Tetrahedron Letters, Vol. 33, No. 34, pp. 4993-4994, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Cyclisation of Aminyl Radicals using Sulfenamide Precursors

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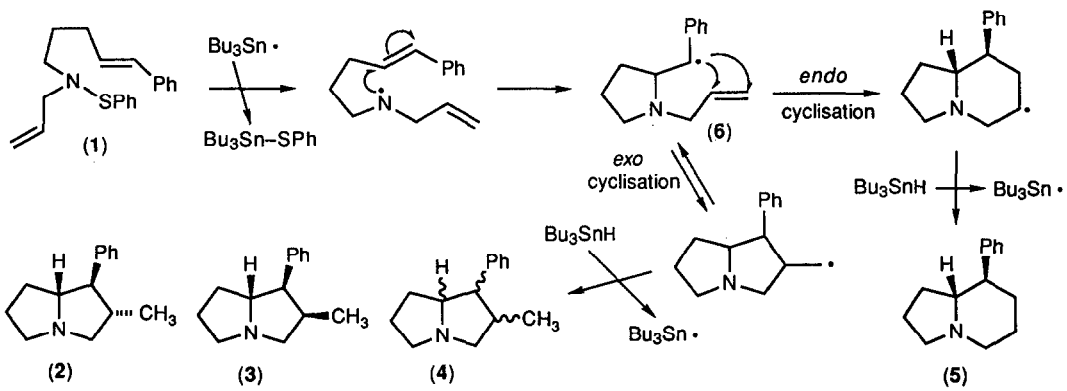
Abstract: *Sulfenamides react readily with tributyltin hydride to yield aminyl radicals, which undergo intramolecular addition to activated double bonds.*

In a previous paper[1] we reported our initial results on the use of sulfenamides as precursors of aminyl radicals, generated using tributyltin hydride (Bu_3SnH) for S_H2 abstraction of the benzenesulfenyl group. Aminyl radicals do not undergo cyclisation onto alkenes in good yield unless the nitrogen centre is electrophilic, *e.g.* protonated as aminium radicals[2] or as amidyl radicals.[3] Initial studies[1,4] using sulfenamides as aminyl radical precursors have confirmed that cyclisation is not favourable, *e.g.* the reaction between Bu_3SnH and *N*-allyl-*N*-benzenesulfenyl-4-pentenylamine[1] gave only the non-cyclised product, *N*-allyl-4-pentenylamine. In this communication we report our preliminary investigations which show that aminyl radicals undergo cyclisation with suitably 'activated' alkenes. Investigation of methods of cyclising aminyl radicals, generated from sulfenamides, has shown that Bu_3SnH can be successfully used. A useful synthesis of pyrrolizidines, involving tandem cyclisation, has been developed using this methodology.

Generation of aminyl radicals from sulfenamide (**1**) (with an activated aryl-alkene) using Bu_3SnH in THF gave a mixture of bicyclised pyrrolizidines (**2-4**) and an indolizidine[5] (**5**) in reasonable yields (Scheme 1).[6] Non-bicyclised products were not detected. The formation of an intermediate stable benzylic radical (**6**) appears to overcome the reported reversibility of the cyclisation of aminyl radicals.[2,3] The unusually large proportion (14% in THF and 8% in PhH) of the thermodynamically more stable isomer (**5**) indicates reversibility in the favoured *exo* cyclisation because of the stable intermediate benzylic radical (**6**). The ratio,[6] but not the yield (49%), of pyrrolizidines altered when the solvent was changed from THF to benzene.

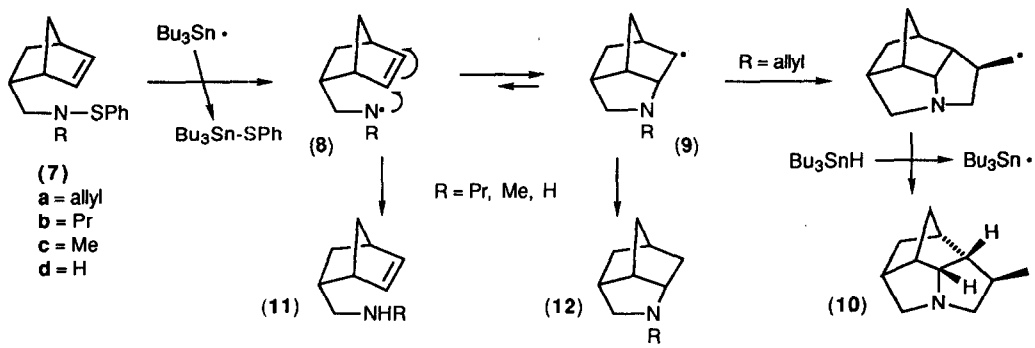


Scheme 1. Tandem cyclisation of (*E*)-*N*-allyl-*N*-benzenesulfenyl-5-phenyl-4-pentenylamine (**1**)

The rate of reaction between Bu_3SnH and aminyl radicals is normally faster than the rate of cyclisation onto alkenes.[1-4] Therefore, we sought a system in which cyclisation would be faster than reduction by

Bu_3SnH, in order to prove that aminyl radicals will cyclise onto alkenes if the reaction is kinetically favourable. The rate of 5-*exo*-trig cyclisation of *endo*-2-(bicyclo[2.2.1]hept-2-en-5-yl)ethyl radicals is one of the fastest reported ($1 \times 10^7\ s^{-1}$)[7] because of the strained alkene and close orientation of the carbon-radical to the alkene. Therefore, we considered that the analogous aminyl radicals should provide a good model for studying the kinetic feasibility of cyclisation. A series of sulfenamide precursors (**7**) were synthesised and the corresponding aminyl radicals generated using Bu_3SnH. As predicted, cyclisation of aminyl radicals was observed, the ratio of non-cyclised (**11**) to cyclised (**12**) products depends on the *N*-substituent on (**7**) (Scheme 2). The quadracyclic pyrrolizidine (**10**)[8] (90%) was the only product formed with a *N*-allyl substituent, *i.e.* an intramolecular trap to prevent equilibrium of (**9**) back to the aminyl radical (**8**). Interestingly, an initial reaction, worked up with CH_2Cl_2, gave the chloromethyl chloride salt of (**10**) (91%), *i.e.* (**10**) is a strong enough nucleophile to undergo a S_N2 reaction with CH_2Cl_2. However, with a *N*-propyl substituent, tricyclic (**12b**) (29% isolated yield) and non-cyclised (**11b**) were obtained in a 8:2 ratio (measured by ^1H NMR). Similar results were obtained for the sulfenamides (**7c**, **7d**, R = Me, H). The formation of non-cyclised material when an intramolecular trap is absent is probably a consequence of the reversible nature of aminyl radical cyclisation.

The use of malonic acid[2] or $MgBr_2.Et_2O$[9] to make the aminyl radicals more electrophilic did not give cyclisation [for (**7a**) the yields of (**11a**) were 48% and 51% resp.]. This supports the observations reported by Newcomb,[2,10] that the rate of reduction of aminium radicals by the nucleophilic Bu_3SnH is faster than for aminyl radicals ($3 \times 10^4\ M^{-1}s^{-1}$), *i.e.* the rate of reduction by Bu_3SnH of aminium radicals (or Lewis acid complexed) of (**8a**) is even faster than the favoured cyclisation.



Scheme 2. Cyclisation of the aminyl radicals of *endo* -2-[(alkylamino)methyl]-bicyclo[2.2.1]hept-5-enes.

Acknowledgements

We gratefully thank Rhône-Poulenc Agriculture for a Post-graduate Research Studentship (DNC) and the S.E.R.C. for a Post-doctoral Fellowship (RJM), and the Warwick SERC NMR service for nOe measurements.

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6. Bu_3SnH and AIBN were dissolved in deoxygenated solvent and added *via* a syringe pump over 5 h to the refluxing solution of sulfenamide. Ratio of pyrrolizidines, (**2**):(**3**):(**4**) = 2.8:1.2:1 (THF), 6.5:2.5:1 (PhH). The stereochemistry of (**2**), (**3**), and (**5**) was assigned by nOe measurements, but the assignment of (**4**) was ambiguous. Yield of (**5**) = 14% (THF), 8% (PhH).
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8. Pyrrolizidine (**10**) was also synthesised from the amine (**11a**) *via* $HgCl_2$ cyclisation (56%), followed by reduction with sodium borohydride *via* radical (**9a**), and the structure confirmed using high field NMR and mass spectroscopy.
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(Received in UK 17 June 1992)