Efficient Method for the Lactonization of ω-Hydroxycarboxylic Acids with Di-2-thienyl Carbonate by the Promotion of Catalytic Amounts of DMAP and $Hf(OTf)_4$

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An efficient method for the synthesis of macrolides from ω-hydroxycarboxylic acids is established by using an equimolar amount of di-2-thienyl carbonate (2-DTC) and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) and group 4 metal triflates such as hafnium(IV) trifluoromethanesulfonate ($Hf(OTf)_4$).

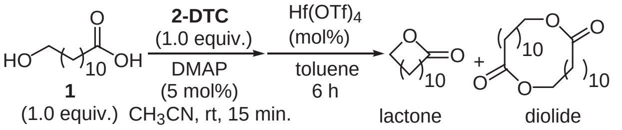
Preparation of macrolactones from ω-hydroxycarboxylic acids is one of the most important topics in organic synthesis because a macrolide structure is contained in a large number of natural products. Therefore, several useful methods for lactonization have been developed.[1–9] Most of them are effective for preparation of 13- to 19-membered ring lactones, however, preparation of 8- to 12-membered ring lactones had a difficult problem of forming a large quantity of diolide at the same time. Recently, Yamamoto et al. reported an effective method for the synthesis of lactones using substituted benzoic anhydride[8] and this was successfully employed in the synthesis of natural product having 9-memberd ring lactone structure.[10]

In our previous communication, a simple and effective method for the synthesis of various macrolactones by using equimolar amounts of ω-hydroxycarboxylic acids and 2-DTC in the presence of a catalytic amount of DMAP and 2–4 equimolar amounts of iodine was reported.[11] Although this reaction affords 13- to 19-membered lactones in good to high yields, 10- to 12-membered ring lactones were obtained in medium or low yields along with large amounts of diolide. Recently, an effective method for esterification of carboxylic acids with alcohols by using a catalytic amount of $Hf(OTf)_4$ was reported from our laboratory.[12] However, lactonization of ω-hydroxycarboxylic acids by using $Hf(OTf)_4$ catalyst was not reported except our one example.[13] These results prompted us to study on 2-DTC-mediated macrolactonization of ω-hydroxycarboxylic acids in the presence of $Hf(OTf)_4$ catalyst.

In this communication, we would like to report that $Hf(OTf)_4$ worked as an efficient catalyst for the synthesis of various macrolactones including 10- to 12-membered ring lactones from the corresponding ω-hydroxycarboxylic acids.

In the first place, lactonization of 12-hydroxydodecanoic acid that uses 2-DTC in the presence of catalytic amounts of DMAP and $Hf(OTf)_4$ was examined (Table 1). It was already reported that 2-thienyl 12-hydroxy dodecanoate, an active ester intermediate, was easily prepared by treating 12-hydroxydodecanoic acid **1** with 2-DTC in the presence of a catalytic amount of DMAP in CH_3CN.[11] On the other hand, corresponding lactone was obtained in low yield (29%) when a solution of 12-hydroxydodecanoic acid, 2-DTC and DMAP in CH_3CN was diluted to 1 mM solution by further addition of toluene and $Hf(OTf)_4$ (Entry 1).

Table 1. Lactonization of 12-hydroxydodecanoic acid by using 2-DTC promoted by catalytic amounts of DMAP and $Hf(OTf)_4$



Entry	$Hf(OTf)_4$ /mol %	Concentration /mM	Temp/°C	Yield[a]/%	
				Lactone	Diolide
1	50	1	rt	29	6
2	50	2	reflux	68	<11
3	20	2	reflux	77	<11
4	10	2	reflux	89	<7
5	5	2	reflux	55	trace
6	10	2	80 °C	61	trace
7	10	2	100 °C	86	3
8	10	2	100 °C	85	3[b]
9	10	4	100 °C	78	3

A solution of 2-thienyl 12-hydroxydodecanoate derived from **1** and 2-DTC in CH_3CN (10 mL) was slowly added to a solution of $Hf(OTf)_4$ in toluene (78 mL) for 5 h. [a]Isolated yield. [b]The reaction time was 10 h.

Next, the above lactonization was tried by using a slow addition procedure: namely, a solution of 2-thienyl 12-hydroxydodecanoate derived from **1** and 2-DTC in CH_3CN (10 mL) was slowly added to a solution of $Hf(OTf)_4$ in toluene (78 mL) at reflux temperature during 5 h and then reaction mixture was continued to stir for 1 h. When 50 mol % of $Hf(OTf)_4$ was used, the desired lactone was obtained in 68% yield (Entry 2). The amounts of $Hf(OTf)_4$, concentration and reaction time were further examined in order to optimize the reaction conditions. Finally, it was found that the desired 12-dodecanolide was obtained in 89% yield in the case when the reaction was carried out in 2 mM solution of toluene in the presence of 10 mol % of $Hf(OTf)_4$ at reflux temperature (Entry 4).

The above reaction was examined in the presence of a catalytic amount of various Lewis acids (Table 2). The corresponding lactones were obtained in low yields when catalysts such as $Cu(OTf)_2$ or $Sc(OTf)_3$ were used (Entries 5 and 6). The desired lactones were not obtained when other Lewis acids were used (Entries 1–4, 7–10). In our previous communication,[12] it was shown that $Hf(OTf)_4$ was effective for 2-DTC mediated esterification since an active chelate complex consisted of $Hf(OTf)_4$ and 2-thienyl ester was formed. Therefore, lactonization in the presence of the other various group 4 metal triflates was tried (Entries 11–15). Then, it was found that the desired lactones were obtained in high yields when $HfCl(OTf)_3$ or $Ti(OTf)_4$, $Zr(OTf)_4$ were used (Entries 12, 14, and 15). These results indi-

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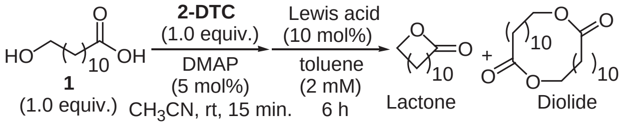
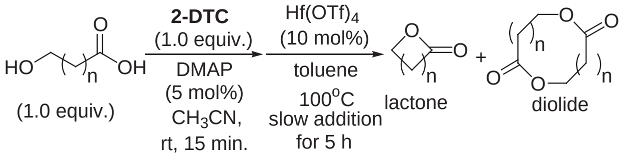
Table 2. Lactonization of 12-hydroxydodecanoic acid by using 2-DTC promoted by DMAP and several Lewis acids



Entry	Lewis acid	Yield^a/%		Entry	Lewis acid	Yield^a/%	
1	BF_3-OEt_2	N.D.	(N.D.)	**9**	$Yb(OTf)_3$	N.D.	(N.D.)
2	$TiCl_4$	N.D.	(N.D.)	**10**	$HfCl_4$	N.D.	(N.D.)
3	$SnCl_4$	N.D.	(N.D.)	**11**	$HfCl_2(OTf)_2$^{b}	41	(N.D.)
4	$Mg(OTf)_2$	N.D.	(N.D.)	**12**	$HfCl(OTf)_3$^{c}	83	(<11)
5	$Cu(OTf)_2$	30	(trace)	**13**	$Hf(OTf)_4$	86	(3)
6	$Sc(OTf)_3$	57	(trace)	**14**	$Ti(OTf)_4$^{d}	82	(<9)
7	$La(OTf)_3$	N.D.	(N.D.)	**15**	$Zr(OTf)_4$^{d}	84	(<2)
8	$Gd(OTf)_3$	trace	(N.D.)				

A solution of 2-thienyl 12-hydroxydodecanoate derived from **1** and 2-DTC in CH_3CN (10 mL) was slowly added to a solution of Lewis acid in toluene (78 mL) at 100 °C. ^{a}Isolated yield of lactone (diolide). ^{b}Generated in situ from 1 equiv. of MCl_4 and 2 equiv. of AgOTf. ^{c}Generated in situ from 1 equiv. of MCl_4 and 3 equiv. of AgOTf. ^{d}Generated in situ from 1 equiv. of MCl_4 and 4 equiv. of AgOTf.

Table 3. Lactonization of various ω-hydroxycarboxylic acids by using 2-DTC promoted by DMAP and $Hf(OTf)_4$



Entry	n (ring size)	Yield^a ( )^b/%			
		Lactone		Diolide	
1	7 (10)	53	(trace)	trace	(<25)
2	8 (11)	70	(23)	5	(30)
3	9 (12)	78	(58)	<9	(18)
4	10 (13)	89^c	(77)	<7	(14)
5	11 (14)	89	(85)	<2	(<8)
6	12 (15)	94	(87)	<6	(<11)
7	13 (16)	92	(90)	<1	(<6)
8	14 (17)	91	(92)	<3	(<7)

^{a}Isolated yield. ^{b}Values in parentheses are those obtained previously by using 2–4 equiv. of iodine instead of $Hf(OTf)_4$.[12] ^{c}Reflux temperature.

cated that group 4 metal triflates exhibit unique characteristic properties of promoting this 2-DTC mediated lactonization.

Results of the lactonization using various ω-hydroxycarboxylic acids are listed in Table 3.[14] Thirteen to seventeen membered ring lactones were obtained in high yields (Entries 4–8) and the desired product was similarly obtained in 78% yield when 11-hydroxyundecanoic acid was used (Entry 3). Eleven membered ring lactone was also obtained in 70% yield when the cyclization was carried out by using the corresponding 10-hydroxydecanoic acid (Entry 2). Although, preparation of 10-membered ring lactone was known to be difficult, the desired lactone was obtained in 53% yield (Entry 1). It is noted that the corresponding lactones were obtained in higher yields and formation of the undesired corresponding diolides was suppressed in comparison with the results obtained by carrying out the same reaction under previously reported conditions of using iodine.[11] Further, it is noted that this reaction provides an excellent method for the synthesis of 10-, 11-membered ring lactones which were known to be difficult by conventional methods. It is also noted that this is effective from the point of view that amounts of the reagent decreased (1equiv. of 2-DTC) and reaction time became shorter (6 h) compared with Yamamoto's method which used 2 equiv. of coupling reagent and the reaction time for 6–20 h.

It is noted that an effective method for the synthesis of various macrolactones was established by using equimolar amounts of ω-hydroxycarboxylic acids and 2-DTC in the presence of a catalytic amount of DMAP and $Hf(OTf)_4$. Other group 4 metal triflates such as $Ti(OTf)_4$ and $Zr(OTf)_4$ were also effective for this lactonization.

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14 A typical experimental procedure was as follows: to a mixture of 12-hydroxydodecanoic acid (38.1 mg, 0.176 mmol), and 2-DTC (40.0 mg, 0.176 mmol) in CH_3CN (10 mL) was added DMAP (1.08 mg, 0.0088 mmol). After stirring for 15 min at rt, the resultant solution was slowly added to solution of $Hf(OTf)_4$ (13.7 mg, 0.0176 mmol) in toluene (78 mL) at 100 °C for 5 h and then reaction mixture was stirred for 1 h. The resultant solution was cooled to room temperature and was evaporated the solvent. The mixture was diluted in ether and was added saturated aqueous sodium hydrogen carbonate under ice cooling. The mixture was extracted with ether, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography to afford the corresponding lactone (30.0 mg, 86%).

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