A new, highly stereoselective approach to pyrrolidines *via* overall 5-*endo*-trig cyclisations of homoallylic tosylamides

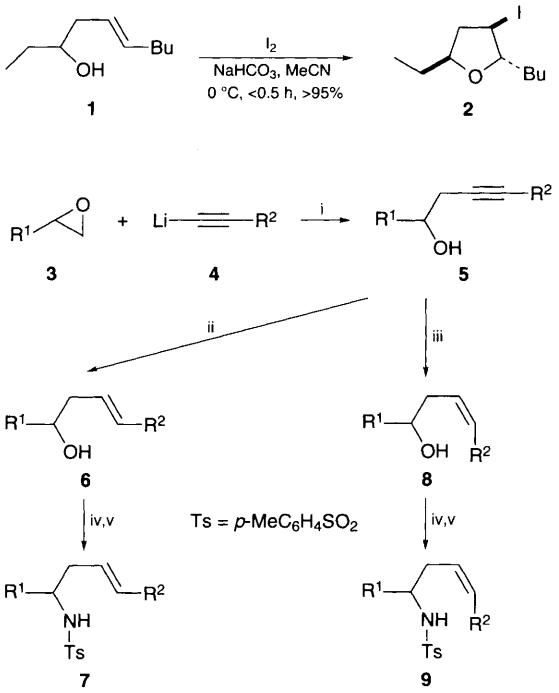
Andrew D. Jones and David W. Knight*†

Chemistry Department, University Park, Nottingham, UK NG7 2RD

Iodocyclisations of *E*-homoallylic tosylamides 7 lead to excellent yields of either 2,5-*trans*- or 2,5-*cis*-3-iodopyrrolidines (10 or 11), depending upon the reaction conditions.

Recent reports[1,2] have outlined the viability of both iodo- and seleno-cyclisations of homoallylic alcohols as highly stereoselective approaches to tetrahydrofurans (*e.g.* **1** → **2**), despite appearing to be violations of Baldwin's rules,[3] being effectively 5-*endo*-trig processes. However, it seems likely that such cyclisations are not exceptions to these rules, as they are electrophile rather than nucleophile driven. The potential of these reactions led us to speculate that similar cyclisations involving other nucleophiles could also be viable. Herein, we report our preliminary studies on iodocyclisations of homoallylic amine derivatives, which have led to the definition of new and highly stereoselective approaches to substituted iodopyrrolidines, *via* reactions which show significant differences to the related tetrahydrofuran syntheses.

The required substrates **7** and **9** were efficiently obtained as outlined in Scheme 1. Alkylation of acetylides **4** with epoxides **3** led[4] to the homoprop-2-ynylic alcohols **5**, which were converted into the corresponding *E*- or *Z*-homoallylic alcohols (**6** and **8**) by hydride or Lindlar reductions respectively. The nitrogen function was then introduced using a Mitsunobu reaction with *N*-(Boc)tosylsulfonamide (TsNHBoc),[5] followed by removal of the carbamate group; all steps gave isolated

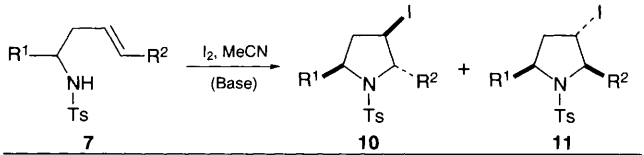


Scheme 1 *Reagents and conditions*: i, BF_3·OEt, THF, −78 °C, ii, $LiAlH_4$, THF–toluene, reflux, 48 h; iii, H_2, 5% Pd–$BaSO_4$, quinoline, EtOAc, 20 °C; iv, TsNHBoc, DEAD, PPh_3, THF, 20 °C; v, TFA, CH_2Cl_2, 20 °C, 0.5 h

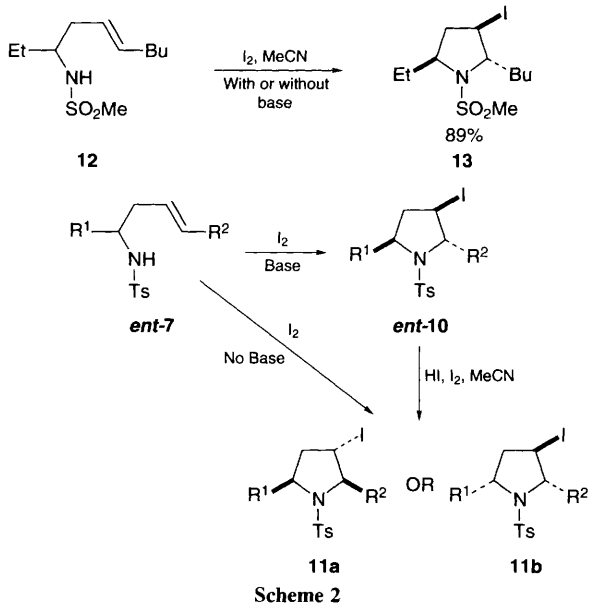
yields in excess of 85%. Our choice of the sulfonamide group was dictated by the realization that many alternatives, such as carbamates, would be likely to compete with the desired 5-*endo*-trig iodocyclisation in a 6-*exo*-trig fashion.‡ Initially, we examined iodocyclisations of the *E*-homoallylic amines **7** using the conditions (3 equiv. I_2 and $NaHCO_3$, dry MeCN, 20 °C) established previously for the conversion **1** → **2**.[2] Encouragingly, our first attempt (entry 1, Table 1) led to the rapid (< 0.25 h) formation of a single *trans*-iodopyrrolidine in excellent yield, the stereochemistry reflecting the anticipated *anti* addition across the double bond. However, a 1-alkene (entry 2) gave poorer yields of an isomeric mixture; more disturbing was that higher homologues (entries 3 and 4) were also converted into isomeric mixtures, although the excellent yields compensated for this. The two isomers obtained (**10** and **11**) differed in their 2,5-stereochemistry, with the 2,5-*trans* isomer dominating.§ A variety of modifications, including changes to the solvent (MeCN–CH_2Cl_2, CH_2Cl_2, Et_2O) and temperature (0 or −78 °C), failed to improve this ratio, which did, however, show slight variations dependent upon the work-up method. We felt that the poor stereoselectivity might thus be due to isomerization of the initially formed pyrrolidines **10**, catalysed by hydrogen iodide, generated during the cyclisation. We therefore added stronger bases and were delighted to find that by using potassium carbonate, the cyclisations (entries 5–8) were highly stereoselective, in favour of the 2,5-*trans*-pyrrolidines **10**. Also of benefit was the addition of small amounts of water, despite our findings in the tetrahydrofuran examples[2] that dry conditions were essential to prevent competing iodohydrin formation. It may be that, in the present examples, water facilitates removal of hydrogen iodide by the heterogeneous base.

The foregoing results made us speculate that if no base were present, the presumed isomerization leading to the 2,5-*cis*

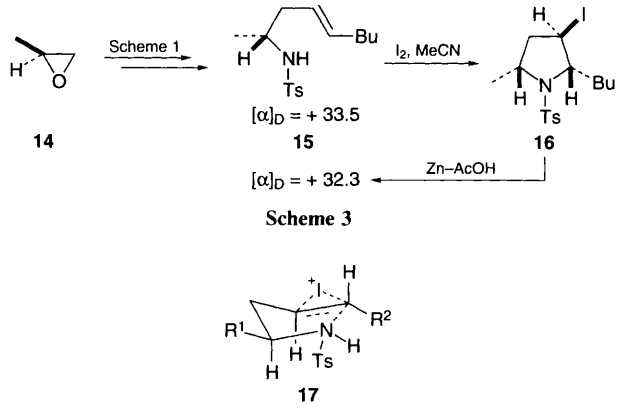
Table 1 Iodocyclisations of (*E*)-homoallylic tosylamides **7**



Entry	R^1	R^2	Base	Yield (%)	Ratio **10**:**11**
1	H	Et	$NaHCO_3$	95	~100:0 *trans*
2	Me	H	$NaHCO_3$	51	3:1
3	Et	Ph	$NaHCO_3$	95	2:1
4	Et	Bu	$NaHCO_3$	91	3:1
5	H	Et	K_2CO_3	85	~100:0 *trans*
6	Et	Ph	K_2CO_3	83	>25:1
7	Pr	Me	K_2CO_3	92	>25:1
8	Bu	C_5H_{11}	K_2CO_3	89	>25:1
9	H	Et	None	96	~100:0 *trans*
10	Et	Ph	None	87	~0:100
11	Me	Bu	None	91	~0:100
12	Et	Bu	None	88	~0:100
13	Bu	C_5H_{11}	None	90	~0:100



Scheme 2



Scheme 3

diastereoisomers **11** might go to completion. We were pleased to find that, by treating the substrates **7** with a solution of iodine in acetonitrile, the 2,5-*cis*-iodopyrrolidines **11** were produced in excellent yields with complete stereocontrol (entries 9–13). Furthermore, these cyclisations were faster than under basic conditions, being complete in less than 5 min at 20 °C, suggesting that hydrogen iodide is catalysing the initial cyclisation as well as the isomerization. In addition, it is clear that the arylsulfonyl group plays a crucial role: cyclisations of the corresponding methylsulfonyl derivatives (*e.g.* **12**) gave only the 2,5-*trans* diastereoisomers (*e.g.* **13**) whether or not a base was present.

We have as yet been unable to secure similar high yields from cyclisations of the *Z*-homoallylic amides **9** under any of the foregoing conditions. The reactions are much slower and isolated yields of the derived iodopyrrolidines are variable, usually 50–80%, and in all cases the products are mixtures (1 : 1–3 : 1) of stereoisomers.

Treatment of selected 2,5-*trans*-pyrrolidines **10** with a solution of iodine and hydrogen iodide in acetonitrile (Scheme 2) resulted in conversion into the corresponding 2,5-*cis*-pyrrolidines **11**, indicating that HI was indeed responsible for the suggested isomerization. One problem remained: which centre was undergoing isomerization? As shown in Scheme 2, this could not be determined using a racemic starting material **7**, as the two isomerization products (**11a** and **11b**) are enantiomeric. However, by starting with a homochiral substrate ***ent*-7** (Scheme 2) and using non-basic cyclisation conditions, the expectation was that one of the 2,5-*cis*-pyrrolidines **11a** or **11b** would be obtained, depending upon which α-centre was undergoing isomerization. That isomerization was occurring about the 2,3-positions was shown by the experiments outlined in Scheme 3. The homochiral tosylamide **15** was prepared from *S*-epoxide **14** (Scheme 1); cyclisation under non-basic conditions led as expected to the pyrrolidine **16**. Deiodination using zinc in acetic acid then led back to the tosylamide **15**, which displayed the same optical rotation as the original sample. It therefore seems that, under basic conditions, the kinetic 2,5-*trans*-pyrrolidines **10** are formed, *via* transition state **17**,[2] wherein the substituent R^1 is pseudoequatorial; subsequent isomerization to the thermodynamically more stable 2,5-*cis*-pyrrolidines **11** then involves cycloreversion and recyclisation, driven by protonation of the sulfonamide function. The poor results from cyclisations of the corresponding *Z*-isomers **9** may reflect a higher energy transition state, wherein the alkenyl substituent (R^2) is pseudoaxial (*cf.* **17**). The failure of the methylsulfonyl pyrrolidine **13** to isomerize remains to be explained, as does the apparent catalytic effect of HI upon the initial cyclisation.

We gratefully acknowledge support of this work from the Royal Society by a Leverhulme Senior Research Fellowship (to D. W. K.) and from the EPSRC (Quota award to A. D. J.).

Footnotes

† Present address: Department of Chemistry, Cardiff University, PO Box 912, Cardiff, UK CF1 3TB.

‡ A variety of trial reactions have shown that this is indeed the case.

§ The stereochemistries of the pyrrolidines were proven by extensive NMR experiments, especially NOE measurements; subsequent X-ray crystallographic determinations of the products from entries 6 (**10**) and 12 (**11**) confirmed these assignments.

References

1 S. H. Kang and S. B. Lee, *Tetrahedron Lett.*, 1993, **34**, 1955 and 7579; B. H. Lipshutz and T. Gross, *J. Org. Chem.*, 1995, **60**, 3572 and references therein; Y. Landais, D. Planchenault and V. Weber, *Tetrahedron Lett.*, 1995, **36**, 2987.

2 J. M. Barks, D. W. Knight and G. G. Weingarten, *J. Chem. Soc., Chem. Commun.*, 1994, 719; J. M. Barks, D. W. Knight, C. J. Seaman and G. G. Weingarten, *Tetrahedron Lett.*, 1994, **35**, 7259 and references therein.

3 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

4 M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391.

5 J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. D. Harris, Jr. and S. M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 5709.

Received, 8th January 1996; Com. 6/00139D