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STEREOCHEMICAL EFFECTS IN THE REACTIONS OF N-ALKYL-4-SUBSTITUTED AZETIDINE 2-CARBOXYLIC ACIDS WITH OXALYL CHLORIDE. REARRANGEMENT TO CHLORO-γ-LACTAMS.

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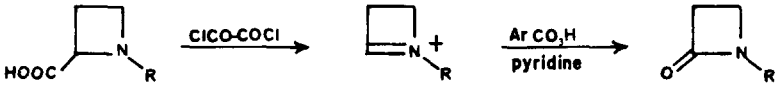
Abstract: Treatment of N-alkylazetidine 2-carboxylates with oxalyl chloride may yield acid chlorides, iminium salts or chloro-γ-lactams depending on the stereochemistry and nature of the substituents on the azetidine ring.

The reactions of α-tertiary amino acids with acid chloride-forming reagents may yield iminium salts by oxidative decarbonylation, and this transformation has had a number of applications in synthesis. [1] In the case of unsubstituted N-alkyl-azetidine-2-carboxylic acids (1) we have recently shown that the iminium salts (2) may be converted to azetidinones (3) by reaction with meta-chloroperbenzoic acid and pyridine (Scheme I). [2]



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During further studies on this procedure we have found that the reactions of 4-substituted systems may take another course depending on the nature and stereochemistry of the substituents at the 1- and 4- positions. Table I, summarizing the action of ClCOCOCl on a series of 4-substituted azetidine 2-carboxylic acids, shows that the reaction may lead to (i) acid chloride, (or equivalent species)[9] (ii) iminium salt (identified as azetidinone) or (iii) stereospecific ring expansion to a chloro-γ-lactam.

In evaluating the stereochemical features of these reactions we propose: (a) that iminium salt formation takes place through a transition state (5) in which the lone pair on nitrogen is disposed anti-periplanar to the acid chloride carbonyl group permitting decarbonylation as shown in path a;[3] (b) that rearrangement to the γ-lactam involves the fused-ring aziridinium salt (6) which undergoes S_N2 ring opening by chloride ion as shown in path b.[4] This picture of the ring expansion is in accord with our findings that trans-N-t-butyl-4-methylazetidine-2-carboxylic acid (4a) leads stereospecifically to trans-N-t-butyl-3-chloro-5-methylpyrrolidone (7a). The trans-relationship of substituents

Table I

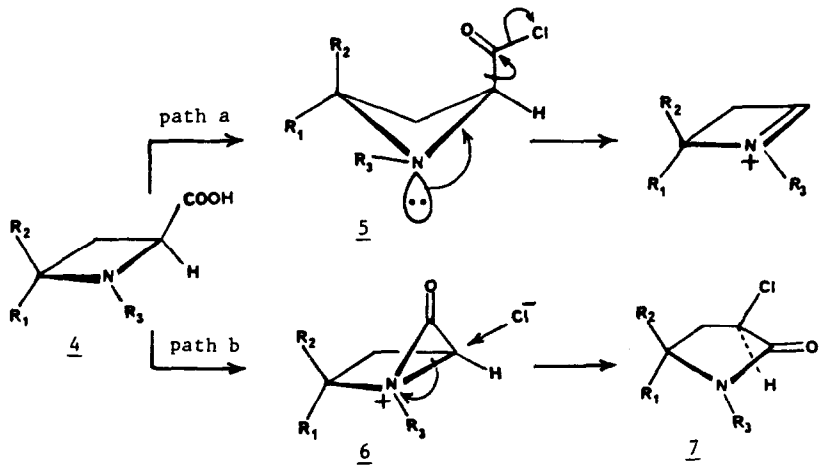
Reaction of Azetidine Carboxylic Acids (4) with Oxalyl Chloride

Azetidine carboxylic acid (4)	R_1	R_2	R_3	(i)	(ii) 3	(iii) 7
4a (trans)	CH_3	H	t-Bu	--	--	69
4b (cis)	H	CH_3	t-Bu	78	--	--
4c (trans)	CH_3	H	CH_2Ph	26	22	30
4d (cis)	H	CH_3	CH_2Ph	57	22	--
*4e (trans)	CH_3	H	CH_3	15	23	--
4f (cis)	H	CH_3	CH_3	54	30	--
4g (trans)	CO_2Me	H	CH_2Ph	--	--	46
4h (cis)	H	CO_2Me	CH_2Ph	--	--	68
4i (trans)	CO_2Me	H	cyclohexyl	--	--	58
4j (cis)	H	CO_2Me	cyclohexyl	--	--	59

*In this case, considerable decomposition occurred under the reaction conditions.

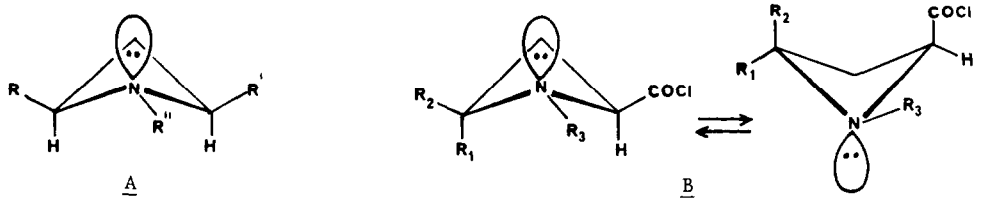
in 4a and 7a was firmly established by single crystal x-ray structure determinations on both of these materials.[5]

It is noteworthy that the acid chloride [9] formed from 4b (cis) is essentially unreactive both toward path a and path b processes. Here, formation of the iminium salt (path a) would require a transition state (5a) in which methyl (R_2) and acid chloride groups are held in an unfavorable 2,4-pseudodiaxial interaction.[5b] Furthermore, in this situation the t-butyl group is located cis to two other substituents. In the path b process, formation of 6 would likewise not be favored since this would involve crowding the carbonyl-containing 3-membered ring with the neighboring cis-4-methyl group. In cases 4d



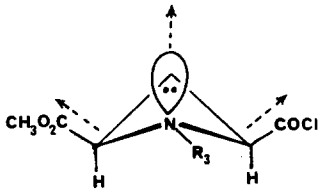
and 4f where the methyl group is cis to the carboxyl derivative, and the N-alkyl substituent is less bulky, the formation of some iminium salt is observed.

In cases (4a, 4c, 4e) where the carboxylate residue is trans to the substituent at the 4-position, there appears to be a competition between paths a and b in which the size of the R_3 group (on nitrogen) is a significant factor. For example, 4a undergoes exclusive ring expansion to the chloro γ-lactam (7a). Here there is no unfavorable interaction of the proposed 3-membered ring intermediate with the (trans)-methyl group (R_1) as observed with 4b. Unlike the unreactive cis cases where the acid chlorides should prefer that conformation which disposes both substituents in pseudo-equatorial positions (Fig.A),[5b] the trans - isomers are expected to exist in two rapidly equilibriating conformers, (Fig B), both of which have one pseudoaxial group adjacent (cis) to the N-alkyl group. The trans - isomers



(R_1=CH_3;R_2=H) would thus be expected to have higher ground state energy with respect to the cis-isomers, and this view is clearly supported by our epimerization studies.[6] The ring expansion of 4a may thus be associated with the relief of strain resulting from the steric congestion in the four membered ring. On the other hand, when the (R_3) substitution on nitrogen is changed from a t-butyl to a benzyl group (4c), iminium salt formation is observed, along with ring enlargement. Further reduction in the size of R_3 to an N-methyl group (4e) leads to iminium salt with no accompanying γ-lactam.

Both cis-and trans-isomers of azetidine carboxylic acids having a carbomethoxy group at the 4-position (entries 4g- 4j) yield only chloro-γ-lactams. The behavior of the trans-isomers can be explained on the same basis as that proposed for the trans-4-methyl analogues. The unexpected rearrangement of the cis-isomers may be associated with the need to alleviate unfavorable dipole-dipole repulsions among carbomethoxy, acid-chloride group and the nitrogen lone pair (Fig.C). Similar dipole-dipole repulsive destabilization has been observed earlier by Allinger for a related cyclobutane system.[8]



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b) More recently, Margerum has shown in a related system of N-chloro-α-amino acids, that fragmentation in such systems requires optimum antiperiplanar relationship between the two bonds being broken. Hand, V.C.; Snyder, M.P.; Margerum, D.W. J. Am. Chem. Soc. 1983, 105, 4022.

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b) This reaction may be viewed as a type of reverse Favorskii reaction of α-chloro-lactams. Henning, R.; Urbach, H. Tetrahedron Lett. 1983, 24, 5339.

5. a) For the x-ray determinations, 4a was converted to the p-bromobenzyl amide.
b) Our structural conclusion is in accord with the recent reassignment by Kingsbury, C.A.; Soriano, D.S.; Podraza, K.F.; Cromwell, N.H. J. Heterocyclic. Chem. 1982, 19, 89.

6. We have carried out the sodium methoxide-catalyzed epimerization of 1-benzyl-2-carbomethoxy-4-methylazetidine in methanol and found that, at equilibrium (65°C), the cis-form predominates over the trans in the ratio of 8:1. This finding which is in accord with the greater stability of the cis-form, is in contradiction with earlier assumptions.[5b,7]

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9) In our discussion, we make no distinction between "acid chloride" and the product initially derived from the reaction of oxalyl chloride with the carboxylic acid. Presence of this species could be determined by conversion to the corresponding amide with NH_3.

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