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

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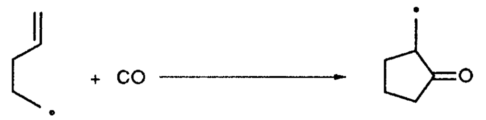
Alk-4-enyl bromides and iodides **1**, when treated with the tributyltin hydride/CO system, undergo carbonylative cyclisation to give cyclopentanones in good yields (AIBN cat., benzene, 75–90 atm, [**1**] = 0.025–0.05 mol dm^{-3}, 80 °C, 2–3 h).

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.[1] 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.[2] 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).[3] Here, we report the first accomplishment of this synthetic scheme based on the tin hydride mediated free-radical carbonylation.[4]

Cyclisation from pent-4-enyl radicals is known to be extremely inefficient, possibly owing to unfavourable interactions in the transition state.[5] In this regard, we felt that CO-trapping by the pent-4-enyl radical and the subsequent 5-*exo-trig* cyclisation process[6] 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^{-3}, 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.[7] 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 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-(phenylvinylidene)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$^n_3$SnH (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.

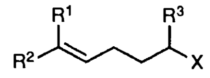


Scheme 1

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

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

[a] *Reaction conditions*: **1**, 0.5 mmol; Bu$_3$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. [b] Isolated yields. GLC yields are underlined. [c] Estimated by GLC. [d] Upon standing, *Z* isomer isomerised to *E* isomer. [e] Mixture of diastereoisomers (50 : 50). [f] Mixture of four stereoisomers (27 : 18 : 19 : 36).



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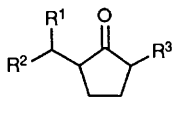

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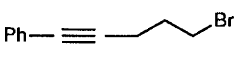
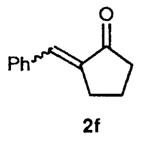
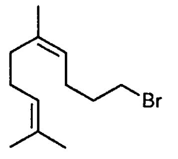
a; R^1 = R^3 = H, R^2 = Me, X = Br
b; R^1 = R^2 = Me, R^3 = H, X = Br
c; R^1 = R^2 = R^3 = Me, X = Br
d; R^1 = R^3 = H, R^2 = Ph, X = Br
e; R^1 = R^3 = H, R^2 = EtO$_2$C, X = I



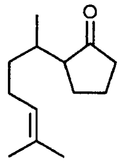
1f



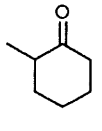
2f



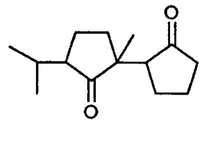
1g



2g



3a



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The precipitated Bu_3^nSnF was removed by filtration at reduced pressure and washed with diethyl ether (3 × 5 ml), and the etheral layers were combined and dried ($MgSO_4$). 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.† 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 free-radical 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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† Since it has been ascertained that free-radical formylation of β-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.