Tetrahedron Letters,Vol.24,No.41,pp 4457-4460,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

THE MECHANISM OF THE RACEMISATION OF α-AMINO ACIDS IN THE PRESENCE OF ALDEHYDES

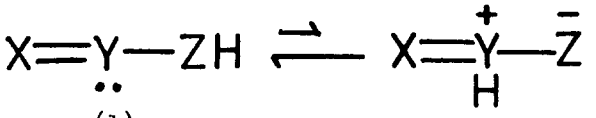
by R. Grigg* and H.Q.N. Gunaratne

(Department of Chemistry, Queen's University, Belfast BT9 5AG, Northern Ireland)

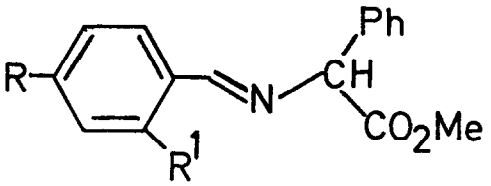
Summary. Heating optically active α-amino acids in the presence of arylaldehydes effects racemisation via stereospecific formation of 1,3-dipolar species from the intermediate imines. These 1,3-dipoles can be trapped as their stereospecific cycloadducts with N-phenylmaleimide.

Over the past five years we have published a series of papers on a new general prototropic process involving 1,3-dipole formation by a formal 1,2-H shift in X=Y-ZH systems (1 ⇌ 2).[1] Of necessity the central Y atom must possess a lone pair of electrons and we have provided many examples of imines[2], hydrazones[1] and oximes[3] which illustrate this process by trapping the 1,3-dipoles as their cycloadducts. In particular we have shown that imines of α-amino acid esters are good examples of this prototropic process.[2] We have also drawn attention to the relevance of this process to the biochemistry of pyridoxal and have shown that pyridoxal imines of α-amino acid esters undergo analogous 1,3-dipolar cycloadditions.[4] It was therefore with some surprise that we read a recent paper[5] in which an identical 1,3-dipole was invoked as an intermediate in the racemisation of α-amino acids in the presence of aldehydes, and in which no mention was made of our extensive prior work.

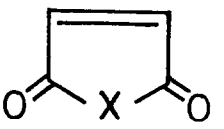
Thus we now report some of our results with α-amino acids which demonstrated stereospecific 1,3-dipole formation. We have shown that 1,3-dipole formation from imines is catalysed by both Lewis and Bronsted acids[6] and this allows many cycloadditions to be carried out at room temperature e.g.(3) reacts (room temperature, 30 min) with (4a) in acetic anhydride containing 6% acetic acid to give (5; 85%); (3b) reacts with (4a) (room temperature, 10 min) in



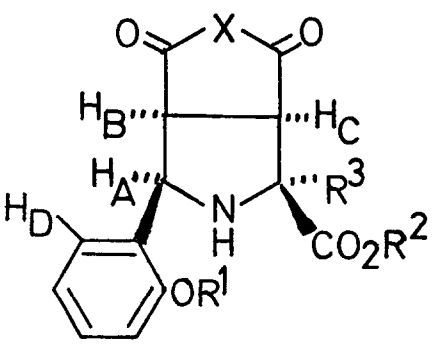
(1) (2)



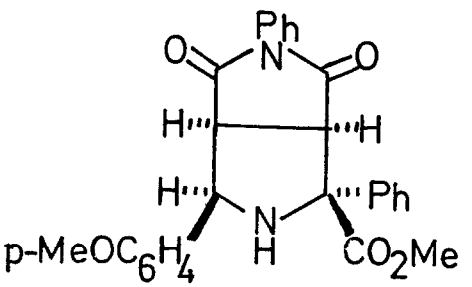
(3) a. R=H, R^1= OMe
b. R=OMe, R^1= H



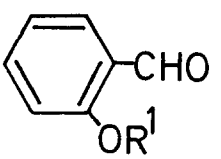
(4) a. X=O
b. X=NPh



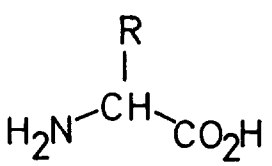
(5) a. X=O, R^1= R^2= Me, R^3= Ph
b. X=NPh, R^1= R^2= H, R^3= CH_2Ph
c. X=NPh, R^1= Me, R^2= H, R^3= CH_2Ph
d. X=NPh, R^1= R^2= H, R^3= CH_2CH_2SMe
e. X=NPh, R^1= R^2= H, R^3=$(CH_2)_4NH_2$
f. X=NPh, R^1= R^2= H, R^3= CH_2CHMe_2
g. X=NPh, R^1= R^2= H, R^3= CH_2OH



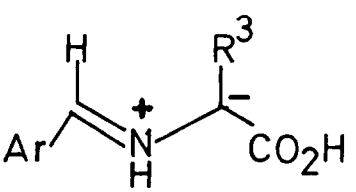
(6)



(8) a. R^1= H
b. R^1= Me



(7) a. R^1= CH_2Ph
b. R^1= CH_2CH_2SMe
c. R^1= $(CH_2)_4NH_2$
d. R^1= CH_2CHMe_2
e. R^1= CH_2OH



(9)

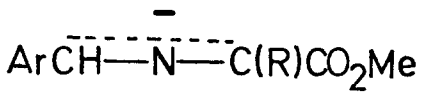
acetic acid to give (6; 85%). Similarly the (L)-amino acids (7a-d) react with aldehydes (8a,b) and dipolarophiles in acetic acid (100^{o}, $<$1h) to give racemic cycloadducts (5b-f) in $>$75% yield.

The stereochemistry of the cycloadducts was established by NOE difference spectroscopy. Thus (5c) in deuteriopyridine solution gave the following NOE enhancements when H_A was irradiated: H_B (16.6%), H_D (19%), and one of the diastereotopic protons of the benzyl group (R^3) (8.3%). The cycloadduct stereochemistry indicates stereospecific trapping of a 1,3-dipole with configuration (9) via an endo transition state. This accords with our previously reported observations on the corresponding imines of α-amino acid esters.[2]

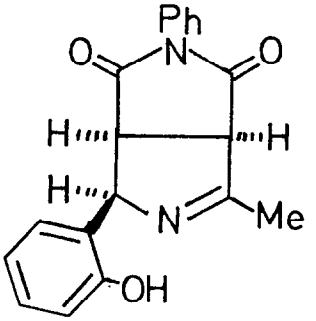
With imines of α-amino acid esters the rate of racemisation is unaffected by (4b). Thus a 0.1M toluene solution of the imine (3b) from methyl (L)-phenylglycinate ($[\alpha]_D^{25}$ = 90.4) racemises at 65^{o}C with an initial pseudo first order rate[7] $k_1 = 0.96 \times 10^{-5}sec^{-1}$. This racemisation rate is essentially unchanged in the presence of 0.1M (4b) ($k_1 = 1.06 \times 10^{-5}sec^{-1}$). The same optically active imine (3b) as a 0.1M solution in acetic acid is completely racemised in 10 mins at room temperature. The ability of organic acids to racemise imines has been used in an elegant conversion of esters of DL-phenyl glycine to the pure (D)- or (L)-phenylglycine esters by use of (+)-tartaric acid.[8] Thus weak acids favour imine racemisation via 1,3-dipole formation whilst bases favour racemisation via azallylic anion formation (10).[9]

Finally, cycloaddition of the imine of serine (7e) and (8a) to (4b) (100^{o}, acetic acid, 15 min) gives an 8:3 mixture of (5g) and (11).[10]

We thank the SERC and Queen's University for support.



(10)



(11)

References.

1. R. Grigg, J. Kemp and N. Thompson, Tetrahedron Letters, 1978, 2827.

2. R. Grigg, J. Kemp, G. Sheldrick and J. Trotter, J. Chem. Soc. Chem. Comm., 1978, 109; R. Grigg and J. Kemp, Tetrahedron Letters, 1980, 2461.

3. R. Grigg, M. Jordan, A. Tangthongkum, F.W.B. Einstein and T. Jones, J. Chem. Soc. Perkin I, in press; R. Grigg and S. Thianpatangul, J. Chem. Soc. Perkin I, in press.

4. R. Grigg and J. Kemp, Tetrahedron Letters, 1978, 2823.

5. S. Yamada, C. Hongo, R. Yoshioka and I. Chibata, J. Org. Chem., 1983, 48, 843.

6. R. Grigg and H.Q.N. Gunaratne, J. Chem. Soc. Chem. Comm., 1982, 384 and footnote therein.

7. The rate data refers to 20-30% reaction. Later data becomes unreliable due to partial breakdown of the imine. Studies with imines of α-amino acids present similar difficulties which we are seeking to overcome. Cyclo additions of imines of α-amino acid esters to (4b) are essentially first order in imine and essentially zero order in (4b). R. Grigg, H.Q.N. Gunaratne and J. Kemp, J. Chem. Soc. Perkin I, in press, and unpublished observations.

8. J.C. Clark, G.H. Phillips and M.R. Steer, J. Chem. Soc. Perkin I, 1976, 475. Resulting from this publication the 1,3-dipolar mechanism for α-aminoacid racemisation in the presence of aldehydes and tartaric acid was suggested by R.G. in discussions and correspondence with Glaxo Research during October 1977.

9. Azallyl anions related to (10) have been extensively studied by Kauffmann, e.g. W. Bannworth, R. Eidenschink and T. Kauffmann, Angew. Chem. Internat. Ed., 1974, 13, 468; T. Kauffmann, H. Ahlers, A. Hamsen, H. Schulz, H.- J. Tilhard and A. Vahrenhorst, ibid, 1977, 16, 119.

10. The ratio of (5g) to (11) remains unchanged after heating in acetic acid at 100° for 1h suggesting (5g) is not a precursor of (11). Assignment of the Δ^1-pyrroline structure (11) rather than the corresponding Δ^2-pyrroline structure is based on nmr evidence and previous examples of Δ^1-pyrrolines produced by dehydrogenation of pyrrolidines such as (6) with DDQ.

(Received in UK 1 August 1983)