

A Convenient Method for Iodolactonization

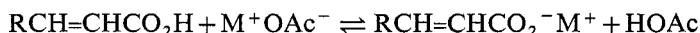
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Abstract

Iodo lactones are conveniently prepared under neutral conditions by treatment of unsaturated carboxylic acids with thallium(i) acetate and iodine in a non-polar solvent.

Recently we reported¹ a method for iodolactonization² wherein an unsaturated thallium(i) carboxylate is treated with iodine in ether at 20°. Although this method is satisfactory for simple compounds it has the disadvantage that pre-formation of the thallium(i) salt requires treatment of the unsaturated acid with thalious ethoxide, a strong base which may be detrimental to substrates possessing base-sensitive functional groups. We now report a simple procedure which circumvents this difficulty, viz. treatment of the parent unsaturated carboxylic acid with thallium(i) acetate (1 equiv.) and iodine in a non-polar solvent at 20°. Despite the low solubility of thallium(i) acetate in such solvents, iodo lactones are formed in yields comparable to those obtained using the pre-formed thallium(i) salt of the acid.¹ Other carboxylate salts, e.g. sodium acetate or ammonium acetate, can also be used (Table 1), but in these cases yields of products are generally lower than with thallium(i) acetate. It is presumed that the acidic substrate reacts with the metal salt to give an equilibrium, i.e.



which is shifted to the right on subsequent iodolactonization. However, treatment of the benzyl ester (2) of 2-(cyclohex-2'-en-1'-yl)acetic acid with thallium(i) acetate and iodine in dichloromethane for 19 h gave the iodo lactone (6) (80%) and benzyl acetate (75%); this suggests that the carboxylate anion may not be involved.

In the case of but-3-enoic acid (4) only thallium(i) acetate gave a reasonable yield of the kinetically controlled product (9), although the addition of sulfolane when sodium acetate was used as the salt resulted in an increase in its yield. A detailed study of the iodolactonization of cyclohex-1-enylacetic acid (5) with thallium(i) acetate and iodine showed that the kinetically controlled γ -iodo β -lactone (10) was

¹ Cambie, R. C., Hayward, R. C., Roberts, J. L., and Rutledge, P. S., *J. Chem. Soc., Perkin Trans. I*, 1974, 1864.

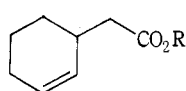
² House, H. O., 'Modern Synthetic Reactions' 2nd Edn, p. 441 (Benjamin: Menlo Park, Cal., 1972).

formed as the major product but, as expected,¹ it rapidly isomerized to the thermodynamically more stable β -iodo γ -lactone (7) after workup. By carrying out this reaction with sodium acetate in a ^1H n.m.r. tube and the instrument on fast scan it was possible to show that the γ -iodo β -lactone (10) was formed initially in this case also, but it rapidly isomerized *in situ*.

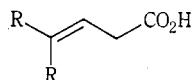
Table 1. Iodo lactones from unsaturated acids

Substrate	Salt	Solvent	Time (h)	Iodo lactone ^A	Yield (%)
(1)	TIOAc	CH_2Cl_2	24	(6) ^B	90
(1)	NaOAc	CH_2Cl_2	24	(6)	85
(1)	NH_4OAc	CHCl_3	21	(6)	99
(1)	AgClO_4	CH_3CN	3	(6)	73
(3)	TIOAc	CH_2Cl_2	0.5 ^C	(8) ^D	65
(3)	NaOAc	CHCl_3	21	(8)	60
(3)	NH_4OAc	CHCl_3	21	(8)	60
(3)	AgClO_4	CH_3CN	10	(8)	65
(4)	TIOAc	CH_2Cl_2	21	(9) ^E	53
(4)	NaOAc	CH_2Cl_2	20	(9)	trace
(4)	NH_4OAc	CHCl_3	5	(9)	12
(5)	TIOAc	CH_2Cl_2	0.2	(7) ^F	32
				(10) ^E	48
(5)	NaOAc	CHCl_3	0.2	(7)	60
(5)	NH_4OAc	CHCl_3	0.75	(7)	51
				(10)	8

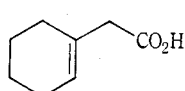
^A All products were identified by direct comparison (mixed m.p., i.r., mass spectrum, and ^1H n.m.r. spectrum) with authentic samples. ^B M.p. 63–65°. ^C Refluxed. ^D M.p. 76–77°. ^E Oil. ^F M.p. 115°.



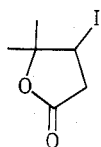
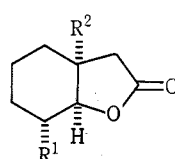
- (1) R = H
(2) R = CH_2Ph



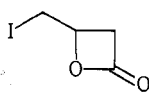
- (3) R = Me
(4) R = H



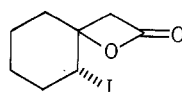
(5)



(8)



(9)



(10)

	R ¹	R ²
(6)	I	H
(7)	H	I

The present procedure provides a convenient method for iodolactonization under neutral and non-aqueous conditions. The use of thallium(I) acetate appears to be particularly valuable when the desired product is unstable or is the kinetically controlled product. Recently Bartlett and Myerson³ have shown that iodine and acetonitrile alone will effect iodo lactone formation, while Corey and Hase⁴ have achieved bromolactonization by a modification of our original procedure.¹

³ Bartlett, P. A., and Myerson, J., *J. Am. Chem. Soc.*, 1978, **100**, 3950.

⁴ Corey, E. J., and Hase, T., *Tetrahedron Lett.*, 1979, 335.

Experimental

Melting points were determined on a Kofler block and are uncorrected. Infrared spectra were measured for CCl_4 solutions with Perkin-Elmer 237, 337 or 397 spectrophotometers, and the u.v. spectrum with a Unicam SP 800A spectrophotometer. ^1H n.m.r. spectra were recorded for deuteriochloroform solutions on a Varian T60 spectrometer and mass spectra with a Varian MAT CH7 instrument. Preparative t.l.c. was carried out on 1 mm plates of Kieselgel PF₂₅₄₊₃₆₆ (Merck).

Iodolactonization of Unsaturated Acids; General Procedure

Iodine (1.5 equiv.) was added over 1 min with swirling to a suspension of the unsaturated acid (1 equiv.) and thallium(i) acetate (1–1.2 equiv.) in dichloromethane or chloroform (20 ml). The mixture was stirred at 20° for the appropriate time (see Table 1) and the precipitate of thallium(i) iodide was filtered off and washed well with solvent. The filtrate was washed with aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and then with water. Removal of solvent gave the iodo lactone which was purified by preparative t.l.c.

When sodium acetate or ammonium acetate was used instead of thallium(i) acetate, the reaction mixture was poured directly into the sodium thiosulfate solution without filtering. When sulfolane was present in the solvent it was removed by passing the organic solution through a short column of silica gel.

Benzyl 2-(Cyclohex-2'-en-1'-yl)acetate

Benzyl alcohol (0.50 g, 4.63 mmol) was added to a solution of 2-(cyclohex-2'-en-1'-yl)acetic acid (1) (0.80 g, 5.71 mmol) in trifluoroacetic anhydride (1.50 g, 7.14 mmol) and the mixture was kept at 20° for 16 h. The solution was poured into 5% aqueous sodium hydroxide (40 ml) and extracted with ether (2 × 50 ml). The extracts were washed with water, dried, and concentrated to give an oil (0.91 g). Preparative t.l.c. of a portion of the oil (0.20 g) with chloroform/hexane (2:1) gave *benzyl 2-(cyclohex-2'-en-1'-yl)acetate* (2) (0.15 g, 75%), b.p. 130–132°/0.7 mm (Found: C, 78.6; H, 7.8. $\text{C}_{15}\text{H}_{18}\text{O}_2$ requires C, 78.2; H, 7.9%). ν_{max} 3025, 2925, 1726, 1450, 1380, 1345, 1240, 1160, 1000, 700 cm^{-1} . λ_{max} 212 nm (ϵ 5370). ^1H n.m.r. δ (CDCl_3) 1.06–2.80 (m, 9H, H 2,1',4',5',6'), 5.10 (s, 2H, benzylic H), 5.56 (m, 2H, H 2',3'), and 7.30 (s, 5H, aryl H).

Iodolactonization of Benzyl 2-(Cyclohex-2'-en-1'-yl)acetate

Iodine (0.10 g, 0.39 mmol) was added over 1 min to a suspension of *benzyl 2-(cyclohex-2'-en-1'-yl)acetate* (2) (40 mg, 0.17 mmol) and thallium(i) acetate (0.10 g, 0.38 mmol) in dichloromethane (7 ml). The mixture was heated under reflux for 19 h, chloroform (20 ml) was added, and the mixture was filtered. Workup gave an oil (62 mg) which was separated by preparative t.l.c. with benzene to give (i) 5 α -iodo-1 α ,6 α -7-oxabicyclo[4,3,0]nonan-8-one (6) (37 mg, 80%), m.p. 63–65° (lit.¹ 64–65°) (correct i.r. and ^1H n.m.r. spectra¹), and (ii) *benzyl acetate* (19.5 mg, 75%) as an oil (correct i.r., mass spectrum and ^1H n.m.r. spectrum).