

Direct Formation of Reactive Alkynyltrichlorotins from 1-Alkynes, SnCl_4 , and Bu_3N .

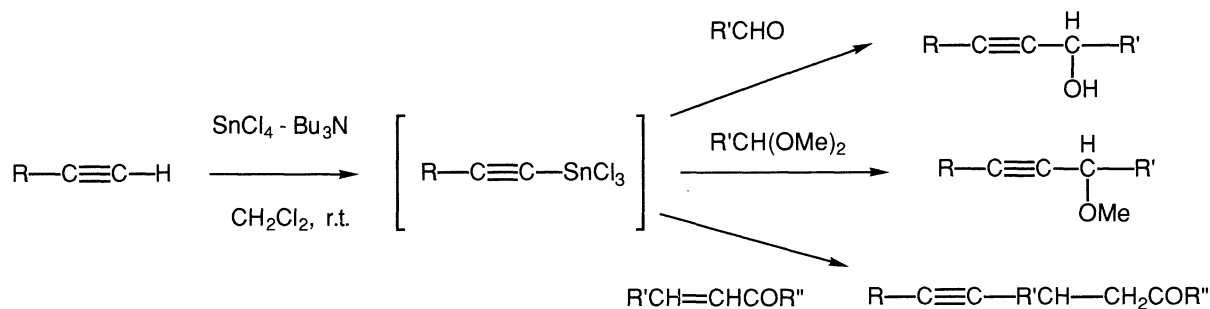
A Mild Alkynylation Reagent of Aldehydes, Acetals, and Enones

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A reagent system of 1-alkyne, SnCl_4 , and Bu_3N alkynylates aldehydes, acetals, and enones under mild reaction conditions giving acetylenic alcohols, acetylenic ethers, and acetylenic ketones, respectively, in high yields. Alkynyltrichlorotins are shown to be the reactive species for these reactions.

Previously, we have reported alkynylation reactions of aldehydes and ketones using combinations of $\text{Sn}(\text{OTf})_2$ and amines.¹⁾ Although intermediacy of alkynyltins was postulated there, studies of the reagent system were not quite fruitful. Recently, it was found that a Sn (IV) reagent system, SnCl_4 - Bu_3N , can be used to alkynylate acetals and enones as well as aldehydes under considerably milder reaction conditions (Scheme 1, Table 1). Alkynyltrichlorotins are shown to be the reactive species for these nucleophilic reactions.



Scheme 1.

When a mixture of 1-alkyne, SnCl_4 , and Bu_3N was treated with an aldehyde in CH_2Cl_2 at r.t., carbonyl addition took place smoothly giving an acetylenic alcohol in a high yield. In case of aromatic 1-alkynes, 1.5 equivalents of the reagent was employed, while use of 3 equivalents gave better results for aliphatic alkynes. As for the amine, higher yields were attained with Bu_3N or Et_3N than with DBU or 1,8-bis(dimethylamino)naphthalene. CH_2Cl_2 was the choice of the solvent, and the yields lowered in THF, C_6H_6 , or CH_3CN . Since the SnCl_4 -based reagent did not react with cyclohexanone, acetophenone, and 2-heptanone, selective transformations of aldehydes in the presence of ketones may be possible. This is contrasted to the properties of the $\text{Sn}(\text{OTf})_2$ -based reagent, which added to certain ketones. Typical procedures are as follows: Under an argon atmosphere, a mixture of phenylacetylene (153 mg, 1.5 mmol) and Bu_3N (0.36 ml, 1.5 mmol) in CH_2Cl_2 (4 mL) was added to a CH_2Cl_2 (2 mL) solution of SnCl_4 (0.18 ml, 1.5

mmol). After stirring for 10 min at r. t., cyclohexanecarbaldehyde (115 mg, 1.0 mmol) in CH_2Cl_2 (2 ml) was added. Stirring was continued for 1.5 h at the temperature., and the reaction was quenched by adding water. The adduct (193 mg, 88%) was obtained by a usual workup.

Table 1. Alkynylation Reactions of Aldehydes, Acetals, and Enones Promoted by SnCl_4 - Bu_3N Reagent^{a)}

R	Electrophiles	Time / h	Yield / % ^{b)}
Ph	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CHO}$	1.5	88
	<i>n</i> - $\text{C}_7\text{H}_{15}\text{CHO}$	1.5	77
	$\text{PhCH}_2\text{CH}_2\text{CHO}$	1	83
<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CHO}$	8	50
<i>n</i> - C_5H_{11}	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CHO}$	2	81 ^{c)} , 52
	$\text{PhCH}_2\text{CH}_2\text{CHO}$	2	74 ^{c)}
	<i>t</i> - BuCHO	24	69 ^{c)}
PhCH_2CH_2	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CHO}$	2	84 ^{c)}
	<i>n</i> - $\text{C}_4\text{H}_9\text{CHO}$	4	67 ^{c)}
PhCOOCH_2	<i>n</i> - $\text{C}_4\text{H}_9\text{CHO}$	7	57 ^{c)}

Ph	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CH}(\text{OMe})_2$	1	81
	$\text{PhCH}_2\text{CH}_2\text{CH}(\text{OMe})_2$	2	78
	$\text{CH}(\text{OMe})_3$	0.15	63 ^{d)}
<i>p</i> - TBSOC_6H_4	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CH}(\text{OMe})_2$	1	73
<i>n</i> - C_5H_{11}	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CH}(\text{OMe})_2$	1	74
PhCH_2CH_2	$\text{PhCH}_2\text{CH}_2\text{CH}(\text{OMe})_2$	1.5	72
PhCOOCH_2	<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{CH}(\text{OMe})_2$	2	64

Ph	PhCH=CHCOCH=CHPh	4	73
	PhCH=CHCOPh	18	57
	<i>n</i> - $\text{C}_5\text{H}_{11}\text{CH=CHCOCH}_3$	20	66 ^{e)}
<i>n</i> - C_5H_{11}	PhCH=CHCOPh	19	70
	<i>n</i> - $\text{C}_5\text{H}_{11}\text{CH=CHCOCH}_3$	36	53 ^{c)}

a) The following molar ratio was employed unless otherwise noted. Alkynylation of aldehydes and enones; substrate : 1-alkyne : Bu_3N : SnCl_4 = 1 : 1.5 : 1.5 : 1.5. Alkynylation of acetals; acetal : 1-alkyne : Bu_3N : SnCl_4 = 1 : 1.5 : 1.5 : 2. b) Satisfactory ^1H -NMR, ^{13}C -NMR, IR, and MS spectra were obtained as well as elemental analysis either by combustion or HRMS. c) Molar ratio; substrate : 1-alkyne : Bu_3N : SnCl_4 = 1 : 3 : 3 : 3. d) Molar ratio; orthoester : 1-alkyne : Bu_3N : SnCl_4 = 1.3 : 1 : 1 : 1.8. e) C_6H_6 was used for the solvent.

The SnCl_4 -promoted reaction can be used for the alkynylation of acetals and enones. High yields of acetylenic ethers were obtained by treating acetals with 1-alkynes (1.5 equivalents) in the presence of SnCl_4 (2 equivalents) and Bu_3N (1.5 equivalents). The yield was substantially reduced with 1.5 equivalents of SnCl_4 , and a slight excess of the Lewis acid may be employed for activation of the electrophile. 1,4-Addition of 1-alkynes to enones took place with the SnCl_4 - Bu_3N reagent, where no 1,2-adduct was detected. It should be emphasized that these transformations are carried out directly from 1-alkynes without involving pre-activation of acetylenic C-H by strong bases, or transmetalation of the alkynylmetal, thus formed, to another species.^{2,3)}

The SnCl_4 - Bu_3N reagent was milder and more chemoselective compared with the $\text{Sn}(\text{OTf})_2$ -amine reagent. When the $\text{Sn}(\text{OTf})_2$ -based reagent was used, both of the acetal and the enone alkynylation gave very low yields of the products. A number of unidentified by-products were formed, and no starting material was recovered. Under the SnCl_4 -reaction conditions, functionalities such as nitro, benzoate, or *t*-butyldimethylsilyloxy groups were not affected. However, substantial desilylation of a *t*-butyldimethylsilyl ether took place with the $\text{Sn}(\text{II})$ method. A reaction of a nitrophenylacetylene using the $\text{Sn}(\text{II})$ reagent gave a complex mixture presumably because of the reduction at the nitro group. Affinity of these tin reagents to a silicon atom also differed. While trimethylsilylacetylenes were obtained from 1-alkynes, TMSCl , and the $\text{Sn}(\text{II})$ -reagent,¹⁾ the silylation did not proceed with the $\text{Sn}(\text{IV})$ reagent.

Several CD_2Cl_2 solutions containing different molar ratio of phenylacetylene- $\text{Bu}_3\text{N}/\text{SnCl}_4$ were prepared, and studied by ^{13}C -NMR. When the ratio was increased from 0.4 to 2, three acetylenic derivatives appeared and then disappeared. Formation of these species was instantaneous, and the composition did not change after standing for several hours. At the ratio of 2, $(\text{PhC}\equiv\text{C})_4\text{Sn}$ (**1**) was the only derivative detected other than phenylacetylene itself. It was isolable by silica gel chromatography,⁴⁾ and the structure was confirmed by elemental analysis as well as comparison of ^1H -NMR and IR spectra with the authentic sample prepared from $\text{PhC}\equiv\text{CLi}$ and SnCl_4 . The other three compounds, therefore, were assigned as $\text{PhC}\equiv\text{CSnCl}_3$ (**4**), $(\text{PhC}\equiv\text{C})_2\text{SnCl}_2$ (**3**), and $(\text{PhC}\equiv\text{C})_3\text{SnCl}$ (**2**), respectively, in the order of the appearance.⁵⁾ The ^{13}C -NMR chemical shifts of the aromatic *para*-carbons in CD_2Cl_2 are as follows: **1**; δ 132.4. **2**; δ 132.5. **3**; δ 132.8. **4**; δ 133.1.

The same alkynylchlorotins could be generated by a transmetalation reaction⁶⁾ of $\text{PhC}\equiv\text{CSnBu}_3$ ⁷⁾ with SnCl_4 , which confirmed the above structure determination. When an aldehyde was added to this mixture, alkynylation took place at r.t. in several hours. The similar reaction rates suggests the same reactive intermediates in the SnCl_4 - Bu_3N method and this transmetalation method. The latter, however, gave several by-products, and the yield of the acetylenic alcohol was lower.

It may be reasonable to assume that **4** is the reactive intermediate in these alkynylation reactions.⁸⁾ Although isolation of **4** was not examined because of the rapid equilibrium between these alkynylchlorotins,^{6,9)} the assumption was supported by the following experiments. Treatment of PhSnCl_3 - Bu_3N or BuSnCl_3 - Bu_3N with phenylacetylene and cyclohexanecarbaldehyde for 16 h gave the product only in 12% and 25% yield, respectively. Bu_2SnCl_2 and Bu_3SnCl were not effective at all. These results indicate the low reactivity of $\text{PhC}\equiv\text{CSnR}_3$, $\text{PhC}\equiv\text{CSnR}_2\text{Cl}$, and $\text{PhC}\equiv\text{CSnRCl}_2$ ($\text{R}=\text{Bu}, \text{Ph}$) towards alkynylation, structure of which are related to **1**, **2**, and **3**, respectively. It is also known that $(\text{CH}_2=\text{CHCH}_2)\text{SnBu}_{3-n}\text{Cl}_n$ ($n=0$ to 3) become more reactive as increasing the number of the chlorine atoms.¹⁰⁾

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