（様式２）

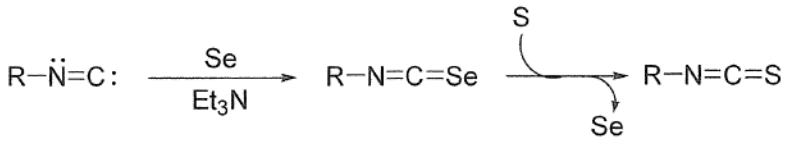
学位論文の概要及び要旨

氏　　名　深町　修平

題　　目　New Syntheses of Heterocycles Utilizing *o*-Functionalized Phenyl Isothiocyanates
（オルト位が官能基化されたフェニルイソチオシアナートを用いるヘテロ環化合物の新規合成）

学位論文の概要及び要旨

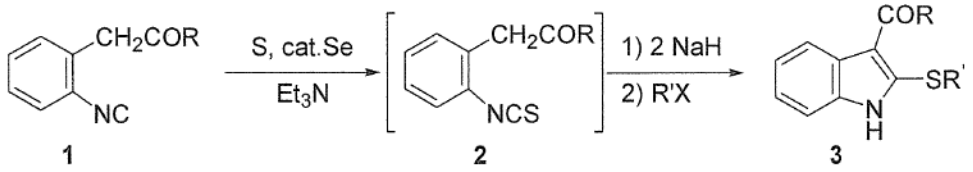
Recently, *o*-functionalized phenyl isocyanides have been used for the preparation of a number of nitrogen-heterocycles, such as quinolines,[1a] 4*H*-3,1-benzoxazines,[1b,e] indoles,[1c,d] and so on,[1f,g] via cyclization reactions initiated by treatment with nucleophiles or electrophiles. On the other hand, the conversion of isocyanides into the corresponding isothiocyanates upon treatment with sulfur in the presence of a catalytic amount of selenium and excess triethylamine has been reported by Fujiwara et al. (Scheme 1).[2] Therefore, I decided to explore the possibility of utilizing *o*-functionalized phenyl isothiocyanates, derived from the respective isocyanides, for the synthesis



Scheme 1

of new types of heterocycles. In this thesis, I describe the results of my studies, which offer new and facile methods for the preparation of interesting heterocyclic derivatives.

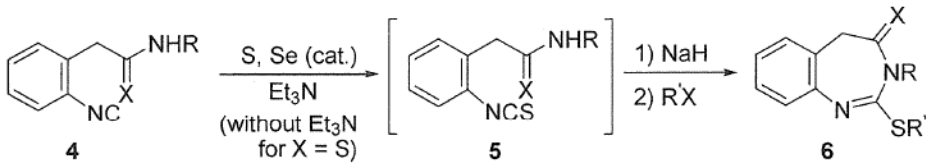
In Chapter 1, I describe a simple one-pot procedure for the synthesis of 3-acyl-2-(alkylsulfanyl)indoles and ethyl 2-(alkylsulfanyl)indole-3-carboxylates **3** from (2-isocyanophenyl)methyl ketones[3] and ethyl 2-(2-isocyanophenyl)acetates[4] **1**, respectively, via the corresponding isothiocyanates **2** (Scheme 2). 2-(Alkylsulfanyl)indoles are medicinally important heterocyclic compounds.[5] Although several methods for the preparation of these indole derivatives have recently been reported,[6] they are of limited generality. The construction of three new indole-containing fused tricyclic structures is also described as an application of the one-pot procedure reported here.



1 2 3

Scheme 2

Benzodiazepine skeletons, such as 3*H*-1,4-benzodiazepine and 2,3-benzodiazepine, are found in many biologically active compounds.[7] Therefore, 3*H*-4,5-dihydro-1,3-benzodiazepine derivatives are also potentially of biological importance. I developed a facile one-pot procedure for the synthesis of 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepin-4-ones **6** (X = O) and 2-alkylsulfanyl-3*H*-4,5-dihydro-1,3-benzodiazepine-4-thione derivatives **6** (X = S) from secondary 2-(2-isocyanophenyl)acetamides **4** (X = O)[8] and 2-(2-isocyanophenyl)thioacetamides **4** (X = S),[8] respectively, via the corresponding isothiocyanates **5** (Scheme 3). This is the first report on the synthesis of these types of benzodiazepine derivatives. The results and efficiency of this synthesis are discussed in Chapter 2.

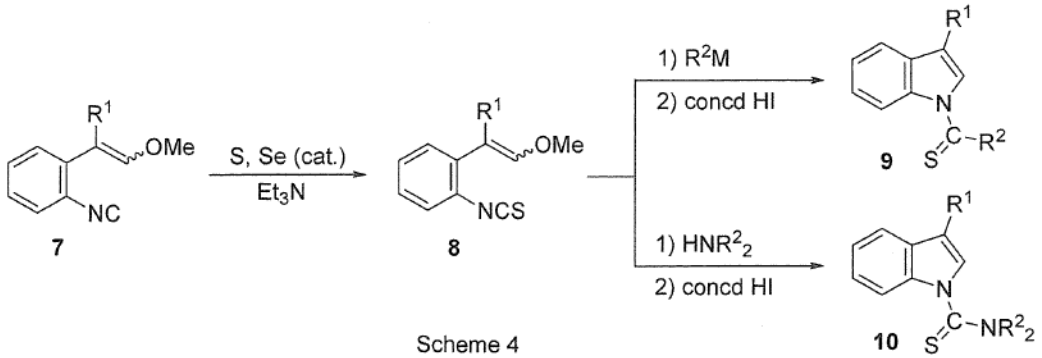


4 5 6

X = O, S

Scheme 3

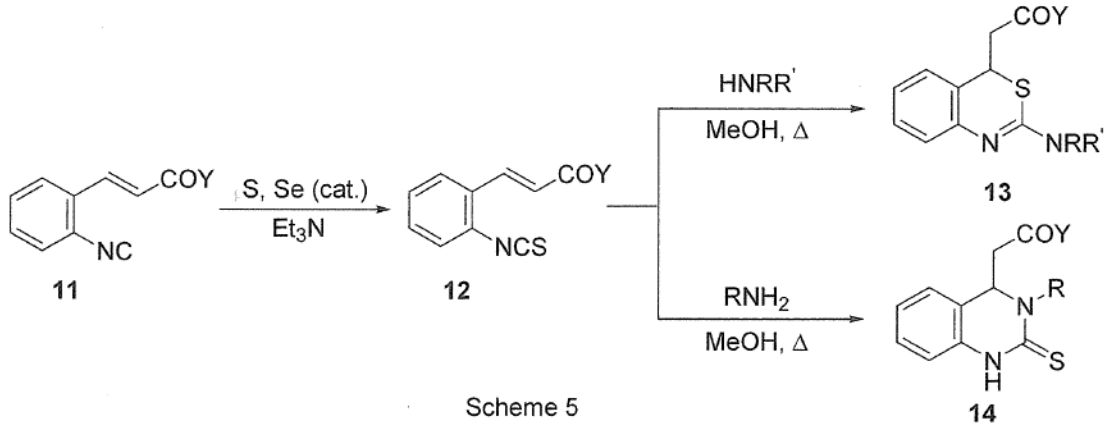
I found that α-substituted 2-isothiocyanato-β-methoxystyrenes **8** are stable and isolable by the reaction of the respective isocyanides **7**[1a] with sulfur under Fujiwara's conditions. Their reactions with nucleophiles, such as organometallic compounds or secondary amines, followed by hydriodic acid mediated cyclization of the resulting adducts, give 1-thioacyl- **9** and 1-thiocarbamoylindoles **10**, respectively (Scheme 4). These types of indole derivatives are thought to be of potential importance in medicinal chemistry. However, few general methods for their preparation have been reported. Chapter 3 describes the results and efficiency of these reactions.



7 8 9 10

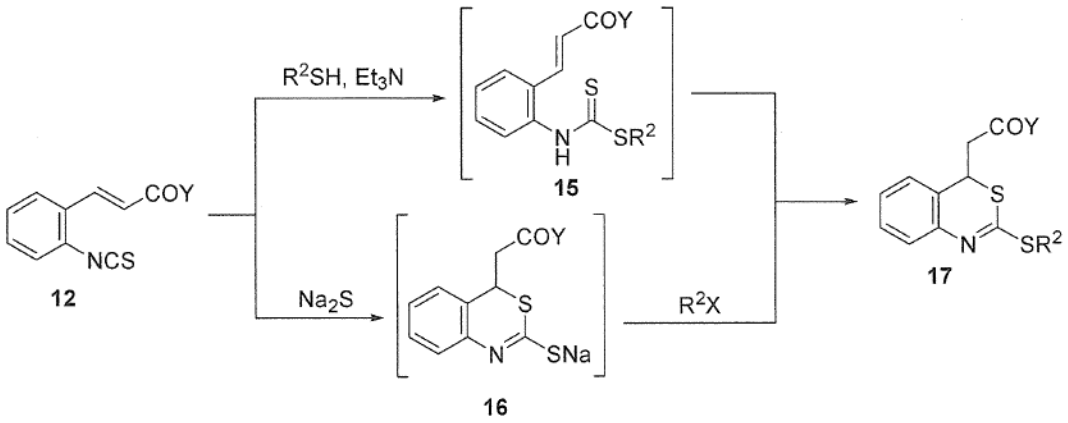
Scheme 4

Compounds having the 4*H*-3,1-benzothiazine skeleton have recently attracted much attention because of their biological activities,[9] and a number of efficient methods for their preparation have been reported.[10] I found that 2-(2-dialkylamino-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives **13** could be obtained by simply heating the respective thiourea intermediates, generated in situ by treating 3-(2-isothiocyanatophenyl)propenoic acid derivatives **12**,[11] with secondary amines in methanol (Scheme 5). I also found that the use of primary amines in place of secondary amines provided an approach for the construction of a new class of quinazoline derivatives, 2-(2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid derivatives **14**. I discuss the results and efficiency of these reactions in Chapter 4.



Scheme 5

In Chapter 5, I describe the synthesis of a new type of 2-(2-sulfanyl-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives **17** from 3-(2-isothiocyanatophenyl)propenoic acid derivatives **12** with thiols, via cyclization of the corresponding dithiocarbamates **15** (Scheme 6). I also found that the use of Na_2S in place of the thiols generated 2-(2-sodiosulfanyl-4*H*-3,1-benzothiazin-4-yl)acetic acid intermediates **16**, which were then allowed to react with alkyl or aryl halides to afford 2-(2-sulfanyl-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives **17**. The 2-sulfanyl-4*H*-3,1-benzothiazine skeleton has attracted much attention because of the biological activities of some derivatives,[12] and some efficient methods for their preparation have been reported.[13]


COY
NCS
12
R2SH, Et3N
Na2S
COY
S
N
H
SR2
15
COY
S
N
SNa
16
R2X
COY
S
N
SR2
17

Scheme 6