Pergamon

Tetrahedron Letters 39 (1998) 3075–3078

TETRAHEDRON
LETTERS

The Birch Reduction of 3-Substituted Pyrroles

Timothy J. Donohoe,* Paul M. Guyo, Rakesh R. Harji and Madeleine Helliwell§

Department of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, U. K.

Rick P. C. Cousins

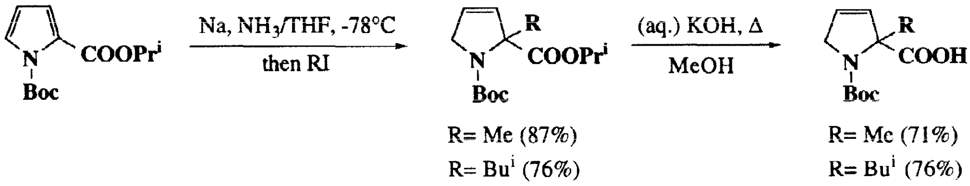
GlaxoWellcome Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, U. K.

Received 26 January 1998; revised 8 February 1998; accepted 13 February 1998

Abstract: The Birch reduction of electron-deficient 3-substituted pyrroles is described. Use of a reductive alkylation procedure involving sodium metal in liquid ammonia gave good yields of 4-alkyl-2-pyrrolines. The identity of these products was proven by an X-ray structure of a crystalline derivative. Moreover, the pyrroles used in this study could be readily prepared by reaction of TOSMIC with acrylic amides and esters and, once the reduction was complete, the ester activating group could be easily removed to yield the corresponding N-protected β-proline derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

We are currently engaged in a programme of research that is aimed at producing stereochemically defined (saturated) heterocycles from their aromatic precursors using a reduction step.[1] Partial reduction is regarded as being potentially more useful than complete reduction, as it gives the opportunity to control one or two stereocentres on the heterocycle nucleus whilst leaving an alkene unit for further elaboration. This approach also has the advantage that the preparation of substituted aromatic heterocycles is well described in the literature.

In this regard, we have recently described a method for achieving the Birch reduction[2] of electron-deficient 2-substituted pyrroles using sodium in liquid ammonia (**Scheme 1**).[3] A reductive alkylation protocol has enabled us to produce N-protected 2-alkyl-dehydroproline derivatives in an efficient manner. In order to investigate further the behaviour of electron-deficient pyrroles under reducing conditions, we next examined the Birch reduction of 3-substituted pyrroles, hoping to develop a route to 4-carboxy-2-pyrrolines. This chemistry should extend the scope of the Birch reduction and provide a short synthesis of β-proline derivatives.



Scheme 1

We used the base-promoted reaction of TOSMIC ($TsCH_2NC$) with either pyrrolidinyl acrylate or cyclohexyl acrylate to generate two pyrroles in reasonable yield (**Scheme 2**).[4] These compounds were

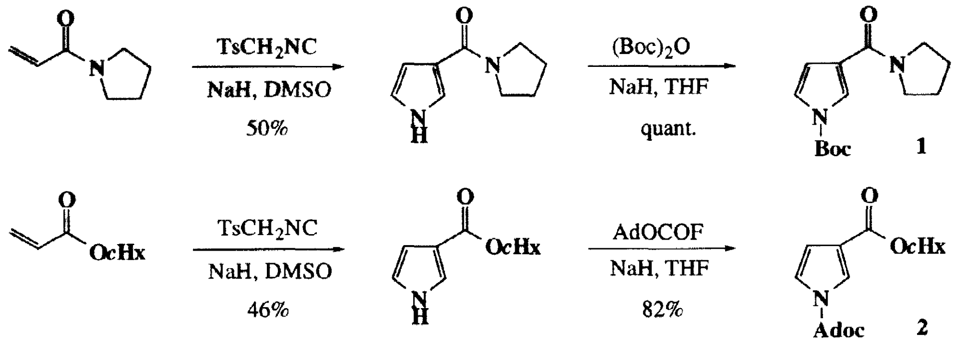
---

* Corresponding author: e-mail t.j.donohoe@man.ac.uk

§ Author to whom correspondence regarding the X-ray crystal structure should be addressed.

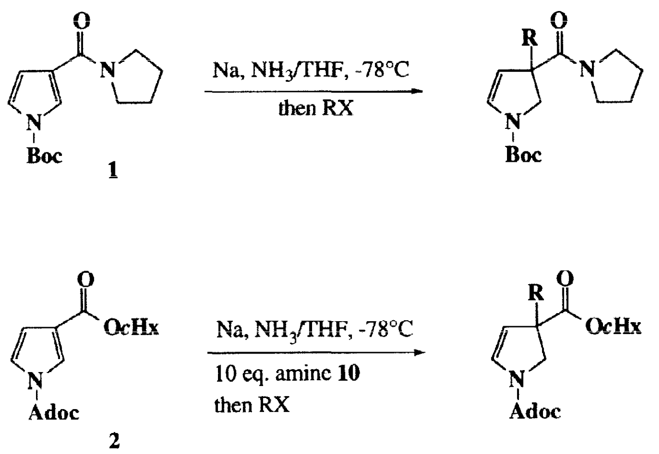
0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00362-1

subsequently protected under standard conditions to yield the N-Boc or N-Adoc pyrroles **1** and **2** respectively.



Scheme 2

The Birch reduction of pyrroles **1** and **2** was best accomplished with sodium metal (3-5 eq.) in liquid ammonia/THF solvent; an alcohol as proton source was not necessary for reaction to occur. After 30 min, the reaction was quenched with a series of alkyl halides and, in each case, a regioselective alkylation ensued to furnish 2-pyrrolines in good yields: the corresponding dehydro-β-proline derivative (**9**) could be obtained by quenching the reaction with ammonium chloride solution (**Scheme 3**). The regiochemical outcome of these reactions is consistent with that observed from the Birch reduction of furan-3-carboxylic acids.[5] During the development of this reaction we discovered that the main by-products consisted of pyrrole and pyrroline compounds which were lacking the Boc and Adoc protecting groups. We reasoned that this was caused by the attack of sodamide [formed in the reaction mixture (*vide infra*)] on both starting material and product. A solution to this problem was discovered by the addition of an excess (10 eq.) of $(MeOCH_2CH_2)_2NH$ (**10**) to the reaction vessel (introduced with the pyrrole substrate). Although the exact role of this amine is unclear, it was designed to be deprotonated in preference to ammonia and produce a chelated (less reactive) anion which would not participate in removal of the Boc and Adoc groups. Moreover, we presume that the amine **10** is not acidic enough to protonate the enolate that is subsequently formed in the reaction and it does not interfere with the alkylation step. Use of this amine was especially beneficial in the reduction of **2** and increased the yields for production of **6** from 55 to 72%.[6]



RX	R	Yield (%)	Compound[a]
MeI	**Me**	**70**	**3**
BnBr	**Bn**	**69**	**4**
Bu^iI	**Bu^i**	**58**	**5**

RX	R	Yield (%)	Compound[a]
MeI	**Me**	72	6
BnBr	**Bn**	53	7
Bu^iI	**Bu^i**	73	8
NH_4Cl	**H**	74	9

Scheme 3

[a] Compounds **3-9** are racemic

The nature of the pyrrolines described above was secured by examination of the nmr data for each compound: signals attributable to the alkyl group at C(4) could be located together with a 2H system at δ 3.5-4.5 ppm (which was assigned to the methylene at C-5). Definitive proof of structure was obtained with an X-ray crystallographic study on compound **3** (**Figure 1**).

We propose that (in the absence of alcohol as a proton source) these reductions proceed *via* a dianion, formed by the addition of two electrons to the electron-deficient pyrrole. This species is sufficiently basic to be protonated at C-5 by ammonia (or amine **10**), thus forming an extended enolate. Presumably, this enolate is stable to the reaction conditions and awaits reaction with an external electrophile. In accordance with literature precedent, this extended enolate reacts at the α-position in preference to the γ-position and so yields a 2-pyrroline isomer.[7]

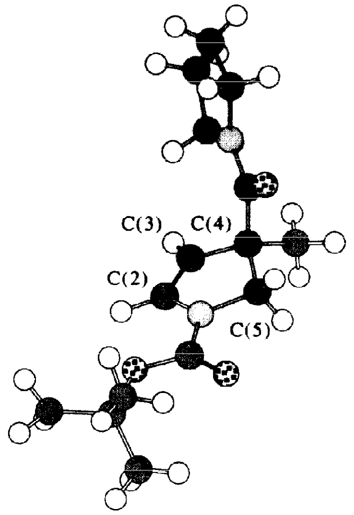
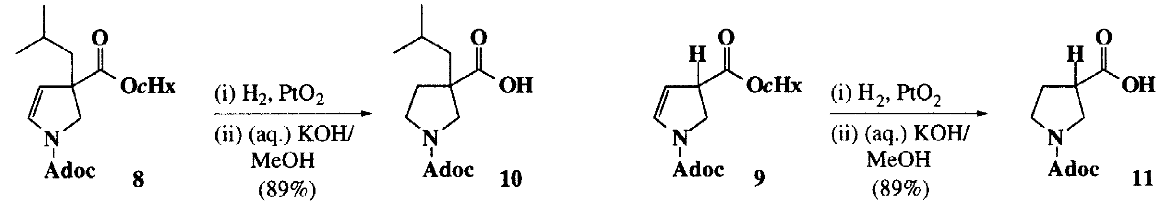


Figure 1: X-ray structure of **3**.

In order to prove the applicability of this chemistry to synthesis, we examined transformations of the activating groups at C-3. Not unexpectedly, the 2-pyrroline nucleus was unstable to the acidic conditions required to hydrolyse the amide and was not particularly compatible with the basic conditions required to hydrolyse the ester. Therefore, a hydrogenation was performed on compounds **8** and **9** prior to treatment with (aq.) KOH/methanol. In each case, the corresponding N-protected β-proline derivatives **10** and **11** were isolated in excellent yield after the two-step protocol (**Scheme 4**). When one considers this facile deprotection step in conjunction with the marginally higher yields obtained for reduction of **2**, the ester clearly becomes the activating group of choice.



Scheme 4

Conclusions

The Birch reduction of electron-deficient 3-substituted pyrroles has been described. Use of either an amide or ester as an activating group enabled a series of regioselective reductive alkylations to be performed and a synthesis of substituted 2-pyrrolines achieved. The choice of protecting group for the pyrrole nitrogen was also important, with Boc and Adoc both being compatible with the reducing conditions. In our hands, reduction of 3-substituted pyrroles was more difficult to achieve than that of the 2-substituted isomers, and care was taken to ensure that the optimum conditions and best protecting group for the pyrrole nitrogen were chosen.

This chemistry should prove interesting in the synthesis of natural products and also in the preparation of unnatural amino acids. Moreover, the real advantage of this chemistry lies in our ability to apply the Birch reduction to more complex pyrroles greatly extending the scope of this methodology.

A representative experimental procedure for the Birch reduction is as follows: Amide **1** (202 mg) in THF (10 ml) was added to a deep blue solution of sodium (100 mg) in THF (30 ml) and ammonia (60 ml), at -78°C under an atmosphere of nitrogen. After 30 min, methyl iodide (1 ml) was added followed immediately by a solution of (aq.) ammonium chloride (1 ml). The reaction was then allowed to warm to room temperature before brine (50 ml) was added and the mixture extracted with diethyl ether (2x 50 ml) and dichloromethane (2x 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by chromatography on a silica column, eluting with acetone/petroleum ether (15:85) gave **3** as a colourless solid (150 mg, 70%): ^1H nmr (300 MHz, $CDCl_3$) δ(ppm): 6.56-6.40 (1H, m, $C\underline{H}$=CH), 5.11 (1H, d, J= 4.2, CH=$C\underline{H}$), 4.22-3.97 (1H, m, $BocNC\underline{H}_2$), 3.65-3.30 (5H, m, $BocNC\underline{H}_2$, $NC\underline{H}_2CH_2$), 1.92-1.68 (4H, m, $NCH_2C\underline{H}_2$), 1.41 (9H, s, $(C\underline{H}_3)_3CO$), 1.32 (3H, s, $C\underline{H}_3C$).

Acknowledgments: We would like to thank Rhône-Poulenc Rorer (TJD), GlaxoWellcome (CASE award to RRH), and Zeneca Pharmaceuticals (Strategic Research Fund) for financial support. We would also like to acknowlege Dr P. Edwards (Zeneca Pharmaceuticals) for helpful discussions.

References

1. Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron Asymmetry*, **1996**, *7*, 317; Donohoe, T. J.; Helliwell, M.; Stevenson, C. A.; Ladduwahetty, T. *Tetrahedron Lett.*, **1998**, *39*, 3071. see also ref 3.
2. For general reviews of the Birch reduction see: Mander, L. N. In *Comprehensive Organic Synthesis*; Ed. Trost, B. M.; Fleming, I.; Pergamon; New York; 1991, vol 8; Rabideau, P. W.; Marcinow, Z. *Organic Reactions*, **1992**, *42*, 1; Rabideau, P. W. *Tetrahedron*, **1989**, *45*, 1579.
3. Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.*, **1996**, *61*, 7664; Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1*, **1998**, in the press.
4. van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.*, **1972**, 5337.
5. Kinoshita, T.; Miwa, T. *Carbohydrate Res.*, **1973**, *28*, 175; Kinoshita, T.; Miyano, K.; Miwa, T. *Bull. Chem. Soc. Japan*, **1975**, *48*, 1865; Kinoshita, T.; Miwa, T. *Bull. Chem. Soc. Japan*, **1978**, *51*, 225; Beddoes, R. L.; Lewis, M. L.; Gilbert, P.; Quayle, P.; Thompson, S. P.; Wang, S.; Mills, K. *Tetrahedron Lett.*, **1996**, *37*, 9119; Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Het. Chem.*, **1996**, *33*, 1313.
6. All new compounds displayed satisfactory spectroscopic data (^1H/^{13}C nmr, mass spec, IR and elemental analysis or HRMS).
7. Extended enolates usually display a penchant for reaction at the α-centre rather than the γ-centre: for example see, Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley; New York; 1976; Caine, D. In *Comprehensive Organic Synthesis*; Ed. Trost, B. M; Fleming, I; Pergamon; New York; 1991, vol 2.