A New Method for the Lactonization of ω-Hydroxy Carboxylic Acids with Di-2-thienyl Carbonate by the Promotion of DMAP and Iodine

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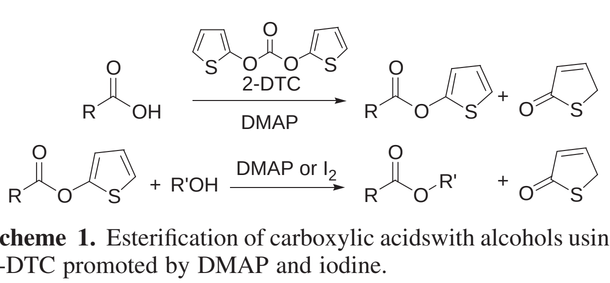
Successive reactions of ω-hydroxycarboxylic acids with an equimolar amount of di-2-thienyl carbonate (2-DTC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) followed by an addition of 2–4 equimolar amounts of iodine afforded the corresponding lactones in good to high yields.

Natural products having macrolide structure are important therapeutic agents in clinical medicine because of their antibiotic, antitumoral, and other various helpful biochemical activities. Accordingly, to prepare macrolactones from ω-hydroxycarboxylic acids is also major concern in synthetic organic chemistry. Several useful methods have therefore been reported; namely, the use of DCC,[1] 2,4,6-trichlorobenzoyl chloride,[2] 2,2′-dipyridyl disulfide/Ph_3P,[3] 1-methyl-2-chloropyridinium iodide/Et_3N,[4] DEAD/Ph_3P,[5] 2-Me-6-NO_2-benzoic anhydride (MNBA),[6] 4-(trifluoromethyl)benzoic anhydride,[7] 4-nitrobenzoic anhydride/$Sc(OTf)_3$,[8] etc.[9]

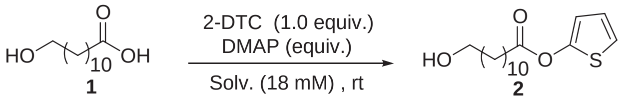
In our previous communication, a new esterification method between nearly equimolar amounts of carboxylic acids and alcohols with the use of di-2-thienyl carbonate (2-DTC) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) was reported.[10] This reaction proceeded via two-step procedure, i.e., i) reaction of carboxylic acid with 2-DTC that formed thienyl ester and ii) formation of ester from thus formed thienyl ester with various alcohols (Scheme 1). It was revealed in both steps then that a catalytic amount of DMAP worked as useful activators although a long reaction time was required for the completion of the second step. Recently, it was reported from our laboratory that this esterification could be accelerated by further addition of an equimolar amount of iodine and to improve the reaction time and the yield.[11] This result prompted us to study 2-DTC-mediated macrolactonization of ω-hydroxycarboxylic acids in the coexistence of iodine.

In the first place, the synthesis of 2-thienyl 12-hydroxy dodecanoate **2**, an active ester intermediate, was examined by reacting 12-hydroxydodecanoic acid **1** with 2-DTC in the presence of a catalytic amount of DMAP (Table 1). The formation of **2** was found to be influenced by the solvents and was obtained most effectively when the reaction was carried out in CH_3CN (Entry 5). The same result was obtained even when 0.05 equivalents of DMAP were used (Entry 6). It is interesting to note that the corresponding lactone was not detected in any cases even when it was allowed to react under more concentrated conditions (35 mM) for 9 h (Entry 7). This indicates that the lactonization is not accelerated by DMAP alone, therefore, it was needed to use the other activator so as to form a lactone in high yield.



Scheme 1. Esterification of carboxylic acidswith alcohols using 2-DTC promoted by DMAP and iodine.

Table 1. Synthesis of 2-thienyl 12-hydroxydodecanoate **2** using 12-hydroxydodecanoic acid and 2-DTC in the presence of DMAP



Entry	Solvent	DMAP/equiv.	Time/min	Yield/%
1	CH_2Cl_2	0.1	60	81
2	toluene	0.1	90	73
3	THF	0.1	120	59
4	Et_2O	0.1	120	49
5	CH_3CN	0.1	15	97
6	CH_3CN	0.05	15	95
7	CH_3CN	0.05	9 h	96[a]

[a]Concentration 35 mM.

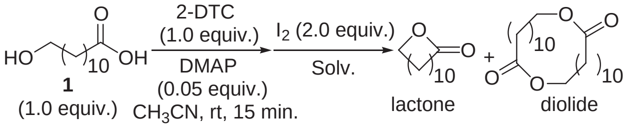
Next, lactonization of 12-hydroxydodecanoic acid that uses 2-DTC in the presence of DMAP and iodine was examined (Table 2). Acetonitrile then turned out to be the most suitable solvent for the preparation of thienyl ester **2** as described above. However, the corresponding lactone was obtained in low yield when a solution of 12-hydroxydodecanoic acid, 2-DTC and DMAP in CH_3CN was diluted to 2 mM by further addition of CH_3CN and iodine at room temperature (Entry 1).

Therefore, thienyl ester **2** was prepared in CH_3CN as mentioned and then the effect of further addition of a solvent in the lactonization step under diluted concentration was examined. After various solvents were screened, the desired lactone was obtained in 47% yield by further addition of toluene (Entry 6). It was found that this reaction proceeded more smoothly in a mixed solvent of CH_3CN and toluene.

It is also noted that the corresponding lactone was not detected when the above reaction was carried out in the presence of DMAP (2.05 equiv.) instead of iodine (Entry 7). This result indicates that iodine works quite effectively in this lactonization step.

With these results in mind, the amounts of iodine and solvents were further examined in order to optimize the reaction conditions (Table 3). Finally, it was found that the desired 12-dodecanolide was obtained in 77% yield in the case when the reac-

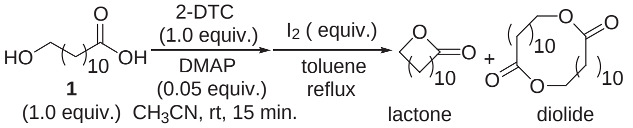
Table 2. Lactonization of 12-hydroxydodecanoic acid by using 2-DTC promoted by DMAP and iodine



Entry	Solvent (2 mM)[a]	Time/h	Yield[b]/%	
			lactone	diolide
1	CH_3CN	24	28	8.6
2	CH_3NO_2	24	25	3
3[c]	Et_2O	8	N.D.	N.D.
4[c]	THF	8	N.D.	trace
5[c]	CH_2Cl_2	8	<26	11
6[c]	toluene	8	47	22
7[c,d]	toluene	8	N.D.	N.D.

A solution of **1** with 2-DTC in CH_3CN (10 mL) was added DMAP and diluted with solvent (78 mL), followed by addition of iodine at room temperature. [a]Values in parentheses was the concentration without consideration of a change of total volume owing to mix plural solvents. [b]Isolated yield. [c]reflux. [d]Reaction was carried by using 2 equivalents of DMAP instead of iodine.

Table 3. Lactonization of 12-hydroxydodecanoic acid by using 2-DTC promoted by DMAP and iodine in CH_3CN–toluene



Entry	I_2 /equiv.	Concentration /mM[a]	Time/h	Yield[b]/%	
				lactone	diolide
1	0.5	2	20	40	21
2	1	2	8	50	19
3	2	2	8	47	19
4	1	1	8	57	16
5	2	1	8	67	15
6	4	1	8	77	14

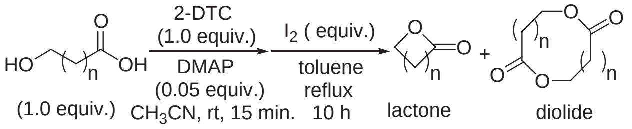
A solution of **1** with 2-DTC in CH_3CN (10 mL) was added DMAP and diluted with toluene (2 mM; 78 mL, 1 mM; 166 mL), followed by addition of iodine at room temperature. [a]The concentration without consideration of a change of total volume owing to mix plural solvents. [b]Isolated yield.

tion was carried in 1 mM solution of toluene in the presence of 4 equimolar amounts of iodine (Entry 6).[12]

Results of the lactonization using various ω-hydroxycarboxylic acids are listed in Table 4. The corresponding macrolactones were obtained in good to high yields along with a small amount of diolide under the reaction conditions mentioned above. The desired product was obtained in 58% yield when 11-hydroxyundecanoic acid was used (Entry 1). Fourteen to seventeen membered ring macrolactones were obtained in high yields when the cyclization was carried out using the corresponding ω-hydroxycarboxylic acids (Entries 3–6).

It is noted that a simple and 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 2–4 equimolar amounts of iodine.

Table 4. Lactonization of various ω-hydroxycarboxylic acids by using 2-DTC promoted by DMAP and iodine



Entry	n	I_2/equiv.	Yield[a]/% (ring size)	
			lactone	diolide
1	9	4	58 (12)	18
2	10	4	77 (13)	14
3	11	4	85 (14)	<8
4	12	4	87 (15)	<11
5	13	2	90 (16)	<6
6	14	2	92 (17)	<7

[a]Isolated yield.

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12 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 room temperature, the resultant solution was diluted by the addition of 166 mL of toluene and treated with iodine (179 mg, 0.707 mmol). The reaction mixture was stirred for 10 h at reflux temperature of toluene and then 10% aqueous sodium thiosulfate was added and the solvent was evaporated. The mixture was extracted with ethyl acetate, 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 (26.8 mg, 77%).

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