Tetrahedron Letters,Vol.25,No.37,pp 4157-4160,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

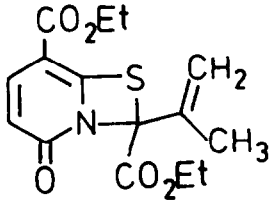
NOVEL CATALYTIC REARRANGEMENTS OF 2-VINYL-1,3-THIAZETIDINES

by Nigel K. Capps[a], Gareth M. Davies[b] and Douglas W. Young*[a]

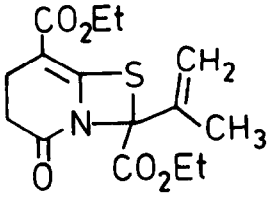
[a]*School of Chemistry and Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ, U.K.;* [b]*ICI Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, SK10 4TG, U.K.*

Abstract - The thiazetidines (1) and (2) undergo a novel and high yielding rearrangement on hydrogenation with heterogeneous catalysis to give the thiazolidines (5) and (8) whilst reaction with the homogeneous catalyst $Rh(Ph_3P)_3Cl$ results in the alternative high yielding rearrangement to give a thiazine.

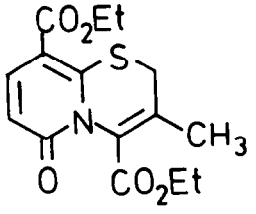
We have recently prepared the fused thiazetidines (1) and (2) in good yield by photolysis of the thiazines (3) and (4).[1] We now wish to report that these strained heterocyclic systems undergo two entirely different novel and high yielding rearrangements under catalytic conditions.



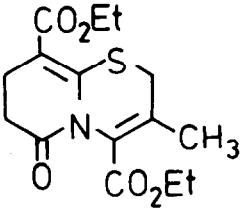
(1)



(2)

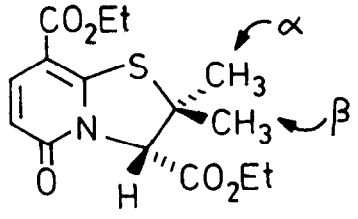


(3)

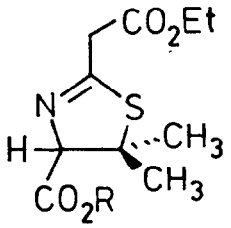


(4)

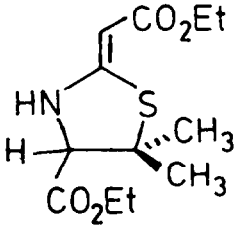
When the thiazetidine (1) was hydrogenated at room temperature and pressure for 3 hours using Adams catalyst and either ethanol or ethyl acetate as solvent, a product, $C_{15}H_{19}NO_5S$† was obtained in 96% yield. The spectra of this compound showed that the pyridone ring was intact. The absorptions due to the CH_3-C= and olefinic groups had however been replaced in the ^1H- and ^{13}C-nmr spectra by absorptions due to two distinct quaternary methyl groups and an uncoupled C-H proton. These data suggested that hydrogenation of the thiazetidine might have been accompanied by rearrangement to give the thiazolidine (5). We elected to confirm the structure of this product by an unambiguous total synthesis.



(5)



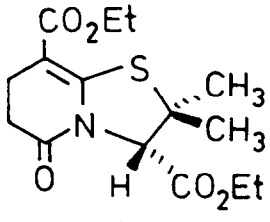
(6)



(7)

We first prepared the thiazoline (6, R=Et)† using an adaptation of the method used to prepare the corresponding methyl ester (6, R=Me)[2] by reacting dl-penicillamine ethyl ester with carbethoxyacetimino ethyl ether hydrochloride in dry tetrahydrofuran/methanol. The nmr spectra of this compound were more in keeping with its formulation as a mixture of the geometric isomers of the vinylogous urethane (7). The compound was reacted with propiolic acid and dicyclohexylcarbodiimide (DCCD) in a modification of our synthesis of fused pyridones[3] to give a product in 63% yield. This had identical spectra to the product of catalytic hydrogenation of the thiazetidine (1) and a mixed melting point was undepressed. The structure (5) for this product was therefore confirmed.

When the dihydropyridone-thiazetidine (2) was hydrogenated under similar conditions a compound $C_{15}H_{21}NO_5S$† was obtained in 60% yield. The spectroscopic data were in keeping with the assignment of the thiazolidine structure (8) to this compound and an independent synthesis by reacting the thiazoline (6, R=Et) with acrylic acid and DCCD confirmed this.



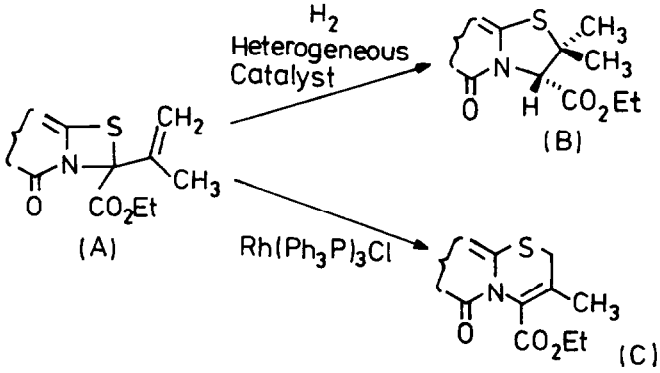
(8)

†All new compounds had satisfactory analytical and spectroscopic data.

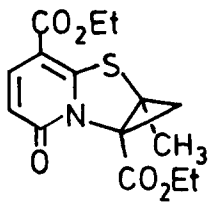
Reaction of the thiazetidine (1) with hydrogen using 10% palladium on charcoal in ethyl acetate also resulted in the novel rearrangement product (5) in 60% yield. Omission of hydrogen in this experiment gave no reaction.

It was of some interest to examine the stereospecificity of hydrogen addition in this new rearrangement. We were fortunately able to assign the relative stereochemistries to the 2α- and 2β-methyl groups in the product (5) with respect to the hydrogen at C-3 since irradiation of the lower field of the singlets due to these methyl groups in the ^{1}H-nmr spectrum caused a 30% nuclear Overhauser enhancement of the signal due to the proton at C-3. Irradiation of the higher field methyl singlet gave but a 5% n.O.e. The lower field singlet was therefore assigned to the methyl group *cis* to the hydrogen at C-3 and the higher field singlet to the methyl group *trans* to this hydrogen. When the hydrogenation-rearrangement reaction using Adams catalyst was repeated using the thiazetidine (1) as substrate, deuterium gas and either EtO^{2}H or ethyl acetate as solvent, a product was obtained which was evidently the dideuteriated product (5) from the mass spectrum and ^{1}H and ^{13}C-nmr spectra. The product showed no absorption in the ^{1}H-nmr spectrum corresponding to the C-3 proton and *both* C-2 methyl (C^{1}H$_3$) singlets were accompanied by a second (C^{1}H$_2$^{2}H) singlet *ca.* 5 Hz to higher field. Further, both methyl singlets in the ^{13}C-nmr spectrum were accompanied by a triplet to slightly higher field. Deuteriation was therefore not stereospecific although the higher field C-2α methyl group in the ^{1}H-nmr spectrum was more highly deuteriated than the C-2β methyl group over several experiments. The 1,3-addition of hydrogen which accompanies the 1,2-migration of sulphur in the reaction is therefore partially *trans* using Adams catalyst so that the mechanism of the process is not clear-cut. Catalytic deuteriation using 10% palladium on charcoal proved, from the ^{1}H-nmr spectrum, to be almost entirely non-stereospecific.

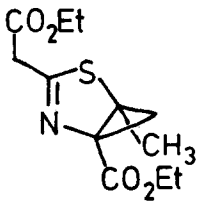
The thiazetidine (1) was now treated with hydrogen in benzene with Rh(Ph$_3$P)$_3$Cl at room temperature and pressure. A product was obtained in 73% yield which had identical spectral properties to an authentic sample of the thiazine (3) and the melting point of a mixture with the authentic specimen was undepressed. Since hydrogenation had evidently not occurred, the reaction was repeated under argon when the rearrangement product (3) was again obtained in undiminished yield. Treatment with a homogeneous catalyst had therefore resulted in a totally different rearrangement to that found on reduction using heterogeneous catalysis.



We have therefore discovered that the strained 2-vinyl-1,3-thiazetidine system (A) undergoes two novel and high-yielding rearrangements. Hydrogenation using heterogeneous catalysis gives the substituted thiazolidine system (B) found in the penicillin series of antibiotics whilst reaction with Wilkinson's catalyst, $Rh(Ph_3P)_3Cl$, yields the 1,3-thiazine system (C) found in the cephalosporin series of antibiotics. The hydrogenative rearrangement to yield the thiazolidine (B) may involve either (a) complexation of the catalyst with the olefinic bond of (A) followed by 1,2-migration of sulphur and 1,3-addition of hydrogen; or (b) hydrogenolysis of the carbon-sulphur bond followed by Markownikoff addition of the resultant thiol to the olefin. The possible intermediacy of the species (9) could be excluded by synthesis of this compound[†] from the bicyclic thiazolidine (10)[4] using propiolic acid and DCCD. The compound (9) was recovered unchanged on reaction with hydrogen and Adams catalyst. The rearrangement to give the thiazine (C) observed on homogeneous catalysis is an allylic rearrangement. The thiazetidine (1) was recovered unchanged on treatment with protic or Lewis acids.



(9)



(10)

The dichotomy in reactions observed with the 2-vinyl-1,3-thiazetidines (A) may reflect the tendency of Pt(II) and Pd(II) to complex with the olefinic bond thus triggering a 1,2-shift. The softer Rh(I) however might be expected to have a greater tendency to complex at sulphur thus generating an allylic carbonium ion and so favouring rearrangement to the thiazine system (C).

The thiazetidines (A) which may readily be prepared in excellent yield[1] would seem to be interesting synthetic intermediates through which compounds with the thiazolidine ring system (B) found in penicillins or the thiazine ring system (C) found in cephalosporins may be approached using the novel and high yielding reactions reported in this work.

Acknowledgement One of us (N.K.C.) thanks the S.E.R.C. and I C I Pharmaceuticals Division for a C.A.S.E. award.

References

1 N.K. Capps, G.M. Davies, P.B. Hitchcock, R.W. McCabe and D.W. Young, *J. Chem. Soc., Chem. Commun.*, 1982, 1418.

2 W.E. Bachmann and M.W. Cronyn in 'The Chemistry of Penicillin', H.T. Clarke, J.R. Johnson and R. Robinson (eds), Princeton University Press, 1949, p885.

3 R.W. McCabe, D.W. Young and G.M. Davies, *J. Chem. Soc., Chem. Commun.*, 1981, 395.

4 P.B. Hitchcock, R.W. McCabe, D.W. Young and G.M. Davies, *J. Chem. Soc., Chem. Commun.*, 1981, 608.

(Received in UK 15 June 1984)