

## SYNTHESIS OF 1,5-DIENES AND 6-AZABICYCLO[3.2.1]OCTANES

VIA  $\omega$ -CARBINOLLACTAMS

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3,3-Disubstituted succinimides are reduced regioselectively at the 2 and 5 positions. The resulting  $\omega$ -carbinol-lactams are used for synthesis of 6-phenyl-1,5-dienes and 6-azabicyclo[3.2.1]octanes, respectively.

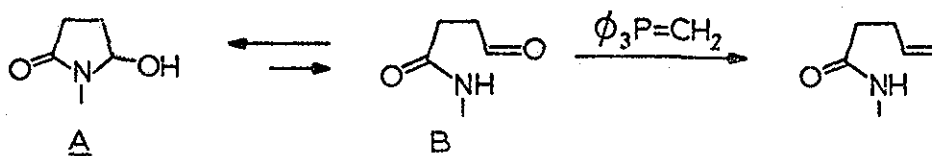
The regioselective reduction of 3,3-disubstituted succinimides<sup>1</sup> with  $\text{NaBH}_4$  at the most hindered carbonyl and the use of the so-obtained  $\omega$ -alkoxylactams as precursors for the reactive  $\alpha$ -acylimmonium ions have been reported to lead to new synthesis of various alkaloids.<sup>2</sup> On the contrary the chemistry of  $\omega$ -carbinol-lactams obtained via reduction at the least hindered carbonyl is almost unexplored although the regioselectivity effect upon reductions of imides with diisobutylaluminum hydride was mentioned earlier by Winterfeldt.<sup>3</sup>

In the present communication both the regioselective  $\text{NaBH}_4/\text{H}^+$ -reduction at the most hindered side and the reduction of 3,3-disubstituted imides with  $\text{DIBALH}^3$  at the least hindered side will be discussed especially in relation with novel synthetic applications. Use of two totally different chemical properties

of  $\omega$ -carbinol-lactams - reaction as a masked aldehyde and as a precursor of the  $\alpha$ -acylimmonium ion - could lead to new syntheses of 1,5-dienes and of azabicyclo[3.2.1]octanes.

### I Synthesis of 1,5-dienes

Wittig type condensations can be carried out with  $\omega$ -carbinol-lactams A, which proceed via the open chain amide-aldehyde tautomer B.<sup>4</sup>



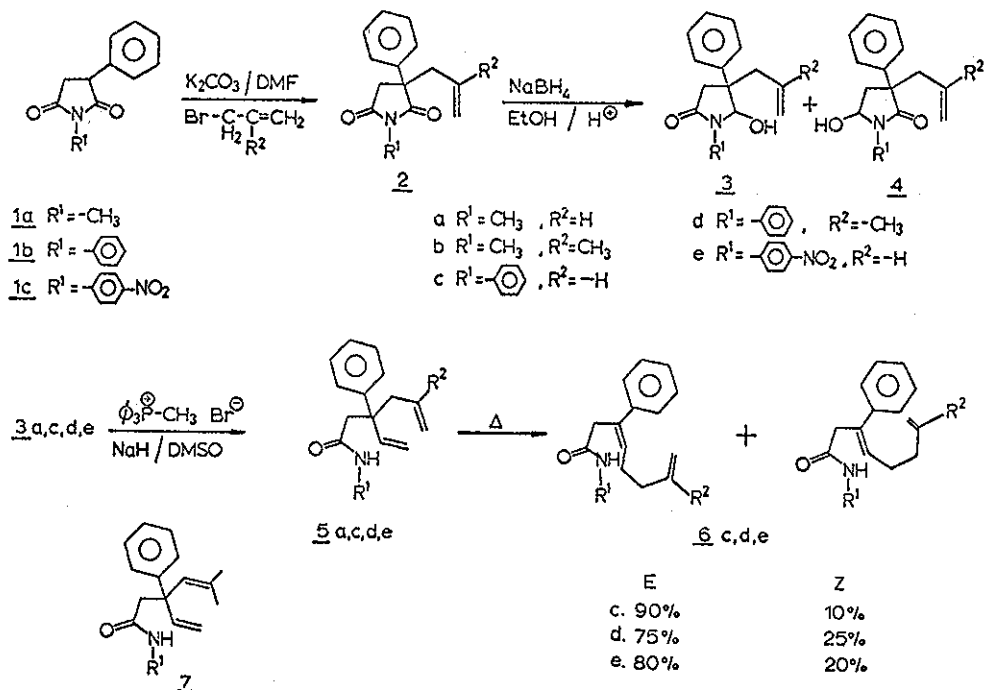
This reaction at the masked aldehyde function coupled with the regioselective  $NaBH_4/H^+$  reduction of disubstituted imides provides a new method for the synthesis of 1,5-dienes (see Scheme 1).

1-Methyl-3-phenylsuccinimide 1a is alkylated with allyl and methallyl bromide by means of  $K_2CO_3$  in DMF to afford imides 2a and 2b

"Acid"  $NaBH_4$ -reduction of imides 2a and 2b produces mixtures of carbinol-lactams 3a,b and 4a,b in which the desired lactams 3a and 3b are existed as a form of epimeric mixtures in more than 80% yield.

Wittig reaction of 3a with triphenylmethylphosphonium bromide and NaH in DMSO proceeds in rather poor yield (25%) affording 5a, ( $^1H$ -NMR  $\delta$  ( $CDCl_3$ ): 4.8-5.2 m(4H)  $=CH_2$  (2x); 5.3-5.7 m(2H) NH and  $CH_2-CH=CH_2$ ; 5.8-6.2 m(1H)  $\phi-C-CH=CH_2$ ). This observation

SCHEME 1



is in marked contrast with the behaviour of carbinol-lactams of which the ring is not substituted<sup>4</sup> and again emphasizes the importance of a favourable tautomeric equilibrium ( $\text{A} \rightleftharpoons \text{B}$ ) in this type of condensation. It was also noticed that a change in external conditions - variation of temperature and/or addition of base - does not improve the yields and instead gives rise to the formation of undesired products. Therefore the substrate itself was changed. Substitution of  $R^1$  by a phenyl and a 3-nitrophenyl group was expected to produce a favourable effect: better stabilization of the developing negative charge at the nitrogen atom by the aromatic substituent during opening of the ring will ultimately influence the equilibrium  $\text{A} \rightleftharpoons \text{B}$  in the desired manner.

Consequently the imides 2c,d and e were synthesized and reduced with  $\text{NaBH}_4$  to give almost exclusively the carbinol-lactams 3c, 3d and 3e as a mixture of epimers. In case of 3c and 3d the latter could be separated via crystallization; 3c: m.p. 148-149°C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 4.8-5.6 m (4H)  $\text{CH}_2\text{OH}$  and  $\text{CH}=\text{CH}_2$ ; 3d: m.p. 148-150°C;  $\delta(\text{CDCl}_3)$ : 5.47 d(1H)  $\text{CH}_2\text{OH}$   $J = 7.5$  c/s; 4.4-4.7 m(2H) =  $\text{CH}_2$ . 3e remained a crystalline mixture of epimers; m.p. 173-174°C;  $^1\text{H-NMR}$  ( $\text{DMSO-D}_6$ ): 5.88 (d,  $J = 9.5$  c/s) and 5.71 (d,  $J = 8$  c/s, 1H,  $\text{CH}_2\text{OH}$ ); 4.8-5.5 (m, 3H,  $\text{CH}=\text{CH}_2$ ). As expected carbinol-lactams 3c reacted in a quantitative manner with methylene triphenylphosphorane to give diene 5c; m.p. 95-97°C;  $^1\text{H-NMR}$   $\delta(\text{CDCl}_3)$  5.0-5.5 (m, 4H,  $=\text{CH}_2 \times 2$ ); 5.5-6.3 (m, 2H,  $\text{CH}=\text{C} \times 2$ ); 6.65 (1H, NH). Wittig condensation with 3d was somewhat complicated by the fact that during the reaction the methallylic double bond partly isomerized. As a result only 70% of diene 5d m.p. 115-117°C;  $^1\text{H-NMR}$   $\delta(\text{CDCl}_3)$ : 4.7-4.9 (m, 2H,  $-(\text{CH}_3)\text{C}=\text{CH}_2$ ); 5.1-5.3 (m, 2H,  $\text{CH}=\text{CH}_2$ ); 6.0-6.3 (m, 1H,  $\text{CH}=\text{C}$ ); 6.7 (1H, NH) was isolated in addition to 30% of 7. Wittig reaction proceeds also quantitatively with the nitrophenyl compound 3e to give 5e; m.p. 121° dec;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 5.0-5.4 (m, 4H,  $=\text{CH}_2 \times 2$ ); 5.4-6.3 (m, 2H,  $\text{CH}=\text{C} \times 2$ ); 6.95 (1H, NH). Thermal rearrangements of 5c,d and e were achieved by heating the dienes at 180°C without solvent in a nitrogen atmosphere. The products 6 (E + Z) were formed quantitatively. The E-isomers which are formed in excess (for ratios: see Scheme 1) crystallize and thus can be purified. Experimental data are collected in Table 1.

TABLE 1

E-isomers	m.p. °C	<sup>1</sup> H-NMR δ (CDCl <sub>3</sub> )		
		$\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \\ \text{R}_2 \end{array} = \text{CH}_2$	$\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \\ \text{R}_2 \end{array} = \text{CH}_2$	$\text{C} = \text{CH} - \text{C}_6\text{H}_5$
<u>6c</u>	113-115	4.9-5.3 m (2H)	R <sup>2</sup> =H 5.6-6.0 m (1H)	6.0-6.2 m (1H)
<u>6d</u>	109-111	4.5-4.8 m (2H)	R <sup>2</sup> =CH <sub>3</sub> 1.5-1.7 m (3H)	6.0-6.2 m (1H)
<u>6e</u>	132-135	5.1-5.3 m (2H)	R <sup>2</sup> =H 5.8 - 6.4 m (2H)	

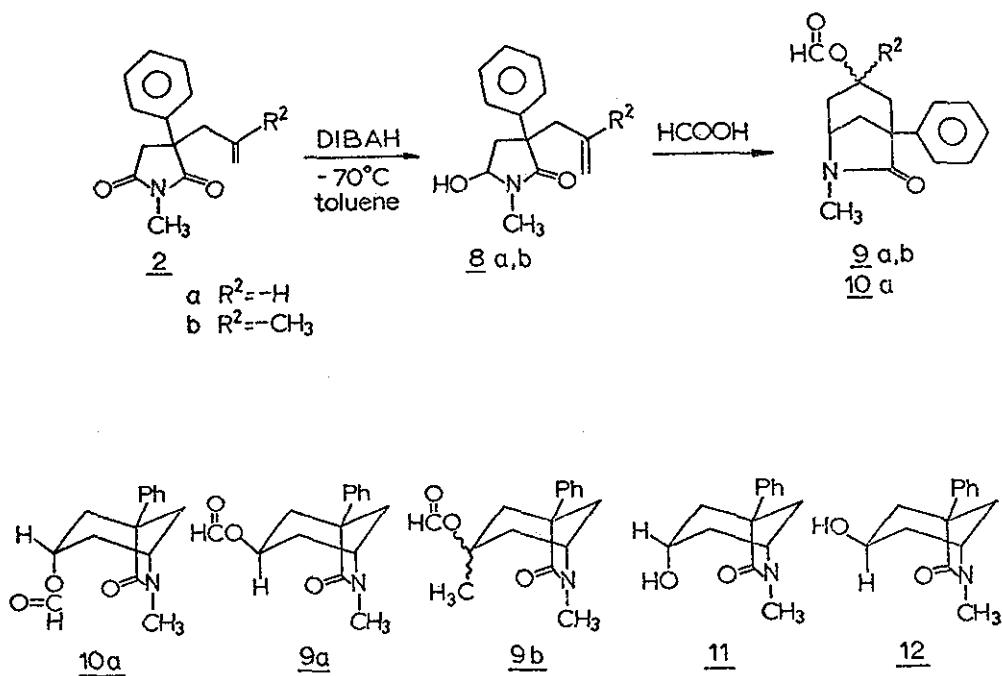
Structural assignment of the E- and Z-isomers 6 were based upon a comparison of δ-values with corresponding ones of substituted styrenes.<sup>5</sup>

## II Synthesis of 6-azabicyclo[3.2.1]octanes.

The recent interest in azabicyclo[3.2.1]octanes because of their potentially analgetic action,<sup>6</sup> prompts us to report our results on a simple synthesis of 1-phenyl-6-azabicyclo[3.2.1]octane derivatives via DIBAH-reduction of 3,3-disubstituted imides.

If a regioselective reduction of appropriate 3,3-disubstituted succinimides at the least hindered side can be effected, imides 2a and 2b are suitable starting materials for this synthesis. Subsequent acid catalyzed cyclization of the so-obtained carbinol-lactams is expected to furnish the azabicyclo[3.2.1]octane skeleton (see Scheme 2).

## Scheme 2



Indeed it showed that upon reduction of 2a and 2b with DIBALH (20% solution in toluene) at  $-70^\circ\text{C}$  exclusively the least hindered carbinol-lactams 8a and 8b were isolated as an oily mixture of epimers. Cyclization<sup>7</sup> of 8a was carried out by heating in formic acid at  $87^\circ\text{C}$  during 70 hr. A mixture of the formates 9a and 10a was formed in 70% yield in a ratio of about 3:2. After purification by chromatography both isomers were characterized by  $^1\text{H-NMR}$ ; 9a  $\delta(\text{CDCl}_3)$ : 2.93 (s, 3H, N- $\text{CH}_3$ ); 3.7-3.85 (m, 1H,  $\text{H}-\text{C}-\text{N}$ ); 4.8-5.2 (m, 1H,  $\text{CH}-\text{OC}$ ); 8.05 (s, 1H,  $-\text{OCH}$ ); 10a  $\delta(\text{CDCl}_3)$ : 2.89 (s, 3H, N- $\text{CH}_3$ ); 3.63-3.8 (m, 1H,  $\text{H}-\text{C}-\text{N}$ ); 5.35-5.52 (m, 1H,  $\text{CH}-\text{OC}$ ); 8.0 (s, 1H,  $\text{OCH}$ ). Basic hydrolysis

afforded the corresponding crystalline alcohols 11, m.p. 121-123°C, and 12, m.p. 181-183°C. Ring closure of carbinol-lactam 8b was accomplished with formic acid at room temperature within 1 hr. Unlike the cyclization of 8a this ring closure proceeds in a stereospecific manner: only one isomer can be detected: 9b, m.p. 106,5-109°C;  $^1\text{H-NMR } \delta(\text{CDCl}_3)$ : 1.67 (s, 3H,  $\text{CH}_3\text{-C-O}$ ); 2.84 (s, 3H,  $\text{N-CH}_3$ ); 3.65-3.78 (m, 1H,  $\text{H-C-N}$ ); 7.93 (s, 1H,  $\text{OCH}$ ).<sup>8</sup>

Although the configuration at C-3 could not be determined unambiguously, the formate residue probably occupies an equatorial position for mechanistic<sup>7</sup> and steric reasons.

## REFERENCES

- 1 J.B.P.A. Wijnberg, W.N. Speckamp and H.E. Schoemaker, Tetrahedron Letters, 1974, 4073.
- 2a J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron Letters, 1975, 3963;
- b J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron Letters, 1975, 4035.
- 3 E. Winterfeldt, Synthesis, 1975, 617.
- 4 J.J.J. de Boer and W.N. Speckamp, Tetrahedron Letters, 1975, 4039.
- 5 M. Barbieux, N. Defay, J. Pecher and R.H. Martin, Bull.Soc. Chim.Belg., 1964, 73, 716.
- 6a M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto and S. Saito, Chem. and Pharm.Bull.Japan, 1976, 24, 1002;

b M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori,  
G. Tsukamoto, Y. Yamawaki and S. Saito, Chem. and Pharm.Bull.,  
Japan, 1976, 24, 1514.

c M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori,  
G. Tsukamoto, Y. Yamawaki, S. Saito, K. Aoe, T. Date,  
S. Nurimoto and G. Hayashi, J.Medicin.Chem., 1977, 20, 221.

7a J. Dijkink and W.N. Speckamp, Tetrahedron Letters, 1975,  
4047;

b J. Dijkink, H.E. Schoemaker and W.N. Speckamp, Tetrahedron  
Letters, 1975, 4043.

8 All new compounds showed satisfactory microanalyses.

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