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A NOVEL SYNTHETIC APPROACH TO PERHYDROHISTRIONICOTOXIN

STEREOSELECTIVE SYNTHESIS OF 1-AZA-SPIRANES

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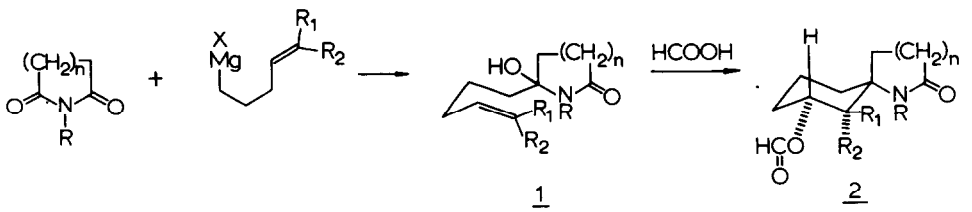
1-Aza-[n,5]-spiranes have recently attracted considerable attention both from a synthetic and from a biological point of view. Typical examples of this class of compounds are histrionicotoxin[1] and its perhydroderivative, for which short and stereocontrolled general syntheses[2] seem of high interest. In this communication we wish to report the preliminary results of a novel approach involving α-acylimmonium-ion initiated olefinic cyclisations[3]. The synthetic plan is outlined in scheme 1.



Scheme 1

Supposedly the key-step 1 → 2 in which the final C-C bond is formed and the desired stereochemistry is brought in, proceeds through a chairlike transition state A with synchronous formation of the new C-C and C-O bonds as is depicted in fig. 1.

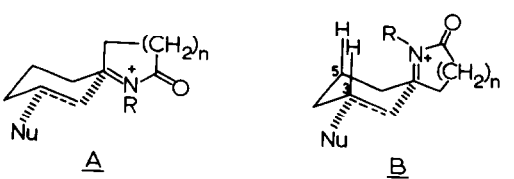
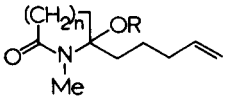
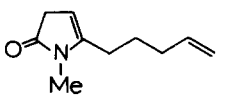


Fig. 1

A reaction via the alternative transition state B (fig. 1) is considered less likely because of steric interactions between the N-substituent R and the hydrogen atoms at C_3 and C_5 of the newly formed cyclohexane ring.



3 n=1 R=H
4 n=1 R=Et
6 n=2 R=H



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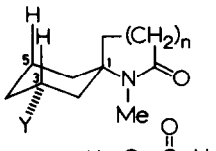
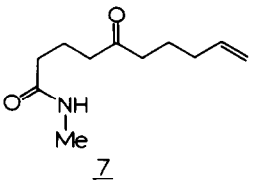


8a n=1 Y=O—C(=O)—H
9a n=1 Y=OH
10a n=2 Y=O—C(=O)—H
11a n=2 Y=OH
12a n=2 Y=I



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To test the synthetic approach outlined in Scheme 1 some model reactions were carried out.

Reaction of N-methylsuccinimide (1 eq) with 4-pentenylmagnesium iodide (1·15 eq) (20 h, room temperature, ether/THF) afforded after aqueous work-up (NH_4Cl/H_2O) 5-hydroxy-5-(4-penten-1-yl)-pyrrolidine-2-one 3 (65%) and unreacted N-methylsuccinimide. In an attempt to convert 3 to the presumably more stable ethoxyderivative 4 only the slightly unstable N-methyl-5(4-penten-1-yl)4-pyrrolin-2-one[4] 5 was formed. IR($CHCl_3$): 1670 cm^{-1} (CO-lactam); ^1H NMR: δ($CDCl_3$): 5·58-6·00 (m, 1H, C<u>H</u>=CH_2) 4·84-5·12 (m, 2H, CH=C<u>H</u>$_2$) 4·49-4·75 (m, 1H, N—C=C<u>H</u>), 2·87 (s, 3H, N—C<u>H</u>$_3$), 1·90-2·78 (m, 8H). Compound 5 could be purified by chromatography (SiO_2/EtOAc) although the isolated yield was only 42% due to severe decomposition on the column.

Cyclisation of the hydroxylactam 3 or the enamide 5 in HCOOH (18 h, room temperature) afforded the spirocyclic formate ester 8a in quantitative yield. IR($CHCl_3$): 1675 cm^{-1} (CO-lactam), 1720 cm^{-1} (CO-ester); ^1H NMR: δ($CDCl_3$): 7·98 (s, 1H, <u>H</u>COO) 4·70-5·10 (m, 1H, C<u>H</u>—O) 2·70 (s, 3H, NC<u>H</u>$_3$) 1·05-2·48 (m, 12H). Compound 8a could be hydrolysed (KOH/H_2O/EtOH) to the azaspiro alcohol 9a[6]. IR($CHCl_3$): 1670 cm^{-1} (CO-lactam); ^1H NMR: δ($CDCl_3$): 3·54-3·91 (m, 1H, C<u>H</u>—OH), 2·70 (s, 3H, N—C<u>H</u>$_3$) 1·00-2·48 (m, 13H).

The cyclisation thus proceeds in a stereospecific manner yielding a spirocyclic lactam with a cis-relation (vide-infra) between the C-N bond and the formate substituent (the occurrence of traces (<5%) of the other isomer 8b[7] could not be excluded).

Since the corresponding glutarimide adduct 6 is known[8] to ring-open extremely fast to the keto amide 7, while the latter form is difficult to cyclize back, the experimental procedure had to be modified. Thus after completion of the Grignard reaction between 4-pentenylmagnesium iodide and N-methylglutarimide (72 h ΔT, Et_2O) the etheral soln was evaporated, the residue dissolved in HCOOH and stirred for 40 h at 35-40°[9]. After work-up and chromatography (SiO_2/EtOAc) two spirocyclic products 10a and 12a were obtained. Compound 10a, obtained as a single stereoisomer in 45% yield possessed the following spectral characteristics: IR($CHCl_3$): 1620 cm^{-1} (CO-lactam), 1710 cm^{-1} (CO-ester); ^1H NMR: δ ($CDCl_3$) 7·96 (s, 1H, HCOO), 4·73-5·10 (m, 1H, CH-O), 2·85 (s, 3H, N-CH_3) 1·20-2·50 (m, 14H). Hydrolysis afforded the crystalline hydroxycompound 11a; m.p.: 142-144°; IR($CHCl_3$): 1620 cm^{-1} (CO-lactam); ^1H NMR: δ($CDCl_3$): 3·58-3·95 (m, 1H - CHOH) 2·90 (s, 3H, N-CH_3), 1·00-2·55 (m, 15H). ^{13}C NMR: δ(d-acetone/$CDCl_3$) 66·36 (d, C-OH), 60·00 (s, quat. C).

The second spirocyclic product (obtained in 15% yield) proved to be the unstable iodo-compound 12a. IR($CHCl_3$): 1620 cm^{-1} (CO-lactam); ^1H NMR: δ($CDCl_3$): 4·02-4·40 (m, 1H, CH-I), 2·93 (s, 3H, N-CH_3), 1·40-2·58 (m, 14H). ^{13}C NMR: (d-acetone) δ = 60·71 (s, quat. C). Presumably formation of this iodocompound 12a (again one stereoisomer) proceeds through transition state A (fig. 1) with I^- acting as the nucleophile.

To establish the stereochemical relationship between the incoming nucleophile and the C-N bond, some additional spectroscopic data were obtained. From the ^1H NMR data the equatorial position ($W_{\frac{1}{2}}$ = 22 Hz for CH-Y) of the substituent Y in the cyclohexane ring was established. Study of the molecular models of the possible trans-isomers 8b-12b[7] showed severe steric interactions between the N-CH_3 atoms and the hydrogen atoms at C_3 and C_5. Upon irradiation of the N-CH_3 a NOE-effect for the CH-Y protons is anticipated in the case of a trans relationship between the substituent Y and the C-H bond. Neither in 11a nor in 12a such

a NOE effect could be detected. The spectroscopic results therefore suggest a cis relationship between the substituent Y and the C-N bond.

The abovementioned results underline the synthetic potential of the α-acyl-immoniumion as a highly versatile intermediate. It may be emphasized, however, that in the present discussion a tertiary instead of a secondary immonium carbon is involved. Since the access into the class of tertiary ω-hydroxylactams may be considered as relatively facile a new area of possible applications has been opened.

Based on this synthetic scheme a new synthesis of a perhydrohistrionicotoxin precursor (Scheme 1, 2, n = 2, R = H, R_1 = n-butyl, R_2 = H) was completed. In the key step the stereocontrolled introduction of three asymmetric carbon atoms was realised. Details on the latter reaction and on the conversion of the cyclisation product will be reported elsewhere.

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6. All new compounds were characterized by IR, NMR, analysis and/or mass spectra
7. The isomers of compounds 8a - 12a possessing a trans relationship between the substituent Y and the C-N bond are represented as compounds 8b - 12b.
8. For a literature survey on the reaction of cyclic imids with Grignard-reagents, see ref. 5.
9. Due to the presence of salts in the reaction medium a reaction temperature of 35-40° is necessary; cf. ref. 3b.