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Formation of Lactones via a Radical Ring Closure Mechanism

Athelstan L. J. Beckwith and Paul E. Pigou

Research School of Chemistry, Australian National University, G.P.O. Box 4, Canberra, A.C.T. 2601, Australia

Suitable alkenoyloxymethyl iodides or selenides are converted into lactones upon treatment with tributyl-stannane or -germane; the reaction involves highly regioselective and stereoselective ring closure of alkenoyloxymethyl radicals (1).

Ring closure *via* radical reactions has recently been applied extensively in natural product synthesis.¹ In view of the widespread occurrence in nature of γ - and δ -lactones we have now examined the practicability of using free radical methods for their formation from suitably constituted unsaturated acids by the general route outlined in Scheme 1.

Initial experiments were conducted with the selenide (2a)

which was readily prepared from the parent acid by treatment with chloromethyl phenyl selenide.² Treatment of (2a) with tributylstannane in the usual way³ gave mixtures of the direct reduction product (2c) and the γ -lactone (8). As expected³ the yield of the latter increased when the concentration of stannane was decreased (see Table 1).

The results obtained when various iodides or phenyl

Table 1. The formation of lactones via radical cyclisation.ª

Entry	Ester/м	Hydride/м	Products (relative yield/%)	Yield/%
1	(2a)(0.2)	Bu ₃ SnH (0.22)	(2c)(66), (8)(34)	95
2	(2a)(0.05)	Bu ₃ SnH (0.055)	(2c)(40), (8)(60)	96
3	(3a)(0.05)	Bu ₃ SnH (0.05)	(3c)(18), (9)(82)	80
4	(4a)(0.03)	$Bu_{3}SnH(0.03)$	(4c)(64), (10)(4), (12)(32)	100
5	(4a) (0.046)	Bu ₃ GeH (0.047)	(4c)(12),(10)+(12)(88)	5ъ
6	(5a) (0.023)	$Bu_3SnH(0.032)$	(5c)(45), (11)(17), (13)(38)	90
7	(5a) (0.048)	$Bu_{3}GeH(0.06)$	(5c)(12),(11)(26),(13)(62)	83
8	(6a)(0.02)	$Bu_3SnH(0.02)$	(6c) (>97)	95
9	(6b) (0.04)	Bu ₃ GeH (0.04)	(6c) (95), ° (14) (5)°	ca. 85°
10	(7b) (0.005)	$Bu_{3}SnH(0.005)$	(7c)(33), (15)(67)	90
11	(7b) (0.02)	$Bu_{3}GeH(0.02)$	(7c) (8), c (15) (92) ^c	<i>ca</i> . 90°

^a Reactions were conducted in benzene or t-butylbenzene under nitrogen at 80 °C. ^b The remainder was starting material (4a). ^c Yields were determined by n.m.r. spectroscopy.

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`CO₂R

(4) R' = H

(5) R' = Me

CO₂Me

Ċ0₂R

(7)

CO2R

Ρh

a; $\mathbf{R} = CH_2SePh$ **b**; $\mathbf{R} = CH_2I$ **c**; $\mathbf{R} = Me$

selenides were treated with tributyl-stannane or -germane are

given in Table 1. In conformity with previously established

guidelines⁴ for regio- and stereo-selectivity in radical cyclisation, each ring closure proceeds exclusively in the *exo*-mode

and, where appropriate, affords only cis-fused products. As

expected,⁵ tributylgermane mediated reactions afford higher

relative yields of cyclised products than do reactions of

tributylstannane, but in some cases (entry 5) it was difficult to

tributylstannane (or germane) to open chain radicals (1) is

unlikely to vary significantly with radical structure, the

relative yields of cyclised and open chain products under

similar experimental conditions should reflect the rates of ring

closure. On this basis the disubstituted double bond in the

radical derived from (3a) is more reactive than the tetrasubsti-

tuted system in (4a) (compare entries 3,4), but the presence of the methyl group in (5a) enhances the cyclisation rate (compare entries 4,6). Formation of the the δ -lactone (14) by

Since the rate constant for hydrogen atom transfer from

sustain the chain and poor overall yields were obtained.

(3)

CO2R

(6)

1,6-ring closure is clearly very slow, but the carbonyl group in the radical leading to (15) has a powerful activating effect.

Most of the systems studied were not suitable for accurate kinetic analysis. However, a series of quantitative experiments with the selenide (2a) and tributylstannane when conducted in the usual way³ gave log $k_c/k_{\rm H} = (2.48 \pm 0.4) (5.52 \pm 0.3)/(2.3 \text{ RT})$ kcal mol⁻¹ and $k_c/k_H = 0.12 \text{ M}^{-1}$ at 80 °C, where $k_{\rm H}$ is the rate constant for hydrogen atom transfer from the stannane to the radical derived from (2a).† Separate work in this laboratory⁶ indicates that the value of $k_{\rm H}$ for radicals of the general type (1) is ca. 0.75 that for simple primary radicals $(6.3 \times 10^6 \text{ s}^{-1} \text{ at } 80 \text{ °C})^7$ and that k_c is therefore *ca*. $5 \times 10^5 \text{ s}^{-1}$ at 80 °C. This is somewhat less than that $(1.5 \times 10^6 \,\text{s}^{-1})$ for ring closure of the hex-5-envl radical at the same temperature⁸ presumably because of stabilisation of the radical centre in (1) by the adjacent oxygen and, more importantly, because barriers to rotation about the CO-O and O-CH₂ bonds retard attainment of the conformation required for ring closure.

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 $\dagger 1 \text{ kcal} = 4.184 \text{ kJ}.$

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(2)