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Rearrangement of pyrrolines derived from the Birch reduction of electron-deficient pyrroles: radical ring-expansion to substituted tetrahydropyridines

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Access to the synthetically important tetrahydropyridine motif has been achieved by radical rearrangement of pyrrolines obtained from the Birch reduction of electron-deficient pyrroles.

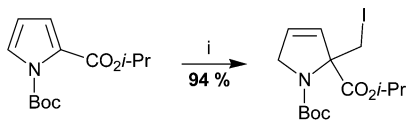
Previously we have reported an extension of the Birch reduction and reductive alkylation reaction[1,2] to encompass electron-deficient pyrroles.[3–5] Herein we report the radical rearrangement of pyrrolines, obtained from the Birch reduction, into functionalised tetrahydropyridines, a substructure commonly found in biologically active natural products.[6] A suitable radical precursor for such a rearrangement would be an α-halomethyl pyrroline (such as **2**, Scheme 1). It was envisaged that access to these pyrrolines could be obtained by alkylating the enolate (formed during reduction of pyrrole **1**) with a 1,1-dihaloalkane, a class of electrophile not previously reported in the Birch reduction. Ensuing one carbon radical ring expansion would then allow access to synthetically useful tetrahydropyridines, complementing our interest in the partial reduction of pyridines.[7–9]

Therefore, use of 1,1-diiodomethane as an electrophile in the Birch reduction of electron-deficient pyrrole **1**[4] furnished pyrroline **2** in excellent yield (Scheme 1). The 400 MHz ^{1}H NMR spectrum of **2** clearly showed the diastereotopic protons of the α-halomethylene (4.40, 4.12 and 3.85, 3.83 ppm) and a 100 MHz ^{13}C NMR spectrum confirmed the presence of the CH_2I moiety with its diagnostic upfield shift (13.7 and 13.4 ppm).

Treatment of pyrroline **2** with tri-n-butyltin hydride and AIBN gave tetrahydropyridine **3** and a dehalogenated pyrroline in 10 : 1 ratio respectively. It quickly became apparent that in order to avoid simple dehalogenation of pyrroline **2**, a low concentration of hydride (0.01 mol dm^{-3}) in conjunction with a 12 hour syringe pump addition of tri-n-butyltin hydride had to be employed. Under these conditions† tetrahydropyridine **3** was formed exclusively in high yield (Scheme 2).

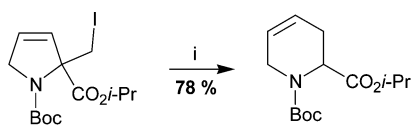
Focus then centred on the general applicability of this methodology by examining substitution patterns around the pyrroline ring. Allylic oxidation[10] of pyrroline **2** furnished lactam **4** in good yield and on exposure to reducing conditions, lactam **4** was smoothly converted to ring-expanded lactam **5** in high yield (Scheme 3).

Use of the Barton–Zard reaction[11] allowed easy access to a range of electron-deficient pyrroles with substitution at both the C-3 and C-4 positions. Reduction of **6** and **7** under Birch conditions gave



1 2

Scheme 1 *Reagents*: i, Li, NH_3, THF, −78 °C, then CH_2I_2.



2 3

Scheme 2 *Reagents*: i, Bu_3SnH and AIBN slow addition, PhH, Δ.

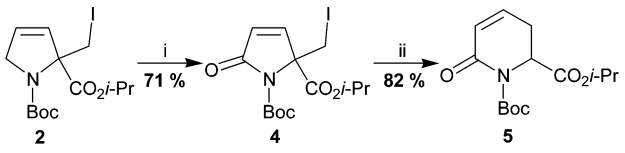
pyrrolines **8** and **9** respectively in high yield. Allylic oxidation then yielded lactams **10** and **11** which upon subjection to the radical conditions furnished ring-expanded lactams **12** and **13** (Scheme 4).

With regard to the mechanism of ring-expansion we postulated that after initial formation of radical **14**, a 3-exo-trig attack onto the double bond forms intermediate **15** (Scheme 5). A retro 3-exo-trig then opens the strained bicycle to give the thermodynamically more stable capto-dative (and tertiary) radical **16**. Abstraction of a hydrogen atom would then furnish the tetrahydropyridine. Although one carbon radical-ring expansions are well documented,[12,13] examples of radicals initially attacking an olefin (rather than a carbonyl) to promote expansion are rare.[14]

Having shown that our methodology is tolerant to substitution around the pyrroline ring, proof of the proposed mechanism in Scheme 5 was sought. As this mechanism involves strain driven cleavage of the bicyclic radical, it was envisaged that this intermediate could be trapped by forming a less strained fused bicycle. Therefore pyrrolines **17** and **18** were duly prepared by the reductive alkylation of electron-deficient pyrrole **1**. Allylic oxidation then furnished lactams **19** and **20** (Scheme 6).

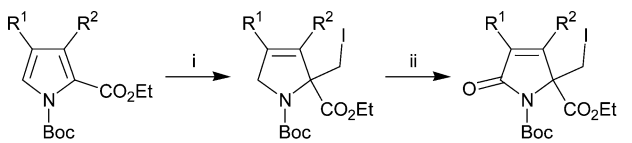
Compounds **17**–**20** were subjected to radical ring-expansion conditions and gratifyingly gave bicycles **21**–**24** directly (Scheme 7). Whereas the sole cyclisation products of lactams **18** and **20** were fused bicycles **22** and **24**, the cyclisation of **17** and **19** not only gave bicycles **21** and **23** but also a small amount of dehalogenated side product (7 : 1 ratio in favour of the bicycle).‡

Interestingly, the yields of the lactams **22** and **24** are significantly higher than their non-lactam counterparts (**21** and **23** respectively). Presumably, this is because the carbonyl group within the lactam



2 4 5

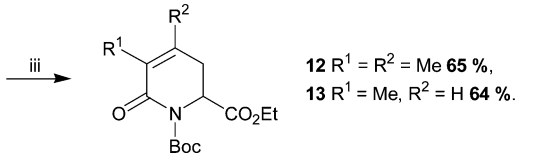
Scheme 3 *Reagents*: i, CrO_3, H_2SO_4, acetone, room temperature; ii, Bu_3SnH, AIBN, PhH, Δ.



6 $R^1 = R^2$ = Me, **7** R^1 = Me, R^2 = H

8 $R^1 = R^2$ = Me **81 %**, **9** R^1 = Me, R^2 = H **89 %**.

10 $R^1 = R^2$ = Me **82 %**, **11** R^1 = Me, R^2 = H **68 %**.



12 $R^1 = R^2$ = Me **65 %**,
13 R^1 = Me, R^2 = H **64 %**.

Scheme 4 *Reagents*: i, Li, NH_3, THF, −78 °C, then CH_2I_2; ii, CrO_3, H_2SO_4, acetone, room temperature; iii, Bu_3SnH, AIBN, PhH, Δ.

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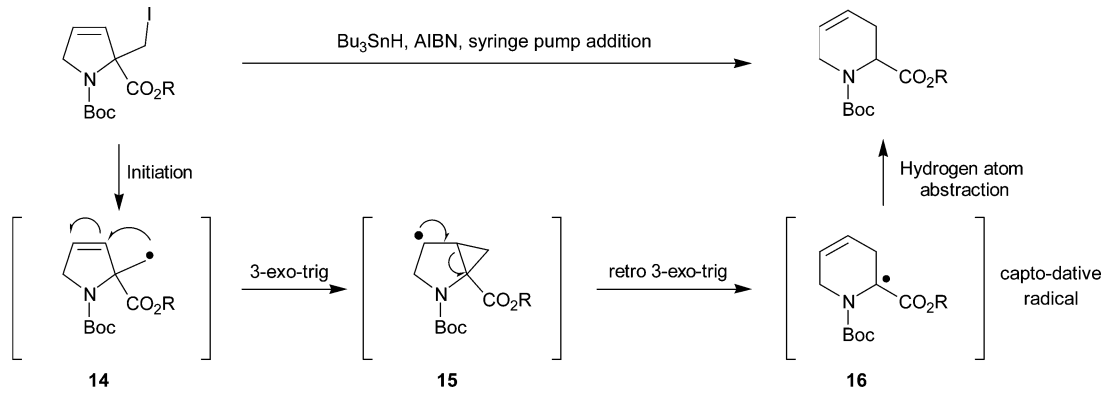
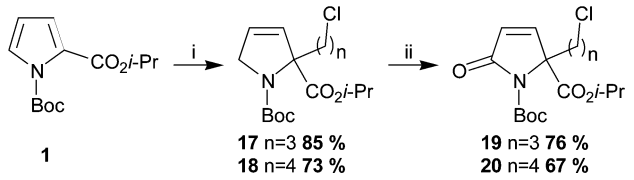
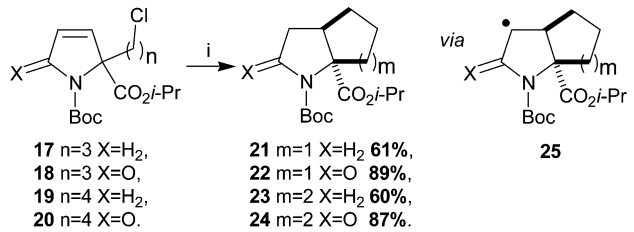


Scheme 5 Proposed mechanism for the formation of tetrahydropyridines by a one carbon radical ring-expansion of pyrrolines.



Scheme 6 *Reagents*: i, Li, NH_3, THF, −78 °C, then $ClCH_2CH_2CH_2I$ or $ClCH_2CH_2CH_2CH_2I$; ii, CrO_3, H_2SO_4, acetone, room temperature.



Scheme 7 Reagents: i, Bu_3SnH, AIBN, PhH, Δ.

promotes addition onto the electrophilic alkene and also stabilises the radical intermediate **25** (X = O) after addition.

Radical cyclisations onto cyclic olefins to form 5- and 6-membered rings is well precedented to form the *cis* diastereoisomer.[15,16] Furthermore, radical cyclisations onto unsaturated lactones to form fused 5,6 bicyclic systems has also been shown to form the *cis* isomer,[17] and therefore, on this precedent, we have assigned compounds **21**–**24** as having a *cis* ring junction.

In summary, we have shown that the Birch reduction of electron-deficient pyrroles is compatible with 1,1-dihaloalkanes. The resulting α-halomethyl pyrrolines can then undergo a radical induced one carbon ring-expansion to furnish the synthetically useful tetrahydropyridine subunit in high yields. Furthermore we have shown that our methodology is tolerant to substitution around the pyrroline ring. A mechanism for the ring-expansion has been given, with supporting evidence provided by the trapping of proposed intermediates by forming stable and potentially useful bicyclic intermediates.

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Notes and references

† *Representative procedure for radical ring-expansions*: Lactam **4** (107 mg, 270 μmol) dissolved in deoxygenated benzene (20 cm^3) was heated at reflux under an atmosphere of argon, heating was continued for 1 hour. Tri-n-butyltin hydride (60 % solution, 0.142 cm^3, 316 μmol, 1.2 eq.) and AIBN (8.8 mg, 54 μmol, 0.2 eq.) dissolved in deoxygenated benzene (10 cm^3) were added over a 12 hour period *via* syringe pump to the hot solution and heating was then continued for a further 12 hours. On cooling the solution was poured into dichloromethane (10 cm^3), stirred for 30 minutes and evaporated under reduced pressure. The residue was dissolved in aqueous sodium hydroxide (1 mol dm^{-3} 10 cm^3), stirred for 30 minutes, poured into ether (30 cm^3), separated and the aqueous layer extracted with ether (2 × 30 cm^3). The combined organics were washed with 10% potassium fluoride solution (4 × 40 cm^3), dried (magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40–60 °C), followed by ethyl acetate–light petroleum (bp 40–60 °C), 20 : 80] to give **5** (63 mg, 82%) as an off white solid, mp 37–39 °C.

‡ As determined by 400 MHz ^1H NMR on the crude reaction mixture.

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