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A New Synthetic Method of Macrocyclic Lactones from ω-Iodoalkylacrylates

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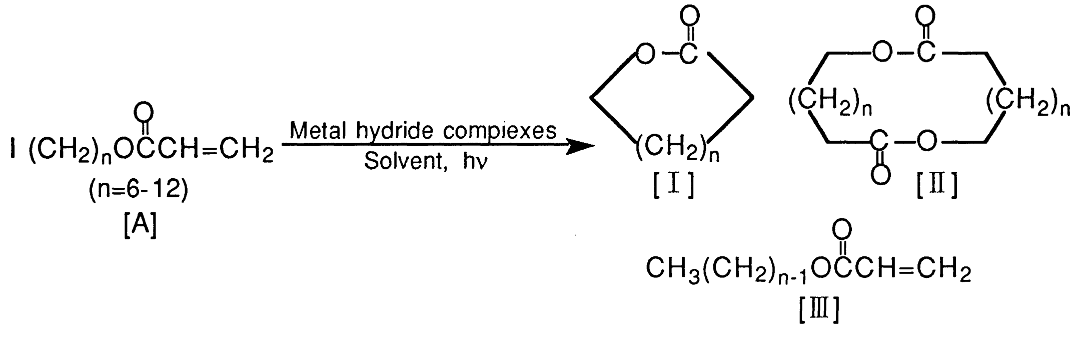
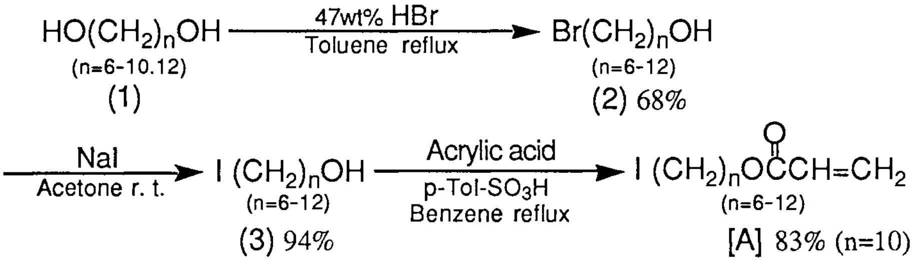
When the photostimulated cyclization reaction of ω-iodoalkylacrylates was performed in the presence of metal hydride complexes such as sodium cyanoborohydride($NaBH_3CN$), sodium borohydride($NaBH_4$) and potassium borohydride (KBH_4), the corresponding macrocyclic lactones were produced. The use of $NaBH_3CN$ led to the highest yield of lactones.

With respect to the synthesis of macrocyclic lactones by intramolecular cyclization reactions, a large number of studies have been reported.1-3) We have recently reported a n-Bu_3SnH mediated intramolecular free radical cyclization reaction.4) Here we report a new synthetic method for producing macrocyclic lactones[I] by the photoirradiation of ω-iodoalkylacrylate[A] in the presence of various kinds of metal hydride complexes (Scheme 1). Although several reports have been concerned with the reduction of organic halides by metal hydride complexes under photoirradiation,5-7) none of them have referred to the photostimulated cyclization reaction giving medium sized ring lactones.



Scheme 1. Cyclization Reaction of ω-Iodoalkylacrylates.

The synthesis of [A] was achieved in 3 steps from α, ω-diols(1) as shown in Scheme 2. ω-Bromoalkanols (2) with different chain lengths(n=6-12) were prepared from their corresponding diols with 47% HBr. These bromides were smoothly converted to the corresponding iodides(3) by the reaction with sodium iodide in acetone. [A] was obtained by esterification of acrylic acid with(3).

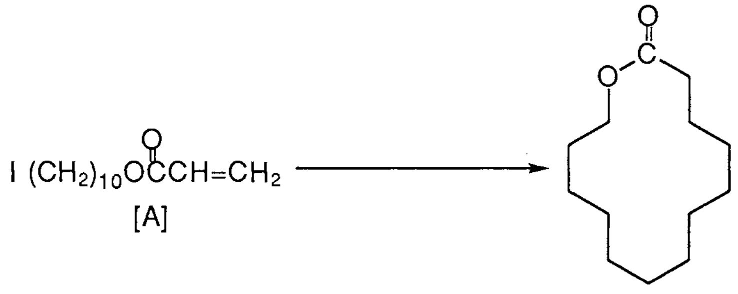


Scheme 2. Preparation of ω-Iodoalkylacrylates.

A mixture of 1mmol of [A] and 5mmol of the metal hydride complex in 400ml of solvent was irradiated with 100W high-pressure mercury lamp for 3 hours under nitrogen. After the reaction was completed, the metal hydride complex was removed by treatment with brine and then the solvent was evaporated *in vacuo*. The products thus obtained were purified by column chromatography on silica-gel (n-hexane : benzene = 40 : 60) and identified by FT-IR, GC-MS, ^{1}H-NMR and ^{13}C-NMR.

Table 1 shows the results of the photostimulated cyclization of 10-iododecylacrylate[A] by using metal hydride complexes.

Table 1. Effects of Metal hydride complex [a)]



[I]

Reagent	Solvent	Conversion / % [b)]	Selectivity / % [b)]			
			[I]	[II]	[III]	Others [c)]
$NaBH_3CN$	Methanol	100	87	12	1	-
$NaBH_4$	Ethanol	87	53	14	19	14
KBH_4	Ethanol	94	43	17	19	21
$LiBH_4$	Ether	92	-	-	14	86
$LiAlH_4$	Ether	100	-	-	-	100

a) Reaction conditions; 10-Iododecylacrylate: 1 mmol, reagent: 5 mmol, solvent: 400 ml, irradiation time: 3 h, temperature: room temp.
b) Determined by GC analysis. c) Reduction products.

From Table 1, it was found that $NaBH_3CN$ led to the highest yield of the lactone[I]. The cyclization reaction also occurred when $NaBH_4$ and KBH_4 were used, but the yield of the lactone decreased. Lithium borohydride($LiBH_4$) and lithium aluminum hydride ($LiAlH_4$), provided the reduction products of the ester group of [A] (for example, $I(CH_2)_{10}OCOCH{=}CH_2 \rightarrow CH_3(CH_2)_9OH + CH_3(CH_2)_2OH$.).

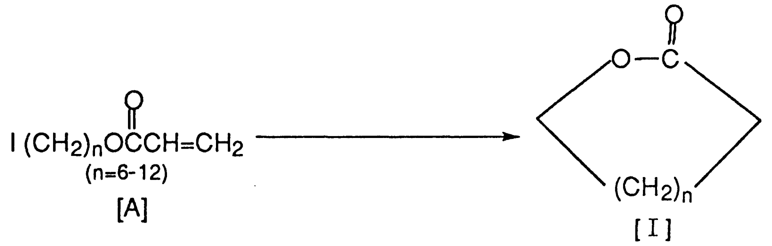
Table 2. Effects of solvent [a)]

Solvent	Conversion / % [b)]	Selectivity / % [b)]			
		[I]	[II]	[III]	Others [c)]
methanol	100	87	12	1	-
ethanol	100	71	29	-	-
acetonitrile	100	65	22	2	11
THF	59	48	11	5	36
DMF	55	36	3	18	33

a) Reaction conditions; 10-Iododecylacrylate: 1 mmol, $NaBH_3CN$: 5 mmol, solvent: 400 ml, irradiation time: 3 h, temperature: room temp.

b) Determined by GC analysis. c) Others consisted of several components.

Table 3. Photocyclization Reaction of ω-Iodoalkylacrylate using $NaBH_3CN$ [a)]



Ring size (n)	Conversion / % [b)]	Selectivity / % [b)]				Isolated yield of [I] / %
		[I]	[II]	[III]	Others [c)]	
10 (6)	97	83	13	4	2	74
11 (7)	98	80	17	3	2	73
12 (8)	100	84	14	2	2	79
13 (9)	100	87	11	2	1	81
14 (10)	100	87	12	1	-	82
15 (11)	100	90	10	-	-	86
16 (12)	100	93	7	-	-	90
14 (10)[d)]	96	75	3	14	8	72

a) Reaction conditions; ω-Iodoalkylacrylate: 1 mmol, $NaBH_3CN$: 5 mmol, methanol: 400 ml, irradiation time: 3 h, temperature: room temp.

b) Determined by GC analysis. c) Unidentified compounds.

d) Reaction conditions; ω-Iodoalkylacrylate: 1 mmol, n-Bu_3SnH: 1 mmol, benzene: 400 ml, AIBN: 0.1 mmol, temperature: room temp.

In order to elucidate the dependence on solvents, the cyclization of 10-iododecylacrylate was carried out using various solvents (Table 2). It was found that methanol was the best solvent. Seven photocyclization reactions giving 10- to 16-membered were investigated. The results in Table 3 show that all the reactions give lactones in high yields. Noteworthy was the fact that the medium sized ring lactones (10, 11-membered), which were difficult to obtain by a standard cyclization method, can also be obtained in good yield. Next, free radical cyclization reaction was carried out using Bu_3SnH and AIBN as a radical initiator (Table 3). Bu_3SnH / AIBN having high conversion of ω-iodoalkylacrylate showed lower yield of [I] than this photocyclization reaction.

Cyclization of 10-iododecylacrylate under variety conditions were investigated(Table 4). From Table 4, $NaBH_3CN$ and photoirradiation has been found very useful for cyclization reaction. And by comparing entry 4 with entry 8, it is assumed that the cyclization reaction proceeds by a radical chain mechanism involving the cyanoborane radical anions($BH_2^{\cdot}CN^-$).

Table 4. Cyclization of 10-Iododecylacrylate under variety conditions [a)]

Entry	Conditions (irradiation time)	Conversion / % [b)]	Selectivity / % [b)]			Others [c)]
			[I]	[II]	[III]	
1	h ν , (3h)	11	-	-	85	15
2	$NaBH_3CN$, dark, (10h)	0	-	-	-	-
3	$NaBH_3CN$, reflux, (3h)	16	-	-	100	-
4	$NaBH_3CN$, AIBN[d)], (3h)	97	61	18	3	18
5	$NaBH_3CN$, h ν , (3h)	100	87	12	1	-
6	$NaBH_3CN$, h ν ,hydroquinone[e)], (3h)	68	59	10	9	22

a) Reaction conditions; 10-Iododecylacrylate: 1 mmol, $NaBH_3CN$: 5 mmol, methanol: 400 ml, temperature: room temp. b) Determined by GC analysis.
c) Others consisted of several components. d) Radical initiator (1 mmol) was used.
e) Radical quencher (1 mmol) was used.

From these results, the present study provides a new synthetic method for macrocyclic lactones.

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