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THE FACILE SYNTHESIS OF MACROCYCLIC LACTONES BY THE USE OF 2-CHLORO-3-METHOXYMETHYL-1-METHYLPYRIDINIUM IODIDE

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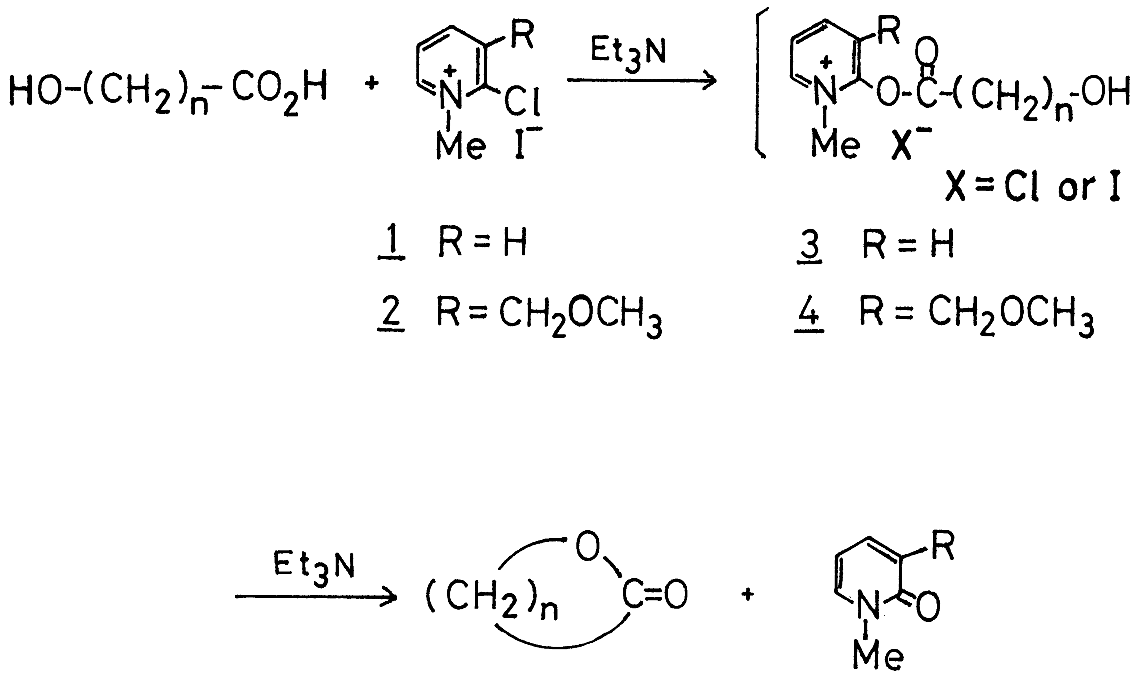
Long chain ω-hydroxycarboxylic acids cyclize to the corresponding lactones in good yields by the treatment with 2-chloro-3-methoxymethyl-1-methylpyridinium iodide (2) and triethylamine in refluxing methylene chloride.

As a part of our continuing investigation on the exploration of new synthetic reactions by utilizing the onium salts of azaaromatics, it was previously reported that lactonization of long chain ω-hydroxycarboxylic acids has been successfully carried out in one step procedure by the treatment of the acids with 2-chloro-1-methylpyridinium iodide (1) in the presence of triethylamine.[1] However, the method required the prolonged heating at an elevated temperature (acetonitrile refluxing temperature) using 4 ~ 8 molar excess amounts of the pyridinium salt (1) and triethylamine for the formation of the corresponding lactones in reasonable yields.

In order to perform the cyclization by the use of slight excess amounts of pyridinium salt and triethylamine at lower temperature, the activation of the assumed intermediate, 2-acyloxy-1-methylpyridinium salt (3), was studied by the introduction of a functional group at 3-position of the pyridinium salt (1).

It has been known that the hydrolysis of esters is facilitated by the introduction of a hetero atom near an ester group,[2] and a hetero atom situating near a carbonyl group interacts each other.[3] Based on these facts, the introduction of a substituent having a hetero atom at 3-position of the 2-halopyridinium salt seems promising for the activation of the key intermediate, 2-acyloxypyridinium salt (4), to accelerate the lactonization reaction.



1 R = H

2 R = CH_2OCH_3

3 R = H

4 R = CH_2OCH_3

First, 2-chloro-3-methoxymethyl-1-methylpyridinium iodide (2) was prepared from nicotinic acid[4)] and then the lactonization of ω-hydroxycarboxylic acids, HO-$(CH_2)_n$-COOH with n=10, 11, and 14, was carried out by utilizing the pyridinium salt (2) in the presence of triethylamine.

The typical experimental procedure is described for Experiment 1: To a refluxing solution of 2-chloro-3-methoxymethyl-1-methylpyridinium iodide (300 mg, 1 mmol) in dry methylene chloride (40 ml) was added a solution of 15-hydroxypentadecanoic acid (129 mg, 0.5 mmol) and triethylamine (121 mg, 1.2 mmol) in dry methylene chloride (60 ml) over a period of 8 h from a mechanically driven syringe, and the reaction mixture was refluxed for additional 30 min after the addition was completed. After evaporation of the solvent under reduced pressure, the residue was separated by column chromatography (silica gel) to afford 15-pentadecanolide (85 mg, 71%). In a similar manner, 12-hydroxydodecanoic acid and 11-hydroxyundecanoic acid were lactonized as summarized in the table.

Table Lactonization of ω-Hydroxy Acids ($HO-(CH_2)_n-COOH$)[*1]

Experiment No.	n	Molar Ratio[*2] a : b : c			Pyridinium Salt	Solvent[*3]	Time h	Yield %
1	14	1	2	2.4	2	CH_2Cl_2	8	71
2		1	2	4	1	CH_2Cl_2	6	34
3		1	4	8	1	CH_3CN	8.5	84
4	11	1	2	2.4	2	CH_2Cl_2	12	56
5		1	1.2	3	1	CH_2Cl_2	6	23
6		1	4	4	1	CH_3CN	8	37
7		1	4	8	1	CH_3CN	8	69
8	10	1	1.5	2.4	2	$ClCH_2CH_2Cl$	11	40
9		1	4	4	1	CH_3CN	8	17
10		1	4	8	1	CH_3CN	9	61

[*1] Each lactone was identified by comparison with authentic sample (NMR and IR spectra, TLC and GLC).

[*2] a = ω-Hydroxycarboxylic acid, b= Pyridinium salt, c = Triethylamine.

[*3] All the reactions were carried out at the refluxing temperature of the solvent.

As shown in table, in the case of the cyclization using 2-chloro-1-methylpyridinium iodide (1), the lactones are obtained in good yields only when the reactions are carried out using 4 molar amounts of the pyridinium salt (1) and 8 molar amounts of triethylamine to hydroxy acids under acetonitrile refluxing temperature (Experiment 3, 7, and 10), and the yields remarkably diminish as the amounts of the pyridinium salt and triethylamine are reduced or the reaction temperature is lowered (Experiment 2, 5, 6, and 9).

Now, it was established that when 2-chloro-3-methoxymethyl-1-methylpyridinium iodide (2) was employed, the lactones were obtained in good yields even at methylene chloride refluxing temperature (40°C) by the use of 2 molar amounts of pyridinium salt (2) and triethylamine (Experiment 1, 4, and 8).

It is noted that the introduction of methoxymethyl group at 3-position of 2-halopyridinium salt efficiently facilitates the lactonization of various long chain ω-hydroxycarboxylic acids.

References and Note

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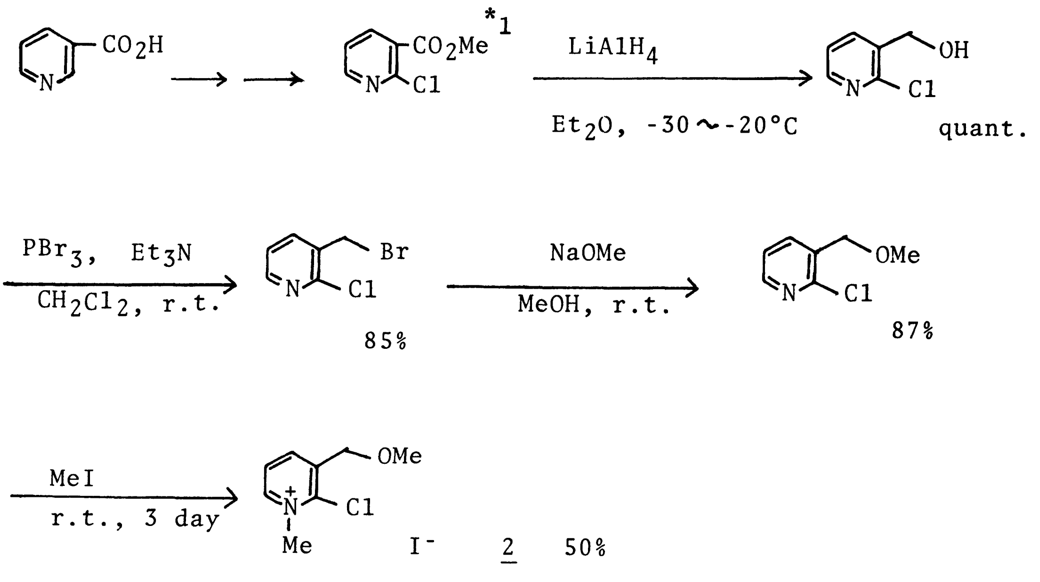
4)



[*1] This compound was prepared according to the method of the literature; E. C. Taylor, Jr. and A. J. Crovetti, J. Org. Chem., 19, 1633 (1954).

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