

การพัฒนารีเอเจนต์เพื่อเตรียมแอซิดคลอไรด์สำหรับการสังเคราะห์  
สารออกฤทธิ์ทางชีวภาพ



นางสาวสกายดาว ฉายศรีพงษ์กุล

ศูนย์วิทยทรัพยากร  
จุฬาลงกรณ์มหาวิทยาลัย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต

สาขาวิชาเคมี ภาควิชาเคมี


คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ปีการศึกษา 2546

ISBN 974-17-5092-7

ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

REAGENT DEVELOPMENT FOR THE PREPARATION OF ACID CHLORIDE  
FOR SYNTHESIS OF BIOACTIVE COMPOUND



Miss Skaydaw Chaysripongkul

ศูนย์วิทยทรัพยากร

จุฬาลงกรณ์มหาวิทยาลัย

A Thesis Submitted in Partial Fulfillment of the Requirements  
for the Degree of Master of Science in Chemistry

Department of Chemistry

Faculty of Science

Chulalongkorn University


Academic Year 2003

ISBN 974-17-5092-7


Thesis Title REAGENT DEVELOPMENT FOR THE PREPARATION OF  
ACID CHLORIDE FOR SYNTHESIS OF BIOACTIVE  
COMPOUND  
By Miss Skaydaw Chaysripongkul  
Field of Study Chemistry  
Thesis Advisor Assistant Professor Warinthorn Chavasiri, Ph.D.

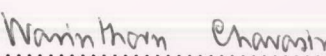
---

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment  
of the Requirements for the Master's Degree

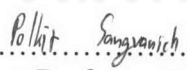
  
..... Dean of the Faculty of Science  
(Professor Piamsak Menasveta, Ph.D.)

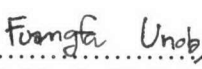
#### THESIS COMMITTEE

  
..... Chairman  
(Professor Udom Kokpol, Ph.D.)

  
..... Thesis Advisor  
(Assistant Professor Warinthorn Chavasiri, Ph.D.)

  
..... Member  
(Associate Professor Pipat Karntiang, Ph.D.)

  
..... Member  
(Assistant Professor Polkit Sangvanich, Ph.D.)

  
..... Member  
(Fuangfa Unob, Ph.D.)

สกายดาว ฉายศรีพงษ์กุล: การพัฒนารีเอเจนต์เพื่อเตรียมแอซิดคลอไรด์สำหรับการสังเคราะห์สารออกฤทธิ์ทางชีวภาพ (REAGENT DEVELOPMENT FOR THE PREPARATION OF ACID CHLORIDE FOR SYNTHESIS OF BIOACTIVE COMPOUND) อ. ที่ปรึกษา: ผศ. ดร.วรินทร์ ชวศิริ, 109 หน้า. ISBN 974-17-5092-7.

ได้ศึกษาวิธีการเตรียมแอซิดคลอไรด์ โดยใช้ฮาโลจีเนตเทตรีเอเจนต์และไทโรเฟนิลฟอสฟิน พบว่าไทโรคลอโรแอเซทามีคู่กับไทโรเฟนิลฟอสฟินเป็นรีเอเจนต์ที่มีประสิทธิภาพในปฏิกิริยานี้ ได้ทดลองเพื่อหาภาวะที่เหมาะสมในการเกิดปฏิกิริยาได้แก่ ชนิดของฮาโลจีเนตเทตรีเอเจนต์, เบส, ระบบตัวทำละลาย, อุณหภูมิและเวลาที่ใช้ในการเกิดปฏิกิริยา แอซิดคลอไรด์ที่เกิดขึ้นสามารถทำปฏิกิริยากับเอมีนหรือแอลกอฮอล์ ให้ผลิตภัณฑ์เป็นแอมิดและเอสเทอร์ตามลำดับ วิธีการนี้สามารถประยุกต์ได้กับกรดคาร์บอกซิลิกชนิดแอมโรมาติกและแอลิฟาติกที่มีความยาวโซ่คาร์บอนสั้น นอกจากนี้สามารถประยุกต์วิธีที่ได้พัฒนาขึ้นสำหรับสังเคราะห์แอมิดและเอสเทอร์ และสามารถเตรียมแอมิดที่มีฤทธิ์ทางชีวภาพ 11 ชนิดและเอสเทอร์ที่แสดงฤทธิ์ทางชีวภาพ 5 ชนิด โดยได้ปริมาณของผลิตภัณฑ์มากกว่าหรือใกล้เคียงกับที่มีรายงานในงานวิจัยก่อนหน้านี้



ศูนย์วิทยทรัพยากร  
จุฬาลงกรณ์มหาวิทยาลัย

ภาควิชา.....เคมี.....	ลายมือชื่อนิสิต..... สกาย ดาว ฉายศรีพงษ์กุล.....
สาขาวิชา.....เคมี.....	ลายมือชื่ออาจารย์ที่ปรึกษา..... วรินทร์ ชวศิริ.....
ปีการศึกษา.....2546.....	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....-.....

# # 4472429023 : MAJOR CHEMISTRY

KEY WORD: REAGENT DEVELOPMENT/ACID CHLORIDE/ BIOACTIVE COMPOUND

SKAYDAW CHAYSRIPOONGKUL: REAGENT DEVELOPMENT FOR THE PREPARATION OF ACID CHLORIDE FOR SYNTHESIS OF BIOACTIVE COMPOUND THESIS ADVISOR: ASSISTANT PROFESSOR WARINTHORN CHAVASIRI, Ph.D., 109 pp. ISBN 974-17-5092-7.

The methodology for the preparation of acid chloride utilizing halogenated reagent and triphenylphosphine was thoroughly explored. Trichloroacetamide coupled with triphenylphosphine was turned out to be an effective reagent for this kind of transformation. A series of experiment to optimize the reaction conditions including type of halogenated reagent, type of base, solvent system, temperature and reaction time was cautiously conducted. The acid chloride generated could be successfully trapped with amine or alcohol yielding amides and esters, respectively. This methodology was applicable for aromatic and short chain aliphatic carboxylic acids. In addition, the application of this developed protocol for the synthesis of amides and esters was fruitfully accomplished. Eleven biologically active amides and five bioactive esters were prepared according to this method with the yield higher or comparable to those cited in literature.

ศูนย์วิทยทรัพยากร  
จุฬาลงกรณ์มหาวิทยาลัย

Department.....Chemistry.....

Field of study...Chemistry.....

Academic year....2003.....

Student's signature.....SKAYDAW CHAYSRIPOONGKUL.....

Advisor's signature.....Warinthorn Chavasiri.....

Co-advisor's signature.....-.....

## ACKNOWLEDGEMENTS

On this thesis's success, the author wishes to express her extremely grateful acknowledgement to her advisor, Assistant Professor Dr. Warinthron Chavasiri for helpful guidance, understanding, valuable suggestions, supervision and continuous encouragements throughout the course of this research. The author also would like to express her appreciation to Professor Dr. Udom Kokpol, Associate Professor Dr. Pipat Karntiang, Assistant Professor Dr. Polkit Sangvanich and Dr. Fuangfa Unob for their comments, corrections and assistance as thesis examiners. Moreover, thanks are extended to the Graduate School and the Department of Chemistry, Faculty of Science, Chulalongkorn University for the financial support. Pursuing the master program at Chulalongkorn University would have been impossible without this financial support. The author acknowledgement to Natural Products Research Unit, Faculty of Science, Chulalongkorn University for the support of chemical and laboratory facilities.

Special thanks are expanded to my friends for friendship, helpful discussion and valuably advice. Besides, the author would like especially to thank Miss Sujittra Deesamer for providing some cinnamic acids. Unforgettably, the author would like to express my parents and family members for their affection, best wish, understanding and encouragement that they have devoted to.

# CONTENTS

	Pages
Abstract in Thai .....	iv
Abstract in English .....	v
Acknowledgements .....	vi
List of Figures.....	x
List of Tables .....	xiii
List of Abbreviations .....	xiv
<b>CHAPTER</b>	
<b>I. INTRODUCTION .....</b>	<b>1</b>
1.1 Introduction of Acid Chlorides .....	1
1.2 Synthesis of Acid Chlorides.....	2
1.2.1 From Carboxylic Acids.....	2
1.2.2 From Aldehydes.....	3
1.2.3 From Aryl <i>1,1,1</i> -Trichloromethanes .....	3
1.2.4 From Ketenes .....	4
1.3 Literature Reviews of Acid Chlorides Synthesis from Carboxylic Acids .....	4
1.3.1 Common Reagents .....	4
1.3.2 Phosphorus Compounds with Halogenated Reagents.....	6
1.4 Literature Reviews of Amides Synthesis.....	7
1.4.1 Synthesis of Amide without Acid Chloride .....	8
1.4.2 Synthesis of Amide <i>via</i> Acid Chloride .....	10
1.5 Literature Reviews of Esters Synthesis.....	11
1.6 Biological Active Amide Compounds .....	12
1.6.1 Agricultural Activity .....	12
1.6.2 Pharmaceutical Activity .....	14
1.7 Biological Active Ester Compounds.....	16

## CONTENTS (continued)

	Pages
1.8 The Objective of This Research.....	17
<b>II. EXPERIMENTAL</b> .....	<b>18</b>
2.1 Instruments and Equipment .....	18
2.2 Chemicals.....	18
2.3 Preparation of Substrates .....	19
2.3.1 Halogenated Reagents .....	19
2.3.2 Starting Materials .....	20
2.4 General Procedure for the Synthesis Amides and Esters.....	21
2.5 Study on the Optimum Conditions .....	21
2.5.1 Effect of Halogenated Reagent.....	21
2.5.2 Effect of Base .....	22
2.5.3 Effect of Solvent System .....	22
2.5.4 Effect of Temperature and Reaction Time .....	22
2.5.5 Variation of Carboxylic Acid .....	22
2.5.6 Variation of Amine.....	22
2.6 Synthesis of Target Molecules.....	22
2.6.1 Amide Compounds.....	22
2.6.2 Ester Compounds.....	27
<b>III. RESULTS AND DISCUSSION</b> .....	<b>29</b>
3.1 Study on Conditions Optimization.....	29
3.1.1 Effect of Halogenated Reagent.....	30
3.1.2 Effect of Base .....	34
3.1.3 Effect of Solvent System .....	35
3.1.4 Effect of Temperature and Reaction Time .....	36
3.2 The General Consideration of Selected Halogenated Reagents and Bases .....	36
3.3 The Mechanism of Acid Chloride Formation.....	39
3.4 Application of Developed Procedures for the Synthesis of Target Molecules .....	39



**CONTENTS (continued)**

	Pages
3.4.1 Biologically Active Amides .....	40
3.4.2 Biologically Active Esters.....	58
<b>IV. CONCLUSION</b> .....	<b>62</b>
REFERENCES .....	65
APPENDICES .....	72
VITA.....	109



ศูนย์วิทยทรัพยากร  
จุฬาลงกรณ์มหาวิทยาลัย

## LIST OF FIGURES

Figures		Pages
1.1	The conversion of organic compounds to amides .....	8
1.2	Structures of agricultural active amide compounds .....	13
1.3	Structures of pharmaceutical active amide compounds .....	15
3.1	The IR spectrum of <i>N</i> -cyclohexylbenzamide .....	32
3.2	The <sup>1</sup> H-NMR spectrum of <i>N</i> -cyclohexylbenzamide .....	32
1	The IR spectrum of <i>N,N</i> -diethylbenzamide ( <b>T1</b> ).....	73
2	The <sup>1</sup> H-NMR spectrum of <i>N,N</i> -diethylbenzamide ( <b>T1</b> ).....	73
3	The IR spectrum of <i>N,N</i> -diethyl- <i>m</i> -toluamide ( <b>T2</b> ) .....	74
4	The <sup>1</sup> H-NMR spectrum of <i>N,N</i> -diethyl- <i>m</i> -toluamide ( <b>T2</b> ).....	74
5	The IR spectrum of mebenil ( <b>T3</b> ).....	75
6	The <sup>1</sup> H-NMR spectrum of mebenil ( <b>T3</b> ).....	75
7	The IR spectrum of benodanil ( <b>T4</b> ).....	76
8	The <sup>1</sup> H-NMR spectrum of benodanil ( <b>T4</b> ) .....	76
9	The IR spectrum of 2-chloro- <i>N,N</i> -diethylcinnamamide ( <b>T5</b> ) .....	77
10	The <sup>1</sup> H-NMR spectrum of 2-chloro- <i>N,N</i> -diethylcinnamamide ( <b>T5</b> ).....	77
11	The IR spectrum of <i>N</i> -(3,4-methylenedioxcinnamoyl)phenethylamide ( <b>T6-1</b> ).....	78
12	The <sup>1</sup> H-NMR spectrum of <i>N</i> -(3,4-methylenedioxcinnamoyl)phenethylamide ( <b>T6-1</b> ).....	78
13	The IR spectrum of <i>N</i> -(3,4-methylenedioxcinnamoyl)piperidide ( <b>T7</b> ).....	79
14	The <sup>1</sup> H-NMR spectrum of <i>N</i> -(3,4-methylenedioxcinnamoyl)piperidide ( <b>T7</b> ).....	79
15	The IR spectrum of cypromid ( <b>T8</b> ) .....	80
16	The <sup>1</sup> H-NMR spectrum of cypromid ( <b>T8</b> ).....	80
17	The IR spectrum of capsaicine synthetic ( <b>T9</b> ).....	81
18	The <sup>1</sup> H-NMR spectrum of capsaicine synthetic ( <b>T9</b> ).....	81

## LIST OF FIGURES (continued)

Figures		Pages
19	The IR spectrum of <i>N</i> -palmitoylethanolamine (T10).....	82
20	The <sup>1</sup> H-NMR spectrum of <i>N</i> -palmitoylethanolamine (T10).....	82
21	The IR spectrum of <i>N,N'</i> -bis(3-chlorophenyl)butanediamide (T11).....	83
22	The <sup>1</sup> H-NMR spectrum of <i>N,N'</i> -bis(3-chlorophenyl)butanediamide (T11).....	83
23	The IR spectrum of benzyl benzoate (T13).....	84
24	The <sup>1</sup> H-NMR spectrum of benzyl benzoate (T13).....	84
25	The IR spectrum of phenethyl cinnamate (T14).....	85
26	The <sup>1</sup> H-NMR spectrum of phenethyl cinnamate (T14).....	85
27	The IR spectrum of cinnamoyl cinnamate (T15).....	86
28	The <sup>1</sup> H-NMR spectrum of cinnamoyl cinnamate (T15).....	86
29	The IR spectrum of cholesteryl butyrate (T16).....	87
30	The <sup>1</sup> H-NMR spectrum of cholesteryl butyrate (T16).....	87
31	The <sup>13</sup> C-NMR spectrum of cholesteryl butyrate (T16).....	88
32	The IR spectrum of cholesteryl nonanoate (T17).....	89
33	The <sup>1</sup> H-NMR spectrum of cholesteryl nonanoate (T17).....	89
34	The <sup>13</sup> C-NMR spectrum of cholesteryl nonanoate (T17).....	90
35	The IR spectrum of <i>N</i> -benzylcyclopropanecarboxamide.....	91
36	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzylcyclopropanecarboxamide.....	91
37	The <sup>13</sup> C-NMR spectrum of <i>N</i> -benzylcyclopropanecarboxamide.....	92
38	The IR spectrum of <i>N</i> -benzylmethacrylamide.....	93
39	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzylmethacrylamide.....	93
40	The IR spectrum of <i>N</i> -benzylbutanamide.....	94
41	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzylbutanamide.....	94
42	The IR spectrum of <i>N</i> -benzyl-6-bromohexanamide.....	95
43	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzyl-6-bromohexanamide.....	95
44	The IR spectrum of <i>N</i> -benzylnonanamide.....	96
45	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzylnonanamide.....	96
46	The IR spectrum of <i>N</i> -benzyl dodecanamide.....	97
47	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzyl dodecanamide.....	97

## LIST OF FIGURES (continued)

Figures		Pages
48	The IR spectrum of <i>N</i> -benzylhexadecanamide .....	98
49	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzylhexadecanamide.....	98
50	The IR spectrum of 4-nitro- <i>N</i> -cyclohexylbenzamide .....	99
51	The <sup>1</sup> H-NMR spectrum of 4-nitro- <i>N</i> -cyclohexylbenzamide.....	99
52	The IR spectrum of 4-methoxy- <i>N</i> -cyclohexylbenzamide .....	100
53	The <sup>1</sup> H-NMR spectrum of 4-methoxy- <i>N</i> -cyclohexylbenzamide .....	100
54	The IR spectrum of <i>N</i> -benzylbenzamide.....	101
55	The <sup>1</sup> H-NMR spectrum of <i>N</i> -benzylbenzamide.....	101
56	The IR spectrum of <i>N</i> -(2,6-dimethylphenyl)benzamide .....	102
57	The <sup>1</sup> H-NMR spectrum of <i>N</i> -(2,6-dimethylphenyl)benzamide .....	102
58	The IR spectrum of <i>N</i> -(4-phenoxyphenyl)benzamide.....	103
59	The <sup>1</sup> H-NMR spectrum of <i>N</i> -(4-phenoxyphenyl)benzamide.....	103
60	The <sup>13</sup> C-NMR spectrum of <i>N</i> -(4-phenoxyphenyl)benzamide.....	104
61	The IR spectrum of <i>N</i> -(2-hydroxyethyl)benzamide .....	105
62	The <sup>1</sup> H-NMR spectrum of <i>N</i> -(2-hydroxyethyl)benzamide .....	105
63	The IR spectrum of 2-benzamidoethyl benzoate .....	106
64	The <sup>1</sup> H-NMR spectrum of 2-benzamidoethyl benzoate.....	106
65	The IR spectrum of <i>N</i> -octadecylbenzamide .....	107
66	The <sup>1</sup> H-NMR spectrum of <i>N</i> -octadecylbenzamide .....	107
67	The IR spectrum of <i>N</i> -(1-naphthyl)benzamide .....	108
68	The <sup>1</sup> H-NMR spectrum of <i>N</i> -(1-naphthyl)benzamide.....	108

จุฬาลงกรณ์มหาวิทยาลัย

## LIST OF TABLES

Tables	Pages
1.1 The conversion of acid chlorides to other organic compounds.....	2
1.2 Fragrances of esters.....	16
3.1 Effects of halogenated reagents on the formation of <i>N</i> -cyclohexylbenzamide	30
3.2 Effects of bases on the formation of <i>N</i> -cyclohexylbenzamide.....	34
3.3 Effects of solvent system on the formation of <i>N</i> -cyclohexylbenzamide.....	35
3.4 Effects of temperature and reaction time on the formation of <i>N</i> -cyclohexylbenzamide .....	36
3.5 The comparison between %yield of <i>N</i> -cyclohexylbenzamide and the cost of some halogenated reagents .....	37
3.6 The comparison between %yield of <i>N</i> -cyclohexylbenzamide and the cost of base .....	38
3.7 The summarization of selected synthesized biological active amides .....	42
3.8 Effect of amines on the synthesis of amides using this developed reaction ....	43
3.9 Comparative study for the synthesis of <b>T7</b> .....	48
3.10 Summarization of selected synthesized biological cinnamamides .....	49
3.11 Effect of carboxylic acids on the synthesis of amides using the developed methodology.....	50
3.12 Effects of substituents on a benzoic acid ring on the yield of amide obtained .....	57
3.13 The summarization of selected synthesized biological active esters .....	61
4.1 The summarization of biologically active amides .....	63
4.2 The summarization of biologically active esters.....	64

**LIST OF ABBREVIATIONS**

br s	broad singlet (NMR)
$\delta$	chemical shift
$J$	coupling constant (NMR)
d	doublet (NMR)
eq	equivalent (s)
Fig	Figure
g	gram (s)
Hz	hertz
IR	infrared
lit.	literature
m.p.	melting point
NMM	<i>N</i> -methylmorpholine
mL	milliliter (s)
mmol	millimole (s)
m	multiplet (NMR)
NMR	nuclear magnetic resonance
ppm	part per million
q	quartet (NMR)
quin	quintet (NMR)
$R_f$	retardation factor
sep	septet (NMR)
s	singlet (NMR)
t	triplet (NMR)
TLC	thin layer chromatography
$\text{cm}^{-1}$	unit of wavenumber