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.†

Reaction of *trans*-ethyl 8-oxonon-2-enoate (**1**; R = 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 improved 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	(1) *n*	R	Reaction conditions	Isolated yield (%)	Isomer ratio[b] *trans*:*cis*
1	1	Me	$2SmI_2$, THF, reflux, 4 h	92	90:10
2	2	Me	$2SmI_2$, THF, reflux, 4 h	56	64:36
3	2	Me	$2SmI_2$, THF–HMPA, 25 °C, 5 h	36 (42)[c]	70:30
4	2	Me	$2SmI_2$, THF–HMPA, reflux, 1 h	47 (54)[c]	79:21
5	2	Me	$2SmI_2$, THF–HMPA, reflux, 1 h, $FeCl_3$ (1%)	38 (43)[c]	66:34
6	2	Me	$4SmI_2$, THF–HMPA, reflux, 1 h	66 (75)[c]	70:30
7	3	Me	$4SmI_2$, THF, reflux, 1 h	45	80:20
8	3	Me	$2SmI_2$, THF–HMPA, reflux, 1 h	40	75:25
9	8	Me	$4SmI_2$, THF–HMPA, reflux, 1 h	40[d]	
10	1	H	$4SmI_2$, THF–HMPA, reflux, 1 h	43	—[e]
11	2	H	$4SmI_2$, THF–HMPA, 25 °C, 5 h	30	75:25
12	2	H	$4SmI_2$, 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.

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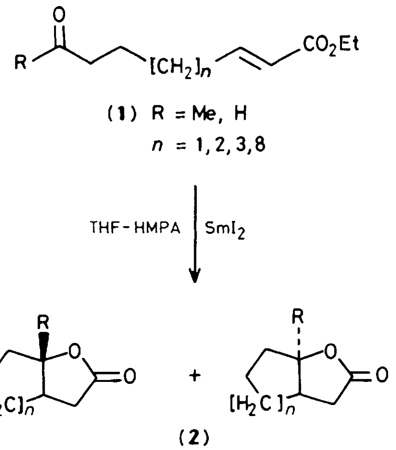
† A typical experimental procedure is as follows. To a refluxing blue-green solution of SmI_2 (0.4 M; 10 ml) in THF–HMPA (9–1 ml) was added a THF (1 ml) solution of 8-oxonon-2-enoate (**1**; R = Me, *n* = 2, 198 mg, 1 mmol) and t-butyl alcohol (1 mmol) with stirring. The refluxing was continued for 1 h, during which period the solution turned yellow-green. After the usual work-up, the bicyclic γ-lactone (**2**; R = 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.



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).

Received, 23rd February 1987; Com 241

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