CHEMISTRY LETTERS, pp. 571-574, 1992.

Lactonization of ω–Hydroxy Esters over Hydrous Zirconium(IV) Oxide

Hideyuki KUNO,* Makoto SHIBAGAKI, Kyoko TAKAHASHI,
Ichiro HONDA, and Hajime MATSUSHITA
Life Science Research Laboratory, Japan Tobacco Inc., 6-2 Umegaoka,
Midori-ku, Yokohama, Kanagawa 227

The lactonization of ω–hydroxy esters was carried out by catalysis with hydrous zirconium(IV) oxide. In the flow reaction system, ω-hydroxy esters were efficiently converted to give the corresponding lactones. In particular, it is noteworthy that heptanolide is obtained in good yield. In addition, it is possible to produce a large quantity of lactones in this catalyst system.

In general, it is very difficult to synthesize lactones which contain a ring of more than 7 members from ω–hydroxy acids or esters, since intermolecular esterification proceeds as the main reaction. It has been reported that some macrolides which contain a ring of more than 12 members were produced from ω-hydroxy acids or their derivatives in good yields.[1-6] However, heptanolide and octanolide have been never efficiently produced. Further, each of these methods necessitates troublesome operations for purifying the product after the reaction.

In a previous paper,[7] we reported that the esterification proceeded efficiently over hydrous zirconium(IV) oxide as a catalyst. It is anticipated that lactonization would proceed efficiently by the use of this catalyst.

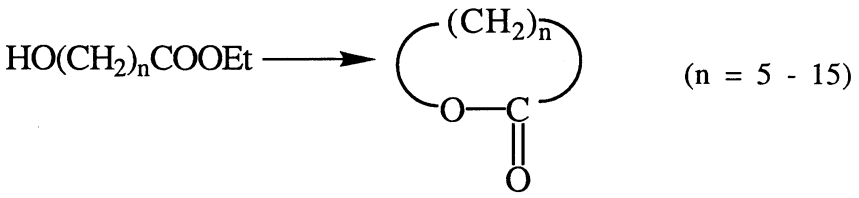
In this paper, we report that ω-hydroxy esters are converted to the corresponding lactones over hydrous zirconium(IV) oxide in good yields. In particular, it is demonstrated that heptanolide and octanolide are also efficiently produced in this catalyst system. With this method, the following advantages can be expected; (1) easy product isolation, (2) water need not be excluded from reaction vessel, (3) reusability of the catalyst, (4) durability of the catalytic activity. Some characteristic properties and preparation of hydrous zirconium(IV) oxide were mentioned in a previous paper.[8]

The reactions were carried out in a glass flow reactor with a fixed-bed catalyst [for instance, flow rate of nitrogen carrier gas: 60 $cm^3 \cdot min^{-1}$; catalyst: 0.5 g, 24-60 mesh; reaction temperature: 275 °C]. A solution of hydroxy ester in toluene (12.0 $mmol \cdot l^{-1}$) and a hydrocarbon as an internal standard was fed, by means of a microfeeder, into the reactor (5 $cm^3 \cdot h^{-1}$). The products were analyzed by gas chromatography (a capillary column SPB-1

30m and PEG 20M 25m), GC-MS (Shimadzu QP-1000), GC-IR, and ^{1}H-NMR. Activity and selectivity of catalyst were determined after a steady state had been reached.

Table 1 shows the lactonization of various ω-hydroxy esters catalyzed by hydrous zirconium(IV) oxide. The results show that all of the ω-hydroxy esters were efficiently converted to the corresponding lactones. For instance, ethyl 6-hydroxyhexanoate was converted to ε-caprolactone in quantitative yield. Further, it was noteworthy that 7-heptanolide, which has been never synthesized from 7-hydroxyheptanoic acid or its derivative, can also be obtained in a 48.7% yield (entry 2). In general, it is extremely

Table 1. Lactonization of ω-Hydroxy Ethyl Ester by Hydrous Zirconium(IV) Oxide[a)]



(n = 5 - 15)

Entry	Substrate	Catalyst/g	Conversion/%	Selectivity/%	Yield/%
1	HO(CH2)5COOEt	0.5	100.0	90.4	90.4
2	HO(CH2)6COOEt	0.5	99.8	48.8	48.7
3	HO(CH2)7COOEt	0.5	73.4	48.4	35.5
4	HO(CH2)11COOEt	0.5	8.3	91.6	7.6
5	HO(CH2)15COOEt	0.5	2.7	100.0	2.7
6[b)]	HO(CH2)5COOEt	0.5	100.0	97.5	97.5
7[b)]	HO(CH2)5COOEt	1.0	100.0	99.0	99.0
8[c)]	HO(CH2)15COOEt	4.0	51.8	100.0	51.8

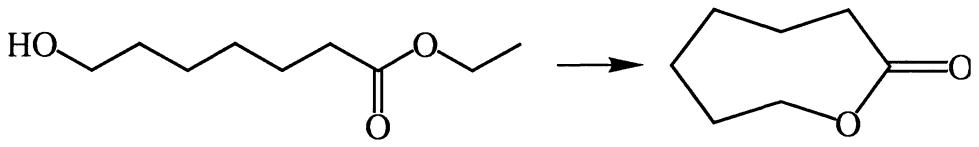
a) Substrate, 0.06 mmol·h^{-1}; solvent, 5 cm^3·h^{-1}; carrier gas, 60 cm^3·min^{-1}; reaction temperature, 275 °C. b) Reaction temperature, 250 °C. c) Substrate, 0.03 mmol·h^{-1}; reaction temperature, 280 °C.

difficult to synthesize a lactone which has a medium-size ring (from 8 to 10 members). Accordingly, it is considered that this catalyst system is useful for the synthesis of medium-size lactones.

From the Table 1, it can be seen that the yield of lactonization decreases with an increase in the length of carbon-chain in the ω-hydroxy esters. However, relatively large ring size lactones (13 or 17 members) could be obtained in a high yield by increasing the amount of catalyst, since a high selectivity was detected for the synthesis of large ring size lactones in this catalyst system (entries 4,5, and 8).

Further, it was found that lactonization by this procedure does not necessitate high-diluted conditions. For instance, ε-caprolactone was obtained in a 86% yield by supplying a large amount of ethyl 6-hydroxyhexanoate (1.8 $mmol \cdot h^{-1}$). In the case of this procedure, the solution was more than 50 times as concentrated than the conventional procedure.[1-6] Accordingly, it is possible to produce a large amount of lactones using this catalyst system.

Table 2. Effect of Reaction Temperature[a]



Temperature/°C	Conversion/%	Selectivity/%	Yield/%
225	68.1	39.2	26.7
250	85.5	40.6	34.7
275	99.8	48.8	48.7
300	100.0	14.1	14.1

a) Conditions: Catalyst, 0.5 g; ethyl 7-hydroxyheptanoate, 0.06 $mmol \cdot h^{-1}$; solvent, 5 $cm^3 \cdot h^{-1}$; carrier gas, 60 $cm^3 \cdot h^{-1}$; temperature, 275 °C.

Table 3. Effect of Solvent[a]

Solvent	Conversion/%	Selectivity/%	Yield/%
Toluene	99.8	48.8	48.7
Xylene	100.0	36.2	36.2
THF	100.0	32.2	32.2
2-Propanol	100.0	3.0	3.0

a) Conditions: Catalyst, 0.5 g; ethyl 7-hydroxyheptanoate, 0.06 $mmol \cdot h^{-1}$; solvent, 5 $cm^3 \cdot h^{-1}$; carrier gas, 60 $cm^3 \cdot min^{-1}$; temperature, 275 °C.

The lactonization of ethyl 7-hydroxyheptanoate was carried out at various reaction temperatures in this catalyst system. The results are shown in Table 2. In the range of 225 to 275 °C, the yield of 7-heptanolide increases with increasing in temperature. However, the yield of 7-heptanolide decreases at even higher temperatures because a side reaction, for instance dehydration, occured over hydrous zirconium(IV) oxide. It is considered that the ω-hydroxy ester was very efficiently converted to the corresponding lactone at 275 °C.

In order to elucidate the dependence on solvent, the lactonization of ethyl 7-hydroxyheptanoate was carried out using various solvents. As shown in Table 3, the use of toluene as the solvent gives an excellent yield of ethyl 7-heptanolide in the lactonization.

References

1) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
2) T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, **1976**, 49.
3) T. Mukaiyama, K. Narasaka, and K. Kikuchi, *Chem. Lett.*, **1977**, 441.
4) J. Inada, K. Harata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull Chem. Soc. Jpn.*, **52**, 1989 (1979).
5) J. Inada, T. Katsuki, S. Takimoto, S. Ouchida, K. Inoue, A. Nakano, N. Okuda, and M. Yamaguchi, *Chem. Lett.*, **1979**, 1021.
6) A. Makita, T. Nihara, and Y. Yamada, *Tetrahedron Lett.*, **28**, 805 (1987).
7) K. Takahashi, M. Shibagaki, and H. Matsushita, *Bull. Chem. Soc. Jpn.*, **62**, 2353 (1989).
8) M. Shibagaki, K. Takahashi, H. Kuno, and H. Matsushita, *Bull. Chem. Soc. Jpn.*, **63**, 258 (1990).

(Received January 20, 1992)