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Radical Cyclisation of Amino Aldehydes Leading to Hydroxy Pyrrolidines and Piperidines

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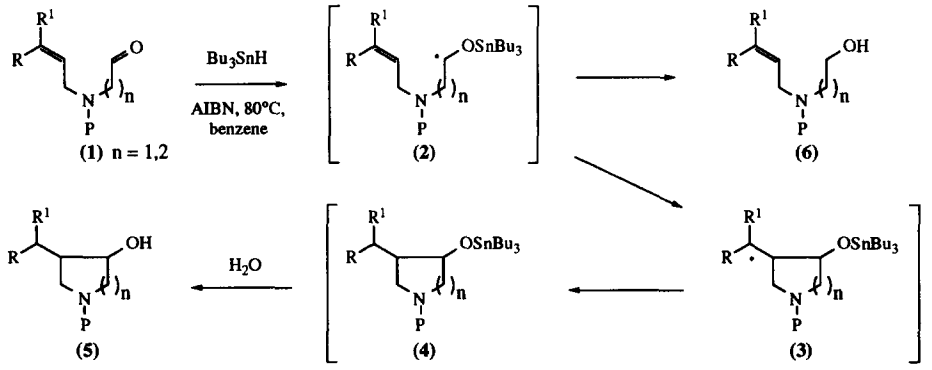
Abstract: The cyclisation of amino aldehydes using Bu_3SnH in boiling benzene is reported. The reaction proceeds *via* addition of a tributyltin radical to the aldehyde forming an *O*-stannyl ketyl and radical cyclisation onto electron poor or rich double bonds gives rise to hydroxy pyrrolidines and piperidines.

Radical cyclisation reactions mediated by Bu_3SnH have attracted considerable interest.[1] Traditional precursors for these reactions include halides, alkenes, alkynes, xanthates, selenides and sulfides that contain a suitably situated radical acceptor, typically a double or triple bond. One drawback to these cyclisations is the loss of two functional groups, namely C-X and C=C, from the precursor. In contrast, Enholm and co-workers[2] have shown that *O*-stannyl ketyls, prepared from reaction of Bu_3SnH[3] with aldehydes, can undergo cyclisation to produce cyclopentanes that retain a versatile hydroxyl functional group. Related cyclisations using allylic *O*-stannyl ketyls (generated from unsaturated ketones) have also recently been reported.[4] As part of our programme aimed at developing new free-radical methods for heterocycle synthesis,[5] we wish to report the application of *O*-stannyl ketyl cyclisations to the preparation of substituted pyrrolidines[6] and piperidines.[7]

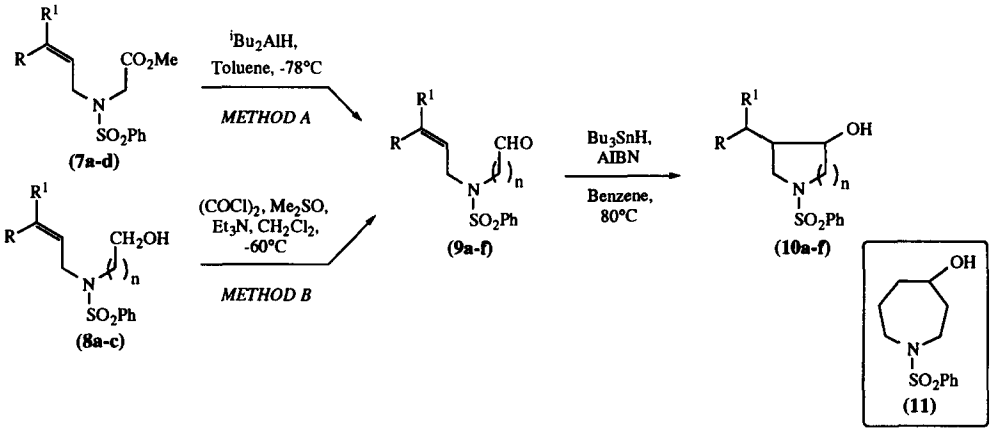


Scheme 1

The cyclisation reaction, shown in scheme 1, centres on the reaction of α- or β-amino aldehydes (**1**) with Bu_3SnH. This is expected[2] to give rise to an intermediate *O*-stannyl ketyl (**2**) which can undergo 5- or 6-*exo* radical cyclisation to afford the cyclic amine (**3**). Subsequent hydrogen atom transfer from Bu_3SnH is expected to produce (**4**) which on aqueous work-up is converted to the cyclic alcohol (**5**). It should be noted

that simple reduction of (**1**), to give the acyclic primary alcohol (**6**), is also possible if the radical (**2**) reacts with Bu_3SnH rather than the double bond.

Initial studies concentrated on the preparation and cyclisation of aldehydes (**9a-d**) which contained electron-rich double bonds (table, entries 1-4). These were prepared on reduction of the corresponding methyl ester (**7a-d**) using diisobutylaluminium hydride at low temperature.[8] The crude aldehyde (**9a-d**) was then immediately reacted with Bu_3SnH (1.5-2 equiv.) and AIBN (0.2 equiv.) in boiling benzene[9] and the progress of the reaction monitored using TLC.[10] Workup and column chromatography (silica) afforded the desired pyrrolidine (**10a-d**) as a mixture of diastereomers in 40-52% yield.[11] No primary alcohol resulting from simple reduction of the aldehyde (**9a-d**) was isolated from any of these reactions. The aldehyde (**9d**) was also prepared on Swern oxidation of the corresponding alcohol (**8a**) (table, entry 5). Treatment of the crude oxidation product with Bu_3SnH gave (**10d**) in identical yield and diastereoselectivity to that observed earlier starting from the methyl ester (**7d**). This method was also shown to have application in piperidine synthesis and the crude β-amino aldehydes (**9e**) and (**9f**) [prepared on oxidation of alcohols (**8b**) and (**8c**)] could be cyclised to secondary alcohols (**10e**) and (**10f**) in 56 and 40% yields respectively (table, entries 6-7). A small amount of primary alcohol (**8a-b**), derived from simple reduction of the aldehyde (**9e-f**), was also isolated from these reactions.[12] The reaction of Bu_3SnH with (**9f**) also gave rise to the hexahydroazepine (**11**) (in 8% yield) and this presumably arises from a 7-*endo* radical cyclisation of the intermediate *O*-stannyl ketyl.

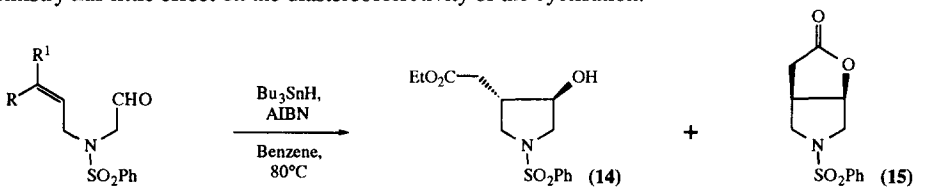


Entry	Precursor	R	R^1	n	Aldehyde (9)	Method of Aldehyde Prep.	Yield of (10) (%)	Diastereomer ratio
1	7a	H	H	1	a	A	40[§]	1.0 : 1[#]
2	7b	H	Me	1	b	A	50	1.2 : 1
3	7c	Me	Me	1	c	A	42	1.2 : 1
4	7d	H	Ph	1	d	A	52	1.6 : 1
5	8a	H	Ph	1	d	B	52	1.6 : 1
6	8b	H	Ph	2	e	B	56*	1.3 : 1
7	8c	H	H	2	f	B	40[¶]	1.2 : 1

*Alcohol (**8b**) was also formed in 4% yield. [¶]Alcohol (**8c**) (7%) and the hexahydroazepine (**11**) (8%) were also isolated. [#]Diastereomer ratio determined from the ^1H NMR spectrum. [§]Yield based on recovered ester (**7a**) (10%).

Table

The intermediate *O*-stannyl ketyl **(2)** (scheme 1) is a nucleophilic radical and previous work has shown the importance of utilising electron-deficient double bond acceptors in cyclopentane and cyclohexane synthesis.[2,3] For comparison, the preparation and subsequent cyclisation of the *cis*- and *trans*-unsaturated esters **(12)** and **(13)** was investigated (scheme 2). These could be prepared on Swern oxidation of the corresponding alcohol and after purification (using column chromatography)[13] reaction with Bu_3SnH afforded *trans*-pyrrolidine **(14)** and the *cis*-bicycle **(15)** in similar yield. [The bicycle **(15)** was thought to arise from a second cyclisation involving attack of the tin alkoxide onto the ester]. Clearly the precursor double bond stereochemistry has little effect on the diastereoselectivity of the cyclisation.

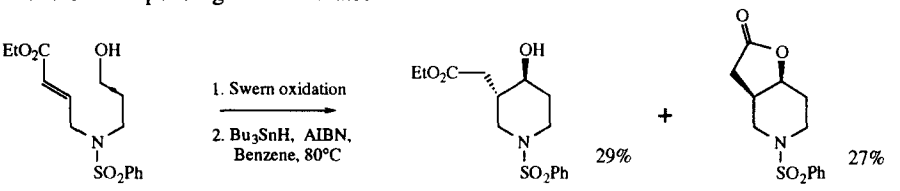


(12) R = CO_2Et; R^1 = H — 27% — 29%

(13) R = H; R^1 = CO_2Et — 33% — 32%

Scheme 2

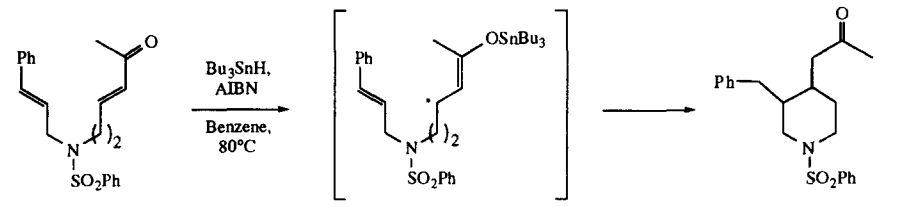
A comparable result was observed on cyclisation of the aldehyde derived from alcohol **(16)** which contained a *trans*-unsaturated ester (scheme 3). Reaction with Bu_3SnH afforded the *trans*-piperidine **(17)** and *cis*-bicycle **(18)**[14] in a combined yield of 56%. A similar ratio of **(17)**:**(18)** was produced on oxidation and cyclisation of the corresponding *cis*-unsaturated ester.



(16) — **(17)** — **(18)**

Scheme 3

The application of the allylic *O*-stannyl ketyl **(20)** in piperidine synthesis was also investigated (scheme 4). Thus treatment of the unsaturated ketone **(19)** with Bu_3SnH gave rise to the disubstituted piperidine **(21)**, as an inseparable mixture of diastereomers, in 76% yield.[15] Cyclisation of **(19)** at higher dilution (*i.e* 0.01M rather than 0.1M) was shown to afford **(21)** in similar yield (71%) and diastereoselectivity (2.6:1) which suggested that the cyclisation was irreversible.[4]



(19) — **(20)** — **(21)** 76% (3:1)

Scheme 4

In conclusion, we have demonstrated that α- or β-amino aldehydes containing a variety of double bond acceptors can be cyclised on reaction with Bu_3SnH to afford substituted pyrrolidines or piperidines. Further studies directed towards the application of this methodology in natural product synthesis are currently underway.

Acknowledgements

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References and Notes

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2. Enholm, E.J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939; Enholm, E.J.; Burroff, J.A. *Tetrahedron Lett.* **1992**, *33*, 1835.
3. For a related reaction using Bu_3SnH (catalytic) and $PhSiH_3$ see: Hays, D.S.; Fu, G.C. *J. Org. Chem.* **1996**, *61*, 4.
4. Enholm, E.J.; Kinter, K.S. *J. Am. Chem. Soc.* **1991**, *113*, 7784; Enholm, E.J.; Kinter, K.S. *J. Org. Chem.* **1995**, *60*, 4850.
5. See for example: Goodall, K.; Parsons, A.F. *Tetrahedron Lett.* **1997**, *38*, 491; Parsons, A.F.; Taylor, R.J.K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1945.
6. For related cyclisations leading to pyrrolidines: (i) Using SmI_2: Baldwin, J.E.; MacKenzie Turner, S.C.; Moloney, M.G. *Tetrahedron* **1994**, *50*, 9411 and 9425; (ii) Using Mg: Lee, G.H.; Choi, E.B.; Lee, E.; Pak, C.S. *J. Org. Chem.* **1994**, *59*, 1428.
7. For a similar electroreduction reaction see: Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545.
8. For a review of the preparation and transformations of α-amino aldehydes see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
9. The concentration of the reaction was 0.1 M. Increasing the concentration (*e.g.* to 0.5 M) has been shown to afford 1,2-pinacol byproducts in related systems (see ref. 2).
10. For slow cyclisation reactions further AIBN was added until all the starting material had been consumed.
11. All new compounds exhibited satisfactory spectral and analytical (high resolution mass and/or combustion) data. Yields are of pure isolated product and are not optimised.
12. The ^1H NMR spectra of the crude aldehydes **(9e-f)** showed that no alcohol starting material **(8b-c)** was present. The isolation of **(8b-c)** was thus attributed to the reduction of **(9e-f)** with Bu_3SnH.
13. Considerably lower yields of **(14)** and **(15)** were isolated using crude alkene **(12)** or **(13)**.
14. Although the formation of both *cis*- and *trans*- lactones was observed in the carbocyclic system (ref 2), the NMR spectra (^1H and ^{13}C) showed the formation of only one lactone diastereomer and this was assigned to be the *cis*- isomer.
15. The isomer ratio was calculated from the ^1H NMR spectrum (270MHz; $CDCl_3$) and was based on integration of the singlets at δ 2.03 and 2.01 for the $COC\underline{H}_3$ group in both compounds.

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