

Intramolecular Reductive Cyclization of Unsaturated Keto- or Aldo-esters by Samarium(II) Di-iodide: A Ready Synthesis of Bicyclic γ -Lactones

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Treatment of unsaturated keto- or aldo-esters with SmI_2 in tetrahydrofuran (THF) or THF–hexamethylphosphoramide affords bicyclic γ -lactones in moderate to good yields.

Numerous efforts have been made to prepare bicyclic γ -lactones, not only because their abundant occurrence in Nature, but also because of their usefulness as versatile synthons. As a result, various methods have been developed, *e.g.*, electrophilic ring-opening of a cyclopropanecarboxylic acid ester,¹ or spiro-oxirane;² the free-radical cyclization of a bromo-acetal;³ the intramolecular lactonization of an unsaturated ester by PhSeCl ;⁴ and the oxidative cyclization of an alkene containing a tertiary hydroxy-group by chromium(v).⁵

We have recently reported the intermolecular reductive coupling of α,β -unsaturated esters and carbonyl compounds by samarium(II) di-iodide (SmI_2), to give γ -lactones.⁶ We thought that if this procedure could be extended to an intramolecular reaction, bicyclic γ -lactones would be produced in one step; and indeed, they may be obtained from unsaturated keto- and aldo-esters in moderate to good yields under mild conditions.

Several *trans*-unsaturated keto- or aldo-esters were prepared by standard procedures.⁷ Treatment of these substrates with SmI_2 in tetrahydrofuran (THF) or THF–hexamethylphosphoramide (HMPA) (10:1) afforded moderate to good yields of bicyclic γ -lactones.[†]

[†] A typical experimental procedure is as follows. To a refluxing blue–green solution of SmI_2 (0.4 M; 10 ml) in THF–HMPA (9–1 ml) was added a THF (1 ml) solution of 8-oxonon-2-enoate (**1**; $\text{R} = \text{Me}$, $n = 2$, 198 mg, 1 mmol) and *t*-butyl alcohol (1 mmol) with stirring. The refluxing was continued for 1 h, during which period the solution turned yellow–green. After the usual work-up, the bicyclic γ -lactone (**2**; $\text{R} = \text{Me}$, $n = 2$, 104 mg, 0.66 mmol) was obtained in 66% yield by flash column chromatography on silica gel (hexane–ethyl acetate, 10:1, as eluant). The isomer ratio was determined by ^1H n.m.r.⁹ and g.l.c. The product gave satisfactory analytical results, and the i.r. spectrum (ν_{CO} 1765 cm^{-1}) and mass spectrum (M^+ 154) were in accord with the structure assigned.

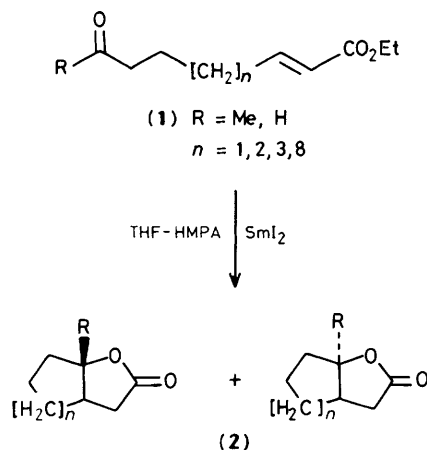
Reaction of *trans*-ethyl 8-oxonon-2-enoate (**1**; $\text{R} = \text{Me}$; $n = 2$) with SmI_2 was examined under a variety of conditions (changing solvent, temperature, time, amount of SmI_2 , and addition of Fe^{III} catalyst). Results are shown in Table 1 (entries 2–6). Reaction proceeded either at room temperature or at reflux; reflux conditions usually gave higher yields. HMPA was not essential as co-solvent, but its addition tended to improve the product yields. Addition of a trace of FeCl_3 is effective for the Barbier-type reaction involving the use of SmI_2 ,⁸ but the yield was not improved in this case. The use of an excess of SmI_2 gave more satisfactory results.

Table 1. Intramolecular reductive cyclization of unsaturated keto- or aldo-esters by SmI_2 .^a

Entry	<i>n</i>	(1) R	Reaction conditions	Isolated yield (%)	Isomer ratio ^b	
					<i>trans</i> : <i>cis</i>	
1	1	Me	2 SmI_2 , THF, reflux, 4 h	92	90 : 10	
2	2	Me	2 SmI_2 , THF, reflux, 4 h	56	64 : 36	
3	2	Me	2 SmI_2 , THF–HMPA, 25 °C, 5 h	36 (42) ^c	70 : 30	
4	2	Me	2 SmI_2 , THF–HMPA, reflux, 1 h	47 (54) ^c	79 : 21	
5	2	Me	2 SmI_2 , THF–HMPA, reflux, 1 h, FeCl_3 (1%)	38 (43) ^c	66 : 34	
6	2	Me	4 SmI_2 , THF–HMPA, reflux, 1 h	66 (75) ^c	70 : 30	
7	3	Me	4 SmI_2 , THF, reflux, 1 h	45	80 : 20	
8	3	Me	2 SmI_2 , THF–HMPA, reflux, 1 h	40	75 : 25	
9	8	Me	4 SmI_2 , THF–HMPA, reflux, 1 h	40 ^d	— ^c	
10	1	H	4 SmI_2 , THF–HMPA, reflux, 1 h	43	— ^c	
11	2	H	4 SmI_2 , THF–HMPA, 25 °C, 5 h	30	75 : 25	
12	2	H	4 SmI_2 , THF–HMPA, reflux, 1 h	34	70 : 30	

^a **(1)** (1 mmol), Bu^tOH (1 mmol), THF (10 ml) or THF–HMPA (10 ml–1 ml). ^b Determined by ^1H n.m.r. and g.l.c. ^c G.l.c. yield.

^d 14-Hydroxypentadec-2-enoate was produced. ^e Not determined.



The bicyclic γ -lactone (2; R = Me, n = 2) was obtained as a mixture of *trans*- and *cis*-isomers in a *trans* to *cis* ratio of 70:30. The ratio was determined by the relative intensity of methyl proton absorption and g.l.c.⁹ It was almost independent of the reaction conditions; thus we infer that the bicyclic γ -lactone was the kinetic product of the reaction.

The analogous reaction occurred with ethyl 7-oxo-oct-2-enoate (1; R = Me, n = 1), ethyl 9-oxodec-2-enoate (1; R = Me, n = 3), ethyl 7-oxohept-2-enoate (1; R = H, n = 1), and ethyl 8-oxo-oct-2-enoate (1; R = H, n = 2) to produce the corresponding bicyclic γ -lactones as mixtures of *trans*- and *cis*-isomers in good yields (Table 1, entries 1, 7—8, 10—12).¹⁰

However, the longer-chain unsaturated keto-esters such as ethyl 14-oxopentadec-2-enoate (1; R = Me, n = 8) did not yield (2); simple carbonyl reduction occurred instead (entry 9).

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