

$\omega$ -Carbinollactams in regioselective  
olefinsynthesis

by

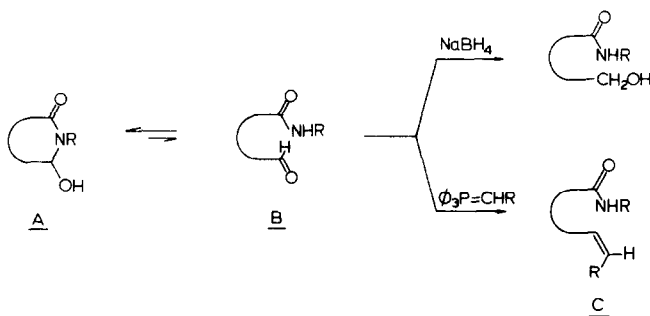
J.J.J. de Boer and W.N. Speckamp\*

Laboratory of Organic Chemistry, University of Amsterdam,  
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

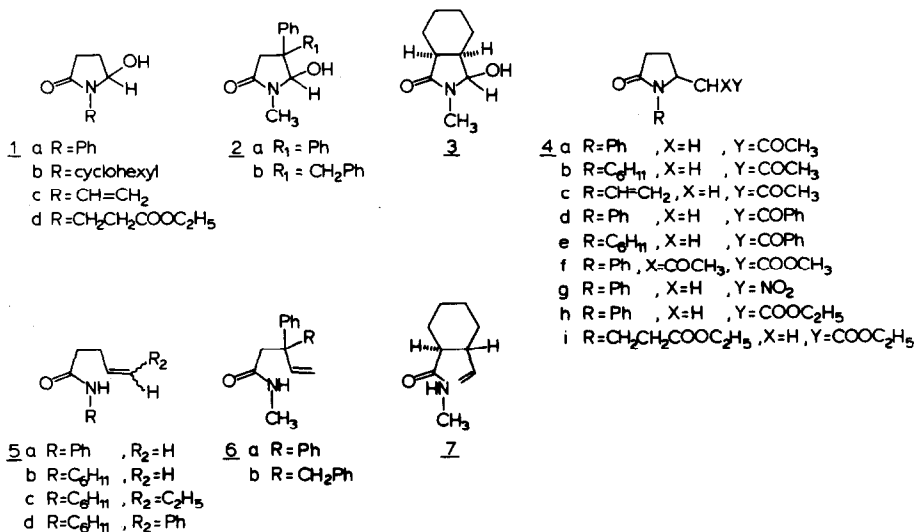
(Received in UK 2 September 1975; accepted for publication 29 September 1975)

The growing synthetic potential of  $\omega$ -carbinollactams as key compounds in the synthesis of polyheterocycles has been recently demonstrated<sup>1)</sup>. As a new class of precursors for the highly reactive cyclic  $\alpha$ -acylimmonium ion<sup>2)</sup> the title compounds serve as easily obtainable starting materials<sup>3)</sup> for a variety of applications.

In the preparation of the  $\omega$ -carbinollactam A one of the pitfalls is the reduction of the so-called open form i.e. the amido aldehyde B<sup>4)</sup>:



Conversely the possible use of A as a reagent - visualized for a Wittig-type condensation to afford C - which is capable of base-catalyzed condensation via its tautomer B can be considered as a novel dimension of the synthetic utility of the  $\omega$ -carbinollactams. In this communication some applications of this principle are reported.



$\omega$ -Carbinollactams undergo reaction with remarkable ease in alkaline medium. Thus active methylene compounds of different structural variety (table I) condense under influence of base<sup>5)</sup> to afford the C-substituted derivatives in good yields. Examples are given in table I.

Table I.

Starting material	$R_1CH_2\overset{O}{\parallel}C R_2$	Conditions	Yield <sup>c)</sup>	Product
<u>1a</u>	R <sub>1</sub> = H    R <sub>2</sub> = CH <sub>3</sub>	2 hr reflux a)	83%	<u>4a</u> mp: 80-82°C
<u>1b</u>	R <sub>1</sub> = H    R <sub>2</sub> = CH <sub>3</sub>	16 hr reflux a)	75%	<u>4b</u> d)
<u>1c</u>	R <sub>1</sub> = H    R <sub>2</sub> = CH <sub>3</sub>	24 hr reflux a)	60%	<u>4c</u> d)
<u>1a</u>	R <sub>1</sub> = H <sub>1</sub> R <sub>2</sub> = Ph	12 hr reflux a)	83%	<u>4d</u> mp: 109.5-110.5
<u>1b</u>	R <sub>1</sub> = H <sub>1</sub> R <sub>2</sub> = Ph	16 hr reflux a)	74%	<u>4e</u> mp: 116-117
<u>1a</u>	R <sub>2</sub> = COEt    R <sub>2</sub> = CH <sub>3</sub>	12 hr reflux b)	68%	<u>4f</u> d)

a) NaOC<sub>2</sub>H<sub>5</sub>/C<sub>2</sub>H<sub>5</sub>OH

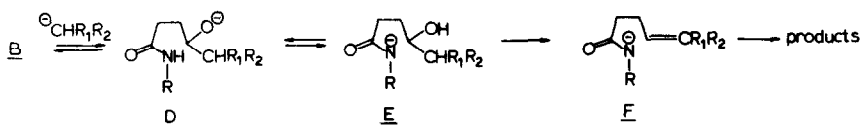
b) Piperidine/C<sub>2</sub>H<sub>5</sub>OH

c) After purification via chromatography

d) Obtained as oily material; characterized via Mass, IR and PMR analysis.

Other types of activated methylenes react equally well with 1a. For instance nitromethane yielded the nitromethylene derivative 4g in 80% yield.

The general course of the reaction can be depicted as follows:



Depending on the  $P_{K_a}$  of the amide D proton transfer will occur more or less readily to yield E which after loss of water via F affords finally the product in a Michael type of addition.

Of additional interest is the behaviour of a variety of  $\omega$ -carbinollactams A towards ylids of different structure. Thus condensation of 1a with triphenylmethylene phosphorane (NaH, DMSO, r.t.) gives a yield of 81% of the alkenylamide 5a, m.p. 93-94°C, PMR  $\delta$  (CDCl<sub>3</sub>) 2.41 (broadened s, 4H, -CH<sub>2</sub>), 5.04 (m, 2H, =CH), 5.80 (m, 1H, =CH). Similarly the *N*-cyclohexyl derivative 1b afforded 5b, m.p. 67-69°C in 81% yield, while triphenyl propylene phosphorane reacted with 1b in a quantitative manner to yield *Z*-5c, m.p. 51-52°C. Analogously 5d was formed from reaction of 1b and benzylidene phosphorane as a 4:1 mixture of *E*- and *Z*-isomers. Reaction of 1a with triethylphosphonoacetate (NaH, DME, r.t.) gave the pyrrolidone 4h, resulting from an intramolecular Michael type of addition of the amide onto the newly formed double bond. In a similar manner 1d afforded the diester 4i in 40% yield (not optimized).

$\alpha, \alpha$ -Disubstituted imides which undergo regioselective NaBH<sub>4</sub>-reduction<sup>7)</sup> proved also possible to serve as starting material, affording  $\beta, \beta$ -disubstituted- $\gamma, \delta$ -unsaturated amides. Thus it now appears possible to achieve highly selective and rational synthesis of this type of structure as indicated by the examples in table II :

Table II.

Compound	Phosphorane <sup>a)</sup>	Conditions	Yield <sup>b)</sup>	Product
<u>2a</u>	$\phi_3\text{P} = \text{CH}_2$	DMSO/80-90°/21 hr	45%	<u>6a</u> m.p. 122-124°C
<u>2b</u>	$\phi_3\text{P} = \text{CH}_2$	DMSO/80-90°/16 hr	70%	<u>6b</u> m.p. 136-139°C
<u>3</u>	$\phi_3\text{P} = \text{CH}_2$	DMSO/65-70°/16 hr	60%	<u>7</u> m.p. 132-133°C

a) Prepared in situ from the corresponding phosphonium salt by addition of 2 eq of NaH,

b) not optimized.

The latter procedure amounts in essence to a selective transformation of one of the carboxyl groups of a nonsymmetric dicarboxylic acid and can be considered as a general method for functionalizing a dicarboxylic acid.

Finally it should be mentioned that the method outlined above seems eminently suitable for the preparation of starting materials in novel synthetic applications of [3,3] sigmatropic rearrangements and for the synthesis of macrocyclic lactams. Results of these will be communicated separately.

#### REFERENCES AND NOTES

- 1) J. Dijkink and W.N. Speckamp, accompanying communication.
- 2) J.C. Hubert, J.P.B.A. Wijnberg and W.N. Speckamp, Tetrahedron, 31, 1437 (1975).
- 3) J.C. Hubert, W. Steege (in part), W.N. Speckamp and H.O. Huisman, Synthetic Comm., 1(2), 103 (1971).
- 4) The amide aldehyde can be obtained quantitatively in form of its hydrazone by reaction of the  $\omega$ -carbinollactam with p-nitrophenylhydrazine.
- 5) It should be noted that  $\omega$ -carbinollactams react also in quantitative yield with sufficiently acidic methylene derivatives as f.i. 1,3-diketones and  $\beta$ -ketoesters under acid conditions. This type of process can be compared with the well-known amido-alkylation of active methylenes<sup>6)</sup>.
- 6) H.E. Zaugg, Synthesis, 2, 49 (1970).
- 7) J.B.P.A. Wijnberg, W.N. Speckamp and H.E. Schoemaker, Tetrahedron Letters, 4073 (1974).

++++++