Tetrahedron Letters,Vol.26,No.23,pp 2809-2812,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain 

# 1,4-DIACETOXY-β-LACTAMS. REACTIONS WITH NUCLEOPHILES

P.A. van Elburg,[a] D.N. Reinhoudt,[a*] S. Harkema[b] and G.J. van Hummel[b]

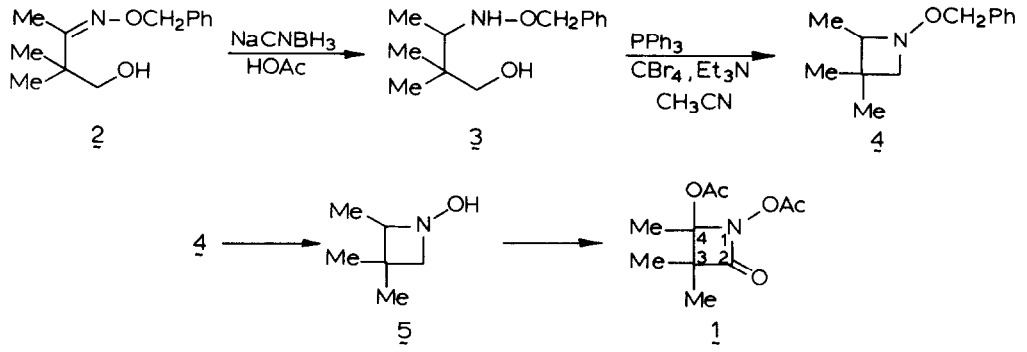
Laboratories of Organic Chemistry[a] and Chemical Physics,[b] Twente University of Technology, Enschede, The Netherlands

Abstract. β-Lactam 1 reacts with hetero nucleophiles under ring cleavage to give 2,2-dimethyl-3-oximinobutanoic esters 6 and 7. N-hydroxyazetidine 5, the precursor of β-lactam 1, is prepared by a new method.

As part of our work on four-membered cyclic nitrones we have recently reported that 1-hydroxyazetidine 5 can be oxidized with lead tetraacetate to 1,4-diacetoxy-3,3,4-trimethyl-2-azetidinone (1).[1] 4-Acetoxy-2-azetidinones have been widely used in β-lactam chemistry[2] and 1-hydroxy-2-azetidinones have recently received much attention after the discovery of the biologically active monocyclic β-lactams.[3]

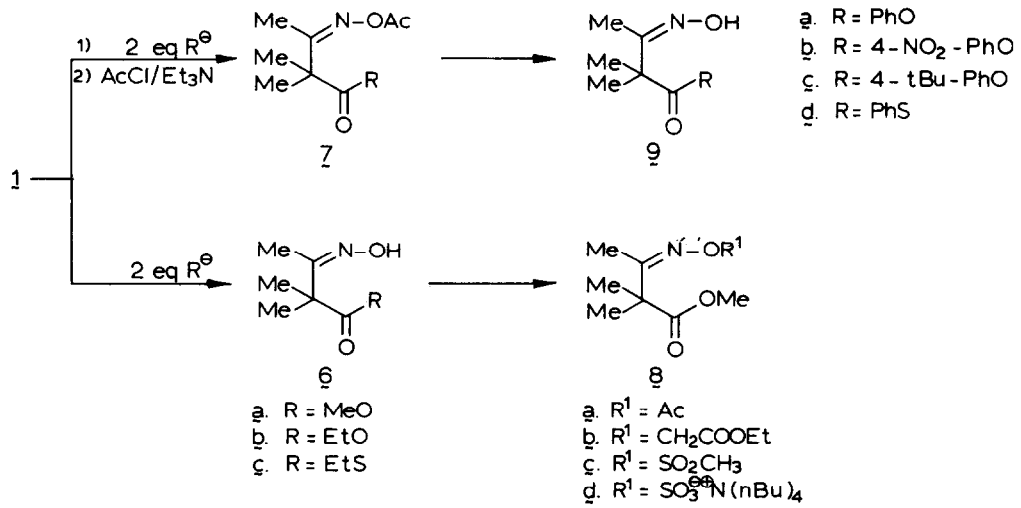
Previously we have shown that the ester function in N,N-diethyl-1-(acetoxy)-4-methyl-3-phenyl-2-azetidinone-4-carboxamide[4] can be saponified with sodium methoxide in diethyl ether without ring opening of the β-lactam. Therefore we have investigated reactions of β-lactam 1 with two equivalents of nucleophile as a possible route to 4-substituted 1-hydroxy-2-azetidinones.

1-Hydroxyazetidines can be synthesized by reductive cyclization of O-benzyl-β-tosyloxy oximes.[1] The disadvantage of this method is the possibility of β-elimination of the leaving group and therefore we have developed an alternative method. Recently Sammes and Smith reported the synthesis of N-substituted azetidines by cyclization of γ-hydroxyamines.[5] We found that the same type of reaction can be used for the cyclization of hydroxylamine derivatives (Scheme I). Reaction of 3,3-dimethyl-4-hydroxy-2-butanone[1] with O-benzylhydroxylamine afforded the oxime 2 in a yield of 79% [bp 86-88 °C/0.1 mm Hg; $n_D^{22}$ 1.5148; $^{13}$C-NMR ($CDCl_3$) δ 163.1 (s, C=N), 70.1 (t, $CH_2OH$); MS: $(M - OH)^+$ 204.138 ($C_{13}H_{18}NO$)]. Reduction of oxime 2 with $NaCNBH_3$ in acetic acid afforded the hydroxylamine 3 in a yield of 79% [bp 98-100 °C/0.07 mm Hg; $n_D^{22}$ 1.5022; $^1$H-NMR ($CDCl_3$) δ 4.48 (bs, 2H, NH and OH), 3.38 (s, 2H, $CH_2OH$); $^{13}$C-NMR ($CDCl_3$) δ 72.6 (t, $CH_2OH$); MS: $M^+$ 223.156 ($C_{13}H_{21}NO_2$)]. The cyclization of compound 3 to 1-benzyloxyazetidine 4 was achieved in a yield of 75% by the addition of carbon tetrabromide and triethylamine to a solution of triphenylphosphine and hydroxylamine 3 in acetonitrile, followed by further reaction at room temperature for 4h. Catalytic debenzylation of the azetidine 4 and subsequent oxidation of the resulting 1-hydroxyazetidine 5 to the 1,4-diacetoxy-2-azetidinone 1 were carried out as described previously.[1]



Scheme I

Reaction of 1,4-diacetoxy-β-lactam 1 with two equivalents of sodium methoxide, at 0 °C in diethyl ether, afforded 3-hydroximino-2,2-dimethylbutanoic acid methyl ester (6a)[7] (Scheme II) [yield 47%; mp 59-60 °C (petroleum ether bp 40-60 °C); $^1$H-NMR ($CDCl_3$) δ 8.70 (bs, 1H, OH), 3.70 (s, 3H, $OCH_3$); $^{13}$C-NMR ($CDCl_3$) δ 175.3 (s, C=O), 159.3 (s, C=N); IR (KBr) 1740 (C=O), 1670 (C=N) $cm^{-1}$; MS: $M^+$ 159.090 ($C_7H_{13}NO_3$)]. The structure and stereochemistry were proven by X-ray analysis (Fig. I). From this figure it can be concluded that compound 6a has the E-configuration. Crystal data: $C_7H_{13}NO_3$; monoclinic; space group $P2_1/c$, a = 7.521 (1), b = 20.122 (2), c = 11.529 (1) Å, β = 94.47 (1)°, Z = 8. Structure determination based on 2631 reflections (Mo Kα radiation, graphite monochromator) with intensity greater than the standard deviation from counting statistics. The structure was solved by direct methods and refined with full matrix least squares to a final R-factor of 4.5%.[8a] Parameters refined: scale factor, extinction parameter, positional and thermal (isotropic for hydrogen atoms, anisotropic for others) parameters.[8b] All hydrogen atoms have been found from a difference Fourier synthesis.



Scheme II

Similar reactions with two equivalents of sodium ethoxide and sodium thioethoxide gave the oximes 6b and 6c in yields of 47% and 52%, respectively.[6] Reaction of β-lactam 1 with sodium phenoxides and sodium thiophenoxides in aqueous acetone (1:1) resulted in a mixture of the acylated oximes 7 and the oximes 9. These compounds could not be separated but acylation of the crude product afforded the oximes 7a-d (Scheme II). Compound 7c[7] [yield 34%; mp 104-105 °C (petroleum ether bp 40-60 °C); $^1$H-NMR ($CDCl_3$) δ 2.21 (s, 3H, $OCH_3$); $^{13}$C-NMR ($CDCl_3$) δ 172.9 (s, C=O), 168.9 (s, $COCH_3$), 165.8 (s, C=N); IR (KBr) 1775 (OAc), 1754 (C=O), 1640 (C=N) cm$^{-1}$; MS: M$^+$ 319.175 ($C_{18}H_{25}NO_4$)]; compound 7d [yield 48%; oil; $^1$H-NMR ($CDCl_3$) δ 2.23 (s, 3H, $COCH_3$); $^{13}$C-NMR ($CDCl_3$) δ 184.1 (s, C=O), 169.0 (s, $COCH_3$), 165.6 (s, C=N); IR (NaCl) 1775 (OAc), 1700 (C=O), 1632 (C=N) cm$^{-1}$; MS: M$^+$ 279.091 ($C_{14}H_{17}NO_3S$)].

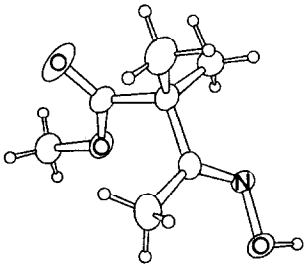


Fig.I View of 6a

Woulfe and Miller have reported that N-hydroxy-O-substituted β-lactams are usually more susceptible to nucleophilic attack at the β-lactam carbonyl moiety than the corresponding N-alkyl β-lactams.[3b] This increased reactivity was also found in the activity of monobactams,[3c] sulfactams[3a] and oxamazins.[3b] The enhanced susceptibility of 1,4-diacetoxy-2-azetidinone 1 to ring opening is illustrated by the difference in the reactivity of β-lactam 1 and 1-acetoxy-β-lactams with sodium carbonate in aqueous methanol. Reaction of β-lactam 1 resulted in the formation of oxime 6a, while the 1-acetoxy-2-azetidinones could be saponified to give the 1-hydroxy-β-lactams.[3b] A similar ring opening of β-lactams as shown in Scheme II has been reported by Page and Proctor in the reaction of cephalosporines with nucleophiles.[9]

The oximes 6 can be acylated with acetyl chloride and triethylamine. Acylation of oxime 6a afforded compound 8a as an oil in quantitative yield (Scheme II) [$^1$H-NMR ($CDCl_3$) δ 2.19 (s, 3H, $COCH_3$), 1.93 (s, 3H, $CH_3$-C=N); $^{13}$C-NMR ($CDCl_3$) δ 174.7 (s, C=O), 169.1 (s, $COCH_3$), 166.1 (s, C=N); IR (NaCl) 1795 (OAc), 1760 (C=O), 1660 (C=N) cm$^{-1}$; MS: M$^+$ 170.082 ($C_9H_{15}NO_4$)]. Catalytic deacylation of oximes 7a-d and 8a with Pd/C (5%) in ethanol afforded the oximes 9a-d and 6a, respectively, in high yields; oxime 9c: [mp 123-125 °C (diisopropyl ether); $^1$H-NMR ($CDCl_3$) δ 8.20 (bs, 1H, OH), 2.26 (s, 3H, $CH_3$-C=N); $^{13}$C-NMR ($CDCl_3$) δ 173.7 (s, C=O), 158.9 (s, C=N), 11.6 (q, $CH_3$-C=N); MS: M$^+$ 277.167 ($C_{16}H_{23}NO_3$)]. Besides acylation, oxime 6a could be alkylated and reacted with methanesulfonyl chloride and pyridine•$SO_3$. Oxime 6a was alkylated by ethyl bromoacetate in diethyl ether to give compound 8b (Scheme II) [yield 58%; oil; $^1$H-NMR ($CDCl_3$) δ 4.60 and 4.58 (s, 2H, $OCH_2CO$), 3.69 (s, 3H, $OCH_3$); MS: M$^+$ 245.127 ($C_{11}H_{19}NO_5$)]. Reaction of 6a with methanesulfonyl chloride afforded compound 8c [yield 88%; oil; $^1$H-NMR ($CDCl_3$) δ 3.72 (s, 3H, $OCH_3$), 3.12 (s, 3H, $SO_2CH_3$); IR (NaCl) 1750 (C=O), 1380 and 1200 ($OSO_2CH_3$) cm$^{-1}$] (Scheme II). Oxime 6a was reacted with pyridine•$SO_3$ in pyridine followed by treatment with tetrabutylammonium hydrogen sulfate to afford compound 8d as a thick colourless oil (Scheme II) [yield 65%; $^1$H-NMR ($CDCl_3$) δ 3.66 (s, 3H, $OCH_3$), 3.28 (t, J = 7.1 Hz, 8H, $NCH_2$); $^{13}$C-NMR ($CDCl_3$) δ 175.7 (s, C=O), 161.3 (s, C=N), 58.8 (t, $NCH_2$); IR (NaCl) 1782 (C=O) cm$^{-1}$].

The above results show that 1,4-diacetoxy-3,3,4-trimethyl-2-azetidinone (1) is much more susceptible to ring opening by nucleophiles than 4-acetoxy-2-azetidinones or 1-acetoxy-2-azetidinones.

Acknowledgement. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

## References and notes

1. M.L.M. Pennings and D.N. Reinhoudt, J. Org. Chem. 48, 4043 (1983).
2. K. Clauss, D. Grimm and G. Prossel, Liebigs Ann. Chem. 539 (1974); M.M. Campbell and B.P. Connarty, Heterocycles 19, 1853 (1982); T. Kobayashi, N. Ishido and T. Hiraoka, J. Chem. Soc., Chem. Commun. 736 (1980); M.D. Bachi and A. Gross, J. Chem. Soc., Perkin Trans. 1 1157 (1983); M. Ihara, A. Nakayama and K. Fukumoto, Tetrahedron 38, 2489 (1982); K. Clauss, H.J. Friedrich and H. Jensen, Liebigs Ann. Chem. 561 (1974); K. Hirai, Y. Iwano and K. Fujimoto, Tetrahedron Lett. 23, 4025 (1982); M. Aratani, K. Sawada and M. Hashimoto, Tetrahedron Lett. 23, 3921 (1982).
3. a) M.J. Miller, A. Biswas and M.A. Krook, Tetrahedron 39, 2571 (1983); b) S.R. Woulfe and M.J. Miller, Tetrahedron Lett. 25, 3293 (1984); c) C.M. Cimarusti, D.P. Bonner, H. Breuer, H.W. Chang, A.W. Fritz, D.M. Floyd, T.P. Kissick, W.H. Koster, D. Kronenthal, F. Massa, R.H. Mueller, J. Pluscec, W.A. Slusarchyk, R.B. Sykes, M. Taylor and E.R. Weaver, Tetrahedron 39, 2577 (1983); d) E.M. Gordon, M.A. Ondetti, J. Pluscec, C.M. Cimarusti, D.P. Bonner and R.B. Sykes, J. Am. Chem. Soc. 104, 6053 (1982); e) D.M. Floyd, A.W. Fritz, J. Pluscec, E.R. Weaver and C.M. Cimarusti, J. Org. Chem. 47, 5160 (1982); f) F.R. Atherton and R.W. Lambert, Tetrahedron 40, 1039 (1984).
4. M.L.M. Pennings and D.N. Reinhoudt J. Org. Chem. 48, 486 (1983).
5. P.G. Sammes and S. Smith, J. Chem. Soc., Perkin Trans. 1 241 (1984).
6. Compound 6b: yield 47%; oil; $^1$H-NMR ($CDCl_3$) δ 9.15 (bs, 1H, OH), 4.17 (q, J = 7.1 Hz, 2H, $OCH_2$); $^{13}$C-NMR ($CDCl_3$) δ 174.8 (s, C=O), 159.3 (s, C=N); IR (KBr) 1740 (C=O) $cm^{-1}$; MS: $M^+$ 173.105 ($C_8H_{15}NO_3$); compound 6c[7]: yield 52%; mp 35-36 °C (petroleum ether bp 40-60 °C); $^1$H-NMR ($CDCl_3$) δ 9.22 (bs, 1H, OH), 2.87 (q, J = 7.3 Hz, 2H, $SCH_2$); $^{13}$C-NMR ($CDCl_3$) δ 202.8 (s, C=O), 158.9 (s, C=N); IR (KBr) 1660 (C=O and C=N) $cm^{-1}$; MS: $M^+$ 189.082 ($C_8H_{15}NO_2S$); compound 7a: yield 33%; oil; $^1$H-NMR ($CDCl_3$) δ 2.21 (s, 3H, $COCH_3$); $^{13}$C-NMR ($CDCl_3$) δ 172.9 (s, C=O), 169.0 (s, $COCH_3$), 166.0 (s, C=N); IR (NaCl) 1780 (OAc), 1765 (C=O), 1660 (C=N) $cm^{-1}$; MS: $M^+$ 263.116 ($C_{14}H_{17}NO_4$); compound 7b[7]: yield 29%; mp 59-60 °C (petroleum ether bp 40-60 °C); $^1$H-NMR ($CDCl_3$) δ 2.20 (s, 3H, $COCH_3$); $^{13}$C-NMR ($CDCl_3$) δ 172.0 (s, C=O), 168.2 (s, $COCH_3$), 165.9 (s, C=N); IR (KBr) 1780-1760 (OAc and C=O), 1640 (C=N) $cm^{-1}$; MS: $(M - 4\text{-}NO_2\text{-}PhO)^+$ 170.082 ($C_8H_{12}NO_3$).
7. Satisfactory elemental analyses were obtained for all new crystalline compounds (C, H, N ± 0.3%).
8. a) The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW, UK. Any request should be accompanied by the full literature citation for this communication. b) Supplementary data available: a list of observed and calculated structure factors. See Announcement to Authors, Tetrahedron Lett. 24, 5154 (1983).
9. M.I. Page and P. Proctor, J. Am. Chem. Soc. 106, 3820 (1984).

(Received in UK 4 March 1985)