CHEMISTRY LETTERS, pp. 49-50, 1976. Published by the Chemical Society of Japan

THE FACILE SYNTHESIS OF LACTONES

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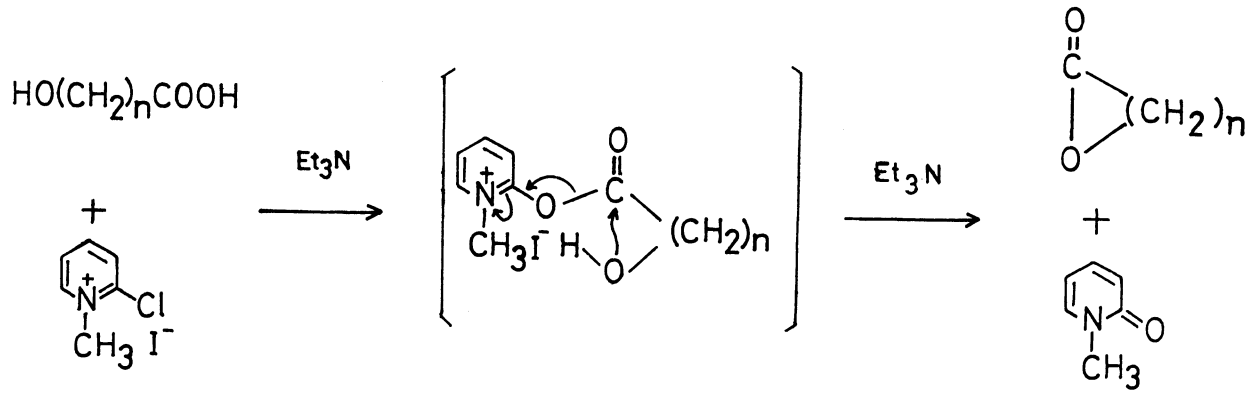
Direct lactonization of ω-hydroxy acids, $HO(CH_2)_nCOOH$ with n=5, 7, 10, 11, 14, has been successfully carried out under mild conditions in good yields by the treatment with 1-methyl-2-chloropyridinium iodide in the presence of triethylamine. In the case of the acid with n=6, only lactide has been produced.

Several literatures[1] exist concerning the lactonization of hydroxy acids, however, in general it is difficult to lactonize hydroxy acids having the hydroxyl group in the epsilon or the more remote position in the chain. Recently, Corey and Nicoloau[2] presented a route to synthesize lactones via 2-pyridinethiol esters, prepared by the oxidation-reduction condensation[3] using triphenylphosphine and 2,2'-dipyridyl disulfide. According to their procedure, rather elevated temperature is required to reflux the thiol esters in a xylene or benzene solution for a long time.

During our study on the development of usuful synthetic methods to prepare carboxylic esters,[4] carboxamides[5] and 2-pyridyl sulfides[6] using 1-alkyl-2-halopyridinium salts, it was assumed that all the reacting species involved in the reactions would be in the close proximity of a central pyridinium salt to make the above mentioned condensations entropically advantageous. Based on this concept, we have studied an intramolecular esterification of ω-hydroxy acids to lactones by utilizing 1-methyl-2-chloropyridinium iodide.

A series of ω-hydroxy acids, $HO(CH_2)_nCOOH$ with n = 5, 6, 7, 10, 11, 14, was employed to prepare medium and large ring lactones as illustrated in the following equation.



An initial investigation was undertaken to determine the effect of a base, a hydrogen halide acceptor, and it was found that triethylamine was the most suitable base for the present lactonization. Further, it was made clear that the lactonization was successfully carried out in a variety of solvents. Of various solvents screened, the optimum yield was given when the reaction was performed in refluxing acetonitrile or dichloromethane.

The typical procedure is described as follows: To a refluxing solution of 510 mg(2.0 mmol) of 1-methyl-2-chloropyridinium iodide in 50 ml of dry acetonitrile, was continuously and uniformly added a solution of 134 mg(0.5 mmol) of 15-hydroxypentadecanoic acid and 404 mg(4.0 mmol) of triethylamine in 40 ml of dry acetonitrile over a period of 8 hr, and the reaction mixture was refluxed for additional 30 min after addition was completed. After evaporation of the solvent under reduced pressure, the residue was separated by silica gel column chromatography to afford 15-pentadecanolide and lactide in 84% and 3% yields respectively.

In a similar manner, various ω-hydroxy acids, except for 7-hydroxyheptanoic acid which resulted in the exclusive formation of lactide, were easily lactonized to give the medium and large ring lactones in good yields as listed in the Table.

Table Lactonization of ω-Hydroxy Acids

n	Solvent	Time(hr)	Lactone Ring Size	Lactone Yield(%)[b]	Lactone Ring Size	Lactone Yield(%)[b]
5[a]	CH_2Cl_2	7.5	7	89	14	0
6	CH_3CN	7.5	8	0	16	93
7	CH_3CN	8.0	9	13	18	34
10	CH_3CN	9.0	12	61	24	24
11	CH_3CN	8.0	13	69	26	14
14	CH_3CN	8.5	16	84	32	3

a) Pyridinium salt (1 mmol) was used. b) Isolated yield.
Each lactone was identified by comparison with authentic sample (ir spectrum and glc).

REFERENCES

1) M. Stoll and A. Rouvé, Helv. Chim. Acta, 17, 1283 (1934); idem, ibid., 18, 1087 (1935); D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, Tetrahedron, 24, 2443 (1968); H. L. Wehrmeister and D. E. Robertson, J. Org. Chem., 33, 4173 (1968); I. Vlattas, I. T. Harrison, L. Tőkés, J. H. Fried, and A. D. Cross, J. Org. Chem., 33, 4176 (1968); E. W. Colvin, T. A. Purcell, and R. A. Raphael, J. Chem. Soc., Chem. Commun., 1031(1972).
2) E. J. Corey and K. C. Nicolaou, J. Amer. Chem. Soc., 96, 5614 (1974).
3) T. Mukaiyama, R. Matsueda, and M. Suzuki, Tetrahedron Lett., 1901 (1970); R. Matsueda, H. Maruyama, E. Kitazawa, H. Takahagi, and T. Mukaiyama, J. Amer. Chem. Soc., 97, 2573 (1975); T. Mukaiyama and M. Hashimoto, ibid., 94, 8528 (1972); idem, Bull. Chem. Soc. Japan, 44, 196 (1971); T. Endo, S. Ikenaga, and T. Mukaiyama, ibid., 43, 2632 (1970).
4) T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, Chem. Lett., 1045 (1975).
5) E. Bald, K. Saigo, and T. Mukaiyama, Chem. Lett., 1163 (1975).
6) T. Mukaiyama, S. Ikeda, and S. Kobayashi, Chem. Lett., 1159 (1975).

(Received November 7, 1975)