

Table I. Formation of Lactones and Dilides by Cyclization of ω -Hydroxy Acids, $\text{HO}-(\text{CH}_2)_n-\text{COOH}$ (1 mmol).

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

* 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.⁴ Since this reaction could also be assumed to involve an alkoxyphosphonium salt, the preparation of cycloalkanes from diols and ethyl cyanoacetate was attempted as expressed by Scheme 2. When diols, $\text{HO}-(\text{CH}_2)_n-\text{OH}$ ($n = 4, 5, \text{ or } 6$), 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

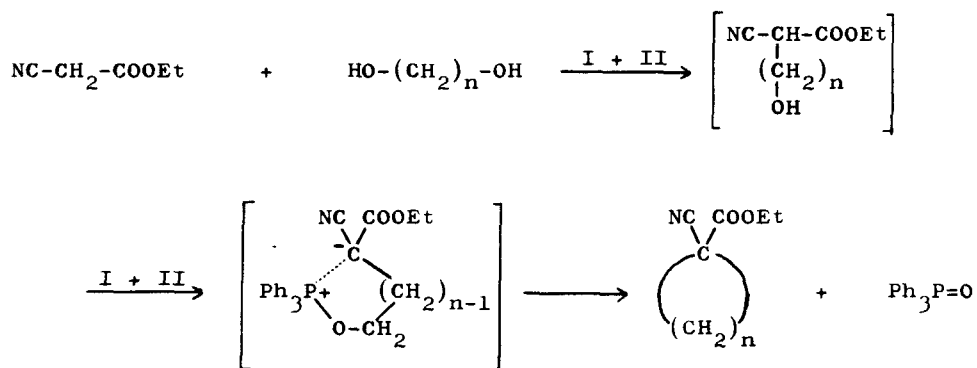


Table II. Formation of 1-Cyano-1-ethoxycarbonylcycloalkanes from Ethyl Cyanoacetate and Diols, HO-(CH₂)_n-OH

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

Experimental procedures for the preparations of lactones and 1-cyano-1-ethoxycarbonylcycloalkanes are as follows.

6-Hexanolide. 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 × 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 12-hydroxydodecanoic acid or 8-hydroxyoctanoic acid, the elution was carried out with ether-petroleum ether = 1 : 9. The lactone appeared first and was followed by dilide.

1-Cyano-1-ethoxycarbonylcyclohexanes. 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).⁵ 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 PF₂₅₄; 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 synthesis of complex macrolide systems.

References and Footnotes

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S-tert-butyl thiolate.⁶

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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,⁷ and N-alkylimides,⁸ no alkylated product could be obtained. T. Kurihara and O. Mitsunobu, in preparation.
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