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A simple and scalable method to prepare 1-aza-5-chloro-5-stannabicyclo[3.3.3]undecane

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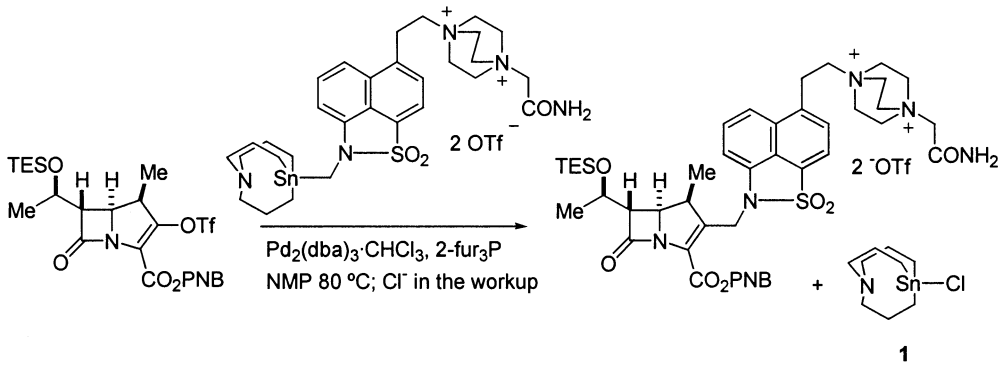
Abstract

A simple and scalable method for the preparation of a potentially versatile organostannane, 1-aza-5-chloro-5-stannabicyclo[3.3.3]undecane (**1**), is described. Stannane **1** was prepared by the disproportionation of $N(CH_2CH_2CH_2SnBu_3)_3$ and $SnCl_4$ at 70–100°C. This reaction requires the addition of water or an alcohol to proceed efficiently. Under typical conditions, **1** was isolated in 50–55% yield after a simple acid/base extraction sequence.

Keywords: tin and compounds; bicyclic heterocyclic compounds; coupling reagents.

Recently, we reported a powerful cross-coupling reaction using a 5-substituted 1-aza-5-stannabicyclo[3.3.3]undecane for the preparation of a carbapenem (Scheme 1).[1] In this reaction, the



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Scheme 1.

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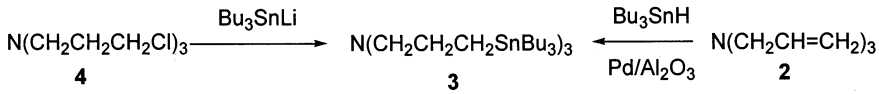
entire side chain of the clinical candidate was coupled to the C-2 position of a readily available carbapenem skeleton in >98% yield. Notably, this route facilitated the transfer of a nitrogen substituted sp^3 carbon to form an sp^2–sp^3 bond, a strategy that failed with typical Bu_3SnCH_2NRR' reagents. Additionally, >98% of stannane **1** was recovered after the coupling reaction and was shown to be suitable for reuse. Previously, Vedejs[2] had pioneered the use of the stannatrane reagent to transfer methyl and CH_2OMOM to aryl halides, yet, surprisingly, no other examples using this promising and potentially versatile reagent have been reported. Part of the reason for this is no doubt due to the difficulty in the preparation of the precursor, the stannatrane chloride **1**. As outlined below, several methods have been reported for its preparation, but they suffer from low yields, hazardous reagents and conditions and/or expensive reagents which make preparation of gram quantities difficult. We now report a straightforward and efficient two-step synthesis of stannatrane chloride **1** from readily available reagents that allows for quick access to multigram quantities of this valuable reagent.

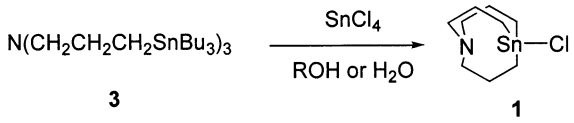
Three methods for the preparation of **1** have been reported. The first is a transmetallation between the Grignard reagent $N(CH_2CH_2CH_2MgCl)_3$ and $SnCl_4$ to provide **1** in 15% yield.[3] The second method is the thermal redistribution of $N(CH_2CH_2CH_2SnMe_3)_3$ and Me_2SnCl_2 at 150–190°C or 19 hours, removing 5 equiv. of Me_3SnCl by vacuum distillation.[4] This method is reported to provide **1** in 40% yield; however, the hazardous reagents and conditions are not suitable for scale-up. Hydrozirconation of triallylamine (**2**) with 3 equiv. of Cp_2ZrHCl (Schwartz's reagent), followed by reaction with $SnCl_4$, affords **1** in 50% yield.[2] While we found that this method works as reported, it is difficult to scale-up because of the high dilution required for the reaction to proceed. The cost of Schwartz's reagent is also a factor. We viewed the thermal redistribution approach as the most promising and investigated this method using $N(CH_2CH_2CH_2SnBu_3)_3$ (**3**). Tributylstannane **3** was chosen over its trimethyl analogue due to concerns of toxicity. Here we report the results of that study which led to a more practical procedure for the preparation of **1**.

Compound **3** was prepared in two ways (Scheme 2). Reaction between $N(CH_2CH_2CH_2Cl)_3$ (**4**)[5,6] and Bu_3SnLi, itself prepared from Bu_3SnH and LDA, afforded **3** in 78% yield. When preparing the Bu_3SnLi, it is important to use a slight excess of Bu_3SnH. If an excess of LDA is used, olefin by-products from the elimination of chloride are observed. Compound **3** was also prepared by the hydrostannylation of triallylamine (**2**) catalyzed by Pd/Al_2O_3.[7] This method gave **3** in 66% isolated yield.



Scheme 2.

When the thermal redistribution of crude **3** prepared from **4**, and $SnCl_4$ was attempted, formation of **1** was observed. Conversely, when **3**, prepared from **2**, was subjected to the same conditions, the reaction failed. Close comparison of **3** prepared by the different routes showed that the material from **4** was wet while that prepared from **2** was anhydrous. The addition of a small amount of water or an alcohol to anhydrous **3** promoted the desired transformation (Scheme 3). With these conditions, the reaction proceeded smoothly at 70–100°C to afford **1** in 50–55% isolated yield. We initially postulated that the promoter was HCl generated by reaction of the water or alcohol and $SnCl_4$. However, addition of dry HCl gas to an anhydrous reaction mixture did not facilitate this redistribution.



3 1

Scheme 3.

The effect of the addition of varying amounts of ethanol to the reaction is summarized in Fig. 1. The best yield was found when 0.5 equivalents of EtOH, based on $SnCl_4$, was added to the reaction. This gave an assay yield of 47%. Addition of more or less EtOH gave a sharp decrease in yield. A similar trend was noted with varying amounts of water. The maximum assay yield in this case was found with the addition of 0.25 equivalents of water based on $SnCl_4$. Again, addition of either more or less water gave a sharp decrease in assay yield.[8]

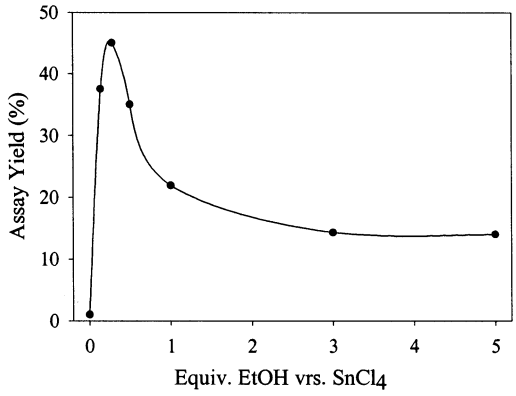


Figure 1. EtOH effect

The effect of using a solvent for this reaction was also explored. Both toluene and xylene functioned well here. The use of solvent however failed to show any advantage in either ease of handling the reaction or yield. From a productivity point of view, the solvent-free method is preferred.

While studying the isolation of **1**, it was found that this compound's behavior is analogous to that of a carboxylic acid, residing primarily in the aqueous phase when the conditions are basic and the organic phase when the conditions are acidic. This observation lead to a simple extractive work-up sequence that easily removed the Bu_3SnCl produced in the thermal redistribution step and provided **1** as a crystalline compound. There is the potential to recover the Bu_3SnCl from this work-up and reduce it to Bu_3SnH for reuse. This tendency for **1** to dissolve in a basic aqueous phase also suggests a simple work-up method for Stille cross-coupling reactions that use cross-coupling reagents based on **1**. The tin by-products produced in such a reaction are easily removed by simple extraction with aqueous base. Stannane **1** can then be recovered for future use by pH adjusting the aqueous phase with HCl and isolating the resulting solids.

In conclusion, we have demonstrated a reliable method for the preparation of 1-aza-5-chloro-5-stannabicyclo[3.3.3]undecane (**1**). This compound has been shown to facilitate a previously difficult Stille cross-coupling reaction. Easy access to **1** will allow the extension of the versatile Stille reaction to include other previously difficult cross-couplings.

*Preparation of **3** from **4***

Tri-*n*-butyltin hydride (121 mL, 456 mmol) was added to a solution of LDA (213 mL of a 2.0 M solution with heptane/THF/ethylbenzene, 426 mmol) and THF (80 mL) while maintaining the internal temperature at −2 to 5°C. After the addition was complete, the solution was stirring at 5°C for 1 h and then a solution of **4** (25.0 g, 101 mmol) and THF (100 mL) was added keeping the internal temperature at 2 to 10°C. The mixture was then stirred at rt. After 12 h, the mixture was diluted with MTBE (200 mL) and washed with saturated aqueous NH_4Cl (2×200 mL) and then water (200 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude material can be used for the next reaction without further purification. Pure **3** was obtained by passing through a short silica gel pad eluting with 10:1 hex/EtOAc. Stannane **3** (80 g, 79%) was isolated as a colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ 2.37 (t, $J=7.7$ Hz, 6H), 1.62 (m, 6H), 1.47 (m, 18H), 1.30 (m, 18H), 0.94–0.78 (m, 45H), 0.71 (t, $J=8.3$ Hz, 6H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 29.3 ($J_{Sn-C}=19.6$ Hz), 27.4 ($J_{Sn-C}=51.9$ Hz), 24.4 ($J_{Sn-C}=16.6$ Hz), 13.7, 8.8 ($J_{Sn-C}=308.2$ Hz), 6.3 ($J_{Sn-C}=299.6$ Hz).

*Preparation of **3** from **2***

A degassed solution of Bu_3SnH (30.0 mL, 113 mmol) and THF (70 mL) was added by syringe pump (60 mL at 13 mL/h then 40 mL at 20 mL/h) to a degassed mixture of **2** (3.4 mL, 20 mmol), THF (20 mL), and 5% Pd on alumina (122 mg) maintaining an internal temperature of 21–22°C to provide **2** in 80% yield (GC assay). The heterogeneous catalyst was removed by filtration through solka floc and the THF was removed by rotary evaporation. The resulting oil was purified by solid phase extraction on silica gel (100 g) using hexanes (700 mL) to elute the hexabutyldistannane by-product and 9:1 hex/EtOAc (750 mL) to elute **3**. The solvents were removed in vacuo to provide **3** (15.6 g, 66%) as a clear colorless oil.

*Typical procedure for preparation of **1***

To a mixture of **3** (10.6 g pure basis, 88 wt%; KF = 50 μg/mL) and water (60 μL) was added $SnCl_4$ (1.8 mL) at 80°C. The reaction mixture was stirred at 95°C for 4 h. The crude mixture was cooled to 20°C and 10 M aqueous NaOH (30 mL) was added to the mixture keeping the temperature around 40°C. The mixture was stirred at 40°C for 40 min. The aqueous layer was separated and extracted with MTBE (30 mL). The pH of the aqueous layer was adjusted to 2.5 by the addition of conc. HCl at 0°C. The mixture was extracted with CH_2Cl_2 (50 mL). The organic extract was dried over Na_2SO_4 and concentrated to give **1** (1.66 g; 53%) as a colorless crystalline compound. The NMR matches that reported.[9]

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8. When **3** was prepared from **4**, the crude compound before chromatography (usually about 55 wt% pure by GC) was wet and could be used directly in the preparation of **1**. The amount of the water should, however, be measured and adjusted prior to the disproportionation reaction.
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