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Substituent Control over the Regiochemistry of Ring Opening of 2-Aziridinylmethyl Radicals

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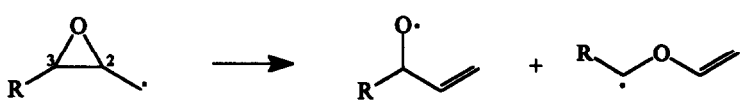
Abstract: **Several substituted 2-aziridinylmethyl radicals have been generated and a rapid ring opening ensues to produce aminyl radicals by way of C-N bond cleavage and in some instances α-aminyl carbon radicals via C-C bond homolysis.**

An important component of radical rearrangement chemistry is the ring opening chemistry of small ring compounds.[1] The cyclopropylmethyl radical and substituted analogs have been shown to have synthetic[2] and mechanistic[3] usefulness. Substituted 2-oxiranylmethyl radicals also have considerable value, particularly in organic synthesis.[4] Unlike cyclopropylmethyl radicals where C-C bond cleavage is the exclusive fate, the 2-oxiranylmethyl radicals may succumb to either C-C or C-O bond cleavage, depending on the nature of the substituent on the 3-position of the oxirane ring (Scheme 1).[5]



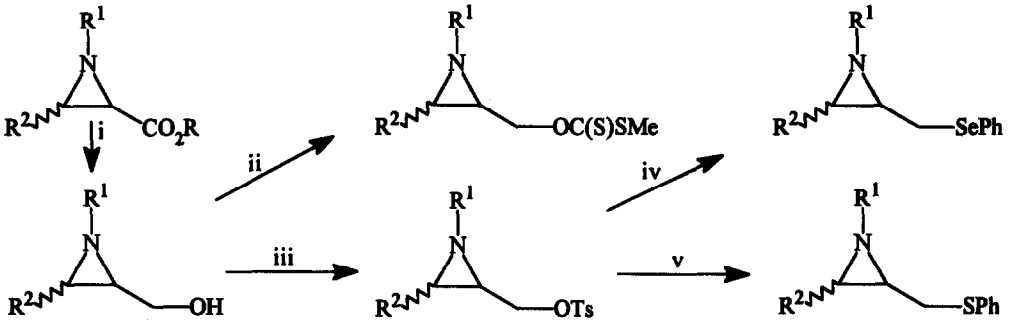
If R = vinyl or aryl

Scheme 1

Some studies have been carried out on related aziridinyl systems. Murphy has shown that highly substituted aziridinyl radicals[6] and ring-fused aziridinyl radicals[6,7] both open to nitrogen bearing radicals, with no evidence for any C-C bond breakage.[8] The absence of this second rearrangement mode is surprising, since the 2-aziridinylmethyl radicals should be at least as responsive to substituent effects as the 2-oxiranylmethyl radicals. Hence we felt the aziridinyl systems warranted further investigation with more diverse substitution patterns and without the constraint of fusion to a larger ring.[9] This preliminary communication of our study reports the discovery of a new mode of 2-aziridinylmethyl radical rearrangement.

The required radical precursors were prepared from 2-carboalkoxy aziridines by the reactions shown in Scheme 2. The 2-carboalkoxy aziridines were either known compounds, or their synthesis was based on known

procedures.[10] The preferred substrates for radical chemistry were found to be 2-aziridinylmethyl selenides although in some cases these compounds were thermally sensitive and therefore unsuitable. Similarly some 2-aziridinylmethyl xanthates were thermolabile. In one instance our only recourse was the use of a 2-aziridinyl sulfide.[11]



Reagents and Yields: i) LAH (39-97%); ii) 1. MeLi 2. CS_2 3. MeI (75-97%); iii) 1. MeLi 2. TsCl; iv) PhSeNa (2 steps: 34, 61-68%); v) PhSLi (2 steps: 34%)

Scheme 2

The conditions of tri-n-butyltin hydride and AIBN in refluxing benzene consistently afforded the best chemical yields of products. Our results are outlined in Tables 1 and 2 (Scheme 3). The products were quantitated in their crude mixture using ^1H nmr. This was accomplished using an added internal standard of dibenzyl sulfide.[12] In most cases the products could eventually be isolated, but not quantitatively.[13] The spectral data of the products compared favorably to published data or to that of the authentic compounds.

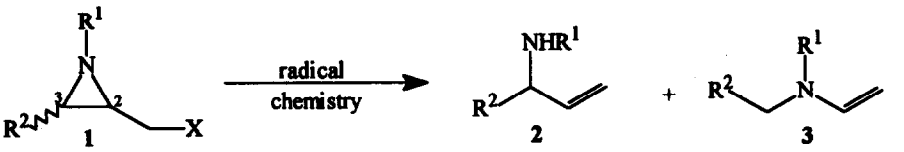
Table 1. Radical Reactions of N-Substituted Aziridines[a]

#	Conditions[b]	Starting Aziridine	Product (% Yield)
1	2.5 eq Bu_3SnH/AIBN/heat/2h	**1a** (R^1=CH_2Ph; X=SePh)	**2a**(R^1=CH_2Ph) (75)
2	2.5 eq Bu_3SnH/AIBN/heat/s.p./2.5h	**1a**	**2a** (79)
3	2.5 eq $(TMS)_3SiH$/AIBN/heat/2h	**1a**	**2a** (67)
4	2.5 eq Bu_3SnH/AIBN/light/26h	**1a**	**2a** (77)
5	2.5 eq Bu_3SnH/AIBN/heat/2h	**1b** (R^1=CH_2Ph; X=OC(S)SMe)	**2a** (45)
6	2.5 eq Bu_3SnH/AIBN/heat/s.p./2.5h	**1b**	**2a** (50)
7	5 eq Bu_3SnH/0.4 eq AIBN/heat/12d[c]	**1c** (R^1=Ph; X=SPh)	**2c** (R^1=Ph) (86)

Footnotes: [a]R^2 = H for all entries in this Table. [b]Solvent was benzene in each case. Substrate concentration was usually 0.05 M. 's.p.' means a syringe pump was used to introduce the tin reagent over 2h. Refluxing continued for another 1/2h. 0.2 eq. of AIBN was used unless otherwise noted. [c]Reaction was not taken to completion; yield is based consumed starting material.

When the nitrogen bears a phenyl or benzyl group (Table 1) the products arise exclusively from C-N bond homolysis as in the case of Murphy's compounds.[6,7] In those instances carbon-3 (C-3) bears only hydrogens. When C-3 bears a phenyl group, then that group increases the rate of C-C homolysis to level

competitive with C-N homolysis. Thus a second type of product is obtained (Table 2). The new products were assigned the structure **3** on the basis of two pieces of evidence. First, resonances consistent with terminal vinyl hydrogens of an N-vinyl functionality could be observed in the ^{1}H nmr spectra of the crude mixtures.[14,15] Second, the eventual isolation of benzyl amines of the structure $R^2CH_2NHR^1$ from the mixtures containing **3** is totally consistent with the expected hydrolytic behavior of enamines such as **3** on a chromatography column.[15] Hence we have discovered the first evidence for a new rearrangement mode of 2-aziridinylmethyl radicals.



Scheme 3

Table 2. Radical Reactions of N- and 3-Substituted Aziridines[a]

#	Cond.[b]	Starting Aziridine	Products (% Yields)[c]
1	B/0.05/2 h	**1d**(R^1=Ph; R^2=*cis*-Ph; X=SePh)	**2d** (R^1=Ph; R^2=Ph) (23) **3d** (45)[d]
2	B/0.05/1 h	**1e** (R^1=Ph; R^2=*cis*-Ph; X=OC(S)SMe)	**2d** (26) **3d** (29)
3	B/0.05/2 h	**1f** (R^1=Ph; R^2=*trans*-Ph; X=OC(S)SMe)	**2d** (34) **3d** (15)
4	A/4 h	**1g** (R^1=CH_2Ph; R^2=*cis*-Ph; X=SePh)	**2g** (R^1=CH_2Ph; R^2=Ph) (15) **3g** (40)
5	B/0.15/4 h	**1h** (R^1=Ar; R^2=*cis*-Ph; X=SePh)[e]	**2h** (R^1=Ar; R^2=Ph) (37) **3h** (29)
6	B/0.15/5 h	**1i** (R^1=Ph; R^2=*cis*-Ar; X=SePh)[e]	**2i** (R^1=Ph; R^2=Ar) (24) **3i** (46)

Footnotes: [a]Solvent was benzene in each case. 2.5 eq. of nBuSnH and 0.2 eq. of AIBN were employed in each instance. [b]Conditions A signify simple reflux of all components for the time indicated with initial substrate concentration = 0.05 M. For conditions B, the tin and AIBN were added to the substrate (0.05 or 0.15 M) via syringe pump over 2 hrs. Additional refluxing was for the time indicated. [c]The R^1 and R^2 substituents of **3** match those of **2**. [d]Based 82% consumption of starting material. [e]Ar = p-methoxyphenyl.

As with oxiranyl examples,[4,5] the additional conjugation of a C-3 substituent seems to offer a new direction for the ring opening rearrangement. We believe this is the first homolytic cleavage of a carbon-carbon bond of an aziridine. Furthermore, the geometry of the carbon substituents also seems to have an effect on the regiochemistry of the ring opening (Table 2: Entries 1, 2 & 3). We are currently investigating other substituted aziridinylmethyl radical systems and will report our results in due course.

ACKNOWLEDGEMENT We gratefully acknowledge NSERC of Canada for funding this research.

REFERENCES AND NOTES

1. Beckwith, K.L.J.; Ingold, K.U. In *Rearrangements in the Ground and Excited States*; de Mayo, Ed.; Academic Press; New York, 1980; Essay 4.

2. (a) Batey, R.A.; Harling, J.D.; Motherwell, W.B. *Tetrahedron* **1992**, *48*, 8031-8052. (b) Batey, R.A.; Motherwell, W.B. *Tetrahedron Letters* **1991**, *32*, 6211-6214. (c) Clive, D.L.J.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 3801-3814. (d)

Feldman, K.S.; Simpson, R.E. *J. Am. Chem. Soc.* **1989**, *111*, 4878-4886. (e) Feldman, K.S.; Kuok Keong Vong, A. *Tetrahedron Letters* **1990**, *31*, 823-826. (f) Singleton, D.A.; Church, K.M. *J. Org. Chem.* **1990**, *55*, 4780-4782. (g) Lei, B.; Fallis, A.G. *J. Org. Chem.* **1993**, *58*, 2186-2195.

3. (a) Griller, D.; Ingold, K.U. *Acc. Chem. Res.* **1980**, *13*, 317-323. (b) Adam, W.; Finzel, R. *J. Am. Chem. Soc.* **1992**, *114*, 4563-4568. (c) Rudolph, A.; Weedon, A.C. *Can. J. Chem.* **1990**, *68*, 1590-1597. (d) Lemieux, R.P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454-5460. (e) Castellino, A.J.; Bruice, T.C. *J. Am. Chem. Soc.* **1988**, *110*, 7512-7519.

4. (a) Rawal, V.H.; Iwasa, S. *Tetrahedron Letters* **1992**, *33*, 4687-4690. (b) Kim, S.; Koh, J.S. *J. Chem. Soc., Chem. Commun.* **1992**, 1377-1378. (c) Feldman, K.S.; Burns, C.J. *J. Org. Chem.* **1991**, *56*, 4601-4602. (d) Bowman, W.R.; Brown, D.S.; Burns, C.A.; Marples, B.A.; Zaidi, N.A. *Tetrahedron* **1992**, *48*, 6883-6896. (e) Kim, S.; Lee, S.; Koh, J.S. *J. Am. Chem. Soc.* **1991**, *113*, 5106-5107. (f) Rawal, V.H.; Newton, R.C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181-5183. (g) Kim, S.; Lee, S. *Tetrahedron Letters* **1991**, *32*, 6575-6578. (h) Dang, H.-S.; Roberts, B.P. *Tetrahedron Letters* **1992**, *33*, 6169-6172.

5. (a) Dickenson, J.M.; Murphy, J.A.; Patterson, C.W.; Wooster, N.F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1179-1184. (b) Feldman, K.S.; Fisher, T.E. *Tetrahedron* **1989**, *45*, 2969-2977.

6. Dickenson, J.M.; Murphy, J.A. *Tetrahedron* **1992**, *48*, 1317-1326. See also: Benbow, J.W.; Schulte, G.K.; Danishefsky, S.J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 915-917.

7. Dickenson, J.M.; Murphy, J.A. *J. Chem. Soc., Chem. Commun.* **1990**, 434-436.

8. Two research groups have studied 1-aziridinylcarbinyl radicals. Such systems can only rearrange via a C-N bond cleavage mechanism. See (a) Werry, J.; Stamm, H.; Lin, P.-Y.; Falkenstein, R.; Gries, S.; Irngartinger, H. *Tetrahedron* **1989**, *45*, 5015-5028. (b) Archier-Jay, D.; Besbes, N.; Laurent, A.; Stamm. H.; Tardivel, R. *Tetrahedron Letters* **1989**, *30*, 2271-2272. (c) Kim, S.; Kee, I.S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882-9883.

9. Ring opening reactions of fused systems under kinetic conditions tend to afford exocyclic radicals (nitrogen, oxygen or primary carbon radicals) regardless of the substitution pattern. See references 3,4,6,7 and Batey, R.A.; Grice, P.; Harling, J.D.; Motherwell, W.B; Rxepa, H.S. *J. Chem. Soc., Chem., Commun.* **1992**, 942-944.

10. (a) Nakamura, I.; Harada, K. *Heterocycles* **1978**, *9*, 473-479. (b) Warski, L. *J. Chem. Soc., Chem. Commun.* **1977**, 602-603.

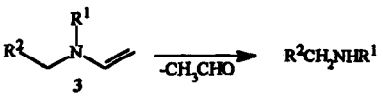
11. Cis and trans isomers are created by the placement of ring carbon substituents. Additional isomers are conceivable due to the two possible orientations of the aziridinyl nitrogen's substituents. No inversion isomers were observed.

12. ^{1}H nmr were run with at least 16 scans and a delay of >15 seconds between scans. The discernable resonances of the products were quantitated against the methylene peak of the dibenzyl sulfide by comparison of peak heights incorporating peak width at half height.

13. Some of the products decompose on silica or alumina (basic and neutral). For instance, an authentic sample of allyl benzyl amine could not be chromatographed quantitatively.

14. Attempts to synthesize the N-vinyl species by condensation of the corresponding amine with acetaldehyde were unsuccessful. For **3i**, ^{1}H nmr of terminal N-vinyl hydrogens: δ 4.04 (d, J=15.4 Hz); 4.01 (d, J=8.8 Hz).

15. The accompanying hydrolysis reaction begins during or before ^{1}H nmr analysis and is complete after chromatography. For instance, **3d** and phenyl benzyl amine can be observed in the nmr simultaneously. Furthermore one can observe the growth of the secondary amine methylene resonance at the expense of the terminal vinyl and methylene peaks of **3d** (and other N-vinyl amines **3**).



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