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Stereoselective reductive alkylation of 2,5-disubstituted pyrroles: a role for naphthalene in the partial reduction of heterocycles

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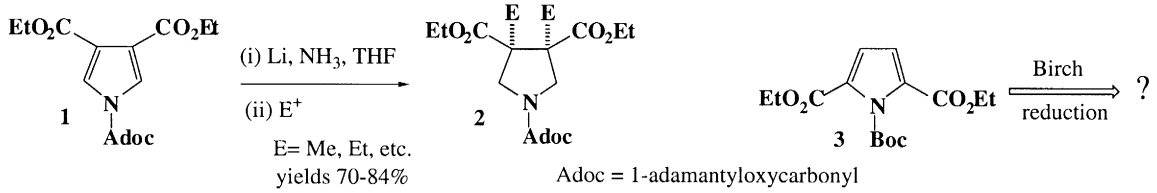
Abstract

Lithium in ammonia promotes the stereoselective reduction of 2,5-disubstituted pyrroles: such reactions proceed with good levels of stereoselectivity, producing the *trans*-isomer. The stereochemistry of one of the reduced compounds was proven by X-ray crystallography. A mechanism is proposed which explains the stereoselectivity and a modification made to the reducing system that includes catalytic naphthalene and obviates the need for liquid ammonia.

Over the last few years we have reported the results of a study into the partial reduction of heterocycles using the Birch reaction.[1] These studies have revealed a high yielding protocol for the transformation of pyrroles into pyrrolines and for the stereoselective reduction of both pyrroles[2] and furans.[3] Recently we disclosed that 3,4-disubstituted pyrroles could be subjected to a double reductive alkylation procedure to furnish (stereoselectively) pyrrolidines with adjacent quarternary centres (see **1**→**2**, Scheme 1).[4]



Scheme 1.

We wanted to extend this methodology to encompass the double reductive alkylation of 2,5-disubstituted pyrroles (e.g. **3**, Scheme 1) as we anticipate that the products from such a reaction may prove useful in synthesis. The requisite starting material **3** was made in good yield via a known procedure which involved bromination of commercially available *N*-Boc pyrrole, followed by double halogen–metal exchange and electrophilic quench with ethylchloroformate (Scheme 2).[5]

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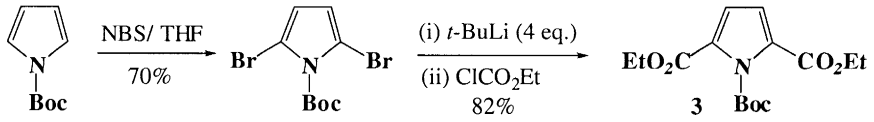
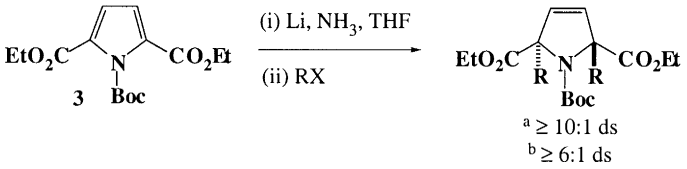


Scheme 2.

We then set about reducing compound **3** (Scheme 3). The best conditions that we found involved lithium metal (5 equivalents), liquid ammonia/THF at −78°C, followed by the addition of an electrophile (excess) after 1 h; application of these conditions gave rise to a series of doubly alkylated pyrrolines in good yield. In each case, the compounds were formed predominantly as single (*trans*) diastereoisomers.[6]

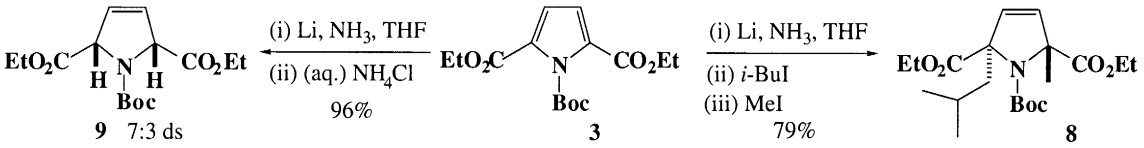


RX	R	Yield (%)	Compound
MeI	Me	85[a]	**4**
EtI	Et	87[a]	**5**
BnBr	Bn	71[a]	**6**
Allyl-Br	Allyl	81[b]	**7**

Scheme 3.

The configuration of the major isomers was proven by HPLC studies: using a standard silica column, compounds **4**–**7** each appeared as a single peak with ≤10% of any other compound present in the crude reaction mixture. And when using a (*R*,*R*) Whelk 01 chiral column for the same analysis, each compound was split into two peaks of equal area. This can only be accounted for when the alkyl groups are *trans* (and the compound racemic) rather than *cis* (and therefore *meso*).

The two alkyl groups that are attached to C-2 and C-5 need not be the same and addition of *i*-butyl iodide, followed by methyl iodide allowed the production of unsymmetrical isomer **8** in good yield (Scheme 4). Moreover, use of ammonium chloride as a protonating agent led directly to the dehydroproline analogue **9** in 96% yield; interestingly, this compound was formed as a 7:3 mixture in favour of the *cis*-isomer.



Scheme 4.

The stereochemistry of **8** was suggested by NOE studies which showed no strong enhancements between the methyl and *i*-butyl groups; the configuration of the minor isomer from protonation, *trans*-**9**, was proven by X-ray crystallography (Fig. 1).

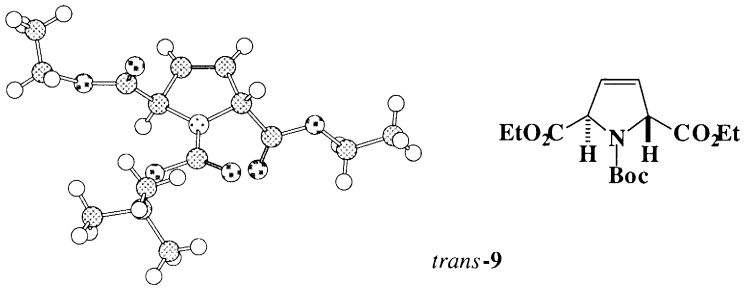


Fig. 1.

We propose that under the reducing conditions, pyrrole **3** is sufficiently electron-deficient to add two electrons and form a dianion, (**A**, Fig. 2). Dianion **A** is stabilised by virtue of being a bisenolate and we presume that it is not, therefore, basic enough to deprotonate ammonia (NH_3 pK_a ~34). Addition of an electrophile to the C-2 and C-5 positions ensues and this process gives rise to the compounds described in Schemes 3 and 4. The relative configuration of these adducts is determined during the second alkylation step (i.e. alkylation of **B**). While a detailed explanation of the origin of this effect awaits further study, we suggest that when R is a tetrahedral carbon atom (as for compounds **4**–**8**) alkylation takes place from the least hindered face, *syn* to the ester group. This model would explain why protonation gives predominantly the *cis*-isomer as reaction of **B** (R=H) will now occur from the least hindered face *syn* to the R group. However, we have not ruled out the possibility that stereoelectronic factors may be operative or that the conformation of the Boc group is important in determining face selectivity.

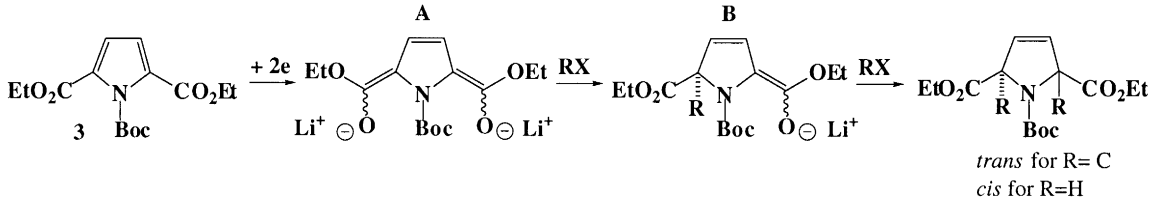
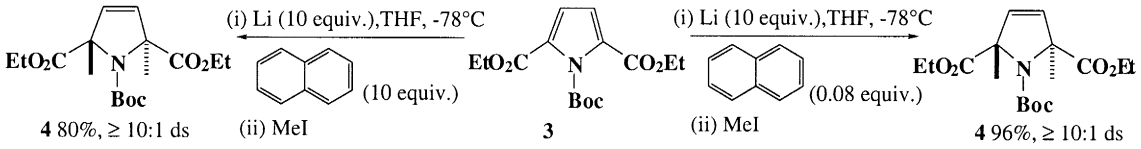


Fig. 2.

During formulation of this mechanistic model we realised that these reductions do not involve transfer of a proton from ammonia to the pyrrole (normally this is an important function for ammonia, in addition to its higher profile role of solvating electrons). Therefore, if we could find a way of getting electrons into solution there would be no need for ammonia at all in this reaction. An obvious approach was to generate the radical anion from naphthalene in THF and to see if this would promote the reduction (Scheme 5).[7] So, addition of lithium powder to **3** with naphthalene (10 equiv.) in THF at −78°C gave a green colouration which disappeared upon addition of methyl iodide. We were delighted to find that pyrroline **4** was formed in 80% yield and with stereoselectivity that was identical to that shown earlier. A further improvement to the procedure was made when we added only *catalytic* amounts of naphthalene to the reduction (8 mol%, Scheme 5) and discovered that the reaction worked equally well.[8]



Scheme 5.

It seems probable that under these conditions naphthalene picks up an electron to form the radical anion (which is green): two separate electron transfers to pyrrole **3** ensue forming the bisenolate **A** and regenerating naphthalene (so allowing it to act in a catalytic role).

To conclude we have demonstrated that 2,5-disubstituted pyrroles can undergo the Birch reduction to furnish highly substituted pyrrolines and that reasonable levels of stereocontrol are observed. We have presented a mechanistic model to explain the reaction and also developed the procedure into one that does not require ammonia as solvent and which utilises catalytic amounts of naphthalene. This raises the intriguing possibility that more standard Birch reductions of heterocycles may be compatible with these conditions and this issue is addressed in the following paper.

Representative experimental procedure: Naphthalene (7 mg, 0.054 mmol) was added to a suspension of pyrrole **3** (174 mg, 0.69 mmol) and lithium powder (39 mg, 5.6 mmol) in THF (5 mL) at −78°C under

an atmosphere of nitrogen. After 1.5 h, the reaction had become deep red and after another 2 h, methyl iodide (0.5 mL, 8.0 mmol) was added and the reaction allowed to warm to room temperature before being quenched with aq. NH_4Cl. The crude mixture was partitioned between ether (20 mL) and water (20 mL) and the aqueous layer further extracted with EtOAc (3×10 mL). The combined organic extracts were dried (Na_2SO_3), filtered and evaporated in vacuo. Purification by chromatoraphy on silica (eluting with EtOAc/hexane, 1:10→1:5) gave **4** as a colourless oil (176 mg, 96%).

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7. For leading references on the use of lithium naphthalenide in organic synthesis, see: *Handbook of Reagents for Organic Synthesis: Oxidising and Reducing Agents*; Burke, S. D.; Danheiser, R. L., Eds.; John Wiley: New York, 1999.
8. For a recent example of reductive lithiation using catalytic naphthalene, see: Huerta, F. F.; Gómez, C.; Yus, M. *Tetrahedron* **1999**, *55*, 4043.