# ACETOXYLATION OF 1-BENZYLOXY β-LACTAMS AT C-4 VIA A REDUCTION-OXIDATION SEQUENCE

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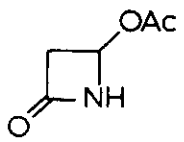
Abstract - Selective dihydroalane reduction of 1-benzyloxy β-lactams **4** affords 1-(benzyloxy)azetidines **6** which can be debenzylated to give the 1-hydroxy azetidines **7**. Oxidation of the compounds **7** either gives a mixture of β-lactams **10** and **11** or selectively β-lactams **10**.

β-Lactams with either a leaving group in 4-position or a hetero substituent at N-1 have recently received much attention. In 1974 Clauss et al. demonstrated the use of 4-(acetyloxy)-2-azetidinone (**1**) in β-lactam synthesis. On reaction with several oxygen, nitrogen, and sulfur nucleophiles **1** yielded the corresponding C-4 substituted products.[1] These displacement reactions have been extended to carbon nucleophiles like cyanide,[2] allylsilanes,[3] silyl enol ethers,[4] and cuprates.[5]

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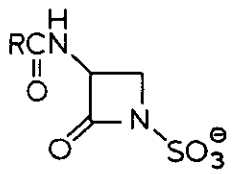


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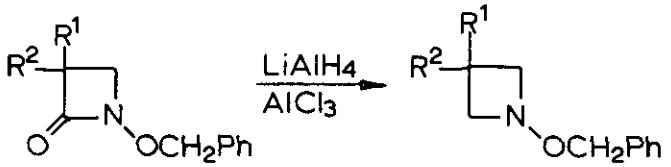
The isolation and structural elucidation of several members of a new class of monocyclic β-lactam antibiotics (monobactams **2**) have initiated work on monocyclic β-lactams with hetero substituents at N-1.[6] 2-Azetidinones with an acetyloxy function in 4-position can be synthesized via several pathways. The first method comprises the (2+2) cycloaddition of vinylic esters and chlorosulfonyl isocyanate.[1,7] Besides, ring opening of penicilline sulfoxide esters to monocyclic 4-acetyloxy derivatives was reported by Suarato et al.[8] Recently the formation of a 4-(acetyloxy)-2-azetidinone was achieved by the lead tetraacetate oxidation of the corresponding 4-carboxyl derivative.[9] Very recently Easton and Love reported the direct introduction of a benzoyloxy function at C-4 of N-alkyl and N-aryl β-lactams[10] and this paper prompts us to report our results on the synthesis of β-lactams that have acetyloxy substituents both at the C-4 and N-1 positions.

To our knowledge the introduction of an acetyloxy function in the 4-position of β-lactams having a hetero substituent at N-1 has not been reported. We have recently described a novel synthesis of 1-(acetyloxy)-2-azetidinones starting from four-membered cyclic nitrones or 1-hydroxyazetidines via oxidation by lead tetraacetate.[11,18] Since Ojima et al.[13] have reported that monocyclic β-lactams can be reduced to the corresponding azetidines we have examined the possibility to introduce an acetyloxy function at C-4 of 1-(benzyloxy)-2-azetidinones via 1-hydroxyazetidines. However, reduction of 1-hydroxy-3,3-dimethyl-2-azetidinone with a mixture of $AlCl_3$ and $LiAlH_4$ gave mixtures of products

possibly due to chelation of the hydroxamic acid function with $Al^{3+}$.[14] In order to circumvent this problem we started from 1-hydroxy-2-azetidinones in which the hydroxyl function had been protected with a benzyl group because it was known from our previous work that the benzyl group in 1-(benzyloxy)azetidines can be removed without cleavage of the N-O bond.[18] The 1-benzyloxy β-lactams **4a-d** were prepared from the corresponding 3-halopropionyl chlorides with O-benzylhydroxylamine and subsequent cyclization of the resulting hydroxamic acids in pyridine.[14,15] The β-lactams **4e** and **4f** were synthesized in 42% and 98% yields, respectively, by cyclization of the corresponding N-(benzyloxy)-propanamides **3e** and **3f** with sodium hydride in DMF. These novel β-lactams were characterized by ir [1780 (C=O) $cm^{-1}$] and $^{13}C$-nmr spectroscopy [ δ 164.4 (s, C=O)]. Debenzylation of the β-lactams **4e** and **4f** by hydrogenation according to literature procedures,[14] afforded the 1-hydroxy-2-azetidinones **5e** and **5f**, respectively, in nearly quantitative yields. Compound **5e** was isolated as a crystalline product, which undergoes slow decomposition at room temperature and β-lactam **5f** was obtained as a red-coloured oil, which decomposes at room temperature within a few days.

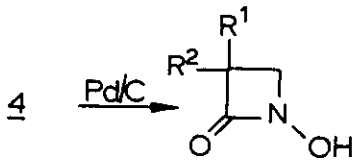



4 6

a. $R^1 = R^2$ = Me (95%) d. $R^1 = R^2$ = Ph (86%)

b. $R^1 = R^2$ = Et (72%) e. $R^1 = R^2$ = H (98%)

c. $R^1 = R^2$ = nBu (70%) f. $R^1$ = H; $R^2$ = Me (67%)

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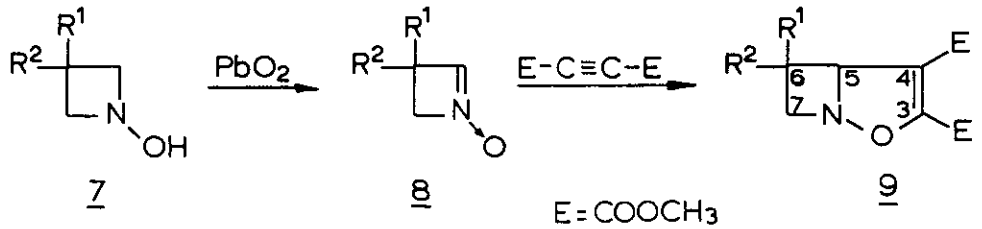
Reaction of the 1-(benzyloxy)-2-azetidinones **4a-f** with a $LiAlH_4/AlCl_3$ suspension in refluxing diethyl ether or tetrahydrofuran for 2.5 h gave the corresponding 1-(benzyloxy)azetidines **6a-f** in good yields. The azetidines **6** were characterized on the basis of $^1H$-nmr and $^{13}C$-nmr spectroscopy and mass spectrometry by comparison of these data with those of **6a**.[18] The azetidines **6a-c**, **6e** and **6f** were isolated as oils which were purified by distillation under reduced pressure. These results show that the monochloroalane reduction can indeed be used for the reduction of 1-(benzyloxy) 2-azetidinones to the corresponding 1-(benzyloxy)azetidines without cleavage of the N-O bond. Although 1-oxy-2-azetidinones are more sensitive towards nucleophilic ring opening than simple β-lactams [12,16] and the $LiAlH_4$ reduction of N-benzyloxy compounds is reported to give deoxygenation [17], this does not occur with this mild reducing agent.

The 1-(benzyloxy)azetidines **6a-d** were debenzylated by hydrogenation in acetic acid (Pd/C)[18], affording the 1-hydroxyazetidines **7a-d** in good to moderate yields. The

1-hydroxy-3,3-dimethylazetidine (**7a**) was identical with an independently prepared sample[18] and the azetidines **7b-d** were characterized by comparison of their spectral data with those of **7a**. We were not able to isolate 1-hydroxyazetidine (**7e**) and 1-hydroxy-3-methylazetidine (**7f**) and $^1$H nmr spectroscopy of the crude reaction mixtures clearly showed that only partial debenzylation of the starting material took place.
Oxidation of the hydroxyazetidines **7b** and **7c** with freshly prepared "active $PbO_2$" [19] gave the four-membered cyclic nitrones **8b** and **8c**, respectively. The nitrones **8b** and **8c** show a characteristic singlet for the C-4 proton in the $^1$H-nmr spectra at $\delta$ 6.8 and were further characterized as the corresponding 1,3-dipolar cycloadducts with dimethyl acetylenedicarboxylate. The cycloadducts **9b** and **9c** show in the $^1$H-nmr spectra a triplet [$\delta$ 4.87 ($J$ = 1 Hz, HC-4)] and an AB pattern [$\delta$ 3.79 and 3.62, (dAB, $J$ = 1 and 10 Hz, 2H, HC-7)] and in the $^{13}$C-nmr spectra absorptions at $\delta$ 163.0 and 159.6 (C=O), 154.0 (C-3) and 108.1 (C-4). Oxidation of hydroxyazetidine **7d** afforded **8d** as a crystalline compound in 59% yield. On the basis of the $^1$H-nmr spectrum [$\delta$ 7.46 (s, 1H, HC-4)], $^{13}$C-nmr spectrum [$\delta$ 142.9 (d, C-4)] and ms [m/z 223.100 ($M^+$, calcd, 223.100)], we assigned the nitrone structure to compound **8d**. Additional proof was obtained by the reduction of **8d** with $NaBH_4$ in methanol, affording 1-hydroxyazetidine **7d** in 80% yield.

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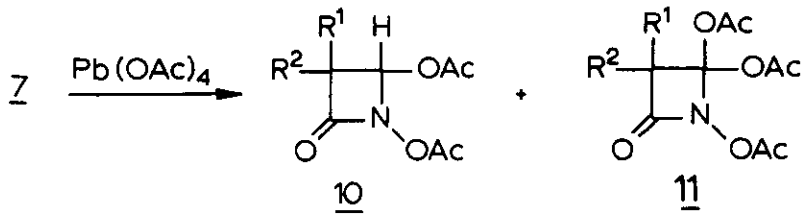


10 11

| 7 | ratio 10/11 | yield (%) |
|---|---|---|
| a. | 60/40 | 59 |
| b. | 100/0 | 46 |
| c. | 100/0 | 42 |
| d. | 100/0 | 50 |

Oxidation of **7a** with 3.3 equivalents of lead tetraacetate afforded a mixture of 1,4-bis(acetyloxy)-2-azetidinone **10a** and 1,4,4-tris(acetyloxy)-2-azetidinone **11a** in a ratio of 3 to 2.[18] However, when the hydroxyazetidines **7b-d** were oxidized with 3.3 equivalents of lead tetraacetate the 1,4-bis(acetyloxy)-2-azetidinones **10b-d** were isolated as the only products. On the basis of three absorptions in the ir spectra (C=O, OAc and NOAc), the

presence of a singlet at low field (1H, HC-4) and two singlets at δ 2.0 ± 0.2 (3H, $COCH_3$) in the $^1$H-nmr spectra and three absorptions in the $^{13}$C-nmr spectra (C=O, OAc and NOAc), we assigned the 1,4-bis(acetyloxy) β-lactam structures **10** to the reaction products.
The introduction of an acetyloxy function at C-4 of these β-lactams is clearly influenced by the substituents in the C-3 position. According to CPK-models the increase in steric hindrance around C-4, when replacing the methyl substituents at C-3 by ethyl, butyl, or phenyl substituents, prevents the introduction of a second acetyloxy function at C-4.

In conclusion we have demonstrated that the use of the monochloroalane reduction followed by lead tetraacetate oxidation of the resulting 1-hydroxyazetidines, enables the introduction of an acetyloxy function at C-4 of 1-oxy-2-azetidinones.

## EXPERIMENTAL

Mps were determined with a Reichert melting point apparatus and are uncorrected. $^1$H-nmr and $^{13}$C-nmr spectra ($CDCl_3$) were recorded with a Bruker WP-80 and a Nicolet MT 200 spectrometer, respectively, with tetramethylsilane as an internal standard. Mass spectra were obtained with a Varian Mat 311A spectrometer. Ir spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by E. Hoogendam of the Laboratory of Chemical Analysis of the Twente University of Technology.
Materials. $LiAlH_4$ (Merck), $AlCl_3$ (Merck), NaH (80% dispersion; Fluka AG), dimethyl acetylenedicarboxylate (Merck) and lead tetraacetate (Merck) are commercially available. Lead tetraacetate was washed with diethyl ether immediately before use to remove the acetic acid. Petroleum ether refers to the fraction boiling at 40-60 °C and glacial acetic acid refers to $CuSO_4$-dried acetic acid.

**N-(Benzyloxy)-3-chloropropanamide (3e).** To a suspension of $HCl.H_2NOBz$ (5.04 g; 31.6 mmol) in dry $CH_2Cl_2$ (80 ml) was added dry triethylamine (6.48 g; 64 mmol), after which a soln of 3-chloropropionyl chloride (4.0 g; 31.6 mmol) in dry $CH_2Cl_2$ (20 ml) was added dropwise at 0 °C. After being stirred for an additional 2 h at room temperature, the reaction mixture was filtered, the organic layer washed twice with water (30 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure, leaving an oil which solidified on rubbing. Trituration with a mixture of ethyl acetate and hexane (1:1) gave **3e** as a white solid. Yield 67%; mp 87 - 88 °C ($CHCl_3$/petroleum ether); ir (KBr): 1660 (C=O) $cm^{-1}$; $^1$H-nmr δ: 8.95 (bs, 1H, NH), 7.37 (s, 5H, PhH), 4.88 (s, 2H, $CH_2Ph$), 3.74 (t, J = 6.8 Hz, 2H, $CH_2Cl$), 2.7-2.3 (m, 2H, $CH_2CO$); $^{13}$C-nmr δ: 167.3 (s, C=O), 78.3 (t, $CH_2Ph$), 39.6 (t, $COCH_2$), 36.4 (t, $CH_2Cl$); ms, m/z 213.054 ($M^+$, calc.: 213.055); Anal. Calc. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 55.83; H, 5.92; N, 6.30.

**N-(Benzyloxy)-3-bromo-2-methylpropanamide (3f).** A soln of $H_2NOBz$ [21] (19.4 g; 157.7 mmol) in dry pyridine (180 ml) was cooled to 0 °C. 3-Bromo-2-methylpropionyl chloride [22] was added dropwise and the resulting mixture was stirred for 0.5 h at 0 °C. After being stirred for 2 h at room temperature, water (150 ml) was added and the reaction mixture was acidified to pH 4 with concentrated HCl and extracted with $CH_2Cl_2$ (3 x 70 ml). The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure, to *give an oil which solidified on rubbing. Trituration with diisopropyl ether gave pure* **3f.** Yield 59%; mp 123-124 °C ($CHCl_3$/petroleum ether); ir (KBr): 1660 (C=O) $cm^{-1}$; $^1$H-nmr δ: 7.70 (bs, 1H, NH), 7.38 (s, 5H, PhH), 4.92 (s, 2H, $CH_2Ph$), 3.59 and 3.31 (dAB, $J_{AB}$ = 10.0

Hz, $J_{vicinal}$ = 8.5 and 5.6 Hz, 2H, $CH_2Br$), 2.8-2.3 (m, 1H, $CHCH_3$), 1.21 (d, $J$ = 6.8 Hz, 3H, $CH_3$); $^{13}$C-nmr δ: 171.0 (s, C=O), 78.6 (t, $CH_2Ph$), 41.2 (d, CH), 33.8 (t, $CH_2Br$), 17.1 (q, $CH_3$); ms, m/z 254.018 [$(M-OH)^+$, calc. for $C_{11}H_{13}{}^{79}BrNO$: 254.018]. Anal. Calc. for $C_{11}H_{14}{}^{79}BrNO_2$: C, 48.54; H, 5.19; N, 5.15. Found: C, 48.10; H, 5.17; N, 4.75.

**1-(Benzyloxy)-2-azetidinone (4e).** To a suspension of NaH (0.40 g; 16.7 mmol) in dry DMF (12 ml) was added dropwise a soln of compound **3e** (2.94 g; 13.8 mmol) in dry DMF (5 ml) at 0 °C. The suspension was stirred for 18 h at 60 °C. Water (50 ml) was carefully added and the resulting mixture was extracted with ethyl acetate (3 x 30 ml). The organic layers were washed with brine (3 x 20 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (first pentane to remove the oil of the NaH suspension, then $CHCl_3$) to give the crude β-lactam, which could be further purified by distillation. Yield 42%; bp 85 °C (0.1 mm); $n_D^{20}$ 1.5372; ir (NaCl): 1780 (C=O) $cm^{-1}$; $^1$H-nmr δ: 7.39 (s, 5H, PhH), 4.94 (s, 2H, $CH_2Ph$), 3.24 (t, $J$ = 4.2 Hz, 2H, $NCH_2$), 2.61 (t, $J$ = 4.2 Hz, 2H, $COCH_2$); $^{13}$C-nmr δ: 167.4 (s, C=O), 78.3 (t, $CH_2Ph$), 39.7 (t, $NCH_2$), 36.2 (t, $COCH_2$); ms, m/z 177.080 ($M^+$, calc. for $C_{10}H_{11}NO_2$: 177.079).

**1-(Benzyloxy)-3-methyl-2-azetidinone (4f).** To a suspension of NaH (2.65 g; 110 mmol) in dry DMF (100 ml) was added dropwise a soln of compound **3f** (22.7 g; 84 mmol) in dry DMF (58 ml). The resulting mixture was stirred for an additional 18 h at 70 °C. The reaction mixture was worked up essentially the same as described for compound **4e**. Yield 98%; bp (kugelrohr) ± 75 °C (0.1 mm); $n_D^{20}$ 1.5300; ir (KBr): 1775 (C=O) $cm^{-1}$; $^1$H-nmr δ: 7.45-7.35 (m, 5H, PhH), 4.94 (s, 2H, $CH_2Ph$), 3.4-3.35 (m, 1H, HC-4), 2.9-2.8 (m, 1H, HC-4), 2.86 (dq, $J$ = 2.1 and 6.8 Hz, 1H, HC-3), 1.21 (d, $J$ = 6.8 Hz, 3H, $CH_3$); $^{13}$C-nmr δ: 167.2 (s, C=O), 77.4 (t, $CH_2Ph$), 52.9 (t, $NCH_2$), 39.6 (d, CH), 13.3 (q, $CH_3$); ms, m/z 191.096 ($M^+$, calc. for $C_{11}H_{13}NO_2$: 191.095).

**1-Hydroxy-2-azetidinone (5e).** A soln of compound **4e** (1.78 g; 10 mmol) in MeOH (40 ml) was hydrogenated at an atmospheric pressure in the presence of Pd/C (10%) to give compound **5e** in 86% yield, after trituration with diisopropyl ether. Mp 73-74 °C ($CHCl_3$/petroleum ether); ir (KBr): 1750 (C=O) $cm^{-1}$; $^1$H-nmr δ: 8.66 (bs, 1H, OH), 3.60 (t, $J$ = 3.4 Hz, 2H, $CH_2N$), 2.72 (t, $J$ = 3.4 Hz, 2H, $COCH_2$); ms, m/z 87.032 ($M^+$, calc. for $C_3H_5NO_2$: 87.032).

**1-Hydroxy-3-methyl-2-azetidinone (5f).** A soln of compound **4f** (0.95 g; 5 mmol) in MeOH (20 ml) was hydrogenated at an atmospheric pressure in the presence of Pd/C (10%) to give compound **5f**, which could not be purified (according to $^1$H-nmr the yield is about 80%). Ir (KBr): 1750 (C=O) $cm^{-1}$; $^1$H-nmr δ: 7.80 (bs, 1H, OH), 3.8-2.9 (m, 3H, HC-3 and HC-4), 1.30 (d, $J$ = 7.1 Hz, 3H, $CH_3$); ms, m/z 101.047 ($M^+$, calc. for $C_4H_7NO_2$: 101.048).

**Reduction of 1-(benzyloxy)-2-azetidinones 4.** A mixture of $AlCl_3$ (22.27 g; 167 mmol) and $LiAlH_4$ (6.53 g; 172 mmol) in dry diethyl ether (380 ml) was refluxed for 30 min with stirring. To the monochloroalane soln, thus prepared, was added dropwise a soln of β-lactam **4** (34 mmol) in dry diethyl ether or tetrahydrofuran (70 ml). The resulting mixture was refluxed an additional 2 h, then cooled to 0 °C and water (80 ml) was added carefully. The organic layer was separated and the water-layer extracted with $CH_2Cl_2$ (3 x 100 ml). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated

under reduced pressure. Purification by silica gel column chromatography (eluent $CH_2Cl_2$) gave pure **6**.

**1-(Benzyloxy)-3,3-dimethylazetidine (6a) from 4a.** Yield 95%. See for spectroscopic data ref. 18.

**1-(Benzyloxy)-3,3-diethylazetidine (6b) from 4b.** Yield 72%; $^1$H-nmr δ: 7.31 (s, 5H, PhH), 4.62 (s, 2H, $CH_2Ph$), 3.32 (bs, 4H, $NCH_2$), 1.54 (bq, J = 7.3 Hz, 4H, $C\underline{H}_2CH_3$), 0.78 (t, J = 7.1 Hz, 6H, $CH_3$). $^{13}$C-nmr δ: 74.7 (t, $CH_2Ph$), 67.3 (t, $NCH_2$), 35.8 (s, C-3), 29.8 and 27.8 (t, $\underline{C}H_2CH_3$), 8.5 (q, $CH_3$); ms, m/z 219.162 ($M^+$, calc.: 219.162). **6b.HCl**; mp 103 - 105 °C ($CHCl_3$/petroleum ether); Anal. Calc. for $C_{14}H_{21}NO.HCl$: C, 65.78; H, 8.61; N, 5.48. Found: C, 65.45; H, 8.98; N, 5.32.

**1-(Benzyloxy)-3,3-dibutylazetidine (6c) from 4c.** Yield 70%; bp 118-120 °C (0.3 mm); $n_D^{20}$ 1.4927; $^1$H-nmr δ: 7.31 (s, 5H, PhH), 4.62 (s, 2H, $CH_2Ph$), 3.32 (bs, 4H, $NCH_2$), 1.6-1.1 (m, 12H, $-(CH_2)_3-$), 0.89 (t, J = 5.4 Hz, 6H, $CH_3$); $^{13}$C-nmr δ: 74.7 (t, $CH_2Ph$), 68.2 (t, $NCH_2$), 37.9 and 35.9 (bt, $\underline{C}H_2$C-3), 34.9 (s, C-3), 14.1 (q, $CH_3$); ms, m/z 275.227 ($M^+$, calc. for $C_{18}H_{29}NO$: 275.225).

**1-(Benzyloxy)-3,3-diphenylazetidine (6d) from 4d.** Yield 86%; mp 53-55 °C ($CHCl_3$ /petroleum ether); $^1$H-nmr δ: 7.2-7.1 (m, 15H, PhH), 4.57 (s, 2H, $CH_2Ph$), 4.05 (bs, 4H, $NCH_2$); $^{13}$C-nmr δ: 75.0 (t, $CH_2Ph$), 70.5 (t, $NCH_2$), 44.2 (s, C-3); ms, m/z 315.164 ($M^+$, calc. for $C_{22}H_{21}NO$: 315.162). Anal. Calc. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.85; H, 7.06; N, 3.96.

**1-(Benzyloxy)azetidine (6e) from 4e.** Yield 98%; bp (kugelrohr) ± 65 °C (0.02 mm); $n_D^{20}$ 1.5182; $^1$H-nmr (40 °C) δ: 7.28 (s, 5H, PhH), 4.61 (s, 2H, $CH_2Ph$), 3.48 (t, J = 7.1 Hz, 4H, $NCH_2$), 1.78 (quint, J = 7.1 Hz, 2H, $CH_2$); $^{13}$C-nmr δ: 74.6 (t, $CH_2Ph$), 59.5 (t, $NCH_2$), 13.3 (t, $CH_2$); ms, m/z 163.101 ($M^+$, calc. for $C_{10}H_{13}NO$: 163.100).

**1-(Benzyloxy)-3-methylazetidine (6f) from 4f.** Yield 67%; bp (kugelrohr) 80 °C (0.1 mm); $n_D^{25}$ 1.5072; $^1$H-nmr δ: 7.27 (s, 5H, PhH), 4.61 (s, 2H, $CH_2Ph$), 3.69 (dt, J = 6.8 and 2.1 Hz, 2H, $NCH_2$), 3.00 (dt, J = 6.8 and 2.1 Hz, 2H, $NCH_2$), 2.18 (octet, J = 6.8 Hz, 1H, HC-3); $^{13}$C-nmr δ: 74.8 (t, $CH_2Ph$), 66.5 (t, $NCH_2$), 22.0 (d, CH), 19.0 (q, $CH_3$); ms, m/z 177.115 ($M^+$, calc. for $C_{11}H_{15}NO$: 177.115).

**Debenzylation of 1-(benzyloxy)azetidines 6.** A soln of the azetidine **6** (4.1 mmol) in glacial acetic acid (20 ml) was hydrogenated at an atmospheric pressure in the presence of 0.1 g Pd/C (5%). After no more hydrogen was taken up, the reaction mixture was filtered over hyflo and the acetic acid removed under reduced pressure at 30 °C. The residue was neutralized with a saturated aqueous $NaHCO_3$ soln and extracted with $CHCl_3$ (3 x 40 ml). The combined extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting 1-hydroxyazetidines **7** were purified either by distillation or by trituration.

**3,3-Diethyl-1-hydroxyazetidine (7b) from 6b.** Yield 62%; bp (kugelrohr) 70 °C (3 mm); $n_D^{20}$ 1.4560; $^1$H-nmr δ: 7.99 (bs, 1H, OH), 3.45 and 3.26 (bAB, 4H, $NCH_2$), 1.54 (bq, J = 7.3 Hz, 4H, $C\underline{H}_2CH_3$), 0.80 (bt, J = 7.3 Hz, 6H, $CH_3$); $^{13}$C-nmr δ: 35.4 (s, C-3), 30.0 and 27.6 (t, $\underline{C}H_2CH_3$), 8.7 and 8.3 (q, $CH_3$); ms, m/z 129.115 ($M^+$, calc. for $C_7H_{15}NO$: 129.115).

**3,3-Dibutyl-1-hydroxyazetidine (7c) from 6c.** Yield 70%; bp (kugelrohr) ± 110 °C (0.5 mm); $n_D^{20}$ 1.4572; $^1$H-nmr δ: 8.47 (bs, 1H, OH), 3.65-3.0 (bAB, 4H, $NCH_2$), 1.6-1.3 (m, 12H, $-(CH_2)_3-$), 0.90 (t, J = 5.6 Hz, 6H, $CH_3$); $^{13}$C-nmr δ: 69.3 (t, $NCH_2$), 37.9 and 35.4 (t, $\underline{C}H_2C$-3), 34.6 (s, C-3), 14.1 (q, $CH_3$); ms, m/z 185.178 ($M^+$, calc. for $C_{11}H_{23}NO$: 185.178).

**1-Hydroxy-3,3-diphenylazetidine (7d) from 6d.** Yield 80%; mp 118-120 °C ($CHCl_3$/petroleum ether); $^1$H-nmr δ: 7.3-7.2 (m, 10H, PhH), 6.15 (bs, 1H, OH), 4.34 and 4.09 (bAB, J = 6.8 Hz, 4H, $NCH_2$); $^{13}$C-nmr δ: 70.9 (t, $NCH_2$), 43.8 (s, C-3); ms, m/z 225.115 ($M^+$, calc.: 225.115); Anal. Calc. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.89; H, 6.61; N, 6.15.

**Oxidation of 1-hydroxyazetidines 7 with lead(IV) oxide.** 1-Hydroxyazetidine **7** (1.9 mmol) was added to a suspension of $PbO_2$ (0.57 g; 2.38 mmol) in dry $CH_2Cl_2$ (10 ml). After being stirred for 45 min, $MgSO_4$ was added and the resulting mixture was filtered over hyflo. The solvent was removed under reduced pressure to give the nitrones **8**.

**3,3-Diethyl-2,3-dihydroazete 1-oxide (8b).** Yield according to $^1$H-nmr about 80%; (unstable oil); $^1$H-nmr δ: 6.92 (s, 1H, =CH), 3.99 (s, 2H, $NCH_2$), 1.73 and 1.71 (q, J = 7.3 Hz, 4H, $C\underline{H}_2CH_3$), 0.96 (t, J = 7.3 Hz, 6H, $CH_2C\underline{H}_3$).

**3,3-Dibutyl-2,3-dihydroazete 1-oxide (8c).** Yield according to $^1$H-nmr about 80%; (unstable oil); $^1$H-nmr δ: 6.87 (s, 1H, =CH), 3.97 (s, 2H, $NCH_2$), 1.8-1.1 (m, 12H, $-(CH_2)_3-$), 0.92 (t, J = 7 Hz, 6H, $CH_3$).

**2,3-Dihydro-3,3-diphenylazete 1-oxide (8d).** Yield 59%; mp 130-132 °C ($CHCl_3$/petroleum ether); $^1$H-nmr δ: 7.46 (s, 1H, =CH), 7.3-7.1 (m, 10H, PhH), 4.76 (s, 2H, $NCH_2$); $^{13}$C-nmr δ: 142.9 (d, =CH), 77.6 (t, $NCH_2$), 48.6 (s, C-3); ms, m/z 223.100 ($M^+$, calc.: 223.100); m/z 193.089 [$(M - CH_2O)^+$ 20; calc. for $C_{14}H_{11}N$: 193.089]; Anal. Calc. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.44; H, 6.22; N, 6.12.

**Characterization of nitrones 8: synthesis of dimethyl 6,6-disubstituted 2-oxa-1-aza bicyclo[3.2.0]hept-3-ene-3,4-dicarboxylates 9.** The crude **8** (1.9 mmol) was dissolved in dry $CH_2Cl_2$ (5 ml) and reacted with dimethyl acetylenedicarboxylate (227 mg; 1.6 mmol) at 0 °C for 30 min after which the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and passed through a small Florisil column, to give pure **9** after removal of the solvent under reduced pressure.

**Dimethyl 6,6-diethyl-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4-dicarboxylate (9b) from 7b.** Yield 42%; ir (KBr): 1758 (C=O) and 1720 (C=O) $cm^{-1}$; $^1$H-nmr δ: 4.87 (t, J = 1 Hz, 1H, H-5), 3.80 and 3.63 (dAB, J = 1 and 10 Hz, 2H, H-7), 3.91 and 3.74 (s, 3H, $COOCH_3$), 1.8-1.4 (m, 4H, $C\underline{H}_2CH_3$), 0.94 and 0.72 (t, J = 7.3 Hz, 3H, $CH_3$); $^{13}$C-nmr δ: 163.0 and 159.5 (s, C=O), 154.2 (s, C-3), 108.1 (s, C-4), 79.2 (d, C-5), 69.2 (t, C-7), 53.4 (s, C-6), 28.3 and 24.3 (t, $\underline{C}H_2CH_3$), 8.4 and 7.5 (q, $CH_3$); ms: m/z 269.126 ($M^+$, calc. for $C_{13}H_{19}NO_5$: 269.126).

**Dimethyl 6,6-dibutyl-2-oxa-1-azabicyclo[3.2.0]hept-3-ene-3,4-dicarboxylate (9c) from 7c.** Yield 28%; $^1$H-nmr δ: 4.87 (t, J = 1 Hz, H-5), 3.79 and 3.62 (dAB, J = 1 and 10 Hz, 2H, H-7), 1.8-0.8 (m, 18H, $-(CH_2)_3-CH_3$); $^{13}$C-nmr δ: 163.0 and 159.6 (s, C=O), 154.0 (s, C-3), 108.1 (s, C-4), 79.9 (d, C-5), 70.7 (t, C-7), 46.5 (s, C-6); ms: m/z 325.188 ($M^+$, calc. for $C_{17}H_{27}NO_5$: 325.189).

**1-Hydroxy-3,3-diphenylazetidine (7d) from 8d.** To a soln of compound **8d** (0.22 g; 0.98 mmol) in dry MeOH (10 ml) was added 0.15 g (3.92 mmol) of $NaBH_4$. The resulting mixture was stirred for 2.5 h at room temperature after which water (30 ml) was added. The reaction mixture was extracted with $CHCl_3$ (3 x 40 ml), the organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Trituration [diisopropyl ether /hexane (1:2)] gave pure **7d** in 80% yield.

**Oxidation of 1-hydroxyazetidines 7 with lead tetraacetate.** A soln of the 1-hydroxy azetidine 7 (3 mmol) in dry toluene (5 ml) was added to a stirred soln of lead tetra acetate (4.43 g; 10 mmol) in dry toluene (40 ml), at 0 °C in an atmosphere of dry $N_2$. After being stirred for 30 min, the mixture was filtered over hyflo and the filtrate was washed with brine (2 x 10 ml). The organic layer was dried and filtered and the solvent was removed under reduced pressure. In the case of **7b** and **7c**, the resulting oil could be purified by silica gel column chromatography with $CHCl_3$ as eluent.

**1,4-Bis(acetyloxy)-3,3-diethyl-2-azetidinone (10b).** Yield 46%; ir (KBr): 1818 (NOAc), 1785 (C=O), 1765 (OAc) $cm^{-1}$; $^1$H-nmr δ: 6.04 (s, 1H, HC-4), 2.17 and 2.14 (s, 3H, $COCH_3$), 1.9-1.7 (m, 4H, $CH_2CH_3$), 1.04 and 1.03 (t, J = 7.5 Hz, 6H, $CH_3$); $^{13}$C-nmr δ: 170.3, 167.9 and 167.8 (C=O), 86.0 (d, C-4), 59.5 (s, C-3), 24.4 and 21.5 (t, $CH_2CH_3$), 20.8 and 17.9 (q, $COCH_3$), 8.9 and 8.5 (q, $CH_3$); ms, m/z 243.112 ($M^+$, calc. for $C_{11}H_{17}NO_5$: 243.111).

**1,4-Bis(acetyloxy)-3,3-dibutyl-2-azetidinone (10c).** Yield 42%; (slightly coloured oil); ir (KBr): 1818 (NOAc), 1785 (C=O) and 1750 (OAc) $cm^{-1}$; $^1$H-nmr δ: 6.02 (s, 1H, HC-4), 2.16 and 2.13 (s, 6H, $COCH_3$), 1.9-1.1 (m, 12H, $-(CH_2)_3-$), 0.92 (m, 6H, $CH_3$); $^{13}$C-nmr δ: 170.3, 168.1 and 167.8 (s, C=O), 86.2 (d, C-4), 58.6 (s, C-3), 20.8 and 17.9 (q, $COCH_3$); ms, m/z 299.164 ($M^+$, calc. for $C_{15}H_{15}NO_5$: 299.173).

**1,4-Bis(acetyloxy)-3,3-diphenyl-2-azetidinone (10d).** Yield 50%; (semi solid); ir (KBr): 1818 (NOAc), 1786 (C=O), 1752 (OAc) $cm^{-1}$; $^1$H-nmr δ: 7.8-7.4 (m, 5H, PhH), 7.3-7.2 (m, 5H, PhH), 6.84 (s, 1H, HC-4), 2.14 and 1.78 (s, 6H, $COCH_3$). $^{13}$C-nmr δ: 169.8, 167.2 and 164.2 (s, C=O), 87.2 (d, C-4), 68.7 (s, C-3), 20.3 and 17.8 (q, $CH_3$); ms, m/z 339.106 ($M^+$, calc. for $C_{19}H_{17}NO_5$: 339.111).

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