Regioselectivity in nucleophilic ring-opening of aziridinones

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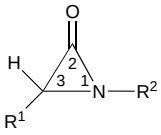
The proportions of products derived from competing modes of ring-opening of 1,3-di-*tert*-butylaziridinone and similar aziridinones by a variety of nitrogen, oxygen, sulfur and halogen nucleophiles do not agree with simple guidelines postulated in the literature for these types of aziridinones.

An important aspect of the chemistry of aziridinones is their mode of ring-opening by nucleophiles and the factors that



1 $R^1 = R^2 = Bu^t$
2 $R^1 = R^2$ = 1-adamantyl
3 R^1 = 1-adamantyl, $R^2 = Bu^t$
4 $R^1 = Bu^t$, R^2 = 1-adamantyl

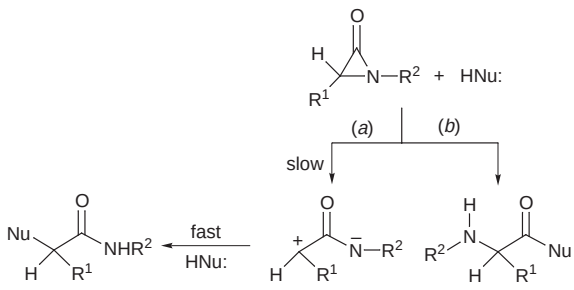
govern the outcome. It has been reported[1,2] that ionic, aprotic nucleophiles (Z^-) cause rupture exclusively of the acyl–nitrogen bond (1,2-bond), whereas non-ionic protic nucleophiles (HZ) afford products derived solely or mainly from scission of the alkyl–nitrogen bond (1,3-bond). Our previous publications[3,4] clearly contradict this sample rule, albeit with a limited set of nucleophiles. We have embarked on a broader study of nucleophilic ring-opening of aziridinones.

An examination of the nitrogen nucleophiles (aprotic) in Table 1 reveals immediately that all of them do not cleave solely the alkyl–nitrogen bond of **1** as alleged in the literature.[1,2] In fact, the only ones that exhibit this pattern are all of the aromatic amines (entries 10–17), none of which was used previously in conjunction with aziridinones **1**–**4**. On the other hand, the simple aliphatic primary amines rupture exclusively the acyl–nitrogen bond of **1**. The secondary amines exhibit varying degrees of ring-opening (entries 3 and 5 giving exactly opposite results) that also seem to depend on the nature of the aziridinone (*e.g.* compare entries 2 and 32), indicating a subtle dependence on steric factors. Roughly speaking, stronger, unhindered nitrogen nucleophiles tend to cleave the acyl–nitrogen bond, whereas sterically hindered, weaker ones favor scission of the alkyl–nitrogen bond. However, there are exceptions to even this rough rule (entries 5, 18 and 19). The aprotic oxygen and sulfur nucleophiles also exhibit considerable variation in their selectivity, the alcohols being most consistent in favoring cleavage of the alkyl–nitrogen bond. The protic ionic nucleophiles also do not all afford products derived from acyl–nitrogen cleavage, as suggested in the literature.[1,2] In fact, the sharp difference between bromides and iodides on one hand and alkoxides on the other hand suggests the intervention of yet another factor, namely, hardness or softness of the nucleophile. Iodide, a soft nucleophile, attacks the soft alkyl carbon of **1**, whereas alkoxide, a hard nucleophile, prefers to attack the harder acyl carbon.

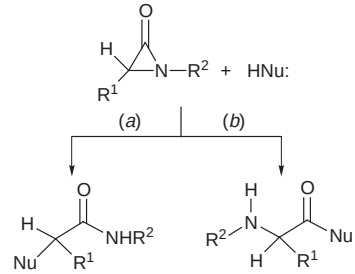
A priori, one can envisage the following two schemes that may determine the selectivity in ring-opening of the aziridinones. Scheme 1 resembles the S_N1/S_N2 type dichotomy encountered in nucleophilic aliphatic substitution [path (*a*) being unimolecular and path (*b*) being bimolecular], whereas Scheme 2 (competing bimolecular pathways) was apparently the basis of the guidelines given in the literature.[1,2] If Scheme 1 were to be the exclusive one prevailing, then the selectivity could be altered proportionately by changing the concentration of a nucleophile that tends to give both types of products. In our case, no such alteration or, at best, minor alterations could be effected in some cases that we examined. Scheme 1 would also indicate a strong dependence on nucleophilicity, path (*b*) being favored by powerful nucleophiles. However, as observed above, an excellent nucleophile such as iodide affords just the opposite type of product. It thus appears that, at least in the case of aziridinones **1**–**4**, no one scheme can satisfactorily explain the competing modes of ring-opening by nucleophiles, a conclusion that does not follow from a study of other types of aziridinones.[9]

We have extended the study of nitrogen nucleophiles to include those that might be synthetically useful as a route to larger heterocycles, as illustrated by the three new examples shown in Scheme 3.[10]

Note that (i) these are the only heterocyclic products isolated in each case; (ii) PhNHCN and $PhNH_2$ (mentioned in Table 1) give products derived from opposite modes of cleavage; (iii) specificity in the substitution pattern of these five-membered heterocyclic compounds can be controlled by the method of synthesis; and (iv) the structures of these three heterocyclic compounds could not have been predicted by previous guidelines.



Scheme 1

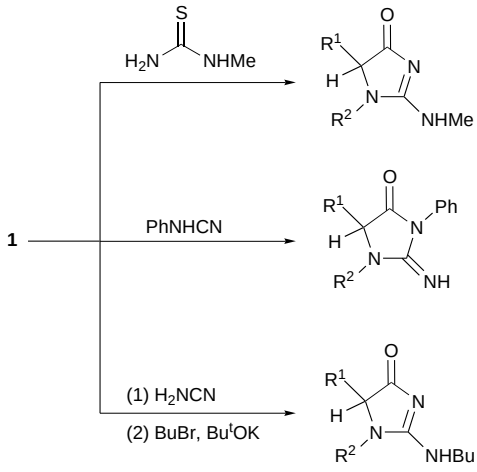


Scheme 2

Table 1 Relative modes of ring opening of aziridinones by various nucleophiles (0.06 mM each) in boiling toluene

					Major product			
						$\delta_H(CDCl_3)$		
Entry	Nucleophile	Aziridinone	Yield[a] (%)	1,2 : 1,3 cleavage (%)	Mp/°C	*C*-Bu^t	*N*-Bu^t	α-CH
1	$PrNH_2$	**1**	88	100 : 0	76–77	0.97	1.04	2.89
2	$BnNH_2$	**1**	92	100 : 0	81.5–82.5	0.97	0.99	2.92
3	Et_2NH	**1**	32	14 : 86	oil	1.02	1.35	2.51
4	Bu_2NH	**1**	54	< 22 : > 78	58–59	1.03	1.35	2.51
5	BnNHMe	**1**	54	86 : 14	oil	0.95	0.99	3.27
6	Pyrrolidine	**1**	65	6 : 94	106–107	1.02	1.33	2.36
7	Morpholine	**1**	48	< 2 : > 98	129–131	1.03	1.37	2.27
8	Piperidine	**1**	52	16 : 84	94–95	1.03	1.36	2.34
9	Piperazine	**1**	42	9 : 91	227	1.02	1.35	2.32
10	$PhNH_2$[b]	**1**	95	0 : 100	172–173	1.09	1.29	3.22
11	*p*-$MeC_6H_4NH_2$	**1**	94	0 : 100	157–157.5	1.08	1.29	3.17
12	*p*-$BrC_6H_4NH_2$	**1**	90	0 : 100	191–192	1.08	1.29	3.18
13	*p*-$MeOC_6H_4NH_2$	**1**	96	0 : 100	146–147	1.09	1.29	3.15
14	1-Aminonaphthalene	**1**	74	0 : 100	105–106	0.98	1.28	2.74
15	4-Aminoazobenzene	**1**	85	0 : 100	212–214	1.12	1.31	3.40
16	4-Aminobiphenyl	**1**	89	0 : 100	229–230	1.11	1.31	3.28
17	Ph_2NH	**1**	12	0 : 100	oil	1.10	1.24	4.23
18	H_2NCN[c]	**1**	94	100 : 0	258 (decomp.)	1.03	1.41	3.54
19	BnNHCN[c]	**1**	65	100 : 0	85–86	0.95	1.26	3.48
20	MeOH	**1**	84	< 7 : > 93	57–58	0.96	1.37	3.08
21	MeONa[d]	**1**	80	100 : 0	oil	0.89	1.00	2.80
22	PhOH	**1**	62	71 : 29	oil	1.04	1.12	3.17
23	Bu^tCH_2OH	**1**	71	5 : 95	oil	0.96	1.36	3.13
24	PhSH	**1**	72	55 : 45	52–53	1.02	1.13	3.20
25	PhSLi	**1**	80	86 : 14	52–53	1.02	1.13	3.20
26	$HSCH_2CO_2Et$	**1**	68	> 93 : < 7	52–53	0.98	1.06	3.12
27	H_2NCSNH_2[e]	**1**	93	55 : 45	258 (decomp.)	1.03	1.41	3.54
28	NaI/acetone	**1**	86	0 : 100	168–169	1.17	1.35	4.05
29	MgI_2 (anhydrous)[f]	**1**	86	0 : 100	168–169	1.17	1.35	4.05
30	$MgBr_2{\cdot}OEt_2$	**1**	87	0 : 100	157–158	1.14	1.36	4.00
31	$Mg(OEt)_2$	**1**	87	100 : 0	oil	0.91	1.01	2.90
32	$BnNH_2$	**3**	89	83 : 17	120–121	—	0.99	2.80
33	Morpholine	**3**	42	8 : 92	171–172	—	1.37	2.05
34	1-Aminonaphthalene	**3**	68	12 : 88	204–205	—	1.26	3.37
35	Morpholine	**2**	40	11 : 89	215–216			
36	1-Aminonaphthalene	**2**	70	7 : 93	121–122			

[a] Combined yield of the two cleavage products after purification. [b] Structure confirmed by using ^{15}N-labelled aniline, which exhibited a doublet (J = 8.05 Hz) at δ 69.22 in its ^{13}C (proton-decoupled) NMR spectrum (Ph^{15}NH*C*HBu^{t}CO). [c] The products are imidazolidinones, obtained by initial acyl–nitrogen cleavage followed by cyclization involving intramolecular nucleophilic attack on the nitrile (ref. 5). [d] See also ref. 6, where reaction was conducted in methanolic solution. [e] The major product is identical with that from entry 18 (net loss of H_2S) (ref. 7). [f] Ref. 8.



Scheme 3

Notes and References

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9 R. V. Hoffman, N. K. Nayyar and W. Chen, *J. Org. Chem.*, 1995, **60**, 4121, have relied exclusively on Scheme 1 to explain products arising from an aziridinone involved as an intermediate (R^1 = Ph or CO_2Et, R^2 = Me) and have correlated products with nucleophilic constants. However, in no case was the aziridinone actually isolated. H. E. Baumgarten, J. F. Fuerholzer, R. D. Clark and R. D. Thompson, *J. Am. Chem. Soc.*, 1963, **85**, 3303; S. Sarel, B. A. Weissman and Y. Stein, *Tetrahedron Lett.*, 1971, 373, studied the reaction of KOBu^t, MeOH or Bu^{t}OH with 1-*tert*-butyl-3-phenylaziridinone and 1-*tert*-butyl-3-bis-norcholanylaziridinone, respectively, the results being in accord with the simple guidelines (refs. 1 and 2).
10 Second and third reactions: work done by S.A. Ismail in our laboratory.

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