Tetrahedron Letters,Vol.23,No.34,pp 3521-3524,1982 0040-4039/82/343521-04$03.00/0
Printed in Great Britain

A NEW SYNTHESIS OF MACROCYCLIC KETO-LACTONES VIA RING EXPANSION OF 2-(3-HYDROXYPROPYL)-2-NITROCYCLOALKANONES

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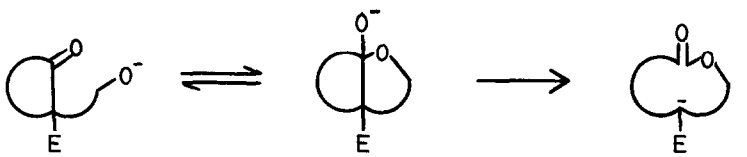
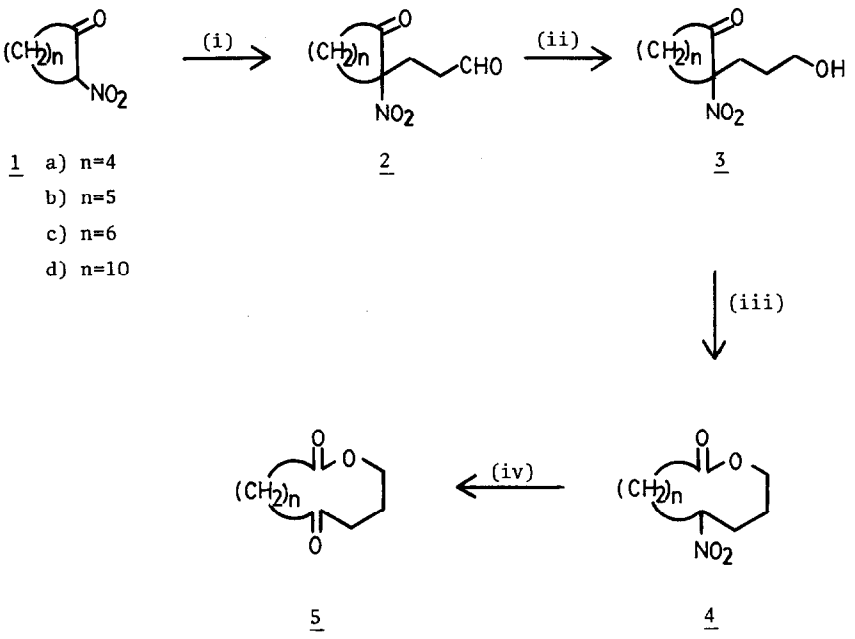
Summary: 2-(3-Hydroxypropyl)-2-nitrocycloalkanones undergo base-catalysed isomerisation into nitro-lactones containing four more atoms in the ring, which can be smoothly converted to the corresponding keto-lactones.

Most syntheses of macrocyclic lactones involve lactonisation as the final step and, therefore, require high dilution and/or very slow mixing of reactants. We have been interested in forming medium and many-membered lactones through ring expansion involving intermediates with the common ring sizes (3 to 7) and thus allowing the use of normal concentrations of reactants (Scheme 1).[1]



E = electronegative group Scheme 1

Since the isomerisation of 2-hydroxyalkyl-2-phenylsulphonylcycloalkanones into phenylsulphonyl-lactones (Scheme 1, E = SO_2Ph) sometimes needed very basic conditions,[1] we have applied the reaction to ketones containing the more strongly electron-withdrawing nitro group (Scheme 1, E = NO_2). The nitro-lactones 4 from expansion of the ring of the cycloalkanones by three carbon atoms can then be converted into the keto-lactones 5 (Scheme 2).



1 a) n=4
b) n=5
c) n=6
d) n=10

2 3 4 5

Scheme 2

Reagents and Conditions: (i) catalytic amount of $(C_2H_5)_3N$ or $P(C_6H_5)_3$ or $(n\text{-}C_4H_9)_4NF$, $(C_2H_5)_2O$, acrolein, RT, 2-4 h; (ii) $NaCNBH_3$, $t\text{-}C_4H_9OH$, HCO_2H, RT, 0.5-1 h for 2a, 2b and 2c; $NaBH_4$, C_2H_5OH, 0^oC, 15 min for 2d; (iii) catalytic amount of NaH, DME, reflux, 0.5-1 h; (iv) $(C_2H_5)_3N$ (3 equivs.), CH_3CN, aq. $(NH_4)_2$ $[Ce(NO_3)_6]$ (3 equivs.), reflux, 2 days.

Table

Percentage yields of isolated products

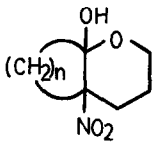
	2	3	4	5
a)	86	84	92	78
b)	82	87	90	76
c)	88	89	95	81
d)	92	93	91	75

Cyclic α-nitroketones[2] are readily available either by nitration of the corresponding enol acetates with acetyl nitrate[3] or from reaction of cycloalkenes with dinitrogen tetroxide and oxygen.[4] Michael addition of 2-nitrocycloalkanones 1a-b to acrolein occurred in good yield (see Table) at room temperature in diethyl ether with a catalytic amount of either triphenylphosphine or tetrabutylammonium fluoride for 1a-c or triethylamine for 1d.

Since selective reduction of the aldehyde group of the keto-aldehydes 2a-c with sodium borohydride in ethanol was unsatisfactory, it was carried out with sodium cyanoborohydride in a mixture of t-butanol and formic acid,[5] which gave the keto-alcohols 3a-c in good yield. Reduction of 2d, however, proceeded smoothly with sodium borohydride in ethanol at 0°C for 15 min. Longer times led to mixtures of 3d, the cyclic hemi-ketal 6d, the nitro-ketone 4d from ring-expansion and the hydroxy-acid from ring-opening. Although work-up of the reaction mixture with dilute acid gave, in addition, some of the keto-lactone 5d, attempts to carry the process through to 5d in one pot gave only low yields. Longer periods for reduction of 2a-c with sodium cyanoborohydride resulted also in the isolation of some of the bicyclic isomers 6a-c.

The keto-alcohols 3a-d or hemi-ketals 6a-d isomerised to the nitro-lactones 4a-d in excellent yield (Table) in boiling 1,2-dimethoxyethane containing a catalytic amount of sodium hydride (0.1 equiv.).*

Most of the procedures for the Nef reaction,[6] when applied to the nitro-lactones 4a-d, gave low yields and some caused opening of the lactone ring. The required transformation to 5a-d was finally achieved very satisfactorily with ceric ammonium nitrate and triethylamine.[7]



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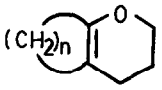

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The conversion of the nitro-ketones 1 into the keto-lactones 5† through the four steps shown in Scheme 2*was carried out in over-all yields of 50-60%, even when each intermediate was separately purified. This general method of ring expansion is being extended by the use of different electronegative groups and different lengths of side chain with a view to its application in the synthesis of natural macrocyclic lactones.

*Recently an isolated example of this rearrangement has been reported without yield in the transformation of 8a-hydroxy-2-methyl-4a-nitro-1-oxadecahydronaphthalene into 9-methyl-6-nitrononanolide by potassium hydride and 18-crown-6 (Von K. Kostova, A. Lorenzi-Riatsch, Y. Nakashita and M. Hesse, Helv. Chim. Acta, 65, 251 (1982).

†The keto-lactones 5 have been made before by oxidation of the dihydropyrans 7 to the diols with moist peractic acid followed by treatment with lead tetra-acetate or by direct oxidation with chromic or m-chloroperbenzoic acid. The ethers 7 were prepared by dehydration of the hydroxypropyl-ketones obtained either by alkylation of the pyrrolidine enamines with 1-acetoxy-3-bromopropane and hydrolysis or by Michael addition of the enamines to methyl acrylate and reduction with lithium aluminium hydride. Alternative syntheses of keto-lactones: 5a, I.J. Borowitz, G. Gonis, R. Kelsey, R. Rapp and G.J. Williams, J. Org. Chem., 31, 3032 (1966); 5b, I.J. Borowitz, G.J. Williams, L. Gross and R. Rapp, J. Org. Chem., 33, 2013 (1968); 5c, I.J. Borowitz, G.J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco and R.D.G. Rigby, J. Org. Chem., 37, 581 (1972); 5d, I.J. Borowitz, V. Bandurco, M. Heyman, R.D.G. Rigby and S. Ueng, J. Org. Chem., 38, 1234 (1973).

‡The compounds listed in the Table were oily liquids but for the following which were crystalline: 2d, m.p. 89-90°C; 3a, 56-58°C; 3b, 59-60°C; 3d, 78°C; 5a, 68-69°C; 5c, 59-60°C; 5d, 31-32°C.

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(Received in UK 10 June 1982)