Convenient One-pot Synthesis of Primary α-Alkoxystannanes

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Abstract: A convenient, general and efficient one-pot synthesis of primary α-alkoxy organostannanes, useful as hydroxymethyl anion equivalents, is reported.

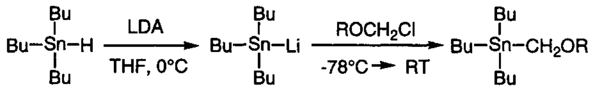
The nucleophilic hydroxy- and alkoxymethylation of carbonyl compounds is a highly useful transformation; therefore, a number of synthetic strategies have been designed to achieve these goals.[1] Among them, Yus[1b] reported an *in situ* synthesis of α-alkoxymethyllithium species by chloro-lithium exchange of α-chloroethers and their reaction with carbonyls; Tamao[1c] has recently employed a silicon-based Grignard reagent which requires a final oxidation step and Castro,[1d] based on Sommelet's work,[1e] prepared α-alkoxy organomagnesium compounds and studied their addition to aldehydes and ketones.

Furthermore, samarium(II)-promoted alkoxymethylation of carbonyl compounds,[1f] cobalt-assisted hydroxymethylation of ketones[1g] and metal-catalyzed photochemical addition of methanol[1h] to carbonyls have been proposed for the same purposes.

In recent years, the unique properties of the tin-carbon bond have been exploited allowing the preparation of versatile reagents and synthetic intermediates. Seebach has used (tributylstannyl)methanol as a hydroxymethyl anion equivalent,[2] but low yields and poor reagent stability induced researchers to protect the carbinol moiety forming ethers or acetals. Upon lithiation, these derivatives readily produce α-alkoxy organolithium species, the addition of which to carbonyls provide high yields of monoprotected glycols.[3]

It is noteworthy that many methods for the elaboration of (benzyloxymethyl)tributyl stannane (**1**),[4] its precursors[5] and congeners[6] have been described and enjoyed some use;[3c,7] nonetheless, they require several steps, involve the preparation of unstable intermediates or are time consuming and, therefore, likely to discourage their more frequent use in synthesis.

This letter reports an alternative route to primary α-alkoxystannanes and related compounds, which makes use (Scheme 1) of the facile replacement of the halogen atom in α-haloethers upon reaction with Bu_3SnLi (readily obtained by lithiation of Bu_3SnH with LDA). This approach has found many applications in the chemistry of cyclic secondary α-haloethers,[8] but surprisingly has two scattered precedents in the case of their less stable acyclic analogs,[9] only one of them involving a primary halide.[9b]



$$Bu_3SnH \xrightarrow[\text{THF, 0°C}]{\text{LDA}} Bu_3SnLi \xrightarrow[\text{-78°C} \rightarrow \text{RT}]{\text{ROCH}_2\text{Cl}} Bu_3Sn{-}CH_2OR$$

Scheme 1

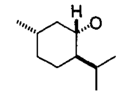
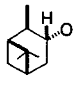
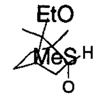
In a typical experiment, a 2.3 M solution of n-BuLi in hexanes (0.323 mL, 0.744 mmol) was added dropwise to a stirred solution of diisopropylamine (0.115 mL, 0.818 mmol) in anhydrous THF (1.5 mL) at 0°C under dry argon. After 5 min, Bu_3SnH (0.200 mL, 0.744 mmol) was introduced in 1 min and the resulting greenish solution was stirred for 15 min; then it was cooled to -78°C and treated with freshly distilled chloromethyl benzyl ether (0.104 mL, 0.744 mmol). After 10 min, the reaction was warmed to room temperature and stirred for 30 min, then it was diluted with hexane (40 mL) and washed with brine (2 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated *in vacuo* and chromatographed (hexane-EtOAc) giving **1** (292 mg, 96%) as an oil, which IR data were in agreement with those previously published.[4,10]

Being operationally simpler and employing easily available starting materials, this novel approach is considerably more convenient than other reported sequences.[4]

To demonstrate the generality and versatility of this strategy, several stannanes were synthesized by the same procedure. As shown in the Table, good to excellent yields were obtained for different acyclic primary α-alkoxymethyl derivatives, including three optically active compounds (entries 4-6). This strategy was also able to provide stannyl thioethers (entry 8) and acyclic secondary α-alkoxy tributylstannanes (entry 7) with the same effectiveness. Yields remained essentially unchanged when the reactions of entries 1 and 4 were run in scales of 12 and 20 mmol, while it was observed that yields decreased up to 10% when the reaction temperature was changed from -78°C to 0°C.

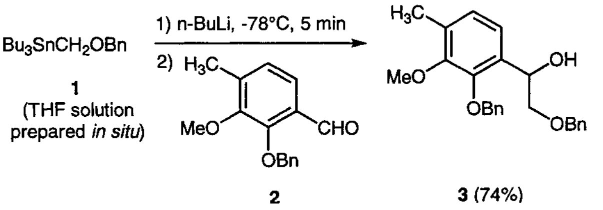
Table. One-flask synthesis of α-(tributylstannyl)ethers by reaction of (tributylstannyl)lithium with α-haloethers[13]

$$Bu_3SnLi + R\text{-}X\text{-}CHR'\text{-}Cl \longrightarrow Bu_3SnCHR'\text{-}X\text{-}R$$

Entry	R-X	R'	Temp./Time (°C/min)	Yield (%)[a,b]
1	BnO	H	-78/10	96
2	MeO	H	-78/10	99
3	$MeOCH_2CH_2O$	H	-78/60	85[c]
4		H	-78/15	91[c]
5		H	-78/15	90[c]
6		H	-78/15	85[c]
7	EtO	Me	-78/15	88[c,d]
8	MeS	H	-78/5	90

[a] Isolated yield after flash chromatography; [b] Spectral data of all compounds were in agreement with their proposed structures; [c] New compounds were characterized by spectral and analytical methods; [d] 1.5 equiv. of freshly prepared α-chloroethyl ethyl ether stabilized with $CaCl_2$ were added

A further proof of the advantages of this synthetic protocol was obtained through the efficient one-pot alkoxymethylation of aldehyde **2**. As depicted in Scheme 2, treatment of a freshly prepared (as described above) THF solution of **1** with n-BuLi at -78°C followed by addition of aldehyde **2** (0.8 equiv.) cleanly afforded 74% of alcohol **3**, an intermediate recently employed in the total synthesis of the β-adrenergic receptor antagonist MY336-a.[11]



Scheme 2

In conclusion, a novel one-flask protocol for the preparation of acyclic primary α-alkoxystannanes and related compounds, which uses inexpensive starting materials and provides high yields of products, has been developed; the generality and versatility of the procedure suggest considerable potential utility in organic synthesis and in the elaboration of the related α-alkoxy organolead compounds.[12]

Acknowledgements

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(10) Spectral data of **1**: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.65-1.15 (15 H, m), 1.20-1.40 (6 H, m), 1.40-1.72 (6 H, m), 3.75 (2 H, s, ^2J (^{119}Sn-^{1}H) = 16, SnC*H*$_2$O), 4.42 (2 H, s, ArC*H*$_2$) and 7.20-7.41 (5 H, m, ArH of benzyl); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 8.89 (^1J ^{119}Sn-^{13}C = 305, Sn*C*H$_2$), 13.59 (CH$_2$*C*H$_3$), 27.21 (^3J ^{119}Sn-^{13}C = 52, *C*H$_2$CH$_3$), 29.03 (^2J ^{119}Sn-^{13}C = 20, SnCH$_2$*C*H$_2$), 61.39 (^1J ^{119}Sn-^{13}C = 347, Sn*C*H$_2$O), 77.11 (Ar*C*H$_2$), 127.18, 127.40 (2 x C), 128.07 (2 x C) and 136.83.

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