博士（薬　学）　今井恵美アリセ

学 位 論 文 題 名

DEVELOPMENT OF RING-EXPANSION REACTION USING $Me_3SiSnBu_3$ AND CsF
- SYNTHESIS OF(+)-and(-)-CYCLOOCTENONE DERIVATIVES -

- $Ms_3SiSnBu_3$-CsF を用いた環拡大反応の開発
-（+）-，（-）-シオロオクテノン誘導体の合成-

学位論文内容の要旨

Introduction

The bimetallic reagent $Me_3SiSnBu_3$ has found valuable applications in organic synthesis, since the obtained products containing C-Sn and C-Si bonds can be further manipulated to intermediates of synthetic interest. Our main attention has been directed to the stannyl anion generated when $Me_3SiSnBu_3$ is treated with R_4NX, CsF or TASF $[(Et_2N)_3SSiMe_3F_2]$ in DMF under mild conditions. Among several useful applications, we reported a novel cyclization reaction that occurs when the stannyl anion attacks a vinyl or aryl halide, leading to the formation of a vinyl or aryl anion, which reacts intramolecularly with a carbonyl group affording a cyclic compound. This methodology was applied to the synthesis of the natural products acorone, coniceine and (-)-cephalotaxine.

A 1,3-cyclodiketone possesing a suitable vinyl iodide in a tether which, upon reaction with the stannyl anion generated from silylstannane and CsF, leads to a bicyclic four-membered intermediate, is presumed to afford products of ring expansion reaction when the ring junction bond undergoes a Grob fragmentation reaction.

Herein it will be reported the ring expansion of cycloalkanones *via* fused 4-membered rings that underwent this intramolecular cyclization promoted by the stannyl anion. We obtained in this way 7- and 8-membered cycloalkanediones and cycloalkenones in a one-pot reaction. The *stereospecific* mode of this reaction made it possible to obtain *cis*- and the constrained *trans*-cyclooctenone selectively. Furthermore, we succeeded in the synthesis of (+)- and (-)-*trans*-cyclooctenones.

I) Ring expansion to cycloalkanediones

When 2-methyl-2[(2-iodo)-2-propenyl]-1,3-cyclopentadione was treated with 2 eq of $Me_3SiSnBu_3$ and 2 eq of CsF in DMF at room temperature for 2 h, although in low yields, expanded 4-methyl-2-methylene-1,5-cycloheptadione and 4-methyl-2-(methyltributyltin)-1,5-cycloheptadione were obtained in 4% and 15%, respectively.

In the same way, 2-methyl-2[(2-iodo)-2-propenyl]-1,3-cyclohexadione afforded 4-methyl-2-methylene-1,5-cyclooctadione and 4-methyl-2-(methyltributyltin)-1,5-cyclooctadione in moderate yields: 39% and 3%, respectively.

II) Ring expansion to cycloalkenones

We tried next to improve the yields of the ring expanded products by replacing one of the keto carbonyls in the starting material by a good leaving group such as methanesulfonate.

II-1) Ring expansion to cycloheptenones and cyclooctenones

The reduction of the cyclopentadione above with 1 eq of DIBAL-H afforded two epimeric alcohols in 61% and 10% yields. The major one, with the hydroxy group and the vinyl iodide containing side chain disposed on the same side of the ring, is designated *cis*-isomer and its stereochemistry was assigned on the basis of a NOE between the methine proton and the methyl group; the minor isomer with these groups on opposite sides is the *trans*-isomer. The*cis*-alcohol was mesylated reacted with 4 eq of $Me_3SiSnBu_3$ and CsF to produce 4-methyl-2(methyltributylstannyl)-4-cycloheptenone in 25% yield and a product resulting from a substituition of the mesylate group by the stannyl anion. This same substitution pattern was observed with the *trans*-mesylate, which afforded the cycloheptenone as the main product (51%). NOE experiments of these 7-membered rings revealed that these reactions were stereospecific with substitution occurring with inversion of configuration.

The reduction of the cyclohexadione was accomplished with $NaBH_4$ at 0 °C. The stereochemistries of the products were determined by NOE experiments after mesylation of the epimeric alcohols.

When the *cis*-substrate reacted with 3 eq of stannyl anion in DMF at room temperature for 3 h, 1,1,6-trimethyl-2-(methytributyltin)-cyclooct-6-en-3-one was obtained in 86% yield. Change solvent to THF led to the formation of 1,1,6-trimethyl-2-methylene-cyclooct-6-en-3-one in 70% yield . Decrease of the amount of sillylstannane to 1.5 eq in DMF now resulted in the cis-enone as the main product (42%). On the other hand, the reaction of *trans*-substrate with 3 eq of stannyl anion afforded *trans*-cyclooctenone in 1% yield together with the cis-Michael adduct in 36% , which was not detected when the amount of $Me_3SiSnBu_3$ was reduced to 1.5 eq (run 5). In this case, *trans*-cyclooctenone was obtained in 33% yield. It is quite interesting that the cyclization/ring expansion reaction for these cyclohexanones is a stereospecific process. *Cis*-substrate leads to the exclusive formation of *cis*-cyclooctenone while *trans*-cyclooctenone, the smallest cycloalkene possible to be isolated at room temperature, is obtained only from the *trans*-substrate. The stereochemistries of products were determined by NOEs.

Other pairs of cis-trans substrates were reacted and it was confirmed the stereospecificity of this ring expansion reaction.

II-2) Isomerization of *Trans*- to *Cis*-cyclooctenone

The formation of the *cis*-cyclooctenone from the corresponding *trans*-substrate in the presence of an excess of silylstannane and CsF was demonstrated to be promoted by the stannyl anion generated *in situ.*, in the reaction of both the *trans*-enone and the *trans*-Michael adduct with 3 eq of this stannyl anion. It is not clear if this mechanism is anionic or radicalic.

III) Synthesis of (+)- and (-)-*trans*-cyclooctenone derivatives

We accomplished the synthesis of both enantiomers of *trans*-cyclooctenones using $Me_3SiSnBu_3$ and CsF. The chiral starting materials were obtained after resolution of the ester derivatives of *(R)*-(-)-*O*-acetylmandelic acid and subsequent transformations. The absolute configuration of the (-)-*trans*-substrate synthesized was determined as *S* by the improved Mosher's method developed by Kusumi and it was obtained in 89% ee, despite the resolution of the diastereomeric pair in 100% de. The ring expansion of it resulted in optically active *trans*-cyclooctenone ($[\alpha]_D^{27}$=+292.7 (*c* 1.17, $CHCl_3$) in 31% yield.

Similarly, the (+)-*trans*-substrate was achieved in 87% ee and upon reaction with stannyl anion, (-)-*trans*-cyclooctenone ($[\alpha]_D^{28}$=-285.8 (*c* 0.98, $CHCl_3$) was obtained in 30% yield.

The values for the optical rotation as well as the sign of the Cotton effects in the CD spectra undoubtedly confirm the enantiomeric relantionship of the cyclooctenones synthesized.

IV) Conclusion

Using the stannyl anion generated from $Me_3SiSnBu_3$ and CsF under mild conditions it was possible to perform a tandem cyclization/ring expansion reaction to obtain medium-sized rings of synthetic value. This reaction proceeds in a stereospecific way and moreover we succeeded in the synthesis of both enantiomers of *trans*-cyclooctenones.

学位論文審査の要旨

主　査　教　授　森　美和子
副　査　教　授　高　橋　保
副　査　助教授　浜　田　辰　夫
副　査　助教授　コトラ・マーテイン

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今井恵美アリセさんは表記の題目で学位論文を提出した。その内容は $Me_3SiSnBu_3$-CsF の系を用いるとスズアニオンの生成することがこれまでの研究で知られていたので、この系を利用して新しい環拡大反応を開発した。その結果非常に興味深いことに立体特異的に反応が進行しシス及びトランスのシクロオクテノンを合成した。更に興味深い事に(+)-,及び(-)-シクロオクテノンの両鏡像異性体を合成することが出来た。その概略を以下に示す。

今井さんの研究計画は 2-アルキルーシクロアルカン-1,3-ジオンの 2 位にハロゲン化ビニルを持つ側鎖を導入し $Me_3SiSnBu_3$-CsF から生じたスズアニオン(Bu_3Sn^-) がハロゲンを攻撃しビニルアニオンを生成し、このアニオンがシクロアルカノンのケトカルボニル基を攻撃すると環化を起こすはずである。その際もう一つのケトカルボニル基の電子的な要因で環が開き環拡大を起こさせようというものである。それゆえ側鎖によって形成される環に歪があるほど環拡大はスムーズに進行するものと思われた。そこ

で始めに形成する環を4員環とし環拡大後の環は炭素数の2個増加した環が形成されることを考えた。この反応がもし成功するならば、生理活性の面から非常に興味の持たれ、しかも最も合成の困難な8員環が比較的容易に合成出来ることが期待された。

まず最初に2-メチル-シクロヘキサ-1,3-ジオンの2位にヨーカビニルを持つ側鎖を導入した基質にCsFを加えDMFを溶媒として$Me_3SiSnBu_3$を加え室温で撹拌したところ8員環に環拡大を起こした生成物を与えた。この反応をシクロペンタジオンに適用したが収率は低かった。そこで次に環化後開環しやすくさせるために脱離基としてメジルオキシ基(OMs)を用いることにした。その結果脱離基と側鎖がシスの関係にある基質を$Me_3SiSnBu_3$-CsFと反応させたところシスの二重結合を持つ8員環化合物を高い収率で得ることが出来た。ところが脱離基と側鎖の関係がトランスである化合物を同様に反応させたところトランスの二重結合を環内にもつ化合物が生成した。トランスの二重結合を環内に持つことが出来るシクロアルケンの最小の環サイズは8員環であることが知られているので本結果は極めて興味が持たれる。この方法を用いて様々なシス及びトランスの8員環化合物を合成した。又今井さんはトランスの8員環化合物はシス体に$Me_3SiSnBu_3$-CsFによって簡単に異性化することも見い出した。

更に今井さんはトランスの8員環が光学活性体であることに気が付き原料のアルコール体をマンデル酸と反応させてジアステレオマーとした後シリカゲルカラムクロマトグラフィーを用いて光学分割することによりそれぞれ光学的にほぼ純粋なトランスの(+)-及び(-)-アルコール体に導いた。一方の異性体を楠見らの改良Mosher法によってその絶対配置を決定した。それぞれのメジラート体を$Me_3SiSnBu_3$-CsFと反応させたところ(+)-及び(-)のシクロオクテノンが得られた。それぞれの機器データー特に比旋光度及びCDのデーターはこれらの化合物が鏡像異性体の関係にあることを示している。ここに光学的にほぼ純粋な(+)-および(-)-トランスシクロオクテ

ノンの合成に成功したことが明らかとなった。これまで光学的に純粋なシクロオクテノンの合成法は未だ知られていず今井さんの得た結果は非常に高く評価される。

２月６日に審査委員会を開催し審査担当者全員が今井恵美アリセさんの博士論文は博士（薬学）の学位に値すると認めた。