行政院國家科學委員會專題研究計畫成果報告

自由基在有機合成上的運用(IV)

The Applications of Free Radical Reactions in Organic Synthesis

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一、中文摘要

我們合成了α -Stannyl bromides 及 xanthates 並研究了其與三丁基錫烷之反應，此環合反應經過了一個 1,3-錫轉移。

關鍵詞：環合, 1,3-錫轉移

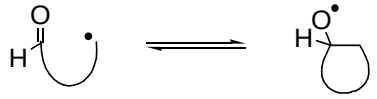
Abstract

α -Stannyl bromides and xanthates are prepared. Reactions of these compounds with tributyltin hydride generate α-stannyl radicals. Intramolecular cyclizations of these radicals with formyl group afford γ-stannyl alkoxy radicals which undergo 1,3-stannyl shift from carbon to oxygen.

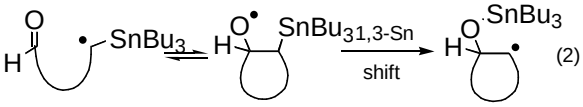
Keywords: α-stannyl radicals, 1,3-stannyl shift

二、緣由與目的

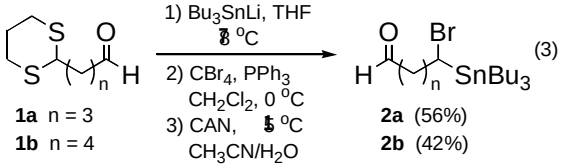
Intramolecular radical addition to carbonyl to give cyclic alcohol is a potentially useful reaction.[1] However, this type of cyclizations (eq 1) is reversible, and the reverse reactions are generally faster than the cyclizations.[2] In the cases of acylgermanes,[3] acylsilanes,[1] thioesters and selenoesters,[4] intramolecular radical additions to the carbonyl moiety in these compounds are followed by irreversible processes. Therefore, these cyclizations can be stopped at the cyclization side.[5] Herein, we wish to report the intramolecular cyclization of formyl group with α-stannyl radical[6] (eq 2). In this cyclization, a heretofore unprecedented homolytic 1,3-stannyl shift from carbon to oxygen[7–10] serves as the driving force.



(1)



(2)



(3)

1a n = 3
1b n = 4

2a (56%)
2b (42%)

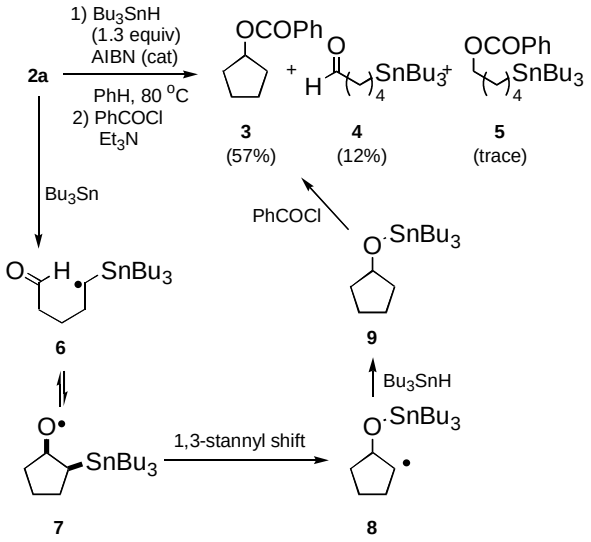
三、研究報告內容

As shown in eq 3, aldehydes **1**[11] were coupled with tributyltin lithium,[12] and the resulting α-stannyl alcohols were converted to α-stannyl bromide by using carbon tetrabromide and triphenylphosphine.[13] The dithiane moiety was then deprotected[14] to give aldehydes **2** in mild yields over three steps. Treatment of aldehyde **2a** with tributyltin hydride[15] (Scheme 1) followed by quenching the reaction with benzoyl chloride gave us the benzoate derivative of cyclohexanol **3** in 57% yield. Uncyclized reduction product aldehyde **4** was also isolated in 12% along with trace amount of benzoate **5**. The benzoate **5** was presumably derived from over-reduction of aldehyde **4** by tributyltin hydride followed by

benzoate formation.

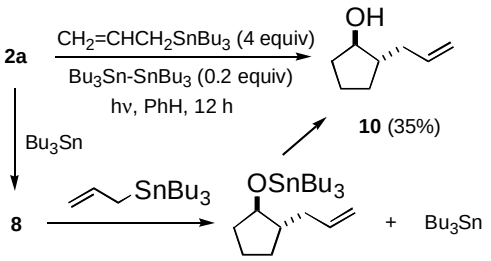
This cyclization reaction occurred through the formation of α-stannyl radical **6** first. This radical then cyclized with the formyl group to generate the γ-stannyl alkoxy radical **7**. Because the carbonyl radical cyclizations are in general reversible,[2] it is likely that the alkoxy radical and stannyl group may have a chance to adopt a *syn*-relationship as shown in **7**. Alkoxy radical **7** presumably underwent 1,3-stannyl shift from carbon to oxygen to generate radical **8**. It is known that O-Sn bond is stronger than C-Sn bond by about 25 kcal/mol.[16] This big difference provides a strong thermodynamic driving force to trap the alkoxy radical **7**. Abstraction of hydrogen from tributyltin hydride by radical **8** gave stannyl ether **9**. Oxygen atom in stannyl ethers is known to be quite nucleophilic.[17] Therefore, we directly added benzoyl chloride to the reaction mixture at the end of the cyclization reaction followed by heating and obtained benzoate **3**.

Scheme 1

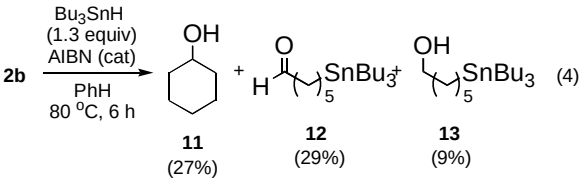


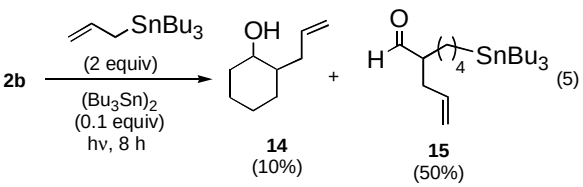
When aldehyde **2a** (Scheme 2) was treated with allyltributyltin (4 equiv) in the presence of hexabutylditin (0.2 equiv) and photolyzed with long wavelength UV light for initiation[18] (12 h), we were able to isolated alcohol **10**[19] in 35% yield. Although this intermolecular process is not very efficient, yet the reaction provided evidence that radical **8** was formed indeed.

Scheme 2



In the case of 6-*exo* cyclization (eq 4), aldehyde **2b** reacted with tributyltin hydride[15] and gave 27% of cyclohexanol (**11**), 29% of uncyclized product aldehyde **12**, and 9% of over-reduction product alcohol **13**. The problem of this reaction was revealed by the reaction of aldehyde **2b** with allyltributyltin (eq 5). In addition to alcohol **14**[20] (10%), we isolated 50% of aldehyde **15** which contains an allyl group at the α-position of the carbonyl group. This result indicated that after the generation of the α-stannyl radical from aldehyde **2b**, a 1,5-hydrogen transfer[21] occurred to give an α-carbonyl radical. The α-carbonyl radical was then trapped by allyltributyltin to give aldehyde **15**.

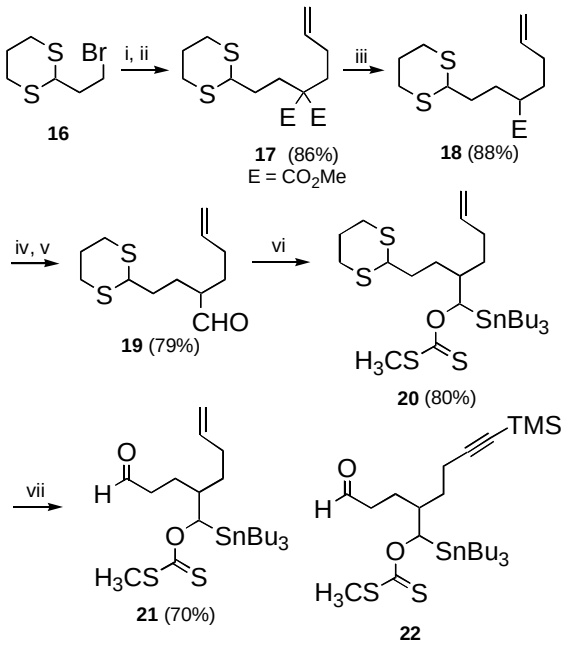




This stannyl shift promoted carbonyl radical cyclization reaction can be employed in a tandem cyclization mode. As shown in Scheme 3, we prepared diester **17** *via* alkylation of dimethyl malonate with bromide **16**[22] and 4-bromo-1-butene. Decarbme-thoxylation of **17** with sodium

cyanide[23] gave ester **18**. Reduction of ester **18** followed by Swern oxidation[24] of the resulting alcohol afforded aldehyde **19**. The aldehyde **19** was

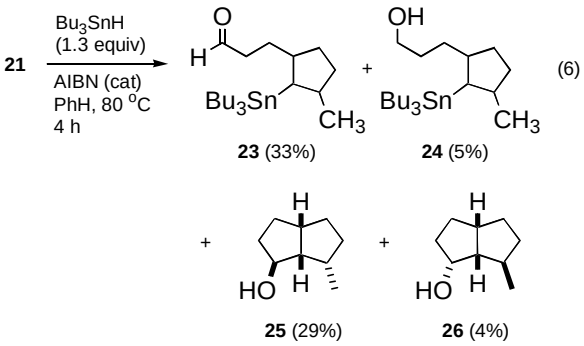
Scheme 3



Reagents and conditions: i, $CH_2(CO_2Me)_2$, NaH, DMF, 80 °C. ii, NaH, DMF; $BrCH_2CH_2CH{=}CH_2$. iii, NaCN, DMF, 120 °C. iv, LAH, THF. v, Swern oxidation. vi, Bu_3SnLi, THF; CS_2,; MeI. vii, MeI (15 equiv), acetone/H_2O.

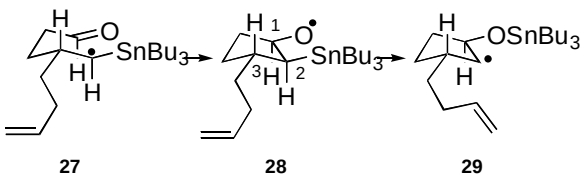
treated with tributyltin lithium, and the resulting oxide was trapped with carbon disulfide and methyl iodide to give xanthate **20**. The dithiane moiety in xanthate **20** was hydrolyzed with excess methyl iodide in wet acetone[25] under reflux to obtain aldehyde **21**. In a similar process we also prepared aldehyde **22**. When we tried to convert aldehyde **19** to the corresponding α-stannyl bromide using the sequence shown in eq 3, low yield of the bromide was obtained. Therefore, the xanthate was used instead for our study.

The reaction of aldehyde **21** with tributyltin hydride[15] (eq 6) gave monocyclic aldehyde **23** in 33% yield. This aldehyde



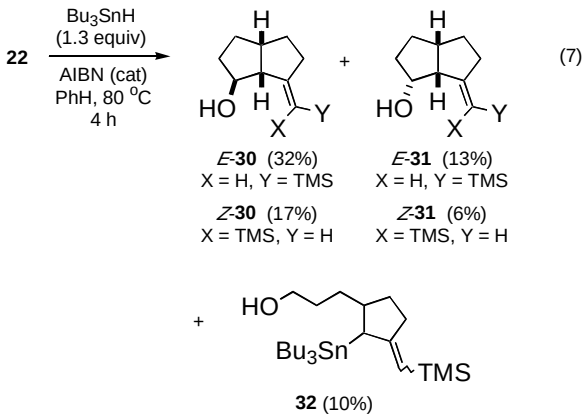
was derived from the addition of α-stannyl radical to the olefin first. An alcohol **24** (5%) was also obtained. This material was presumably derived from reduction of aldehyde **23** by tributyltin hydride. Bicyclic alcohol **25** was isolated in 29% yield. Small amount of bicyclic alcohol **26** was also present in about 4% yield. To determine the stereochemistry of alcohols **25** and **26**, we treated the cyclization crude product with benzoyl chloride. The benzoates derived from alcohols **25** and **26** thus obtained are identical to that reported by Wilcox *et al.*[26] There appeared to be other stereoisomers of alcohol **25** and **26** present; however, the amount was very small and we were not able to identify these minor isomers. Bicyclic alcohols **25** and **26** were tandem cyclization products derived from addition of α-stannyl radical **27** (Scheme 4) to formyl group first. The cyclization presumably prefers to adopt a chair transition state[27] with large groups located at equatorial position as shown in **27**. This led to the formation of alkoxy radical **28** with a predominant *trans*-1,3-relationship. A stannyl shift of **28** gave radical **29** which cyclized with the olefin with the known *endo*-selectivity[28] to give bicyclic alcohol **25** as the major isomer.

Scheme 4



Because the total yields of monocyclic products **23** and **24** are close to that of

bicyclic alcohols **25** and **26**, the addition rates of α-stannyl radical to olefin and formyl group appeared to be similar. With this information available, it is possible to attenuate the tandem system to favor the bicyclic product. For example, it is known that 5-*exo* cyclization of 5-hexynyl radical is slower than the corresponding 5-hexenyl radical cyclization by about ten fold.[29] Therefore, for aldehyde **22**, one would expect the carbonyl cyclization to be faster than the alkyne cyclization. As shown in eq 7, the cyclization of aldehyde **22** gave four isomeric bicyclic alcohols **30** and **31** in a combined yields of 68%.[30] Monocyclic alcohol **32** was isolated in 10% yield. The rates of carbonyl addition product versus alkyne addition product was improved to about 7/1.



(7)

In conclusion, a 1,3-stannyl shift promoted cyclization of α-stannyl radical with formyl group was developed. This process is successful for 5-*exo* cyclization; however, the corresponding 6-*exo* cyclization has serious competition of 1,5-hydrogen transfer. The 5-*exo* cyclization of α-stannyl radical with formyl group has similar rate as that with terminal olefin. This information will be useful in the design of tandem cyclizations. In the tandem cyclizations, the α-bromostannane moiety serves as a novel *gem*-diyl equivalent.[31]

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