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THE 2-AZA-COPE N-ACYLIMINIUM CYCLIZATION

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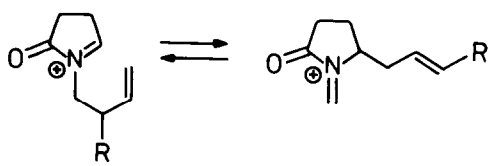
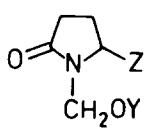
The 2-aza-Cope N-acyliminium ring closure is shown to proceed in a stereoselective fashion via the primary N-acyliminium intermediate 1B. The latter ion can also be generated from the open hydroxymethyllactam 6b.

The recently reported aza-Cope variant[1] of the N-acyliminium induced heterocyclization[2] is assumed to proceed via ring closure of the primary N-acyliminium ion 1B. The transient nature of such a species, however, thusfar precluded the characterization of the corresponding carbinollactam 2 and its subsequent conversion into the pyrrolizidine system. A similar case in which the allene derivative 3 was involved[3] failed to produce the 5,5-cyclization product upon further reaction. We now report (i) the isolation of 2 (R = Ph) (ii) its stereoselective conversion into 5 and (iii) the marked influence of the introduction of a p-methoxy substituent in the aromatic ring. In addition the synthetic conversion of the newly synthesized ring system is described.



1A 1B

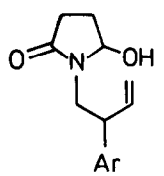


2 Z = $CH_2CH{=}CHR$ Y = H

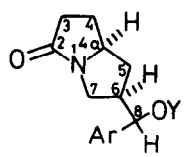
3 Z = $-C(=CH_2)-CH{=}CH_2$ Y = H, $CH(=O)$

Upon cyclization of the hydroxylactam 4[4] in formic acid (r.t., 18 h) and work-up[8] a 1:1 mixture of the isomeric pyrrolizidines 5a was obtained in 77% yield, while in addition two minor products, the pyrrolidine 6b (4%) and the indolizidine

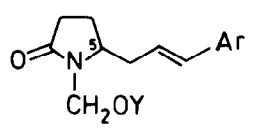
7 (7%) were isolated. Hydrolysis of the formates 5a and subsequent chromatographic separation (SiO_2 , acetone : CH_2Cl_2 = 2 : 9) gave the pure alcohols 5b-I[9]; m.p. 131-131.5°C; ^{1}H NMR δ($CDCl_3$): 4.47 (d, J = 8 Hz, H_8), 3.83 (m, H_{4a}), 3.55 (dd, J = 12 and 8 Hz, H_7), 3.22 (dd, J = 12 and 9 Hz, H_7), 2.77 (m, H_6) and 5b-II[9]; m.p. 137-138°C; ^{1}H NMR δ($CDCl_3$): 4.53 (d, J = 7 Hz, H_8), 3.91 (m, H_{4a}), 3.23 (m, H_7), 2.73-2.88 (2H, m, $H_7 + H_{4a}$). From extensive ^{1}H NMR analysis it appeared that the cis-stereochemistry of C_{4a}-H and C_6-H in both isomers was the same, the difference thus resulting from the configurations at C_8. Upon carrying out the cyclization of 4, using CF_3COOH in CH_2Cl_2 (5°C, 0.5 h), and work-up 53% of the alcohol 6b[9] was obtained; m.p. 125-128°C; ^{1}H NMR δ($CDCl_3$): 6.53 (d, J = 16 Hz, =CH), 6.15 (dt, J = 16 Hz and 7 Hz, =CH), 4.99 (d, J = 11 Hz, 1H, CH_2O), 4.78 (d, J = 11 Hz, 1H, CH_2O), 3.97 (m, H_5) together with 1 : 1 mixtures of isomers of 5b (17%) and 5c (27%). Treatment of the alcohol 6b with HCOOH (r.t., 18 h) gave the 1 : 1 isomeric mixture of 5a in 84% yield (according to ^{1}H NMR analysis), thereby indicating the alcohol as the precursor for the intermediate 1B in the 2-aza-Cope rearrangement and establishing the proposed pathway. Most significantly the indolizidine 7 is also formed in 8% yield.



4 Ar = C_6H_5



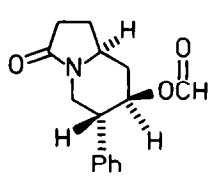
5 Ar = C_6H_5



6 Ar = C_6H_5

8 Ar = p-$MeOC_6H_4$ 9 Ar = p-$MeOC_6H_4$ 10 Ar = p-$MeOC_6H_4$

a Y = $-\overset{\overset{O}{\|}}{C}H$, b Y = H , c Y = $-\overset{\overset{O}{\|}}{C}CF_3$



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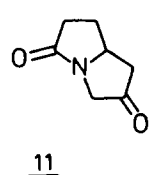

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The hydroxylactam 8[4] underwent ring closure (HCOOH, r.t., 18 h) solely to the 1 : 1 formate mixture 9a (91%) which could be saponified and chromatographed to the alcohols 9b-I[9]; m.p. 138-139.5°C and 9b-II[9]; m.p. 103-104°C. CF_3COOH treatment in CH_2Cl_2 (5°C, 0.5 h) also afforded a mixture of the trifluoroacetate 9c (69%)

and the alcohol 9b (25%), both as a 1 : 1 mixture of C_8 stereoisomers. Under the latter circumstances no trace of 10 could be detected. In view of the marked difference in the cyclizations of 4 and 8 we decided to follow both reactions in the time, the results of which are given in tables I and II.

TABLE I[a]

Cyclization of 4 (1.3 mmol) in HCO_2H (6 ml) at 20°C

Reaction time	Product composition (mol %; ± 2%)			
(h)	4	6a	5a	7
0.17	84	16	-	-
1	32	56	12	<1
4	4	65	26	5
20	-	27	66	7
68	-	2	88	10

TABLE II[a]

Cyclization of 8 (0.77 mmol) in HCO_2H (5ml) at 20°C

Reaction time	Product composition (mol %, ± 2%)		
(h)	8	10a	9a
0.12	65	9	26
1	16	11	73
3.5	-	<1	99

[a] Samples were taken, worked up and analyzed by ^1H NMR spectrometry.

As can be judged from the data the reaction of 8 → 9a is much faster than the reaction 4 → 5a, which is due predominantly to the faster ring closure 10a → 9a in comparison with 6a → 5a. Given the fact, however, that the amount of indolizidine 7 is slowly increasing while ring closure of pure 6b also affords 7, the results can be interpreted as good evidence for the existence of a dynamic equilibrium between secondary N-acyliminium ion 1A and the primary N-acyliminium ion 1B. In case of a fast reaction via 1B the pyrrolizidine system is formed; the slow process proceeds via 1A to form the indolizidine, presumably via a chairlike six-membered transition state. Since the allylic aryl substituent is not directly involved in the establishment of the equilibrium between 1A and 1B it may be postulated that this is an intrinsic property of the N-acyliminium intermediate[10].

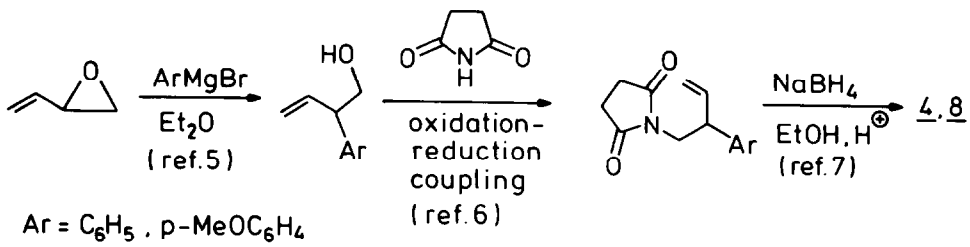
The pyrrolizidine alcohol 9b can be smoothly converted into the unknown dione 11 via a standard sequence. After elimination of water (H_2SO_4-AcOH, 70°C, 1 min.) the alkene is ozonized (-78°C, CH_2Cl_2; Me_2S) to form 11[9], oil; ^1H NMR $\delta(CDCl_3)$: 4.19 (m, H_{4a}), 4.05 (d, J = 19 Hz, H_7), 3.32 (d, J = 19 Hz, H_7), 2.71 (dd, J = 18 and 6 Hz, H_5), 2.18 (dd, J = 18 and 10 Hz, H_5); IR($CHCl_3$): 1764, 1686 cm^{-1} (C=O).

Further progress will be reported in due course.

ACKNOWLEDGEMENT. We wish to thank Mr. C. Kruk and his staff for recording the NMR spectra.

LITERATURE AND REFERENCES

1. P.M.M. Nossin, J.A.M. Hamersma and W.N. Speckamp, Tetrahedron Lett., 23, 3807 (1982).
2. W.N. Speckamp, Recl.Trav.Chim.Pays-Bas, 100, 345 (1981).
3. P.M.M. Nossin and W.N. Speckamp, Tetrahedron Lett., 22, 3289 (1981).
4. Hydroxylactams 4 and 8 were obtained in the following manner:



5. C.B. Rose and C.W. Smith Jr., Chem.Commun., 248 (1969).
6. O. Mitsunobu, M. Wada and T. Sano, J.Amer.Chem.Soc., 94, 679 (1972).
7. J.C. Hubert, J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron, 31, 1437 (1975).
8. Usual work-up procedure for cyclizations:
   Following evaporation in vacuo of formic acid, the residue is dissolved in dichloromethane and the solution washed with aqueous bicarbonate and with brine, dried over $MgSO_4$, concentrated in vacuo and chromatographed.
9. For all new compounds satisfactory ^1H NMR and IR and in some cases MS and ^{13}C NMR spectra have been obtained.
10. For the aza-Cope rearrangement of secondary N-acyliminium ions see also:
    D.J. Hart and Y.-M. Tsai, Tetrahedron Lett., 22, 1567 (1981);
    D.J. Hart and T.-K. Yang, Tetrahedron Lett., 23, 2761 (1982).

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