Tetrahedron Letters, Vol.31, No.30, pp 4351-4354, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

STEREOSELECTIVE APPROACHES TO TRISUBSTITUTED PYRROLIDINES

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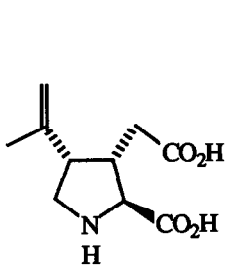
Abstract: 5,6-Alkyl substituted 1,2,5,6-tetrahydropyridine salts undergo Stevens [3,2] rearrangement with ring contraction to give 2,3,4 or 2,3,5-trisubstituted pyrrolidines with 100% stereoselectivity.

The trisubstituted pyrrolidine moiety is an important structural unit in many biologically active substances e.g. kainic acid (**1**),[1] borrecapine (**2**)[2] and quinocarcin (**3**).[3] Recently Ireland Claisen [3,3] rearrangement with ring contraction of ketene acetals (**4**→**5**) has been utilised to construct trisubstituted pyrrolidines stereoselectively.[4] Because of the nature of the bicyclic transition state the stereoselectivity is 100%. The major drawback with this procedure is that it is difficult to synthesise the precursor medium sized ring lactones. We now report our findings on Stevens [3,2] rearrangement with ring contraction, (proceeding through a bicyclic transition state), as a method for producing trisubstituted pyrrolidines stereoselectively. The precursors for making the salts are the readily available alkyl substituted 1,2,5,6-tetrahydropyridines.[5]



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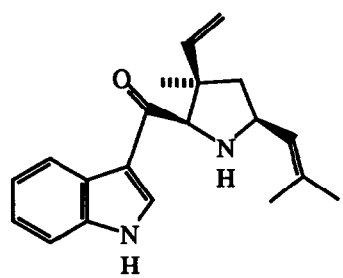

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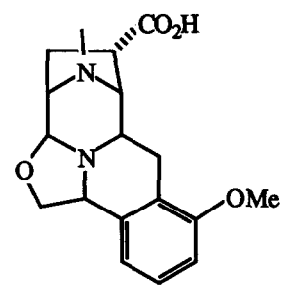

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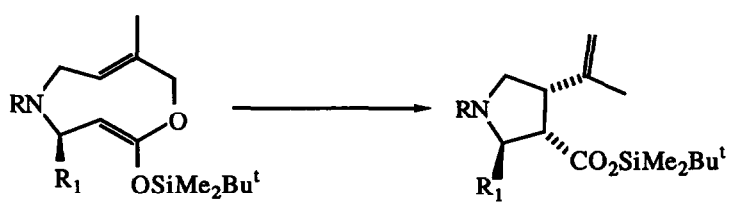
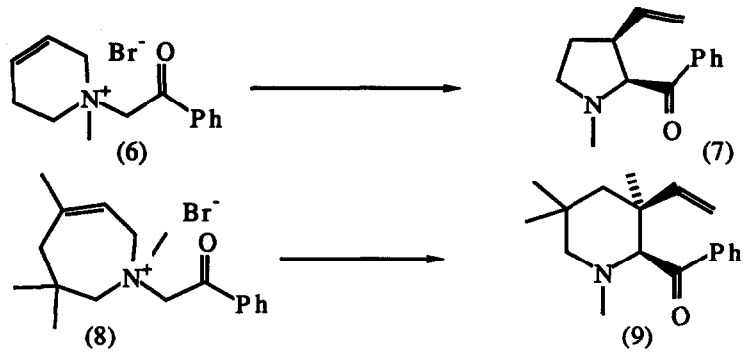
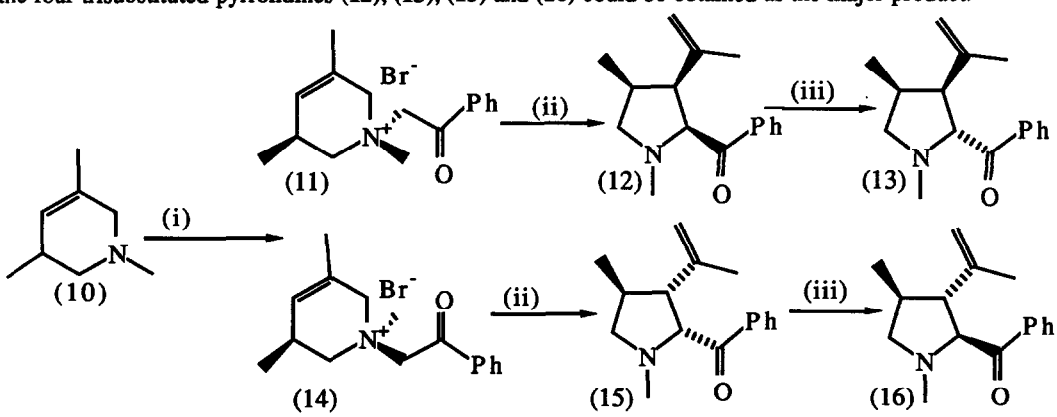


(4) (5)

It is known that salts (**6**) and (**8**) undergo Stevens [3,2] rearrangement with ring contraction to give the *cis*-disubstituted pyrrolidines (**7**) and piperidines (**9**) respectively as the sole diastereoisomers in high yield.[6] The high degree of stereocontrol in these reactions suggests that it could easily be modified to give a trisubstituted pyrrolidine stereoselectively.

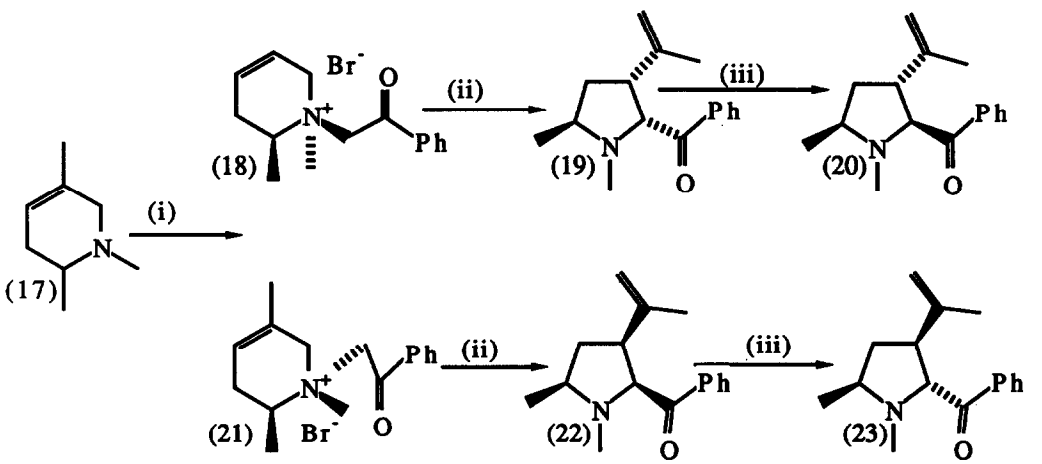


Treatment of 1,3,5-trimethyl pyridinium iodide with sodium borohydride give 1,3,5-trimethyl-1,2,5,6--tetrahydropyridine (**10**). It is known that quaternisation of 4-phenyl-5-methyl-1,2,5,6-tetrahydropyridines is a stereoselective process[7]. It is usually found that the major diastereoisomer upon quaternisation is the one resulting from axial attack of the electrophile onto the nitrogen lone pair[8], and isomer ratios ranging from 3:1 to 9:1 are common. Therefore by choosing which group is used in the quaternisation step in principle any of the salt diastereoisomers could be obtained as the major product. When (**10**) was treated with phenacyl bromide a 55:45 mixture of salts (**11**) and (**14**) was formed in 91% yield. The selectivity of salt formation in this case is disappointingly low. Diastereoisomers (**11**) and (**14**) were readily separated by fractional crystallisation. On treatment with sodium methoxide in methanol and then boiling in benzene for 1 hr (**11**) cleanly rearranged to give (**12, 54%**) as the sole product. The stereochemistry of (**12**) was established using n.O.e. difference spectroscopy and the *cis* relationship between the keto and the vinyl groups was further confirmed by equilibration studies. Hence when (**12**) was treated with a catalytic quantity of sodium methoxide in boiling benzene it isomerised to give a 10:1 mixture of (**13**):(**12**). Likewise (**14**) underwent Stevens [3,2] rearrangement under identical conditions giving (**15, 78%**) as the sole diastereoisomer. Again (**15**) could be isomerised to (**16**) (ratio at equilibrium **16:15** 9:1) The isomer ratios in the equilibration studies are synthetically useful. Therefore, if the stereoselectivity of salt formation could be properly controlled then any of the four trisubstituted pyrrolidines (**12**), (**13**), (**15**) and (**16**) could be obtained as the major product.



Reagents: (i) Phenacyl bromide, (ii) sodium methoxide in methanol then heat in boiling benzene for one hour, (iii) sodium methoxide in boiling benzene.

This approach can be extended to 2,3,5-trisubstituted pyrrolidines. Treatment of 1,2,5-trimethylpyridinium iodide with sodium borohydride give 1,2,5-trimethyl-1,2,3,6-tetrahydropyridine (**17**). Treatment of (**17**) with phenacyl bromide give a 50:50 mixture of (**18**) and (**21**). As expected (**18**) and (**21**) cleanly rearranged to (**19**) and (**22**) respectively. Again the stereochemistry of (**19**) and (**22**) was established using n.O.e. difference spectroscopy and the *cis* relationship between the keto and the vinyl group was further confirmed by isomerisation studies. Hence when (**19**) and (**22**) were treated with sodium methoxide in boiling benzene they cleanly isomerised to give 9:1 mixture of (**20**):(**19**) and a 10:1 mixtures of (**23**):(**22**) respectively.



Reagents: (i) Phenacyl bromide, (ii) sodium methoxide in methanol then heat in boiling benzene for one hour, (iii) sodium methoxide in boiling benzene.

In conclusion we have demonstrated that Stevens [3,2] rearrangement of alkyl substituted tetrahydropyridine salts is a highly selective reaction giving rise to only one diastereoisomer. New routes to alkyl substituted tetrahydropyridines via Diels Alder reactions have recently been published[9] and new routes to optically pure alkyl substituted tetrahydropyridines have also appeared[10]. This makes this new route to trisubstituted pyrrolidines attractive.

Typical experimental procedure: Salt (**11**, 1.0g, 3.3mmol) was added to a solution of sodium methoxide (50 ml, 1M) and this was stirred at room temperature for six hours. The methanol was removed under reduced pressure, water (10ml) was added to the residue and this was extracted with benzene. The combined benzene extracts were dried over magnesium sulphate and the red solution was boiled for 1 hr under reflux. Removal of the benzene gave a red oil which nmr analysis showed to be exclusively (**12**). Purification by column chromatography on neutral aluminia gave (**12**, 53%) as a yellow oil.

We thank the Department of Education N. Ireland and The Queen's University of Belfast for support.

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(Received in UK 5 June 1990)