Tetrahedron Letters, Vol.32, No.24, pp 2827-2828, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Stereoselective Route To Highly Functionalised Amino Alcohols

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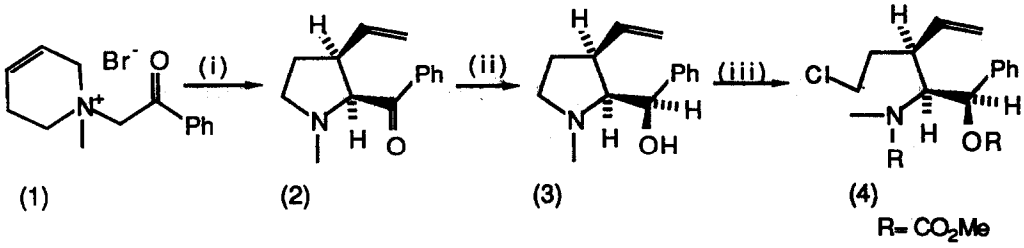
Keywords; [2,3] Sigmatropic rearrangement; amino ketone; amino alcohol; chelation controlled reduction.

Abstract: Acyclic amino alcohols can be obtained in high stereoisomeric purity by Stevens [2,3] rearrangement of tetrahydropyridine salts followed by reduction of the ketones and ring opening of the disubstituted pyrrolidine.

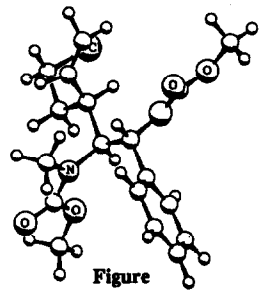
It is well known that [3,3] sigmatropic rearrangements are an excellent method for controlling stereochemistry in acyclic systems[1]. In contrast [2,3] sigmatropic rearrangements usually show much poorer selectivities in new carbon-carbon bond formation[2]. If these rearrangements are forced to proceed via bicyclic transition states then further constraints are placed on the transition state and the stereoselectivity of new carbon-carbon bond formation approaches 100% for both [3,3] and [2,3] rearrangements[3]. Therefore if a [2,3] rearrangement can be forced to proceed via a bicyclic transition state and then the extra ring can be unravelled this would provide a method for controlling stereochemistry in acyclic systems using [2,3] rearrangements. We now report our findings in this area.

Stevens [2,3] rearrangement of the racemic tetrahydropyridine salt (1) proceeded smoothly in boiling benzene to give the *cis*-disubstituted pyrrolidine (2) in high yield and with greater than 95% selectivity; Scheme. Reduction of the amino-ketone (2) with sodium borohydride in methanol gives the amino alcohol (3) as the sole diastereoisomer. Careful nmr analysis of the crude reaction product failed to reveal any other diastereoisomers. The high degree of stereocontrol in this reduction must be due, in part, to chelation of the tertiary nitrogen to the reducing agent and then delivery of the hydrogen from the least hindered face. Reductions in other similar systems are known to show the same degree of control, again delivering the hydrogen from the least hindered face of the sp^2 hybridised moiety[4]. Finally the pyrollidine ring was readily cleaved by treating (3) with a five-fold excess of methyl chloroformate in boiling benzene for three hours to give (4, 58%) as a crystalline solid, mp 104-106°C. This appears to be the first example of an N-methylated pyrollidine ring opening in preference to N-demethylation when treated with methyl chloroformate[5]. The relative stereochemistry of the protected amino alcohol (4) was established by a single-crystal X-ray analysis* (Figure) and thus the relative stereochemistry of (3) is as shown. Therefore the highly functionalised protected amino alcohol (4) is obtained isomerically pure in 42% overall yield from the salt (1). The convenience and high stereoselectivity of these processes make this a viable route to other protected amino alcohols of type (4).



Reagents (i) Sodium methoxide then heat in benzene for one hour. (ii) Sodium borohydride. (iii) Methyl chloroformate in boiling benzene.

Scheme



Figure

We thank the Nuffield Foundation (M.T.McC) and Queens University for support.

References and Notes

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*Crystal Data for (4): $C_{18}H_{24}NO_5Cl$. M = 369.9. Monoclinic, a = 12.758(13), b = 16.888(19), c = 9.462(14)Å, β = 109.51(9)°, V = 1921.6(38)Å^3, Z = 4, Dc = 1.28 g cm^{-3}, F(000) = 784, space group $P2_1/c$ (No. 14), λ(MoKα) = 0.71073Å, μ(MoKα) = 1.83 cm^{-1}. Siemens P3/V2000 diffractometer, θ-2θ scans, θ scan range 1.2°, 3 < 2θ < 50°, 3397 unique reflections measured, direct methods (SHELXS86) solution, least squares refinement (SHELX76), non-hydrogen atoms anisotropic, hydrogens included at calculated positions. In the final cycles the 868 data with F > 6σ(F) gave R = .088, Rw = .093 with weighting scheme w = .88/[σ^2(F) + .0126F^2] .

Full crystallographic results have been deposited with the Director, Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, U.K

(Received in UK 18 March 1991)