



## Synthesis and reactions of a novel chlorostannane resin: coupling with functionalized organozinc halides

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### Abstract

A novel resin-bound chlorostannane has been developed from Merrifield resin for use in solid-phase organic synthesis. This polymer was coupled with functionalized aryl-, heterocyclic-, benzyl- and styryl-zinc halides to afford resin-bound functionalized organostannanes with complete conversion as shown by gel-phase  $^{13}\text{C}$  NMR analysis. © 2000 Published by Elsevier Science Ltd.

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Solid-phase organic synthesis has attracted much attention in the last few years due to the rapid development of combinatorial chemistry.<sup>1</sup> While library synthesis continues to drive most solid-phase synthetic research, other applications are being explored such as the use of resins in the rapid on-site synthesis of radiopharmaceuticals.<sup>2</sup> The most important facet of solid-phase synthesis is the choice of an appropriate resin and linker. Linkers need to be attachable to the synthetic scaffold to survive the desired synthetic transformations without degradation and to be cleavable. Linker and resin development is necessary for improving reaction yields and for extending the range of reaction types and substrate diversity.

The Group IV elements, silicon and tin, have been used as linkers in solid-phase synthesis. Ellman developed arylsilicon resins, which are synthesized by the reaction of aryllithium reagents with a chlorosilane resin.<sup>3</sup> The silicon–aryl bond can be cleaved with hydrogen fluoride or basic fluoride ion releasing the desired product with no trace of the point of linkage. These types of linkers are called traceless. Arylstannane resins have also been synthesized by the reaction of aryllithium reagents with a chlorostannyl resin.<sup>2,4,5</sup> While a tin–aryl bond is generally not as robust as a silicon–aryl bond, it can be cleaved with a wider variety of electrophiles increasing its diversity potential.<sup>5</sup> Arylstannane resins can also act as traceless linkers by reaction with acid.

One problem with these methodologies is that the attachment of the scaffolds in both instances requires the generation of a highly reactive organolithium reagent. This limits the

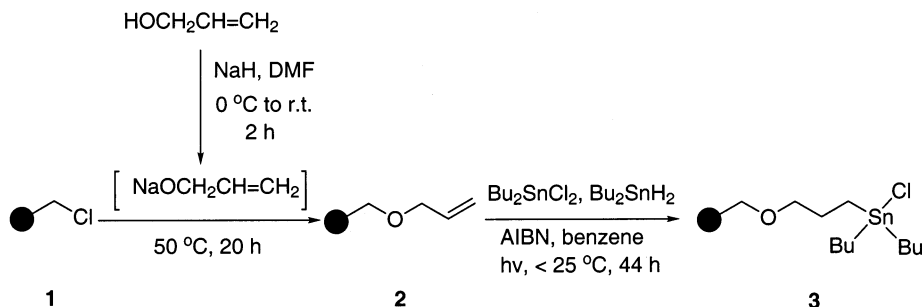
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choice of scaffolds to those without exposed electrophilic functionalities such as esters, nitriles, and ketones. A solution to this problem could be attachment via organozinc reagents, which are not as nucleophilic as organolithium reagents and are compatible with many electrophilic functionalities. Herein we report the development of a stable chlorostannane resin and its reaction with aryl-, heterocyclic-, benzyl-, and styrylzinc halides to form resin-bound functionalized organostannanes.

Organozinc reagents are known to react with stannyl or silyl chlorides in solution after conversion to cuprates. However, the direct coupling of organozinc reagents with either electrophile has not been extensively explored.<sup>6</sup> In order to establish the feasibility of this approach and to determine which resin would be most suitable, we showed that treatment of 3-ethoxycarbonylphenylzinc iodide with tributyltin chloride, but not trimethylsilyl chloride, in tetrahydrofuran at room temperature gave the expected coupled product. This suggested that it should be possible to generate resin-bound functionalized organostannanes utilizing organozinc reagents.

The resin-bound chlorostannane, **3**, used in this study was derived from a Merrifield resin (1.26 mmol/g) (**1**) as shown in Scheme 1. Deprotonated allyl alcohol was reacted with the Merrifield resin to form a resin-bound allyl ether **2**. Hydrostannation<sup>7</sup> of polymer **2** in the presence of 2,2'-azobisisobutyronitrile under irradiation (120 V, 4.2 A, 60 Hz) below 25°C afforded **3** as a white polymer which was characterized by gel-phase <sup>13</sup>C NMR (CDCl<sub>3</sub>).<sup>8,9</sup> Reaction temperature is very important in the radical hydrostannation step. When the reaction was conducted below 25°C, a white product was obtained. At elevated reaction temperatures, the product takes on a grayish color that may indicate side reactions.<sup>7b</sup> The chlorine loading on resin **3** was 0.83 mmol/g which was measured by Mohr titration of Cl<sup>-</sup> released from resin **3** after hydrolysis with sodium hydroxide in a mixture of water/methanol/THF.<sup>5</sup> This is very close to the theoretical loading of 0.89 mmol/g, indicating complete hydrostannation. The resin also has good swellability in most organic solvents which is necessary for further manipulation.



Scheme 1.

Polymer **3** reacted with various functionalized organozinc reagents as summarized in Table 1.<sup>10</sup> All of the organozinc reagents, except 4-acetylphenylzinc iodide (entry 4) and 4-bromophenylzinc iodide (entry 5), were purchased from Rieke Metals, Inc. 4-Acetylphenylzinc iodide and 4-bromophenylzinc iodide were prepared by following Knochel's procedure.<sup>11</sup> Gel-phase <sup>13</sup>C NMR (CDCl<sub>3</sub>) analysis showed that most reactions proceeded to completion at room temperature. The reaction of 2-ethoxy-carbonyl phenylzinc bromide with polymer **3** did not go to completion at room temperature but proceeded to completion at 62°C, probably due to the steric effect of the *ortho* substituent. One interesting observation is that the *para*-substi-

tuted ethoxycarbonyl phenylstannane polymer **4a** was white but the *ortho*-substituted ethoxycarbonyl phenylstannane polymer **4b** was yellow in color. A possible explanation of this is the formation of the penta-coordinated polymer **4b** when the ethoxycarbonyl group is at the *ortho* position. The only reaction that did not proceed to completion was that with 4-acetylphenylzinc iodide (entry 4) as indicated by gel-phase  $^{13}\text{C}$  NMR. Cleavage with 5% trifluoroacetic acid (TFA) in methylene chloride at room temperature for 15 min afforded acetophenone in 20% isolated yield based on the chlorostannane loading of 0.83 mmol/g. Gel-phase  $^{13}\text{C}$  NMR spectrum of the TFA treated polymer indicated complete removal of acetophenone from the resin.

Table 1

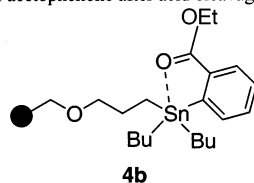
**3** +  $\text{RZnX}$   $\xrightarrow[\text{r.t., overnight}]{\text{THF, N}_2}$  **4a-j**  
X = I or Br

R	Transformation % of <b>3</b> <sup>a</sup>	Entry
	<b>(4a)</b> >95%	1
	<b>(4b)</b> >95% <sup>b</sup>	2
	<b>(4c)</b> >95%	3
	<b>(4d)</b> 20% <sup>c</sup>	4
	<b>(4e)</b> >95%	5
	<b>(4f)</b> >95%	6
	<b>(4g)</b> >95%	7
	<b>(4h)</b> >95%	8
	<b>(4i)</b> >95%	9
	<b>(4j)</b> >95%	10

<sup>a</sup>Determined by gel-phase  $^{13}\text{C}$  NMR.

<sup>b</sup>Reaction at 62 °C (bath).

<sup>c</sup>Based on isolated yield of acetophenone after acid cleavage.



Polymer **3** was shown to be recyclable by treating a mixture of polymers, consisting of polymer **3**, hydrolyzed polymer **3**, and recycled arylstannane polymers, with a mixture of concentrated hydrochloric acid and methanol (1:2) overnight at reflux to afford pure white

polymer **3** as indicated by gel-phase  $^{13}\text{C}$  NMR. The chlorine loading on the recycled chlorostannane polymer was identical to the initial polymer **3**.

Currently, we are investigating the loading of resin-bound stannanes possessing ketone groups and exploring the potential of using this methodology for the solid-phase synthesis of radiopharmaceuticals such as [ $^{125}\text{I}$ ]-3 $\beta$ -(4-iodophenyl)tropane-2 $\beta$ -carboxylic acid methyl ester ([ $^{125}\text{I}$ ]-RTI-55, DOPASCAN<sup>®</sup>) and of compound libraries with biological activities.

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- To a mixture of polymer **2** (2.0 g),  $\text{Bu}_2\text{SnCl}_2$  (1.22 g), benzene (40 mL) and AIBN (26.4 mg) was slowly added  $\text{Bu}_2\text{SnH}_2$  (0.94 g) under irradiation of light (120 V, 4.2 A, 60 Hz) under argon. The reaction flask was merged in a water bath below 25°C. More AIBN was added after 4 h (27 mg) and 25 h (10 mg). Total reaction time was 44 h. The polymeric material was then collected by filtration and was washed with toluene, acetone and toluene. After further washing with toluene and methanol in a Soxhlet extractor, the polymeric material was dried under vacuum at room temperature. A white polymer (2.4 g, 91 wt% yield) was obtained.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz, rt):  $\delta$  13.8, 15.0, 18.6, 26.0, 26.3, 26.8, 27.3, 28.0, 40.4 (br), 70.9 (br), 73.1, 126.0 (br), 127.9 (br), 144.9 (br).
- In this study, gel-phase  $^{13}\text{C}$  NMR was a very convenient and useful tool for characterization as well as the monitoring of reactions on resins **1** and **3**. The samples were swelled with  $\text{CDCl}_3$  and performed as the routine  $^{13}\text{C}$  NMR experiment. All experiments were run on a Bruker AVANCE DPX 300 spectrometer using a Bruker 5 mm QNP probe.
- To a suspension of chlorostannane polymer **3** (0.40 g, 0.33 mmol) in THF (5.0 mL), cooled at 0°C, was added ethyl 3-ethoxycarbonylzinc iodide/THF solution (0.50 M, 2.0 mL, 1.0 mmol) through a syringe. After stirring for 5 h at 0°C under argon, a mixture of methanol (3.0 mL) and 1.0 N HCl (1.0 mL) was added to quench the excess zinc reagent. The pH of the quenched mixture was around 4. The white polymeric material was collected by filtration and washing with distilled water (3 $\times$ 2.0 mL), methanol (3 $\times$ 2.0 mL), acetone (3 $\times$ 2.0 mL) and chloroform (3 $\times$ 3.0 mL). After drying in air, a white polymer (364 mg, 86 wt% yield) was obtained.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz, rt):  $\delta$  5.8, 9.7, 13.6, 14.3, 18.6, 26.8, 27.3, 29.0, 40.3, 42.0 (br), 60.8, 70.9, 72.0, 72.7, 73.1, 117.0, 125.8 (br), 127.7 (br), 129.1, 134.8, 136.3, 137.2, 140.8, 144.9 (br), 167.0.
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