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REDUCTIVE METHYLATION OF ω-CARBINOLLACTAMS VIA ANOMALOUS WITTIG REACTION

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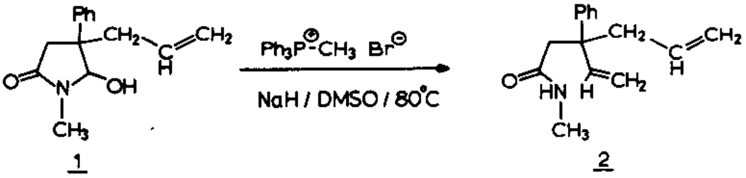
Abstract - Methylene phosphorane reacts with carbinollactams 4 with unexpected formation of 5-Me-substituted lactams 5. Reaction of phosphorane homologs with 4 afforded the γ,δ-alkenylamides 6.

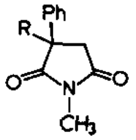
Reactions of ω-carbinollactams with phosphonates[1] and phosphoranes[2] have been shown to yield useful synthetic results. The success of the reaction is governed by several factors such as the presence of substituents, the reaction temperature, the size of the lactam ring and the excess of reagent used, all of which are influencing the final results. The N-methyl derivative which is disubstituted adjacent to the lactam hydroxyl group appeared to undergo this type of condensation in rather poor yield. Thus 1 gives alkene 2 in only 25% yield.



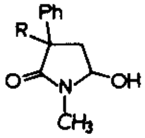
In order to investigate whether this behaviour was due to steric hindrance by the adjacent ring substituents we decided to prepare the corresponding carbinollactams at the least hindered side. For this purpose the imides 3 (a, b and c) were reduced with diisobutylaluminium hydride (DIBAH)[1,3].

The resulting carbinollactams 4a and 4b were obtained as oily mixtures of epimers in yields of about 75% after purification by column chromatography. Reduction of 3c gave 4c (52% yield) as off-white crystals (m.p. 139-140°C). Subsequently the Wittig reactions were carried out with triphenylmethylphosphonium bromide (5 equiv.) and NaH (3 equiv.) in DMSO at 80°C during 26 hr after which the products were purified by column chromatography.

Reaction of <u>4a</u> resulted in an oil (yield 75%) of which the IR-spectrum surprisingly did not show the characteristic secondary amide absorption. The conspicuous peaks of additional Me-absorptions in 'H NMR indicated the presence of a methyl substituted lactam ring. Furthermore decoupling experiments revealed the structure of the product as a C_5-Me epimer mixture of the methylated lactam <u>5a</u> instead of alkene <u>6</u>.



3	R
a	$-CH_2-CH=CH_2$
b	$-CH_2-C(CH_3)=CH_2$
c	$-Ph$



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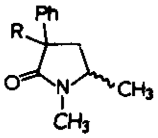

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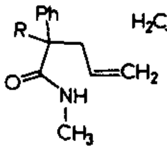

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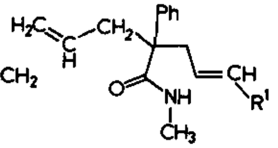

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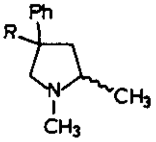
d $R^1 = C_3H_7$
e $R^1 = C_2H_5$



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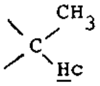
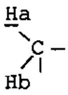
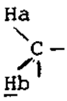
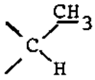
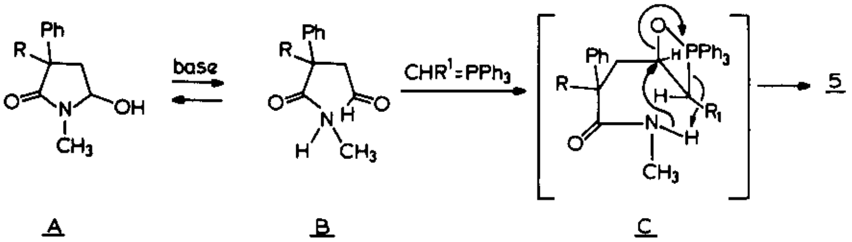
(^{1}H NMR $\delta(CDCl_3)$: 7.15-7.6 m (5H) arom; 5.45-6.0 m (1H) $-C\underline{H}=C$; 4.9-5.2 m (2H) $=\underline{CH}_2$; 3.2-3.6 m (1H) $-\mathrm{C}\overset{\mathrm{CH_3}}{\underset{\underline{\mathrm{H}}}{}}$; 2.83 m and 2.80 s (2x) (3H) N-$\underline{C}H_3$; 2.4-2.7 and 1.4-2.1 (4H) $-\underline{CH}_2-\overset{\varnothing}{\underset{|}{\overset{|}{C}}}-\underline{CH}_2-C=C$; 1.23 d and 1.13 d (2x) (J = 6.5 Hz) (3H) $\mathrm{C}\overset{\mathrm{H}}{\underset{\underline{\mathrm{CH}}_3}{}}$.

Reduction of 5a with DIBAH gave the amines 8a as a mixture of epimers of which a single picrate could be isolated via crystallization (m.p. 115-118°, elemental analysis calc. for C: 56.75%, H: 5.44%; found C: 56.80%, H: 5.37%).

In an analogous manner the condensation of 4b resulted in 5b (80% yield) also as a mixture of two epimers of which one isomer could be purified by crystallization (m.p. 56-58°C). In conclusion 4c gives 5c (yield 44%) as off-white crystals (115° dec.). (^{1}NMR ($CDCl_3$): 7.1-7.4 m (10H) arom.; 3.3-3.65 m (1H)  $>C<^{CH_3}_{\underline{H}c}$; 2.85-3.04 m (1H)  $\overset{\underline{H}a}{\underset{Hb}{>C-}}$; 2.05-2.3 m (1H)  $\overset{Ha}{\underset{\underline{H}b}{>C-}}$ ($J_{ab} = 13$ Hz, $J_{ac} = 8.5$ Hz, $J_{bc} = 5.5$ Hz); 2.83 s (3H) N-$C\underline{H}_3$; 1.98 d (3H)  $>C<^{\underline{C}H_3}_{H}$ $J = 6$ Hz. Thus all three lactams 4a-4c showed an unprecedented reductive methylation at the masked aldehyde carbonyl group while none of the anticipated alkene 6 could be detected.

In order to elucidate this unexpected behaviour several additional experiments were carried out. Most remarkably reaction of 4a with triphenylpropylphosphonium bromide/NaH/DMSO gives - albeit in rather low yield of 20% - the "normal" open product 7d while no trace of abnormal product could be detected. Furthermore reaction of 4a with triphenylethylphosphonium iodide/NaH/DMSO also failed to produce any abnormal product and again a low yield of 35% of 7e was obtained. It was independently established that γ,δ-alkenylamides of type 7 do not cyclize spontaneously under the reaction conditions or even at a temperature of 250°C and therefore the products 5a-c have to be formed via a different reaction pathway. Moreover the results of above Wittig condensations tend to indicate that the mechanistic course of the "abnormal" reaction is strongly influenced by steric factors. Although a conclusive proof for the observed anomalous reaction course at this moment is lacking it seems plausible that after base-catalyzed ring-opening of A the reaction starts with the formation of the betaine C from the open aldehyde form B.



If $R^1 = H$ the amide nitrogen may appoach the oxygen bearing carbon atom close enough to induce an abnormal collaps of the betaine. Substitution of the latter carbon atom by the amide nitrogen and concomitant proton transfer then account for the observed product formation. Eventually the betaine collaps may also be induced by the amide anion in which case the proton has to come from an external source. Subtle changes in the steric environment in case $R^1 \neq H$ may prevent the attainment of a favorable conformation for the process described, thus resulting in a normal breakdown of the betaine.

Further investigation will be carried out to clarify the observed anomalous reaction pathway.

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