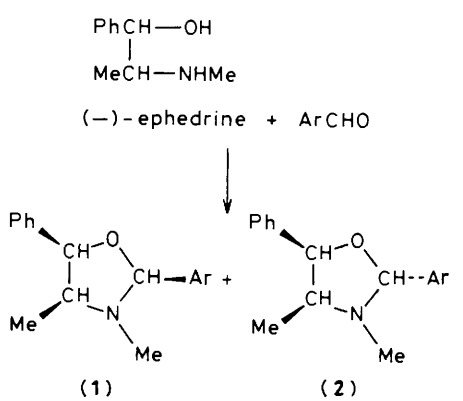
Role of Solvent on the Diastereoselectivity of Oxazolidine Formation from (−)-Ephedrine

Claude Agami* and Toufic Rizk

Laboratoire de Chimie Organique, Equipe de Recherche Associée au CNRS No. 127, Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France

Under kinetic control, the stereochemical course of the condensation between (−)-ephedrine and *p*-cyano- or *p*-nitro-benzaldehyde is solvent dependent; no noticeable stereoselectivity was observed in chloroform whereas diastereo-differentiation occurred in methanol.

There has been recent interest in the use of chiral oxazolidines as starting materials for asymmetric induction.[1–3] Oxazolidine formation from (−)-ephedrine is a stereo-differentiating reaction giving rise to a major epimer (**1**) with the (*S*)-configuration[4–6] at C-2; the proportion of the (*R*)-epimer (**2**) does not exceed 10% in the isolated products. This stereochemical result remains to be explained though it should be noticed that Beckett and Jones[4] demonstrated the greater thermodynamic stability of the (2*S*)-epimer derived from acetaldehyde compared to the (2*R*)-epimer.



(**1**) (**2**)

We have found that benzaldehyde itself reacted with (−)-ephedrine in chloroform yielding the epimer (**1**) as the major product (90%), irrespective of the reaction time and *p*-methoxybenzaldehyde reacted similarly. In contrast, kinetic control was observed with benzaldehydes containing electron-withdrawing substituents (*p*-cyano and *p*-nitro); both epimers (**1**) and (**2**) were then observed in a 50:50 ratio at the beginning of the reaction† (extent of reaction: 10%, temperature: 0 or

† Representative procedure: the aldehyde (2.4 mmol) and (−)-ephedrine (2.4 mmol) were dissolved in the appropriate solvent ($CHCl_3$ or CD_3OD; 5 ml) in the presence of 5A molecular sieves. Aliquot samples were analysed over a period of 48 h.

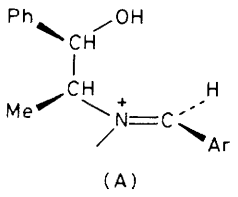
20 °C) and, here again, the epimer (**1**) was the major product (85%) at the end of the reaction. Configurations were determined classically by ^{1}H n.m.r. spectroscopy; C-2-H and C-5-H are more shielded[6] in (**1**) than in (**2**).

As deduced from the well known reverse reaction[7] (oxazolidine hydrolysis), the stereo-directing step is the addition of the ephedrine hydroxy-group onto the iminium double bond [structure (A)]. The observed absence of diastereoselectivity could be ascribed to a non-selective ring closure owing to the planarity of the prochiral sp^2 carbon atom. Thus these observations clearly show that the former reported diastereoselectivities were only the result of thermodynamic control.

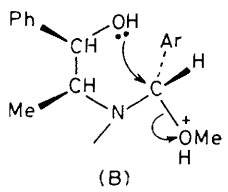
When the condensations were carried out in methanol instead of chloroform, a completely different stereochemical result was observed; at the beginning of the reaction only epimers (**2**) were detected (with *p*-cyano- and *p*-nitro-benzaldehyde) while, as above, the epimers (**1**) were still the major components of the final mixtures.

The effect of methanol can be explained by stereoselective ring closure‡ in the methanol adduct (B) whose nitrogen and reacting carbon atoms are no longer planar.

This dramatic solvent effect also explains a puzzling earlier report; Neelakantan[9] claimed the (2*R*)-configuration for the oxazolidine resulting from *p*-bromobenzaldehyde and (−)-ephedrine and this result was seriously disputed.[1,5,6] Actually,



(A)



(B)

as this experiment was performed in absolute ethanol, this apparently conflicting result could merely be due to the solvent effect described above.

Received, 13th June 1983; Com. 783

‡ An analogous cyclisation process is well documented in the aldose acetal series.[8]

References

1 H. Abadallah, R. Gree, and R. Carrie, *Tetrahedron Lett.*, 1982, **23**, 503.
2 P. Mangenay, A. Alexakis, and J. F. Normant, *Tetrahedron Lett.*, 1983, **24**, 373.
3 M. Huche, J. Aubouet, G. Pourcelot, and J. Berlan, *Tetrahedron Lett.*, 1983, **23**, 585; Y. Besace, J. Berlan, G. Pourcelot, and M. Huche, *J. Organomet. Chem.*, 1983, **247**, C11.
4 A. H. Beckett and G. R. Jones, *Tetrahedron*, 1977, **33**, 3313.
5 R. J. De Neale, *Diss. Abstr. Int.*, 1973, **34B**, 2119.
6 M. Baudet and M. Gelbcke, *Anal. Lett.*, 1979, **12B**, 325, 641.
7 T. H. Fife and L. Hagopian, *J. Am. Chem. Soc.*, 1968, **90**, 1007.
8 B. Capon, *Chem. Rev.*, 1969, **69**, 407.
9 L. Neelakantan, *J. Org. Chem.*, 1971, **36**, 2256; L. Neelakantan and J. A. Molin-Case, *ibid.*, 1971, **36**, 2261.