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Article / Book Information

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（博士課程）
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論 文 要 旨

THESIS SUMMARY

専攻： Department of	生体分子機能工学　専攻	申請学位（専攻分野）： Academic Degree Requested	博士 Doctor of　（　工学　）
学生氏名： Student's Name	山岸優仁	指導教員（主）： Academic Advisor(main)	占部弘和
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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

This thesis, entitled "Development of Novel Synthetic Methods Based on Nucleophilic Addition to Haloalkynes," describes the development of nucleophilic addition of various nitrogen nucleophiles to 1-halo-1-alkynes and its application to the synthesis of heterocyclic and other related compounds.

Chapter 1. "Introduction."

The reason why the nucleophilic addition to haloalkynes has been overlooked is mentioned. Its recent discovery and synthetic applications found by us and other groups are briefly summarized. In addition, the outline of this research together with its scientific and practical significance is described.

Chapter 2. "Facile Preparation of 1,2-Dihydroisoquinolines from Haloalkynes and *N*-Benzylsulfonamides."

Facile preparation of pyrroles, indoles, and 1,2-benzothiazine 1,1-dioxides by the nucleophilic addition of sulfonamides to haloalkynes and the subsequent Pd-catalyzed cyclization has been established in the Master's Thesis of the author. The same method was applied to the synthesis of 1,2-dihydroisoquinolines. For example, when a mixture of *N*-benzylethanesulfonamide, 1-bromo-1-octyne, and K_3PO_4 in DMF was heated at 120 °C for 2 h, the regio- and stereoselective nucleophilic addition of the sulfonamide to the bromoalkyne took place to give (*Z*)-*N*-(1-bromo-1-octen-2-yl)-*N*-benzylethanesulfonamide. The Pd-catalyzed cyclization via C-H bond activation of this adduct afforded 2-(ethanesulfonyl)-3-hexyl-1,2-dihydroisoquinoline as the desired product. As 1,2-dihydoisoquinolines are useful synthetic intermediates for isoquinoline alkaloids, their synthetic transformations including halogenation, acylation, etc. are also illustrated.

Chapter 3. "Preparation of Functionalized Tetrahydropyridines and CF_3-substituted Tetrahydrofuropyridines via Intramolecular Addition of Amines."

Intramolecular nucleophilic addition of an amine to a haloalkyne in the presence of a carboxylic acid gave 6-(acyloxymethyl)-1,2,3,4-tetrahydropyridine or 5-(trifluoromethyl)-1,2,3,4-tetrahydrofuropyridine via incorporation of the carboxylic acid. For example, when a solution of a (6-halo-5-hexynyl)ammonium trifluoroacetate was heated under basic conditions in the presence of an externally added carboxylic acid, a 6-(acyloxymethyl)-1,2,3,4-tetrahydropyridine was obtained in good yield. This reaction was

applied to the racemic synthesis of (+)-isosolenopsin, which is an alkaloid exhibiting anti-HIV activities. On the other hand, when a solution of a (6-halo-5-hexynyl)ammonium trifluoroacetate was heated under basic conditions without an externally added carboxylic acid, a 5-(trifluoromethyl)-1,2,3,4-tetrahydrofuro[3,4-*b*]pyridine was obtained. In this reaction, trifluoroacetate itself behaves as the carboxylate to give a 6-[(trifluoroacetyl)oxymethyl]-1,2,3,4-tetrahydropyridine, which spontaneously undergoes the second cyclization, finally giving the tetrahydrofuropyridine. These reactions demonstrated the first synthetic application of the nucleophilic addition of amine to haloalkyne, allowing the novel preparation of the aforementioned heterocyclic compounds. Furthermore, through the development of these reactions, it was shown that the reaction pathway of the nucleophilic addition of nitrogen nucleophiles to haloalkynes is dependent on the electronic character of the nucleophiles. For example, when a sulfonamide was allowed to react with a haloalkyne, a simple adduct, (*Z*)-*N*-(1-halo-1-alken-2-yl)sulfonamide, was formed and it remained as it was. On the other hand, when an amine is a nucleophile to a haloalkyne, the reaction proceeded as above to give an alternative product.

Chapter 4. "Facile Preparation of Dihydro-1,4-oxazines by the Nucleophilic Addition of 2-Aminoalkanols."

In Chapter 3, the new synthesis of tetrahydropyridines via incorporation of an amine and a carboxylic acid to haloalkynes is described. In this chapter, a novel preparation of dihydrooxazines via the addition of amino and hydroxy groups of 2-amino-1-alkanols to 1-halo-1-alkynes is described. For example, when a mixture of a 2-amino-1-ethanol, 1-bromo-1-octyne, and a base was heated, a dihydro-1,4-oxazine was obtained. This reaction may involve the double nucleophilic addition of the amino and hydroxy groups of aminoalkanol to the haloalkyne. However, the actual reaction course may be more complicated as evidenced by control experiments.

Chapter 5. "Cleavage of the Acetylenic Bond via Nucleophilic Addition of 1,2-Ethylenediamines with Air."

Cleavage of the acetylenic bond of a haloalkyne was accomplished by the addition of 1,2-ethylenediamine to it and the subsequent aerial oxidation. For example, when a mixture of an ethylenediamine, 1-bromo-1-octyne, and a base was heated and treated with air, the corresponding *N*-[(formylamino)ethyl]amide was obtained. Although the primary product of this reaction may be a tetrahydropyrazine, the cleavage of its olefinic bond takes place by aerial oxidation to give the final product. This reaction has attractive points from the stand point of the cleavage of an acetylenic bond: (i) a transition metal catalyst-free process and (ii) an aerial oxidation.

Chapter 6. "Summary."

New synthetic reactions based on the nucleophilic addition to haloalkynes have been disclosed in this thesis. Applications to the facile and novel preparation of heterocyclic compounds, frequently found in natural or artificial bioactive compounds, proved the above transformations a useful synthetic method in organic, synthetic, and medicinal chemistry.

The contribution of this nucleophilic addition to haloalkynes to organic chemistry and a related field of industry is also discussed.

備考 ： 論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。

Note : Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1copy of 800 Words (English).

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