A Route to the Pyrrolizidine Ring System using a Novel Radical Cyclisation

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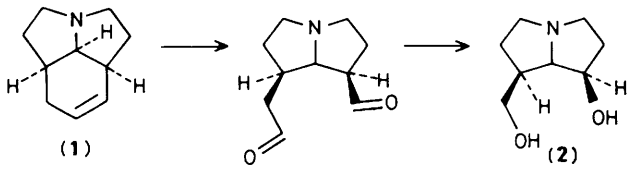
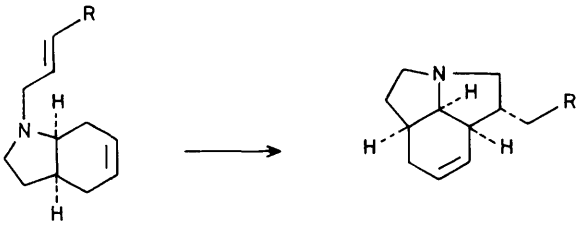
A method for the construction of pyrrolizidine rings is described using a new radical cyclisation procedure, which involves generation of an allylic radical from a preformed vinylic radical followed by cyclisation of the allylic radical onto a pendant double bond.

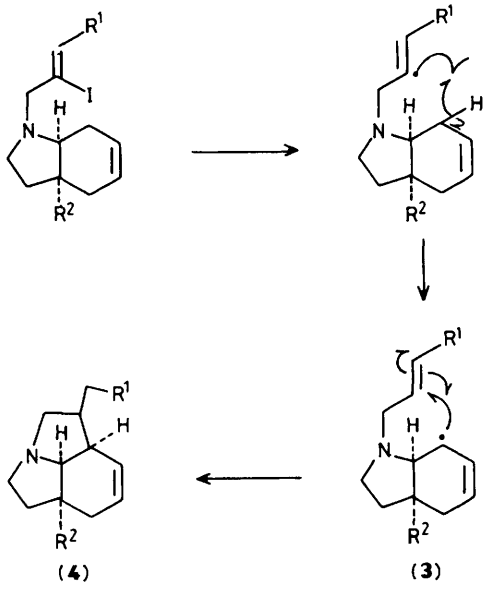
The pyrrolizidine alkaloids are a family of biologically active azabicyclo[3.3.0]bicyclo-octanes which can possess anti-tumour, and also, in contrast, carcinogenic properties.[1] In view of the wide spectrum of biological activity exhibited by these molecules we became interested in their synthesis. Our analysis of this problem relied on the efficient synthesis of the tricyclic amine (**1**) which on ozonolysis would provide the desired ring system (**2**) (Scheme 1). In order to construct the



Scheme 1



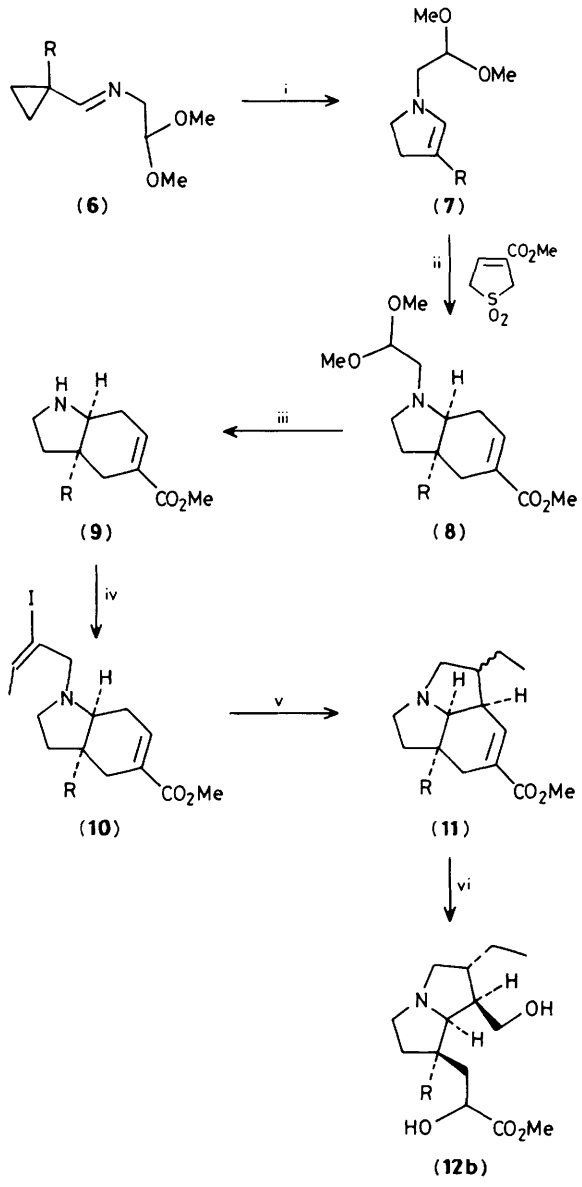
Scheme 2



Scheme 3. R^1 = Ph or SPh; R^2 = H or Me.

desired tricyclic amine (**1**) we envisaged a cyclisation involving the addition of an allylic radical to a suitably positioned double bond (Scheme 2). We eventually discovered that the allylic radical (**3**) could be generated using the novel hydrogen atom abstraction–addition sequence illustrated in Scheme 3.

The key radical cyclisation precursor (**8**) was easily made using a Diels–Alder reaction of 2-methoxycarbonylbuta-1,3-diene, produced *in situ* from 2,5-dihydro-3-methoxycarbonylthiophene *S,S*-dioxide,[2] with pyrrolines[3] (Scheme 4). The dimethoxyethyl group in (**8**) was removed by hydrolysis with acid followed by treatment of the resulting aldehyde with aqueous *N*-phenylhydroxylamine hydrochloride in dilute aqueous sodium carbonate, a method we have found to be particularly good for the protection and deprotection of amines.[5] *N*-Alkylation of the secondary amines (**9**) proceeded smoothly providing the iodides (**10**). Irradiation of a dilute solution of (**10**) and tributyltin hydride[4] in benzene (10 mM) with a 150 W tungsten lamp led to the isolation of the desired cyclic amines (**11**)† (60—85%), a mixture of ethyl epimers (4:1 α:β) being formed. The viability of this new radical cyclisation as a route to highly substituted pyrrolidines was



a; R = Ph
b; R = SPh

Scheme 4. *Reagents and conditions*: i, 110 °C; ii, PhMe, 110 °C; iii, $(CO_2H_2)_2$ then aq. PhNHOH·HCl in aq. Na_2CO_3, room temp.; iv, *trans*-MeCH=ClCH$_2$Br, solid K_2CO_3 (powder); v, Bu^n_3SnH, C_6H_6, *hν*; vi, O_3, then $NaBH_4$, MeOH.

demonstrated by ozonolysis of the hydrochloride salt of (**11b**) followed by reduction of the ozonide to provide (**12b**)† (63%).

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† (**11a**): 4:1 mixture of ethyl epimers: δ (^{1}H); ($CDCl_3$) 7.23 (m, 5H), 7.05 (m, 1H), 3.90 (m, 1H), 3.70 (s, 3H), 3.2—3.05 (m, 2H), 2.85—1.90 (m, 8H), 1.55 (m, 2H), and 1.0 (2 × t, 3H, *J* 6 Hz); *m/z* (*M*$^+$) 311.1913 (calc. 311.1895); $\nu_{max.}$ 1715 cm^{-1}; (**11b**): 3:1 mixture of ethyl epimers: δ (^{1}H); ($CDCl_3$) 7.70—7.25 (m, 5 H), 6.96 (m, 1H), 3.95 (d, *J* 6 and Hz), 3.85 (d, *J* 6 Hz) (together 1H), 3.80 (s, 3H), 3.75—1.20 (m, 12H), and 0.95 (2 × t, 3H, *J* 6 Hz); *m/z* (*M*$^+$) 343.1604 (calc. 343.1606); $\nu_{max.}$ 1715 cm^{-1}; (**12b**): δ (^{1}H); ($CDCl_3$) 7.30 (m, 5H), 5.40 (m, 1H), 5.15 (br.d, 1H, *J* 8 Hz), 3.70 (s, 3H), 4.10—1.90 (m, 14H), 1.55 (m, 2H), and 0.9 (br.t, 3H, *J* 6 Hz); *m/z* (*M*$^+$ −2) 345.1929 (calc. 345.1940); $\nu_{max.}$ 1740 cm^{-1}.

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