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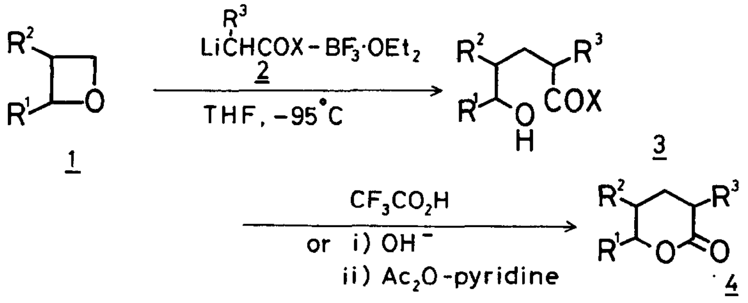
A NEW SYNTHESIS OF δ-LACTONES FROM OXETANES

Masahiko Yamaguchi*, Keisuke Shibato, and Ichiro Hirao
Department of Industrial Chemistry, Kyushu Institute of Technology,
Sensui-cho, Tobata, Kitakyushu 804, JAPAN

Abstract: Oxetanes were reacted with lithium enolates generated from esters or amides in the presence of boron trifluoride etherate to give δ-hydroxyesters or amides in high yield, which were hydrolyzed and converted to δ-lactones.

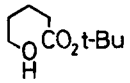
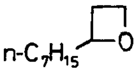
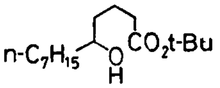
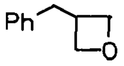
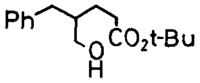
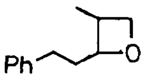
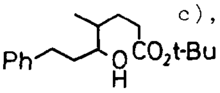
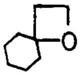
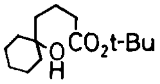
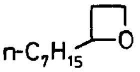
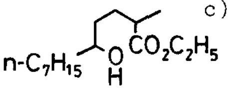
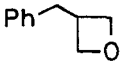
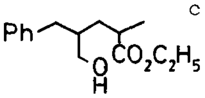
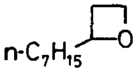
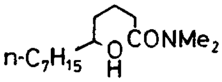
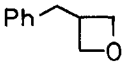
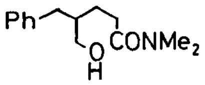
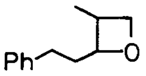
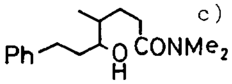
Lactones are one of the most familiar class of compounds in organic chemistry and many methods were reported for the synthesis of the compounds[1]. As for five-membered γ-lactones, one of the general synthetic method would be the ring cleavage of oxiranes with various carboxylic acid derivatives to form γ-hydroxy acids followed by the lactone formation[2]. Though the ring opening reaction of oxetanes (1), a higher homologue of oxiranes, was expected to be a method for the synthesis of δ-lactones (4), few report, to our knowledge, appeared concerning this approach[3]. One of the reasons for the difficulties to carry out this synthesis was a rather low reactivity of 1 against nucleophiles compared with oxiranes. Previously, we have found that boron trifluoride etherate promotes the ring opening of 1 with lithium acetylides and that γ-hydroxyacetylenes were obtained in high yield[4]. As a further extention of this new methodology, we now wish to describe a new synthesis of δ-lactones (4) utilizing the ring opening of oxetanes (1) with lithium enolates (2) by effecting a Lewis acid[5].

Thus, lithium enolates generated from esters or an amide were treated with several oxetanes (1) in the presence of boron trifluoride etherate in tetrahydrofuran (THF) at -95°C to -40°C, and the corresponding δ-hydroxycarboxylic acid derivatives (3) were obtained in high yield (Scheme I, Table I).



Scheme I

Table I. A synthesis of δ-hydroxyesters and amides.

entry	esters/amides	oxetanes	products[a]	yield (%)
1	$CH_3CO_2t\text{-}Bu$			90[b]
2				87 (57)[e]
3				84
4		 [c]	 [c], [d]	77
5				35
6	$C_2H_5CO_2C_2H_5$		 [c]	84
7			 [c]	73
8	CH_3CONMe_2			77
9				60
10		 [c]	 [c]	72

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a) All the products gave satisfactory spectral data (^1H-NMR, IR, and/or ^{13}C-NMR).

b) The reaction was carried out with 3 mmol of oxetane and 15 mmol of ester, and the product was isolated by short path distillation.

c) A 1:1 mixture of diastereomers determined by ^{13}C-NMR.

d) A satisfactory elemental analysis was obtained by high resolution mass spectrometry.

e) The reaction was performed at -78°C.

The examination of the reaction conditions showed some aspects of the present synthesis. The Lewis acid was playing an important role in the activation of oxetanes (1), as 3 was not detected in the absence of boron trifluoride etherate even at r.t. It was also observed that 3 were obtained in higher yield when the reaction was carried out at -95°C rather than at -78°C (entry 2).

On the synthetic stand point of view, the following feature should be noted: 1) Several types of substituted oxetanes were available in the present synthesis. And, when unsymmetrically substituted oxetanes were used, C-O bond fission at the less hindered site occurred (entries 2,4,5,6,8, and 10). 2) In case of 1,2-disubstituted oxetanes, cis- or trans-oxetanes seemed to be equally reactive to the nucleophile (entries 4 and 10). 3) In the reaction of the enolate generated from ethyl propionate, 1,3- or 1,4-asymmetric induction was not observed under the present reaction conditions (entries 6 and 7).

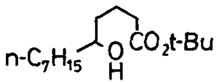
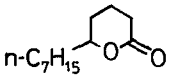
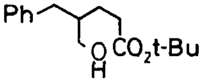
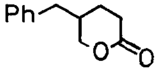
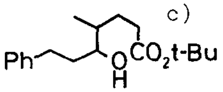
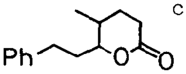
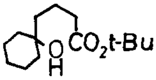
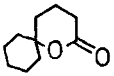
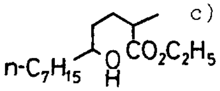
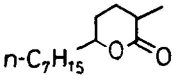
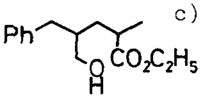
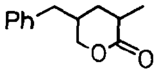
Next, we turned to the lactonization of the δ-hydroxyesters (3) as depicted in Scheme I and Table II. t-Butyl esters were treated with trifluoroacetic acid in methylene chloride for 1 h, and were directly converted to the corresponding δ-lactones (entries 1,2,3, and 4) in high yield. In case of ethyl esters, hydrolysis of ester moiety was performed with 3N potassium hydroxide at refluxing temperature for 1 h, followed by the cyclization with acetic anhydride in pyridine at r.t. (entries 5 and 6). In either method, the stereochemistry of 3 was preserved throughout the lactone formation step (entries 3,5, and 6). Thus, δ-lactones (4) with various substituents were synthesized from oxetanes (1) by two-carbon homologation.

A typical procedure is described for the synthesis of 5-undecanolide: Under nitrogen atomosphere, a tetrahydrofuran (THF, 2 ml) solution of t-butyl acetate (290 mg, 2.5 mmol) was added to a THF-hexane (2 ml and 1.5 ml) solution of lithium diisopropyl amide (LDA, 2.5 mmol) at -78°C. After stirring for 25 min, 2-heptyloxetane (88 mg, 0.5 mmol) in THF (2 ml) and boron trifluoride etherate (0.3 ml, 2.4 mmol) were added at -95°C. Bath temperature was slowly raised to -40°C for 1.5 h and the reaction was quenched by adding aqueous ammonium chloride. A usual work up gave t-butyl 5-hydroxyundecanoate (134 mg, 87%). NMR ($CDCl_3$) δ 0.6-1.0 (3H, m), 1.0-1.9 (16H, m), 1.44 (9H, s), 2.24 (2H, t, J=7Hz), 2.79 (1H, s), 3.3-3.8 (1H, m). IR (neat) 3400, 1720 cm^{-1}.

Under nitrogen atomosphere, trifluoroacetic acid (0.2 ml) was added to a methylene chloride (2 ml) solution of t-butyl 5-hydroxyundecanoate (199 mg, 0.73 mmol) and the mixture was stirred for 1 h. A usual work up gave 5-undecanolide (153 mg, quant.).

NMR ($CDCl_3$) δ 0.6-1.0 (3H, m), 1.0-2.1 (16H, m), 2.2-2.6 (2H, m), 4.0-4.4 (1H, m). IR (neat) 1730 cm^{-1}. MS m/e 198 (M^+), 167. Found: 198.1612. Calcd for $C_{12}H_{22}O_2$: 198.1619.

Table II. A synthesis of δ-lactones.[a)]

entry	δ-hydroxyesters	δ-lactones[b)]	yield (%)
1		 d)	quant.
2			90
3	 c)	 c), d)	72
4			63
5	 c)	 c), d)	90
6	 c)	 c)	73

a) Entry 1,2,3,4: CF_3CO_2H, CH_2Cl_2, r. t., 1 h.
Entry 5,6: i) 3N-KOH, THF, refl., 1h, ii) Ac_2O-pyridine, r. t., 2 h.

b) All the products gave satisfactory spectral data (^{1}H-NMR, IR, and/or ^{13}C-NMR).

c) A 1:1 mixture of diastereoisomers determined by ^{13}C-NMR.

d) A satisfactory elemental analysis was obtained by high resolution mass spectrometry.

References

1) For recent examples for the synthesis of δ-lactones by C-C bond formation: R. W. Dugger and C. H. Heathcock, J. Org. Chem., 45, 1181 (1980); M. Chmielewski and J. Jurczak, ibid, 46, 2230 (1981); G. Solladié and F. Matloubi-Moghadam, ibid, 47, 91 (1982); R. H. Schlessinger and M. A. Poss, J. Am. Chem. Soc., 104, 357 (1982). 2) For recent examples: J. W. Scheeren, F. J. M. Dahmen, and C. G. Bakker, Tetrahedron Lett., 1979, 2925; A. I. Meyers, Y. Yamamoto, E. D. Mihelich, and R. A. Bell, J. Org. Chem., 45, 2792 (1980); L. Strekowski, M. Visnick, and M. A. Battiste, Synthesis, 1983, 493. 3) The reaction of metalated enamine or nitrile with a oxetane is known: P. F. Hudrlik and C.-N. Wan, J. Org. Chem., 40, 2963 (1975); L. L. Darko and J. G. Cannon, ibid, 32, 2352 (1967). 4) M. Yamaguchi, Y. Nobayashi, and I. Hirao, Tetrahedron Lett., 24, 5121 (1983). 5) A reaction of lithium enolate in the presence of boron trifluoride etherate is known: M. Suzuki, A. Yanagisawa, and R. Noyori, Tetrahedron Lett., 23, 3595 (1982).

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