# Stereoselectivity in the Synthesis of 2,5-Disubstituted Pyrrolidines

**Richard Kinsman, David Lathbury, Peter Vernon, and Timothy Gallagher***

*School of Chemistry, Bath University, Bath, Avon BA2 7AY, U.K.*

Under homogeneous conditions, the silver(I)-catalysed cyclisation of the allenic amine derivatives (**3a**—**c**), though not (**3d**), is stereoselective giving *cis*-2,5-disubstituted pyrrolidines in high yield; cyclisation of (**3a**), using a heterogeneous silver(I)-catalyst, is nonstereoselective.

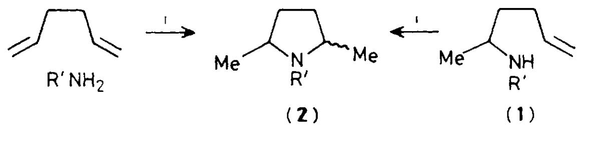
The electrophile-initiated cyclisation of δ-alkenyl amines, amides, and carbamates provides a useful route to substituted pyrrolidines.[1] Considerable attention has been focused on the stereochemistry of this cyclisation reaction with particular emphasis on the process leading to *cis*- and *trans*-2,5-disubstituted pyrrolidines. For example, the synthesis of 2,5-dimethylpyrrolidine (**2**) (Scheme 1) from either alkene (**1**) or hexa-1,5-diene has been extensively studied and conditions found yielding either *cis*- or *trans*-(**2**) selectively.[2]

Despite these studies there is still a need to extend this methodology to the stereoselective construction of more highly functionalised, and therefore synthetically more useful, disubstituted pyrrolidines. With this objective in mind we report on the silver(I)-catalysed cyclisation of allenic amino esters (**3a**—**d**) leading to 2,5-disubstituted pyrrolidines (**4a**—**d**).

The requisite amino allenes (**3a**—**d**), varying only in the nature of the substituent on nitrogen, were prepared as shown in Scheme 2 *via* the alkylation of a glycine derivative.[3]

Efficient cyclisation of (**3a**—**d**) was effected using $AgBF_4$ (0.1—1.0 equiv.) in $CH_2Cl_2$ (Scheme 3). The products were isolated following a simple aqueous wash and, if necessary, chromatographic purification. High stereoselectivity (see Table 1) was observed in the cyclisation of (**3a**—**c**) with the *cis*-2,5-disubstituted pyrrolidine *cis*-(**4a**—**c**) being the only product observed. The primary amine (**3d**), however, underwent nonstereoselective cyclisation under these conditions.

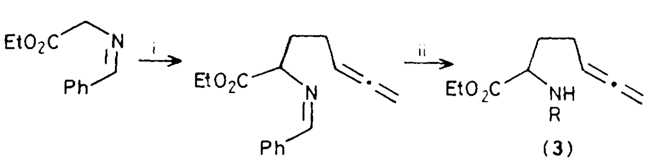
The configuration of *cis*-(**4a**) was established by conversion, *via* the corresponding carboxylic acid, into a single iodolactone (**5**) [m.p. 185 °C (benzene), $\nu_{max.}$ ($CHCl_3$) 1765 $cm^{-1}$; $\delta_H$ 4.72—4.66 (2H, m), 4.31 (1H, dd, *J* 10, 4 Hz), 3.28 (1H, dd, *J* 10, 4 Hz), 3.17 (1H, t, *J* 10 Hz), 2.16—1.79 (4H, m)].† The structure of *cis*-(**4b**) was established in a similar fashion;



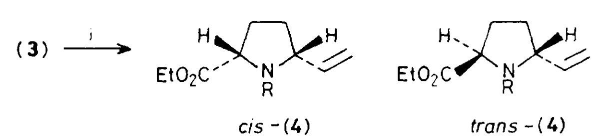
**Scheme 1.** *Reagents and conditions:* i, $HgX_2$ then $NaBH_4$.

---

† $^1H$ N.m.r. (400 MHz, $CDCl_3$) signals due to *N*-$SO_2$Tol have been omitted.



**Scheme 2.** *Reagents and conditions:* i, Bu$^t$OK, tetrahydrofuran (THF), −78 °C, 5 min followed by 5-bromopenta-1,2-diene, −78 °C to 0 °C; ii, (**3a**): aq. HCl followed by $ClSO_2Tol$, pyridine, 55%; (**3b**): $NaBH_4$, methanol, 60%; (**3c**): aq. HCl followed by $Boc_2O$, $CH_2Cl_2$, 30%; (**3d**): aq. HCl, 60%.



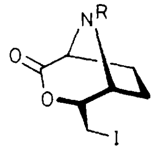
**Scheme 3.** *Reagents and conditions:* i, $AgBF_4$ (0.1—1.0 equiv.), $CH_2Cl_2$, 20 °C, 0.5—4 h.

both *cis*-(**4c**) and *cis*-(**4d**) were readily correlated with *cis*-(**4a**).‡

The success of homogeneous silver(I)-catalysis in effecting the cyclisation of a variety of allenic alcohols[4] and amines[5] prompted us to examine the use of an alternative procedure utilizing a supported catalyst, specifically silica gel impregnated with silver nitrate (5% w/w).§ Elution of a solution of (**3a**) though a column of this catalyst resulted in a clean, though nonstereoselective cyclisation, with *cis*- and *trans*-(**4a**) being formed in approximately equal amounts.[6]¶

Mechanistically, the results shown in Table 1 would suggest that the physical bulk, and not necessarily the electronic nature of the nitrogen substituent, is a determining factor in terms of the overall stereoselectivity observed. However, until more is known about the mode of action of silver(I) in this catalytic reaction and how the catalyst is modified by silica gel this rationale must be treated cautiously.

The synthetic potential of the transformations described above is easily appreciated. Heterocycles (**4**) bear two quite distinct and readily manipulated functional groups and the versatility of these products has been illustrated by the use of *cis*-(**4a**) [m.p. 64 °C (diethyl ether–hexane), $\delta_H$ 5.78 (1H, m), 5.36 (1H, m), 5.08 (1H, m), 4.38 (1H, q, *J* 7 Hz), 4.27—4.13 (3H, m), 2.02—1.97 (2H, m), 1.85 (1H, m), 1.77 (1H, m), 1.27 (3H, t, *J* 7 Hz)] as a key intermediate in the synthesis of the neurotoxic alkaloid, anatoxin-a.[7]



(**5**) R = $SO_2Tol$

**Table 1.**

| | (3) | *cis*-(4) : *trans*-(4) | % Yield[b] |
|---|---|---|---|
| **a**; | R = $SO_2Tol$[a] | >50 : 1 | 100 |
| **b**; | R = $CH_2Ph$ | >50 : 1 | 93 |
| **c**; | R = Boc[a] | >50 : 1 | 70 |
| **d**; | R = H | 1 : 1[c] | 60 |

[a] Tol = tolyl; Boc = t-butoxycarbonyl. [b] Yields refer to isolated material and isomeric purity was determined by g.c. and $^1H$ n.m.r. analysis. [c] This mixture was treated with $ClSO_2Tol$-pyridine to give *cis*-(**4a**) and *trans*-(**4a**) which were separated by flash chromatography.

We thank Dr. O. Howarth (Warwick University) for help in the acquisition and interpretation of 400 MHz $^1H$ n.m.r. spectra and the S.E.R.C. and Bath University for providing invaluable financial support.

*Received, 20th October 1986; Com. 1509*

---

‡ Control experiments, using *trans*-(**4a**), showed that no equilibration occurred under the conditions used to convert *cis*-(**4a**) (LiOH, aq. THF followed by $I_2$–KI, $NaHCO_3$–$H_2O$) into (**5**).

§ Similar results were obtained if silica gel was added to a solution of $Ag^I$ and (**3a**). No reaction occurred in the absence of $Ag^I$ nor was any equilibration [*cis*-(**4a**) to *trans*-(**4a**)] observed on prolonged exposure to this heterogeneous catalyst.

¶ The precise ratio of *cis*-(**4a**) : *trans*-(**4a**) showed a small solvent dependance: dichloromethane (2 : 3); diethyl ether (1 : 1); ethyl acetate (3 : 2). Similar experiments using (**3b**) gave only *cis*-(**4b**) but this more basic amine stripped the support of silver nitrate and cyclisation is presumed to have taken place in solution.

## References

1 M. B. Gasc, A. Lattes, and J. J. Perie, *Tetrahedron*, 1983, **39**, 703; R. R. Webb and S. Danishefsky, *Tetrahedron Lett.*, 1983, **24**, 1357, and references therein; L. Stella, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 337; T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, *J. Org. Chem.*, 1983, **48**, 3644; K. E. Harding and S. R. Burks, *ibid.*, 1984, **49**, 40; Y. Tamura, S. Kawarmura, K. Tanaka, and Z. Yoshida, *Tetrahedron Lett.*, 1984, **25**, 1063.

2 K. E. Harding and S. R. Burks, *J. Org. Chem.*, 1981, **46**, 3920; J. Barluenga, C. Jimenez, C. Najera, and M. Yus, *J. Chem. Soc., Chem. Commun.*, 1981, 1178; J. Barluenga, C. Najera, and M. Yus, *J. Heterocycl. Chem.*, 1981, **18**, 1297; J. Barluenga, C. Jimenez, C. Najera, and M. Yus, *ibid.*, 1984, **21**, 1733; *J. Chem. Soc., Perkin Trans. 1*, 1984, 721; K. E. Harding and T. H. Marman, *J. Org. Chem.*, 1984, **49**, 2838, and references therein. See also M. Tokuda, Y. Yamada, T. Takagi, and H. Suginome, *Tetrahedron Lett.*, 1985, **26**, 6085.

3 G. Stork, A. Y. W. Leong, and A. M. Touzin, *J. Org. Chem.*, 1976, **41**, 3493.

4 L.-I. Olsson and A. Claesson, *Synthesis*, 1979, 743; P. Audin, A. Doutheau, and J. Gore, *Bull. Soc. Chim. Fr.*, 1984, 297; T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1984, 1554.

5 S. Arseniyadis and J. Gore, *Tetrahedron Lett.*, 1983, **24**, 3997; S. Arseniyadis and J. Sartoretti, *ibid.*, 1985, **26**, 729; D. Lathbury and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1986, 114.

6 Silica gel has been observed to improve the efficiency of related cyclisations involving olefinic urethanes and benzeneselenyl chloride: D. L. J. Clive, V. Farina, A. Singh, C. K. Wong, W. A. Kiel, and S. M. Menchen, *J. Org. Chem.*, 1980, **45**, 2120.

7 P. Vernon and T. Gallagher, following communication.