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INTRAMOLECULAR CYCLISATION OF ENAMIDE DERIVATIVES

Miss Kunlayanee Hansuthirakul

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By	Miss Kunlayanee Hansuthirakul
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Thesis Advisor	Associate Professor Mongkol Sukwattanasinitt, Ph.D.
Thesis Co-Advisor	Anawat Ajavakom, 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

(Associate Professor Supawan Tantayanon, Ph.D.)

..... Thesis Advisor

(Associate Professor Mongkol Sukwattanasinitt, Ph.D.)

..... Thesis Co-Advisor

(Anawat Ajavakom, Ph.D.)

..... Member

(Assistant Professor Warinthorn Chavasiri, Ph.D.)

..... Member

(Duangamol Nuntasri, Ph.D.)

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วิทยานิพนธ์นี้เกี่ยวข้องกับการจัดเป็นวงภายในโมเลกุลด้วยกรดเป็นตัวเร่งปฏิกิริยาของอนุพันธ์เอนาไมด์ที่มีหมู่ปกป้องเป็นเทอร์เชียรีบิวทอกซีคาร์บอนิลที่ประกอบด้วย หมู่ β และ γ ไดแอลคอกซีแอซีแทล ในการจัดเป็นวงของอนุพันธ์เอนาไมด์ปกป้องด้วยเทอร์เชียรีบิวทอกซีคาร์-บอนิลที่มีหมู่ β ไดแอลคอกซีแอซีแทลได้ผลิตภัณฑ์เป็นอนุพันธ์ออกซาโซลิดิโนนที่มีหมู่แทนที่บนอะตอมของไนโตรเจนให้เปอร์เซ็นต์ผลิตภัณฑ์ที่สูง โดยการจัดเป็นวงภายในโมเลกุลนี้เกิดจากออกซิเจนอะตอมบนหมู่ปกป้องคาร์บอนิลเข้าชนที่แอซีแทลคาร์บอนที่ถูกโปรโตรเนตได้อนุพันธ์ออกซาโซลิดิโนนเป็นผลิตภัณฑ์ ส่วนในการจัดเป็นวงของอนุพันธ์เอนาไมด์ที่ประกอบด้วยหมู่ γ ไดแอลคอกซีแอซีแทลได้ผลิตภัณฑ์เป็นอนุพันธ์ไพริดีนให้เปอร์เซ็นต์ผลิตภัณฑ์ที่ต่ำ โดยปฏิกิริยาการจัดเป็นวงภายในโมเลกุลนี้เกิดจากการที่คาร์บอนอะตอมของหมู่แอลคีนของเอนาไมด์เข้าชนที่หมู่แอลคอกซีแอซีแทลคาร์บอนที่ถูกโปรโตรเนตได้อนุพันธ์ไพริดีนเป็นผลิตภัณฑ์สุดท้าย ซึ่งน่าจะเกิดจากกระบวนการหลุดของหมู่ปกป้องที่เป็นเทอร์เชียรีบิวทอกซีคาร์บอนิล นอกจากนี้สามารถสังเคราะห์อนุพันธ์ออกซาโซลิดิโนนที่เกิดจากการจัดเป็นวงของเอไมด์ที่ปกป้องด้วยเทอร์เชียรีบิวทอกซีคาร์บอนิลได้

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KUNLAYANEE HANSUTHIRAKUL : INTRAMOLECULAR CYCLISATION OF ENAMIDE DERIVATIVES. THESIS ADVISOR : ASSOC. PROF. MONGKOL SUKWATTANASINITT, Ph.D. THESIS CO-ADVISOR : ANAWAT AJAVAKOM, Ph.D. 91 pp. ISBN 974-14-3249-6

This thesis studied acid-induced intramolecular cyclisation of Boc-enamides containing β and γ dialkyl acetal group. The cyclisation of Boc-enamides containing β dialkyl acetal group yielded *N*-substituted oxazolidin-2-one derivative in good yield. The cyclisation was proposed to undergo a nucleophilic attack on the acid activated acetal carbon by an oxygen atom on the Boc carbonyl. The cyclisation Boc-enamides containing γ dialkyl acetal group gave pyridine derivative in low yield. The reaction presumably occurred through an attack of carbon atom of the alkene in enamide with an assist of decarboxylation in the Boc deprotection process. The cyclisation to form oxazolidin-2-ones was also extended successfully to Boc-amides.

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Finally, I owe very deep thanks to my family for their love, encouragement and support.

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LIST OF ABBREVIATIONS

Anal.	Analysis
Ar	Aromatic
$BF_3{\cdot}OEt_2$	borontrifluoride diethyl etherate
Boc	*tert*-butoxy carbonyl
br	broad (NMR)
brd	broad doublet (NMR)
Calcd.	Calculated
$^{\circ}C$	degree Celsius
d	doublet (NMR)
dd	doublet of doublet (NMR)
DMAP	4-(dimethyl amino)pyridine
dt	doublet of triplet (NMR)
2,4-DNP	2, 4-dihydrophenylhydrazine
E	*E*ntgegen (opposite)
Elem.	Elemental
eq	equivalent
Et	ethyl
EtO	ethoxy
EtOAc	ethyl acetate
h	hour
Hz	Hertz
J	coupling constant
J.	journal
Lett.	Letters
m	multiplet (NMR)
M	Molar
Me	methyl
mL	Milliliter
MeO	methoxy
MHz	Megahertz

min	minute
mmol	Millimole
MS	mass spectroscopy
m/z	Mass per charge
n-	normal
NMR	Nuclear Magnetic Resonance
Org.	Organic
p-TsOH	*para*-toluenesulfonic acid
q	quartet
Rev.	Reviews
Rf.	Retention factor
rt	room temperature
s	singlet (NMR)
Sci.	Science
Soc.	Society
Syn.	Synthesis
t	*tertiary*
t	triplet (NMR)
TEA	triethylamine
tert-	tertiary
TFA	trifluoroacetic acid
TLC	thin layer chromatography
UV	Ultraviolet
Z	*Z*usammen (together)

CHAPTER I

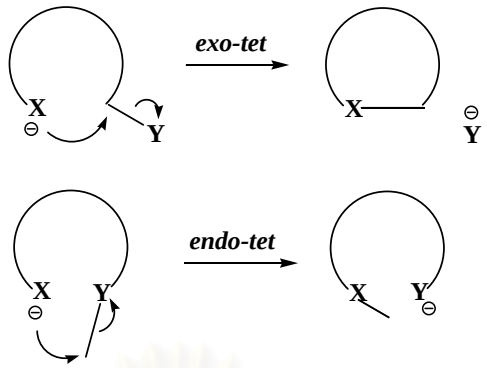
INTRODUCTION

Thailand petroleum industry has rapidly grown into one of the biggest industries in South East Asia. It does not only full-fill the national needs but also does expand to produce large amount of fine chemicals enough to export to other countries among the region, which can gain a big profit for our country. In general, most chemicals can be obtained from by-products of the oil-refining process, which are massively produced and therefore relatively cheap. To bring out most benefits from such cheap starting materials, the most efficient fine chemical technologies are required. Hence the development of such methodologies is compulsory for fine chemical industry.

1.1 Intramolecular cyclisation

Intramolecular cyclisation is one of the most important reactions useful for the synthesis of various types of heterocycles such as dihydropyrroles, oxazolidinones and pyridines. Metal mediated catalysts, [1] radical initiators, [2] bases [3] and acids [4] have been used to induce the intramolecular cyclisation to form valuable intermediates of natural products and medicines from simple fine chemicals [5], which means increase the value of cheap petrochemical starting materials.

In 1976, Baldwin [6] formulated a number of rules for ring closure to predict relative facility of ring forming reactions. He reported that there were two basic states in which ring-closure could happen, which are *exo* and *endo*. When nucleophile attacks an electrophile, if electrons stay within the ring, the process is called *endo* cyclisation and if electrons shift away from the ring it is called *exo* cyclisation **(Scheme 1)**.



Scheme 1 The ring-closure of *endo-tet* and *exo-tet* cyclisations

He also reported that the geometry of the acceptor atom was important, and the feasible states tetrahedral (sp^3), trigonal (sp^2), and diagonal (*sp*) were determined as *tet*, *trig*, and *dig*, respectively. Baldwin's Rule can be summarized, as the following systems.

a. Tetrahedral systems

i) 3 to 7-*exo–tet* are all favoured.

ii) 3 to 6-*endo-tet* are disfavoured; 7-*endo-tet* is favoured

b. Trigonal systems

i) 3 to 7-*exo-trig* are all favoured.

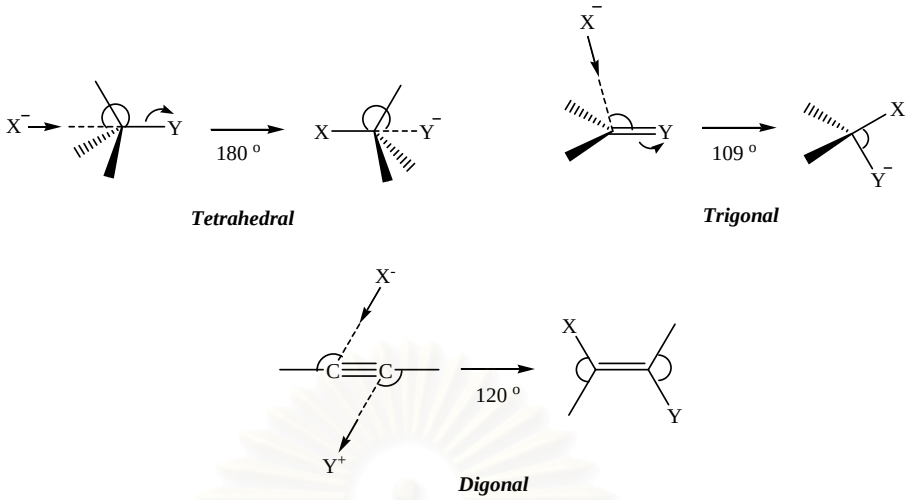
ii) 3 to 5-*endo-trig* are disfavoured; 6 to 7-*endo-trig* are favoured.

c. Digonal systems

i) 3 to 4-*exo-dig* are disfavoured; 5 to 7-*exo-dig* are favoured.

ii) 3 to 7-*endo–dig* are all favoured.

"Disfavoured" does not imply whether the reaction can not or will not occur. It only means that the reaction is more difficult than the favoured one.



Scheme 2 The favoured trajectories for a nucleophile to a carbon atom

For the ring closure, the favoured trajectories for a nucleophile to a carbon atoms can be described by the fact that subtended angle between the three interacting atoms is sustained during the reaction pathway, becoming the angle between these atoms in the product **(Scheme 2)**. Consequently the favoured ring closure is up to the length and nature of linking chain which enables the terminal atoms to achieve the required trajectories to form the final ring bond. Hence the cases that demand more distortion of bond angles and distances to achieve such trajectories are clarified as the disfavoured processes.

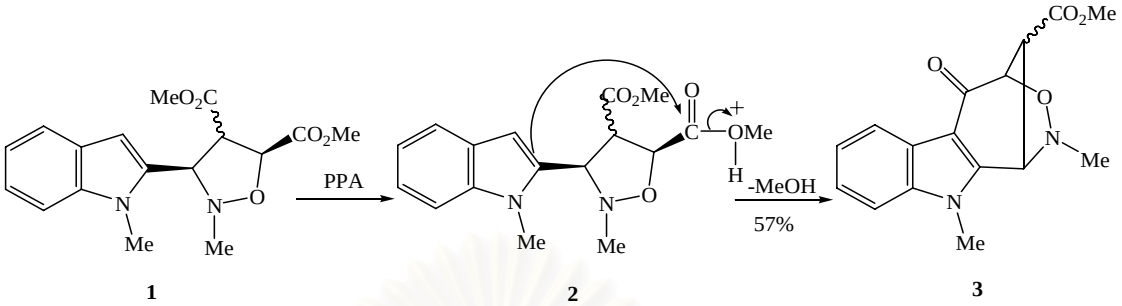
1.2 Acid-induced intramolecular cyclisation

As the way to promote the intramolecular cyclisation previously mentioned, acid-induced cyclisation is one of the most popular methods as there are acidic reagents applicable for the purpose. Herein, some intramolecular cyclisation induced by important acids such as PPA, [7] formic acid [8] and Lewis acid [9] are examplified.

1.2.1 Polyphosphoric acid (PPA)

Malamidou-Xenikakiand and his colleagues reported that the intramolecular cyclisation of the isooxazolidine by using PPA as an acid catalyst gave product **3** in moderate yield **(Scheme 3)**. The ester group of the substrate **1** was protonated by PPA

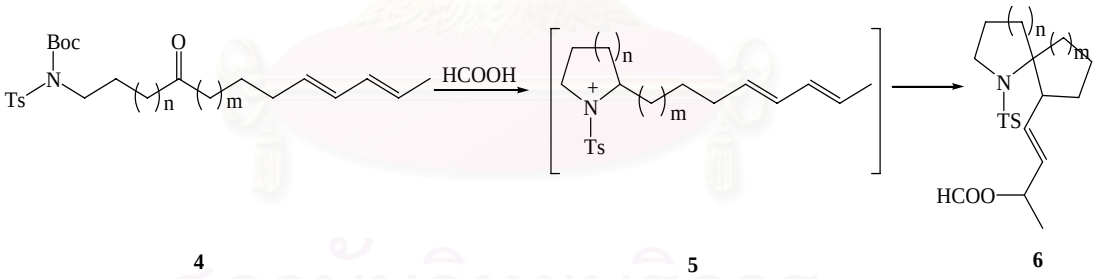
to generate intermediate **2** on which the enamine double bond can easily attack to form the fused *tetra* cyclic **3**.



Scheme 3 Polyphosphoric acid-induced intramolecular cyclisation

1.2.2 Formic acid

Kibayashi and his colleagues reported that formic acid had been utilized to induce the cyclisation of various conjugated diene-ketoamides **(Scheme 4)**. The effect of the subtituent on the nitrogen atom was investigated. This spirocyclisation of ketoamides **4** using formic acid likely occurred *via* the intermediate of five-membered ring *N*-tosyliminium ions **5** giving the spirocyclics **6** in good yields.

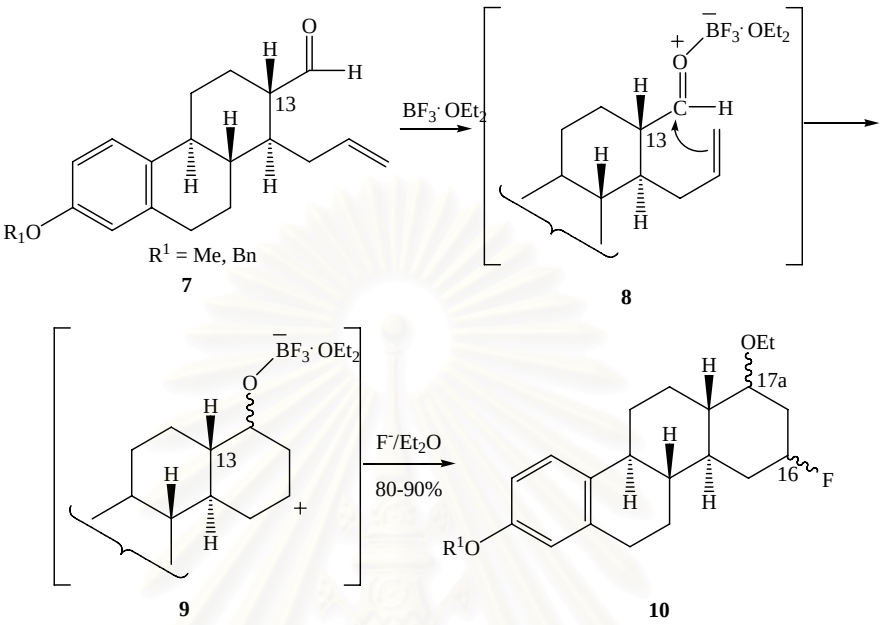


Scheme 4 Formic acid-induced intramolecular cyclisation

1.2.3. Lewis acid

Schneider and his colleagues established a novel synthetic route to halogen-containing-13-α-*D*-homoestrone derivatives **10** by Lewis acid-induced intramolecular Prins reaction through a stepwise ionic pathway **(Scheme 5)**. First the aldehyde **7** was treated with $BF_3{\cdot}OEt_2$ to chemoselectively produce the corresponding halohydrins. They believed that compound **10** were derived from a two-step mechanism, which has

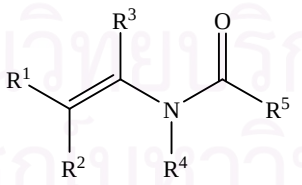
the oxonium ion **8** and the secondary carbocation **9** as intermediates. The addition of a halide as nucleophile terminates the reaction to give tetracyclic product **10** in a good yield.



Scheme 5 Lewis acid-induced intramolecular cyclisation

1.3 Enamide

Enamide, so call “eneamide”, is an α, β- unsaturated amide **11 (Fig. 1)**. Normally enamides are reactive compounds. They can be hydrolyzed to give carbonyl compound and amines under acidic or basic conditions.



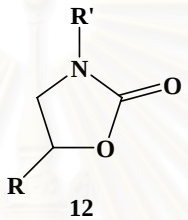
11

Fig. 1 The structure of an α, β- unsaturated amide **11**

1.4 Oxazolidin-2-one derivatives

1.4.1 Pharmaceutical background of oxazolidinone derivatives

Oxazolidin-2-ones **12** are five-membered ring of azoles, oxazolidines with the carbon between the nitrogen and oxygen oxidized to a ketone, hence oxazolidin-2-ones. Some oxazolidin-2-ones are possibly used as the stereoselective chiral auxiliaries (Evans's chiral auxiliary [10]) in asymmetric synthesis. Some oxazolidin-2-ones possess biological activities such as antibiotic, [11] antibacterial, [12] antianaerobic [13] etc.



12

Fig. 2 The structure of oxazolidin-2-one derivatives **12**

In 1983, oxazolidinone sulfonamide **13** was utilized for treating antibacterial. [14] The first member of commercially available oxazolidinone antibiotics was linezolid **14**, which has been successfully developed by Pharmacia Corporation. [15] It was confirmed and released by the US Food and Drug Administration (FDA), in April, 2000. Linezolid is effective against gram-positive pathogens, including staphylococci, enteococci and pneumococi. [16] AZD2563 **15** is the most recent oxazolidinone that developed by AstraZeneca has an alike structure to the linezolid, [17] but only at the positions 3 and 4 of the aryl ring on the C-5 side chain are different. AZD2563 has a stronger interaction than linezolid against some strains, and AZD2563 may offer the availability of once-daily dosing, while the linezolid used to receive twice-daily dosing in adults. AZD2563 can be consumed through an oral as well as intravenous therapy. Considerable attention has been gathered to the synthesis of oxazolidinone derivatives, in order to find better antibiotic candidates. Lois and his colleagues [18] reported that AZD2563 and linezolid were active against most Gram-positive anaerobes. AZD2563 has excellent activity against gram-positive bacterial **(Fig.3)**.

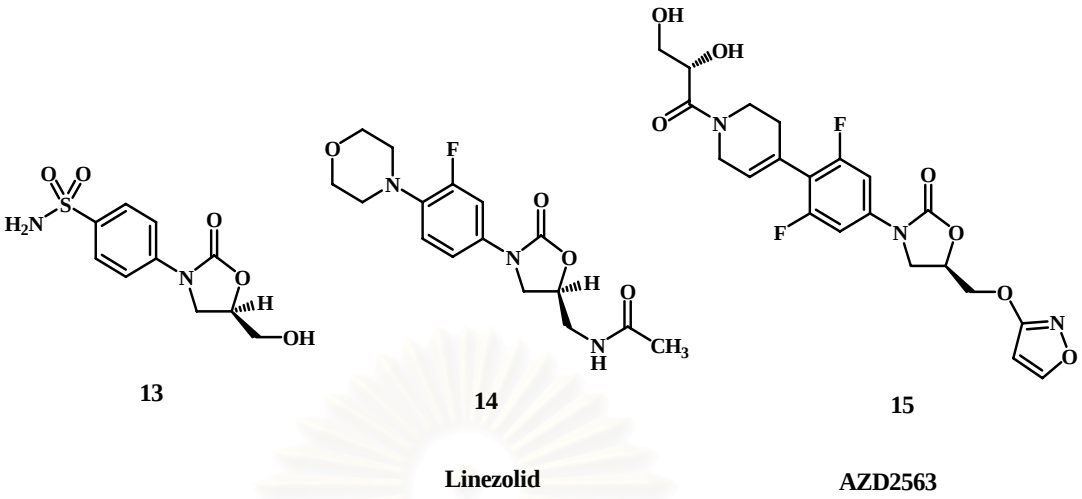


Fig. 3 The structures of oxazolidin-2-one derivatives

The oxazolidinones act in an early stage by inhibiting the bacterial protein synthesis. This means linezolid **14** interacted with 50s ribosomal subunit near to the interface with the 30s subunit to inhibit 70s initiation complex **(Fig. 4)**. [19-20] It is caused to inhibit the bacterial protein synthesis.

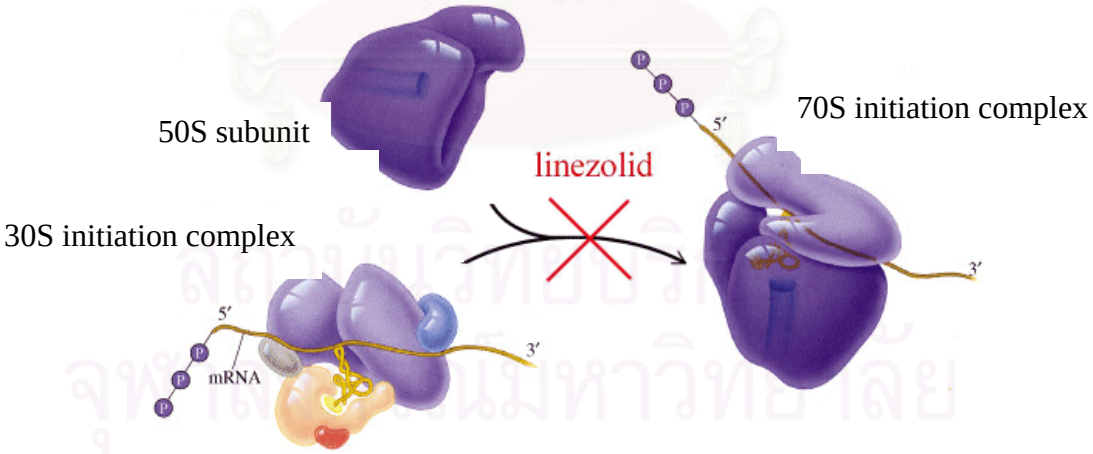


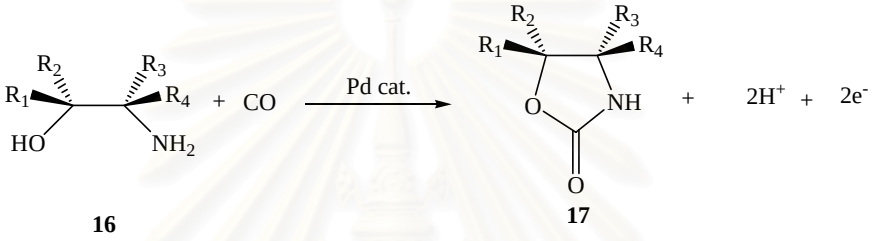
Fig. 4 The mechanism of inhibition

1.4.2 Synthesis of oxazolidin-2-ones derivatives

The oxazolidin-2-ones can be synthesized by using amino alcohols, [21] aziridines [22] or epoxides [23] as precursors.

1.4.2.1 Amino alcohol as starting material

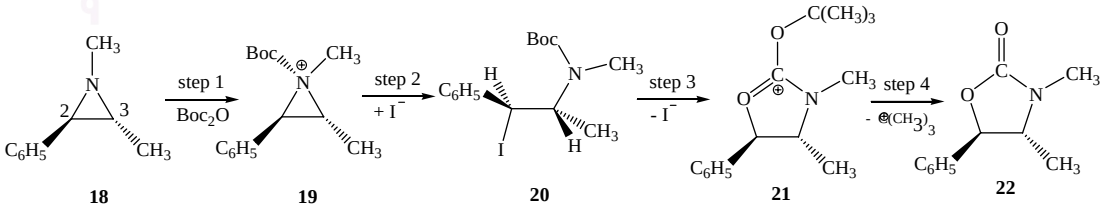
In the past, oxazolidin-2-ones were generally produced by reaction of 1,2-amino alcohol with harmful reagent such as phosgene, isocyanates sometimes involving high temperature condition. [24] In 2001, Chiarotto and Feroci synthesized oxazolidin-2-one **17** by using 1,2-amino alcohol **16** with palladium (II) complex as a catalyst and carbon monoxide (pCO = 1 atm) **(Scheme 6)**. They found that the reactions of primary amino group are faster than the reactions of secondary amino group. This method using amino alcohols as precursor was thus not suitable for synthesis of *N*-substituted oxazolidin-2-ones.



Scheme 6 The synthesis of oxazolidin-2-one from amino alcohol **16**

1.4.2.2 Aziridine as starting material

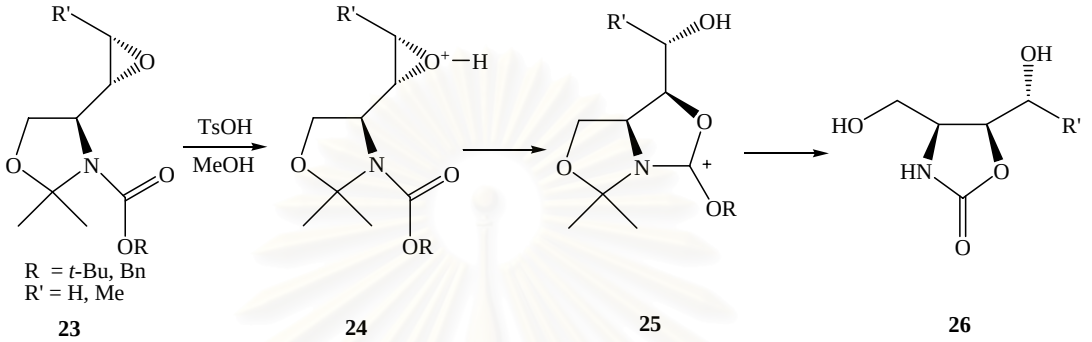
The synthesis of *trans*-oxazolidin-2-ones **22** from *trans*-1,2,3-trisubtituted aziridine **18** was reported by Domigo and his colleagues **(Scheme 7)**. It is an obvious stepwise mechanism. The first step is the nucleophilic attack of the nitrogen atom of the *trans*-aziridine **18** to a carbonyl group of Boc_2O, giving aziridium cation intermediate **19**. The nucleophilic attack of an iodide anion to C2 carbon atom gives iodo compound **20** by the ring opening of aziridinium **19**. The intramolecular cyclisation of compound **20** by substitution of iodide gives the cationic *O*-alkylated oxazolidin-2-one intermediated **21**. The lost of *tert*-butyl group of intermediate **21** provides the final oxazolidin-2-one **22** as a product in good yield.



Scheme 7 The synthesis of oxazolidin-2-one from aziridine **18**

1.4.2.3 Epoxide as starting material

Sepúlveda-Arques and his colleagues established the new synthetic route to oxazolidin-2-one **26** from chiral *α*-amino epoxides **23 (Scheme 8).** In this reaction *tert*-butyl carbamates reacted faster and with higher yields than their benzyl analogues.



Scheme 8 The synthesis of oxazolidin-2-one from epoxide **23**

The synthesis of oxazolidin-2-one derivatives by using aziridine and epoxide as starting materials required a three-membered ring reactive intermediate, which is sometimes hard to be formed. In this research, the synthesis of oxazolidin-2-ones was proposed to start from small linear molecules using simple reactions to generate Boc-protected enamines or secondary amines and then using an acid-induced intramolecular cyclisation to give oxazolidin-2-one derivatives.

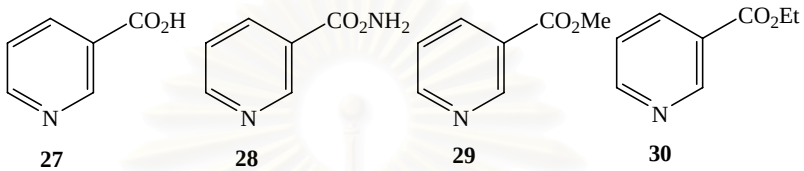
1.5 Pyridines derivatives

1.5.1 Pharmaceutical background of pyridine derivatives

Pyridine derivatives have many biological activities, such as antibacterial, [25] antidepressant, [26] fungicide, [27] herbicide [28] etc.

Niacin (vitamin B_3), commonly nicotinic acid (3-Pyridincarboxylic acid) **27** and niacinamide, commonly nicotinamide (3-Pyridincarboxamide) **28**, are water soluble vitamin B complexes **(Fig 5).** Commercial niacin is made from *ß*-picoline or from quinoline, which both of them could be produced from coal tar. But free nicotinic acid and nicotinamide are found in nature in only small amounts. Nicotinic acid is mostly bound to macromolecules in plants, while nicotinamide is normally a component of NADP in the animal bodies. Significant sources of niacin include beef,

pork, wheat flour, corn flour, eggs and milk. Nicotinamide in the active form functions as a component of two coenzymes, namely, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). They are the principal forms of niacin, which exist in animal tissues. In human, the daily need of nicotinic acid is within the range of 10-20 mg. The B vitamins niacin and niacinamide are well known as preventives of pellagra. [29]



27 **28** **29** **30**

Fig. 5 The structures of nicotin derivatives

One way to synthesize vitamin moiety nicotinic acid is to hydrolyze methyl nicotinated **29** and ethyl nicotinated **30 (Fig 5)**. Methyl nicotinate **29** is the methyl ester of nicotinic acid. It is an active ingredient of a number of veterinary preparations aimed for topical application as a rubefacient for the cure of many diseases, such as respiratory diseases, vascular disorders (oedema, haematoma), and rheumatoid disorders in cattle and horse. It is also used as an intermediate for agrochemicals, food additives, pharmaceuticals, flavors and fragrances. For example; methyl nicotinate **29** and ethyl nicotinate **30**, which are classified as a vasodilator, were used to be counterirritant in small concentration (0.25-1 %) for three or four times a day. [30]

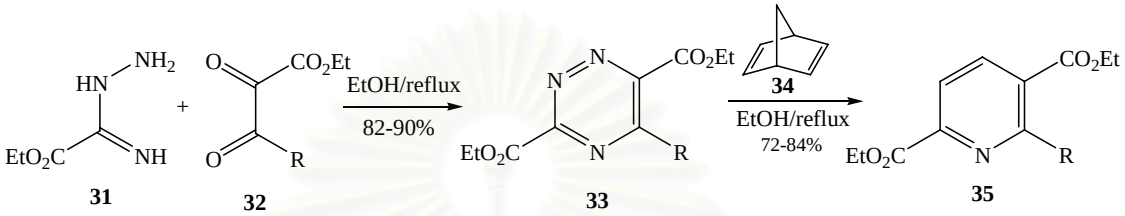
1.5.2 Synthesis of pyridine derivatives

The purpose of this research was to find novel route to the alkyl nicotinate based on an acid-induced intramolecular cyclisation approach.

Pyridine is an aromatic nitrogen analogue of benzene, which have a nitrogen atom substituted to one of the six C-H units of benzene. The nonbonding electron pair on nitrogen are sp^2 hybrid orbital perpendicular to the π system. Pyridines often proceed substitution rather than addition. Many methods have been developed to synthesize pyridine derivatives for more than a century. For example, pyridine can be synthesized by using Aza Diels-Alder [31] or Bohlmann-Rahtz [32] methodology.

1.5.2.1 Aza Diels-Alder

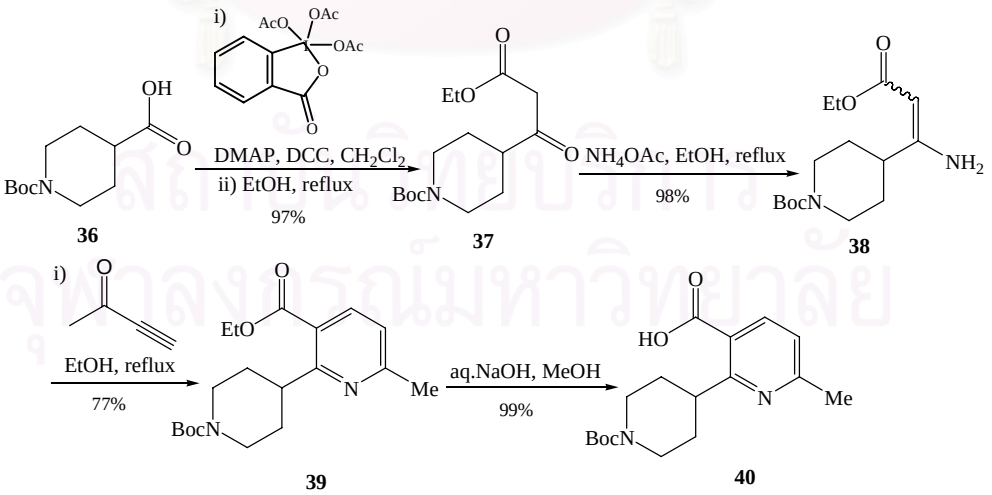
In 2002, Stanforth and his colleagues prepared pyridine derivatives using the Aza Diels-Alder reaction **(Scheme 9).** The condensation of amidrazone **31** with tricarbonyl derivatives **32** gave triazine derivatives **33** in good yields. The corresponding triazines **33** were then refluxed in ethanol with 2,5-norbornadiene **34** to give pyridine derivatives **35** also in good yields.



Scheme 9 The Aza Diels-Alder reaction

1.5.2.2 Bohlmann-Rahtz

In 2003, Robertson and his colleagues established pyridine scaffolds by using the Bohlmann-Rahtz route **(Scheme 10)**. In the first step, *N*-Boc-isonipecotic acid **36** coupled with Meldrum's acid, followed by ethanolysis to give *ß*-ketoester **37** in excellent yield. The *ß*-ketoester was treated with ammonium acetate in EtOH to give pure enamine **38** in great yield. Under Bohlmann-Rahtz condition, enamine **38** reacted with butynone in boiling ethanol to provide pyridine **39**, which is hydrolyzed to give carboxylic acid **40** in excellent yield for the use in library synthesis.



Scheme 10 The Bohlmann-Rahtz reaction

Although there are a few methods for synthesis of nicotinic acid, approach using simple acid-induced cyclisation of acyclic enamines has not been reported.

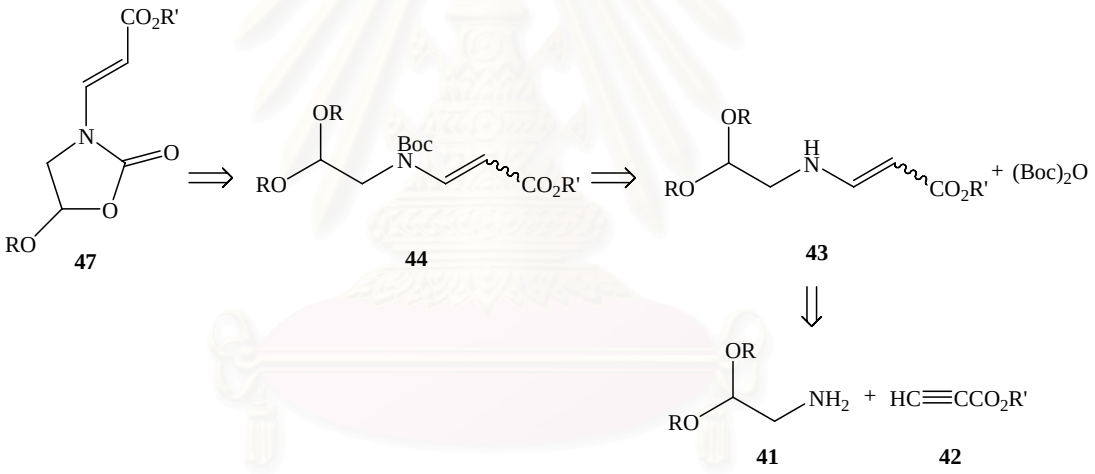
CHAPTER II

RESULTS AND DISCUSSION

2.1 Synthesis of oxazolidin-2-ones

2.1.1 Retrosynthesis of oxazolidin-2-ones

From the retrosynthetic strategy of oxazolidinones **47**, the required substrate for the cyclisation would be enamides **44**, which could be synthesized by protecting enamines **43** with Boc_2O. The enamines **43** could be synthesized from the simple coupling between dialkoxy amines **41** and alkyl propiolates **42 (Scheme 11)**.



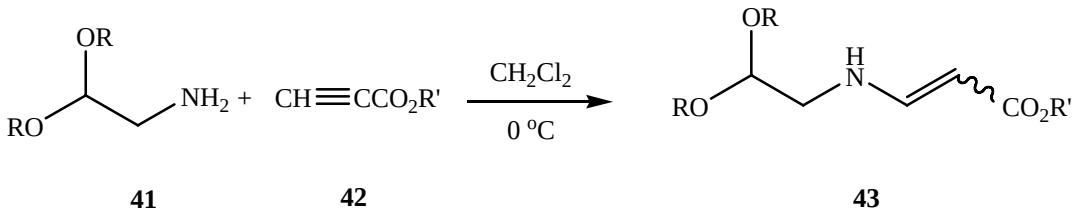
Scheme 11 Retrosynthesis of oxazolidin-2-one derivatives **47**

2.1.2 Synthesis of enamine by Michael addition reaction

In 2000, Macdonald and his colleagues [33] synthesized an enamine from a Michael type addition reaction of 1-amino-3,3-diethoxy propane with ethyl propiolate at room temperature with quantitative yield. The enamine product was obtained as a 1:1 mixture of *cis/trans* isomers.

The experiments were undertaken following Macdonald's method. The initial coupling reaction between 1-amino-dialkoxys and alkyl propiolates for 20 h gave the

desired secondary enamines **43** as a 7:3 mixture of *cis/trans* isomers at 0°C in quantitative yields **(Table 1)**.



41 **42** **43**

Scheme 12 The synthesis of enamine derivatives **43**

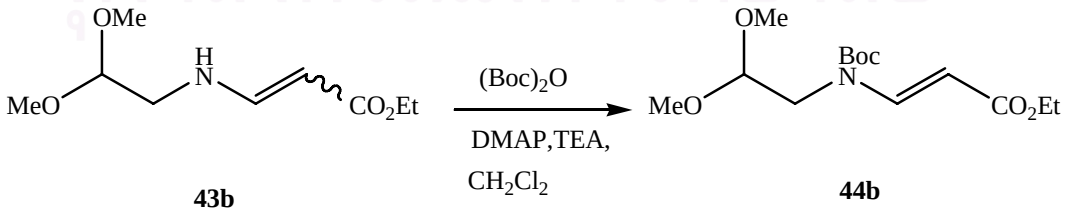
Table 1 Synthesis of enamine derivatives **43** by Michael addition reaction[a]

No.	R	R'	% yield
a	Me	Me	quant.
b	Me	Et	quant.
c	Et	Me	quant.
d	Et	Et	quant.

[a]Reaction conditions: solvent = CH_2Cl_2, temp = 0 °C ,time = 4 h, and allowed to room temperature , time = 20 h.

2.1.3 Synthesis of *N*-Boc protected secondary enamine

The synthesis of *tert*-butoxycarbonyl protected enamine precursor started from the reaction of enamine **43b** and Boc_2O using TEA as a base and DMAP as a catalyst to give *trans*-Boc-enamide **44b** in moderate yield **(Scheme 13)**. In this step the % yield of enamide product was monitored by GC. Further optimization of this reaction included reagent concentrations, amount of TEA and amount of DMAP.

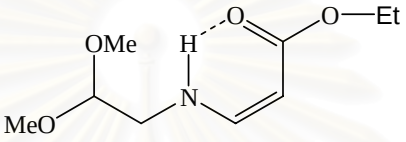


43b **44b**

Scheme 13 The synthesis of enamide derivative **44b**

2.1.3.1 Effect of the reagent concentrations on protection with Boc_2O

The reagent concentrations used in the Boc-protection reaction were varied **(Table 2)**. The % yield of enamide product **44b** was increased from 11% to 46% as the reagent concentrations increased. The reactions gave only moderate yields, probably due to the intramolecular hydrogen bonding in *Z* isomer that prevent the steric *tert*-butoxyl carbonyl group from undergoing the reaction with enamine **43b (Fig. 6)**.



43b

Fig. 6 The hydrogen bond formation in (*Z*)-enamine **43b**

Table 2 Effect of concentration of reagents in enamine protection reaction[a]

Conc. of enamines (M)	TEA (M)	DMAP (M)	Boc_2O (M)	% yield[b]	% yield[c]
0.023	0.0097	0.0098	0.024	11	-
0.047	0.019	0.020	0.047	26	-
0.230	0.097	0.096	0.240	46	38

[a]Reaction conditions: TEA 4 eq, DMAP 0.4 eq, Boc_2O 1 eq, solvent = CH_2Cl_2, room temperature, time = 20 h. [b]Determined by GC analysis with benzophenone as an internal standard. [c]Isolated yield by column chromatography.

2.1.3.2 Effect of the amount of TEA

The amount of TEA was varied from 1 to 4 eq of substrate **(Table 3)**. The amount of TEA that gave the highest % yield of enamide was 2 eq, when the amount of TEA was increased to 4 eq, the % yield of enamide decreased.

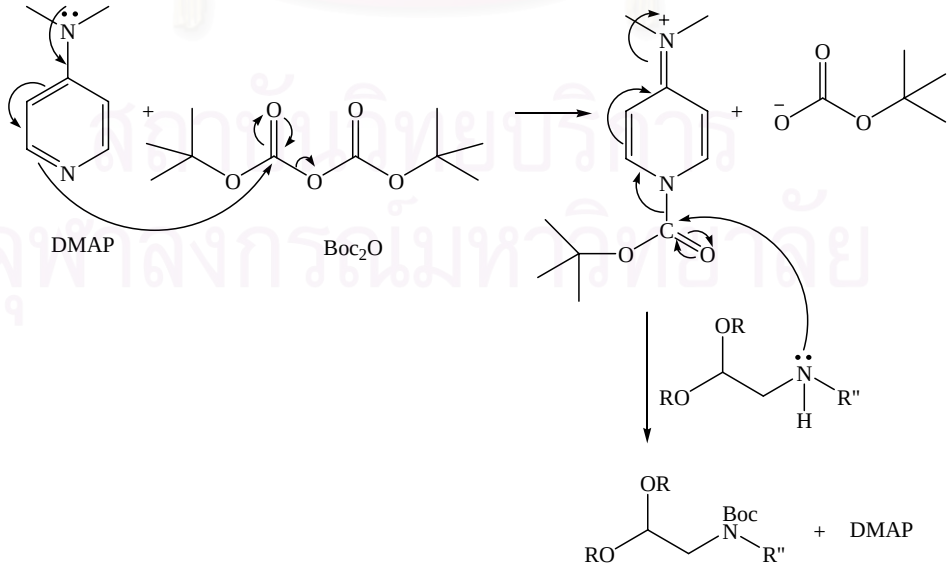
Table 3 Effect of amount of TEA in enamine protection reaction[a]

Amount of TEA (eq)	% yield[b]
1	56
2	65
4	46

[a]Reaction conditions: enamines **43b** (0.23 M), DMAP 0.4 eq, Boc_2O 1 eq, solvent = CH_2Cl_2, room temperature, time = 20 h. [b]Determined by GC analysis with benzophenone as an internal standard.

2.1.3.3 Effect of the amount of catalyst (DMAP)

The effect of the amount of DMAP (4-dimethylamino pyridine) catalyst was studied. Although Boc_2O is widely used for the protection of amine and alcohol substrates, alcohols and some amines do not often react readily with Boc_2O in the presence of only TEA. DMAP is well known as super acylation catalysts for alcohols, amines, phenols and enolates, and are used in case of difficult acylation. [34] The addition of a catalytic amount 0.1 eq of DMAP can increase the reaction rate by nucleophilic catalysis mechanism **(Scheme 14)**. [35] The results showed that DMAP is necessary for this reaction **(Table 4)**. The amount of 0.2 eq DMAP was sufficient in the reaction.



Scheme 14 The mechanism of the protection of amine using DMAP as catalyst

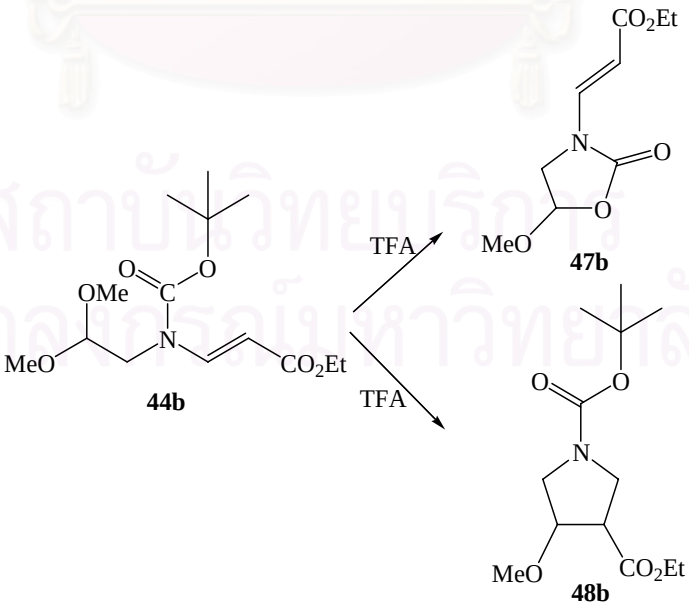
Table 4 Effect of amount of catalyst (DMAP) in enamine protection reaction[a]

Amount of catalyst (eq)	% yield[b]
0	0
0.2	36
0.4	38

[a]Reaction conditions: enamines **43b** (0.23 M), TEA 2 eq, Boc_2O 1 eq, solvent = CH_2Cl_2, room temperature, time = 20 h. [b]Isolated yield by column chromatography.

2.1.4 Synthesis of oxazolidin-2-one derivatives

The initial main objective of this work was investigated the synthesis of oxazolidin-2-ones by acid-induced intramolecular cyclisation of enamines. Simple enamide **44b** was chosen as the first substrate. Under acidic condition, two pathways of 5-*exo*-*tet* cyclisation are possible **(Scheme 15).** One involves the attack of the carbonyl oxygen to the acetal carbon to form oxazolidin-2-one derivative **47b,** and the other involves the attack of the vinylic carbon to the acetal carbon to form pyrolidine derivative **48b**. The reaction induced by TFA gave oxazolidin-2-one exclusively. Further optimization of this reaction included the amount of TFA, solvent, and type of acid.



Scheme 15 The cyclisation of enamide derivative **44**b

2.1.4.1 Effect of amount of TFA

The cyclisation of enamide derivative **44b** at various concentrations of TFA in CH_2Cl_2 were conducted at room temperature for 20 h to give the oxazolidin-2-one **47b** as a product. The result showed that the greater amount of TFA was used. The higher % yield was obtained **(Table 5)**. Even though 10 eq of TFA gave the highest yield (88%) but the large excess of this acid used was unacceptably high. The amount of 2 eq of acid was chosen for further optimization. It is interesting to note that even at 100 eq of TFA there was no deprotection of Boc observed but the % yield of oxazolidin-2-one dropped slightly to 73%.

Table 5 Effect of amount of TFA in enamide cyclisation reaction[a]

Amount of TFA (eq)	% yield[b]
0.2	-
1.2	27
2	68
10	88
100	73

[a]Reaction conditions: enamides **44b** (0.063 M), solvent = CH_2Cl_2, room temperature, time = 20 h. [b]Determined by GC analysis with benzophenone as an internal standard.

2.1.4.2 Effect of solvents

Four different kinds of solvents were investigated in the acid-induced intramolecular cyclisation of enamide **44b (Table 6)**. The cyclisation of enamide in CH_2Cl_2 as a solvent conclusively gave the highest yield for a shorter time.

Table 6 Effect of solvents in enamide cyclisation reaction[a]

Solvent	reaction time (h)	% yield[b]
acetone	5	26
toluene	5	49
acetonitrile	5	60
dichloromethane	2	97

[a]Reaction conditions: enamides **44b** (0.063 M), TFA 2 eq

[b]Determined by GC analysis with benzophenone as an internal standard.

2.1.4.3 Effect of types of acid

Four different types of acid were examined in the acid-induced intramolecular cyclisation. When the CH_3COOH and TsOH were used in the reaction using CH_2Cl_2 at reflux temperature for 2 h, the desired product was not observed. The reason was considered as these 2 acids are weaker than TFA, and especially for TsOH, it is not soluble in CH_2Cl_2. The high % yield was obtained by using $BF_3{\cdot}OEt_2$ (lewis acid) and TFA. But $BF_3{\cdot}OEt_2$ is more expensive than TFA. Then TFA was chosen as an acid to intramolecular cyclisation.

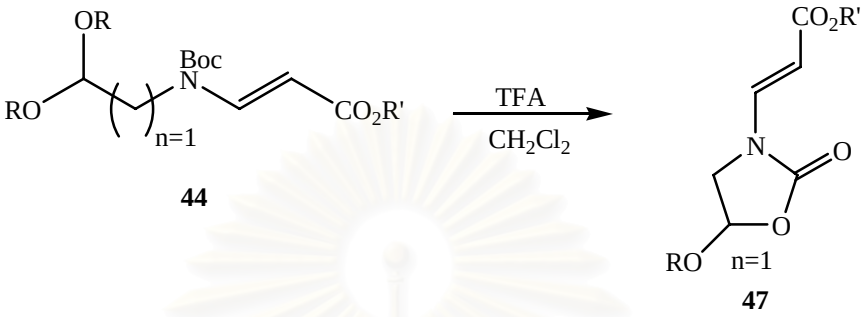
Table 7 Effect of types of acid in enamide cyclisation reaction[a]

Acid	% yield[b]
CH_3COOH	-
TsOH	-
$BF_3{\cdot}OEt_2$	98
TFA	95

[a]Reaction conditions: enamides **44b** (0.063 M), acid 2 eq, solvent = CH_2Cl_2, reflux temperature, time = 2 h. [b]Determined by GC analysis with benzophenone as an internal standard.

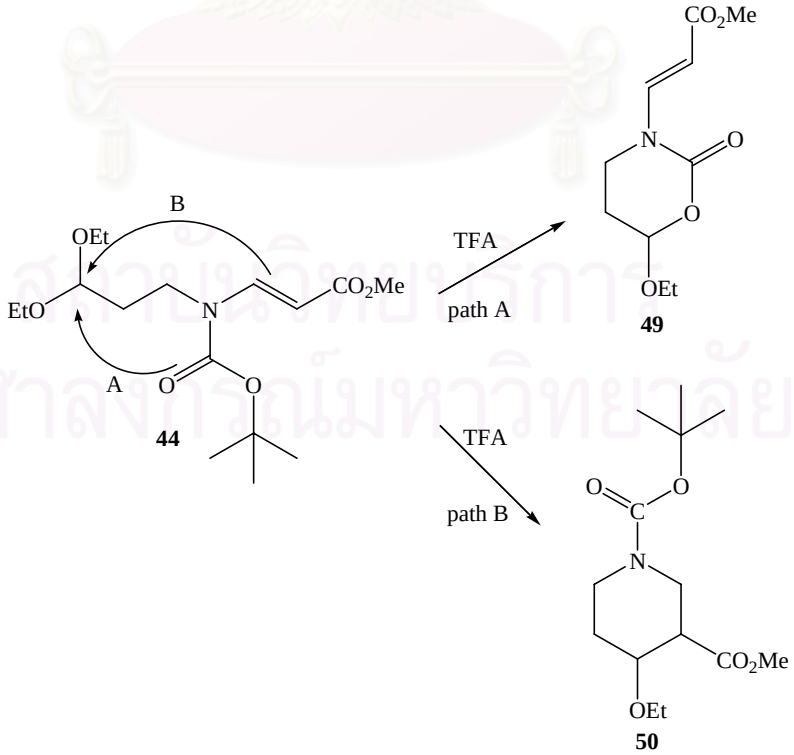
2.2 Cyclisation of enamide derivatives

Under acidic condition, the enamide **44** was cyclised to give oxazolidin-2-one **47** in good yield, involving the attack of the carbonyl oxygen to the acetal carbon **(Scheme 16).**



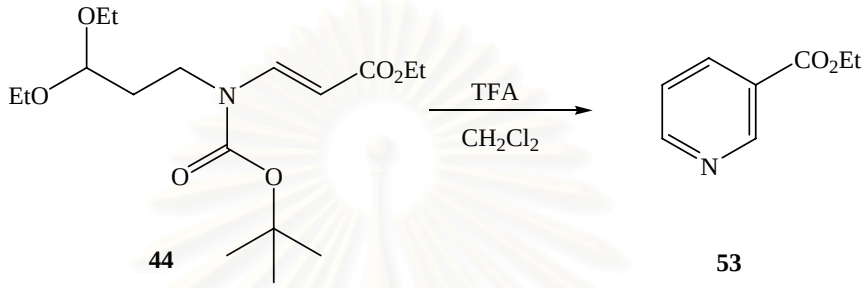
Scheme 16 The synthesis of oxazolidin-2-one derivative **47**

Cyclisation of enamide derivative **44** is interesting to increase carbon length from n=1 to n=2 under the same condition. Two pathways of 6-*exo-tet* cyclisation are possible **(Scheme 17).** One involves the attack of the carbonyl oxygen to the acetal carbon to form oxazolidinone derivative **49,** and the other involves the attack of the vinylic carbon to the acetal carbon to form pyrolidine derivative **50**.



Scheme 17 The cyclisation of enamide derivative **44** (n=2**)**

From the results**,** the cyclisation of enamide derivative **44** (n=2) was not produced oxazolidinone derivative **49** or pyrolidine derivative **50** but it was obtained pyridine derivative **53** as a major product **(Scheme 18).** The influence of alkyl chain length of enamide **44** (n=1) and enamide derivative **44** (n=2) affect the pathway of intramolecular cyclisation under same condition.

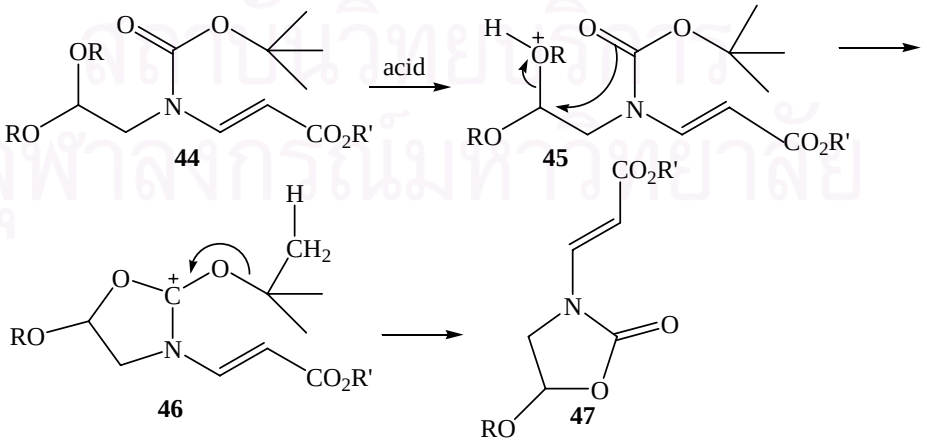


Scheme 18 The cyclisation of enamide derivative **44** (n=2**)**

2.3 The proposed mechanism

The proposed mechanism for the cyclisation of enamide derivative **44** (n=1) by TFA could be illustrated in **scheme 19.** The protonation of one of the alkoxy groups, followed by the attack of oxygen atom of the carbonyl double bond to the activated acetal carbon, forms the cyclised cation intermediate **46**. The lost of *tert*-butyl group gives the oxazalidin-2-one derivative **47** as the final product.

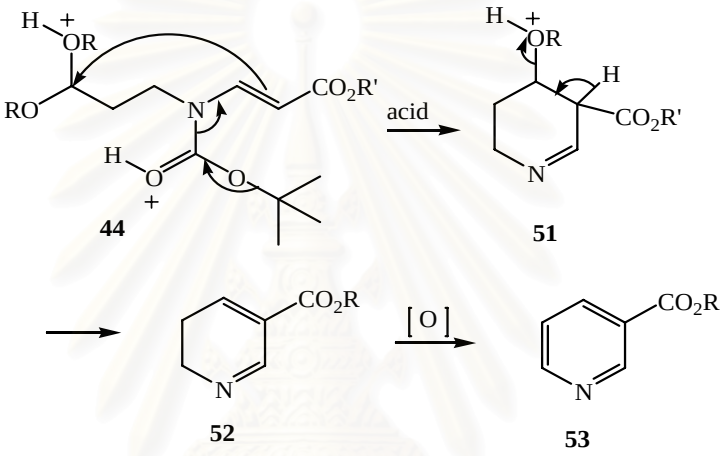
< n =1 >



Scheme 19 The proposed mechanism of oxazolidin-2-one derivative formation

The proposed mechanism of the cyclisation of enamide derivative **44** (n=2) by TFA also involves the protonation of an alkoxy group in the first step **(Scheme 20).** However the cyclisation of 6-membered ring is kinetically slower than the 6-membered ring that allows the acid catalyzed deprotection of Boc group. The deprotection in turn initiates the cyclisation of 6-membered ring through the attack of vinylic carbon to the activated carbon to provide intermediated **51**. The elimination of alcohol followed by autooxidation gave the aromatic pyridine derivative **53**.

< n = 2 >

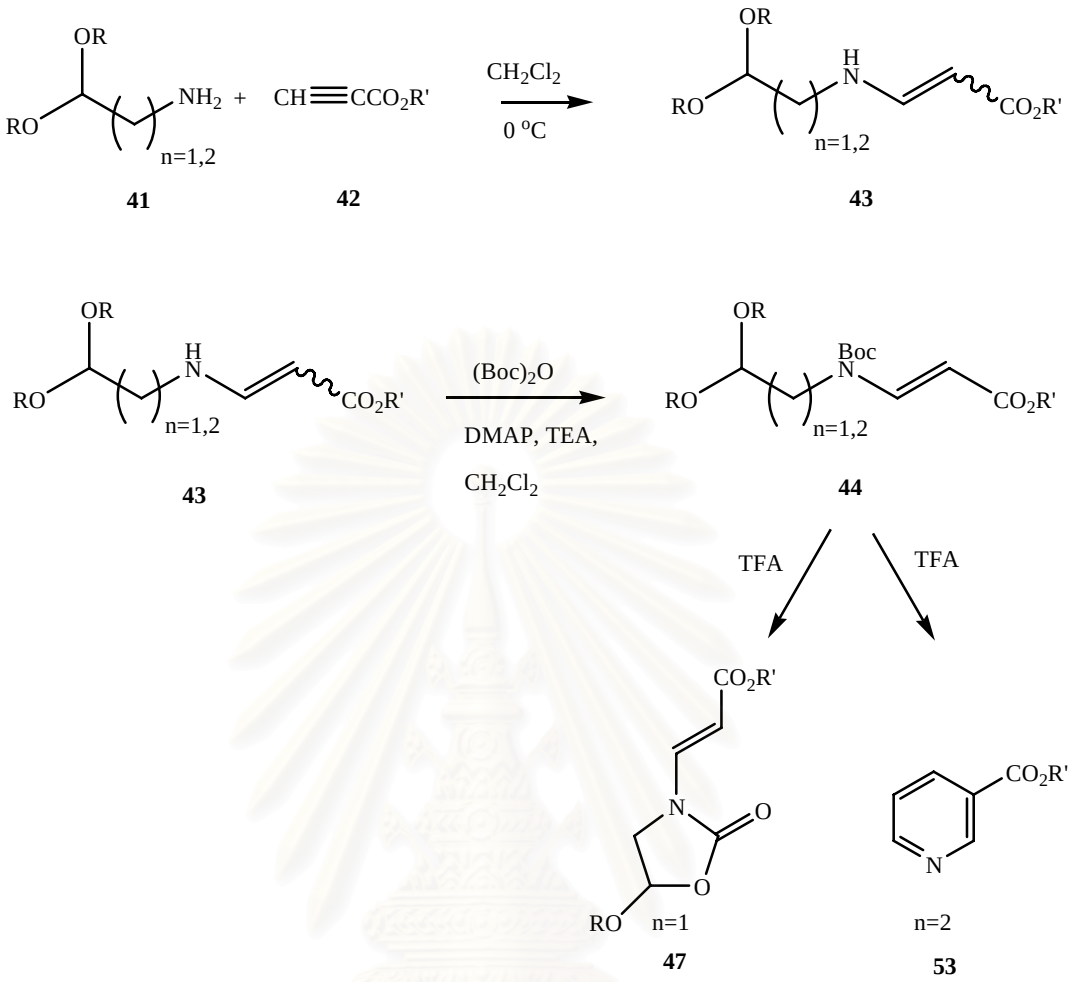


Scheme 20 The proposed mechanism of pyridine derivative formation

2.4 Variation of alkyl substituents of alkoxy and ester groups

After the synthesis of oxazolidin-2-one derivative and pyridine derivative were successfully synthesized. The variation of alkyl substituents of alkoxy and ester groups was investigated.

In the first step, the enamine derivatives could be synthesized in quantative yields by coupling dialkyl amines **41** (n=1, 2) with alkyl propiolates **42**. The second step is to protect the enamine nitrogens **43** by Boc-group donating *E*-isomer substrates **44** (n=1, 2) in moderate yields. The third step is the cyclisation of enamides **44** (n=1) by using TFA to obtain the oxazolidin-2-ones **47** in good yields. And also the cyclisation of enamides (n=2) by using TFA provided the pyridine derivatives **53** in relatively low yields **(Scheme 21)**.



Scheme 21 The synthesis of oxazolidin-2-one derivatives **47** and pyridine derivatives **53**

The protection with Boc_2O at various temperatures was investigated in the reaction **(Table 8)**. To increase the reaction rate, the reaction temperature was thus increased from room temperature to 5 hours reflux temperature, the % yields of enamides (n=1) by column chromatography was however not improved due to the intramolecular hydrogen bonding of *Z*-isomer that preventing substrates from the Boc-protection **(Table 9)**. But for the protection of enamines **43** (n=2) the % yield were increased from 38 to 45-49, when the temperature was changed from room temperature overnight to 5 hours reflux. This is because that the enamines **43** (n=2) have longer side chain and less steric hindrance from alkoxy groups than enamines **43** (n=1), so the Boc-protection of enamines **43** (n=2) was undergone much more easily.

Table 8 Synthesis of oxazolidin-2-one derivatives

No.	R	R′	% yield **43**[a]	%yield **44**[b,c]	%yield **44** [b,d]	%yield **47** [b,e]
a	Me	Me	quant.	35	34	59
b	Me	Et	quant.	38	-	66
c	Et	Me	quant.	35	-	58
d	Et	Et	quant.	36	38	63

[a]Reaction conditions: solvent = CH_2Cl_2, temp = 0 ^oC, time = 4 h, and allowed to room temperature, time = 20 h. [b]Isolated yield by column chromatography. [c]Reaction conditions: enamines **43a-d** (0.23 M), TEA 2 eq, DMAP 0.2 eq, Boc_2O 1.3 eq, solvent = CH_2Cl_2, room temperature, time = 20 h. [d]Reaction conditions: enamines **43a-d** (0.23 M), TEA 2 eq, DMAP 0.2 eq, Boc_2O 1.3 eq, solvent = CH_2Cl_2, reflux temperature, time = 5 h. [e]Reaction conditions: enamides **44b** (0.063 M), TFA 2 eq, solvent = CH_2Cl_2, reflux temperature, time = 5 h.

Table 9 Synthesis of pyridine derivatives[a]

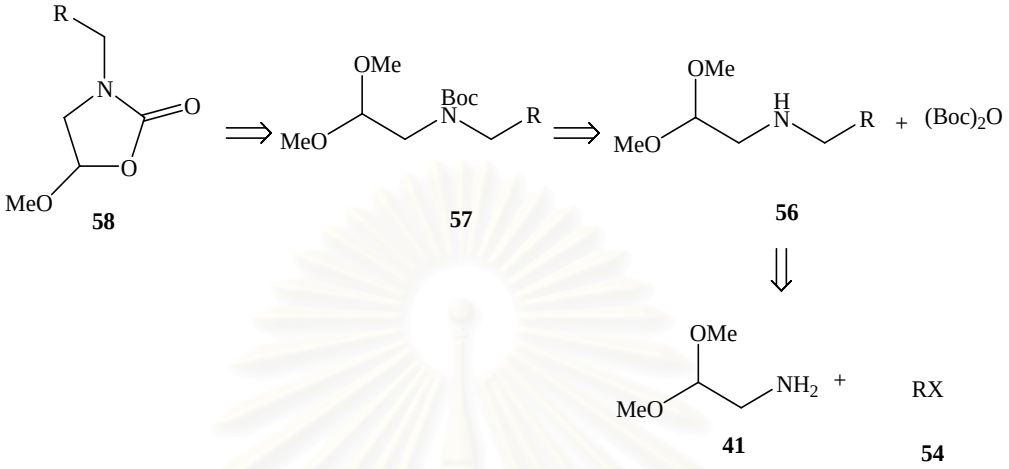
No.	R	R′	% yield **43**[a]	%yield **44**[b,c]	%yield **44** [b,d]	%yield **53** [b,e]
e	Et	Me	quant.	38	49	17
f	Et	Et	quant.	38	45	22

[a]Reaction conditions: solvent = CH_2Cl_2, temp = 0 ^oC, time = 4 h, and allowed to room temperature, time = 20 h. [b]Isolated yield by column chromatography. [c]Reaction conditions: enamines **43e**, **43f** (0.23 M), TEA 2 eq, DMAP 0.2 eq, Boc_2O 1.3 eq, solvent = CH_2Cl_2, room temperature, time = 20 h. [d]Reaction conditions: enamines **43e**, **43f** (0.23 M), TEA 2 eq, DMAP 0.2 eq, Boc_2O 1.3 eq, solvent = CH_2Cl_2, reflux temperature, time = 5 h. [e]Reaction conditions: enamides **44e**, **44f** (0.063 M), TFA 2 eq, solvent = CH_2Cl_2, reflux temperature, time = 5 h.

2.5 Generalization of oxazolidin-2-one synthesis from acid-induced intramolecular cyclisation of enamide

Hence the acid catalyzed cyclisation involving the *O*-nucleophile from Boc-group to form oxazolidin-2-one unprecedentedly gave high yield of the oxazolidin-2-one, therefore it would be interesting to investigate whether it could be used as a general method for synthesis *N*-alkylated oxazolidin-2-ones **58.** The required substrate to synthesize oxazolidin-2-one derivatives **58** would be amides **57**, which could be

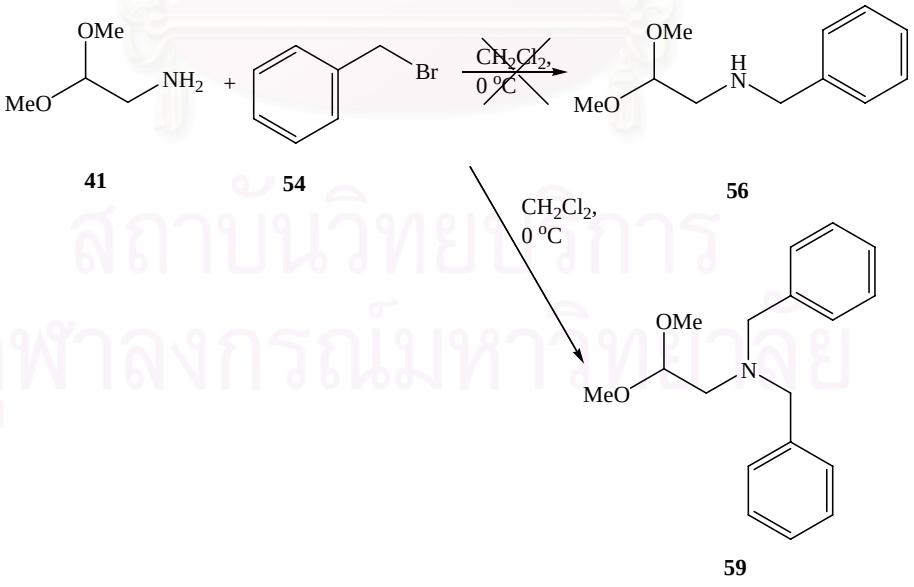
synthesized by protecting secondary amines **56** with Boc_2O. These secondary amines **56** may be synthesized by an alkylation reaction of dialkoxy amine **41** with alkyl halides **54 (Scheme 22)**.



Scheme 22 Retrosynthesis of the oxazolidin-2-one derivatives **58**

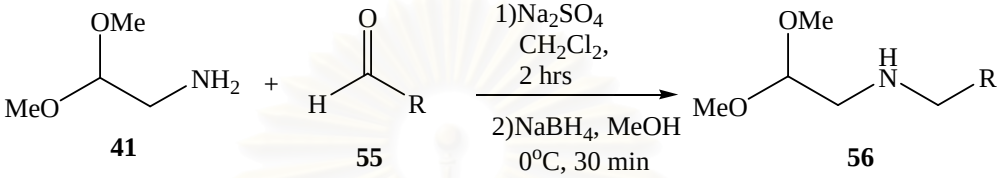
2.5.1 Synthesis of secondary amine substrates

The initial coupling reaction between 1-amino-dialkoxy **41** and benzyl bromide **54** at 0^oC did not give the desired secondary amine **56** but it gave only the tertiary amine **59** in 62% yield **(Scheme 23)**.



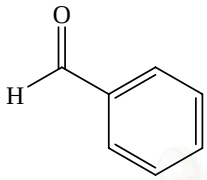
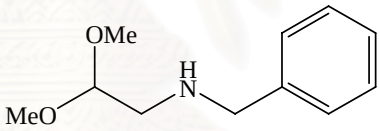
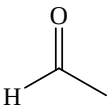
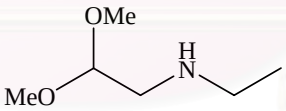
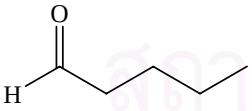
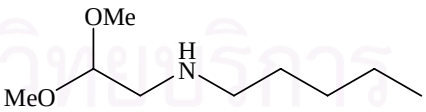
Scheme 23 The synthesis of secondary amine substrates

Reductive amination to avoid double substitution, the synthesis of secondary amine **56** was thus opted to use. The reductive amination included the reaction between 1-amino-dialkoxy **41** and aldehydes **55** at 0°C to give imine intermediates, which were reduced by using $NaBH_4$ **(Scheme 24)** to give the desired secondary amines **56** in high yields (63-80%) **(Table 10)**.



Scheme 24 The synthesis of amine derivatives **56**

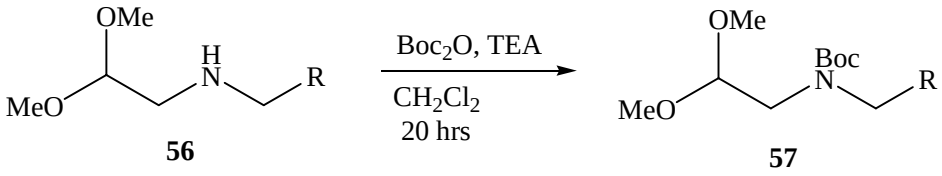
Table 10 Synthesis of amine derivatives **56** by reductive amination reaction[a]

aldehyde **55**	2° amine product **56**	% yield[b]
		70
		80
		63

[a]Reaction conditions: i) solvent = CH_2Cl_2, Na_2SO_4, room temperature, time = 2 h. ii) $NaBH_4$, solvent = MeOH, temp = 0 °C, time = 30 minute [b]Isolated yield by column chromatography.

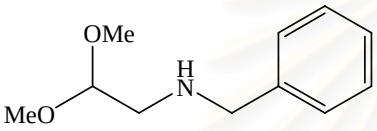
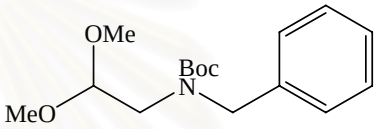
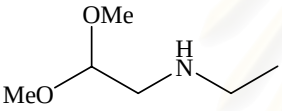
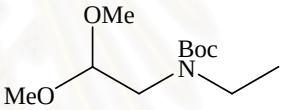
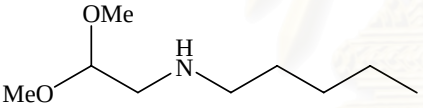
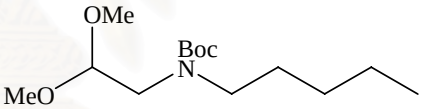
2.5.2 Synthesis of *N*-Boc protected secondary amines

The secondary amines **56** were treated with Boc_2O by using TEA as a base to give Boc-amides **57** in moderate to high yields (28-80%) **(Scheme 25)**.



Scheme 25 The synthesis of amide derivatives **57**

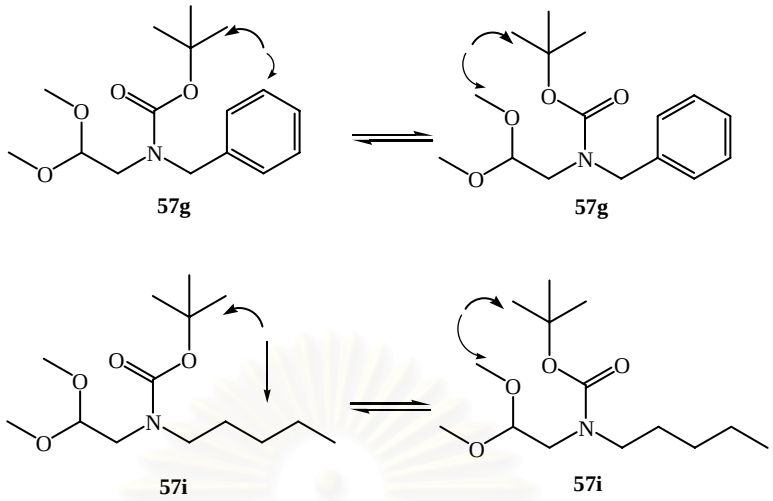
Table 11 Synthesis of amide derivatives **57** by amine protection reaction

amine **56**	amide product **57**	% yield[b]
		79
		28
		80

[a]Reaction conditions: TEA 2 eq, Boc_2O 1.2 eq, solvent = CH_2Cl_2, room temperature, time = 20 h.

[b]Isolated yield by column chromatography.

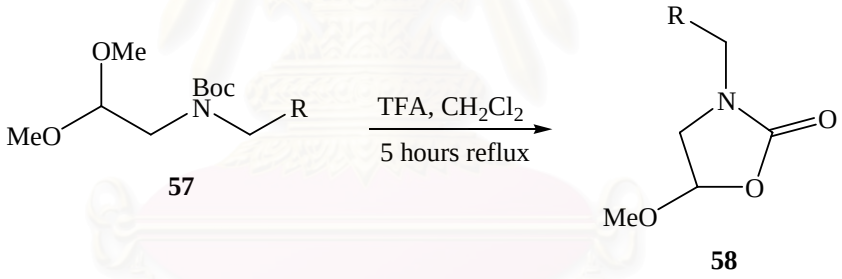
It is interesting to note that the ^{1}H-NMR spectrum of **57** in which R = benzyl and pentyl showed the presence of rotomers with a ratio of 50 : 50 and 60 : 40, respectively **(Scheme 26)**. The sigma amide bond between carbon and nitrogen atom can not freely rotate because of the steric hindrance between Boc-group and benzyl or pentyl group. But the spectrum of **57** with R = methyl has rotomer did not show any because the steric hindrance between Boc-group and methyl group is not large enough to prevent free rotation of the sigma amide bond at room temperature.



Scheme 26 The rotomers of amide derivatives **57g** and **57i**

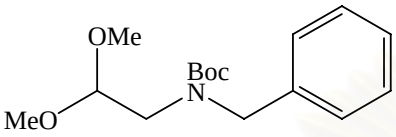
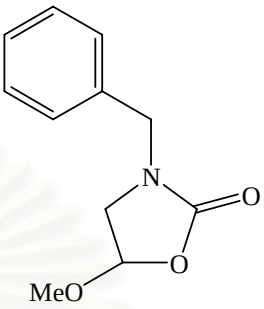
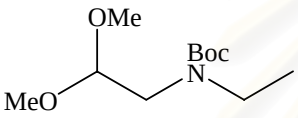
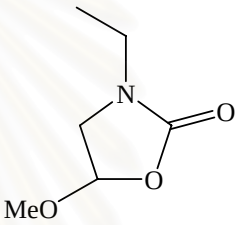
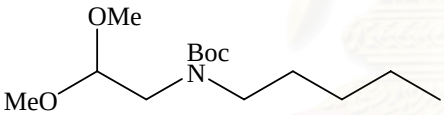
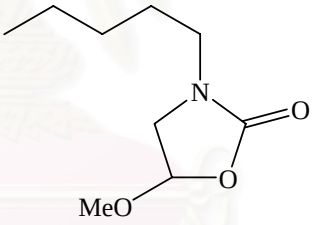
2.5.3 Synthesis of oxazolidin-2-one substrates

The acid-induced intramolecular cyclisation of amides **57** by using TFA gave oxazolidin-2-ones **58** by using TFA as acid in high yields (81-88%) **(Scheme 27)**.



Scheme 27 The synthesis of oxazolidin-2-one derivatives **58**

Table 12 Synthesis of oxazolidin-2-one derivatives **58** by amine cyclisation reaction[a]

amide **57**	oxazolidin-2-one product **58**	% yield[b]
		84
		83
		88

[a]Reaction conditions: TFA 2 eq, solvent = CH_2Cl_2, reflux temperature, time = 5 h. [b]Isolated yield by column chromatography.

CHAPTER III

EXPERIMENTAL

3.1 General Experimental

All reagents were either reagent or analytical grade, purchased from Fluka (Switzerland) or Merck (Germany) and used without purification. Solvents were analytical and commercial grade. Commercial grade solvents such as ethyl acetate, petroleum ether, hexane, and methanol were distilled prior to use and the fraction boiling between 40^{o}C and 60^{o}C were used throughout. Flash column chromatography was performed on silica gel column (Kieselgel 60, 63-200 μm, Merck) Thin layer chromatography (TLC) was carried out using silica plates (Kieselgel 60 F_{254}, 1 mm, Merck).

3.2 Instrumental

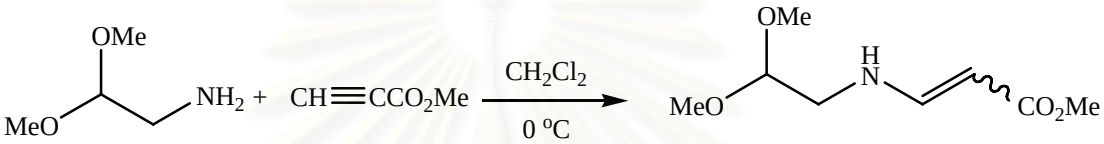
The ^{1}H-NMR spectra, ^{13}C-NMR, cosy spectra, and ^{1}H - ^{13}C-NMR spectra were recorded on a Bruker ACF 200 nuclear magnetic resonance spectrometer operating at 400 MHz (^{1}H-NMR) and 100 MHz (^{13}C-NMR). Chemical shifts were reported using a residual chloroform signal as an internal reference. Gas chromatographic analyzes were conducted on a Shimadzu GC-14A chromatograph equipped with a 30-m long and 0.25-mm o.d. HP-5 column. Elemental analysis was determined at the Instrumental Center of Chulalongkorn University. Compounds were named using the program from Chemdraw version 9.0 and www.chemfinder.com

3.3 Synthesis of oxazolidin-2-ones

3.3.1 Preparation of methyl 3-(2,2-dimethoxyethylamino)acrylate (43a)

Following is a modified version of method by Macdonald.[33]

Methyl propiolate **42a** (314 mg, 3.74 mmol) in CH_2Cl_2 (5 mL) was added dropwise into 1-amino-2,2-dimethoxy ethane **41a** (393 mg, 3.74 mmol) in CH_2Cl_2 (10 mL) at 0^oC for 4 hours, before being allowed to warm to room temperature for 20 hours. The reaction was removed *in vacuo* to give enamine **43a** (708 mg, 100 %) as a colourless oil and as a 3: 7 mixture of *E* and *Z* isomers.



41a **42a** **43a**

Scheme 28 The synthesis of enamine derivative **43a**

TLC:Rf = 0.24 (EtOAc : Hexane (1:3 v/v))

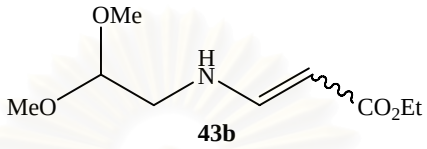
δ_H (400 MHz, $CDCl_3$) : 7.82 (1H, br, N*H*), 7.50 (0.3H, dd, *J* 8, 13.2, (*E*)-NHC*H*=CH), 6.61 (0.7H, dd, *J* 8, 13.2, (*Z*)-NHC*H*=CH), 4.76 (0.3H, d, *J* 13.2, (*E*)-NHCH=C*H*), 4.51 (0.7H, d, *J* 8, (*Z*)-NHCH=C*H*), 4.10 (0.3H, t, *J* 5.2, (*E*)-C*H*(OCH_3), 4.33 (0.7H, t, *J* 5.2, (*Z*)-C*H*(OCH_3), 3.66 (1H, s, (*E*)-CO_2CH_3), 3.65 (2H, s, (*Z*)-CO_2CH_3), 3.41 (6H, s, OCH_3), 3.24 (1.4H, t, *J* 5.6, (*Z*)-CH_2CH_2NH), 3.16 (0.6H, t, *J* 5.6, (*E*)-$CHCH_2$NH)

δ_C (100 MHz, $CDCl_3$) : 171.0 (C_Z) and 169.8 (C_E), 152.5 (CH_Z) and 149.5 (CH_E), 103.9 (CH_Z) and 101.6 (CH_E), 86.1 (CH_E) and 82.5 (CH_Z), 54.6 (CH_{3Z}) and 54.1 (CH_{3E}), 50.6 (CH_{3E}) and 50.4 (CH_{3Z}), 50.2 (CH_2)

3.3.2 Preparation of ethyl 3-(2,2-dimethoxyethylamino)acrylate (43b)

Following is a modified version of method by Macdonald.[33]

Ethyl propiolate **42b** (371 mg, 3.78 mmol) in CH_2Cl_2 (5 mL) was added dropwise into 1-amino-2,2-dimethoxy ethane **41b** (412 mg, 3.92 mmol) in CH_2Cl_2 (10 mL) at 0^oC for 4 hours, before being allowed to warm to room temperature for 20 hours. The reaction was removed *in vacuo* to give enamine **43b** (768 mg, 100 %) as a colourless oil and as a 3: 7 mixture of *E* and *Z* isomers.



43b

Fig. 7 The structure of ethyl 3-(2,2-dimethoxyethylamino)acrylate **43b**

TLC:Rf = 0.27 (EtOAc : Hexane (1:3 v/v))

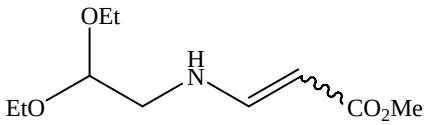
δ_H (400 MHz, $CDCl_3$) : 7.82 (0.7H, br, (*Z*)-N*H*), 7.49 (0.3H, dd, *J* 8.0, 13.2, (*E*)-NHC*H*=CH), 6.60 (0.7H, dd, *J* 8.0, 13.2, (*Z*)-NHC*H*=CH), 4.76 (0.3H, d, *J* 13.3, (*E*)- NHCH=C*H*), 4.61 (0.3H, br, (*E*)-N*H*), 4.49 (0.7H, d, *J* 8.1, (*Z*)-NHCH=C*H*), 4.33 (1H, t, *J* 5.4, C*H*$(OMe)_2$, 4.10 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.40 (4.2H, s, (*Z*)-$(OCH_3)_2$), 3.39 (1.8H, s, (*E*)-$(OCH_3)_2$), 3.24 (1.4H, t, *J* 5.5, (*Z*)-CH_2CH_2NH), 3.15 (0.6H, t, *J* 5.5, (*E*)-$CHCH_2NH$), 1.25 (3H, t, *J* 8.5, $CO_2CH_2CH_3$)

δ_C (100 MHz, $CDCl_3$) : 170.7 (C_Z) and 169.5 (C_E), 152.4 (CH), 103.9 (CH), 86.6 (CH_E) and 82.9 (CH_Z), 59.0 (CH_{3E}) and 58.7 (CH_{3Z}), 54.6 (CH_{2Z}) and 54.3 (CH_{2E}), 50.4 (CH_2), 14.5 (CH_3)

3.3.3 Preparation of methyl 3-(2,2-diethoxyethylamino)acrylate (43c)

Following is a modified version of method by Macdonald.[33]

Methyl propiolate **42c** (319 mg, 3.79 mmol) in CH_2Cl_2 (5 mL) was added dropwise into 1-amino-2,2-diethoxy ethane **41c** (498 mg, 3.74 mmol) in CH_2Cl_2 (10 mL) at 0^oC for 4 hours, before being allowed to warm to room temperature for 20 hours. The reaction was removed *in vacuo* to give enamine **43c** (812 mg, 100 %) as a colourless oil and as a 3: 7 mixture of *E* and *Z* isomers.



43c

Fig. 8 The structure of methyl 3-(2,2-diethoxyethylamino)acrylate **43c**

TLC:Rf = 0.30 (EtOAc : Hexane (1:3 v/v))

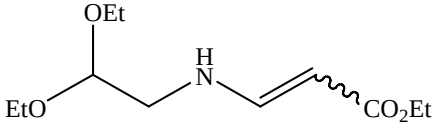
δ_H (400 MHz, $CDCl_3$) : 7.50 (1H, br, N*H*), 7.50 (0.3H, dd, *J* 8.4, 13.2, (*E*)-NHC*H*=CH), 6.62 (0.7H, dd, *J* 8, 13.2, (*Z*)-NHC*H*=CH), 4.76 (0.3H, d, *J* 13.2, (*E*)-NHCH=C*H*), 4.59 (0.3H, t, *J* 5.2, (*E*)-C*H*$(OEt)_2$, 4.50 (0.7H, d, *J* 8, (*Z*)-NHCH=C*H*), 4.44 (0.7H, t, *J* 5.2, (*Z*)-C*H*$(OEt)_2$), 3.75-3.68 (2H, m, OC$H_AH_BCH_3$), 3.66 (0.9H, s, (*E*)-CO_2CH_3), 3.64 (2.1H, s, (*Z*)-CO_2CH_3), 3.58-3.50 (2H, m, $OCH_AH_BCH_3$), 3.24 (1.4H, t, *J* 5.6, (*Z*)-CH_2CH_2NH), 3.15 (0.6H, t, *J* 5.6, (*E*)-CHCH_2NH), 1.22 (6H, t, *J* 7.2, OCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 171.0 (C), 152.6 (CH), 102.2 (CH), 82.2 (CH),63.3 (CH_2), 51.4 (CH_3), 50.2 (CH_2), 15.3 (CH_3)

3.3.4 Preparation of ethyl 3-(2,2-diethoxyethylamino)acrylate (43d)

Following is a modified version of method by Macdonald.[33]

Ethyl propiolate **42d** (368 mg, 3.75 mmol) in CH_2Cl_2 (5 mL) was added dropwise into 1-amino-2,2-diethoxy ethane **41d** (507 mg, 3.8 mmol) in CH_2Cl_2 (10 mL) at 0^oC for 4 hours, before being allowed to warm to room temperature for 20 hours. The reaction was removed *in vacuo* to give enamine **43d** (867 mg, 100 %) as a colourless oil and as a 3: 7 mixture of *E* and *Z* isomers.



43d

Fig. 9 The structure of ethyl 3-(2,2-diethoxyethylamino)acrylate **43d**

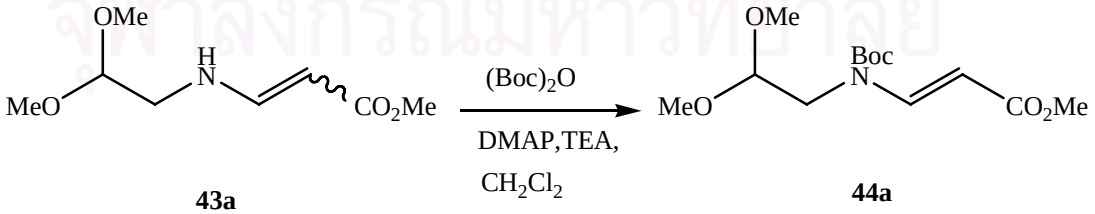
TLC:Rf = 0.42 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 7.79 (0.7H, br, (*Z*)-N*H*), 7.47 (0.3H, dd, *J* 8.2, 13.0, (*E*)-NHC*H*=CH), 6.58 (0.7H, dd, *J* 8.2, 13.0, (*Z*)-NHC*H*=CH), 4.79 (0.3H, br, (*E*)-N*H*), 4.71(0.3H, d, *J* 13.3, (*E*)-NHCH=C*H*), 4.44 (0.7H, d, *J* 8.1, (*Z*)-NHCH=C*H*), 4.40 (1H, t, *J* 5.4, C*H*$(OEt)_2$, 4.06 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 3.71-3.62 (2H, m, $OCH_AH_BCH_3$), 3.56-3.46 (2H, m, $OCH_AH_BCH_3$), 3.19 (1.4H, t, *J* 5.6, (*Z*)-$CHCH_2NH$), 3.11 (0.6H, t, *J* 5.6, (*E*)-$CHCH_2NH$), 1.21 (3H, t, *J* 7.1, $COCH_2CH_3$), 1.18 (6H, t, *J* 7.0, OCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 170.6 (C_Z) and 169.4 (C_E), 152.4 (CH), 102.2 (CH), 86.3 (CH_E), and 82.6 (CH_Z), 63.2 (CH_{2Z}) and 62.7 (CH_{2E}), 58.9 (CH_{2E}) and 58.6 (CH_{2Z}), 51.3 (CH_2),15.2 (CH_3), 14.4 (CH_3)

3.3.5 Preparation of methyl 3-(tert-butoxycarbonyl(2,2-dimethoxyethyl) amino)acrylate (44a)

Enamine **43a** (662 mg, 3.50 mmol), TEA (1 mL, 2eq) and DMAP (86 mg, 0.2 eq), were dissolved in CH_2Cl_2 (5 mL). Boc_2O (1.06 g, 1.3 eq) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give enamide **44a** (358 mg, 35 %) as a colourless oil.



43a **44a**

Scheme 29 The synthesis of enamide derivative **44a**

TLC:Rf = 0.32 (EtOAc : Hexane (1:3 v/v))

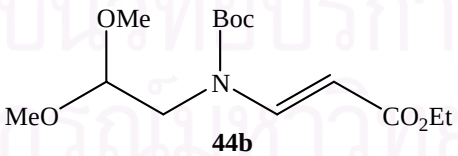
δ_H (400 MHz, $CDCl_3$) : 8.20 (1H, d, *J* 14.2, NC*H*=CH), 5.31 (1H, d, *J* 14.2, NCH=C*H*), 4.52 (1H, t, *J* 5.4, C*H*$(OMe)_2$, 3.72 (3H, s, CO_2CH_3), 3.67 (2H, d, *J* 5.4 , $CHCH_2N$), 3.38 (6H, s, OCH_3), 1.53 (9H, s, $C(CH_3)_3$)

δ_C (100 MHz, $CDCl_3$) : 168.4 (C), 152.1 (C), 143.2 (CH), 101.6 (CH), 97.5 (CH), 83.4 (C), 54.6 (CH_3), 51.2 (CH_3), 46.4 (CH_2), 28.0 (CH_3)

Elem. Anal.: Calcd. for $C_{13}H_{23}NO_6$; C, 53.97%; H, 8.01%; N, 4.84%
Found: C, 53.98%; H, 8.04%; N, 4.77%

3.3.6 Preparation of ethyl 3-(tert-butoxycarbonyl(2,2-dimethoxyethyl)amino) acrylate (44b)

Enamine **43b** (725 mg, 3.57 mmol), TEA (1 mL, 2eq) and DMAP (87 mg, 0.2 eq), were dissolved in CH_2Cl_2 (5 mL). Boc_2O (1.01 g, 1.3 eq) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give enamide **44b** (407 mg, 38 %) as a colourless oil.



44b

Fig. 10 The structure of ethyl 3-(*tert*-butoxycarbonyl(2,2-dimethoxyethyl)amino) acrylate **44b**

TLC:Rf = 0.42 (EtOAc : Hexane (1:3 v/v))

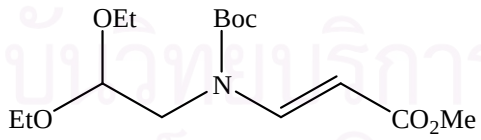
δ_H (400 MHz, $CDCl_3$) : 8.20 (1H, d, *J* 14.2, NC*H*=CH), 5.29 (1H, d, *J* 14.2, NCH=C*H*), 4.52 (1H, t, *J* 5.3, C*H*$(OMe)_2$, 4.18 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.66 (2H, d, *J* 5.4, $CHCH_2N$), 3.38 (6H, s, OCH_3), 1.53 (9H, s, $C(CH_3)_3$), 1.28 (3H, t, *J* 7.1, $COCH_2CH_3$)

δ_C (100 MHz, $CDCl_3$) : 167.8 (C), 152.1 (C), 142.9 (CH), 101.4 (CH), 97.9 (CH), 83.2 (C), 59.9 (CH_3), 54.4 (CH_2), 46.2 (CH_2), 27.9 (CH_3), 14.3 (CH_3)

Elem. Anal.: Calcd. for $C_{14}H_{25}NO_6$; C, 55.43%; H, 8.31%; N, 4.62%
Found: C, 55.44%; H, 8.59 %; N, 4.73%

3.3.7 Preparation of methyl 3-(tert-butoxycarbonyl(2,2-diethoxyethyl)amino) acrylate (44c)

Enamine **43c** (793 mg, 3.65 mmol), TEA (1 mL, 2eq) and DMAP (89 mg, 0.2 eq), were dissolved in CH_2Cl_2 (5 mL). Boc_2O (1.04 g, 1.3 eq) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give enamide **44c** (402 mg, 35 %) as a colourless oil.



44c

Fig. 11 The structure of methyl 3-(*tert*-butoxycarbonyl(2,2-diethoxyethyl)amino) acrylate **44c**

TLC:Rf = 0.40 (EtOAc : Hexane (1:3 v/v))

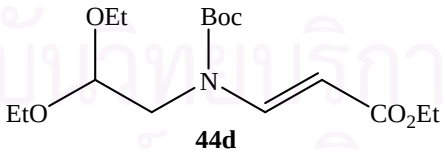
δ_H (400 MHz, $CDCl_3$) : 8.21 (1H, d, *J* 15.0, NC*H*=CH), 5.34 (1H, d, *J* 15.0, NCH=C*H*), 4.64 (1H, t, *J* 5.3, C*H*$(OEt)_2$, 3.72 (3H, s, CO_2CH_3), 3.67 (2H, d, *J* 5.3 ,CHCH_2N), 3.54-3.45 (4H, m, OCH_2CH_3), 1.53 (9H, s, C(CH_3)$_3$), 1.18 (6H, t, *J* 7.0, OCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 168.4 (C), 152.2 (C), 143.2 (CH), 99.8 (CH), 97.6 (CH), 83.2 (C), 63.3 (CH_2), 51.2 (C), 47.3 (CH_2), 28.0 (CH_3), 15.3 (CH_3)

Elem. Anal.: Calcd. for $C_{15}H_{27}NO_6$; C, 56.77%; H, 8.57%; N, 4.41%
Found: C, 56.83%; H, 8.60%; N, 4.42%

3.3.8 Preparation of ethyl 3-(tert-butoxycarbonyl(2,2-diethoxyethyl)amino) acrylate (44d)

Enamine **43d** (501 mg, 3.46 mmol), TEA (1 mL, 2eq) and DMAP (84 mg, 0.2 eq), were dissolved in CH_2Cl_2 (5 mL). Boc_2O (982 mg, 1.3 eq) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give enamide **44d** (415 mg, 36 %) as a colourless oil.



44d

Fig. 12 The structure of ethyl 3-(*tert*-butoxycarbonyl(2,2-diethoxyethyl)amino) acrylate **44d**

TLC:Rf = 0.47 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 8.20 (1H, d, *J* 14.0, NC*H*=CH), 5.33 (1H, d, *J* 14.2, NCH=C*H*), 4.64 (1H, t, *J* 5.4, C*H*$(OEt)_2$, 4.17 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.75-3.69

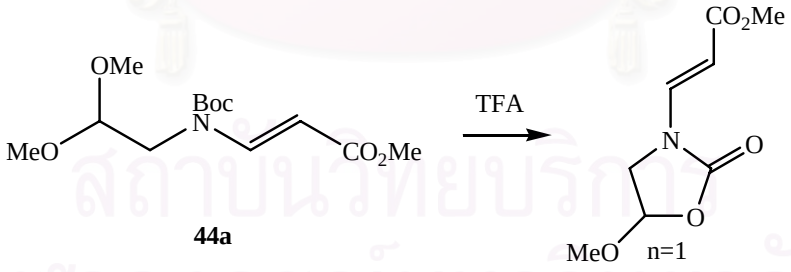
(2H, m, OC*H*$_A$H$_B$CH$_3$), 3.68 (2H, d, *J* 5.5 ,CHC*H*$_2$N), 3.53-3.45 (2H, m, OCH$_A$*H*$_B$CH$_3$), 1.52 (9H, s, C(C*H*$_3$)$_3$), 1.28 (3H, t, *J* 7.1, COCH$_2$C*H*$_3$) , 1.18 (6H, t, *J* 7.0, OCH$_2$C*H*$_3$)

δ_C (100 MHz, $CDCl_3$) : 167.8 (C), 152.1 (C), 142.9 (CH), 99.6 (CH), 97.9 (CH), 83.1 (C), 63.1 (CH_2), 59.8 (CH_2), 47.1 (CH_2), 27.9 (CH_3), 15.2 (CH_3), 14.2 (CH_3)

Elem. Anal.: Calcd. for $C_{16}H_{29}NO_6$; C, 57.99%; H, 8.82%; N, 4.23%
Found: C, 57.99%; H, 8.71%; N, 4.29%

3.3.9 Preparation of (E)-methyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate) (47a)

Enamide **44a** (89 mg, 0.31 mmol) was stirred with TFA (0.05 mL, 2 eq) in CH_2Cl_2 (25 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide oxazolidin-2-one **47a** (36 mg, 59%) as a yellow oil.



44a **47a**

Scheme 30 The synthesis of oxazolidin-2-one derivative **47a**

TLC:Rf = 0.05 (EtOAc : Hexane (1:3 v/v))

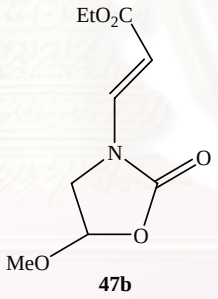
δ_H (400 MHz, $CDCl_3$) : 7.93 (1H, d, *J* 14.1, NC*H*=CH), 5.55 (1H, dd, *J* 2.4, 6.4, MeOC*H*O), 5.14 (1H, d, *J* 14.1, NCH=C*H*), 3.84 (1H, dd, *J* 6.4, 10.7,

NC*H*$_A$H$_B$CH), 3.74 (3H, s, CO$_2$C*H*$_3$), 3.57 (3H, s, OC*H*$_3$), 3.52 (1H, dd, *J* 2.4, 10.7, NCH$_A$*H*$_B$CH)

δ_C (100 MHz, $CDCl_3$) : 166.8 (C), 153.1 (C), 137.8 (CH), 100.3 (CH), 98.9 (CH), 56.9 (CH_3), 51.5 (CH_3), 48.8 (CH_2)

3.3.10 Preparation of (E)-ethyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate) (47b)

Enamide **44b** (98 mg, 0.32 mmol) was stirred with TFA (0.05 mL, 2 eq) in CH_2Cl_2 (25 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide oxazolidin-2-one **47b** (47 mg, 66%) as a yellow oil.



47b

Fig. 13 The structure of (*E*)-ethyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate) **47b**

TLC:Rf = 0.08 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 7.93 (1H, d, *J* 14.2, NC*H*=CH), 5.55 (1H, dd, *J* 2.5, 6.4, MeOC*H*O), 5.13 (1H, d, *J* 14.1, NCH=C*H*), 4.20 (2H, q, *J* 7.2, CO$_2$C*H*$_2$CH$_3$), 3.84 (1H, dd, *J* 6.4, 10.6, NC*H*$_A$H$_B$CH), 3.53 (1H, dd, *J* 2.5, 10.6, NCH$_A$*H*$_B$CH), 1.29 (3H, t, *J* 7.1, CO$_2$CH$_2$C*H*$_3$)

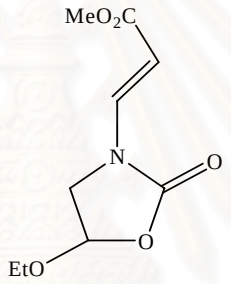
δ_C (100 MHz, $CDCl_3$) : 166.4 (C), 153.1 (C), 137.5 (CH), 100.8 (CH), 98.9 (CH), 60.3 (CH_3), 56.9 (CH_2), 48.8 (CH_2), 14.3 (CH_3)

Elem. Anal.: Calcd. for $C_9H_{13}NO_5$; C, 50.23%; H, 6.09%; N, 6.51%

Found: C, 50.56%; H, 6.45%; N, 6.56%

3.3.11 Preparation of (E)-methyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) (47c)

Enamide **44c** (98 mg, 0.31 mmol) was stirred with TFA (0.05 mL, 2 eq) in CH_2Cl_2 (25 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide oxazolidin-2-one **47c** (67 mg, 58%) as a yellow oil.



47c

Fig. 14 The structure of (*E*)-methyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) **47c**

TLC:Rf = 0.11 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 7.93 (1H, d, *J* 14.2, NC*H*=CH), 5.65 (1H, dd, *J* 2.5, 6.4, OC*H*CH_2), 5.13 (1H, d, *J* 14.2, NCH=C*H*), 3.99-3.91 (1H, m, OC$H_AH_BCH_3$), 3.84 (1H, dd, *J* 6.4, 10.6, NCH_AH_BCH), 3.73 (3H, s, CO_2CH_3), 3.72-3.64 (1H, m, $OCH_AH_BCH_3$), 3.53(1H, dd, *J* 2.5, 10.6, NCH_AH_BCH), 1.26 (3H, t, *J* 7.1, CH_2CH_3)

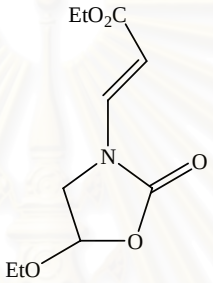
δ_C (100 MHz, $CDCl_3$) : 166.9 (C), 153.2 (C), 137.9 (CH), 100.2 (CH), 97.8 (CH), 65.7 (CH_2), 51.2 (CH_3), 48.9 (CH_2),14.8 (CH_3)

Elem. Anal.: Calcd. for $C_9H_{13}NO_5$; C, 50.23%; H, 6.09%; N, 6.51%

Found: C, 50.44%; H, 6.12%; N, 6.51%

3.3.12 Preparation of (E)-ethyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) (47d)

Enamide **44d** (107 mg, 0.32 mmol) was stirred with TFA (0.05 mL, 2 eq) in CH_2Cl_2 (25 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide oxazolidin-2-one **47d** (74 mg, 63 %) as a yellow oil.



47d

Fig. 15 The structure of (*E*)-ethyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) **47d**

TLC:Rf = 0.14 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 7.93 (1H, d, *J* 14.1, NC*H*=CH), 5.65 (1H, dd, *J* 2.3, 6.4, OC*H*CH_2), 5.12 (1H, d, *J* 14.1, NCH=C*H*), 4.19 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 3.99-3.91 (1H, m, $OCH_AH_BCH_3$), 3.84 (1H, dd, *J* 6.4, 10.6, NCH_AH_BCH), 3.72-3.64 (1H, m, $OCH_AH_BCH_3$), 3.52 (1H, dd, *J* 2.3, 10.6, NCH_AH_BCH), 1.28 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.26 (3H, t, *J* 7.2, OCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 166.4 (C), 153.2 (C), 137.6 (CH), 100.6 (CH), 97.8 (CH), 65.6 (CH_2), 60.2 (CH_2), 48.9 (CH_2), 14.7 (CH_3), 14.2 (CH_3)

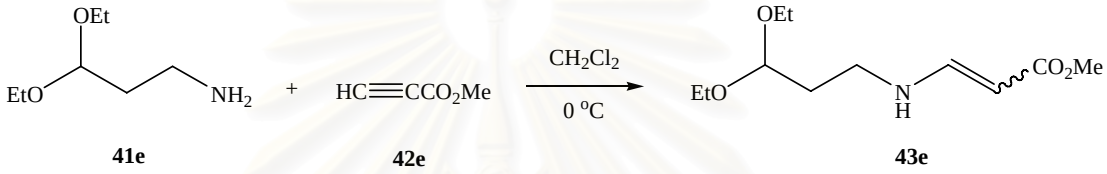
Elem. Anal.: Calcd. for $C_{10}H_{15}NO_5$; C, 52.40%; H, 6.60%; N, 6.11%
Found: C, 52.31%; H, 6.68%; N, 6.16%

3.4 Synthesis of pyridines

3.4.1 Preparation of methyl 3-(3,3-diethoxypropylamino)acrylate (43e)

Following is a modified version of method by Macdonald.[33]

Methyl propiolate **42e** (628 mg, 7.47 mmol) in CH_2Cl_2 (10 mL) was added dropwise into 1-amino-3,3-diethoxy propane **41e** (1.13 g, 7.68 mmol) in CH_2Cl_2 (20 mL) at 0^{o}C for 4 hours, before being allowed to warm to room temperature for 20 hours. The reaction was removed *in vacuo* to give enamine **43e** (1.73 g, 100 %) as a colourless oil and as a 3: 7 mixture of *E* and *Z* isomers.



41e **42e** **43e**

Scheme 31 The synthesis of enamine derivative **43e**

TLC:Rf = 0.21 (EtOAc : Hexane (1:3 v/v))

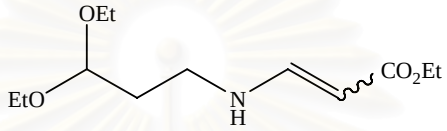
δ_H (400 MHz, $CDCl_3$) : 7.83 (0.7H, br, (*Z*)-N*H*), 7.49 (0.3H, dd, *J* 7.8, 13.2, (*E*)-NHC*H*=CH), 6.61 (0.7H, dd, *J* 8, 13.2, (*Z*)-NHC*H*=CH), 5.02 (0.3H, br, (*E*)-N*H*), 4.70 (0.3H, d, *J* 13.2, (*E*)-NHCH=C*H*), 4.56 (1H, t, *J* 5.6, C*H*$(OEt)_2$, 4.46 (0.7H, d, *J* 8.1, (*Z*)-NHCH=C*H*), 3.72-3.62 (2H, m, $OCH_AH_BCH_3$), 3.65 (3H, s, CO_2CH_3), 3.54-3.46 (2H, m, $OCH_AH_BCH_3$), 3.26 (1.4H, q, *J* 6.6, (*Z*)-CH_2CH_2NH), 3.14 (0.6H, t, *J* 5.6, (*E*)-$CHCH_2$NH), 1.89 (0.6H, q, *J* 5.9, (*E*)-$CHCH_2CH_2$), 1.85 (1.4 H, q, *J* 6.6, (*Z*)-$CHCH_2CH_2$), 1.21 (6H, t, *J* 7.0, OCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 170.6 (C_Z) and 169.8 (C_E), 151.9 (CH), 101.3 (CH_E) and 100.4 (CH_Z) , 84.1 (CH_E) and 81.0 (CH_Z), 61.5 (CH_{2E}) and 61.2 (CH_{2Z}), 50.0 (CH_{3E}) and 49.6 (CH_{3Z}), 44.3 (CH_2), 34.7 (CH_2), 14.9 (CH_3)

3.4.2 Preparation of ethyl 3-(3,3-diethoxypropylamino)acrylate (43f)

Following is a modified version of method by Macdonald.[33]

Ethyl propiolate **42f** (732 mg, 7.46 mmol) in CH_2Cl_2 (10 mL) was added dropwise into 1-amino-2,2-dimethoxy ethane **41f** (1.10 g, 7.50 mmol) in CH_2Cl_2 (20 mL) at 0^oC for 4 hours, before being allowed to warm to room temperature for 20 hours. The reaction was removed *in vacuo* to give enamine **43f** (1.83 g, 100 %) as a colourless oil and as a 3: 7 mixture of *E* and *Z* isomers.



43f

Fig. 16 The structure of ethyl 3-(3,3-diethoxypropylamino)acrylate **43f**

TLC:Rf = 0.24 (EtOAc : Hexane (1:3 v/v))

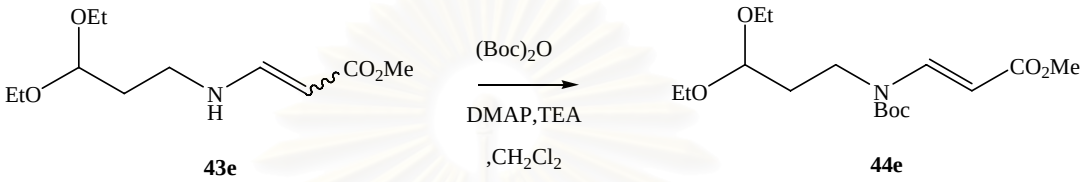
δ_H (400 MHz, $CDCl_3$) : 7.82 (0.7H, br, (*Z*)-N*H*), 7.47 (0.3H, dd, *J* 8.0, 13.1, (*E*)-NHC*H*=CH), 6.58 (0.7H, dd, *J* 8.0, 13.1, (*Z*)-NHC*H*=CH), 5.05 (0.3H, br, (*E*)-N*H*), 4.68 (0.3H, d, *J* 13.2, (*E*)-NHCH=C*H*), 4.54 (1H, t, *J* 5.6, C*H*$(OEt)_2$, 4.42 (0.7H, d, *J* 8.0, (*Z*)-NHCH=C*H*), 4.13-4.05 (2H, m, $CO_2CH_2CH_3$), 3.68-3.59 (2H, m, $OCH_AH_BCH_3$), 3.51-3.44 (2H, m, $OCH_AH_BCH_3$), 3.23 (1.4H, q, *J* 6.6, (*Z*)-CH_2CH_2NH), 3.11 (0.6H, t, *J* 5.8, (*E*)-$CHCH_2NH$), 1.86 (0.6H, q, *J* 6.0, (*E*)-$CHCH_2CH_2$), 1.82 (1.4 H, q, *J* 6.7, (*Z*)-$CHCH_2CH_2$), 1.23 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.19 (6H, t, *J* 7.0, OCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 170.7 (C_Z) and 169.7 (C_E), 152.2 (CH), 102.0 (CH_E) and 100.6 (CH_Z) , 85.3 (CH_E) and 81.7 (CH_Z), 61.9 (CH_{2E}) and 61.5 (CH_{2Z}), 58.8 (CH_{2E}) and 58.5 (CH_{2Z}), 44.6 (CH_2), 35.0 (CH_2), 15.2 (CH_3), 14.5 (CH_3)

3.4.3 Preparation of methyl 3-(tert-butoxycarbonyl(3,3-diethoxypropyl) amino)acrylate (44e)

Enamine **43e** (1.73 g, 7.48 mmol), TEA (2.08 mL, 2eq) and DMAP (183 mg, 0.2 eq), were dissolved in CH_2Cl_2 (10 mL). Boc_2O (1.65 g, 1.0 eq) in CH_2Cl_2 (20 mL)

was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give enamide **44e** (937 mg, 38 %) as a colourless oil.



43e **44e**

Scheme 32 The synthesis of enamide derivative **44e**

TLC:Rf = 0.36 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 8.18 (1H, d, *J* 14.3, NC*H*=CH), 5.23 (1H, d, *J* 14.3, NCH=C*H*), 4.50 (1H, t, *J* 5.4, C*H*$(OEt)_2$, 3.72 (3H, s, CO_2CH_3), 3.69-3.62 (2H, m, $OCH_AH_BCH_3$), 3.60 (2H, t, *J* 7.7 ,CH_2CH_2N), 3.52.-3.44 (2H, m, $OCH_AH_BCH_3$), 1.87 (2H,q, *J* 5.7, $CHCH_2CH_2$), 1.52 (9H, s, $C(CH_3)_3$), 1.21 (6H, t, *J* 7.1, OCH_2CH_3)

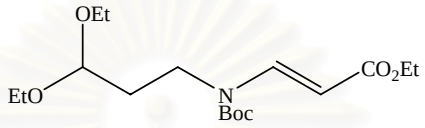
δ_C (100 MHz, $CDCl_3$) : 168.2 (C), 151.8 (C), 142.6 (CH), 100.6 (CH), 96.5 (CH), 82.9 (C), 61.3 (CH_2), 51.0 (CH_3), 40.2 (CH_2), 30.9 (CH_2), 27.9 (CH_3), 15.1 (CH_3)

Elem. Anal.: Calcd. for $C_{16}H_{29}NO_6$; C, 57.99%; H, 8.82%; N, 4.23%
Found: C, 57.92%; H, 8.92%; N, 4.23%

3.4.4 Preparation of ethyl 3-(tert-butoxycarbonyl(3,3-diethoxypropyl) amino)acrylate (44f)

Enamine **43f** (888 mg, 3.61 mmol), TEA (1.05 mL, 2eq) and DMAP (92 mg, 0.2 eq), were dissolved in CH_2Cl_2 (5 mL). Boc_2O (840 mg, 1.1 eq) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The

reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give enamide **44f** (479 mg, 38 %) as a colourless oil.



44f

Fig. 17 The structure of ethyl 3-(*tert*-butoxycarbonyl(3,3-diethoxypropyl)amino) acrylate **44f**

TLC:Rf = 0.43 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 8.16 (1H, d, *J* 14.0, NC*H*=CH), 5.21 (1H, d, *J* 14.3, NCH=C*H*), 4.49 (1H, t, *J* 5.4, C*H*$(OEt)_2$, 4.16 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.67-3.59 (2H, m, $OCH_AH_BCH_3$), 3.59 (2H, t, *J* 7.5 ,CH_2CH_2N), 3.50-3.43 (2H, m, $OCH_AH_BCH_3$), 1.86 (2H,q, *J* 7.4, $CHCH_2CH_2$), 1.50 (9H, s, $C(CH_3)_3$), 1.26 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.20 (6H, t, *J* 7.0, OCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 167.9 (C), 151.8 (C), 142.4 (CH), 100.7 (CH), 97.0 (CH), 82.9 (C), 61.4 (CH_2), 59.8 (CH_2), 40.3 (CH_2), 31.0 (CH_2), 28.0 (CH_3), 15.2 (CH_3) , 14.3 (CH_3)

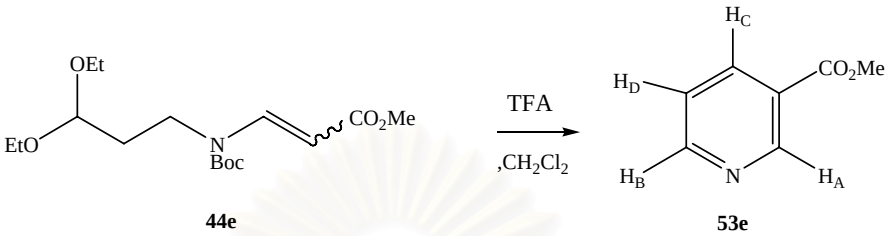
Elem. Anal.: Calcd. for $C_{17}H_{31}NO_6$; C, 59.11%; H, 9.05%; N, 4.05%

Found: C, 59.12%; H, 9.15%; N, 4.06%

3.4.5 Preparation of methyl nicotinate (53e)

Enamide **44e** (519 mg, 1.57 mmol) was stirred with TFA (0.24 mL, 2 eq) in CH_2Cl_2 (25 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected

organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide methyl nicotinate **53e** (36 mg, 17%).



44e **53e**

Scheme 33 The synthesis of pyridine derivative **53e**

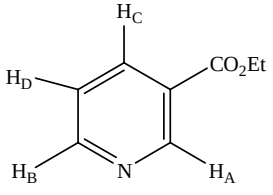
TLC:Rf = 0.22 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 9.23 (1H, s, ArH_A), 8.78 (1H, brd, *J* 4.9, ArH_B), 8.32 (1H, dt, *J* 1.9, 7.8, ArH_C), 7.41 (1H, dd, *J* 4.9, 7.8, ArH_D), 3.96 (3H, s, CO_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 165.6 (C), 153.0 (CH), 150.6 (CH), 137.4 (CH), 123.4 (C), 52.5 (CH_3)

3.4.6 Preparation of ethyl nicotinate (53f)

Enamide **44f** (541 mg, 1.57 mmol) was stirred with TFA (0.24 mL, 2 eq) in CH_2Cl_2 (25 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide methyl nicotinate **53f** (51 mg, 22%).



53f

Fig. 18 The structure of ethyl nicotinate **53f**

TLC:Rf = 0.21 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 9.24 (1H, s, ArH_A), 8.76 (1H, brd, *J* 4.2, ArH_B), 8.30 (1H, dt, *J* 1.8, 7.9, ArH_C), 7.39 (1H, dd, *J* 4.2, 7.9, ArH_D), 4.41 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 1.41 (3H, t, *J* 7.2, $CO_2CH_2CH_3$)

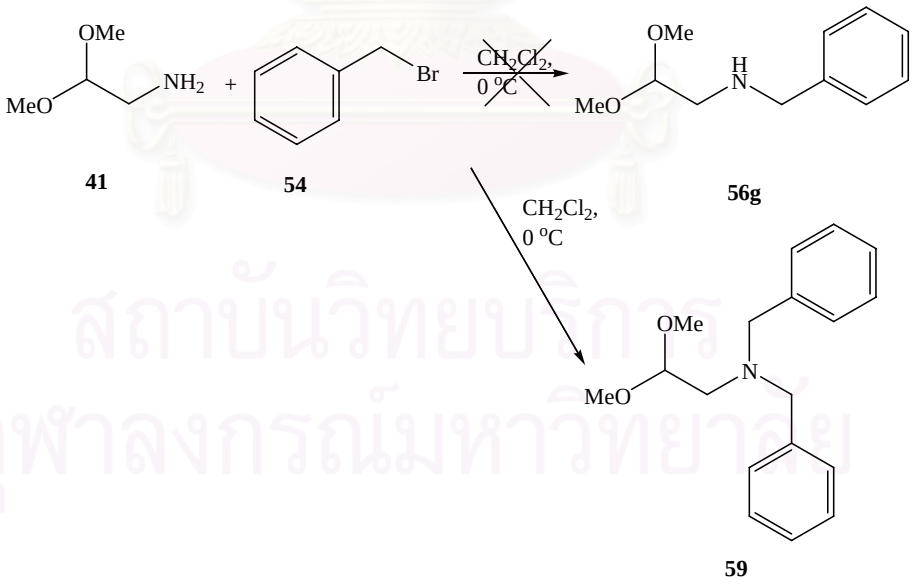
δ_C (100 MHz, $CDCl_3$) : 165.2 (C), 153.2 (CH), 150.8 (CH), 137.1 (CH), 123.3 (C), 61.4 (CH_2), 14.2 (CH_3)

3.5 Synthesis of applied oxazolidin-2-ones

3.5.1 Preparation of N-benzyl-2,2-dimethoxyethanamine (56g)

Method 1.

Benzylbromide **54** (891 mg, 5.21 mmol) in CH_2Cl_2 (100 mL) was added dropwise into 1-amino-2,2-dimethyl ethane **41** (549 mg, 5.22 mmol) in CH_2Cl_2 (5 mL) at 0^{o}C for 4 hours, before being allowed to warm to room temperature for 20 hours. The reaction was removed *in vacuo*. This step was purified by column chromatography (SiO_2) to give tertiary amine **59** (461 mg, 62%) as a colourless oil.



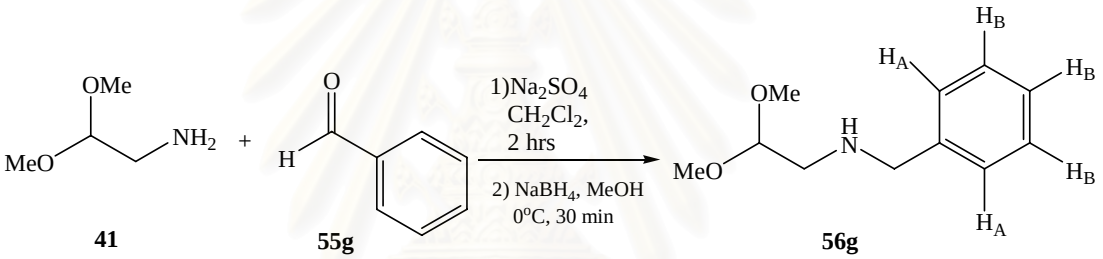
Scheme 34 The synthesis of amine derivative **56g** by method 1

TLC:Rf = 0.47 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 7.38 (4H, d, *J* 7.2, ArH_B), 7.31 (4H, t, *J* 7.2, ArH_A), 7.23 (2H, t, *J* 7.2, ArH_C), 4.47 (1H, t, *J* 5.2, C*H*$(OMe)_2$), 3.66 (4H, s, CH_2Ar), 3.26 (6H, s, OCH_3), 2.64 (2H, d, *J* 5.2, CHCH_2N)

Method 2.

In the first step, benzaldehyde **55g** (10.10 mL, 10.5 mmol) was added dropwise into 1-amino-2,2-dimethyl ethane **41** (1.28 g, 1.2 eq) in CH_2Cl_2 (10 mL). After the reaction mixture was left stirring for 10 minutes, the mixture was added Na_2SO_4 (5.74 g, 40.4 mmol). The mixture was stirred for 2 hours, and followed the reaction by TLC. The solvent was removed in *vacuo* to obtain crude imine intermediate as a pale yellow oil. This step was not purified by column chromatography (SiO_2).



41 **55g** **56g**

Scheme 35 The synthesis of amine derivative **56g** by method 2

TLC:Rf = 0.47 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 8.29 (1H, s, N=C*H*-Ar), 7.74 (2H, d, *J* 4.4, ArH_A), 7.55-7.40 (3H, m, ArH_B), 4.68 (1H, t, *J* 5.2, C*H*$(OMe)_2$), 3.78 (2H, d, *J* 5.2, CHCH_2N), 3.42 (6H, s, OCH_3)

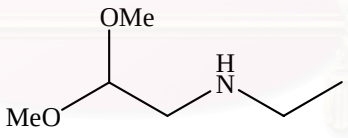
In the second step, the imine mixture (10.5 mmol) was stirred with $NaBH_4$ (0.80 g, 2 eq) at 0^oC in MeOH (30 mL) for 30 minutes. The round bottom flask connected to the drying tube. The mixture was quenched with water to get rid of $NaBH_4$. Aqueous layer was extracted with EtOAc (2 x 20 mL), and also the combined organic extracts were dried (Na_2SO_4). The solvent was withdrawn in *vacuo* to get the product **68g** (1.66 g, 8.50 mmol, 70%) as a colourless oil.

TLC:Rf = 0.08 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 7.40-7.20 (5H, m, Ar*H*), 4.51 (1H, t, *J* 5.6, C*H*$(OMe)_2$), 3.82 (2H, s, NHCH_2Ar), 3.37 (6H, s, OCH_3), 2.76 (2H, d, *J* 5.6, CHCH_2NH)

3.5.2 Preparation of N-ethyl-2,2-dimethoxyethanamine (56h)

Acetaldehyde **55h** (1.00 mL, 12.1 mmol) was added dropwise into 1-amino-2,2-dimethyl ethane **41** (1.27 g, 1.21 mmol) in CH_2Cl_2 (10 mL). After the reaction mixture was left stirring for 10 minutes, the mixture was added Na_2SO_4 (5.68 g, 40.0 mmol). The mixture was stirred for 2 hours, and followed the reaction by TLC. The solvent was removed in *vacuo* to obtain crude imine intermediate as a pale yellow oil. The imine mixture (12.1 mmol) was stirred with $NaBH_4$ (0.80 g, 2 eq) at 0^oC in MeOH (30 mL) for 30 minutes. The round bottom flask connected to the drying tube. The mixture was quenched with water to get rid of $NaBH_4$. Aqueous layer was extracted with EtOAc (2 x 20 mL), and also the combined organic extracts were dried (Na_2SO_4). The solvent was withdrawn in *vacuo* to get the product **56h** (840 mg, 6.30 mmol, 63%) as a colourless oil.



56h

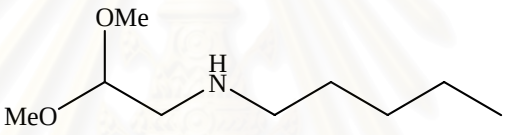
Fig. 19 The structure of *N*-ethyl-2,2-dimethoxyethanamine **56h**

TLC:Rf = 0.08 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 4.49 (1H, t, *J* 5.4, C*H*$(OMe)_2$), 3.39 (6H, s, OCH_3), 2.75 (2H, d, *J* 5.4, NHCH_2CH), 2.68 (2H, q, *J* 7.2, NHCH_2CH_3), 1.12 (3H, t, *J* 7.2, NHCH_2CH_3)

3.5.3 Preparation of N-(2,2-dimethoxyethyl)pentan-1-amine *(56i)*

Valeraldehyde **55i** (1.10 mL, 10.4 mmol) was added dropwise into 1-amino-2,2-dimethyl ethane **41** (1.05 g, 10.0 mmol) in CH_2Cl_2 (10 mL). After the reaction mixture was left stirring for 10 minutes, the mixture was added Na_2SO_4 (5.68 g, 40.0 mmol). The mixture was stirred for 2 hours, and followed the reaction by TLC. The solvent was removed in *vacuo* to obtain crude imine intermediate as a pale yellow oil. The imine mixture (10.0 mmol) was stirred with $NaBH_4$ (0.80 g, 2 eq) at 0^oC in MeOH (30 mL) for 30 minutes. The round bottom flask connected to the drying tube. The mixture was quenched with water to get rid of $NaBH_4$. Aqueous layer was extracted with EtOAc (2 x 20 mL), and also the combined organic extracts were dried (Na_2SO_4). The solvent was withdrawn in *vacuo* to get the product **56i** (1.03 g, 5.87 mmol, 59%) as a colourless oil.



56i

Fig. 20 The structure of *N*-(2,2-dimethoxyethyl)pentan-1-amine **56i**

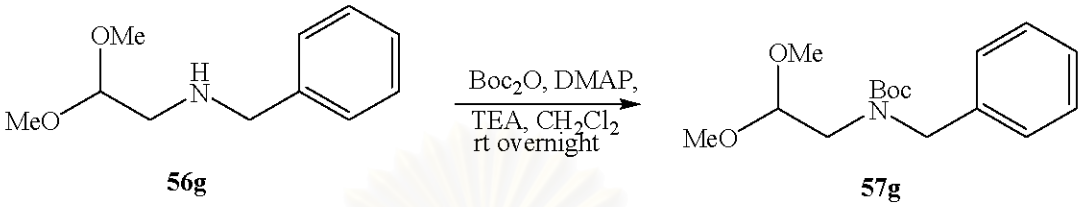
TLC:Rf = 0.13 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 4.48 (1H, t, *J* 5.6, C*H*$(OMe)_2$), 3.37 (6H, s, OC*H*$_3$), 2.67 (2H, d, *J* 5.6, NHC*H*$_2$CH), 2.01 (2H, q, *J* 8.0, NHC*H*$_2$CH$_2$), 1.40-1.10 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.00-0.70 (3H, m, CH$_2$C*H*$_3$)

3.5.4 Preparation of tert-butyl benzyl(2,2-dimethoxyethyl)carbamate (57g)

Phenyl amine **56g** (1.01 g, 5.17 mmol) was dissolved in CH_2Cl_2 (5 mL). TEA (0.70 mL, 1.5 eq) was added in the reaction. The reaction mixture was stirred for 10 minutes. Boc_2O (1.41 g, 1.0 eq) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried

(Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give protected phenyl amine **57g** (1.21 g, 4.08 mmol, 79 %) as a colourless oil.



56g **57g**

Scheme 36 The synthesis of amide derivative **57g**

TLC:Rf = 0.40 (EtOAc : Hexane (1:3 v/v))

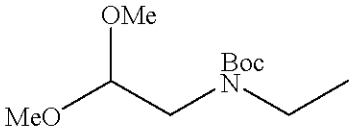
δ_H (400 MHz, $CDCl_3$) : 7.33-7.20 (5H, m, Ar*H*), 4.52 (2H, d, *J* 16.4, NCH_2Ar), 4.52 (0.5H, t, *J* 16.4, $CH_A(OMe)_2$), 4.44 (0.5H, br, $CH_B(OMe)_2$), 3.40 (3H, s, OC*H*$_3$), 3.36 (3H, s, OC*H*$_3$), 3.28 (1H, d, *J* 4.4, CHC*H*$_2$N), 3.26 (1H, d, *J* 4.4

Fig. 21 The structure of *tert*-butyl 2,2-dimethoxyethyl(ethyl)carbamate **57h**

TLC:Rf = 0.51 (EtOAc : Hexane (1:3 v/v))

3.5.5 Preparation of tert-butyl 2,2-dimethoxyethyl(ethyl)carbamate (57h)

Ethyl amine **56h** (503 mg, 3.78mmol) was dissolved in CH_2Cl_2 (5 mL). TEA (0.57mL, 10.7 mmol) was added in the reaction. The reaction mixture was stirred for 10 minutes. Boc_2O (823 mg, 3.77 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give protected ethyl amide **57h** (242 mg, 1.04mmol, 27 %) as a colourless oil.



57h

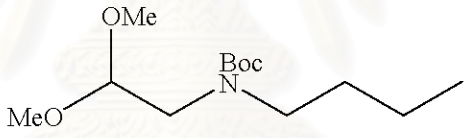
Fig. 21 The structure of *tert*-butyl 2,2-dimethoxyethyl(ethyl)carbamate **57h**

TLC:Rf = 0.51 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 4.50-4.33 (1H, br m, C*H*$(OMe)_2$), 3.39 (6H, s, OC*H*$_3$), 3.35-3.20 (4H, br, C*H*$_2$NC*H*$_2$), 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.08 (3H, t, *J* 6.8, NCH_2CH_3)

3.5.6 Preparation of tert-butyl 2,2-dimethoxyethyl(pentyl)carbamate (57i)

Pentyl amine **56i** (474 mg, 2.71 mmol) was dissolved in CH_2Cl_2 (5 mL). TEA (0.37 mL, 10.7 mmol) was added in the reaction. The reaction mixture was stirred for 10 minutes. Boc_2O (710 mg, 3.26 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at room temperature for 20 hours. The reaction was quenched with dil.aq.HCl (15 mL), and followed by washing with water (2 x 50 mL). Aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4). After removal of solvent *in vacuo*, the crude oil was purified by column chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:9.5 → 1:9 v/v) to give protected pentyl amine **57i** (599 mg, 2.18 mmol, 80 %) as a colourless oil.



57i

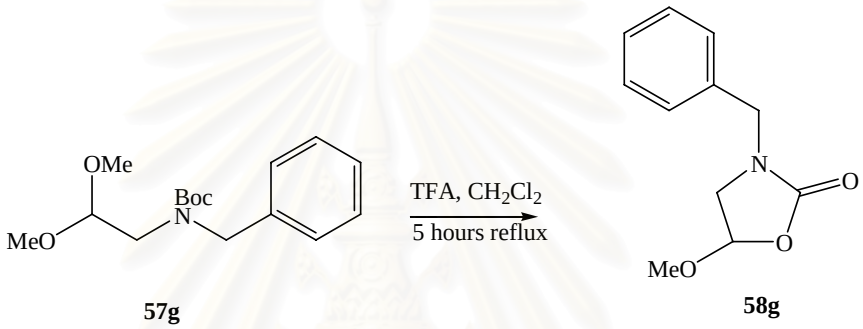
Fig. 22 The structure of *tert*-butyl 2,2-dimethoxyethyl(pentyl)carbamate **57i**

TLC:Rf = 0.56 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 4.53 (0.6H, t, *J* 5.2, C*H*$_A$$(OMe)_2$), 4.43 (0.4H, 2t, *J* 5.2, C*H*$_B$$(OMe)_2$), 3.38 (3.6H, s, OC*H*$_{3A}$), 3.37 (2.4H, s, OC*H*$_{3B}$), 3.21-3.19 (1.2H, d, *J* 5.2, NC*H*$_{2A}$CH), 3.17-3.14 (0.8H, d, *J* 5.2, NC*H*$_{2B}$CH), 2.10-2.00 (2H, br m, NC*H*$_2$$CH_2$), 1.47 (3.6H, s, C(C*H*$_{3B}$)$_3$), 1.44 (5.4H, s, C(C*H*$_{3A}$)$_3$), 1.40-1.10 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$$CH_3$), 1.00-0.70 (3H, m, CH_2C*H*$_3$)

3.5.7 Preparation of 3-benzyl-5-methoxyoxazolidin-2-one (58g)

Protected phenyl amide **57g** (500 mg, 1.69 mmol) was stirred with TFA (0.26 mL, 2 eq) in CH_2Cl_2 (30 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide oxazolidin-2-one **58g** (295 mg, 1.42 mmol, 84%) as a pale yellow oil.



57g **58g**

Scheme 37 The synthesis of oxazolidin-2-one derivative **58g**

TLC:Rf = 0.05 (EtOAc : Hexane (1:3 v/v))

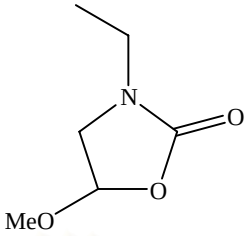
δ_H (400 MHz, $CDCl_3$) : 7.37-7.25 (5H, m, Ar*H*), 5.34 (1H, dd, *J* 2.4, 6.4, OC*H*CH_2), 4.45 (2H, d, *J* 10.4, NCH_2Ar), 3.53 (1H, dd, 6.4, 10.4, NC$H_A$$CH_B$CH), 3.51 (3H, s, OC$H_3$), 3.21 (1H, dd, *J* 2.4, 10.4, NC$H_A$$H_B$CH)

δ_C (100 MHz, $CDCl_3$) : 156.3 (C), 135.1 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 97.8 (CH), 55.8 (CH_2), 49.8 (CH_3), 47.3 (CH_2)

3.5.8 Preparation of 3-ethyl-5-methoxyoxazolidin-2-one (58h)

Protected ethyl amide **57h** (201 mg, 0.86 mmol) was stirred with TFA (0.10 mL, 2 eq) in CH_2Cl_2 (30 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with

EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide oxazolidin-2-one **58h** (104 mg, 0.72 mmol, 83%) as a pale yellow oil.



58h

Fig. 23 The structure of 3-ethyl-5-methoxyoxazolidin-2-one **58h**

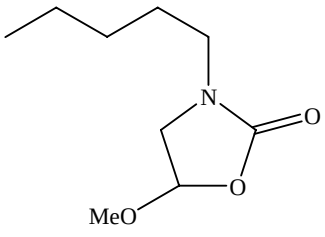
TLC:Rf = 0.10 (EtOAc : Hexane (1:3 v/v))

δ_H (400 MHz, $CDCl_3$) : 5.36 (1H, dd, *J* 2.0, 6.4, OC*H*CH_2), 3.67 (1H, dd, *J* 6.4, 10.4, NC$H_A$$H_B$CH), 3.52 (3H, s, OC$H_3$), 3.42-3.20 (3H, m, NC$H_A$$H_BCH, NCH_2$$CH_3$), 1.16 (3H, t, *J* 7.2, NCH_2CH_3)

δ_C (100 MHz, $CDCl_3$) : 156.2 (C), 97.7 (CH), 56.0 (C), 50.1(CH_3), 38.1 (CH_2), 12.4 (CH_3)

3.5.9 Preparation of 5-methoxy-3-pentyloxazolidin-2-one (58i)

Protected pentyl amide **57i** (318 mg, 1.16 mmol) was stirred with TFA (0.15 mL, 10.7 mmol) in CH_2Cl_2 (30 mL) at reflux 5 hours. The reaction was quenched by aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The collected organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2), eluting with EtOAc/petroleum ether (1:7 → 1:3 v/v), to provide oxazolidin-2-one **58i** (189 mg, 1.01 mmol, 88%) as a pale yellow oil.



58i

Fig. 24 The structure of 5-methoxy-3-pentyloxazolidin-2-one **58i**

TLC:Rf = 0..25 (EtOAc : Hexane (1:3 v/v))

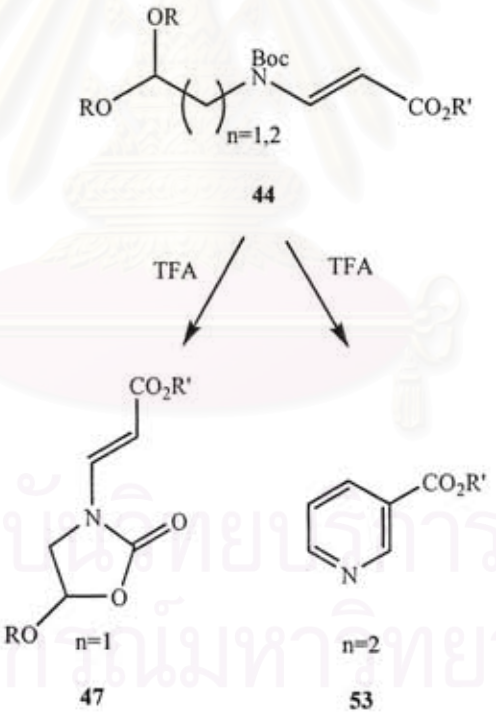
δ_H (400 MHz, $CDCl_3$) : 5.34 (1H, dd, *J* 2.4, 6.4, OC*H*CH_2), 3.52-3.50 (1H, dd, *J* 6.4, 10.4, NC*H*$_A$H$_B$CH), 3.51 (3H, s, OC*H*$_3$), 3.18 (1H, dd, *J* 2.4, 10.4, NCH$_A$*H*$_B$CH), 1.95 (2H, t, *J* 7.4, NC*H*$_2$CH$_2$), 1.48-1.36 (2H, m, NCH$_2$C*H*$_2$), 1.35-1.29 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.89 (3H, t, *J* 7.4, CH$_2$C*H*$_3$)

δ_C (100 MHz, $CDCl_3$) : 156.5 (C), 97.9 (CH), 56.0 (CH_3), 49.7 (CH_2), 29.8 (CH_2), 22.3 (CH_2), 21.1(CH_2), 21.1(CH_2), 13.9 (CH_3)

CHAPTER IV

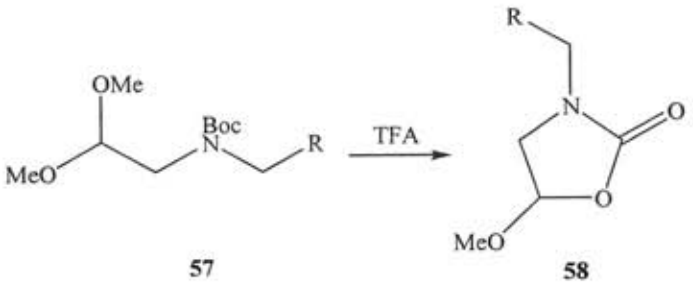
CONCLUSION

The acid-induced cyclisation of Boc-enamide **44** was studied. The cyclisation reaction of Boc-enamide **44** with n=1 and n=2 gave oxazolidin-2-one **47** and pyridine **53**, respectively. The oxazolidin-2-one was produced from the cyclisation through the attack of *O*-nucleophile of carbonyl group in Boc group. The reaction was fast and occurred readily to give high yield of product. On the other hand, the cyclisation of Boc-enamide **44** with n=2 was a slower reaction and the acid-induced deprotection of Boc group occurred prior to the cyclisation, resulting in the cyclisation through the attack of *C*-nucleophilic of alkene to give pyridine **53** as a final product in low yield.



Scheme 38 The formation of oxazolidin-2-one **47** and pyridine **53**

Since the formation of oxazolidin-2-one derivatives **47** was new and facile, the methodology was applied to synthesize several *N*-substituted oxazolidin-2-one derivatives **58** in very good yields **(Scheme 39).**

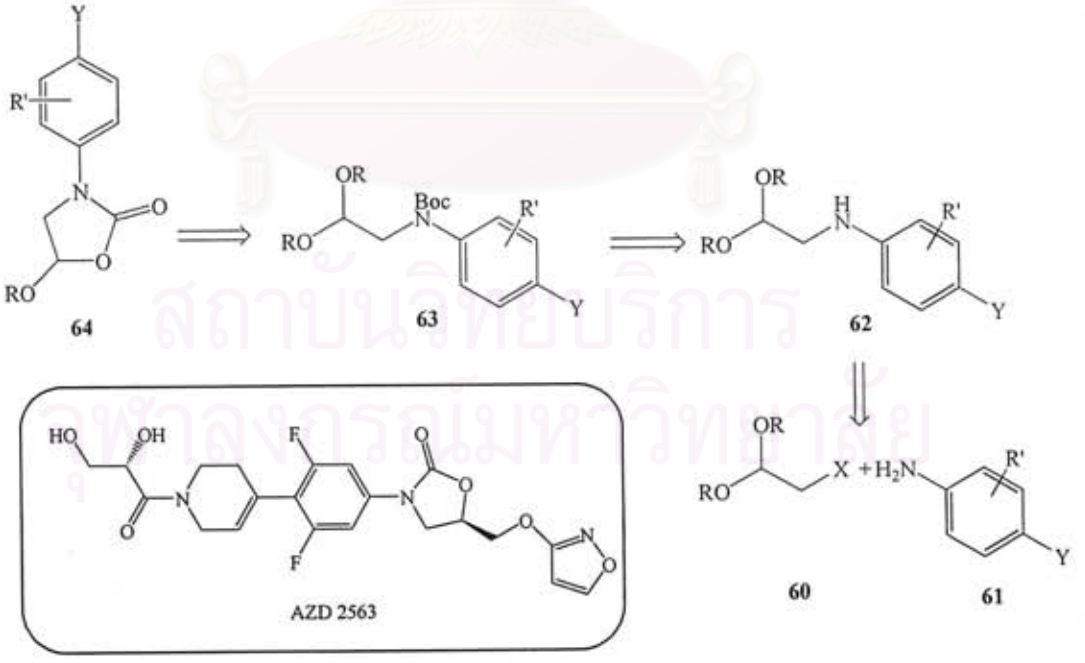


57 58

Scheme 39 The synthesis of oxazolidin-2-one derivatives **58**

Suggestion for the future work:

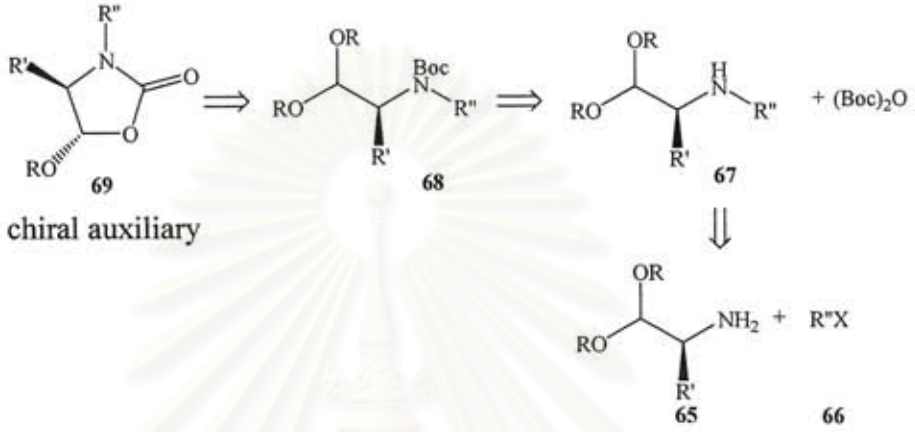
Hence the novel route to synthesize oxazolidin-2-ones has been successfully developed; therefore it would allow the efficient preparation of novel analogues AZD 2563 antibiotics from amide derivatives. For the retrosynthesis, the oxazolidin-2-one **64** may be derived from amide **63**, which may be synthesized by protecting amine **62** with Boc_2O. This amine **62** may be synthesized from the simple coupling halides **60** and aniline derivatives **61**. With variation of substituents on aromatic ring, the antibiotic activity could be investigated. This kind of oxazolidin-2-ones is also very valuable intermediates of many natural products and medicines **(Scheme 40)**.



64 63 62 60 61

Scheme 40 Retrosynthesis of the oxazolidin-2-one derivative **64**

Oxazolidin-2-ones **69** as the stereoselective chiral auxiliaries may possibly be synthesized through the acid-induced cyclisation of *N*-Boc protected secondary amine **68**, which may be synthesized by protecting amine **67** with Boc_2O. The amine **67** may be synthesized from the reaction of chiral dialkoxy amine **65** with alkyl halide or aldehyde **66 (Scheme 41)**.



Scheme 41 Retrosynthesis of the oxazolidin-2-one derivatives **69**

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APPENDICES

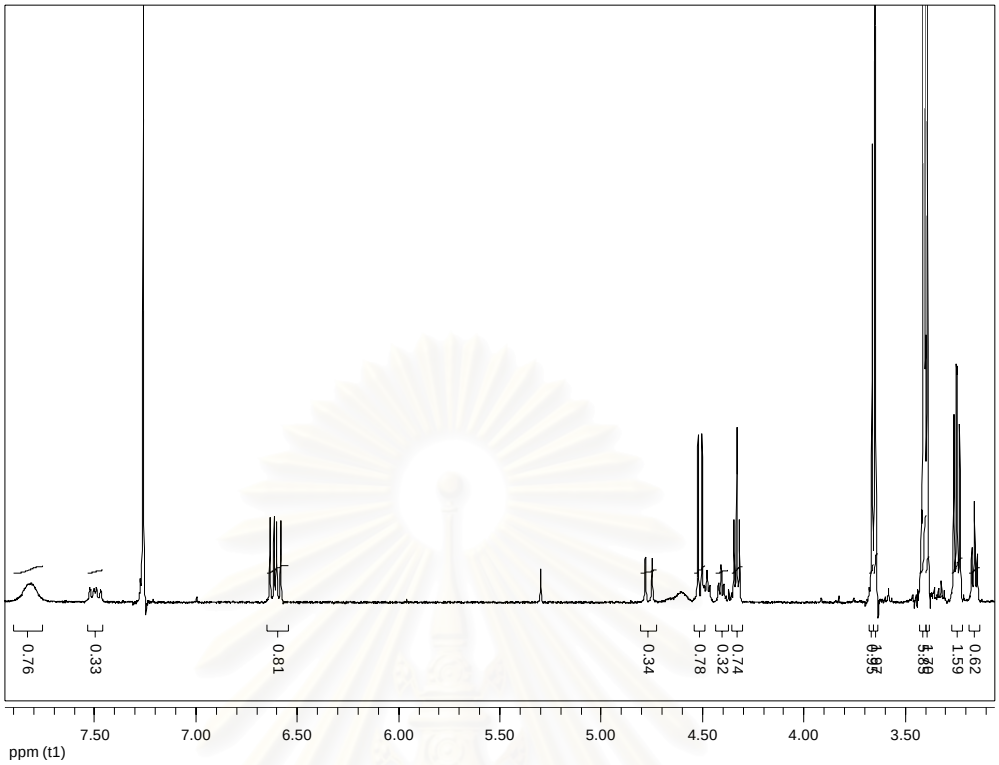


Fig. A.1 The ^{1}H-NMR spectrum of methyl 3-(2,2-dimethoxyethylamino)acrylate **43a**

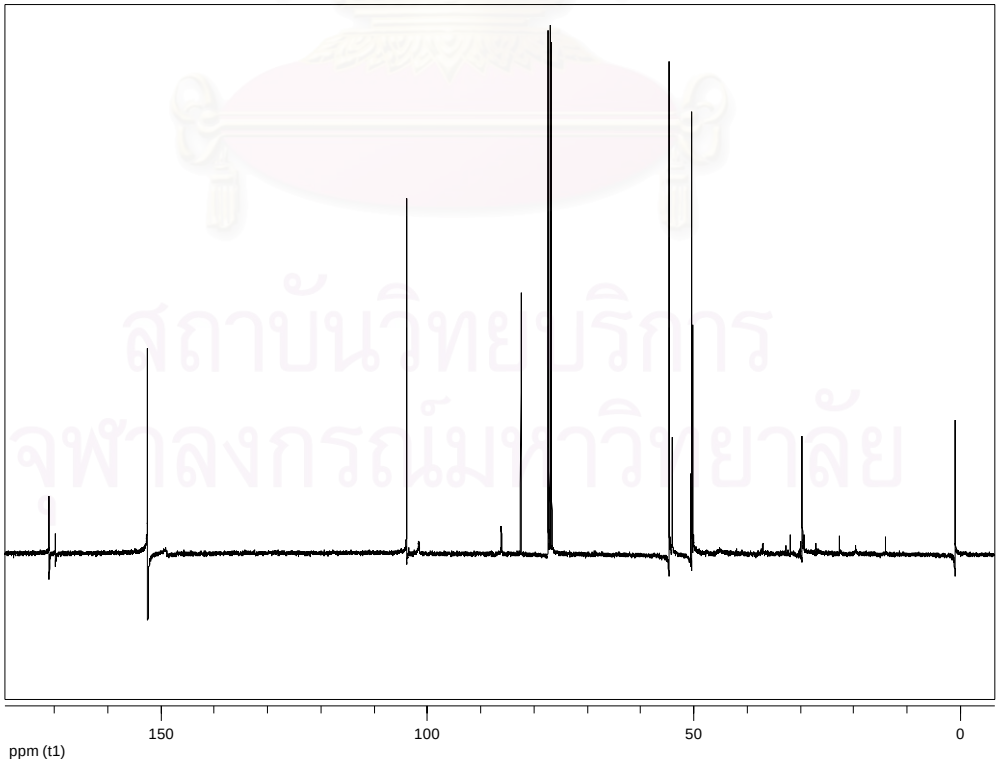


Fig. A.2 The ^{13}C-NMR spectrum of methyl 3-(2,2-dimethoxyethylamino)acrylate **43a**

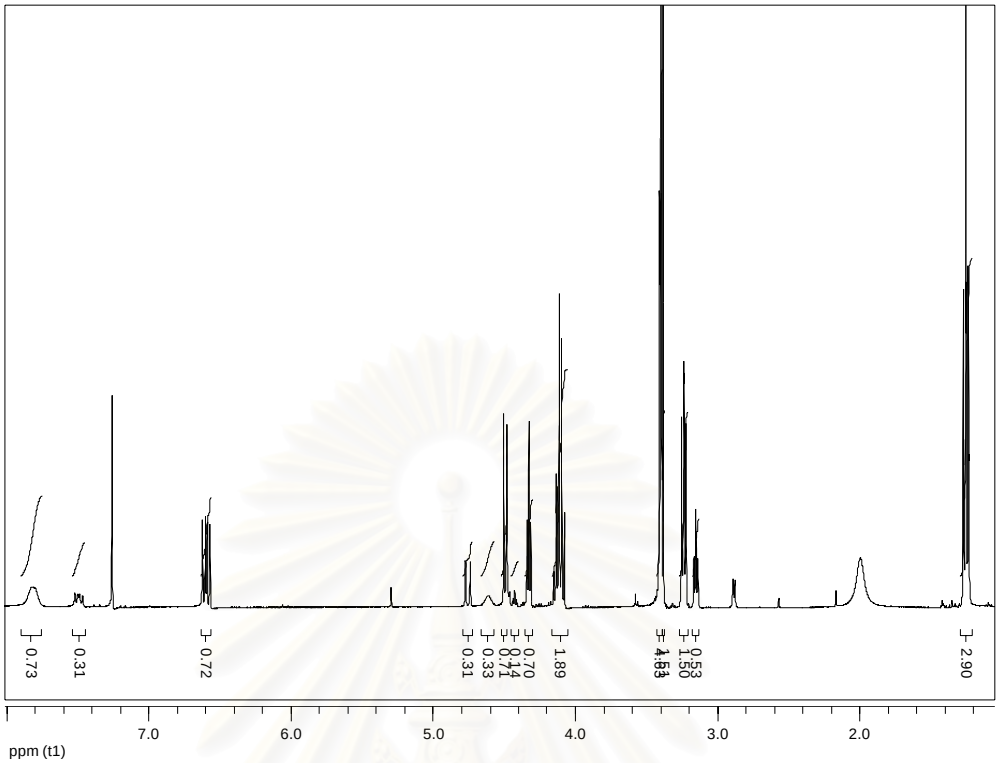


Fig. A.3 The ^{1}H-NMR spectrum of ethyl 3-(2,2-dimethoxyethylamino)acrylate **43b**

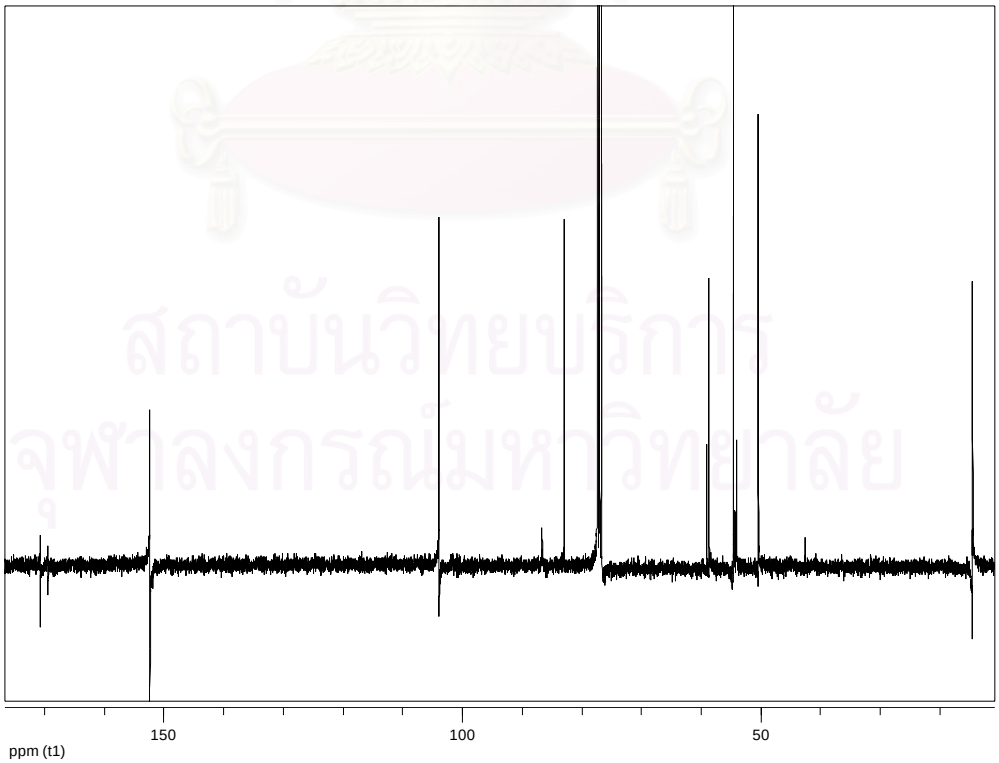


Fig. A.4 The ^{13}C-NMR spectrum of ethyl 3-(2,2-dimethoxyethylamino)acrylate **43b**

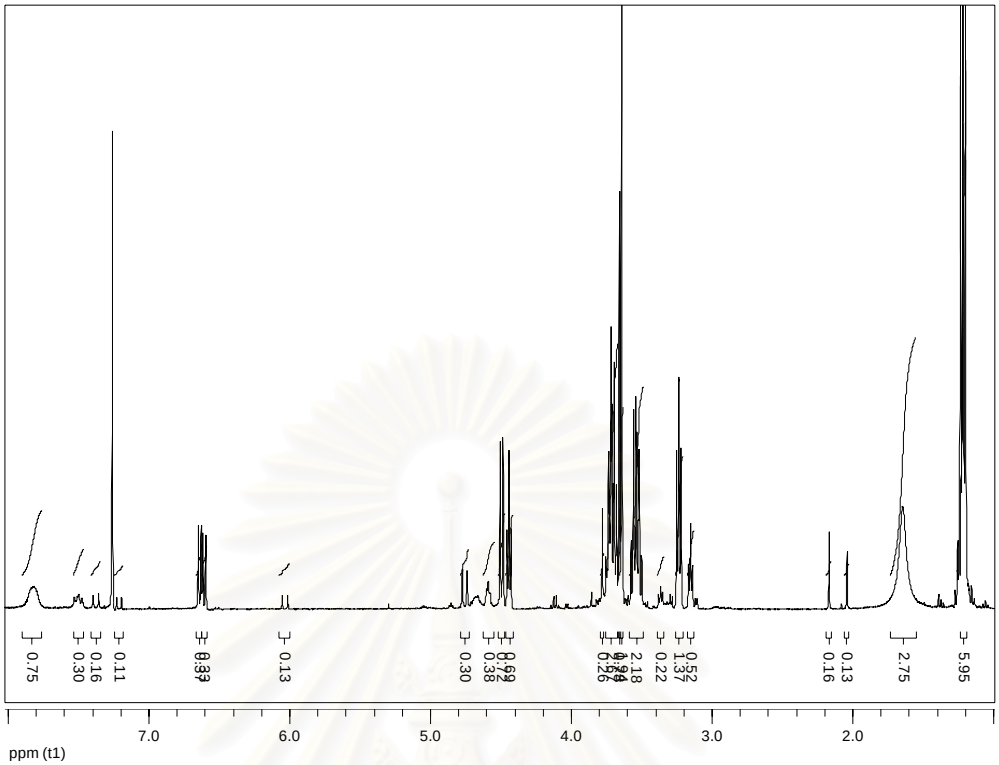


Fig. A.5 The ^{1}H-NMR spectrum of methyl 3-(2,2-diethoxyethylamino)acrylate **43c**

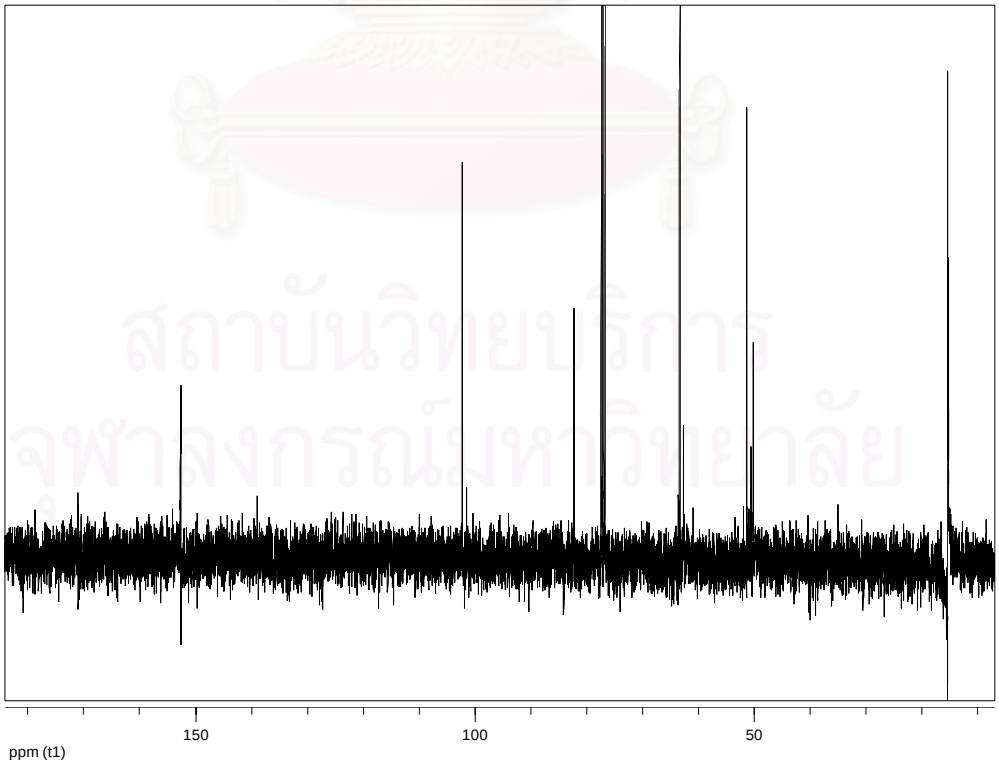


Fig. A.6 The ^{13}C-NMR spectrum of methyl 3-(2,2-diethoxyethylamino)acrylate **43c**

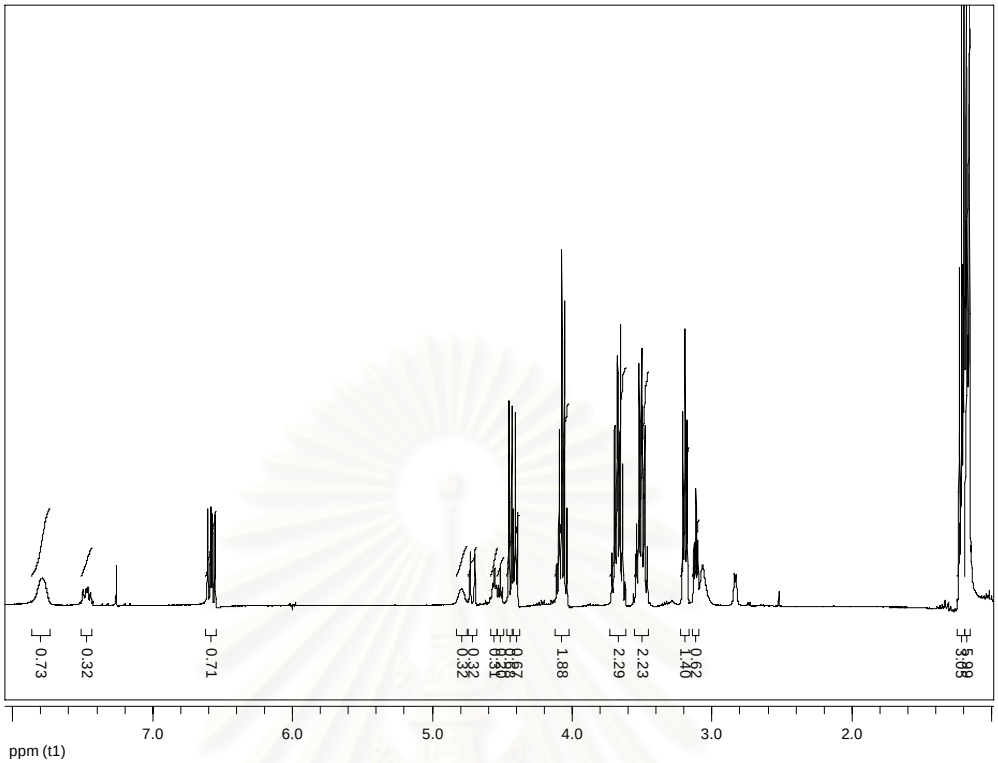


Fig. A.7 The ^{1}H-NMR spectrum of ethyl 3-(2,2-diethoxyethylamino)acrylate **43d**

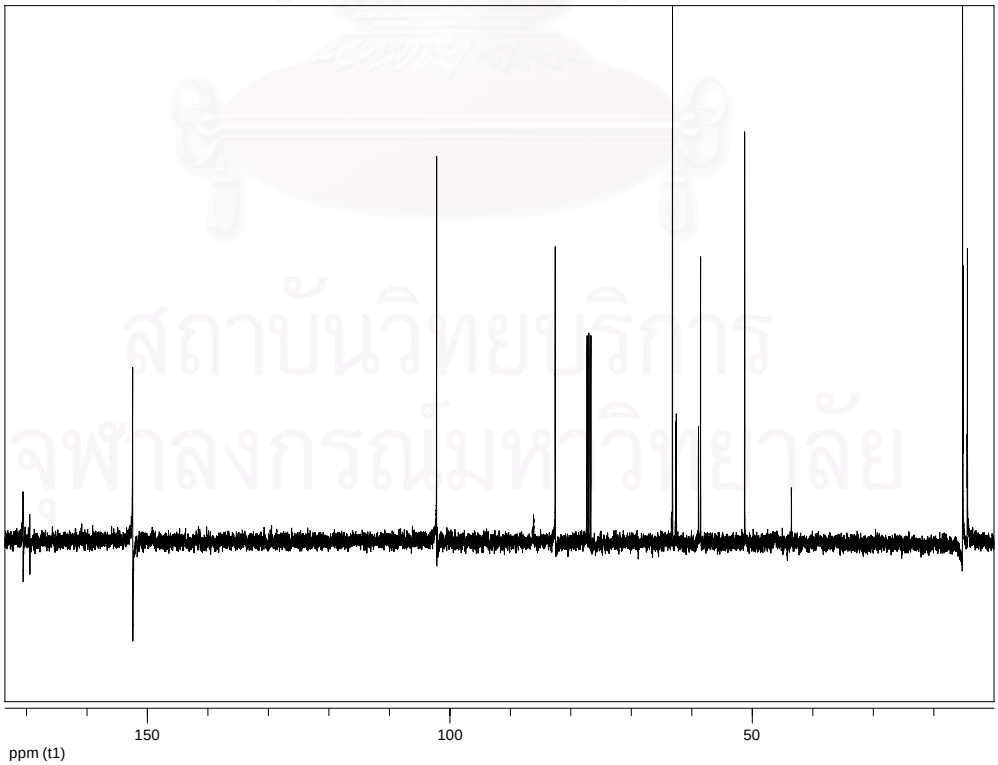


Fig. A.8 The ^{13}C-NMR spectrum of ethyl 3-(2,2-diethoxyethylamino)acrylate **43d**

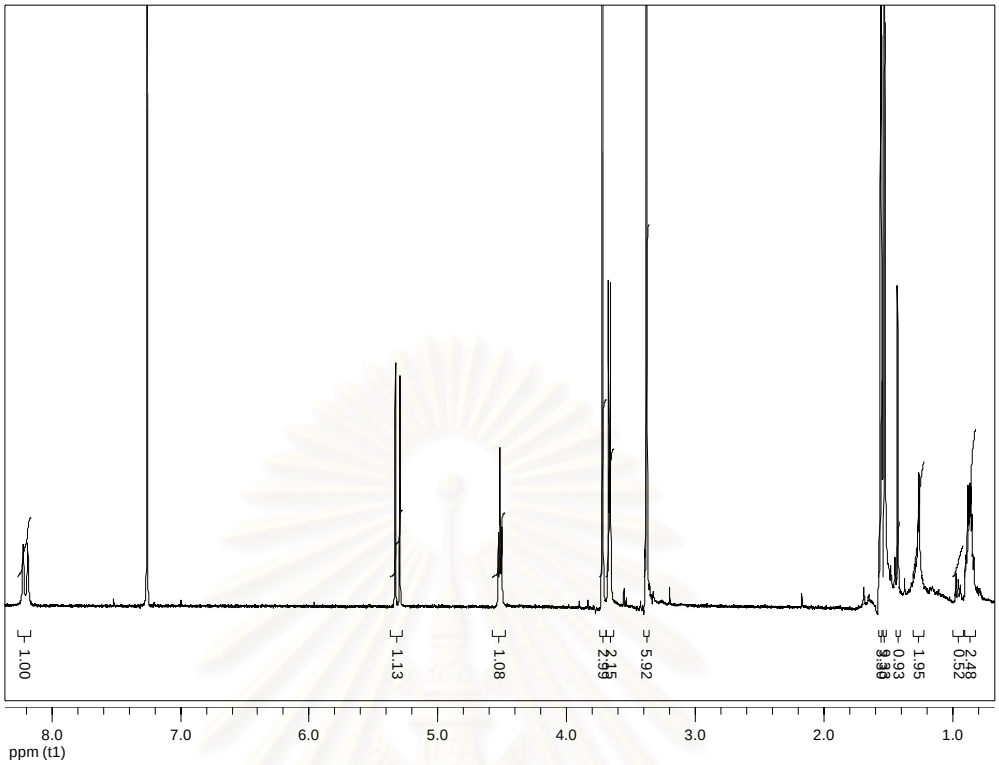


Fig. A.9 The ^{1}H-NMR spectrum of methyl 3-(*tert*-butoxycarbonyl(2,2-dimethoxyethyl)amino)acrylate **44a**

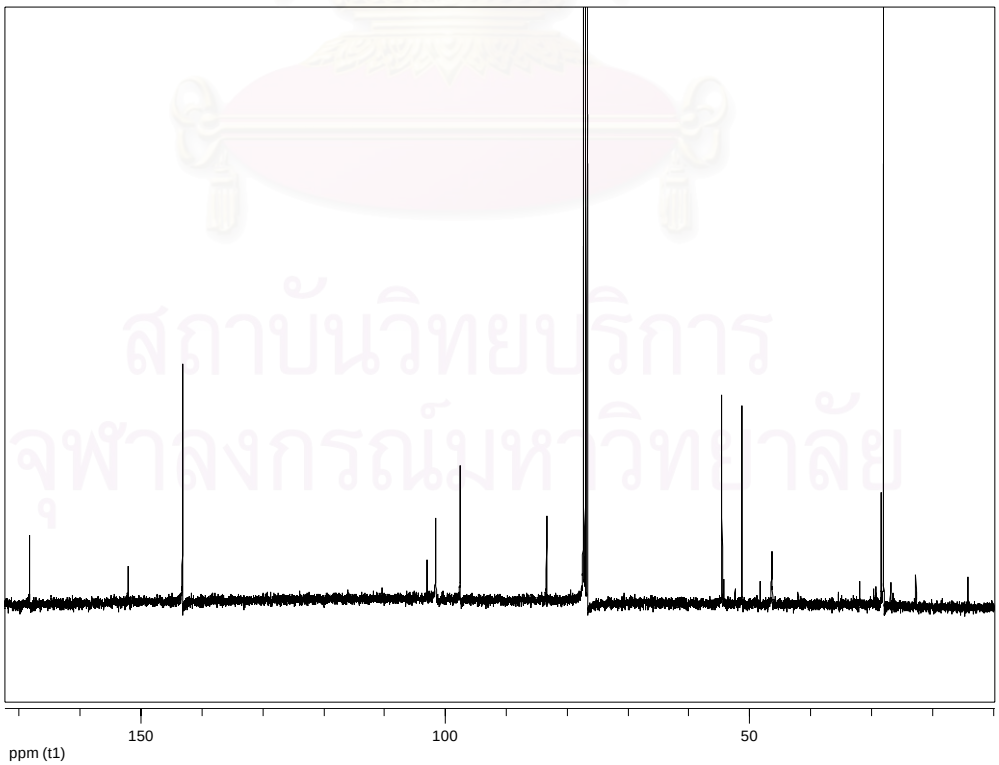


Fig. A.10 The ^{13}C-NMR spectrum of methyl 3-(*tert*-butoxycarbonyl(2,2-dimethoxyethyl)amino)acrylate **44a**

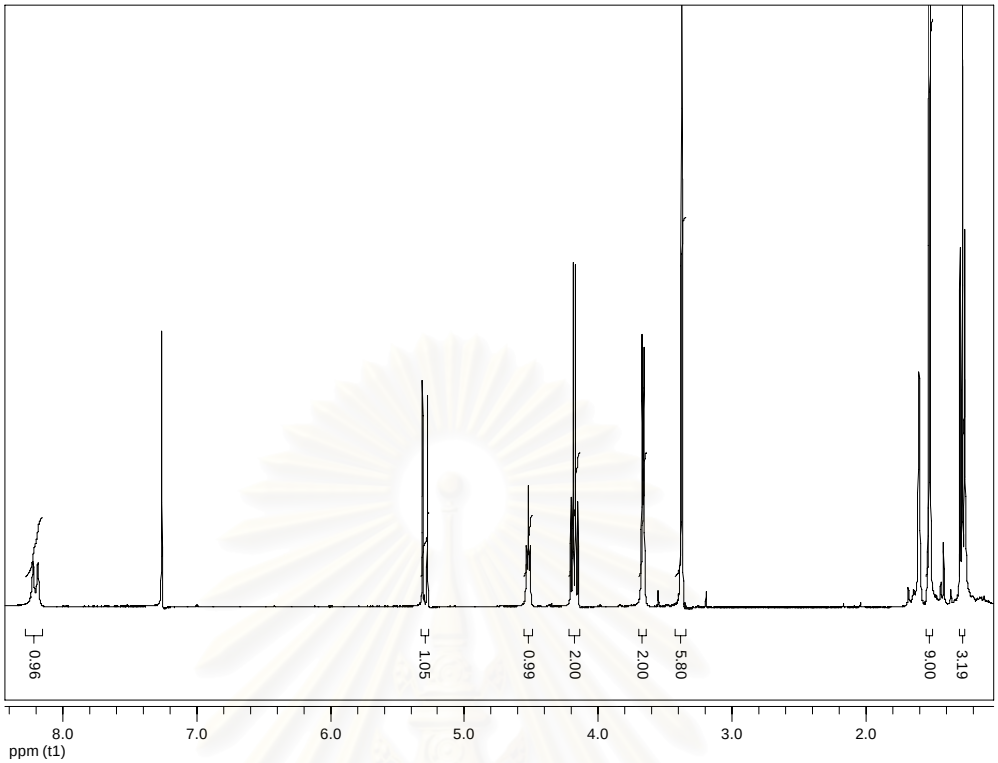


Fig. A.11 The ^{1}H-NMR spectrum of ethyl 3-(*tert*-butoxycarbonyl(2,2-dimethoxyethyl)amino)acrylate **44b**

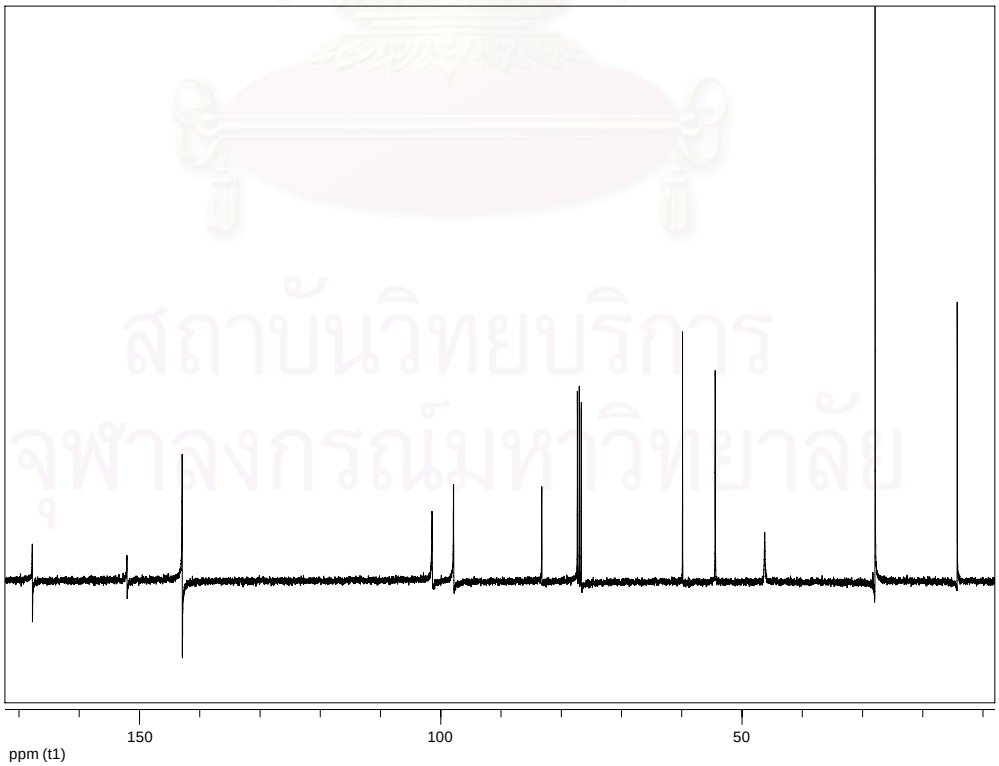


Fig. A.12 The ^{13}C-NMR spectrum of ethyl 3-(*tert*-butoxycarbonyl(2,2-dimethoxyethyl)amino)acrylate **44b**

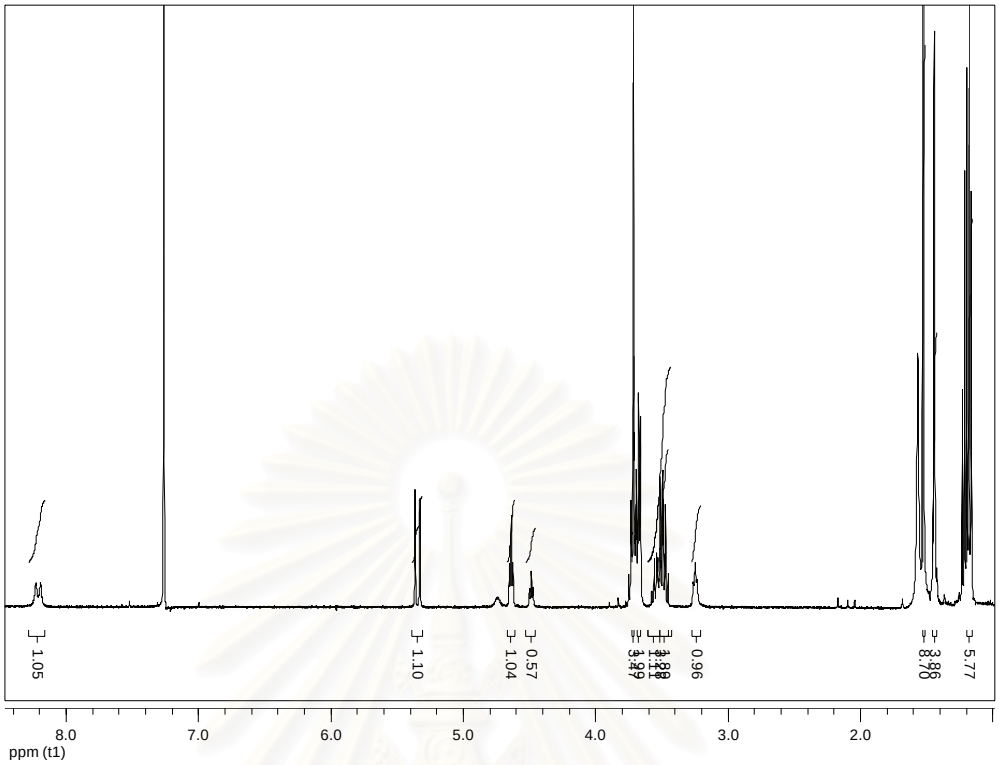


Fig. A.13 The ^{1}H-NMR spectrum of methyl 3-(*tert*-butoxycarbonyl(2,2-diethoxyethyl)amino)acrylate **44c**

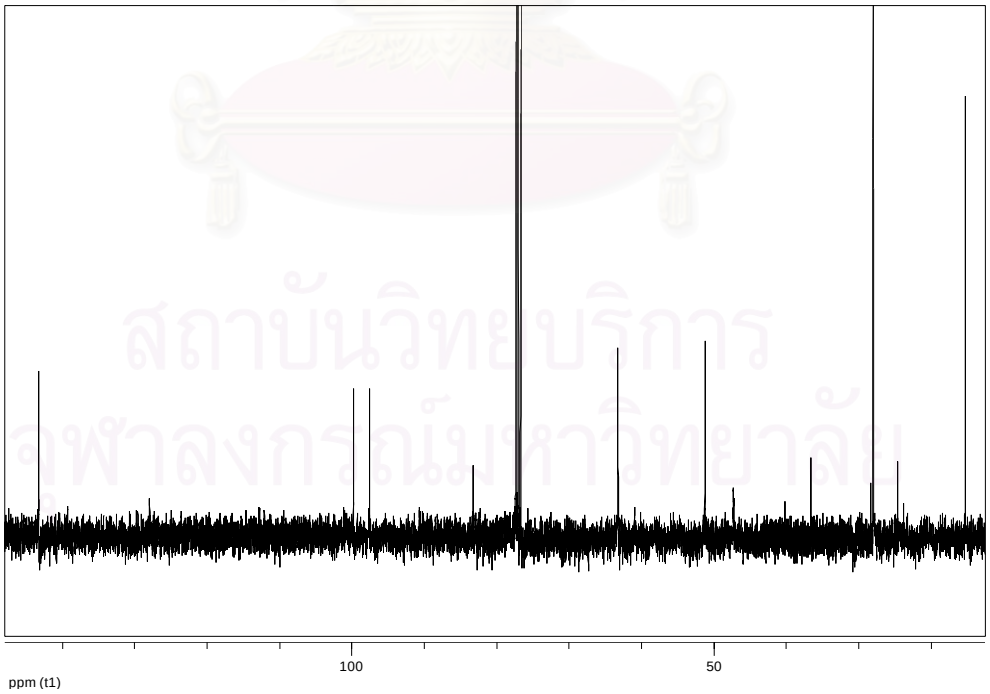


Fig. A.14 The ^{13}C-NMR spectrum of methyl 3-(*tert*-butoxycarbonyl(2,2-diethoxyethyl)amino)acrylate **44c**

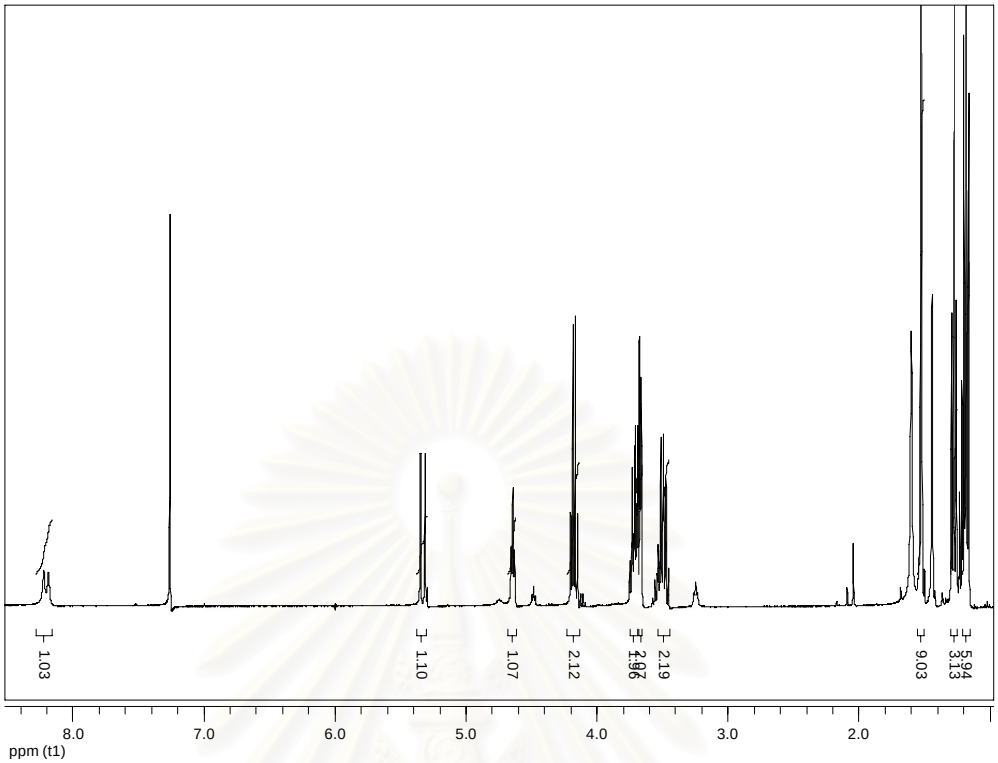


Fig. A.15 The ^{1}H-NMR spectrum of ethyl 3-(*tert*-butoxycarbonyl(2,2-diethoxyethyl)amino)acrylate **44d**

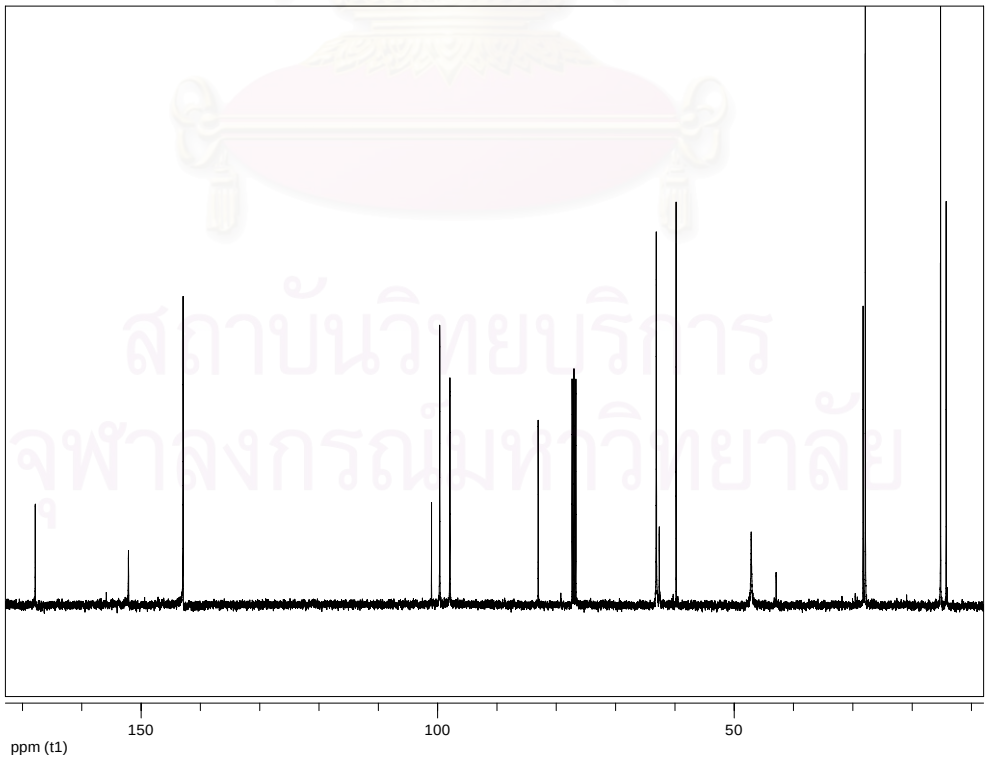


Fig. A.16 The ^{13}C-NMR spectrum of ethyl 3-(*tert*-butoxycarbonyl(2,2-diethoxyethyl)amino)acrylate **44d**

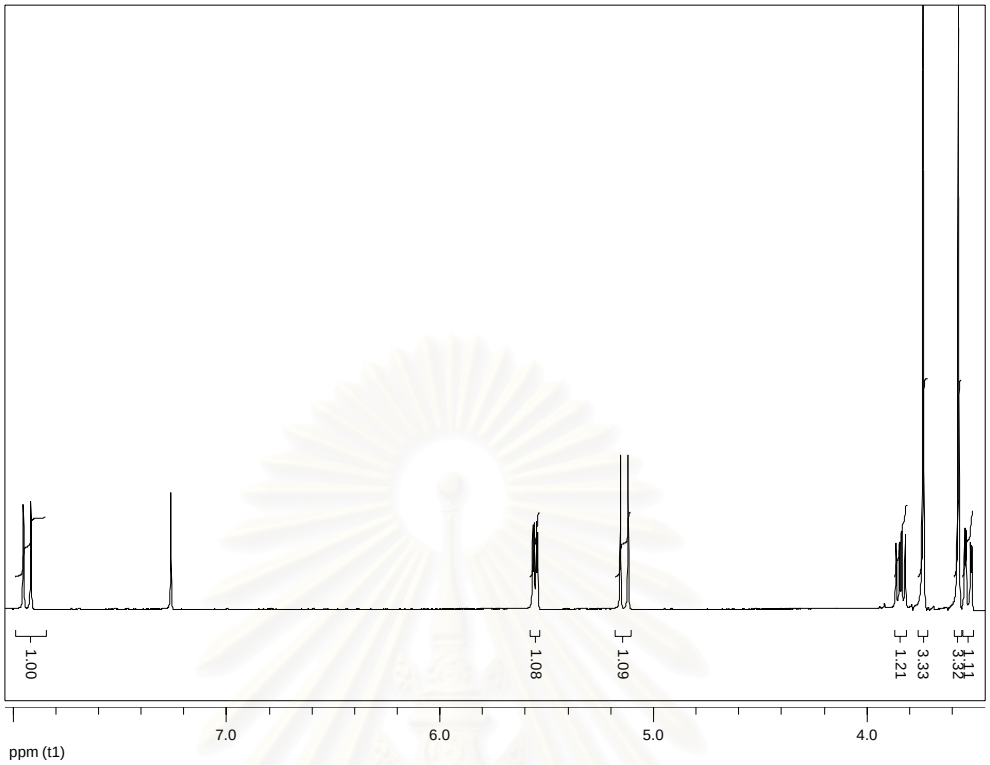


Fig. A.17 The ^{1}H-NMR spectrum of (*E*)-methyl 3-(5-methoxy-2-oxooxazolidin-*3*-yl)acrylate) **47a**

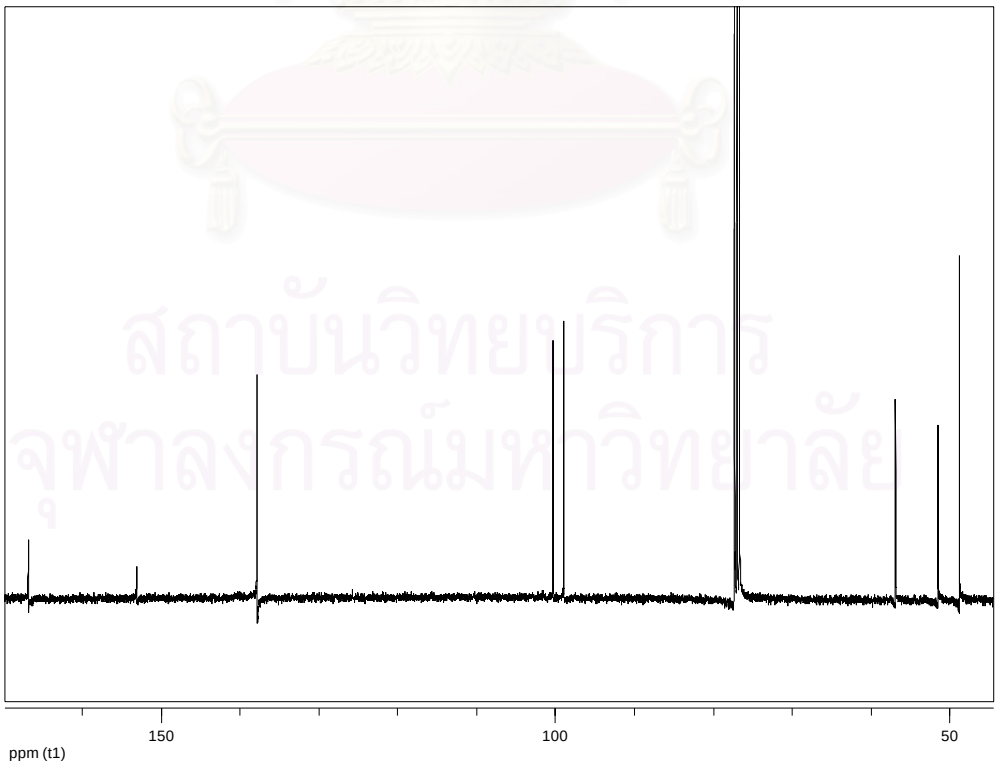


Fig. A.18 The ^{13}C-NMR spectrum of (*E*)-methyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate) **47a**

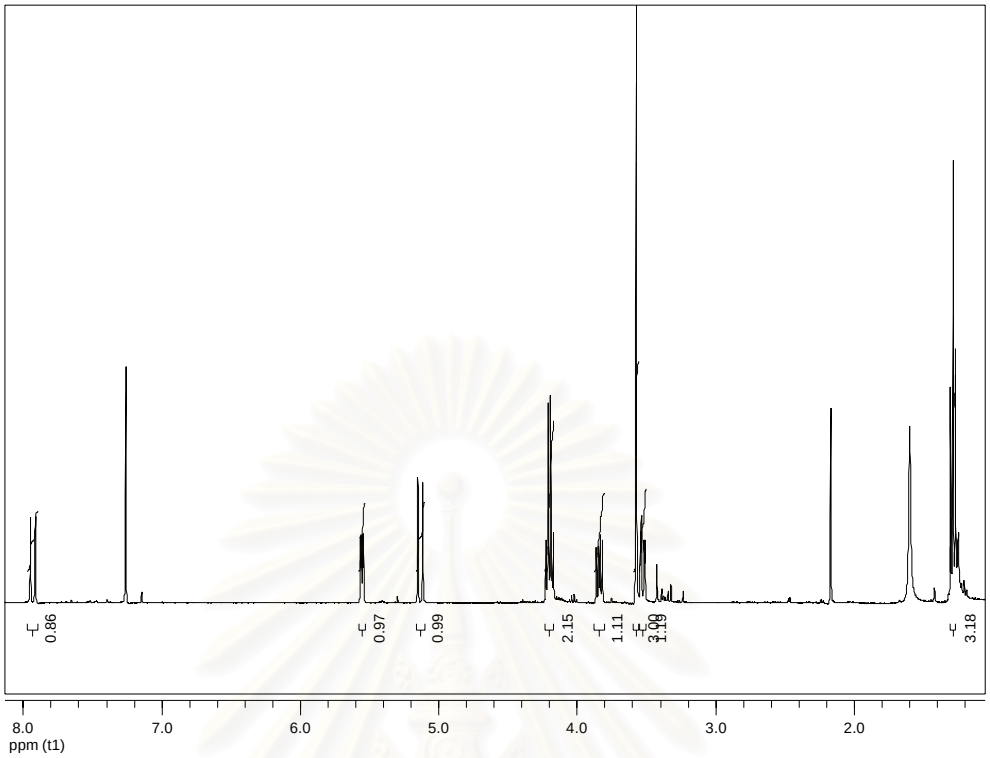


Fig. A.19 The ^{1}H-NMR spectrum of (*E*)-ethyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate) **47b**

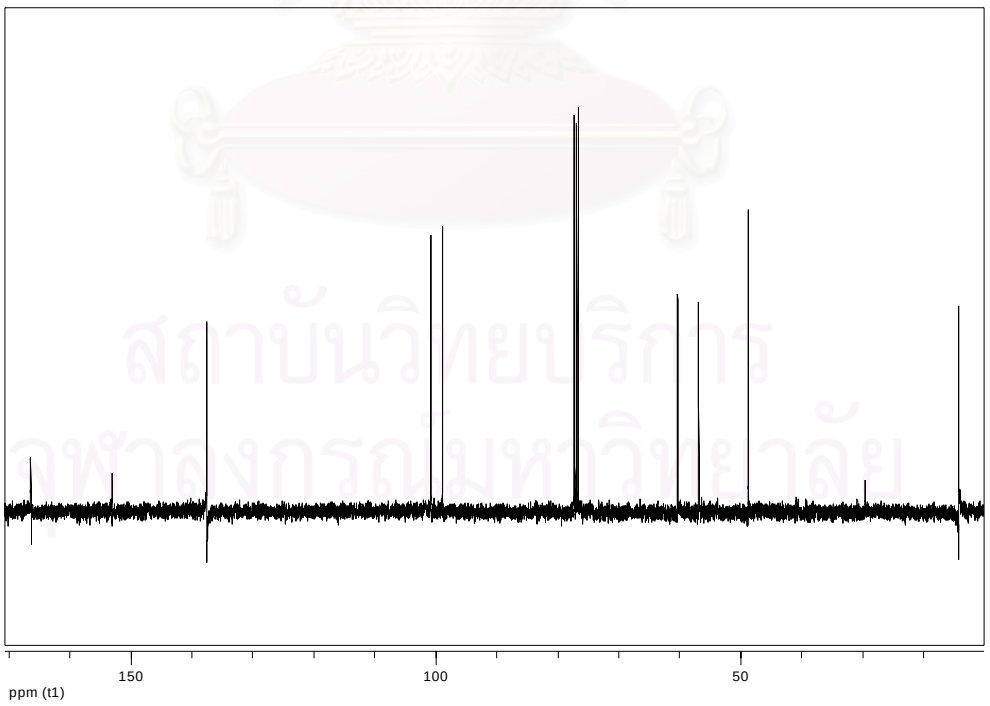


Fig. A.20 The ^{13}C-NMR spectrum of (*E*)-ethyl 3-(5-methoxy-2-oxooxazolidin-3-yl)acrylate) **47b**

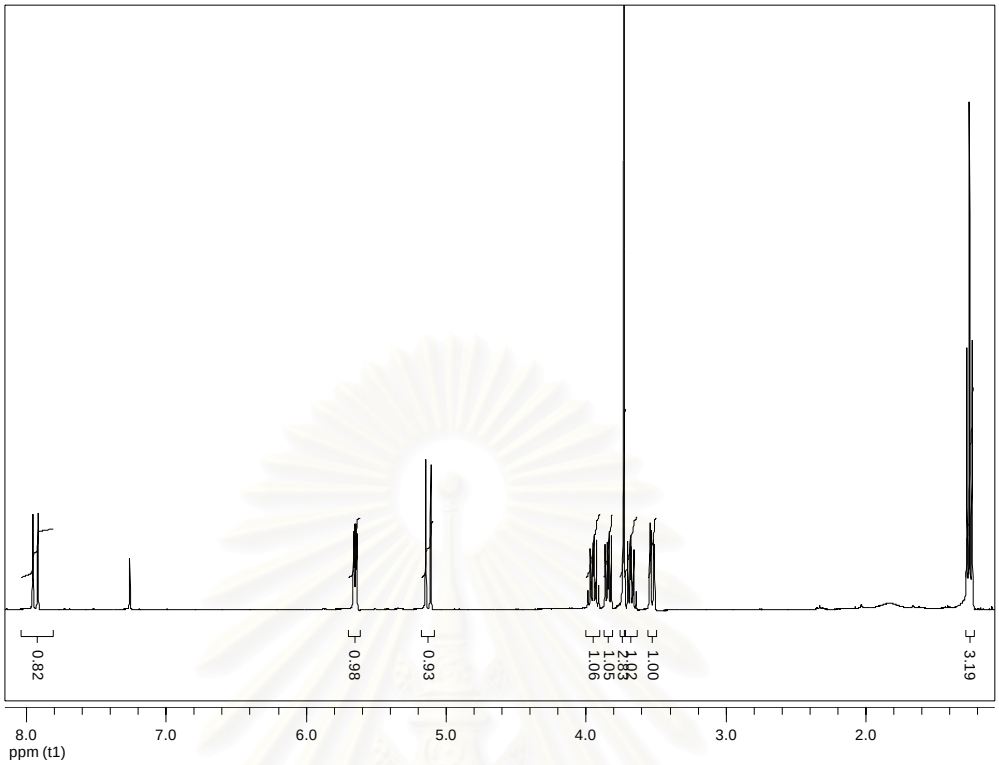


Fig. A.21 The ^{1}H-NMR spectrum of (*E*)-methyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) **47c**

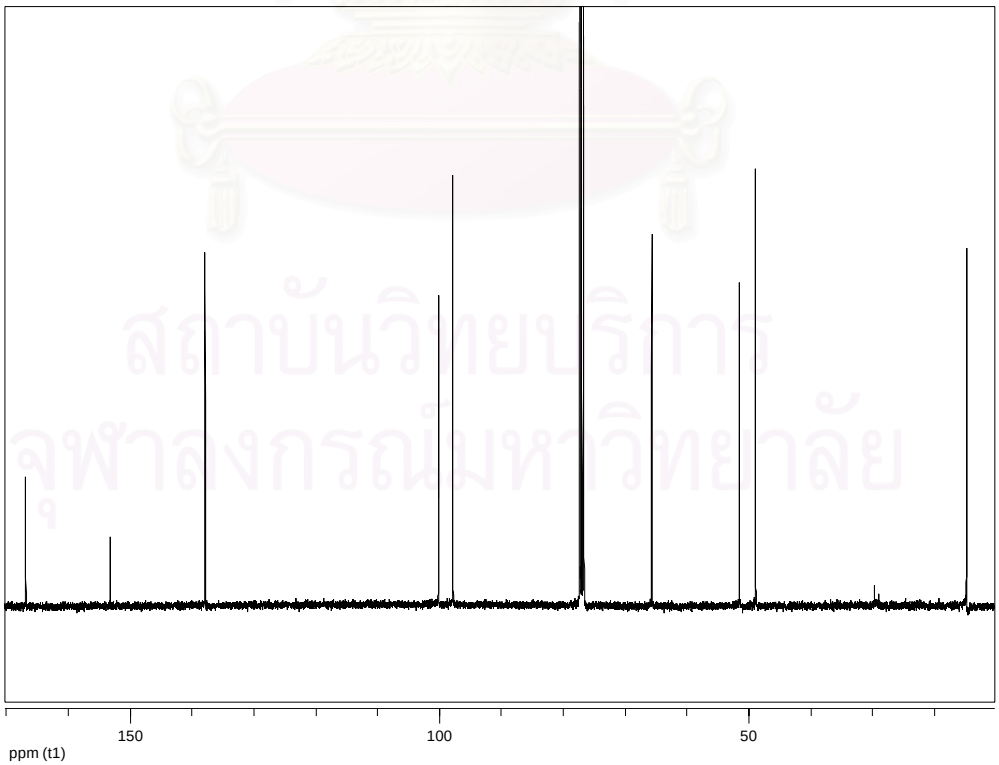


Fig. A.22 The ^{13}C-NMR spectrum of (*E*)-methyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) **47c**

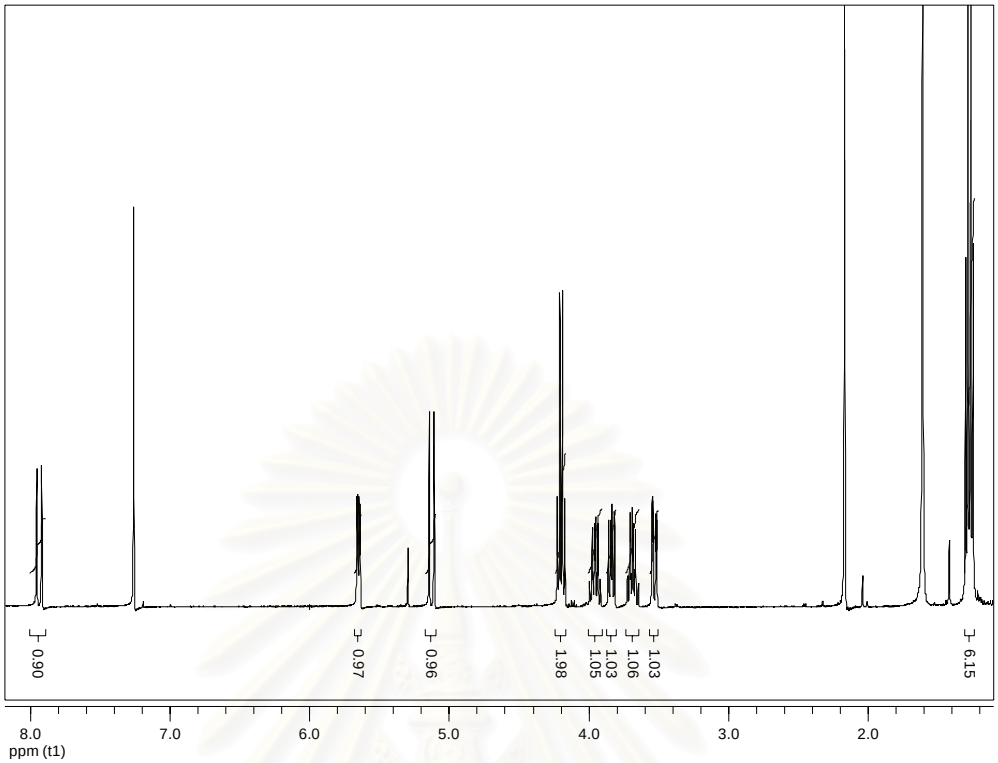


Fig. A.23 The ^{1}H-NMR spectrum of (*E*)-ethyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) **47d**

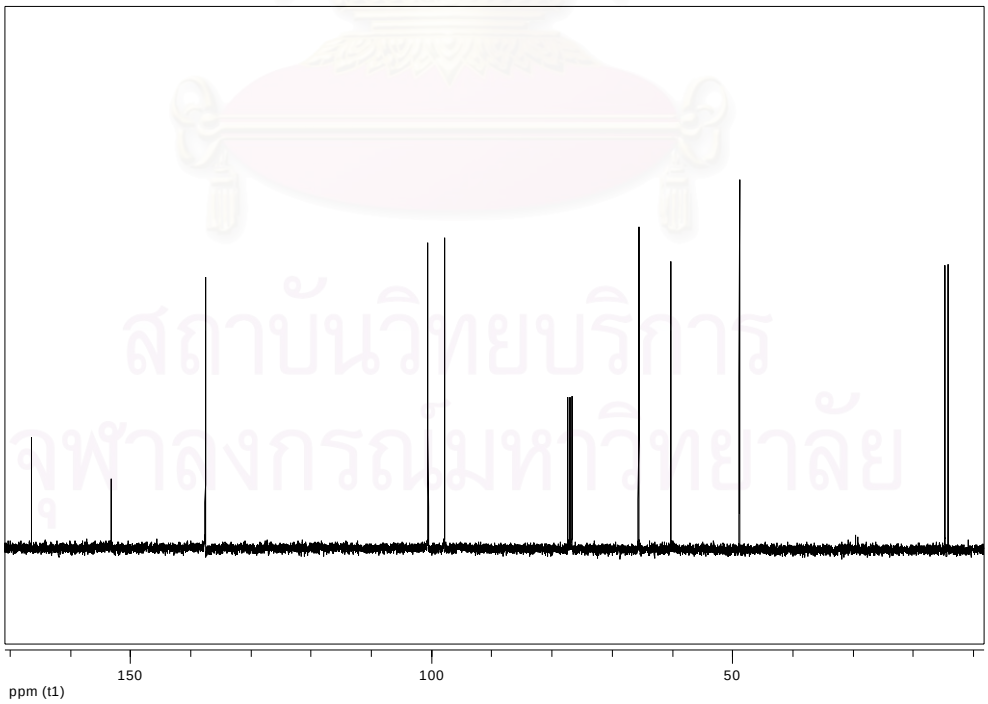


Fig. A.24 The ^{13}C-NMR spectrum of (*E*)-ethyl 3-(5-ethoxy-2-oxooxazolidin-3-yl)acrylate) **47d**

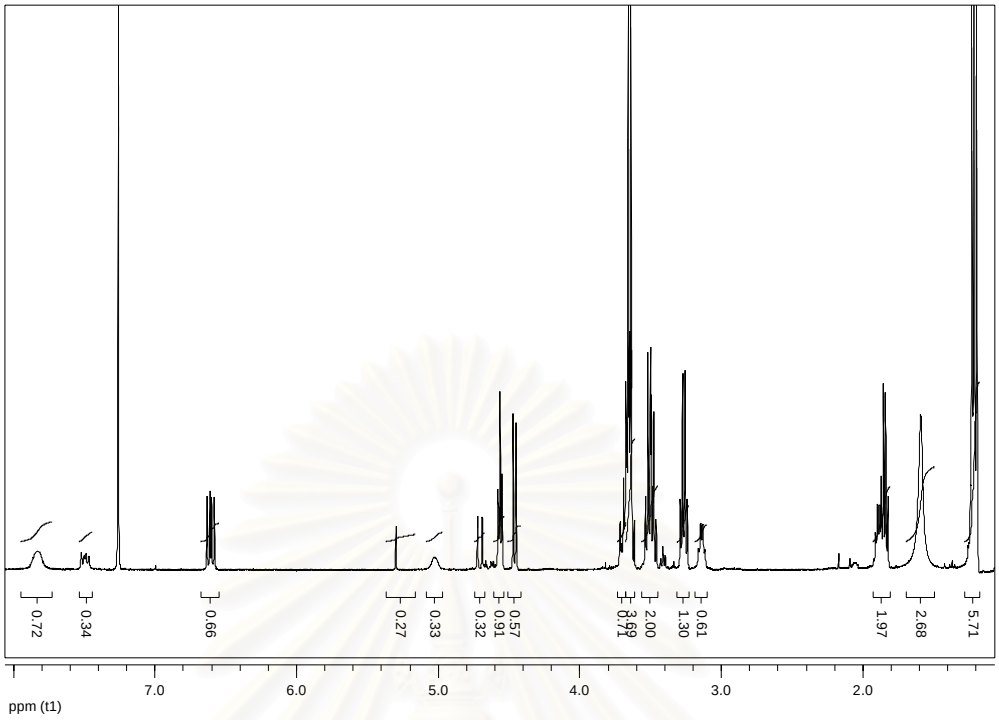


Fig. A.25 The ^{1}H-NMR spectrum of methyl 3-(3,3-diethoxypropylamino)acrylate **43e**

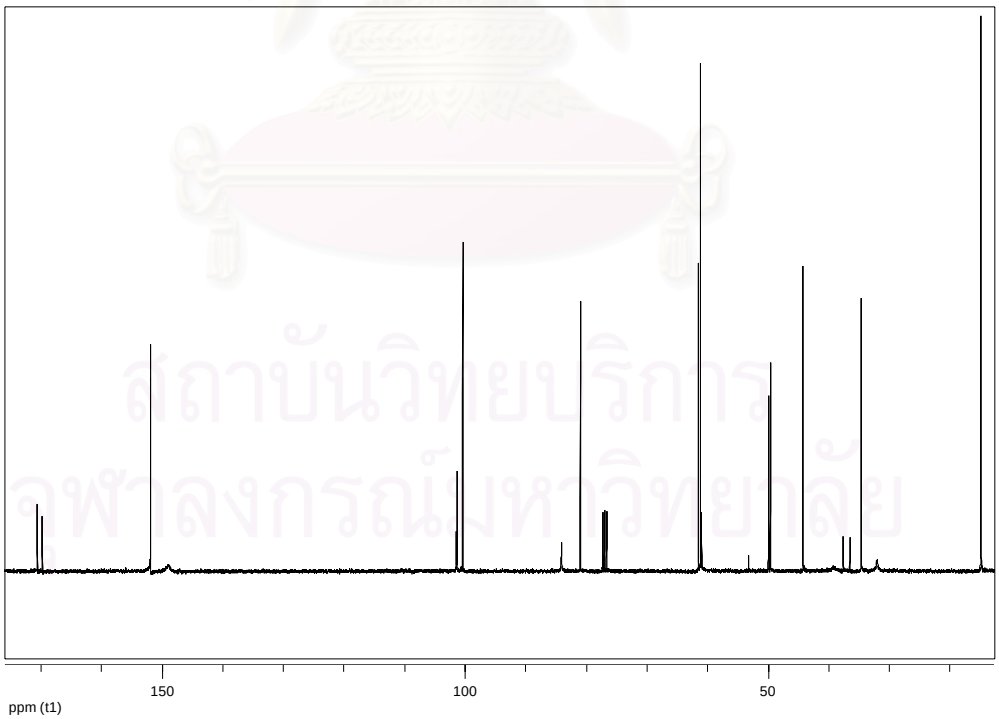


Fig. A.26 The ^{13}C-NMR spectrum of methyl 3-(3,3-diethoxypropylamino)acrylate **43e**

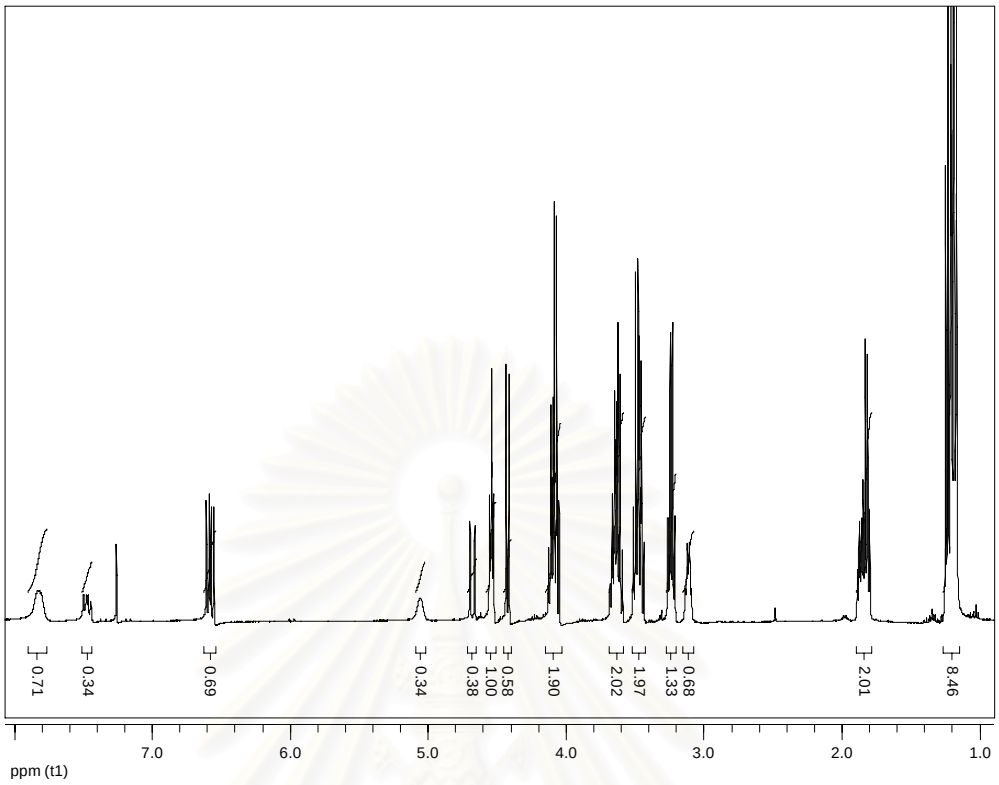


Fig. A.27 The ^{1}H-NMR spectrum of ethyl 3-(3,3-diethoxypropylamino)acrylate **43f**

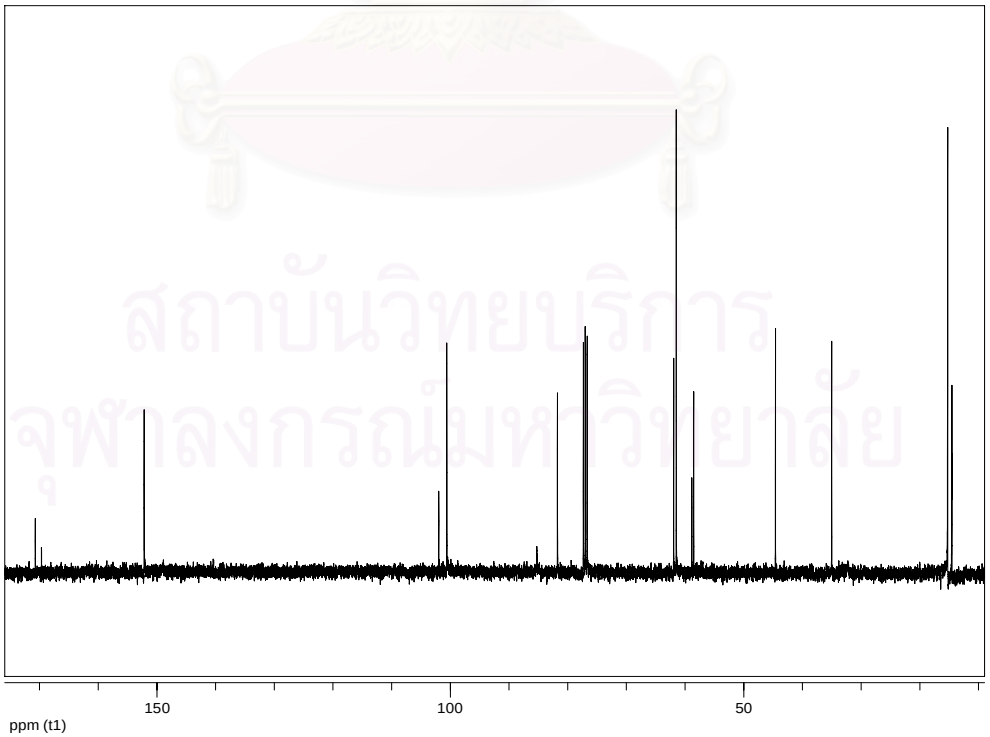


Fig. A.28 The ^{13}C-NMR spectrum of ethyl 3-(3,3-diethoxypropylamino)acrylate **43f**

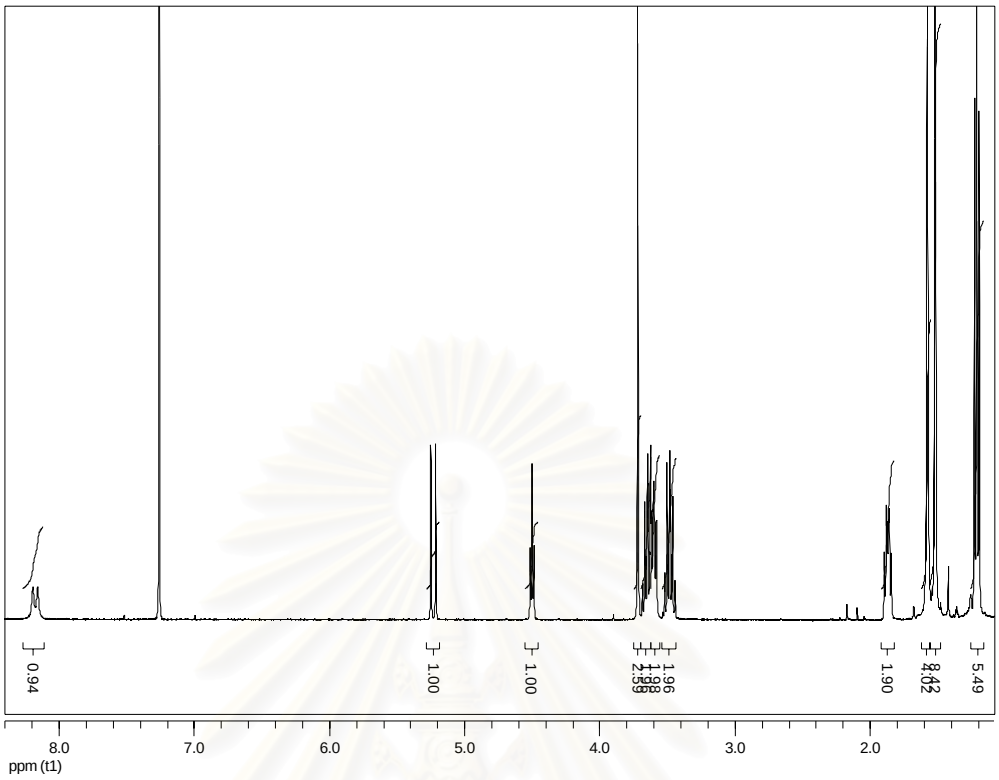


Fig. A.29 The ^{1}H-NMR spectrum of methyl 3-(*tert*-butoxycarbonyl(3,3-diethoxypropyl)amino)acrylate **44e**

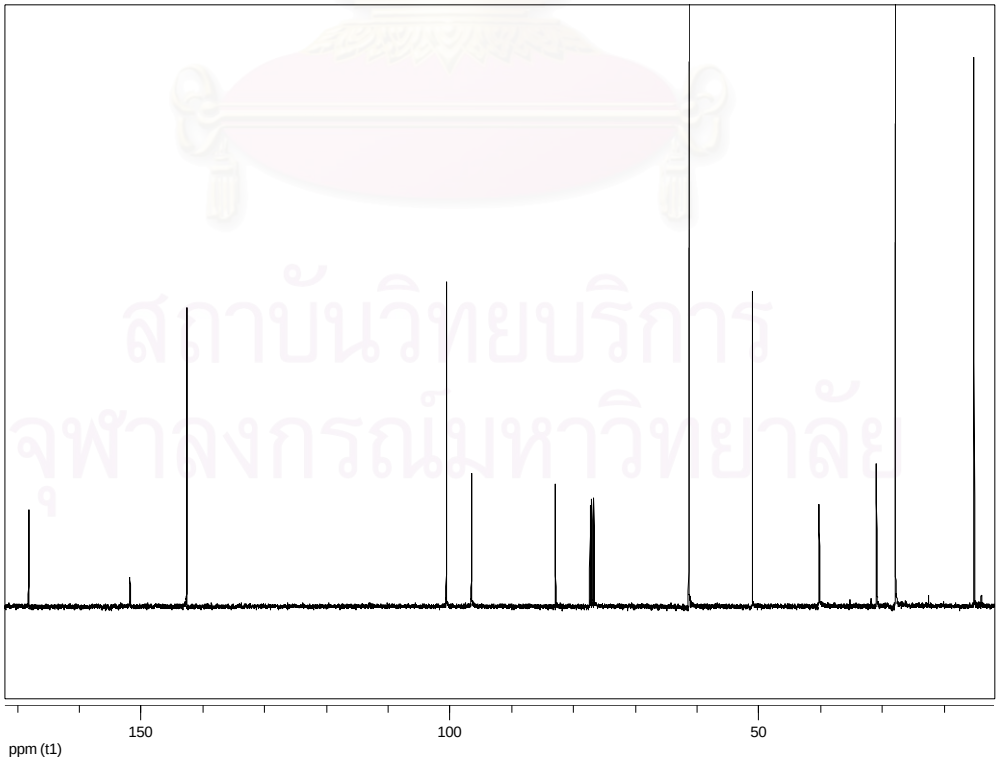


Fig. A.30 The ^{13}C-NMR spectrum of methyl 3-(*tert*-butoxycarbonyl(3,3-diethoxypropyl)amino)acrylate **44e**

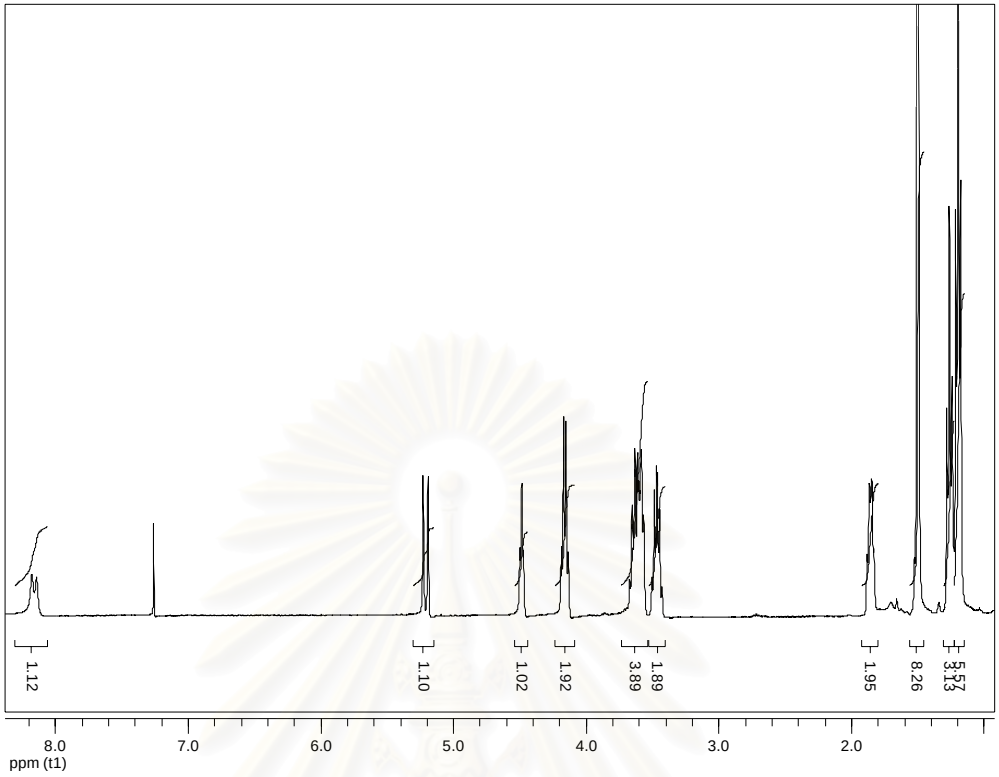


Fig. A.31 The ^{1}H-NMR spectrum of ethyl 3-(*tert*-butoxycarbonyl(3,3-diethoxypropyl)amino)acrylate **44f**

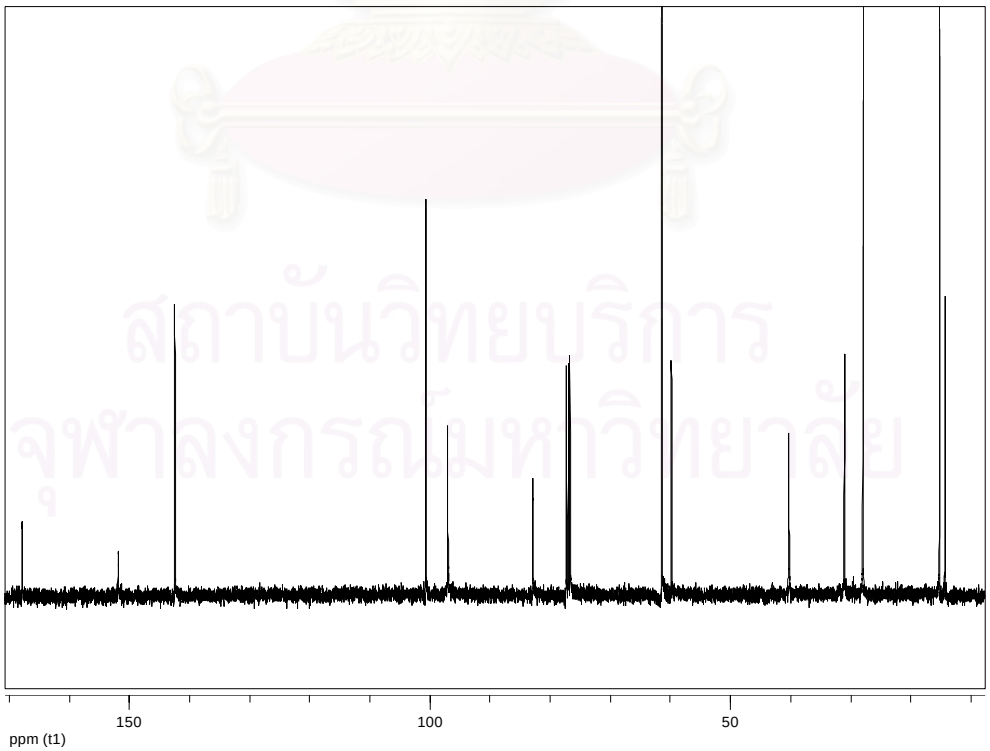


Fig. A.32 The ^{13}C-NMR spectrum of ethyl 3-(*tert*-butoxycarbonyl(3,3-diethoxypropyl)amino)acrylate **44f**

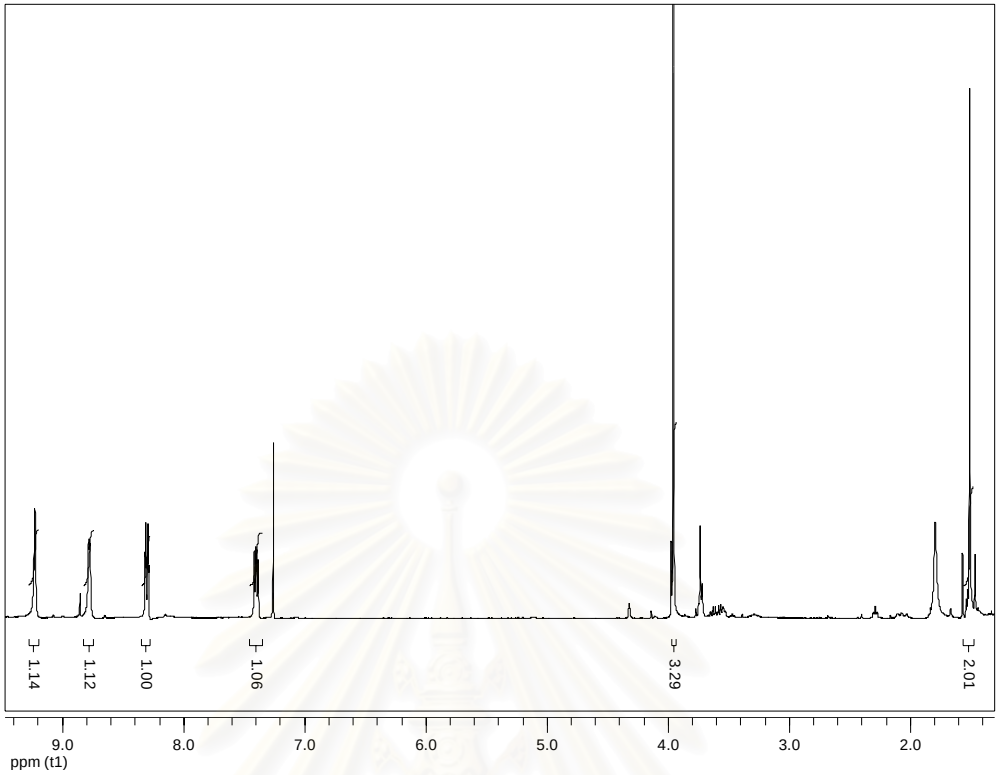


Fig. A.33 The ^{1}H-NMR spectrum of methyl nicotinate **53e**

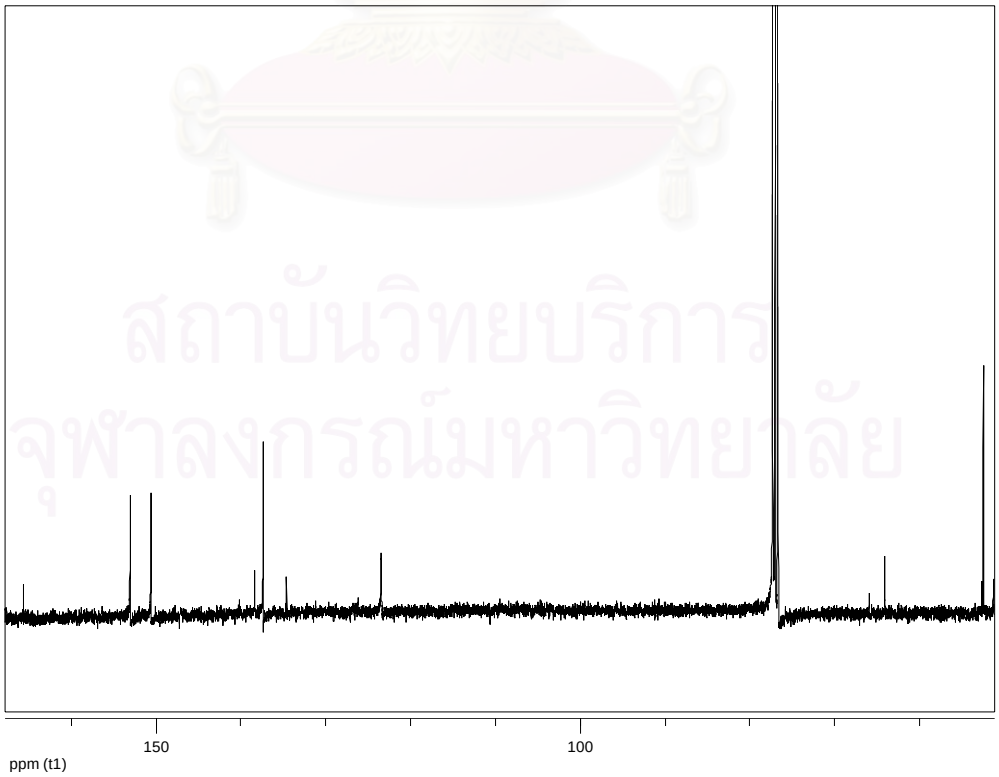


Fig. A.34 The ^{13}C-NMR spectrum of methyl nicotinate **53e**

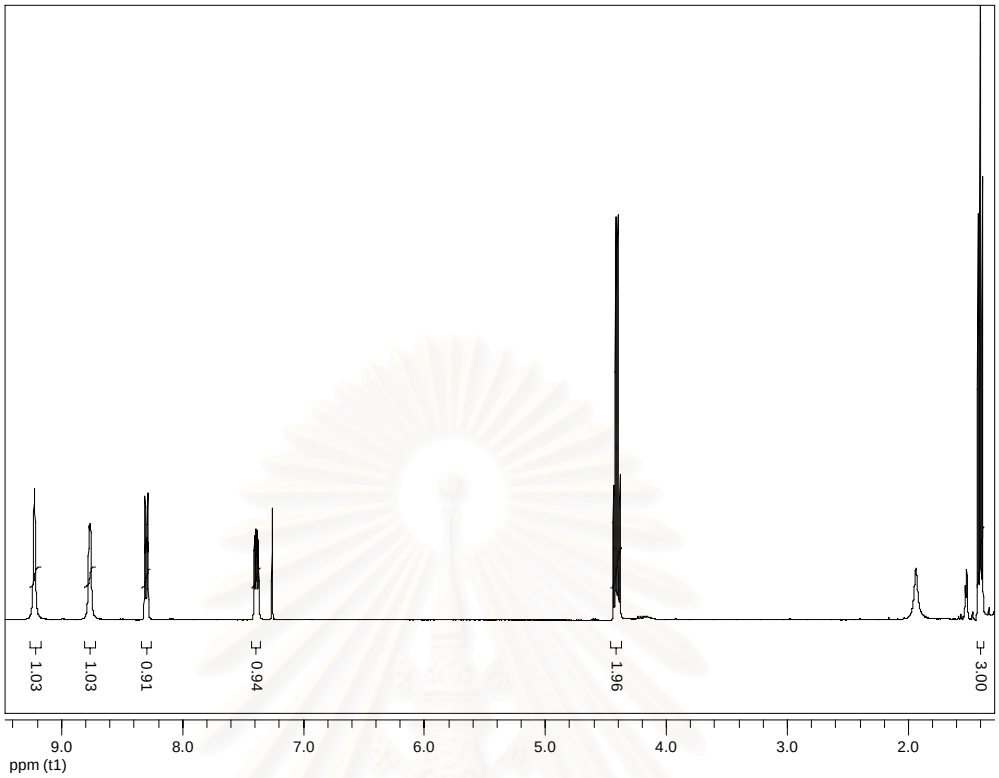


Fig. A.35 The ^{1}H-NMR spectrum of ethyl nicotinate **53f**

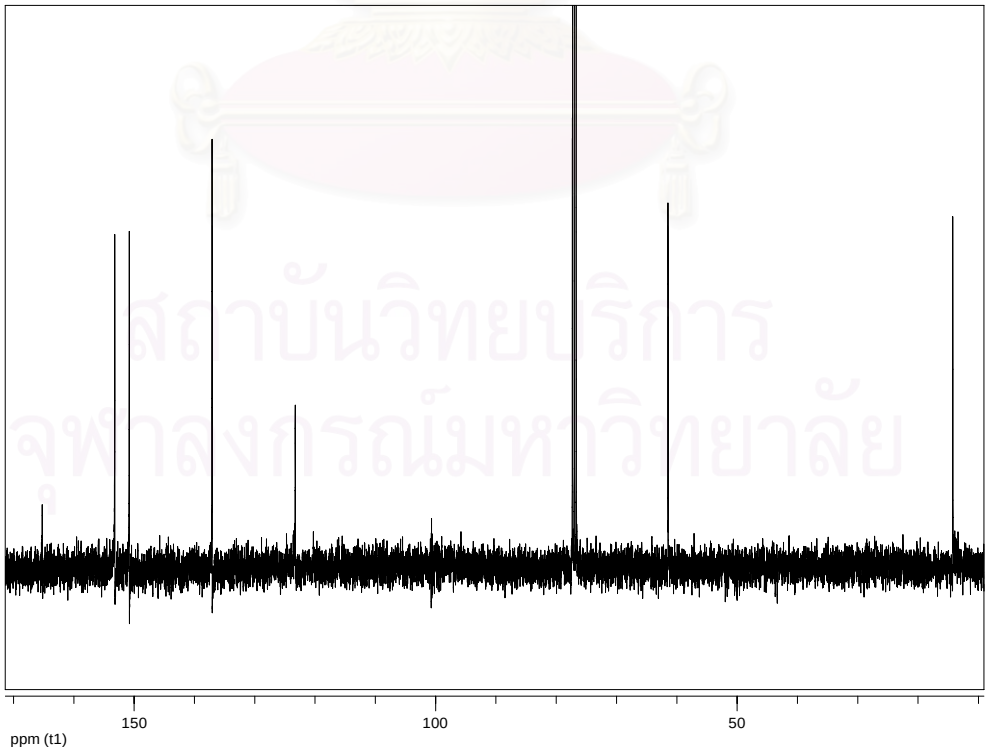


Fig. A.36 The ^{13}C-NMR spectrum of ethyl nicotinate **53f**

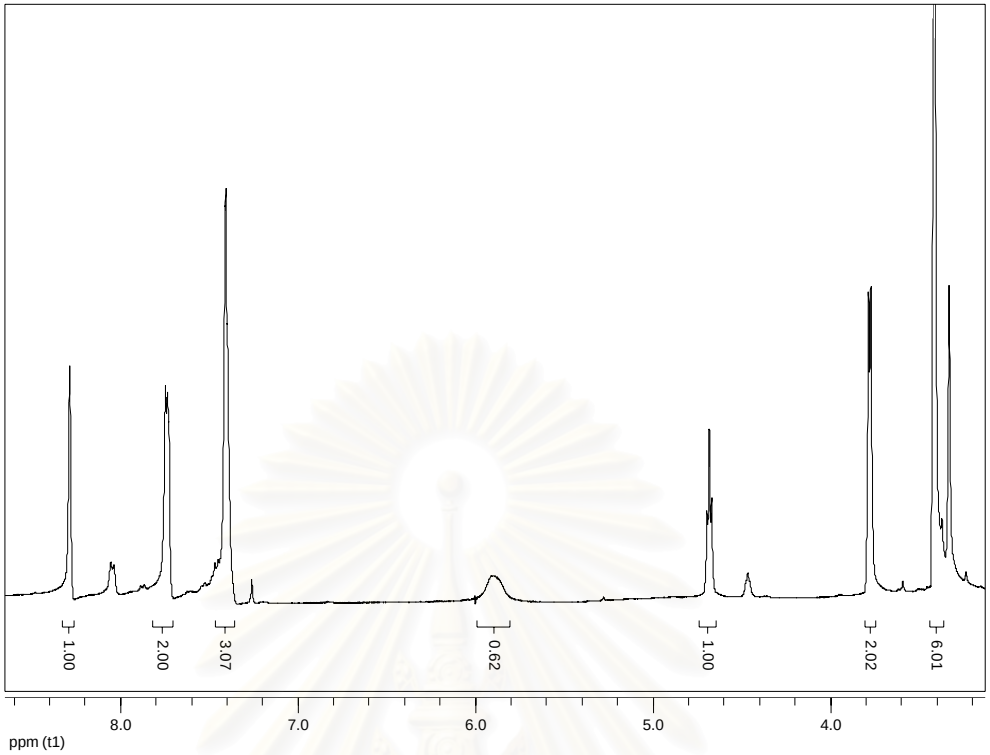


Fig. A.37 The ^{1}H-NMR spectrum of (*E*)-*N*-benzylidene-2,2-dimethoxyethanamine intermediate

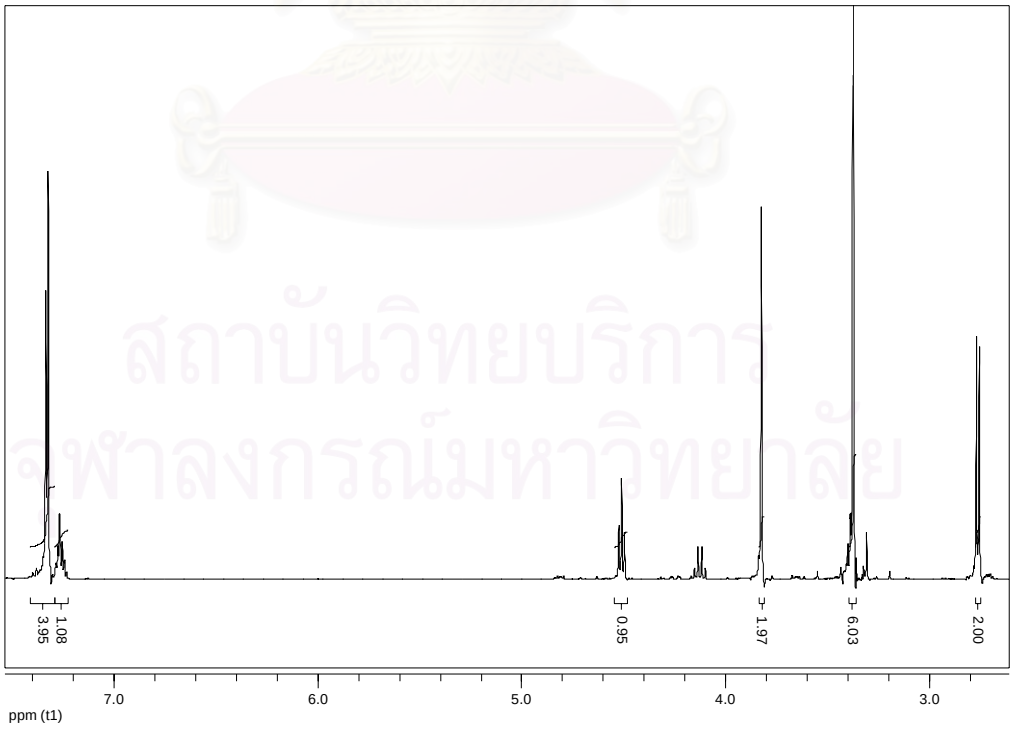


Fig. A.38 The ^{1}H-NMR spectrum of *N*-benzyl-2,2-dimethoxyethanamine **56g**

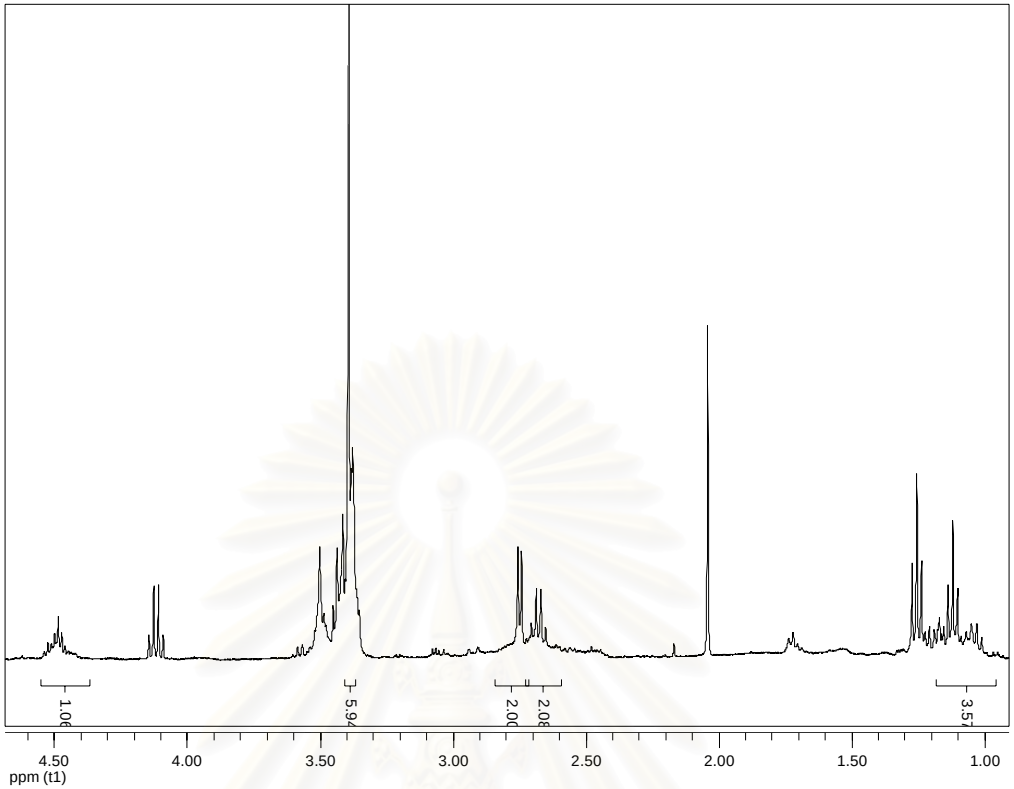


Fig. A.39 The ^{1}H-NMR spectrum of *N*-ethyl-2,2-dimethoxyethanamine **56h**

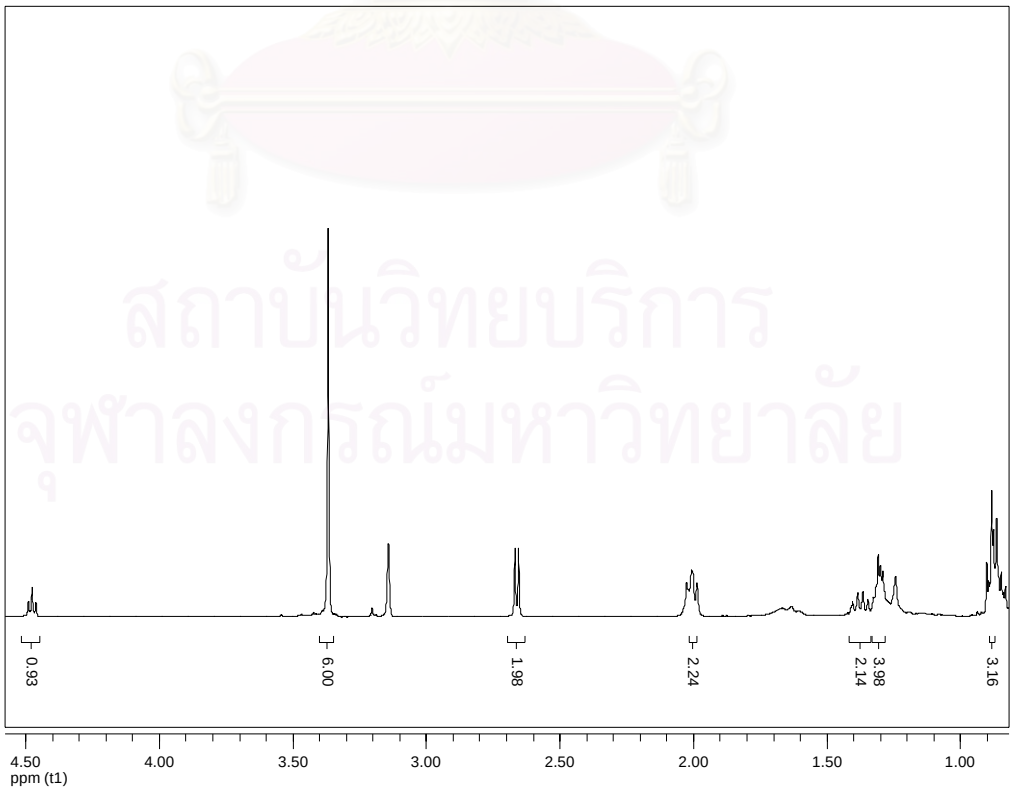


Fig. A.40 The ^{1}H-NMR spectrum of *N*-(2,2-dimethoxyethyl)pentan-1-amine **56i**

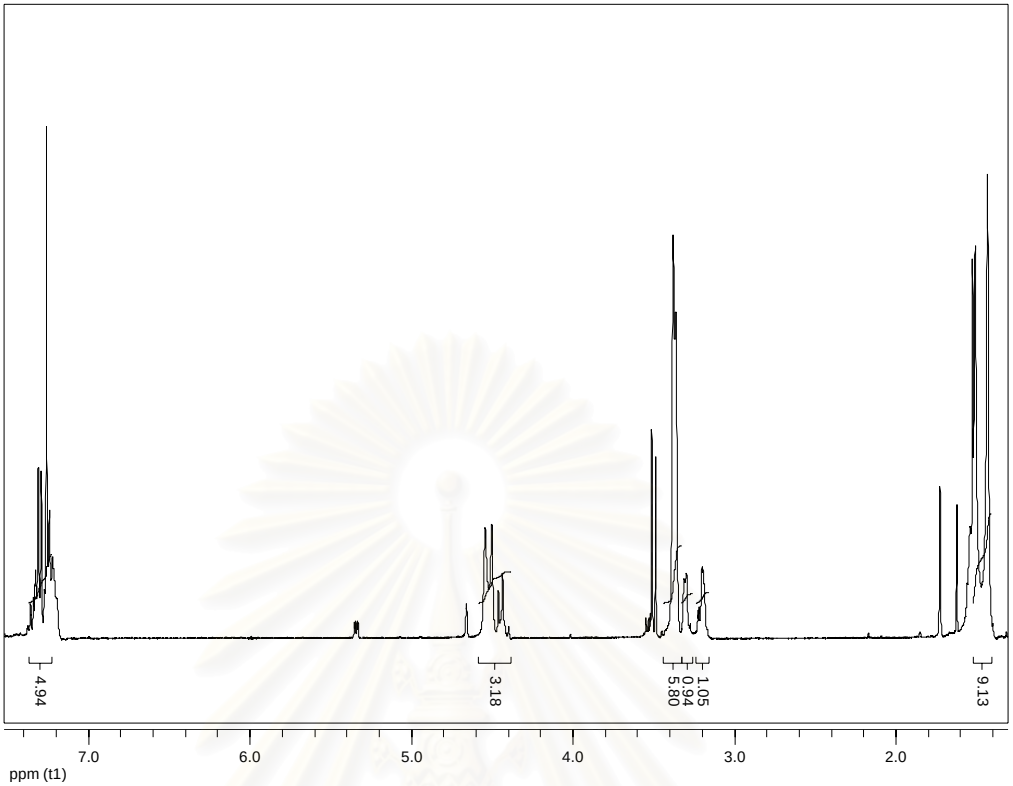


Fig. A.41 The ^{1}H-NMR spectrum of *tert*-butyl benzyl(2,2-dimethoxyethyl) carbamate **57g**

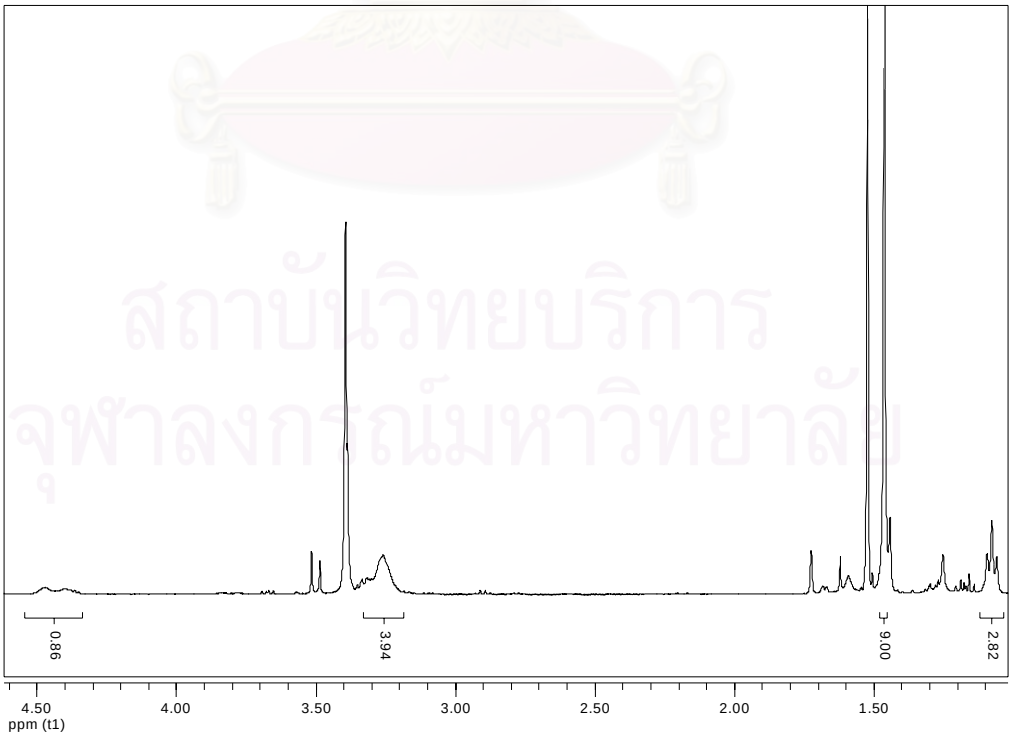


Fig. A.42 The ^{1}H-NMR spectrum of *tert*-butyl 2,2-dimethoxyethyl(ethyl) carbamate **57h**

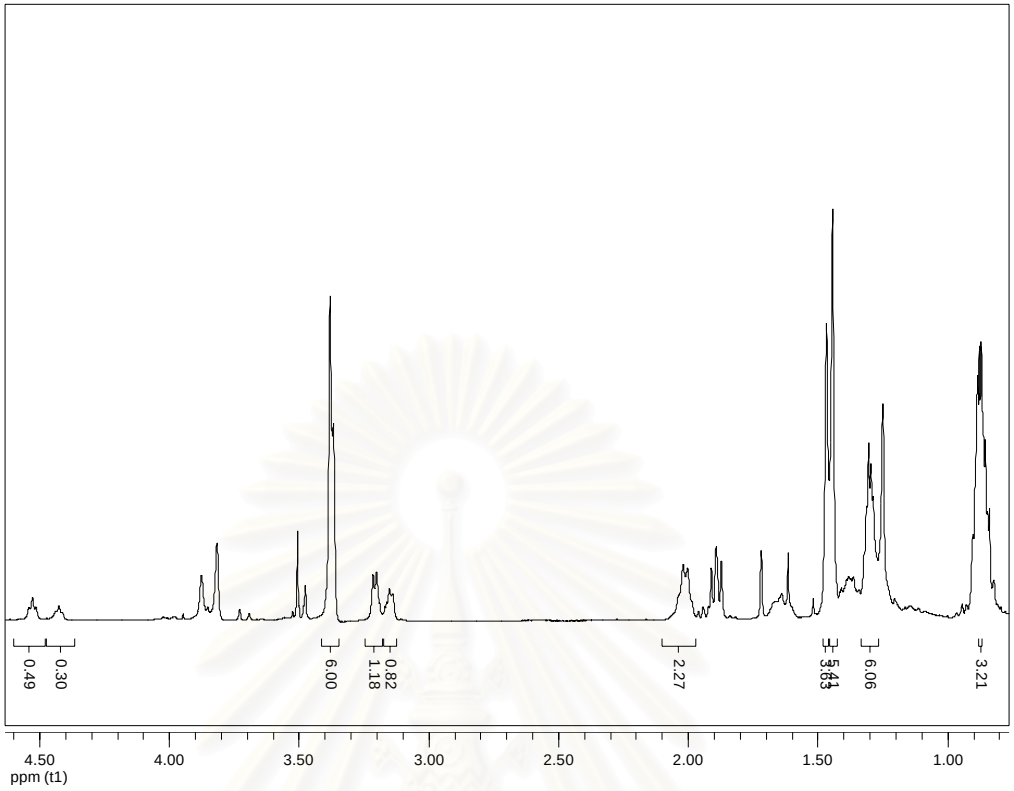


Fig. A.43 The ^{1}H-NMR spectrum of *tert*-butyl 2,2-dimethoxyethyl(pentyl) carbamate **57i**

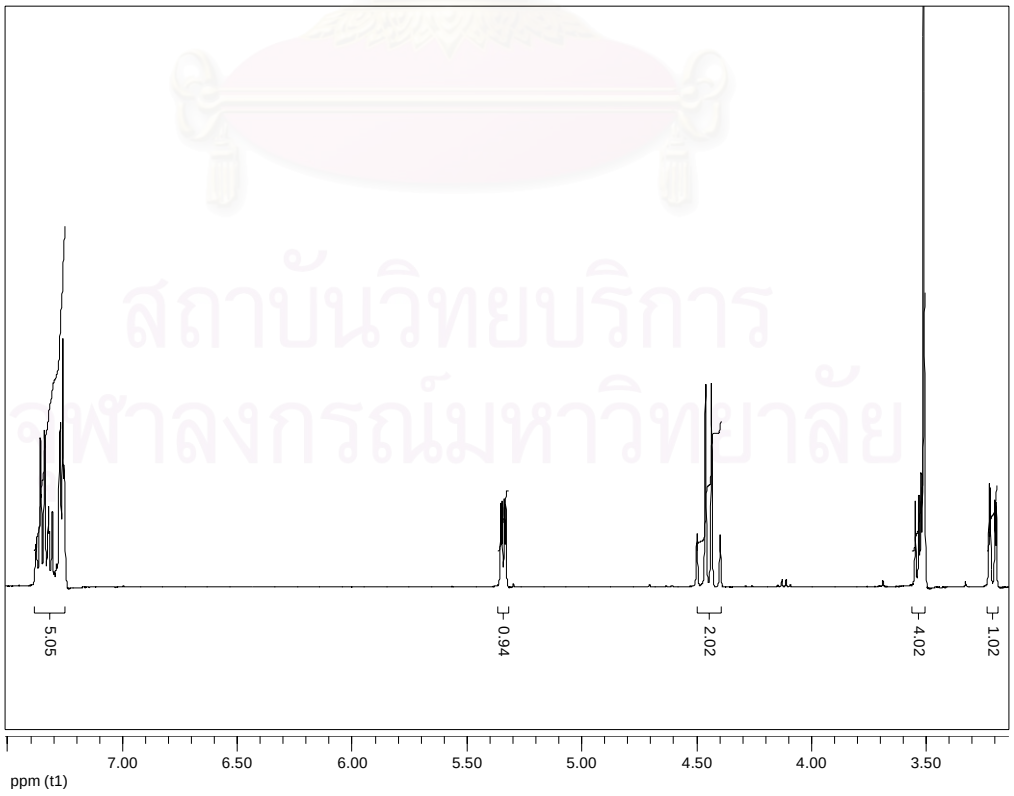


Fig. A.44 The ^{1}H-NMR spectrum of 3-benzyl-5-methoxyoxazolidin-2-one **58g**

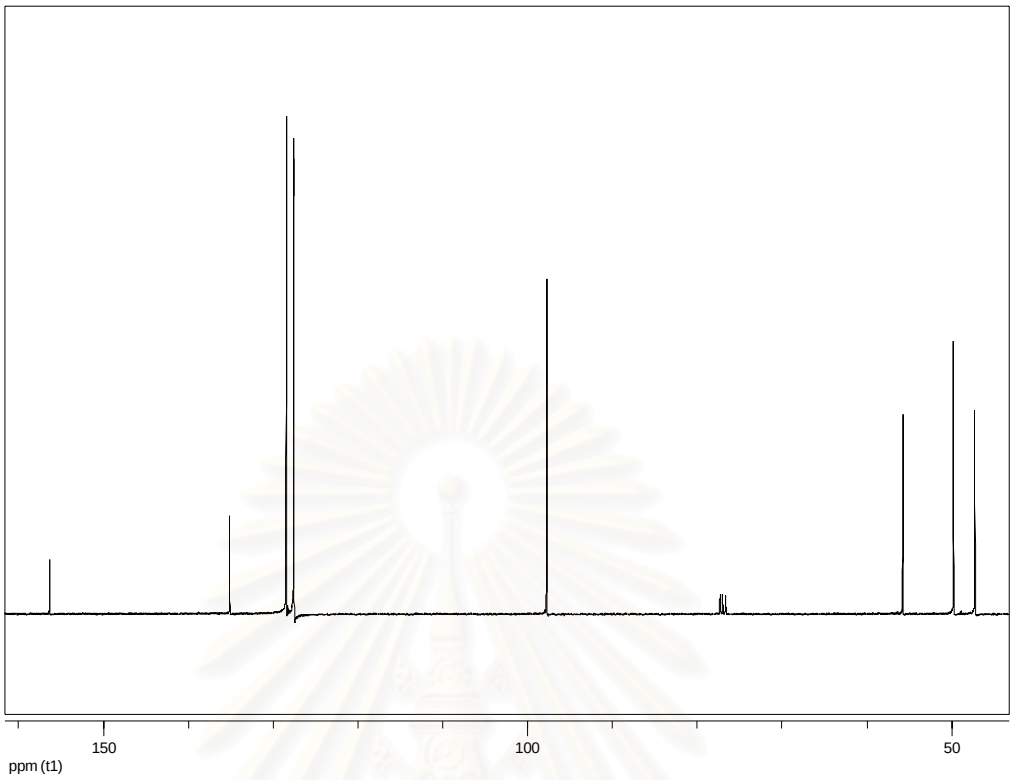


Fig. A.45 The ^{13}C-NMR spectrum of 3-benzyl-5-methoxyoxazolidin-2-one **58g**

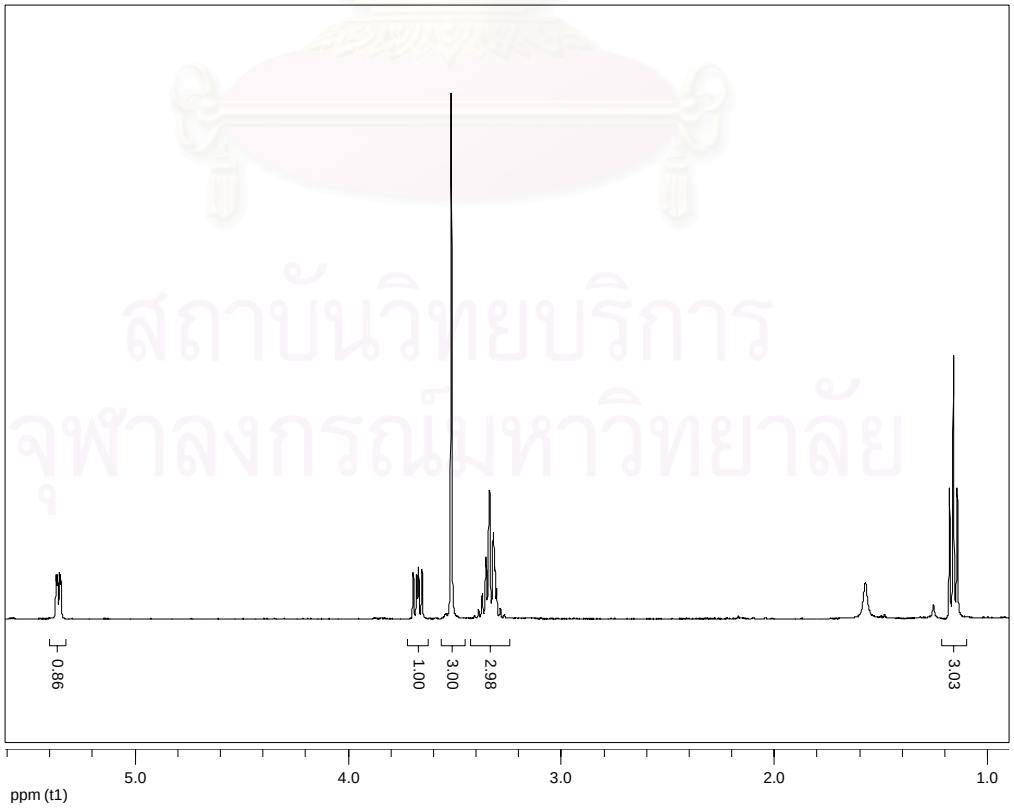


Fig. A.46 The ^{1}H-NMR spectrum of 3-ethyl-5-methoxyoxazolidin-2-one **58h**

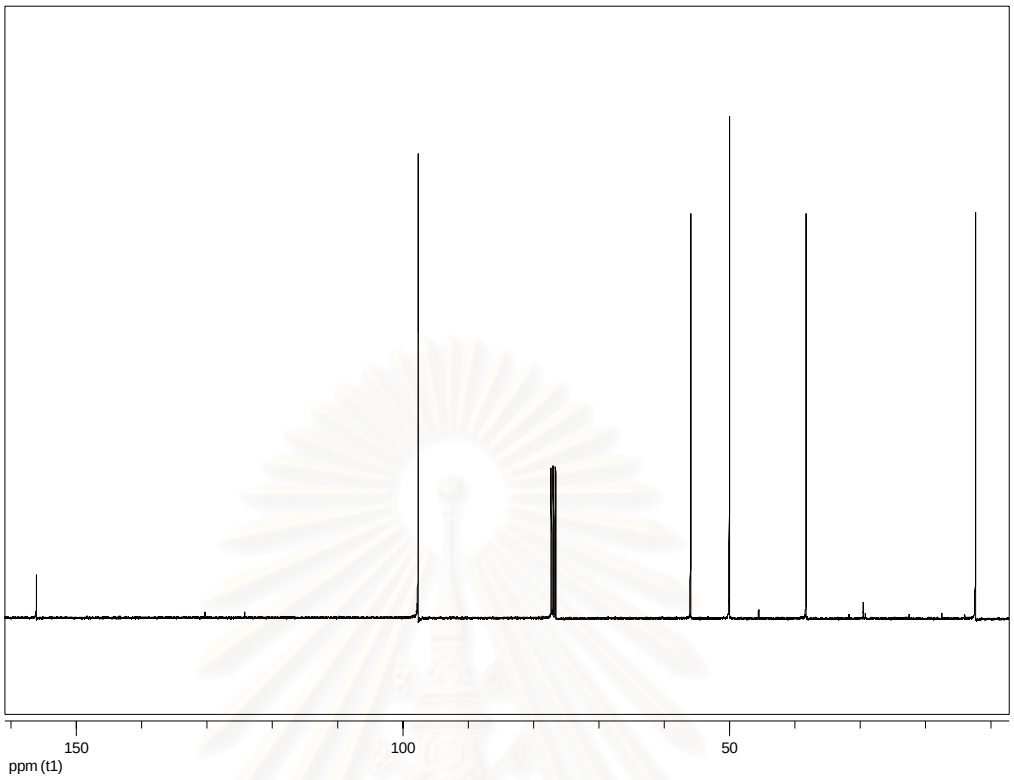


Fig. A.47 The ^{13}C-NMR spectrum of 3-ethyl-5-methoxyoxazolidin-2-one **58h**

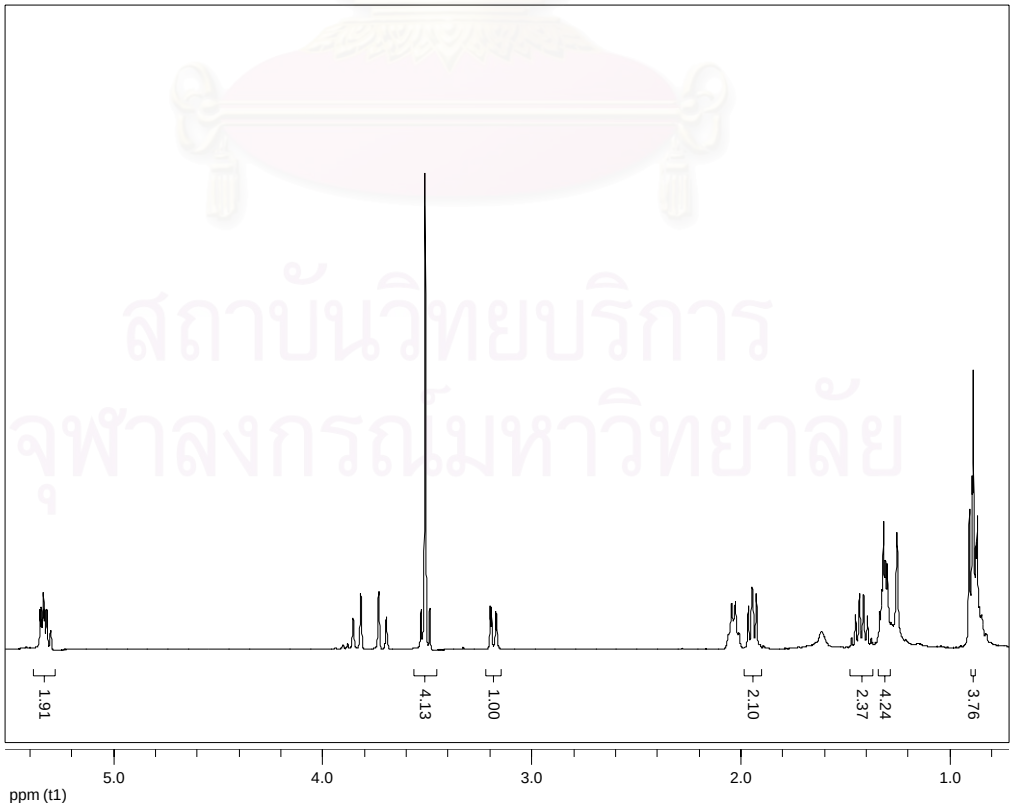


Fig. A.48 The ^{1}H-NMR spectrum of 5-methoxy-3-pentyloxazolidin-2-one **58i**

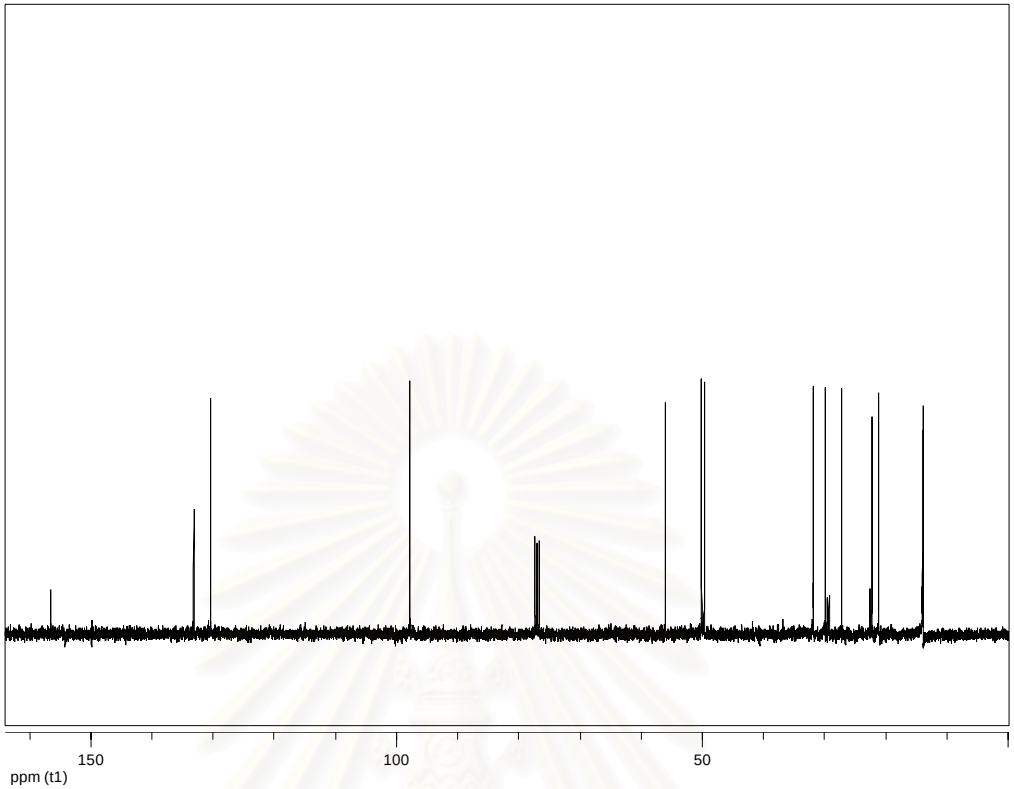


Fig. A.49 The ^{13}C-NMR spectrum of 5-methoxy-3-pentyloxazolidin-2-one **58i**

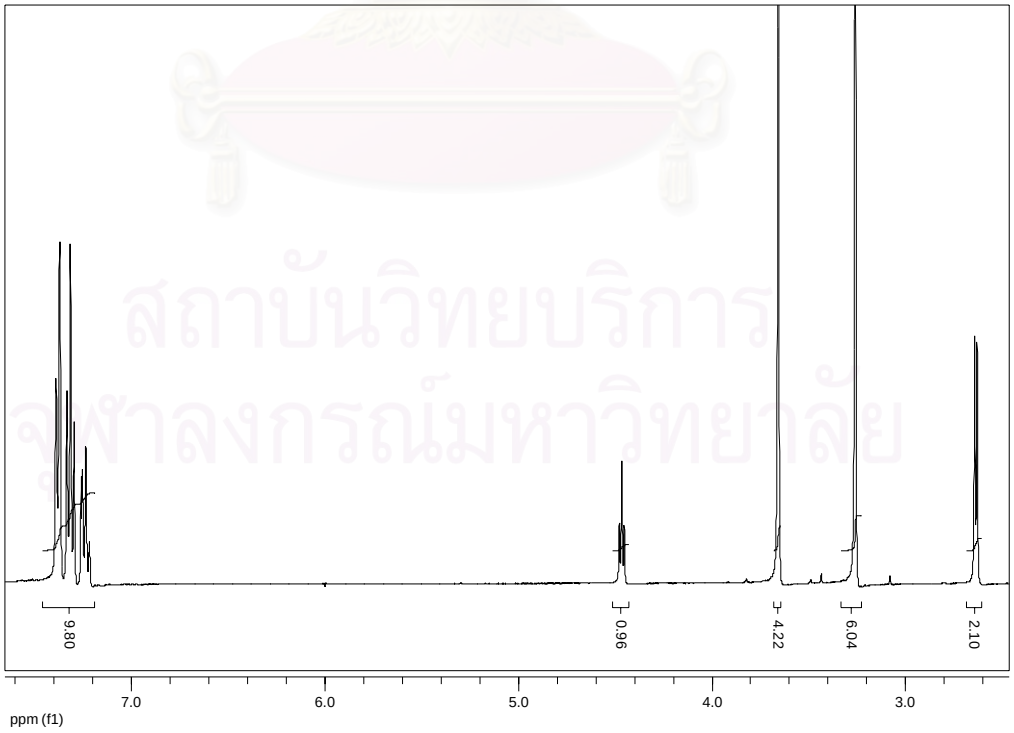
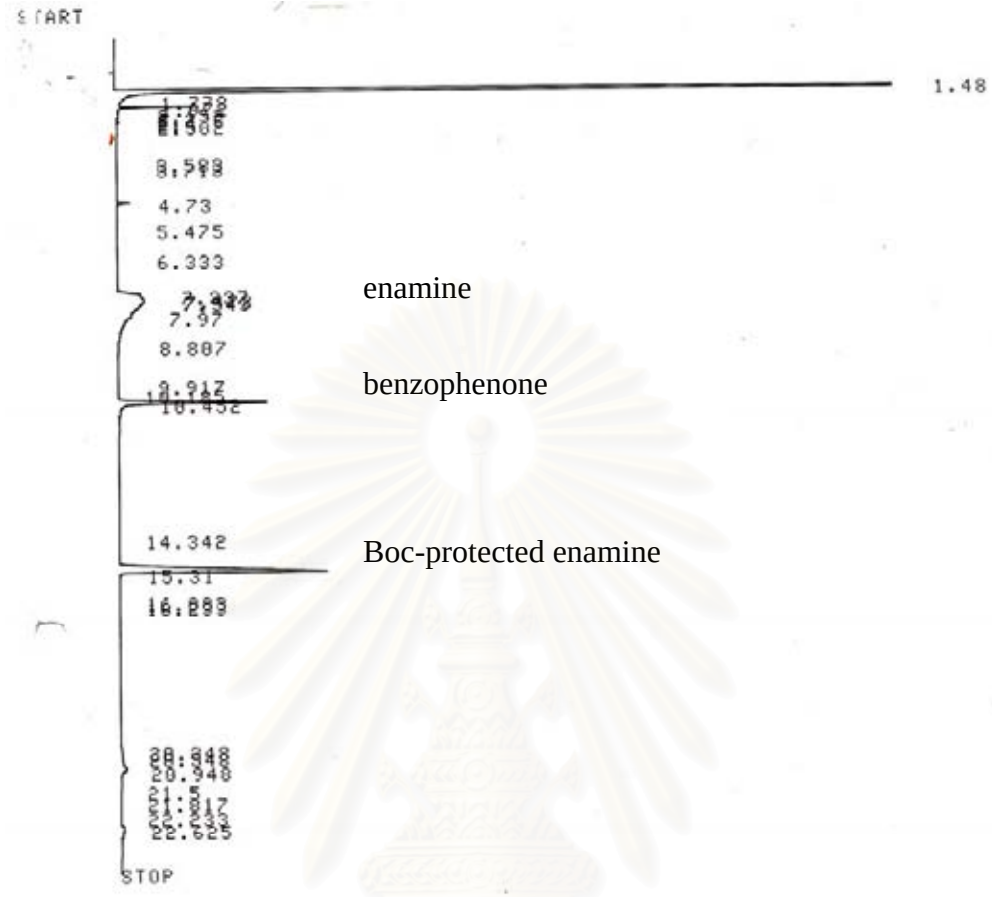


Fig. A.50 The ^{1}H-NMR spectrum of *N*,*N*-dibenzyl-2,2-dimethoxyethanamine **59**



CHROMATOPAC C-R3A FILE 0
SAMPLE NO 0 METHOD 41
REPORT NO 16

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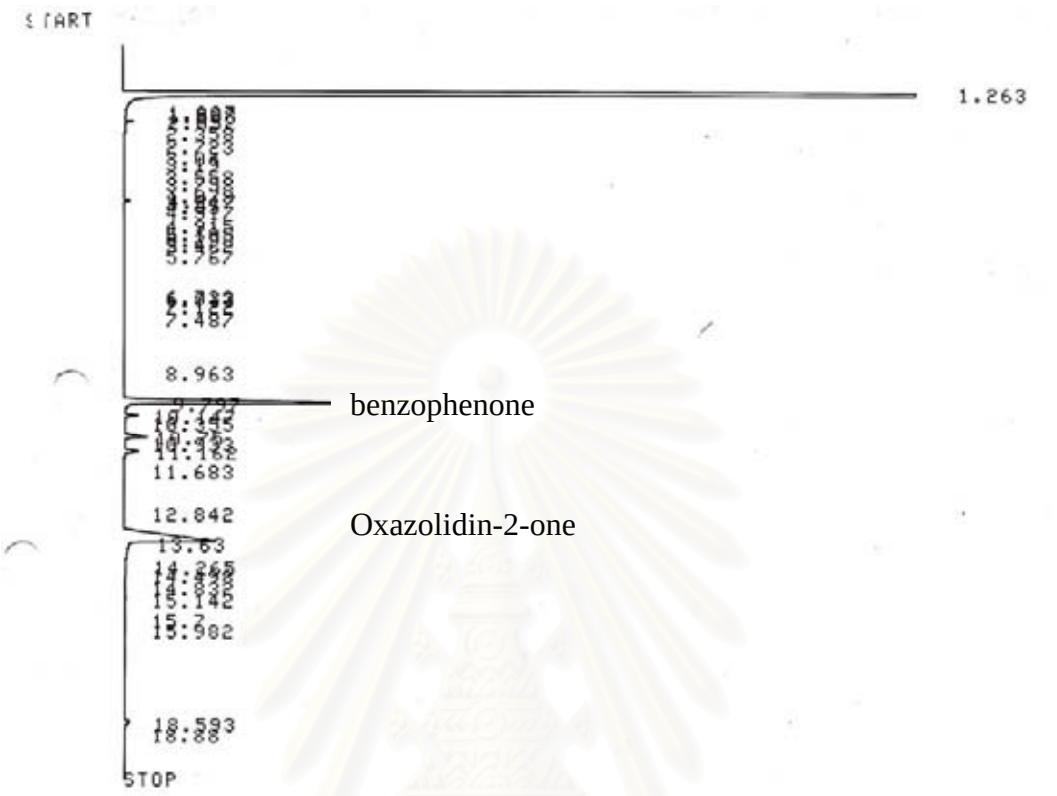
3	4.73	780			0.0602	
4	7.337	2493			0.1924	
5	7.478	4855	V		0.3747	
6	7.543	10640	V		0.8212	
7	7.97	5149	V		0.3974	
8	10.452	14206			1.0963	
9	15.31	30504			2.3541	
10	20.348	631			0.0487	
11	20.548	450	V		0.0347	
12	20.948	2688	SV		0.2075	
13	22.625	1414	V		0.1092	
	TOTAL	1295763			100	

Fig. A.51 The GC chromatogram of the protection of enamine **43b**, using benzophenone (internal standard), temp = room temperature, time = 20 h.



CHROMATOPAC C-R3A FILE 0
SAMPLE NO 0 METHOD 41
REPORT NO 8

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	2.052	310	T		0.0191	
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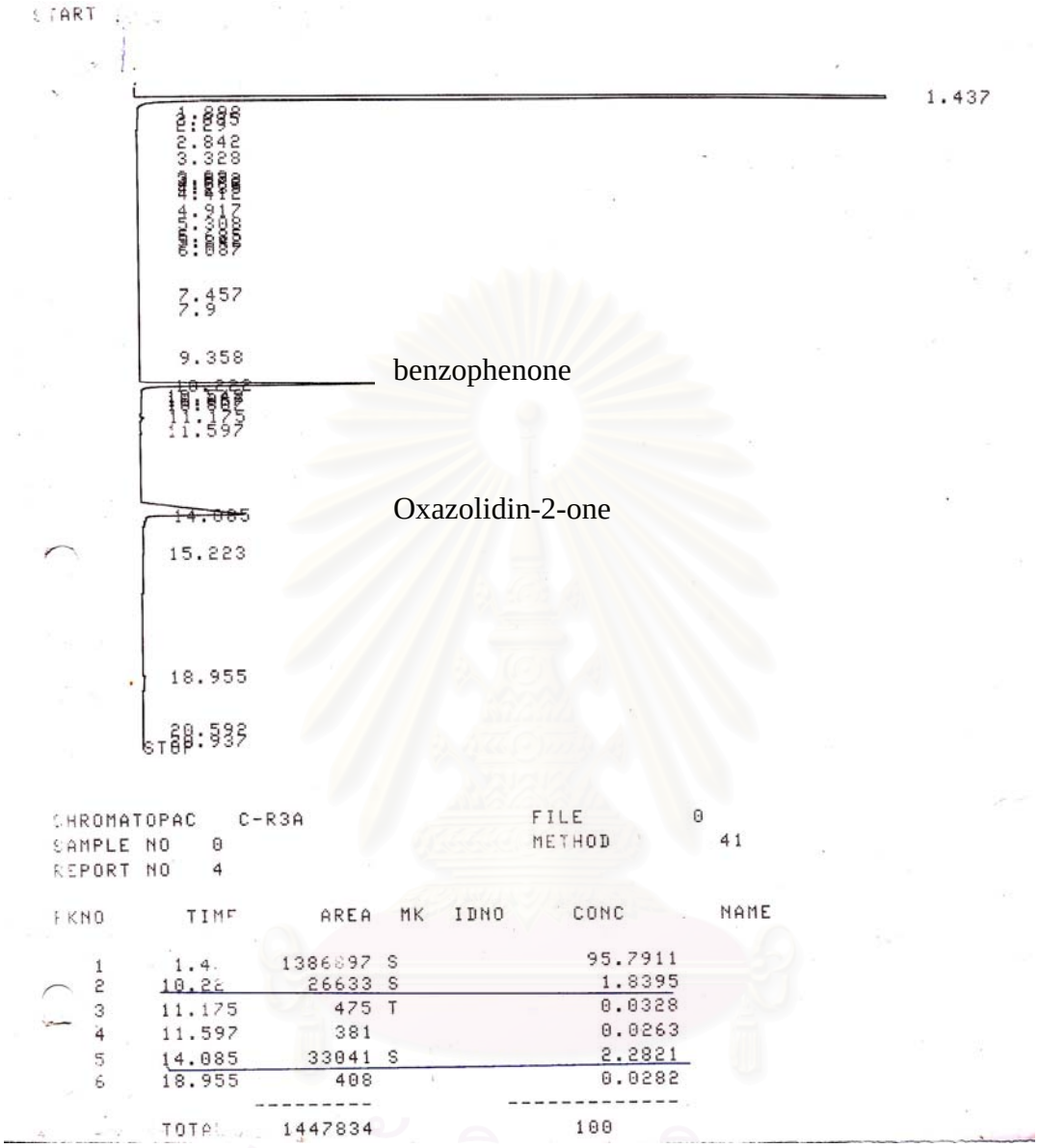
4	9.292	29228			1.7972	
5	10.147	1204	V		0.0739	
6	10.75	2346	V		0.1441	
7	11.162	1595	V		0.0979	
8	13.63	24010	S		1.4742	
9	18.593	849	S		0.0521	
	TOTAL	1628697			100	

Fig. A.52 The GC chromatogram of cyclisation of enamide **44b,** using benzophenone (internal standard), temp = room temperature, time = 20 h.



CHROMATOPAC C-R3A FILE 0
SAMPLE NO 0 METHOD 41
REPORT NO 4

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3	11.175	475	T		0.0328	
4	11.597	381			0.0263	
5	14.085	33041	S		2.2821	
6	18.955	408			0.0282	
	TOTAL	1447834			100	

Fig. A.53 The GC chromatogram of cyclisation of enamide **44b,** using benzophenone (internal standard), temp = reflux temperature, time = 2 h.

VITA

Miss Kunlayanee Hansuthirakul was born on January 17, 1980 in Bangkok, Thailand. She finished high school at St. Joseph Bangna, 10270, Samutprakarn in 1999. She received a Bachelor's Degree of Science, in Department of Chemistry, Kasetsart University, Bangkok, in 2003. In the same year she was accepted as a graduate student in Program of Petrochemisrty and Polymer Science, Chulalongkorn University, Bangkok. She received a Master's Degree Program of Science in Polymer Science, in 2005.