SYNTHESIS OF LACTONES AND CYCLOALKANES. CYCLIZATION OF  $\omega$ -hydroxy acids and ethyl  $\alpha$ -cyano- $\omega$ -hydroxycarboxylates

Toshio Kurihara, Yoshisada Nakajima, and Oyo Mitsunobu\* Department of Chemistry, College of Science and Engineering, Aoyama Gakuin University, Chitosedai, Setagaya-ku, Tokyo 157, Japan

(Received in Japan 7 May 1976; received in UK for publication 1 June 1976)

Corey et al. and Mukaiyama et al. have recently reported efficient routes to synthesize medium and large ring lactones. 1, 2 Intramolecular associations in the reaction intermediates were assumed to play an important role in these reactions. We wish to report herein convenient methods for the preparations of lactones and cycloalkanes under mild neutral conditions.

In the previous papers we described the preparation of carboxylic esters using reagent combinations of diethyl azodicarboxylate (I) and triphenylphosphine (II).<sup>3</sup> The reaction could be explained by assuming an alkoxyphosphonium carboxylate as a key intermediate. If a hydroxy acid is allowed to react with I and II, a dipolar intermediate (III) would therefore be formed in which reaction sites are brought so close together that would favor lactonization (Scheme 1).

Scheme 1

$$\begin{array}{c} 0 & 0 \\ \mathbb{E} \text{to}-\mathbb{C}-N=N-\mathbb{C}-\text{OEt} \\ \text{I} \\ \end{array} + \begin{array}{c} Ph_{3}P \\ \text{H} \\ \end{array} + \begin{array}{c} Ho_{-}(\mathbb{C}H_{2})_{2}-\text{COOH} \\ \end{array} + \begin{array}{c} -(\mathbb{E} \text{to}_{2}\mathbb{C}NH_{-})_{2} \\ \end{array} \\ \end{array} \\ \left[ \begin{array}{c} Ph_{3}P_{+} \\ -O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \end{array} \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \end{array} \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \end{array} \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \end{array} \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \end{array} \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \end{array} \right] \xrightarrow{} O_{-}C \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ O_{-}C \\ 0 \end{array} \right] \xrightarrow{} O_{-}C \\ \left[ \begin{array}{c} O_{-}C \\ O_{-}C \\ O_{-}C \\ O_{-}C \\ O_{-}C \\ O_{-}C \\ \end{array} \right] \xrightarrow{} O_{-}C \\ \left[ \begin{array}{c} O_{-}C \\ O_{$$

A series of  $\omega$ -hydroxy acids, HO-(CH<sub>2</sub>)<sub>n</sub>-COOH with n = 5, 7, or 11, was utilized in the cyclization studies. The reaction of hydroxy acids with I and II went to completion within 2 days at room temperature giving the corresponding lactones and dilides in varying amounts as is indicated in Table I. The identity of each lactone was proved by comparison (infrared, proton magnetic

n	Solvent* (ml)	Reaction Time	Isolated Yield, %	
		(day)	Lactone	Dilide
5	THF (25)	2	[8]**	
	B (25)	2	40	53
7	B (25)	2	~0 [0.8]	70
11	в (25)	2	60	17
	B (200)	1	63	32
	B(25) + THF(4)	1	[5]	

Table I. Formation of Lactones and Dilides by Cyclization of  $\omega$ -Hydroxy Acids, HO-(CH<sub>2</sub>)<sub>n</sub>-COOH (1 mmol).

\* THF = Tetrahydrofuran; B = Benzene. \*\* Glc yields are parenthesized.

resonance, and gas chromatography) with an authentic sample. The dilides were identified by proton magnetic resonance and mass spectra.

Intermolecular dehydration between active hydrogen compounds and alcohols has also been accomplished by the use of I and II.<sup>4</sup> Since this reaction could also be assumed to involve an alkoxyphosphonium salt, the preparation of cyclo-alkanes from diols and ethyl cyanoacetate was attempted as expressed by Scheme 2 When diols,  $HO-(CH_2)_n-OH$  (n = 4, 5, or 6), were allowed to react with an equimolar amount of ethyl cyanoacetate in the presence of excess I and II at room temperature, the corresponding 1-cyano-1-ethoxycarbonylcycloalkanes were isolated by preparative layer chromatography (Table II). The cycloalkanes were identified by infrared, proton magnetic resonance, and mass spectra.

Scheme 2

$$NC-CH_2-COOEt + HO-(CH_2)_n-OH \xrightarrow{I + II} \begin{bmatrix} NC-CH-COOEt \\ (CH_2)_n \\ OH \end{bmatrix}$$



n	Ring Size	Solvent (ml)	Isolated Yield, %	
4	5	THF (15)	46	
		<b>Toluene (21) + THF</b> (4)	60	
5	6	THF (25)	40	
6	7	THF (25)	21	

Table II.	Formation of 1-Cyano-1-ethoxycarbonylcycloalkanes fr	ют
	Ethyl Cyanoacetate and Diols, $HO-(CH_2)_n-OH$	

Experimental procedures for the preparations of lactones and l-cyano-lethoxycarbonylcycloalkanes are as follows.

<u>6-Hexanolide</u>. To a stirred mixture of 6-hydroxyhexanoic acid (5 mmol) and II (7.5 mmol) in benzene (125 ml) was added dropwise I (7.5 mmol) over a period of 5 min at room temperature. After the solution was stirred for 2 days at room temperature, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel column (Merck, 230 mesh; 3.3 cm  $\times$  70 cm) with ether as eluant, 3 g fractions being collected. Each fraction was monitored by gas chromatography. Dilide appeared first and followed by diethyl hydrazinedicarboxylate. 6-Hexanolide appeared in the third peak.

In the case of the cyclization of  $l_2-hydroxydodecanoic acid or 8-hydroxy$ octanoic acid, the elution was carried out with ether-petroleum ether = 1 : 9.The lactone appeared first and was followed by dilide.

<u>1-Cyano-1-ethoxycarbonylcyclohexanes</u>. A solution of I (3 mmol) in THF (1 ml) was added dropwise to a stirred solution of II (3 mmol) in THF (20 ml) at -20°C, followed by addition of the diol (1 mmol) and ethyl cyanoacetate (1 mmol) in THF (4 ml).<sup>5</sup> After stirring was continued for 1 day at -20°C, 1 day at -20°C, 0°C, 1 day at 0°C, and then 1 day at room temperature, the solvent was removed under reduced pressure. The 1-cyano-1-ethoxycarbonylcycloalkane was isolated by preparative layer chromatography (Merck silica gel PF<sub>254</sub>; benzene-methanol = 30 : 1), homogeneous by gas chromatography (SE-30, 10%, 1 m column).

Work is continuing to find optimum conditions and to study stereochemistry of the cyclization method disclosed above as well as application of the present reaction to the synthesize of complex macrolide systems.

## References and Footnotes

E. J. Corey and K. C. Nicolaou, <u>J. Amer. Chem. Soc.</u>, <u>96</u>, <u>5614</u> (1974): E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., <u>ibid.</u>, <u>97</u>, 653, 654 (1975):
E. J. Corey, K. C. Nicolaou, and T. Toru, <u>ibid.</u>, <u>97</u>, 2287 (1975). See also
H. Gerlach and A. Thalmann, <u>Helv. Chim. Acta</u>, <u>57</u>, 2661 (1974). Masamune et al. have reported an efficient method for the synthesis of lactone from

S-tert-butyl thiolate.6

- 2. T. Mukaiyama, M. Usui, and K. Saigo, Chemistry Letters, 49 (1976).
- 3. O. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Japan, 44. 3427 (1971):
- O. Mitsunobu, J. Kimura, K. Iiizumi, and N. Yanagida, <u>ibid.</u>, <u>49</u>, 510 (1976.)
- 4. M. Wada and O. Mitsunobu, <u>Tetrahedron Letters</u>, 1279 (1972).
- 5. Active methylene compound and alcohol should be added to the pre-formed intermediate prepared by the reaction of I with II at low temperature. Under the same conditions as were used for the preparation of carboxylic esters, phosphoric esters,<sup>7</sup> and N-alkylimides,<sup>8</sup> no alkylated product could be obtained. T. Kurihara and O. Mitsunobu, in preparation.
- 6. S. Masamune, S. Kamata, and W. Schilling, <u>J. Amer. Chem. Soc.</u>, <u>97</u>, 3515 (1975).
- 7. O. Mitsunobu, K. Kato, and J. Kimura, <u>ibid</u>., <u>91</u>, 6510 (1969), and ref 3.
- H. Morimoto, T. Furukawa, K. Miyazima, and O. Mitsunobu, <u>Chemistry Letters</u>, 821 (1973): M. Wada, T. Sano, and O. Mitsunobu, <u>Bull. Chem. Soc. Japan</u>, <u>46</u>, 2833 (1973).