Stereoselectivity in the double reductive alkylation of pyrroles: synthesis of *cis*-3,4-disubstituted pyrrolidines

Timothy J. Donohoe,*[a] Rakesh R. Harji[a] and Rick P. C. Cousins[b]

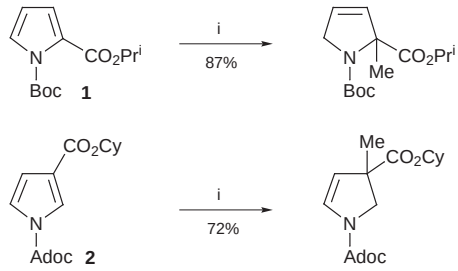
[a] *Department of Chemistry, The University of Manchester, Oxford Road, Manchester, UK M13 9PL. E-mail: t.j.donohoe@man.ac.uk*

[b] *GlaxoWellcome Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, UK SG1 2NY*

Received (in Liverpool, UK) 23 November 1998, Accepted 26th November 1998

The preparation and Birch reduction of a 1,3,4-tri-substituted pyrrole is described: the heterocycle is loaded with electron-withdrawing groups and undergoes a double reductive alkylation reaction to yield *cis*-3,4-disubstituted pyrrolidines.

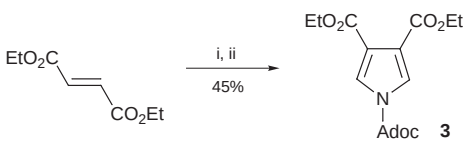
The Birch reduction is a particularly useful synthetic reaction capable of transforming aromatic substrates into partially unsaturated products.[1] We have recently investigated and developed the partial reduction of heterocycles and found that Birch reductive alkylation of electron-deficient pyrroles takes place readily (Scheme 1).[2] For example, the transformation of pyrroles **1** and **2** into either 2- or 3-pyrroline isomers is a high yielding process that enables introduction of an alkyl group adjacent to the activating ester.[3–5] In each case, we believe that addition of electrons to the pyrrole forms a dianion which deprotonates ammonia to furnish an enolate; this reacts with an external electrophile to produce the observed products.



Scheme 1 *Reagents and conditions*: i, Na (3 equiv.), NH_3/THF, then MeI (excess), −78 °C.

Recently we have attempted to expand this work by using more highly-substituted pyrroles as substrates for the Birch reduction. In these cases diastereoisomeric products can be formed and we now present data that shows a high level of stereochemical control is possible. In addition, we also describe a *double* reductive alkylation reaction whereby two alkyl groups can be introduced onto the heterocycle in one step.

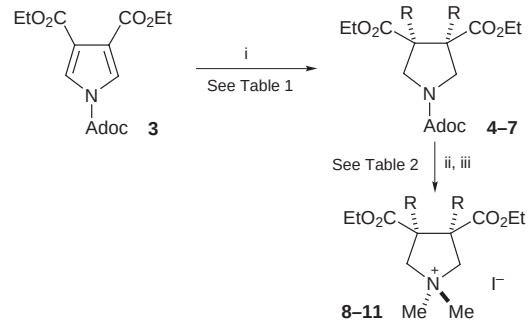
Studies began with the preparation of electron-deficient pyrrole **3** using standard methodology (Scheme 2). Reaction of $TsCH_2NC$,[6] $KOBu^t$ and diethyl fumarate gave a 3,4-disubstituted pyrrole which was protected, on nitrogen, as a adamantyloxycarbonyl (Adoc) derivative using adamantyl fluoroformate (45% overall yield from diethyl fumarate).



Scheme 2 *Reagents and conditions*: i, $TsCH_2NC$, Bu^tOK, THF; ii, Adoc-F, MeCN, Et_3N.

Subjection of pyrrole **3** to reductive alkylation conditions (6 equiv. Li in NH_3) is described in Scheme 3. We routinely add $(MeOCH_2CH_2)_2NH$ (10 equiv.) to Birch reductions as this amine appears to 'mop-up' lithium amide formed during the reaction and reduces the presence of undesirable by-products.[5]† Isoprene 'quenches' excess electrons in the reaction after reduction is complete (addition of isoprene caused the reaction to turn from deep blue to yellow—this colour was dissipated upon addition of an alkyl halide). The first reaction was quenched with MeI and produced a single product in good yield. We identified the pyrrolidine **4** (R = Me) from ^{1}H NMR spectroscopic data (Table 1).‡ We were then able to repeat the reaction and quench with a variety of electrophiles to generate compounds **5**–**7** in good yields (Table 1). In every case ^{1}H NMR spectroscopy showed that an alkyl group had been introduced α to each of the two esters, and also revealed the presence of the four protons adjacent to the pyrrolidine nitrogen.

Unfortunately, the NMR spectra of **4**–**7** did not allow us to assign relative stereochemistry and this was subsequently proved by conversion to the corresponding quarternary ammonium salts *via* a two step sequence (Scheme 3). Assignment of *cis* relative stereochemistry to compounds **4**–**7** would mean that the two *N*-methyl groups on (*meso*) salts **8**–**11** are diastereotopic, and could therefore resonate at different chemical shifts. On the other hand, *trans* stereochemistry would make the *N*-methyl groups of **8**–**11** (now C_2 symmetrical) homotopic and they would therefore have identical chemical shifts. Gratifyingly, salts **8**–**11** each displayed two (3H) singlets in the ^{1}H NMR spectrum,‡ thus allowing us to assign with confidence the stereochemistry of **4**–**7** as shown (Table 2).



Scheme 3 *Reagents and conditions*: i, Li (6 equiv.), NH_3, THF, $(MeOCH_2CH_2)_2NH$, −78 °C, then isoprene (3 drops), then RI (excess); ii, TFA, CH_2Cl_2; iii, MeI, $KHCO_3$, MeOH.

Table 1 Birch reduction of **5**

Entry	RX	*cis*/*trans*	Yield (%)	Compound
1	MeI	⩾20:1	77	**4**
2	EtI	⩾10:1	82	**5**
3	Bu^iI	⩾10:1	79	**6**
4	Allyl-I	⩾10:1	70	**7**

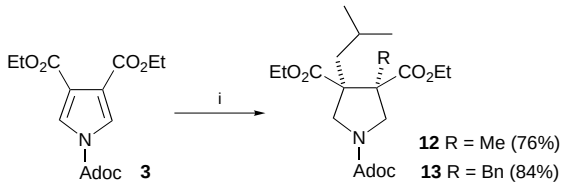
Table 2 Quaternary ammonium salts

Entry	R	δ_H(NMe) ($CDCl_3$)	Yield (%)	Compound
1	Me	3.52, 3.77	52	**8**
2	Et	3.67, 3.81	61	**9**
3	Bu^i	3.69, 3.77[a]	55	**10**
4	Allyl	3.65, 3.83	58	**11**

[a] NMR run in acetone-d_6.

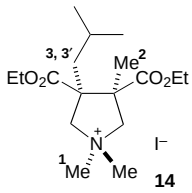
Compounds **4**–**7** were formed with high levels of stereoselectivity; such ratios were formulated by examination of the NMR spectra of the crude reaction mixtures. As far as the formation of **4** is concerned we were able to prepare an authentic sample of the *trans* isomer by another route and (in comparison with this standard) could not observe the *trans* isomer in the crude reduction reaction. Although each of the other cases was assigned ⩾10:1 selectivity without comparison to a standard, we believe this is a conservative estimate. Not only were the Birch reduced products **5**–**7** free from detectable impurities but also the amines formed by Adoc deprotection and the salts **8**–**11** appeared as single isomers by NMR spectroscopy.

We noticed that the alkylation step of the Birch reduction proceeded at different rates with the electrophiles that were used. Not surprisingly, reaction with Bu^{i}I was much slower than reaction with MeI. Using this information we developed a protocol for the sequential dialkylation of the pyrrole with two different electrophiles (Scheme 4). So, reaction of **3** with



Scheme 4 *Reagents and conditions*: i, Li (6 equiv.), NH_3, THF, $(MeOCH_2CH_2)_2NH$, −78 °C, then isoprene (3 drops), then Bu^{i}I (excess) , then RX (excess).

lithium metal as before but quenching with excess Bu^{i}I and then (after 2 min) excess MeI (or BnBr) enabled the synthesis of **12** and **13** in good yields. In both cases the reaction gave a single product as judged by ^{1}H NMR spectroscopy. Further proof of the identity of **12** was obtained by conversion to **14** under standard conditions (**14** appeared as one isomer) and subsequent NOE studies (Fig. 1). The NOE experiment described shows that **14** is the *cis* isomer. With all of this evidence for *cis* stereoselectivity in the dialkylation reaction, compound **13** was assigned as *cis* by analogy.



14

Irradiate	Percent NOE observed 1	2	3	3'
1	X	1	0	3
2	1	X	4	5
3	1	4	X	9
3'	3	6	8	X

Fig. 1 NOE studies on **14**

In terms of mechanism, we suggest that **3** accepts two electrons and forms dianion **A** (Fig. 2). Dianion **A** is then basic enough to deprotonate ammonia and form enolate **B**. Presumably, the presence of an ester group at C-4 means that the C-4,5 alkene in **B** is susceptible to further reduction by addition of two electrons and protonation at C-5 (by ammonia) to give **C**,[7] which is then alkylated twice. Presumably, the relative stereochemistry is determined by the facial selectivity of the second alkylation step (reaction of **D**) and it is surprising that such high levels of control are observed. Additional experiments show that both potassium and sodium metals give identical selectivity to lithium, thus dampening arguments based on chelation. However, we have preliminary results which show that, remarkably, the ammonia solvent is essential in order to achieve high stereoselectivity. We cannot comment on the exact role of the ammonia at this point, but note that Schultz has previously observed a similar relationship between solvent and the stereoselectivity displayed by enolates generated in the Birch reduction.[8]

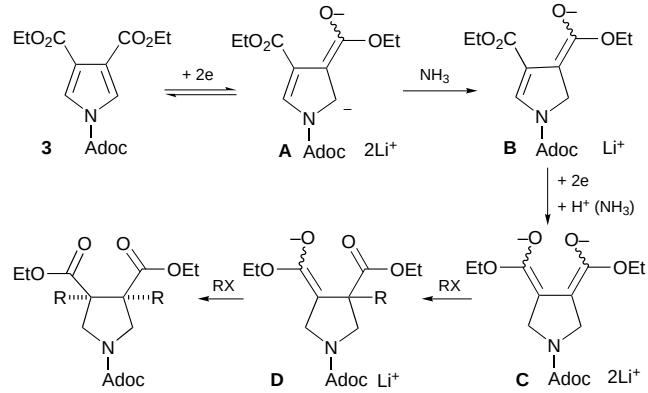


Fig. 2

We believe this type of reaction will be of use in both natural product synthesis and medicinal chemistry and that, as this reaction results in the formation of two adjacent quarternary chiral centres with control of relative stereochemistry, it is worthy of further study.

We wish to thank GlaxoWellcome (CASE award to R. R. H.) and Zeneca Pharmaceuticals (Strategic Research Fund) for financial support.

Notes and references

† We assume that $(MeOCH_2CH_2)_2NH$ is acidic enough to become deprotonated by lithium amide. Presumably, the anion derived from the amine additive is chelated and is a relatively unreactive species compared to lithium amide itself. We also note that $(MeOCH_2CH_2)_2NH$ is not acidic enough to protonate any enolate formed in the reaction, hence allowing us to add 10 equiv. without complication.

‡ *Selected data for* **4**: δ_H(140 °C, 1,2-$Cl_2C_6H_4$) 4.28 (2H, AB, CH_2N), 4.24 (4H, q, *J* 7.5, CH_2O), 3.38 (2H, AB, CH_2N), 2.32 (6H, br s, Adoc), 2.22 (3H, br s, Adoc), 1.75 (6H, br s, Adoc), 1.50 (6H, s, CH_3), 1.33 (6H, t, *J* 7.5 , CH_3CH$_2$); HRMS (CI): $C_{23}H_{35}NO_6$ requies 422.2542, found 422.2534. For **8**: δ_H($CDCl_3$) 4.40 (AB, 2H, CH_2N), 4.20–4.08 (4H, m, CH_2O), 4.05 (2H, AB, CH_2N), 3.77 (3H, s, NCH_3), 3.52 (3H, s, NCH_3), 1.58 (s, 6H, CH_3), 1.23 (6H, t, *J* 7.1, CH_3CH$_2$); Calc. for $C_{14}H_{26}NO_4I$: C, 42.12; H, 6.56; N, 3.51. Found C, 42.39; H, 6.40; N, 3.40%.

1 L. N. Mander, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, New York, 1991, vol. 8; P. W. Rabideau and Z. Marcinow, *Org. React*., 1992, **42**, 1; P. W. Rabideau, *Tetrahedron*, 1989, **45**, 1579.
2 T. J. Donohoe, R. Garg and C. A. Stevenson, *Tetrahedron*: *Asymmetry*, 1996, **7**, 317.
3 T. J. Donohoe and P. M. Guyo, *J. Org. Chem*., 1996, **61**, 7664.
4 T. J. Donohoe, P. M. Guyo, R. L. Beddoes and M. Helliwell, *J. Chem Soc*., *Perkin Trans. 1*, 1998, 667.
5 T. J. Donohoe, P. M. Guyo, R. R. Harji, M. Helliwell and R. P. C. Cousins, *Tetrahedron Lett*., 1998, **39**, 3075.
6 A. M. van Leusen, H. Siderius, B. E. Hoogenboom and D. van Leusen, *Tetrahedron Lett*., 1972, 5337; D. P. Arnold, L. J. Nitschinsk, C. H. L. Kennard and G. Smith, *Aust. J. Chem*., 1991, **44**, 323.
7 S. Li, X. Fang, Z. Wang, Y. Yang and Y. Li, *Synth. Commun*., 1993, **23**, 2051; A. G. Schultz, M. Macielag, D. E. Podhorez, J. C. Suhadolnik and R. K. Kullnig, *J. Org. Chem*., 1988, 53, 2456.
8 See A. G. Schultz, M. Macielag, P. Sundararaman, A. G. Taveras and M. Welch, *J. Am. Chem. Soc*., 1988, **110**, 7228.

Communication 8/09193E