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# N-ACYLIMINIUM CYCLIZATIONS VIA REVERSIBLE 2-AZA-COPE REARRANGEMENTS

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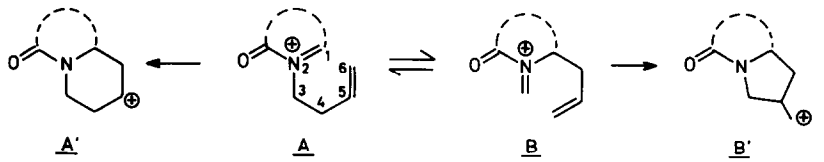
Summary: The existence of a reversible 2-aza-Cope rearrangement in cyclizations of N-acyliminium ions derived from 1'- and 2'-vinyl-N-(3'-butenyl)-5-hydroxy-2-pyrrolidinones is established.

Substituent effects in the rearrangement of N-acyliminium ions of the 2-aza-1,5-hexadienyl type A have previously been described in reports from our laboratory[1] and the Hart group[2]. Although cyclizations of this type of N-acyliminium ions generally afford piperidine derivatives A', gem-dimethyl[1b,2c], methoxy[1b], or phenyl[1c] substitution at C-4 of the initially formed N-acyliminium ions A encourages rearrangement to isomeric ions B, which upon cyclization lead to (partial) formation of pyrrolidine derivatives B'. In case of (substituted) phenyl substituents at C-4 the existence of a dynamic equilibrium between the two N-acyliminium ions, via a formal 2-aza-Cope process, has been proved[1c].

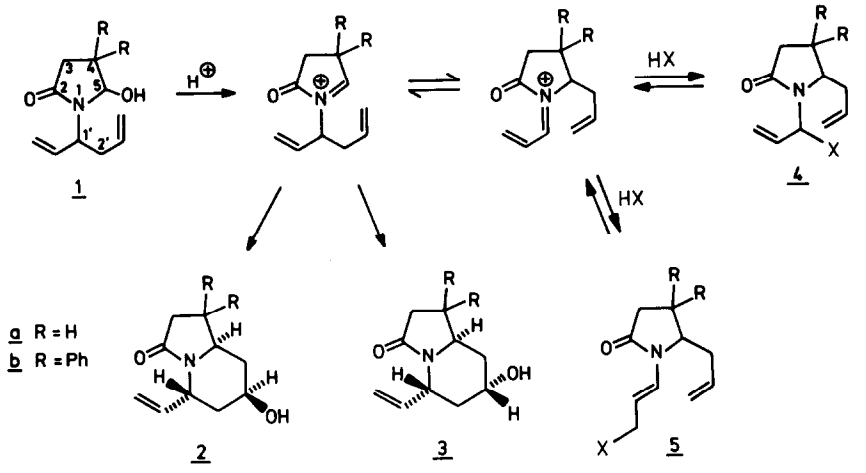



For gem-dimethyl, n-propyl or phenyl substitution at C-3 Hart[2c] found, besides formation of piperidine derivatives, products which could only be explained via a preceding 2-aza-Cope process, but the reversibility of the rearrangement was not established.

We now report the existence of a dynamic equilibrium in case of a vinyl substituent at C-3 or C-4 of the initial N-acyliminium ion A.

Cyclization of C-1' substituted hydroxylactam 1a in $HCO_2H$ for 1 h at r.t., followed by saponification of the formate ester, gave indolizidine 2a[3] in 70% yield, besides some unidentified minor products. However, when 1a was stirred in $HCO_2H$/AcOH (2:3) for 40 min at 20°C and subsequently treated with ethanolic KOH, the alcohols 4a[3] (X=OH) and 5a[3] (X=CH) could be isolated in 49.5% and 25% yield, respectively. The reversibility of the aza-Cope process

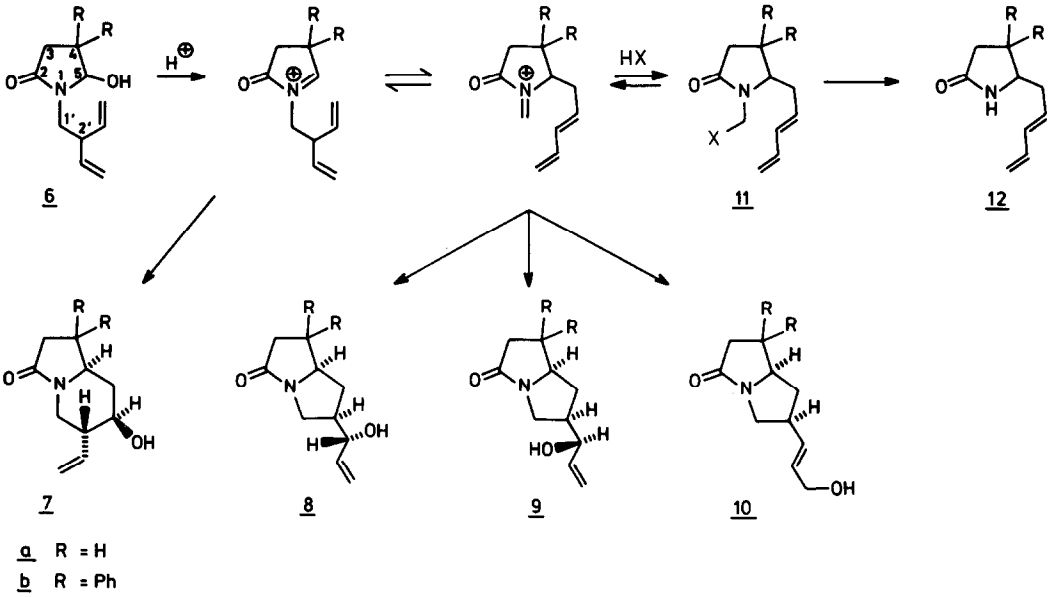
followed from treatment of 4a (X=OH) or 5a (X=OH) with $HCO_2H$ at r.t. for 1½ h which showed, upon work-up, exactly the same crude product as obtained from 1a in $HCO_2H$ according to $^1H$ NMR spectra. Upon cyclization of the sterically more hindered gem-diphenylhydroxylactam 1b for 1.75 h at 20°C in $HCO_2H$ again only indolizidine formation was observed: main product 2b[3] (65%) and the epimeric alcohol 3b[3] (4.5%) were isolated.




After cyclization of C-2' substituted hydroxylactam 6a in $HCO_2H$ for 1½ h at 22°C and saponification of the formate esters, flash chromatography[4] gave indolizidine 7a[3] (14%) and a 1:1:2 mixture (61%) of the pyrrolizidines 8a[3], 9a[3] and 10a[3]. The pyrrolizidines, characteristic of an aza-Cope rearrangement, could be separated by careful chromatography. When 6a was treated for 45 min at 20°C in $HCO_2H$/AcOH (2:3), the crude product saponified in ethanolic KOH for 10 min at 0-5°C and then flash-chromatographed, the aza-Cope intermediate could be captured: 11a[3] (X=OH, 49%) was isolated in addition to a 7:3 mixture (22%) of 12a and 6a. Here again, the aza-Cope rearrangement appeared to be reversible, because treatment of 11a (X=OH) with $HCO_2H$ at 21°C for 1 h afforded the same mixture of products as described for 6a.

Cyclization of 6a in the stronger acid medium $CF_3CO_2H$ for 1½ h at 22°C gave only pyrrolizidine derivatives, while in the weaker acid mixture $HCO_2H$/AcOH (2:3) after 5 d at r.t. a 31:69 mixture of the indolizidine and pyrrolizidines was obtained. After reaction of 6a in AcOH for 10 months at r.t. only 11a (X=OAc) + 12a were formed, while reaction for 69 h at 100°C in AcOH gave a mixture of butadiene derivatives (11a + 12a), indolizidine and pyrrolizidine derivatives in a 3:1:1 ratio, though some decomposition occurred.

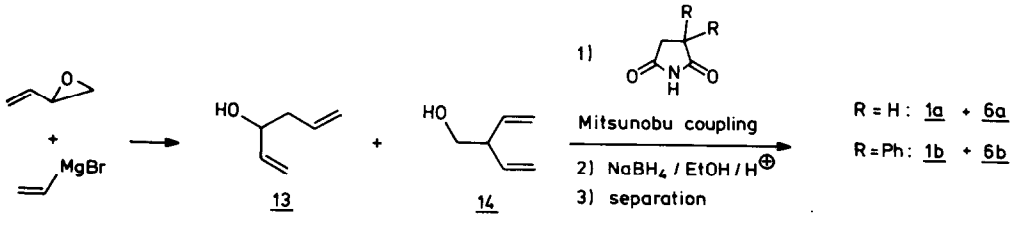
Upon introduction of gem-diphenyl substitution in the hydroxylactam pyrrolizidine formation was slightly more favoured. Thus, cyclization of 6b in $HCO_2H$ and subsequent saponification gave 7b[3] (10%), 8b[3] (32%) and a mixture (49%) of 9b + 10b.




a R = H
b R = Ph

The aforementioned results unequivocally prove the existence of a fast equilibrium of the two N-acyliminium forms A and B. Further reaction of these ions is dependent on factors as substitution patterns and/or acid-solvent systems.

The required hydroxylactams were prepared in the following way: Reaction of vinylmagnesium bromide with butadiene monoxide in ether gave a 4:5 mixture of the alcohols 13 and 14 in 53% yield. N-Alkylation of succinimide with the mixture of alcohols under Mitsunobu[5] conditions in 72% yield, followed by reduction[6] with $NaBH_4/H^+$ and flash chromatography afforded the pure hydroxylactams 1a[3] (38%) and 6a[3] (49%). The diphenylhydroxylactams 1b[3] (21%) and 6b[3] (38%) were obtained from 3,3-diphenylsuccinimide[7] in an analogous procedure.



## References and Notes

1. (a) P.M.M. Nossin and W.N. Speckamp, Tetrahedron Lett., 22, 3289 (1981); (b) P.M.M. Nossin, J.A.M. Hamersma and W.N. Speckamp, ibid., 23, 3807 (1982); (c) H. Ent, H. de Koning and W.N. Speckamp, ibid., 24, 2109 (1983).
2. (a) D.J. Hart and Y.-M. Tsai, Tetrahedron Lett., 22, 1567 (1981); (b) D.J. Hart and T.-K. Yang, ibid., 23, 2761 (1982); (c) D.J. Hart and T.-K. Yang, J.Org.Chem., 50, 235 (1985).
3. All new compounds reported herein gave IR, $^{1}H$ NMR, and exact mass spectral data consistent with the assigned structures.
4. W.C. Still, M. Kahn and A. Mitra, J.Org.Chem., 43, 2923 (1978).
5. O. Mitsunobu, M. Wada and T. Sano, J.Amer.Chem.Soc., 94, 679 (1972).
6. J.C. Hubert, J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron, 31, 1437 (1975).
7. F. Salmon-Legagneur, Bull.Soc.Chim.Fr., 580 (1952).

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