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The First Preparation of β-Lactones by Radical Cyclization

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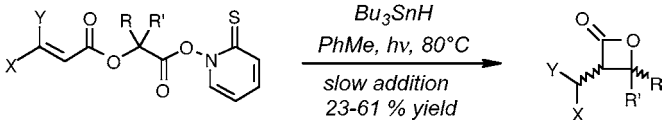
ABSTRACT



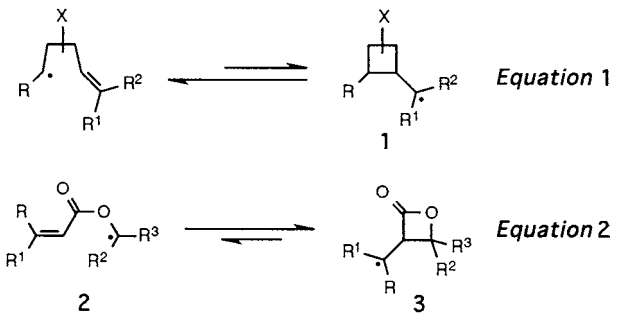
***β*-Lactones have, for the first time, been prepared by 4-*exo-trig* radical cyclization. Thus, α-ethenoyloxy radicals react in the presence of tributylstannane in a photothermal process to give *β*-lactones. Highest yields were obtained when groups capable of stabilizing a carbon-centered radical were present at the 3-position of the alkenoate acceptor.**

The use of radical cyclization for construction of four-membered rings has, until recently,[1] been problematic as a result of the preference for cyclobutylalkyl radicals **1** to undergo ring-opening (eq 1, Scheme 1).[2] In particular, *β*-lactams have been prepared via several different types of radical cyclization,[3−5] However, to date no method has been adumbrated that allows an analogous 4-*exo-trig* radical cyclization to prepare *β*-lactones.

We reasoned that cyclization of an *O*-(alkenoyl)oxyalkyl radical **2** (eq 2, Scheme 1), bearing radical-stabilizing substituents R and R[1], would allow for an unprecedented 4-*exo-trig* preparation of *β*-lactones (via (3-oxetanonyl)-methyl radical **3**). We here report the results of our preliminary investigation of this reaction, which indicate that the generation of radicals such as **2** is facile and that these radicals do cyclize to give *β*-lactones. Thus, a dilute benzene solution of (1-bromopropyl)-cinnamate (**4**)[6] and Bu_3SnH (9 mM in each reagent) was added via syringe pump to a refluxing solution of AIBN (0.25 equiv) in the same solvent, and the reaction was heated at reflux for 4 h (final concentration 1.3 mM), yielding 3-benzyl-4-ethyloxetan-2-one (**5**) in 17% yield (*cis*:*trans* 1:1)[7] and the directly reduced product, propyl cinnamate (**6**), in 20% yield (Scheme 2). It is noteworthy that butyrolactone **7**, the product of the alternative 5-*endo*-cyclization, was not observed in the product mixture.

When the reaction was repeated under the same conditions, using toluene in the place of benzene, similar yields of the same products were obtained (Table 1, entries 1−3). Again no trace of the 5-*endo*-cyclization product (**7**) was observed among the crude reaction products. In these reactions, the

Scheme 1. Radical Cyclization to Prepare Four-Membered Rings



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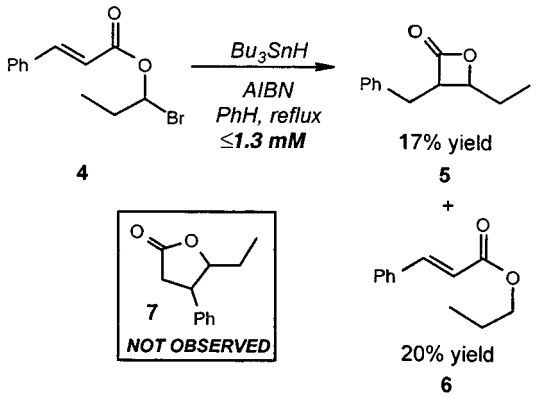
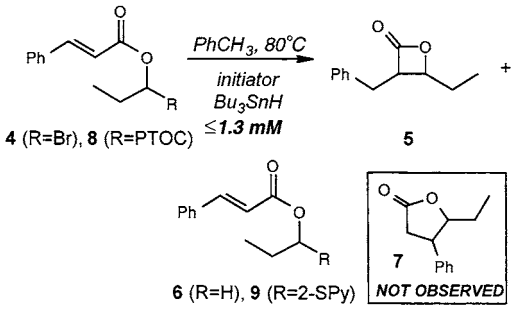
Scheme 2. Preparation of 3-Benzyl-4-ethyl Oxetan-2-one 5 by 4-*exo*-Cyclization



mode of addition of the reagents and the concentration was crucial. When a solution of stannane and AIBN was added slowly to a heated toluene solution of bromide **4**, no cyclized products were isolated, and after chromatography **6** was the only product of the reaction, (45% yield, entry 5), while increasing the final concentration (to 28 mMol, entry 6) also encouraged reduction and obviated cyclization. When slow addition of the reagents was not employed, no lactone was obtained (entry 7). To examine the effect of the nature of the radical precursor, we prepared *N*-hydroxypyridine thione ester (**8**)[8] and subjected it to the conditions described above (Table 1, entries 8−10). Once again, cyclization to give **5** was observed, but the yield of β-lactone was lower than previously observed (cf. entries 1−4); in this case, excluding AIBN and utilizing in its place photothermal initiation (using a simple desk lamp fitted with a 300-W tungsten bulb) gave the best yield of **5** (entry 10). Observing that in no reaction of **8** did the yield of β-lactone surpass that obtained using bromide **4**, it seemed reasonable to deduce that the manner of generation of the first-formed radical (**2**) was not as important as the stabilization of the radical (**3**) produced via cyclization. Thus, we examined the use of 3,3-disubstituted enoates bearing groups capable of stabilizing an unpaired electron, in the desire of improving cyclization yields by enhancing the stability of **3**. The results are summarized in Table 2.

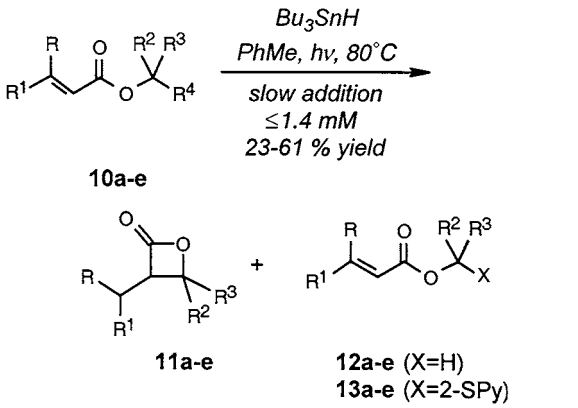
Table 1. 4-*exo-trig* Radical Cyclization of Functionalized Cinnamate Esters **4** and **8**



entry	R	addition time[a] (h)	reaction time[b] (h)	initiation	yield (%) 5	6	9
1	Br	1	2.5	AIBN	20	24	
2	Br	1	3.5	AIBN	20	20	
3	Br	1	4.5	AIBN	17	23	
4	Br	2	3	AIBN	23	23	
5	Br	3	5	AIBN	tr	45	
6[c]	Br	3	12	AIBN	tr	45	
7[d]	Br	-	4.5	AIBN	0	50	
8	PTOC[e]	2	3	AIBN	0	71	0
9	PTOC	2	3	AIBN	10	40	7
10	PTOC	2	4	300 W[f]	22	38	4

[a] Time taken to add solution of reagents to reaction vessel. [b] Total reaction time. [c] Final concentration of 28 mM. [d] Reagents combined directly. [e] PTOC = pyridine-2-thione-*N*-oxycarbonyl. [f] Flask irradiated (300-W tungsten bulb).

Table 2. Preparation of β-Lactones (**11**) via Radical Cyclization of α-Functionalized Esters of Substituted Enoates (**10**)



entry[a]	R	R^1	R^2	R^3	R^4	yield (%)[b] 11	12	13
1	Ph	Ph	Et	H	PTOC	59	5	2
2[c]	Ph	Ph	Et	H	PTOC	47	10	3
3[d]	Ph	Ph	Et	H	PTOC	56	7	8
4	Ph	Ph	Me	Me	PTOC	61	7	8
5[e]	Ph	Ph	Me	Me	PTOC	57	6	10
6[f]	Ph	Ph	Me	Me	PTOC	13	49	15
7	Ph	Ph	H	H	PTOC	32	23	10
8[g]	Ph	Ph	H	H	PTOC	15	50	13
9[h]	Ph	Ph	H	H	PTOC	27	39	12
10	PhS	PhS	Et	H	PTOC	55	14	4
11[h]	PhS	PhS	Et	H	PTOC	51	21	8
12	TolS	TolS	Et	H	PTOC	52	18[i]	0

[a] General procedure: 50 mL of a 0.5 mM toluene solution of ester and hydride was added over a 2 h period via syringe pump to a heated vessel (irradiated by a 300-W tungsten lamp) containing toluene (300 mL), after which the reaction was continued until the substrate had been consumed (5−8 h). [b] Isolated yield (*cis:trans* ≈ 1:1). [c] Heated at 110°C. [d] 150-W lamp used. [e] Separate solutions of substrate and hydride added via syringe pumps. [f] Solution of hydride added to solution of ester in toluene. [g] AIBN used in place of 300-W lamp. [h] Final concentration of 2.5 mM. [i] Solvent acetonitrile/hexane (1/1), reaction temperature 59 °C.

Thus, the presence of an additional phenyl substituent in the 3-position of the enoate (compound **10a**, prepared from 3-phenyl cinnamic acid) greatly enhanced cyclization at the

expense of reduction and lactone **11a** (R = R^1 = Ph, R^2 = H, R^3 = Et) was isolated in 59% yield as a roughly 1:1 mixture of (separable) *cis*- and *trans*-isomers (entry 1). The reaction of an analogous ester containing a *gem*-dimethyl substituent pattern (compound **10b**, entry 4) led to lactone **11b** (R = R^1 = Ph, R^2 = Me, R^3 = Me) in 61% yield, while the parent ester **10c** gave **11c** (R = R^1 = Ph, R^2 = R^3 = H) less efficiently (entries 7−9), presumably because of the high reactivity of the intermediate primary radical.

These reactions have shown for the first time that the inherent instability of (oxetan-2-one-4-yl)methyl radicals of the general structure **3** can be tamed to allow for the preparation of β-lactones. However, although of utility in this transformation, the *gem*-diphenyl motif of the products of these latter reactions does not readily lend itself to subsequent synthetic transformations.

In an attempt to ameliorate this deficiency, we next examined the reactions of arylthio-substituted analogues in the reaction process.[4] We were gratified to observe that compounds **10d** and **10e** (both prepared from 3,3-dichloroacrylic acid) undergo 4-*exo*-cyclization in synthetically useful yields, to give thioacetal lactones **11d** (R = R^1 = SPh, R^2 = H, R^3 = Et) and **11e** (R = R^1 = STol, R^2 = H, R^3 = Et) (Table 2, entries 10−12). The thioacetal functionality of these lactones is far riper for further reaction than in the case of lactones **11** and **12**, thereby offering a new potential entry to bioactive β-lactones and their analogues by this methodology.

Thus we have demonstrated for the first time that, despite the inherent instability of the intermediate radicals, functionalized β-lactones may be prepared via 4-*exo*-*trig* radical cyclization. The extrapolation of these preliminary data is currently the focus of intense scrutiny in our laboratories.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5** and **11a**, **b**, and **e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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