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BIOMIMETIC HETEROCYCLIZATION

by

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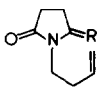
Nature often uses the immonium intermediate to construct C – C bonds[1]. Also in daily synthetic practice numerous examples can be given of the versatility of the $\rangle C = \overset{\oplus}{N}\langle$ function[2].

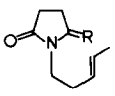
However, the immediate precursors of this reactive species, like f.i. carbinolamines, enamines, are not always easily obtainable. Therefore a generally applicable substitute, which would satisfy requirements in terms of stability, ready accessibility and facile conversion into a highly reactive $\rangle C = \overset{\oplus}{N}\langle$ derivative would be of potential value for expanding the synthetic importance of the immonium method.

Previously, we have already indicated the advantages connected with the use of the cyclic acylimmonium ion especially in heterocyclic synthesis[3]. The added carbonyl allows selective reduction of an amide function, stabilizes the carbinolamine and adds on to the desired reactivity pattern of the $C = \overset{\oplus}{N}\langle$ function[4]. In this communication some results are presented which elaborate further on the extremely versatile synthetic character of the acylimmonium intermediate.

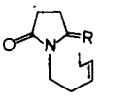
Non-enzymatic olefine cyclizations are currently well-defined processes[5]. Introduction of this reaction principle to heterocyclic synthesis may lead to a novel approach in the synthesis of nitrogen containing natural compounds. In a preliminary exploration cyclization reactions of a number of simple model compounds were investigated[6], of which three representative imides are selected :



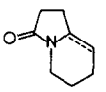
1 R=O
4 R=H, OEt



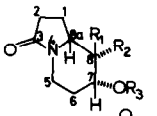
2 R=O
5 R=H, OEt



3 R=O
6 R=H, OEt



7 8,8a dehydro-
8 8,8a saturated



9 $R_1=R_2=H$ $R_3=-CH$ (O)
10 $R_1=R_2=H$ $R_3=H$
11 $R_1=CH_3$, $R_2=H$, $R_3=-CH$ (O)
12 $R_1=H$, $R_2=C_2H_5$, $R_3=-CH$ (O)
13 $R_1=H$, $R_2=C_2H_5$, $R_3=H$

Since the usually employed methods for N-alkylation of imides require fairly drastic conditions[7] and in the actual case the coupling has to be carried out between unsubstituted imides and difficultly obtainable alkenyl halides, other methods were investigated. Among them the procedure of Mitsunobu[8] proved particularly convenient and afforded high yield of product in relatively simple operation. Thus the synthesis of imides 1-3 proved to be straightforward via coupling of succinimide and the corresponding unsaturated alcohol in presence of triphenylphosphine-dimethylazodicarboxylate.

$NaBH_4/H^{\oplus}$ reduction of 1-3 gave the corresponding lactams 4-6 in essentially quantitative yield. Initially ring closures were performed under a variety of acidic conditions leading to mixtures of desired and undesired products. For example with H_2SO_4/r.t. 6 cyclized to the enamide 7 in good yield, which could be hydrogenated to the saturated lactam 8. Later it was discovered that all of the ethoxy-lactams underwent smooth cyclization in formic acid at r.t.

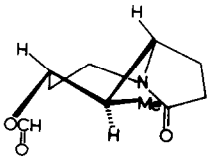
Upon stirring a soln of 4 in HCOOH/r.t. for 18 hr a highly stereoselective formation of crystalline 9 occurred in nearly quantitatve yield, m.p. 82-87° (dec)

IR 1710 and 1675 cm^{-1} (C=O); PMR $\delta(CDCl_3)$ 2.76 (m, 1H, H_{5ax}), 3·62 (m, 1H, H_{8a}), 4·25 (m, 1H, H_{5eq}) 5·06 (m, 1H, H_7) and 8·05 (S, 1H, OOCH). From the shape of the H_7 signal (triplet of triplets $J_1 = J_2 = 4$ cps, $J_3 = J_4 = 11$ cps) an equatorial position for the formate residue is established. The axial position for H_{8a} follows from a $W_{\frac{1}{2}}$ of 28 cps. Thus the cyclization proceeds according to the commonly encountered pattern for this type of reaction[9]. Hydrolysis of 9 (CH_3OH/HCl aq) gave the crystalline alcohol 10 m.p. 99-101°C (diisopropylether), PMR $\delta(CDCl_3)$ 2·67 (m, 1H, J_1= 13·0, 13·0 and 2·0 cps, H_{5ax}); 3·35 - 4·0 (m, 2H, H_{8a}+ H_7) 4·13 (m, 1H, J = 13·0, 5·0 and 2·0 cps, H_{5eq}).

Cyclization of the E-pentenyl derivative 5 gave the methyl derivative 11 with high (>90%) stereoselectivity PMR $\delta(CDCl_3)$ 2·68 (m, 1H, J = 11·0, 11·0 and 2·0 cps, H_{5ax}), 3·11 (m, 1H, J = 10·0, 6·0 and 6·0 cps, H_{8a}), 4·11 (m, 1H, J = 11·0 5·0 and 2·0 cps, H_{5eq}), 4·68 (m, 1H, J = 11·0, 11·0, 4·0 cps, H_7) and 8·00 (s, 1H OOCH). The equatorial positions for both formate and methyl groups and the axial H_8 stereochemistry follow without ambiguity from the values of the coupling constants.

In a similar manner 6 was cyclized (HCOOH, r.t./18 hr) to yield the indolizidine 12 in quantitative yield and with a degree of stereoselectivity greater than 95%. Its stereochemistry was inferred from the PMR spectrum : $\delta(CDCl_3)$ 2·76 (m, 1H, H_{5ax}), 3·74 (m, 1H, J = 6·0, 6·0 and 3·0 cps, H_{8a}); 4·11 (m, 1H, J = 11·0, 5·0 and 2·0 H_5 eq), 5·10 (m, 1H, $W_{\frac{1}{2}}$ = 25 cps , H_7 and 8·08 (s, 1H, OOCH). The magnitude of $W_{\frac{1}{2}}$ and the low value (3·0 cps) for $J_{7,8a}$ indicate an equatorial position for the formate and axial position for both the ethyl substituent and H_{8a} HCl-CH_3OH hydrolysis of 12 gave the crystalline alcohol 13 m.p. 104-106° (ether-diisopropylether) PMR $\delta(CDCl_3)$ 2·67 (m, 1H, J = 13·0, 13·0 and 5·0 cps, H_{5ax}), 3·66 (m, 1H, J = 7·0, 7·0 and 3·0 cps , H_{8a}) 3·9 (m, 1H, H_7) and 4·12 (m, 1H, J = 13·0, 5·0 and 2·0 cps, H_{5eq}).

The foregoing results clearly demonstrate the usefulness of the cyclic acylimmonium ion in olefin cyclizations. Coupled with the most facile practical handling of this type of intermediate its synthetic applicability seems highly promising. Moreover, the cyclizations occur almost stereospecific, provided a chairlike 6-membered transition state is possible as indicated in 14 and 15.



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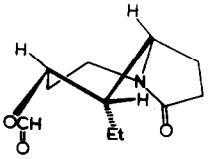

15

Therefore this type of ring closure can be generally classified as biomimetic heterocyclization. Other examples as well as some comments on the mechanism are presented in accompanying papers.

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