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Synthesis of Pyrrolizidines by Cascade Reactions of N-Alkenylaziridinylmethyl Radicals

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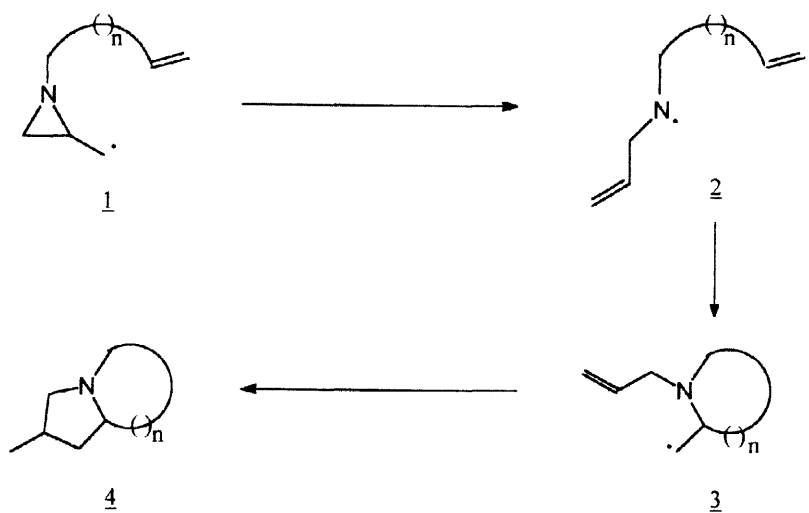
Abstract : Pyrrolizidines were synthesized in a one-step-reaction from 2-(bromomethyl)aziridines *via* a cascade of radical reactions involving aziridinylmethyl radicals, N-allylaminyl radicals and carbon-centered pyrrolidinyl radicals. © 1998 Elsevier Science Ltd. All rights reserved.

Cyclopropylmethyl radicals have been shown to be useful intermediates in organic synthesis.[1] Ring opening reactions of cyclopropanes and oxiranes via cyclopropylmethyl radicals and oxiranylmethyl radicals, respectively, have received much attention.[1-3] In principle, the nitrogen analogues, i.e. 2-aziridinylmethyl radicals, have a similar synthetic potential, which has not been fully exploited yet.[4] 2-(Bromomethyl)aziridines easily afford N-allylamines upon radical mediated cleavage.[4a,b] This generation of aziridinylmethyl radicals and ring cleavage to aminyl radicals offers the possibility to construct more complex frameworks of molecu-



Scheme 1

les. The selective preparation of complex polycyclic molecules via radical mediated cascade reactions[5-7] (also correctly assigned as domino reactions[8]) is a very attractive route. By retrosynthetic analysis of the

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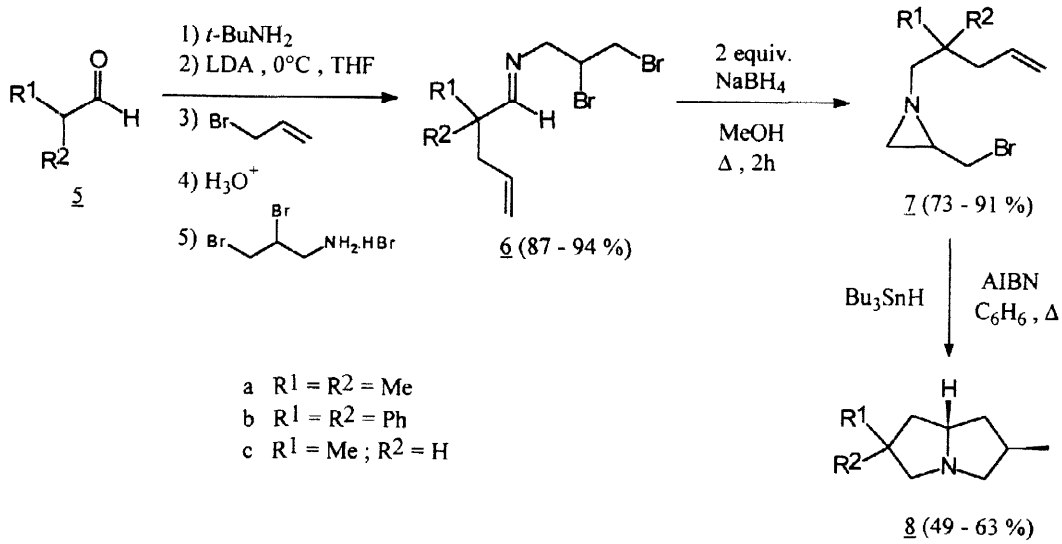
cascade reactions, the use of 1-(ω-alkenyl)-2-(bromomethyl)aziridines **1** in the radical initiated process could lead to pyrrolizidines (n=3) or indolizidines (n=4) in a one-step-reaction (Scheme 1). Indeed, the rate of cyclization of neutral aminyl radicals is similar to the rate of ring opening which has limited their use for monocyclization reactions [4c,9-10] By trapping the monocyclized carbon radical intermediate by an internal olefin, the cyclization process is forced to occur. The use of cascade radical cyclizations of carbon-centered radicals in synthetic reactions has been extensively reported[5-7,11,12] but there are only a few examples of the use of aminyl radicals.[13-15] In the present communication, it is shown that 2-(bromomethyl)aziridines 7, carrying a N-bishomoallyl substituent, are valuable building blocks for transformation into pyrrolizidine skeletons via radical cascade reactions.

2-(Bromomethyl)aziridines 7, carrying a 4-alken-1-yl substituent, are accessible from aldehydes **5** via a sequence of reactions involving (a) imination with t-butylamine, (b) α-alkylation with an allylic bromide, (c) hydrolysis to the corresponding aldehyde, (d) imination with 2,3-dibromopropylamine to give the corresponding N-(alkylidene)-2,3-dibromopropylamine and (e) reductive cyclization with sodium borohydride in methanol (Scheme 2).[4a,b] Reaction of 2-(bromomethyl)aziridines 7 with tributyltin hydride [1.7 equiv.; added via a syringe pump at a rate of 3 ml / h in benzene in the presence of azoisobutyronitrile (0.85 equiv.)] under

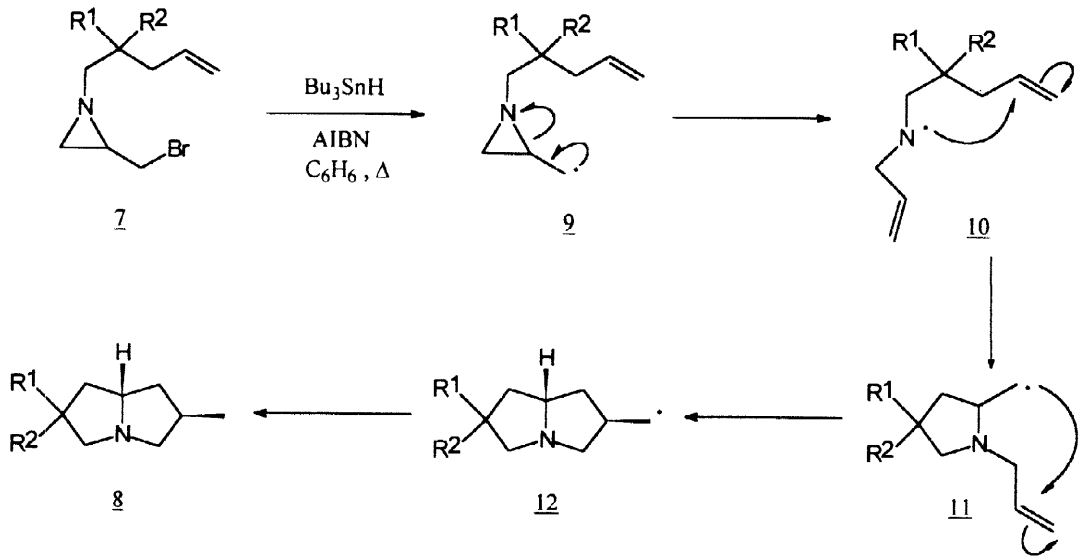


Scheme 2

reflux afforded pyrrolizidines **8** in 49-63% yield after purification by flash chromatography. The use of a syringe pump is essential as otherwise the formation of substantial amounts (up to 20%) of monocyclized N-allyl-N-bishomoallylamines is observed. The cascade reaction of aziridines 7 to pyrrolizidines **8** seems to be a stereoselective process as it leads to one stereoisomer with respect to the methyl substituent and the bridge-

head hydrogen, the stereochemistry of compounds **8** being secured by NOE and spin-spin decoupling experiments. Compound **8c** was obtained as a 1:1 mixture of isomers, the stereochemistry of which was not determined.

The radical-induced formation of pyrrolizidines **8** from 2-(bromomethyl)aziridines **7** can be interpreted as the result of a cascade of carbon centered and nitrogen centered radicals. Tributyltin hydride led to the formation of aziridinylmethyl radicals **9**, which rearranged into N-allylaminyl radicals **10**.[4a,b] The aminyl radicals **10** were trapped in an intramolecular fashion to give (2-pyrrolidinyl)methyl radicals **11** which underwent cyclization to the bicyclic skeleton, after which the radical cascade terminated into azabicyclic compounds **8** (Scheme 3).



7 9 10 11 12 8

Scheme 3

The sonification of aziridine **7a** (R^1=R^2=Me) with a zinc-copper couple in aqueous methanol for 4h at room temperature only gave rise to N-allyl-2,2-dimethyl-4-pentenylamine in 86% yield.

All attempts to synthesize an indolizidine via the radical-induced cascade reaction of 2-(bromomethyl)-1-(2,2-dimethyl-5-hexenyl)aziridine with tributyltin hydride / AIBN in benzene, even in the presence of the activating magnesium bromide diethyl etherate,[4c] failed. Only variable amounts of the corresponding N-allyl-2,2-dimethyl-5-hexenylamine were isolated.

Pyrrolizidines, being known as a class of alkaloids from the animal and plant kingdom, have been prepared already via free radical-induced cyclization of N-allyl-N-bishomoallylsulfenamides,[14] N-chloro-N-alkylbishomoallylamines[16] and N-allyl-N-benzoyloxy-5-pentenamide.[17] A similar strategy to produce a cascade of radical cyclizations utilising N-(ω-selenenylallyl)-α-cinnamylimines failed for pyrrolizidines but was successful for indolizidines.[18]

Acknowledgements

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