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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. THE STEREOCHEMISTRY AND REGIOCHEMISTRY OF CYCLOADDITION REACTIONS OF IMINES OF α-AMINO-ACID ESTERS.

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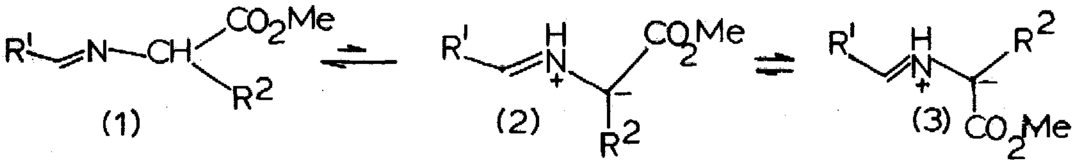
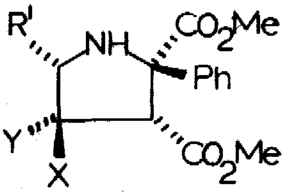
Summary. The stereochemistry and regiochemistry of cycloadditions of α-amino acid ester imines is dependent both on imine structure and on the reactivity of the dipolarophile. Phenylglycine imines undergo competing dipole stereomutation and cycloaddition with some dipolarophiles.

We have suggested that X=Y-ZH systems are potential sources of 1,3-dipoles via tautomerism[1] and have described many examples of cycloadditions of X=Y-ZH systems involving both inter- and intra-molecular reactions.[2-4] We indicated that cycloadditions to imines of α-amino acid esters were *stereospecific*[2] *but* recent publications briefly reporting on the stereochemistry of the cycloaddition of (1; R^1=Ph, R^2=H)[5] and on an intramolecular case[6] prompts us to report our results that show the stereochemistry and regiochemistry of these processes are dependent on imine structure and dipolarophile reactivity.

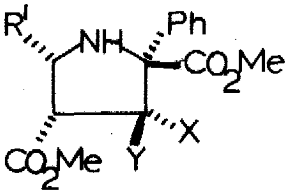
In cycloadditions of (1) with dipolarophiles one must consider the stereochemistry of the process with respect to both the 1,3-dipolar species and the dipolarophile. Thus we showed that only one 1,3-dipole stereoisomer (2) is involved in cycloadditions with N-phenylmaleimide, a reactive dipolarophile.[2] This suggested that (2) was the kinetically generated 1,3-dipole and this is confirmed by the results reported below and by our observations on intramolecular cycloadditions[4]. However, with less reactive dipolarophiles such as dimethyl maleate and fumarate, we observe that stereomutation (2 $\rightleftharpoons$ 3) of the 1,3-dipole sometimes occurs. Thus imines (1; R^1= 2-furyl, p-$MeOC_6H_4$, p-$NO_2C_6H_4$, Ph; R^2= Ph) give pyrrolidines (4a and 5a; ca. 3:1) with dimethyl maleate and (4b and 5b; ca. 3:1) with dimethyl fumarate in essentially quantitative yield (110°, toluene, 48h). The stereochemical assignments are based (i) on ^{1}H nmr spectra[7] and (ii) on chemically relating maleate adducts to maleic anhydride adducts.[2] The adducts are configurationally stable under the reaction conditions as shown (i) by the appropriate blank experiments and (ii) an nmr study of the reaction of (1; $R^1 = R^2 =$ Ph) with dimethyl maleate which showed that the two products (4a; $R^1 =$ Ph) and (5a; $R^1 =$ Ph) are formed concurrently and that one is not the precursor of the other. Imines (1; $R^1 =$ Ph, $R^2 =$ Me or CH_2Ph) give a mixture of (6a and 6b; ca. 3:1) with maleate and a mixture of (7a and 7b) with fumarate. The cycloadditions are therefore always stereospecific with respect to the dipolarophiles and are also stereospecific with respect to the imines (1; $R^2 =$ alkyl) and involve the dipole stereoisomer (2). However, with imines (1; $R^2 =$ Ph) stereomutation ($2 \rightleftharpoons 3$) occurs as dipolarophile reactivity is decreased, due to phenyl substitution lowering the barrier to stereomutation. Our observations on intramolecular cycloadditions,[4] where stereomutation ($2 \rightleftharpoons 3$) occurred to give an approximately 50:50 mixture in some cases, indicates that maleate and fumarate are sufficiently reactive to prevent complete dipole equilibration. Other workers failed to detect the second stereoisomer in the intramolecular processes.[6] Thus the extent of dipole equilibration ($2 \rightleftharpoons 3$) is dependent on both imine structure and dipolarophile reactivity.





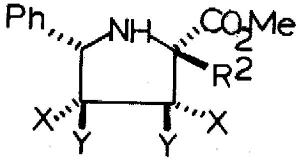
(4) a. X = H, Y = CO_2Me

b. X = CO_2Me, Y = H



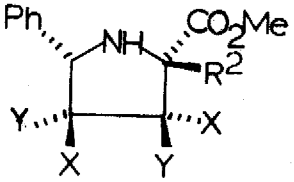
(5) a. X = CO_2Me, Y = H

b. X = H, Y = CO_2Me.



(6) a. X = CO_2Me, Y = H

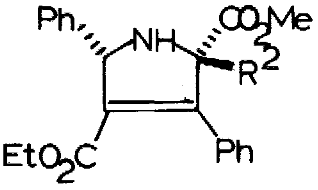
b. X = H, Y = CO_2Me



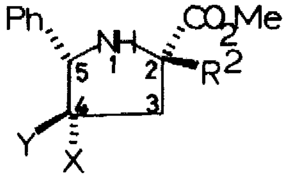
(7) a. X = CO_2Me, Y = H

b. X = H, Y = CO_2Me

A similar dichotomy is observed in the regiochemistry of cycloadditions of imines (1) to unsymmetrical dipolarophiles. Thus the cycloaddition (xylene, 135°, 48h) of imines (1; R^1= Ph; R^2= Me, Et and Ph) to ethyl phenylpropiolate appears to be regiospecific. The adduct (8) comprises at least 80% of the crude product but minor amounts of other isomers cannot be ruled out at present. The imines (1; R^2= H or Me) also undergo regiospecific cycloaddition to acrylates. Thus (1; R^1= Ph, R^2= Me) and methyl acrylate gives a 95:5 mixture of (9a; R^2= Me) and (9b; R^2= Me) in quantitative yield. Treatment of (9a; R^2= Me) with 1 equiv. of benzyltrimethylammonium methoxide (BTAM) in benzene gives (9b; R^2= Me), thus establishing the identical configuration of the two isomers at C(2). The relative configuration of the C(2) and C(5) substituents is assigned by analogy with the cycloadducts from (1; R^2= Me) and maleate and fumarate. The imine (1; R^1= Ph, R^2= H) and methyl acrylate undergo regiospecific cycloaddition with concomitant dipole stereomutation to give a 1:0.5 : 2:0.75 mixture of four pyrrolidines (9a,b; R^2= H) and (10a, b; R^2= H).[8] In contrast to (1; R^2= H or alkyl) the imines (1; R^1= *p*-H-, Me-, MeO-, NO_2-C_6H_4; R^2= Ph) undergo regioselective cycloaddition, accompanied by dipole stereomutation, to acrylates to give high yields of mixtures of three pyrrolidines (11a,b) and (12) in a ratio of ca. 2:1:1.[9] In a blank experiment, the major product (11a; Ar=Ph) was found to be configurationally stable when heated in boiling toluene for 48h. The same mixture of pyrrolidines, in a slightly different ratio is formed when the imine and acrylate are stirred in pyridine at room temperature for 1-5dy. Assignment of configuration to the pyrrolidines (11a,b) is based on epimerisation to (11c,d) with 1 equiv. of BTAM and on an X-ray crystal structure of (11; Ar=Ph, R^2= Y=CO_2Me, R^3= *p*-$MeOC_6H_4$, X=H).[10]

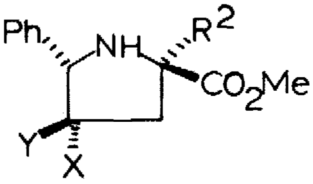


(8)



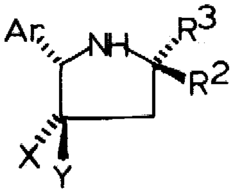
(9) a X=CO_2Me, Y=H

b. X=H, Y=CO_2Me



(10) a. X=CO_2Me, Y=H

b. X=H, Y=CO_2Me

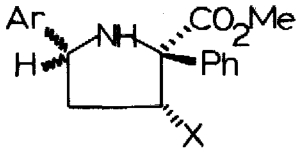


(11) a. R^2=Ph, R^3=X=CO_2Me, Y=H

b. R^2=X=CO_2Me, R^3=Ph, Y=H

c. R^2=Ph, R^3=Y=CO_2Me, X=H

d. R^2=Y=CO_2Me, R^3=Ph, X=H



(12) a X=CO_2Me

b X=CO_2Et

Cycloadditions of imines (1) with acrylonitrile broadly parallel the acrylate results although acrylonitrile cycloadditions are less stereoselective e.g. (1; R^1= p-$MeOC_6H_4$; R^2= Me) gives (11; Ar=p-$MeOC_6H_4$, R^2=Me, R^3=CO_2Me, X=CN, Y=H) and (11; Ar=p-$MeOC_6H_4$, R^2= Me, R^3= CO_2Me, X = H, Y = CN) in 1.2:1 ratio.

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References

1. R. Grigg, J. Kemp and N. Thompson, Tetrahedron Letters, 1978, 2827.
2. R. Grigg, J. Kemp, G. Sheldrick and J. Trotter, Chem.Comm., 1978, 109.
3. R. Grigg and J. Kemp, Chem.Comm., 1977, 125; R. Grigg and J. Kemp, Tetrahedron Letters, 1978, 2823.
4. R. Grigg, M. Jordan and J.F. Malone, Tetrahedron Letters, 1979, 3877.
5. M. Joucla and J. Hamelin, Tetrahedron Letters, 1979, 3877; M Joucla and J. Hamelin, Tetrahedron Letters, 1978, 2885.
6. O. Tsuge, K Ueno and K. Oe, Chemistry Letters, 1979, 1407.
7. R. Huisgen, W. Scheer, G. Szeimies and H. Huber, Tetrahedron Letters, 1966, 397; P.B. Woller and N.H. Cromwell, J.Org.Chem., 1970, **35**, 888; J.H. Hall and R. Huisgen, Chem.Comm., 1971, 1187 and 1188.
8. This may not represent the initial product mixture since we observe that (10a; R^2=H) epimerises on vacuum distillation to give predominantly (9a; R^2=H).
9. In ref.2 we reported (12b; Ar=Ph) as the major isomer (35%) from the reaction of (1; R^1=R^2=Ph) and ethyl acrylate. It was subsequently found that (12b) was contaminated with some (11a; Ar=R^2=Ph, R^3=CO_2Me, X=CO_2Et, Y=H) with which it had co-crystallised.
10. R. Grigg, J. Kemp, J. Malone and A. Tangthongkum, Chem.Comm., 1980, in press.

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