New Stereoselective Synthesis of *trans*-2,5-Disubstituted Pyrrolidines by Cyclization of Aminyl Radicals Generated from 2- and/or 5-Substituted *N*-Chloro-*N*-alkylalk-4-enylamines with Bu_3SnH-Azoisobutyronitrile

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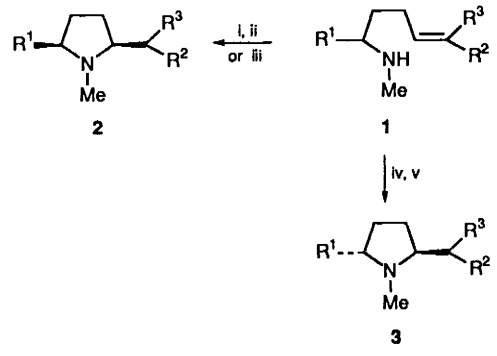
trans-*N*-Alkyl-2- and/or 5-substituted pyrrolidines are stereoselectively formed in up to 63% yields by *N*-chlorination of 2- and/or 5-substituted *N*-methylpent-4-enylamine with *N*-chlorosuccinimide, followed by heating a solution of the resulting *N*-chloro-unsaturated amines in benzene with Bu_3SnH–azoisobutyronitrile under reflux; a pathway involving stereoselective cyclization of neutral aminyl radicals is proposed.

Protonated aminyl radicals (aminium radicals) or metal ion-complexed aminyl radicals have been reported to undergo intramolecular cyclization to give five-membered nitrogen heterocycles.[1] It has also been reported that neutral aminyl radicals can be generated by the photolysis or thermolysis of a variety of substrates, such as *N*-chloroamines,[2] *N*-nitrosoamines,[3] 2-tetrazenes,[4] *N*-hydroxypyridine-2-thione carbamates,[5] sulfenylamines,[6a] sulfenylimines,[6b,c] and azides;[7] they also undergo cyclization to give heterocyclic molecules.

In previous papers[8] we reported that anodic oxidation of lithium amides of 1- and/or 5-substituted *N*-methylalk-4-enylamines **1** or the treatment of 1- and/or 5-substituted *N*-methylalk-4-enylamines **1** with a catalytic amount of butyllithium gave *cis*-*N*-methyl-2,5-disubstituted pyrrolidines **2** stereoselectively in good yields (Scheme 1).[9] We have proposed



Scheme 1 *Reagents and conditions:* i, BuLi; ii, −e; iii, BuLi (0.1 equiv.); iv, NCS, benzene; v, Bu_3SnH–AIBN, benzene, reflux

pathways for these pyrrolidine formations in terms of either a cyclization of the aminyl radical intermediate on the electrode surface[8] or of an anionic cyclization of intermediary lithium amides.[9] †

In a continuation of these studies concerning the formation of pyrrolidines by the cyclization of unsaturated amines, we report here that the aminyl radicals can be efficiently generated by the reaction of *N*-chloroalk-4-enylamines with Bu_3SnH–azoisobutyronitrile (AIBN) and that, in contrast to the above-mentioned electrolytic or anionic formation of *cis*-2,5-disubstituted pyrrolidines **2**, they undergo a stereoselective cyclization to give *trans*-2,5-disubstituted pyrrolidines in fair to good yields. Thus, typically, *N*-chlorination of alk-4-enylamines **1d** (R^1 = R^2 = Ph, R^3 = H) in benzene with 1 equiv. of *N*-chlorosuccinimide (NCS), followed by heating of the resulting *N*-chloroalk-4-enylamines with Bu_3SnH (1 equiv.) and AIBN (1 equiv.) in benzene under reflux for 8 h, gave the corresponding *trans*-2,5-disubstituted pyrrolidines **3d** (R^1 = R^2 = Ph, R^3 = H) in 63% yield. The yields of the pyrrolidines **3** from alk-4-enylamines **1** with different substituents attached to the 2- and/or 5-positions are summarized in Table 1. It is notable that all of the cyclizations gave exclusively *trans*-2,5-disubstituted pyrrolidines, the stereochemistry of which was established by either a direct comparison with an authentic sample prepared by aminomercuriation[8a,b,10] or by their ^1H NMR spectra. *N*-Unsubstituted *trans*-2,5-disubstituted pyrrolidines, such as pyrrolidine **6**, can be prepared by the present method; *N*-benzylalk-4-enylamine **4** is cyclized to *N*-benzylpyrrolidine **5**, which is subjected to hydrogenolysis with Pd/C as catalyst to give pyrrolidine **6** (Scheme 2).

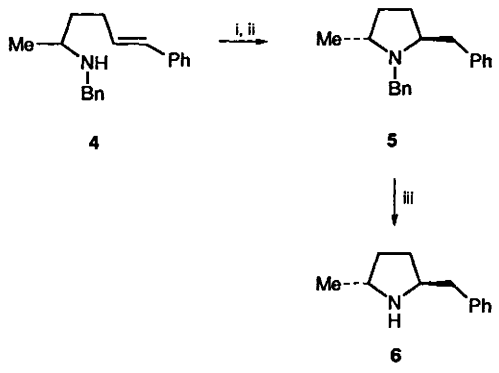
Table 1 Aminyl radical cyclization of alk-4-enylamines **1**

Alkenylamine **1a–f**					Yield of **3a–f** (%)[b]
	R^1	R^2	R^3	Product[a]	
1a	Ph	H	H	**3a**	19
1b	Ph	Me	H	**3b**	42
1c	Ph	Me	Me	**3c**	53
1d	Ph	Ph	H	**3d**	63
1e	Me	Ph	H	**3e**	57
1f	H	Ph	H	**3f**	37

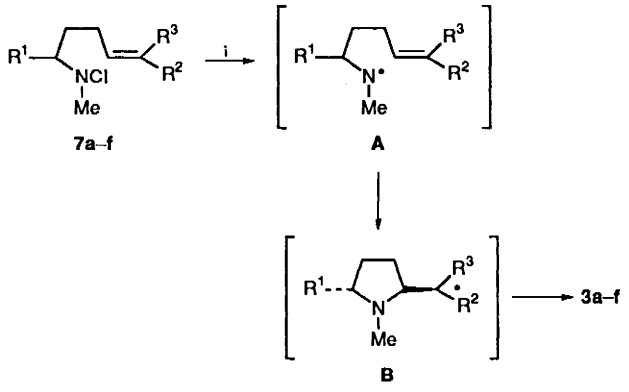
[a] Satisfactory analytical and spectroscopic results were obtained for these products. [b] Isolated yields by PLC.

The suggested pathway of the present pyrrolidine formation is outlined in Scheme 3; the reaction of *N*-chloroalk-4-enylamines **7a–f** with Bu_3SnH–AIBN generates the corresponding aminyl radical **A** which undergoes stereoselective cyclization to give the *trans*-2,5-disubstituted pyrrolidines **3a–f**. Involvement of the aminyl radicals in this pyrrolidine formation is supported by the following findings. (*a*) The pyrrolidines are formed in appreciably higher yields from 5-dialkyl- and 5-phenylalk-4-enylamines than from 5-unsubstituted alk-4-enylamines. The formation of pyrrolidines from the 5-substituted amines involves the more stabilized tertiary and benzylic radicals as the intermediates, while those from the 5-unsubstituted amines involve less stabilized primary radicals.

† The yields of the pyrrolidines formed by the electrolytic and non-electrolytic procedures differ considerably in some cases; no cyclization to the pyrrolidines takes place from (*E*)- and (*Z*)-(2*S*,3*S*)-2,3-bis-(methoxymethoxy)-5-(4-methoxyphenyl)-*N*-methylpent-4-enylamines merely by a treatment with butyllithium, while the corresponding pyrrolidines can be obtained in 50–53% yields by anodic oxidation of their lithium amides.[8d] This difference in the results implies that the mechanisms involved in the two procedures differ.

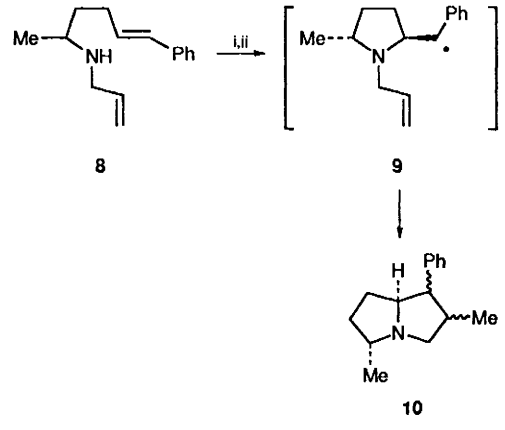


Scheme 2 *Reagents and conditions:* i, NCS; ii, Bu_3SnH–AIBN, benzene, reflux; iii, H_2, Pd/C



Scheme 3 *Reagents and conditions:* i, Bu_3SnH–AIBN, benzene, reflux

(*b*) Pyrrolizines **10** (a 29:71 mixture of diastereoisomers) can be obtained in 53% yield by the reaction of *N*-allyl-*N*-chloropent-4-enylamine **8**. This tandem cyclization should require a carbon-centred radical **9**, as outlined in Scheme 4.



Scheme 4 *Reagents and conditions:* i, NCS; ii, Bu_3SnH–AIBN, benzene, reflux

The stereoselectivity of the present cyclization of unsaturated amines is remarkable in view of the results of cyclization by another method; the aminium radicals generated from *N*-hydroxypyridine-2-thione carbamate of *N*-butyl-1-methylpent-4-enylamine have been reported to give a 3:1 mixture of *trans*- and *cis*-2,5-disubstituted pyrrolidines.[5a,c] We found that photolysis or thermolysis of the *N*-chloro amine of **1a** in the presence of benzoyl peroxide (0.02 equiv.) in methanol gave a 6:4 mixture of *trans*- and *cis*-2-methoxymethyl-*N*-methyl-5-phenylpyrrolidines (10–16%). We also found that thermolysis of the *N*-chloro amine of **1d** in the presence of benzoyl peroxide in methanol gave a 8:2 mixture of *trans*- and *cis*-2-(1-methoxybenzyl)-*N*-methyl-5-phenylpyrrolidines (90%).

We believe that the present method should be of value for the synthesis of some five-membered nitrogen heterocycles in view of the simplicity of the procedure and the stereoselectivity of the reaction.

Experimental

Typical Procedure for the Synthesis of Pyrrolidines **3** *by Aminyl Radical Cyclization.*—To *N*-methyl-1,5-diphenylpent-4-enylamine **1d** (100.5 mg, 0.4 mmol), prepared by reductive amination of 1,5-diphenylpent-4-en-1-one with methylamine and sodium cyanoborohydride according to the method reported previously by us,[8c] in dry benzene (5 cm^3) was added *N*-chlorosuccinimide (53.5 mg, 0.4 mmol) under a nitrogen atmosphere; the mixture was stirred at room temperature for 5 min. Tributyltin hydride (116.4 mg, 0.4 mmol) and azoisobutyronitrile (54.5 mg, 0.4 mmol) were added to the reaction mixture which was then heated under reflux for 8 h. The mixture was then cooled to room temperature, and dissolved in diethyl ether (30 cm^3). After the ethereal solution had been treated with 10% aqueous potassium fluoride (0.5 cm^3) it was stirred for 1 h. The ethereal solution was separated and washed with water (3 × 5 cm^3) and brine (10 cm^3). Evaporation of the solvent gave a crude product which was made acidic (pH 2–3) with concentrated hydrochloric acid. The aqueous solution was washed with diethyl ether (2 × 10 cm^3) and then made basic (pH 9–10) with aqueous sodium hydroxide (4 mol dm^{-3}) at 0 °C. The resulting aqueous solution was extracted with diethyl ether (3 × 20 cm^3); the combined ether solutions were washed with brine (20 cm^3) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by preparative layer chromatography (PLC) (silica gel, dichloromethane–methanol–25% ammonia solution, 150:10:1) gave *trans*-2-benzyl-1-methyl-5-phenylpyrrolidine **3d** (63.4 mg, 63%) as an oil.

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