SYNTHESIS OF 1,5-DIENES AND 6-AZABICYCLO[3.2.1]OCTANES VIA ω-CARBINOLLACTAMS

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

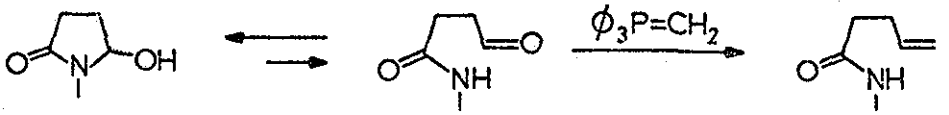
The regioselective reduction of 3,3-disubstituted succinimides[1] with $NaBH_4$ at the most hindered carbonyl and the use of the so-obtained ω-alkoxylactams as precursors for the reactive α-acylimmonium ions have been reported to lead to new synthesis of various alkaloids.[2] On the contrary the chemistry of ω-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.[3]

In the present communication both the regioselective $NaBH_4/H^+$-reduction at the most hindered side and the reduction of 3,3-disubstituted imides with DIBAH[3] at the least hindered side will be discussed especially in relation with novel synthetic applications. Use of two totally different chemical properties

of ω-carbinol-lactams - reaction as a masked aldehyde and as a precursor of the α-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 ω-carbinol-lactams A, which proceed via the open chain amide-aldehyde tautomer B.[4]



A B

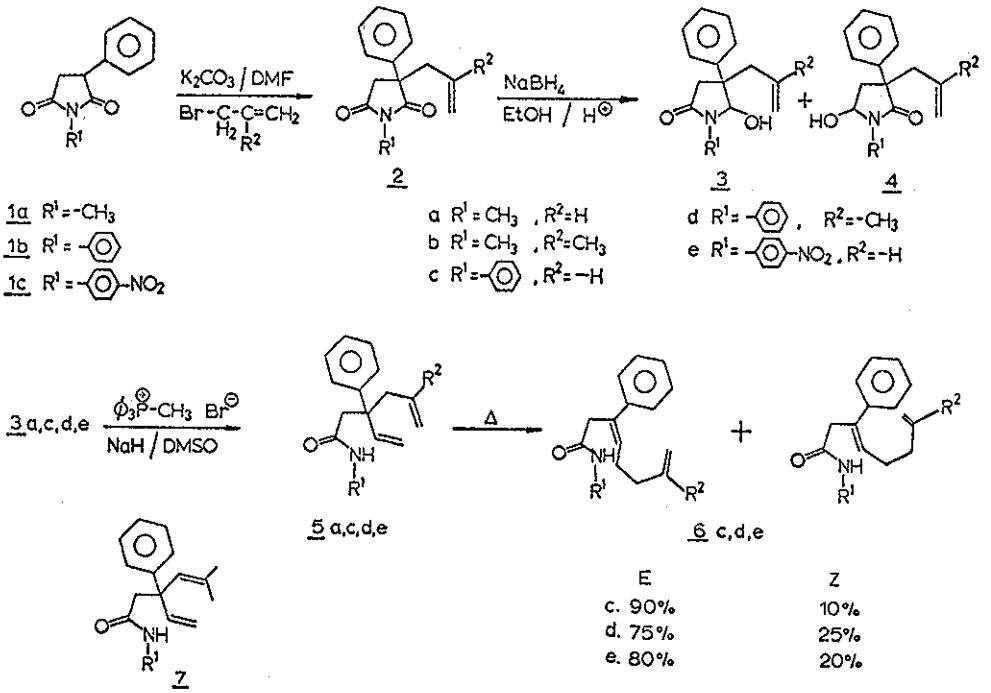
This reaction at the masked aldehyde function coupled with the regioselective $NaBH_4/H^+$- reduction of disubstituted imides provides a new method for the synthesis of 1,5-dienes (see Scheme 1).

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, (^{1}H-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) Ø-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[4] and again emphasizes the importance of a favourable tautomeric equilibrium (A ⇌ 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 A ⇌ B in the desired manner.

Consequently the imides 2c,d and e were synthesized and reduced with $NaBH_4$ 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}H-NMR ($CDCl_3$): 4.8-5.6 m (4H) CHOH and $CH=CH_2$; 3d: m.p. 148-150°C; δ($CDCl_3$): 5.47 d(1H) CHOH J = 7.5 c/s; 4.4-4.7 m(2H) = CH_2. 3e remained a crystalline mixture of epimers; m.p. 173-174°C; ^{1}H-NMR (DMSO-D_6): 5.88 (d, J = 9.5 c/s) and 5.71 (d, J = 8 c/s, 1H, CHOH); 4.8-5.5 (m, 3H, $CH=CH_2$). As expected carbinol-lactams 3c reacted in a quantitative manner with methylene triphenylphosphorane to give diene 5c; m.p. 95-97°C; ^{1}H-NMR δ($CDCl_3$) 5.0-5.5 (m, 4H, $=CH_2$x2); 5.5-6.3 (m, 2H, CH=Cx2); 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}H-NMR δ($CDCl_3$): 4.7-4.9 (m, 2H, -(CH_3) $C=CH_2$); 5.1-5.3 (m, 2H, $CH=CH_2$); 6.0-6.3 (m, 1H, CH=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}H-NMR ($CDCl_3$): 5.0-5.4 (m, 4H, $=CH_2$x2); 5.4-6.3 (m, 2H, CH=Cx2); 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	^{1}H-NMR δ($CDCl_3$): $R_2C=CH_2$	R^2-C=CH-	Ø-C=CH-
6c	113-115	4.9-5.3 m (2H)	R^2=H 5.6-6.0 m (1H)	6.0-6.2 m (1H)
6d	109-111	4.5-4.8 m (2H)	R^2=CH_3 1.5-1.7 m (3H)	6.0-6.2 m (1H)
6e	132-135	5.1-5.3 m (2H)	R^2=H 5.8 - 6.4 m (2H)	

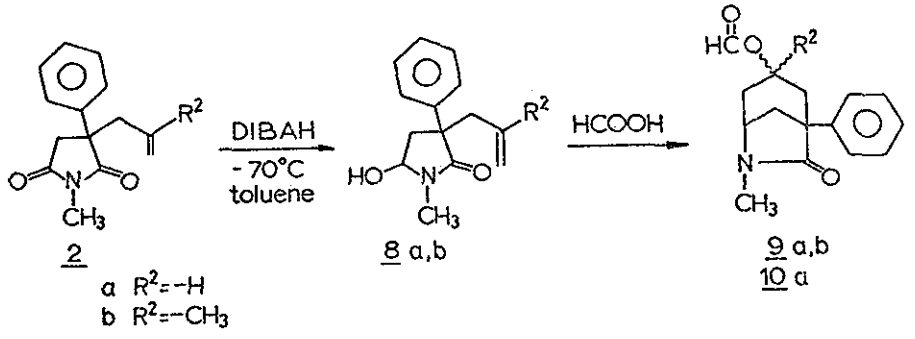
Structural assignment of the E- and Z-isomers 6 were based upon a comparison of δ-values with corresponding ones of substituted styrenes.[5]

II Synthesis of 6-azabicyclo[3.2.1]octanes.

The recent interest in azabicyclo[3.2.1]octanes because of their potentially analgetic action,[6] 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

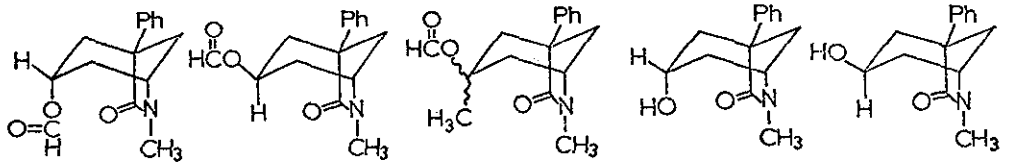


2

a R^2=-H
b R^2=-CH_3

8 a,b

9 a,b
10 a



10a 9a 9b 11 12

Indeed it showed that upon reduction of 2a and 2b with DIBAH (20% solution in toluene) at -70°C exclusively the least hindered carbinol-lactams 8a and 8b were isolated as an oily mixture of epimers. Cyclization[7] of 8a was carried out by heating in formic acid at 87°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}H-NMR; 9a δ($CDCl_3$): 2.93 (s, 3H, N-C<u>H</u>$_3$); 3.7-3.85 (m, 1H, <u>H</u>-C-N); 4.8-5.2 (m, 1H, C<u>H</u>-OC(=O)); 8.05 (s, 1H, -OC(=O)<u>H</u>); 10a δ($CDCl_3$): 2.89 (s, 3H, N-C<u>H</u>$_3$); 3.63-3.8 (m, 1H, <u>H</u>-C-N); 5.35-5.52 (m, 1H, C<u>H</u>-OC(=O)); 8.0 (s, 1H, OC(=O)<u>H</u>). 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}H-NMR $\delta(CDCl_3)$: 1.67 (s, 3H, CH_3-C-O); 2.84 (s, 3H, N-CH_3); 3.65-3.78 (m, 1H, H-C-N); 7.93 (s, 1H, O$\overset{O}{\overset{\|}{C}}$H).[8]

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

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8 All new compounds showed satisfactory microanalyses.

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