Tributyltin Hydride as a Selective Reducing Agent for Aryl Enones

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Abstract: Aryl enones undergo selective 1,4-reduction to the corresponding saturated ketones with two equivalents of tributyltin hydride in the presence of a wide range of other potentially reducible functional groups, including alkyl enone. Additionally during this investigation reductive cyclization of bisenones to give five- and six-membered carbocycles via an α , β -coupling process was observed.

Key words: chemoselectivity, selective 1,4-reduction, cyclization, stannane, enone

During the course of our synthetic studies we required a chemoselective method for the 1,4-reduction of aryl enones, particularly in the presence of alkyl vinyl ketones. While a large variety of methods are reported for the conjugate reduction of α,β -unsaturated carbonyl compounds,^{1–8} none appeared to possess the degree of selectivity we desired. However, in a study by the Noltes group⁹ on the use of organotin hydride compounds as reducing agents for unsaturated carbonyl compounds it was shown that aryl enones underwent 1,4-reduction in the presence of tributyltin hydride while methyl vinyl ketone was inert. In contrast, other organotin hydrides examined in the paper such as triphenyltin hydride reduced both types of enones, however no direct 'one-pot' comparison was made and no study was carried out to determine the scope of the reaction. Herein we describe the expanded scope and synthetic utility of this selective reduction in addition to providing mechanistic insight.

An initial investigation into the reduction of phenyl 1-propenyl ketone (**1a**; Equation 1) with tributyltin hydride revealed two equivalents of the stannane in refluxing benzene at 0.3 M concentration to be the optimum conditions, in which case the reaction was complete in three hours. With one equivalent, the reaction failed to go to completion and a mixture of starting material and reduced product was obtained, while additional equivalents of tin hydride beyond two were not beneficial to the reaction rate or efficiency.



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Gratifyingly, when these conditions were applied to bisenone 2a, (Equation 2), the phenyl vinyl ketone was reduced selectively in good yield in the presence of the methyl vinyl ketone.

A variety of functionalized aryl enones were subsequently screened to test the utility and scope of the method (Table 1). In general it was found that the reaction exhibited excellent selectivity for aryl enones in the presence of a wide range of substituents and functional groups. Both aromatic and aliphatic groups were tolerated at the enone β -carbon (entry 1 vs. entry 2). A variety of substituents on the aryl ring were acceptable and no unwanted reduction was seen (entries 3–5). However, it appeared from the extremely slow reduction in entry 5, that substituents at the α -position inhibited the reduction, probably due to steric constraints in the transition state (vida infra). Potentially reducible substituents on other positions on the molecule were also found to be compatible with the method (entries 6-8). Aryl enones were also reduced selectively and in high yields in the presence of an α,β -unsaturated aldehyde, ketone or ester (entries 9-12).

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 Table 1
 Reaction Scope^a (continued)



^a Reaction conditions: n-Bu₃SnH (2 equiv), benzene (0.3 M), 80 °C, 3 h, resealable tube.

^b Yield estimated from ¹H NMR spectrum, reaction incomplete after 18 h.

Investigations were also carried out to determine the mechanism of the reaction. The Noltes group⁹ reported that the reaction proceeds via initial hydrostannylation

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followed by quenching of the resultant tin enolate with water. We found that reactions conducted in the presence of D_2O resulted in deuterium incorporation at the α -position. The possibility of a radical reaction pathway was ruled out when the presence of the radical inhibitor, galvinoxyl, was found to have no detrimental effect on the outcome of the reaction. Given the sluggishness of the reaction in the case where an α -substituent was present on the enone (Table 1, entry 5), we suspected that the initial hydrostannylation proceeded through a cyclic transition state **A** (Scheme 1), as the adoption of such a conformation would result in steric crowding between the α -substituent and an aromatic *ortho* proton, as in **C** (Scheme 1).





Reduction via transition state **A** was supported by the observation that cyclic enone **13**, which cannot adopt a cyclic transition state owing to the conformational constraints imposed by the seven-membered ring, was inert to reduction (Equation 3).

Equation 3

Interestingly, it was found that in the presence of tributyltin hydride certain bisenones, (Table 2), underwent a reductive cyclization via a net α,β -coupling of the unsaturated systems to give five- and six-membered saturated carbocycles. Related processes involving the cyclization of electron-deficient alkenes have been reported by the Montgomery¹⁰ and Enholm¹¹ groups, although in their cases cyclization results from coupling at the β -positions. Presumably, in our case Michael addition of the tin enolate onto the second unsaturated system occurs in preference to further reduction of the second phenyl vinyl ketone functionality by stannane (entries 1 and 3, Table 2; Scheme 2). Bisphenyl enone 15a (entry 1, Table 2), gave the cyclized product in 95% yield while bisenone 16a (entry 2) gave 70% of the monocycle along with 30% of the reduced product 16c (Figure 1) as an inseparable mixture.



Scheme 2

In the case of six-membered ring formation (entries 3 and 4, Table 2), the reactions were messier leading to lower yields. Bisenone **17a** (entry 3) gave the *trans*-disubstituted cyclized product along with the fully reduced product, **17c** (Figure 1), as an inseparable mixture. Increasing the



Figure 1

amount of tributyltin hydride to four equivalents resulted in a slightly higher proportion of the reduced product. With phenyl enone **18a** (entry 4), it was possible to isolate the cyclized product exclusively as the *trans* diastereomer in 66% yield. Employing more dilute conditions resulted in a cleaner reaction and improved yield in the case of **17a**, although the product selectivity was not affected. In the reaction of **18a** no beneficial effect was observed however.

In conclusion, we have found that under ionic conditions Bu_3SnH can act as a selective reducing agent for aryl enones in the presence of a wide range of other functional groups.^{12,13} Furthermore, a mode of reactivity has been uncovered whereby bisenones can undergo reductive cyclization to give the five- and six-membered saturated carbocycles.

Table 2 Reductive Cyclization of Bisenones in the Presence of Tributyltin Hydride

Entry ^a	Substrate	Product	Yield (%) Cyclized product	Yield (%) Reduced product
1	Ph O	Ph Ph	95 ^b	0
2	15a Ph 16a	15b Ph	70 ^{c.d}	30° (16c)
3	Ph Ph	Ph	$54^{c,e}$ $n-Bu_3SnH$ (2 equiv $43^{c,e}$ $n-Bu_3SnH$ (4 equiv $62^{c,e}$ $n-Bu_3SnH$ (2 equiv $(0.1 M \text{ in benzene})$) $13^{\circ} (17c)$) $22^{\circ} (17c)$) $16^{\circ} (17c)$
4	17a Ph	17b Ph	66 ^e 58 ^e (0.1 M in benzene)	0 0

^a Reaction conditions: *n*-Bu₃SnH (2 equiv), benzene (0.3 M), 80 °C, 3 h, resealable tube.

^b Only the *cis* isomer was detected by ¹H NMR.

^c Yields estimated from ¹H NMR spectra. Inseparable mixture of products.

^d A mixture of *cis* and *trans* was observed.

^e Only the *trans* isomer detected by ¹H NMR.

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- (12) All commercially procured chemicals were used as received. Dichloromethane, triethylamine, diethyl ether, benzene (C_6D_6) were distilled from calcium hydride. THF was distilled from lithium aluminum hydride. Reagent grade solvents were used for solvent extraction and organic extracts were dried over anhyd Na₂SO₄. Silica gel 60 (230– 400 mesh ASTM) was used for flash chromatography with anhyd hexane–EtOAc. ¹H NMR spectra were recorded on 500 MHz Varian, 500 MHz Bruker or 300 MHz Varian spectrometers. The proton chemical shifts (δ) are reported as parts per million relative to 7.26 ppm for CDCl₃, 7.14 ppm for C₆D₆, 5.32 for CD₂Cl₂.

Typical Procedure for the Selective Reduction of Aryl Enones: To a stirred solution of the aryl vinyl ketone (1.0 mmol) in benzene (3.3 mL, 0.3 M) in a resealable tube at r.t. under argon was added tributyltin hydride (0.58 g, 2.0 mmol). The reaction mixture was subsequently heated to 80 °C for 3 h. Upon completion the reaction mixture was concentrated en vacuo and purified by flash column chromatography to give the reduced product as a clear oil.

- (13) NMR data: 1b, ¹⁴ 3b, ² 4b, ¹⁵ 5b, ¹⁶ 6b, ¹⁷ 7b, ¹⁸ 8b, ¹⁹ 9b, ²⁰ 11b, ²¹ 15b,²² 17b and 18b,²³ 17c.²⁴ Compound 2b: ¹H NMR (300 MHz, CD_2Cl_2): δ = 7.95 (m, 2 H), 7.55 (m, 1 H), 7.47 (m, 2 H), 6.78 (dt, J = 15.95, 6.9 Hz, 1 H), 6.09 (dd, J = 16.0, 1.4 Hz, 1 H), 2.96 (t, J = 7.2 Hz, 2 H), 2.20 (s, 3 H), 2.09 (tdd, *J* = 7.0, 7.0, 1.5 Hz, 2 H), 1.71 (tt, *J* = 7.15, 7.15 Hz, 2 H), 1.29–1.53 (m, 10 H). ¹³C NMR (75 MHz, CD_2Cl_2): $\delta =$ 200.5, 198.6, 148.8, 137.7, 133.2, 131.7, 129.0, 128.4, 38.9, 32.9, 29.9, 29.7, 29.6, 28.6, 27.0, 24.7. Compound 10b: ¹H NMR (300 MHz, CD_2Cl_2): $\delta = 9.48$ (d, J = 8.0 Hz, 1 H), 7.95 (m, 2 H), 7.55 (m, 1 H), 7.47 (m, 2 H), 6.85 (dt, J = 15.7, 6.6 Hz, 1 H), 6.09 (dd, J = 15.2, 7.7 Hz, 1 H), 2.96 (t, J = 7.2 Hz, 2 H), 2.32 (dt, J = 7.4, 7.2 Hz, 2 H), 1.71 (tt, J = 7.2, 6.9 Hz, 2 H), 1.50 (tt, J = 6.9, 6.9 Hz, 2 H) 1.35 (m, 8 H). ¹³C NMR $(75 \text{ MHz}, \text{CD}_2\text{Cl}_2): \delta = 200.2, 194.1, 159.17, 137.4, 133.1,$ 132.9, 128.7, 1281, 38.7, 32.8, 29.6, 29.5, 29.4, 29.3, 28.0, 24.4. Compound **12b**: ¹H NMR (300 MHz, CD_2Cl_2): $\delta =$ 7.93 (m, 2 H), 7.55 (m, 1 H), 7.46 (m, 2 H), 6.94 (dt, J = 15.7),6.9 Hz, 1 H), 5.80 (dd, J = 15.4, 1.4 Hz, 1 H), 3.67 (s, 3 H), 2.94 (t, J = 7.4 Hz, 2 H), 2.19 (tdd, J = 7.9, 6.9, 1.1 Hz, 2 H), 1.71 (tt, J = 7.2, 6.8 Hz, 2 H), 1.24 - 1.52 (m, 10 H). ¹³C NMR $(75 \text{ MHz}, \text{CD}_2\text{Cl}_2): \delta = 200.3, 167.1, 149.8, 137.9, 132.9,$ 128.7, 128.1, 120.9, 51.4, 38.7, 32.3, 29.6, 29.5, 29.4, 29.2, 28.2, 24.4.
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