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COMPETITIVE ATTACK OF NUCLEOPHILES AT RING CARBON VS CARBONYL. REACTIONS OF AZIRIDINECARBAMATES[1]

Alfred Hassner and Albert Kascheres

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

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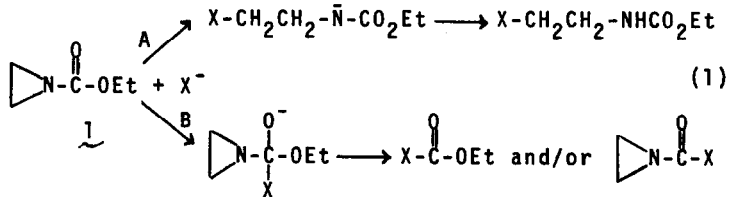
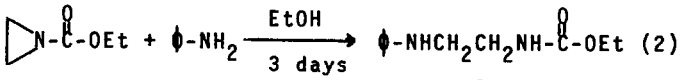
O-Alkyl aziridinecarbamates (ie. 1) are of interest as enzyme substrates and permit an evaluation of the relative importance of nucleophilic reactions on carbon (paths A and B in eq. 1).



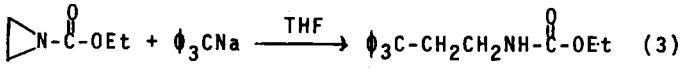
(1)

The susceptibility of aziridine derivatives of type 1 toward ring opening by a variety of nucleophilic reagents, for the most part aryl and alkyl amines, has been well established.[2a,3,4] Thus, the reaction of ethyl aziridinecarbamate 1 with aniline has been reported to result in a slow, quantitative conversion to ethyl N-(β-anilinoethyl) carbamate 2 (eq. 2).[3] The NaI catalyzed rearrangement of ethyl



(2)

aziridinecarbamate to an oxazoline[5] presumably also involves initial ring opening by iodide anion. Furthermore, tritylsodium (a comparatively strong base) has been observed[6] to give 30% of the product 3 resulting from attack at the ring carbon (eq. 3).



(3)

Our own results with tritylllithium,[7] indicate that 3 is the only product formed in yields as high as 85%. The driving force behind these reactions is evidently relief of ring strain and the formation of a transition state wherein considerable negative charge is placed on N adjacent to a carbonyl function.

In conjunction with the above reports of ring attack, there have been cases cited involving reaction at the other electrophilic site in the molecule, namely the carbonyl function.[2b,2c] Thus, the reaction of 1 with sodium ethoxide in ethanol has been observed[2c] to yield diethyl carbonate along with free aziridine. We have observed an analogous rapid reaction with sodium methoxide in methanol, the nmr spectrum of the crude material showing no evidence of ring opened products. Attack at the carbonyl group has been assumed in the NaOH[8] and the enzyme catalyzed[9] hydrolysis of aziridinecarbamates to aziridines.

In order to determine more definitively the effect of the nature of the nucleophile on the course of the above reactions (paths A and B in eq. 1), and at the same time gain some insight into the relative propensity as a leaving group of alkoxide versus aziridinyl anion in these carbamates, several strong nitrogen and carbon bases were generated and reacted with the ambident substrate 1. The results of these reactions are indicated in Tables I and II, respectively.

When the conjugate bases of several amines were used as nucleophiles (Table I), only products arising from carbonyl attack, with ethoxide expulsion, were observed.

Table I

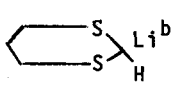
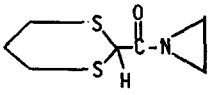
Products obtained in theReaction of 1 with Lithium Amides

Lithium Amide	Product	% Yield[c]
ø-NHLi[a,b]	ø-NH-C(=O)-N 	65
t-BuNHLi[a]	t-BuNH-C(=O)-N 	70
$(isopr)_2NLi$[a]	$(isopr)_2N$-C(=O)-N 	60
n-prNHLi[a]	n-prNH-C(=O)-N 	50

(a) Ethyl ether used as solvent.
(b) Glyme used as solvent.
(c) These are the only products found. No ring opened products were observed in the nmr spectra of the crude materials.

Table II

Products obtained in the Reaction of 1 with Alkyllithiums

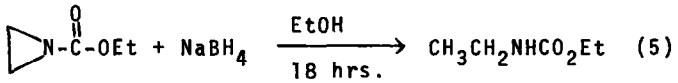
Alkyllithium	Products	Overall Yield
ϕ_3CLi[b]	$\phi_3C\text{-}CH_2CH_2NHCOOEt$	85%
ϕ_2CHLi[b]	ϕ_2CHCON (33%) $\phi_2CH\text{-}CH_2CH_2\text{-}NHCOOEt$ (66%)	90%
ϕCH_2Li[a](2equiv)	$\phi CH_2COCH_2\phi$	70%
t-BuLi[a,b](2equiv)	t-Bu-C(=O)-t-Bu	(a) 95% (b) 70%
$\phi\text{-}C{\equiv}CLi$[a](2equiv)	$\phi\text{-}C{\equiv}C\text{-}C(=O)\text{-}C{\equiv}C\text{-}\phi$	95%
		85%

(a) Ethyl ether used as solvent.
(b) Glyme used as solvent.

These findings contrast sharply with those reported,[2a,3,4] and confirmed by us, for the reactions of 1 with neutral amines, which gave only ring opened adducts.

In the case of alkyllithiums (Table II), a most striking structure relationship is revealed. Whereas benzyllithium or even the bulky t-butyllithium gave only products of carbonyl attack, tritylllithium produced solely ring opening. Phenyl substitution in the alkyllithium appears to enhance ring opening over carbonyl attack, and preliminary results with lithium diphenylamide suggest that there may be some ring opening in this case too. It appears that nucleophilicity, rather than basicity, governs the course of the reaction; the better nucleophiles attacking the carbonyl function and the weaker nucleophiles attacking the ring carbon.[10]

It is known that reaction of $LiAlH_4$ with 1-acylaziridines results only in attack at the carbonyl site.[11] By contrast, we have found that reaction of 1 with $NaBH_4$ (a weaker nucleophilic reagent) affords a slow, clean conversion to the N-ethyl derivative 5 (eqs).



Further investigation regarding the relative electrophilicity of the ring versus carbonyl carbon in these and related systems is underway.

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2b. ibid., pp. 312-314.

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