## Free-radical-mediated Carbonylative Cyclisation of Alk-4-enyl Halides Leading to Cyclopentanones

## Ilhyong Ryu,\* Kazuya Kusano, Mitsuharu Hasegawa, Nobuaki Kambe and Noboru Sonoda\*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

Alk-4-enyl bromides and iodides **1**, when treated with the tributyltin hydride/CO system, undergo carbonylative cyclisation to give cyclopentanones in good yields (AIBN cat., benzene, 75–90 atm, [1] = 0.025-0.05 mol dm<sup>-3</sup>, 80 °C, 2–3 h).

Modern synthetic chemistry requires a new efficient methodology for the introduction of carbon monoxide into organic molecules. Free-radical carbonylation has considerable potential and indeed we have previously demonstrated free-radical formylation starting with organic halides.<sup>1</sup> The development of methods for construction of five-membered carbocycles largely owes its importance to the widespread occurrence of such substructures in natural and biologically active compounds.<sup>2</sup> Thus, we have planned the free-radical approach based on the carbonylative cyclisations of alk-4-enyl radicals, in which carbon monoxide constitutes one of the five carbon units of the ring (Scheme 1).<sup>3</sup> Here, we report the first accomplishment of this synthetic scheme based on the tin hydride mediated free-radical carbonylation.<sup>4</sup>

Cyclisation from pent-4-enyl radicals is known to be extremely inefficient, possibly owing to unfavourable interactions in the transition state.<sup>5</sup> In this regard, we felt that CO-trapping by the pent-4-enyl radical and the subsequent 5-*exo-trig* cyclisation process<sup>6</sup> could be achieved. Thus, when the free-radical reaction of 5-methylpent-4-enyl bromide **1a** with tributyltin hydride (1.2 equiv.) was conducted at 75 atm of CO (1 atm = 101 kPa) (10 mol% of AIBN, benzene, **[1a]** = 0.05 mol dm<sup>-3</sup>, 80 °C, 3 h), 2-ethylcyclopentanone **2a** was obtained as a major product (43%) together with 2-methylcyclohexanone **3a** (21%) (Table 1, run 1), derivatised from a thermodynamically more stable (3-keto)cyclohexyl radical.<sup>7</sup> The CO trapping/cyclisation sequence of alk-4-enyl radicals was examined for some other cases (Table 1). Terminal dialkyl or phenyl substitution at C-5 position of pent-4-enyl bromide



 
 Table 1 Carbonylative cyclisations of alk-4-enyl and alk-4-ynyl halides under free-radical conditions of tin hydride

Run	Substrate	Conditions <sup>a</sup>	Product(s)	Yield $(\%)^b$
1	1a	CO 75 atm, 80 °C, 3 h	2a	43
		0.05 mol dm <sup>-3</sup>	3a	$\overline{21}$
2	1b	CO 75 atm, 80 °C, 3 h	2b	<u>65</u>
		0.05 mol dm <sup>-3</sup>		<i>^</i>
3	1c	CO 80 atm, 80 °C, 3 h	2c	77,68
		$0.05  \text{mol}  \text{dm}^{-3}$		$\overline{(Z/E)} = 32/68)^c$
4	1d	CO 80 atm, 80 °C, 3 h	2d	62
		$0.025  \text{mol}  \text{dm}^{-3}$		
5	1e	CO 90 atm, 80 °C, 2 h	2e	60
		$0.025 \text{ mol dm}^{-3}$		
6	lf	CO 80 atm, 80 °C, 3 h	2f	40
		$0.05  \text{mol}  \text{dm}^{-3}$		$(E/Z = 40/60)^{c,d}$
7	1g	CO 80 atm, 80 °C, 2 h	$2g^e$	15
	0	$0.025 \text{ mol dm}^{-3}$	<b>4</b> Ĭ	53

<sup>*a*</sup> Reaction conditions: 1, 0.5 mmol; Bu<sub>3</sub>SnH, 0.6–0.7 mmol; AIBN, 0.06 mmol; benzene 10 or 20 ml; CO 75–90 atm. For the general procedure, see text. <sup>*b*</sup> Isolated yields. GLC yields are underlined. <sup>*c*</sup> Estimated by GLC. <sup>*d*</sup> Upon standing, Z isomer isomerised to E isomer. <sup>*e*</sup> Mixture of diastereoisomers (50:50). <sup>*f*</sup> Mixture of four stereoisomers (27:18:19:36).

caused selective 5-exo type of cyclisation leading to the cyclopentanones (runs 2-4). The 4-keto ester 2e was obtained similarly by carbonylative cyclisation of 1e (run 5). The substrate having the carbon-carbon triple bond could be also subjected to this reaction, giving a E/Z mixture of 2-(phenyl-vinylidene)cyclopentanone 2f (run 6). Usually, the formation of aldehydes via direct hydrogen abstraction of hex-5-enoyl radicals from tributyltin hydride is not observed, whereas the simple reduction by hydrogen abstraction of alk-4-enyl radicals is recognized as the side reaction. For example, in the cases of 1c and 1e, 2-methylhept-2-ene and ethyl hex-2-enoate were formed as the byproducts in 14 and 13% yield, respectively.

The following procedure is typical: 6-bromo-2-methylhept-2-ene (1c; 95.6 mg, 0.5 mmol),  $Bu_3^nSnH$  (189.2 mg, 0.6 mmol), AIBN (9 mg, 0.06 mmol) and benzene (10 ml) were placed in a 50 ml stainless steel autoclave with an inserted glass tube. The reaction mixture was stirred under carbon monoxide pressure (80 atm) at 80 °C for 3 h. After removal of the excess of carbon monoxide at room temperature *in vacuo* benzene was removed by evaporation and the resultant residue was dissolved in 5 ml of diethyl ether. The ethereal solution was treated with saturated aqueous potassium fluoride solution.



The precipitated Bu<sub>3</sub><sup>n</sup>SnF was removed by filtration at reduced pressure and washed with diethyl ether  $(3 \times 5 \text{ ml})$ , and the etheral layers were combined and dried (MgSO<sub>4</sub>). Removal of the solvent gave a colourless oil that was chromatographed on silica gel (9:1 pentane-diethyl ether) yielding the 2-methyl-5-isopropylcyclopentanone **2c** in 68%.

The absence of aldehydes as products implies the occurrence of very rapid carbonylative cyclisation rather than formylation.<sup>†</sup> This prompted us to investigate the serial carbonylative cyclisation starting from dienyl bromide 1g, in which the first carbonylative cyclisation is designed to give rise to another alk-4-enyl radical. Indeed, 1,4-diketone 4 was obtained as the major product (53%) along with the monocarbonylated product 2g (15%) (run 7).

The results described in this paper establish that a freeradical carbonylative approach starting with readily available alk-4-enyl halides is capable of serving as a useful method for the construction of the cyclopentanone framework.

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<sup>†</sup> Since it has been ascertained that free-radical formylation of  $\beta$ -keto alkyl halides proceeds effectively, the possibility of obtaining 4-keto aldehydes by tuning the reaction conditions still remains. We are currently studying this problem.

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