การสังเคราะห์ออกซาโซลิดิโนนผ่านการจัดเป็นวงภายในโมเลกุลด้วยการเหนี่ยวนำแบบกรดและแบบแฮโล

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SYNTHESIS OF OXAZOLIDINONES VIA ACID- AND HALO-INDUCED INTRAMOLECULAR CYCLIZATION

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ธนกฤต จันทรา: การสังเคราะห์ออกซาโซลิดิโนนผ่านการจัดเป็นวงภายในโมเลกุลด้วยการเหนี่ยวนำแบบกรดและแบบแฮโล (SYNTHESIS OF OXAZOLIDINONES VIA ACID- AND HALO-INDUCED INTRAMOLECULAR CYCLIZATION) อ. ที่ปรึกษาวิทยานิพนธ์หลัก : อ.ดร.อนวัช อาชวาคม, อ. ที่ปรึกษาวิทยานิพนธ์ร่วม : รศ. ดร.มงคล สุขวัฒนาสินิทธิ์, 135 หน้า.

งานวิจัยนี้ได้พัฒนาวิธีการใหม่ในการสังเคราะห์สารประกอบ 2-ออกซาโซลิดิโนน สองวิธี วิธีการแรกเป็นการจัดเป็นวงภายในโมเลกุลโดยของอนุพันธ์บีตาเอ็นแอริลคาร์บามิลอิ-พอกไซด์การเหนี่ยวนำด้วยกรด ด้วยการทำปฏิกิริยาอนุพันธ์บีตาเอ็นแอริลคาร์บามิลอิพอกไซด์กับกรดไตรฟลูออโรอาซิติกสามารถสังเคราะห์แอโรมาติกออกซาโซลิดิโนนในเปอร์เซ็นต์ผลิตภัณฑ์ที่ดีมาก โดยกลไกการเกิดปฏิกิริยาเกิดจากออกซิเจนอะตอมของหมู่ปกป้องคาร์บอ-นิลเข้าชนที่อิพอกไซด์คาร์บอนภายใต้ภาวะที่เป็นกรดและปิดวงตามรูปแบบ 5-เอกโซ-เทต ได้อนุพันธ์ 2-ออกซาโซลิดิโนนที่ต้องการ นอกจากนี้ยังสามารถใช้วิธีการนี้เพื่อการสังเคราะห์ยาแก้โรคซึมเศร้า โทลอกซาโทน และ ยาปฏิชีวนะต้านแบคทีเรียชนิดแกรมบวก ลิเนโซลิดได้ วิธีการที่สองเกี่ยวข้องกับการจัดเป็นวงภายในโมเลกุลด้วยการเหนี่ยวนำของแฮโล ของเทอร์-เชียรรีบิวทิลแอลริล คาร์บาเมตโดยการใช้แฮโลจีเนติ้งรีเอเจนต์หลายชนิด ทำให้สามารถสังเคราะห์อนุพันธ์ออกซาโซลิดิโนนที่ถูกแทนที่ด้วยคลอโร โบรโม หรือ ไอโอโด หนึ่งหรือสองอะตอมได้สำเร็จ โดยปฏิกิริยาสามารถเลือกเกิดให้ผลิตภัณฑ์ออกซาโซลิดิโนนที่มีหรือไม่มีการแทนที่ของแฮโลเจนอะตอมที่ตำแหน่ง*พารา*บนวงแอริล ได้อย่างจำเพาะ เมื่อเลือกใช้แฮโลจีเน-ติ้งรีเอเจนต์อย่างเหมาะสม

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THANAKRIT CHANTRA : SYNTHESIS OF OXAZOLIDINONES VIA ACID- AND HALO-INDUCED INTRAMOLECULAR CYCLIZATION. THESIS ADVISOR : ANAWAT AJAVAKOM, Ph.D., THESIS CO-ADVISOR : ASSOC. PROF. MONGKOL SUKWATTANASINITT, Ph.D., 135 pp.

Two novel synthetic pathways toward 2-oxazolidinone derivatives were developed. The first pathway is the acid-induced intramolecular cyclization of β-(*N*-arylcarbamyl) epoxides. Simple treatment of a β-(*N*-arylcarbamyl)epoxide with trifluoroacetic acid exclusively gave the corresponding *N*-aryl-2-oxazolidinone in excellent yield. Mechanistically, the Boc carbonyl oxygen intramolecularly attacks the acid-activated epoxide ring in *5-exo-tet* fashion to form the desired oxazolidin-2-ones. Toloxatone, a well known antidepressant, and Linezolid (Zyvox®) antibacterial medicine were successfully synthesized from this cyclization method. The second synthetic pathway involves halo-induced cyclization of *tert*-butyl allyl(phenyl)carbamate. Various halogenated reagents were evaluated for reaction optimization. The synthesis of oxazolidinone derivatives containing one or two halogen atoms were successfully established for all chloro, bromo and iodo compounds. Either unsubstituted-aryl oxazolidinone or *p*-halo-substituted-aryl oxazolidinone were selectively produced with appropriate choice of halogenated reagents.

Department : Chemistry	Student's Signature .....
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LIST OF ABBREVIATIONS

Ar	Aromatic
$BF_3 \cdot OEt_2$	boron trifluoride diethyletherate
Boc	*tert*-butoxy carbonyl
Boc_2O	di-*tert*-butyl dicarbornate
br	broad (NMR)
Bu	butyl
^{13}C-NMR	Carbon nuclear magnetic resonance
cm	Centimeter
^{o}C	Degree Celsius
d	doublet (NMR)
dd	doublet of doublet (NMR)
ddd	doublet of doublet of doublet(NMR)
dt	doublet of triplet (NMR)
DMF	*N*,*N*'-dimethyl formamide
DMAP	4-(dimethyl amino)pyridine
DuP	DuPont's compound (medicine)
%ee	percent enantiomeric effect
equiv.	equivalent
EtOAc	ethyl acetate
FID	flame ionization detector
g	Gram
GC	Gas Chromatography
h	hour
^{1}H-NMR	Proton nuclear magnetic resonance
HPLC	High Performance Liquid Chromatography
Hz	Hertz
J	Coupling constant
JC	Jacobsen catalyst
LiHMDS	lithium bis(trimethylsilyl)amide

m	multiplet (NMR)
M	Molar
MAOI	monoamine oxidase inhibitor
Me	methyl
MHz	megaherz
min	minute
mL	Millilitre
mmol	Millimole
MS	mass spectroscopy
m/z	Mass per charge
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
m-CPBA	*meta* chloroperbenzoic acid
nm	Nanometer
NMO	*N*-methyl morpholine n-oxide
MRSA	methicillin resistant *Staphylococcus aureus*
MRSE	methicillin resistant *Staphylococcus epidermitis*
OAc	acetate
OD	OD type chiral column
OJ	OJ type chiral column
OMe	methoxy
ppm	Part per million
R	R configuration
rfx.	reflux
rt	room temperature
S	S configuration
t	tertiary
t	triplet (NMR)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
VRE	Vancomycin resistant

CHAPTER I

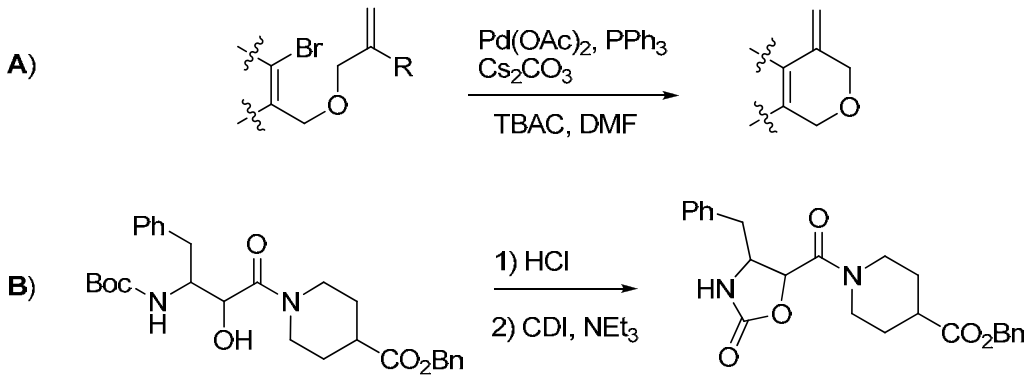
INTRODUCTION

Organic compounds can be commonly divided into two types depending on the structural dissimilarity, acyclic and cyclic compounds. The cyclic compound is a series of carbon atoms and/or other atoms connected together to form a ring structure. Carbocyclic compounds are a cyclic compound containing only carbon atoms in the ring structure, while heterocyclic compounds are a cyclic organic compound containing at least one atom of carbon and at least one atom of other element usually sulfur, nitrogen or oxygen within the ring structure. The heterocyclic compound, probably the largest and the most varied class of organic compounds, possesses numerous attractive properties. Mostly, a class of this compound has much potential as bioactive medicines in clinical therapy [1-4], catalysts in asymmetric synthesis [5-8], and polymers [9-11]. Because of its importance, a great deal of effort has been expanded in attempts to develop the new methodologies based on intramolecular cyclization reaction.

1.1 Intramolecular cyclization

Recently, the construction of heterocyclic compound *via* cyclization has played a considerable role in organic chemistry for many years. In general, there are various reactions, which can be used for the synthesis of heterocyclic compounds such as Hetero-Diels-Alder cycloaddtion reaction [12], and intramolecular cyclization [13]. The intramolecular cyclization is one of the most important reactions which can be commonly used for the preparation of this type of compounds. For example, pyrans, the six-membered oxygenated heterocycle accommodated as a usual moiety in natural products [14], can be prepared from the intramolecular cyclization of an oxygenated precursor [15] (Scheme1.1A). A five-membered ring heterocyclic oxazolidinone, also often found in various natural products [16], can be potentially

synthesized from N-C-O precursor [17] (Scheme 1.1B). Focusing on the intramolecular cyclization, metal mediated catalysts [18], radical initiator [19], bases [20], and acids [21] have been used for inducing intramolecular cyclization reaction.



Scheme 1.1 Preparation of pyrans and oxazolidinone from oxygenated and N-C-O precursor

The rule of ring-forming reaction

Ring-forming reactions are important and common process in organic chemistry. In 1976, Jack E. Balwin [22-23], has established simple rules for ring closure useful for organic chemists in planning syntheses. He described a ring forming process with the prefix *exo*, when nucleophilic attacks an electrophile and electrons shift away from the ring or prefix *endo*, if electrons stay within the ring (Scheme 1.2). In addition, a numerical prefix is used to indicate the ring size, and the suffixes *tet*, *trig*, and *dig* refer to geometry of the carbon atom accepter undergoing the ring-closure reaction, tetrahedral (sp^3), trigonal (sp^2), and digonal (*sp*) respectively.

Tetrahedral Systems

a) 3 to 7-*exo-tet* are all favoured.

b) 5 to 6-*endo-tet* are disfavoured.

Trigonal Systems

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

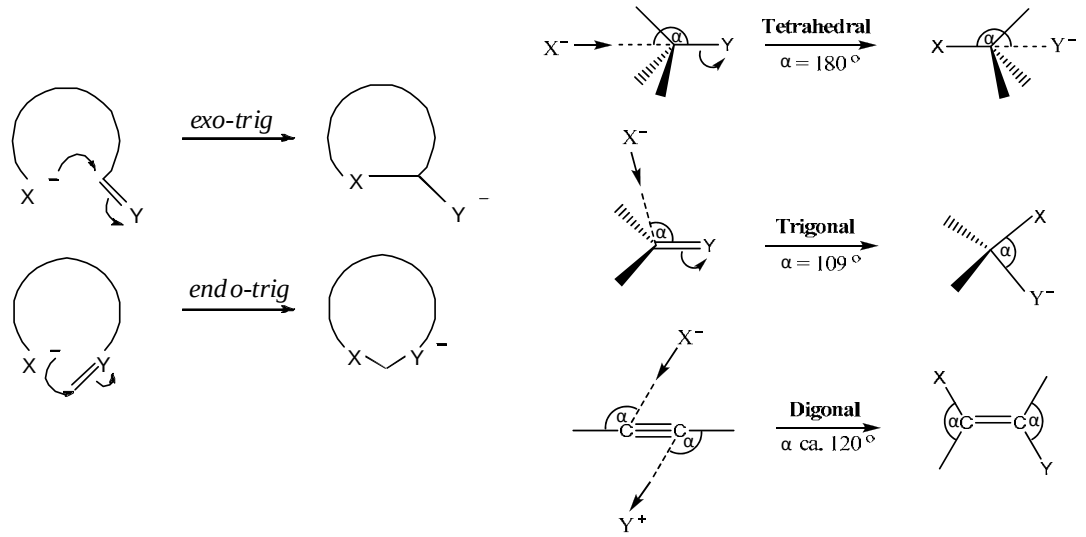
b) 3 to 5-*endo-trig* are disfavoured; 6 to 7-*endo-trig* are favoured.

Digonal Systems

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

b) 3 to 7-*endo-dig* are favoured.

Notably, a disfavoured ring closure does not mean the reaction is completely impossible, it only means that the possibility of having such a ring formation happened is very low.



Scheme 1.2 The ring-closure of *exo-trig* and *endo-trig* cyclization (right), and the favoured subtended angle for a nucleophilic to carbon atom (left)

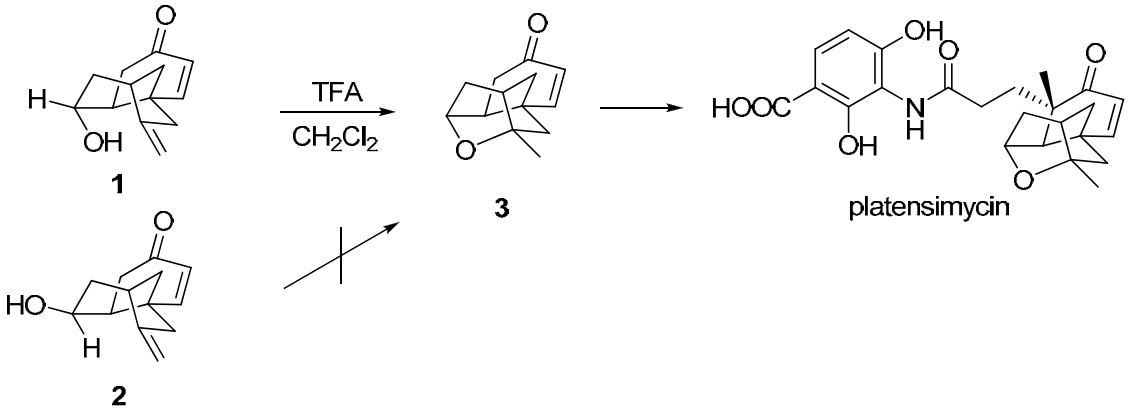
According to this Balwin's Rule, the favoured ring closure of the tetrahedral, trigonal, and digonal ring closure process are represented in Scheme 1.2. By description for these processes based on the suitable stereochemical transition states, the subtended angle (α) between the three interacting atoms is retained during the reaction pathway, becoming the angle between these atoms in the final products. Additionally, the length and nature of the chain enable the terminal atom to achieve the required trajectories to form the ring linking bond, while the require distortion of bond angles and distance to achieve trajectories is clearly the reason for the disfavoured cases. In summary, the tetrahedral systems correspond to the inversion of the configuration, S_N2 type reaction, while the trigonal systems represent the addition reaction to the carbonyl group, and lastly, the digonal systems are supported by the general predominance of *endo*-ring closures (Scheme 1.2).

1.2 Acid-induced intramolecular cyclization

In order to proceed the intramolecular cyclization, however, a general procedure for synthesizing organic compounds by using an acid-induced intramolecular cyclization reaction is one of the most popular methods for construction of numerous heterocyclic compounds. Acids such as trifluoroacetic acid [24], chlorosulfonic acid [25], and such Lewis acid [26] are exemplified.

1.2.1 Trifluoroaceticacid (TFA)

Nicolaou and co-workers [24] reported that the synthesis of platensimycin was accomplished from the treatment of diastereomers of hydroxyl alkene **1** and **2** in the presence of strong Brønsted acid, TFA. Percent yield of the cage-like product **3** was calculated to be 87% based on the isomer **1** remained in the mixture. Interestingly, the diastereomer **2** is unreacted and fully recovered because their regioselectivity is usually controlled by the Markovnikov tenet (Scheme 1.3).

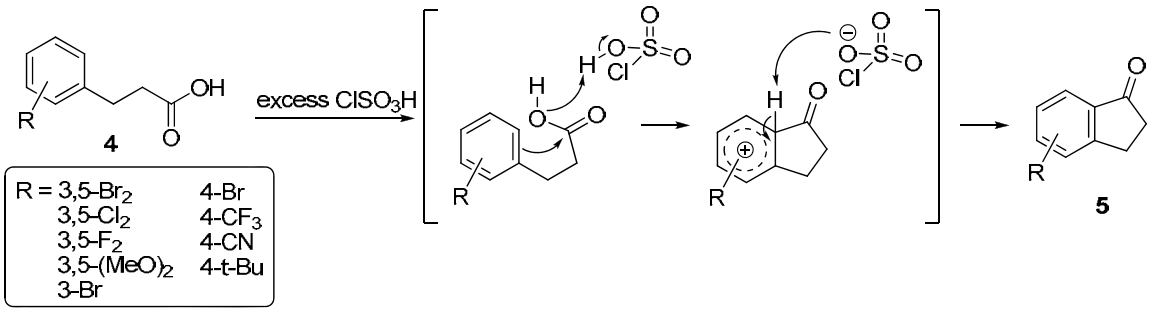


Scheme 1.3 TFA acid-induced intramolecular cyclization

1.2.2 Chlorosulfonic acid ($ClSO_3H$)

Anil and co-workers [25] reported that the chlorosulfonic acid ($ClSO_3H$) had been utilized to induce the intramolecular cyclization of various aryl propionic acids **4** to produce halogen-substituted indanone derivatives in high yields (70-94%). This cyclization with $ClSO_3H$ acid as an acidic dehydrating agent

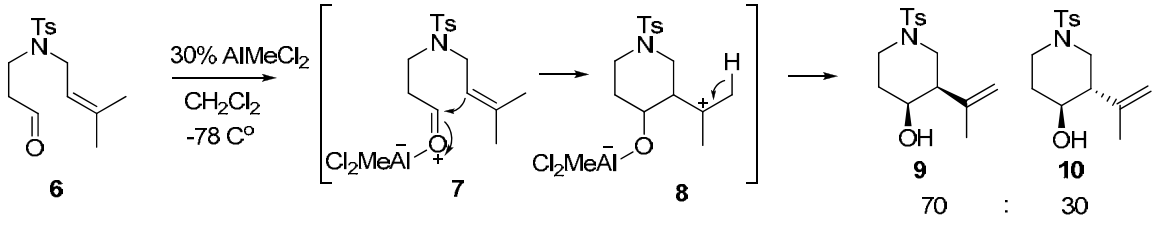
generated the desired indanone products **5** mechanistically through five-six fused membered ring cationic intermediate (Scheme 1.4).



Scheme 1.4 $ClSO_3H$ acid-induced intramolecular cyclization

1.2.3 Lewis acid

Snaith and co-workers [26] have recently explored the intramolecular cyclization of carbonyl enes **6** by using catalytic amount of Lewis acid $AlMeCl_2$ to give piperidine diastereomers **9** and **10**. The aldehyde **6** was treated with $AlMeCl_2$ to chemoselectively create the oxonium ion **7** subsequently cyclic **8** as intermediates which then deprotonated to furnish piperidine as desired products **9** and **10** in high diastereomeric ratio (Scheme 1.5).



Scheme 1.5 $AlMeCl_2$ acid-induced intramolecular cyclization

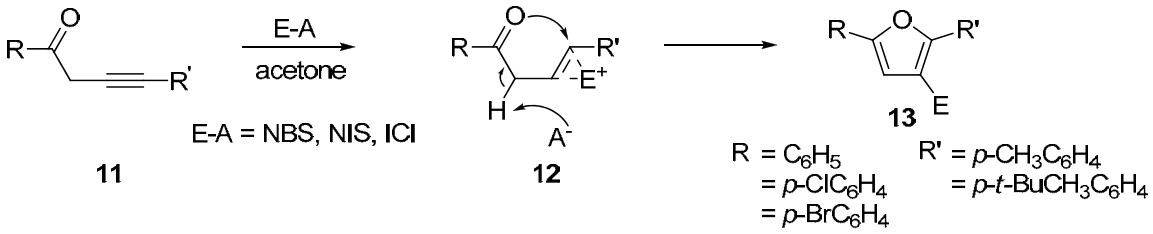
1.3 Halo-induced intramolecular cyclization

Likewise an acid-induced intramolecular cyclization, halo-induced intramolecular cyclization of unsaturated compound has been proven to be an efficient method for one step construction and functionalization of many heterocyclic compounds. For instance, it could provide an important building block for

combinatorial chemistry [27]. The developments of synthetic routes leading to further opportunity for substituted heterocycle *via* various halo-reagents are exemplified.

1.3.1 NBS, NIS, and ICl

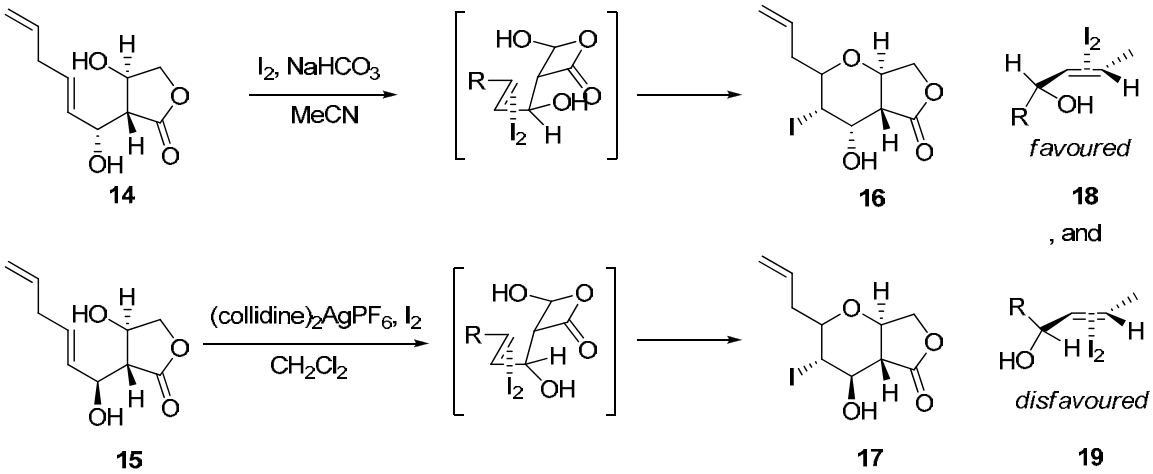
Adam Snidy and co-workers [28] reported that the intramolecular cyclization of 1,4-diaryl but-3-yn-1-ones **11** using *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), and iodine monochloride (ICl) as electrophilic halo-reagent produced 2,5-disubstituted 3-bromo-and 3-iodofurans **13** in high yield (82-94%). The cyclization involving the reaction of alkynyl ketone with various halogenating electrophiles generated a cationic intermediate **12**, which was immediately cyclised to halofurans (Scheme 1.6).



Scheme 1.6 NBS, NIS, and ICl for halo-induced intramolecular cyclization

1.3.2 Iodine and bis(*sym*-collidine)$_2$IPF$_6$

Gao and co-workers [29] have investigated that the preparation of tetrahydropyrans *via* iodoetherifiacation of substrates containing an allylic alcohol with iodine. The reaction turned out to be highly dependent on conformation of allylic moiety of allylic alcohol. Allylic diol **14** proceeds rapidly through the favoured **18** π-complex (C-OH eclipses the carbon-carbon double bond) and cyclised to yield 2,6-cis-tetra-hydropyran **16**, while disfavoured **19** π-complex (C-H eclipses the carbon-carbon double bond) cyclization requires a more reactive iodinating reagent, bis(*sym*-collidine)$_2$IPF$_6$. This iodinating reagent was used to prepare *in situ* from bis(*sym*-collidine)$_2$AgPF$_6$ and iodine, to overcome this defect could be convert allylic diol **15** into the desired tetrahydropyran **17** in high yield (Scheme 1.7).



Scheme 1.7 I_2 and bis(*sym*-collidine)$_2$IPF$_6$ for halo-induced intramolecular cyclization

1.4 2-Oxazolidinone

Oxazolidinone, a five membered heterocycle consists of oxygen, carbonyl and nitrogen as shown as a core unit in Figure 1.1. Particularly, they are useful as chiral auxiliaries in asymmetric synthesis [30-33]. One of the best known chiral auxiliaries of this class is Evans auxiliary used in enantioselective Aldol reactions [34]. Another major issue is the use of oxazolidinones as a new class of synthetic antibacterial medicines with marvellous inhibition against gram-positive pathogenic and anaerobic bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant *Staphylococcus epidermitis* (MRSE) and Vancomycin resistant enterococci (VRE) [35-36]. The examples show DuPont's compound DuP-105 and DuP-721 [37-39] that were not enter advanced chinical testing. First commercial available oxazolidinone antibiotic is the Linezolid (Zyvox®), which has been successfully developed by Phamacia Corporation [12-14] and approved by U.S Food and Drug Administrative (FDA) on April, 2000. Moreover, Toloxatone (Humoryl) is an antidepressant and monoamine oxidase inhibitor (MAOI) activity [40]. Nowadays, synthesis and investigation of this newly intriguing oxazolidinone family, RX-01, is one of the most focusing area in oxazolidinone research field. Despite of the fascinating properties of this class compound, using as an antibacterial medicine is undergoing clinical trial period [41].

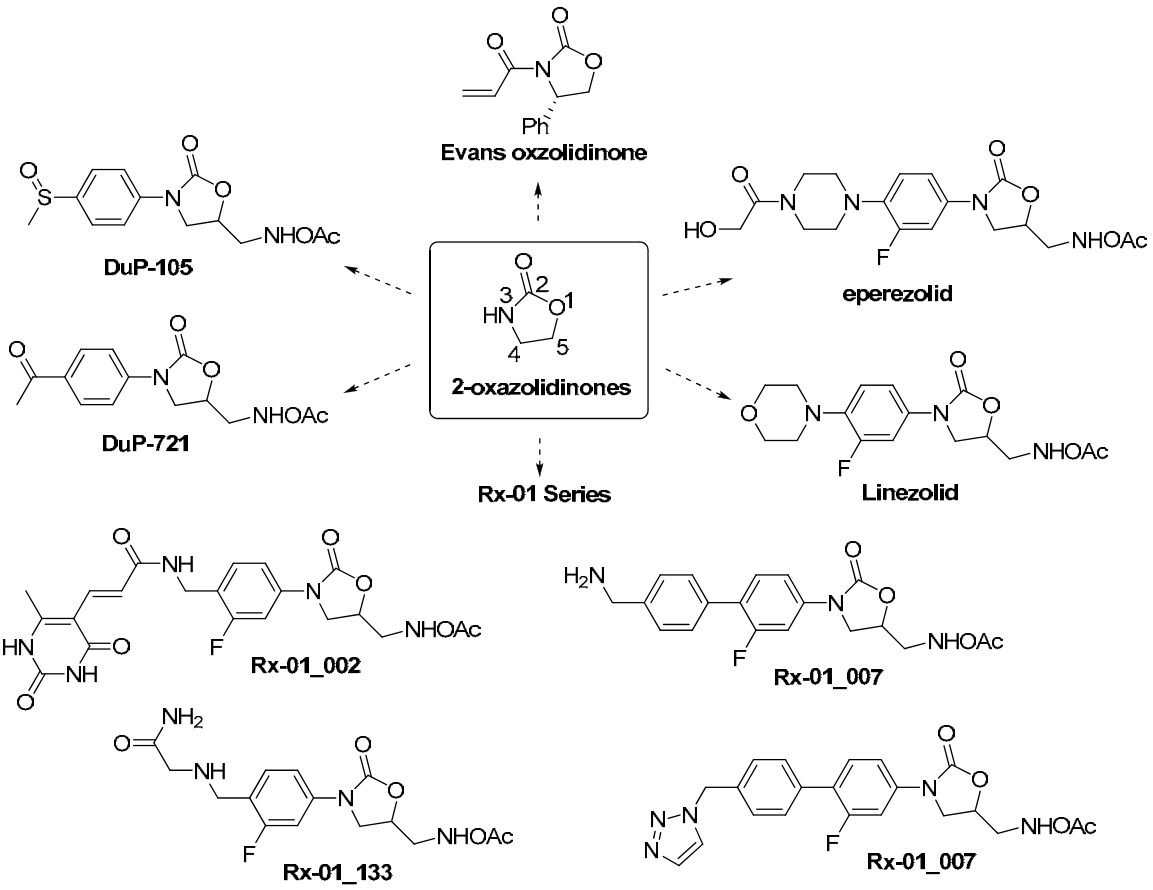


Figure 1.1 2-oxazolidinones and various 2-oxazolidinone derivatives

The oxazolidinones appear to inhibit bacterial translation at the initiation phase of protein synthesis. The preferred binding of oxazolidinones, in this case Linezolid, to the A site of the 50S ribosomal subunit interferes the initial complexation between fMet-tRNA and mRNA to this site. As a result of this interference of the RNA interaction during the initiation phase that involves the bacterial translation from initiating complex toward the 50S ribosomal subunit [2, 4, 42], the bacterial protein synthesis is therefore completely inhibited (Figure 1.2).

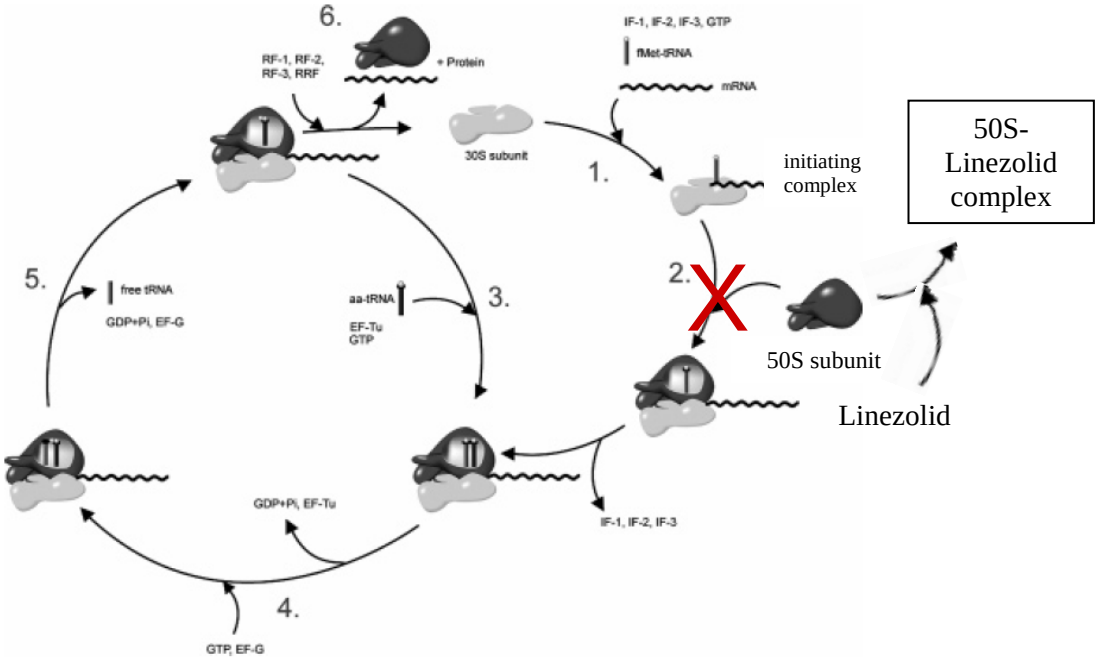


Figure 1.2 The mechanism of action

1.4.1 Synthesis of 2-oxazolidinone

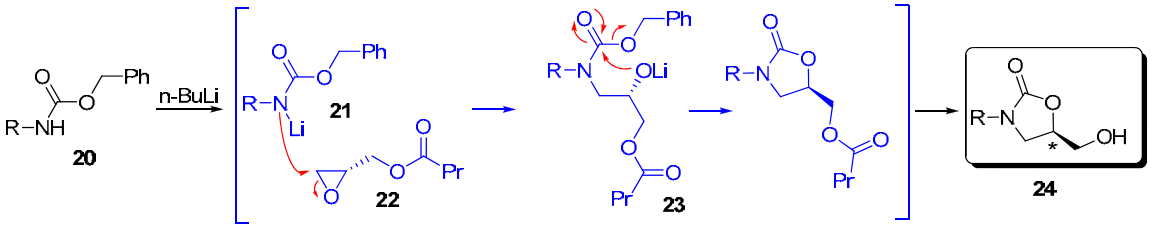
Due to the remarkable functionalities of 2-oxazolidinones, their preparations have become a continuous challenge for organic chemists. In general, 2-oxazolidinone derivatives can be synthesized from various precursors such as carbamate [35, 43-55], amino alcohol [60], epoxide [56], β-lactam [57], azidoformate [58], and isocyanate [59]. The classification of these precursors is considered based on ring forming cyclization process.

a) Carbamate-mediated cyclization

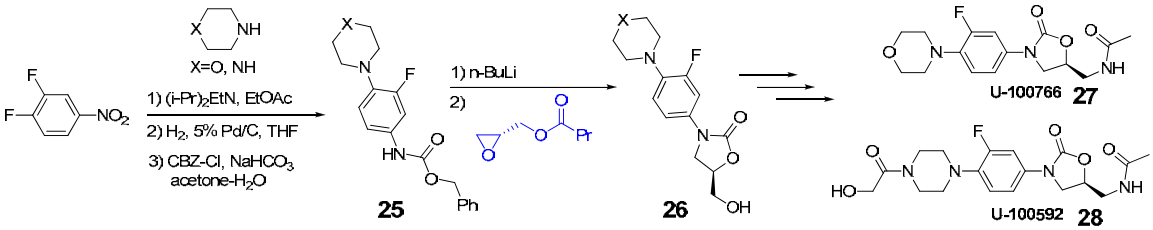
- Aryl carbamates with *(R)*-glycidyl butyrate

This 2-oxazolidinone ring forming process is generally undertaken by deprotonation of aryl carbamate **20** with base, especially *n*-BuLi. Then generated essential reactive species, in the case of *n*-BuLi, *N*-lithioarylcarbamate **21** is treated with *(R)*-glycidyl butyrate **22** to form alkoxide intermediated **23**, which immediately cyclised into 2-oxazolidinone **24** (Scheme 1.8). For instance, Steven J. Brickner and

co-workers [35] have successfully prepared two potent antibacterial synthetic oxazolidinones, Linezolid (U-100592) **27** and Eperezolid (U-100766) **28**. The synthetic pathway started from 3,4-difluoronitrobenzene with morpholine or piperazine by nucleophilic aromatic substitutions furnishing the substitution at para position. Reduction with catalytic hydrogenation with Pd/C, followed by protection with benzyl chloroformate (CBZ) produced carbamate **25**. Treatment of *n*-BuLi with of (*R*)-glycidyl butyrate provided the corresponding (5*R*)-(hydroxymethyl)-2-oxazolidinone **26**, which would be thus used in the further synthesis of Linezolid and Eperezolid (Scheme 1.9).

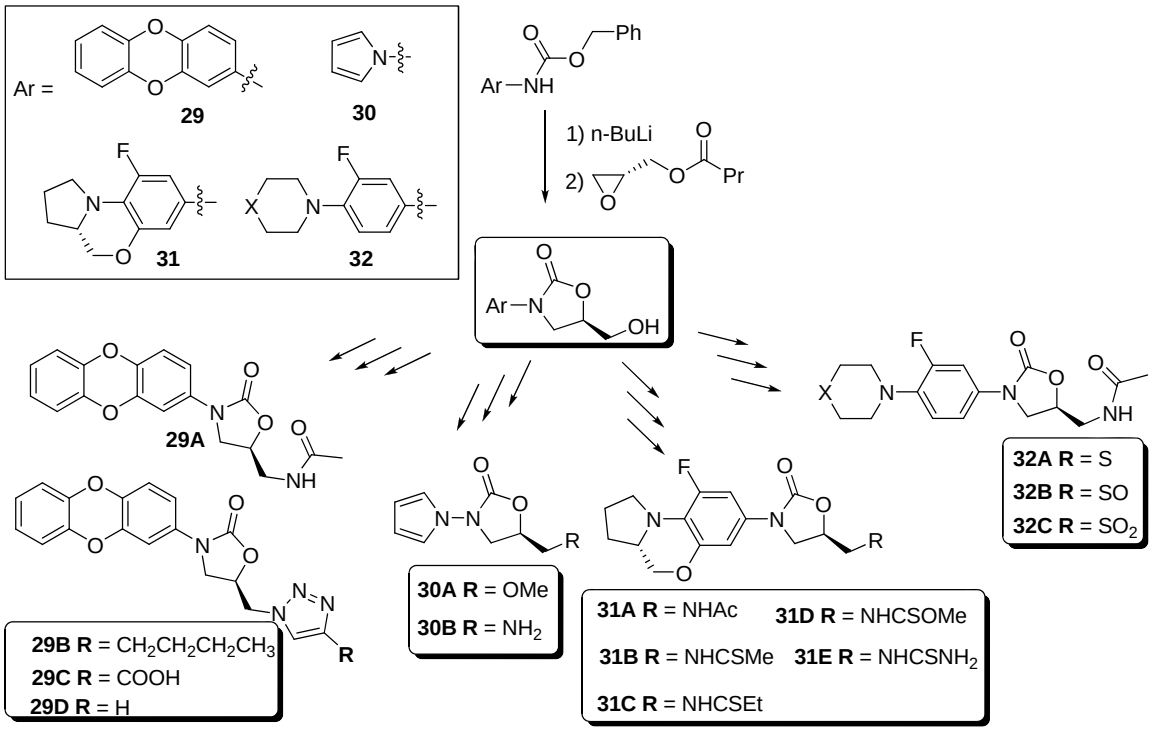


Scheme 1.8 General procedure of *N*-lithiocarbamates with *(R)*-glycidyl butyrate cyclization



Scheme 1.9 Synthesis of antibiotic Linezolid (U-100592) and Eperezolid (U-100766)

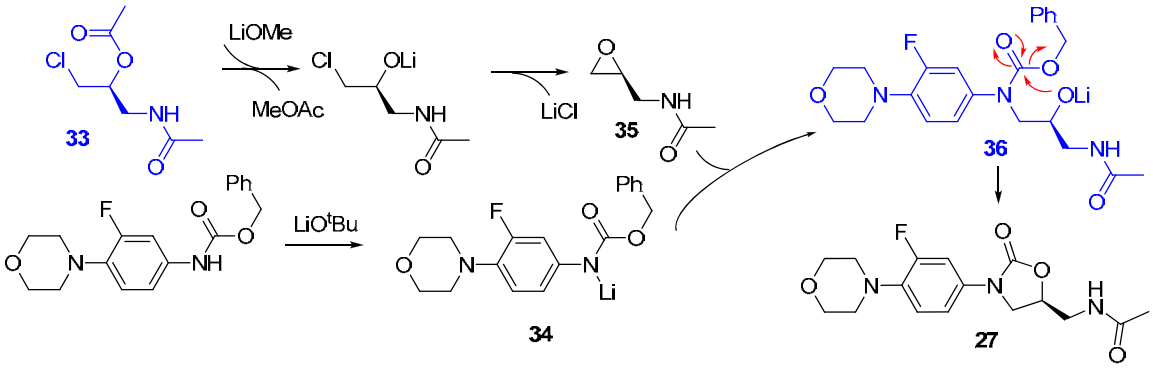
For the novel discovery of antimicrobial activity, David C. Ebner and co-workers [43] have explored four novel oxazolidinones **29A-29D** in benzodioxin style. Moreover, useful process valuable chiral *(R)*-glycidyl butyrate reagent is widely utilized in the preparation of various 2-oxazolidinone antibacterial agents such as pyrrole ring substituted oxazolidinones **30A-30B** [44], tricyclic oxazolidinone derivatives **31A-31E** [45], and oxazolidinones **32A-32C** with thiomorpholine moiety [46] (Scheme 1.10).



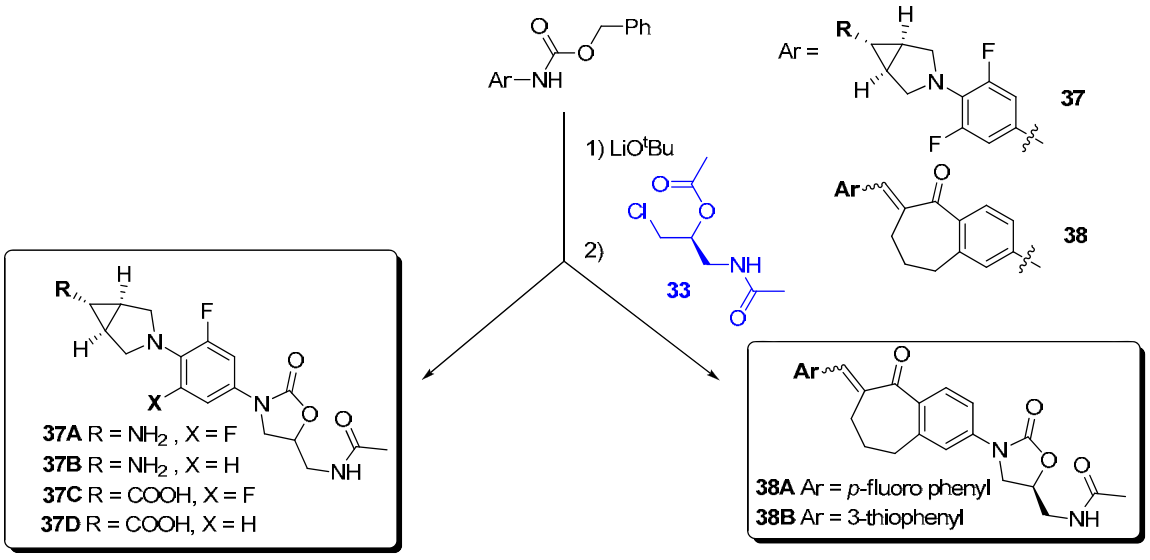
Scheme 1.10 Synthesis of analogues antimicrobial 2-oxazolidinones

- Aryl carbamates with *(S)*-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester

William R. Perrault and co-workers [47] have developed the current commercial process to produce Zyvox (Linezolid) by preparing economical chiral synthons *N*-[(2S)-2-(acetyloxy)-3-chloropropyl]acetamide **33** from commercially available (*S*)-epichlorohydrin. The reaction of *N*-lithiocarbamate **34** with chiral epoxide **35** generated the alkoxide intermediate **36**, which was subsequently cyclized into *N*-aryl-5(*S*)-aminomethyl-2-oxazolidinone derivative in one step. The oxazolidinone ring formation was explained as scheme 1.11. Likewise the *N*-lithioaryl carbamates with *(R)*-glycidyl butyrate case, these reagents and procedures have also proven to be applicable in the preparation of a diverse array of 2-oxazolidinones such as azabicyclic oxazolidinone antibacterial agent **37** [48], and benzocycloheptanone **38** [49] (Scheme 1.12).



Scheme 1.11 One-Pot Conversion of *N*-Aryl carbamates to *N*-Aryl-5(*S*)-acetamido-methyl-2-oxazolidinones

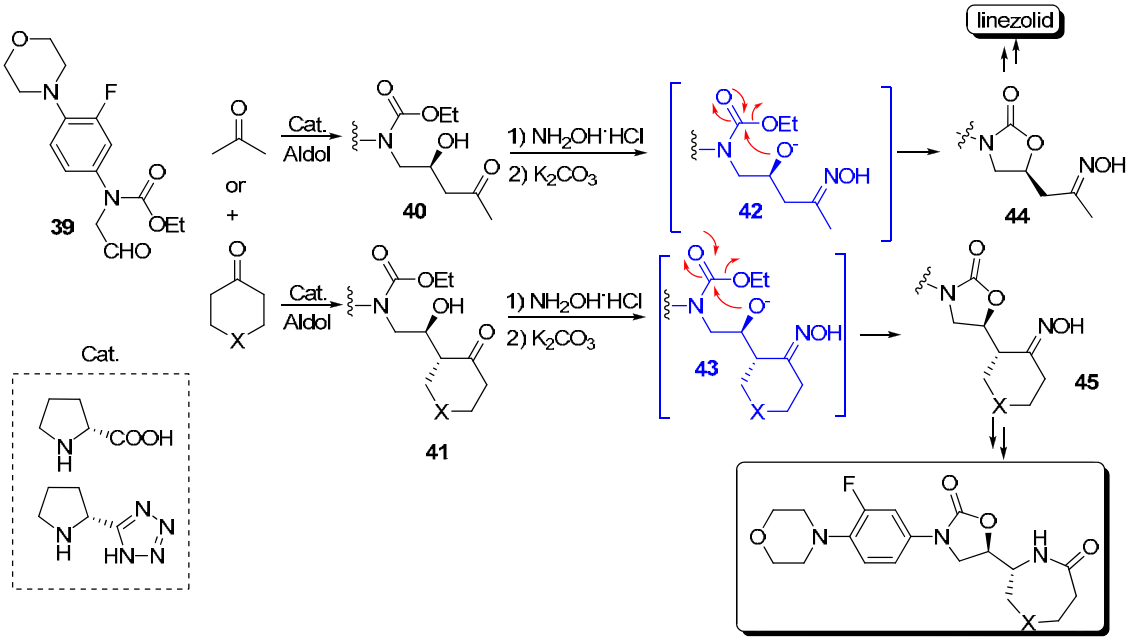


Scheme 1.12 Synthesis of antimicrobial 2-oxazolidinones *via* (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester

- Hydroxyl carbamates with base

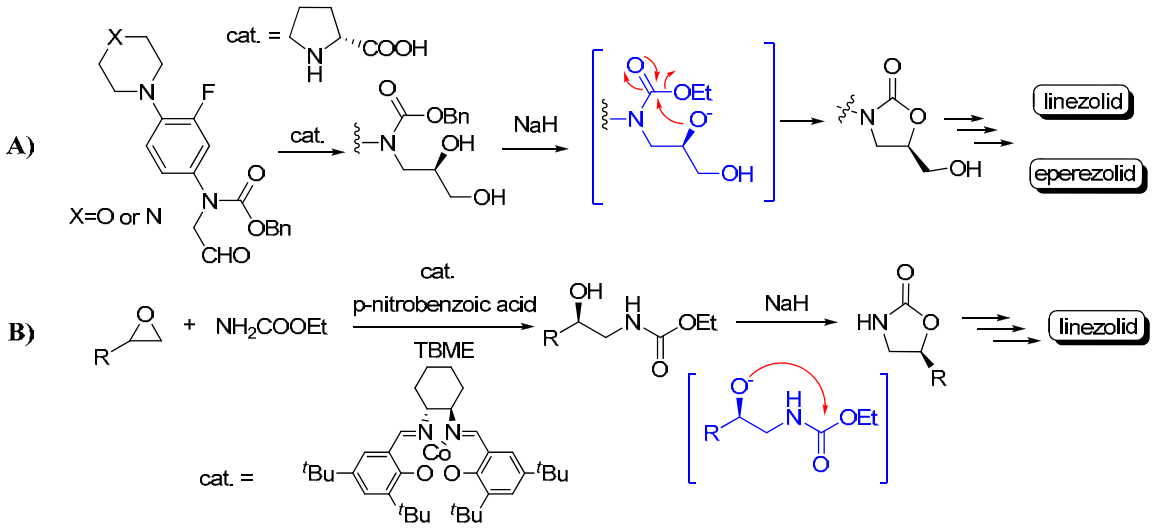
Hydroxyl carbamate is also one of the precursors for the synthesis of 2-oxazolidinone derivative. In 2008 Wei Wang and co-workers [50] reported that oxazolidinone analogues could be synthesized from the intramolecular cyclization of hydroxyl carbamates in the presence of base. The hydroxyl carbamates **40** and **41** were prepared from the reaction of aldehyde **39** with ketones in the presence of proline catalyst *via* catalytic enantioselective aldol reaction. Treatment this hydroxyl carbamate with base gave alkoxide intermediates **42** and **43** ready for the cyclization

into chiral oxazolidinones **44** and **45**. Then two-step Beckman rearrangement was performed to afford Linezolid. Moreover, the successful preparation of novel α-substituted analogues of Linezolid with high enantio- and diastereoselectivity can open the new synthetic route for α-substituted analogues oxazolidinone (Scheme 1.13).



Scheme 1.13 Synthesis of Linezolid and α-substituted analogues of Linezolid *via* intramolecular cyclization of hydroxy carbamate

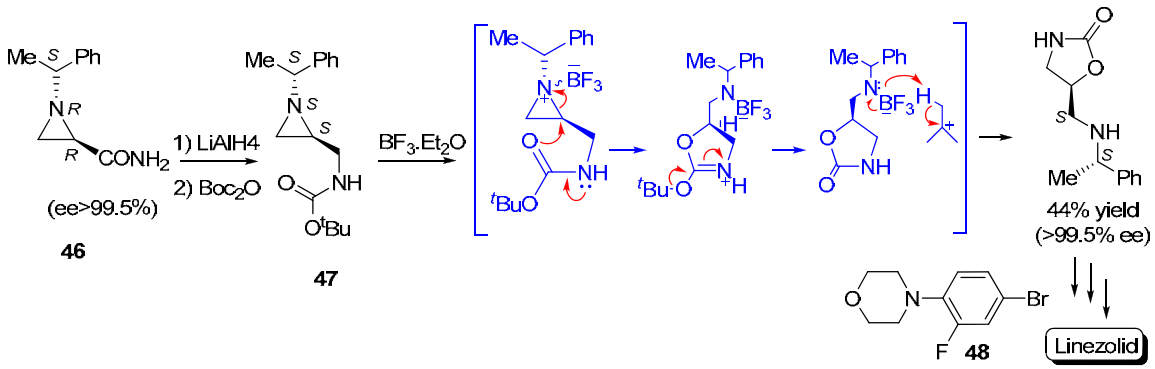
Many reports have used this procedure to synthesize oxazolidinone derivatives. For instance, Srinivasarao V. and co-workers [51] used this methodology to prepare Linezolid and Eperezolid in high yield and %ee (Scheme 1.14 A.**)**. Giuseppe B. and co-workers [52] successfully generated chiral synthons that can be used in the synthesis of Linezolid (Scheme 1.14 B).



Scheme 1.14 The intramolecular cyclization of hydroxy carbamate in the synthesis Linezolid and Eperezolid

- Chiral aziridine carbamates with BF_3·OEt_2

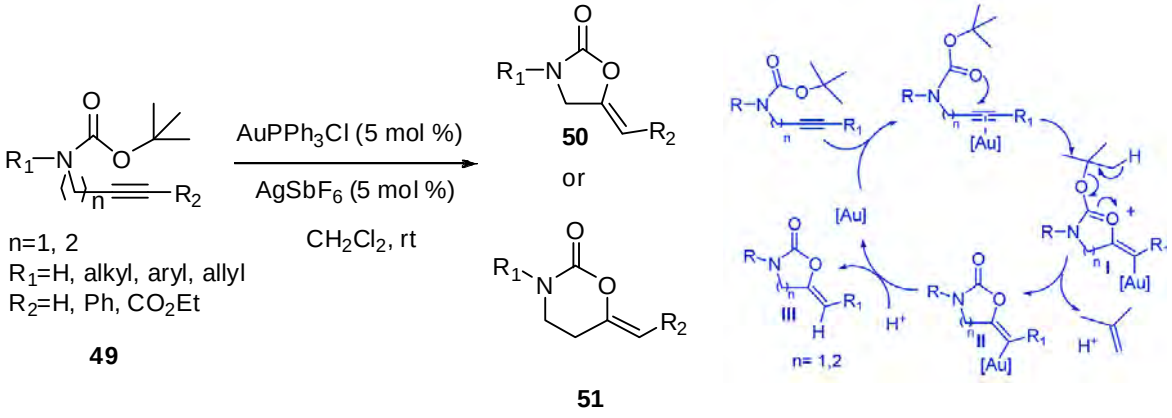
Roberto, Mora´n-R. and co-workers [53] have successful developed another Linezolid synthesis procedure. The starting enantiopure 1-substituted aziridine-2-carboxamide **46** was reduced with $LiAlH_4$, followed by Boc protection to obtain chiral aziridine carbamate **47**. Aziridine ring opening in *5-exo-tret* gave chiral oxazolidinone synthon upon treatment with Lewis acid BF_3·OEt_2. The C-N coupling reaction was introduced this compound with aryl halide **48** to provide Linezolid in high yield (Scheme 1.15).



Scheme 1.15 Synthesis of Linezolid *via* acid-mediated intramolecular cyclization

- Alkynyl carbamates with gold-catalyzed

Due to the excellent ability of transition metals to activate alkynes toward nucleophilic attack, numerous novel catalytic cyclizations have been developed. Juan, C. C. and co-workers [54] reported that alkylidene 2-oxazolidinones **50** and 1,3-oxazin-2-ones **51** can be prepared from the catalytic cyclizations of alkynyl carbamate **49** in the presence of catalytic amount of $AuPPh_3Cl/AgSbF_6$ under mild reaction conditions. A tentative mechanism for this gold-catalyzed cyclization involves the nucleophilic attack of the carbamate carbonyl group on the activated Au(I)-alkyne complex to afford the cationic vinyl-gold intermediate **I**. Subsequently *tert*-butyl fragmentation **19** by releasing isobutene and a proton, would give raise to the oxazolidinone-Au complex **II**, which after protonation would provide the observed oxazolidinone **III** or 1,3-oxazin-2-ones (Scheme 1.16). Remarkably, this novel procedure was applicable in the preparation of unsaturated 2-oxazolidinone.

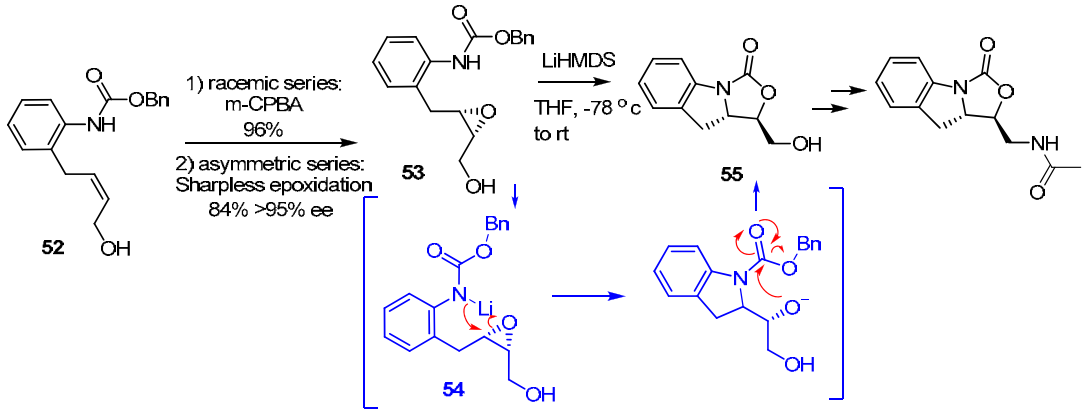


Scheme 1.16 Preparation of unsaturated cyclic carbamates *via* catalytic cyclization

- Epoxy aryl carbamates with base

Steven J. B. and co-workers [55] developed the synthesis of tricyclic fused oxazolidinone antibacterial agents by using intramolecular cyclization of aryl epoxycarbamates in base conditions. The synthesis started from the epoxidation of unsaturated carbamate **52** producing aryl epoxycarbamate **53**, which was converted to tricyclic fused oxazolidinone by using LiHMDS as base. Firstly, the amide was deprotonated with base to obtain *N*-lithio-intermediate **54**, which would then

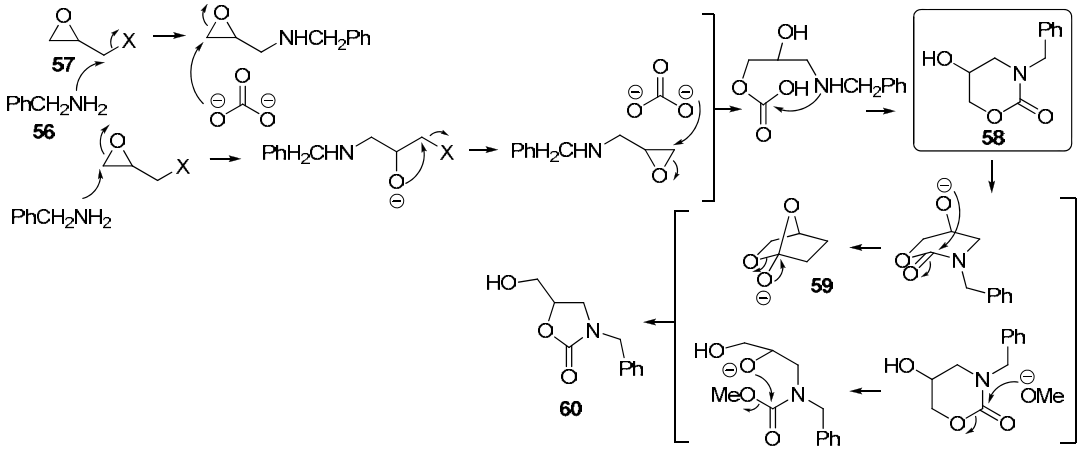
intramolecularly cyclize to afford tricyclic fused oxazolidinone **55** in high yield (Scheme 1.17).



Scheme 1.17 Preparation of tricyclic fused oxazolidinone *via* base-mediated intramolecular cyclization

b) Epoxide-mediated cyclization

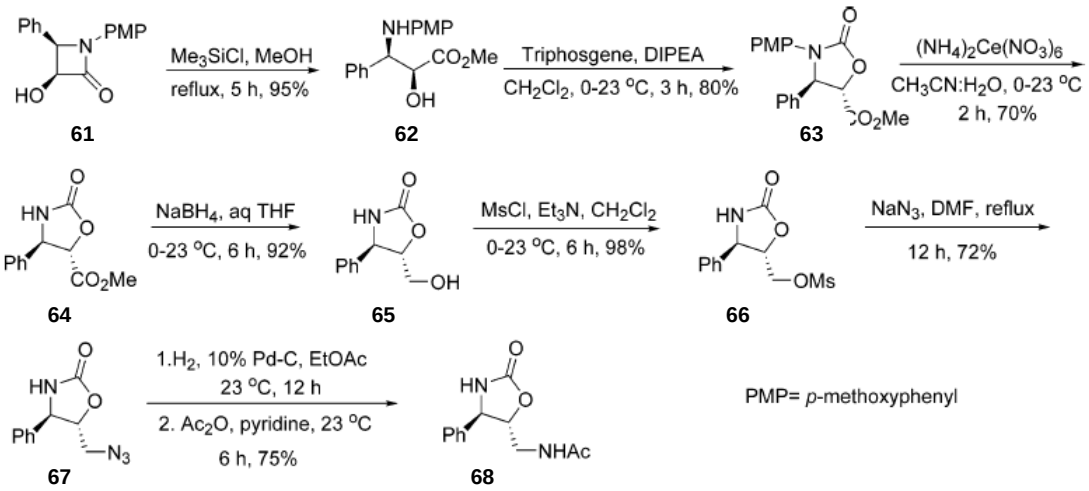
Yumiko, O. and co-workers [56] have explored the convenient synthesis of useful *N*-substituted oxazolidinones, by treating benzyl amine **56** and halomethyl oxiranes **57** with carbonate salts (Na_2CO_3, K_2CO_3, Cs_2CO_3, and Ag_2CO_3) in the presence of a base such as DBU or TEA to give oxazolidinones **60** in high yields. A reaction mechanism was proposed. The corresponding oxazolidinone produced the ring opening of an oxazinanone intermediate **58** through a bicyclo[2.2.1] intermediate **59** (Scheme. 1.18).



Scheme 1.18 Preparation 2-oxazolidinones *via* intramolecular cyclization reaction

c) β-Lactam with triphosgene cyclization

Rajesh, K. M. and co-workers [57] described that the novel synthesis of 2-oxazolidinones could be prepared form 3-hydroxy β-lactams in stereomerically pure by a ring-opening-cyclization isomerization process. Lactam **61** was hydrolyzed with Me_3SiCl by refluxing in methanol to afford the *syn*-aminol **62** in 95% yield. Upon treatment of **62** with triphosgene and Hunig's base in dichloromethane oxazolidinone **63** was obtained in 80% yield. The *N*-methoxyphenyl moiety on the oxazolidinone ring was then cleaved with ceric ammonium nitrate in acetonitrile and water to yield the *N*-protio oxazolidinone **64** in 70% yield. Selective reduction of **64** with sodium borohydride in aqueous THF furnishes the alcohol **65** in 92% yield. Conversion of the hydroxy **65** into the azide **67** proceeded through mesylate **66** in 72% yield. Catalytic hydrogenation of the azide and subsequent acetylation afforded the acetamide **68** in 75% yield for the final one-pot synthesis (Scheme 1.19).

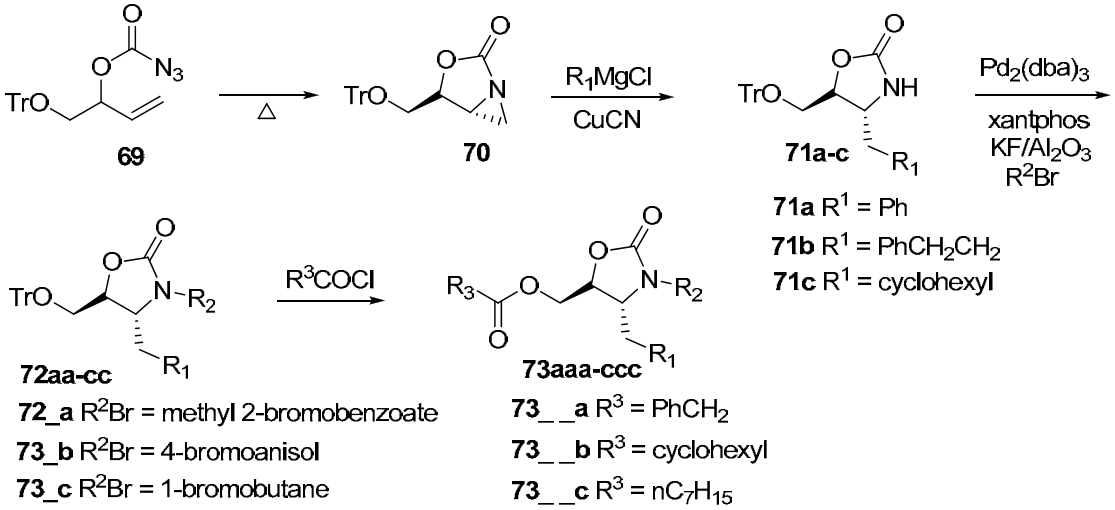


Scheme 1.19 Synthesis of 2-oxazolidinones from 3-hydroxy β-lactams

d) Azidoformate cyclization

Stephen, C. B. and co-workers [58] presented a 3x3x3 array synthesis yielding 27 different products in one time that was suitable for the preparation of oxazolidinone libraries. The starting material bicylic aziridine **70** was prepared from the thermolysis of the azidoformate **69** in good yield as a single diastereomer. The synthesis starts with the opening of the aziridine ring of **70** with copper-catalyzed and

commercially available Grignard reagents (R^1) produced substituted compounds **71** in high yield. The *N*-atom was substituted with both aryl and alkyl groups (R^2) *via* KF/Al_2O_3 method and $Pd_2(dba)_3$/xantphos system to yield compounds **72**. In the final substitution step, trityl protecting group of compounds **72** was removed *via* esterification then subsequently treated with three different acid chlorides to provide desired products **73** (Scheme 1.20).

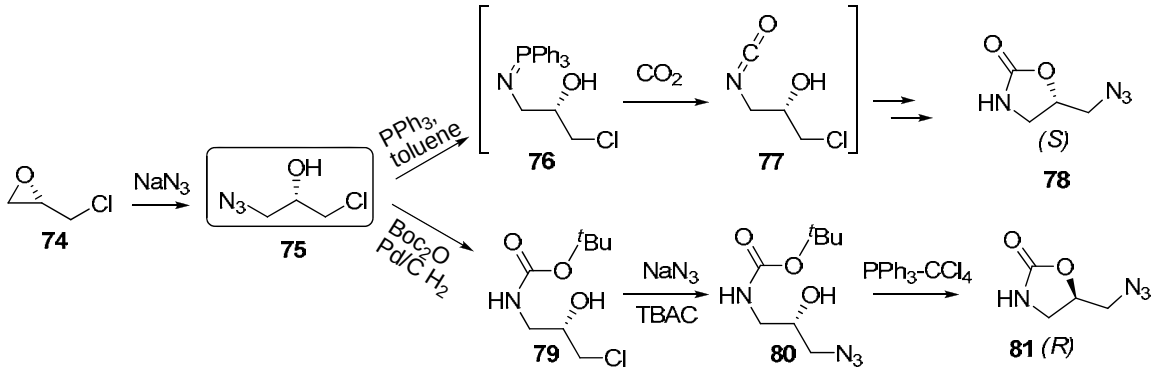


Scheme 1.20 Synthesis of 2-oxazolidinones from azidoformate cyclization

e) Isocyanate with carbondioxide

Madhusudhan G. and co-workers [59] reported the facile synthesis of *(R)*-and *(S)*-5-azidomethyl-2-oxazolidinones from *(S)*-epichlorohydrin. *(S)*-epichlorohydrin **74** was stereoselectively ring-opened with NaN_3 in mild acidic conditions using NH_4Cl to give *(2S)*-1-azido-3-chloropropan-2-ol **75** without racemization. The treatment of azido alcohol **75** with Ph_3P and carbon dioxide in toluene under reflux gave oxazolidinone **78**. The mechanism involved an intermediate iminophosphorane **76** that reacts with carbon dioxide to generate an intermediate isocyanate **77**, which was further treated with NaN_3 to give the corresponding oxazolidinone **78**. Furthermore, oxazolidinone **81** was obtained by converting compound **75** into *tert*-butyl carbamate derivative **79** by reductive protection with Boc using Pd/C. Treatment this chloride **79** with NaN_3 in the presence of tetrabutylammonium chloride (TBAC) yielded azido compound **80**, which then

cyclized with PPh_3-CCl_4-NEt_3 to *(R)*-oxazolidinone **81** by S_N2 inversion **(**Scheme 1.21**)**.

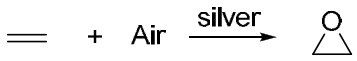


Scheme 1.21 Synthesis of 2-oxazolidinones from *via* isocyanate-CO_2 cyclization

Although many 2-oxazolidinone constructions have been reported, the increasing incidence of bacterial resistance to a large number of antibacterial agents and the requirement of optically pure new Evans chiral auxiliary analogs in asymmetric synthesis are becoming a major issue. Thus, the finding and developing more efficient methodologies of 2-ozazolidinones are still among the interest of organic chemists.

1.5 Epoxidation of alkenes

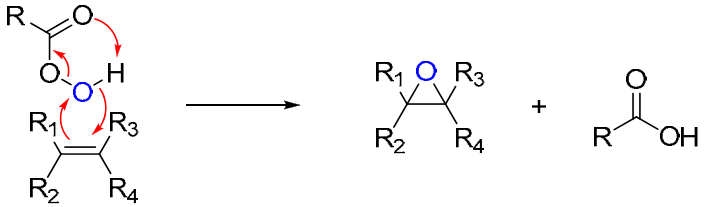
An epoxide, or oxirane, is reactive three membered-ring cyclic ether which is important synthetic precursor for organic synthesis. Epoxides are usually used to convert alkenes to several other functional groups. The simplest and the most important epoxide, is ethylene oxide prepared from a direct oxidation of ethylene by air in the presence of silver catalyst [61] (Scheme 1.22).



Scheme 1.22 Synthesis of ethylene oxide by air oxidation

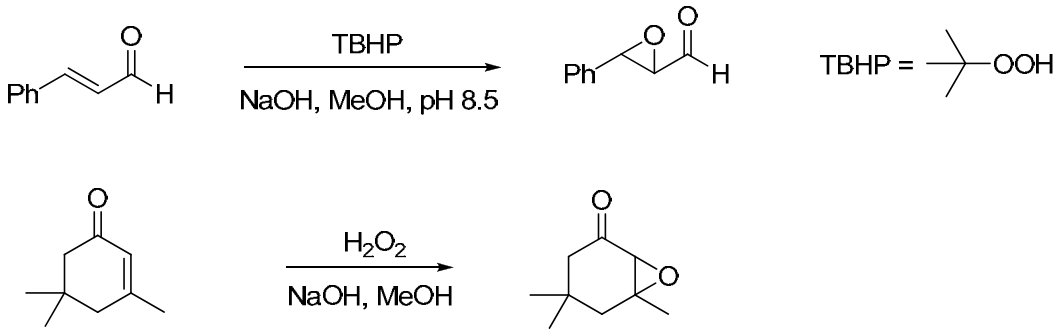
1.5.1 Epoxidation of alkenes with peroxy acids and peroxides

The ordinary oxidation of alkene to produce epoxides has been used for many decades without metal catalyst. The most important oxidizing agents are peroxy acids and peroxides, for which the mechanism of peracid epoxidation is believed to go through a cyclic concerted transition state. The carbon-carbon bond is broken when the oxygen transferred to alkene causing the simultaneous proton transfer toward the carbonyl oxygen [62] (Scheme 1.23).



Scheme 1.23 The mechanism of alkene epoxidation with peroxy acid

In the case of using peroxides, as an oxidizing agent, α,β unsaturated aldehydes and ketones can be much selectively epoxidise, especially sodium salt of H_2O_2 or sodium salt of *tert*-butyl hydroperoxide (TBHP) more than peroxy acid [63]. (Scheme 1.24)

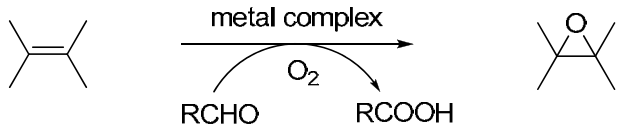


Scheme 1.24 The epoxidation of α,β unsaturated ketones and aldehydes by using peroxides

1.5.2 Epoxidation of alkenes catalyzed by metal complexes

The oxidation of alkenes have been developed using metalloporphyrins and metal complex of non-porphyrin-ligands, normally requires oxidants [64, 65], *e.g.* H_2O_2, organic peroxides, or iodosyl benzene. It has been observed that olefins can be

epoxidized by O_2 in the presence of aldehydes and transition metal-containing catalysts to yield epoxides in satisfactory yield [66]. (Scheme 1.25)



Scheme 1.25 Synthesis of epoxide by using alkenes catalyzed by metal complexes

1.5.3 Asymmetric epoxidation of alkenes catalyzed by metal complexes

Catalytic asymmetric epoxidation is a remarkably powerful technique for the stereoselective synthesis. The development of the chiral catalysts inducing highly efficient and above all highly stereoselective asymmetric epoxidation has always been the most focusing area of asymmetric synthesis. Many chemists have proposed their successful chemistry, in which some of them are picked up for brief introduction.

Sharpless epoxidation

The most well known and fascinating method to convert allylic alcohols into the corresponding epoxides with high yield and highly stereoselective in only one step was developed by Sharpless and coworkers [67]. By using a complex of titanium-*iso*-propoxide, the TBHP as an oxidant and enantiomerically pure diethyl tartrate as catalyst (DET), the desired epoxide enantiomers can be obtained with high enantiomeric excess (ee). The high enantioselectivity for Sharpless epoxidation reason may be due the important playing role of the hydroxyl function of the allylic alcohol. A wide range of allylic alcohol can be epoxidized with significant enantiomeric excess usually more than 90% and high yield above 80% [68]. The mechanism relies on the first step, the rapid ligand exchange of $Ti(O\textit{i}\text{-}Pr)_4$ with DET. The resulting complex undergoes further ligand exchange with the allylic alcohol and then TBHP. The hydroperoxide and the allylic alcohol occupy the axial coordination site on the titanium and this model conceivably accounts for the facial enantioselectivity. (Figure 1.3)

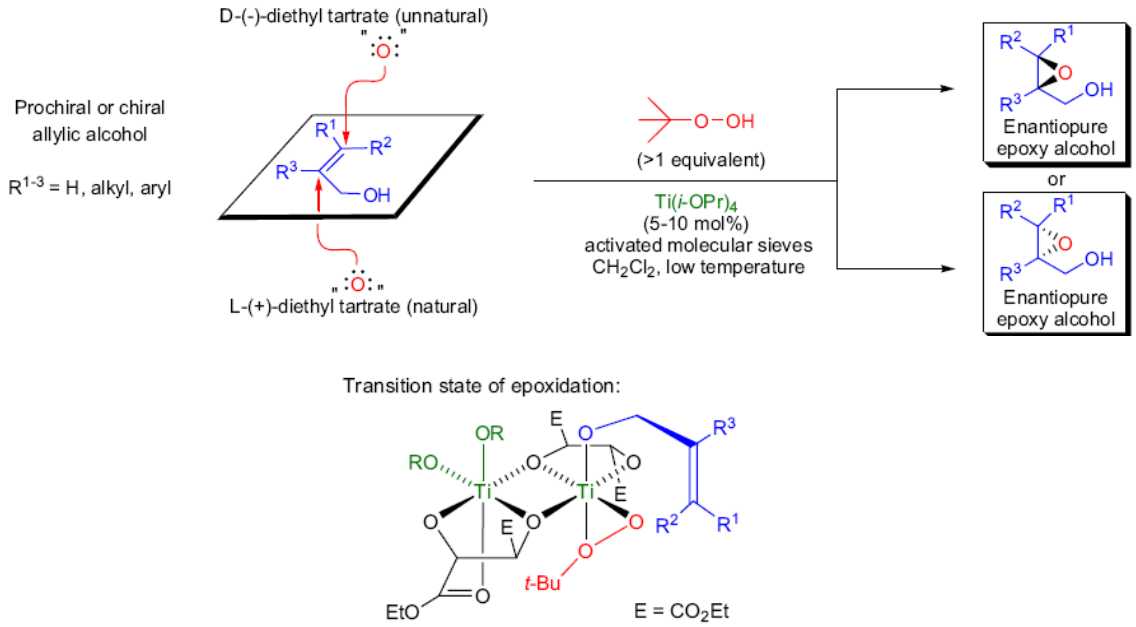


Figure 1.3 The mechanism of Sharpless epoxidation [68]

Katsuki-Jacobsen epoxidation

Another interesting efficient epoxidation of non-functionalized alkenes with high enantioselectivity was firstly introduced by Katsuki-Jacobsen and coworkers [69]. The catalyst is chiral salen-Mn (III) was used with simple oxidants e.g. PhIO, NaOCl, and H_2O_2. The perfect matching catalyst and reaction condition is required to achieve and optimal enantioselectivity. The condensations of diamine with salicylaldehyde derivatives make a unique tune of the steric an electronic property of the catalyst [70]. Notably, the Jacobsen's catalysts is air-stable that can be kept for a long period without decomposition [71] and Katsuki's catalysts is also effective [72]. (Figure 1.4**)**

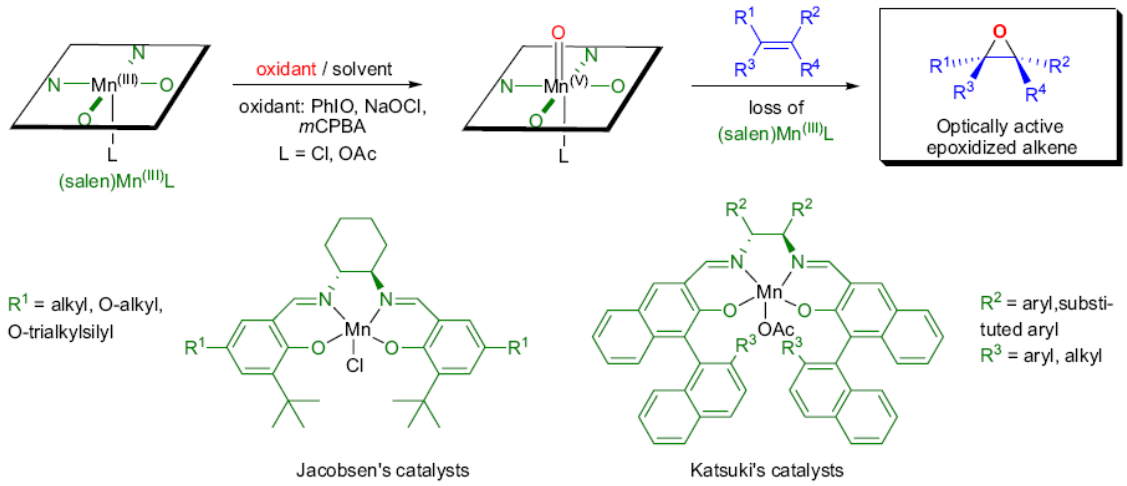


Figure 1.4 Katsuki-Jacobsen epoxidation [73]

The conceivably mechanism is most likely a manganese(V) specie as the reactive intermediate, which is formed upon the oxidation of the Mn(III)-salen complex. The enantioselectivity is explained by either a “top-on” approach (Jacobsen) or by a “side-on” approach (Katsuki) of the olefin. The three major mechanistic pathways are shown below. The radical intermediate accounts for the formation of mixed epoxides when conjugated olefins are used as substrates [73]. **(**Figure 1.5**)**

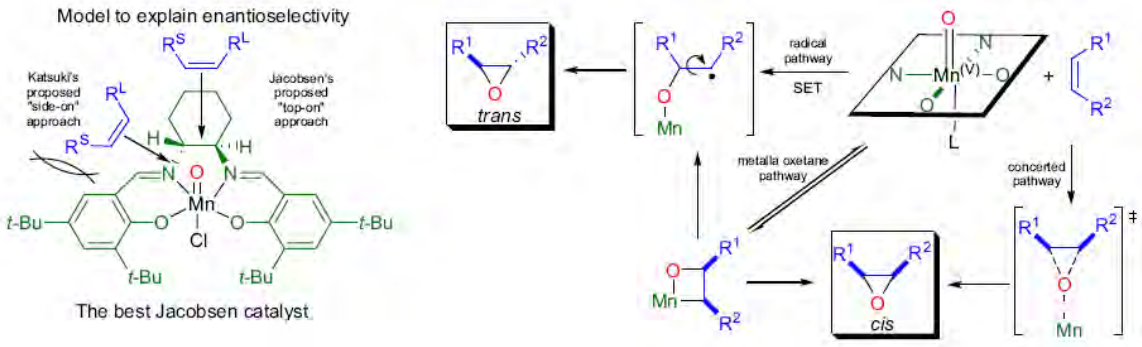


Figure 1.5 The mechanism of Katsuki-Jacobsen epoxidation [72]

1.6 Enantiomeric excess (ee)

The term “enantiomeric excess” was introduced in 1971 by Morison and Mosher to describe the relationship of two enantiomers in a mixture and was equated

with optical purity (op) [74]. The following relationships define the term op (equation 1.1) and ee (equation 1.2).

$$op = \frac{[\alpha]_{obs}}{[\alpha]_{\max}} \qquad \text{(equation 1.1)}$$

where; $[\alpha]_{obs}$ = observed specific rotation

$[\alpha]_{max}$ = maximum specific rotation

$$ee = \frac{R-S}{R+S} = R-S \qquad \text{(equation 1.2)}$$

where; R and S are respective fraction of enantiomers

$R + S = 1$

$$\%ee = \frac{R-S}{R+S} x100 \qquad \text{(equation 1.3)}$$

It is most often expressed as a percent enantiomeric excess (%ee)**.** For mixtures of diastereomer, there are similarity defined and used for diastereomeric excess (de) and percent diastereomeric excess (%de)

1.7 Specific rotation

The specific rotation [α] value occurred in solution of chiral molecule [75], is defined as the observed angle of optical rotation α from resulting in plane-polarized light is passed through certain sample with a part length of 1 dm and concentration of 1 g/1mL. As results, a negative value means levorotatory rotation and a positive value means dextrorotatory rotation. Specific rotation can be calculated by using two equations depending on the sample. The equation 1.4 and equation 1.5 are used when sample is pure liquid and solution respectively.

Liquid;

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{lxd} \qquad \text{(equation 1.4)}$$

where; α = optical rotation T = temperature (°C) d = density (g/mL)

l = path length (dm) λ = wavelength of sodium D line (589 nm)

Solution;

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{lxc} \qquad \text{(equation1.5)}$$

where; α = optical rotation T = temperature (ºC) c = concentration (g/mL)

l = path length (dm) λ = wavelength of sodium D line (589 nm)

CHAPTER II

EXPERIMENTAL

Synthesis

Materials: Aniline, 3,4-difluoronitro benzene, allyl bromide, 3-chloro perbenzoic acid (*m*-CPBA), oxone®, 4-methylbenzene-1-sulfonyl chloride (TsCl), *(R)*-glycidyltosylate, 4-phenylpyridine *N*-oxide (PPNO), manganesesulfate(*R,R*)-(−)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride ((*R,R*)-Jacobsen's catalyst), *N*-methylmorpholine-*N*-oxide (NMO), bis(trimethylsilyl)amide (LiHMDS), *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), Iodine monochloride (ICl) were purchased from Aldrich (USA). Morpholine, iodine, di-*tert*-butyl dicarbornate, 10% palladium on carbon, celite, *tert*-butyl alkoxide, ammonium chloride, triethylamine (TEA), sodium thiosulphate, sodium sulphate anhydrous, sodium hydrogen carbonate, magnesium sulphate anhydrous, ammonium acetate, calcium carbonate, 30% hydrogen peroxide, glycidol, *N,N*-dimethylpyridin-4-amine (DMAP), epichlorohydrin, trifluoroacetic acid (TFA), titanium(IV)chloride ($TiCl_4$), boron trifluoride diethyletherate ($BF_3{\cdot}OEt_2$), aluminium trichloride ($AlCl_3$) and acetic acid (CH_3COOH), 10% palladium on activated charcoal were purchased from Fluka (Switzerland). Diethylether (reagent grade) was purchased from AnalaR® (UK). Toluene (AR grade) was purchased from Fisher Scientific (UK). Hexane (HPLC grade), 2-propanol (HPLC grade), EtOAc(HPLC grade), Methanol (AR grade), tetrahydrofuran (AR grade), acetone (AR grade), dimethylfomamide (DMF) (AR grade), dimethyl sulfoxide (DMSO) (AR grade), chloroform ($CHCl_3$) (AR grade), methylene chloride (CH_2Cl_2) (AR grade) were purchased from Labscan (Thailand). Bromine solution, sodium azide, acetic anhydride were purchased from Carlo Alba. Commercially available sodium hypochlorite (Clorox) was used as bleaching agent. Tetrahydrofuran (THF) was distilled over sodium and benzophenone, acetonitrile (CH_3CN) was distilled over calcium hydride and stored over molecular sieves. Other

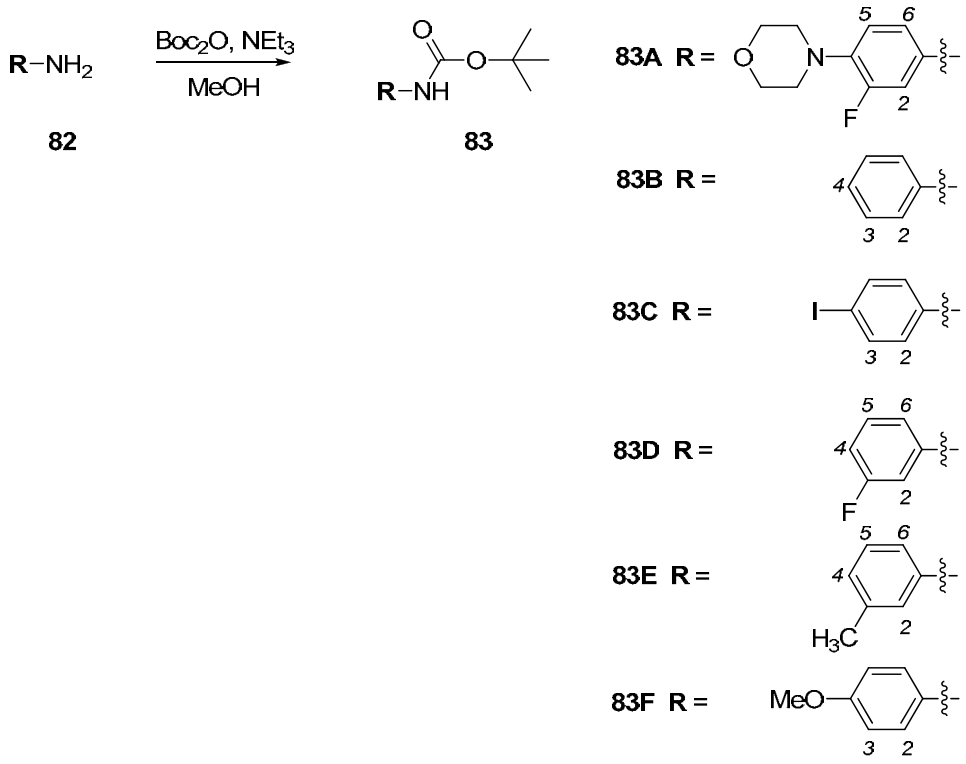
analytical grade solvents were used as received without further distillation. For extraction and chromatography, solvents were commercial grade and they were distilled prior to use. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere. Column chromatography was performed using Merck silica gel 60 (70-230 mesh). Analytical TLC was carried out on silica gel plates with detection by UV lights.

Analytical instruments: ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury at 400 MHz NMR spectrometer (Varian, USA) using residual solvent ($CDCl_3$, 7.26 ppm and 77.0 ppm) as the reference. Low resolution Mass Analysis was conducted with Quattro micromass (Waters, France) using the electrospray ionization (ESI) in its positive or negative modes. Either percent enantiomeric excess (%ee) were studied using normal phase HPLC or GC analysis. For HPLC, a Water 600^{TM} controller system equipped with gradient pump and Water 996^{TM} photo diode array detector. A Chiralcel® OJ-H column Cellulose tris (4-methylbenzoate)coated on 5μm silica-gel HPLC column 250 x 20 mm ID was used for the analysis of percent enantiomeric excess (%ee) by real-time HPLC Chromatogram monitoring. Peak monitoring and data processing were performed on the based Empower software. For GC, an Agilent 6890 equipped with split injector and flame ionization detector (FID) detector. 30% BSiMe in OV-1701 column 15.356 m x 0.25 mm x 0.25 μm was used. Optical rotations were measured using sodium light (D line, 589.3 nm) at ambient temperature on Jasco P-1010 Polarimeter. Infrared spectra were measured from neat on a Nicolet Impact 410 FT-IR spectrophotometer (Thermo Nicolet, USA). The melting points were recorded on Electrothermal 9100 (Electrothermal Engineering LTD.).

2.1 Preparation of aryl carbamates

Method I

General procedure 1



Scheme 2.1 Preparation of aryl carbamates **83A-F**

Amine and NEt_3 were dissolved in MeOH. After stirring for 10 minutes, Boc_2O was added into the reaction. The reaction mixture was stirred at ambient temperature for 2 hours under nitrogen atmosphere. After the removal of solvent in *vacuo*, aqueous HCl (2 M) was added and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo.* The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (9:1).

2.1.1 *tert*-Butyl 3-fluoro-4-morpholinophenylcarbamate (83A): Compound **83A** was synthesized from 3-fluoro-4-morpholinoaniline (5.65 g, 28.84 mmol), NEt_3 (12.00 mL, 86.52 mmol) and Boc_2O (8.00 mL, 34.61 mmol) in MeOH 50 mL to afford **83A** as a clear crystal (5.75 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.28 (d, *J* = 14.0 Hz, 1H, 2-Ar*H*), 6.92 (d, *J* = 8.5 Hz, 1H, 6-Ar*H*), 6.82 (t, *J* =

9.0 Hz, 1H, 5-Ar*H*), 6.68 (s, br, 1H, N*H*), 3.84 (m, 4H, OCH_2), 3.00 (m, 4H, NCH_2), 1.49 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 156.8, 154.4, 152.7, 135.2, 133.9, 119.0, 114.4, 107.7, 107.5, 80.5, 66.9, 51.1, 28.2.

2.1.2 *tert*-Butyl phenylcarbamate (83B): According to carbamate formation above, compound **83B** was synthesized from aniline (2.00 mL, 2.10 mmol), NEt_3 (1.00 mL, 7.19 mmol) and Boc_2O (0.80 ml, 3.48 mmol) in MeOH (10 mL) to afford **83B** as a clear white crystal (400 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 (d, J = 8.0 Hz, 2H, 2-Ar*H*), 7.30 (m, 2H, 3-Ar*H*), 7.03 (t, J = 7.0 Hz, 1H, 4-Ar*H*), 6.45 (s, br, 1H, N*H*), 1.52 (s, 9H, C(CH_3)$_3$).

2.1.3 *tert*-Butyl 4-iodophenylcarbamate (83C): Compound **83C** was synthesized from 4-iodoaniline (1.00 g, 4.57 mmol), NEt_3 (1.90 mL, 13.7 mmol) and Boc_2O (1.60 mL, 6.96 mmol) in MeOH (30 mL) to afford **83C** as a clear white crystal (752 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 (d, J = 9.0 Hz, 2H, 2-Ar*H*), 7.14 (d, J = 8.5 H, 2H, 3-Ar*H*), 6.45(s, br, 1H, N*H*), 1.51 (s, 9H, C(CH_3)$_3$).

2.1.4 *tert*-Butyl 3-fluorophenylcarbamate (83D): Compound **83D** was synthesized from 3-fluoroaniline (1.00 g, 9.01mmol), NEt_3 (3.80 mL, 27.3 mmol) and Boc_2O (2.7 mL, 11.7 mmol) in MeOH (20 mL) to afford **83D** as a white solid (555 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31 (d, J = 11.0 Hz, 1H, 2-Ar*H*), 7.21 (dd, J = 8.0, 15.0 Hz, 1H, 5-Ar*H*), 6.97 (d, J = 8.0 Hz, 1H, 6-Ar*H*), 6.72 (dt, J = 2.0, 8.0 Hz, 1H, 4-Ar*H*), 6.53 (s, 1H, N*H*), 1.52 (s, 9H, C(CH_3)$_3$).

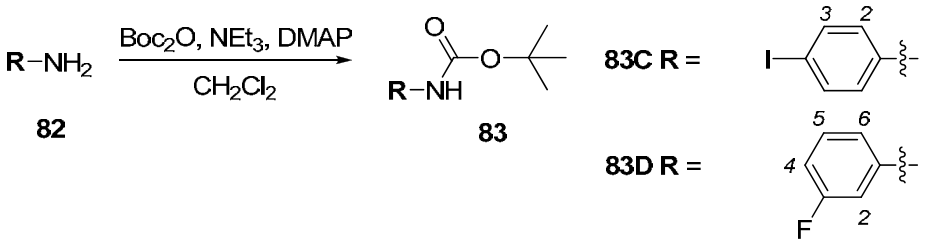
2.1.5 *tert*-Butyl *m*-tolylcarbamate (83E): Compound **83E** was synthesized from *m*-toluidine (0.500 mL, 4.67 mmol), NEt_3 (2.00 mL, 14.4 mmol) and Boc_2O (1.60 mL, 6.96 mmol) in MeOH (20 mL) to afford **83E** as a clear pale yellow solid (873 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 (s, 1H, 2-Ar*H*), 7.16 (t, J = 7.5 Hz, 1H, 6-Ar*H*), 7.09 (d, J = 8.0 Hz, 1H, 5-Ar*H*), 6.85 (d, J = 7.5 Hz, 1H, 4-Ar*H*), 6.41 (s, 1H, N*H*), 2.32 (s, 3H, CH_3), 1.52 (s, 9H, C(CH_3)$_3$).

2.1.6 *tert*-Butyl 4-methoxyphenylcarbamate (83F): Ccompound **83F** was synthesized from 4-methoxyaniline (403 mg, 3.27 mmol), NEt_3 (1.40 mL, 10.1 mmol) and Boc_2O 1.20 mL, 5.22 mmol) in MeOH (15 mL) to afford **83F** as a clear white

crystal (738 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 (d, J = 8.0 Hz, 2H, 2-Ar*H*), 6.83 (d, J = 9.0 Hz, 2H, 3-Ar*H*), 6.34 (s, 1H, N*H*), 3.78 (s, 3H, OCH_3), 1.51 (s, 9H, C(CH_3)$_3$).

Method II

General procedure 2



Scheme 2.2 Preparation of aryl carbamates **83C** and **83D** using DMAP as catalyst

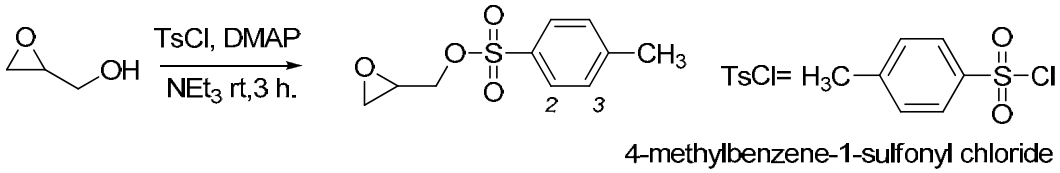
To a stirred solution of amine in CH_2Cl_2 (20 mL) was added NEt_3 and DMAP (10 mol%). After stirring for 10 minutes, Boc_2O was added into the mixture by syringe. The reaction mixture was stirred at ambient temperature for 2 hours under nitrogen atmosphere and quenched with aqueous HCl (2 M). The organic layer was separated and the aqueous layers was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (9:1).

2.1.7 *tert*-Butyl 4-iodophenylcarbamate (83C): Compound **83C** was synthesized from 4-iodoaniline (200 mg, 0.913 mmol), NEt_3 (0.400 mL, 2.88 mmol) and Boc_2O (0.320 g, 1.39 mmol), DMAP (11 mg) in CH_2Cl_2 (20 mL) to afford **83C** as a clear white crystal (218 mg, 75%).

2.1.8 *tert*-Butyl 3-fluorophenylcarbamate (83D): Compound **83D** was synthesized from 3-fluoroaniline (0.20 mL, 2.08 mmol), NEt_3 (1.00 mL, 7.19 mmol) and Boc_2O (0.70 mL, 3.04 mmol), DMAP (10 mg) in CH_2Cl_2 (20 mL) to afford **83D** as a white solid (406 mg, 88%).

2.2 Preparation of glycidyltosylate

General procedure



Scheme 2.3 Preparation of glycidyltosylate

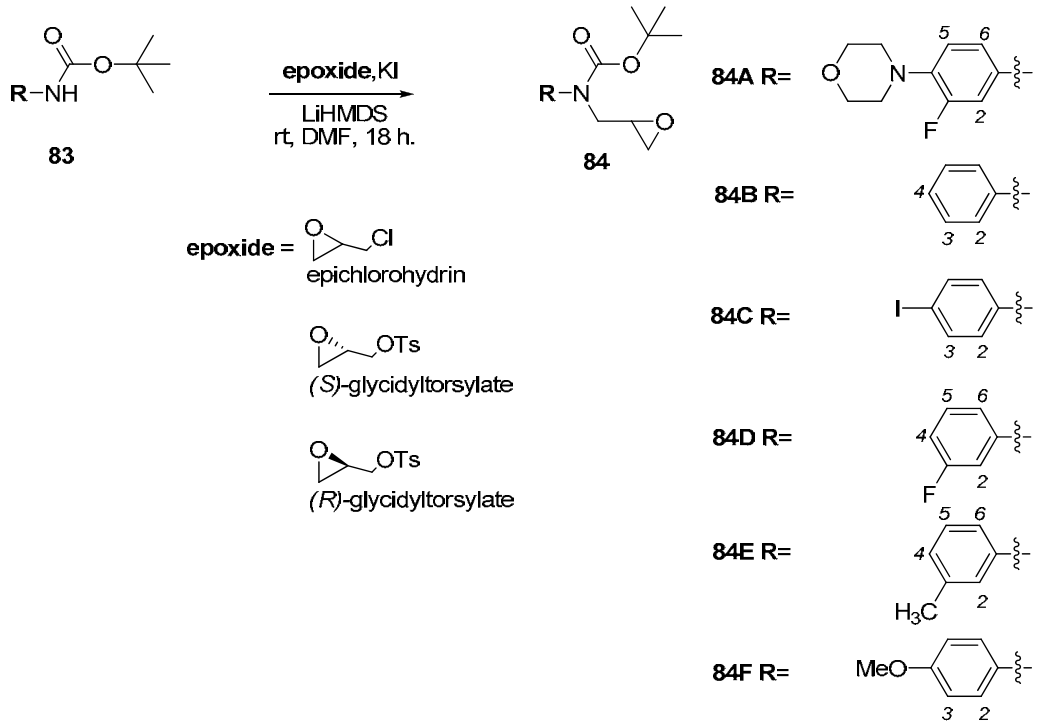
To a stirred solution of amine in CH_2Cl_2 (20 mL) was added NEt_3 and DMAP (10 mol%). After stirring for 10 minutes, a solution of TsCl in CH_2Cl_2 was added. The reaction mixture was stirred at ambient temperature for 3 hours under nitrogen atmosphere before being quenched with aqueous HCl (2 M) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (9:1).

2.2.1 Glycidyltosylate: The compound was synthesized from glycidol (0.38 mL, 5.72 mmol), TsCl (1.70 g., 8.92 mmol), NEt_3 (1.90 mL, 13.7 mmol), and 10 mol% DMAP in CH_2Cl_2 (20 mL) to afford glycidyltosylate as a clear oil (1.08 g., 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 (d, J=8.0 Hz, 2H, 2-Ar*H*), 7.35 (d, J = 8.0 Hz, 1H, 3-Ar*H*), 4.25 (dd, J = 3.5, 11.5 Hz, 1H, OCH_2CHO), 3.94 (dd, J = 6.0, 11.5 Hz, 1H, OCH_2CHO), 3.18 (m, 1H, OCH$_2$C*H*O), 2.81 (t, J = 4.5 Hz, 1H, OCH_2CHCH$_2$), 2.58 (dd, J = 2.5, 4.5 Hz, 1H, OCH_2CHCH$_2$), 2.44 (s, 3H, CCH_3).

2.2.2 *(S)*-Glycidyltosylate: The compound was synthesized from glycidol (0.50 mL, 7.53 mmol), TsCl (2.15 g., 11.3 mmol), NEt_3 (3.2 mL, 23.0 mmol), and 10% mol DMAP in CH_2Cl_2 20 mL to afford glycidyltosylate as a clear oil (882 mg, 57%). Physical and spectroscopic data were found to be identical to that of racemic glycidyltosylate.

2.3 Preparation of β-(*N*-arylcarbamyl)epoxides

General procedure



Scheme 2.4 Preparation of β-(*N*-arylcarbamyl)epoxides **84A-F**

To a stirred solution of aryl carbamate in DMF was added KI and epoxide. The 1 M solution of LiHMDS in THF was added dropwise. The reaction mixture was stirred at ambient temperature under nitrogen atmosphere for 18 hours before being quenched with deionized water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with deionized water several times to remove DMF, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo.* The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15).

2.3.1 *tert*-Butyl 3-fluoro-4-morpholinophenyl(oxiran-2-ylmethyl) carbamate (**84A**)**:** Compound **84A** was synthesized from *tert*-butyl 3-fluoro-4-morpholino phenylcarbamate (**83A**) (100 mg, 0.338 mmol), epichlorohydrin (0.0800 mL, 1.02 mmol), KI (160 mg, 1.00 mmol) and LiHMDS (0.80 mL, 0.80 mmol) in DMF 10 mL to afford **84A** as a clear oil (101 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.00 (m, 2H, 2-Ar*H*, 6-Ar*H*), 6.87 (t, J = 9.0, 1H, 5-Ar*H*), 3.87 (m, 4H,

NCH_2CH, OCH_2), 3.52 (dd, J = 5.5, 15.0 Hz, 1H, NCH_2CH), 3.22 (m, 1H, CH_2CHO), 3.07 (m, 4H, NCH_2), 2.81 (t, J = 4.5 Hz, 1H, CHCH_2O), 2.52 (dd, J = 2.5, 4.5 Hz, 1H, CHCH_2O), 1.45 (s, 9H, C(CH_3)$_3$).

2.3.2 *(S)*-*tert*-Butyl3-fluoro-4-morpholinophenyl(oxiran-2-ylmethyl) carbamate (*(S)*-84A): Compound ***(S)*-84A** was synthesized from **83A** (100 mg, 0.337 mmol), *(R)*-glycidyltosylate (230 mg, 1.00 mmol), KI (168 mg, 1.00 mmol) and LiHMDS (1.4 mL, 1.10 mmol) in DMF 10 mL to afford ***(S)*-84A** as a clear oil (98 mg, 83%). Physical and spectroscopic data were found to be identical to that of racemic **84A**.

2.3.3 *tert*-Butyl oxiran-2-ylmethyl(phenyl)carbamate (84B): Compound **84B** was synthesized from *tert*-butyl phenylcarbamate (**83B**) (200 mg, 1.04 mmol), KI (170 mg, 10.2 mmol), epichlorohydrin (0.82 mL, 10.5 mmol) and LiHMDS (2.00 mL, 2.00 mmol) in DMF 20 mL to afford **84A** as a clear oil (210 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40-7.20 (m, 5H, ArH), 3.87 (dd, J = 3.5, 14.5 Hz, 1H, NCH_2CH), 3.63 (dd, J = 5.5, 14.5 Hz, 1H, NCH_2CH), 3.24 (m, 1H, NCH_2CHCH_2), 2.79 (t, J = 4.5 Hz, 1H, NCH_2CHCH_2), 2.51 (dd, J = 2.5, 4.5 Hz, 1H, NCH_2CHCH_2), 1.44 (s, 9H, C(CH_3)$_3$).

2.3.4 *(R)*-tert-butyl oxiran-2-ylmethyl(phenyl)carbamate (*(R)*-84B): Compound ***(R)*-84B** was synthesized from **83B** (100 mg, 0.518 mmol), KI (260 mg, 1.57 mmol), *(S)*-glycidyltosylate (350 mg, 1.53 mmol) and LiHMDS (1.00 mL, 1.00 mmol) in DMF 10 mL to afford ***(R)*-84B** as a clear oil (210 mg, 85%). Physical and spectroscopic data were found to be identical to that of racemic **84B**.

2.3.5 *tert*-Butyl4-iodophenyl(oxiran-2-ylmethyl)carbamate (84C): Compound **84C** was synthesized from *tert*-butyl 4-iodophenylcarbamate (**83C**) (200 mg, 0.627 mmol), KI (312 mg, 1.88 mmol) epichlorohydrin (0.150 mL, 1.91 mmol) and LiHMDS (1.25 mL, 1.25 mmol) in DMF 20 mL to afford **84C** as a clear oil (170 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (d, J = 8.5 Hz, 2H, 3-ArH), 7.03 (d, J = 8.5 Hz, 2H, 2-ArH,), 3.93 (dd, J = 3.5, 15.0 Hz, 1H, NCH_2CH), 3.49

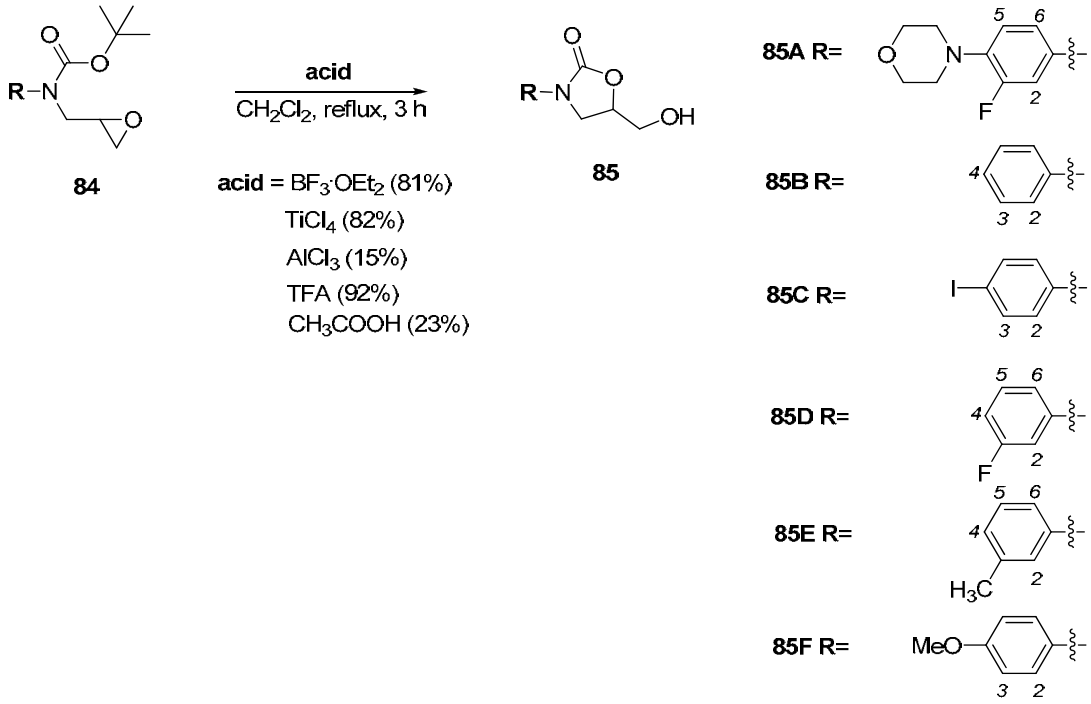
(dd, *J* = 6.0, 15.0 Hz, 1H, NC*H*$_2$CH), 3.23 (m, 1H, CH$_2$C*H*O), 2.80 (t, *J* = 4.5 Hz, 1H, CHC*H*$_2$O), 2.51 (dd, *J* = 2.5, 4.5 Hz, 1H, CHC*H*$_2$O), 1.44 (s, 9H, C(C*H*$_3$)$_3$).

2.3.6 *tert*-Butyl-3-fluorophenyl(oxiran-2-ylmethyl)carbamate (84D): Compound **84D** was synthesized from *tert*-butyl-3-fluorophenylcarbamate (**83D**) (103 mg, 0.486 mmol), KI (240 mg, 1.45 mmol), epichlorohydrin (0.11 mL, 1.40 mmol) and LiHMDS (0.95 mL, 0.95 mmol) in DMF 10 mL to afford **84D** as a clear oil (97.0 mg, 60%). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.28 (m, 1H, 2-Ar*H*), 7.06 (m, 2H, 5-Ar*H*, 6-Ar*H*), 6.91 (m, 1H, 4-Ar*H*), 3.94 (dd, *J* = 3.5, 14.5 Hz, 1H, NC*H*$_2$CH), 3.55 (dd, *J* = 5.5, 14.5 Hz, 1H, NC*H*$_2$CH), 3.24 (m, 1H, CH$_2$C*H*O), 2.82 (t, *J* = 4.5 Hz, 1H, CHC*H*$_2$O), 2.53 (dd, *J* = 2.5, 4.5 Hz, 1H, CHC*H*$_2$O), 1.46 (s, 9H, C(C*H*$_3$)$_3$). $[\alpha]_D^{24.8}$ = -36.85º (*c* = 1.00, CHCl$_3$).

2.3.7 *tert*-Butyl oxiran-2-ylmethyl(*m*-tolyl)carbamate (84E): Compound **84E** was synthesized from *tert*-butyl-*m*-tolylcarbamate (**83E**) (200 mg, 0.965 mmol), KI (800 mg, 4.80 mmol), epichlorohydrin (0.400 mL, 5.10 mmol) and LiHMDS (2.00 mL, 2.00 mmol) in DMF 20 mL to afford **84E** as a clear oil (156 mg, 62%). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.21 (t, *J* = 7.5 Hz, 1H, 2-Ar*H*), 7.10-7.00 (m, 3H, 4-Ar*H*, 5-Ar*H*, 6-Ar*H*), 3.83 (dd, *J* = 3.5, 14.5 Hz, 1H, NC*H*$_2$CH), 3.63 (dd, *J* = 5.5, 14.5 Hz, 1H, NC*H*$_2$CH), 3.23 (m, 1H, CH$_2$C*H*O), 2.79 (t, *J* = 4.5 Hz, 1H, CHC*H*$_2$O), 2.51 (dd, *J* = 2.5, 4.5 Hz, 1H, CHC*H*$_2$O), 2.34 (s, 3H, CC*H*$_3$), 1.45 (s, 9H, C(C*H*$_3$)$_3$).

2.3.8 *tert*-Butyl 4-methoxyphenyl(oxiran-2-ylmethyl) carbamate (84F): Compound **84F** was synthesized from *tert*-butyl-4-methoxyphenylcarbamate (**83F**) (200 mg, 0.857 mmol), KI (430 mg, 2.59 mmol), epichlorohydrin (0.20 mL, 2.55 mmol) and LiHMDS (1.70 mL, 1.70 mmol) in DMF 20 mL to afford **84F** as a clear oil (181 mg, 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.15 (d, *J* = 5.5 Hz, 2H, 2-Ar*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 3-Ar*H*), 3.79 (m, 4H, OC*H*$_3$, NC*H*$_2$CH), 3.58 (dd, *J* = 4.5, 15.0 Hz, 1H, NC*H*$_2$CH), 3.21 (m, 1H, CH$_2$C*H*O), 2.78 (t, *J* = 4.5 Hz, 1H, CHC*H*$_2$O), 2.49 (dd, *J* = 2.5, 4.5 Hz, 1H, CHC*H*$_2$O), 1.42 (s, 9H, C(C*H*$_3$)$_3$).

2.4. Preparation of *N*-aryl-2-oxazolidinones



Scheme 2.5 Preparation of *N*-aryl-2-oxazolidinones **85A-F**

2.4.1 Acid optimization

General procedure

To a solution of *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate **(84B)** in CH_2Cl_2 (10 mL) was added a variety of acid (5 equiv), acetic acid (CH_3COOH), trifluoroacetic acid (TFA), boron trifluoride diethyletherate ($BF_3{\cdot}OEt_2$), titanium (IV) chloride ($TiCl_4$), or aluminium trichloride ($AlCl_3$) and then refluxed for 2 hours. The reaction mixture was quenched with $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (4:1) to obtain 5-(hydroxymethyl)-3-phenyloxazolidin-2-one **(85B)**.

Using $BF_3{\cdot}OEt_2$ as acid: According to acid optimization procedure above, the *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate **(84B)** (210 mg, 0.844 mmol), $BF_3{\cdot}OEt_2$ (0.530 mL, 4.18 mmol) to afford **85B** as a white solid (133 mg, 81%).

Using $TiCl_4$ as acid: The *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate **(84B)** (112 mg, 0.450 mmol), $TiCl_4$ (0.25 mL, 2.27 mmol) to afford **85B** as a white solid (71 mg, 82%).

Using $AlCl_3$ as acid: The *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate **(84B)** (123 mg, 0.495 mmol), $AlCl_3$ (356 mg, 2.67 mmol) to afford **85B** as a white solid (40.0 mg, 15%).

Using TFA as acid: The *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate **(84B)** (209 mg, 0.822 mmol), TFA (0.315 mL, 4.11 mmol) to afford **85B** as a white solid (146 mg, 92%).

Using CH_3COOH as acid: The *tert*-butyl oxiran-2-ylmethyl(phenyl) carbamate **(84B)** (161 mg, 0.648 mmol), CH_3COOH (0.200 mL, 3.49 mmol) to afford **85B** as a white solid (28.8 mg, 23%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (d, J = 8.5 Hz, 2H, 2-Ar*H*), 7.38 (t, J = 7.5 Hz, 2H, 3-Ar*H*), 7.15 (dt, J = 1.0, 7.0, 7.0 Hz, 1H, 4-Ar*H*), 4.76 (m, 1H, CH_2CHO), 4.02 (m, 3H, NCH_2CH, $CHCH_2OH$), 3.77 (m, 1H, NCH_2CH), 2.14 (t, J = 6.5 Hz, 1H, O*H*).

2.4.2 Synthesis 2-oxazolidinone derivatives by acid cyclization

General procedure

To a solution of β-(*N*-arylcarbamyl)epoxides **84** in CH_2Cl_2 10 mL was added TFA and then refluxed for 2 hours. The reaction mixture was then quenched with aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo.* The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (4:1) to obtain 2-oxazolidinone derivatives.

3-(3-Fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one (85A): The *tert*-Butyl 3-fluoro-4-morpholinophenyl(oxiran-2-ylmethyl)carbamate **(84A)** (66.8 mg, 0.190 mmol) was used as a starting material, TFA (0.070 mL, 0.914

mmol) to afford **85A** (41 mg, 75%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.45 (dd, *J* = 2.5, 14.5 Hz, 1 H, 2-Ar*H*), 7.12 (ddd, *J* = 1.0, 2.5, 9.0 Hz, 1H, 6-Ar*H*), 6.92 (t, *J* = 9.0 Hz, 1H, 5-Ar*H*), 4.74 (m, 1H, CH_2CHO), 3.97 (m, 3H, NCH_2CH, $CHCH_2OH$), 3.87 (m, 4H, OCH_2), 3.75 (d, *J* = 12.5 Hz, 1H, NCH_2CH), 3.05 (m, 4H, NCH_2), 2.39 (s, 1H, O*H*).

***(R)*-3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one (*(R-)*85A):** The *tert*-Butyl 3-fluoro-4-morpholinophenyl(oxiran-2-ylmethyl)carbamate **(*(S)*-84A)** (144 mg, 0.408 mmol) was used as a starting material, TFA (0.16 mL, 2.04 mmol) to afford the corresponding ***(R)*-85A** (118 mg, 81%). Physical and spectroscopic data were found to be identical to that of racemic **85A**

5-(Hydroxymethyl)-3-phenyloxazolidin-2-one (85B): The *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate **(84B)** (209 mg, 0.822 mmol), TFA (0.315 mL, 4.11 mmol) to afford **85B** as a white solid (146 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (d, *J* = 8.5 Hz, 2H, 2-Ar*H*), 7.38 (t, *J* = 7.5 Hz, 2H, 3-Ar*H*), 7.15 (dt, *J* = 1.0, 7.0, 7.0 Hz, 1H, 5-Ar*H*), 4.76 (m, 1H, CH_2CHO), 4.02 (m, 3H, NCH_2CH, $CHCH_2OH$), 3.77 (m, 1H, NCH_2CH), 2.14 (s, *J* = 6.5 Hz, 1H, O*H*).

***(S)*-5-(hydroxymethyl)-3-phenyloxazolidin-2-one (*(S)*-85B):** The *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate **(*(S)*-84B)** (209 mg, 0.822 mmol), TFA (0.315 mL, 4.11 mmol) to afford the corresponding ***(S)*-85B**as a white solid (146 mg, 90%). Physical and spectroscopic data were found to be identical to that of racemic **85B**.

5-(Hydroxymethyl)-3-(4-iodophenyl)oxazolidin-2-one (85C): The *tert*-butyl 4-iodophenylcarbamate **(84C)** (141 mg, 0.376 mmol) was used as a starting material, TFA (0.15 mL, 1.96 mmol) to afford **85C** (100 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67 (d, *J* = 9.0 Hz, 2H, 3-Ar*H*), 7.33 (d, *J* = 9.0 Hz, 2H, 2-Ar*H*), 4.76 (m, 1H, CH_2CHO), 3.99 (m, 3H, NCH_2CH, $CHCH_2OH$), 3.76 (m, 1H, NCH_2CH), 2.08 (dd, *J* = 6.03, 7.17 Hz, 1H, O*H*).

3-(3-Fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one (85D): The *tert*-butyl-3-fluorophenyl(oxiran-2-ylmethyl)carbamate (**84D**) (97.0 mg, 0.364 mmol) was used as a starting material, TFA (0.20 mL, 2.07 mmol) to afford **85D** (71 mg, 93%).

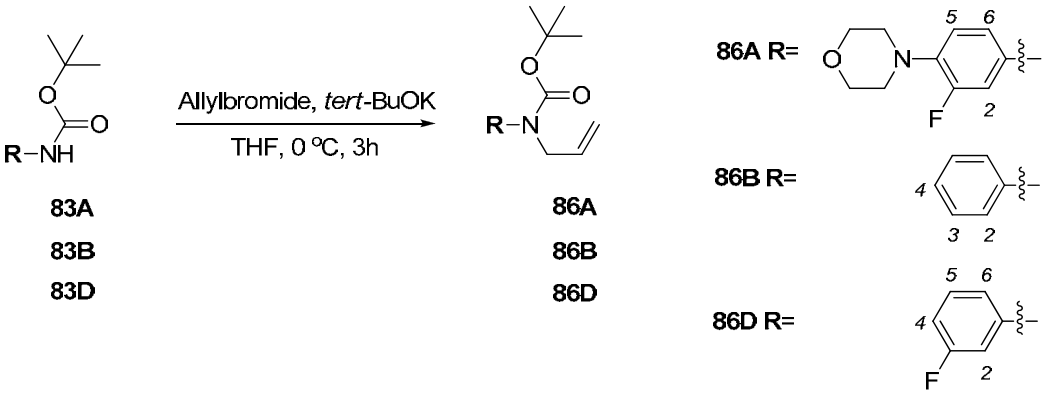
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (ddd, J = 2.0, 4.0, 11.0 Hz, 1H, 2-Ar*H*), 7.31 (m, 1H, 6-Ar*H*), 7.22 (d, J = 7.0 Hz, 1H, 5-Ar*H*), 6.83 (m, 1H, 4-Ar*H*), 4.75 (m, 1H, CH_2CHO), 4.00 (m, 3H, NCH_2CH, $CHCH_2OH$), 3.75 (m, 1H, NCH_2CH), 2.73 (t, J = 6.0 Hz, 1H, O*H*).

5-(Hydroxymethyl)-3-*m*-tolyloxazolidin-2-one (85E): The *tert*-butyl oxiran-2-ylmethyl(*m*-tolyl)carbamate (**84E)** (68.0 mg, 0.258 mmol) was used as a starting material, TFA (0.10 mL, 1.31 mmol) to afford **85E** (46.0 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (s, 1H, 2-Ar*H*), 7.28 (d, J = 8.5 Hz, 1H, 6-Ar*H*), 7.22 (t, J = 7.5 Hz, 1H, 5-Ar*H*), 6.93 (d, J = 7.0 Hz, 1H, 4-Ar*H*), 4.67 (m, 1H, CH_2CHO), 3.95 (m, 3H, NCH_2CH, $CHCH_2OH$), 3.73 (m, 1H, NCH_2CH), 2.44 (s, 1H, O*H*), 2.33 (s, 3H, CH_3).

5-(Hydroxymethyl)-3-(4-methoxyphenyl)oxazo-lidin-2-one (85F): The *tert*-butyl 4-methoxyphenyl(oxiran-2-ylmethyl) carbamate **(84F)** (181 mg, 0.648 mmol) was used as a starting material, TFA (0.25 mL, 3.27 mmol) to afford **85F** (109 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44 (d, J = 8.0 Hz, 2H, 2-Ar*H*), 6.91 (d, J = 8.0 Hz, 2H, 3-Ar*H*), 4.73 (m, 1H, CH_2CHO), 3.99 (m, 3H, NCH_2CH, $CHCH_2OH$), 3.77 (m, 4H, OCH_3, NCH_2CH), 2.19 (t, J = 5.5 Hz, 1H, O*H*).

2.5 Preparation of allylcarbamates

General procedure



Scheme 2.6 Preparation of allyl carbamates **86A**, **86B** and **86D**

Carbamates in THF were cooled to 0 ºC. A 1 M solution of *tert*-BuOK in THF was added dropwise to reaction mixture. After stirring at 0 ºC for an hour, allylbromide was added at 0 ºC and stirred for 2 hours under nitrogen atmosphere. The reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with hexane/CH_2Cl_2 (4:1).

2.5.1 *tert*-Butyl (3-fluoro-4-morpholinophenyl)allylcarbamate (86A): According to allyl formation above, compound **86A** was synthesized from *tert*-butyl 3-fluoro-4 morpholinophenylcarbamate **(83A)** (0.217 g, 0.730 mmol), 1 M solution of *tert*-BuOK in THF (1.00 mL, 1.00 mmol) and allylbromide (0.25 mL, 3.00 mmol) in THF (20 mL) to afford **86A** as clear white crystal (0.23 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 6.95 (m, overlapping, 2H, 2-Ar*H*, 6-Ar*H*), 6.85 (t, *J* = 9.0 Hz, 1H, 5-Ar*H*), 5.88 (m, 1H, CH_2CHCH_2), 5.13 (dd, *J* = 2.0, 13.5 Hz, 2H, NCH_2CHCH_2), 4.16 (d, *J*=5.5 Hz, 1H, NCH_2CHCH_2), 3.86 (m, 4H, OCH_2), 3.05 (s, 4H, NCH_2), 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 154.3, 137.7, 137.6, 134.0, 125.5, 122.1, 118.1, 116.5, 114.9, 114.5, 80.6, 66.9, 52.9, 50.9, 30.3, 28.2.

2.5.2 *tert*-Butyl (phenyl)allylcarbamate (86B): Compound **86B** was synthesized from *tert*-butyl phenylcarbamate **(83B)** (324 mg, 1.67 mmol), 1 M solution of *tert*-BuOK in THF (2.50 mL, 2.50 mmol) and allylbromide (0.57 mL, 6.70 mmol) in THF (20 mL) to afford **86B** as colorless oil (374 mg, 96%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.24 (m, 5H, Ar*H*), 5.92 (m, 1H, NCH_2CHCH_2), 5.14 (m, 2H, NCH_2CHCH_2), 4.22 (s, 2H, NCH_2CHCH_2), 1.44 (s, 9H, $C(CH_3)_3$).^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 154.5, 142.8, 134.3, 128.6, 126.3, 135.7, 116.4, 80.3, 52.9, 28.3. ν_{max}(neat) 3075, 2975, 1702, 1592, 1380, 1149.

2.5.3 *tert*-Butyl (3-fluorophenyl)allylcarbamate (86D): Compound **86D** was synthesized from *tert*-butyl 3-fluorophenylcarbamate **(83D)** (635 mg, 3.01mmol), 1 M solution of *tert*-BuOK in THF (4.5 mL, 4.5 mmol) and allylbromide (1.0 mL, 12.0 mmol) in THF (20 mL) to afford **86D** as clear white crystal (640 mg, 85%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.25 (dd, *J* = 8.0, 15.0 Hz, 1H, 2-Ar*H*), 7.01 (dd, *J* =

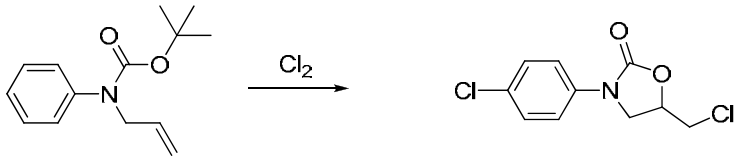
9.5, 14.0 Hz, 2H, 5-Ar*H*, 6-Ar*H*), 6.87 (ddt, *J* = 1.0, 2.5, 8.5, 8.5 Hz, 1H, 4-Ar*H*), 5.90 (m, 1H, $NCH_2C\mathit{H}CH_2$), 5.15 (m, 1H, $NCH_2CHC\mathit{H}_2$), 4.22 (td, *J* = 1.5, 1.5, 5.5 Hz, 2H, $NC\mathit{H}_2CHCH_2$), 1.45 (s, 9H, $C(C\mathit{H}_3)_3$)

2.6 Halogenation of alkene

2.6.1 Chlorination

- Synthesis of chloro 2-oxazolidinones

Method I



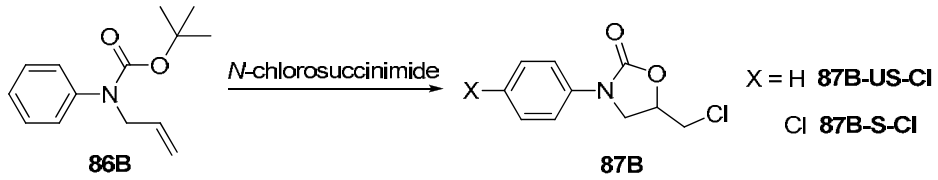
86B **87BCl$_2$**

Scheme 2.7 Preparation of 5-(Chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one (**87BCl$_2$**) using Cl_2

Chlorine gas (generated from $KMnO_4$ with conc. HCl) was added into the solution of *tert*-butyl allyl(phenyl)carbamate **86B** (100 mg, 0.429 mmol) in $CHCl_3$ 10 mL at ambient temperature and stirred for 1 hour. The reaction mixture was added with aqueous solution of $NaHCO_3$ for neutralization then extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product. Purification was accomplished by column chromatography (SiO_2) eluting with hexane/EtOAc (4:1) to obtain the 5-(chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one (**87BCl$_2$**) as white solid (53 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.49 (d, *J*=9.0 Hz, 2H, Ar-H_{ortho}), 7.34 (d, *J* = 9.0 Hz, 2H, Ar-H_{meta}), 4.90 (m, 1H, $NCH_2C\mathit{H}CH_2Cl$), 4.14 (t, *J* = 9.0 Hz, 1H, $NCH_2CHC\mathit{H}_2Cl$), 3.92 (m, 1H, $NCH_2CHC\mathit{H}_2Cl$), 3.79 (m, 2H, $NC\mathit{H}_2CHCH_2Cl$). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 153.7, 136.3, 129.5, 129.1, 119.4, 70.8, 47.9, 44.5. ν_{max} (neat) . HRMS m/z: 267.9960 $[M+Na]^+$

Method II

General procedure



Scheme 2.8 Preparation of 5-(Chloromethyl)-3-phenyloxazolidin-2-one (**87BCl**) and 5-(Chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one (**87BCl$_2$**) using NCS

N-chlorosuccinimide (NCS) was added into the solution of *tert*-butyl allyl(phenyl)carbamate in $CHCl_3$ 10 mL at ambient temperature and stirred 24 hours under an nitrogen atmosphere. The reaction mixture was added with cold water until a solution turned to turbid then extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as the pale yellow oil. Purification was accomplished by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15).

5-(Chloromethyl)-3-phenyloxazolidin-2-one (87BCl): According to bromo 2-oxazolidinone preparation above, compound **87BCl** was synthesized from the NCS (172 mg, 1.29 mmol), *tert*-butyl allyl(phenyl)carbamate (100 mg, 0.429 mmol) in $CHCl_3$ 10 mL to afford **87BCl** as white solid (6.0 mg, 6%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.55 (dd, J=1.0, 8.5 Hz, 2H, Ar-H_{ortho}), 7.39 (m, 1H, Ar-H_{ometa}), 7.16 (t, J = 7.5 Hz, 1H, Ar-H_{para}), 4.88 (m, 1H, NCH_2CHCH_2Cl), 4.18 (t, J = 9.0 Hz, 1H, NCH_2CHCH_2Cl), 3.97 (dd, J = 5.5, 9.0 Hz, 1H, NCH_2CHCH_2Cl), 3.78 (m, 2H, NCH_2CHCH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 153.9, 137.7, 129.16, 124.3, 118.3, 70.8, 48.1, 44.5. ν_{max} (neat) 3029, 2957, 1731, 1594, 1501, 1479, 1408. HRMS m/z: 234.0354 $[M+Na]^+$

5-(Chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one(87BCl$_2$): Compound **87BCl$_2$** was synthesized from the NCS (172 mg, 1.29 mmol), *tert*-butyl

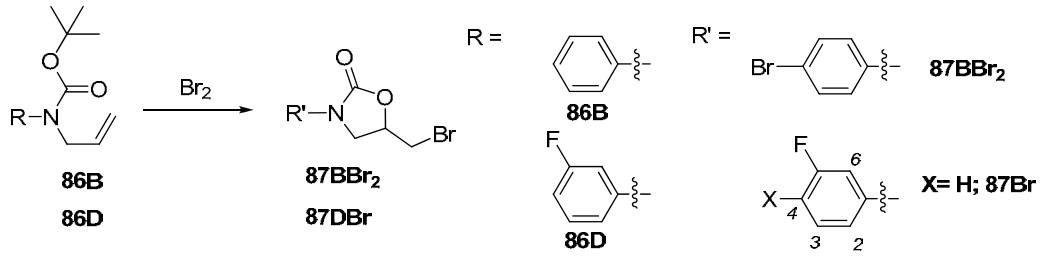
allyl(phenyl)carbamate (100 mg, 0.429 mmol) in DMF 10 mL to afford **87BCl$_2$** as white solid (28 mg, 26%).

2.6.2 Bromination

- Synthesis of bromo 2-oxazolidinones

Method III

General procedure I



Scheme 2.9 Preparation of 5-(Bromomethyl)-3-(4-bromophenyl)oxazolidin-2-one (**87BBr$_2$**), 5-(bromomethyl)-3-(3-fluorophenyl)oxazolidin-2-one (**87DBr**)

Bromine (Br_2) was added into the solution of *tert*-butyl allyl carbamate in $CHCl_3$ at ambient temperature, stirred for 1 hour under nitrogen atmosphere. The reaction mixture was added with saturated aqueous solution of $Na_2S_2O_3$ until an orange solution turned to a colorless solution, neutralized solution with saturated $NaHCO_3$ then extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (4:1).

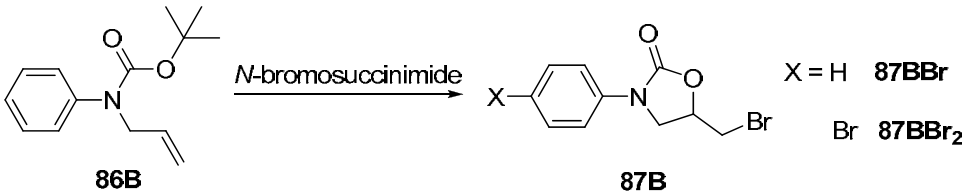
5-(Bromomethyl)-3-(4-bromophenyl)oxazolidin-2-one(87BBr$_2$): According to bromo 2-oxazolidinone preparation above, compound **87BBr$_2$** was synthesized from *tert*-butyl allyl(phenyl)carbamate (100 mg, 0.429 mmol, bromine (0.070 mL, 1.36 mmol) in $CHCl_3$ 10 mL to afford **87BBr$_2$** as a white solid (136 mg, 94 %). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.48 (m, 4H, Ar-H_{ortho}, Ar-H_{meta}, Ar-H_{para}), 4.88 (m, 1H, NCH_2CHCH_2Br), 4.16 (m, 1H, NCH_2CHCH_2Br), 3.90 (dd, J = 6.0, 9.0 Hz, 1H, NCH_2CHCH_2Br), 3.65 (dd, J = 4.0, 11.0 Hz, 1H, NCH_2CHCH_2Br), 3.57 (dd, J =

7.5, 11.0 Hz, 1H, NC*H*$_2$CHCH$_2$Br). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 153.7, 136.8, 132.0, 119.7, 117.1, 70.5, 49.0, 32.5. Mp124-125 ºC. ν_{max} (neat) 3102, 2961, 1754, 1498, 1417, 1403. HRMS m/z: 357.8845 $[M+Na]^+$

5-(bromomethyl)-3-(3-fluorophenyl)oxazolidin-2-one (87DBr): Compound **87DBr** was synthesized from **87D** (50 mg, 0.182 mmol and bromine (0.030 mL, 0.585 mmol) in $CHCl_3$ 10 mL. to afford **87BBr$_2$** as a white solid (44 mg, 88 %).^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.44 (m, 1H, 6-Ar*H*), 7.33 (m, 1H, 2-Ar*H*), 7.24 (dd, *J* = 7.0, 13.0 Hz, 1H, 3-Ar*H*), 6.85 (dd, *J* = 8.0, 14.0 Hz, 1H, 4-Ar*H*), 4.88 (m, 1H, NCH$_2$C*H*CH$_2$Br), 4.16 (m, 1H, NC*H*$_2$CHCH$_2$Br), 3.90 (m, 1H, NC*H*$_2$CHCH$_2$Br), 3.64 (m, 1H, NCH$_2$CHC*H*$_2$Br), 3.57 (m, 1H, NCH$_2$CHC*H*$_2$Br).

Method IV

General procedure II



Scheme 2.10 Preparation of 5-(Bromomethyl)-3-phenyloxazolidin-2-one (**87BBr**) and 5-(Bromomethyl)-3-(4-bromophenyl)oxazolidin-2-one (**87BBr$_2$**) using NBS

N-bromosuccinimide (NBS) was added into the solution of *tert*-butyl allyl(phenyl)carbamate in CH_3CN 20 mL at ambient temperature and stirred 24 hours under an nitrogen atmosphere. Cold water was added until a solution turned to turbid then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as the pale yellow oil. Purification was accomplished by column chromatography (SiO_2) eluting with hexane/EtOAc (4:1).

5-(Bromomethyl)-3-phenyloxazolidin-2-one (87BBr): According the preparation above, compound **87BBr** was synthesized from the NBS (84 mg, 0.472 mmol), *tert*-butyl allyl(phenyl)carbamate (0.050 mg, 0.214 mmol) in CH_3CN 20 mL

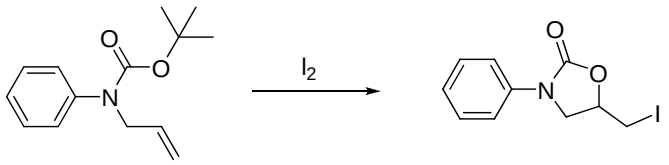
to afford **87BBr** as white solid (71 mg, 99%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.55 (dd, *J* = 1.0, 9.0 Hz, 1H, Ar-H_{ortho}), 7.40 (m, 1H, Ar-H_{meta}), 7.17 (tt, *J* = 1.0, 7.5 Hz, 1H, Ar-H_{para}), 4.87 (m, 1H, NCH_2CHCH_2Br), 4.19 (t, *J* = 9.0, Hz, 1H, NCH_2CHCH_2Br), 3.94 (dd, *J* = 6.0, 9.0 Hz, 1H, NCH_2CHCH_2Br), 3.66 (dd, *J* = 4.0, 10.5 Hz, 1H, NCH_2CHCH_2Br), 3.56 (dd, *J* = 7.5, 10.5 Hz, 1H, NCH_2CHCH_2Br). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 153.9, 137.7, 129.2, 124.4, 118.4, 70.6, 49.3, 32.6. Mp 97-98 ºC. ν_{max} (neat) 3034, 2917, 1755, 1594, 1504, 1480, 1410. HRMS m/z: 277.9750 $[M+Na]^+$

5-(bromomethyl)-3-(4-bromophenyl)oxazolidin-2-one(87BBr$_2$): Compound **87BBr$_2$** was synthesized from the NBS (380 mg, 2.13 mmol) *tert*-butyl allyl(phenyl)carbamate (100 mg, 0.429 mmol) in CH_3CN 10 mL to afford **87BBr$_2$** as white solid (98 mg, 68%).

2.6.3 Iodination

- Synthesis of iodo 2-oxazolidinones

Method V



86B **87BI**

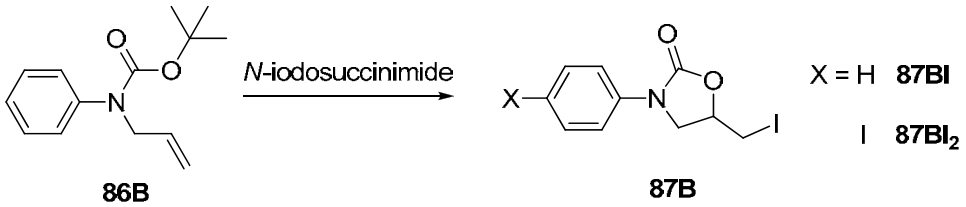
Scheme 2.11 Preparation of 5-(iodomethyl)-3-phenyloxazolidin-2-one (**87BI**) using I_2

Iodine (I_2) (913 mg, 3.60 mmol) was dissolved with toluene 20 mL at 50 ºC. Then *tert*-butyl allyl(phenyl)carbamate (150 mg, 0.643 mmol) was added into the solution at 50 ºC and stirred 24 hours under an nitrogen atmosphere. The reaction mixture was added with saturated aqueous solution of saturated $Na_2S_2O_3$ until a dark brown solution turned to a colorless solution then extracted with EtOAc(3 x 10 mL). The combined organic extracted layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as the pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with

hexane/EtOAc (85:15) to afford 5-(iodomethyl)-3-phenyloxazolidin-2-one (**87BI**) as white solid (410 mg, 64%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.53 (d, *J* = 8.0 Hz, 1H, Ar-H_{ortho}), 7.38 (t, *J* = 8.0 Hz, 1H, Ar-H_{meta}), 7.15 (t, *J* = 7.5 Hz, 1H, Ar-H_{para}), 4.70 (m, 1H, NCH_2CHCH_2I), 4.16 (t, *J* = 9.0 Hz, 1H, NCH_2CHCH_2I), 3.78 (dd, *J* = 6.0, 9.0 Hz, 1H, NCH_2CHCH_2I), 3.45 (dd, *J* = 4.0, 10.5 Hz, 1H, NCH_2CHCH_2I), 3.35 (dd, *J* = 8.0, 10.5 Hz, 1H, NCH_2CHCH_2I). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 154.0, 137.7, 129.0, 124.3, 118.3, 71.1, 50.9, 6.2. Mp 97-98 ºC. ν_{max}(neat) 3041, 2916, 1742, 1602, 1502, 1473, 1403. HRMS m/z: 325.9623 $[M+Na]^+$

Method VI

General procedure



Scheme 2.12 Preparation of 5-(Iodomethyl)-3-phenyloxazolidin-2-one (**87BI**) and 5-(Iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one (**87BI$_2$**) using NIS

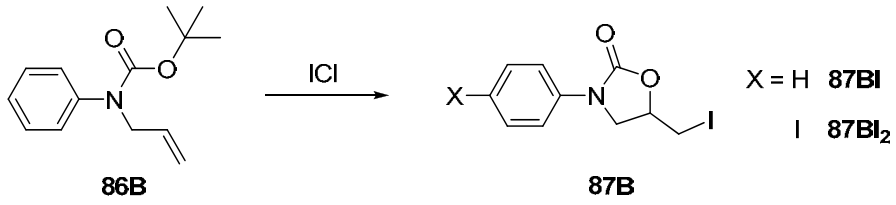
N-iodosuccinimide (NIS) was added into the solution of *tert*-butyl allyl(phenyl)carbamate in CH_3CN at ambient temperature and stirred overnight under an nitrogen atmosphere. DI water and saturated $Na_2S_2O_3$ were added until a orange solution turned to a colorless solution then extracted with EtOAc (3 x 10 mL). The combined organic extracted layer were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15).

5-(Iodomethyl)-3-phenyloxazolidin-2-one (87BI): According the preparation above, compound **87BI** was synthesized from the *N*-iodosuccinimide (NIS) (212 mg, 0.946 mmol) *tert*-butyl allyl(phenyl)carbamate (100 mg, 0.429 mmol) in CH_3CN 20 mL to afford **87BI** as white solid (121 mg, 93%).

5-(Iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one (87BI$_2$): Compound **87BI$_2$** was synthesized from the NIS (480 mg, 2.13 mmol), *tert*-butyl allyl(phenyl)carbamate (100 mg, 0.429 mmol) and TFA (0.23 mL, 3.00 mmol) in CH_3CN 20 mL to afford **87BI$_2$** as white solid (137 mg, 74%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.68 (d, *J* = 8.5 Hz, 1H, Ar-H_{meta}), 7.32 (d, *J* = 8.5 Hz, 1H, Ar-H_{ortho}), 4.74 (m, 1H, NCH_2CHCH_2I), 4.15 (t, *J* = 9.0 Hz, 1H, NCH_2CHCH_2I), 3.76 (dd, *J* = 6.0, 9.0 Hz, 1H, NCH_2CHCH_2I), 3.47 (dd, *J* = 4.0, 10.0 Hz, 1H, NCH_2CHCH_2I), 3.35 (dd, *J* = 8.5, 10.0 Hz, 1H, NCH_2CHCH_2I). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 153.7, 137.9, 137.5, 120.0, 87.8, 71.1, 50.6, 6.0. Mp 148-149 ºC. ν_{max}(neat) 3095, 2914, 1747, 1487, 1417, 1394. HRMS m/z: 451.8568 $[M+Na]^+$

Method VII

General procedure



Scheme 2.13 Preparation of 5-(Iodomethyl)-3-phenyloxazolidin-2-one (**87BI**) and 5-(Iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one (**87BI$_2$**) using ICl

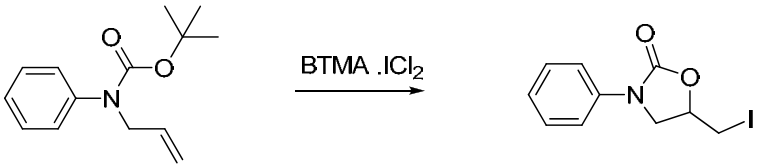
Iodinemonochloride (ICl) was added into the solution of *tert*-butyl allyl(phenyl)carbamate and $CaCO_3$ in mixed solvent $CHCl_3$ and MeOH (3:1) at ambient temperature and stirred 24 hour under an nitrogen atmosphere. A solution of 40% sodiumbisulfite was added to the reaction mixture until a dark brown solution turned to a colorless solution extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracted layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15).

5-(Iodomethyl)-3-phenyloxazolidin-2-one (87BI): According the preparation above, compound **87BI** was synthesized from ICl (24 mg, 0.517 mmol), *tert*-butyl

allyl(phenyl)carbamate (100 mg, 0.429 mmol), $CaCO_3$ (86 mg, 0.86 mmol) in mixed solvent $CHCl_3$ and MeOH (3:1) to afford **87BI** as white solid (93 mg, 71%).

5-(Iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one (87BI$_2$): Compound **87BI$_2$** was synthesized from ICl (0.10 mL, 1.20 mmol), *tert*-butyl allyl(phenyl)carbamate (100 mg, 0.429 mmol), $CaCO_3$ (386 mg, 3.86 mmol) in mixed solvent $CHCl_3$ and MeOH (3:1) to afford **87BI$_2$** as white solid (137 mg, 74% yield).

Method VIII



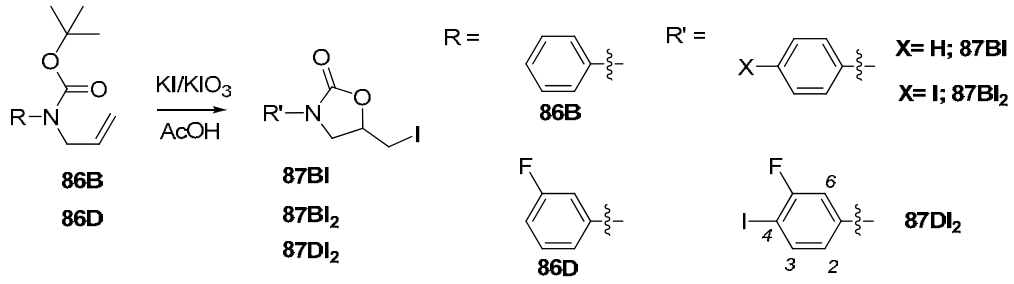
86B 87BI

Scheme 2.14 Preparation of 5-(Iodomethyl)-3-phenyloxazolidin-2-one (**87BI**) using BTMA·ICl_2

Benzyltrimethylaluminium dichloroiodate (BTMA·ICl_2) (158 mg, 0.472 mmol) was added into the solution of *tert*-butyl allyl(phenyl)carbamate (50 mg, 0.214 mmol) in $CHCl_3$ at ambient temperature and stirred 24 hours under an nitrogen atmosphere. A saturated $Na_2S_2O_3$ was added to the reaction mixture until a yellow solution turned to a colorless solution then extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracted layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo.* The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15) to afford 5-(iodomethyl)-3-phenyloxazolidin-2-one (**87BI**) as white solid (93 mg, 71%).

Method IX

General procedure



Scheme 2.15 Preparation of 5-(Iodomethyl)-3-phenyloxazolidin-2-one (**87BI**), 5-(Iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one (**87BI$_2$**), and 3-(3-fluoro-4-iodophenyl)-5-(iodomethyl)oxazolidin-2-one (**87DI$_2$**) using KI/KIO_3

KI and KIO_3 was added into the solution of *tert*-butyl allyl(phenyl)carbamate (**86B**) in acetic acid 5 mL at 120 ºC and stirred until the pink vapor of iodine fade away from reaction (about 3 hours) under an nitrogen atmosphere. DI-water and saturated $Na_2S_2O_3$ was added to the reaction mixture until a dark brown solution turned to a colorless solution then extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracted layers were neutralized with saturated aqueous solution of saturated $NaHCO_3$, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15).

5-(Iodomethyl)-3-phenyloxazolidin-2-one (**87BI**): According to the preparation above, compound **87BI** was synthesized from KI (43 mg, 0.260 mmol), KIO_3 (55 mg, 0.0.259 mmol), **86B** (50 mg, 0.214 mmol) in acetic acid 5 mL to afford **87BI** as white solid (59 mg, 91%).

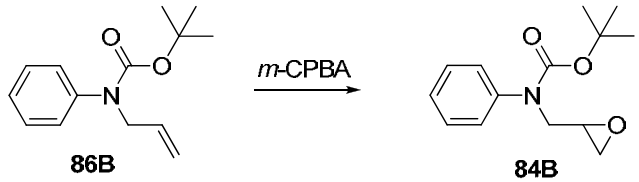
5-(Iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one (**87BI$_2$**): Compound **87BI$_2$** was synthesized from KI (156 mg, 0.940 mmol), KIO_3 (202 mg, 0.948 mmol), **86B** (100 mg, 0.429 mmol) in acetic acid 5 mL to afford **87BI$_2$** as white solid (163 mg, 89% yield).

3-(3-fluorophenyl)-5-(iodomethyl)oxazolidin-2-one (**87DI$_2$**): Compound **87DI** was synthesized from KI (100 mg, 0.602 mmol), KIO_3 (128 mg, 0.600 mmol), **86D** (50 mg, 0.200 mmol) in acetic acid 5 mL to afford **87BI$_2$** as pale yellow oil (57 mg, 64% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.71 (dd, *J* = 7.0, 8.5 Hz, 1H, 6-Ar*H*), 7.48 (dd, *J* = 2.5, 10.0 Hz, 1H, 2-Ar*H*), 7.07 (dd, *J* = 2.5, 8.5 Hz, 1H, 3-Ar*H*), 4.75 (m, 1H, NCH_2CHCH_2I), 4.15 (t, *J* = 9.0 Hz, 1H, NCH_2CHCH_2I), 3.76 (dd, *J* = 6.0, 9.0 Hz, 1H, NCH_2CHCH_2I), 3.48 (dd, *J* = 4.0, 10.5 Hz, 1H, NCH_2CHCH_2I), 3.36 (dd, *J* = 9.0, 10.5 Hz, 1H, NCH_2CHCH_2I). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 163.1, 160.7, 153.5, 139.3, 115.1, 106.2, 105.9, 74.7, 74.4, 71.2, 50.8, 5.9. ν_{max}(neat) 3099, 2942, 1752, 1595, 1471, 1402. HRMS m/z: 469.8629 $[M+Na]^+$

2.7 Oxidation of terminal alkene

Method I

General procedure



Scheme 2.16 Preparation of *tert*-Butyl oxiran-2-ylmethyl(phenyl)carbamate (**84B**)

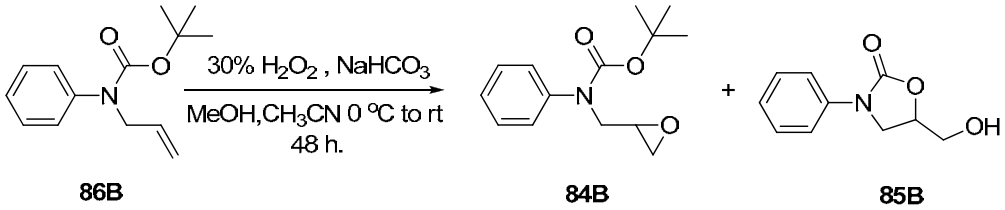
70% 3-chloroperbenzoic acid (*m*-CPBA) was added into a solution mixture of *tert*-butyl allyl carbamate (**86**) in CH_2Cl_2 (20 mL) at 0 ºC to ambient temperature and stirred overnight under nitrogen atmosphere. The reaction mixture was added with the solution of saturated $NaHCO_3$ for neutralization then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracted layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as the dark brown oil. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (85:15).

***tert*-Butyl oxiran-2-ylmethyl(phenyl)carbamate 84B**: According to the preparation above, compound **84B** was synthesized from 70% 3-chloroperbenzoic

acid *(m*-CPBA) (2.65 g, 15.3 mmol), **86B** (511 mg, 2.19 mmol) in CH_2Cl_2 20 mL to obtain **3B** as clear oil (25 mg, 5%).

***tert*-Butyl oxiran-2-ylmethyl(phenyl)carbamate 84B**: Compound **84B** was synthesized from *m*-CPBA (214 mg, 1.24 mmol), **83B** (203 mg, 0.868 mmol) and *(R,R)* Jacobsen catalyst (22 mg, 0.035 mmol)in CH_2Cl_2 20 mL to obtain **84B** as clear oil (24 mg, 11%).

Method II



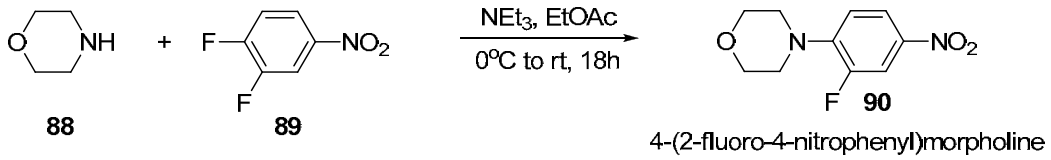
86B 84B 85B

Scheme 2.17 Preparation of **84B** using Payne oxidation

30% H_2O_2 (1.00 mL, 14 equiv.) was added into a solution mixture *tert*-butyl allyl(phenyl)carbamate (150 mg, 0.643 mmol) and $NaHCO_3$ (54 mg, 0.643 mmol) in MeOH (3.21 mL) and CH_3CN (0.68 mL, 20 equiv) at 0 ºC and stirred for 48 hours at ambient temperature. The reaction mixture was evaporated under reduced pressure, extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as the pale yellow oil. Purification was accomplished by column chromatography with 5-50% EtOAc in hexane, and 10 % Methanol in EtOAc to obtain the *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate (**84B**) (54 mg, 34%) as clear oil and 5-(hydroxymethyl)-3-phenyloxazolidin-2-one (**85B**) as white solid. (27 mg, 22%)

2.8 Preparation of Linezolid

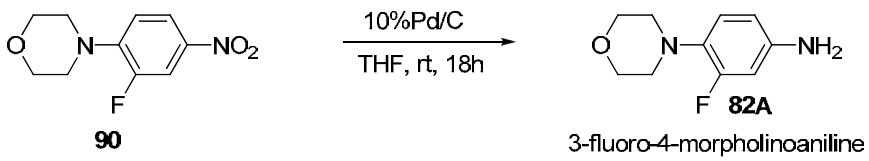
2.8.1 Preparation of 4-(2-fluoro-4-nitrophenyl)morpholine



Scheme 2.18 Preparation of 4-(2-fluoro-4-nitrophenyl)morpholine (**90**)

In a 250 mL, a round bottomed flask equipped with a magnetic stirring bar, to a stirred of a solution of morpholine (**88**) (2.75 mL, 31.58 mmol) and NEt_3 (4.40 mL, 31.60 mmol) in EtOAc(20 mL) was added dropwise into 3,4-difluoronitrobenzene (**89**) (3.18 mL, 31.49 mmol) at 0 ºC to ambient temperature and stirred for 18 h under an nitrogen atmosphere. The reaction mixture was added with saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as a yellow solid. Purification was accomplished by mixed solvent crystallization using acetone and water to afford a 4-(2-fluoro-4-nitrophenyl)morpholine (**90**) as yellow crystal (6.65 g, 93%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.99 (ddd, J = 0.96, 2.5, 9.0 Hz, 1H, Ar-H_{ortho}), 7.91 (dd, J = 2.5, 13.0 Hz, 1H, Ar-H_{ortho}), 6.92 (t, J = 8.76, 1H, Ar-H_{meta}), 3.87 (m, 4H, OCH_2), 3.28 (m, 4H, NCH_2) ^{13}C NMR (100 MHz,$CDCl_3$) δ_C (ppm): 154.2, 151.7, 145.4, 140.7), 120.9, 116.8, 112.6, 66.5, 49.8. ESIMS m/z: 227.1 $[M+H]^+$

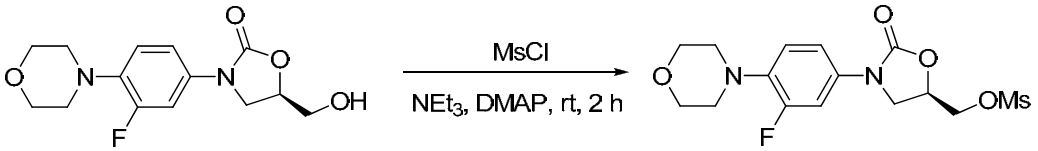
2.8.2 Preparation of 3-fluoro-4-morpholinoaniline



Scheme 2.19 Preparation of 3-fluoro-4-morpholinoaniline (**82A**)

Hydrogen gas (in balloon) was added into a solution mixture of 4-(2-fluoro-4-nitrophenyl)morpholine (**83A**) (6.12 g., 27.05 mmol) and 10% palladium on carbon (2.88 g, 2.70 mmol) in dry tetrahydrofuran (100 mL) at ambient temperature. The mixture was stirred for 18 h at room temperature under hydogen atmosphere. The reaction mixture was filtered through celite and the solids were washed with tetrahydrofuran. The filtrate was concentrated *in vacuo* to yield the crude product as a white and pale red solid. Purification was accomplished by column chromatography (SiO_2) eluting with hexane/EtOAc (4:1) to obtain the 3-fluoro-4-morpholinoaniline (**82A**) as white solid (4.76 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 6.79 (t, J=9.02 Hz, 1H, Ar-H_{meta}), 6.41 (m, 2H, Ar-H_{ortho}), 3.85 (m, 4H, OCH_2), 3.57 (s, 2H, NH), 2.96 (m, 4H, NCH_2).

2.8.3 Preparation of (3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methylmethanesulfonate (91)

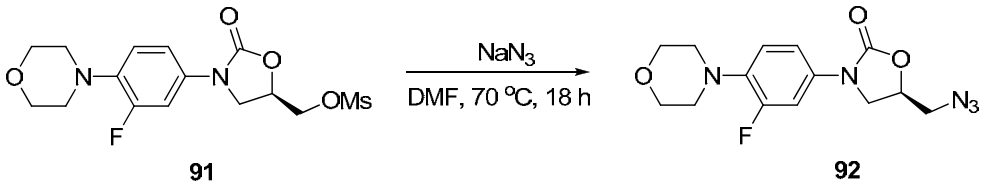


Scheme 2.20 Preparation of (3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methylmethanesulfonate (**91**)

In a 100 mL, a round bottomed flask equipped with a magnetic stirring bar a mixture of 3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one (**85A**) (100 mg, 0.338 mmol), NEt_3 (0.14 mL, 1.00 mmol) and 10%mol DMAP in dried CH_2Cl_2 20 mL was stirred at 0 ºC. The solution of MsCl was added into the mixture by syringe. The mixture was stirred at 0 ºC to ambient temperature for 2 hours under a nitrogen atmosphere. The reaction mixture was added with aqueous solution of 2 M HCl and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (1:1) to furnish (3-(3-fluoro-4-morpholinophenyl)-2-

oxooxazolidin-5-yl) methylmethanesulfonate (**91**) as a white solid (120 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.45 (dd, *J* = 2.5, 14.0 Hz, 1H, Ar-H_{ortho}), 7.10 (ddd, *J* = 1.0, 2.5, 8.5 Hz, 1H, Ar-H_{ortho}), 6.98 (t, *J* = 9.0 Hz, 1H, Ar-H_{meta}), 4.92 (m, 1H, CH_2CHO), 4.50 (dd, *J* = 4.0, 11.5 Hz, 1H, $CHCH_2OMs$), 4.42 (dd, *J* = 4.0, 11.5 Hz, 1H, $CHCH_2OMs$), 4.12 (t, *J* = 9.12 Hz, 1H, NCH_2CH), 3.91 (m, 5H, NCH_2CH, OCH_2), 3.10 (s, 1H, OSO_2CH_3), 3.07 (m, 4H, NCH_2).

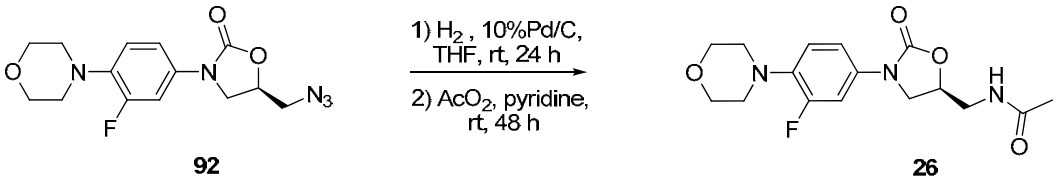
2.8.4 Preparation of 5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one (92)



Scheme 2.21 Preparation of 5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one (**92**)

Sodium azide (190 mg, 1.15 mmol) was added into the solution of **91** (109 mg, 0.292 mmol) in DMF (20 mL). The mixture was heated up to 70 ºC for 18 hours. After cooling, the reaction mixture was added with DI-water and ethyl acetate. The phases were separated, and the aqueous portion was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to yield the crude product as the pale yellow oil. The crude product was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (1:1) to obtain 5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazo lidin-2-one (**92**) as a colorless oil (175 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.44 (dd, *J* = 2.5, 14.5 Hz, 1H, Ar-H_{ortho}), 7.11 (ddd, *J* = 1.0, 2.5, 8.5 Hz, 1H, Ar-H_{ortho}), 6.93 (t, *J* = 9.0 Hz, 1H, Ar-H_{meta}), 4.78 (m, 1H, CH_2CHO), 4.04 (t, *J* = 9.0 Hz, 1H, NCH_2CH), 3.86 (m, 4 H, OCH_2), 3.81 (dd, *J* = 6.0, 9.0 Hz, 1H, NCH_2CH), 3.70 (dd, *J* = 4.49, 13.24 Hz, 1H, $CHCH_2N_3$), 3.58 (dd, *J* = 4.5, 13.0 Hz, 1H, $CHCH_2N_3$), 3.05 (m, 4H, NCH_2).

2.8.5 Preparation of N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl methyl)acetamide (26)



92 26

Scheme 2.22 Preparation of N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl methyl)acetamide (**26**)

Hydrogen gas (in balloon) was added into a solution mixture azido compound **92** (85 mg, 0.266 mmol) and 10% palladium on carbon in dried tetrahydrofuran (10 mL) at ambient temperature. The mixture was stirred for 18 h at room temperature under hydogen atmosphere and concentrated *in vacuo* then equipped with a magnetic stirring bar. The reaction mixture was added with pyridine (1.0 mL, 12.4 mmol), flushed with nitrogen gas and cooled to 0 ºC. An acetic anhydride (0.08 ml, 0.85 mmol) was added slowly in the reaction mixture. The reaction mixture was stirred for 18 h under nitrogen atmosphere at room temperature. The reaction mixture was filtered through celite and the solids were washed with ethyl acetate. The filtrate was concentrated *in vacuo* to yield the crude product as a white and pale red solid. Purification was accomplished by column chromatography (SiO_2) eluting with MeOH/EtOAc (1:4) to obtain **26** as orange solid and then recrystallization with EtOAc and hexane to obtain pale yellow solid (37 mg, 42%). ^{1}H NMR (400 MHz,$CDCl_3$) δ_H (ppm): 7.41 (dd, *J* = 2.0, 14.5 Hz, 1H, Ar-H_{ortho}), 7.05 (d, *J* = 9.0 Hz, 1H, Ar-H_{ortho}), 6.90 (t, *J* = 9.0 Hz, 1H, Ar-H_{meta}), 6.59 (t, *J* = 6.0 Hz, 1H, (CO)N*H*), 4.76 (dt, *J* = 4.5, 9.5, 9.5 Hz, 1H, NCH_2CHCH_2), 4.00 (t, *J* = 9.0 Hz, 1H, $NCH_2CHCH_2NH(CO)$), 3.85 (m, 4H, OCH_2CH_2N), 3.75 (dd, *J* = 7.0, 9.0 Hz, 1H, $NCH_2CHCH_2NH(CO)$), 3.63 (t, *J* = 6.0 Hz, 2H, $NCH_2CHCH_2NH(CO)$), 3.03 (m, 4H, OCH_2 CH_2N), 2.00 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm): 171.2, 156.6, 154.4, 136.5, 136.4, 132.9, 132.8, 118.8, 113.9, 113.9, 107.6, 107.3, 72.0, 66.9, 50.9, 47.5, 41.8, 23.0. ESIMS m/z: 338.4 $[M+H]^+$

2.9 Stereochemistry study

2.9.1 High performance liquid chromatography (HPLC)

Normal-phase HPLC, the %ee was performed on normal-phase HPLC with UV detector at 260 nm. The samples 1 mg in hexane and a little amount of isopropanol were filtered through a nylon membrane filtter (0.45 μm). A Chiralcel® OJ-H column (cellulose tris(4-methylbenzoate)coated on 5μm silica gel particle HPLC column 250 x 4.6 mm ID) analytical column and Chiralcel® OD column (cellulose tris (3,5-dimethylphenylcarbamate)coated on 10μm silica gel particle HPLC column 250 x 4.6 mm ID) analytical column were used for analytical purpose. The eluents were hexane (solvent A) and isopropanol (solvent B). The isocratic system was A : B (70 : 30) over a period of 40 minutes at flow rate 0.8 mL/min. on OJ-H column, and A : B (99 : 1) over a period of 30 minutes at flow rate 1.0 mL/min. on OD column. The %ee value was calculated by peak area data.

2.9.2 Gas chromatography (GC)

Chiral GC, the %ee were performed on chiral GC with FID detector (makeup gas, N_2 : 30 mL/min, hydrogen : 30 mL/min, air : 300 mL/min). Samples 1 mg were dissolved in a little amount of acetone. 30%BSiMe in OV-1701 as stationary phase (15.356 m x 0.25 mm x 0.25 μm) analytical column was use for analytical purpose. The carrier gas was hydrogen 50 cm/s. The injector temperature was 250 ℃. The isothermal system depended on each samples over a period of 30 to 60 minutes. The %ee value was calculated by peak area data.

2.9.3 Optical rotations

The sample 20 mg was dissolved in $CHCl_3$ 2 mL and added in cuvett (10 mm length). The specific rotation was measured using sodium light (D line, 589.3 nm) at ambient temperature on Jasco P-1010 Polarimeter.

2.9.5 Percent inversion (%inv)

To determine the quantitative value of inversion products compared with retention products, the percent of *R* and *S* configuration products were translated into percent inversion (%inv) representing percent occurrences of S_N2 products. In the case of the reaction that convert *S* to *R* configuration, %inv can be calculated according to the following equation 2.1

$$\%inv = \frac{100(Pdt.\ (R) - Sm.(R))}{Sm.(S)\text{-}Sm.(R)} \qquad \text{(equation 2.1)}$$

where; *Pdt. (R)* = *R* products

Sm. (R) = *R* starting material

Sm. (S) = *S* starting material

Moreover, it can be calculated following equation 2.2

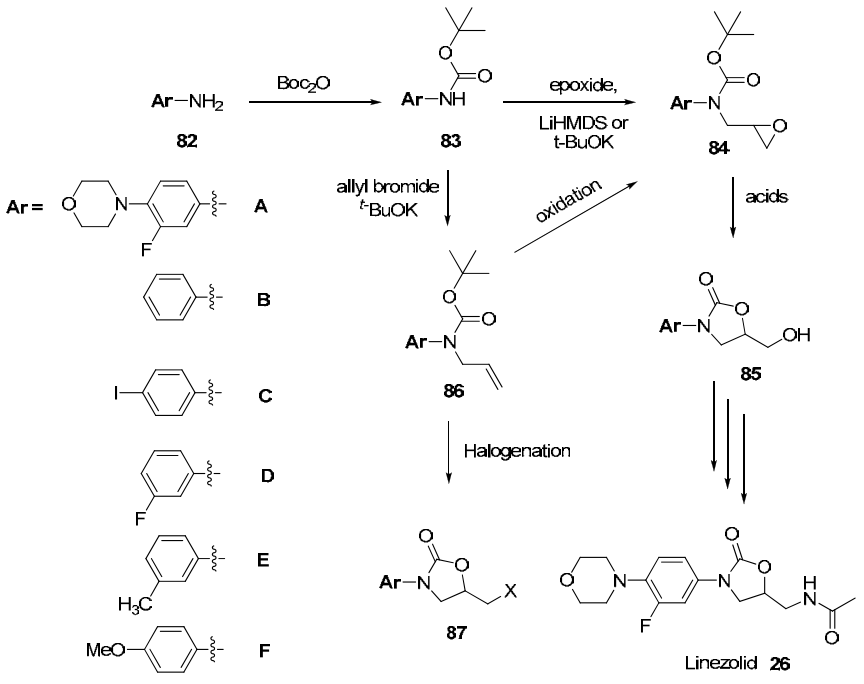
$$\%S_N2 = \frac{50(\%ee\ Pdt. - \%ee\ Sm.)}{\%ee\ Sm.} \qquad \text{(equation 2.2)}$$

CHAPTER III

RESULTS AND DISCUSSION

Synthesis

Two synthesis pathways of *N*-Aryl-2-oxazolidinone involving two different cyclizations of two types of *tert*-butyl carbamates were investigated. In the first pathway, β-(*N*-arylcarbamyl)epoxides (**84**) were prepared as cyclization substrate by either alkylation of aryl carbamates (**83**) with epoxides or epoxidation of aryl allylcarbamates (**86**) (Scheme 3.1). Acid induced cyclization of **84** afforded *N*-aryl-2-oxazolidinone (**85**) applicable for the synthesis of the antibacterial medicine, Linezolid (Zyvox) (**26**). In the second pathway, allylcarbamates (**86**) were prepared as key intermediates by allylation of an aryl carbamate (**83)**. The cyclization of intermediates **86** was carried out by treating with various halogenating reagents to provide either a monohalogenated or dihalogenated *N*-aryl-2-oxazolidinone (**87**) (Scheme 3.1).

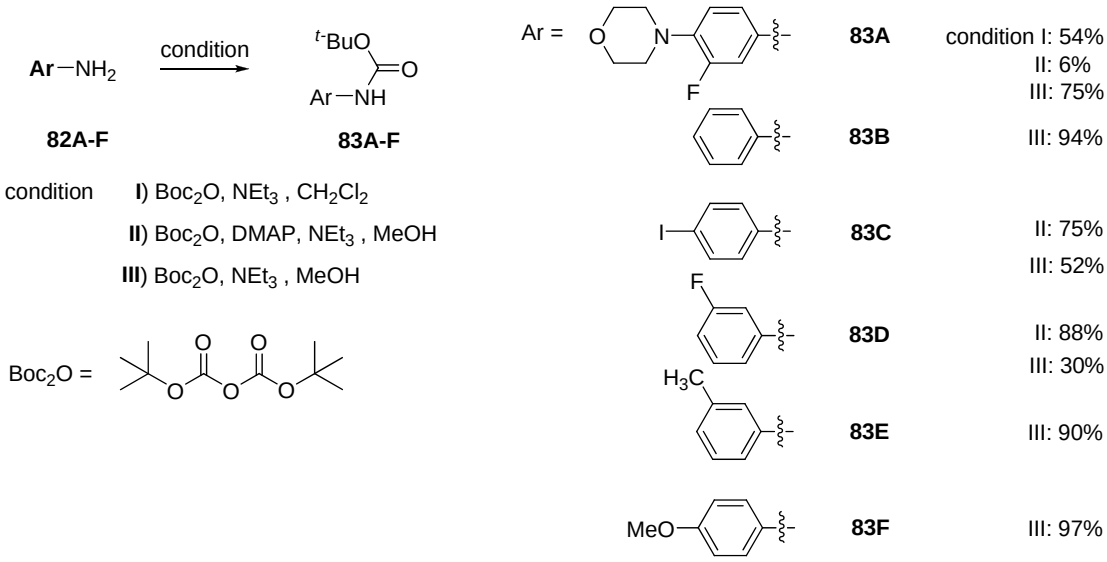


Scheme 3.1 Synthesis of *N*-aryl-2-oxazolidinones.

3.1 The first synthetic pathway: acid-induced intramolecular cyclization of propylene oxide carbamates

3.1.1 Synthesis of aryl carbamates

Di-*tert*-butyl dicarbonate (Boc_2O) is one of the most popular reagents frequently used for amine protection in organic synthesis [76]. Boc group is easy to be incorporated, highly stable in basic conditions, and easily deprotected in strong acid conditions [77]. The protection of primary aromatic amine, 3-fluoro-4-morpholinoaniline (**82A**) was initially performed by reacting Boc_2O in dichloromethane in the presence of triethylamine base at room temperature for 24 hours (Scheme 3.2 condition I). The protected primary aromatic amines, *tert*-butyl 3-fluoro-4-morpholinophenylcarbamate (**83A**) was obtained in moderate yield as the starting material **82A** did not completely react and remained in the reaction mixture. In an attempt to improve the reaction efficiency, 4-dimethylaminopyridine (DMAP) [78] was used in condition II. However, the yield dropped dramatically from 54 to 6% and the reaction gave a complex mixture indicating that many side reactions occurred under this condition. In condition III where the solvent was changed from dichloromethane to methanol, the higher yield was obtained (75%). This condition was also used effectively for the synthesis of other carbamates **83B**, **83E** and **83F**. Surprisingly, condition III gave relatively low yields of carbamates **83C** and **83D** (52 and 30%) but the higher yields (75 and 88%) were obtained using condition II (Scheme 3.2). With all the information available at this stage, no clear explanation can be made for these observations.



Scheme 3.2 Synthesis of *O-tert*-butyl-*N*-arylcarbamates **83A-F** with Boc_2O

The ^1H NMR spectra of *O-tert*-butyl-*N*-arylcarbamates **83A-F** in $CDCl_3$ are illustrated in Figure 3.1. Most characteristically, the methyl protons of *t*-butyl group (**a**) were observed as a singlet in the range of 1.50-1.60 ppm and the NH protons (**b**) were observed as a broad peak in the range of 6.40-6.60 ppm. The aromatic protons were observed in the range of 6.80-7.50 ppm depending on its substituents. For instance, in the case of 3-fluoro-4-morpholinophenylcarbamate, a starting material for Linezolid, the two *ortho* aromatic protons (**c** and **c′**) were observed as a pair of doublet signals at 7.28 ppm and 6.92 ppm respectively, the *meta* protons (**d**) was observed as a triplet signal at 6.82 ppm. Two multiplet signals at 3.00 and 3.84 ppm belong to two methylene protons (**x** and **z**) respectively.

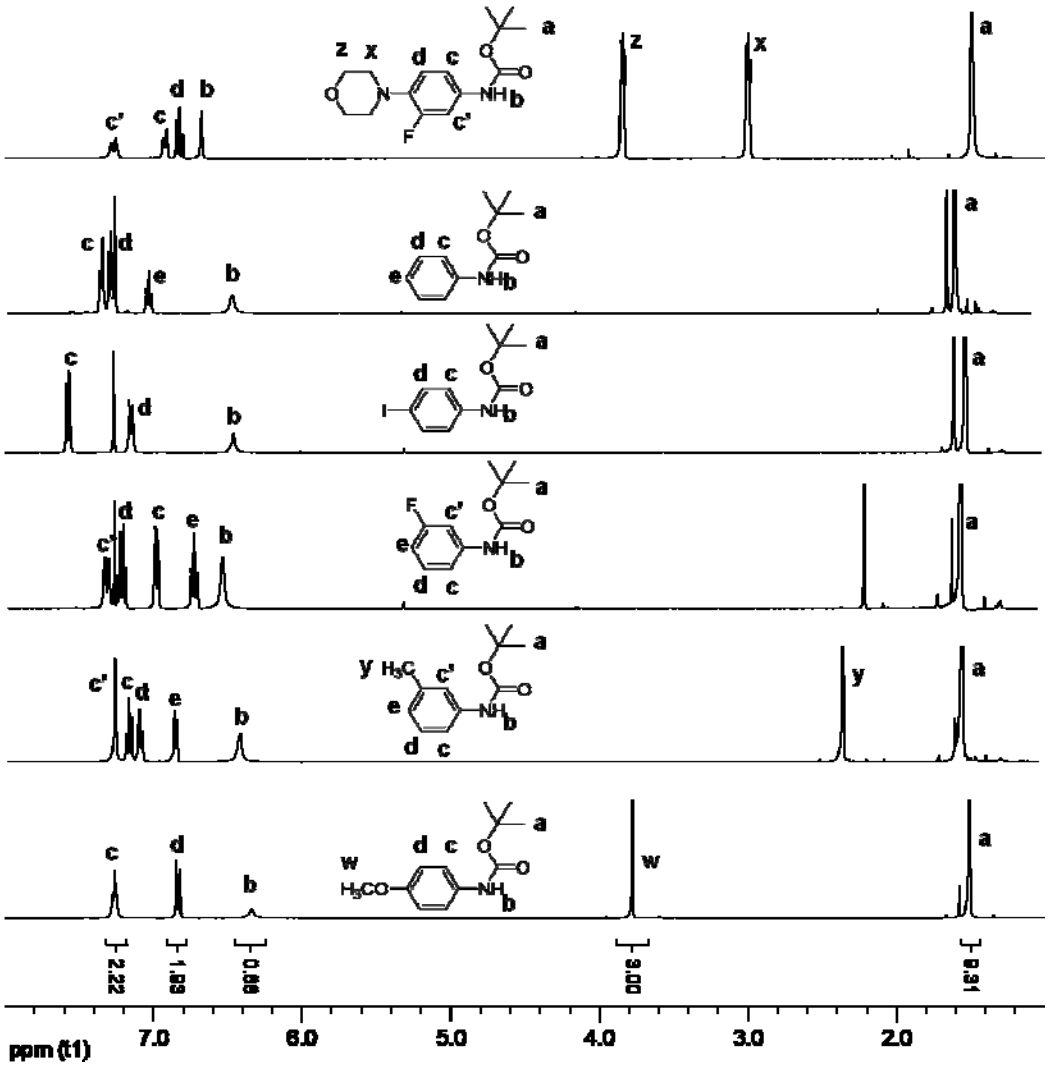
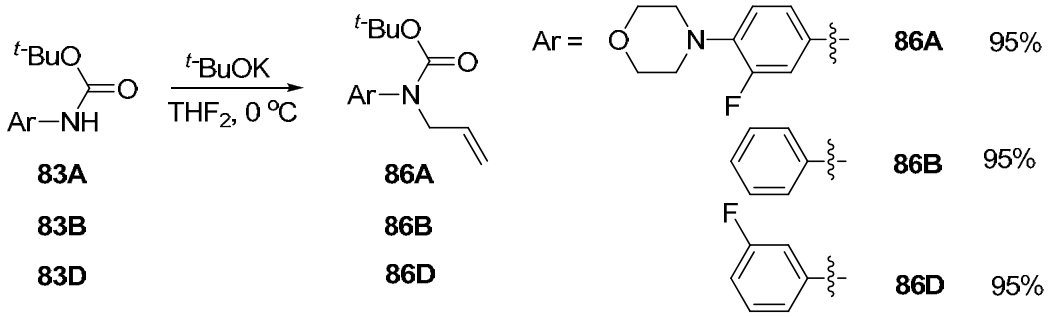


Figure 3.1 ^{1}H NMR spectra of aryl carbamate **83A-F** in $CDCl_3$

3.1.2 *N*-allylation of *tert*-butylarylcarbamates

The *N*-allylation of **83A**, **83B** and **83D** was achieved with four equivalents of allylbromide in the presence of 1M *tert*-BuOK in dried THF as a base at 0 °C to give the corresponding *N*-allyl carbamates (**86A, 86B** and **86D**) in excellent yields (95%) (Scheme 3.3).



Schemes 3.3 *N*-allylation of *O-tert*-butyl-*N*-arylcarbamates **83A**, **83B** and **83D**

The ^{1}H NMR spectra of **86A**, **86B** and **86D** in $CDCl_3$ are shown in Figure 3.2. Upon the allylation, the broad peak of N-H proton disappeared with the emergence of a new doublet signal corresponding to the two methylene protons (**f** and **g**) of the allyl moiety at 4.30-4.10 ppm. The signals of methyne proton (**h**) appeared as a multiplet around 6.00-5.80 ppm and those of two terminal alkene protons (**i** and **j**) appeared around 5.20-5.10 ppm. The signals of the aromatic protons were observed in the range of 7.80-6.60 ppm depending on the substituent.

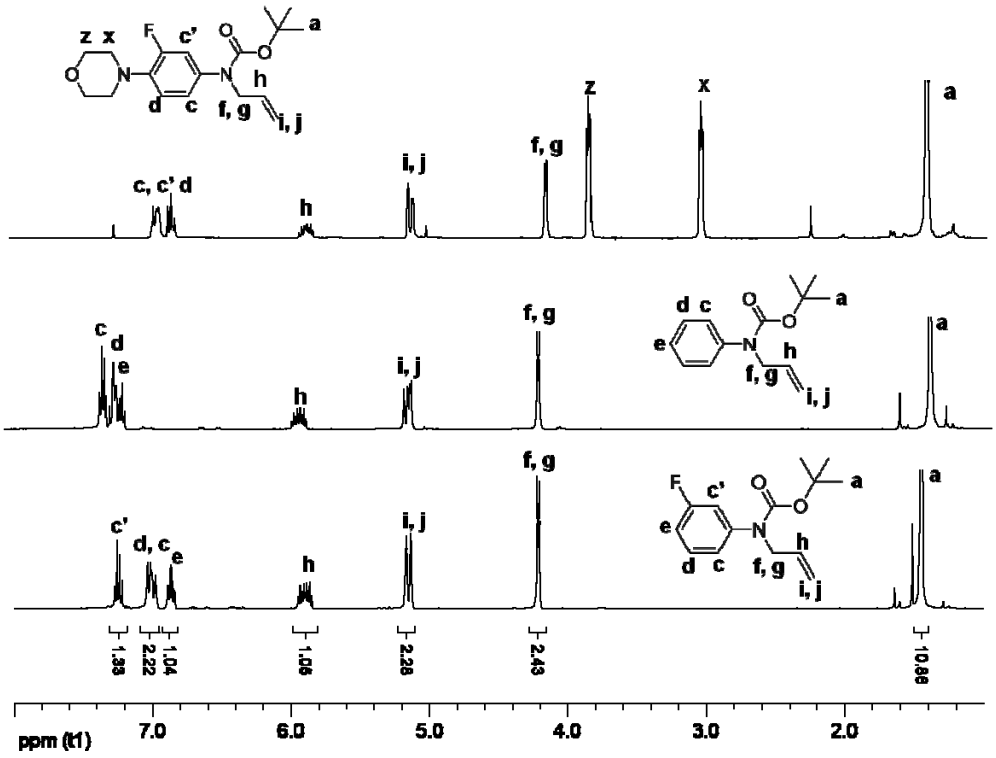


Figure 3.2 ^{1}H NMR spectra of *N*-aryl-*N*-allylcarbamates **86A, 86B** and **86D** in $CDCl_3$

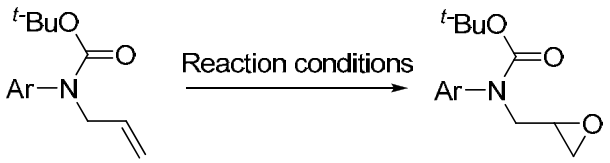
3.1.3 Synthesis of β-(*N*-arylcarbamyl)propylenoxides (*N*-aryl-*N*-(2,3-propyleneoxy)carbamate)

In order to prepare the desired epoxide, direct epoxidation of alkene by various types of oxidants [62-64] or either alkylation of aryl carbamate with commercial epoxide [79] may be used. The methods performed and their results are discussed as follows.

- Attempt in epoxidation of *O*-*tert*-butyl-*N*-aryl-*N*-allylcarbamates

Chloroperbenzoic acid (*m*-CPBA) is a common oxidizing agent used for oxidation of unfunctionalized alkene [62, 80]. Initially, the oxidation reaction was carried out on *tert*-butyl (phenyl)allylcarbamate (**86B**) by using *m*-CPBA as the oxidizing agent for finding suitable reaction condition (Scheme 3.4). In the first attempt the desired aryl epoxycarbamate **84B** was not observed (Table 3.1, entry 1 and 2).

The hydrogen peroxide in the presence of sodium hydrogen carbonate, Payne oxidation, was used successfully for the oxidation of unfunctionalized alkene [81]. Interestingly, when this oxidation was applied to **86B,** the desired epoxide **84B** was obtained in 34% along with 22% of 5-(hydroxymethyl)-3-phenyloxazolidin-2-one, the cyclization product (entry 3). The epoxidation yield was worse with other solvents such as MeOH to ^{t}BuOH, or DMF or upon addition of some additives, which have been reported to improve the epoxidation yield [81], such as manganese sulfate, sodium acetate and salicylic acid. The poor epoxidation yields for this particular *N*-allylcarbamate probably stem from either the steric hindrance nature of the Boc group or the sensitivity of the N atom to oxidation.



Scheme 3.4 Epoxidation of *N*-allylcarbamates **86A** and **86B**

Epoxidation of alkene **86A** were also investigated using both *m*-CPBA and Oxone® as an oxidizing agent. Unfortunately, the desired product **84A** was not obtained for both cases (entry 10 and 11). The reaction gave only the N-oxide product as previously reported in the literature work [82].

Table 3.1 The epoxidation of **86A** and **86B** with various oxidants

Entry	SM	Reaction conditions	% Yield[c]	% Recovery	By Product
1	**86B**	*m*-CPBA[a], $CHCl_3$, rt, 3h	-[d]	66	-
2		*m*-CPBA, CH_2Cl_2, 0 °C, on	5	75	-
3		H_2O_2[b], $NaHCO_3$, MeOH/CH_3CN, 0 °C, 48h	34	38	22
4		H_2O_2, $NaHCO_3$, $MnSO_4$, MeOH/CH_3CN, 0 °C, 48h	-	72	-
5		H_2O_2, $NaHCO_3$, ^{t}-BuOH/CH_3CN, 0 °C, 48h	-	85	-
6		H_2O_2, $NaHCO_3$, NaOAc, ^{t}-BuOH/CH_3CN, 0 °C, 48h	-	77	-
7		H_2O_2, $NaHCO_3$, DMF, 0 °C, 48h	-	91	-
8		H_2O_2, $NaHCO_3$, $MnSO_4$, DMF, 0 °C, 48h	-	93	-
9		H_2O_2, $NaHCO_3$, salicylic acid, DMF, 0 °C, 48h	-	95	-
10	**86A**	*m*-CPBA, CH_2Cl_2, 0 °C, 1h.	-	-	?
11		Oxone®, $NaHCO_3$, Acetone/H_2O, 0 °C, 3h	-	-	-

[a] 70% *m*-CPBA, [b] 30% H_2O_2, [c] isolated yield, [d] not observed

Metal catalyzed epoxidations were also investigated because they have been utilized successfully for epoxidation of unfunctionalized alkenes in many literature reports [83]. The Katsuki-Jacobsen Mn-salen complex has been proven to be general and efficient catalyst for enantioselective epoxidation of various unfunctionalized alkenes [84]. If this catalyst was applicable for epoxidation of **86A**, it would provide a straight forward stereoselective synthetic route of linezolid (Zyvox®). Initially, the model compound **86B** was used for condition optimization in the catalytic asymmetric epoxidation. In the presence of *(R,R)* Jacobsen catalyst (JC), *tert*-butylallyl(phenyl)carbamate **86B** was epoxidized by *m*-CPBA to give **84B** in low yield (Table 3.2, entry 1). The variation of the solvent (from CH_2Cl_2 to $CHCl_3$, CH_3CN or THF), the addition of a radical stabilizer NMO, changing the oxidant to H_2O_2, led to poorer results (entry 2-7). Surprisingly, chlorinated oxazolidinone (**87BCl**) was obtained in 31% yield when NaOCl was use as the oxidant without the expected epoxide **84B** (entry 8). The trial to use Katsuki-Jacobsen catalyst for

epoxidation of **86A** also did not give any positive results. Only a complex mixture of oxidized starting material, especially the oxidezed morpholonyl group of **86A,** was obtained. Therefore, this epoxidation pathway is not likely to give linezolid synthesis.

Table 3.2 The epoxidation of **86A** and **86B** with various oxidants in the presence of *(R,R)* Jacobsen catalyst (JC)

Entry	SM	Reaction conditions	% Yield[d]	% Recovery	By product
1	**86B**	*m*-CPBA,*(R,R)*JC, CH_2Cl_2, 0 °C, 6h	11	82	-
2		*m*-CPBA[a], *(R,R)*JC, $CHCl_3$, 0 °C, 6h	-[e]	78	-
3		*m*-CPBA,*(R,R)*JC, CH_3CN, 0 °C, 3h	-	92	-
4		*m*-CPBA, *(R,R)JC*, THF, 0 °C, 48h	-	52	-
5		*m*-CPBA, *(R,R)*JC, NMO, CH_2Cl_2, 0 °C, 48h	-	63	-
6		H_2O_2[b], $NaHCO_3$, *(R,R)*JC, MeOH/CH_3CN, 0 °C, 48h	-	73	-
7		H_2O_2, NH_4OAc, *(R,R)*JC, MeOH/CH_2Cl_2, 0 °C, 48h	-	64	-
8		NaOCl[c], *(R,R)*JC, 4-PPNO, CH_2Cl_2, pH 11.3, rt, 20h	-	47	31
9	**86A**	*m*-CPBA, *(R,R)*JC, CH_2Cl_2, 0 °C, 3h	-	-	?
10		*m*-CPBA, *(R,R)*JC, $NaHCO_3$/CH_2Cl_2, 0 °C, 48h	-	-	-
11		H_2O_2, *(R,R)*JC, NH_4OAc, MeOH/CH_2Cl_2, 0 °C, 1h	-	-	-
12		H_2O_2, *(R,R)*JC, $NaHCO_3$, MeOH/CH_3CN, 0 °C, 1h	-	-	-
13		NaOCl, *(R,R)*JC, 4-PPNO, CH_2Cl_2, pH 11.3, rt, 48h	-	-	-

[a] 70% *m*-CPBA, [b] 30% H_2O_2, [c] 5% NaOCl, [d] isolated yield, [e] not observed

The ^{1}H NMR spectrum of the β-(*N*-arylcarbamyl)epoxides **84B** in $CDCl_3$ showed that the signals of the two methylene protons (**f** and **g**) next to the N atom shifted from 4.20 ppm to 3.80-3.58 ppm and split in to a pair of doublet of doublets. (Figure 3.3). The oxirane methyne proton (**h**) gave a multiplet signal in the range of 3.20-3.00 ppm. The signals at 2.72 and 2.44 ppm belonged to two oxirane methylene protons (**i** and **j**). All of the *ortho*, *meta* and *para* aromatic protons were observed at 7.26, 7.18 and 7.13 ppm, respectively.

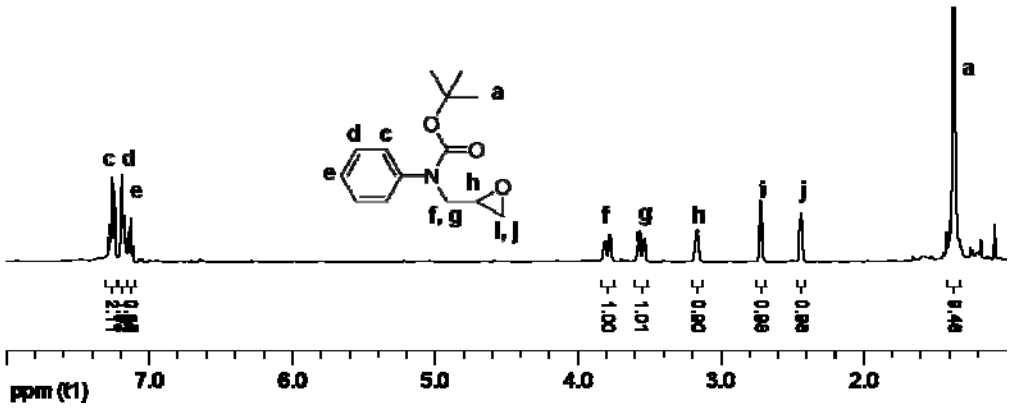
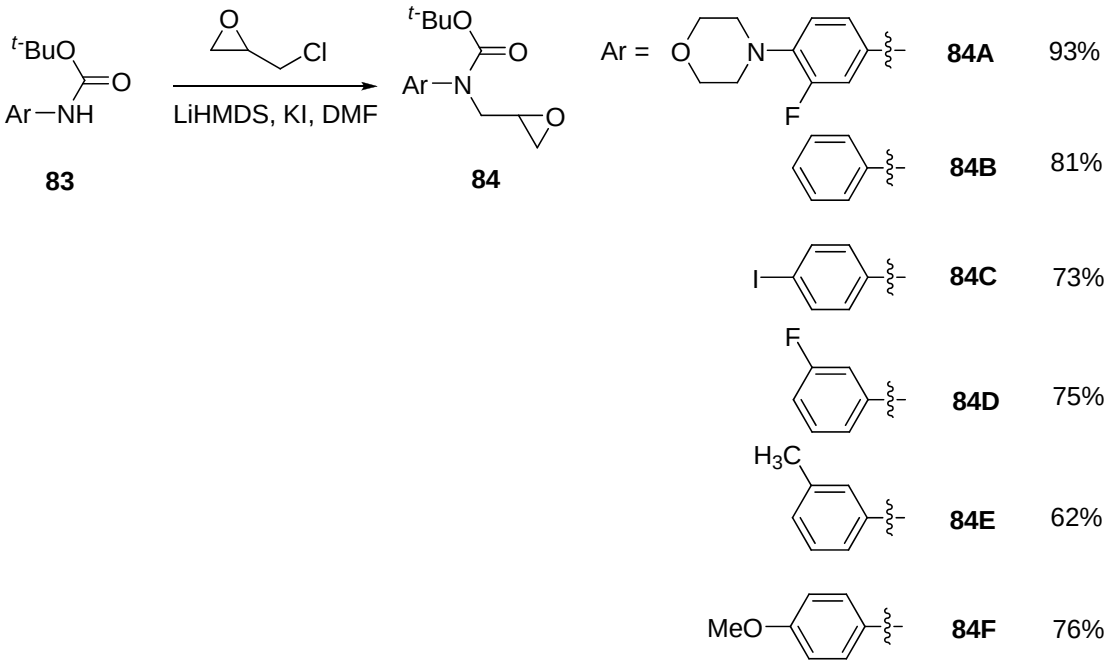


Figure 3.3 ^{1}H NMR spectrum of epoxy aryl carbamate **86B** in $CDCl_3$ by epoxidation

- Alkylation reaction of *O*-*tert*-butyl-*N*-arylcarbamate

Alkylation reaction of the carbamates with an appropriate alkylating reagent containing epoxide group can be an alternative route to synthesize carbamylepoxides. In this work, **84A-F** were prepared from the alkylation reaction of aryl carbamates (**83A-F**) with epichlorohydrin in the presence of potassium iodide lithium bis(trimethylsilyl)amide (LiHMDS) in moderate to good yields (Scheme 3.5).



Scheme 3.5 Synthesis of β-(*N*-arylcarbamyl)epoxides **84A-F** by alkylation

The ^{1}H NMR spectra of **84A-F** in $CDCl_3$ are shown in Figure 3.4. The characteristic signals of epoxide protons were clearly observed in the range of 4.00-2.30 ppm indicating the successful incorporation of the epoxide group into the carbamates. The signals of oxirane methyne (**h**) and methylene protons (**i** and **j**) were observed around 3.20-3.00 ppm and 2.80-2.50 ppm, respectively. The signal of methylene protons next to N atom (**f** and **g**) were observed as near 4.00-3.20 ppm.

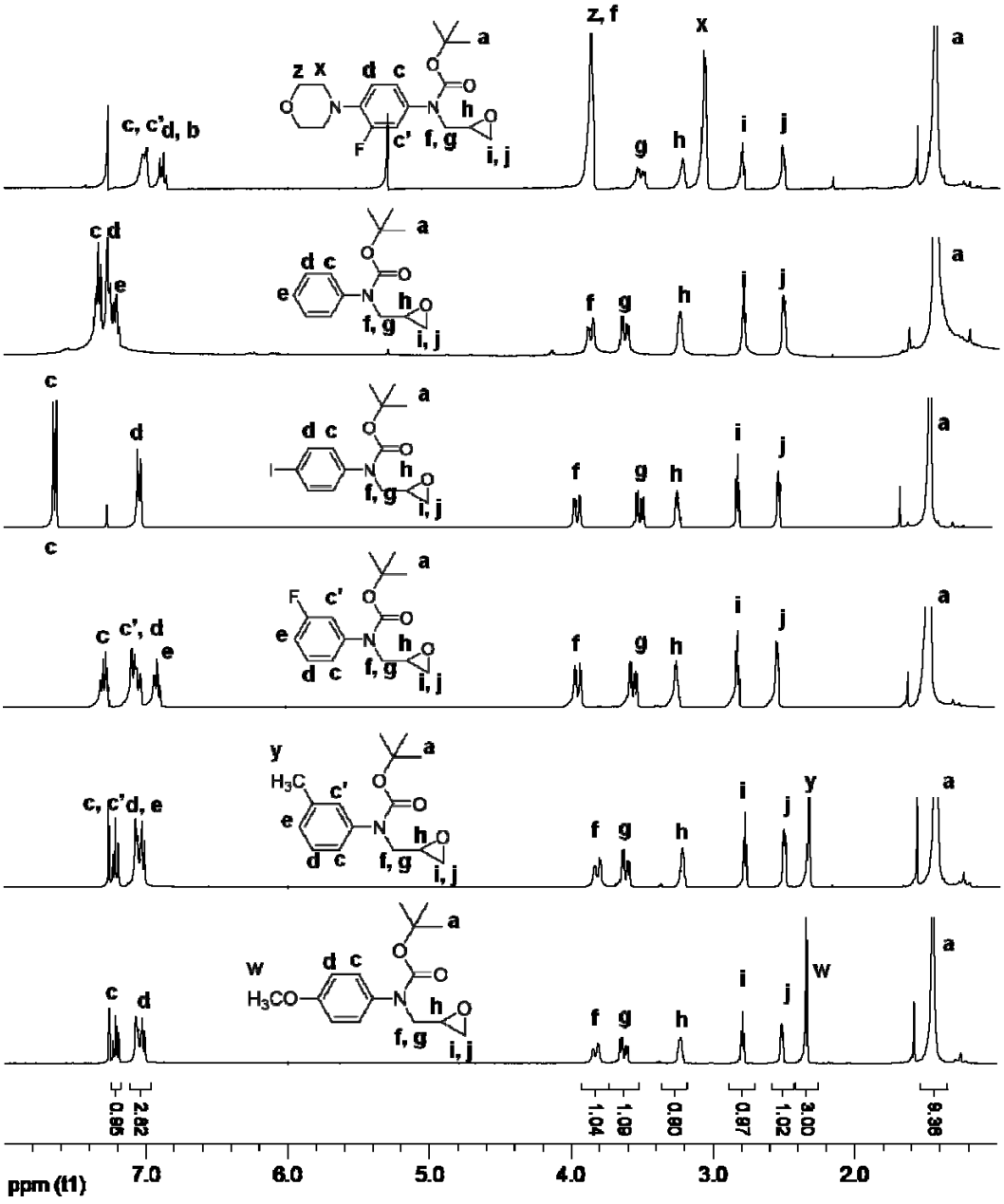
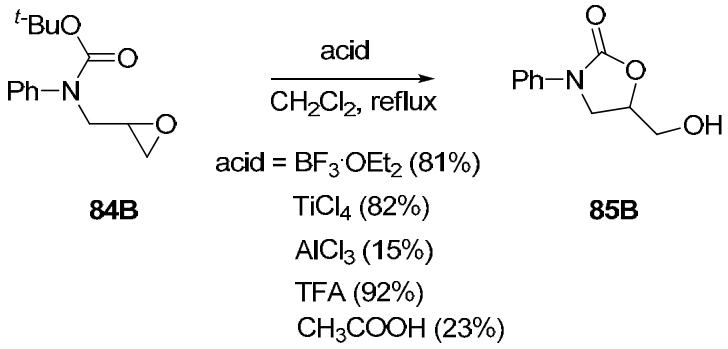


Figure 3.4 ^{1}H NMR spectra of *O*-*tert*-butyl-β-(*N*-arylcarbamyl)epoxides **84A-F** in $CDCl_3$

3.1.4 Formation of 2-oxazolidinone ring

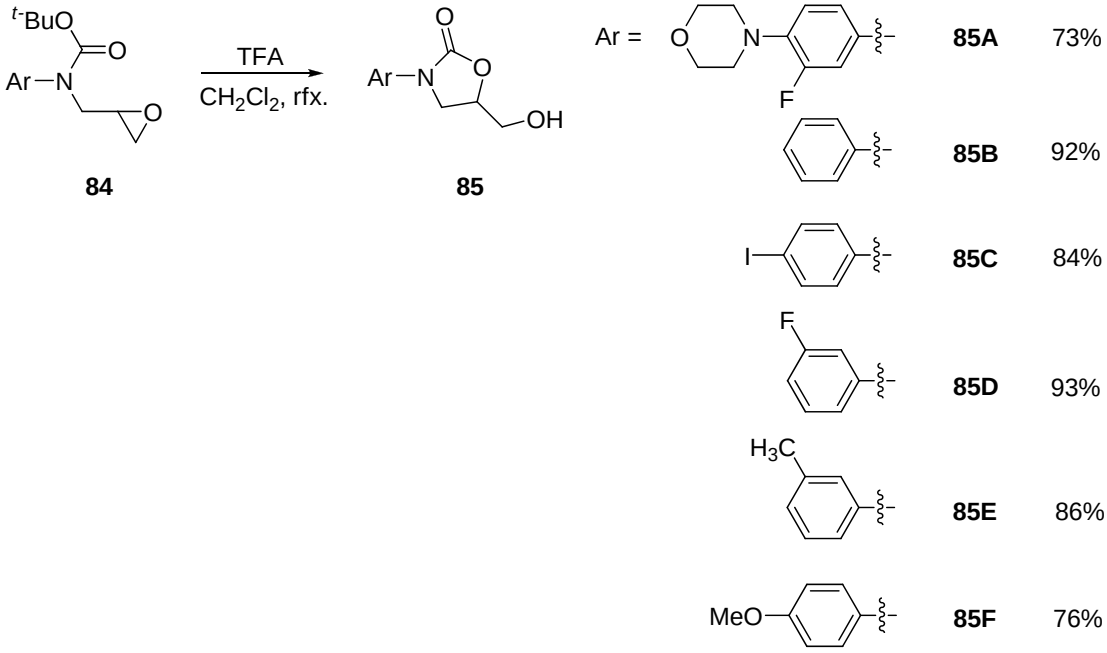
First, the formation of 2-oxazolidinone ring from β-(*N*-arylcarbamyl)epoxide by acid induced cyclization reaction was studied using **84B** as a model compound (Scheme 3.6). Using an excess amount of acid (5 equiv), under reflux condition for 3 hours, the effect of the types of acids *i.e.* trifluoroacetic acid (TFA), acetic acid (CH_3COOH), boron trifluoride diethyletherate ($BF_3{\cdot}OEt_2$), titanium(IV) chloride ($TiCl_4$), and aluminium trichloride ($AlCl_3$) on the reaction yield was investigated. The corresponding 2-oxazolidinone **85B** was obtained in high yields (81-92%) when strong acid such as $BF_3{\cdot}OEt_2$, TFA and $TiCl_4$ was used under the default condition. When weaker acid such as CH_3COOH or $AlCl_3$ was used, the reactions resulted in much poorer yields (15-23%). The reaction induced by CH_3COOH was not completed under this condition and the starting material remained in the reaction mixture. The longer reflux time however did not significantly increase the yield. In the case of $AlCl_3$, long reflux time led to a complex unidentified mixture.



Scheme 3.6 Optimization of acid induced cyclization of β-(*N*-arylcarbamyl)epoxide **84B** to form 2-oxazolidinone **85B**

According to the optimization results, TFA is the reagent of choice for the synthesis of other oxazolidin-2-ones (**85A-F**) as it gave the highest yield with its ease of handling and relatively low cost. Although TFA is commonly used for the deprotection of Boc group, in this particular cyclization, the Boc carbonyl oxygen participated in the cyclization and remained as part of the oxazolidin-2-one structure (Scheme 3.7). It is also important to point out here that compound **85E** which is Toloxatone, a well known antidepressant and monoamine oxidase inhibitor (MAOI),

was produced from **84E** in 86% yield [40]. Furthermore, **84A** can be used as a precursor for the synthesis of linezolid antibacterial medicine [35].



Scheme 3.7 Synthesis of 2-oxazolidinones **85A-F** using TFA for cyclization

The ^{1}H NMR spectra of the various 2-oxazolidinone (**85A-85F**) in $CDCl_3$ are shown in Figure 3.5. The signals of aliphatic protons in the 2-oxazolidinone ring appeared around 4.80-3.60 ppm with the disappearance of the Boc signal. In details, the methyne protons next to ester group (**h**) are observed as a multiplet signal in the range of 4.60-4.80 ppm. The two groups of overlapping signals in the range of 4.20-3.60 ppm correspond to the methylene protons next to hydroxyl group (**i** and **j**) and methylene protons next to N atom within the 2-oxazolidinone ring (**f** and **g**)

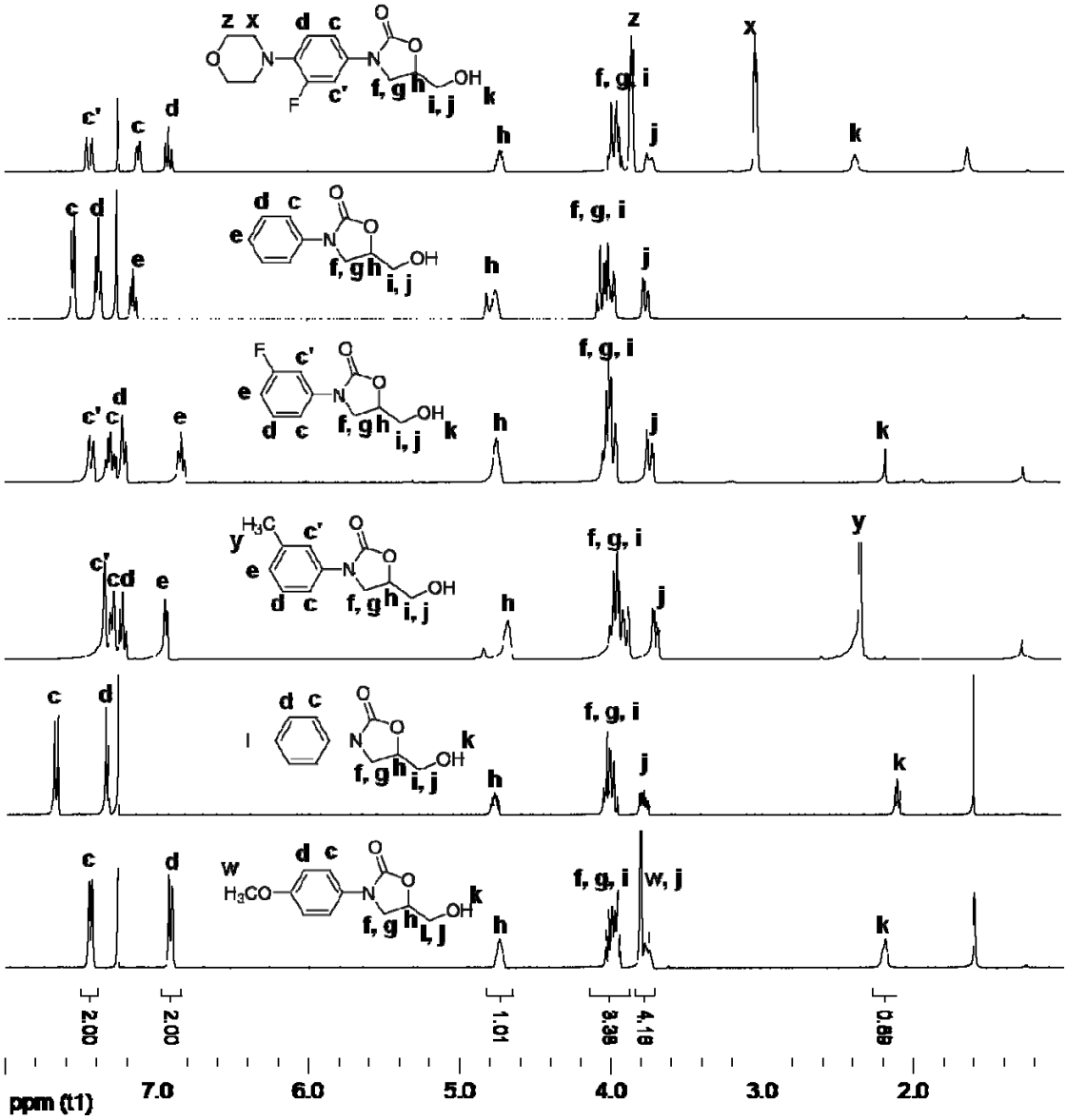
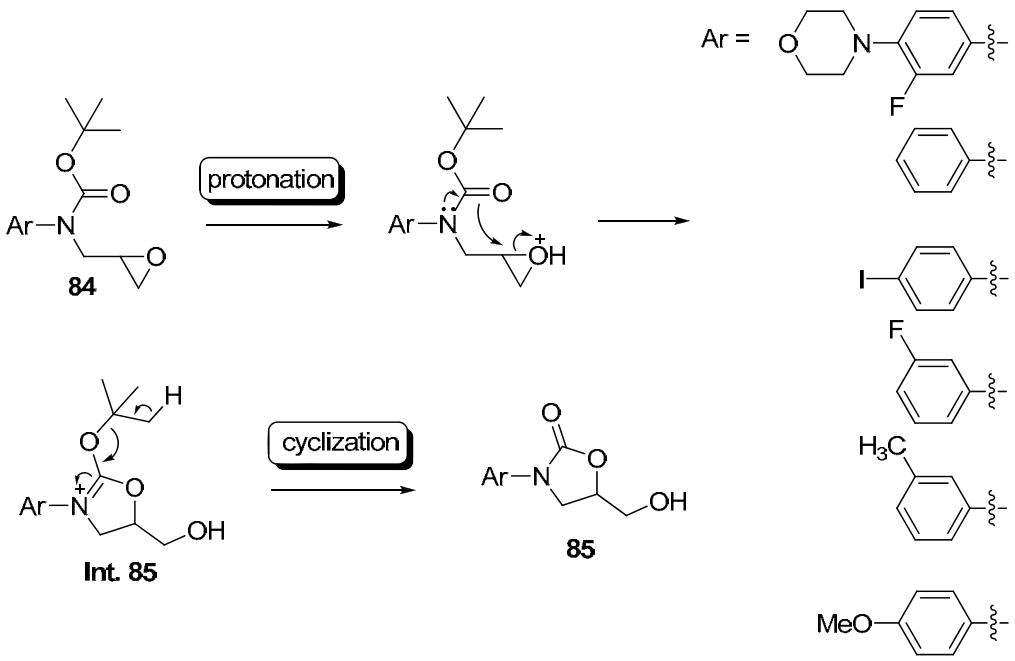


Figure 3.5 ^{1}H NMR spectra of *N*-aryl 2-oxazolidinones **85A-F** in $CDCl_3$

3.1.5 Mechanism of acid-induced intramolecular cyclization

The proposed mechanism for the acid induced cyclization of β-(*N*-arylcarbamyl)epoxide **84** is illustrated in Scheme 3.8. It begins with the protonation of an epoxide moiety which in turn attacked by the carbonyl oxygen atom in a 5-*exo*-*tet* fashion to form a 5-mebered iminium ring intermediate. In the final step, the lost of *tert*-butyl group in the form of *iso*-butene is probably the thermodynamic driving force to create the 2-oxazolidinone **85** as the final product.

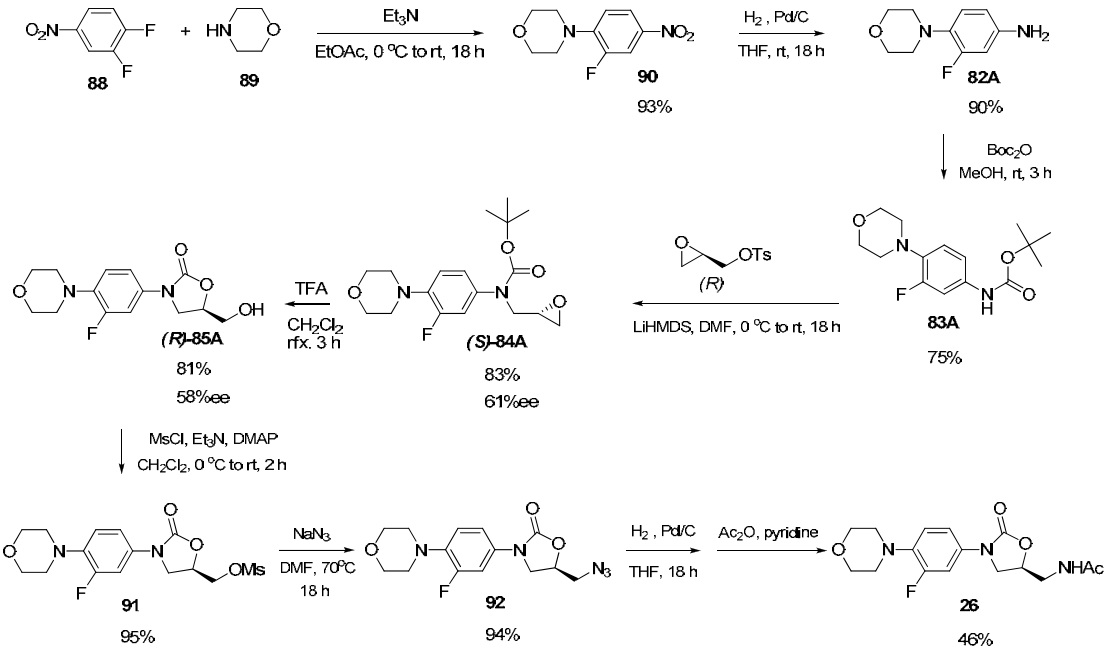


Scheme 3.8 Proposed mechanism for acid-induced intramolecular cyclization of β-(*N*-arylcarbamyl)epoxide **84**

3.1.6 Synthesis of Linezolid

The best condition for acid induced oxazolidinone formation from **84A**, described in the previous section, was incorporated into the total synthesis of antibacterial linezolid (Scheme 3.9). The synthesis started with a nucleophilic substitution of 3,4-difluoronitrobenzene (**88**) with morpholine (**89**) in ethylacetate in the presence of triethylamine base. The reaction afforded 3-fluoro-4-morpholinylnitrobenzene (**90**) in excellent yield (93%). The conversion of the nitro group of **90** to amino group was readily achieved by a catalytic hydrogenation on Pd/C in THF giving **82A** in 90% yield. Upon treatment of **82A** with Boc_2O and triethylamine in methanol, *O*-*tert*-butyl- *N*-(3-fluoro-4-morpholinophenyl)carbamate (**83A**) was obtained in good yield (75%). An aryl carbamate **83A** was alkylated with *(R)*-glycidyl tosylate in the presence of KI and LiHMDS base to furnish carbamylepoxide **84A** in high yield (83%). The carbamylepoxide **84A** was cyclized to oxazolidinone **85A** in high yield (81%) by the TFA induced cyclization as described in section 3.1.4. The hydroxyl group of oxazolidinone **85A** was converted to **91**, having an active methanesulfonate leaving group, in high yield (95%)by reacting with

methanesulfonyl chloride (MsCl) in the presence of triethylamine and 10% mol DMAP in dicloromethane. Substition of mesylate group with an azide using sodium azide in 75 °C DMF overnight gave 5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (**92**) in excellent yield (94%). In the final step, catalytic hydrogenation of the azide group to produce an amino group and subsequent acetylation with AcO_2 in pyridine afforded linezolid **26** in moderate yield (46%) [35] (Scheme 3.9).



Scheme 3.9 The total synthesis of Linezolid

The ^{1}H NMR spectra of **85A**, **91**, **92** and linezolid **26** are illustrated in Figure 3.6. As the broad peak of hydroxy proton (**k**) around 2.20-2.40 ppm of **85A** disappeared, the new signals of three methyl protons (**m**) corresponding to the mesyl moiety appeared at 3.20 ppm. Substitution of N_3 deleted signal of methyl protons **m.** The reduction followed by acetylation generated acetamide moiety which showed methyl protons (**o**) at 2.00 ppm and NH proton (**n**) at 6.40 ppm. For the signals of aromatic part, they are almost identical to those of the starting material, as it is far from the molecular part being modified.

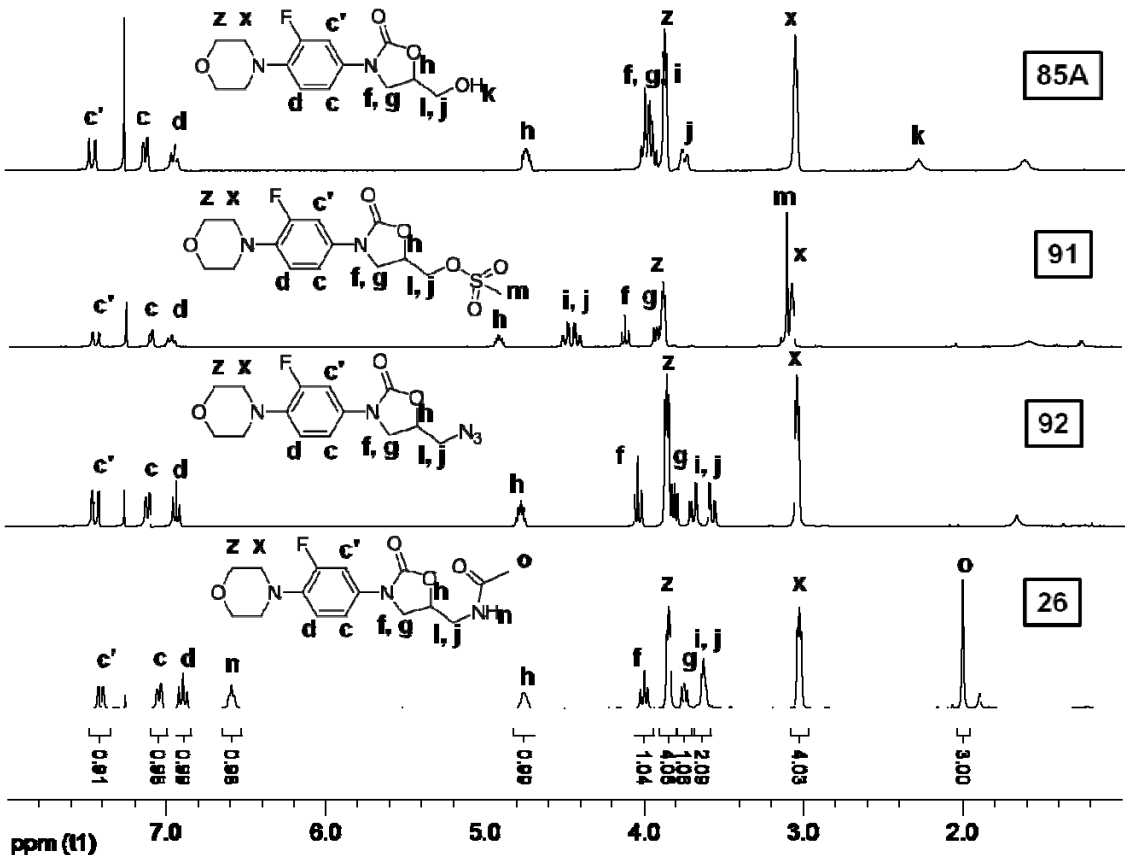
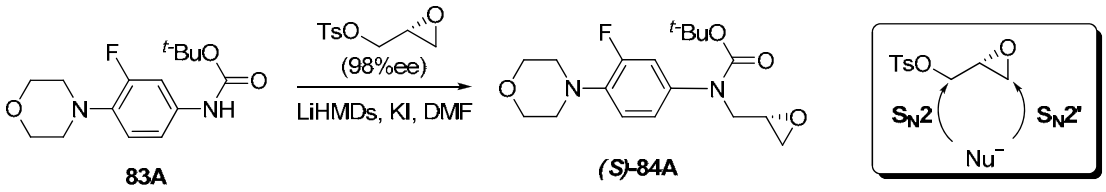


Figure 3.6 ^{1}H NMR spectra of the total synthesis of Linezolid (**26**) and some of its precursors (**85A**, **91** and **92**) in $CDCl_3$

3.1.7 Study of stereochemistry of the products from alkylation and cyclization

Stereochemistry of β-(*N*-arylcarbamyl)epoxides **84** and 2-oxazolidinones **85** were analyzed by chiral HPLC in the synthesis using commercially available *(R)*-glycidyl tosylate (98 %ee). In the synthesis of ***(R)*-84A** (similar to scheme 3.5), the aryl carbamate **83A** and was allowed to react with *(R)*-glycidyl tosylate in the presence of KI and LiHMDS as base in DMF solvent at various temperatures. At -60 °C, the reaction gave **84A** in moderate yield (40%) (Table 3.3, entry 3) but much improved yields were obtained at higher temperatures (57-79 %, entry 1-2). It is important to note that %ee of the product (~60%) is significantly lower than the %ee of the starting epoxide (~98%) and the reaction starting temperature did not affect this %ee. The lower %ee of the product comparing to the starting glycidyl tosylate suggests that the generated carbamate anion may nucleophilically attack at either the

tosylated carbon (S_N2 fashion) or the less steric epoxide carbon (S_N2' fashion) (Scheme 3.10).



Scheme 3.10 Synthesis of β-(*N*-arylcarbamyl)epoxides ***(S)*-84A**

The S_N2 and S_N2' attack produce the product with opposite configurations: *S* and *R*, respectively. Thereby, %ee can be used to calculate the S_N2:S_N2' regioselective ratio (equation 1). As the product was obtained in 60%ee from the starting material with 98%ee, the reaction thus proceeded through S_N2: S_N2' at 81:19% giving the regioselectivity of 4:1.

$\%S_N2 = 50(\%ee\ Product + \%ee\ Starting\ Material)/\%ee\ Starting\ Material$ (equation 1)

Table 3.3 Alkylation of carbamate **83A** with *(R)*-glycidyl tosylate (98 %ee)

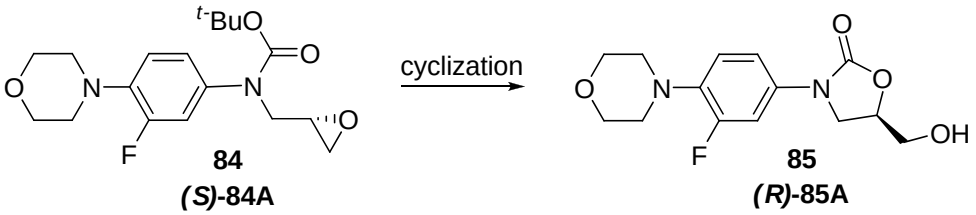
Entry	Reaction Temperature	%Yield *(S)*-84A	%ee[a]	$\%S_N2$[b]	Regio selectivity
1	rt	79	59.9	81	4:1
2	0 ºC to rt	57	59.7	81	4:1
3	-60 ºC to rt	40	60.7	81	4:1

[a] determined from Chiral HPLC, [b] calculated from eq.1

After the epoxide *(S)*-**84A** (~60% ee) was obtained, treating this epoxide with TFA produced 2-oxazolidine ***(R)*-85A** in high yield (72-81%) with 52-58% ee (Table 3.4). Under acidic condition, the epoxide ring may be opened by stereospecific S_N2 or non-stereoselective S_N1 mechanisms (Scheme 3.11) [85]. In S_N2 mechanism, the carbonyl oxygen attacks the protonated epoxide ring from the back-side to generate ***(R)*-85A**. In S_N1 mechanism, the epoxide ring opens after the protonation to give achiral carbocation that consequently lead to racemic products. Using equation 1, the

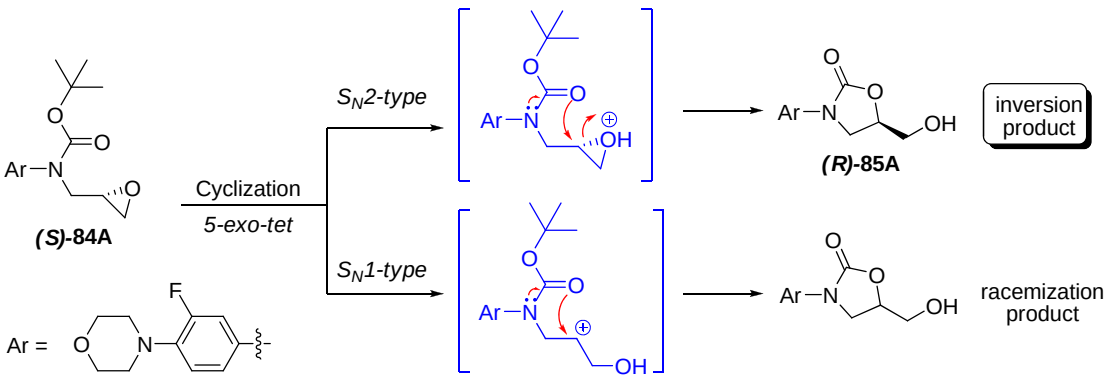
%ee of the product obtained from four trials of cyclization can be translated into % inversion of 94% or higher indicating that the cyclization proceed mostly through S_N2 mechanism.

Table 3.4 Acid induced cyclization of carbamylepoxide ***(S)*-84A** to form oxazolidinone ***(R)*-85A**



Entry	%ee[a]	Condition	%Yield ***(R)*-85A**	%ee[b]	%inversion[c]
1	59.9	reflux	81	52.4	94
2	59.7	reflux	71	53.4	95
3	59.7	room temp.	81	53.0	94
4	60.7	reflux	72	58.3	98

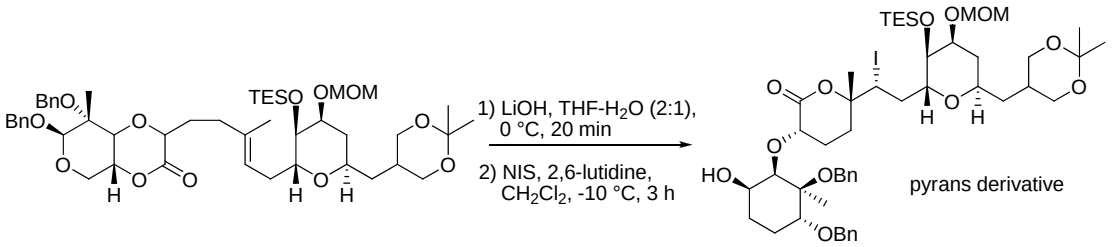
[a] from alkylation reaction, [b] determined from Chiral HPLC, [c] calculated from eq.1



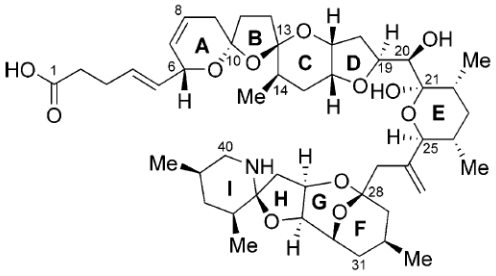
Scheme 3.11 Possible S_N1- and S_N2-type mechanism for the formation of 2-oxazolidinones **85A** from acid induced intramolecular cyclization of ***(S)*-84A**

3.2 The second synthetic pathway: halo-induced intramolecular cyclization

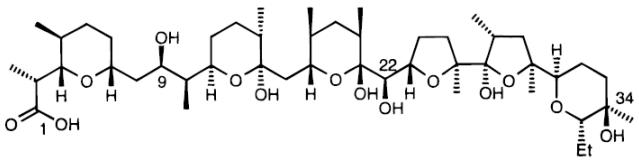
Closely related to the epoxide-mediated cyclization, halo-induced cyclization is a unique method for cyclization of alkene based on the intramolecular attack of the nucleophilic atom on an olefin activated electrophilic halogen [86]. In 2003, Armen, Z. and co-workers reported that the halo-mediated cyclization (iodolactonization) to synthesize the corresponding pyrans from alkene as starting material [87] (Scheme 3.12). It is similar to the processes using mercury (II) salts for stoichiometric cyclization that was used in the total synthesis of the antibiotic X-206 [88] (Figure 3.7). Moreover, Nicolaou, K. C. and co-workers have found the advantage of iodine or *N*-iodosuccinimide (NIS) as compound using intramolecular halo-etherification reactions. NIS-induced iodoetherification play a crucial role in the G-ring azaspiracid-1, as a result of marine metabolites responsible for human poisoning from the consumption of tained shellfish [89] (Figure 3.7). Our investigation on the halo-induced cyclizations of alkene, simpler synthesis of oxazolidinone was discovered. In this work allylcarbamate (**86**) was treated with various halogenated sources. The synthesis of halogen containing oxazolidinone proceeded smoothly from *tert*-butyl (phenyl) allylcarbamate with several halogenated reagents such as chlorine, bromine, iodine, *N*-chlorosuccinimide, *N*-bromosuccinimide, *N*-iodosuccinimide, iodinemonochloride, $PhCH_2NMe_3ICl_2$, and mixed solution of potassium iodide and potassiumiodate in acetic acid. These reagents do not only play a critical role in cyclization step to form the oxazolidinone ring but also generate the halo substituted aromatic derivatives in which the substitution position is *para* one. Moreover, the great thing about this *p*-halo-substituted product can be further functionalized by various reagents to make a series of oxazolidinone derivatives (Scheme 3.8). In details, the investigation of the halo-induced cyclization was accomplished by using a conventional halogen reagent such as chlorine (Cl_2), bromine (Br_2) and iodine (I_2) first, compared to the other halogenated sources reagent. In each condition, the halogen amount, solvent type and other related factors were systematically validated to obtain the optimized condition.



Scheme 3.12 Synthesis of diastereoselective iodolactonization from alkene



Azaspiracid-1



X-206

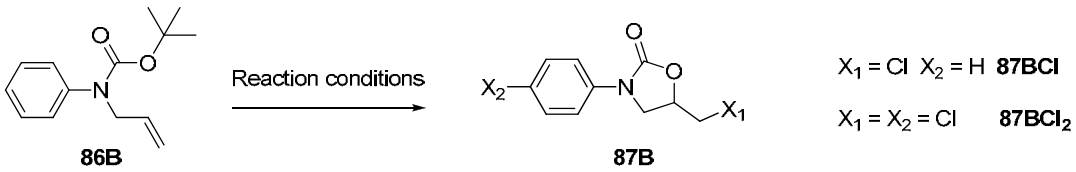
Figure 3.7 The structure of Azaspiracid-1 and antibiotic X-206

3.2.1 Using chlorine (Cl_2) and *N*-chlorosuccinimide (NCS)

Cl_2: The different types of solvent were examined for optimization in the chloro-induced intramolecular cyclization. As the results, it is important to note that not only halo-induced intramolecular cyclization was proceeded but the electrophilic aromatic substitution (S_EAr) triggered by a reactive Cl^+ ion from Cl_2 also occurred to produce 5-(chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one (**87BCl$_2$**). (In order to make the product name easily understandable, **87BX$_2$** will represent the *p*-halo-substituted aryl product and sometimes it may be called as *p*-halo-aryl, while **87BX** represents the unsubstituted aryl and sometimes it may be called as unsubstituted product. When the CH_3CN, CH_2Cl_2, $CHCl_3$ and were used as solvent at ambient temperature for 1 hour, the desired chloro-substituted cyclization product (**87BCl$_2$**) was observed as major product in low to moderate yield, 29%, 47% and 50% respectively (Table 3.5, entry 1, 2 and 3). However, even the long reaction time did not provide higher yield but mixture was presented. Because of the fairly low yielding and high toxicity of using Cl_2 as a reagent, continuing to study the chloro-induced cyclization by using other reagent in order to obtain a higher yield and lower toxicity.

NCS: Using an *N*-chlorosuccinimide (NCS) as a Cl^+ ion source in solvents such as CH_2Cl_2, $CHCl_3$, CH_3CN, THF, and DMF were systematically verified, and the suitable solvent for chlorination reaction was found to be acetonitrile (Table 3.5, entry 8-11). To improve the yield, using reflux condition to complete the reaction was done but the yield did not increase significantly (entry 9). Moreover, the increasing amount of NCS also did not improve the yields (entry 5, 7, and 11) as much as expected. From these chlorination results, almost all products were obtained as unsubstituted oxazolidinone (**87BCl**). The % yield of these conditions, lower than 35%, suggested the low reactivity of NCS which was supported by the remaining of the starting material in % recovery of higher than 70%. Interestingly, changing the solvent to DMF produced the *p*-Cl-aryl product (**87BCl$_2$**) occurred in low yield (27%) but the starting material was not recovered at all (entry 14).

Table 3.5 Preparation of various chloro-2-oxazolidinones using Cl_2 and NCS



86B 87B

Entry	Halogen sources	Reaction conditions	%Yield[a]	
			87BCl	**87BCl$_2$**
1	Cl_2	Excess, CH_3CN, rt, 1h	-[b]	29
2		Excess, CH_2Cl_2, rt, 1h	-	47
3		Excess, $CHCl_3$, rt, 1h	-	50
4	NCS	**2.2** equiv, CH_2Cl_2, rt, 48h	-	-
5		**3.0** equiv, CH_2Cl_2, rt, 48h	trace	-
6		**2.2** equiv, $CHCl_3$, rt, 48h	-	-
7		**3.0** equiv, $CHCl_3$, rt, 48h	6	-
8		**2.2** equiv, CH_3CN, rt, 48h	25	-
9		**2.2** equiv, CH_3CN, rfx., 48h	32	-
10		**2.2** equiv, CH_3CN, TFA, 48h	trace	-
11		**3.0** equiv, CH_3CN, rt, 48h	trace	-
13		**3.0** equiv, THF, rt, 24h	-	-
14		**3.0** equiv, DMF, rt, 24h	-	27

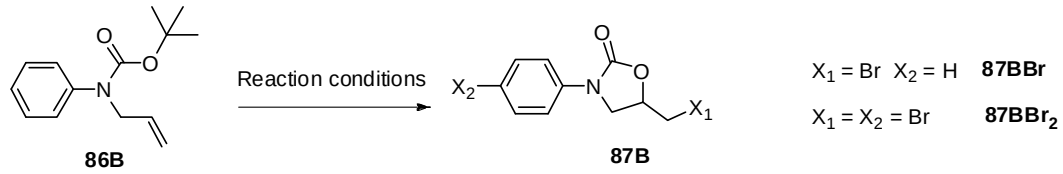
[a] isolated yield, [b] not observed

3.2.2 Using bromine (Br_2) and *N*-bromosuccinimide (NBS)

Br_2: In this experimental, three kinds of solvents CH_2Cl_2, $CHCl_3$ and CH_3CN were mainly used for optimization. The reaction at room temperature for 1 hour, the desired bromo-substituted cyclization product (**87BBr$_2$**) in good to excellent yields (73%-94%) (Table 3.6, entry 1-5). Among these conditions, the bromo-cyclization reaction in $CHCl_3$ conclusively gave the highest yield with the shortest time. It is worth to pointing out that this cyclization product can be suitably used as oxazolidinone scaffold for the preparation of oxazolidinone derivatives because the two bromides, on aromatic (X_2) or aliphatic (X_1) moiety, could be easily replaced by the variety of functional groups. In the aromatic moiety (X_2=Br), this bromide was usually substituted with the amines by the Buchwald-Hartwig reaction [90]. However, using Br_2 could only produce **87BBr$_2$** but not the **87BBr**. Because of the toxicity, difficult handling and harmfulness of bromine (Br_2), changing the reagent to others brominated source reagent would be able to avoid such unsafe situation and hopefully exclusively provide **87BBr$_2$**.

NBS: Using an *N*-bromosuccinimide (NBS) is safer than Br_2 and it acts as a Br^+ ion source in various solvents, CH_2Cl_2, $CHCl_3$, CH_3CN, and DMF. As the results, this reagent could produce both of unsubstituted products (**87BBr**) and *p*-Br-aryl product **(87BBr$_2$)**. Acetonitrile was found to be an effective solvent for bromination of **86B** to **87BBr$_2$** in excellent yield (99%) (Table 3.6, entry 9). Adding more amounts of NBS leads to the desired scaffold oxazolidinone (**87BBr$_2$**) (68%, entry 11). There is an information reported by Anne, S. C. and co-worker indicating that the addition of TFA could generate more reactive bromonium ion then NIS itself and improve the yield of **87BBr$_2$** [91] (Scheme 3.13). Therefore, addition of 5 equiv of NBS and TFA was attempted the desired *p*-Br-aryl product (**87BBr$_2$**) could be successfully provide in 81 % (entry 12). Interestingly, In the case of using DMF as solvent, both unsubstituted product (**87BBr**) and *p*-Br-aryl product (**87BBr**) were equally obtained (entry 13).

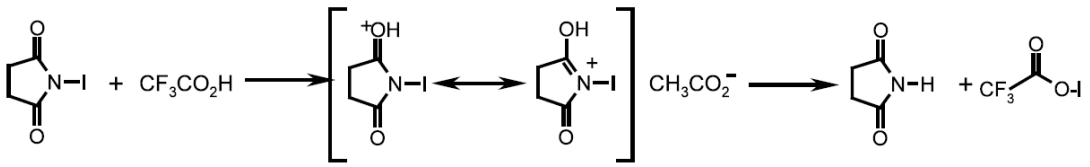
Table 3.6 Preparation of various bromo-2-oxazolidinones using Br_2 and NBS



86B 87B

Entry	Halogen sources	Reaction conditions	%Yield[a]	
			87BBr	**87BBr$_2$**
1	Br_2	**3.0** equiv, CH_3CN, rt, 1h	-[b]	73
2		**2.2** equiv, CH_2Cl_2, rt, 1h	-	81
3		**3.0** equiv, CH_2Cl_2, rt, 1h	-	83
4		**2.2** equiv, $CHCl_3$, rt, 1h	-	91
5		**3.0** equiv, $CHCl_3$, rt, 1h	-	94
6	NBS	**2.2** equiv, CH_2Cl_2, rt, 24h	47	-
8		**2.2** equiv, $CHCl_3$, rt, 24h	34	-
9		**2.2** equiv, CH_3CN, rt, 24h	99	-
10		**3.0** equiv, CH_3CN, rt, 24h	88	-
11		**5.0** equiv, CH_3CN, rt, 24h	-	68
12		**5.0** equiv, TFA, CH_3CN, rt, 24h	-	81
13		**3.0** equiv, DMF, rt, 24h	46[c]	44[c]

[a] isolated yield, [b] not observed, [c] calculated from the ratio of ^{1}HNMR analysis



Scheme 3.13 Active species for the iodination

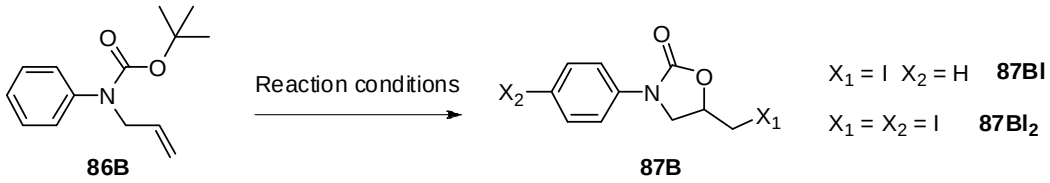
3.2.3 Using iodine (I_2) and iodinated reagents

From the easiness of further functionalization point of view, as seen in various organometallic coupling reactions [92], the scaffold development of iodo-substituted oxazolidinone (**87**) is far more interesting than chloro- and bromo-substituted cases. It has high potential to open the new useful and convenient pathway for oxazolidinone derivatization.

I_2: To obtain a desired iodide substituted oxazolidinone scaffold (**87BI$_2$**), the synthesis was started with the iodination of allylcarbamate using iodine (I_2) in toluene at 50 ºC (Table 3.7, entry 4). After the addition follow by an iodonium bridge formation was completed, the cyclization step was subsequently occurred. Only an unsubstituted product (**87BI**) was obtained in fair yield (64%) without the occurrence of the aromatic iodo-substitution. The changing of solvent from toluene to chloroform and acetonitrile was performed (entry 1-3), in order to see the solvent effect on the reaction. However, in the both case of $CHCl_3$ and CH_3CN, the reaction either at room temperature or at 60 ºC for 24 hours gave the product **87BI**, the only the product **87BI** in moderate yield (53-60%, entry 1-3). From the results of iodo-induced cyclization that were mentioned above, It can be summarized that only halo-induced intramolecular cyclization was successful but electrophilic aromatic substitution (S_EAr) of I^+ at aromatic position did not occur under these conditions due to the low reactivity of iodonium ion.

NIS: Using *N*-iodosuccinimide (NIS) in various solvents could produce only unsubstituted product (**87BI**). In the case of using acetonitrile as a solvent, the highest yield of **87BI** was obtained. The increasing of NIS from 2.2 equiv to 3 and 5 equiv were also investigated (Table 3.7, entry 6, 8, 10, and 11). Unfortunately, these conditions did not give the desired *p*-I-aryl product (**87BI$_2$**) but only the **87BI** in high yield (88-97%) which may due to the lower reactivity of iodonium ions compared to that of bromonium ions. When TFA was added to the reaction, both **87BI** and **87BI$_2$** were observed as the mixture (entry 12 and 13). Then, increasing of the amount of both NIS up to 5 equiv and TFA led to the absence of the **87BI** and completely converted starting material **86B** to the **87BI$_2$** in high yield (74%, entry 14).

Table 3.7 The preparation of various iodo-2-oxazolidinones using I_2, NIS, ICl, BTMA·ICl_2 and KI/KIO_3



86B **87B**

Entry	Halogen sources	Reaction conditions	%Yield[a]	
			87BI	**87BI$_2$**
1	I_2	**3.0** equiv, $CHCl_3$, rt, 24h	60	-[b]
2		**3.0** equiv, $CHCl_3$, rfx., 24h	55	-
3		**3.0** equiv, CH_3CN, rt, 24h	53	-
4		**3.0** equiv, Toluene, 50 ℃	64	-
5	NIS	**2.2** equiv, CH_2Cl_2, rt, 24h	89	-
6		**3.0** equiv, CH_2Cl_2, rt, 24h	88	-
7		**2.2** equiv, $CHCl_3$, rt, 24h	90	-
8		**3.0** equiv, $CHCl_3$, rt, 24h	92	-
9		**2.2** equiv, CH_3CN, rt, 24h	93	-
10		**3.0** equiv, CH_3CN, rt, 24h	96	-
11		**5.0** equiv, CH_3CN, rt, 24h	97	-
12		**2.2** equiv, TFA, CH_3CN, rt, 24h	46[c]	41[c]
13		**2.2** equiv, TFA, CH_2Cl_2, rt, 24h	60[c]	8[c]
14		**5.0** equiv, TFA, CH_3CN, rt, 24h	-	74
15	ICl	**1.2** equiv, $CaCO_3$, $CHCl_3$/MeOH, rt, 24h	71	-
16		**3.0** equiv, $CaCO_3$, $CHCl_3$/MeOH, rt, 24h	33[c]	55[c]
17		**3.0** equiv, $CaCO_3$, $CHCl_3$/MeOH, rfx., 24h	20[c]	72[c]
18		**4.0** equiv, $CaCO_3$, $CHCl_3$/MeOH, rt, 24h	44[c]	46[c]
19		**5.0** equiv, $CaCO_3$, $CHCl_3$/MeOH, rt, 24h	-	96
20	BTMA·ICl_2	**3.0** equiv, CH_2Cl_2, rt, 24h	61	-
21		**2.2** equiv, $CHCl_3$, rt, 24h	87	-
22		**2.2** equiv, $CaCO_3$, $CHCl_3$/MeOH, rfx., 24h	60	-
23		**3.0** equiv, $CaCO_3$, $CHCl_3$/MeOH, rfx., 24h	61	-
24	KI/KIO_3	**1.2** equiv, KI/KIO_3, AcOH, rt, 3h	91	-
25		**2.2** equiv, KI/KIO_3, AcOH, rfx., 3h	-	89
26		**3.0** equiv, KI/KIO_3, AcOH, rfx., 3h	-	86

[a] isolated yield, [b] not observed, [c] Yields calculated from the ratio of ^{1}HNMR analysis

BTMA·ICl_2: Using a BTMA·ICl_2 in conditions describe in Table 3.7 produced **87BI** in high yield without the substitution product **$87BI_2$** (entry 20-23). The product only occurred in unsubstituted from due to the low reactivity of iodonium ions.

ICl(I): An iodinemonochloride (ICl) was used as an I^+ ion source in $CHCl_3$/MeOH at room temperature for 24 h, the amount of ICl(I) seemed to play an important role in this reaction. When using only 1.2 equiv of ICl, unsubstituted product (**87BI**) was solely occurred in good yield (71%, Table 3.7, entry 15). However, in the case of 3.0-4.0 equiv of ICl, the reaction gave both products in the raio shown in entry 16-18. And if the reaction was carried on 5 equiv the reaction give only the *p*-I-aryl product (**$87BI_2$**) in high yield (96%) (entry 19).

KI/KIO_3: In order to obtain the desired iodonium ions for the iodination reaction, a mixed solution of KI and KIO_3 in acetic acid is an effective and convenient method. When the amount of KI/KIO_3 is below 2.2 equiv, the unsubstituted product (**87BI**) was observed in excellent yield (91%, Table 3.7, entry 24). Additionally, using the amount of KI/KIO_3 equal to or more than 2.2 equiv in refluxing acetic acid, the desired substituted oxazolidinone scaffold product (**$87BI_2$**) could be obtained in high yield (86-89%, entry 25 and 26) due to the highly reactive iodonium ions.

The ^{1}H NMR spectra of the various 2-oxazolidinones **87B** in $CDCl_3$ show the different signals of various protons in the chemical shift between 7.80–3.20 ppm (Figure 3.8). As the singlet peak of Boc proton disappeared, new signals corresponding to 2-oxazolidinone around 4.80-3.20 ppm, two methylene protons (**f** and **g**), (4.20-3.80 ppm), methyne protons (**h**), (5.00-4.60 ppm) and two other methylene protons (**i** and **j**) (3.80-3.20 ppm), were observed. Notably, the chemical shift values of protons **i** and **j** are slightly down field when the adjacent atom are Cl, Br and I depending on the electronegativity value of Cl, Br and I, respectively. In the aromatic part, the signals are observed in the range of 6.80-7.50 ppm depending on different environments(**c**, **d** and **e**). When the electrophilic aromatic substitution reaction was occurred, the signal of aromatic are changed from three multiplet signal

of **c, d** and **e** (unsubstituted product, **87BX**, **X = Cl**, **Br** and **I**) to two doublet signal of **c** and **d** (substituted product, **87BX$_2$**, **X = Cl**, **Br** and **I**).

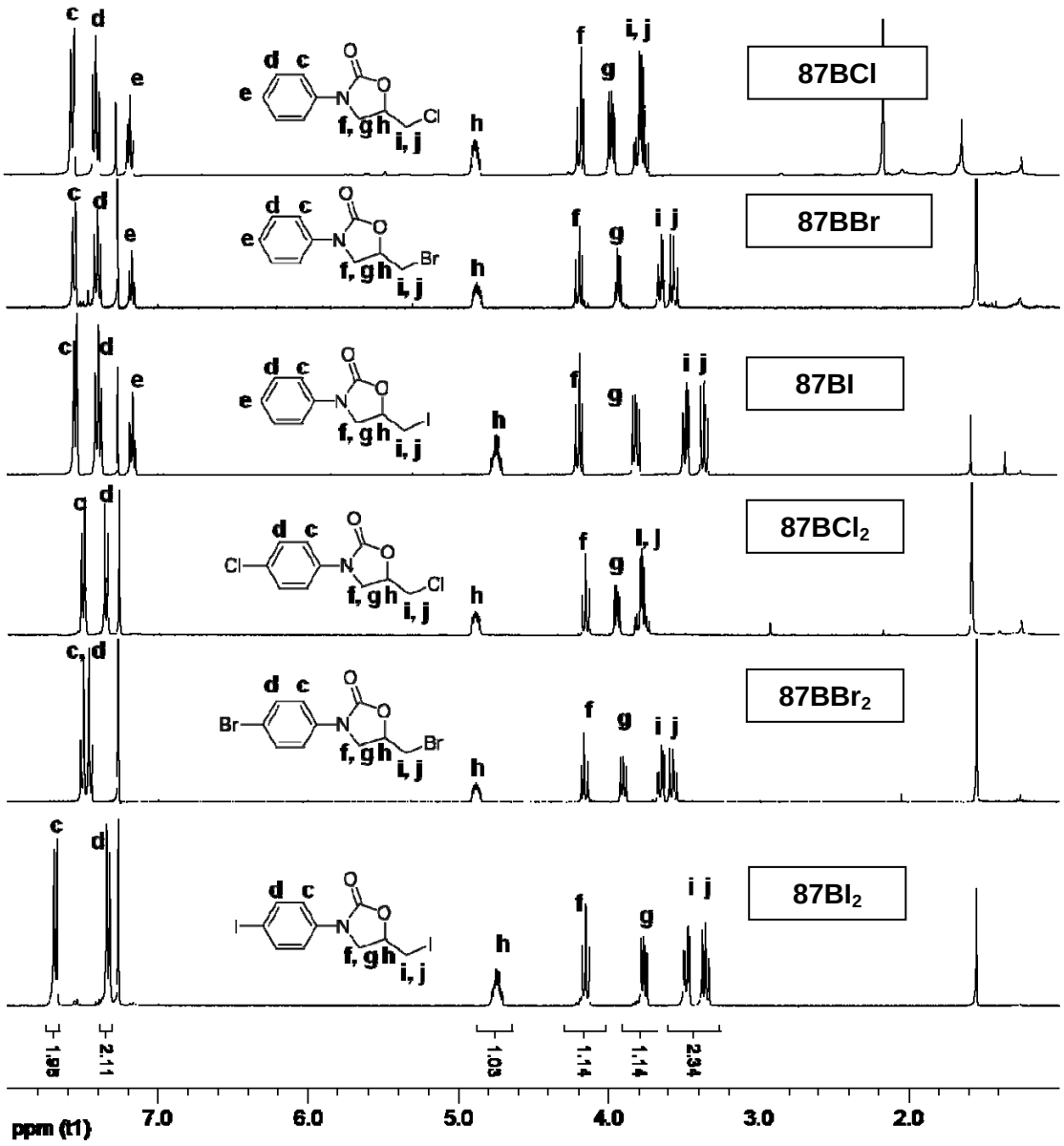
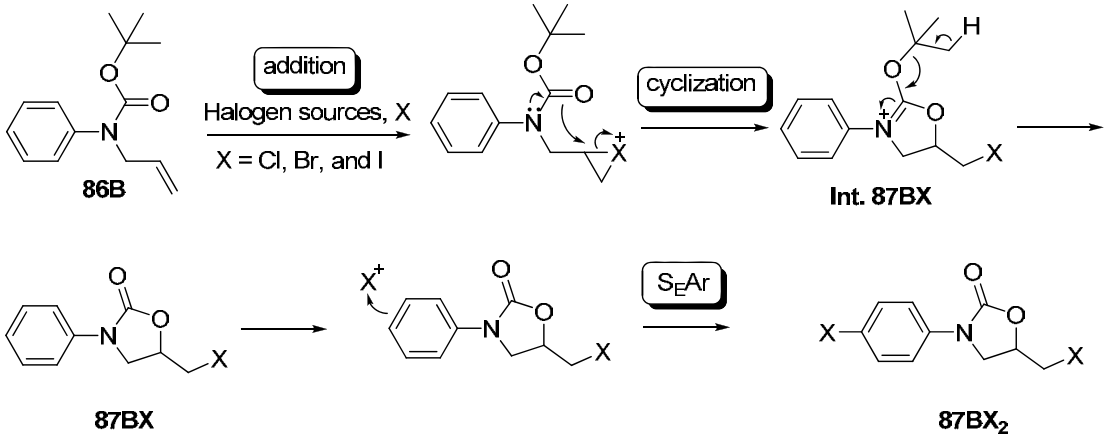


Figure 3.8 ^{1}H NMR spectra of various *N*-aryl 2-oxazolidinones **87B** in $CDCl_3$

3.2.4 Mechanism of halo-induced intramolecular cyclization

The mechanism for the halo-induced-cyclization of *tert*-butyl (phenyl)allylcarbamate **86B** by various halogen sources was proposed herein. The addition reaction of alkene moiety allowed the protonation of the halogenbridge

cation, on which the carbonyl oxygen would immediately attack to form the cyclized 5-memberd-ring cation intermediate **Int. 87BX**. The lost of *tert*-butyl group gives the corresponding 2-oxazolidinone containing halogen atom derivative **87BX**. Additionally, the electrophilic aromatic substitution reaction was occurred to produce 2-oxazolidinone containing two halogen atom derivative **87BX$_2$** as the final product (Scheme 3.14).



Scheme 3.14 The proposed mechanism of halo-induced intramolecular cyclization

CHAPTER IV

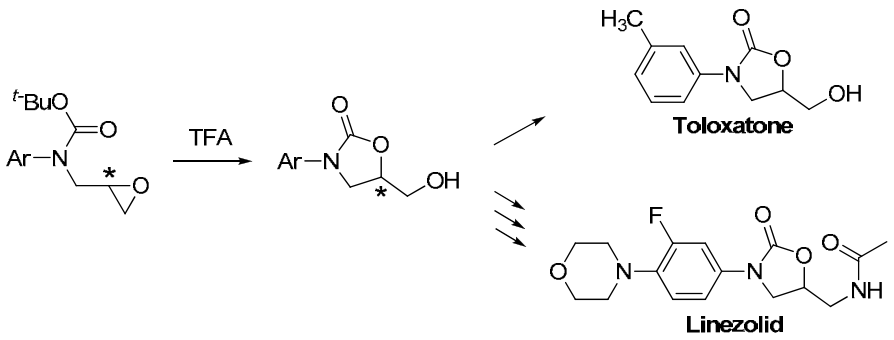
CONCLUSION

4.1 Conclusion

The series of *N*-aryl-2-oxazolidinone, containing various aromatic moieties were synthesized in novel two synthetic pathways and their key intramolecular cyclizations were systematically and thoroughly optimized.

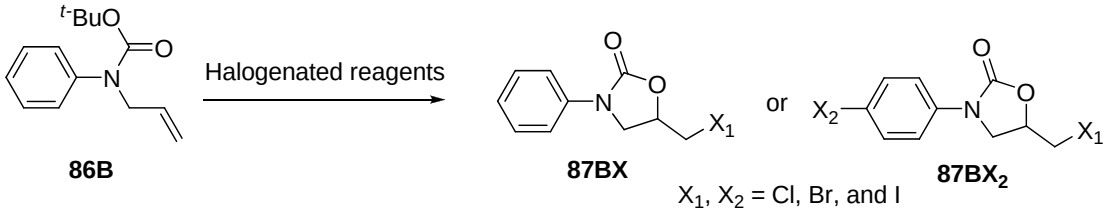
1) Acid-induced cyclization of β-(*N*-arylcarbamyl)epoxides

β-(*N*-arylcarbamyl)epoxides, cyclization substrates, were easily synthesized from the alkylation of epichlorohydrin and *N*-arylcarbamates. Cyclization of β-(*N*-arylcarbamyl)epoxides with acid readily gave the corresponding *N*-aryl-2-oxazolidinones in excellent yields (73%-93%). Mechanistically, the Boc carbonyl oxygen intramolecularly attacks the epoxide ring under acidic conditions in *5-exo-tet* fashion to give the desired oxazolidin-2-ones. The cyclization reaction conditions were thoroughly optimized by varying acids. Trifluoroacetic acid was found to be the most effective acid in cyclization step. Toloxatone, a well known antidepressant and monoamine oxidase inhibitor (MAOI), was successfully produced from this method in high yield. Linezolid (Zyvox®), our main target antibacterial medicine, was also stereochemically synthesized by using this optimized acid-induce cyclization with overall percent yield of 27%.



2) Halo-induced intramolecular cyclization

Simple and facile halo-induced intramolecular cyclization method was developed. The target halo-oxazolidinone products were obtained in excellent yields by treating *tert*-butyl allyl (phenyl)carbamate with halogenated reagents. Several halogenated reagents were used such as chlorine, bromine, iodine, *N*-Chlorosuccinimide, *N*-Bromosuccinimide, *N*-Iodosuccinimide, iodinemonochloride, $BTNMe_3ICl_2$, and mixed reagent of potassium iodide and potassiumiodate in acetic acid. The condition optimization was also accomplished by varying factors e.g. amount of reagent, solvent, temperature and reaction time. Interestingly, two halo-oxazolidinone scaffolds, unsubstituted oxazolidinone (**87BX**) and *p*-halo-aryl oxazolidinone (**87BX$_2$**), could be produced from this halo-induced intramolecular cyclization reaction depending on the reactivity of the particular halonium ion. Moreover, the selective syntheses for only **87BX** derivative or **87BX$_2$** derivative were successfully developed. In general, cyclization reaction to yield **87BX** prefers the relatively unreactive halonium ion (NCS, NBS, NIS, I2, $BTNMe_3ICl_2$), on the other hand, the relatively more reactive halonium ion (Cl_2, Br_2, KI/KIO_3) tend to have both cyclization reaction and electrophilic aromatic substitution to produce **87BX$_2$**. From the easiness of further functionalization point of view, the scaffold development of iodo-substituted oxazolidinone (**87BI$_2$**) is far more interesting than chloro and bromo-substituted cases with high potential to open the new useful and convenient pathway for oxazolidinone derivatization.



4.2 Suggestion for the future work

Further research in continuation of this thesis may include:

- To synthesize oxazolidinone derivatives based on using **87BX$_2$** oxazolidinone scaffold.

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APPENDICES

APPENDIX A

NMR SPECTRA

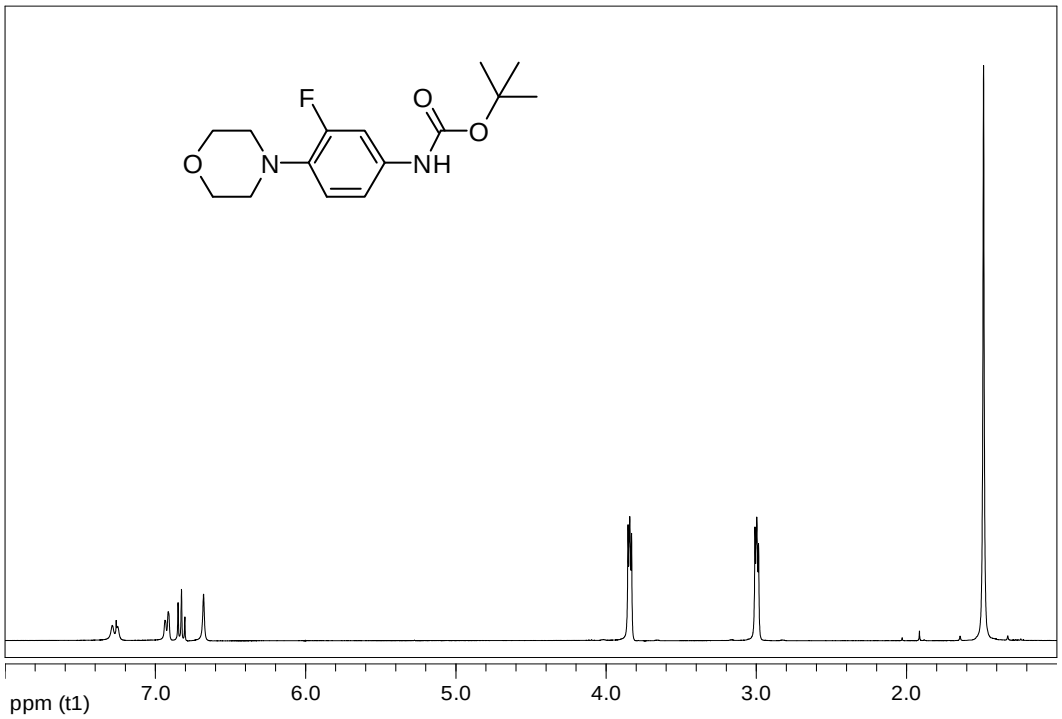


Figure A1 ^{1}H NMR spectrum of *tert*-butyl 3-fluoro-4-morpholinophenylcarbamate

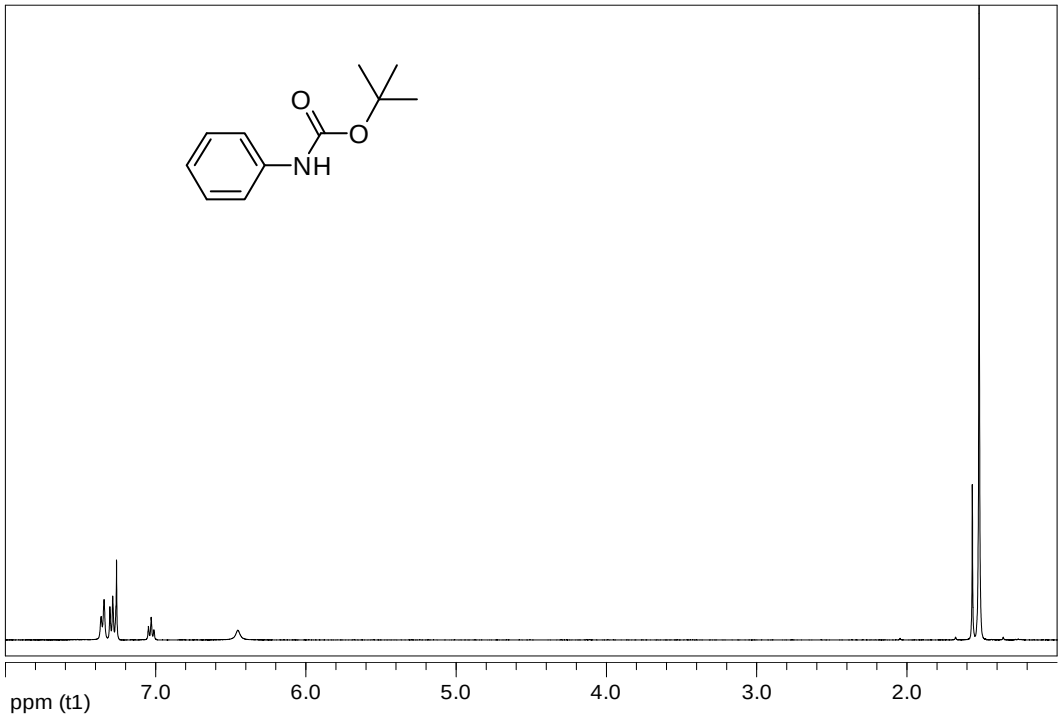


Figure A2 ^{1}H NMR spectrum of *tert*-butyl phenylcarbamate

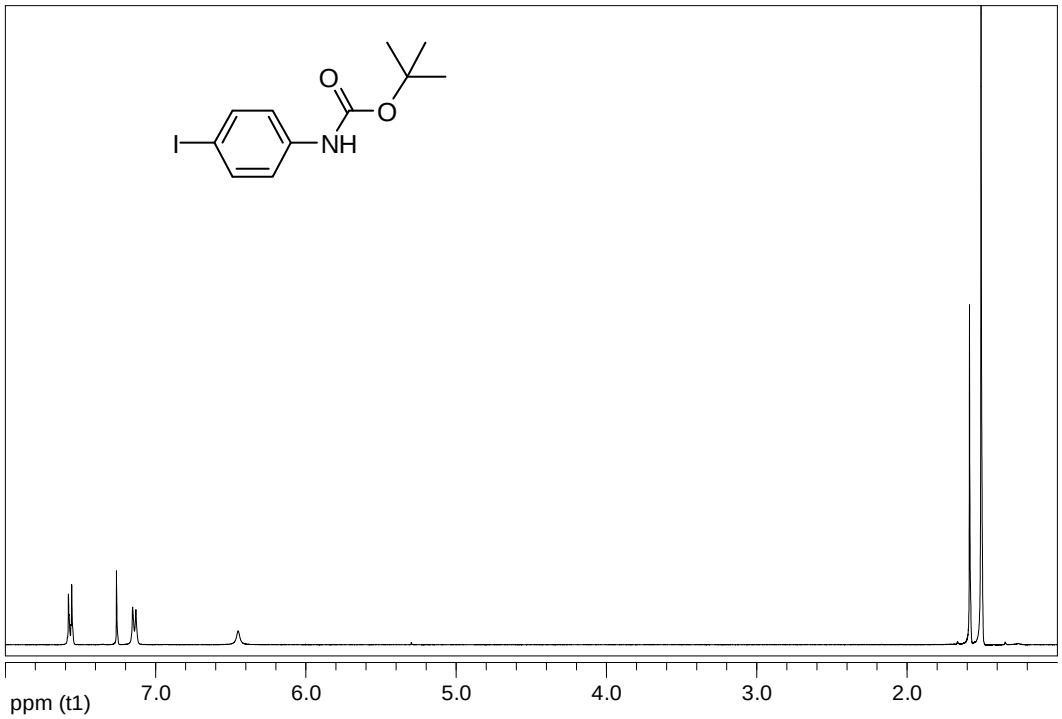


Figure A3 ^{1}H NMR spectrum of *tert*-butyl 4-iodophenylcarbamate

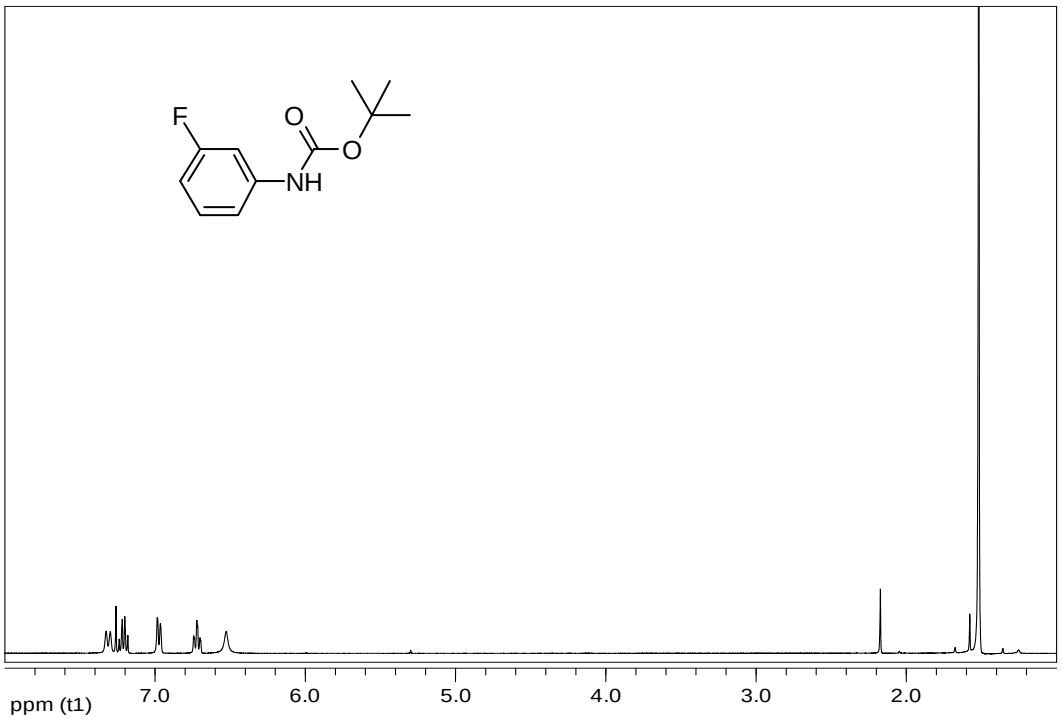


Figure A4 ^{1}H NMR spectrum of *tert*-butyl 3-fluorophenylcarbamate

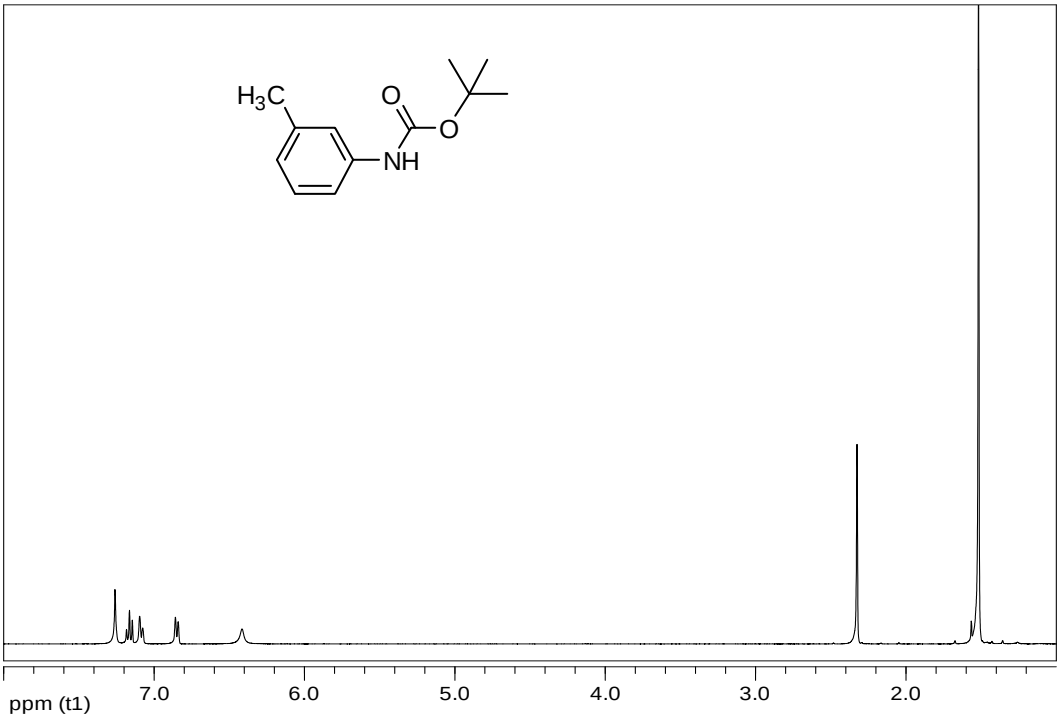


Figure A5 ^{1}H NMR spectrum of *m*-tolylcarbamate

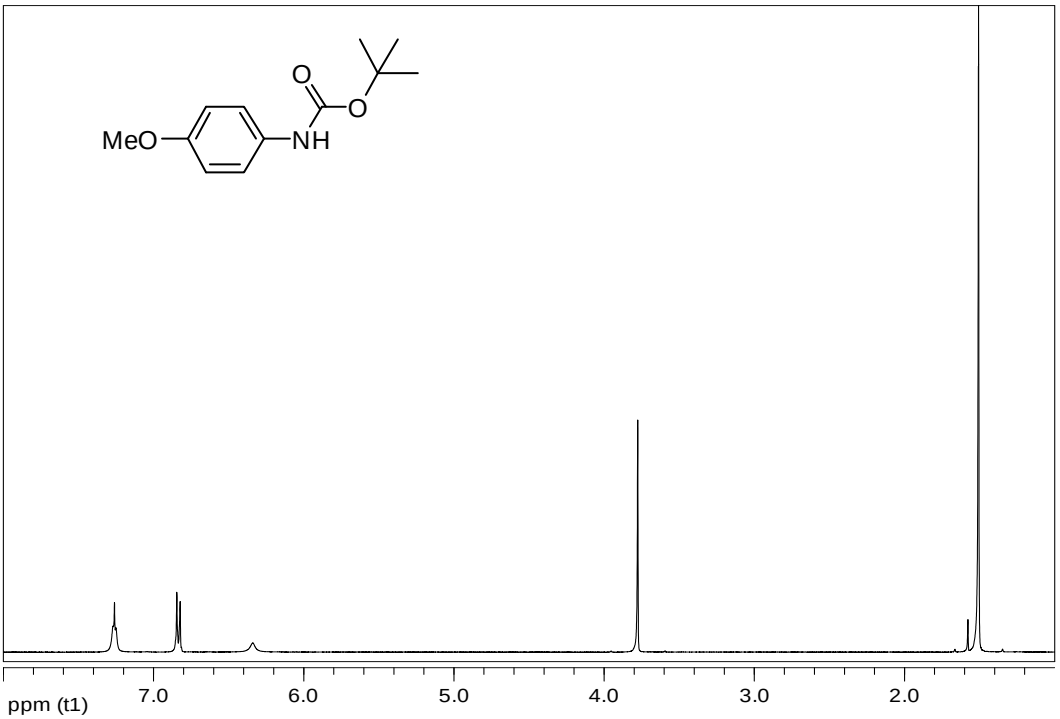


Figure A6 ^{1}H NMR spectrum of *tert*-butyl 4-methoxyphenylcarbamate

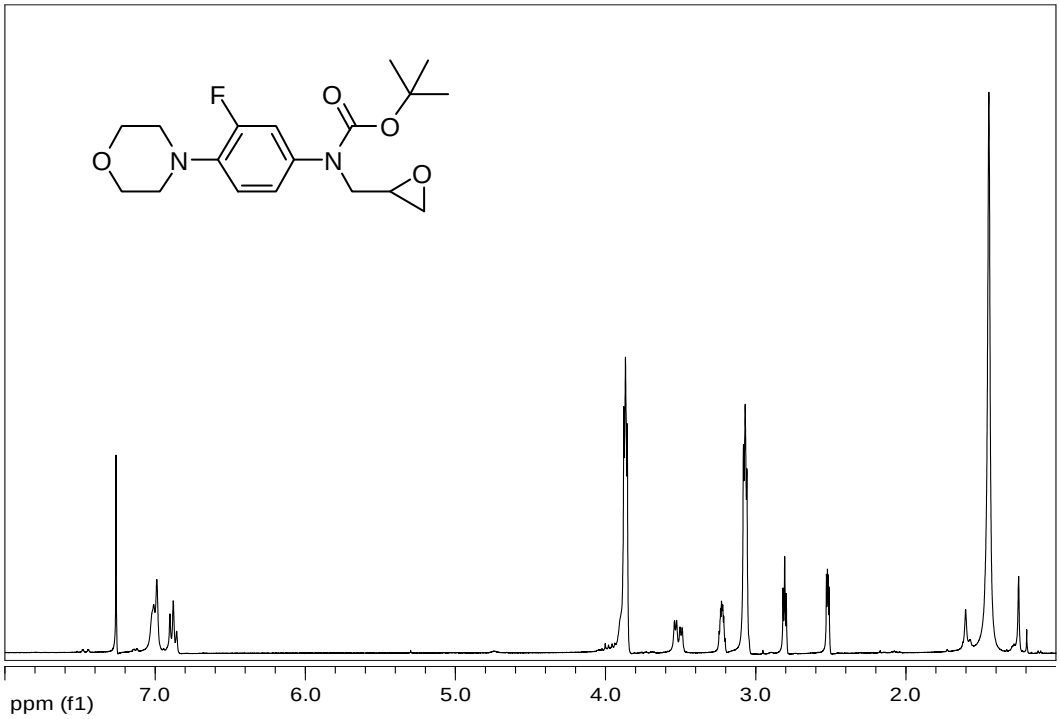


Figure A7 ^{1}H NMR spectrum of 3-fluoro-4-morpholinophenyl(oxiran-2-ylmethyl) carbamate

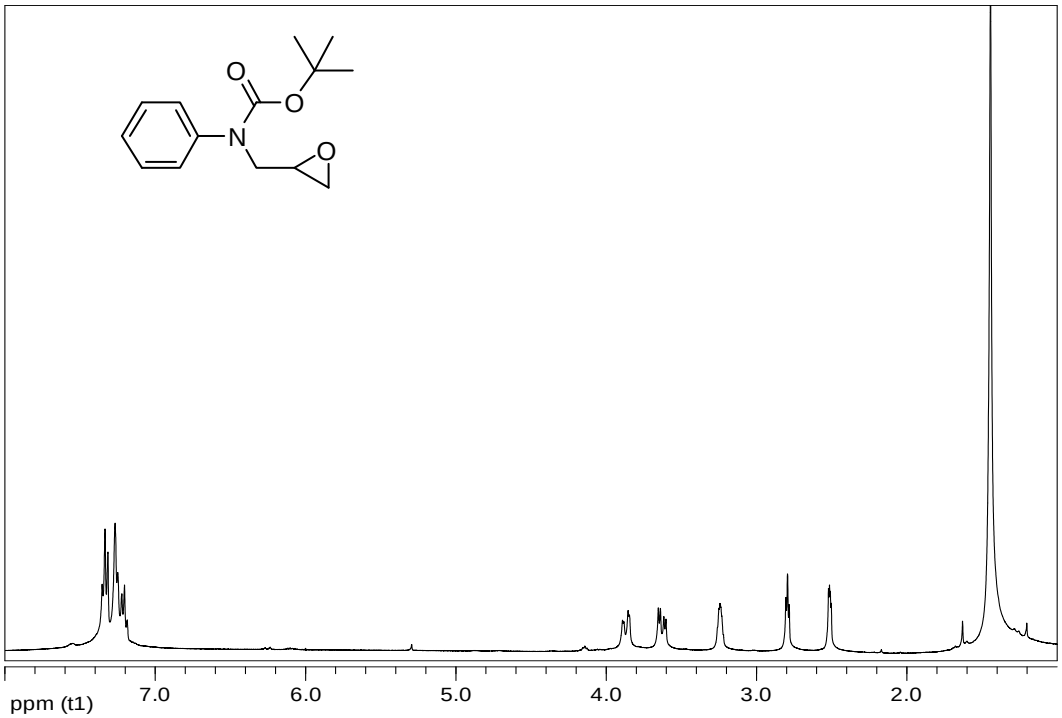


Figure A8 ^{1}H NMR spectrum of *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate

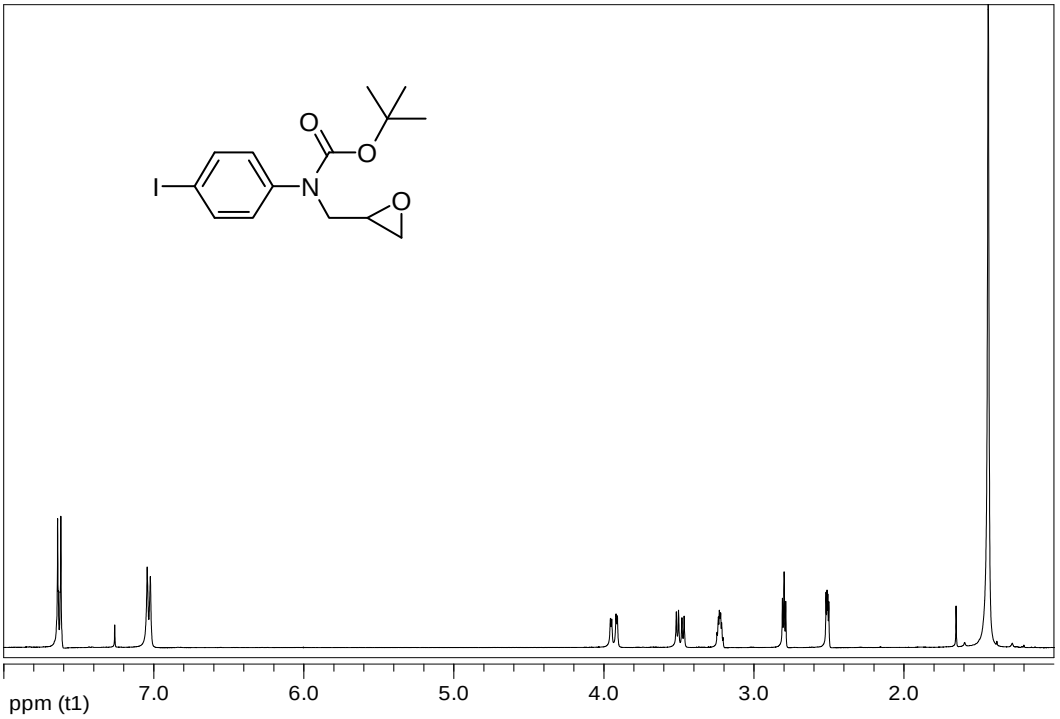


Figure A9 ^{1}H NMR spectrum of *tert*-butyl-4-iodophenyl(oxiran-2-ylmethyl) carbamate

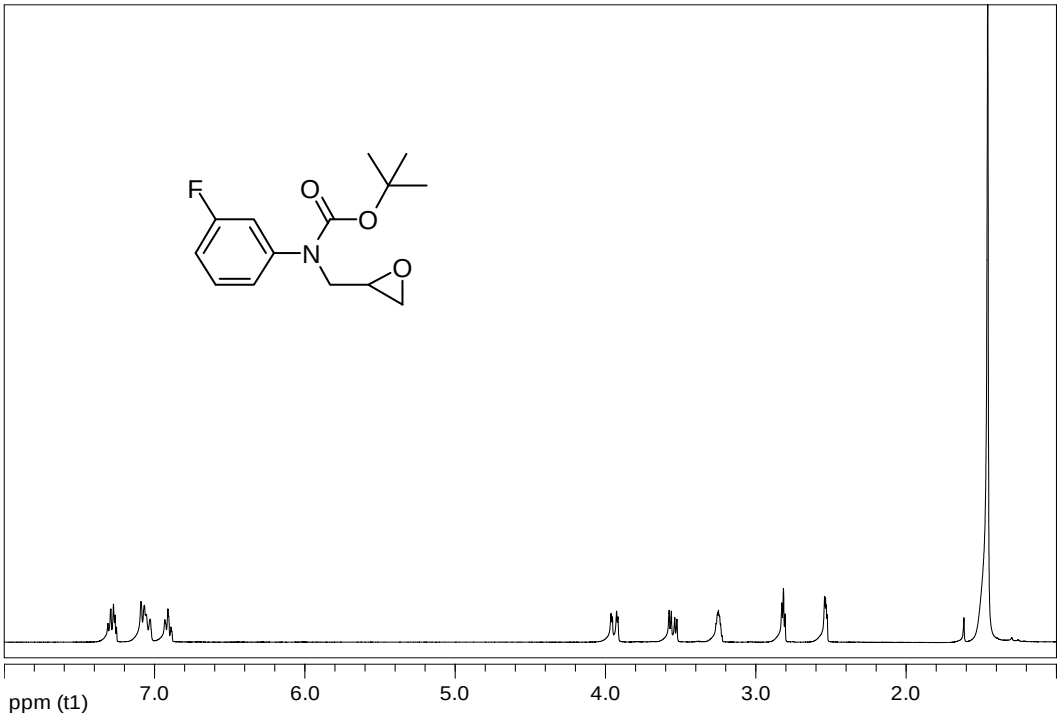


Figure A10 ^{1}H NMR spectrum of *tert*-butyl-3-fluorophenyl(oxiran-2-ylmethyl) carbamate

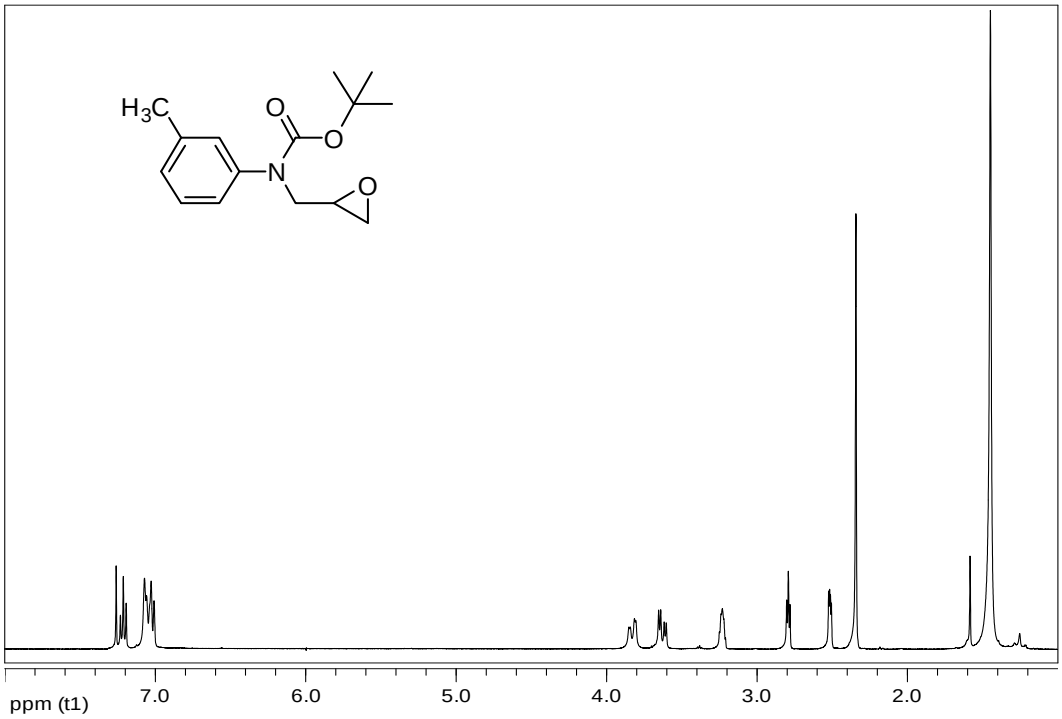


Figure A11 ^{1}H NMR spectrum of *tert*-butyl oxiran-2-ylmethyl(*m*-tolyl)carbamate

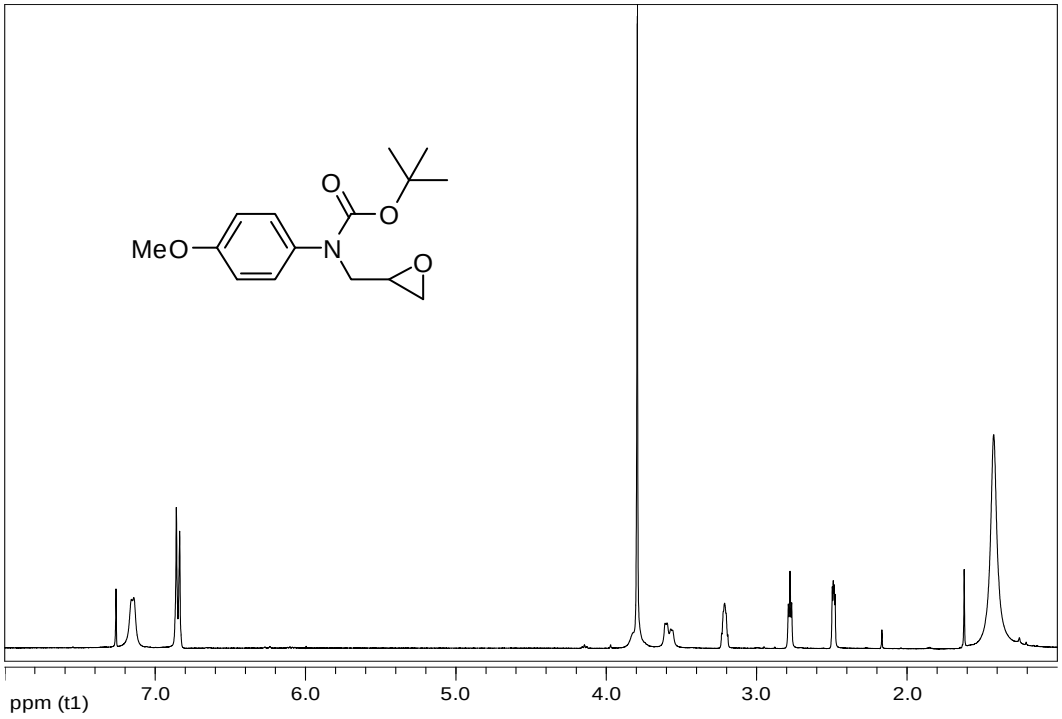


Figure A12 ^{1}H NMR spectrum of *tert*-butyl 4-methoxyphenyl(oxiran-2-ylmethyl) carbamate

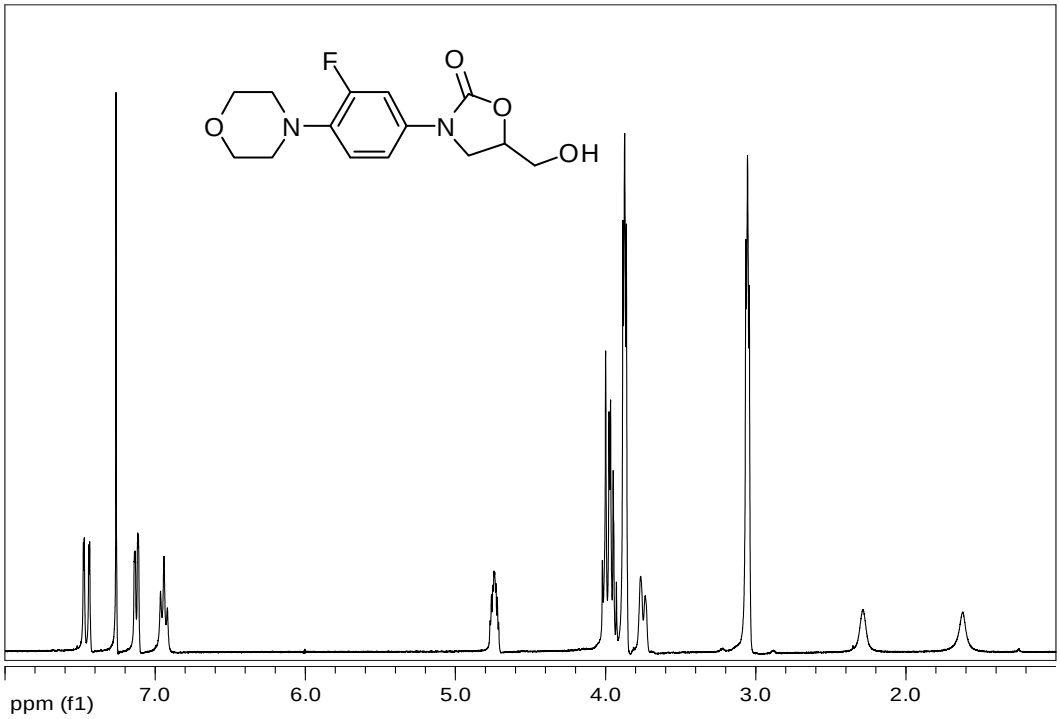


Figure A13 ^{1}H NMR spectrum of 3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one

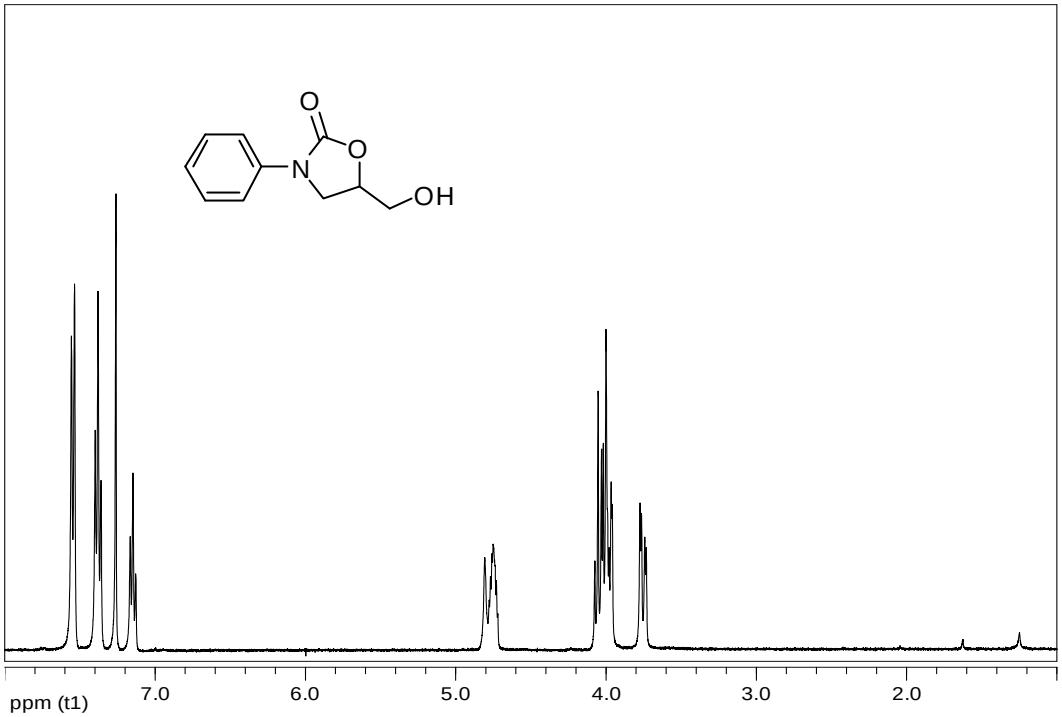


Figure A14 ^{1}H NMR spectrum of 5-(hydroxymethyl)-3-phenyloxazolidin-2-one

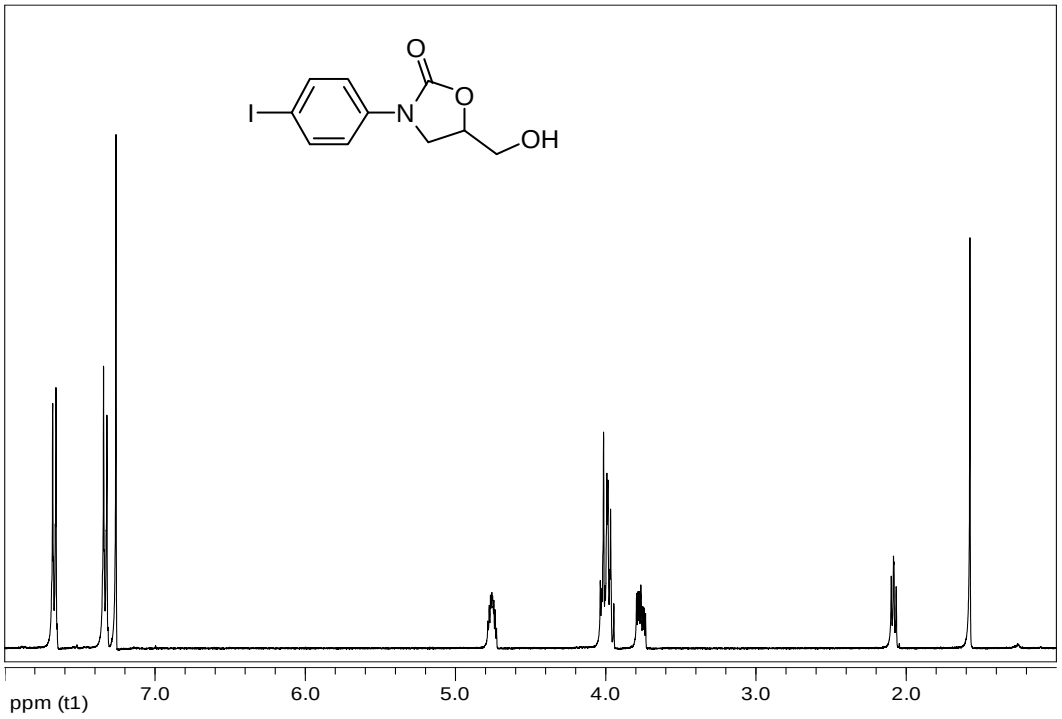


Figure A15 ^{1}H NMR spectrum of 5-(hydroxymethyl)-3-(4-iodophenyl)oxazolidin-2-one

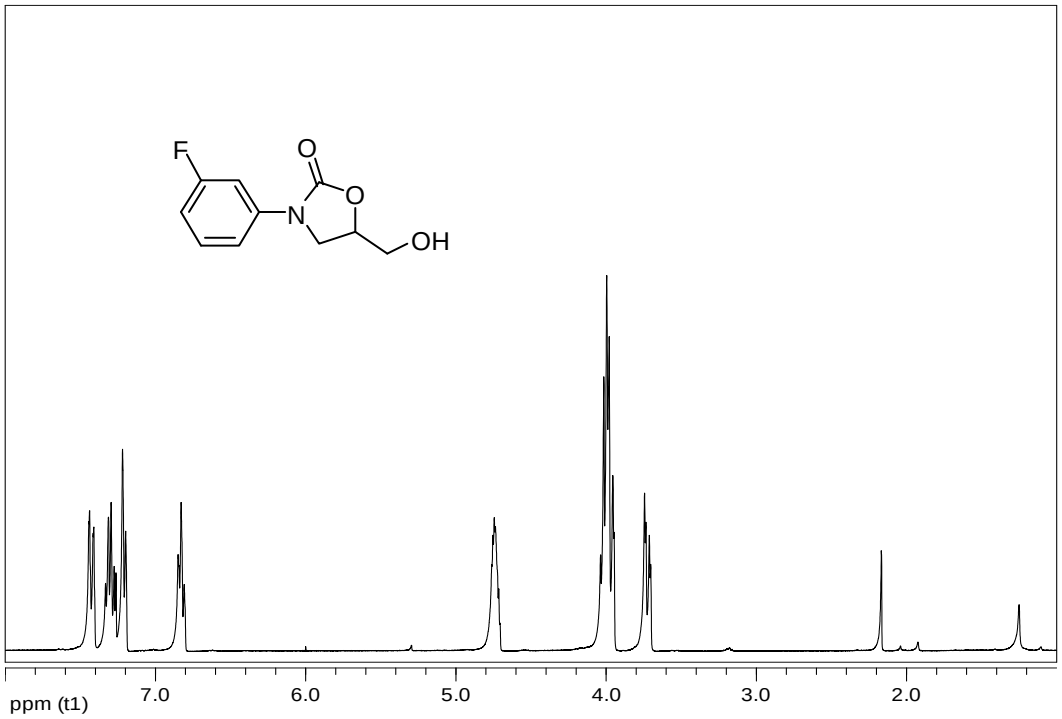


Figure A16 ^{1}H NMR spectrum of 3-(3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one

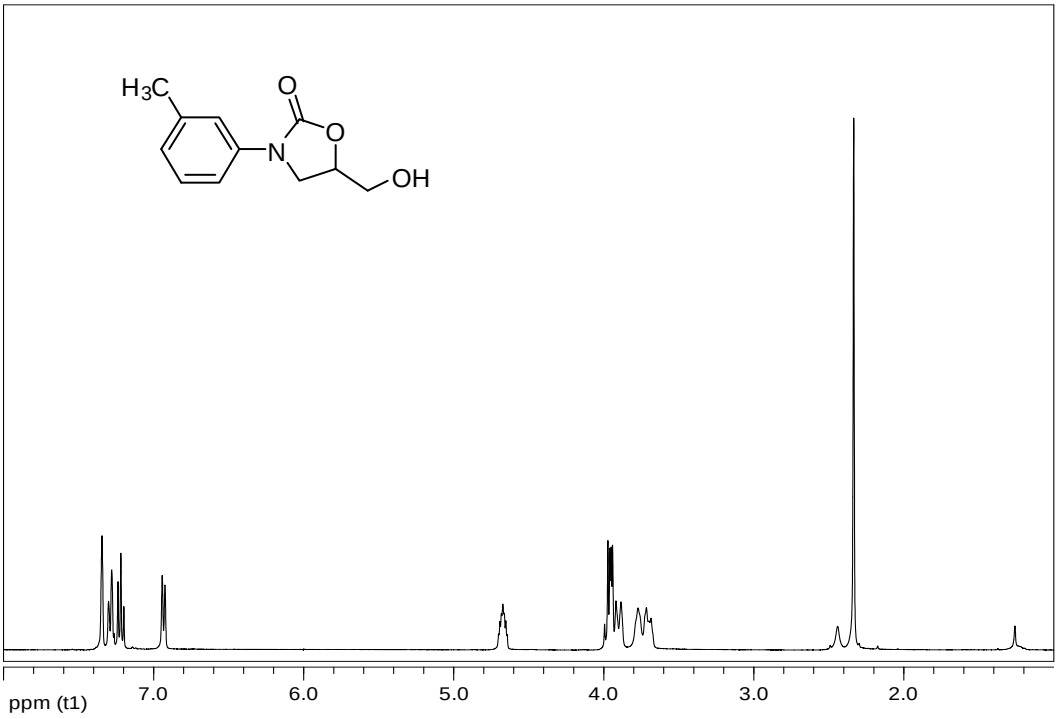


Figure A17 ^{1}H NMR spectrum of 5-(hydroxymethyl)-3-*m*-tolyloxazolidin-2-one

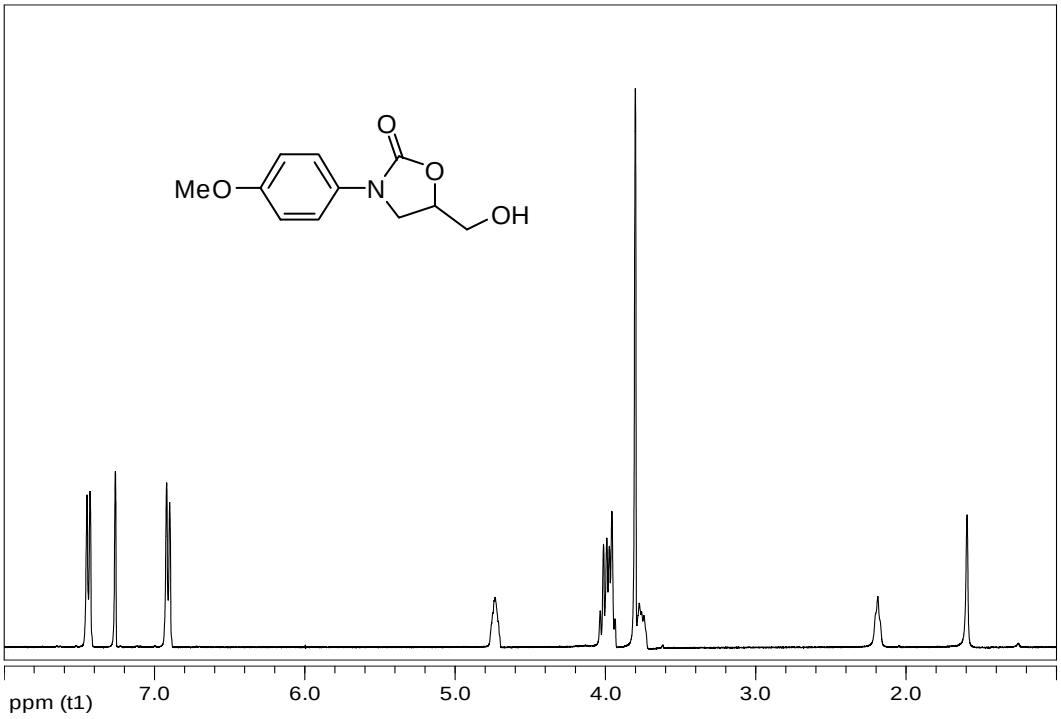


Figure A18 ^{1}H NMR spectrum of 5-(hydroxymethyl)-3-(4-methoxyphenyl)oxazolidin-2-one

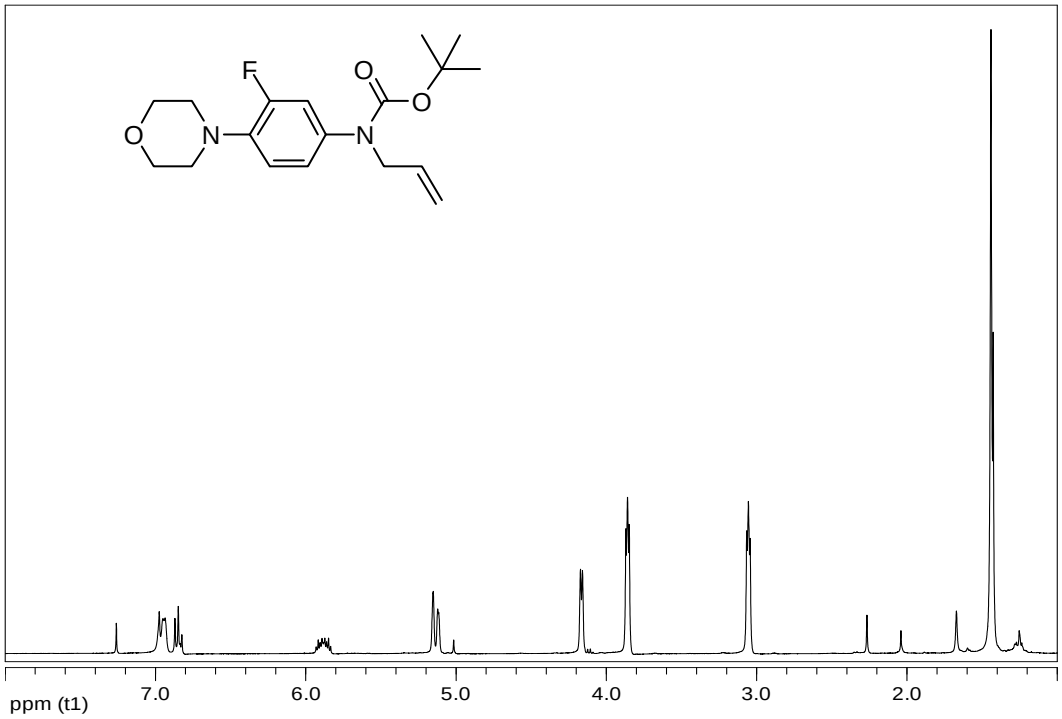


Figure A19 ^{1}H NMR spectrum of *tert*-butyl allyl(3-fluoro-4-morpholinophenyl) carbamate

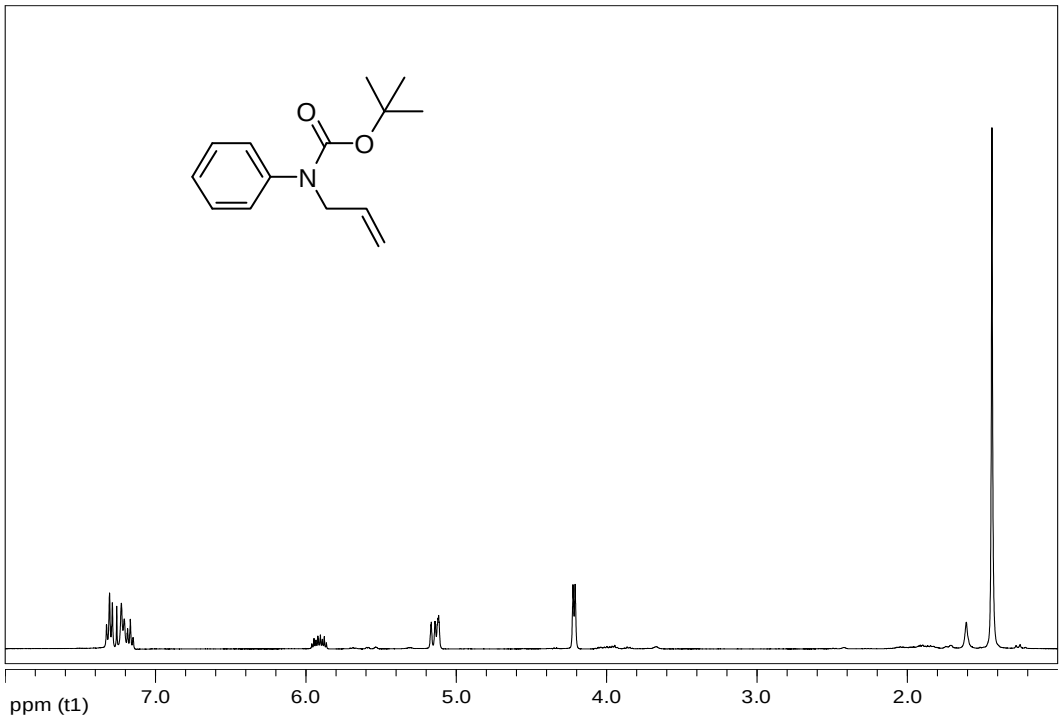


Figure A20 ^{1}H NMR spectrum of *tert*-butyl allyl(phenyl)carbamate

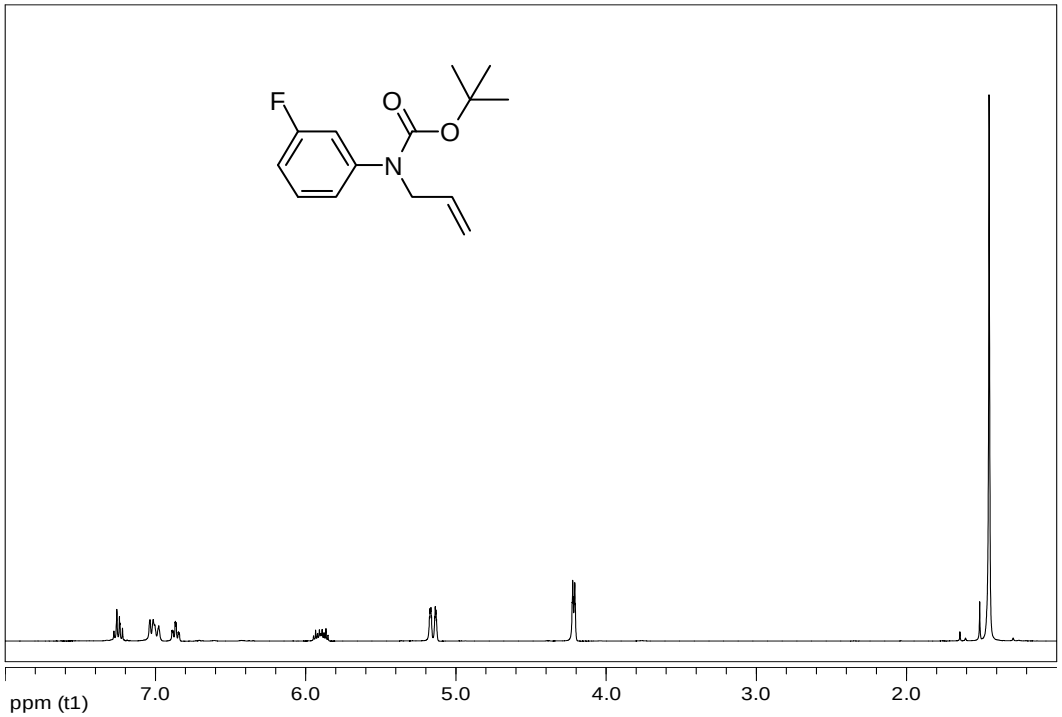


Figure A21 ^{1}H NMR spectrum of *tert*-butyl allyl(3-fluorophenyl)carbamate

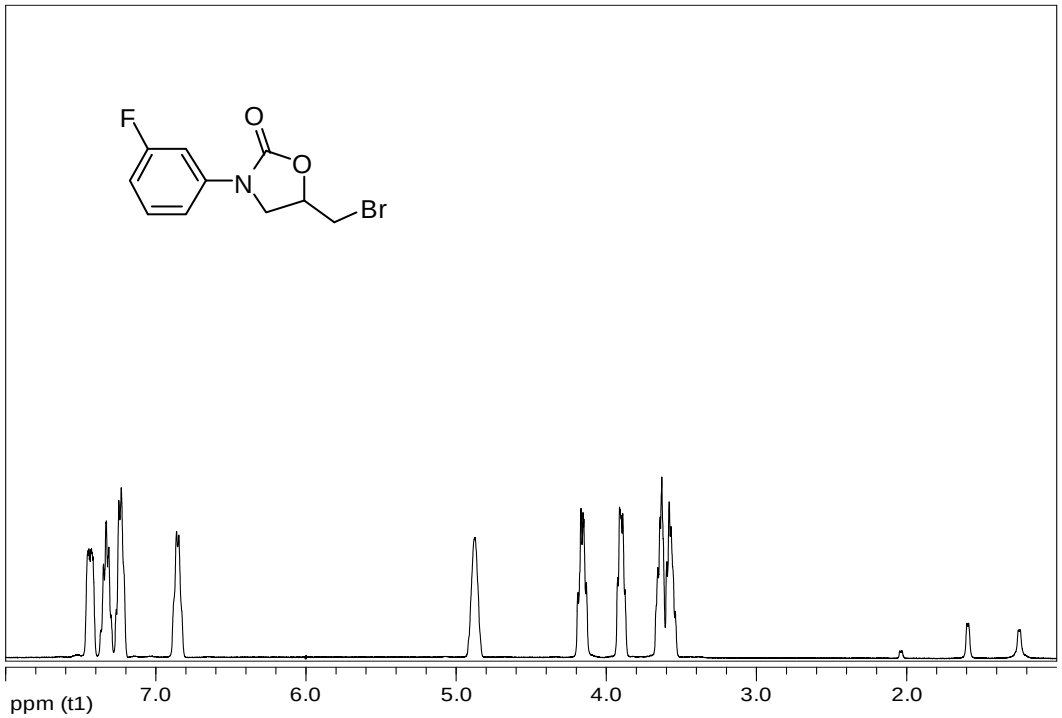


Figure A22 ^{1}H NMR spectrum of 5-(bromomethyl)-3-(3-fluorophenyl)oxazolidin-2-one

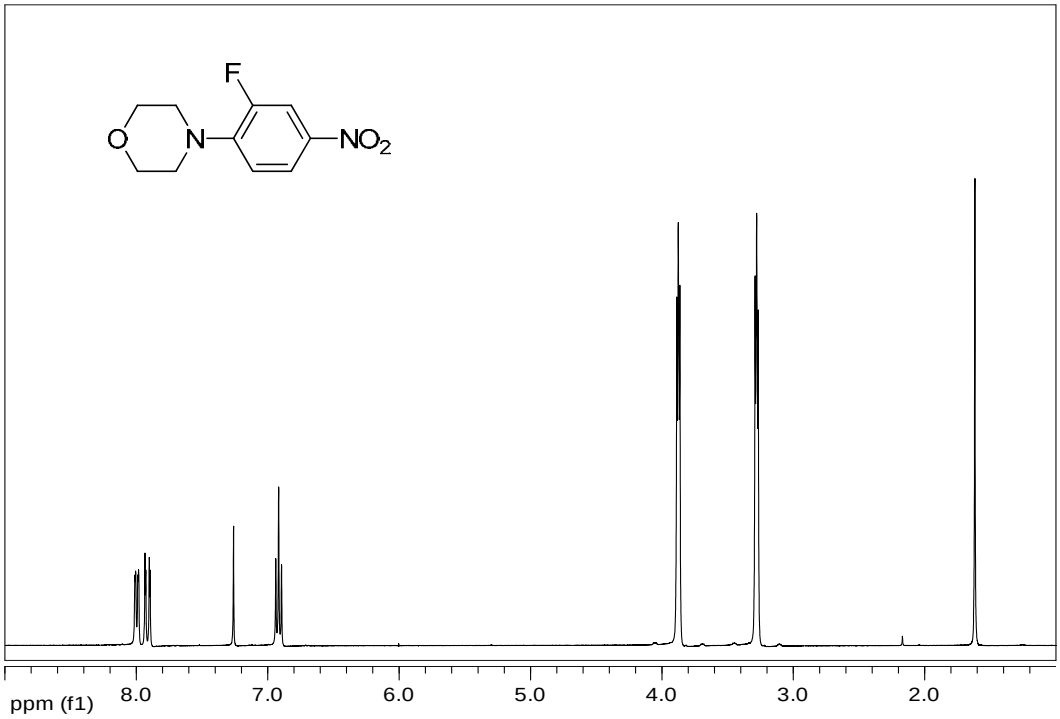


Figure A23 ^{1}H NMR spectrum of 4-(2-fluoro-4-nitrophenyl)morpholine

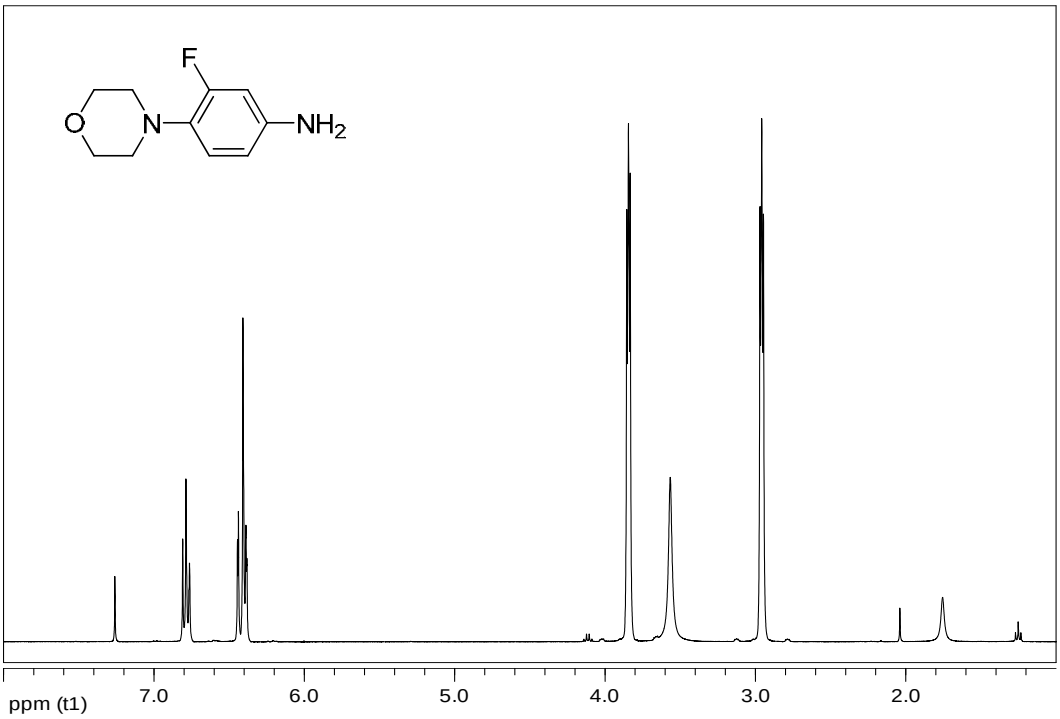


Figure A24 ^{1}H NMR spectrum of 3-fluoro-4-morpholinoaniline

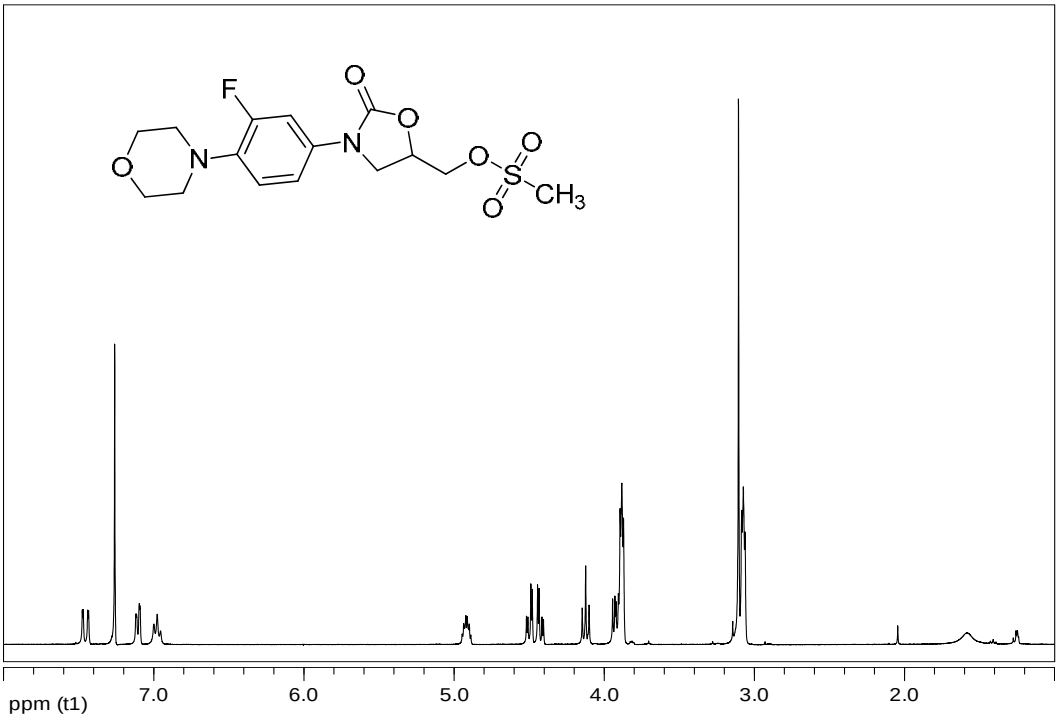


Figure A25 ^{1}H NMR spectrum of (3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methylmethanesulfonate

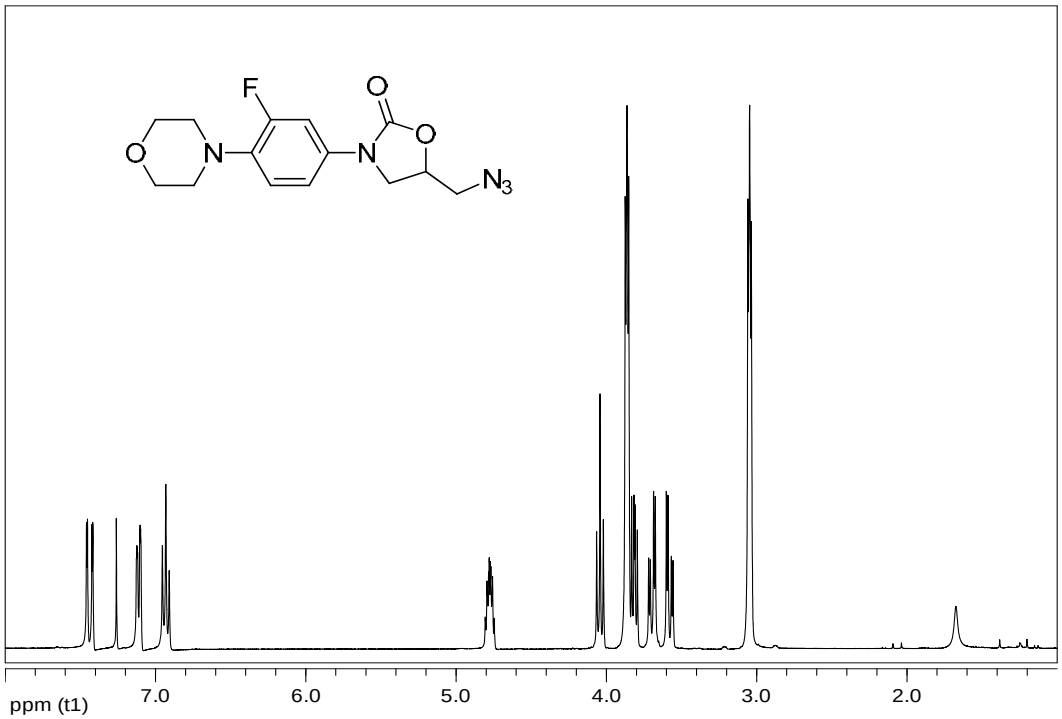


Figure A26 ^{1}H NMR spectrum of 5-(azidomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one

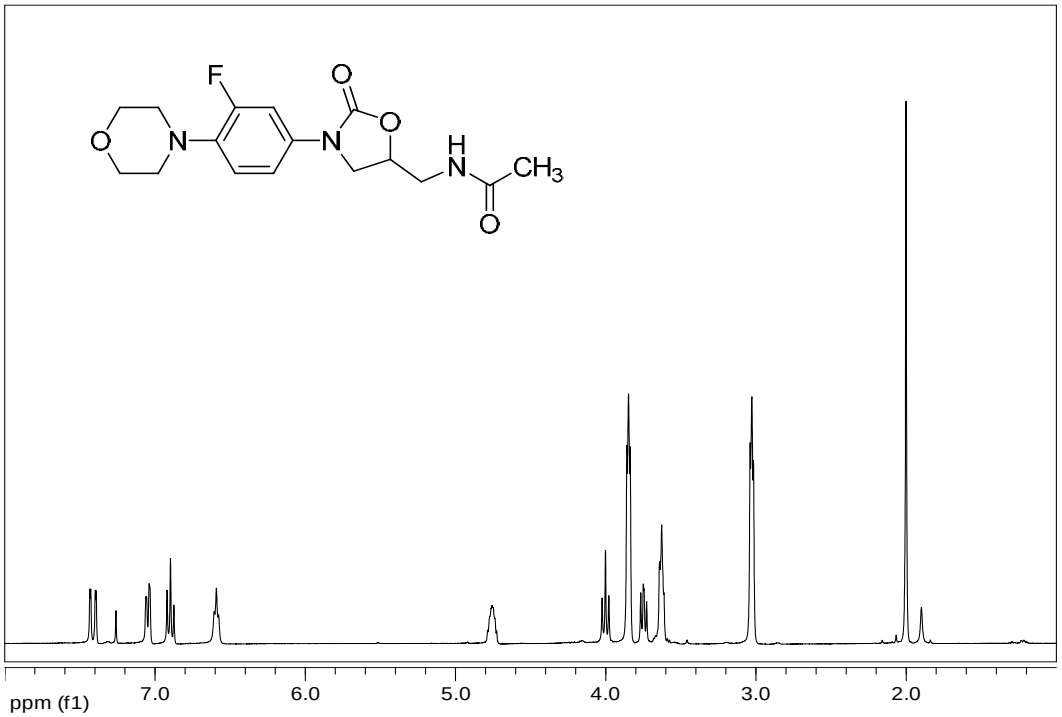


Figure A27 ^{1}H NMR spectrum of N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl methyl)acetamide

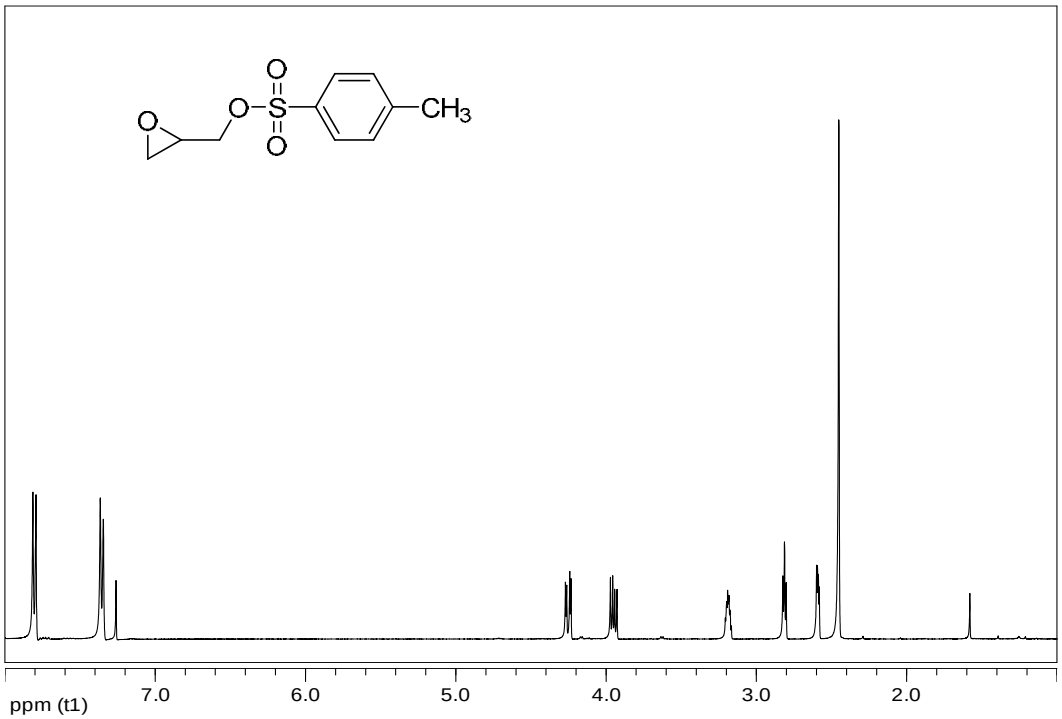


Figure A28 ^{1}H NMR spectrum of glycidyltosylate

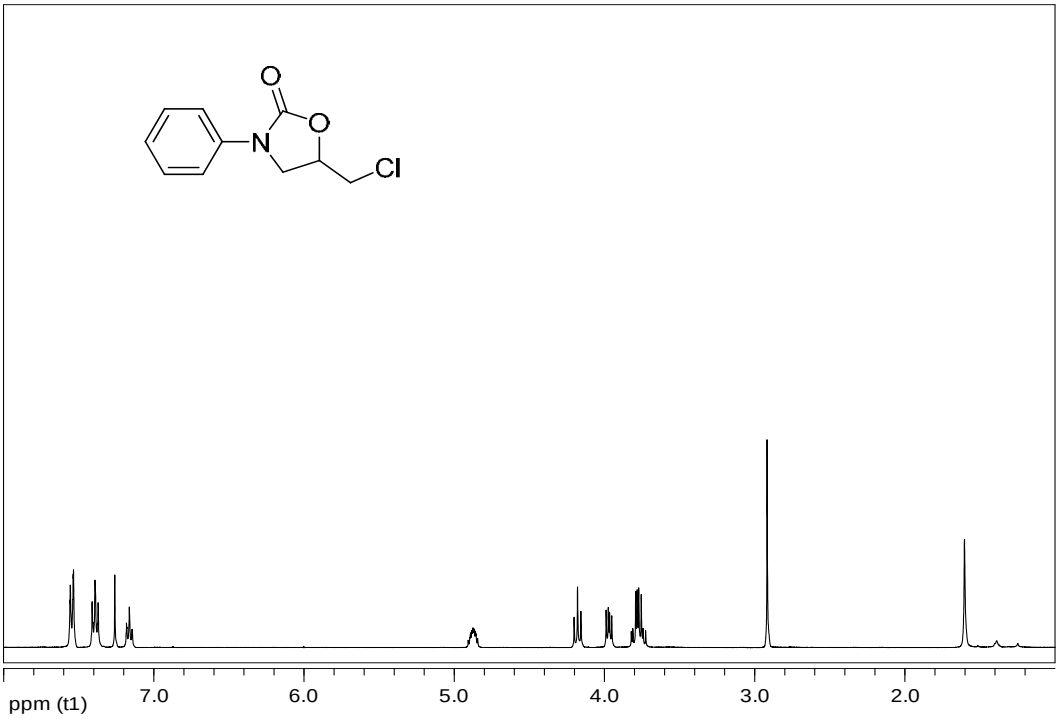


Figure A29 ^{1}H NMR spectrum of 5-(chloromethyl)-3-phenyloxazolidin-2-one

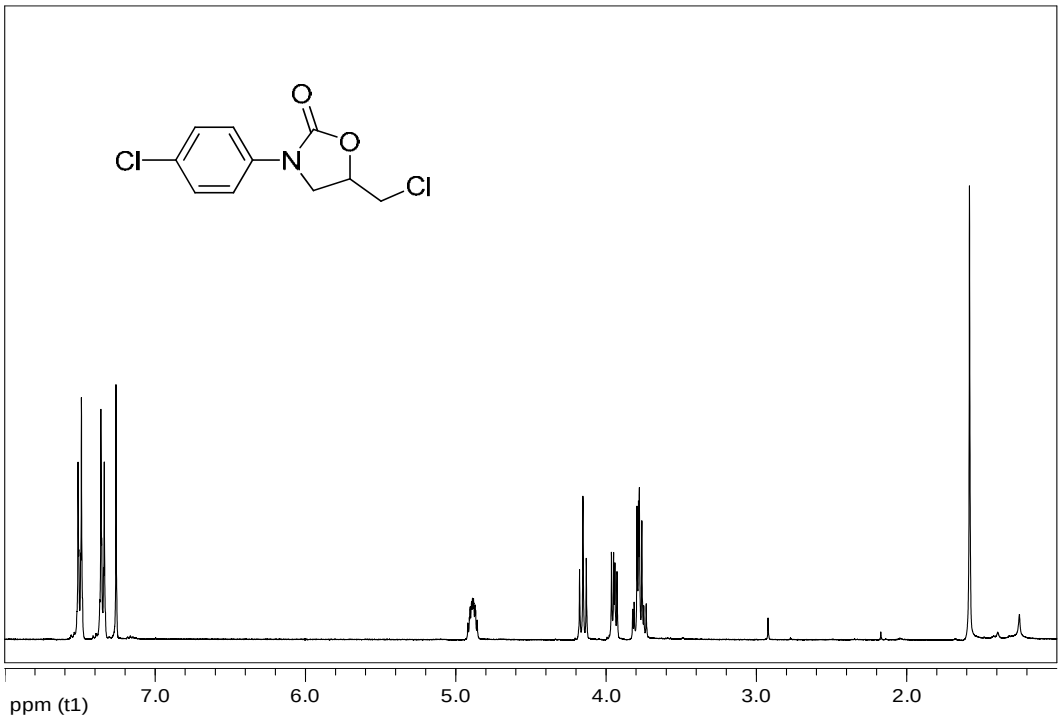


Figure A30 ^{1}H NMR spectrum of 5-(chloromethyl)-3-(4-chlorophenyl) oxazolidin-2-one

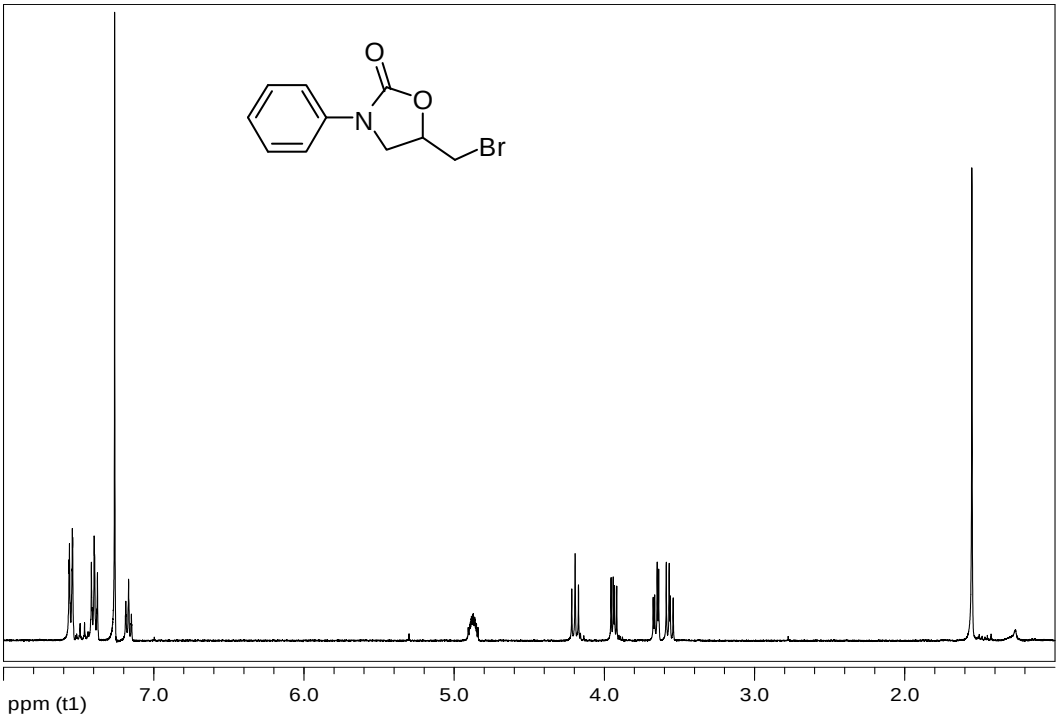


Figure A31 ^{1}H NMR spectrum of 5-(bromomethyl)-3-phenyloxazolidin-2-one

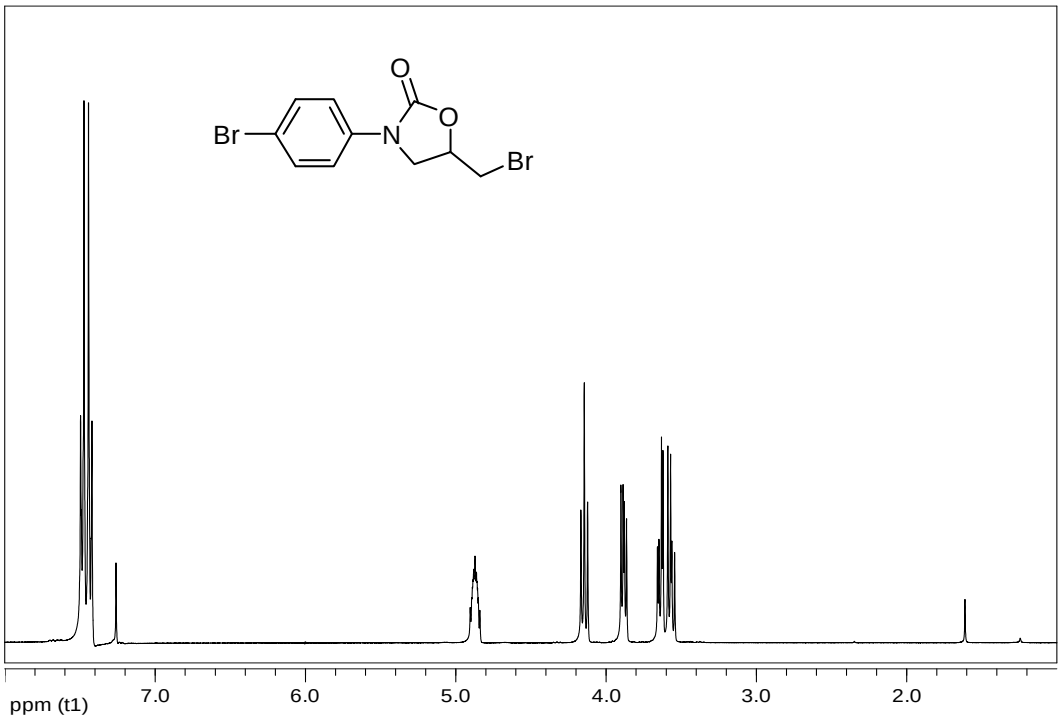


Figure A32 ^{1}H NMR spectrum of 5-(bromomethyl)-3-(4-bromophenyl)oxazolidin-2-one

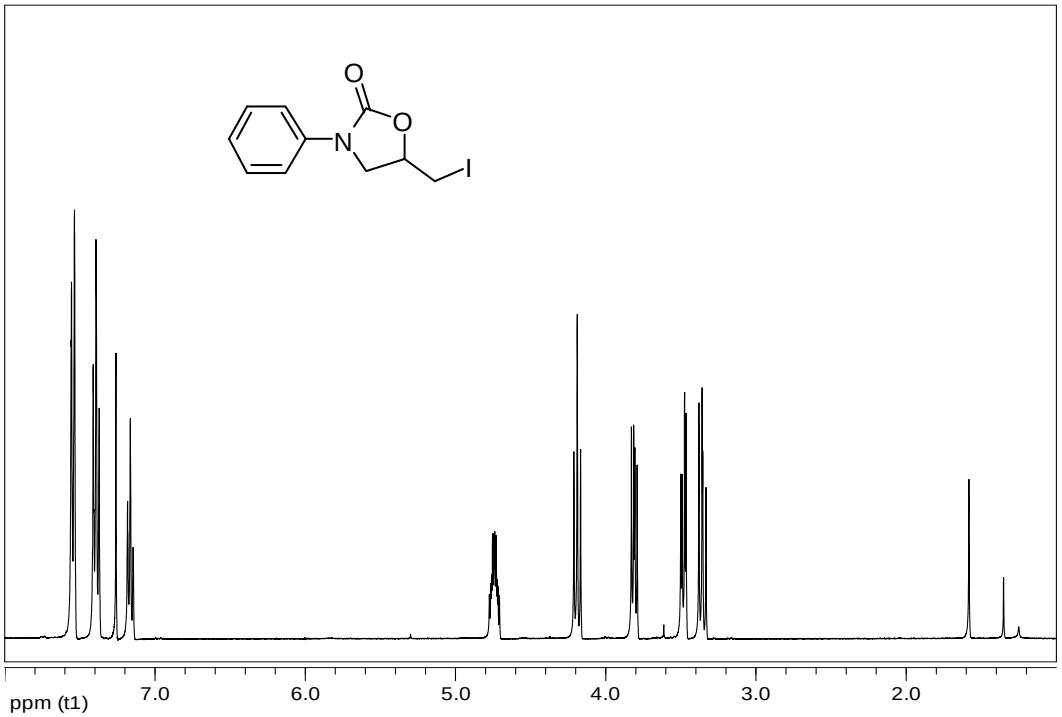


Figure A33 ^{1}H NMR spectrum of 5-(iodomethyl)-3-phenyloxazolidin-2-one

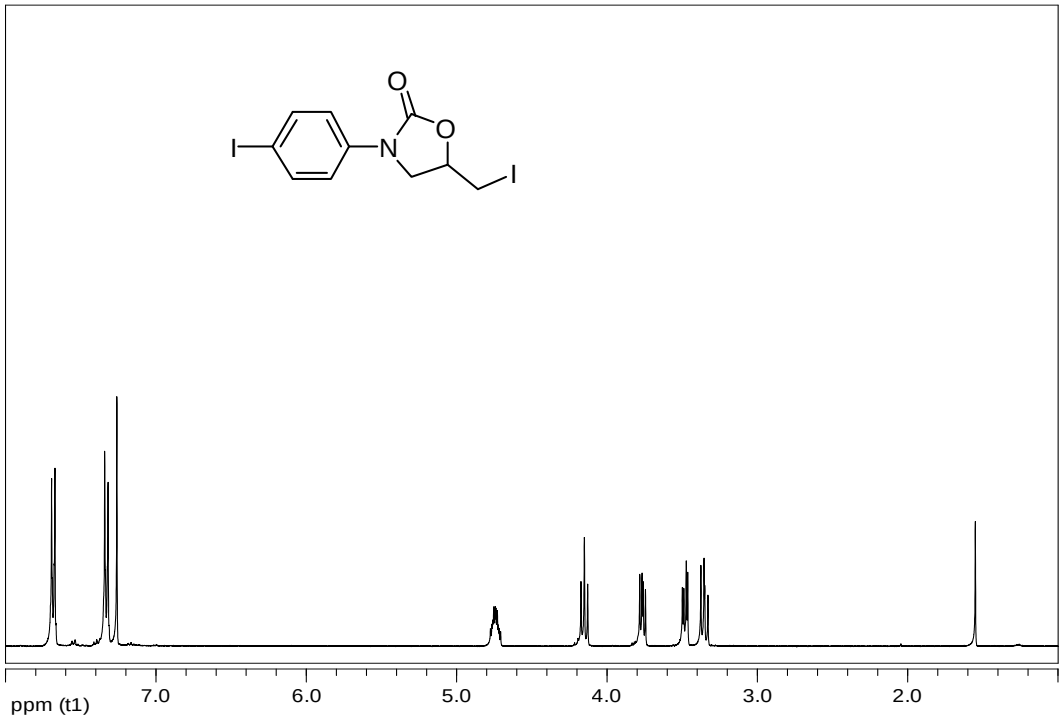


Figure A34 ^{1}H NMR spectrum of 5-(iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one

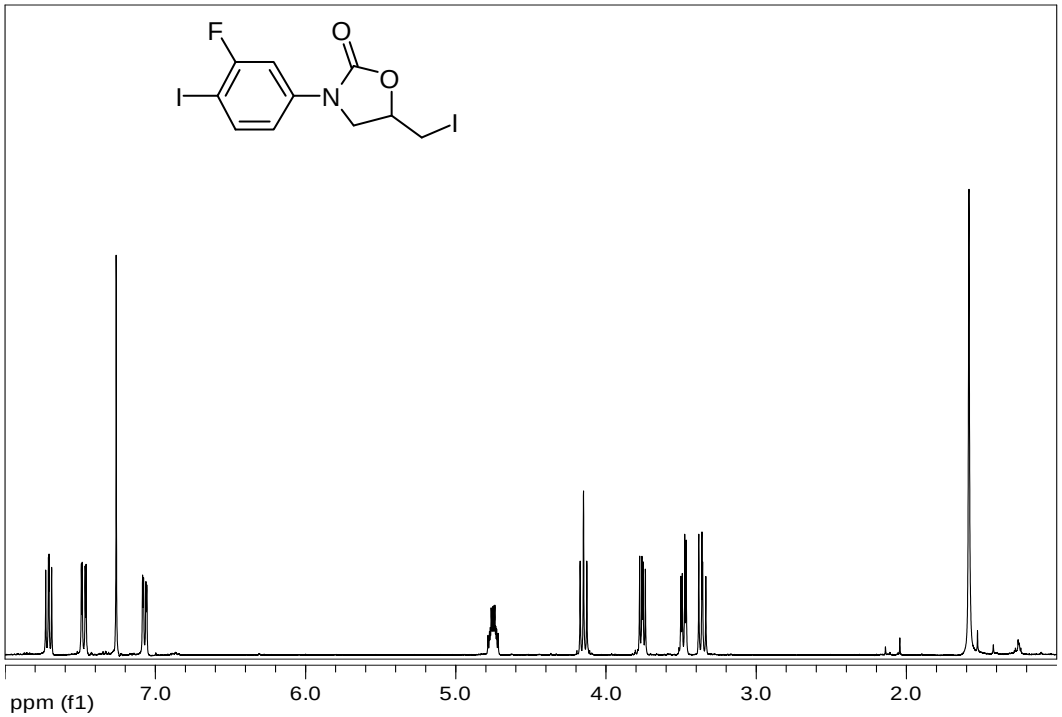


Figure A35 ^{1}H NMR spectrum of 3-(3-fluoro-4-iodophenyl)-5-(iodomethyl) oxazolidin-2-one

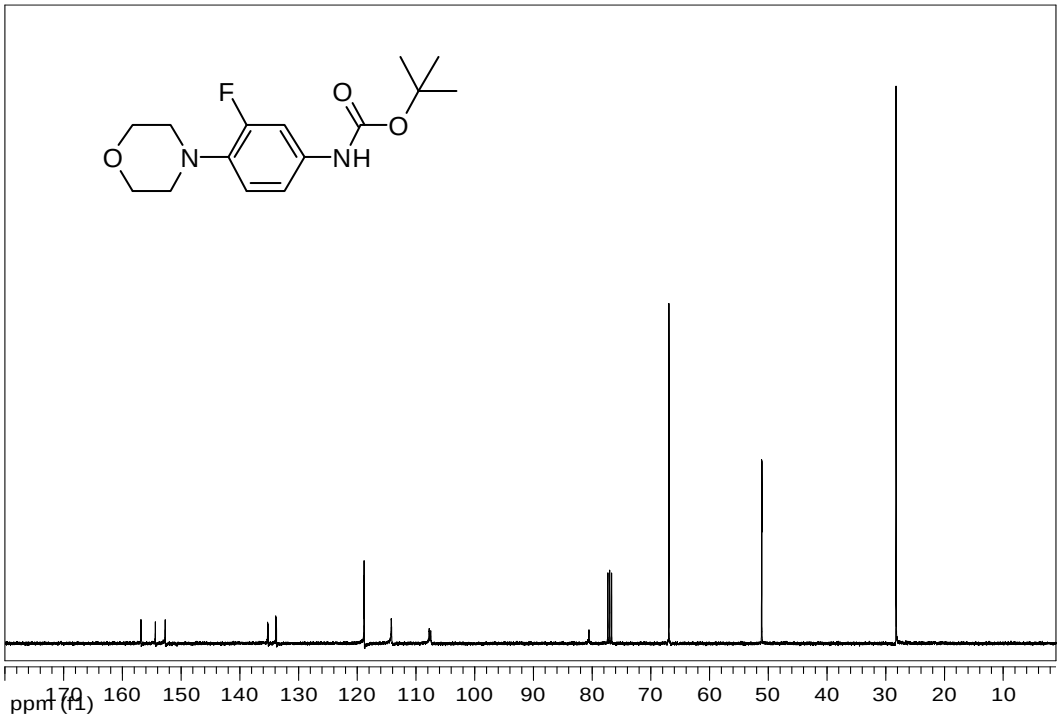


Figure A36 ^{13}C NMR spectrum of *tert*-butyl 3-fluoro-4-morpholinophenylcarbamate

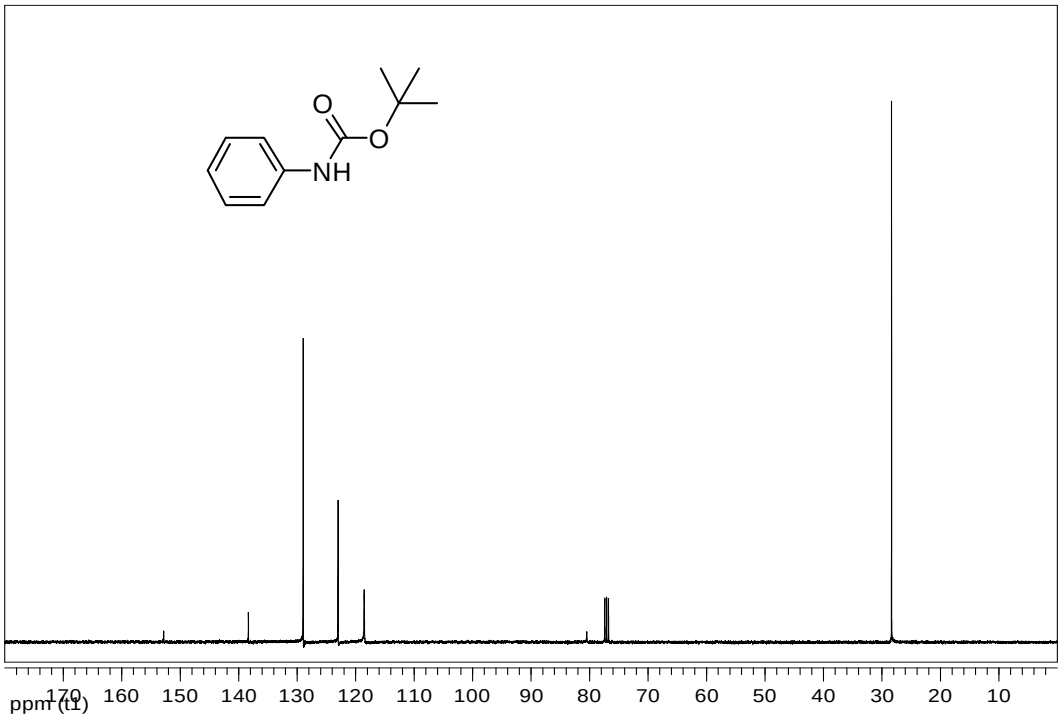


Figure A37 ^{13}C NMR spectrum of *tert*-butyl phenylcarbamate

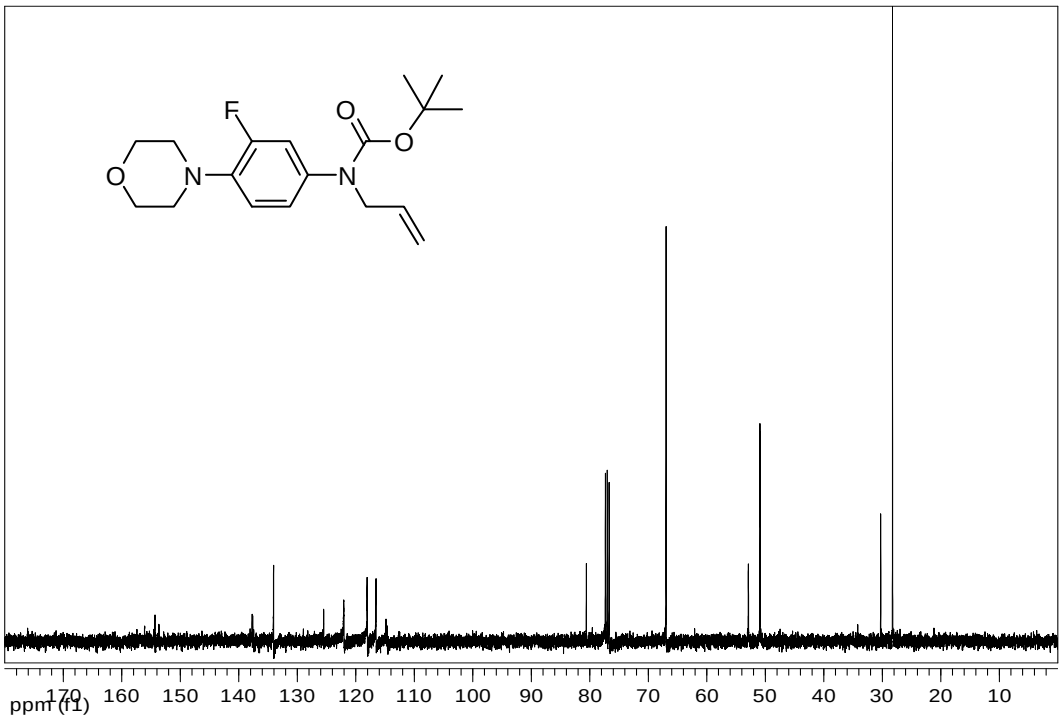


Figure A38 ^{13}C NMR spectrum of *tert*-butyl allyl(3-fluoro-4-morpholinophenyl) carbamate

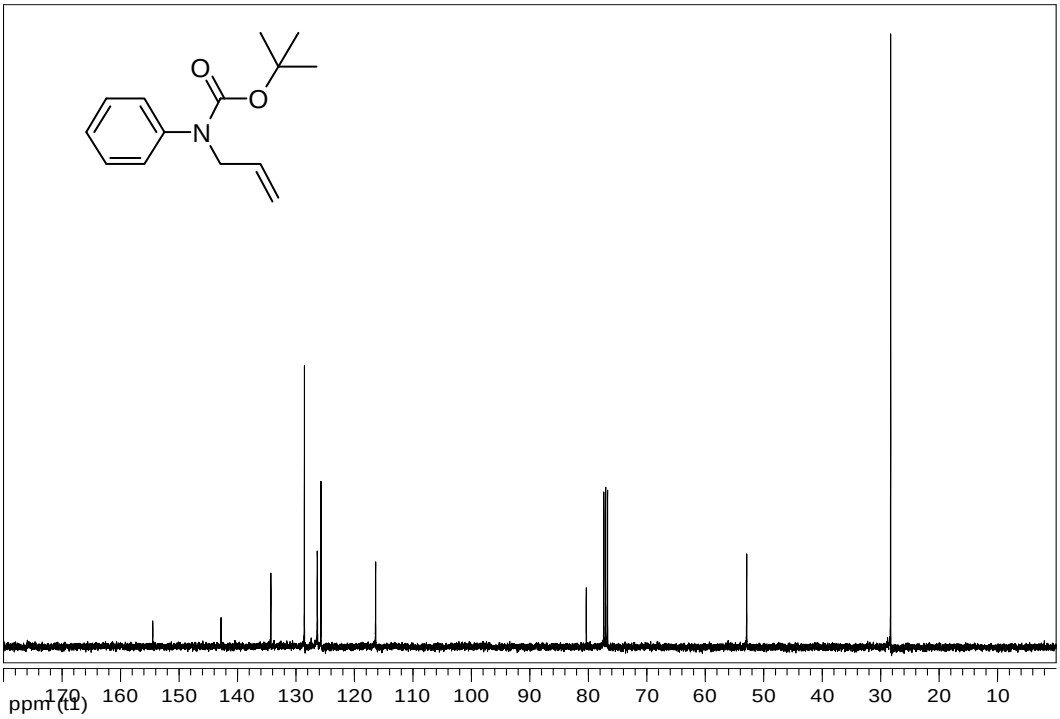


Figure A39 ^{13}C NMR spectrum of *tert*-butyl allyl(phenyl)carbamate

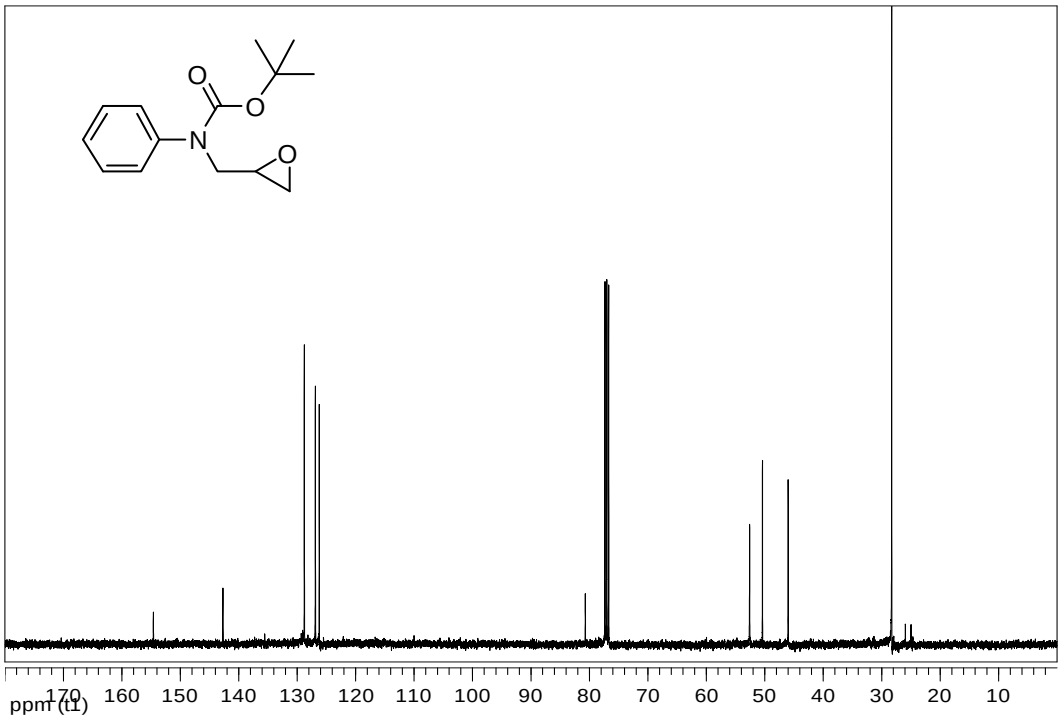


Figure A40 ^{13}C NMR spectrum of *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate

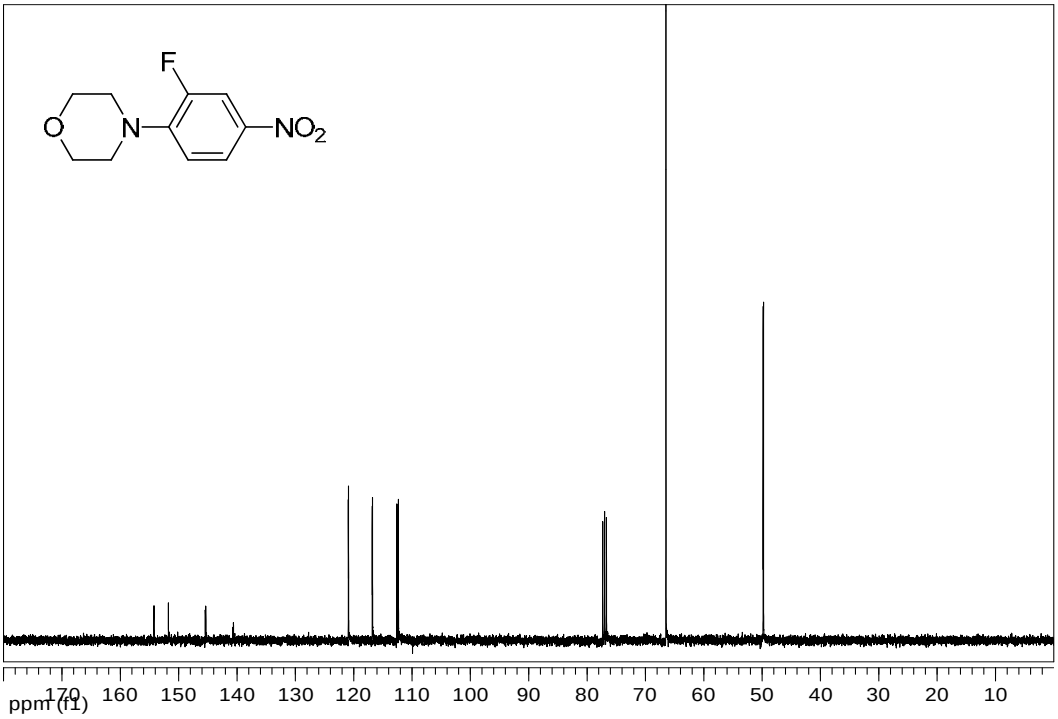


Figure A41 ^{13}C NMR spectrum of 4-(2-fluoro-4-nitrophenyl)morpholine

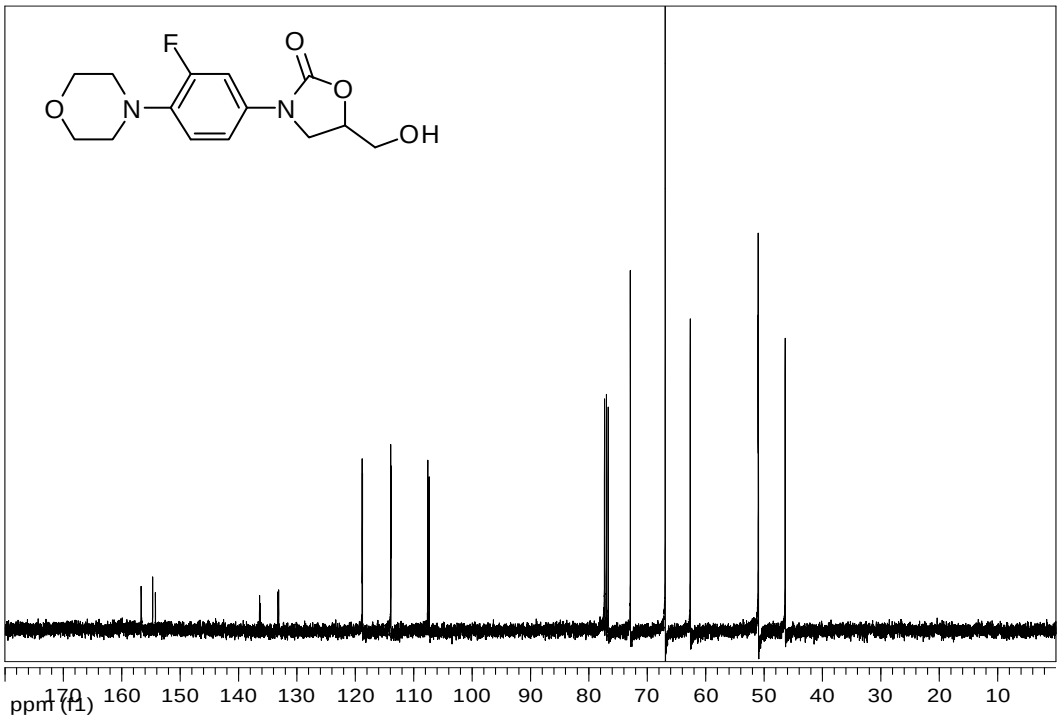


Figure A42 ^{13}C NMR spectrum of 3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one

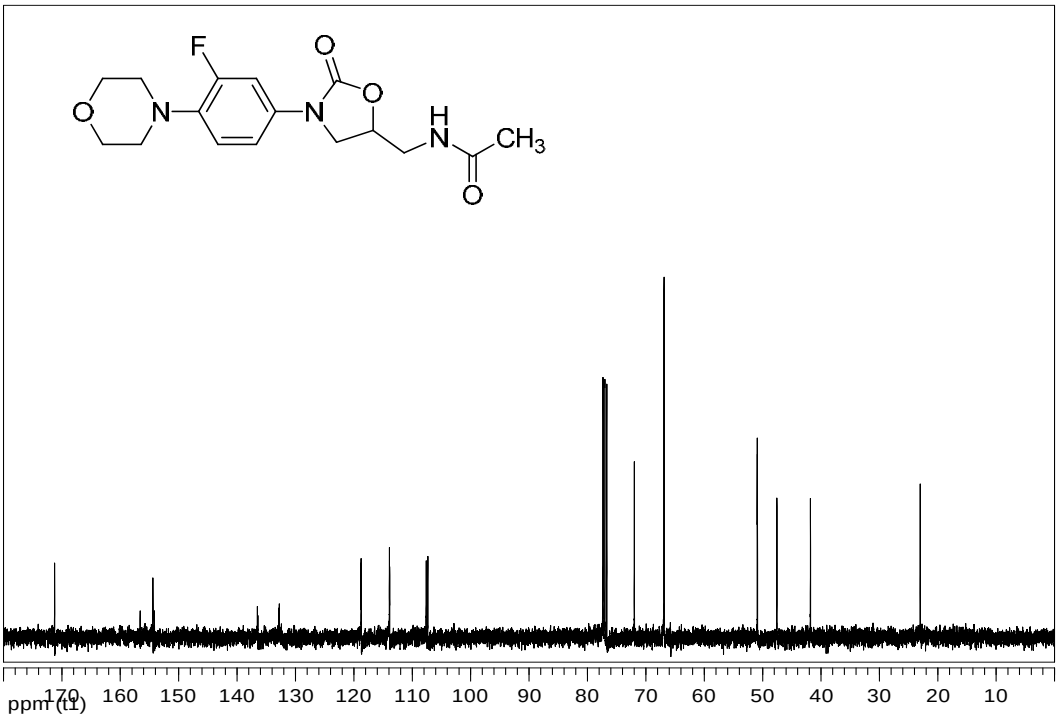


Figure A43 ^{13}C NMR spectrum of *N*-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl methyl)acetamide

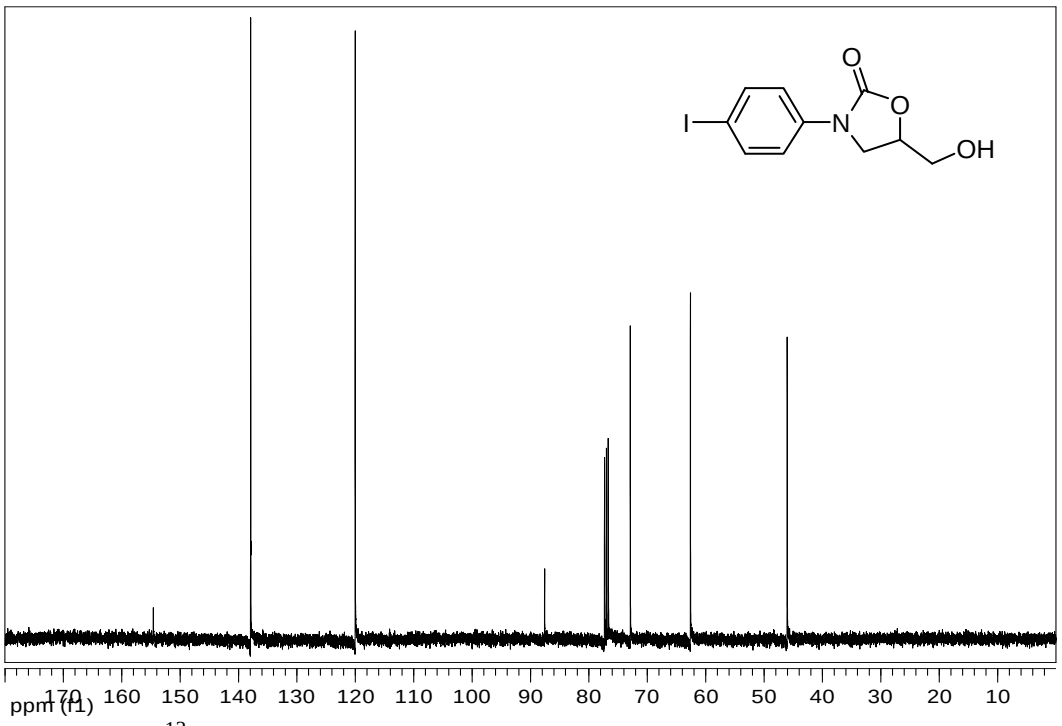


Figure A44 ^{13}C NMR spectrum of 5-(hydroxymethyl)-3-(4-iodophenyl)oxazolidin-2-

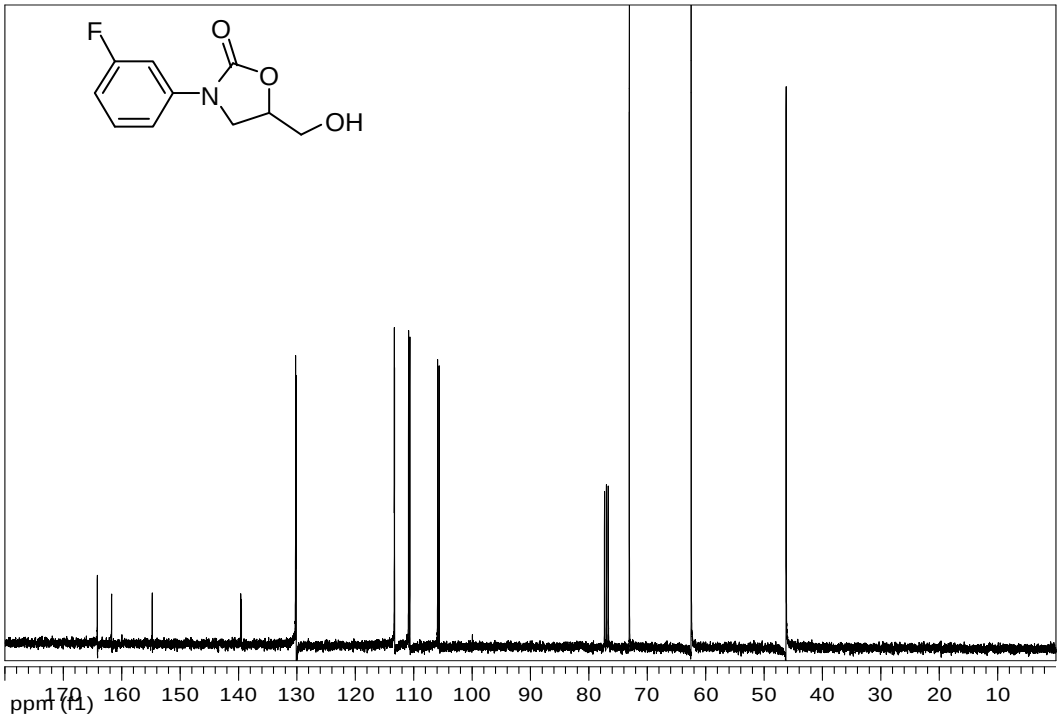


Figure A45 ^{13}C NMR spectrum of 3-(3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one

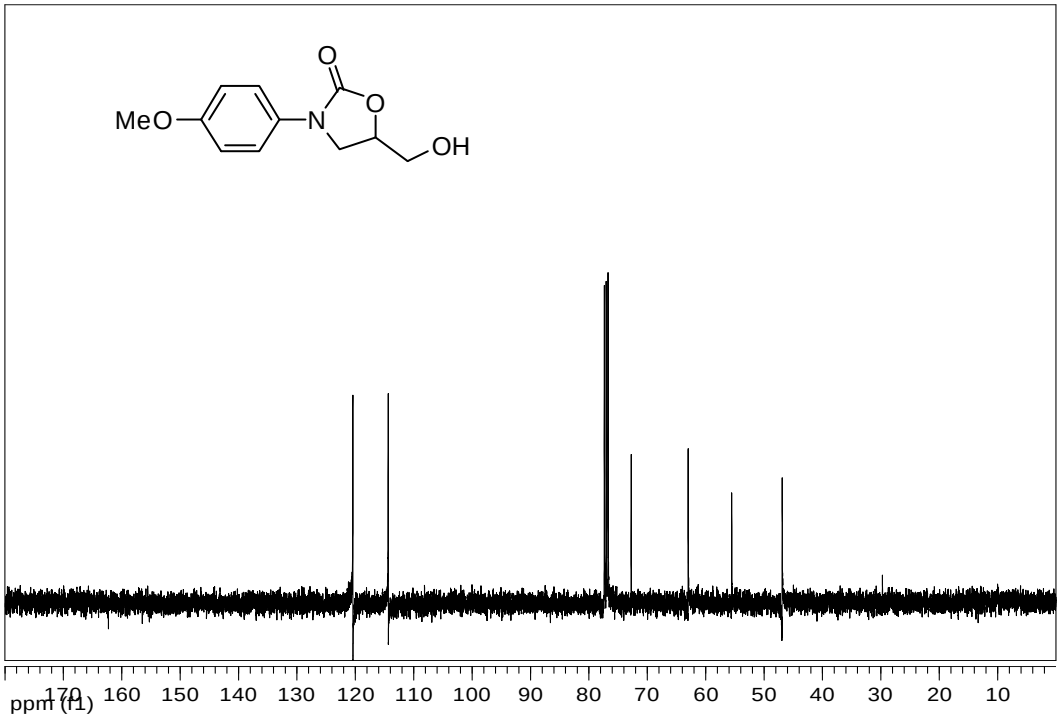


Figure A46 ^{13}C NMR spectrum of 5-(hydroxymethyl)-3-(4-methoxyphenyl)oxazolidin-2-one

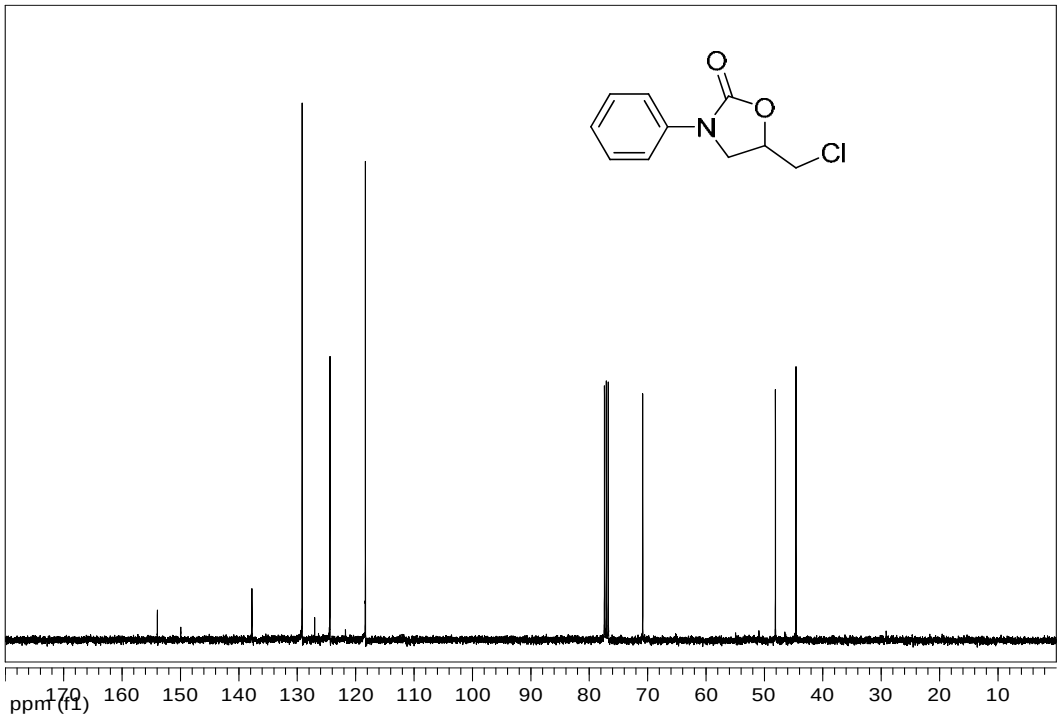


Figure A47 ^{13}C NMR spectrum of 5-(chloromethyl)-3-phenyloxazolidin-2-one

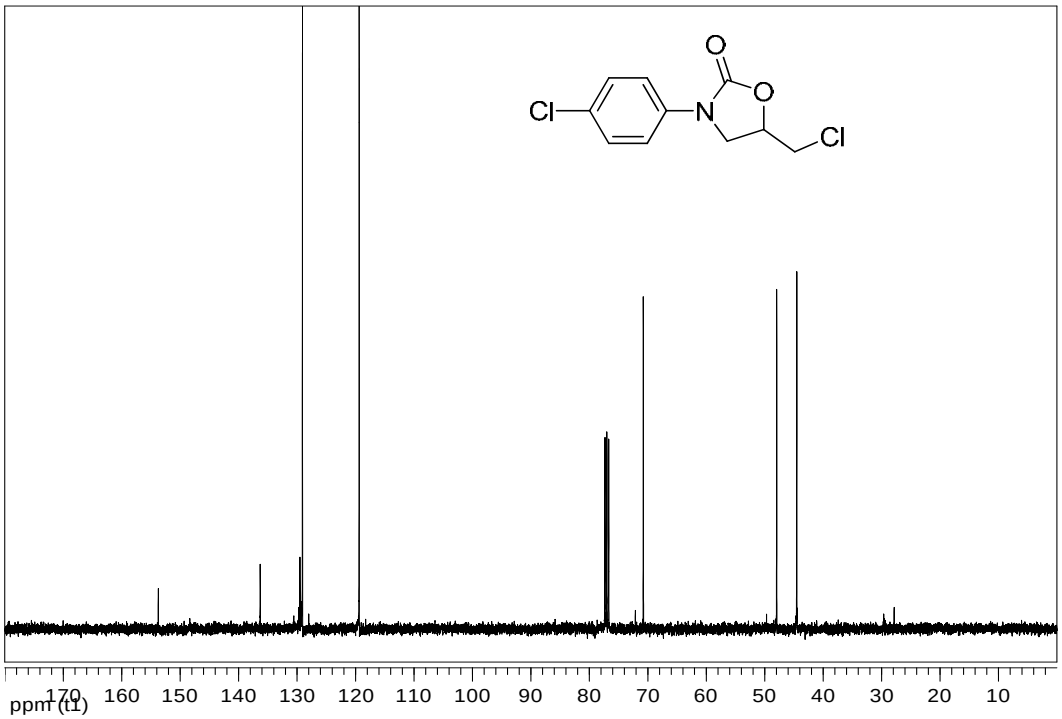


Figure A48 ^{13}C NMR spectrum of 5-(chloromethyl)-3-(4-chlorophenyl)oxazolidin-2-one

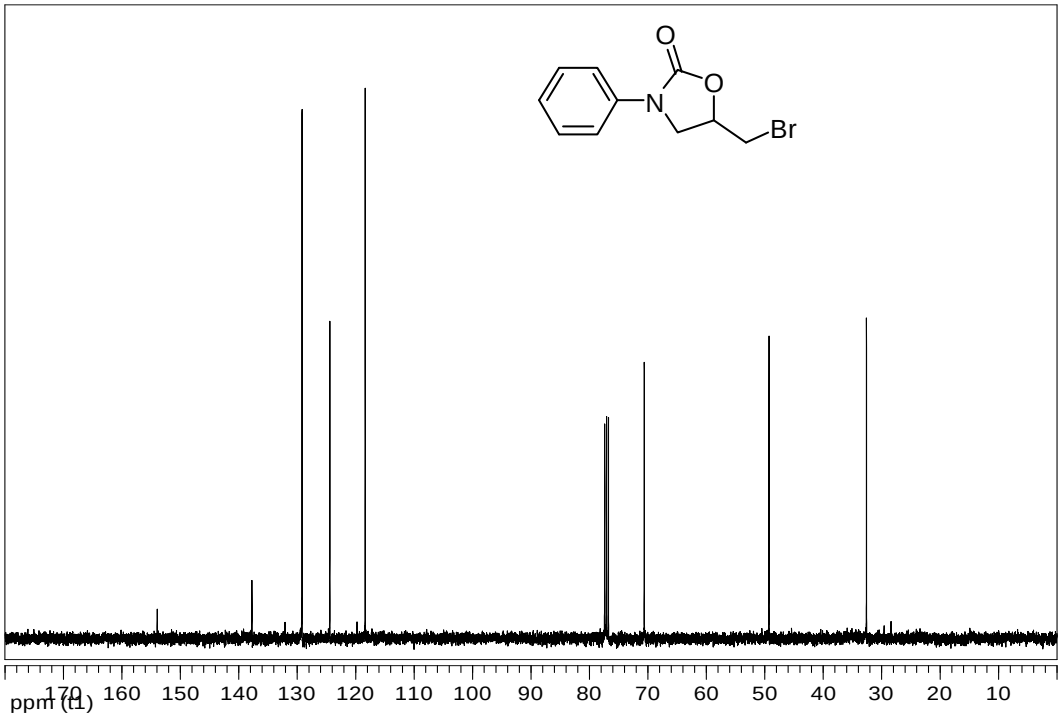


Figure A49 ^{13}C NMR spectrum of 5-(bromomethyl)-3-phenyloxazolidin-2-one

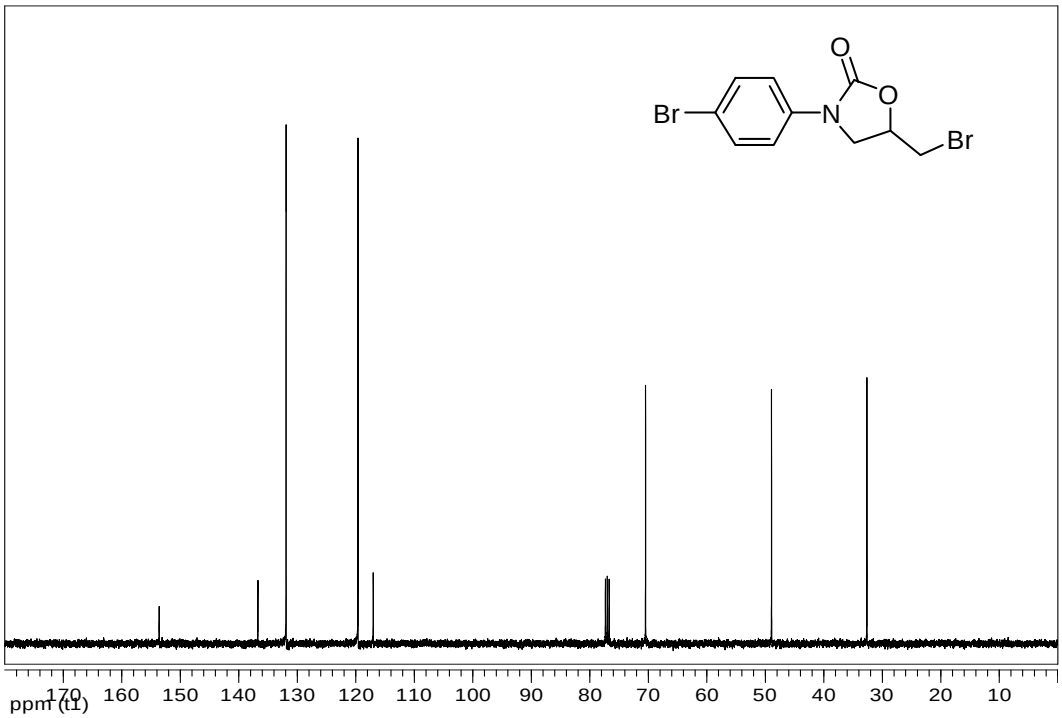


Figure A50 ^{13}C NMR spectrum of 5-(bromomethyl)-3-(4-bromophenyl)oxazolidin-2-one

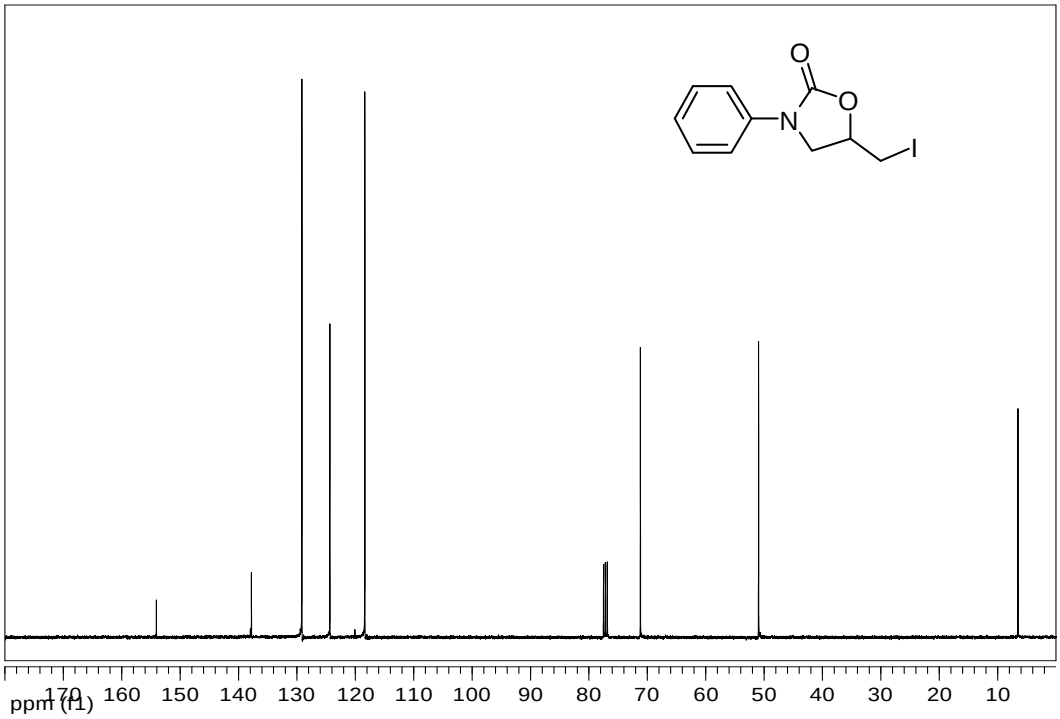


Figure A51 ^{13}C NMR spectrum of 5-(iodomethyl)-3-phenyloxazolidin-2-one

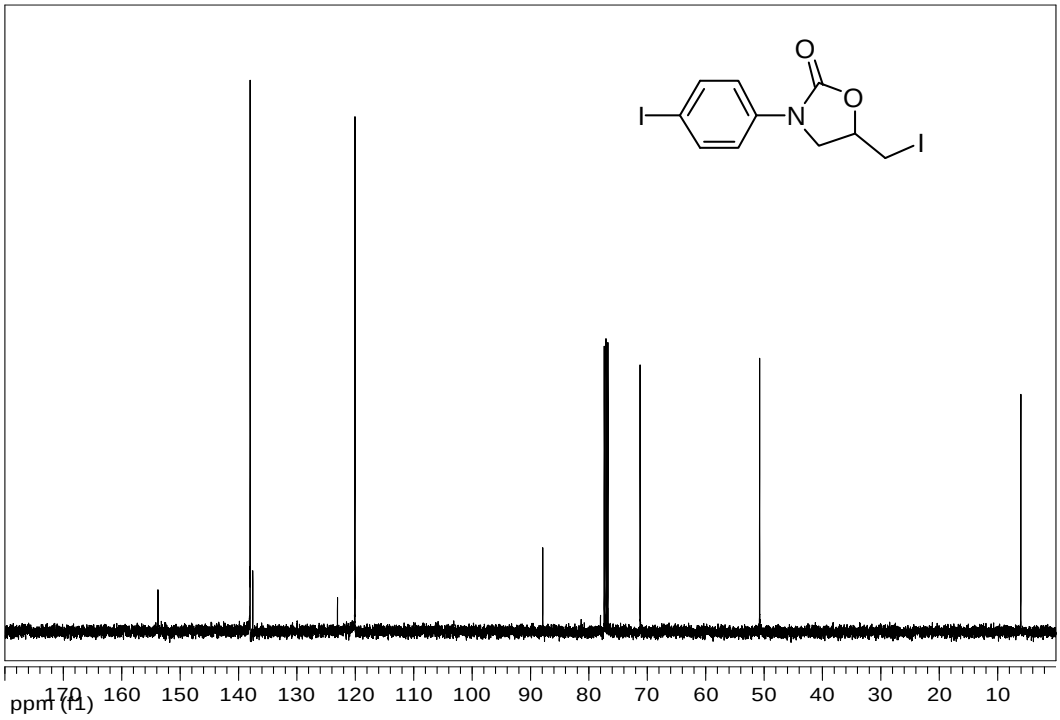


Figure A52 ^{13}C NMR spectrum of 5-(iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one

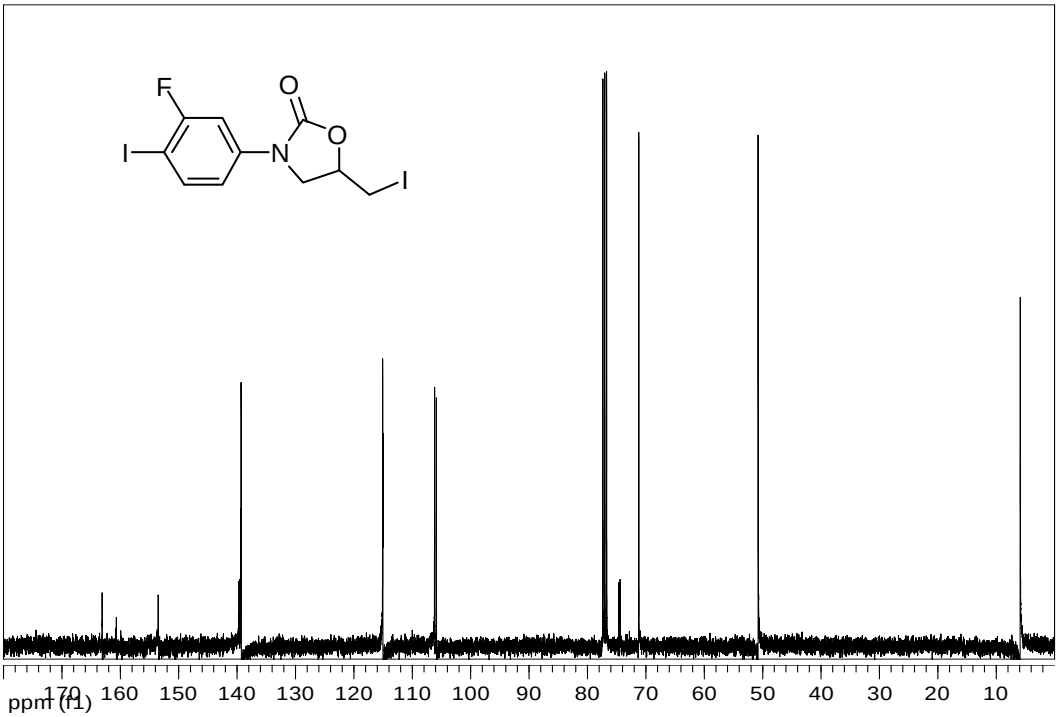


Figure A53 ^{13}C NMR spectrum of 3-(3-fluoro-4-iodophenyl)-5-(iodomethyl) oxazolidin-2-one

APPENDIX B

MASS SPECTRA

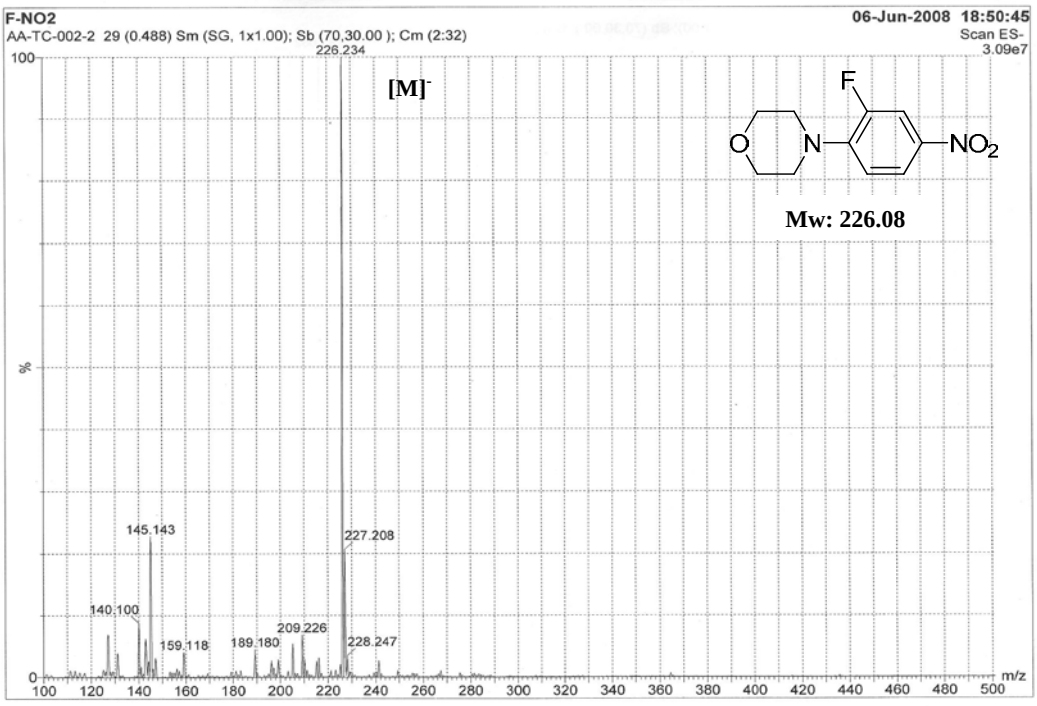


Figure B1 Mass spectrum (ESI-) of 4-(2-fluoro-4-nitrophenyl)morpholine

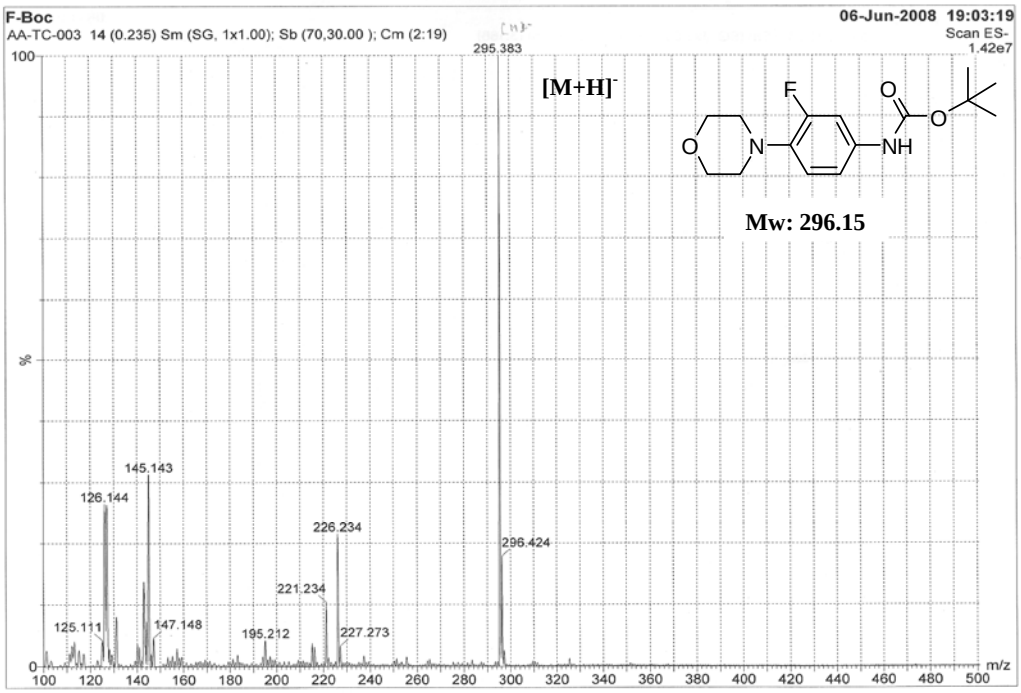


Figure B2 Mass spectrum (ESI-) of *tert*-butyl 3-fluoro-4-morpholinophenylcarbamate

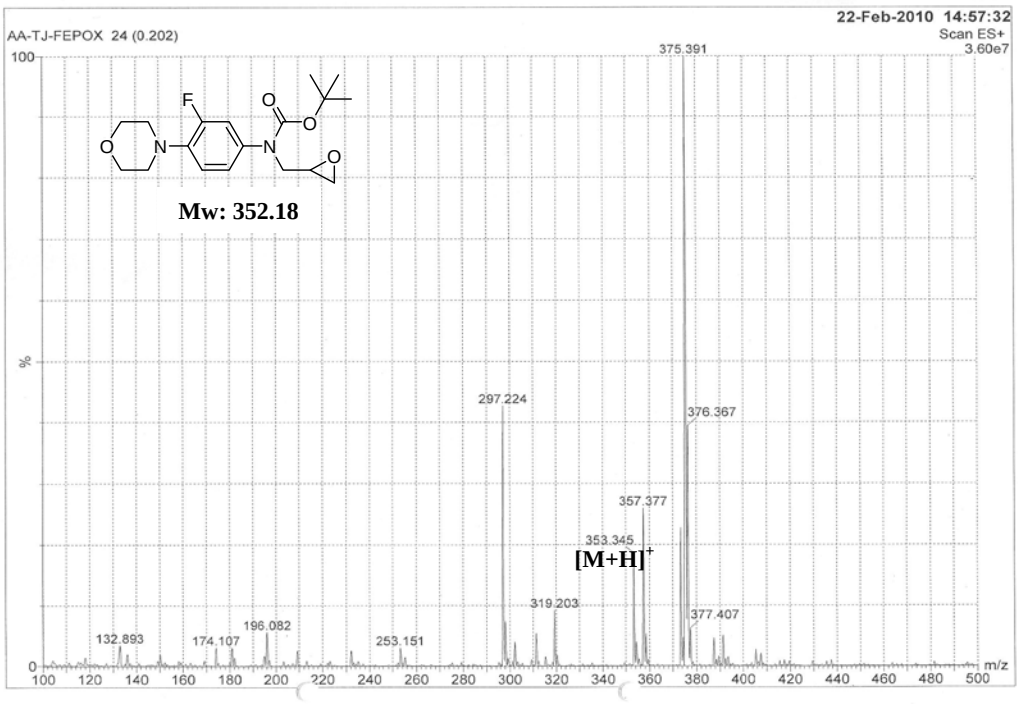


Figure B3 Mass spectrum (ESI+) of *tert*-butyl 3-fluoro-4-morpholinophenyl (oxiran-2-ylmethyl)carbamate

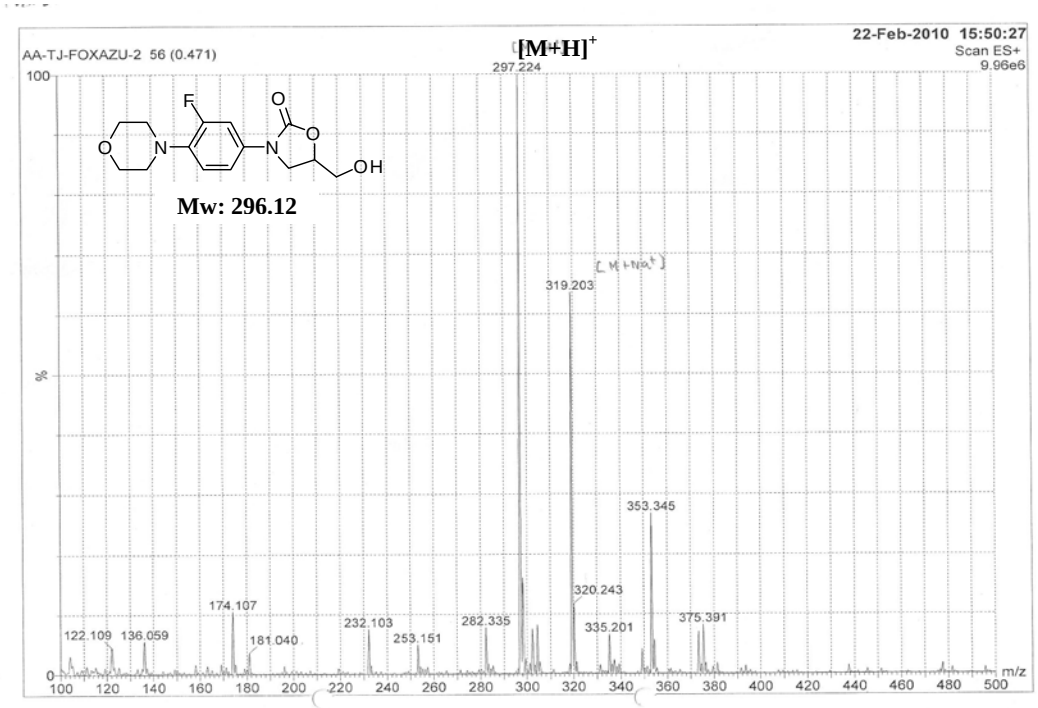


Figure B4 Mass spectrum (ESI+) of 3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one

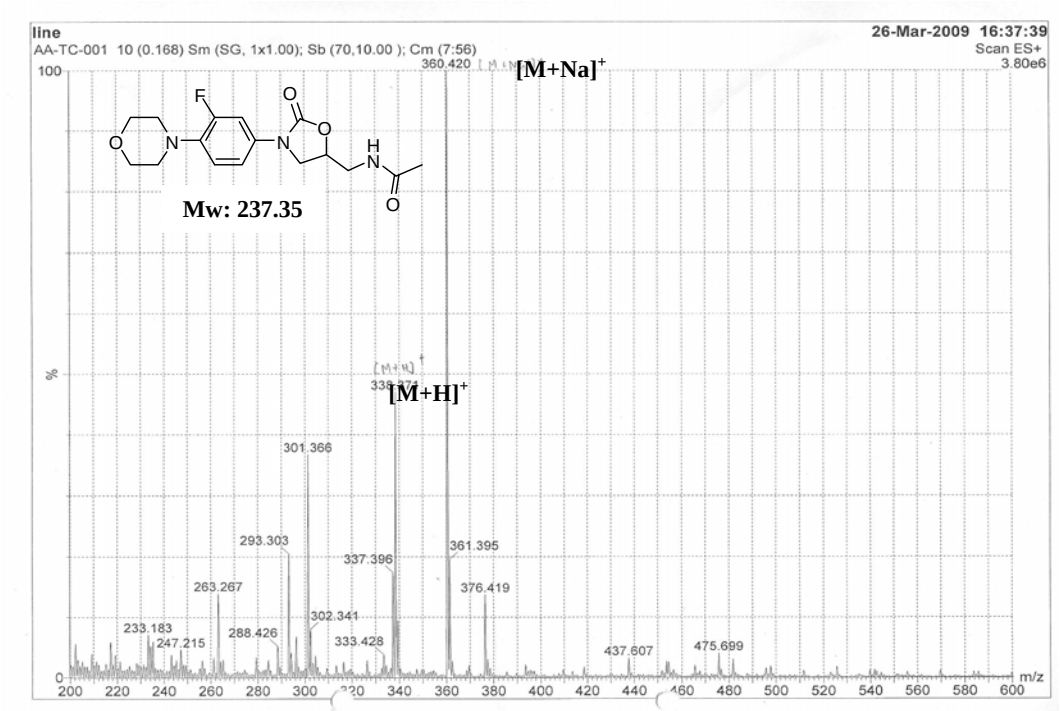


Figure B5 Mass spectrum (ESI+) of *N*-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide

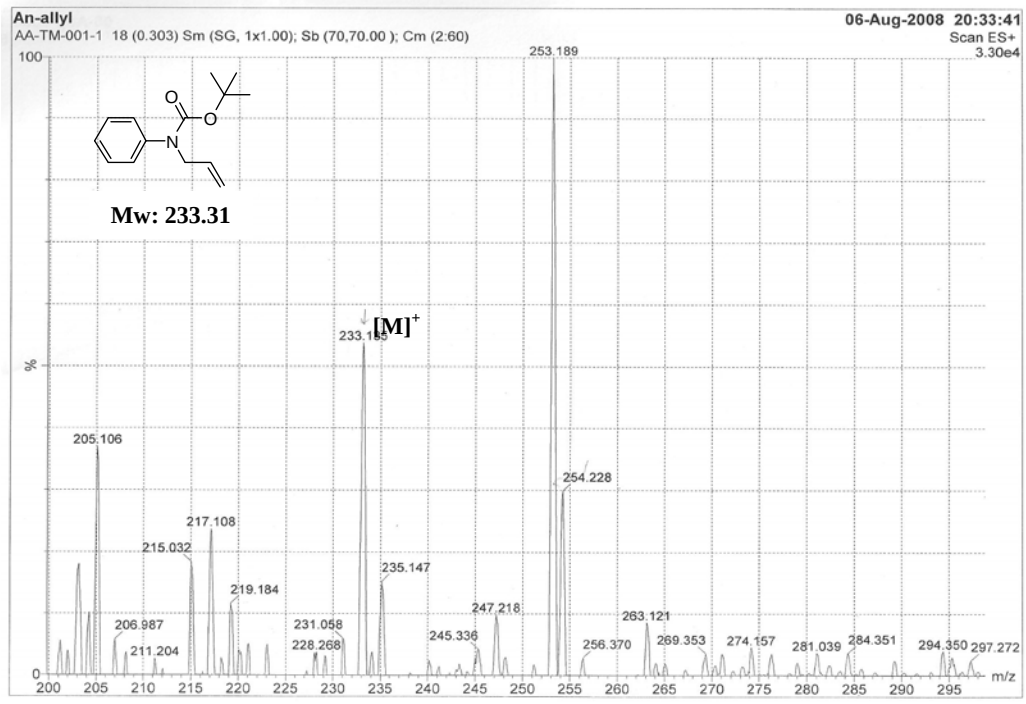


Figure B6 Mass spectrum (ESI+) of *tert*-butyl allyl(phenyl)carbamate

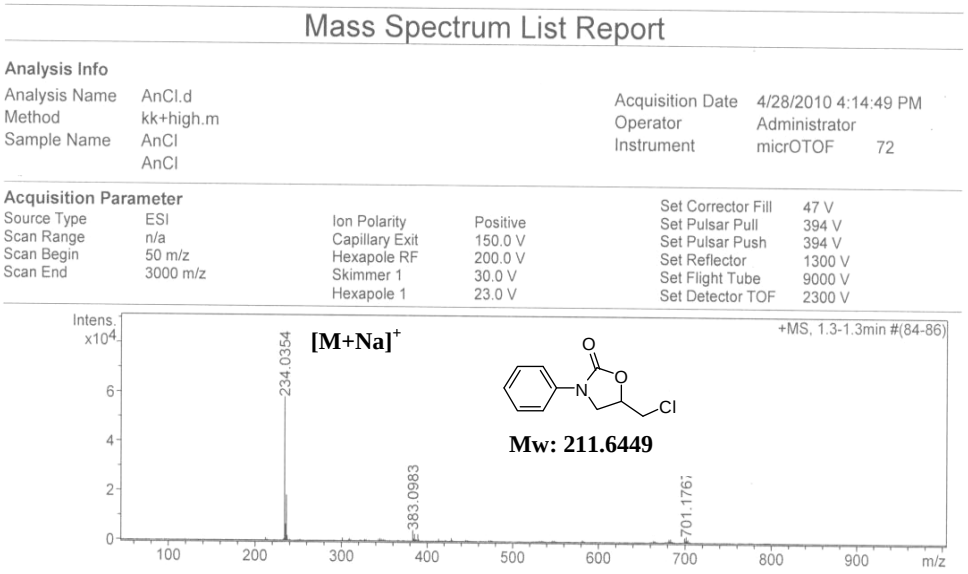


Figure B7 Mass spectrum (ESI+) of 5-(chloromethyl)-3-phenyloxazolidin-2-one

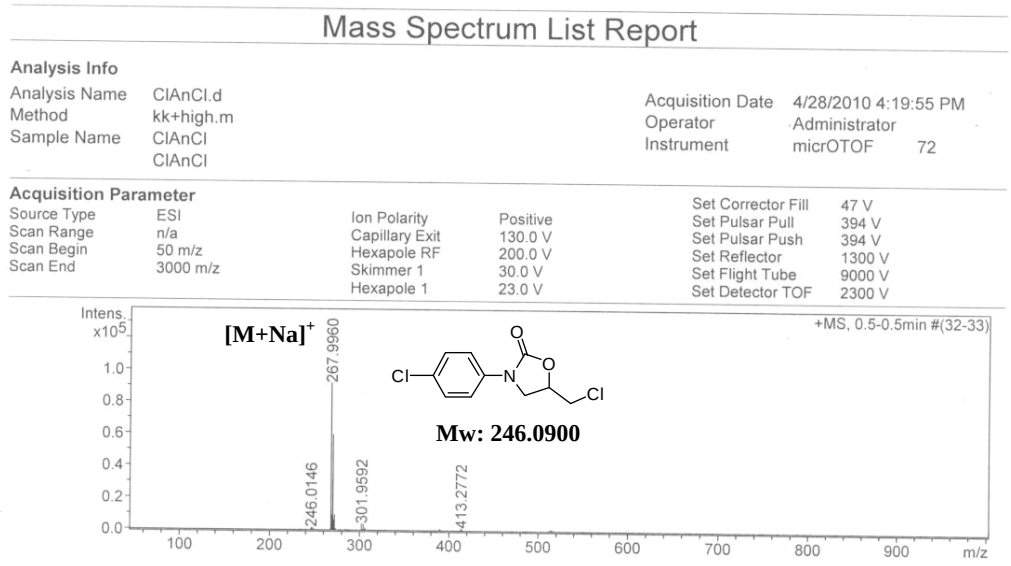


Figure B8 Mass spectrum (ESI+) of 5-(chloromethyl)-3-(4-chlorophenyl) oxazolidin-2-one

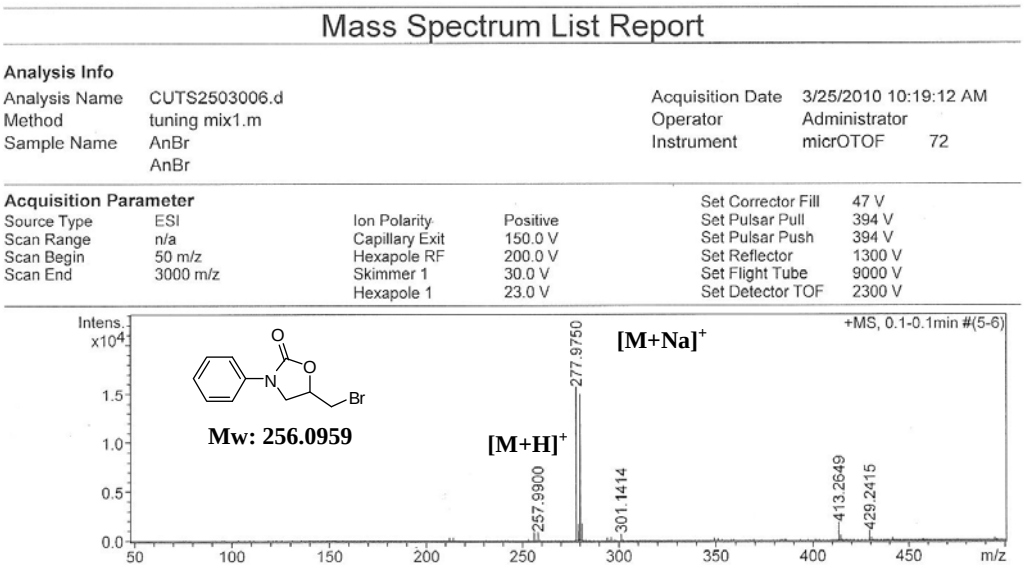


Figure B9 Mass spectrum (ESI+) of 5-(bromomethyl)-3-phenyloxazolidin-2-one

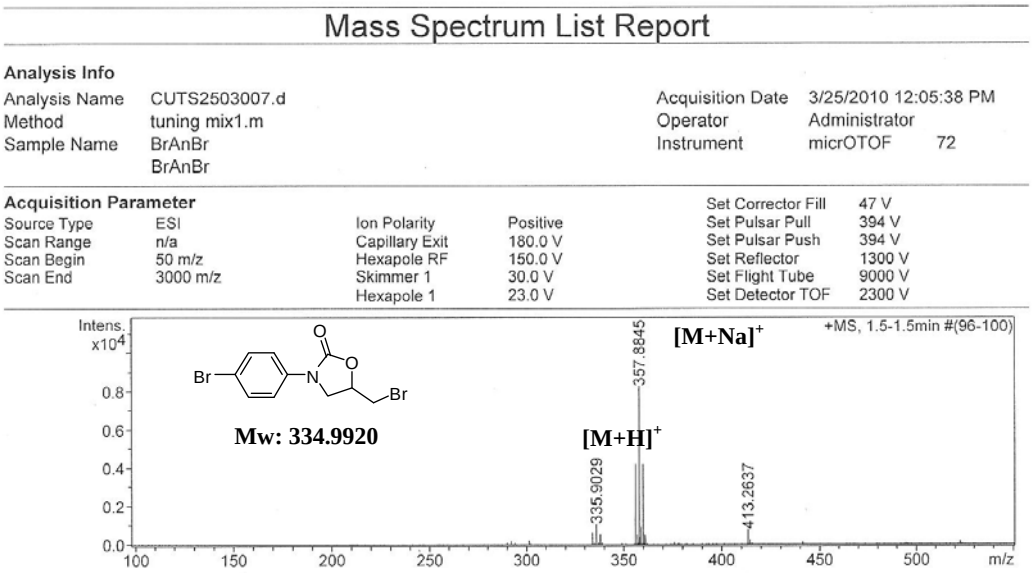


Figure B10 Mass spectrum (ESI+) of 5-(bromomethyl)-3-(4-bromophenyl) oxazolidin-2-one

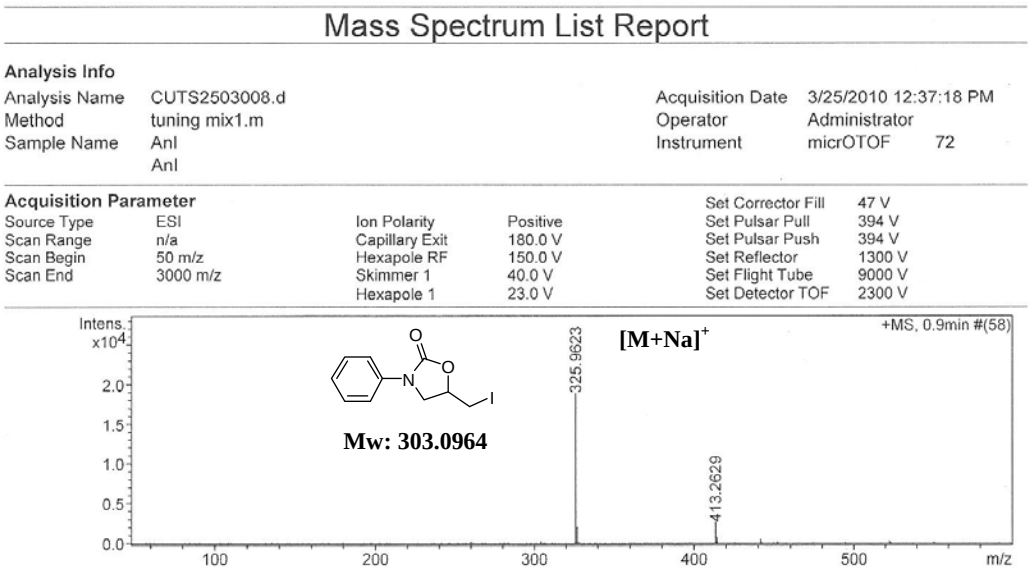


Figure B11 Mass spectrum (ESI+) of 5-(iodomethyl)-3-phenyloxazolidin-2-one

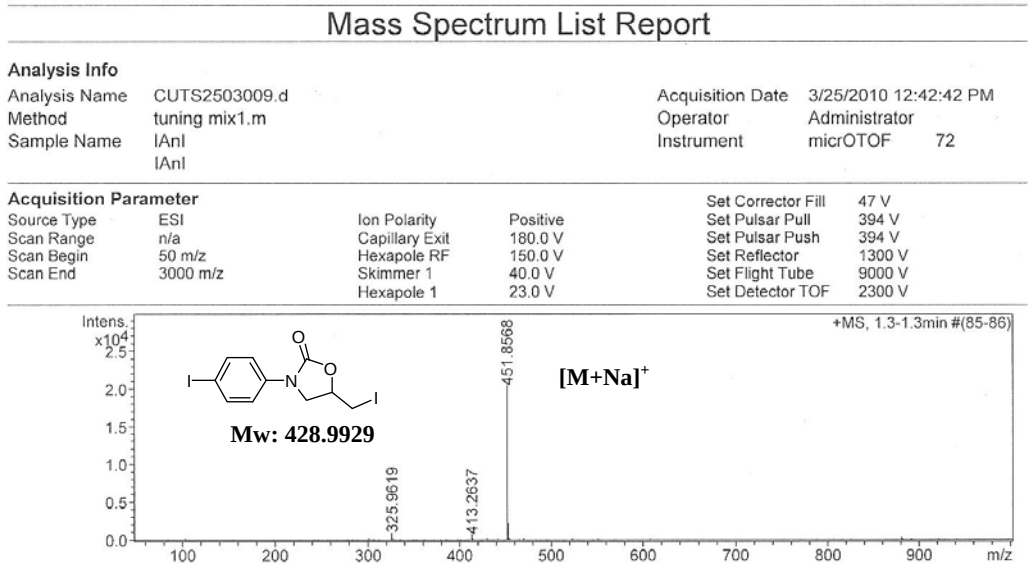


Figure B12 Mass spectrum (ESI+) of 5-(iodomethyl)-3-(4-iodophenyl)oxazolidin-2-one

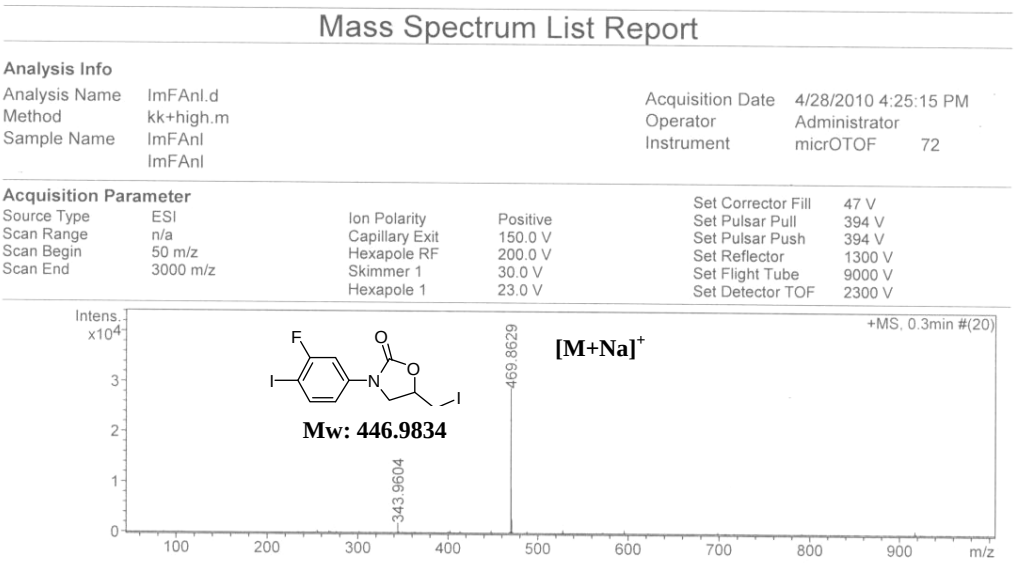


Figure B13 Mass spectrum (ESI+) of 3-(3-fluoro-4-iodophenyl)-5-(iodomethyl) oxazolidin-2-one

APPENDIX C

CHROMATROGRAMS

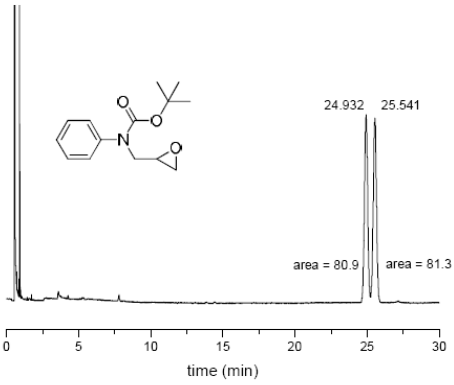


Figure C1 GC chromatogram of *tert*-butyl oxiran-2-ylmethyl(phenyl)carbamate

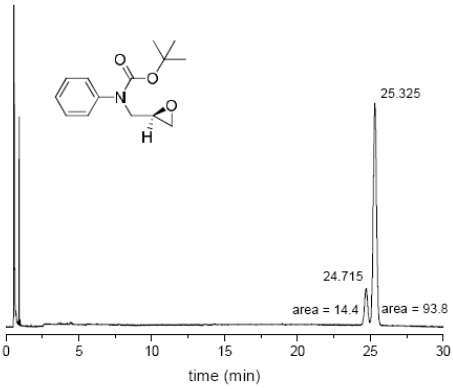


Figure C2 GC chromatogram of *(R)*-tert-butyl oxiran-2-ylmethyl(phenyl)carbamate

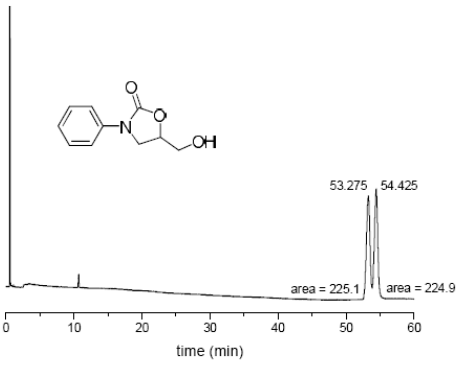


Figure C3 GC chromatogram of 5-(hydroxymethyl)-3-phenyloxazolidin-2-one

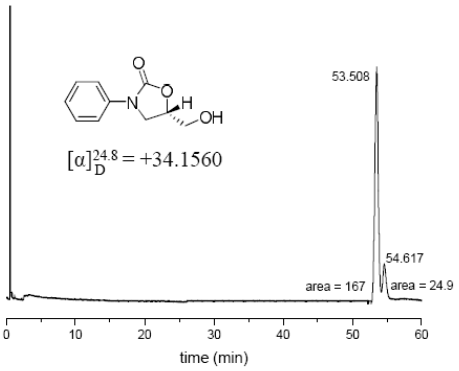


Figure C4 GC chromatogram of *(S)*-5-(hydroxymethyl)-3-phenyloxazolidin-2-one

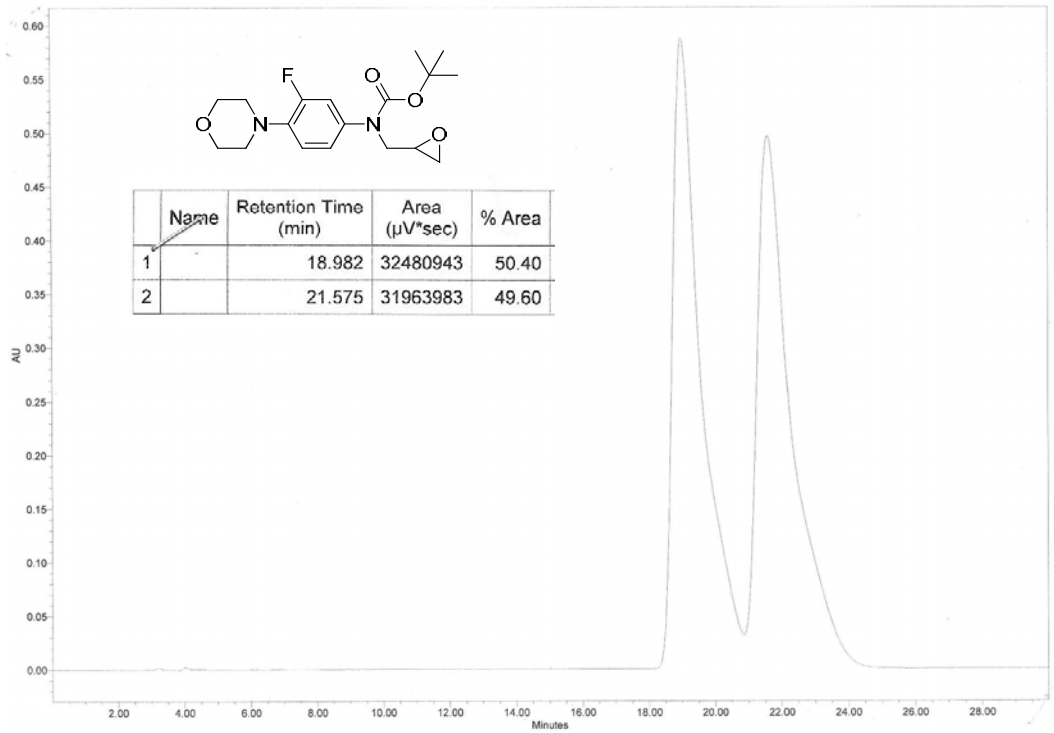


Figure C5 HPLC chromatogram of chromatogram of *tert*-butyl 3-fluoro-4-morpholinophenyl(oxiran-2-ylmethyl)carbamate

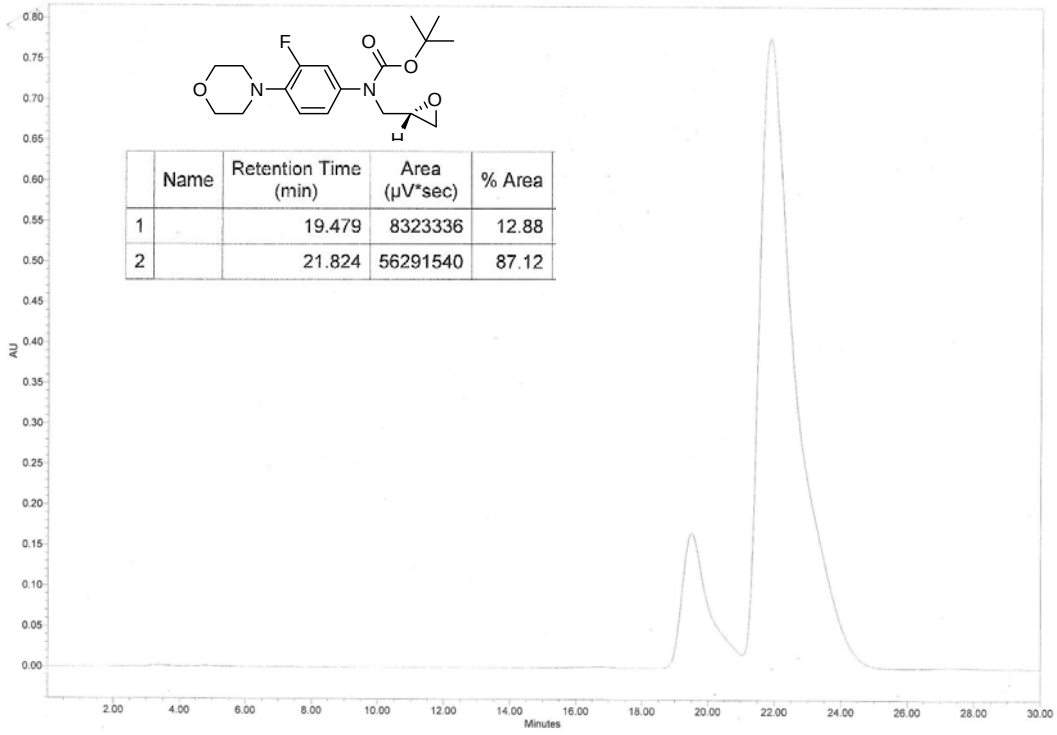
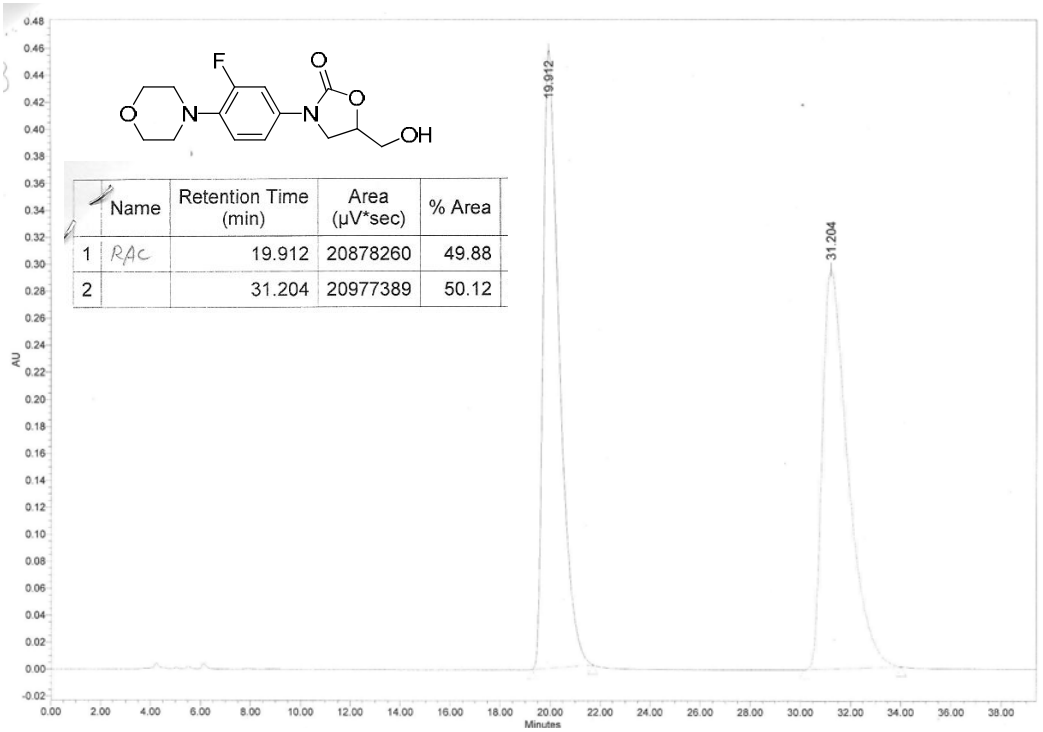
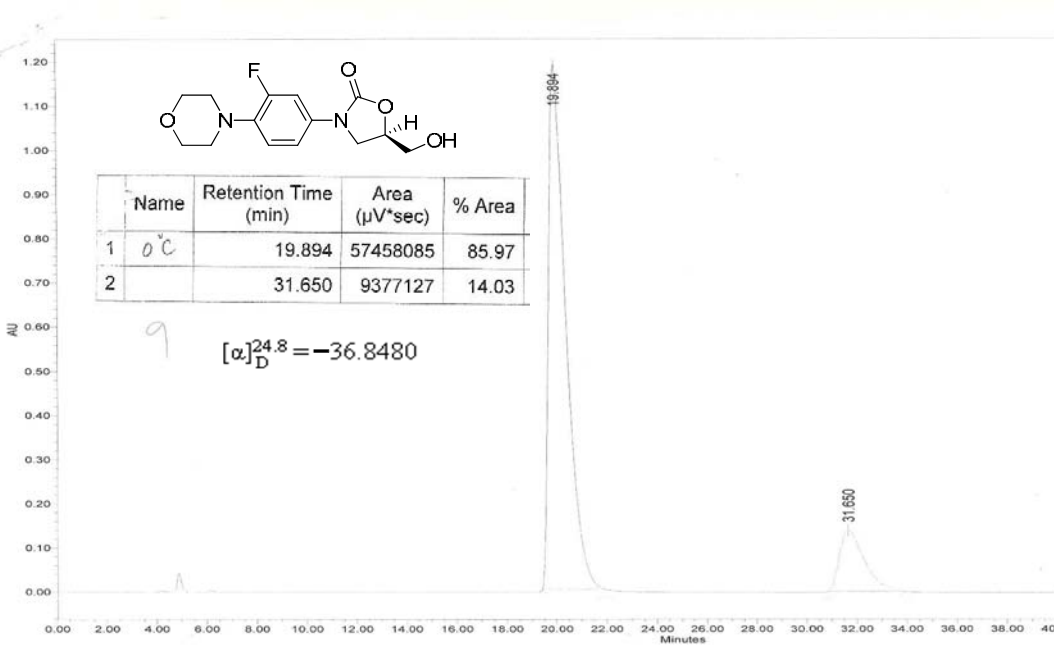


Figure C6 HPLC chromatogram of *(S)-tert*-butyl 3-fluoro-4-morpholinophenyl (oxiran-2-ylmethyl)carbamate



	Name	Retention Time (min)	Area (μV*sec)	% Area
1	RAC	19.912	20878260	49.88
2		31.204	20977389	50.12

Figure C7 HPLC chromatogram of 3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one



	Name	Retention Time (min)	Area (μV*sec)	% Area
1	0°C	19.894	57458085	85.97
2		31.650	9377127	14.03

$[\alpha]_D^{24.8} = -36.8480$

Figure C8 HPLC chromatogram of *(R)*-3-(3-fluoro-4-morpholinophenyl)-5-(hydroxymethyl)oxazolidin-2-one

VITAE

Mr. Thanakrit Chantra was born on September 10th, 1984 in Pichit, Thailand. He received a Bachelor's Degree of Science, majoring in Chemistry from Faculty of Science, Chulalongkorn University in 2007. He has been graduate student in organic chemistry under supervision of Dr. Anawat Ajavakom and Assoc. Prof. Dr. Mongkol Sukwattanasinitt. He graduated with a master degree in organic chemistry at Chulalongkorn University in 2010. His current address is 10/3, Klongkum, Bungkum, Bangkok, 10240.