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An investigation into the β-cleavage of aziridinylcarbinyl radicals.

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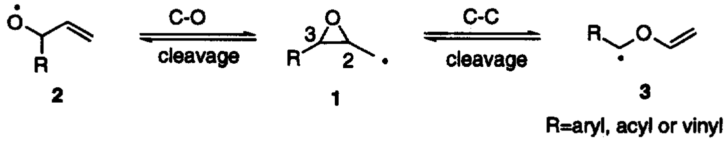
Abstract: In contrast to similar oxiranylcarbinyl radical systems, 3-arylaziridinylcarbinyl radicals have been shown to give only products of C-N bond cleavage.

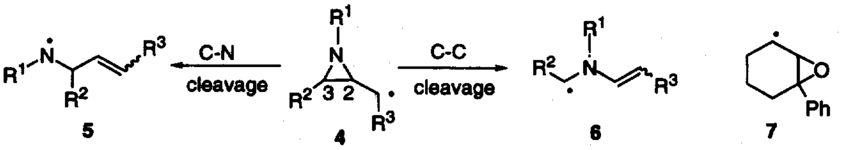
Keywords: Aziridines; amines; radical; cleavage reactions.

The cyclopropylcarbinyl-homoallylic rearrangement has been widely studied and it is recognised that stereoelectronic factors are important in controlling the direction of β-cleavage [1-6]. The related β-cleavage reactions of the C-O and C-C bonds (Scheme 1) of oxiranylcarbinyl radicals **1** have also been widely reported [4-11], but the influence of stereoelectronic effects is less clear [7]. In general calculations and experimental data suggest that C-O and C-C bond cleavage are reversible and that C-O bond cleavage is favoured kinetically [9-11]. When radical stabilising groups are present at position 3 products of C-C bond cleavage are usually observed particularly under thermodynamically-controlled conditions [7-11]. However, other factors including steric hindrance may affect the reactivity of the first-formed radicals **2** and **3** and determine product formation [8, 9].



Scheme 1

In the few examples of β-cleavage reactions of aziridinylcarbinyl radicals **4**, products derived from **5** arising from C-N bond cleavage are observed except when R^2=aryl in which case evidence of products of C-C bond cleavage *via* **6** is also reported (Scheme 2) [12-14]. The related SmI_2-mediated cleavage of 2-acylaziridines also leads to C-N bond cleavage [15].



Scheme 2

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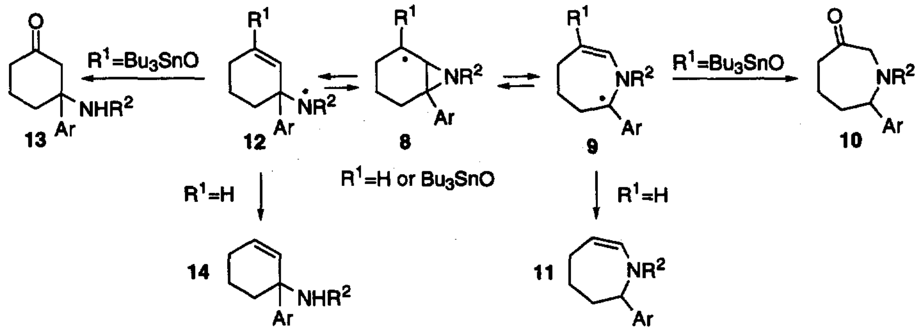
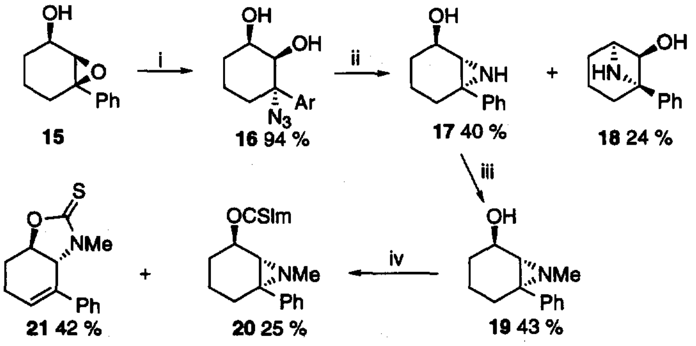


Scheme 3

Calculations suggest for the aziridinylmethyl radical **4** (R^1, R^2, R^3 = H) that C-N bond cleavage would be kinetically preferred whereas C-C bond cleavage would be thermodynamically preferred [10]. In view of these observations and our earlier work with oxiranylcarbinyl radicals **7** [8], in which ring-expanded products arising from C-C bond cleavage were observed, we anticipated that the generation of radicals **8** would lead to tetrahydroazepines **11** or azepanones **10** (Scheme 3). We report here that only products of C-N cleavage are observed with **8** [16].

The syntheses of precursors to **8** are shown in Schemes 4 and 5 [17]. Reaction of the epoxide **15** with NaN_3 gave the azidodiol **16** [8]. A Staudinger reaction gave the aziridine **17** along with some of the azetidinol **18**. Methylation of the aziridine **17** gave **19** which on reaction with 1,1-thiocarbonyldiimidazole gave the cyclic compound **21** and the desired thiocarbonylimidazolide **20**.



i) NaN_3, NH_4Cl, 8:1 MeOH:water ii) PPh_3, rt 5 days , reflux 5 hr iii) MeI, K_2CO_3, 18-Crown-6, iv) $CS(Im)_2$, DCM, reflux.

Scheme 4

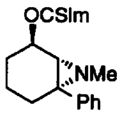
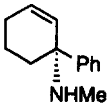
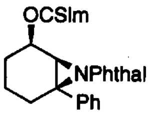
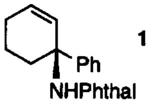
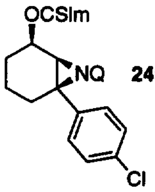
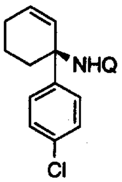
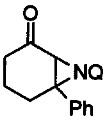
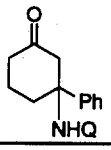
Reactions of the allylic alcohols **22** with 3-amino-2-ethyl-4(3*H*)-quinazolinone (QNH_2) or *N*-aminophthalimide ($PhthalNH_2$) with lead tetraacetate (LTA) in the presence of a base (Scheme 5) gave the *N*-substituted aziridines **23a/b** [18-20]. These reactions are known to proceed with *syn*-selectivity [18]. A similar reaction on 3-phenyl-2-cyclohexen-1-one gave the aziridine **25** in 59 % yield. Further reaction of the aziridino alcohols **23** with 1,1'-thiocarbonyldiimidazole gave the radical precursors **24a/b**.

a, Ar=Ph, R=Phthal; b, Ar=p-ClC_6H_4, R=Q (66-98 %) i) $CS(Im)_2$, DCM, reflux (50 %).

Scheme 5

Table :

Products of the β-cleavage of 3-arylaziridines.

Substrate	**Product**	**Isolated Yield %$^{a, b}$**
 20	 14, R^2=Me	15^{c}
 24a	 14, R^2=Phthal	67
 24b	 14, R^2=Q	40^{d}
 25	 13, R^2=Q	54^{d}

a) $[Bu_3SnH]$=0.05-0.07M, 2.5-2.8 eq., added at a rate of 40-60 ml/hr to a refluxing solution of the substrate 003-0.08M in THF.

b) TLC showed no evidence for any other products.

c) low yield obtained due to small scale reactions and difficult purifications-estimated purity 90 %.

d) NMR spectra resolved at 80°C for 14 (R^2=Q) and 50°C for 13, owing to hindered rotation at 25°C.

The isolated yields of products are shown in the Table. The contrast between the aziridinyl and oxiranyl systems is striking. The reaction conditions used should favour thermodynamic control and it would be reasonable to assume that some evidence of C-C bond cleavage would be detected in the products owing to the stabilisation of the carbon-centred radical **9** by the aryl group.

The isolation of only products of C-N bond cleavage may be explained by stereoelectronic control in the cleavage of radical **8** in which overlap of the singly occupied p-orbital with the C-C bond of the aziridine would not be possible except in a very unfavourable conformation. No such constraints would operate in radical **4**. In view of the absence of such stereoelectronic effects in similar oxiranylcarbinyl radicals, it may be more likely that **9** is reversibly formed but is unreactive to reduction owing to the close proximity of the *N*-substituent (cf ref. 9). The observed tributyltin hydride reductions of **12** are analogous to that reported for one other *N*-quinazolinonyl aminyl radical [13].

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