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# Tandem Radical Cyclisations Leading to Indolizidinones and Pyrrolizidinones

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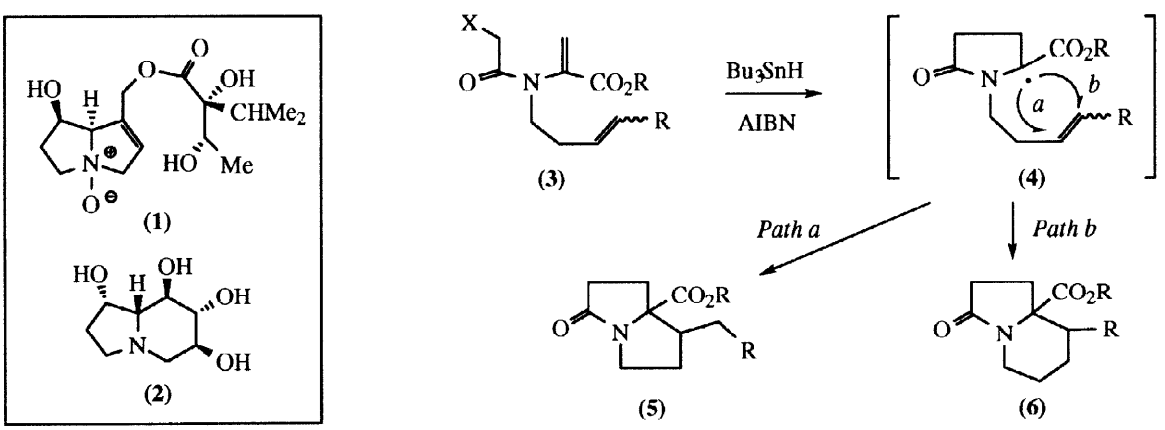
***Abstract:*** Reaction of various dehydroamino esters with tin hydrides resulted in 5-*endo*-5-*exo* or 5-*endo*-6-*endo* tandem cyclisation reactions. The preferred pathway was dependent on alkene substitution and the bicyclic products have potential application in indolizidine and pyrrolizidine alkaloid synthesis. © 1998 Elsevier Science Ltd. All rights reserved.

***Keywords:*** Cyclisation; tin and compounds; alkaloids; bicyclic heterocyclic compounds.

The considerable variety and widespread occurrence of pyrrolizidine and indolizidine alkaloids has attracted the attention of synthetic chemists for many years.[1,2] These types of compound exhibit a wide range of physiological and pharmacological activites and most are toxic. Pyrrolizidines are known to promote a form of cirrhosis in mammals and many livestock deaths have resulted from animals grazing on plants containing these alkaloids. Many of these compounds are of medicinal importance and notable examples include indicine *N*-oxide **(1)** (a pyrrolizidine anti-cancer agent) and the indolizidine castanospermine **(2)** which is a potent glycosidase inhibitor and potential AIDS drug.




**SCHEME 1**

We became interested in developing a quick and efficient approach to the ring systems present in these alkaloids and envisaged employing a tandem radical cyclisation reaction starting from dehydroamino ester derivatives **(3)** (Scheme 1). Reaction of **(3)** with $Bu_3SnH$ was expected (from our previous work[3] on related systems) to lead to 5-*endo* cyclisation of the carbamoylmethyl radical to give the tertiary pyrrolidinone radical **(4)**. Intramolecular trapping of this radical by a suitably situated double bond could then proceed in a 5-*exo*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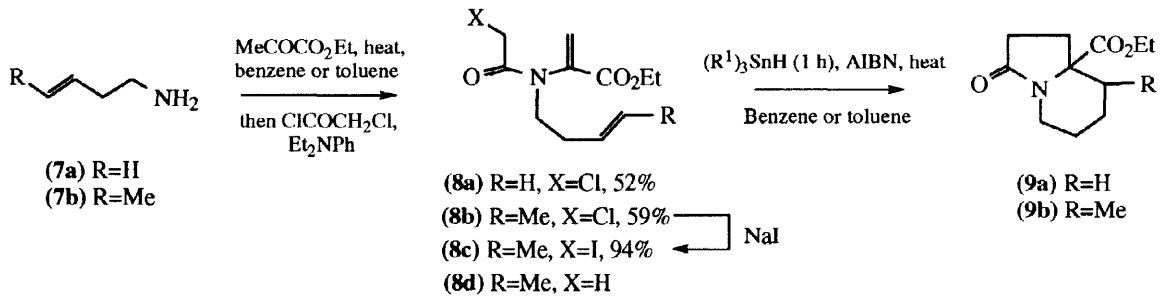
(path a) or 6-*endo* (path b) manner to give pyrrolizidinone (**5**) or indolizidinone (**6**) respectively (after hydrogen atom abstraction from $Bu_3SnH$). It was anticipated that pyrrolizidinone ring formation would be preferred as 5-*exo* radical cyclisations are generally much faster than their 6-*endo* counterparts.[4]

Initial studies concentrated on the preparation of dehydroamino esters (**8a-c**) starting from unsaturated amines (**7a-b**)[5] (Scheme 2). Previous work from our group[6] had shown that similar compounds could be prepared using a one-pot procedure involving condensation of the primary amine with a pyruvate followed by *N*-acylation of the intermediate imine. This approach was used to prepare chlorides (**8a-b**) and (**8b**) could be converted to the corresponding iodide (**8c**) in good yield.[7]




(**7a**) R=H
(**7b**) R=Me

(**8a**) R=H, X=Cl, 52%
(**8b**) R=Me, X=Cl, 59%
(**8c**) R=Me, X=I, 94%
(**8d**) R=Me, X=H

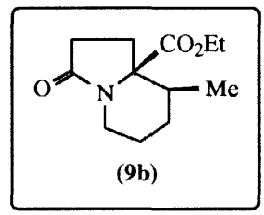
(**9a**) R=H
(**9b**) R=Me

**SCHEME 2**

| Entry | Halide (**8**) | $R^1$ | Products (yield %) |
|---|---|---|---|
| 1 | a | Bu | **9a** (21*) |
| 2 | b | Bu | **9b** (25/27*) |
| 3 | b | Ph | **9b** (40) |
| 4 | c | Bu | **8d** (21) + **9b** (38) |
| 5 | c | Ph | **8d** (13) + **9b** (40) |

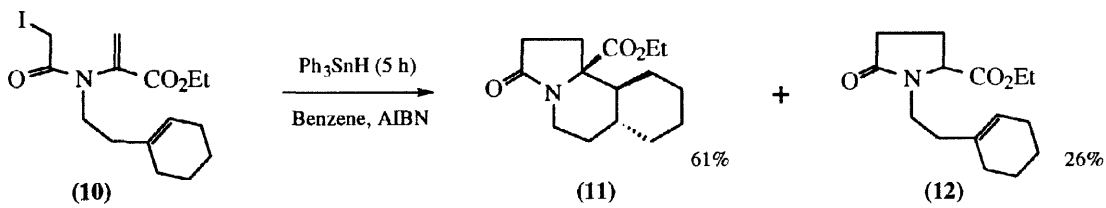
*$Bu_3SnH$ added over 5 rather than 1 h

**TABLE 1**: Tin hydride mediated cyclisations of (**8a-c**).




**FIGURE**

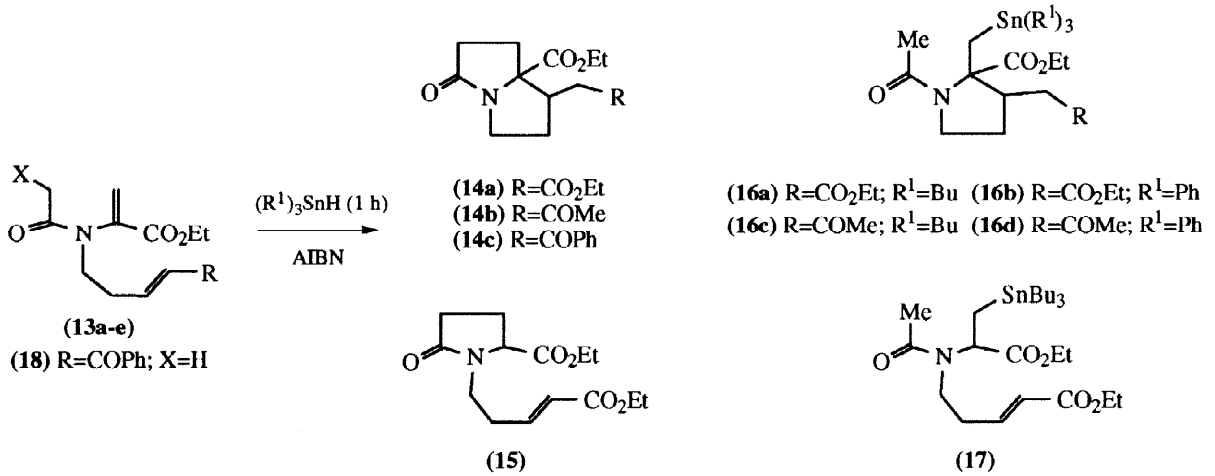
Treatment of (**8a**) with 1.1 equivalents of $Bu_3SnH$ gave rise to the indolizidinone (**9a**) in 21% yield (Table, entry 1). This resulted from a 5-*endo*-6-*endo* cyclisation sequence and no pyrrolizidinone product was isolated. A similar result was observed on cyclisation of (**8b**) and (**9b**) was isolated in good yield particularly when using $Ph_3SnH$ (entries 2-3). The use of iodide (**8c**) was found to result in the best overall product recovery but now acetamide (**8d**), derived from simple reduction, was formed in significant yield (entries 4-5). Although 6-*endo* radical cyclisations have been observed in related systems,[8] the selectivity and high yield of (**9b**) is of particular note. Only one diastereomer was isolated from these reactions and NMR experiments[9] together with literature precedent[8] supported the formation of the isomer shown in the Figure.




(**10**) (**11**) (**12**)

**SCHEME 3**

Reaction of the *N*-2-(cyclohex-1-enyl)ethyl derivative (**10**) with $Ph_3SnH$ also resulted in tandem cyclisation and the tricycle (**11**) was isolated as one diastereomer[10] in good yield (Scheme 3). Only 6-*endo* cyclisation on to the trisubstituted double bond was observed and this can be explained by steric considerations.[11] The reaction also gave rise to the pyrrolidinone (**12**) derived from trapping of the intermediate trisubstituted radical [of type (**4**)].




**SCHEME 4**

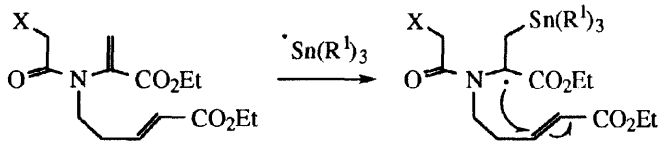
| Entry | Halide (13) | X | R | $R^1$ | Solvent* | Products (yield %) | (14) d.r. |
|---|---|---|---|---|---|---|---|
| 1 | a | Cl | $CO_2Et$ | Bu | Toluene | **14a** (19) + **15** (11) + **16a** (19) | 2.6 : 1 |
| 2 | a | Cl | $CO_2Et$ | Ph | Toluene | **14a** (18)+ **15** (8) + **16b** (22) | 2.7 : 1 |
| 3 | b | I | $CO_2Et$ | Bu | Toluene/EtOAc | **14a** (40) + **16a** (3) +**17** (11) | 2.3 : 1 |
| 4 | b | I | $CO_2Et$ | Ph | Toluene/EtOAc | **14a** (30) + **16b** (35) | 2.8 : 1 |
| 5 | c | Cl | COMe | Bu | Toluene | **16c** (37) | - |
| 6 | c | Cl | COMe | Ph | Toluene | **16d** (47) | - |
| 7 | d | I | COMe | Bu | Toluene/EtOAc | **14b** (65) | 2.6 : 1 |
| 8 | d | I | COMe | Ph | Toluene/EtOAc | **14b** (66) | 2.6 : 1 |
| 9 | e | I | COPh | Bu | Toluene/EtOAc | **14c** (55) | 1.7 : 1[+] |
| 10 | e | I | COPh | Ph | Toluene/EtOAc | **14c** (52) | 1.6 : 1[+] |
| 11 | e | I | COPh | Ph | EtOAc | **14c** (57) + **18** (8) | 1.8 : 1[+] |

*When using a mixed solvent system the ratio of toluene:EtOAc was ca. 10:1. [+] Ratio determined from the $^1H$ NMR spectrum.

**TABLE 2:** Tin hydride mediated cyclisations of (**13a-e**).

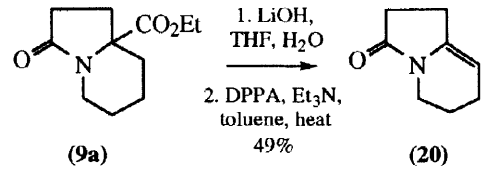
The cyclisation of dienes (**13a-e**) was then explored (Scheme 4, Table 2). Reaction of (**13a**) with $Bu_3SnH$ or $Ph_3SnH$ gave rise to pyrrolizidinone (**14a**) derived from 5-*endo*-5-*exo* cyclisation; the change in regioselectivity [from that observed on cyclisation of (**8**)] could be attributed to the ester substituent which is expected to stabilise the radical in the transition state for 5-*exo* cyclisation. In addition, pyrrolidinone (**15**) and the tin adducts (**16a-b**) were formed in reasonable yields. The formation of (**16a-b**) can be explained by a Michael-type addition of the tin radical to (**13a**) followed by 5-*exo* cyclisation on to the acrylate double bond (Scheme 5). Hydrogen atom transfer followed by reduction of the chloride, using a further equivalent of tin hydride, would then produce (**16a-b**). It should be noted that addition of the tin radical to (**13a**) may well be reversible and chloride reduction of (**13a**) to give (**19**) could proceed the cyclisation reaction. Reaction of iodide (**13b**) improved the yield of pyrrolizidinone (**14a**) to 30-40% (Table 2, entries 3-4), a mixed EtOAc/toluene solvent system was employed because of the poor solubility of (**13b**) in toluene. The effect of

changing the leaving group from Cl to I was most pronounced on reaction of methyl ketones (**13c-d**) (entries 5-8). Excellent yields of pyrrolizidinone (**14b**) were isolated when using iodide (**13d**) while the related pyrrolizidinone (**14c**) could be prepared in >50% yield starting from iodide (**13e**) (entries 9-11).




(**13a**) X=Cl; (**19**) X=H

SCHEME 5




(**9a**) (**20**)

SCHEME 6

The preparation of naturally occurring indolizidines and pyrrolizidines requires the decarboxylation of amino esters (**9a-b**) and (**14a-c**). This type of transformation is well-known and has been exploited in a number of alkaloid syntheses.[12] We found that hydrolysis of ester (**9a**) followed by heating the crude acid with diphenylphosphorazide (DPPA)[13] produced the enamide (**20**) in an unoptimised 49% yield (Scheme 6). Enamide (**20**) is a versatile intermediate and has previously been converted to δ-coniccine, 8,8a-*trans*-8-hydroxyindolizidine and 8a-hydroxyindolizidine.[13]

This tandem cyclisation approach provides a quick and mild entry to both indolizidine and pyrrolizidine ring systems. The resulting α-amino esters can be readily decarboxylated and the method should be applicable to a wide range of natural and unnatural alkaloids. Further work in this area is currently underway.

**Acknowledgements**

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**References and Notes**

1. (a) Michael, J.P. *Nat. Prod. Rep.*, 1997, **14**, 619. (b) J.R. Liddell, *Nat. Prod. Rep.*, 1996, **13**, 187.
2. For examples of recent synthetic approaches see: (a) Denmark, S.E.; Parker, D.L.; Dixon, J.A. *J. Org. Chem.*, 1997, **62**, 435. (b) McAlonan, H.; Stevenson, P.J.; Thompson, N.; Treacy, A.B. *Synlett*, 1997, 1359. (c) Li, Y; Marks, T.J. *J. Am. Chem. Soc.*, 1998, **120**, 1757. (d) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett*, 1997, 1179. (e) Goti, A.; Cardona, F.; Brandi, A. *Synlett*, 1996, 761. (f) Carretero, J.C.; Arráyas, R.G. *J. Org. Chem.*, 1998, **63**, 2993.
3. (a) Baker, S.R.; Parsons, A.F.; Wilson, M. *Tetrahedron Lett.*, 1998, **39**, 2815. (b) Goodall, K.; Parsons, A.F. *J. Chem. Soc., Perkin Trans. 1*, 1994, 3257. (c) Goodall, K.; Parsons, A.F. *Tetrahedron*, 1996, **52**, 6739. (d) Goodall, K.; Parsons, A.F. *Tetrahedron Lett.*, 1997, **38**, 491.
4. (a) Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron*, 1985, **41**, 3925. (b) Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.*, 1987, **52**, 959.
5. Amines (**7a**) and (**7b**) were prepared from reduction ($LiAlH_4$, $AlCl_3$, $Et_2O$, -10 to 0°C) of 3-butenenitrile and *trans*-3-pentenenitrile (95%) respectively.
6. Davies, D.T; Goodall, K.; Kapur, N.; O'Brien, M.; Parsons, A.F. *Synth. Commun.*, 1997, **27**, 3815.
7. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
8. (a) Hart, D.J.; Tsai, Y.M. *J. Am. Chem. Soc.*, 1982, **104**, 1430. (b) Burnett, D.A..; Choi, J-K.; Hart, D.J.; Tsai, Y-M. *J. Am. Chem. Soc.*, 1984, **106**, 8201. (c) Hart, D.J.; Tsai, Y-M. *J. Am. Chem. Soc.*, 1984, **106**, 8209.
9. The stereochemistry was assigned based on $^1H$–$^1H$ nOes and $^3J_{1H-1H}$, $^3J_{1H-13C}$ coupling constants but because of spectral overlap the assignment was not totally unambiguous.
10. The $^1H$–$^1H$ nOes and $^3J_{1H-1H}$, $^3J_{1H-13C}$ coupling constants were consistent with the stereochemistry as drawn but an unambiguous assignment was not possible because of spectral overlap.
11. For a related cyclisation see Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1*, 1992, 2399.
12. See for example Hernández, A.S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.*, 1996, **61**, 314.
13. (a) Martín-López, M.J.; Bermejo-González, F. *Tetrahedron Lett.*, 1994, **35**, 4235 and 8843. (b) Rodríquez, R.; Bermejo, F. *Tetrahedron Lett.*, 1996, **37**, 5581.