-lactams from the reaction of *N*-sulfonyloxyamides with bases is largely derived from mechanistic studies[12] that showed that a 1,3-elimination was occurring. Moreover, the products obtained from these reactions were typical of those obtained from α-lactams. It was logical to deduce that the 1,3-elimination did, in fact, produce an α-lactam in situ that was converted to products. The recent suggestion[10a] that an intermediate other than an α-lactam could be involved in the reactions of *N*-mesyloxyamides with amine bases was the genesis of this study.

It is assumed that 1,3-elimination in **6** would give α-lactam **7**.[12] Moreover, α-lactam **7** can be prepared and isolated as a pure compound. [16,18] Comparison of the chemistry of **6** with the chemistry of **7** would reveal if the reacting species are the same. The reaction of **6** and **7** with diethylamine was used for comparison. To maintain similar reaction conditions for **7**, the equivalents of amine were adjusted to reflect the different stoichiometry of the two systems (**7** requires one less amine equivalent than **6**). Moreover, a solution of 1 equiv of diethylammonium mesylate and α-lactam **7** was added slowly to a solution of diethylamine to simulate the slow production of **7** and the ammonium salt from the 1,3-elimination of **6**. These adjustments provided similar, but not identical, reaction conditions for the two systems. The C-2/C-3 product ratio was used to compare the chemistry of the two systems.

The response of the C-2/C-3 ratio for **6** and **7** to changes in temperature, amine concentration, and ammonium salt concentration are nearly identical (Figures 1−3). These results show that the chemical properties of the intermediate produced from **6** and α-lactam **7** are the same. The results provide convincing evidence that α-lactam **7** is produced in situ from **6**. It is also reasonable to assume that other *N*-sulfonyloxyamides react with bases to produce α-lactams as well.

In conjunction with the above study, a study of the regiochemistry of the reaction of **7** with nucleophiles was initiated. Regioselectivity has been a core problem in the chemistry of α-lactams and has yet to be resolved. The source of regioselectivity in nearly all previous work has focused on the nucleophile and whether it attacks the C-2 or the C-3 carbon. The protic nature of the nucleophile and some steric concerns have been at the center of most discussions.

Our work with *N*-sulfonyloxyamide **2** as the precursor to α-lactam **3** led us to conclude that two different pathways were involved in the production of the C-2 and C-3 products (Scheme 3).[13] The C-2 product results from direct nucleophilic attack on the acyl carbon of **3**. The C-3 product results from N-protonation of the α-lactam, which activates the C-3 carbon toward nucleophilic attack so even weak nucleophiles can attack C-3. Protonation of the α-lactam requires an acid, and thus, we became interested in the role of acid catalysts in changing the regioselectivity.

The results of this study show that for α-lactam **7** there are two different pathways for the formation of the C-2 and C-3 products, and *both* the C-2 and C-3 pathways are subject to some type of acid catalysis. Tables 2−4 show that acids of nearly any type increase the overall rate of conversion to products markedly. Furthermore, significant rate increases are seen for reactions that give C-2 products or C-3 products; thus, both pathways are acid catalyzed.

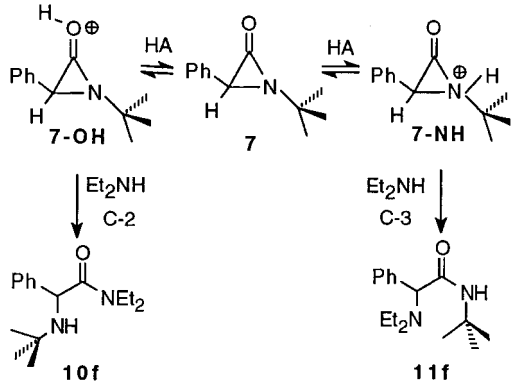
For example, the reaction of **7** with diethylamine in dichloromethane at room temperature takes 1.5 h for completion and gives only the C-3 product (Table 6). Addition of 1 equiv of diethylammonium mesylate causes the reaction to be complete in 30 min but still gives the C-3 product as the major product (Table 2). The same reaction of diethylamine with **7** in 2-propanol at room temperature is complete in less than 10 min and gives only C-3 product. Thus, the C-3 pathway is catalyzed by weak acids and protic solvents.

A similar analysis can be made for the C-2 pathway. Reaction of diethylamine with **7** at room temperature in dichloromethane gives only the C-3 product (Table 6). Addition of 1 equiv of diethylammonium mesylate gives 14% of the C-2 product. Reaction of **7** with diethylamine in methanol gave 84% of the C-2 product and shortens the reaction time to less than 10 min (Table 7). Thus, the C-2 path is also catalyzed by weak acids and protic solvents.

One difference between these two pathways is that the C-2 pathway is favored at low temperatures, whereas the C-3 pathway is favored at higher temperatures. While it might appear that this results from a kinetic vs thermodynamic partitioning, the C-2 and C-3 products do not interconvert under the reaction conditions. While there are obviously different activation barriers for the two pathways, the product formation steps are irreversible. Thus, both pathways must be multistep processes involving intermediates.

(18) Baumgarten, H. E. *J. Am. Chem. Soc.* **1962**, *84*, 4975.

SCHEME 5



Nucleophilicity also plays an important role in these pathways. Poor nucleophiles such as alcohols or mesylate give only the C-3 product, irrespective of whether acids are present or not. Better nucleophiles such as unhindered amines are capable of adding to the acyl carbon and give C-2 products. The nucleophilicity of bulkier amines is reduced, and they give only C-3 products. Diethylamine and *tert*-amylamine fall in a middle ground and give mixtures of C-2 and C-3 products. Furthermore the amount of C-2 product does not increase in a first-order fashion for these amines reacting with **7** as it did for the reactions of the less hindered **3**.[12] Thus, it is fair to say that direct attack on the C-2 carbon is not possible for **7** because the phenyl and *tert*-butyl groups block nucleophilic approach to the acyl carbon. In order for C-2 attack to be successful, the acyl group of **7** must be activated by acid catalysis.

A reaction mechanism based on these requirements is pictured in Scheme 5. Two distinct protonated species are proposed. One is an O-protonated (or hydrogen bonded) α-lactam **7-OH**. The second is an N-protonated (or hydrogen bonded) α-lactam **7-NH**. These protonated species do not interconvert directly. The N-H proton in **7-NH** is nearly orthogonal to the lone pair on oxygen while the O-H proton in **7-OH** is anti and orthogonal to the lone pair on nitrogen.[19] To interconvert they must pass through the unprotonated α-lactam **7**. The product formation steps are irreversible.

The proposed mechanism shows that O-protonation **7-OH** leads to C-2 attack while N-protonation **7-NH** leads to C-3 attack. Two factors led to this choice. First the effect of temperature requires that the less stable protonated form gives the C-2 product. Calculations on 1,3,3-trimethylazridinone have shown that the N-protonated species is of slightly lower energy than the anti O-protonated species. This difference should be greater for **7**, which has a conjugating phenyl group at C-3.[13] Thus, if **7-OH** is of higher energy than **7-NH**, then it is the intermediate that leads to the C-2 product.

Second, protonation on oxygen causes significant flattening of the nitrogen atom in **7-OH** (it is pyramidal in the unprotonated compound).[14] This would reduce steric hindrance to nucleophilic attack at C-2 and should facilitate C-2 addition relative to the unprotonated α-lactam. Conversely, protonation on nitrogen should cause little change in the steric environment of the carbonyl group and C-2 addition should be sterically retarded as it is in the unprotonated α-lactam.

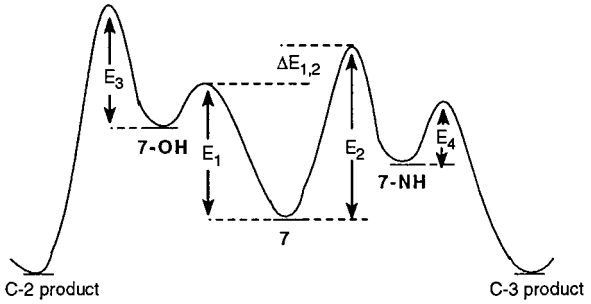


FIGURE 4. Energy diagram for the reaction of **7** with nucleophiles.

This mechanistic assignment differs from the theoretical study of the reaction of protonated 1,3,3-trimethylaziridinone with chloride ion. [14] In that study, four transition states were located for chloride addition to C-2 or C-3 of N-protonated and O-protonated species in the gas phase. Significant H-bonding between the protonated species and the chloride ion nucleophile appears to play an important role in the transition state energies amd structures. It was concluded that C-3 attack on the anti-O-protonated form had the lowest energy barrier, and C-2 attack on the N-protonated form was energetically favored for C-2 addition. In the present case, particularly where general acid catalysis is observed, there should be minimal H-bonding with the incoming nucleophile. Moreover, steric effects are probably much more important for reactions of **7** with amines than for the reaction of 1,3,3-trimethylaziridinone with chloride ion. Thus, it is not unreasonable that the mechanisms of the two systems have different energy profiles.[20]

An energy diagram consistent with this mechanism is shown in Figure 4. Assuming that the N-protonated species is of lower energy than the anti-O-protonated species, the temperature data suggest that the energy barrier for O-protonation is lower than the energy barrier for N-protonation. The lower barrier for O-protonation means that at lower temperatures, it is possible to achieve equilibrium between **7** and **7-OH** but not between **7** and **7-NH**. Thus, the concentration of **7-OH** is greater than the concentration of **7-NH** at low temperature.[19]

The energy barrier (E_3) for nucleophilic attack at C-2 of **7-OH** is significant because of steric hindrance despite the activation by protonation. At lower temperature where **7** and **7-OH** are in equilibrium, the Curtin−Hammett principle applies. Thus, E_3, the energy barrier for acyl attack on **7-OH**, must be less than E_2, the energy barrier for protonation of **7** ($E_3 < E_2$), because the C-2 process proceeds but N-protonation and hence the C-3 process does not. As the temperature increases, the protonation equilibrium between **7** and **7-NH** can be established and the concentration of **7-NH** increases because of its greater stability. Protonation on nitrogen makes C-3 susceptible to attack by even weak nucleophiles. The energy barrier for nucleophilic attack on C-3

(19) The syn protonated form of **7-OH** is about 2 kcal/mol higher in energy than the anti form shown in Scheme 5,[14] and the proton is nearly orthogonal to the lone pair on nitrogen as well.

(20) How much greater is not known because the relative energies of **7-OH** and **7-NH** are not known. The temperature dependence suggests, however, that the difference in concentration is large.

(E_4) is small and **7-NH** proceeds rapidly to the C-3 product. The rapid conversion of **7-NH** to product shifts the protic equilibrium toward **7-NH** and the C-3 product becomes favored at higher temperatures.

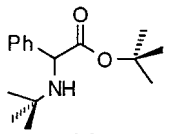
The data in Table 7 illustrates these considerations. The use of low temperature, methanol solvent, and the ammonium salt as an acid catalyst would favor the C-2 process. Thus, for diethylamine and *tert*-amylamine, only the C-2 product is observed under these conditions. The use of higher temperature and the less acidic *tert*-butyl alcohol as solvent produces only the C-3 product for these same amines. Thus the energy barrier E_3 for these two amines is smaller than, but comparable to, E_2 as shown in Figure 4.

The nucleophile also plays an important role in determining the regiochemistry in reactions of **7**. Good nucleophiles lower the energy barrier E_3 between **7-OH** and the C-2 product (Figure 4) and make the C-2 process faster. If the nucleophile is very good, E_3 can become sufficiently low that N-protonation and, hence, the C-3 process cannot compete. Thus, in Table 7, isopropylamine is a better nucleophile than *tert*-amylamine (both primary) by virtue of its smaller size so that even under conditions favoring the C-3 process, some C-2 product is found. Poor nucleophiles (bulky or otherwise poor, e.g., MsO^-) result in an increase in E_3. If E_3 becomes much larger than E_2, then the C-2 process does not compete and the C-3 product is favored. Thus, in Table 7, *N*-methyl-*tert*-butylamine is a poorer nucleophile than diethylamine (both secondary) by virtue of its steric bulk so that even under conditions favoring the C-2 process, very little C-2 product is obtained.

The mechanism shown in Scheme 5 shows activation by protonation of either oxygen or nitrogen. Such activation does not require complete proton transfer to be effective. Similar arguments can be made for activation of the acyl carbon by hydrogen bonding to the oxygen or activation of the C-3 carbon by hydrogen bonding to nitrogen. In fact, the rate accelerations seen for ammonium salts and alcohol solvents suggest that general acid catalysis or H-bonding rather than complete proton transfer is the dominant mode of catalysis under the conditions investigated. Theoretical investigations have shown that hydrogen bonding to either the oxygen or nitrogen of 1,3,3-trimethylazridinone result in similar (but less developed) changes in structure as complete proton transfer.[14]

This scenario is consistent with several observations of the system. At low temperatures, the addition of ammonium salts or more acidic solvents increases the concentration of **7-OH** and the rate of conversion to the C-2 product increases. (At low temperatures, protonation of nitrogen is not competitive.) At higher temperatures, only protic solvents are needed to give sufficient quantities of **7-NH** for reaction by the C-3 pathway. Greater amounts of stronger acids increase the concentration of both **7-OH** and **7-NH** and some of the **7-OH** could form the C-2 product.

This scenario also explains the stringent moisture control necessary in the synthesis of **7**. Although not emphasized in the literature,[18] we found that if freshly dried ether and freshly sublimed potassium *tert*-butoxide were not used, the product **7** was contaminated with significant amounts of *tert*-butyl amino ester **12**. It appears that even trace amounts of water activate the acyl carbon by protonation or H-bonding toward nucleophilic attack by *tert*-butoxide.



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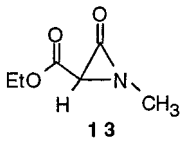
The competing pathways in Scheme 5 are independent of whether the nucleophile is protic or aprotic, but only depend on the nucleophilicity of the nucleophile, the presence of Bronsted acids (general or specific) and/or protic solvents, and the temperature. This mechanism is thus a departure from earlier mechanisms in which the protic nature of the nucleophile and competing C-2 and C-3 attacks were invoked.[1,2,7,10]

It is important to note that the mechanism in Scheme 5 was developed for α-lactam **7**. This α-lactam is sterically stabilized, and thus, direct nucleophilic attack on the acyl carbon is greatly retarded. This also translates to a significant energy barrier E_3 between **7-OH** and the C-2 product. Furthermore, the phenyl group at C-3 facilitates positive charge development at C-3. Thus, **7** is structurally set up to favor the C-3 process.

It is likely that the same general pathways are present in the reactions of α-lactams that lack steric stabilization. In such cases, acyl attack is much faster, i.e., the energy barrier E_3 between the O-protonated (or H-bonded) α-lactam and its C-2 product is low. In fact, for good nucleophiles there is the additional pathway of direct nucleophilic attack on the acyl carbon of the unprotonated (or non-H-bonded) α-lactam. This is the case for α-lactam **3**, which undergoes direct nucleophilic attack at C-2 by *tert*-butylamine.[13] Nevertheless, very bulky nucleophiles can increase energy barrier E_3 to the point that the C-3 process becomes competitive.[12]

Groups at C-3 that do not stabilize electron deficiency at the C-3 carbon should raise the barrier E_2 for N-protonation and thus slow the C-3 pathway. This is precisely the behavior of α-lactam **13**, which gives no C-3 products, even with very bulky amine nucleophiles. Only C-2 products are found.[13]



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In summary, the mechanism developed in Scheme 5 and the energy diagram in Figure 4 are very useful for understanding the changes in rates and product distributions in the reactions of sterically stabilized α-lactams with nucleophiles. They also can be extrapolated to other α-lactams so that a more coherent picture of α-lactam reactivity can be developed.

Experimental Section

General Methods. Ether was distilled from benzophenone ketyl. Pentane and dichloromethane were dried and distilled from P_2O_5. Acetonitrile was dried with CaH_2 and distilled. Alcohols were dried using magnesium turnings and distilled.

Potassium *tert*-butoxide was freshly sublimed. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Melting points are uncorrected. Thin-layer chromatography was performed on silica gel 60 F254 plates and visualized by UV irradiation or vanillin in a mixture of methanol and sulfuric acid. *N*-Mesyloxyamide **6**[11e] and *N*-*tert*-butyl-2-bromophenylacetamide **8**[16] were prepared by literature procedures.

General Procedure for Preparing Ammonium Mesylate Salts. Methanesulfonic acid (25 mmol) in 10 mL of ethyl acetate was added over a period of 20 min to a 0 °C solution of the amine (25 mmol) in 30 mL of ethyl acetate. The mixture was stirred for an additional 10 min. The solvent was evaporated. The products were recrystallized.

Diethylammonium mesylate was obtained as an oil in 90% yield after low-temperature recrystallization from acetone: ^{1}H NMR δ 1.38 (t, 6H, J = 7.28 Hz), 2.77 (s, 3H), 3.04 (m, 4H), 8.95 (bs, 2H).

***tert*-Amylammonium mesylate** was obtained as a white solid in 93% yield after recrystallization from ethyl acetate: mp 103−104 °C; ^{1}H NMR δ 0.98 (t, 3H, J = 7.56 Hz), 1.36 (s, 6H), 1.72 (q, 2H), 2.79 (s, 3H), 7.50 (bs, 3H).

General Procedure for the Reaction of 6 with Amines. To a 0 °C solution of *N*-mesyloxyamide **6** (130−250 mg, 0.456−0.876 mmol) in dichloromethane (10 mL) was added a neat amine (1.03−1.97 mmol). The reaction mixture was stirred at room temperature until TLC analysis showed no starting material to be present (hexane/ethyl acetate = 4:1). After rotary evaporation, the residue was treated with 1.0 M potassium carbonate (10 mL) and extracted with ethyl acetate (2 × 10 mL). The organic extracts were washed with water (2 × 10 mL) and brine (10 mL) and dried (MgSO4). After rotary evaporation, the crude products were placed under high vacuum for several hours. ^{1}H NMR was used to measure the product ratio by measuring the relative height of the *tert*-butyl group of the C-2 product (δ = 1.1) and the C-3 product (δ = 1.3). The results are collected in Table 1. Individual regioisomers were separated and characterized.

Reaction of 6 with isopropylamine gave a mixture of **10a** and **11a** (27.6:1) in 88% crude yield. These were separated by flash chromatography (hexane/ethyl acetate = 4/1).

10a was obtained as a white solid in 80% yield: mp 66−67 °C; ^{1}H NMR δ 1.048 (s, 9H), 1.10 (s, 3H), 1.14 (s, 3H), 4.19 (s, 1H), 3.95−4.12 (m, 1H), 7.22 (m, 5H), 7.75 (bs, 1H); ^{13}C NMR δ 172.79, 140.85, 128.95, 127.70, 127.19, 61.71, 52.02, 40.77, 29.28, 22.95, 22.60; IR 3296, 1651 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 73.02; H, 9.16; N, 11.29.

11a was obtained as a white solid in 3% yield: mp 67−68 °C; ^{1}H NMR δ 1.36 (s, 9H), 1.10 (d, 3H, J = 1.3), 1.07 (d, 3H, J = 1.5), 2.81 (septet, 1H, J = 6.3), 4.08 (s, 1H), 7.32 (m, 5H), 7.75 (bs, 1H); ^{13}C NMR δ 171.87, 140.76, 128.66, 127.61, 127.04, 66.25, 50.42, 48.42, 28.64, 23.26, 23.02; IR 3404, 1645 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C 72.42; H 9.57; N, 11.12.

Reaction of 6 with pyrrolidine gave a mixture of **10b** and **11b** (21.1:1) in 93% crude yield.

10b was obtained as a crystalline solid in 79% yield after recrystallization (ethyl acetate) of the crude product: mp 148−149 °C; ^{1}H NMR δ 1.13 (s, 9H), 1.81 (m, 4H), 3.22 (m, 1H), 3.54 (m, 3H), 4.40 (s, 1H), 7.31 (m, 5H); ^{13}C NMR δ 172.34, 140.82, 128.93, 127.80, 127.46, 58.79, 51.42, 46.30, 46.12, 29.61, 26.08, 24.13; IR 2976, 1636 cm^{-1}. Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.71; H, 9.09; N, 10.68. **11b** was not isolated.

Reaction of 6 with piperidine gave a mixture of **10c** and **11c** (7.04:1) in 81% crude yield. These were separated by flash chromatography (hexane/ethyl acetate = 5/1).

10c was obtained as a white solid in 66% yield: mp 95−96 °C; ^{1}H NMR δ 1.15 (s, 9H), 1.47−1.53 (m, 6H), 3.31−0.3.35 (m, 2H), 3.55−5.59 (m, 2H), 4.57 (s, 1H), 7.23 (m, 5H); ^{13}C NMR δ 171.72, 141.39, 128.62, 127.12, 126.89, 56.61, 50.91, 46.02, 43.38, 29.29, 25.56, 25.22, 24.25; IR 1631 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55; N, 10.21. Found: C, 74.29; H, 9.46; N, 10.11.

11c was obtained as a white solid in 9% yield: mp 107−108 °C; ^{1}H NMR δ 1.36 (s, 9H),1.41−1.58 (m, 6H), 2.32 (t, 4H, J = 5.14), 3.70 (s, 1H), 7.26−7.28 (m, 5H); ^{13}C NMR δ 170.99, 136.55, 129.09, 128.34, 127.79, 52.80, 50.55, 18.82, 26.51, 24.40; IR 3415, 1661 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55; N, 10.21. Found: C, 74.28; H, 9.86; N, 10.21.

Reaction of 6with morpholine gave a mixture of **10d** and **11d** (6.7:1) in 90% crude yield. These were separated by flash chromatography (hexane/ethyl acetate = 5/1).

10d was obtained as a white solid in 73% yield: mp 96−97 °C; ^{1}H NMR δ 1.12 (s, 9H), 3.15−3.59 (m, 8H), 4.52 (s, 1H), 7.23−7.32 (m, 5H); ^{13}C NMR δ 172.53, 141.02, 128.92, 127.35, 127.22, 66.36, 56.99, 51.12, 45.96, 29.48; IR 3296, 1650 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H 8.75; N, 10.14. Found: C 69.70; H 8.66; N, 10.10.

11d was obtained as a white solid in 11% yield: mp 138−139 °C; ^{1}H NMR δ 1.35 (s, 9H), 2.41 (m, 4H), 3.68 (s, 1H), 3.70 (m, 4H), 6.97 (bs, 1H), 7.31 (s, 5H); ^{13}C NMR δ 169.80, 135.79, 128.60, 128.43, 128.02, 66.95, 52.06, 50.58, 28.60; IR 3436, 1662 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H 8.75; N, 10.14. Found: C, 69.69; H, 8.63; N, 9.96.

Reaction of 6 with 1-adamantylmethylamine gave a mixture of **10e** and **11e** (5.45:1) in 89% crude yield.

10e was obtained as a crystalline solid in 76% yield after recrystallization of the crude product (ethyl acetate): mp 153−154 °C; ^{1}H NMR δ 1.14 (s, 9H), 1.49−1.97 (m, 15H), 2.96 (d, 2H J = 6.22), 4.34 (s, 1H), 7.26−7.34 (m, 5H), 8.03 (bs, 1H); ^{13}C NMR δ 173.93, 141.99, 129.32, 128.20, 127.74, 62.27, 52.27, 51.31, 40.74, 37.40, 34.31, 29.68, 28.69; IR 1651 cm^{-1}. Anal. Calcd for $C_{23}H_{34}N_2O$: C, 77.92; H 9.67; N, 7.90. Found: C, 77.68; H 9.49; N, 7.98. **11e** was not isolated.

Reaction of 6 with diethylamine gave a mixture of **10f** and **11f** (0.20:1) in 86% crude yield. These were separated by flash chromatography (hexane/ethyl acetate = 4/1).

10f was obtained as a white solid in14% yield: mp 47−48 °C; ^{1}H NMR δ 1.01 (t, 3H, J = 7.14), 1.11 (t, 3H, J = 7.10), 1.12 (s, 9H), 3.02−3.50 (m, 4H), 7.24−7.29 (m, 5H); ^{13}C NMR δ 12.68, 14.00, 29.61, 40.75, 41.55, 51.51, 57.35, 127.42, 127.62, 129.05, 141.49, 172.80; IR 3026, 2970, 1682 cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 73.50; H, 9.85; N, 10.71.

11f was obtained as a white solid in 67% yield: mp 65−66 °C; ^{1}H NMR δ 0.99 (t, 6H, J = 7.10), 1.36 (s, 9H), 2.29−2.47 (sextet, 2H, J = 6.96), 2.54−2.72 (sextet, 2H, J = 7.08), 4.09 (s, 1H), 7.27−7.32 (m, 5H); ^{13}C NMR δ 11.88, 28.79, 43.75, 50.63, 72.35, 127.80, 128.29, 129.41, 136.44, 171.57; IR 3018, 2976, 1691 cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 73.30; H, 9.77; N, 10.73.

Reaction of 6 with *tert*-amylamine gave a mixture of **10g** and **11g** (0.18:1) in 91% crude yield. These were separated by flash chromatography (hexane/ethylethyl acetate = 4/1)

10g was obtained as a solid in 12% yield: mp 71−72 °C; ^{1}H NMR δ 0.86 (t, 7.40, 3H), 1.13 (s, 9H), 1.32 (s, 3H), 1.34 (s, 3H), 1.74 m, 2H), 4.18 (s, 1H), 7.30 (m, 5H), 7.85 (bs, 1H); ^{13}C NMR δ 8.31, 26.07, 29.13, 34.22, 51.85, 53.03, 62.11, 127.03, 127.52, 128.76, 141.94, 172.68; IR 3056, 1681 cm^{-1}. Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.84; H, 10.05; N, 9.81.

11g was obtained as a solid in 68% yield: mp 69−70 °C; ^{1}H NMR δ 0.83 (t, 3H, J = 7.32), 1.03 (s, 3H), 1.08 (s, 3H), 1.38 (m, 2H), 4.12 (s, 1H), 7.28 (m, 5H), 7.86 (bs, 1H); ^{13}C NMR δ 8.31, 25.59, 26.84, 28.57, 34.50, 50.26, 54.17, 61.76, 127.03, 127.46, 128.78, 141.93, 172.97; IR 3415, 3029, 1661 cm^{-1}. Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.04; H, 9.97; N, 9.69.

Reaction of 6 with diisopropylamine gave a mixture of **10h** and **11h** (0.16:1) in 83% crude yield.

11h was obtained as a white solid in 68% yield after flash chromatography (hexane/ethyl acetate = 7:3): mp 89−90 °C; ^{1}H NMR δ 0.82 (d, 3H, J = 6.58 Hz), 1.12 (d, 3H, J = 6.68 Hz), 1.42 (s, 9H), 3.23 (m, 2H), 4.51 (s, 1H), 7.27 (s, 5H), 7.78 (bs, 1H); ^{13}C NMR δ 174.32, 139.42, 130.98, 128.47, 127.48, 64.80, 51.14, 47.06, 29.27, 24.23, 21.56; IR 3315, 2967, 1661 cm^{-1}. Anal. Calcd for $C_{18}H_{30}N_2O$: C, 74.44; H, 10.41; N, 9.65. Found: C, 74.42; H 9.95; N, 9.42. **10h** was not isolated.

Reaction of 6 with dicyclohexylamine gave a mixture of **10i** and **11i** (0.10:1) in 81% crude yield.

11i was obtained as a white solid in 69% yield after flash chromatography (hexane/ethyl acetate = 3/1): mp 109−110 °C; ^{1}H NMR δ 0.99−1.82 (m, 20H), 1.41 (s, 9H), 2.66 (m, 2H), 4.56 (s, 1H), 7.26 (s, 5H), 7.85 (bs, 1H); ^{13}C NMR δ 174.46, 139.99, 130.87, 128.32, 127.40, 65.62, 57.06, 51.16, 35.28, 33.31, 29.32, 27.38; IR 2927, 1666 cm^{-1}. Anal. Calcd for $C_{24}H_{38}N_2O$: C, 77.79; H, 10.34; N, 7.56. Found: C, 77.64; H, 10.12; N, 7.48. **10i** was not isolated.

Reaction of 6 with 1-adamantanamine gave a mixture of **10j** and **11j** (0.083:1) in 86% crude yield.

11j was obtained as a white solid in 67% yield after recrystallization (methanol−water): mp 101−102 °C; ^{1}H NMR δ 1.38 (s, 9H), 1.58−1.75 (m, 12H), 2.07 (bs, 3H), 4.29 (s, 1H), 7.26−7.29 (m, 5H), 7.97 (bs, 1H); ^{13}C NMR δ 173.04, 142.11, 128.75, 127.16, 59.86, 51.87, 50.25, 42.97, 36.28, 29.29, 28.55; IR 3414, 1661 cm^{-1}. Anal. Calcd for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23; Found: C, 77.73; H, 9.29; N, 8.31. **10j** was not isolated.

Reaction of 6 with *N*-methyl-*tert*-butylamine gave only **11k** in 89% crude yield. **11k** was obtained as a white solid in 78% yield after flash chromatography (hexane/ethyl acetate = 3/1): mp 88−89 °C; ^{1}H NMR δ 1.17 (s, 9H), 1.42 (s, 9H), 1.99 (s, 3H), 4.58 (s, 1H), 7.15−7.29 (m, 5H), 7.921 (bs, 1H); ^{13}C NMR δ 172.85, 137.75, 130.23, 127.77, 126.90, 66.49, 55.29, 50.18, 32.17, 28.55, 27.17; IR 3435, 1661 cm^{-1}. Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.84; H, 10.05; N, 9.81.

N-*tert*-Butyl-3-phenylaziridinone 7. A stirred suspension of freshly sublimed potassium *tert*-butoxide (0.5516 g, 4.913 mmol) in dry ether (40 mL) was added over a period of 1 h to a well-stirred solution of **8** (1.021 g, 3.779 mmol) in dry ether (70 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was filtered quickly. The filtrate was placed on a rotary evaporator, and the solvent was removed. The residue was recrystallized from dry pentane at −18 °C. α-Lactam **7** was obtained as a white crystalline solid in 65% yield: mp 32−33 °C; IR 1845 cm^{-1}; ^{1}H NMR δ 1.37 (s, 9), 3.87 (s, 1H), 7.34 (s, 5H). The physical properties of the product are identical to literature values.[16] Pure **7** can be stored for at least 1 month at −18 °C, but only a few days at room temperature.

Effect of Temperature on Reactions of 6 and 7. Mesyloxyamide **6** (20−40 mg, 0.07−0.14 mmol) in dichloromethane (5 mL) was added to a solution of diethylamine (0.157−0.315 mmol) in dichloromethane (5 mL) at −18, 0, +23, or +40 °C. The reaction mixture was stirred until TLC showed no starting material present. After rotary evaporation, the residue was treated with 1 M potassium carbonate (10 mL) and extracted with ethyl acetate (2 × 10 mL). The organic extracts were washed with water (2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). After rotary evaporation, the crude product was placed under high vacuum for several hours. ^{1} H NMR was used to measure the ratio of the C-2 and C-3 regioisomers by measuring the relative height of the *tert*-butyl groups at δ = 1.1 (C-2) and 1.3 (C-3) in the crude product. The results are presented in Figure 1.

In a similar sets of experiments, α-lactam **7** (15−30 mg, 0.0792−0.158 mmol) and diethylammonium mesylate (13.4−26.7 mg, 0.0792−0.158 mmol) in dichloromethane (3 mL) were added to a solution of diethylamine (10−20 (L, 0.0991−0.197 mmol) in dichloromethane (5 mL) at −18, 0, +23, and +40 °C. This gave a final molar ratio of 1:1.25:1 of **7**/amine/salt, which was the same as the final ratio used for **6**. The mixture was stirred for 3 h. After rotary evaporation, the residue was treated with 1 M potassium carbonate (10 mL) and extracted with ethyl acetate (2 × 10 mL). The organic extracts were washed with water (2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). After rotary evaporation, the crude product was placed under high vacuum for several hours. ^{1} H NMR was used to measure the ratio of the C-2 and C-3 regioisomers in the crude product. The results are presented in Figure 1.

A second comparison was done using *tert*-amylamine and *tert*-amylammonium mesylate as the amine and salt, respectively, and similar results were obtained.

Effect of Amine Concentration on Reactions of 6 and 7. -Sulfonoxyamide **6** (25 mg, 0.0876 mmol) in dichloromethane (5 mL) was added to a solution of diethylamine (0.197, 0.394, 0.788, and 1.183 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C until TLC showed no starting material to be present. The reaction was worked up as above. Changes of the product ratio were observed as a function of amine concentration. The results are presented in Figure 2.

In a similar set of experiments, a solution of **7** (17 mg, 0.0898 mmol) and diethylammonium mesylate (0.0898 mmol) in dichloromethane (3 mL) was added to a solution of diethylamine (0.112, 0.314, 0.718, 1.122 mmol) in dichloromethane (5 mL) at 0 °C over a period of 1.5 h. The mixture was stirred at 0 °C for 3 h. The reaction was worked up as above. The results are presented in Figure 2.

A similar set of experiments using *tert*-amylamine gave similar results.

Effect of Ammonium Salt Concentration on Reactions of 6 and 7. *N*-Sulfonyloxyamide **6** (40 mg, 0.14 mmol) and diethylammonium mesylate (0.315, 0.63, 1.26, 1.89, mmol) in dichloromethane (5 mL) were added to a solution of diethylamine (0.315 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C until TLC showed no starting material to be present. The reaction was worked up as above. Changes of the product ratio were observed as a function of ammonium mesylate salt concentration. The results are shown in Figure 3.

In a similar set of experiments, α-lactam **7** (30 mg, 0.158 mmol) and diethylammonium mesylate (0.513, 0.869, 1.58, 2.29 mmol) in dichloromethane (5 mL) was added to a solution of diethylamine (20 (L, 0.197 mmol) in dichloromethane (5 mL) at 0 °C over a period of 1.5 h. The mixture was stirred at 0 °C for 3 h. The reaction was worked up as above. The results are presented in Figure 3.

A set of experiments using *tert*-amylamine and *tert*-amylammonium mesylate gave similar results.

NMR Monitoring of Reaction Times. The time required for the disappearance of the α-lactam was determined by monitoring ^{1}H NMR peaks at δ 3.87 and 1.37. Different reaction conditions were evaluated by adding **7** to deuterated solvent (0.75 mL) containing nucleophiles and/or acid catalysts to be evaluated. The mixture was well shaken and kept at a specified temperature (either room temperature or 0 °C). The tube was periodically placed in the NMR probe and the spectrum recorded. The reaction time was taken as the time required for complete disappearance of the starting material.

Effect of Diethylammonium Mesylate α-Lactam **3** (26 mg, 0.14 mmol) was added to an NMR tube containing diethylamine (18 μL, 0.17 mmol) and diethylammonium mesylate (0.14 mmol) in CD_2Cl_2 at room temperature. A similar reaction mixture that did not contain diethylammonium mesylate was used for comparison. A similar set of experiments was carried out using *tert*-amylamine and *tert*-amylammonium mesylate. The results are collected in Table 2.

Effect of Specific Acid. α-Lactam **3** (37 mg, 0.195 mmol) was added to a mixture of methanol (10 μL, 0.24 mmol) and methanesulfonic acid (4μL, 0.054 mmol) in CD_2Cl_2 at room temperature. A similar reaction mixture that did not contain methanesulfonic acid was run for comparison.

α-Lactam **3** (35 mg, 0.185 mmol) was added to a solution of methanesulfonic acid (4 μL. 0.054 mmol) in 2-propanol-d_8 at room temperature. Reaction of **3** in 2-propanol-d_8 was used for comparison. The results are shown in Table 3.

Effect of Protic Solvents α-Lactam **3** (20 mg, 0.106 mmol) was added to methanol-d_4, ethanol-d_6, 2-propanol-d_8, and *tert*-butyl alcohol-d_{10} at room temperature. For comparison, α-lactam **3** (20 mg, 0.106 mmol) was added to solutions of diethylamine (14 μL, 0.132 mmol) in CD_2Cl_2, acetonitrile-d_3, and 2-propanol-d_8 at room temperature. The results are collected in Table 4.

Reaction **3** (0.16 mmol) with diethylamine (0.2 mmol) in 3.0 mL solutions of methanol, ethanol, 2-propanol, and *tert*-butyl alcohol were carried out at room temperature. The solvent was evaporated, and the residue was worked up as described above. The ratio of the C-2/C-3 isomers in the crude product was measured by NMR. The results are collected in Table 5.

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