CHEMISTRY LETTERS, pp. 441-444, 1977. Published by the Chemical Society of Japan

AN EFFICIENT METHOD FOR THE SYNTHESIS OF MACROCYCLIC LACTONE

Teruaki MUKAIYAMA, Koichi NARASAKA, and Kazunori KIKUCHI
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Long chain ω-hydroxycarboxylic acids were quantitatively converted to 6-phenyl-2-pyridyl esters by the treatment of the acids with 6-phenyl-2-pyridone and 2-chloro-1-methylpyridinium iodide in the presence of triethylamine. These esters were cyclized in refluxing methylene chloride by the promotion of p-toluenesulfonic acid to give macrocyclic lactones in high yields.

The discovery of numerous macrolides has generated a recent surge of interest in new solutions to the problem of macrocyclic lactone synthesis.1) Corey et al., presented one of the effective routes to lactonize ω-hydroxycarboxylic acids via active thiol esters,1a) i.e., 2-pyridinethiol esters or 2-imidazolethiol esters, prepared by employing oxidation-reduction condensation.2) Recently, the efficient method for preparation of carboxylic esters was developed in our laboratory utilizing the onium salts of azaaromatics.3) This method was applied to the lactonization, and ω-hydroxycarboxylic acids, $HO\text{-}(CH_2)_n\text{-}COOH$, n=10, 11, 14 were cyclized in good yields by employing 4 molar amounts of 2-halopyridinium salts in refluxing acetonitrile.1b)

In the course of further investigation, it was newly found that several active esters of carboxylic acid such as succinimido ester and 1-benzotriazolyl ester were readily prepared by the use of 2-halopyridinium salts.4) These results prompted us to prepare active esters of long chain ω-hydroxycarboxylic acids, which might be potential intermediates for the lactonization under mild conditions.

We wish to describe herein (i) an efficient preparation of 6-phenyl-2-pyridyl-esters (II) of ω-hydroxy acids (I) using 2-chloro-1-methylpyridinium iodide, and

(ii) a successful macrocyclic lactone (IV) formation by the treatment of the active esters (II) with 1 molar amount of p-toluenesulfonic acid at room temperature or methylene chloride refluxing temperature (40°C).

When a series of ω-hydroxycarboxylic acids, $HO\text{-}(CH_2)_n\text{-}COOH$ with n=10, 11, 14 (Ia, b, c), were treated with 2-chloro-1-methylpyridinium iodide and 6-phenyl-2-pyridone[5)] in the presence of triethylamine, the corresponding 6-phenyl-2-pyridyl esters (IIa, b, c) were obtained in quantitative yields. The 6-phenyl-2-pyridyl esters so prepared were subjected to lactonization by slow addition to a refluxing methylene chloride solution of p-toluenesulfonic acid, and macrocyclic lactones were obtained in high yields. The results are summarized in Table.

The following general procedure was used in the experiments.

Preparation of 6-phenyl-2-pyridyl 12-hydroxydodecanoate (IIb): A mixture of 6-phenyl-2-pyridone (4.0mmol), 2-chloro-1-methylpyridinium iodide (2.0mmol) and triethylamine (4.0mmol) in methylene chloride (40ml) were stirred for 1 h at room temperature under argon.[6)] To this solution was slowly added a methylene chloride solution (60ml) of 12-hydroxydodecanoic acid (0.5mmol) and triethylamine (0.5mmol) from a mechanically driven syringe over a period of 9 h. The reaction mixture was refluxed for additional 30 min after the addition was completed. The solvent was removed under reduced pressure and the residue was subjected to column chromotography (silica gel, 2% methanol in methylene chloride for development) to afford 6-phenyl-2-pyridyl ester (IIb) in quantitative yield.

Synthesis of 12-dodecanolide (IIIb): A methylene chloride solution (40ml) of the active ester (IIb, 0.34mmol) was added from a mechanically driven syringe to a refluxing solution of p-toluenesulfonic acid in methylene chloride (60ml) over a period of 9 h under argon. The reaction mixture was refluxed for additional 30 min. The solvent was removed under reduced pressure and the residue was eluted through a column of silica gel (mixture of hexane and ether (5:1) for development) to give pure lactone (IIIb) in 99% yield along with a trace amount (less than 1%) of dilactide (IVb).

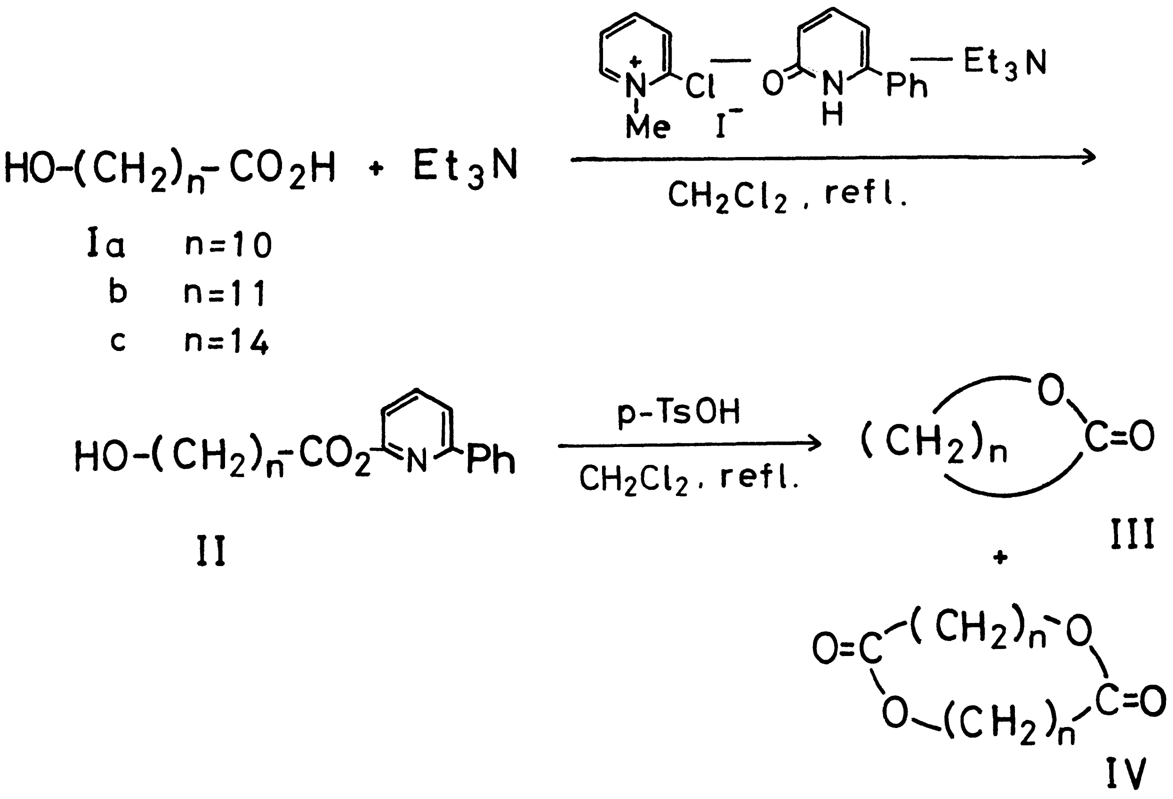

Table. Yields of Macrocyclic Lactones.[7)]

n	Yield (%) Lactone (III)	Yield (%) Dilactide (IV)
10	73 (32)*	25 (23)*
11	99 (72)*	<1 (16)*
14	quant.(92)*	0 (trace)*

( )* Yields of the products when the lactonization was carried out at room temperature.

It is noted that 6-phenyl-2-pyridyl esters (II) prepared quantitatively from ω-hydroxycarboxylic acids (I) and 6-phenyl-2-pyridone were lactonized in high yields by the treatment with p-toluenesulfonic acid under mild conditions. The efficiency of this method is apparent from the results that macrocyclic lactones (III) were obtained in higher yields as compared with those obtained by any other methods previously reported.

We are now investigating the improvement of this method to synthesize macrocyclic lactones by one-step procedure.

References and Notes

1 a) E. J. Corey, P. Ulrich, and J. M. Fitzpatrick, J. Am. Chem. Soc., 98, 222 (1976); E. J. Corey and D. J. Brunelle, Tetrahedron Lett., 3409 (1976), and preceding papers in the series.

b) T. Mukaiyama, M. Usui, and K. Saigo, Chem. Lett., 49 (1976).

c) S. Masamune, S. Kamata, and W. Schilling, J. Am. Chem. Soc., 97, 3515 (1975); S. Masamune, Y. Hayase, W. K. Chan, and R. I. Sobczak, ibid., 98, 7874 (1976).

d) H. Gerlach and A. Thalmann, Helv. Chim. Acta, 57, 2661 (1974); H. Gerlach, K. Oertle, and A. Thalmann, ibid., 59, 755 (1976).

e) L. T. Scott and J. O. Naples, Synthesis, 738 (1976).

2) T. Mukaiyama, R. Matsueda, and M. Suzuki, Tetrahedron Lett., 1901 (1970); T. Mukaiyama, Angew. Chem. Int. Ed. Engl, 15, 94 (1976).

3) T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, Chem. Lett., 1163 (1975).

4) Unpublished results.

5) 6-Phenyl-2-pyridone was prepared according to Thesing's procedure; J. Thesing and A. Müller, Chem. Ber., 90, 711 (1957).

6) At this stage, 2-chloro-1-methylpyridinium iodide was consumed completely to result in the formation of 1-methyl-2-(6-phenyl-2-pyridyloxy)pyridinium halide, which was used for the following reaction without isolation.

7) Each lactone (III) was identified by comparison with authentic sample (ir, nmr, tlc, and glc).

(Received March 3, 1977)