# Base-Promoted Ring-Opening and Elimination of 4-Chloro- and 4-(Methylthio)azetidinones

S. Nagaraja Rao and R. A. More O'Ferrall*

*Department of Chemistry, University College, Belfield, Dublin 4, Ireland*

*Received December 12, 1989*

In a search for elimination within the β-lactam ring, reactions of *N*-phenyl- and *N*-benzyl-, 4-chloro-, and 4-(methylthio)azetidinones with sodium methoxide in methanol have been investigated. The products formed are enamine esters, consistent with the occurrence of both an elimination reaction and opening of the β-lactam ring. Substituent and leaving-group effects indicate, however, that ring-opening is the first and rate-controlling reaction and that elimination occurs from an initially formed ring-opened intermediate. Thus a small leaving-group rate ratio ($k_{Cl}/k_{SMe}$) and insensitivity of the rate to the stereochemistry of *cis*- and *trans*-3-(tosyloxy)-4-chloro substituents rule out elimination by a concerted mechanism (E2), while similar substituent effects at the 3- and 4-positions, and reaction at the predicted rate for β-lactam methanolysis, exclude a carbanion mechanism (E1cB). Also, for the thiomethyl leaving group, 1,2-rearrangement, a reaction almost certainly occurring after ring-opening, competes with elimination. For β-lactams with a 4-chloro substituent and a relatively basic nitrogen atom, solvolysis accompanies ring-opening, but substitution and not elimination products are formed. It is concluded that more effective carbanion and double bond stabilizing substituents than used in this investigation will be required to observe the sought for elimination.

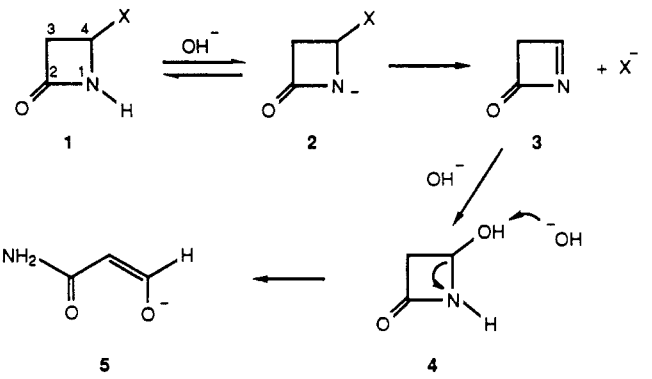
Nucleophilic attack upon the β-lactam ring normally occurs at the carbonyl carbon atom and leads to opening of the ring.[1] When the ring contains a leaving group at the 4-position, however, nucleophilic displacement can also occur[2-5] and is exemplified by substitution of the readily available 4-acetoxyazetidinone (**1**, X = OAc) by sulfur[6] and oxygen[7] nucleophiles, which has provided initial steps in syntheses of a number of β-lactam antibiotics.[6-8]

The mechanism of these substitutions has been investigated by Fedor[3] who has shown that reaction occurs by an E1cB elimination-addition pathway in which an azetidinone anion **2** and, by implication, a 1,4-unsaturated azetinone[9] **3** are intermediates, as shown in Scheme I. In aqueous sodium hydroxide the initial product is probably the 4-hydroxyazetidinone **4**, which fragments to the 3-hydroxyacrylamide anion (**5**, $pK_a$ = 9.3).

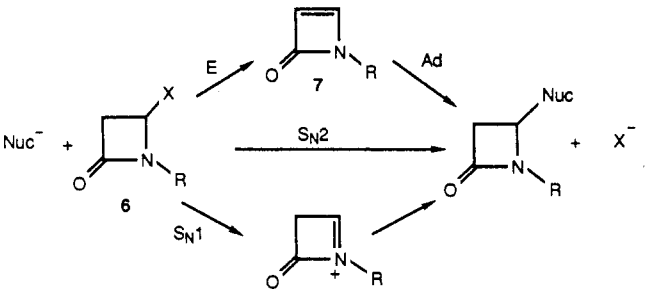
Fedor's mechanism applies when the nitrogen of the β-lactam ring bears a hydrogen atom. For *N*-alkyl or *N*-aryl β-lactams **6**, substitution at the 4-position must involve either elimination-addition via an azetinone containing a 3,4 carbon-carbon double bond **7** or direct displacement by $S_N2$ or $S_N1$ mechanisms, as shown in Scheme II. The elimination-addition pathway would again presumably occur by an E1cB mechanism, but with anion formation now occurring at the 3- rather than the 1-position.

The possibility of carbon-carbon double bond formation within a β-lactam ring is suggested by the known tendency of penicillins with electron-withdrawing substituents such as *p*-nitrophenylimino or phthalimido at the 6-position to undergo base-promoted rearrangement to thiazepinones,[10] a reaction for which the azetinone **9** is reasonably proposed as an intermediate (Scheme III).[11] Although the only

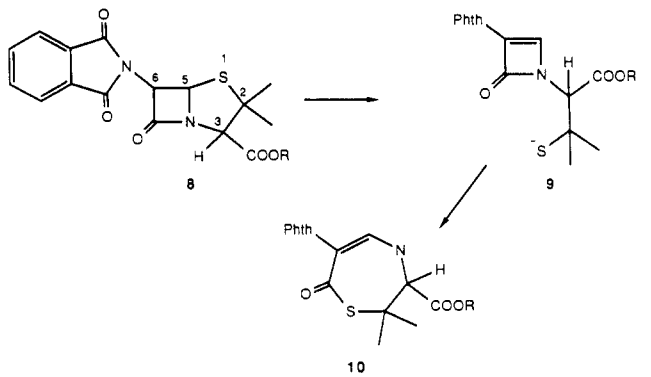
**Scheme I**



**Scheme II**



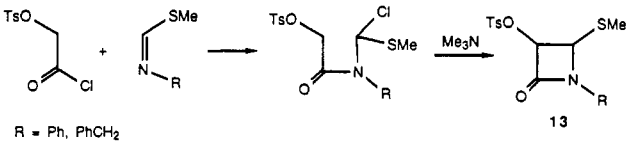
**Scheme III**



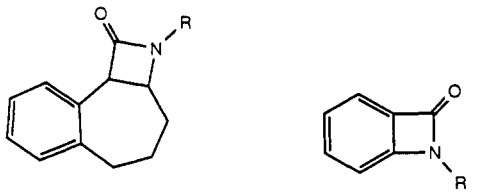
(1) Page, M. I. *Adv. Phys. Org. Chem.* **1987**, *23*, 165-270.
(2) Claus, K.; Grimm, D.; Prossel, G. *Justus Liebigs Ann. Chem.* **1974**, *49*, 539-560.
(3) Fedor, L. R. *J. Org. Chem.* **1984**, *49*, 5094-5097.
(4) Wolfe, S.; Lee, W. S. Kannengiesser, G., Ducep, J.-B. *Can. J. Chem.* **1972**, *50*, 2894-2897.
(5) Wolfe, S.; Goeldner, M. P. *Tetrahedron Lett.* **1973**, *14*, 5131-5134.
(6) Schnabel, H. W.; Grimm, D.; Jensen, H. *Justus Liebigs Ann. Chem.* **1974**, 477-495.
(7) Bentley, P. H.; Hunt, E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2222-2227 and references cited.
(8) *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Wiley: New York, 1980; Vol. 4. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Chemical Society Special Publication, No. 28; Elks, J., Ed.; The Chemical Society: London, 1976; p 9.
(9) *Chemical Abstracts* refers to the unsaturated β-lactam ring as "azetone", but "azetinone" is consistently used in the organic chemical literature.
(10) Ramsey, B. G.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1971**, 450-452.

0022-3263/90/1955-3244$02.50/0 

**Scheme IV**




confirmed example of a 3,4-unsaturated β-lactam (detected spectroscopically[12]) appears to be **11**, azetinones fused to benzene or pyridine rings (e.g., **12**) are well-known.[13,14] The




R = adamantyl

**11** **12**

parent structure has been the subject of a number of theoretical calculations.[15]

The purpose of the present investigation was to establish the scope of 3,4-eliminations in simple *N*-alkyl or *N*-aryl β-lactams. At the outset, it was recognized that, as a base-catalyzed reaction, elimination must compete with the normal mode of attack by base, upon the carbonyl group of the ring. In choosing a substrate for study it seemed reasonable that elimination would be favored by a good leaving group at the 4-position and a carbanion stabilizing substituent at the 3-position. However, as such substituents are normally electron withdrawing they will also, in some degree, favor reaction at the carbonyl group.

It is also likely that elimination and reaction at the carbonyl group would occur not only in competition but successively. Thus although in Scheme III elimination is the first step in formation of the thiazepinone **10**, it is followed by nucleophilic opening of the β-lactam ring. The ring-opening in this instance is intramolecular, and there is no ambiguity as to which reaction occurs first. However, in the absence of an internal nucleophile, ring-opening by a solvent or base molecule may occur, and indeed for the bicyclic azetinones **12** this is the observed reaction.[13] For monocyclic azetinones **7** attack of the nucleophile could occur at the carbon–carbon double bond as shown in Scheme II, but it could also take place at the carbonyl group. In the latter case, the product from elimination and ring-opening would be the same as from these reactions occurring in the reverse order and give no clue as to which took place first.

In practice, choice of substrates was determined largely by ease of synthesis. Substituted *N*-alkyl and *N*-aryl β-lactams are conveniently prepared by the reaction of acid chlorides with imines.[16-18] The efficiency of this reaction depends on the structure of the reactants, but toluenesulfonoxyacetyl chloride reacts with a variety of alkyl and aryl thioimidates (Scheme IV) to give azetidinones **13** containing SMe at the 4-position and OTs as 3-substituent.[16,17] These substituents have the advantage that SMe is easily converted to the more reactive chloro leaving group,[19] while the tosylate may be transformed to an azide which, on reduction and further reaction, yields the corresponding amine, amide, arylimine and isonitrile. This gives access to a combination of good and poor leaving groups (Cl and SMe) which might be expected to react by elimination and β-lactam ring-opening, respectively, together with a variety of moderately electron-withdrawing 3-substituents.

In this paper we describe measurements for *N*-benzyl and *N*-phenyl β-lactams containing tosyloxy and azido 3-substituents, and in a further paper[20] extend the study to a wider range of activating and leaving groups.

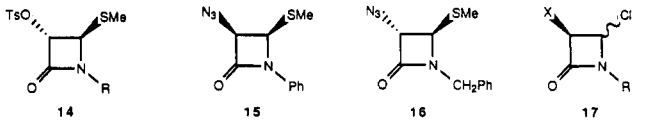
**Table I. Rate Constants for Reaction of 3,4-Substituted Azetidinones 18 in NaOMe–MeOH and NaOH–$H_2O$ at 25 °C**

| substituents[a] | | | | $10^2k$/L mol$^{-1}$ s$^{-1}$ | |
|---|---|---|---|---|---|
| 3-X | 4-Y | N-R | config | MeOH | $H_2O$ |
| OTs | $SCH_3$ | Ph | trans | 36.0 | |
| OTs | $SCH_3$ | $PhCH_2$ | trans | 2.5 | |
| $N_3$ | $SCH_3$ | Ph | cis | 85.0 | 50.0 |
| $N_3$ | $SCH_3$ | $PhCH_2$ | trans | 4.5[b] | |
| OTs | Cl | Ph | cis | 1650.0 | |
| OTs | Cl | Ph | trans | 1350.0 | |
| OTs | Cl | $PhCH_2$ | trans | 102.0 | 35.0[c] |
| $N_3$ | Cl | Ph | cis | 1030.0 | |
| $N_3$ | Cl | $PhCH_2$ | trans[d] | 100.0 | 90.0[c] |
| $N_3$ | Cl | $PhCH_2$ | trans[d] | 43.0[e] | |
| $N_3$ | Cl | $PhCH_2$ | trans[d] | 0.0018[f] | |

[a] Cf. structure **18** for substituent positions. [b] Rate constant less accurate than normal because of interference from further reaction of product (estimated error 20%). [c] 50:50 $H_2O$–$CH_3CN$. Poor solubility interfered with measurements in pure $H_2O$, but approximate rate constants differed by 20% only from this value. [d] Containing 15% cis isomer. [e] In MeOD, $k_{MeOD}/k_{MeOH}$ = 2.33. [f] First-order constant ($s^{-1}$) for solvolysis in MeOH.

## Results

**Syntheses.** Cycloaddition of tosyloxyacetyl chloride and *N*-phenyl or *N*-benzyl thioimidates as in Scheme IV gave 3-(tosyloxy)-4-(methylthio)azetidinones **14** which on reaction with sodium azide formed the corresponding 3-azido derivatives **15** and **16**.[16,17] NMR coupling constants




**14** **15** **16** **17**

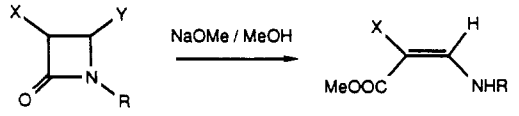
R = Ph, $PhCH_2$ R = Ph, $PhCH_2$; X = OTs, $N_3$

between the 3- and 4-hydrogens[16,21] indicated that the 3-(tosyloxy)azetidinones were trans in configuration and that the corresponding azides were cis for the *N*-phenyl derivative and trans for *N*-benzyl. Presumably the cis azide arose from $S_N2$ displacement of OTs and the trans from neighboring-group participation by SMe;[22] the latter reaction is perhaps favored by the more basic *N*-benzyl than *N*-phenyl β-lactam. Chlorinolysis of the methylthio

(11) Jackson, J. R.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1971**, 647–648.
(12) Olofson, R. A.; Morrison, D. S.; Banerji, A. *J. Org. Chem.* **1984**, *49*, 2653–2654.
(13) (a) Olofson, R. A.; Van der Meer, P. K.; Hoskin, D. H.; Bernheim, M. Y.; Stournas, S.; Morrison, D. S. *J. Org. Chem.* **1984**, *49*, 3367–3372.
(14) Bashir, N.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 868–872. Wentrup, C.; Gross, G. *Angew. Chem., Int Ed. Engl.* **1983**, *22*, 543.
(15) Nguyen, M. T.; Tae-Kyu Ha; More O'Ferrall, R. A. *J. Org. Chem.*, following paper in this issue.
(16) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 870–900.
(17) Lattrell, R.; Lohaus, G.; *Justus Liebigs Ann. Chem.* **1974**, 901–920.
(18) Bose, A. K.; Anjaneyulu, B.; Bhattacharya, S. K.; Manhas, M. S. *Tetrahedron* **1967**, *23*, 4769–4776. Bachi, M. D.; Goldberg, O. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2332.
(19) Kukolja, S. *J. Am. Chem. Soc.* **1971**, *93*, 6267. Sheehan, J. C.; Ben-Ishai, D.; Piper, J. U. *J. Am. Chem. Soc.* **1973**, *95*, 3064.
(20) Rao, S. N.; More O'Ferrall, R. A. *J. Am. Chem. Soc.*, in press.
(21) *Cephalosporins and Penicillins: Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972.
(22) Jackson, J. R.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 895.

groups[24] gave cis and trans chlorides **17** with predominant retention of configuration. The 3-azido chlorides were obtained as single isomers and the 3-tosyloxy as mixtures, which were separated by chromatography in the case of the *N*-phenyl substrate but not *N*-benzyl. Product configurations are summarized in Table I.

**Product Analyses.** Reactions of the 4-chloro and 4-(methylthio) 3-(tosyloxy)- and 3-azidozetidinones in methanolic sodium methoxide, methanolic triethylamine, and aqueous sodium hydroxide were investigated. The products from triethylamine in methanol were isolated and identified by NMR. For reaction of 4-chloro-3-azido and 3-toluenesulfonoxy azetidinones **17** mixtures of *E*- and *Z*-enamino esters **19** were obtained with *E* (probably)

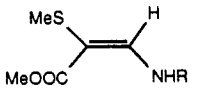



**18** **19**

X = OTs, $N_3$

R = Ph, $PhCH_2$

predominating. These are the products of β-lactam ring-opening and elimination of chloride ion. For the corresponding methylthio derivatives, however, additional products were observed arising from elimination of azide or tosylate and rearrangement of MeS, e.g., **20**.

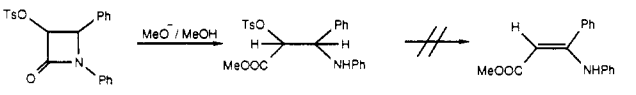



**20** E and Z

Product analyses were made with triethylamine as base rather than sodium methoxide, the base normally used in kinetic studies, because isolation of the products was easier. A check on the identity of the products from the two bases was provided by UV spectra which normally consisted of a peak and a shoulder[23] (probably corresponding to *E* and *Z* isomers) in the range 280–330 nm. For 4-chloroazetidinones UV spectra indicated that the products in the two basic media were the same. For the (methylthio)azetidinones, however, small but probably significant differences in $\lambda_{max}$ of product solutions were observed. With sodium methoxide the UV spectra were usually the same as from the corresponding chloroazetidinone, but for triethylamine they differed; e.g., for the *N*-phenylazetidinone $\lambda_{max}$ = 315 and 319 nm from NaOMe and $Et_3N$, respectively. This is consistent with base-promoted elimination leading to **19** being the dominant reaction for the stronger base (NaOMe) and rearrangement of the thiomethyl group (e.g., to give **20**) competing more effectively with elimination for the weaker base. For *N*-benzyl(tosyloxy)azetidinones, on the other hand, a difference in product spectra between methylthio and chloro leaving groups is observed even for sodium methoxide ($\lambda_{max}$ = 287 and 277 nm, respectively), although for *N*-phenyl azido substrates the methylthio and chloro products were the same in both sodium methoxide and triethylamine (327 nm). These observations suggest that rearrangement is also favored by *N*-benzyl relative to *N*-phenyl and 3-(tosyloxy) relative to 3-azido substituents.

The possibility was also considered that rearrangement of the methylthio group occurs intermolecularly, e.g., with expulsion of $MeS^-$ to form an imine following β-lactam ring-opening and then $S_N2$ displacement of the tosylate or azide. However, monitoring of the reactions under preparative conditions gave the same UV spectra as measured kinetically, where the concentration of substrate and $MeS^-$ would have been too small ($10^{-4}$ M) for a bimolecular reaction to occur.

Elimination of tosylate without participation of sulfur can also be excluded. Thus 4-phenyl-3-(tosyloxy)azetidinone **21** was found to undergo β-lactam ring-opening

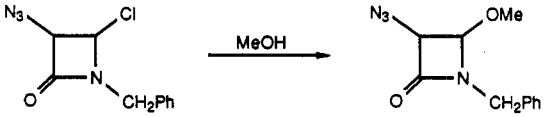



**21** **22**

without subsequent elimination,[24] even though the base used was sodium methoxide and the ring-opening ester might be expected to be more reative than the corresponding structure in which phenyl is replaced by $SCH_3$.

Although product analyses were not carried out in water, the similarity of the product UV spectra to those in methanol (e.g., $\lambda_{max}$ = 322 nm from $H_2O$ compared with 327 nm from MeOH for 4-(methylthio)- and 4-chloro-3-azido-*N*-phenylazetidinones, and 274 compared with 277 nm for 3-(tosyloxy)-*N*-benzyl) suggests that the products formed are enamino acid anions, i.e., **19** with the ester replaced by a carboxylate group.

**Kinetic Measurements.** Reactions of the azetidinones with base were kinetically first order in substrate and in base. Rate constants for methanolic sodium methoxide and aqueous sodium hydroxide are listed in Table I. Also in the table is a measurement in MeOD for *N*-phenyl-3-(tosyloxy)-4-chloroazetidinone, which yields a solvent isotope effect ($k_{MeOD}/k_{MeOH}$ = 2.33) consistent with reaction of methoxide ion as either a base or nucleophile.[25] In the absence of methoxide ion, *N*-benzyl-3-azido-4-chloroazetidinone **23** in methanol undergoes solvolysis leading




**23** **24**

to replacement of the chloro by a methoxy group. Measurement of an approximate rate constant for the solvolysis ($1.8 \times 10^{-5}$ $s^{-1}$) showed that the reaction was too slow to compete with attack by methoxide ion at normal base concentrations ($k_2$ = 1.0 l $mol^{-1}$ $s^{-1}$), and this was confirmed by the lack of intercept in a plot of first-order rate constants for the reaction with base against [$MeO^-$]. The configuration of the chloride was 85% trans, and isolation and the 3-azido-4-methoxy-*N*-benzylazetidinone product from methanol as a 3:1 ratio of cis to trans isomers indicated that the reaction occurred with predominant inversion of configuration.

## Discussion

**Ring-Opening and Elimination.** As expected, in the presence of sodium methoxide, azetidinones with a leaving

(23) Huisgen, R.; Herbig, K.; Siegel, A.; Huber, H. *Chem. Ber.* **1966**, *99*, 2546–2555.

(24) Martin, F.; More O'Ferrall, R. A.; Rao, S. N., to be published.

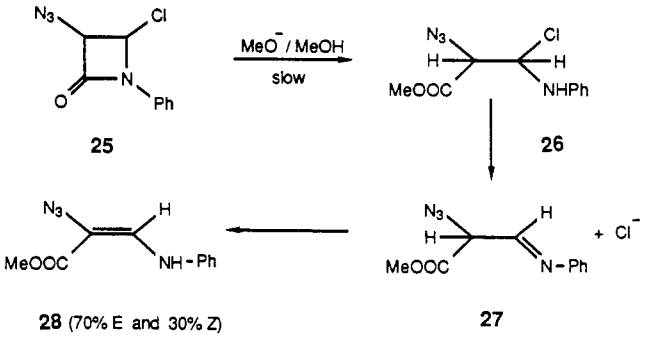
(25) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, 1987; Vol. 7, p 229.

(26) Dittmer, D. C.; Patwardhan, B. H. *The Chemistry of the Sulphonium Group*; Stirling, C. J. M., Patai, S., Eds.; Wiley: New York, 1981; pp 387–521.

(27) A comparable reaction has been suggested recently in β-lactam-ring-opened 6-bromopenicillin.[28]

(28) Pratt, R. F.; Cahn, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 5096–5104.

**Scheme V**




group at the 4-position undergo both β-elimination and opening of the β-lactam ring. Thus 3-azido-4-chloro-*N*-phenylazetidinone **25** yields a mixture of *Z* and *E* enamino esters **28** as shown in Scheme V. In principle, elimination of HCl may occur before or after opening of the β-lactam ring, and Scheme V shows the alternative that ring-opening occurs first. It also shows elimination as occurring via formation of the imine **27** followed by an imine-to-enamine rearrangement, rather than the more straightforward but less likely expulsion of HCl from the initially formed amino ester **26** to yield the product **28** directly.

That β-lactam ring-opening indeed does occur before elimination is suggested by several observations. The simplest, if not most compelling, is that in aqueous sodium hydroxide elimination yields a product with a chromophore similar to that obtained in methanol. Had elimination preceded ring-opening, analogy with Schemes I and II might suggest that trapping of an azetinone (**7**) by hydroxide ion[3] followed by fragmentation to a hydroxy acrylamide anion **5** would be the expected reaction, and this was not observed. Elimination from the β-lactam ring is not rigorously excluded, however, because hydroxide attack on an azetinone could occur at the carbonyl group, in which case no difference in products from ring-opening followed by elimination would be expected.

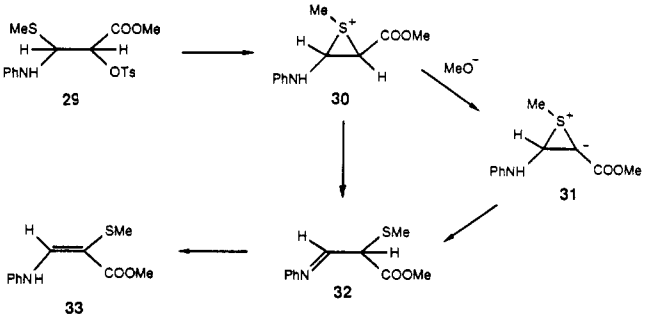
Further evidence of initial ring-opening comes from observation of a difference in products from reactions of 4-chloroazetidinones and the corresponding methylthio compounds.

**4-(Methylthio)azetidinones.** In contrast to 4-chloroazetidinones which show exclusively elimination of HCl, 4-(methylthio)-3-(tosyloxy)- and -3-azidoazetidinones in the presence of trimethylamine undergo elimination of tosylate and azide in competition with loss of MeSH. Examination of the products of these eliminations reveals that the methylthio group has also undergone rearrangement, from the 4-carbon atom to the 3-carbon atom. It seems unlikely that rearrangement would occur under such mild conditions before opening of the β-lactam ring, and this is confirmed by the lack of reaction in the absence of base. It follows that rearrangement takes place in the initial product of β-lactam ring-opening.

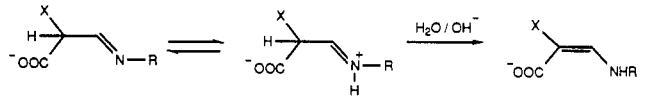
The most likely mechanism for this rearrangement is via formation of the epi-sulfonium ion **30** resulting from intramolecular displacement of tosylate or azide ions by the neighboring methylthio group of the ring-opened ester **29** as in Scheme VI.[26,27] The observed product **33** then arises either from direct fragmentation of **30** to the imine **32** or via an initial ionization to the zwitterion **31** followed by ring-opening.

Whatever the mechanism, however, rearrangement presumably occurs in competition with elimination of the methylthio group. Thus the UV spectra of the products suggest that the rearrangement is suppressed by factors favoring elimination, such as a stronger base or poorer

**Scheme VI**



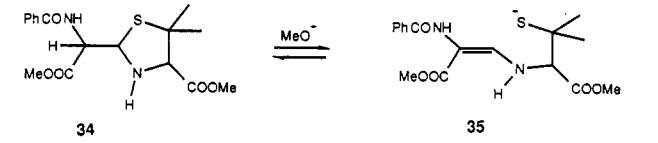

**Scheme VII**




leaving group at the 3-position. If so, attack of base at the carbonyl group opening the β-lactam ring must precede both the rearrangement *and* elimination steps.

Further evidence suggests that β-lactam ring-opening is not only the initial but also the rate-determining reaction. For *N*-phenyl β-lactams, ring-opening and elimination can be monitored independently from disappearance of the *N*-phenyl lactam chromophores of the reactants[29] and appearance of the enamino ester chromophore of the product. Both processes occur at the same rate, and it follows that elimination and rearrangement are fast steps following the rate-determining step. This conclusion is based on the reasonable assumption that opening of the β-lactam is not reversible.

It is interesting that this behavior differs from that of benzylpenicillin methyl ester in methanolic sodium methoxide where formation of the β-lactam ring-opened penicilloate **34** occurs 10 times more rapidly than the




subsequent (intramolecular and reversible) elimination of sulfur accompanying fission of the thiazolidine ring **35**.[30,31]

Also deserving comment is the fact that ring-opening is slower than elimination not only in methanol but in water. In water the initial product is a carboxylate anion, and this should provide less activation than the corresponding ester for the imine to enamine isomerization presumed to be the rate-determining step of the elimination reaction (Scheme V). However, there is some indication that this reaction is base-catalyzed in methanol but acid-catalyzed (or pH-independent) in water, where it occurs via an iminium ion intermediate (Scheme VII).[30,31] If so, it is understandable that the carboxylate anion should not disfavor elimination.

**4-Chloroazetidinones.** It does not follow that because β-lactam ring-opening is rate-determining for 4-(methylthio)azetidinones the same must be true of the corresponding chlorides. Chloride is a better leaving group than methylthiolate, and elimination could become the pre-

(29) Blackburn, G. M.; Plackett, J. D. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1366–1371.
(30) Davis, A. M.; Page, M. I. *J. Chem. Soc., Chem. Commun.* **1985**, 1702–170
(31) Golden, P.; More O'Ferrall, R. A.; Rao, S. N., to be published.
(32) Exner, O. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; pp 439–590.

**Table II. Leaving-Group Effects $k_{Cl}/k_{SMe}$ for Reaction of 4-Substituted β-Lactams with NaOMe–MeOH at 25 °C**

| 3-subst | N-subst | confign | $k_{Cl}/k_{SMe}$ |
|---|---|---|---|
| $N_3$ | Ph | cis | 12 |
| $N_3$ | $PhCH_2$ | trans | 22 |
| OTs | Ph | trans | 38 |
| OTs | $PhCH_2$ | trans[a] | 41 |

[a] The chloride contains 15% cis isomer.

ferred reaction. An obvious criterion of mechanism then is the magnitude of the leaving-group effect $k_{Cl}/k_{SMe}$. A change of mechanism should be signalled by an enhanced rate for the chloro substrate.

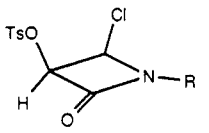
To use this criterion substituent effects of chloro and methylthio groups upon β-lactam ring-opening need to be estimated. Chloride is more electronegative than sulfur and should accelerate attack by hydroxide or methoxide ions at the carbonyl group of the ring. Only if the rate ratio $k_{Cl}/k_{SMe}$ exceeds the expected magnitude of this effect can an elimination be inferred.

In practice, measured chloro/methylthio rate ratios are quite variable. As shown in Table II values fall in the range 12–41 for the four *N*-phenyl or *N*-benzyl, 3-(tosyloxy), and 3-azido substrates. This might seem to imply that competing elimination and β-lactam ring-opening does occur, with different contributions for each substrate.

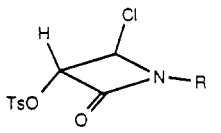
Almost certainly this is not the case. The smallest rate ratio, $k_{Cl}/k_{SMe} = 12$, is consistent with nucleophilic attack at the β-lactam ring. From the Taft inductive substituent constants[35] $\sigma_I = 0.47$ for Cl and 0.25 for MeS, the ratio 12 corresponds to a reaction constant $\rho_I = 4.9$ which is comparable to that reported for ring-opening of β-lactams not subject to elimination by methoxide or hydroxide ions.[20] It follows that, at least for the *N*-phenyl-3-azido chloride, the leaving-group effect gives no evidence of a rate-determining elimination reaction.

With respect to the larger rate ratios, there is evidence that β-lactam ring-opening is sensitive to steric as well as electronic effects and that these become significant when the ring bears two aryl substituents.[20] From Table II it is noticeable that the leaving-group effects are larger for the bulky 3-(tosyloxy) group ($k_{Cl}/k_{SMe}$ = 41 and 38) than the 3-azido ($k_{Cl}/k_{SMe}$ = 12 and 22). Moreover, the smallest rate ratio is associated with a cis configuration of 3- and 4-substituents, which presumably allows unencumbered access of a reagent to the unsubstituted face of the β-lactam ring, whereas for all the other substrates the configuration is trans.[33] Since the largest leaving-group effect is less than four times greater than expected from an electronic effect alone, it seems more likely that the differences represent a minor steric influence upon reactivity than a contribution from elimination. Indeed a more detailed correlation of substituent effects indicates that the chlorides react at a normal rate for β-lactam ring-opening whereas the methylthio derivatives are slow.[20] Had the chlorides been subject to elimination their rates should have been enhanced.

Confirmation that the chlorides are not eliminating comes from their insensitivity to the stereochemistry of 3-substituents in the β-lactam ring. Rates of reaction of *cis*- and *trans*-3-(tosyloxy)-4-chloroazetidinones (**36** and **37**) are almost the same ($k_{cis}/k_{trans}$ = 1.2). For elimination, a faster reaction might have been expected for the cis isomer **36**, in which the leaving group and reacting β-hydrogen are anti to each other, than in the trans (**37**) where




**36**




**37**

they are syn. With respect to β-lactam ring-opening, steric effects should also lead to a slower reaction of the trans than cis isomer, and the observed difference appears to be less than implied for methylthio substituents above. This is discussed in more detail elsewhere,[34] but the result is consistent with a role for inductive as well as steric effects in determining the stereochemistry of reaction.

Strictly speaking the stereochemical result and leaving-group effect exclude only E2 and reversible E1cB mechanisms of elimination. An E1cB mechanism in which formation of the carbanion is rate-determining is not ruled out. However, independent evidence of carbanion formation in monocyclic β-lactams, namely, epimerization and hydrogen isotope exchange, exists only for more strongly activating substituents than tosylate and azide, for example, isocyano.[34-36] Moreover, investigation of a wider range of β-lactam structures indicates that substituents at the 3- and 4-positions have similar effects on reactivity.[20] Had an E1cB mechanism been operating, larger effects would have been expected at the 3-position, which is the site of carbanion formation.

The sum of evidence that neither chloro- or (methylthio)azetidinones are undergoing elimination before opening of the β-lactam ring thus seems overwhelming. Nevertheless, the dilemma presented by the elimination step in Scheme III for the thiazepinone rearrangement remains, and the present discussion may be seen as establishing mechanistic criteria to be used in a continuing attempt to identify examples of elimination within the β-lactam ring.

**Solvolysis Reactions.** An important difference between methylthio and chloro substrates is that *N*-benzyl-4-chloroazetidinones are subject to solvolysis in methanolic and aqueous solution. In principle, this reaction also could lead to elimination, but in practice only products of substitution are observed. The importance of the solvolysis reaction depends strongly upon the basicity of the nitrogen atom in the β-lactam ring. Thus no solvolysis is seen for the *N*-phenyl chlorides, and even for *N*-benzyl the reaction fails to compete with ring-opening except at low concentrations of methoxide ion in methanol. On the other hand, solvolysis of *N*-methyl-4-chloroazetidinone has been shown to be fast,[20] and in this case ring-opening competes only at high base concentrations. These results are useful in delineating the scope of competing solvolytic reactions for different leaving groups and N-substituents. Solvolysis is certainly unimportant for leaving groups much less reactive than chloride either for mono or bicyclic β-lactams.

## Conclusions

Despite the strong implications of the thiazepinone rearrangement of penicillins that elimination can occur in the β-lactam ring (Scheme III), no example of this reaction has been uncovered for monocyclic β-lactams, even for a leaving group as reactive as chloride. In basic solutions hydrolysis or methanolysis of the β-lactam ring take pre-

(33) For reaction of *N*-phenyl-3-bromo azetidinones in NaOMe–MeOH, $k_{Cl}/k_{SMe}$ = 15 and 56 for cis and trans substrates, respectively.[34]

(34) More O'Ferrall, R. A.; Rao, S. N. *Proc. R. Ir. Acad., Sect. B* **1989**, *89*, 273–286.

(35) More O'Ferrall, R. A.; Rao, S. N., to be published.

(36) Clayton, R. J.; Naylor, J. H. C.; Southgate, R.; Stove, E. R. *J. Chem. Soc., Chem. Commun.* **1969**, 129.

cedence. The only reaction competing with ring-opening is solvolysis, and this leads to substitution rather than elimination products.

One way of avoiding ring-opening would be to use amine bases in aprotic solvents. These are the conditions under which the thiazepinone rearrangement is observed. So far, however, even the chloro substrates have proved unreactive under these conditions. It appears, therefore, that at least better carbanion and double bond stabilizing substituents than tosyloxy and azido will be required to effect elimination. However, preparative pathways combining these substituents with a good leaving group are less straightforward than those described here.

## Experimental Section

**Reagents and Instrumentation.** Products were purified by column chromatography on silica (Merck Kieselgel 60, 230–400 mesh ASTM) using ethyl acetate and petroleum ether as eluting solvents. Methanol used in kinetic measurements was distilled from magnesium methoxide under nitrogen; sodium methoxide was prepared by dissolving sodium (5 g, Pierce Inorganics 99.9% purity) in methanol (ca. 200 mL) also under nitrogen. Deuteromethanol was Aldrich Gold Label grade (>99% D). NMR measurements were made with a Perkin-Elmer R12B 60-MHz instrument or Jeol GX 270 MHz. Spectrophotometric measurements were made with Perkin-Elmer 124 or Pye Unicam SP8-400 or PU8800 spectrophotometers, usually with on-line data processing by an Apple IIe microcomputer for kinetic measurements. Infrared measurements were made with Perkin-Elmer 283B or FT1710 spectrometers.

**Synthesis and Structure of β-Lactams.** 3,4-Substituted β-lactams were prepared by published methods. *N*-Phenyl- and *N*-benzyl-3-(tosyloxy)-4-(methylthio)azetidinones **14** were obtained from reaction of toluenesulfonoxyacetyl chloride with the corresponding *N*-phenyl and *N*-benzyl thioformimidate esters in the presence of triethylamine as described by Lattrell and Lohaus[16,17] (Scheme IV). The products showed a β-lactam carbonyl peak at 1775–1780 $cm^{-1}$ and coupling constants $J$ = 2.0 Hz between the 3- and 4-hydrogens indicating a trans stereochemistry of tosyloxy and methylthio substituents. Chlorinolysis[19] in methylene chloride at −70 °C with excess chlorine gave the chlorides (**17**, X = OTs; R = Ph, $PhCH_2$) as a cis–trans mixture in which cis and trans isomers predominated for *N*-phenyl and *N*-benzyl products, respectively (80–85%); the isomers were separated chromatographically for the *N*-phenyl but not *N*-benzyl chlorides. Displacement of the tosyloxy groups in **14** with $NaN_3$ gave the azides **15** and **16**, with inversion of configuration in the case of the *N*-phenyl tosylate and retention for *N*-benzyl; chlorinolysis again gave the chlorides (**17**, X = OTs), this time as single isomers with retention of configuration. Details of reaction procedures and structural assignments are available in the literature.[21,22] NMR and IR data and outlines of representative reactions are given below.

Chemical shifts and coupling constants of 3- and 4-hydrogens, on the basis of which configurations were assigned,[17,21] are summarized in Table III. In general, cis isomers are distinguished from trans by their larger coupling constants (≥3.5 Hz compared with ≤2 Hz). In the case of the *N*-phenyl-3-(tosyloxy)-4-chloroazetidinones, for which both isomers were available, NOE measurements showed, as expected, a greater enhancement of the signal for the vicinal hydrogen (6% compared with 2%) upon irradiating the 3- or 4-hydrogen in the isomer assigned a cis structure than in the trans. A further feature of the spectra of *N*-benzylazetidinones is the splitting and coupling ($J$ = 15 Hz) of the prochiral methylene hydrogens of the benzyl group.

Together with IR and NMR data for the azetidinones themselves, UV spectra ($\lambda_{max}$) are reported for the products of their reactions with methanolic sodium methoxide and (if measured) aqueous sodium hydroxide. The small differences in $\lambda_{max}$ from reaction of 4-(methylthio)azetidinones with sodium methoxide and triethylamine, apparently associated with rearrangement of the methylthio group (as discussed above), are also recorded where observed. Extinction coefficients of products were in the range 4000–11 000.

**Table III. Chemical Shifts and Coupling Constants for 3- and 4-Substituted Azetidinones 18**

| substituents | | | | δ, ppm | | |
|---|---|---|---|---|---|---|
| 3-X | 4-Y | N-R | confign | 3-H | 4-H | $J_{3,4}$, Hz |
| OTs | $SCH_3$ | Ph | trans | 5.35 | 5.02 | 2.0 |
| OTs | $SCH_3$ | $PhCH_2$ | trans | 5.2 | 4.50 | 2.0 |
| $N_3$ | $SCH_3$ | Ph | cis | 5.05 | 5.30 | 4.0 |
| $N_3$ | $SCH_3$ | $PhCH_2$ | trans | 4.8 | 5.0 | 1–1.5 |
| OTs | Cl | Ph | cis | 5.8 | 6.2 | 4.0 |
| OTs | Cl | Ph | trans | 5.58 | 5.93 | 1.0 |
| OTs | Cl | $PhCH_2$ | trans | 5.3 | 5.65 | 2.0 |
| $N_3$ | Cl | Ph | cis | 4.95 | 6.15 | 4.0 |
| $N_3$ | Cl | $PhCH_2$ | trans | 4.7 | 5.1 | 1–1.5 |
| $N_3$ | $OCH_3$ | $PhCH_2$ | cis | 4.80 | 4.30 | 3.5 |
| $N_3$ | $OCH_3$ | $PhCH_2$ | trans | 4.56 | 4.41 | 1.0 |

***trans*-1-Phenyl-3-(tosyloxy)-4-(methylthio)-2-azetidinone (14, R = Ph).** To a cold solution of *N*-phenyl-*S*-methylthioformimidate (15.1 g, 0.1 M) was added a freshly prepared solution of (tosyloxy)acetyl chloride (29.8 g, 0.12 M) in 150 mL of $CH_2Cl_2$ over a period of 2 h with stirring (for structures, see Scheme IV). Stirring was continued for a further 30 min and the mixture poured into 300 mL of water. The organic phase was washed with brine and dried. Evaporation of the solvent afforded an oil which was chromatographed over silica to give a solid product: mp 107–108 °C; IR 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.05 (s, $CH_3$), 2.5 (s, Ar-$CH_3$), 5.02 (d, $J$ = 2 Hz, 4-H), 5.35 (d, $J$ = 2 Hz, 3-H), 7.2–8.0 (m, aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 315 nm, 285 (sh), (after reaction with $Et_3N$–MeOH) 319 nm.

***cis*-1-Phenyl-3-(tosyloxy)-4-chloro-2-azetidinone (17, X = OTs, R = Ph).** Into a solution of 1-phenyl-3-(tosyloxy)-4-(methylthio)-2-azetidinone (**14**, R = Ph, 0.5 g, 0.00138 M) in 20 mL of $CH_2Cl_2$ cooled to −78 °C was bubbled 2 equiv of chlorine generated from a calculated quantity of potassium permanganate and hydrochloric acid. The mixture was allowed to stand at −78 °C for a further 15 min and the solvent evaporated to give an oil (yield 80%): IR 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.5 (s, Ar-$CH_3$), 5.8 (d, $J$ = 4 Hz, 3-H), 6.2 (d, $J$ = 4 Hz, 4-H), 7.3–8.0 (m, aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 315 nm.

***cis*-1-Phenyl-3-azido-4-(methylthio)-2-azetidinone (15).** A solution of 1-phenyl-3-(tosyloxy)-4-(methylthio)-2-azetidinone (**14**, R = Ph, 3.63 g, 0.01 M) and sodium azide (6.5 g, 0.1 M) in DMSO (60 mL) was stirred at 55 °C for 24 h, cooled, diluted with 150 mL of water, and extracted with ethyl acetate (3 × 75 mL). The extract was washed with water and dried, and the solvent was evaporated. Chromatography gave pure **15**: IR 2120 (azide) 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 2.1 (s, $CH_3$), 5.05 (d, $J$ = 4 Hz, 4-H), 5.30 (d, $J$ = 4 Hz, 3-H), 7.2–8.0 (aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 327 nm, (after reaction with NaOH–$H_2O$) 322 nm.

***cis*-1-Phenyl-3-azido-4-chloro-2-azetidinone (17, X = $N_3$; R = Ph).** The same method used to prepare **17** (X = OTs) was followed: IR 1780 $cm^{-1}$; $^1H$ NMR δ ($CDCl_3$) 4.95 (d, $J$ = 4 Hz, 3-H), 6.15 (d, $J$ = 4 Hz, 4-H), 7.2–7.6 (aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 327 nm.

***trans*-1-Benzyl-3-(tosyloxy)-4-(methylthio)-2-azetidinone (14, R = $PhCH_2$).** The same method used to prepare **14** (R = Ph); was followed: IR 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.05 (s, $CH_3$) 2.5 (s, Ar-$CH_3$), 4.0 and 4.7 (d, $J$ = 15 Hz, $PhCH_2$), 4.5 (d, $J$ = 2 Hz, 4-H), 5.3 (d, $J$ = 2 Hz, 3-H), 7.2–8.0 (m, aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 287 nm.

***trans*-1-Benzyl-3-(tosyloxy)-4-chloro-2-azetidinone (17, R = $PhCH_2$; X = OTs).** The method used to prepare **17** (R = Ph) was followed: IR 1775 $cm^{-1}$; $^1H$ NMR δ ($CDCl_3$) 2.5 (s, Ar-$CH_3$), 4.1 and 4.8 (d, $J$ = 15 Hz, $PhCH_2$), 5.3 (d, $J$ = 1.5 Hz, 3-H), 5.65 (d, $J$ = 1.5 Hz, 4-H), 7.2–7.9 (aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 277 nm, (after reaction with NaOH–$H_2O$) 274 nm.

***trans*-1-Benzyl-3-azido-4-(methylthio)-2-azetidinone.** The method used to prepare **15** was followed: IR 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 2.1 (s, $SCH_3$), 4.1 and 4.8 (d, $J$ = 15 Hz $PhCH_2$), 4.8–5.0 (d, $J$ = 1.5 Hz 3-H and 4-H), 7.4 (aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 295 nm.

***trans*-1-Benzyl-3-azido-4-chloro-2-azetidinone.** The method used to prepare **17** (R = Ph) was followed: IR 1775 $cm^{-1}$, $^1H$ NMR

($CDCl_3$) $\delta$ 4.05–4.75 (d, $J$ = 15 Hz, $PhCH_2$), 4.7 (d, $J$ = 1.0–1.5 Hz, 3-H), 5.1 (d, $J$ = 1.0–1.5 Hz, 4-H), 7.4 (aromatic); UV $\lambda_{max}$ (after reaction with NaOMe–MeOH) 295 nm, (after reaction with $NaOH-H_2O$) 290 nm.

**Product Analyses.** Triethylamine was used as a base instead of sodium methoxide because the reactions were more easily controlled and worked up, and product decomposition was minimized. UV spectra showed no difference in products between $Et_3N$ and NaOMe from 4-chloroazetidinones; however, for 4-(methylthio)azetidinones, small but distinct differences were apparent. The reactions were monitored by UV spectra; upon completion, $Et_3N$ and methanol were evaporated and the products, which were obtained as oils, were chromatographed on silica and analyzed by NMR. Products from the 3-(tosyloxy) and 3-azido chlorides were eluted as a single band showing two NMR peaks at $\delta$ 8.0 ppm consistent with the presence of $E$ and $Z$ isomers, each containing a vinyl hydrogen. The chemical shifts of the vinyl hydrogens were comparable with those of the 2-unsubstituted acrylic esters[23] **38**, and other signals were consistent with structure


**19** (R = Ph or $PhCH_2$); in particular, the $S$-methyl signal was absent from the spectrum while the tosyloxy signals were retained.

Chromatography of the products from 4-(methylthio) tosylates by contrast gave $E$ and $Z$ enamines showing loss not, as expected, of the 4-(methylthio) group but of the 3-(tosyloxy). Two chromatographic fractions were isolated. The spectrum of the major product from the less polar fraction was consistent with rearrangement of the methylthio group to the adjacent carbon atom. This was revealed by the similarity of the spectrum to that of **19** but with the vinyl and NH hydrogens now appearing as doublets with a coupling constant ($J$ = 13.9 Hz) similar to that of **38** ($J$ = 13.0 Hz for both $E$ and $Z$ isomers). In the (minor) product from the more polar fraction the spectrum was similar but showed no coupling of these hydrogens. The same product was obtained from reaction of the 4-azidoazetidinone as from the 4-(tosyloxy); it was not definitely identified.

No independent evidence that the appearance of two vinyl peaks in the NMR represents $E$ and $Z$ isomers was obtained, but UV spectra of the products often showed a shoulder 30 nm below the main peak, consistent with the presence of major and minor components. As judged by $\lambda_{max}$ for $E$ and $Z$ isomers of **39**, the major form is probably $E$. As expected,[23] $\lambda_{max}$ for $N$-benzyl enamino esters occurred at shorter wavelengths than $N$-phenyl, and shorter wavelengths were also observed for products from reactions in aqueous than in methanolic solutions, where presumably an enamine carboxylate anion rather than an ester is formed.

Products were also isolated from reaction of the $N$-benzyl-3-azido-4-chloroazetidinone (**17**) (R = $PhCH_2$, X = trans $N_3$) with methanol in the absence of base. The spectrum obtained indicated a 3:1 mixture of *cis*- and *trans*-3-azido-4-methyl ethers **24**. Details of spectra of these products and of the enamino esters are given below.

**(*E*)- and (*Z*)-2-(Tosyloxy)-3-anilinoacrylic Acid Methyl Ester (19, X = OTs; R = Ph).** These structures were assigned to products of reaction of 3-(tosyloxy)-4-chloro-$N$-phenylazetidinone with $Et_3N$ in MeOH: $^1H$ NMR ($CDCl_3$) $\delta$ 2.5 (s, Ar-$CH_3$), 3.57 (s, $COOCH_3$), 7.0–8.0 (aromatic) 7.75 and 7.95 (vinyl). The product ratio was 60:40 with the higher field vinyl peak predominating.

**(*E*)- and (*Z*)-2-(Tosyloxy)-3-(benzylamino)acrylic Acid Methyl Ester (19, X = OTs; R = $CH_2Ph$).** The $N$-benzyl modification of the $N$-phenyl acrylic esters above were obtained from the corresponding (trans) $N$-benzyl chloride in the same way: $^1H$ NMR $\delta$ ($CDCl_3$) 2.35 (s, $SCH_3$), 3.5 (s, $COOCH_3$), 4.4 and 4.5 ($ArCH_2$), 5.5 (s [broad] NH), 7.3 (s aromatic) 7.75 and 7.95 (vinyl).

**(*E*)- and (*Z*)-2-(Methylthio)-3-anilinoacrylic Acid Methyl Ester (20, R = Ph).** These structures were assigned to the compound from the less polar fraction after chromatography of products from reaction of 3-(tosyloxy)-4-(methylthio)-$N$-phenylazetidinone with $Et_3N$ in MeOH: $^1H$ NMR $\delta$ ($CDCl_3$) 2.16 (s, $ArCH_3$), 3.77 (s, $COOCH_3$), 6.9–7.2 (m, aromatic), 7.81 and 8.17 (intensity ratio 3.8:1, d, $J$ = 13.9 Hz, $E$- and $Z$-vinyl-H), 10.38 (d, $J$ = 13.9 Hz, NH).

**(*E*)- and (*Z*)-3-(Methylthio)-3-anilinoacrylic Acid Methyl Ester.** These structures were tentatively assigned to the compound from the more polar fraction following chromatography of products of the preceding reaction and from reaction of 3-azido-4-(methylthio)-$N$-phenylazetidinone in $Et_3N$ and MeOH: $^1H$ NMR $\delta$ ($CDCl_3$) 2.25 (s, $SCH_3$), 3.9 (s, $COOCH_3$), 6.9–7.2 (m, aromatic) 8.3 and 8.5 (s, $E$- and $Z$-vinyl-H).

**(*E*)- and (*Z*)-2-(Methylthio)-3-(benzylamino)acrylic Acid Methyl Ester (20, R = $PhCH_2$).** These structures were assigned to compounds from chromatography (more polar fraction) of products from reaction of 3-(tosyloxy)-4-(methylthio)-$N$-benzyl-2-azetidinone (**14**, R = $PhCH_2$) with $Et_3N$ in MeOH: $^1H$ NMR ($CDCl_3$) $\delta$ 2.2 (s, $SCH_3$), 3.9 (s, $COOCH_3$), 4.6 and 4.7 ($E$ and $Z$ $ArCH_2$), 6.0 (s, broad, NH) 7.5 (m, Ar), 7.9 and 8.2 (s, intensity ratio 2:1, $E$- and $Z$-vinyl-H).

***cis*- and *trans*-3-Azido-4-methoxy-*N*-benzylazetidinones 24.** These products were obtained from the reaction of 3-azido-4-chloro-$N$-benzylazetidinone with methanol (overnight at room temperature) in the absence of base: cis and trans products in ratio 3:1; $^1H$ NMR ($CDCl_3$) (cis) $\delta$ 3.41 (s, $OCH_3$), 4.23 and 4.68 (d, $J$ = 15 Hz, $PhCH_2$), 4.30 (d, $J$ = 3.5 Hz, 4-H), 4.80 (d, $J$ = 3.5 Hz, 3-H), 7.2–7.4 (aromatic); (trans) 3.32 (s, $OCH_3$), 4.16 and 4.67 (d, $J$ = 15 Hz, $PhCH_2$), 4.41 (d, $J$ = 1.0 Hz, 4-H), 4.56 (d, $J$ = 1.0 Hz, 3-H), 7.2–7.4 (aromatic).

**Kinetics.** Kinetic measurements were made spectrophotometrically by monitoring an increase in $\lambda_{max}$ in the range 270–320 nm of the enamino ester products. Reactions were initiated by injecting 10-30 $\mu$L of concentrated stock solution of substrate in methanol or acetonitrile into a 10-mm spectrophotometric cell containing 2–3 mL of aqueous methanolic base in the thermostated cell compartment of the spectrophotometer.

Kinetics were normally cleanly first order, but at higher concentrations of methoxide ion in methanol the product (**19**) underwent a further reaction leading to loss of the long-wavelength chromophore. The rate of this reaction was the same for Cl and MeS leaving groups but was faster for $N$-phenyl than $N$-benzyl and for 4-azido than 4-(tosyloxy) substrates. The reaction may have involved attack of methoxide ion on the enamino ester with displacement of the amine and formation of the acetal **39**. Simple


**39** **40**

addition to the amine to form the adduct **40** is unlikely because for $N$-methyl-4-methoxy azetidinone this is the initial product of ring-opening which, nevertheless, eliminated methanol to form the enamine, as judged by development of a strong chromophore at 255 nm. In any event, for the $N$-benzyl azide, this reaction was accompanied and followed by a further reaction leading to a new long-wavelength chromophore at 365 nm. Possibly this involved cyclization of an azido vinyl ether, but an attempt to isolate the product was unsuccessful. No attempt was made to isolate the adducts **39**. In water, a base-independent reaction of the enamino acid anions occurred; probably this was hydrolysis.

Usually, decomposition of the product was slow enough not to interfere with the initial formation of enamino ester, for which rate constants could be calculated from absorbance measurements over 3–4 half-lives, with the limiting absorbance iterated to optimize linearity of a first-order kinetic plot. Rate constants were normally measured at four or more base concentrations and an average value, or a value extrapolated to zero base concentration, derived. In no case was variation in the second-order rate constant with base concentration greater than 20%. Only in the case of 3-azido-4-(methylthio)-$N$-benzyl-2-azetidinone did product decomposition seriously affect rate measurements for the initial reaction.

Solvolysis of 3-azido-4-chloro-$N$-benzyl-2-azetidinone with methanol in the absence of base was monitored from the change

in absorbance of 1,8-bis(dimethylamino)naphthalene (proton sponge) accompanying protonation by HCl produced in the reaction.[37] Excess of substrate was used to give zero-order kinetics and reasonable linearity of plots of absorbance against time were obtained. The second-order rate constant $1.8 \times 10^{-5}$ $M^{-1}$ $s^{-1}$ was based on measurements at several substrate concentrations in the range 0.5–2.5 $\times 10^{-3}$ M, and was derived from the expression $k = \Delta A/(\Delta t \epsilon[S])$, where $\Delta A/\Delta t$ is the slope of the plot of absorbance against time, $\epsilon$ is the extinction coefficient of the proton sponge, and [S] is the concentration of substrate; the initial concentration of proton sponge was $10^{-5}$ M.

(37) Luton, P. R.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1507.

**Acknowledgment** is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. We thank Frances Martin for experimental assistance.

# An ab Initio Study of the Cyclization and Rearrangement of Vinyl-, Imidoyl-, and Formylketene

Minh Tho Nguyen

*Department of Chemistry, University of Leuven, B-3030 Leuven, Belgium*

Tae-Kyu Ha*

*Laboratory of Physical Chemistry, Swiss Federal Institute of Technology, CH-8092 Zurich, Switzerland*

Rory A. More O'Ferrall

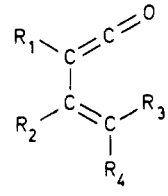
*Department of Chemistry, University College—Belfield, Dublin 4, Ireland*

*Received November 6, 1989*

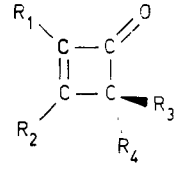
The 1,4-cyclization was studied in three model systems; formylketene, imidoylketene, and vinylketene, using ab initio MO methods. Structures of stationary points on the reaction potential energy surfaces were located at the HF/6-31G** level. Relative energies, estimated at the MP4SDQ/6-31G** level together with zero-point contributions, are as follows (in kcal/mol): formylketene (-17) → TS(4) → oxetone (0); imidoylketene (-10) → TS(15) → azetinone (0); and vinylketene (0) → TS(31) → cyclobutenone (0). The ring-opening of cyclobutenone is energetically more favorable than that of cyclobutene. The electronic reorganization accompanying the ring-closure of substituted ketenes was also examined using a localized orbital analysis. The process is found to be similar to the 1,5-cyclization of vinylazide and imidoylazide. Finally, the ketoketene–ketoketene rearrangement, including migration of a hydrogen in the formylketene, was considered. This 1,3-hydrogen shift is calculated to be a quite difficult chemical process requiring a large activation energy (even larger than that in formic acid).

## 1. Introduction

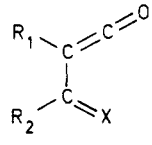
Vinylketenes **1** have been shown to be intermediates in several thermal and photochemical reactions of cyclobutenones **2**, and the ring–chain tautomerization reactions **2** → **1** have been extensively studied.[1,2] From a mechanistic point of view, the electrocyclic ring-opening of cyclobutenones **2** resembles, in many aspects, that of cyclobutenes.[3] In contrast, relatively little is known about the tautomeric equilibria either between imidoylketenes **3** and azetinones **4** or between acylketenes **5** and oxetones **6**. The oxetones and azetinones possess the additional feature that resonance of the carbonyl group leads to formally antiaromatic structures.



**1**

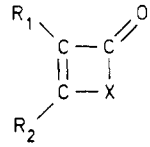


**2**



**3** (X = NR)

**5** (X = O)



**4** (X = NR)

**6** (X = O)

Azetinones **4** have been considered as potential intermediates in the nucleophilic ring-opening of β-lactams. Although these structures have occasionally been proposed in the literature[4] and are well-characterized in their benzo-fused forms,[5] the best evidence of their existence probably comes from either the base-catalyzed rearrangement of penicillins to thiazepinones[6] or the treatment of isoxazoles with tertiary amines and nucleophiles.[7]

* Author to whom correspondence should be addressed.

(1) For recent reviews, see: (a) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (b) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797.

(2) For recent works, see: (a) Perri, S. T.; Foland, L. D.; Moore, H. W. *Tetrahedron Lett.* **1988**, *29*, 3529. (b) Foland, L. D.; Karlsson, J. D.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.

(3) Huisgen, R.; Mayr, H. *J. Chem. Soc., Chem. Commun.* **1976**, *55*, 57.

(4) See, for example: Brandt, A.; Bassignani, L.; Re, L. *Tetrahedron Lett.* **1976**, 3979. The azetinone structure was disproved subsequently by: Gane, P. A. C.; Boles, M. O. *Acta Crystallogr. B* **1979**, *35*, 2664. Bachin, M. D.; Goldberg, O.; Gross, A.; Vaya, J. *J. Org. Chem.* **1980**, *45*, 1481.

(5) (a) Burgess, E. M.; Milne, G. *Tetrahedron Lett.* **1966**, 93. (b) Ege, G. *Chem. Ber.* **1968**, *101*, 3079, 3089. (c) Bashir, N.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 868. (d) Olofson, R. A.; Van der Mer, A. K.; Hoskin, D. H.; Bernheim, M. Y.; Stournas, S.; Morrison, D. S. *J. Org. Chem.* **1984**, *49*, 3367.

(6) Jackson, J. R.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1971**, 647.

0022-3263/90/1955-3251$02.50/0 