STEREOSELECTIVE OLEFIN CYCLISATIONS OF TERT α-ACYLIMINIUM IONS.

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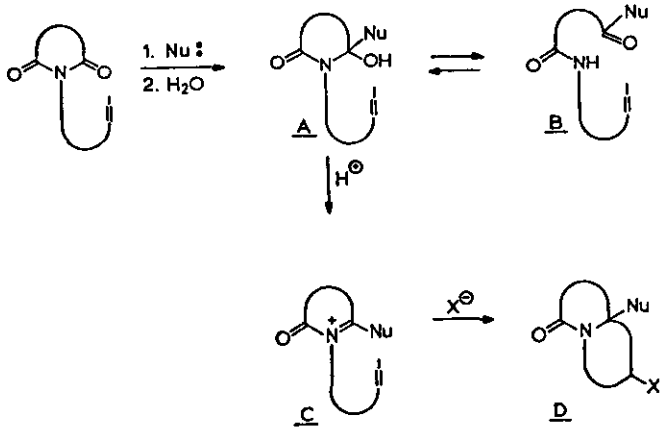
Abstract - Tert α-acyliminium ions are shown to exhibit excellent properties for inducing stereoselective olefin cyclisations. Starting from the appropriate alkene precursor bicyclic and tetracyclic ring systems are formed in good to excellent yields.

In the last few years sec α-acyliminium ion intermediates were found to operate as remarkably good initiating centres for stereoselective olefin cyclisations.[1] Recently the utility of tert α-acyliminium ions was demonstrated in the stereocontrolled synthesis of perhydrohistrionicotoxin.[2]

In this communication more general results are communicated on the exploration of tert α-acyliminium ion initiated olefin cyclisations.

Nucleophilic substitution reactions at the imide carbonyl have been shown to result in mixtures of tertiary hydroxylactams and the corresponding tautomeric open keto amides.[3] As Chiron and Graff[3b,c] have demonstrated, the tautomeric equilibrium A⇌B is among other factors depending on the nature of the N-substituent. Under the conditions investigated the cyclic form A is a necessary starting point for the cyclisation sequence A → C → D; therefore useful synthetic results are only expected if the formation of C favourably competes with the rate of interconversion between A and B.



In a first investigation the N-alkenyl imides[1a,b,4] 1a-9a were treated with MeMgCl in order to obtain the Me-hydroxylactams, all of which were found to appear in the ring closed form A except for 8b where a mixture of 8b and 10 was formed in a ratio of 5:4. As was observed in a later stage a complete conversion of the imides, however, necessitated the use of 2 equiv. of MeMgCl (THF, r.t., 3 hr, work-up NH_4Cl). The hydroxylactams were purified by crystallization prior to use or submitted to cyclisation in their crude form to prevent decomposition upon distillation and chromatography.

I Mono unsaturated N-substituents.

The ethoxylactams 1b-4b were selected for reasons of comparison with earlier results on cyclisation studies with sec $\diagdown\!\!\diagup C=\overset{\oplus}{N}(R)CO-$. Especially with reference to the stereoselectivity of the C-C bond formation process the unactivated N-alkenyl substituents 1b-3b have served useful purposes.[1a] Furthermore an evaluation of the experimental conditions for connecting the new C-C bond indirectly provides information on the reactivity of the cationic initiating centre. The ethoxylactam 1b was stirred for 18 hr/r.t. in HCOOH and afforded after work-up a crude yield of 71% of 11. 11: Mp. 88-90°C, (isopropyl ether); IR($CHCl_3$): 1715 cm^{-1} (C=O ester), 1670 cm^{-1} (C=O lactam); ^{1}H-NMR δ($CDCl_3$): 1.32 (s, C_6-Me); 2.80 (d of tr, J=14 and 3 Hz H_2-ax); 4.15 (m, 1H, H_2-eq); 5.22 (tr of tr, J=11.5 and 5 Hz H_4-ax); 8.03 (s, 1H, O$\overset{\overset{O}{\|}}{C}$H). The latter data are in good accord with the spectral data of the corresponding sec acyliminium cyclisation product.[1a] Therefore the trans relationship of C_6-methyl and formate group is highly probable and thus the formation of the C-C bond proceeds via a chairlike transition state. In the same way E-pentenyl imide 3a could be transferred into indolizidine 12 which was isolated in 60% after distillation (bulb to bulb 200°/0.01 mm). IR($CHCl_3$): 1710 cm^{-1} (C=O ester), 1670 cm^{-1} (C=O lactam); ^{1}H-NMR δ($CDCl_3$): 0.95 (d, C_5-Me); 1.19 (s, C_6-Me); 2.80 (d of tr, 1H, H_2-ax); 4.14 (m, 1H, H_2-eq); 4.99 (tr of d, J_{tr}=11 Hz, J_d=4.5 Hz, H_4-ax); 8.10 (s, 1H, O$\overset{\overset{O}{\|}}{C}$H). The foregoing examples already indicated a close analogy in reaction behaviour of tert vs sec acyliminium ions, although the overall yields of the ring closures are somewhat lower due to differences in the hydroxylactam preparation.

The Z-hexenyl derivative 2b [79% from 2a, mp. 56-58°; IR($CHCl_3$): 3380 cm^{-1} (OH), 1670 cm^{-1} (C=O lactam); ^{1}H-NMR δ($CDCl_3$): 0.96 (t, Me); 1.50 (s, Me); 4.25 (s, OH)] when exposed to cyclisation conditions (HCOOH r.t., 18 hr) did not afford a trace of a cyclic product. Both upon extension of the reaction time as well as upon

raising of the temperature to 45°C ring closure could not be induced while in stronger acids only decomposition was observed. This negative result is of remarkable theoretical interest. Supposedly unfavorable steric interactions prevent the attainment of the necessary chairlike conformation for ring closure. Yet in compounds of similar geometry cyclisation does occur as will be discussed in the sequel.

A similar rate enhancement as observed for the sec α-acyliminium analogue[1a] was found in the ring closure experiment of 4b. After 30 min at r.t. in HCOOH a 1:1 mixture of the epimeric formates 13 was formed in 85% yield. The latter result agrees with earlier findings on Me-substituted olefins in which the overall high stereoselectivity of the cyclisation reaction is lost upon stabilization of the newly developing cationic charge.[4]

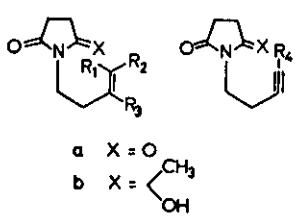
The mixture of tautomers 8b and 10 needed a considerably longer reaction time (90 hr, HCOOH, r.t.). After column chromatography 45% of compound 14 was isolated, mp. 49-53°. IR($CHCl_3$): 1710 cm^{-1} (C=O ketone), 1670 cm^{-1} (C=O lactam); ^{1}H-NMR δ ($CDCl_3$): 1.28 (s, C_6-Me); 3.02 (m, 1H, H_2-ax); 4.41 (m, 1H, H_2-eq). The relatively lower yield on azabicyclic ketone 14 is probably due to the slower rate of cyclisation thereby allowing side reactions to interfere.

All of the results so far obtained for tert α-acyliminium ions point to a similar reaction pattern with respect to stereoselectivity and ease of bond formation as encountered in the behaviour of sec α-acyliminium intermediates. A further test for the reactivity of these initiating systems is the reaction behaviour towards aryl olefins.

II Aryl unsaturated N-substituents.

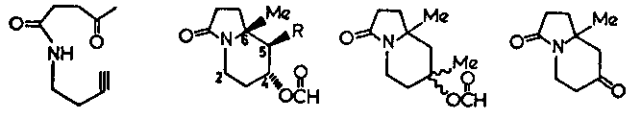
The E- and Z-aryl olefin hydroxylactams show a similar reaction behaviour as compared to corresponding sec hydroxylactam.[1b] HCOOH cyclisation of 5b (18 hr, r.t) gave a single isomer of tetracyclic product 15 (56% from 5a), structure assignment of which was based upon comparison with previous results[1b], mp. 94-96°; ^{1}H-NMR δ($CDCl_3$): 1.22 (s, C_{14}-Me); 4.23 (m, 1H, H_{12}-eq).

Most surprisingly the Z-isomer 6b also gave complete ring closure (HCOOH, 115 hr, r.t.) to a single cis-syn isomer 16 (yield 41% from 6a after distillation and crystallization), mp. 130-133°; ^{1}H-NMR δ($CDCl_3$): 1.46 (s, C_{14}-Me); 3.24 (m, 1H, H_{12}-ax); 4.09 (m, 1H, H_{12}-ax). Thus although it remained impossible to effect ring closure of Z-olefin 2b the aryl olefin 6b yet cyclized in a stereoselective manner albeit in a rather slow reaction. The retention of stereochemistry observed in the latter process once more lends support to the idea of concerted formation of both C-C bonds[5] and the ability of the aryl group to activate the double bond in this reaction,



a X = O
b X = CH3, OH

	1	2	3	4	5	6	7	8	9
R_1	H	Et	H	H	H	CH_2CH_2Ph	H	–	–
R_2	H	H	Me	H	CH_2CH_2Ph	H	CH_2CH_2Ph	–	–
R_3	H	H	H	Me	H	H	Me	–	–
R_4	–	–	–	–	–	–	–	H	CH_2CH_2Ph



10 11 R = H 12 R = Me 13 14

15 R = H 8,9 trans — 8,14 anti
16 R = H 8,9 cis — 8,14 syn
17 R = Me 8,9 trans — 8,14 anti

18

either by some form of electronic interaction or by promoting the attainment of a favourable conformation for cyclisation. When 7b was treated with HCOOH (r.t., 1 hr) 17 was formed in 68% yield. The latter yield could be raised considerably upon cyclisation in $CHCl_2COOH$ (r.t., 30 min) affording 93% of a single product, which on the basis of previous results[1b] and according to ^{1}H-NMR analysis proved to be the trans-anti dimethyl compound 17, mp. 119-121°; ^{1}H-NMR δ($CDCl_3$): 1.25 (s, C_{14}-Me) 1.32 (s, C_8-Me); 4.19 (m, 1H, H_{12}-eq). Cyclisation of 7b therefore showed an even better selectivity than the comparable sec hydroxylactam.[1b]

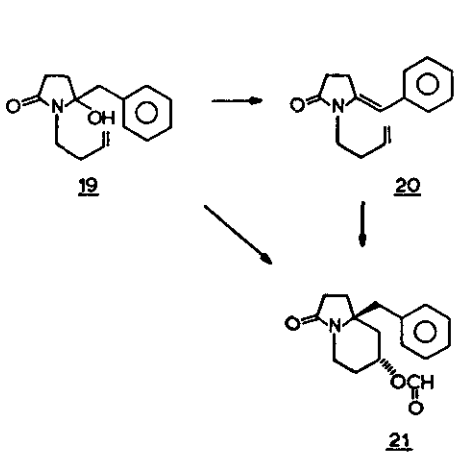
HCOOH cyclisation (70 hr, r.t.) of 9a afforded among polymerisation products the tetracyclic compound 18, which was isolated by chromatography in 38%, mp. 115-118°; ^{1}H-NMR δ($CDCl_3$): 1.41 (s, C_{14}-Me); 4.34 (m, 1H, H_{12}-eq).

Miscellaneous tert acyliminium ions.

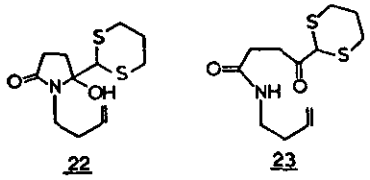
In order to expand further on the α-acyliminium method several other types of nucleophiles were condensed with the starting imide 1a, two of which being particularly relevant to the results discussed before.

With benzyl magnesium bromide 1a could be quantitatively transformed into hydroxylactam 19: IR($CHCl_3$): 3360 cm^{-1}, 1670 cm^{-1} (C=O lactam); ^{1}H-NMR δ($CDCl_3$): 2.94 and

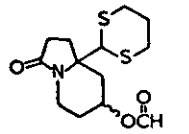
3.07 (AB J=14 Hz, 2H, $C\underline{H}_2PH$). Chromatography of the reaction mixture over silica-gel induced elimination of H_2O resulting in partial formation of enamide 20. Upon treatment with HCl/EtOH or CF_3COOH/CH_2Cl_2 water elimination of 19 was complete; 20 was isolated as an unstable oil. IR($CHCl_3$): 1700 and 1640 cm^{-1} (enamide). ^{1}H-NMR $\delta(CDCl_3)$: 3.68 (t, 2H, NCH_2); 5.0-6.0 (4H, olefin H). It is most important that under the latter conditions no trace of mono-cyclisation product is formed.



19 20 21



22 23



24 OCH eq.

25 OCH ax.

On the contrary reaction of enamide 20 as well as hydroxylactam 19 with HCOOH (18 hr, r.t.) afforded the formate 21 (65% from 1a), mp. 108-110°; IR($CHCl_3$): 1715 cm^{-1} (C=O ester), 1670 cm^{-1} (C=O lactam); ^{1}H-NMR $\delta(CDCl_3)$: 2.76 and 3.02 (AB J=19.5 Hz, 2H, CH_2Ph); 3.00 (m, 1H, H_2-ax); 4.31 (m, 1H, H_2-eq); 5.39 (tr of tr, H_4-ax); 8.02 (s, 1H, $O\overset{O}{\overset{\|}{C}}\underline{H}$). The virtual absence of any dicyclisation product can be understood since in this case the process involved would formally amount to a cis-addition to the C-C double bond.

An excellent nucleophile for substitution on the imide carbonyl appeared to be the 1,3-dithiane anion.[6] Since the dithiane moiety could be viewed upon as a latent functionality allowing obvious ramifications of the α-acyliminium method, its behaviour in cyclisations was also investigated. Reaction of 1a with 2 eq 1,3 dithiane anion (THF -10°— 0°, 3 hr, work-up sat aq NH_4Cl) afforded a mixture of the tautomers 22 and 23 in a 1:1 ratio from which keto amide 23 could be crystallized; mp. 90-91°. IR($CHCl_3$): 3450 cm^{-1} (NH), 1710 cm^{-1} (C=O ketone) 1660 cm^{-1} (C=O amide), 1510 cm^{-1} (amide II). Ring closure of 22 could be effected in 18 hr (HCOOH, r.t.), while the cyclisation of 23 necessitated a longer reaction time (HCOOH, r.t., 7 days). Obviously cyclisation of 23 proceeds via hydroxy lactam 22 where by the interconversion of 23 into 22 seems to be the rate determing step. When the crude

mixture of tautomers 22 and 23 was exposed to cyclisation conditions (HCOOH, r.t. 7 days) 24 could be obtained in 62% yield (from 1a), mp. 178-181°; IR($CHCl_3$): 1715 cm^{-1} (C=O ester), 1675 cm^{-1} (C=O lactam); ^{1}H-NMR δ ($CDCl_3$): 4.20 (m, 1H, H_2-eq); 4.62 (s, 1H, SCHS); 5.23 (tr of tr, J=13 Hz and J=4.5 Hz, H_4-ax); 8.02 (s, 1H, O$\overset{O}{\overset{\|}{C}}$H). From the mother liquor a second compound could be isolated in 5% yield, which appeared to be the axial formate isomer 25; IR($CHCl_3$): 1720 cm^{-1} (C=O ester), 1675 cm^{-1} (C=O lactam); ^{1}H-NMR δ($CDCl_3$): 4.11 (m, 1H, H_2-eq); 5.08 (s, 1H, SCHS); 5.33 (m, $W_{½}$=8 Hz, 1H, H_4-eq); 8.13 (s, 1H, O$\overset{O}{\overset{\|}{C}}$H). Presumably the latter isomer has been formed in a discreet manner.

All of the abovementioned results point to reactivity of the tert α-acyliminium species which under given conditions is of similar magnitude as compared with the sec α-acyliminium ion. Further work on the various synthetic aspects is in progress.

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Received, 30th May, 1979

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