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Tributyltin hydride-mediated radical cyclisation of aldehydes and unsaturated ketones: the synthesis of hydroxy tetrahydrofurans, chromanols and related compounds

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Abstract

The tributyltin hydride-mediated cyclisation of unsaturated ethers bearing an aldehyde or α,β-unsaturated ketone group is reported. Cyclisation proceeds via addition of the tributyltin radical to the carbonyl double bond and the resultant *O*-stannyl ketyl can add intramolecularly to electron-rich double bonds to form hydroxy tetrahydrofurans, chromanols or related compounds.

Keywords: cyclisation; oxygen heterocycles; radicals and radical reactions; tin and compounds.

Radical cyclisation of unsaturated organohalides, or related compounds, using tributyltin hydride has attracted considerable synthetic interest in recent years.[1] A wide variety of five- and six-membered rings, in particular, can be prepared under mild reaction conditions using this method of cyclisation. However, one important drawback to these types of reactions is the loss of two functional groups (e.g. C–X and C=C) on cyclisation of the halide precursor to the cyclic product. In contrast, Enholm and co-workers have shown that *O*-stannyl ketyls, prepared from reaction of tributyltin hydride with aldehydes, can undergo cyclisation to produce cyclopentanes bearing a versatile hydroxyl group.[2] Allylic *O*-stannyl ketyls were also shown to undergo related cyclisations leading to cyclopentanes possessing a ketone group.[3] In these reactions an activating or electron-withdrawing group on the alkene double bond was found to be essential for cyclisation. More recently, we have extended this method of cyclisation to the formation of substituted pyrrolidines and piperidines.[4] Both *O*-stannyl ketyls and allylic *O*-stannyl ketyls were shown to undergo cyclisation, onto electron-rich or -poor alkenes, to produce five- or

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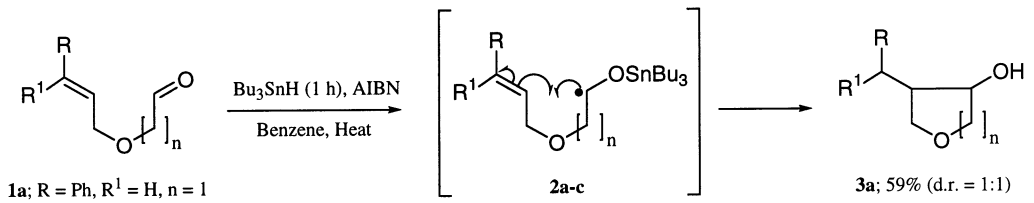
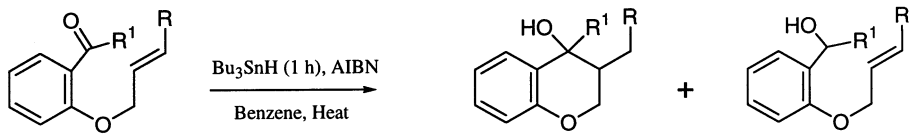
six-membered nitrogen heterocycles. Having established that these types of (nucleophilic) radical can undergo cyclisation on to electron-rich alkenes, we now report the application of this method to the formation of saturated oxygen heterocycles for the first time.[5]

Initial work concentrated on the formation and cyclisation of aldehydes **1a–b** (Scheme 1). These were prepared by mono-alkylation of ethylene glycol using allylic bromides (in 61–82% yield), followed by Swern oxidation of the resulting primary alcohols (in 67–73% yield). The cyclisation of **1a–b** was then investigated by reaction with tributyltin hydride. Thus, slow addition of tributyltin hydride (1.1 equiv.) and AIBN (0.3 equiv.) over 1 h, to a solution of **1a–b** (1 equiv.) in boiling benzene produced the desired hydroxy tetrahydrofurans **3a–b** in 59–64% yield.[6] The cyclic products were isolated as a 1:1 mixture of diastereomers (as indicated by the NMR spectra), which were inseparable by column chromatography. These reactions are expected to proceed via 5-*exo*-*trig* cyclisation of the intermediate *O*-stannyl ketyls **2a–b** followed by hydrogen-atom transfer from tributyltin hydride and hydrolysis of the tributyltin alkoxide on aqueous workup. It is of interest to note that no alicyclic alcohols, derived from the reaction of **2a–b** with tributyltin hydride, were isolated from these reactions. This method could also be extended to the formation of tetrahydropyrans. Hence, reaction of aldehyde **1c** with tributyltin hydride (added over 1 h) produced the desired 6-ring product **3c** in 44% yield. The lower yield of **3c** compared to **3a** is presumably due to the slower rate of 6-*exo*-*trig* radical cyclisation and the possibility of a competing 1,5-hydrogen atom transfer. Indeed, the reaction of **1c** also resulted in the isolation of cinnamyl alcohol (in 40% yield), which may have been formed via an initial 1,5-hydrogen atom transfer.



Scheme 1.

The cyclisation of aromatic aldehydes was then investigated and reaction of benzaldehyde **4a**, under the same conditions as for **1a–c**, produced chromanol **5a**, as a 5.5:1 mixture of (separable) *trans*-:*cis*-isomers,[7] in an excellent 78% yield (Scheme 2). A similar diastereomer ratio was observed when the tributyltin hydride was added to **4a** over 5 h. This contrasts with the much

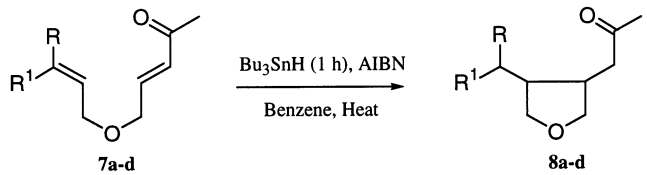


Scheme 2.

lower yield of 44% for **3c**. The introduction of a benzene ring, which is expected to lead to the formation of a more stable *O*-stannyl ketyl, clearly has a pronounced effect on the efficiency of the 6-*exo*-*trig* cyclisation. The substitution of the alkene also influences the cyclisation; when the corresponding *O*-allyl derivative **4b** was reacted under the same conditions the main product was benzyl alcohol **6b**, which was derived from simple reduction. Even when the tributyltin hydride was added over 5 h (rather than 1 h), benzyl alcohol **6b** was formed in 62% yield while chromanol **5b** was only isolated in 24% yield. Chromanol **5b** was isolated as an inseparable 5:1 mixture of diastereomers, the major isomer of which was tentatively assigned (from the NMR spectra) as the *trans*-isomer. Cyclisation of aromatic ketones, as well as aldehydes, is also possible as illustrated by the reaction of acetophenone **4c**. This underwent cyclisation to afford chromanol **5c**, as an inseparable (4.2:1) mixture of diastereoisomers, in an excellent 82% yield. The stereochemistry of the major diastereomer was assigned as *trans*- on the basis of NOE experiments.

The cyclisation of allylic *O*-stannyl ketyls was also investigated by treating α,β-unsaturated ketones **7a**–**d**, which were prepared from the corresponding aldehydes, and $Ph_3P{=}CHCOMe$ (in 59–76% overall yield for the alcohol oxidation and Wittig reaction steps), with tributyltin hydride (Table 1). These 5-*exo*-*trig* cyclisations proceeded smoothly to give the expected disubstituted tetrahydrofurans **8a**–**d** in 50–82% yield. The *trans*-diastereomer of **8a**–**d** was the major product isolated from each of these reactions and the predominant formation of the thermodynamically more stable isomer could be explained by a reversible radical cyclisation mechanism.[9]

Table 1
Cyclisation of unsaturated ketones **7a**–**d** to tetrahydrofurans **8a**–**d**



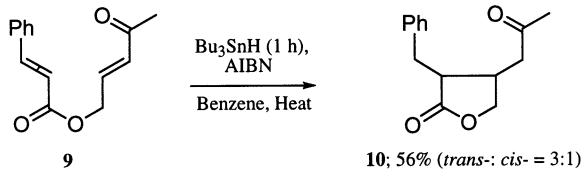
7a-d **8a-d**

8	R	R^1	Yield (%)	D.r[a] *cis*-:*trans*-
a	H	H	50	1:3.1
b	Me	H	80	1:3.7
c	Me	Me	63	1:9.0
d	Ph	H	82	1:1.8

[a] Assigned on the basis of the ^{13}C NMR spectra.[8]

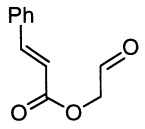
This method of cyclisation could also be applied to the synthesis of butyrolactone **10** (Scheme 3). Hence, reaction of unsaturated ketone **9** with tributyltin hydride resulted in the formation of **10** in 56% yield as a 3:1 mixture of (inseparable) *trans*-:*cis*-isomers, respectively.[10] In contrast, reaction of the related aldehyde **11** (under the same conditions) did not lead to any butyrolactone formation. Cyclisations of similar unsaturated esters are known to be relatively slow (due to conformer effects)[11] and so the intermediacy of a more stable allylic *O*-stannyl ketyl (compared to the *O*-stannyl ketyl) is crucial, presumably because this allows time for cyclisation on to the unsaturated ester double bond. An allylic *O*-stannyl ketyl can also undergo 6-*exo*-*trig*

cyclisation to form a substituted tetrahydropyran (Scheme 4). Hence, reaction of the unsaturated ketone **12** with tributyltin hydride afforded tetrahydropyran **13** in 48% yield (as a 2:1 mixture of diastereomers).



9 **10**; 56% (*trans*-: *cis*- = 3:1)

Scheme 3.



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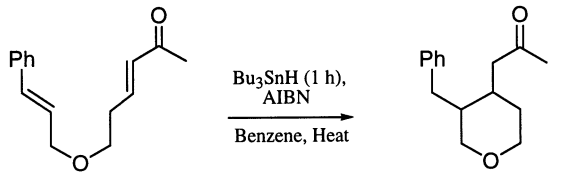

12 **13**; 48% (d.r. = 2 : 1)

Scheme 4.

This work has demonstrated that aldehydes or α,β-unsaturated ketones can undergo cyclisation to form substituted tetrahydrofurans, or related compounds, on reaction with tributyltin hydride. The intermediate *O*-stannyl ketyls, which are nucleophilic, have been shown to cyclise on to a variety of electron-rich double bonds to give a range of oxygen heterocycles. In addition, the importance of using intermediate allylic or benzylic *O*-stannyl ketyls in slow (6-*exo*-*trig* or unsaturated ester) radical cyclisation reactions is reported for the first time. Further studies directed towards the application of this methodology in natural product synthesis are underway.

Acknowledgements

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