Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 2825–2828
Tetrahedron Letters

On the rapid synthesis of highly substituted proline analogues by 5-*endo*-trig iodocyclisation

Muhammad Amjad and David W. Knight*

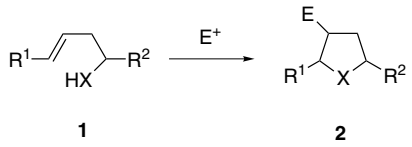
Centre for Heterocyclic Synthesis, School of Chemistry, Cardiff University, Main College, Park Place, Cardiff CF10 3AT, UK

Received 8 December 2005; revised 23 January 2006; accepted 1 February 2006
Available online 21 February 2006

Abstract—Highly substituted α-alkenyl-α-amino esters undergo smooth if rather slow 5-*endo*-iodocyclisations both in the presence or absence of base to give good to excellent yields of substituted proline derivatives. The stereoselectivities are often only moderate, except when the amino ester residue carries a substituent, which is branched at its α-position.

The utility of 5-*endo*-trig cyclisations for the usually highly stereoselective synthesis of tetrahydrofurans[1] or pyrrolidines[2,3] has been demonstrated by a number of groups. Generally, these are best induced by species such as halonium or phenylselenenonium ions;[4] the transformation, overall, can also be achieved using protons[5] or palladium(II) salts[6] in the case of homoallylic sulfonamides. Despite initial appearances, this general transformation (Scheme 1) of homoallylic precursors **1** into heterocycles **2**, being electrophile-driven, probably does not represent an exception to Baldwin's rules.[7,8]

Our experiments towards defining a pyrrolidine synthesis based on Scheme 1 have revealed a marked tendency for equilibration in favour of the thermodynamically more stable 2,5-cis diastereoisomers, in the presence of protons. Thus, while exposure of the (*E*)-homoallylic sulfonamides **3** to an excess of iodine in the presence of potassium carbonate showed a distinct preference for formation of the 2,5-trans isomers **5**, omission of the base leads to the corresponding 2,5-cis isomers **6**, often as the sole products (Scheme 2).

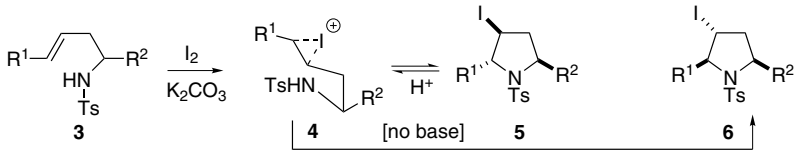


1 **2**

Scheme 1.

We have ascribed these results to an initial cyclisation via a chair-like transition state conformation **4**, which leads to the 2,5-trans isomers **5** and which can then be followed by proton-induced cyclo-reversion and re-closure and hence equilibration towards, eventually only, the more stable 2,5-cis isomers **6**.

This led us to question whether such cyclisations could be applied successfully to much more highly substituted examples and, if so, whether these would show useful levels of stereoselection. A prime motivation was that, if successful, this would represent a rapid approach to highly substituted proline analogues. As one of the 20 or so ubiquitous α-amino acids, the synthesis of such analogues is an important aspect of drug discovery.

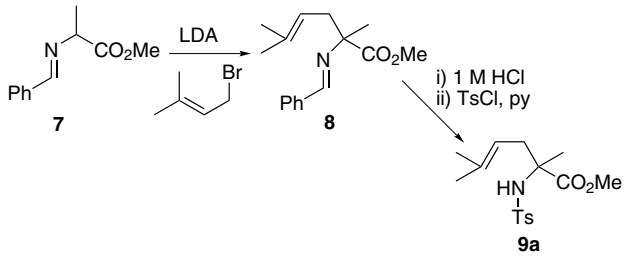


3 **4** **5** **6**

Scheme 2.

* Corresponding author. Fax: +44 02920 874 210; e-mail: knightdw@cf.ac.uk

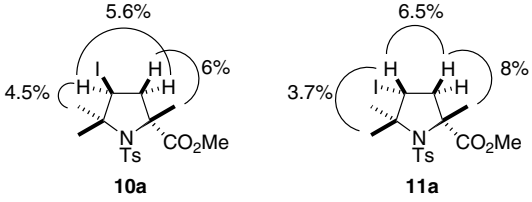
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.02.017



Scheme 3.

However, at the outset, it was far from clear if such highly crowded substrates would indeed undergo cyclisation, especially as the overall 5-*endo*-trig process is already disfavoured.[7,8] Fortunately, a relevant substrate, the *C*-prenyl derivative of alanine **9a** was readily prepared, in racemic form, using the excellent Stork procedure, by C-alkylation of the carbanion derived from Schiff's base **7** (Scheme 3).[9]

The resulting homologated product **8** was subsequently hydrolysed by brief exposure to 1 M hydrochloric acid then the resulting free amine N-tosylated to give the precursor **9a** in good overall yield. Gratifyingly, the desired iodocyclisation was found to proceed smoothly using 3 equiv of iodine in acetonitrile under both sets of conditions, that is, either in the presence or absence of potassium carbonate (Table 1). However, in both cases, there was virtually no stereocontrol. Careful column chromatography and crystallisation separated samples of both diastereomers **10a** and **11a**, the stereochemistry of which was determined using a GOSEY experiment at 500 MHz. The key results are shown below. All other enhancements were below 2%, except for those of the geminal methyls and protons.

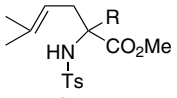
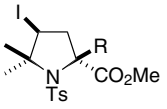
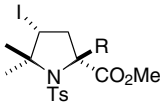
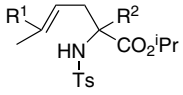
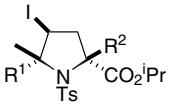
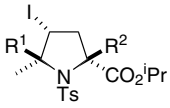


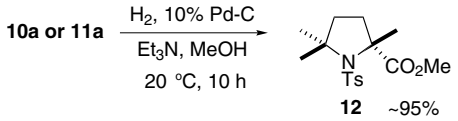
Evidence for these two structures was also obtained by hydrogenolytic removal of the iodine atom; as expected, both iodopyrrolidines [**10a** and **11a**] gave the same deiodinated product **12a** (Scheme 4).

Subsequently, the same route[9] was used to prepare all other substrates tested in such iodocyclisations. In all cases, similar GOSEY experiments were used to determine product stereochemistry, often using (partly separated) mixtures.

A similar result was obtained upon cyclisation of the prenylated derivative **9b** of *N*-tosyl phenylglycinate, under basic conditions. Although the overall yield was excellent, the cyclisation was rather slow, taking over

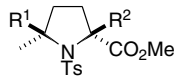
Table 1. Cyclisations of 1,2,2-trisubstituted alkenyl derivatives **9** and **13**

Precursor	Products	
 **9**	 **10**	 **11**
(a) R = Me		
Basic: $3I_2$, 2 h, 76%	48%	52%
Acidic: $3I_2$, 16 h, 82%	62%	38%
(b) R = Ph		
Basic: $3I_2$, 96 h, 88%	38%	62%
Acidic: $3I_2$, 96 h, 91%	20%	0%
	[80% deiodo **16a**]	
(c) R = CH_2Ph		
Basic: $3I_2$, 2 h, 75%	26%	74%
Acidic: $3I_2$, 2 h, 76%	0%	25%
	[75% deiodo **16b**]	
 **13**	 **14**	 **15**
(a) R^1 = Pr^n; R^2 = H		
Basic: $3I_2$, 24 h, 87%	35%	65%
Acidic: $3I_2$, 24 h, 87%	60%	40%
(b) R^1 = Ph; R^2 = H		
Basic: $3I_2$, 48 h, 96%	22%	78%
Acidic: $3I_2$, 24 h, 90%		[Mainly deiodo **16c**]
(c) R^1 = Ph; R^2 = Me		
Basic: $5I_2$, 48 h, 96%	42%	58%
Acidic: $5I_2$, 48 h, 97%	75%	25%

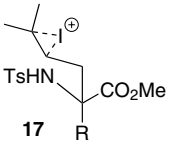


Scheme 4.

90 h to reach completion at ambient temperature. Again, the predominant isomer **11b** was that having the ester and iodine atom disposed cis to each other. However, a quite different result arose in the absence of base, when the preferred pathway was acid-catalysed cyclisation[5] to give pyrrolidine **16a**, together with a minor amount of iodopyrrolidine **10b**, in excellent overall yield. Much the same result was obtained from the prenylated phenylalanine derivative **9c**: under basic conditions, isomer **11c** predominated while, under acidic conditions, pyrrolidine **16b** was the major product. In both cases, however, the rates of cyclisation were much higher, reflecting the lower degree of steric crowding relative to the phenylglycinate derivative **9b**. In line with the originally proposed chair-like transition state conformation **4** (Scheme 2), the foregoing results are consistent with the predominant intermediary, albeit only slightly, of a conformation **17** in which the ester occupies an equatorial position.



16 a) R^1 = Me; R^2 = Ph
b) R^1 = Me; R^2 = CH_2Ph
c) R^1 = Ph; R^2 = H



17

Highly efficient cyclisations of the (*E*)-alkenyl glycinate **13a** followed a similar pattern: under basic conditions, isomer **15a** predominated whereas under acidic conditions, an alternative, presumably more thermodynamically stable isomer **14a** was the major product, in which the larger α-substitutes (propyl and CO_2Me) are orientated cis to each other. The formation of only two diastereoisomers is also notable indicating a highly stereocontrolled cyclo-reversion process. More peculiar results were obtained from the phenyl-substituted glycinate **13b**: whilst under basic conditions, the predominance of isomer **15b** suggested control arising from a chair conformation related to structure **17**, under acidic conditions, pyrrolidine **16c** lacking iodine was formed almost exclusively. However, cyclisation of the homologous alanine derivative **13c** was found to require 5 equiv of iodine to reach completion and, even then, only after an extended reaction period of 48 h. The stereochemical patterns, however, followed a now familiar sequence, even though the molecules are now very sterically crowded.

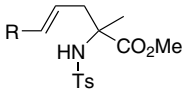
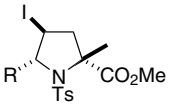
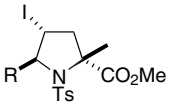
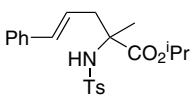
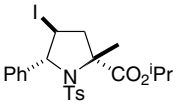
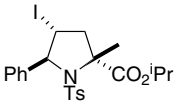
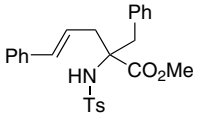
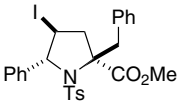
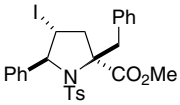
A similar pattern of results was observed in iodocyclisations of a series of alanine derivatives **18** having monosubstituted (*E*)-alkenyl substituents (Table 2). Five equivalents of iodine were necessary to achieve a reasonable rate of cyclisation as well as completion of the reaction.

Once again, while chemical yields were very good, the levels of stereoselection were not particularly exciting, showing only a moderate preference for those isomers **20** with a trans disposition between the ester and 5-substituent under basic conditions but the reverse (**19**) under acidic conditions, at least when R = Ph. In an effort to encourage greater stereocontrol, the methyl ester precursor **18b** was transesterified into the bulkier isopropyl ester **21**. This resulted in a marginal increase in formation of the '2,5-trans' isomer **23** together with a pronounced reluctance to undergo acid-catalysed isomerisation to the '2,5-cis' isomer **22**, presumably because of the increase in the size of the ester. Placing the bulk of a substituent further away from the reacting centres, as in the phenylalanine derivative **24** resulted in little stereocontrol under both extremes of conditions, probably reflecting the relatively similar steric influences of the benzyl and methoxycarbonyl groups.

Really high levels of stereocontrol were only observed when the α-amino ester residue was substituted by a group having an α-branch, in the present cases, isopropyl or phenyl (Table 3).

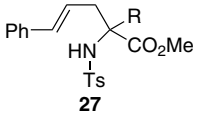
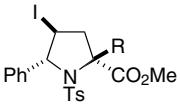
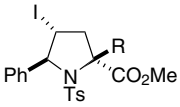
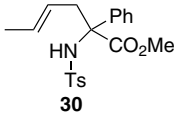
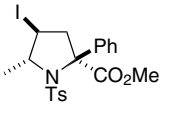
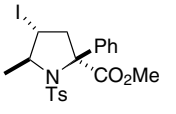
Thus, the valine-derived cinnamyl derivative **27a** gave largely the '2,5-*trans*' proline homologue **29a** under basic conditions, but showed a contrary stereoselection in favour of the '2-5-cis' isomer **28a** under acidic conditions. Both the requirements for 5 equiv of iodine and the relatively slow rate of cyclisation reflect the high level of steric congestion. Similarly, the phenylglycine derivative **27b** gave the '2,5-trans' isomer **29b** as a

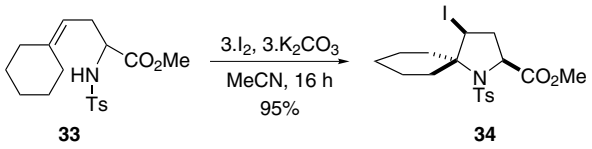
Table 2. Cyclisations of 1,2-disubstituted alkenyl derivatives **18**, **21** and **24**

Precursor	Products	
 **18**	 **19**	 **20**
(a) R = Me		
Basic: $5I_2$, 16 h, 80%	30%	70%
Acidic: $5I_2$, 16 h, 85%	35%	65%
(b) R = Ph		
Basic: $5I_2$, 48 h, 73%	44%	56%
Acidic: $5I_2$, 16 h, 80%	76%	24%
 **21**	 **22**	 **23**
Basic: $5I_2$, 16 h, 83%	18%	82%
Acidic: $5I_2$, 16 h, 76%	33%	67%
 **24**	 **25**	 **26**
Basic: $5I_2$, 16 h, 51%[a]	42%	58%
Acidic: $5I_2$, 16 h, 95%	58%	42%

[a] 37% starting material **24** recovered.

Table 3. Cyclisations of α-branched-cinnamyl and crotyl derivatives **27** and **30**

Precursor	Products	
 **27**	 **28**	 **29**
(a) R = ^{i}Pr		
Basic: $5I_2$, 48 h, 88%	20%	80%
Acidic: $5I_2$, 16 h, 89%	82%	18%
(b) R = Ph		
Basic: $3I_2$, 48 h, 95%	12%	88%
Acidic: $3I_2$, 48 h, 98%	35%	65%
 **30**	 **31**	 **32**
Basic: $3I_2$, 40 h, 88%	6%	94%
Acidic: $3I_2$, 40 h, 82%	92%	8%



33 34

Scheme 5.

predominant product in the presence of potassium carbonate. Oddly, this was also the major product under acidic conditions, perhaps suggesting a contribution from a favourable interaction between the two phenyl rings (π–π-stacking?). Enhanced levels of stereoselection were observed in the phenylglycine-derived crotyl derivative **30**, the '2,5-trans' product **32** being formed nearly exclusively under basic conditions at the expense of the '2,5-cis' isomer **31**, favoured under acidic conditions.

A curiosity associated with the use of 5 equiv of iodine was that it was found essential to add this quantity at the outset of a reaction. Adding two further equivalents to a cyclisation, which already contained 3 equiv of iodine but which appeared to be progressing extremely slowly had almost no effect. We have no explanation for this phenomenon. Indeed, beyond a supposition of the necessity for formation of a suitable reactive iodonium species such as $I^+I_5^-$, we have no certain rationale of the need for 3 equiv[2] in most iodocyclisations, including lactonisations, etherifications and aminations, whether of an *exo*- or *endo*-type.

The stereochemical outcomes appear to follow largely the chair-like conformation **4** (Scheme 2), wherein the ester group adopts an equatorial position during the initial cyclisation (which predominates under basic conditions), hence leading to the kinetic product. Acid-catalysed cyclo-reversion and equilibration to the thermodynamic isomers then follows in the absence of base (Scheme 2). However, the highly crowded nature of some of the precursors, together with the often low levels of stereoselection could be concealing a more complicated picture involving alternative transition state conformations, making clear stereochemical predictions rather difficult. Further, none of this takes into account the possible influence of the relatively large *N*-tosyl substituent. In any event, the foregoing results clearly show that this route, overall, represents a very rapid, flexible and efficient approach to highly substituted proline derivatives and no doubt many other pyrrolidines in general. High levels of stereoselection are, however, not usually observed except when an α-branched substituent is included adjacent to the central ring.

A further demonstration of the utility of this chemistry, perhaps not surprising in view of the results shown in Table 1, was the finding that *spiro*-pyrrolidine **34** is obtained highly selectively and efficiently from the cyclohexylidene derivative **33** (Scheme 5). We would therefore anticipate that, at the very least, this chemistry should be useful for the rapid synthesis of a great diversity of proline analogues.

Acknowledgements

We are grateful to Robert Jenkins for assistance with spectroscopic analysis and to the EPSRC and the National Mass Spectrometry Service, Swansea, for the provision of high resolution NMR and mass spectroscopic data, respectively.

References and notes

1. Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950; Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 1955, and 7579; Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084; Mihelich, E. D.; Hite, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7318; Barks, J. M.; Knight, D. W.; Seaman, C. J.; Weingarten, G. G. *Tetrahedron Lett.* **1994**, *35*, 7259; Bedford, S. B.; Bell, K. E.; Bennett, F.; Hayes, C. J.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2143.
2. Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1182, and references cited therein.
3. Jones, A. D.; Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1999**, *40*, 3267; For selenocyclisations onto indoles, see: Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143; Crich, D.; Huang, X. *J. Org. Chem.* **1999**, *64*, 7218.
4. French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354; Knight, D. W. *Prog. Heterocycl. Chem.* **2002**, *14*, 19.
5. Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471; Haskins, C. M.; Knight, D. W. *Chem. Commun.* **2002**, 249.
6. Koh, J. H.; Mascarenhas, C.; Gange, M. R. *Tetrahedron* **2004**, *60*, 7405, and references cited therein.
7. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734; Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
8. Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1998**, *39*, 8909.
9. Stork, G.; Leong, A. Y.; Touzin, A. M. *J. Org. Chem.* **1976**, *41*, 3491.