Tetrahedron Letters, Vol. 33, No. 35, pp. 5141-5144, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Synthesis of Medium-Sized Lactones by Copper(I) Catalyzed Atom Transfer Cyclization

Frank O.H. Pirrung, Werner J.M. Steeman, Henk Hiemstra* and W. Nico Speckamp*

Department of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Bernard Kaptein, Wilhelmus H. J. Boesten, Hans E. Schoemaker and Johan Kamphuis

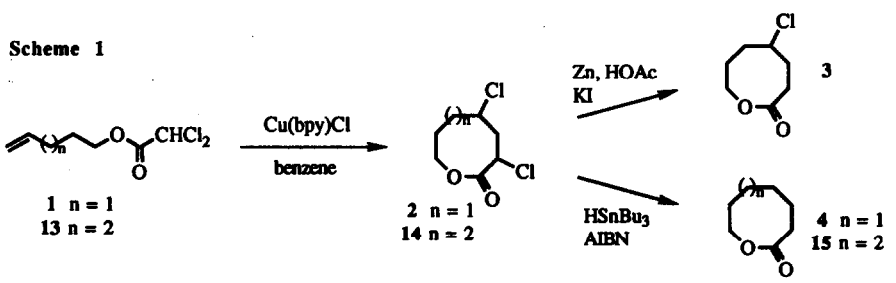
DSM Research, P. O. Box 18, 6160 MD Geleen, The Netherlands

Abstract: Several ω-alkenyl dichloroacetates cyclize in moderate to excellent yields to 3,5-dichloro-oxocan-2-ones (8-membered ring lactones) when heated in benzene at 80-180 °C in the presence of a catalytic amount of the cuprous chloride 2,2'-bipyridine complex.

The increasing number of natural and man-made products containing a medium sized heterocyclic ring as an essential structural element has spurred the interest in synthetic methods for this type of compound.[1] Although significant advances have been made in various cyclization procedures[2] the use of radical based techniques[3] is not well developed. Herein we wish to report a novel and unprecedented formation of eight- and nine-membered lactones through Cu(I) catalyzed cyclization of ω-alkenyl dichloroacetates. The latter substrates are directly available from ω-alken-1-ols and dichloroacetyl chloride. Earlier observations on the intramolecular addition of glycine derived radicals[4] provided the stimulus for this work.

Upon refluxing the dichloroacetate **1** in the presence of 30% of the *in situ* prepared complex of copper(I)chloride and 2,2'-bipyridine (Cu(bpy)Cl) in a 0.1 M solution in benzene for 18 h, the dichlorolactone **2** (IR 1760 cm^{-1}) was obtained in 92% yield as a 70:30 mixture of diastereomers (Scheme 1). The oxocan-2-one structure was proved by the usual spectroscopic techniques,[5] in combination with chemical evidence obtained by conversion of **2** to the monochloro derivative **3** (IR 1715 cm^{-1}) with Zn in acetic acid[6] (63%) and to the known parent oxocan-2-one **4**[7] by Bu_3SnH/AIBN reduction (60%). The *endo* cyclization mode corresponds to earlier observations and calculations on the radical ring closure of monosubstituted alkenes to 8-membered carbocycles.[8] The reaction was successful in several solvents, but benzene gave the best results. A higher reaction temperature led to a much faster reaction, as for instance 10% Cu(bpy)Cl in benzene in a sealed tube at 140 °C for 2 h gave **2** in ca. 90% yield.

Scheme 1

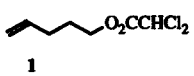
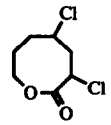
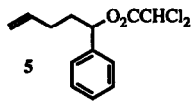
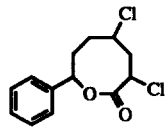
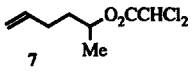
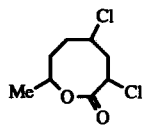
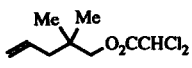
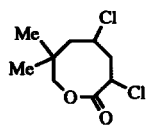
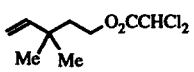
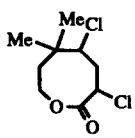
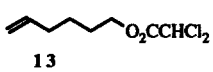
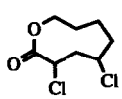


1 n = 1
13 n = 2

2 n = 1
14 n = 2

4 n = 1
15 n = 2

Table 1: Results of the Cu(bpy)Cl catalyzed cyclisation of dichloroacetates

entry	dichloroacetate	conditions[a]	product	yield	(ratio of diastereomers)
1	 **1**	0.1 M PhH reflux, 18 h		**2**	92% (70:30)
2		0.1 M DCE reflux, 18 h			75% (70:30)
3	 **5**	0.2 M PhH sealed tube 180 °C, 1.75 h		**6**	51% (68:18:13) mp (major isomer) = 71-76 °C
4	 **7**	0.1 M PhH sealed tube 130 °C, 5 h		**8**	68% (70:20:10)
5	 **9**	0.2 M PhH sealed tube 180 °C, 1.5 h		**10**	81% (75:25) mp (major isomer) = 77-81 °C
6	 **11**	0.5 M PhH sealed tube 140 °C, 3 h		**12**	70% (70:30)
7	 **13**	0.1 M DCE reflux, 18 h		**14**	57% (70:30)

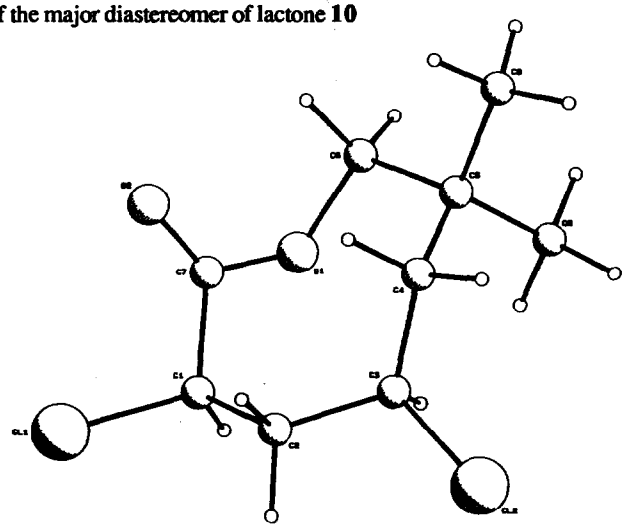
a) Cu(bpy)Cl (0.3 equiv) was employed in all cases.

As the reaction itself could serve as a highly useful method for the direct preparation of a variety of substituted oxocan-2-ones, a number of substituted 4-pentenyl dichloroacetates (entries 3-6, Table 1) were subjected to the cyclization conditions. The presence of a C-1 substituent (**5** and **7**) necessitated the use of higher temperatures, because at reflux in benzene the starting material remained unchanged. Although some intermolecular radical addition[9] took also place, the expected cyclization products **6**[5] and **8**[5] were obtained in satisfactory yields as mixtures of 3 diastereomers on heating the starting materials at 130-180 °C in benzene in a sealed tube. In a similar fashion the 4-pentenyl dichloroacetates **9** and **11** containing two geminal methyl groups were cyclized in good yields to the lactones **10**[5] and **12**[5], respectively, as mixtures of two diastereomers. The major isomer of **10**, obtained crystalline, was subjected to an X-ray analysis.[10] This crystal structure determination proved the oxocan-2-one skeleton beyond doubt and furthermore showed a *cis* orientation of the chlorine substituents (Figure 1). The ring conformation can be characterized as a *chair-chair* (or *crown*) with the chlorine substituents in *pseudo*-equatorial positions and a *trans*-lactone conformation.[11,12]

The ^{1}H NMR data of the major isomers of lactones **2**, **6**, **8**, and **10** showed a remarkable similarity, in particular the signals from the C-4 methylene hydrogens.[5] The *pseudo*-axial C-4 hydrogen of these compounds

was found at ca. 2.55 ppm as a double triplet with a geminal coupling of ca. 13.5 Hz and two vicinal couplings of ca. 11.4 Hz. The *pseudo*-equatorial C-4 hydrogen always showed a double doublet at ca. 2.95 ppm with the expected geminal coupling of 13.5 Hz and only one vicinal coupling of ca. 6.2 Hz with the hydrogen at C-3. These observed vicinal coupling constants are in excellent agreement with the expected data (Karplus equation) for a solution conformation similar to the crystal conformation as shown in Figure 1. On this basis we tentatively assign the major isomers of **2**, **6**, and **8** also as *cis*-3,5-dichlorolactones. The C-8 substituent in the major isomers of **6** and **8** will probably assume a *pseudo*-equatorial orientation, thus *trans* to the chlorine atoms. On the basis of ^{1}H NMR coupling constants the conformation of the major isomer of **12** was clearly different.

Figure 1 Crystal structure of the major diastereomer of lactone **10**



To further investigate the scope of the lactone formation, 5-hexen-1-ol and higher homologues were also tested. Upon refluxing of **13** with 30% of Cu(bpy)Cl in a 0.1 M solution of 1,2-dichloroethane for 18 h, a 57% yield of the nine-membered lactone **14**[5] as a 70:30 mixture of diastereomers was obtained. Removal of the chlorine atoms (2 equiv Bu_3SnH, benzene, reflux) gave the unsubstituted lactone **15**[7] thus again confirming the exclusive *endo* ring closure. The formation of **14** was accompanied by substantial amounts of oligomers the structures of which were not investigated in detail. The latter intermolecular addition appeared to be the exclusive process with higher homologues of **13** (n = 3, 6, and 7, see Scheme 1).

The carbon-carbon bond formation by intramolecular Kharash type cyclization is a well-studied process and is thought to proceed via metal-coordinated radicals.[13] Although the use of dichloroacetates is known for this type of olefin cyclization[14] its efficacy in the ring closure to medium-sized lactones is unprecedented. In this respect it is of interest to note that in our hands the formation of analogous γ-lactones from dichloroacetates as reported recently[15] could not be reproduced only teleomerization being observed. We observed similar results on attempted δ- and ε-lactone formation. However, our present work which will be reported in due course indicates that cyclizations of trichloroacetates have a considerably broader scope.[15]

Although the observed regioselectivity in the cyclizations reported here (see Table) closely corresponds to earlier results of medium-ring[8] and large ring radical cyclizations[16] the marked preference for this type of ring closure may be connected with a template effect. If the Cu(bpy)Cl complex is not only involved in the electron transfer process, but also is intimately attached to the reacting termini, one might predict the folding of the carbon chain to happen in accord with the geometry of the complex. As can be inferred from model studies an acceptable fit is possible with the number of atoms involved. Although we have no convincing proof for the

existence of such a template effect, the observed decrease in reaction rate upon introduction of methyl groups at one of the chain carbons as well as at the ortho position of the bipyridine ligand[17] agrees with such rationale. Finally, the great number of variations possible in the starting alcohol hold promise for further synthetic applications, several of which are currently being actively pursued.

ACKNOWLEDGEMENT

K. Goubitz and J. Fraanje of the Department of Crystallography are kindly acknowledged for the X-ray crystal structure determination.

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5. The assigned structures were in complete agreement with IR, ^{1}H NMR and ^{13}C NMR data. Some selected data are as follows. Major isomer of **2**: ^{1}H NMR (300 MHz) δ($CDCl_3$) 1.83-2.15 (m, 3 H), 2.33-2.45 (m, 1 H), 2.57 (ddd, *J* = 14.0, 11.5, 11.1 Hz, H-4), 2.91 (ddd, *J* = 14.0, 5.8, 1.2 Hz, H-4), 4.10 (ddd, *J* = 11.1, 4.9, 4.1 Hz, H-8), 4.17-4.27 (m, H-8), 4.48 (dd, *J* = 11.5, 6.2 Hz, H-3), 4.75-4.88 (m, H-5); ^{13}C NMR (50 MHz) δ($CDCl_3$) 29.3, 37.7, 50.0 (C-4), 54.6, 58.6, 68.0 (C-8), 170.3 (C-2). Major isomer of **6**: ^{1}H NMR (300 MHz) δ($CDCl_3$) 2.0-2.15 (m, 2H, 2 H-6), 2.15-2.25 (m, 1H, H-7), 2.45-2.55 (m, 1H, H-7), 2.66 (dt, 1H, *J* = 13.6, 11.4 Hz, H-4), 3.01 (dd, 1H, *J* = 13.6, 6.4 Hz, H-4), 4.31 (ddt, 1H, *J* = 11.2, 6.5 Hz, H-5), 4.62 (dd, 1H, *J* = 11.5, 6.5 Hz, H-3), 6.05 (dd, 1H, *J* = 7.0, 7.6 Hz, H-8), 7.30-7.45 (m, 5H, 5 Ar-H); ^{13}C NMR (50 MHz) δ($CDCl_3$) 37.9, 38.3, 51.5 (C-4), 54.7, 59.2, 80.6 (C-8), 125.9, 125.9, 128.3, 128.5, 138.0, 171.3 (C-2). Major isomer of **10**: ^{1}H NMR (300 MHz) δ($CDCl_3$) 0.86 (s, 3H, Me), 1.20 (s, 3H, Me), 1.91 (dd, 1H, *J* = 16.4, 6.6 Hz, H-6), 2.09 (d, 1H, *J* = 16.4 Hz, H-6), 2.47 (dt, 1H, *J* = 13.4, 11.5 Hz, H-4), 2.90 (dd, 1H, *J* = 13.4, 6.3 Hz, H-4), 3.59 (d, 1H, *J* = 11.0 Hz, H-8), 4.35-4.45 (m, 1H, H-5), 4.52 (dd, 1H, *J* = 11.7, 6.4 Hz, H-3), 4.58 (d, 1H, *J* = 11.0 Hz, H-8); ^{13}C NMR (75.5 MHz) δ($CDCl_3$) 23.6 (Me), 26.9 (Me), 38.1 (C-7), 51.2, 51.6, 54.0, 54.5, 76.3 (C-8), 171.6 (C-2).
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10. The major isomer of **10** formed monoclinic cristals, $P2_1/a$ [a = 10.3946 (8); b = 9.9835 (6); c = 11.4685 (16); β = 111.933 (8); Z = 4]. The final R-value was 0.061 for 1705 reflections [$F_o \geq 2.5\ (\sigma(F_o))$]. Lists of refined coordinates and e.s.d.'s were deposited at the Cambridge Crystallographic Data Centre.
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12. No data were available in the Cambridge Crystallographic Database on X-ray crystal structures of monocyclic eight-membered lactones at the time of this writing.
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17. Details will be discussed in a forthcoming paper.

(Received in UK 3 June 1992)