เฮโลจิเนตเทตรีเอเจนต์และไทรเฟนิลฟอสฟีนสำหรับสังเคราะห์เอมีด เอสเทอร์และซัลโฟนามีด

นางสาว อรพิน จันทรศรีวงศ์

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HALOGENATED REAGENTS AND TRIPHENYLPHOSPHINE FOR THE SYNTHESES OF AMIDES, ESTERS AND SULFONAMIDES

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อรพิน จันทรศรีวงศ์: เฮโลจิเนตเทตรีเอเจนต์และไทรเฟนิลฟอสฟีนสำหรับสังเคราะห์เอมีด เอสเทอร์และซัลโฟนามีด (HALOGENATED REAGENTS AND TRIPHENYL-PHOSPHINE FOR THE SYNTHESES OF AMIDES, ESTERS AND SULFONAMIDES) อ. ที่ปรึกษา: ผศ. ดร. วรินทร ชวศิริ, 98 หน้า. ISBN 974-14-3381-6.

ได้ประยุกต์การใช้ประโยชน์ของไทรคลอโรแอเซทามีดและไทรเฟนิลฟอสฟีนเพื่อเตรียมเบนซามีด 9 ชนิด ที่มีโครงสร้างสัมพันธ์กับ DEET รีเอเจนต์นี้สามารถนำไปใช้ประโยชน์เพื่อสังเคราะห์เอสเทอร์ได้อย่างมีประสิทธิภาพ การศึกษาขอบเขตของปฏิกิริยาพบว่ารีเอเจนต์นี้เหมาะสมสำหรับไพรมารีและเซกันดารีแอลกอฮอล์ ในขณะที่เทอร์เชียรีแอลกอฮอล์ไม่สามารถเกิดปฏิกิริยาได้ อย่างไรก็ตามเทอร์เชียรีคาร์บอกซิลิกแอซิดสามารถเปลี่ยนเป็นเอสเทอร์ได้อย่างมีประสิทธิภาพ การศึกษากลไกการเกิดปฏิกิริยาสนับสนุนโดยข้อมูลอินฟราเรด โปรตอนและคาร์บอนสเปกโทรสโกปีอย่างชัดเจนว่าปฏิกิริยานี้เกิดผ่านแอซิดคลอไรด์ นอกจากนี้ได้ศึกษาวิธีใหม่สำหรับเตรียมซัลโฟนามีดโดยใช้เฮโลจิเนตเทตรีเอเจนต์และไทรเฟนิลฟอสฟีน ได้ศึกษาผลของชนิดและปริมาณของเฮโลจิเนตเทตรีเอเจนต์ ชนิดของเบส และระบบของตัวทำละลายเพื่อได้ภาวะที่เหมาะสม ไทรคลอโรแอซีโทไนไตร์ลร่วมกับไทรเฟนิลฟอสฟีนเป็นรีเอเจนต์ที่ว่องไวอย่างสูงสำหรับเปลี่ยนซัลโฟนิกแอซิดปืนซัลโฟนิลคลอไรด์ภายใต้อุณหภูมิรีฟลักซ์ไดคลอโรมีเทนเป็นเวลา 1 ชั่วโมง เมื่อทำปฏิกิริยากับเอมีน ให้เบนซีนซัลโฟนามีดที่สอดคล้องกันในปริมาณสูง วิธีนี้มีประสิทธิภาพกับเอมีนทุกประเภท เช่น ไพรมารีแอลิฟาติก เซกันดารีแอลิฟาติกและแอโรมาติกเอมีน

ภาควิชา.....เคมี..... ลายมือชื่อนิสิต.....อรพิน จันทรศรีวงศ์.....

สาขาวิชา.....เคมี..... ลายมือชื่ออาจารย์ที่ปรึกษา.....

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ORAPHIN CHANTARASRIWONG: HALOGENATED REAGENTS AND TRIPHENYLPHOSPHINE FOR THE SYNTHESES OF AMIDES, ESTERS AND SULFONAMIDES. THESIS ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., 98 pp. ISBN 974-14-3381-6.

The utilization of Cl_3CCONH_2 and PPh_3 could be applied to prepare nine benzamides whose structures are related to DEET. This reagent could also be successfully utilized to synthesize esters. Examining the scope of the reaction revealed that this reagent was suitable for primary and secondary alcohols while tertiary alcohol did not proceed well. However, tertiary carboxylic acid could transform efficiently to ester. The mechanistic studies supported by IR, ^{1}H- and ^{13}C-NMR spectral data clearly exhibited that these reactions occur *via* acid chlorides. The new methodology for the preparation of sulfonamides using halogenated reagents and PPh_3 was in addition disclosed. The effects of type of halogenated reagents, amount of reagents, type of bases and solvent system were investigated to optimize the reaction conditions. Cl_3CCN in combination with PPh_3 approved to be a highly reactive reagent for conversion of sulfonic acids to the corresponding sulfonyl chlorides in refluxing CH_2Cl_2 within 1 hour. Upon treating with amines, the corresponding benzenesulfonamides were achieved in good to excellent yields. This reaction worked well for all amines selected: primary aliphatic, secondary aliphatic and aromatic amines.

Department.....Chemistry..... Student's signature. Oraphin Chantarasriwong
Field of study.....Chemistry..... Advisor's signature. Warinthorn Chavasiri
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LIST OF ABBREVIATIONS

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

CHAPTER I

INTRODUCTION

The utilization of halogenated reagents and triphenylphosphine (PPh_3) has been continuously developed as a versatile reagent in organic synthesis. These reagents could be adopted to prepare organic halides such as alkyl or acyl halides. Acyl chlorides generated could be used as a reliable intermediate for the synthesis of other classes of organic compounds such as amides, esters and sulfonamides. At the first time, the combination of CCl_4 and PPh_3 [1] was examined with the aim to search for an alternative reagent to replace $SOCl_2$ [2], PCl_3 [3], or oxalyl chloride [4] in the preparation of acyl chlorides or alkyl chlorides due to their strong acidic conditions; provided those methods being not compatible for acid-sensitive molecules. Later, other reagents such as cyanuric chloride [5], tetramethyl-α-chloroenamine [6], or hexachloroacetone (CCl_3COCCl_3) [7] were also addressed. Nevertheless, these reagents have their disadvantages such as toxicity, long reaction time required or expensive. It was thus rationalized for the development of a new compatible, selective and viable reagent.

Certain amides and esters have been widely known to possess biological activities such as antioxidant [8] and antifungal activity [9]. Moreover, sulfonamides are also found in many therapeutic agents, including drug for the treatment of bacterial and viral infections [01].

During the last few years, Natural Products Research Unit, Department of Chemistry, Chulalongkorn University has developed a new methodology to synthesize amides and esters using Cl_3CCONH_2 and PPh_3[11]. This combined reagent was attractive since it could be utilized under mild and acid-free condition. In this research, the extention of the utilizations of this developed system for the synthesis of both amides and esters will be mainly focused. The mechanistic studies for the conversion of carboxylic acids to its corresponding acid chlorides using this reagent would carefully explore. In addition, there is no report concerning the preparation of sulfonamides using the combination of halogenated reagent and PPh_3 reacted with

sulfonic acids. Thus, the synthesis of this class of compound also needed the development of a generally useful, mild and novel methodology.

1.1 The Objective of This Research

This research was divided into two parts:

1. Application of Cl_3CCONH_2/PPh_3 for the synthesis of amides and esters
    - To utilize Cl_3CCONH_2 and PPh_3 for the synthesis of bioactive benzamides and to investigate the scope of this developed system for the synthesis of esters.
    - To explore the mechanism under these reaction conditions.
2. Application of Cl_3CCN/PPh_3 for the synthesis of sulfonamides
    - To search for the optimum conditions and a new halogenated reagent/PPh_3 system for the synthesis of sulfonamide under mild reaction condition as a novel methodology.

CHAPTER II

APPLICATIONS OF TRICHLOROACETAMIDE FOR THE SYNTHESES OF AMIDES AND ESTERS

2.1 Introduction

The amide and ester functional groups are important in organic and biological chemistry. The preparation of amides and esters from their corresponding carboxylic acids are an important and well-known transformation in organic synthesis [12]. In general, the activation of carboxylic acids and their subsequent conversion to esters or amides is a key transformation. Carboxylic acid activation can be achieved either by conversion into more reactive functional groups such as acyl halide, anhydride, acyl azide, active esters or by *in situ* activation by coupling reagents such as carbodiimides [13]. In this case the poor reactivity of the deactivated aromatic amine in concomitance with the conjugated nature of the activated carboxylic acid derivative may explain the failure of the coupling reaction.

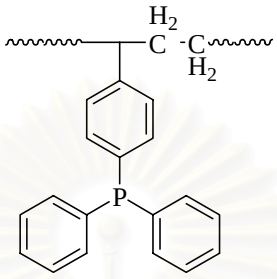
Acid chlorides are valuable intermediates in organic synthesis and are generally prepared by the reaction of carboxylic acids with reagents such as thionyl chloride, PCl_3, PCl_5, and oxalyl chloride, among others [14]. However, such protocols cannot be applied to acid-sensitive compounds due to the vigorous conditions required and the formation of strong acid (HCl) during the process [15]. Moreover, the application of triphenylphosphine (PPh_3) and halogenated reagent has been explored extensively within the last decade [1]. These reagents could also be used to convert carboxylic acids into a more reactive functional group efficiently.

2.1.1 Literature Review on Halogenated Reagents

The methodologies for the preparation of amides and esters utilizing halogenated reagents have been extensively studied in many research groups. For instance, Lee and co-workers [1] was the first group who reported the treatment of carboxylic acids with carbon tetrachloride (CCl_4) and PPh_3 leading to the formation of the corresponding acyl chlorides in good yield. This method required however temperatures above room temperature in order to proceed the reaction. Later, Barstow

and Hruby in 1970 [16] displayed the synthesis of amides using a mixture of PPh_3 and CCl_4 or $BrCCl_3$ in THF at reflux temperature.

Harrison and co-workers [17] in 1983 described that carboxylic acids and amines could react to form amides by the reaction with CCl_4 and 1% cross-linked polystyrenes containing phosphine residues (I). The reactions proceeded in high yield.



I

Sucheta [18] in 1994 addressed that carboxylic acids were conveniently esterified with alcohols and thiols by the use of PPh_3 and *N*-bromo/iodo succinimide to afford the corresponding esters and thiol esters. Later, Froyen [19] in 1995 reported that amides can be generated in very high yields under mild conditions from the corresponding carboxylic acid and amine in the presence of equivalent amounts of PPh_3 and *N*-halosuccinimides, *e.g.*, NCS or NBS.

Villeneuve and Chan [7] in 1997 demonstrated the use of hexachloroacetone (HCA) and PPh_3 for the conversion of carboxylic acids at -78 °C in CH_2Cl_2 to the corresponding acyl chlorides. Formic acid can be used to generate formyl chloride at -78 °C in order to perform formylation under very mild conditions.

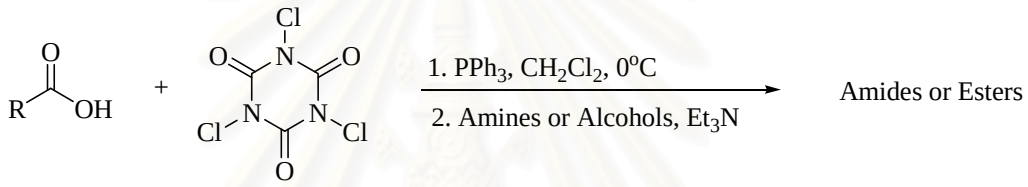
Jang and co-workers [20] in 1999 developed an alternative method for obtention of the respective acid chlorides from carboxylic acids by the combination use of PPh_3 and CCl_3CN. Subsequent addition of primary amines resulted in the acquirement of secondary amides in high yield. Later, in 2003 Jang and co-workers [21] applied that developed system to prepare various esters from carboxylic acids. Racemic α-tocopherol, clofibrate and flavoxate could be prepared in high yields using this method.

Plubchang in 2000 [22] addressed the preparation of amides using Cl_3CCN and PPh_3 at room temperature. This reaction proceeded efficiently with aromatic carboxylic acid. Certain bioactive amides could be synthesized according to this methodology.

Vago and Greiner [23] in 2002 reported a novel acylation procedure using polymer supported synthesis, with *in situ* generated acyl chlorides using Cl_3CCN and PPh_3.

Azumaya and colleagues [24] in 2003 reported the conversion of carboxylic acids to the corresponding acid halides by using dichlorotriphenylphosphorane in $CHCl_3$.

Hiegel and co-workers [25] in 2005 showed that PPh_3 treated with trichloroisocyanuric acid (TCICA) in CH_2Cl_2 at 0 °C could convert carboxylic acids to the respective acid chlorides under very mild conditions. Subsequent addition of amines or alcohols, in the presence of a tertiary amine, afforded the corresponding amides or esters in a one-pot procedure.



2.1.2 Literature Review on Trichloroacetamides as Halogenated Reagents for Synthesis of Amides and Esters

Chaysripongkul [11] addressed for the first time the methodology for the synthesis of amides and esters using CCl_3CONH_2 and PPh_3 at reflux temperature of CH_2Cl_2. This method provided a viable procedure as a mild reaction using short reaction time. In addition, this reagent could be also applied to prepare bioactive ester compounds efficiently such as benzyl benzoate [26].

Despite the fact that there are many coupling reagents and the methods for coupling carboxylic acids and amines or alcohols, certain methods still have their own disadvantages such as long reaction time or using toxic substrate.

From the literature review, there has been only one report on the direct synthesis of amides and esters from carboxylic acid acids by this means. Nevertheless, the thoroughly investigation on the scope of this method for the preparation of esters did not mention. Thus a mild, cost effective alternative of CCl_3CONH_2 was prompted to apply this reagent to synthesize certain bioactive amides and esters. Furthermore, the study on the effect of various carboxylic acids and alcohols were also challenged to fulfil the fundamental knowledge of this developed system.

2.2 Experimental

The synthesis of the amides and esters was carried out using the reaction conditions described in the general procedure of Chaysripongkul [11].

2.2.1 Instruments and Equipment

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel (Merck's, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's silica gel 60 G Art 7734 (70-230 mesh))

The IR spectra were recorded on Nicolet model Impact 410 FT/IR spectrophotometer. Solid samples were incorporated into a pellet of KBr. Liquid samples were dropped on sodium chloride plates. The ^{1}H- and ^{13}C-NMR spectra were performed in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference on Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

2.2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology. The reagents used for synthesis were purchased from Fluka chemical company or otherwise stated and were used without further purification.

2.2.3 Synthesis of Target Molecules

2.2.3.1 Synthesis of Benzamide Derivatives

***N*,*N*-Diethylbenzamide:** [27, 28] yellow liquid (95%), R_f 0.50 (50% EtOAc/hexane). IR (neat): 3049, 2970, 1629, 1524, 1427, 1372, 1273 and 1088 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.10 (3H, br s, CH_2CH_3), 1.25 (3H, br s, CH_2CH_3), 3.26 (2H, br s, CH_2CH_3), 3.55 (2H, br s, CH_2CH_3) and 7.38 (5H, br s, Ar*H*).

***N*,*N*-Diethyl-3-methylbenzamide or *N*,*N*-diethyl-*m*-toluamide or DEET**: [29,30] yellow liquid (99%), R_f 0.75 (50% EtOAc/hexane). IR (neat): 2970, 1619, 1564, 1460, 1372, 1219 and 1091 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.10 (3H, br s,

CH_2CH_3), 1.25 (3H, br s, CH_2CH_3), 2.36 (3H, s, ArCH_3), 3.25 (2H, br s, CH_2CH_3), 3.54 (2H, br s, CH_2CH_3) and 7.17-7.26 (4H, m, Ar*H*).

***N,N*-Diethyl-3-methoxybenzamide:** [31] yellow liquid (quant), R_f 0.56 (50% EtOAc/hexane). IR (neat): 2970, 1622, 1463, 1421, 1293 and 1031 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.21 (3H, br s, CH_2CH_3), 1.22(3H, br s, CH_2CH_3), 3.26 (2H, br s, CH_2CH_3), 3.53 (2H, br s, CH_2CH_3), 3.80 (3H, s, ArOCH_3) and 7.15-7.28 (4H, m, Ar*H*).

***N,N*-Diethyl-3-nitrobenzamide:** yellow liquid (quant), R_f 0.40 (50% EtOAc/hexane). IR (neat): 2981, 1628, 1531, 1346, 1293 and 1114 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.15 (3H, br s, CH_2CH_3), 1.27 (3H, br s, CH_2CH_3), 3.25 (2H, br s, CH_2CH_3), 3.58 (2H, br s, CH_2CH_3) and 7.60-8.28 (4H, m, Ar*H*).

***N,N*-Diethyl-4-methylbenzamide:** [29] yellow liquid (90%), R_f 0.49 (50% EtOAc/hexane). IR (neat): 2967, 1719, 1607, 1427, 1273 and 1114 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.17 (6H, br s, CH_2CH_3), 2.35 (3H, s, ArCH_3), 3.29 (2H, br s, CH_2CH_3), 3.50 (2H, br s, CH_2CH_3) and 7.17-7.27 (4H, m, Ar*H*).

***N,N*-Diethyl-4-*tert*-butylbenzamide:** [32] yellow liquid (79%), R_f 0.51 (50% EtOAc/hexane). IR (neat): 2963, 1704, 1607, 1422, 1294 and 1109 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.22 (3H, br s, CH_2CH_3), 1.15 (3H, br s, CH_2CH_3), 1.25 (9H, s, $(CH_3)_3$), 3.29 (2H, br s, CH_2CH_3), 3.54 (2H, br s, CH_2CH_3) and 7.26-7.40 (4H, m, Ar*H*).

***N,N*-Diethyl-2-chlorobenzamide:** [33] yellow liquid (6%), R_f 0.53 (50% EtOAc/hexane). IR (neat): 3183, 2977, 1620, 1435, 1381, 1293 and 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.06 (3H, t, *J*= 7.20 Hz, CH_2CH_3), 1.27 (3H, t, *J*= 7.20 Hz, CH_2CH_3), 3.15 (2H, quin, *J*= 7.20 Hz, CH_2CH_3), 3.38 (1H, t, *J*= 6.80 Hz, CH_2CH_3), 3.78 (1H, t, *J*= 6.80 Hz, CH_2CH_3),and 7.20-7.80 (4H, m, Ar*H*).

***N,N*-Diethyl-2-bromobenzamide:** [33] yellow liquid (39%), R_f 0.62 (50% EtOAc/hexane). IR (neat): 2976, 1715, 1628, 1439, 1375, 1293 and 1108 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.06 (3H, t, *J*= 7.20 Hz, CH_2CH_3), 1.27 (3H, t, *J*= 7.20 Hz, CH_2CH_3), 3.14 (2H, sep, *J*= 6.80 Hz, CH_2CH_3), 3.38 (1H, sex, *J*= 6.80 Hz, CH_2CH_3), 3.83 (1H, sex, *J*= 6.80 Hz, CH_2CH_3) and 7.20-7.80 (4H, m, Ar*H*).

***N,N*-Diethyl-2-chloro-4-nitrobenzamide:** yellow liquid (14%), R_f 0.49(50% EtOAc/hexane). IR (neat): 2977, 1629, 1445, 1371 and 1293 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.28 (3H, t, *J*= 7.20 Hz, CH_2CH_3), 1.84 (3H, t, *J*= 7.20 Hz, CH_2CH_3), 3.14

(2H, m, C*H*$_2$CH$_3$), 3.38 (1H, sex, *J*= 6.80 Hz, C*H*$_2$CH$_3$), 3.80 (1H, sex, *J*= 6.80 Hz, C*H*$_2$CH$_3$) and 7.20-7.80 (3H, m, Ar*H*).

2.2.3.2 Synthesis of Ester Compounds

1-Octyl benzoate: colorless liquid (98%), R_f 0.77 (50% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87-1.80 (15H, m, alkyl group), 4.31 (2H, t, *J*= 6.80 Hz, OC*H*$_2$), 7.41 (2H, t, *J*= 7.20 Hz, *m*-Ar*H*), 7.57 (1H, t, *J*= 7.20 Hz, *p*-Ar*H*) and 8.02 (2H, d, *J*= 7.20 Hz, *o*-Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.6, 26.0, 28.7, 29.2, 29.3, 31.8, 65.1, 128.3, 129.5, 130.5, 132.8 and 166.7.

2-Octyl benzoate: colorless liquid (77%), R_f 0.71 (50% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.85-1.78 (15H, m, alkyl group), 5.16 (1H, sex, *J*= 6.40 Hz, OC*H*), 7.42 (2H, t, *J*= 7.20 Hz, *m*-Ar*H*), 7.57 (1H, t, *J*= 7.20 Hz, *p*-Ar*H*) and 8.04 (2H, d, *J*= 7.20 Hz, *o*-Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 20.1, 22.6, 25.4, 29.2, 31.7, 36.1, 71.7, 128.3, 129.5, 130.9, 132.7 and 166.2.

Cyclooctyl benzoate: colorless liquid (66%), R_f 0.71 (50% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.45-2.00 (14H, m, alkyl group), 5.20 (1H, quin, *J*= 4.40 Hz, OC*H*), 7.40 (2H, t, *J*= 7.20 Hz, *m*-Ar*H*), 7.60 (1H, t, *J*= 7.20 Hz, *p*-Ar*H*) and 8.00 (2H, d, *J*= 7.20 Hz, *o*-Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 22.1, 24.5, 26.3, 31.5, 75.8, 128.0, 129.5, 130.8, 132.8 and 166.2.

Cinnamoyl benzoate: colorless liquid (90%), R_f 0.70 (50% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.00 (2H, dd, *J*= 6.40 Hz, OC*H*$_2$), 6.42 (1H, m, C*H*=CHAr), 6.75 (1H, d, *J*= 16.00 Hz, CH=C*H*Ar), 7.20-7.60 (8H, m, Ar*H*) and 8.05 (2H, d, *J*= 7.20 Hz, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 65.6, 123.2, 126.6, 128.6, 128.4, 128.6, 129.7, 130.2, 133.0, 134.3, 136.2 and 166.4.

4-Chlorophenyl benzoate: white solid (78%), R_f 0.60 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.20-8.20 (9H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 123.1, 128.6, 129.1, 129.5, 130.2, 131.3, 133.8, 149.4 and 164.9.

4-*iso*-Propyl-2-methylphenyl benzoate: white solid (75%), R_f 0.43 (15% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.27 (3H, d, *J*= 7.20 Hz, CH(C*H*$_3$)$_2$), 2.21 (3H, s, C*H*$_3$), 2.90 (1H, m, C*H*(CH$_3$)$_2$ and 7.21-7.29 (8H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 15.9, 23.9, 33.6, 119.9, 124.2, 127.4, 128.6, 129.6, 130.1, 130.9, 133.5, 148.1, 149.4 and 164.9.

(-)-2-(6,6-Dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-ethyl benzoate: [35] colorless liquid (77%), R_f 0.71 (50% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.84 (3H, s, CC*H*$_3$), 1.27 (3H, s, CC*H*$_3$), 2.08-2.44 (8H, m, alkyl group), 4.33 (2H, m, OC*H*$_2$), 5.36 (1H, t, *J*= 1.60 Hz, C*H*=C), 7.43 (2H, t, *J*= 7.20 Hz, *m*-Ar*H*), 7.55 (1H, t, *J*= 7.20 Hz, *p*-Ar*H*) and 8.02 (2H, d, *J*= 7.20 Hz, *o*-Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.1, 26.2, 31.4, 31.7, 36.0, 38.0, 40.7, 45.7, 63.3, 118.3, 129.5, 130.4, 132.8, 144.2 and 166.6.

Cholesteryl benzoate: white solid (81%), R_f 0.81 (50% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.69 (3H, s, C*H*$_3$), 0.87 (6H ,d, *J*= 6.80 Hz, (C*H*$_3$)$_2$CH), 0.92-2.04 (30H, m, alkyl group), 2.46 (2H, d, *J*= 7.60 Hz, CC*H*$_2$), 4.86 (1H, m, C*H*O), 5.41 (1H, d, *J*= 4.40 Hz, *H*C=C), 7.43 (2H, t, *J*= 7.20 Hz, *m*-Ar*H*), 7.54 (1H, t, *J*= 7.20 Hz, *p*-Ar*H*) and 8.03 (2H, d, *J*= 7.20 Hz, *o*-Ar*H*). (^{13}C-NMR ($CDCl_3$) δ (ppm): 11.9, 18.7, 19.4, 21.0, 22.6, 22.8, 23.8, 24.3, 27.9, 28.0, 28.2, 31.8, 31.9, 35.8, 36.2, 36.6, 37.0, 38.2, 39.5, 39.7, 42.3, 50.0, 56.1, 56.7, 74.6, 122.8, 128.2, 129.5, 130.8, 132.7, 139.6 and 165.9.

(*E*)-3,7-Dimethylocta-2,6-dienyl benzoate: [36] colorless liquid (70%), R_f 0.67 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60-1.77 (9H, s, CH=CC*H*$_3$), 2.09 (4H, m, CC*H*$_2$), 4.84 (2H, d, *J*= 7.20 Hz, OC*H*$_2$), 5.09 (1H, t, *J*= 4.80 Hz, (CH$_3$)$_3$C=C*H*), 5.47 (1H, t, *J*= 7.20 Hz, C=C*H*CH$_2$O), 7.43 (2H, t, *J*= 7.20 Hz, *m*-Ar*H*), 7.55 (1H, t, *J*= 7.20 Hz, *p*-Ar*H*) and 8.05 (2H, d, *J*= 7.20 Hz, *o*-Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 16.6, 17.7, 25.7, 26.3, 39.5, 61.9, 118.3, 123.7, 128.3, 129.6, 130.5, 131.8, 132.8, 142.3, 166.6.

(-)-1,7,7-Trimethyl-bicyclo[2.2.1]hept-2-yl benzoate: [37] colorless liquid (81%), R_f 0.67 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.92 (6H, s, C(C*H*$_3$)$_2$), 0.97 (3H, s, CC*H*$_3$), 1.11-2.48 (7H, m, alkyl group), 5.11 (1H, dd, *J*= 10.0 Hz, OC*H*, 7.43 (2H, t, *J*= 7.20 Hz, *m*-Ar*H*), 7.55 (1H, t, *J*= 7.20 Hz, *p*-Ar*H*) and 8.05 (2H, d, *J*= 7.20 Hz, *o*-Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.6, 18.9, 19.7, 27.4, 28.1, 36.9, 44.9, 47.9, 49.1, 80.5, 128.3, 129.5, 130.9, 132.7 and 166.8.

Phenethyl acetate: colorless liquid (59%), R_f 0.53(23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.04 (3H, s, C*H*$_3$), 2.94 (2H, t, *J*= 6.80 Hz, C*H*$_2$Ph), 4.28 (2H, t, *J*= 6.80 Hz, C*H*$_2$O) and 7.21-7.33 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.9, 35.1, 64.9, 126.5, 128.5, 128.9, 137.8 and 171.0.

(+)-1,7,7-Trimethyl-bicyclo[2.2.1]hept-2-yl acetate: colorless liquid (67%), R_f 0.67 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.82 (3H, s, C*H*$_3$), 0.87 (3H, s, C*H*$_3$), 0.90 (3H, s, C*H*$_3$), 1.25-2.35 (7H, m, alkyl group), 2.06 (3H, s, OOCC*H*$_3$) and 4.88 (1H, dd, *J*= 9.60 Hz, OC*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.5, 18.8, 19.7, 21.3, 27.0, 28.0, 36.7, 44.8, 47.7, 48.7, 79.9 and 171.5.

Phenethyl palmitate: white solid (74%), R_f 0.82 (50% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, *J*= 6.40 Hz, C*H*$_3$), 1.25 (24H, s, alkyl group), 1.57 (2H, m, C*H*$_2$CH$_2$C=O), 2.28 (2H, t, *J*= 7.60 Hz, CH$_2$C*H*$_2$C=O), 2.93 (2H, t, *J*= 6.80 Hz, C*H*$_2$Ph), 4.29 (2H, t, *J*= 6.80 Hz, C*H*$_2$O) and 7.21-7.30 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.7, 24.9, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 34.3, 35.1, 64.7, 126.5, 128.4, 128.9, 137.9 and 173.8.

Phenethyl penta-2,4-dienoate: colorless liquid (51%), R_f 0.60 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.85 (2H, d, *J*= 5.60 Hz, C*H*$_3$), 2.98 (2H, t, *J*= 6.80 Hz, C*H*$_2$Ph), 4.35 (2H, t, *J*= 6.80 Hz, C*H*$_2$O), 5.75 (1H, d, *J*= 15.60 Hz, C=C*H*CO$_2$), 6.20 (2H, t, *J*= 9.20 Hz, C*H*=CHCO$_2$), 7.23-7.27 (5H, m, Ar*H*) and 7.31 (2H, m, CH$_3$C*H*=C*H*) .

Phenethyl pivalate: colorless liquid (87%), R_f 0.65 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.16 (9H, s, C(C*H*$_3$)$_3$), 2.94 (2H, t, *J*= 6.80 Hz, C*H*$_2$Ph), 4.27 (2H, t, *J*= 6.80 Hz, C*H*$_2$O) and 7.21-7.29 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.2, 35.1, 64.8, 126.4, 128.4, 128.9, 137.9 and 178.5.

Phenethyl abietate: yellow oil (34%), R_f 0.65 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.80-2.00 (27H, m, abietic group), 2.91 (2H, t, *J*= 6.80 Hz, C*H*$_2$Ph), 4.25 (2H, t, *J*= 6.80 Hz, C*H*$_2$O), 5.40 (1H, d, *J*= 4.00 Hz, C=C*H*), 5.77 (1H, s, C=C*H*), and 7.20-7.28 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 17.0, 18.1, 20.9, 21.5, 22.5, 25.6, 27.5, 34.5, 34.9, 35.2, 37.1, 38.3, 45.0, 46.5, 50.9, 65.1,120.7, 122.5, 126.4, 128.4, 128.9, 135.4, 138.0, 145.1 and 178.4.

Phenethyl 1-naphthoate: colorless liquid (75%), R_f 0.63 (23% EtOAc/hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.15 (2H, t, *J*= 6.80 Hz, C*H*$_2$Ph), 4.65 (2H, t, *J*= 6.80 Hz, C*H*$_2$O), 7.26-8.78 (12H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 35.3, 65.7, 124.5, 125.9, 126.2, 126.7, 127.7, 128.5, 128.6, 129.1, 130.2, 133.3, 133.8, 138.0 and 167.6.

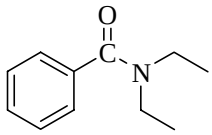
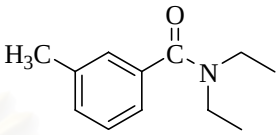
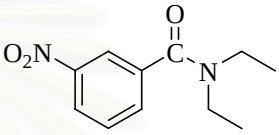
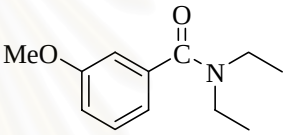
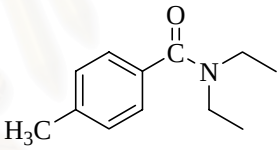
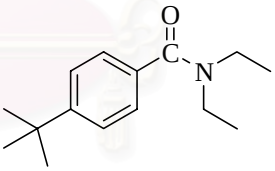
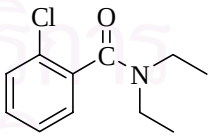
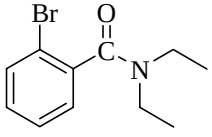
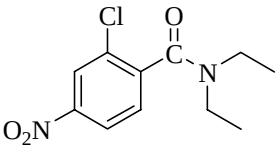
2.3 Results and Discussion

2.3.1 Further Study on the Use of CCl_3CONH_2/PPh_3 for the Synthesis of Bioactive Benzamides

Benzamides are reported to possess a wide range of biological activity including anticonvusant [38], antiemetic [39] and insect repellent [29]. *N*,*N*-Diethyl-*m*-toluamide or DEET was one of the benzamide derivatives presented an effective repellent for many insects with the *meta* isomer being the most effective [40]. Since DEET was first marketed in 1956, it has remained the best repellent in the 40 years of comparative testing on tens of thousands of the other compounds. An estimated 200 million people worldwide use DEET repellents each year [41]. These facts provided benzamide derivatives as fascinated molecules to prepare, particularly those compounds whose structures closely related to DEET. Therefore, the utilization of CCl_3CONH_2 and PPh_3 was attempted to apply for preparing these bioactive benzamides.

Upon the collaboration with Department of Agriculture, Faculty of Agriculture, Khon Kaen University, related compounds based on DEET were planned to synthesize and test for insect repellant activity. The synthesis part was the responsibility of natural products research unit, while the activity testing was assigned to be done at Khon Kaen University. Nine benzamides including DEET were synthesized by the use of CCl_3CONH_2/PPh_3 protocol and the results are demonstrated in Table 2.1.

Table 2.1 The synthesis of benzamide derivatives

Entry	Starting carboxylic acid	Amide	% Isolated yield
1	benzoic acid		95
2	3-methylbenzoic acid		99
3	3-nitrobenzoic acid		quant
4	3-methoxybenzoic acid		quant
5	4-methylbenzoic acid		90
6	4-*tert*-butylbenzoic acid		79
7	2-chlorobenzoic acid		6
8	2-bromobenzoic acid		39
9	2-chloro-4-nitrobenzoic acid		14

Treating with CCl_3CONH_2/PPh_3, benzoic acid reacted smoothly with diethylamine provided *N*,*N*-diethylbenzamide in excellent yield (95%, entry 1). Gratefully, DEET could be prepared from the reaction of 3-methylbenzoic acid and diethylamine to give the desired product in excellent yield under the reaction conditions (99%, entry 2). This compound was characterized its identity by IR and ^{1}H NMR spectra. IR spectrum (Fig 2.1) clearly presented a strong absorption carbonyl band of amide at 1619 cm^{-1}. The characteristic peaks of an aromatic ring exhibited the medium intensity bands at 1566 and 1462 cm^{-1}. Finally, the C-H and C-N bands were observed from the presence of bands at 2971 and 1370 cm^{-1}. The ^{1}H NMR spectrum (Fig 2.2) displayed five aromatic protons at δ_H 7.15-7.28 and a methyl group substituted at *meta*- position on an aromatic ring at δ_H 2.40. Two ethyl groups were inferred from the presence of four broad singlet signals at δ_H 1.10, 1.28, 3.25 and 3.58.

In addition, the presence of electron-releasing and electron-withdrawing substituents on the aromatic ring at *meta*- position was intentionally designed to imitate the structure of DEET. *N*,*N*-Diethyl-3-nitrobenzamide and *N*,*N*-diethyl-3-methoxybenzamide could be afforded in quantitative yields (entries 3 and 4). Moreover, there were no report on *N*,*N*-diethyl-3-nitrobenzamide, thus this compound is the new compound synthesized in benzamide class. From these results, it was suggested that the substituents at *meta*- position of benzoic acid was unaffected with the yield of the desired product.

The IR spectrum of *N*,*N*-diethyl-3-nitrobenzamide (Fig 2.3) displayed a strong absorption band of the carbonyl at 1628 cm^{-1}. The medium intensity band at 1531 cm^{-1} was the characteristic peak of an aromatic ring. The absorption bands at 2981 and 1346 cm^{-1} indicated the presence of the C-H and C-N bonds. The ^{1}H-NMR spectrum (Fig 2.4) of this compound presented a multiplet signal of five aromatic protons at δ_H 7.60-8.28. Four broad singlet signals were presented at δ_H 1.15, 1.27, 3.25 and 3.58 belonging to the signals of two ethyl groups of diethylamine.

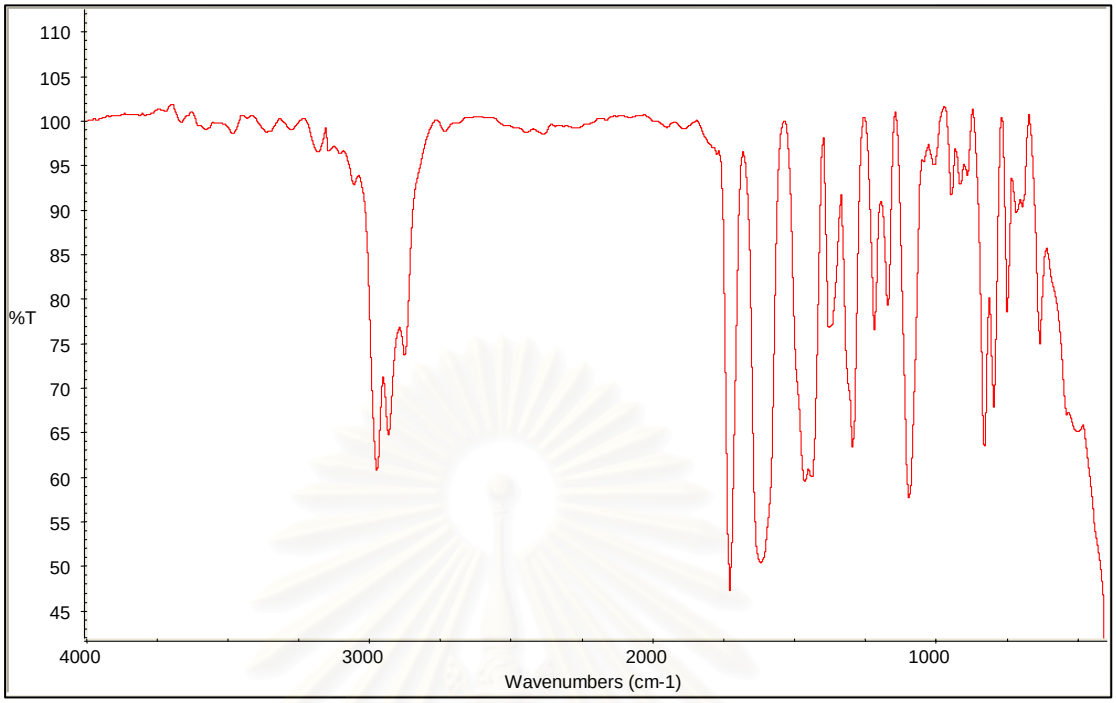


Figure 2.1 The IR spectrum of *N*,*N*-diethyl-*m*-toluamide

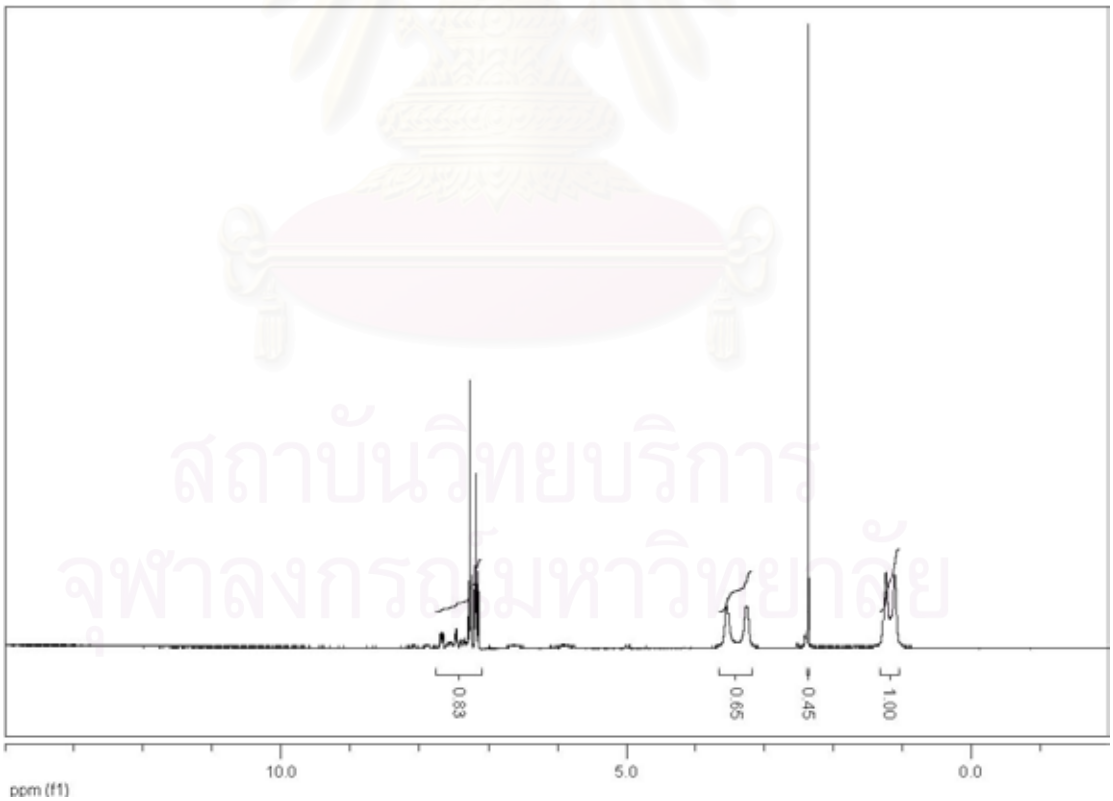


Figure 2.2 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-*m*-toluamide

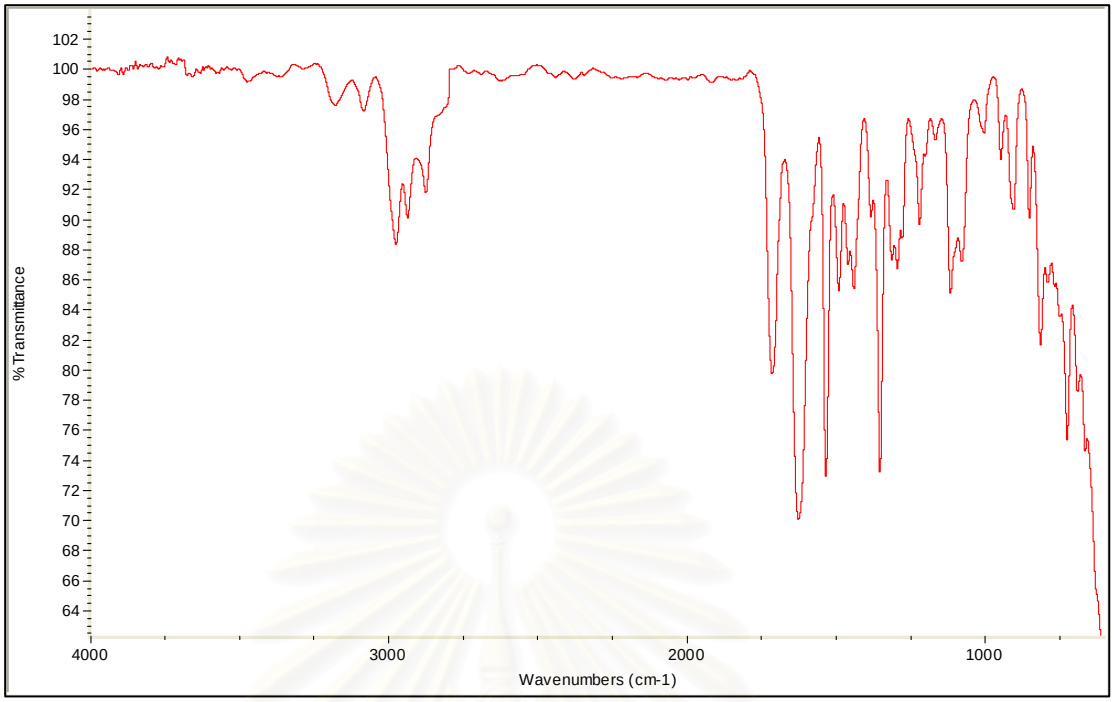


Figure 2.3 The IR spectrum of *N*,*N*-diethyl-3-nitrobenzamide

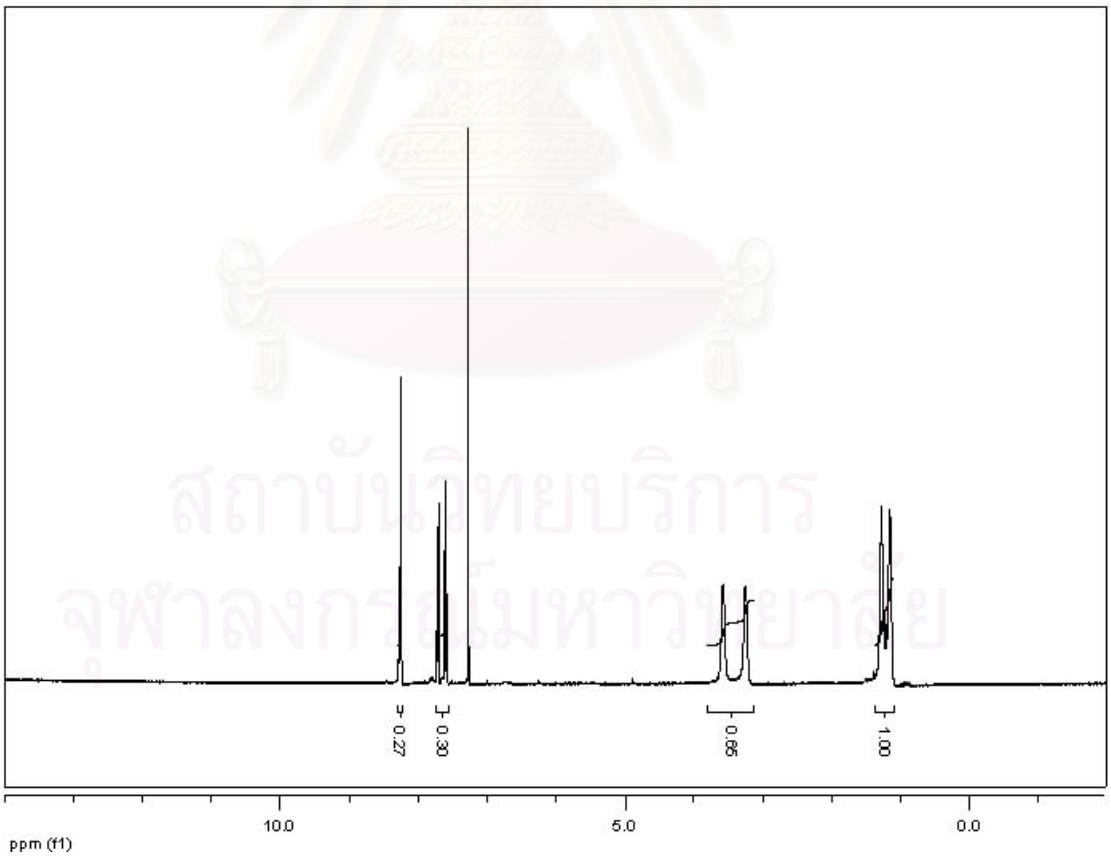


Figure 2.4 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-3-nitrobenzamide

The IR spectrum of *N*,*N*-diethyl-3-methoxybenzamide (Fig 2.5) exhibited a strong absorption band at 1622 cm^{-1}, pointing out the presence of amide carbonyl. Other absorption bands at 2970 and 1463 cm^{-1} indicated for the C-H and C-N bonds. The ^{1}H-NMR spectrum (Fig 2.6) of this compound displayed the signals around δ_H 7.15-7.28, indicating the presence of an aromatic ring. Four broad signals around δ_H 1.21, 1.22, 3.26 and 3.53 were ascribed for ten protons of two ethyl groups. The singlet signal at δ_H 3.80 was assigned to three protons of methoxy group.

4-Methylbenzoic acid and 4-*tert*-butylbenzoic acid bearing the substituent at *para*- position were tried to synthesize. The desired benzamides were also obtained in good yield (entries 5-6).

The IR spectrum of *N*,*N*-diethyl-4-methylbenzamide (Fig 2.7) displayed a strong absorption band of carbonyl at 1607 cm^{-1}, indicating the presence of amide carbonyl. The medium intensity band at 2967 and 1427 cm^{-1} were indicated for the C-H and C-N bonds. The ^{1}H-NMR spectrum (Fig 2.8) of this compound displayed a singlet methyl proton substituted on an aromatic ring signal at δ_H 2.35. The multiplet signal at δ_H 7.17-7.27 was due to four aromatic protons. Two ethyl groups were observed from the presence of four broad singlet signals at δ_H 1.17, 2.35, 3.29 and 3.50.

The IR spectrum of *N*,*N*-diethyl-4-*tert*-butylbenzamide (Fig 2.9) showed an amide carbonyl absorption band at 1607 cm^{-1}. The presence of C-H and C-N bonds was inferred from the occurrence of bands at 2963 and 1422 cm^{-1}. The ^{1}H-NMR spectrum (Fig 2.10) of this compound displayed four aromatic protons at δ_H 7.26-7.40. The singlet signal around δ_H 1.25 was typical of nine butyl group protons. The four broad signals around δ_H 1.22, 1.15, 3.29 and 3.54 were belonged to ten protons of diethylamine.

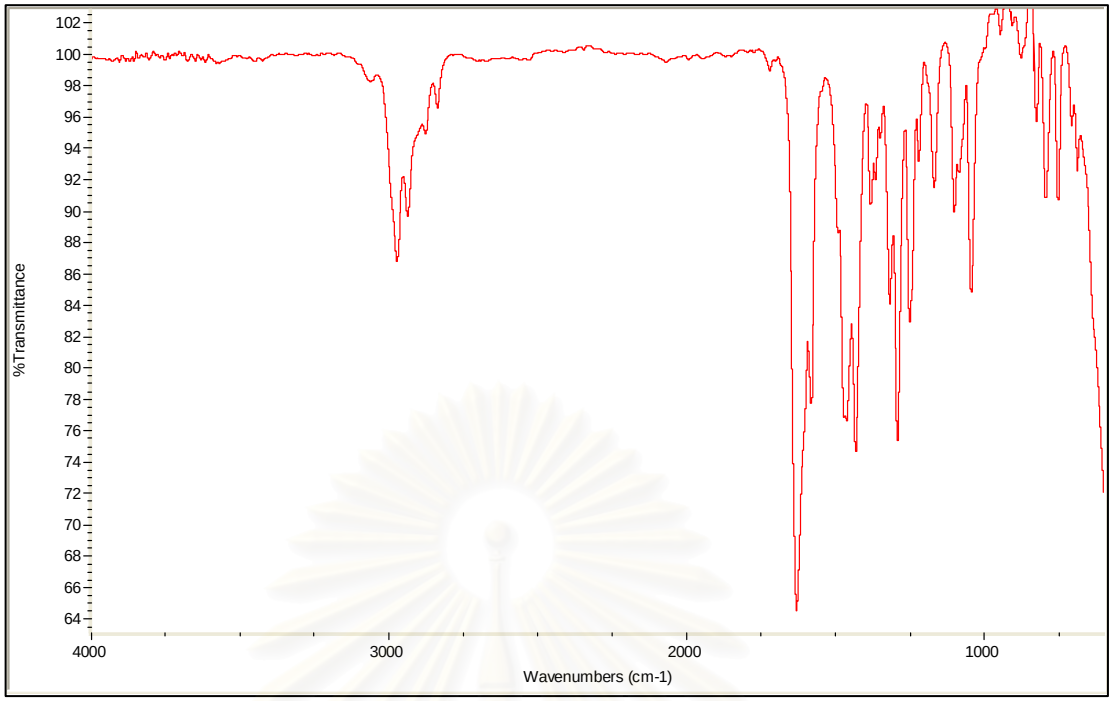


Figure 2.5 The IR spectrum of *N*,*N*-diethyl-3-methoxybenzamide

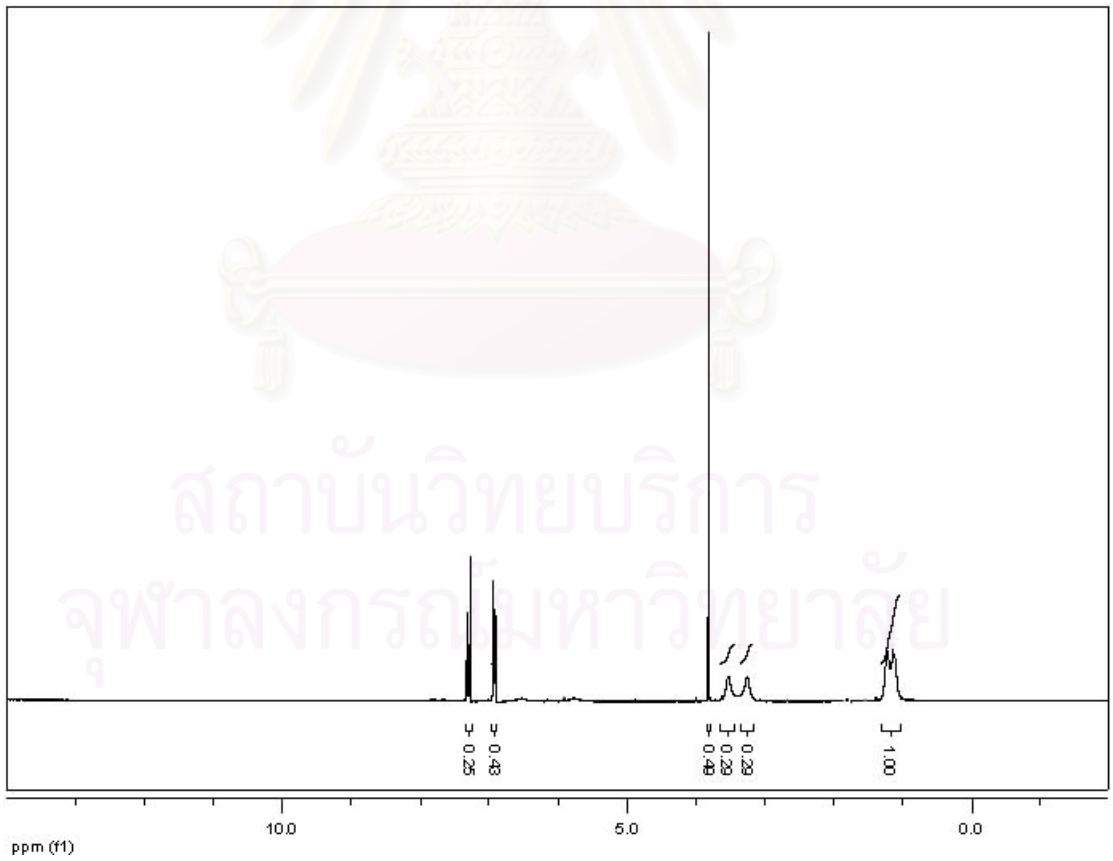


Figure 2.6 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-3-methoxybenzamide

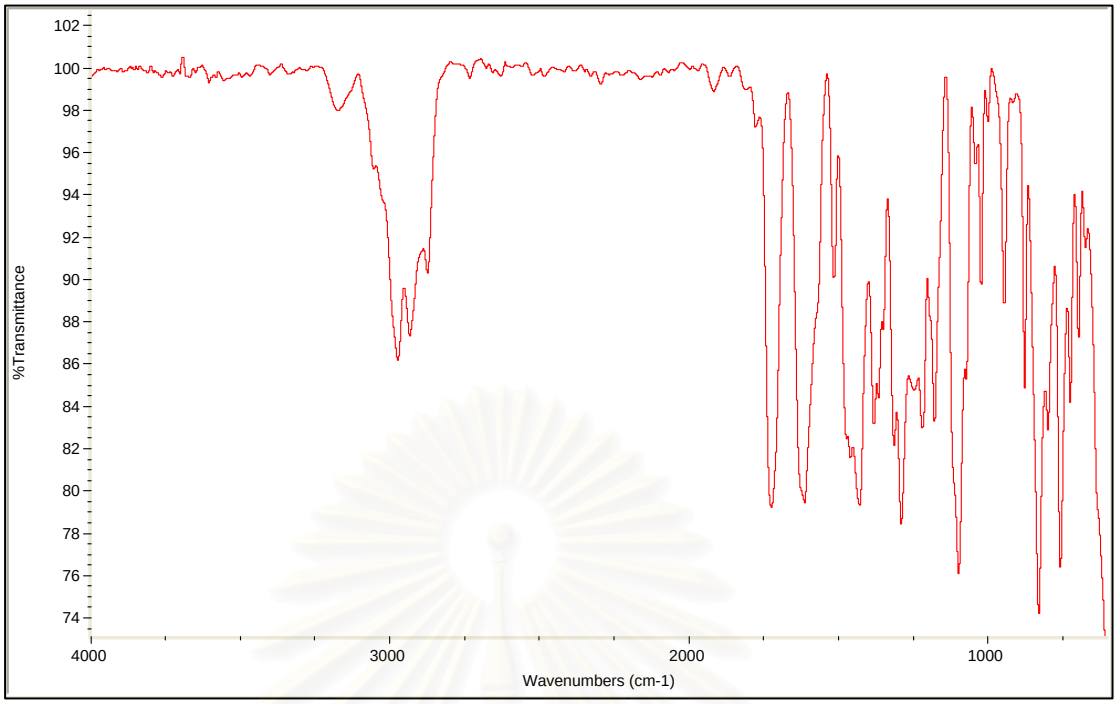


Figure 2.7 The IR spectrum of *N*,*N*-diethyl-4-methylbenzamide

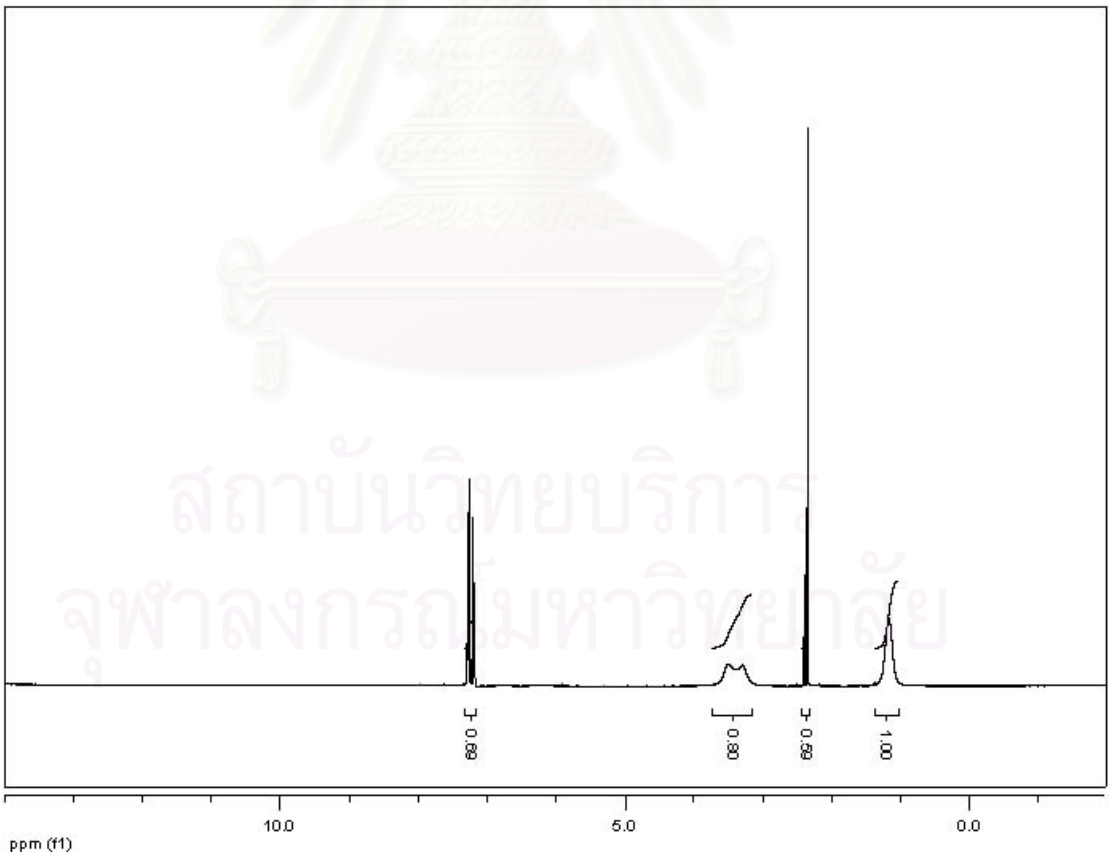


Figure 2.8 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-4-methylbenzamide

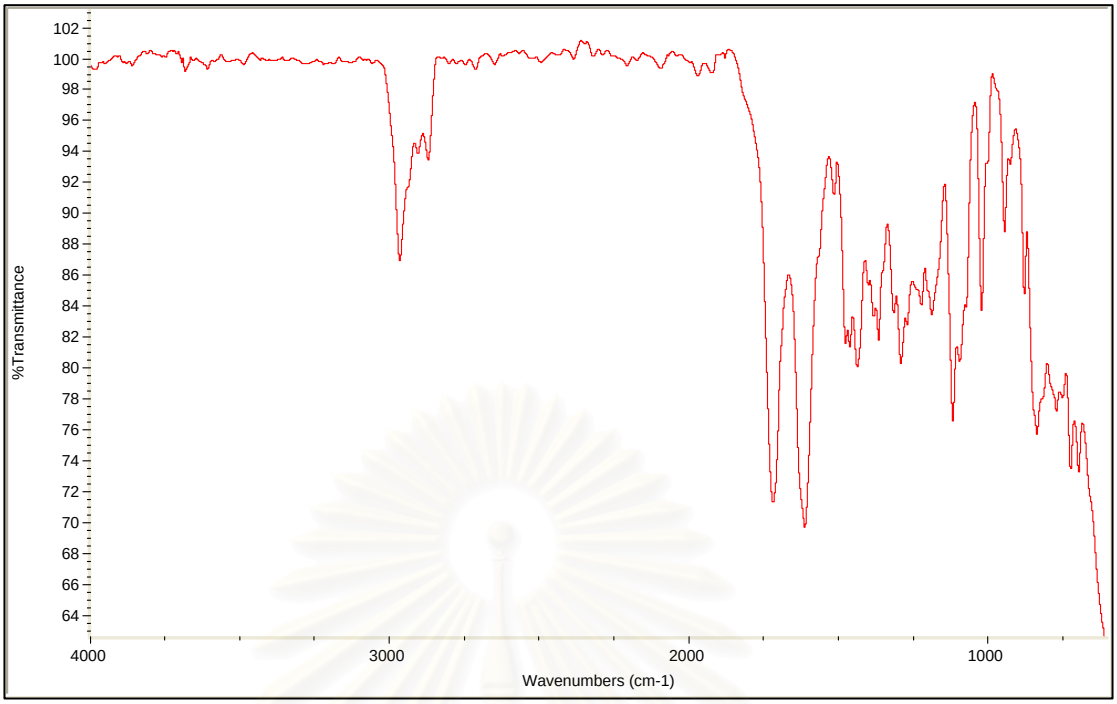


Figure 2.9 The IR spectrum of *N*,*N*-diethyl-4-*tert*-butylbenzamide

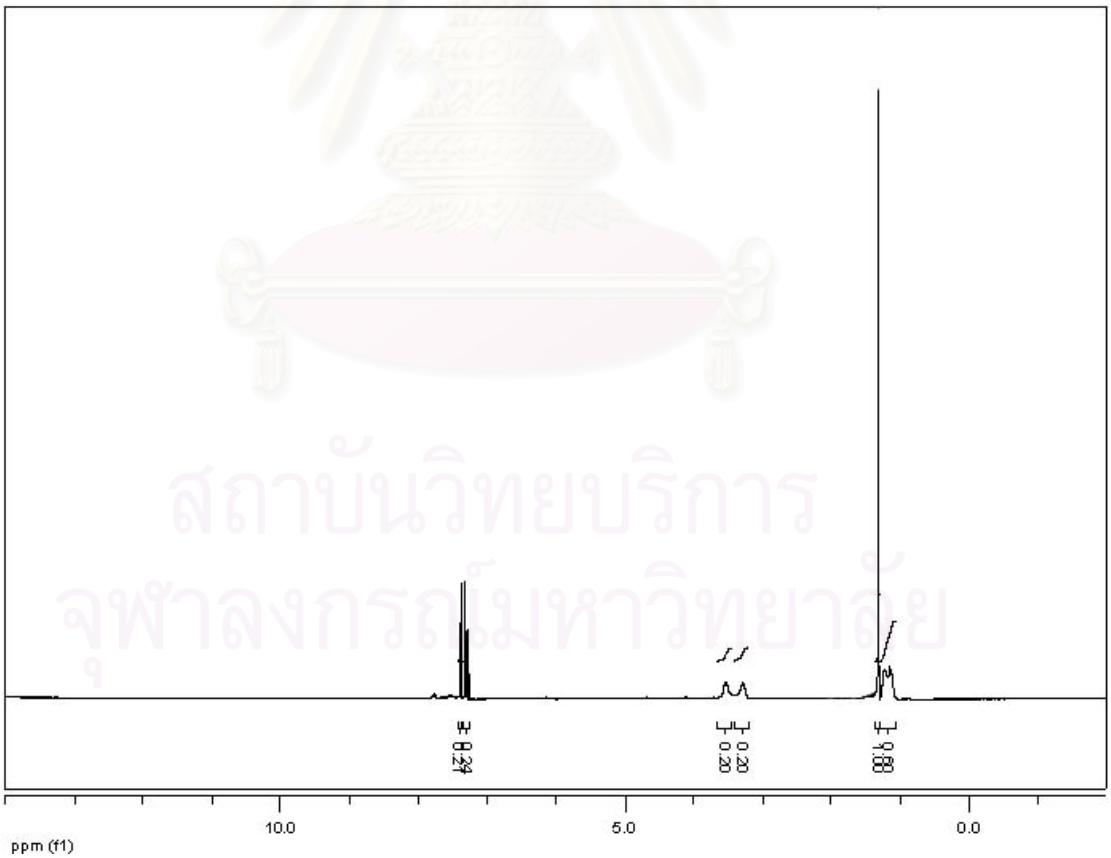


Figure 2.10 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-4-*tert*-butylbenzamide

Finally, compounds with one substituent at *ortho*- position and the other with two substituents at *ortho*- and *para*- positions such as 2-chlorobenzoic acid, 2-bromobenzoic acid and 2-chloro-4-nitrobenzoic acid were planned to synthesize, the corresponding benzamides were obtained in only a poor yield (entries 7-9). In the later case, the steric effect of the substituent at *ortho*- position may take a major role to control the reactivity of the reaction; resulted in the decrease yield of the desired benzamides.

The IR spectrum of *N*,*N*-diethyl-2-chlorobenzamide (Fig 2.11) revealed a strong absorption peak at 1620 cm^{-1}, indicating the presence of carbonyl. The presence of C-H and C-N bonds was observed from the absorption bands at 2977 and 1381 cm^{-1}. The ^{1}H-NMR spectrum (Fig 2.12) of this compound displayed a multiplet signal of aromatic ring at δ_H 7.20-7.80. Two methyl groups were observed from two triplet signals (J = 7.20 Hz) of diethylamine at δ_H 1.06 and 1.27. Two methylene groups present could be assigned for a triplet (J = 6.80 Hz) and quintet (J = 6.80 Hz) signals of diethylamine at δ_H 3.38 and 3.78.

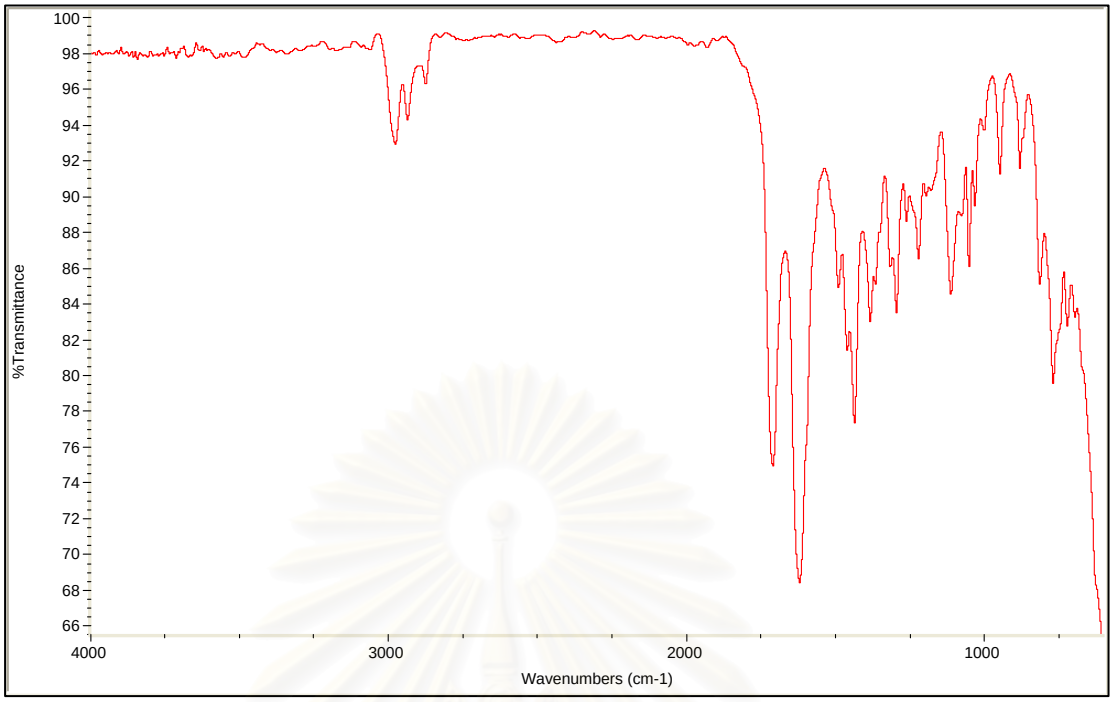


Figure 2.11 The IR spectrum of *N*,*N*-diethyl-2-chlorobenzamide

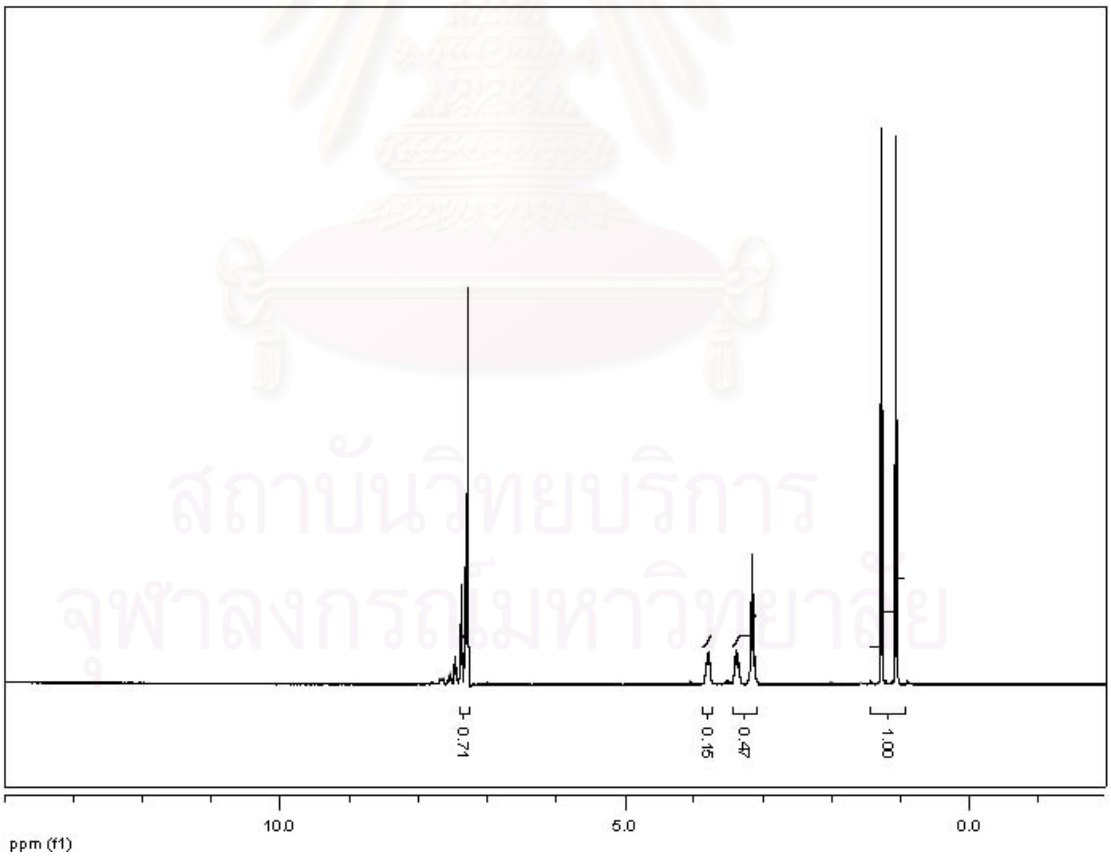


Figure 2.12 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-2-chlorobenzamide

The IR spectrum of *N*,*N*-diethyl-2-bromobenzamide (Fig 2.13) presented a strong absorption band at 1628 cm^{-1}, indicating the presence of amide carbonyl. The presence of bands at 2976 and 1375 cm^{-1} belonged to C-H and C-N bonds. The ^{1}H-NMR spectrum (Fig 2.14) of this compound showed a multiplet signal of aromatic ring at δ_H 7.20-7.80. Two methyl groups were revealed from the presence of two triplet signals (J = 7.20 Hz) of diethylamine at δ_H 1.06, and 1.27. The one methylene group was presented from the presence of one septet (J = 6.80 Hz) signal of diethylamine at δ_H 3.14. Another methylene group was displayed from the presence of two sextet (J = 6.80 Hz) signals of diethylamine at δ_H 3.38-3.83.

The IR spectrum of *N*,*N*-diethyl-2-chloro-4-nitrobenzamide (Fig 2.15) exhibited a strong absorption band at 1619 cm^{-1}, pointing out the presence of amide carbonyl. The medium intensity band at 2967 and 1427 cm^{-1} were indicated for the C-H and C-N bonds. The ^{1}H-NMR spectrum (Fig 2.16) of this compound displayed a multiplet signal at δ_H 7.20-7.80 due to three aromatic protons. Two methyl groups were observed from the presence of two triplet signals (J = 7.20 Hz) at δ_H 1.28 and 1.84. One methylene group was displayed from the presence of multiplet signals of diethylamine at δ_H 3.14. Another methylene group was observed from the presence of two sextet signals (J = 6.80 Hz) at δ_H 3.38 and 3.80. Additionally, according to chemical database this benzamide was found to be a new synthesized compound.

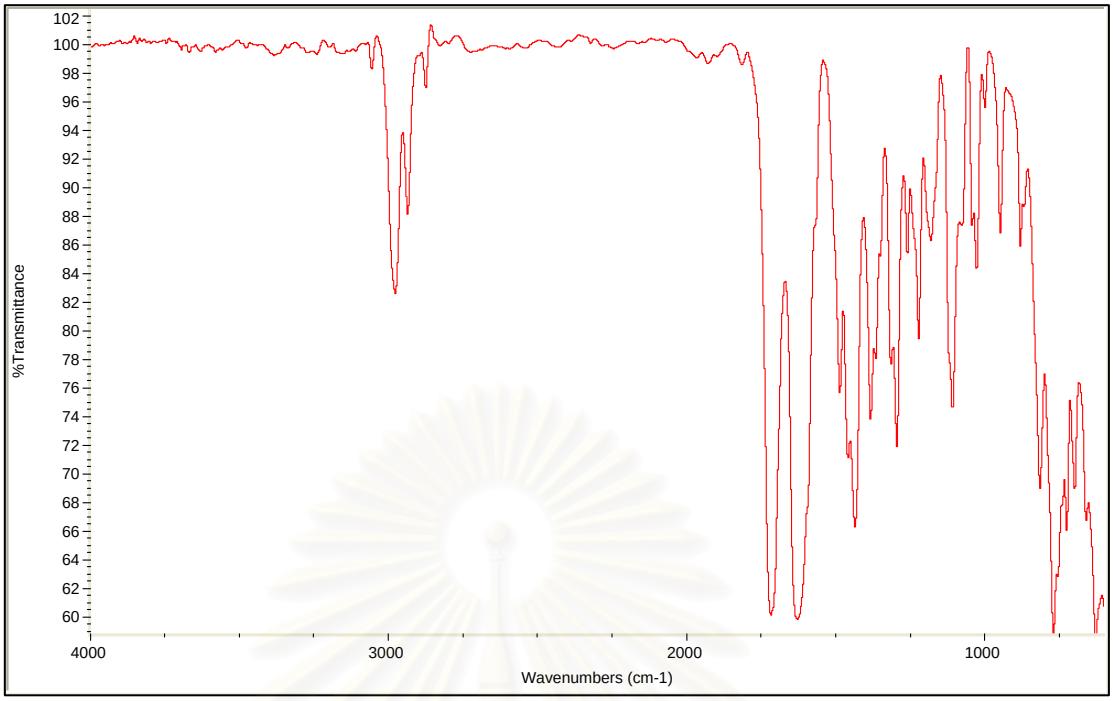


Figure 2.13 The IR spectrum of *N*,*N*-diethyl-2-bromobenzamide

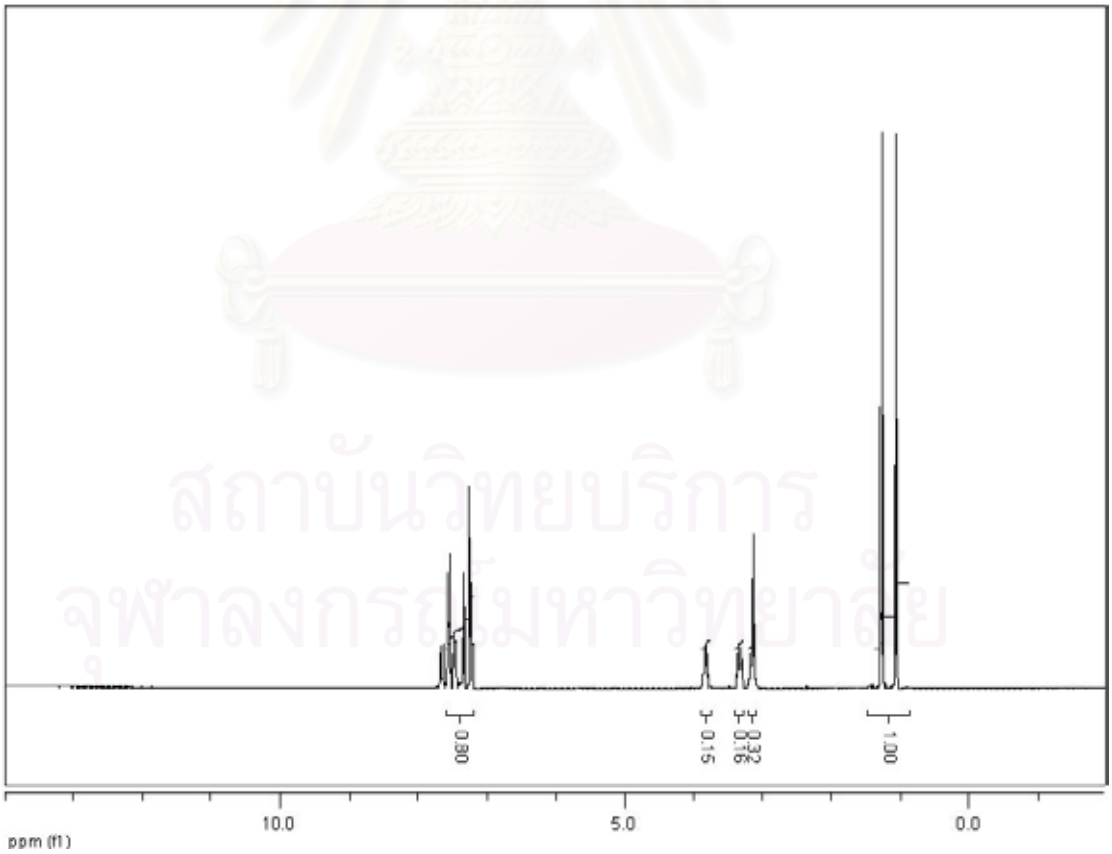


Figure 2.14 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-2-bromobenzamide

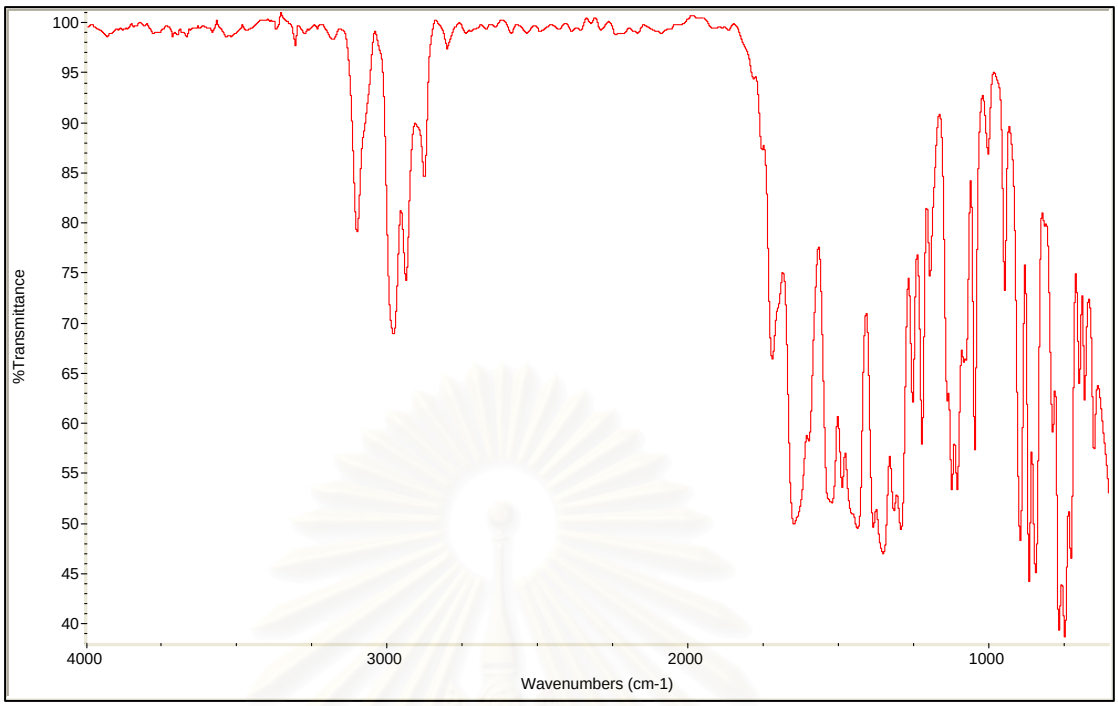


Figure 2.15 The IR spectrum of *N*,*N*-diethyl-2-chloro-4-nitrobenzamide

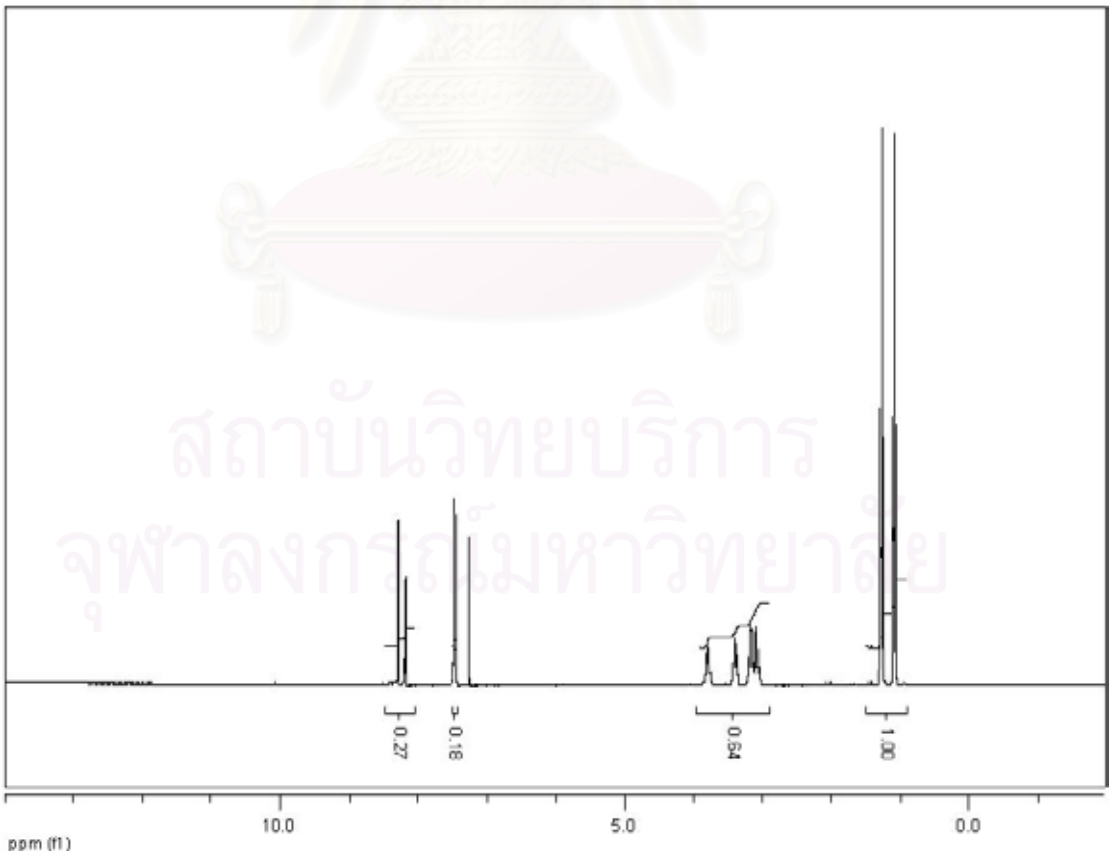


Figure 2.16 The ^{1}H-NMR spectrum of *N*,*N*-diethyl-2-chloro-4-nitrobenzamide

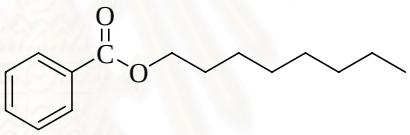
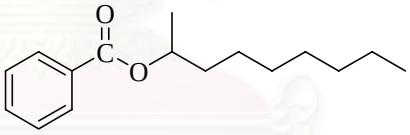
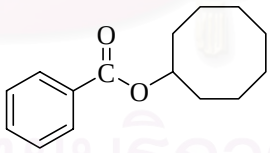
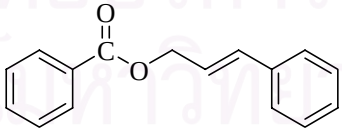
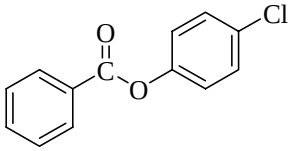
2.3.2 Using CCl_3CONH_2/PPh_3 for the Synthesis of Esters

From literature review, Chaysripongkul [11] first addressed the use of CCl_3CONH_2/PPh_3 to prepare some esters. Nevertheless, the scope of the preparation of esters using the reagents was not explored. The procedure for the preparation of esters was similar to that for amides: 1 equiv of carboxylic acid, 2 equiv of CCl_3CONH_2 and 2 equiv of PPh_3 in refluxing CH_2Cl_2 for 1 h, followed by 1 equiv of alcohol and 3 equiv of *4*-picoline under refluxing CH_2Cl_2 for 1 h.

2.3.2.1 The Effect of Alcohols on the Formation of Benzoate Esters

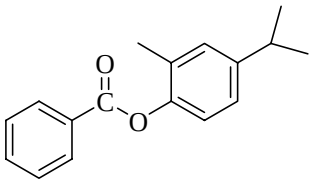
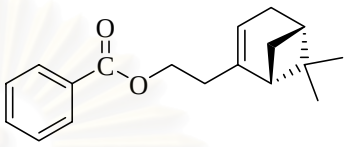
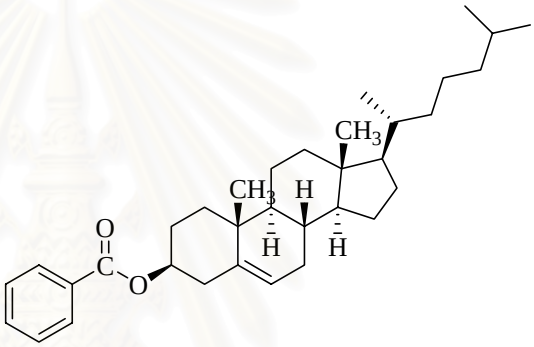
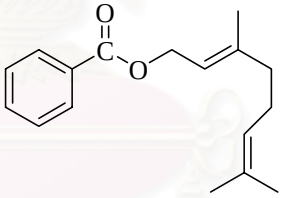
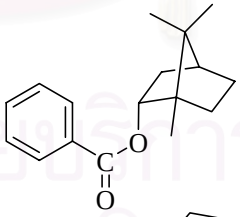
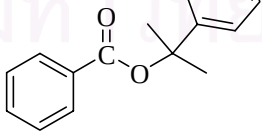
To investigate the generality and scope of this developed method, the reaction was extended for various structurally diverse alcohols. These results are summarized in Table 2.2.

Table 2.2 The effect of alcohols for the synthesis of esters

Entry	Starting alcohol	Ester	% Isolated yield
1	1-octanol		98
2	2-octanol		77 (78)[a]
3	cyclooctanol		66
4	cinnamyl alcohol		90
5	4-chlorophenol		78

[(a)] 3 h

Table 2.2 (Conti)

Entry	Starting alcohol	Ester	% Isolated yield
6	carvacrol		75
7	(-)-nopol		77
8	cholesterol		81(3)[b]
9	geraniol		70
10	(-)-borneol		81
11	2-methyl-2-phenylethanol		0

[b] the corresponding chloride was isolated.

As it was clearly seen from Table 2.2, when primary alcohol such as 1-octanol was employed, the reaction proceeded cleanly and the desired benzoate was obtained in excellent yield (98 %, entry 1). When secondary alcohols such as 2-octanol and cyclooctanol were employed, the corresponding benzoates were afforded in 77 and 66%, respectively (entries 2 and 3). The refluxing time in step II of the reaction of 2-octanol was increased from 1 to 3 h with the expectation to lift up the yield of benzoate ester; the desired benzoate was slightly increased. This result indicated that refluxing time did not affect to this reaction. In the case of allylic alcohol and cinnamyl alcohol, the reaction can efficiently undergo to furnish the target alcohol in good yields under conditions (entry 4). In addition, when phenols such as 4-chlorophenol and carvacrol were employed, the desired benzoates were obtained in good yields (75-78%, entries 5 and 6). Moreover, the method could be applied to preparing benzoate esters of (-)-nopol, cholesterol and geraniol, natural occurring alcohols containing C=C in the molecule. The reaction proceeded smoothly; C=C was intact (entries 7 and 9). In the case of cholesterol, it was found that the corresponding chloride was obtained as white solid in 3% yield. This result suggested that the adduct generated from Cl_3CCONH_2 and PPh_3 was still remained in the reaction due to the excess of these reagents employed in step I. Additionally, when (-)-borneol, another natural product, was employed to react with benzoic acid, the corresponding ester was obtained in a good yield (81%, entry 10). Nevertheless, in the case of 2-methyl-2-phenylethanol, a sterically hindered alcohol, the reaction did not proceed. All starting material was recovered with a bulkier tertiary alcohol (entry 11). This may be because the steric hindrance of two methyl and phenyl groups may control the reactivity of the reaction.

The structures of benzoate esters prepared were fully confirmed by ^{1}H- and ^{13}C-NMR. The ^{1}H-NMR spectrum of 1-octyl benzoate (Fig 2.17) contained a multiplet signal of fifteen aliphatic protons and a triplet signal of two protons connecting with oxygen atom at δ_H 0.87-1.80 and 4.31, respectively. The signals around δ_H 7.40-8.02 were assigned for five aromatic protons. The^{13}C-NMR spectrum (Fig 2.18) of this compound displayed seven sp^3 carbon signals of alkyl group and one sp^3 carbon connecting with oxygen at δ_C 14.09- 31.8 and 65.1 respectively. The signals around δ_C 128.3-132.8 with six sp^2 carbons and one sp^2 carbon were assigned to aromatic carbons and a carbonyl carbon of ester, respectively.

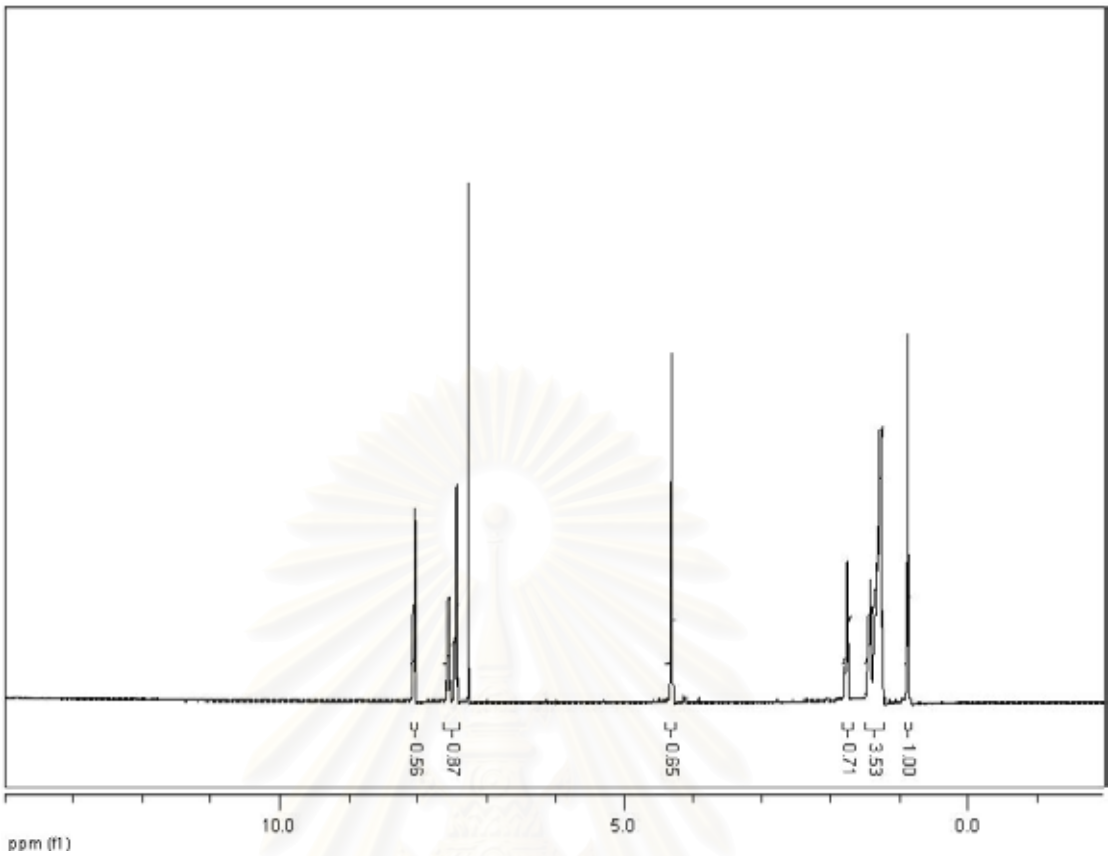


Figure 2.17 The ^{1}H-NMR spectrum of 1-octyl benzoate

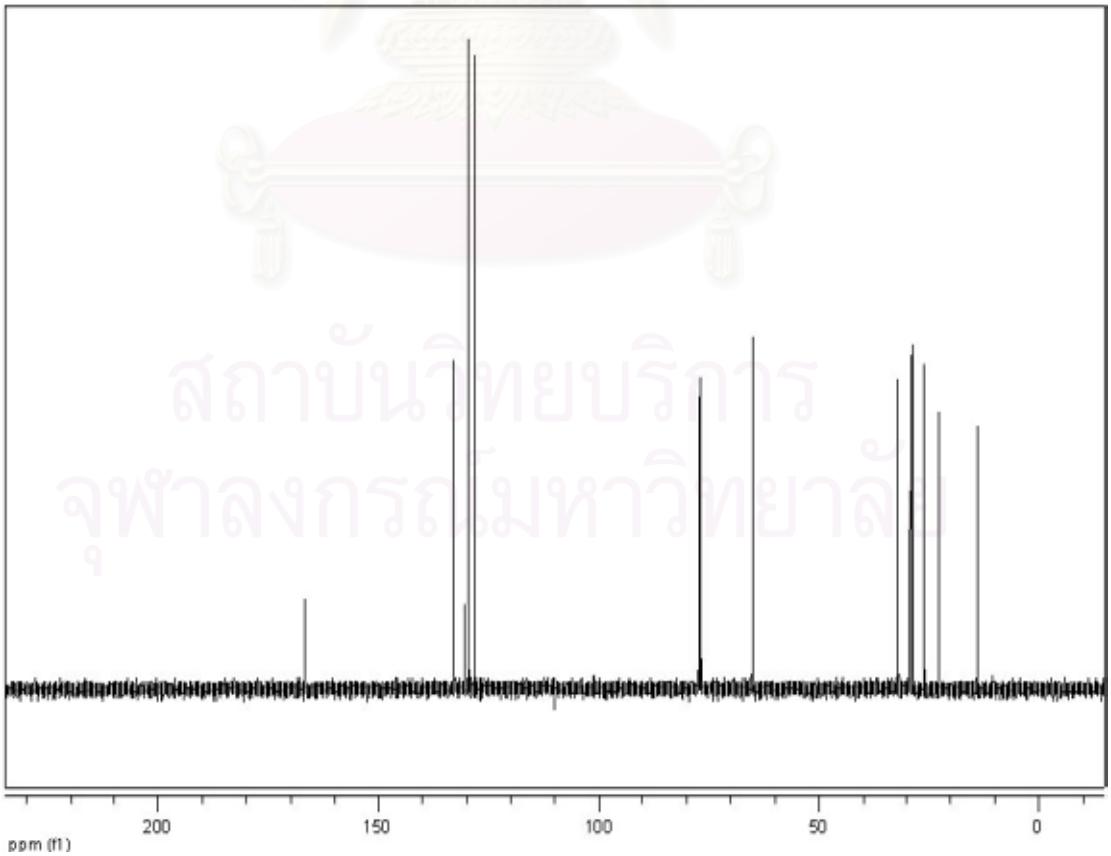


Figure 2.18 The ^{13}C-NMR spectrum of 1-octyl benzoate

The ^{1}H-NMR spectrum of 2-octyl benzoate (Fig 2.19) displayed multiplet signal of alkyl group at δ_H 0.85-1.78. The sextet signal (J= 6.40 Hz) around δ_H 5.16 was one proton on the carbon connected with oxygen atom. The five protons on aromatic ring showed a multiplet signal at δ_H 7.57-8.05. The^{13}C-NMR spectrum (Fig 2.20) of this compound contained seven signals at δ_C 14.1-36.1 and a signal at δ_C 71.7. These could be assigned for sp^3 carbon of alkyl groups and carbon adjoined to oxygen atom, respectively. The presence of six aromatic carbons and a carbonyl carbon was inferred from the presence of peaks at δ_C 128.3-132.7 and 166.2, respectively.

The ^{1}H-NMR spectrum of cyclooctyl benzoate (Fig 2.21) showed a multiplet signal of alkyl groups at δ_H 1.45-2.00. The presence of quintet signal (J= 4.40 Hz) at δ 5.20 could be assigned for a proton of OC*H*. The signals around δ_H 7.40-8.00 were typical of five aromatic protons. The^{13}C-NMR spectrum (Fig 2.22) of this compound contained four signals and one signal at δ_C 22.1-31.5 and 75.8, respectively, indicative of seven sp^3 carbons of alkyl groups and a carbon connected with oxygen atom, respectively. The four signals at δ_C 128.0-132.8 and another signal at δ_C 168.2 could be assigned for six sp^2 carbons of aromatic ring and a carbonyl group, respectively.

The ^{1}H-NMR spectrum of cinnamoyl benzoate (Fig 2.23) displayed a doublet of doublet signal (J= 6.40 Hz) at δ_H 5.00 and multiplet signals at δ_H 6.42 of methylene groups connecting with oxygen and an olefinic proton, respectively. Another olefinic proton connecting with the phenyl ring was observed as doublet signal (J= 16.00 Hz) at δ_H 6.75. A signal at δ_H 7.20-8.05 was due to ten aromatic protons. The ^{13}C-NMR spectrum (Fig 2.24) of this compound exhibited a signal at δ_C 65.6, indicating the presence of one sp^3 carbon connected with oxygen atom. The ten signals at δ_C 123.2-136.2 and a signal at δ_C 168.2 were belonging to six sp^2 carbons of aromatic ring and carbonyl group, respectively.

The ^{1}H-NMR spectrum of 4-chlorophenyl benzoate (Fig 2.25) displayed a multiplet signal of nine aromatic protons of two benzene rings at δ_H 7.20-8.20. The^{13}C-NMR spectrum (Fig 2.26) of this compound presented eight signals of twelve aromatic carbons at δ_C 123.1-131.3. The signal at δ_C 164.9 was belonged to a carbonyl carbon of ester group.

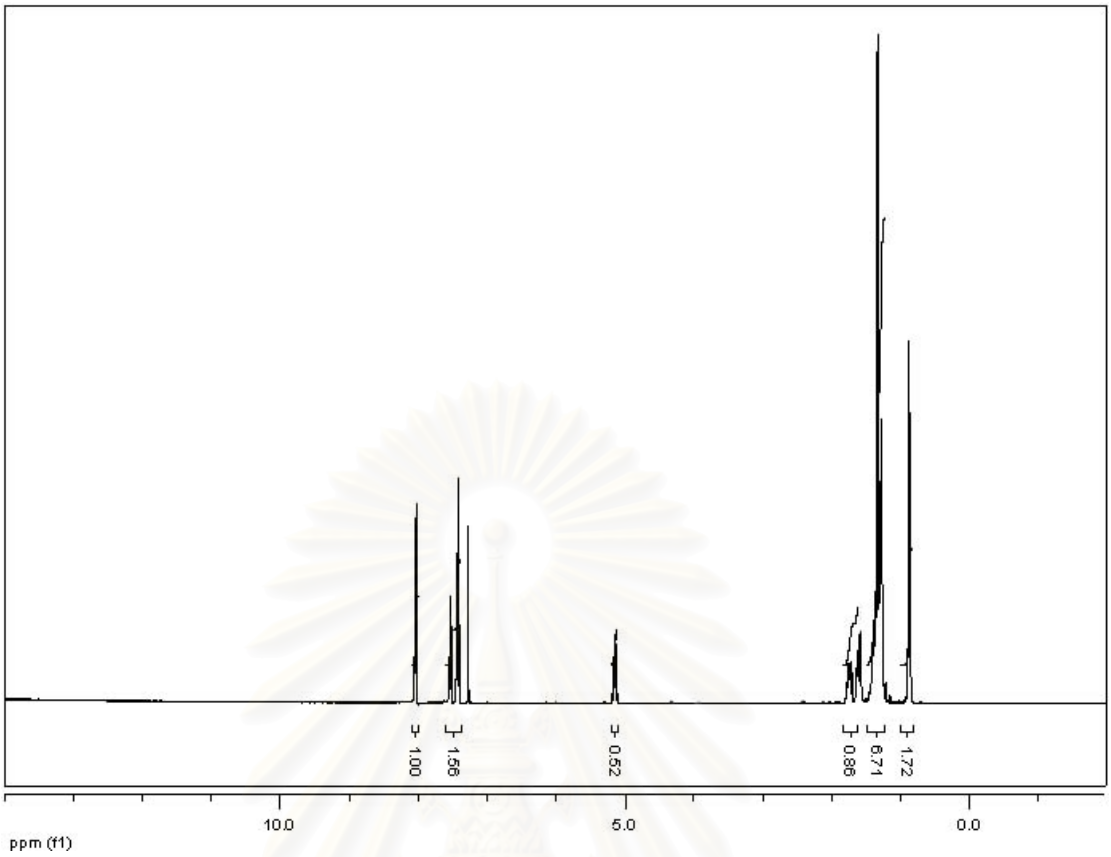


Figure 2.19 The ^{1}H-NMR spectrum of 2-octyl benzoate

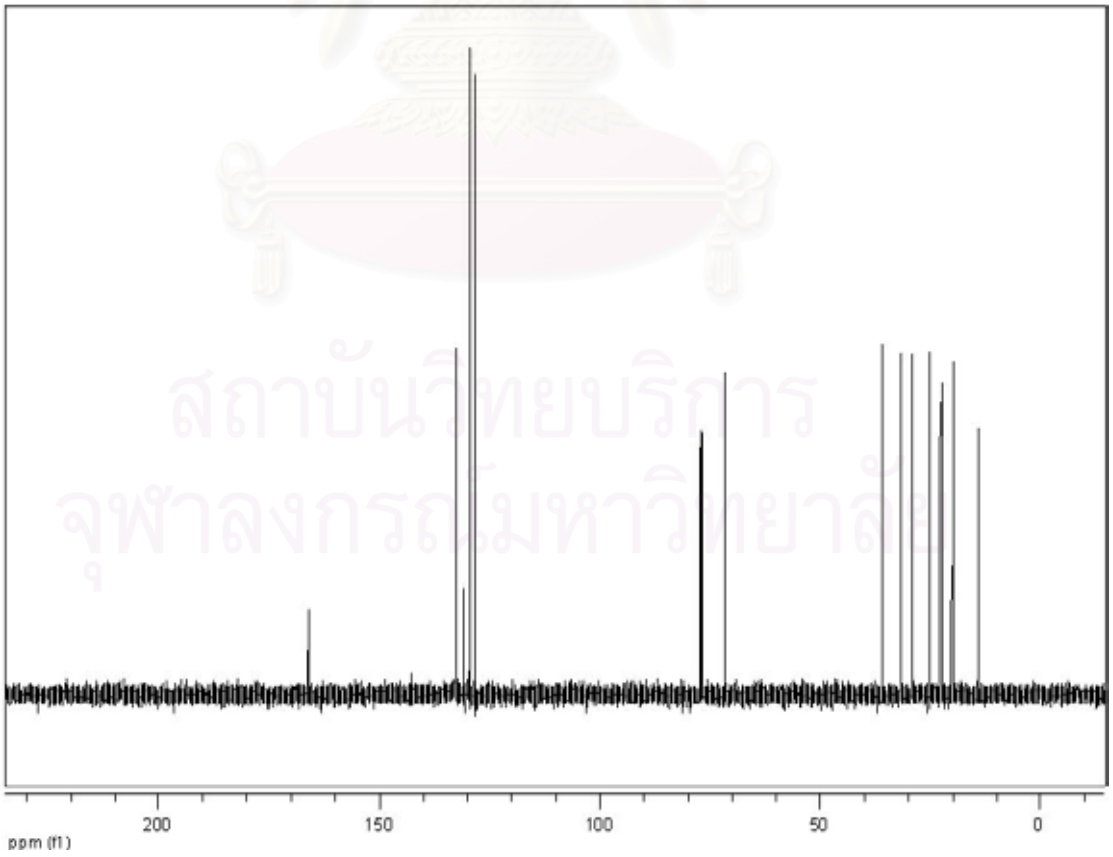


Figure 2.20 The ^{13}C-NMR spectrum of 2-octyl benzoate

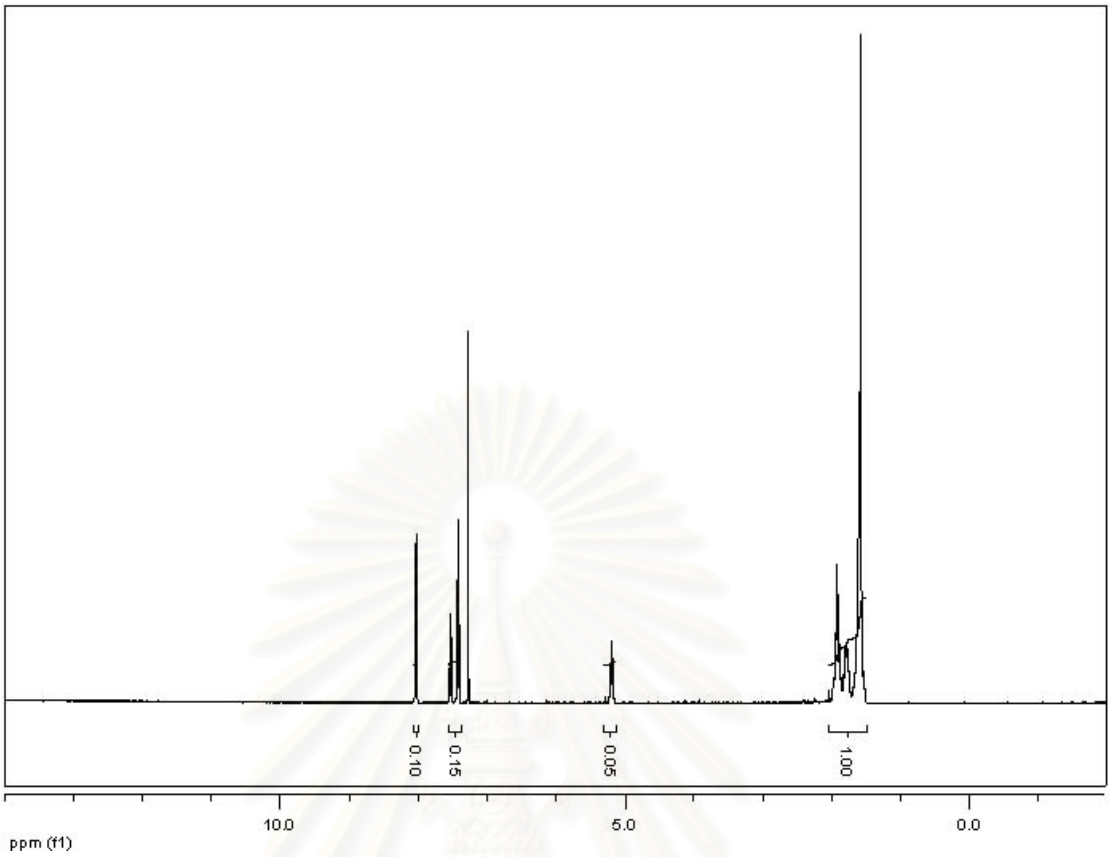


Figure 2.21 The ^{1}H-NMR spectrum of cyclooctyl benzoate

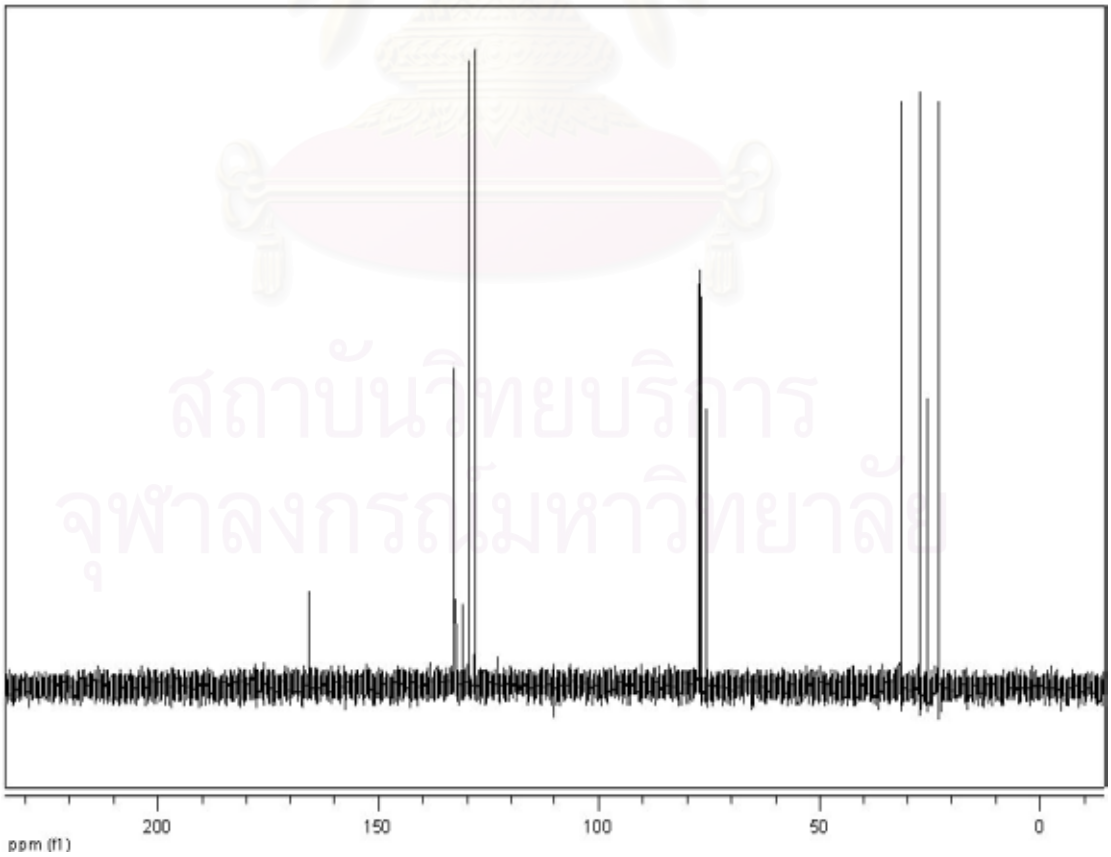


Figure 2.22 The ^{13}C-NMR spectrum of cyclooctyl benzoate

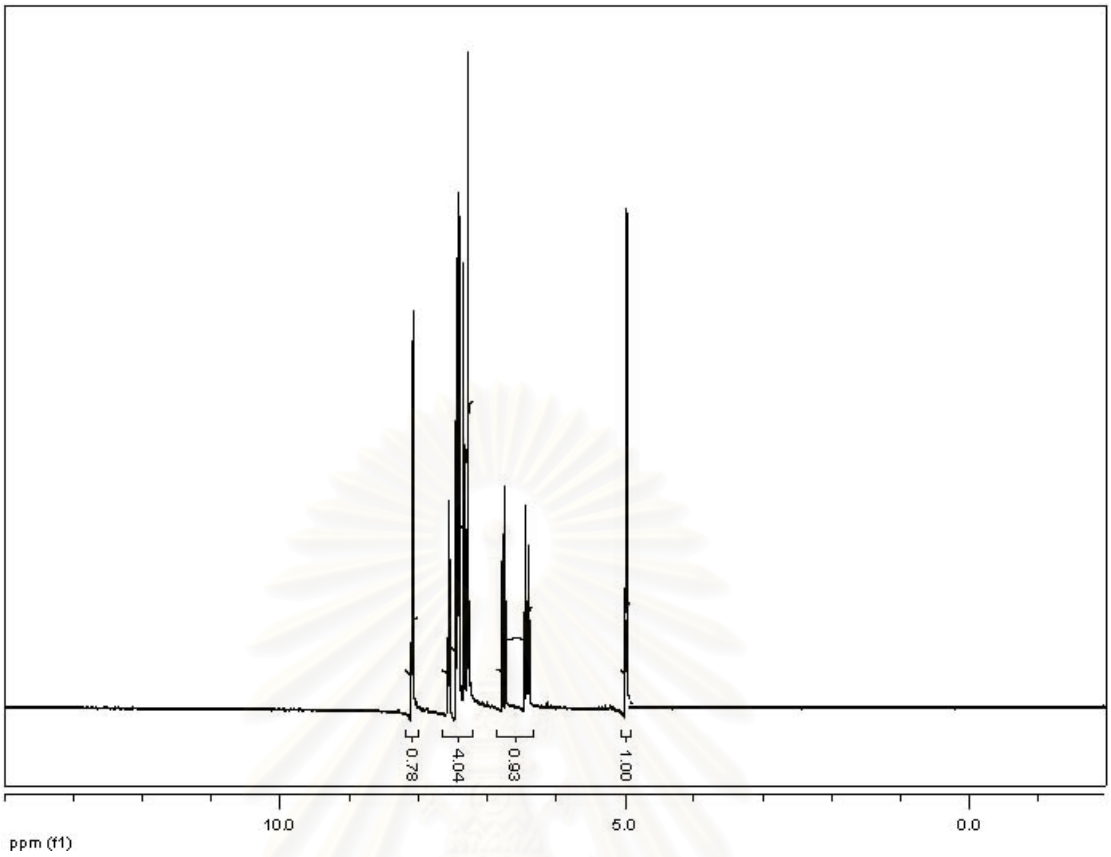


Figure 2.23 The ^{1}H-NMR spectrum of cinnamoyl benzoate

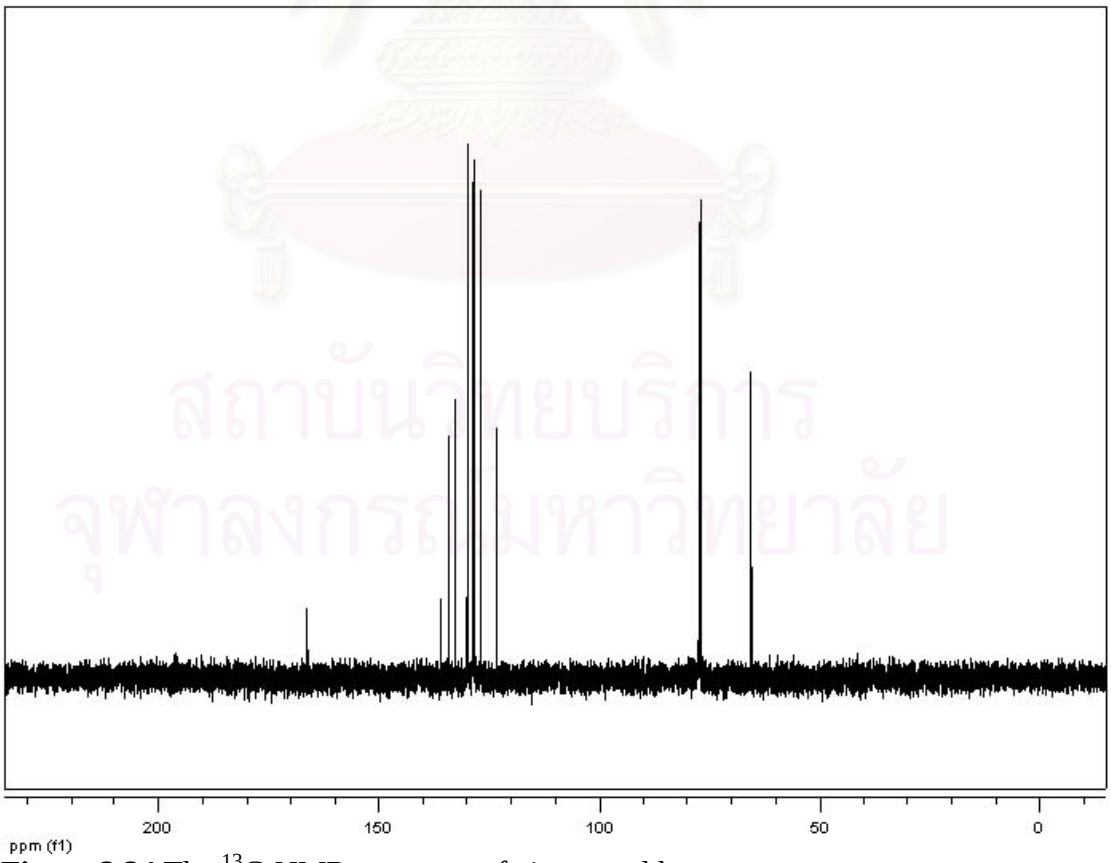


Figure 2.24 The ^{13}C-NMR spectrum of cinnamoyl benzoate

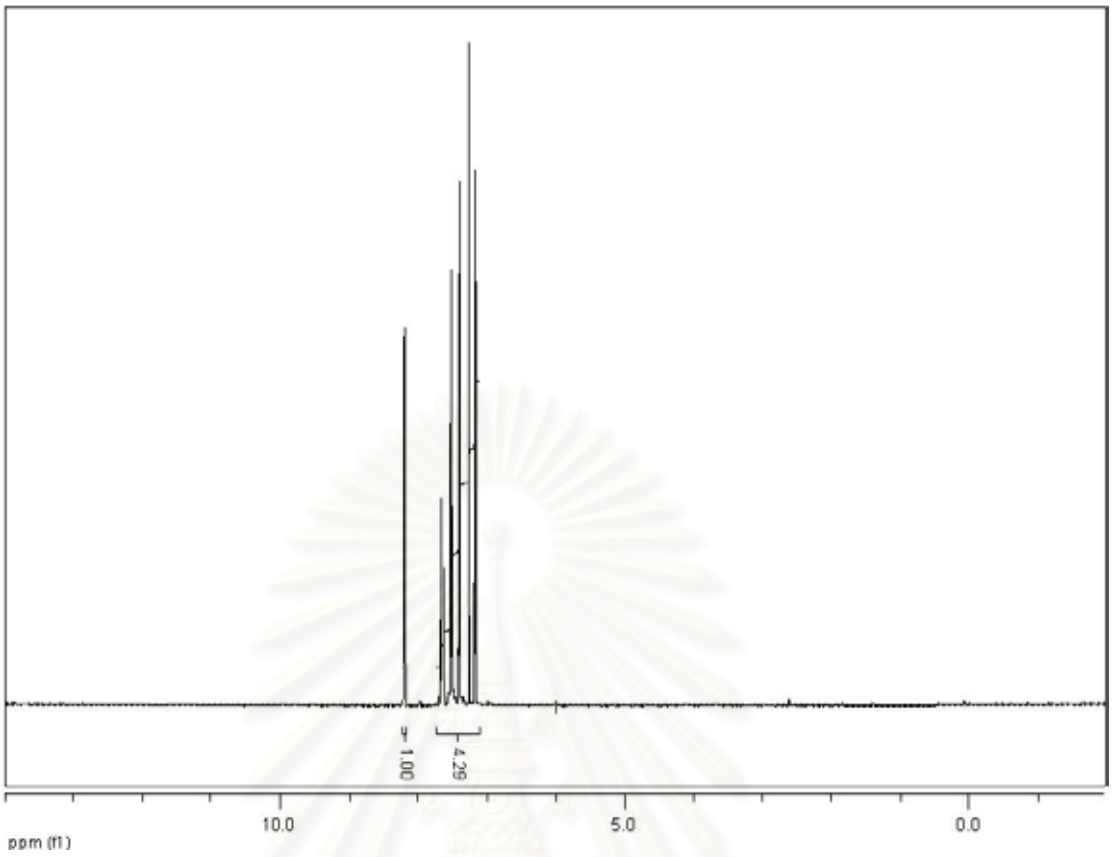


Figure 2.25 The ^{1}H-NMR spectrum of 4-chlorophenyl benzoate

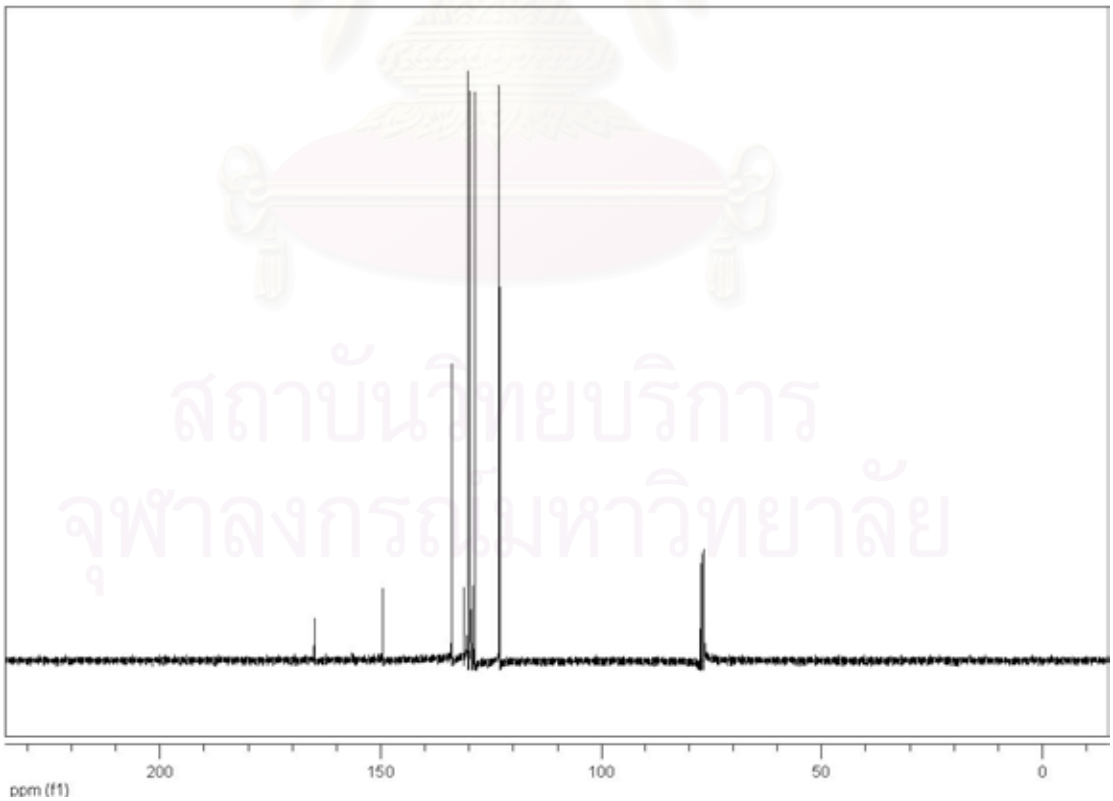


Figure 2.26 The ^{13}C-NMR spectrum of 4-chlorophenyl benzoate

The ^{1}H-NMR spectrum of 4-*iso*-propyl-2-methylphenyl benzoate (Fig 2.27) presented a doublet signal of six protons of two methyl groups at δ_H 1.27. The singlet signal at δ_H 2.90 was belonged to a proton on a carbon connecting with methyl group of *iso*-propyl group. The presence of three protons of methyl group substituted on an aromatic ring was observed at δ_H 2.21. The presence of a multiplet signal of eight aromatic protons was observed at δ_H 7.65-8.25. The^{13}C-NMR spectrum (Fig 2.28) of this compound contained three signals of four sp^3 carbons at δ_C 15.9-33.6. Twelve aromatic carbons were inferred from the observation of the twelve signals at δ_C 119.9-149.4. The signal at δ_C 164.9 was belonged to a carbonyl carbon of ester.

The ^{1}H-NMR spectrum of (-)-2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-ethyl benzoate (Fig 2.29) displayed two singlet signals of two methyl groups at δ_H 0.84 and 1.27. The doublet signal (J= 8.80 Hz) of olefinic proton was observed at δ_H 1.17. The signals around δ_H 2.08-2.44 were ascribed to eight protons of alkyl group. The presence of a multiplet signal at δ_H 4.33, indicating the presence of two protons on a carbon connecting with oxygen atom. The olefinic proton was inferred from the presence of triplet signal at δ_H 5.36. The signals around δ_H 7.43-8.02 were assigned for five aromatic protons. The^{13}C-NMR spectrum (Fig 2.30) of this compound exhibited eight signals at δ_C 21.1-45.7 and another signal at δ_C 63.3, indicating the presence of nine aliphatic carbons and a sp^3 carbon connected with oxygen atom. The six signals and a signal at δ_C 128.3-132.8 and 168.2 were belonging to six sp^2 carbons of aromatic ring and a carbonyl carbon, respectively. Two olefinic carbons were in addition observed at δ_C 118.9 and 144.2.

The ^{1}H-NMR spectrum of cholesteryl benzoate (Fig 2.31) showed a doublet at δ_H 5.43 of an olefinic proton. A multiplet signal at δ_H 4.86 was due to a proton on a carbon connecting with an ester group. A multiplet at δ_H 0.69-2.45 was indicated to protons of cholesterol group. The^{13}C-NMR spectrum (Fig 2.32) of this compound exhibited twenty-five peaks at δ_C 11.9-74.6, indicated alkyl carbons of cholesterol. Two signals of olefinic carbons were observed at δ_C 122.8 and 139.6. The six signals at δ_C 128.3-132.8 belonging to six sp^2 carbons of aromatic ring were detected. The peak at δ_C 166.0 appropriated for a carbonyl carbon was also observed.

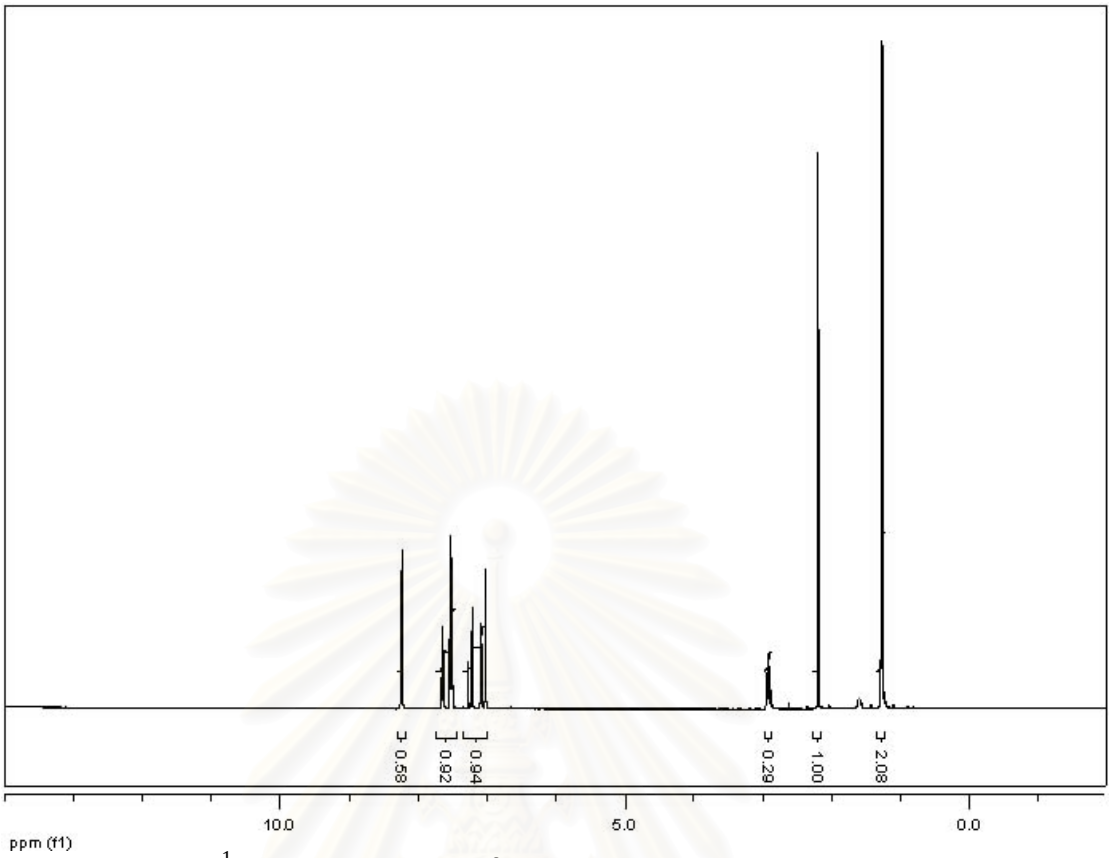


Figure 2.27 The ^{1}H-NMR spectrum of 4-*iso*-propyl-2-methylphenyl benzoate

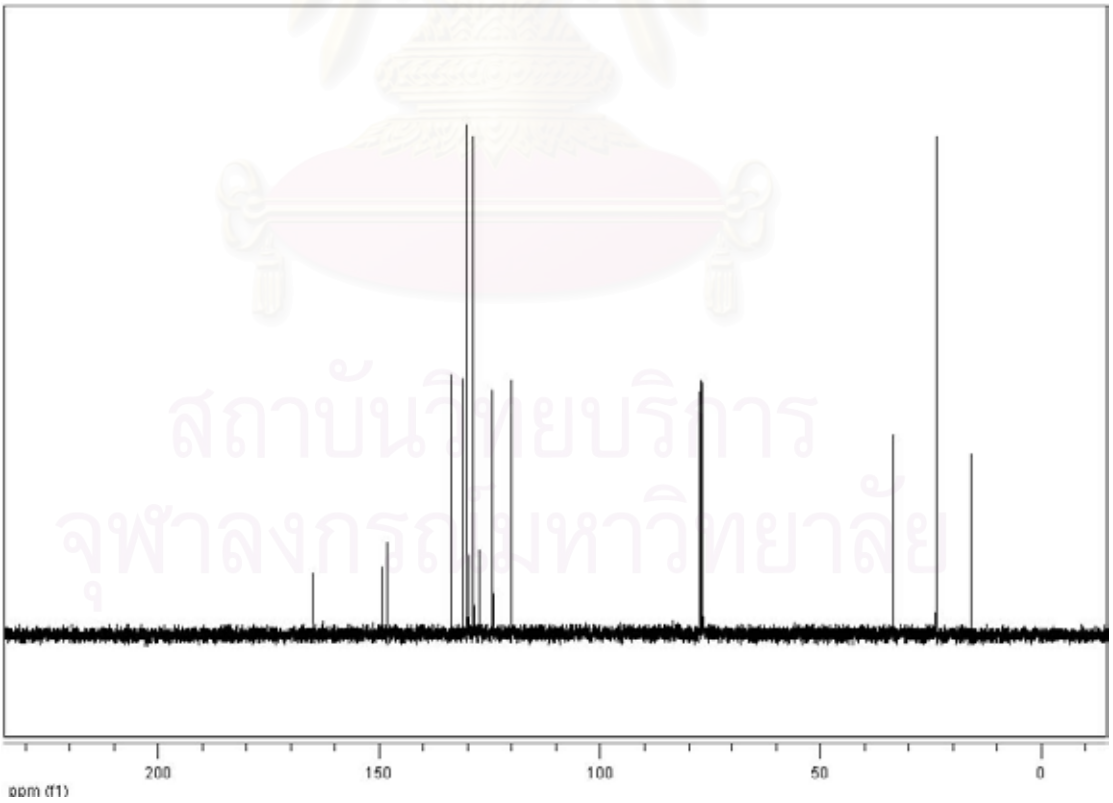


Figure 2.28 The ^{13}C-NMR spectrum of 4-*iso*-propyl-2-methylphenyl benzoate

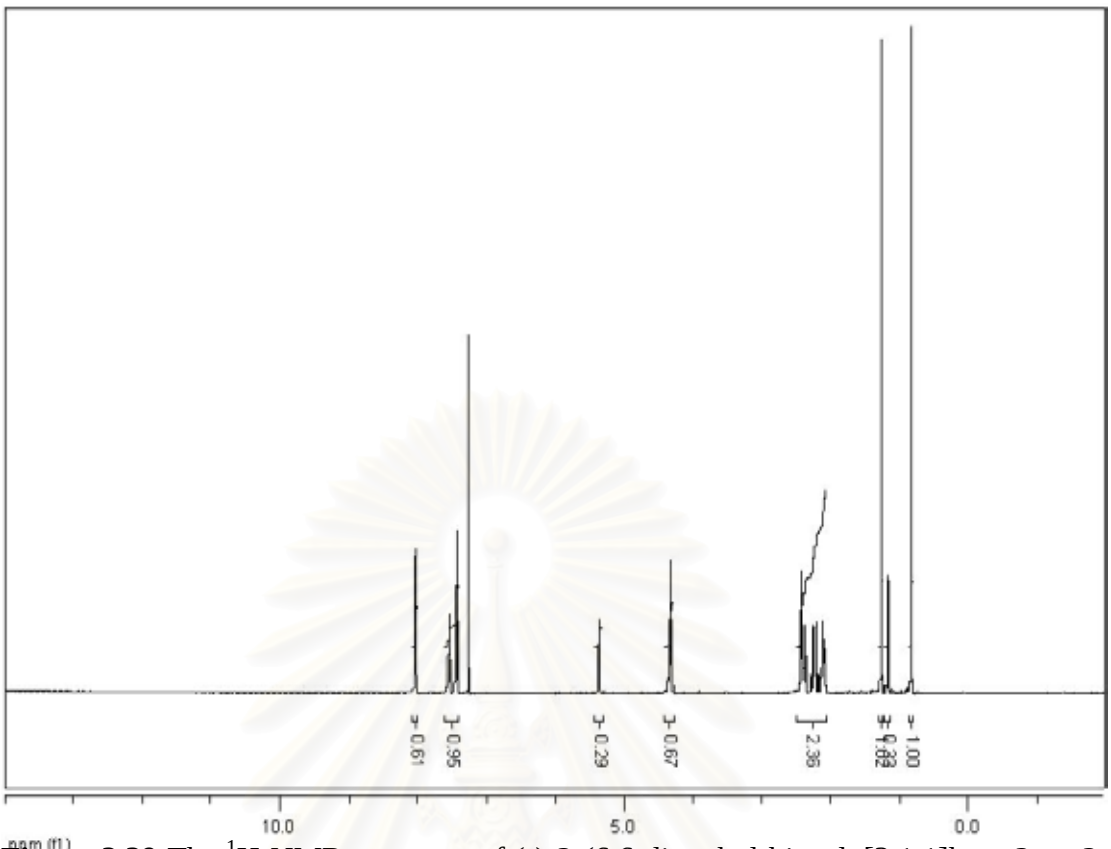


Figure 2.29 The ^{1}H-NMR spectrum of (-)-2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-ethyl benzoate

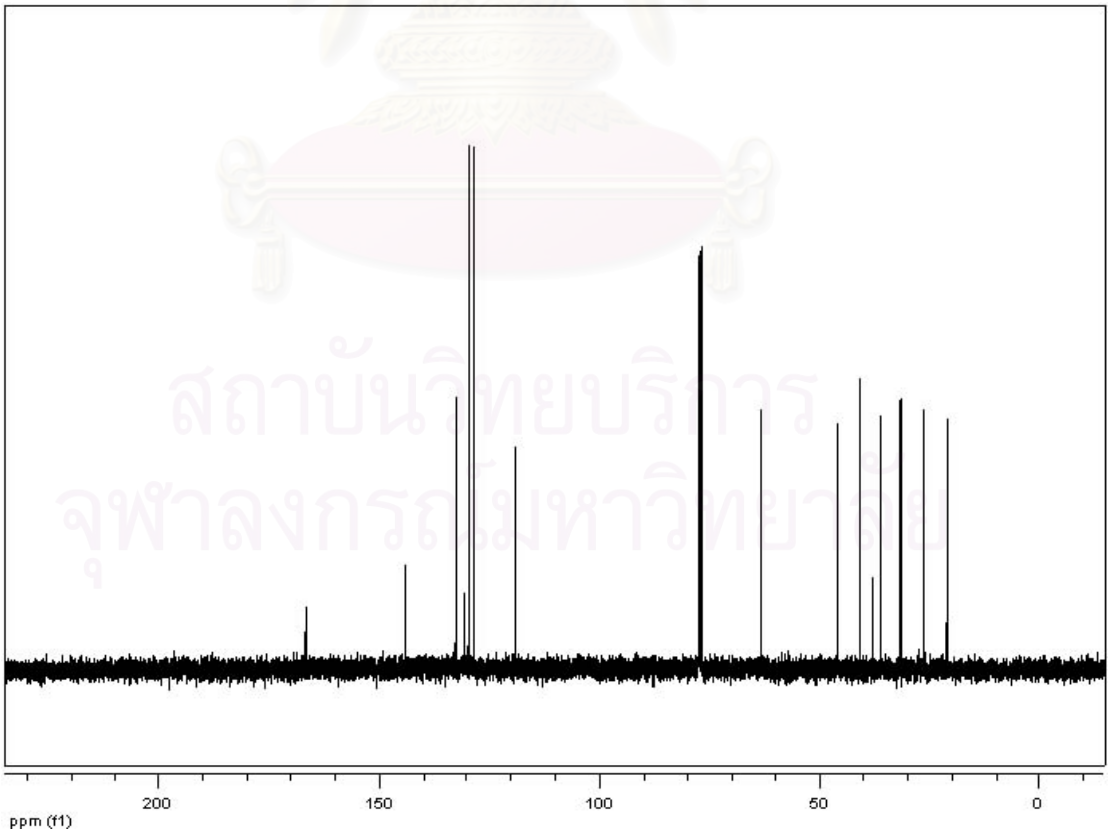


Figure 2.30 The ^{13}C-NMR spectrum of (-)-2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-ethyl benzoate

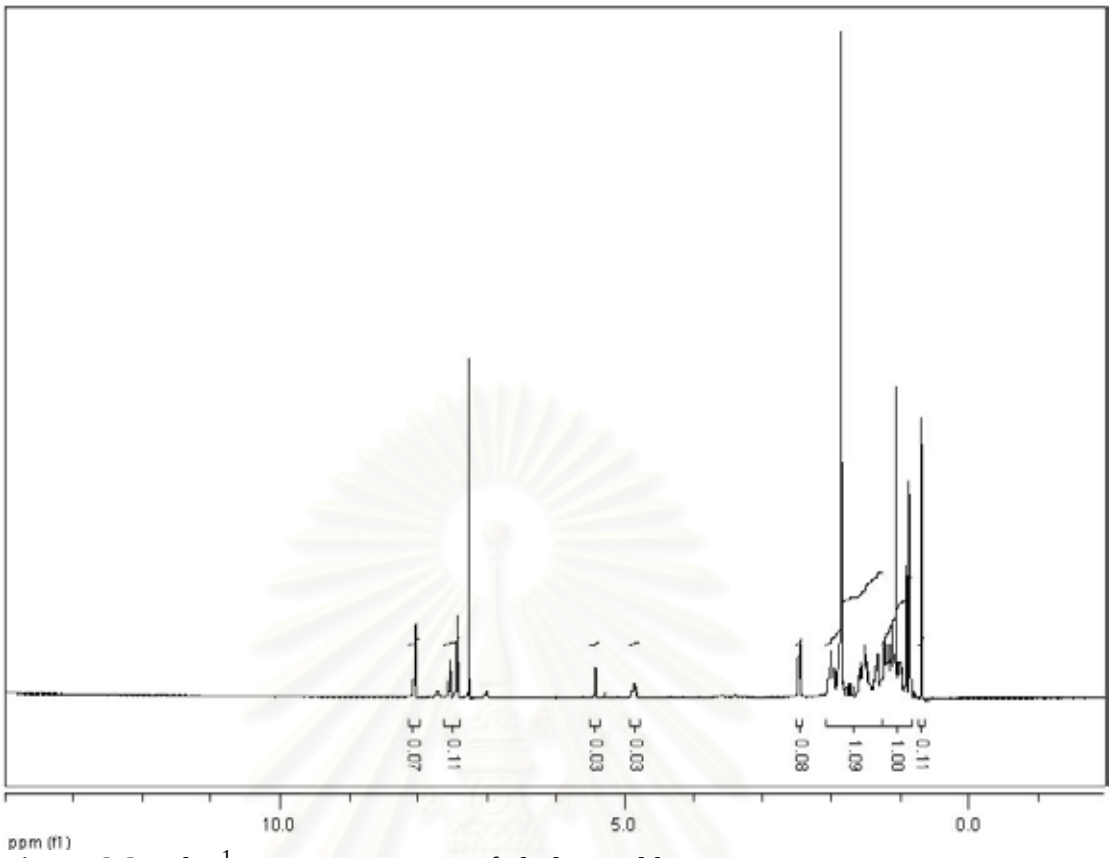


Figure 2.31 The ^{1}H-NMR spectrum of cholesteryl benzoate

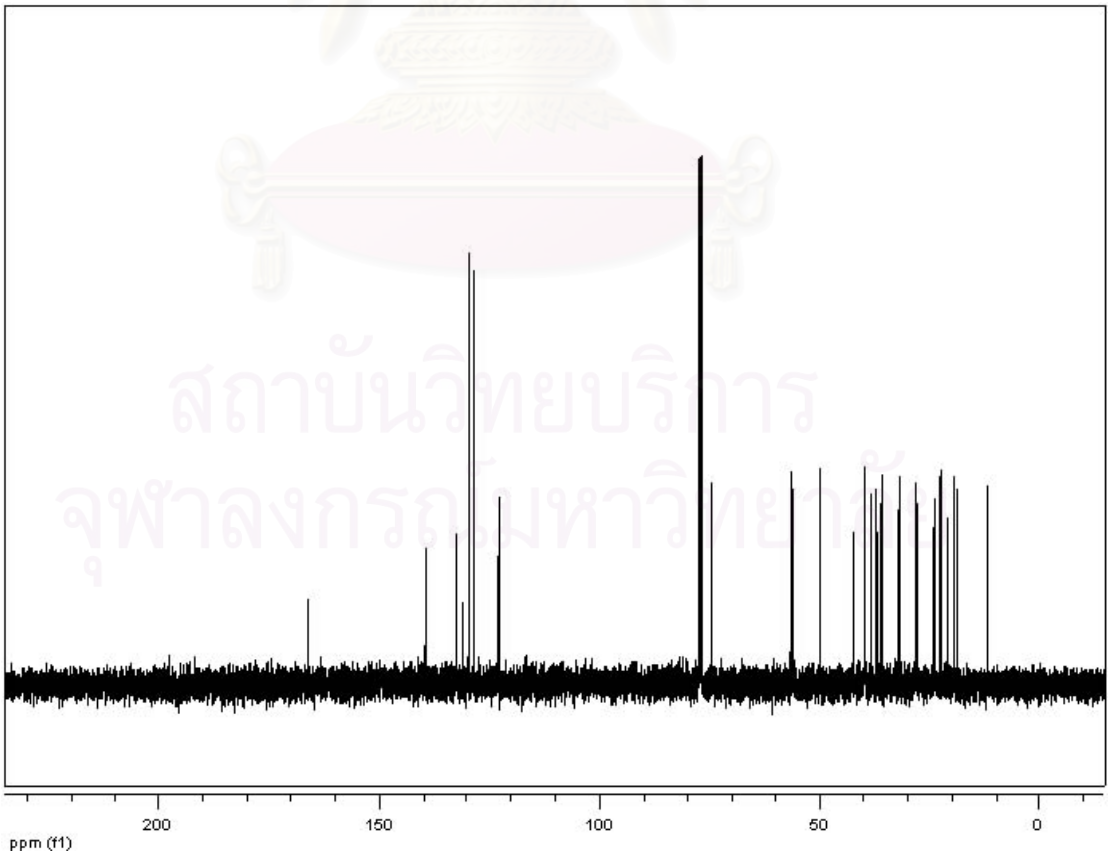


Figure 2.32 The ^{13}C-NMR spectrum of cholesteryl benzoate

The ^{1}H-NMR spectrum of (*E*)-3,7-dimethylocta-2,6-dienyl benzoate (Fig 2.33) showed three singlet signals of three methyl groups at δ_H 1.60-1.77. A multiplet signal of two methylene groups was revealed at δ_H 2.09. A signal of two protons on a carbon connecting with oxygen atom was observed from the presence of a doublet signal (*J*= 7.20 Hz) at δ_H 4.84. Two triplet signals at δ_H 5.09 (*J*= 4.80 Hz) and 5.47 (*J*= 7.20 Hz) were assigned to two olefinic protons. The signals around δ_H 7.43-8.05 were indicated to five protons of aromatic ring. The^{13}C-NMR spectrum (Fig 2.34) of this compound displayed six peaks at δ_C 16.6-61.9 of geraniol group. The four signals of olefinic carbons at δ_C 118.3, 123.7, 131.8 and 142.3 were detected. The four signals at δ_C 128.3-132.8 belonging to six carbons of aromatic ring were visualized. The peak at δ_C 166.6, coincided to a carbonyl carbon was manifestly revealed.

The ^{1}H-NMR spectrum (-)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl benzoate (Fig 2.35) presented two singlet signals of three methyl groups at δ_H 0.92 and 0.97. A multiplet signal around δ_H 1.10-2.48 was belonged to seven protons of borneol group. A signal of a proton on a carbon connecting with oxygen atom was observed from the presence of doublet of doublet signal (*J*= 10.00 Hz) at δ_H 5.11. The signals around δ_H 7.43-8.05 could be assigned for five aromatic protons. The^{13}C-NMR spectrum (Fig 2.36) of this compound displayed ten peaks at δ_C 13.6-80.5 of borneol. The four signals at δ_C 128.0-132.7 were assigned for six carbons of aromatic ring. The peak at δ_C 166.8 could be ascribed for a carbonyl carbon of ester.

This protocol is a new methodology for the preparation of benzoate derivatives since it is convenient, rapid and efficient while the conventional methods are delicate to prepare these compounds.

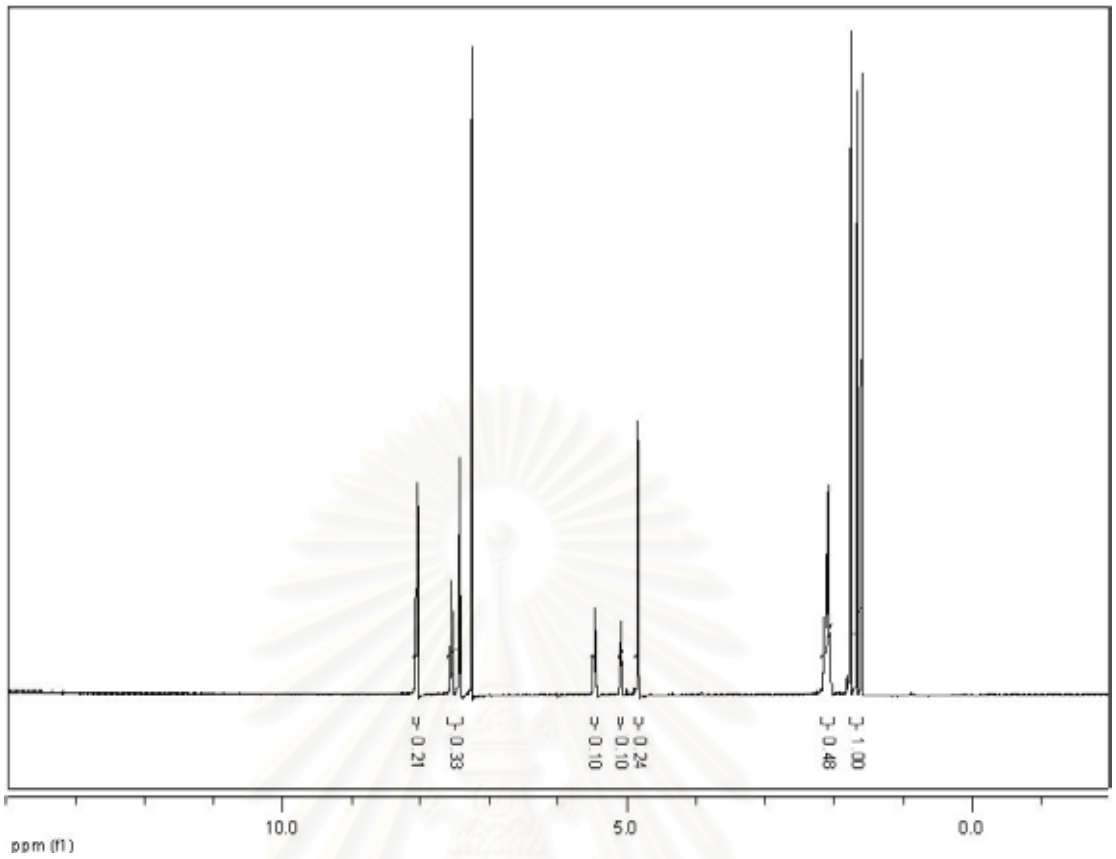


Figure 2.33 The ^{1}H-NMR spectrum of (*E*)-3,7-dimethylocta-2,6-dienyl benzoate

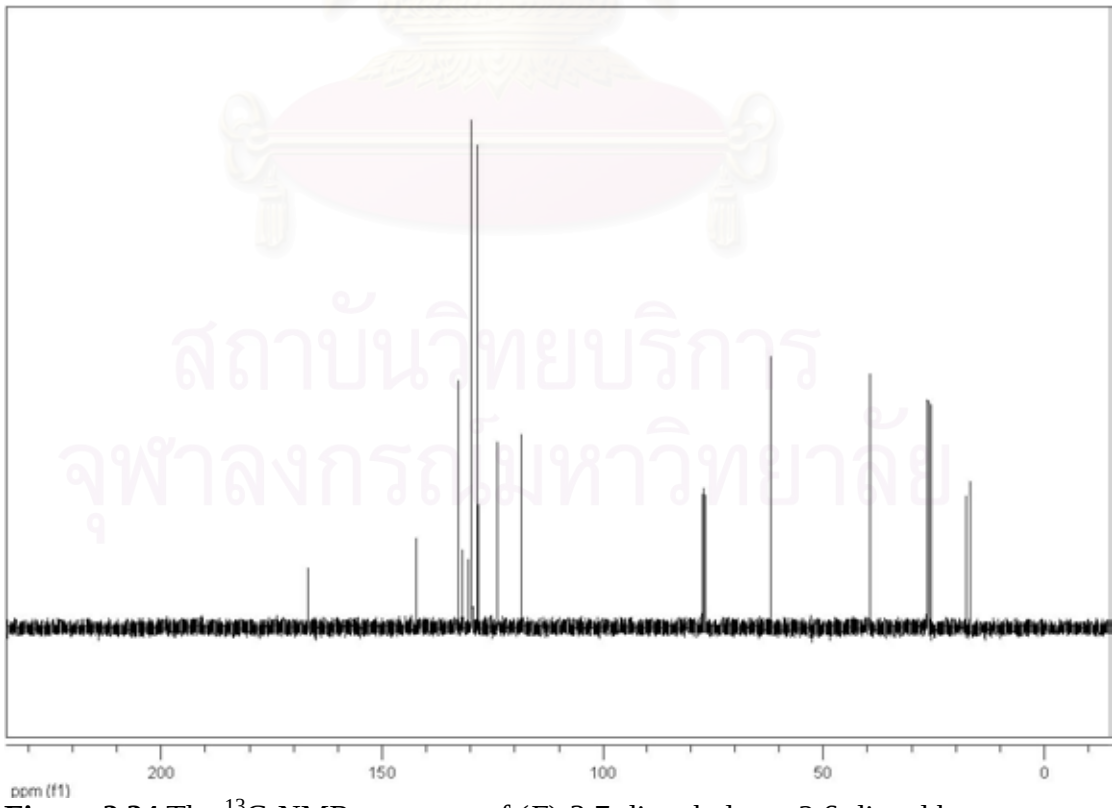


Figure 2.34 The ^{13}C-NMR spectrum of (*E*)-3,7-dimethylocta-2,6-dienyl benzoate

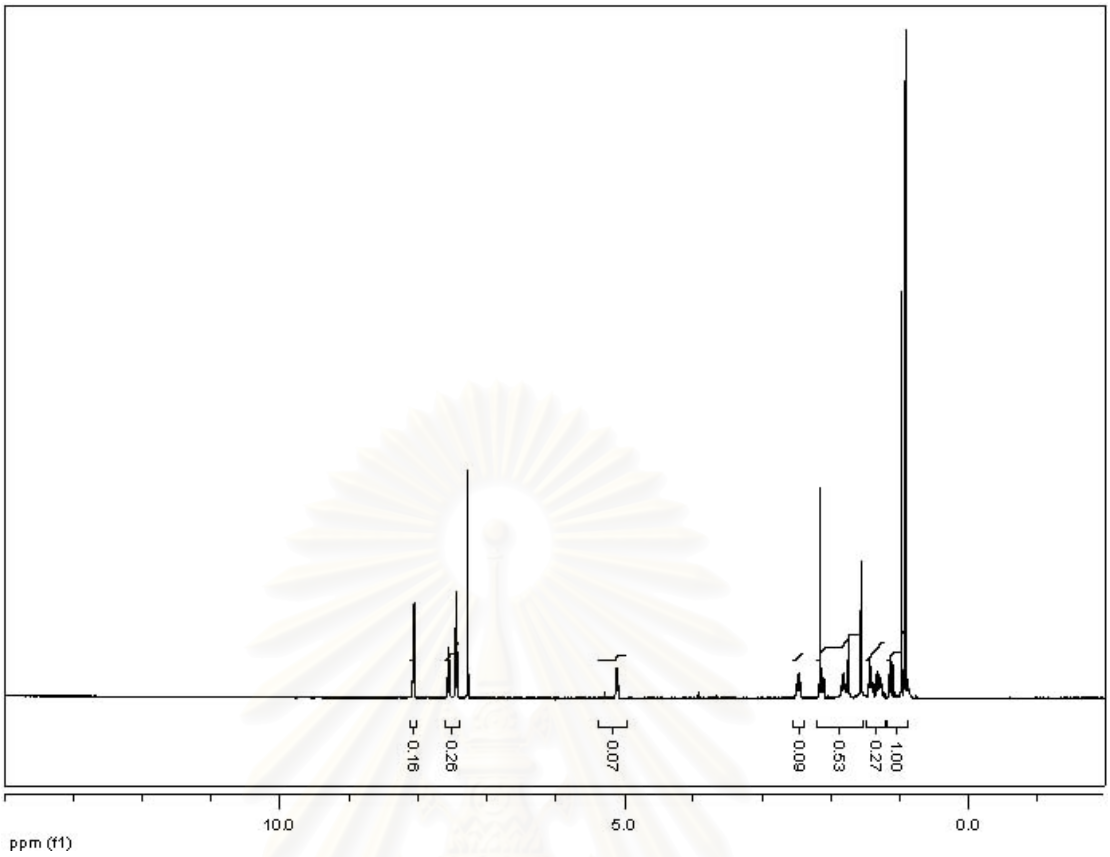


Figure 2.35 The ^{1}H-NMR spectrum of spectrum (-)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl benzoate

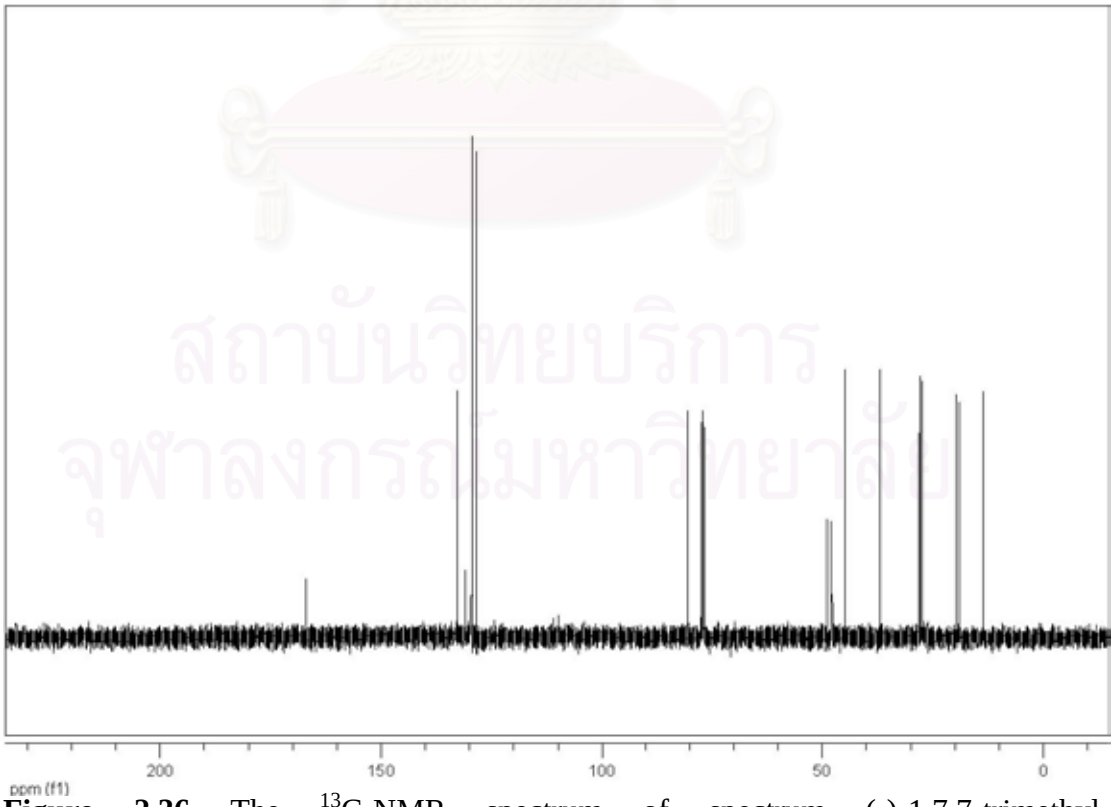
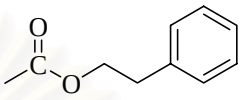
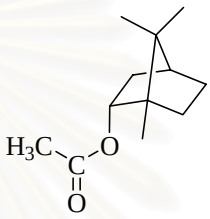
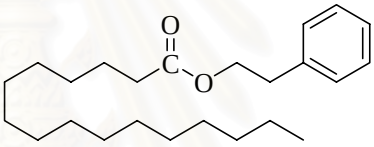
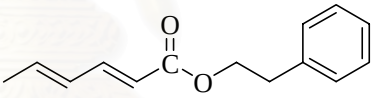
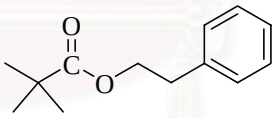
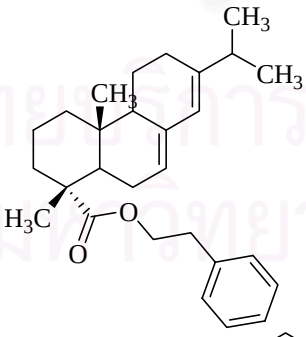
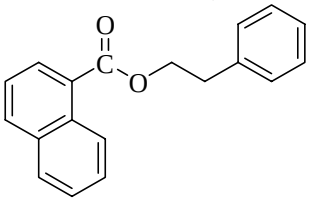


Figure 2.36 The ^{13}C-NMR spectrum of spectrum (-)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl benzoate

2.3.2.2 The Effect of Carboxylic Acids on the Formation of Esters

The preparation of esters was performed on a variety of carboxylic acids to determine the limitations of this method. The results are presented in Table 2.3

Table 2.3 The effect of carboxylic acids for the synthesis of esters

Entry	Starting carboxylic acid	Ester	% Isolated yield
1	acetic acid		59[a]
2	acetic acid		67[b]
3	palmitic acid		74
4	sorbic acid		51
5	pivalic acid		87 (0)[c]
6	abietic acid		34
7	naphthalic acid		68

[a] 1.2 equiv of acetic acid was used, [b] 2 equiv of acetic acid was used, [c] room temperature in step II

Treating PPh_3/Cl_3CCONH_2 with acetic acid and phenethyl alcohol furnished the formation of phenethyl acetate in moderate yield (59%, entry 1). To try to lift up the yield of the desired acetate ester, the amount of acetic acid (2 equiv) was increased to react with (+)-borneol under the reaction conditions. Unfortunately, the acetate esters were isolated only in moderate yields similar to the case of phenethyl acetate. This may be because acetyl chloride formed was volatile resulting in the limited amount of acetyl chloride to react with alcohol. Therefore, the preparation of acetate ester still needed to optimize the reaction conditions. For example, the increase of the amount of either acetic acid or other reagents. Treatment of palmitic acid, a long chain aliphatic carboxylic acid, with Cl_3CCONH_2 and PPh_3, followed by phenethyl alcohol furnished the formation of the corresponding ester in high yield (74%, entry 3). In the case of sorbic acid, the desired ester was attained in moderate yield (51%, entry 4). The attempt to establish the convenient procedure to prepare acetate derivatives was carried out. Satisfyingly, the reaction of tertiary carboxylic acid such as pivalic acid can proceed smoothly to gain the corresponding ester in high yield (87%, entry 5). In addition, when the reaction was performed at room temperature in step II, no desired ester was attained. The capability of this developed protocol to manipulate the ester directly from tertiary carboxylic acid made this system far superior to certain systems [42]. Another tricyclic compound containing both tertiary carboxylic acid and two olefinic groups, abietic acid, was selected as a chemical probe. This compound was allowed to react with phenethyl alcohol under the standard conditions utilized in the presence of Cl_3CCONH_2/PPh_3. The corresponding ester was obtained in 34% isolated yield along with recovered substrate (60%). Even the lower yield was obtained propably because of steric hindrance of the starting carboxylic acid, the other functional group present was not interfered the formation of the ester. In order to improve the yield of target molecule, the system needed some modification such as the increment of the ratio of Cl_3CCONH_2/PPh_3 or reaction time. Finally, in the case of naphthalic acid being employed, the corresponding ester was afforded in moderate yield (68%, entry 7).

Esters prepared in this study were characterized by ^{1}H- and ^{13}C-NMR. The ^{1}H-NMR spectrum of phenethyl acetate (Fig 2.37) presented a singlet signal of methyl groups at δ_H 2.04. Two triplet signals at δ_H 2.94 (J= 6.80 Hz) and 4.28 (J= 6.80 Hz) of aliphatic protons were ascribed to four protons of two ethyl groups. A multiplet signal at δ_H 7.21-7.33 was due to five aromatic protons. The ^{13}C-NMR spectrum of this compound (Fig 2.38) displayed a peak at δ_C 20.9 of methyl group. Two peaks at δ_C 35.1 and 64.9 belonging to two ethyl groups were observed. Four signals at δ_C 126.5-137.8 were assigned for six carbons of aromatic ring. The peak at δ_C 171.0 was indicated to a carbonyl carbon of ester.

The ^{1}H-NMR spectrum of (-)-2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-ethyl acetate (Fig 2.39) displayed four singlet signals of three methyl groups of borneol and a methyl group of acetate at δ_H 0.82- 0.90 and 2.06 respectively. The signals around δ_H 1.25-2.35 were ascribed to seven protons of borneol group. The doublet of doublet signal at δ_H 4.88 was indicated to a proton on a carbon connecting with oxygen atom. The^{13}C-NMR spectrum of this compound (Fig 2.40) exhibited eleven signals around δ_C 13.5-79.9, indicating the presence of nine aliphatic carbons of borneol and acetyl groups. The peak at δ_C 171.5 was a carbonyl carbon of ester.

The ^{1}H-NMR spectrum of phenethyl palmitate (Fig 2.41) showed two triplet signals at δ_H 0.87 (J= 6.40 Hz) and 2.28 (J= 7.60 Hz) of methyl group and two protons on a carbon connecting with a carbonyl of palmitate, respectively. The presence of a singlet signal at δ_H 1.25 could be assigned for twenty four protons of palmitate group. Two triplet signals of two ethyl groups of phenethyl alcohol were observed at δ_H 2.93 (J= 6.80 Hz) and 4.29 (J= 6.80 Hz). The signals around δ_H 7.21-7.30 were typical of five aromatic protons. The^{13}C-NMR spectrum of this compound(Fig 2.42) contained fifteen peaks at δ_C 14.1-34.3 and two peaks at δ_C 35.1-64.7 respectively, which were indicative of carbons of palmitate and two ethyl groups respectively. Four signals at δ_C 126.5-137.9 and 173.8 were assigned for six sp^2 carbons of aromatic ring and a carbonyl carbon, respectively.

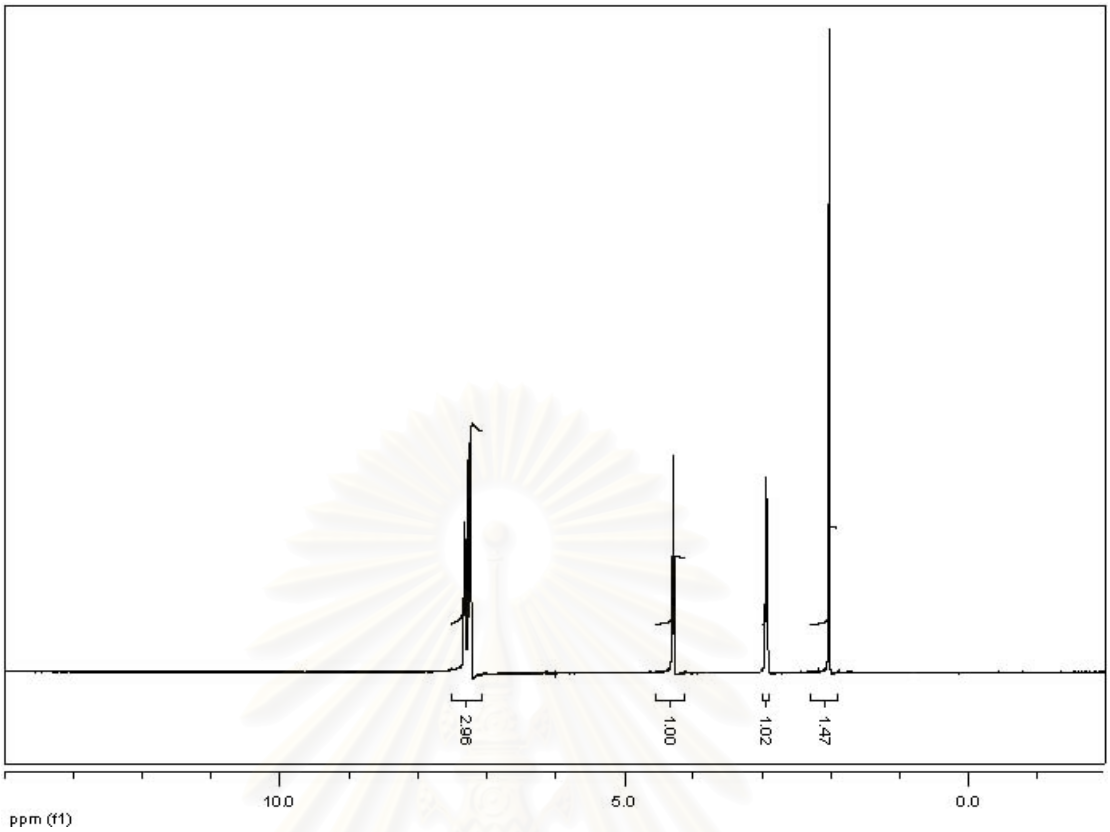


Figure 2.37 The ^{1}H-NMR spectrum of phenethyl acetate

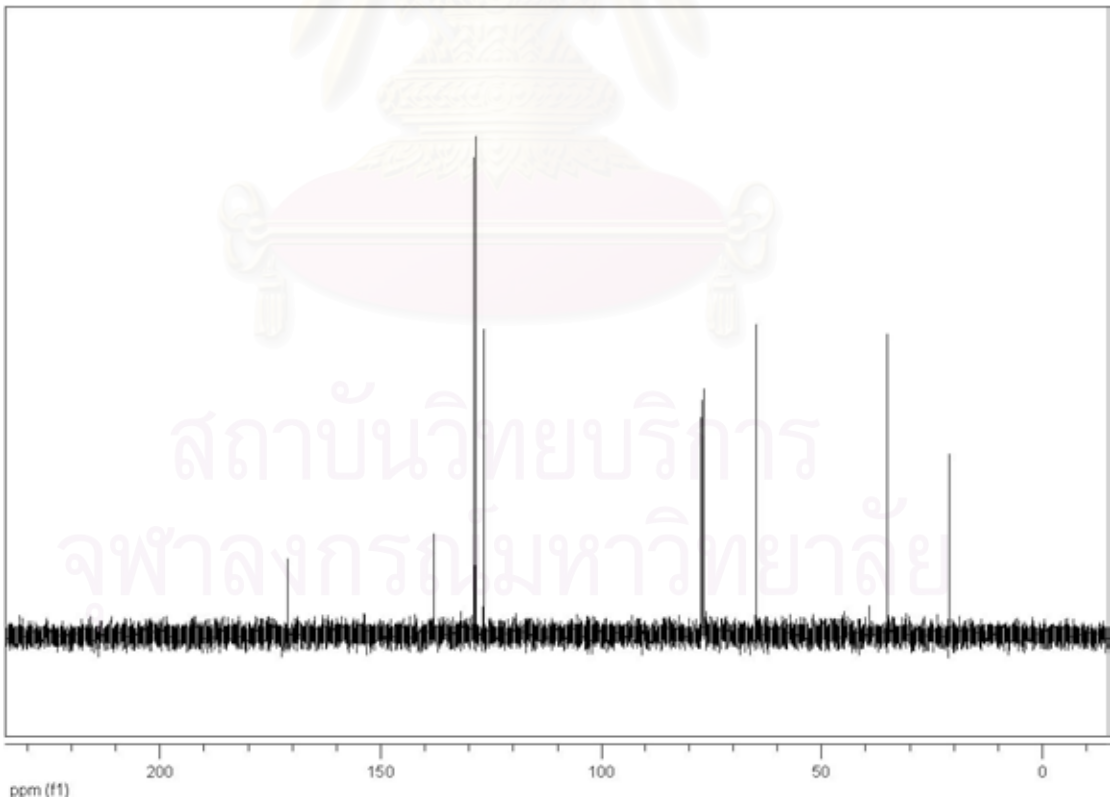


Figure 2.38 The ^{13}C-NMR spectrum of phenethyl acetate

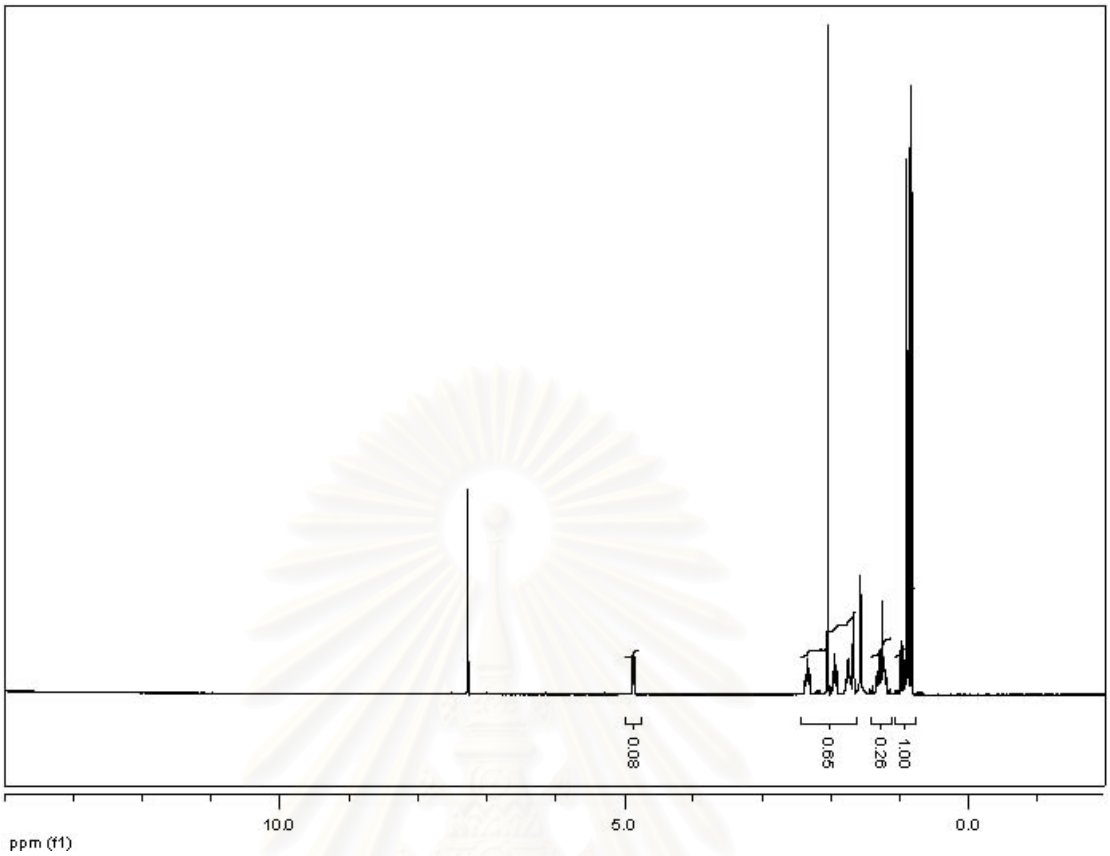


Figure 2.39 The ^{1}H-NMR spectrum of (-)-2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-ethyl acetate

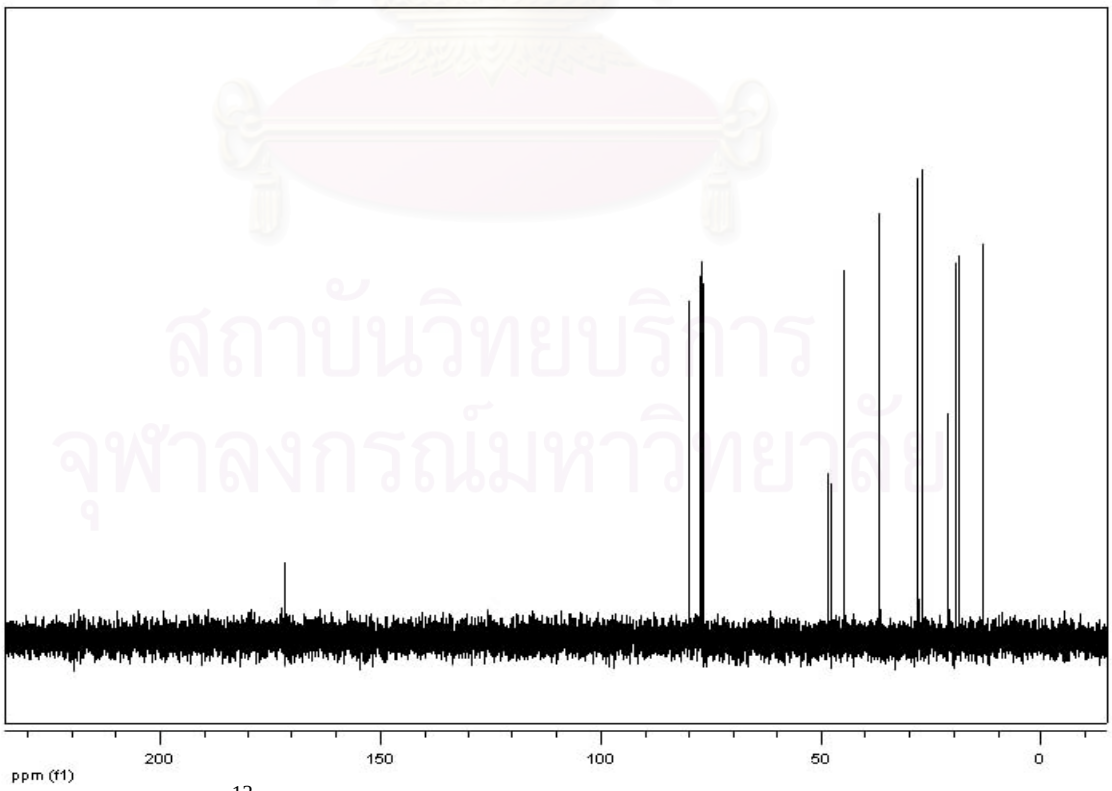


Figure 2.40 The ^{13}C-NMR spectrum of (-)-2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl)-ethyl acetate

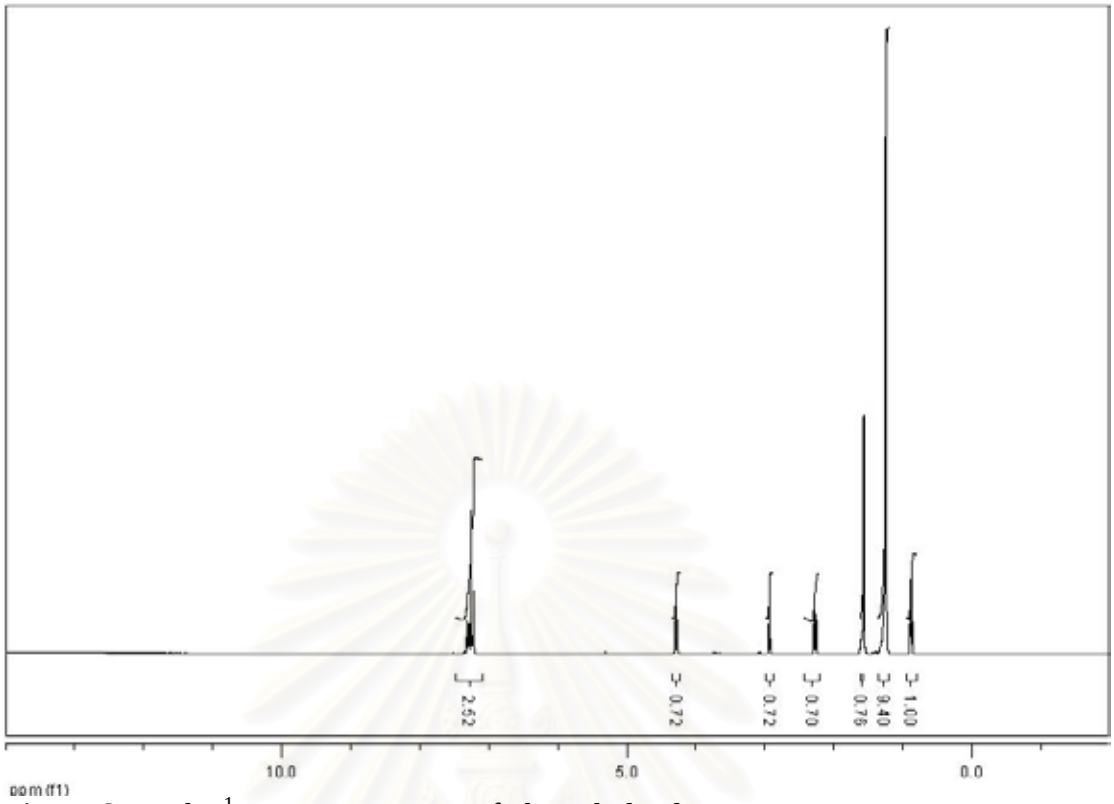


Figure 2.41 The ^{1}H-NMR spectrum of phenethyl palmitate

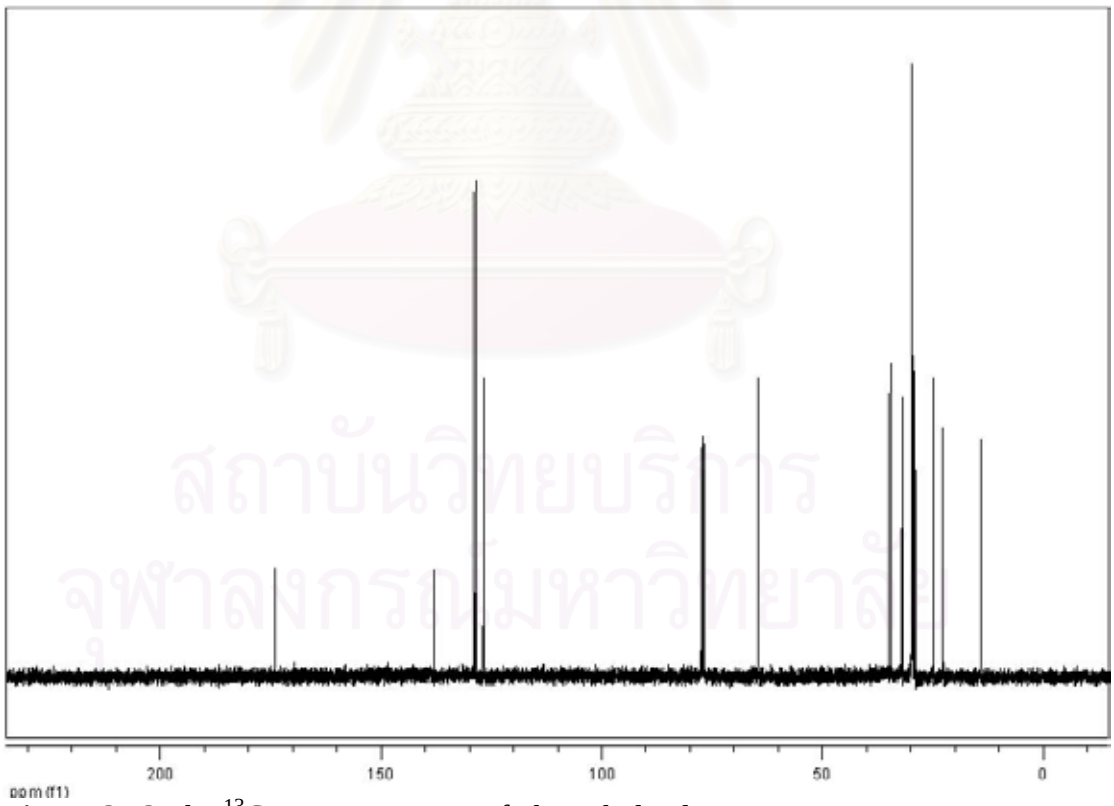


Figure 2.42 The ^{13}C-NMR spectrum of phenethyl palmitate

The ^{1}H-NMR spectrum of phenethyl sorbate (Fig 2.43) displayed a doublet signal at δ_H 1.85 (*J*= 5.60 Hz) of methyl group. A pair of triplet signals at δ_H 2.98 (*J*= 6.80 Hz) and δ_H 4.35 (*J*= 6.80 Hz) was assigned to four protons of two methylene groups. An olefinic proton on a carbon next to a carbonyl group was observed from the presence of doublet signal at δ_H 5.75 (*J*= 15.60 Hz). Other three olefinic protons were detected as a triplet signal (*J* = 9.20 Hz) at δ_H 6.20 and a multiplet signal at δ_H 7.31. Five aromatic protons were assigned for a multiplet signal at δ_H 7.23-7.27.

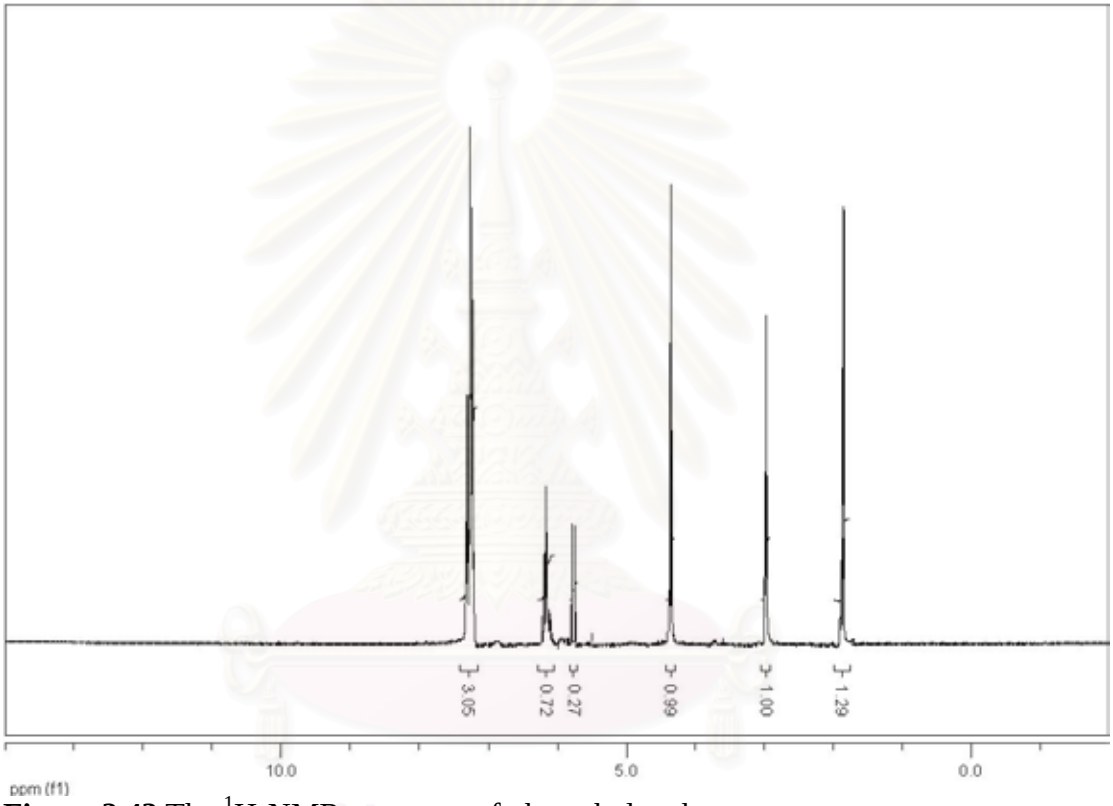


Figure 2.43 The ^{1}H-NMR spectrum of phenethyl sorbate

The ^{1}H-NMR spectrum of phenethyl pivalate (Fig 2.44) showed a singlet signal of tertiary butyl group at δ_H 1.16. Two triplet signals of two ethyl groups appeared at δ_H 2.94 (*J*= 6.80 Hz) and 4.27 (*J*= 6.80 Hz). A multiplet signal could be ascribed for five aromatic protons. The ^{13}C-NMR spectrum of this compound (Fig 2.45) displayed two peaks at δ_C 27.2 and 38.1 belonging to methyl carbon and quaternary carbon of tertiary butyl group, respectively. Two peaks at δ_C 35.1 and 64.8 of two ethyl groups and four signals at δ_C 126.4-137.9 for six carbons of aromatic ring could be fitted assigned. The peak at δ_C 178.5 indicated a carbonyl carbon of ester.

The ^{1}H-NMR spectrum of phenethyl abietate (Fig 2.46) showed a multiplet signals around δ_H 0.81-1.71 of abietyl group. Two triplet signals of two methylene groups of phenethyl alcohol were observed at δ_H 2.91 (*J*= 6.80 Hz) and 4.24 (*J*= 6.80 Hz). The presence of a doublet (*J*= 4.00 Hz) signal at δ_H 5.40 and a singlet signal at δ 5.78 could be assigned for two olefinic protons of abietic group. The signals around δ_H 7.21-7.30 were typical of five aromatic protons. The^{13}C-NMR spectrum of this compound (Fig 2.47) contained sixteen peaks at δ_C 14.0-65.1, indicating of carbons of abietic ester and two methylene groups, respectively. The signals around δ_C 120.7-145.1 and 178.4 were assigned for ten aromatic carbons and a carbonyl carbon, respectively.

The ^{1}H-NMR spectrum of phenethyl 1-naphthoate (Fig 2.48) exhibited the signals around δ_H 7.26-8.81, indicating the presence of twelve aromatic protons. Two triplet signals at δ_H 3.15 (*J*= 6.80 Hz) and 4.64 (*J*= 6.80 Hz) were ascribed for four protons of two methylene groups. The ^{13}C-NMR spectrum of this compound (Fig 2.49) contained two peaks at δ_C 35.3 and 65.7 of two methylene groups. The signals around δ_C 124.5-140.0 could be assigned for sixteen carbons of phenyl and naphthalene groups. The peak at δ_C 165.6 indicated a carbonyl carbon of ester.

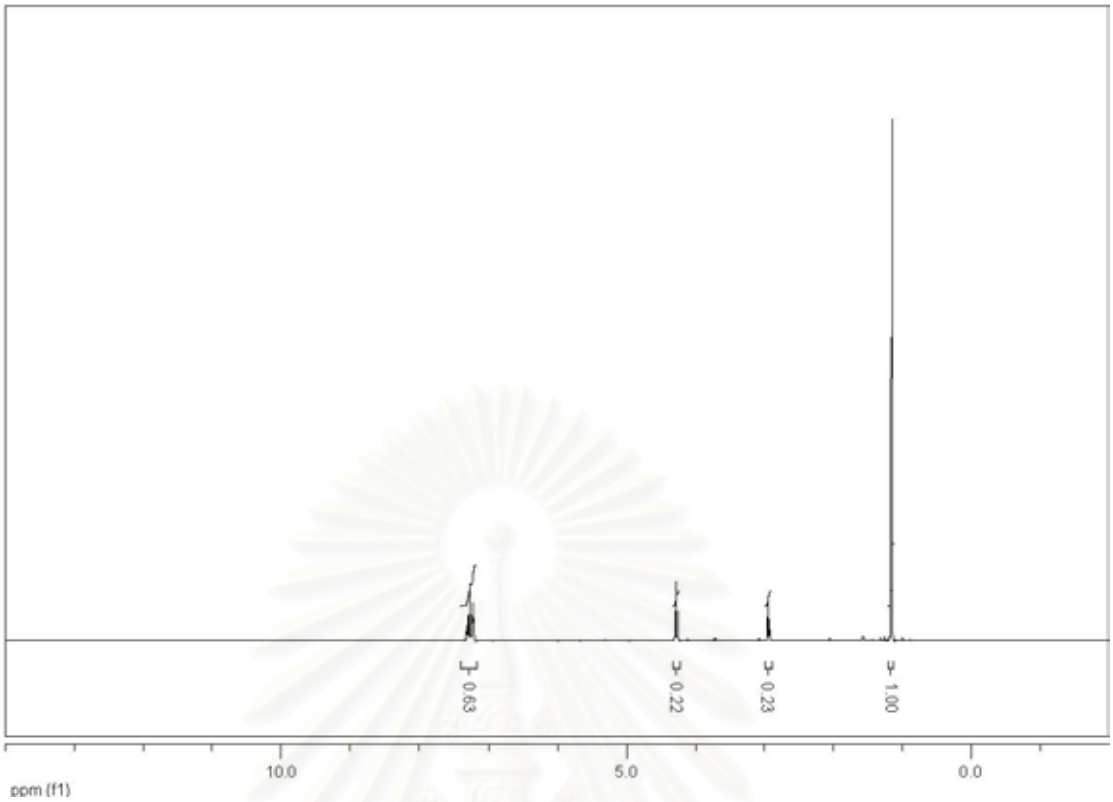


Figure 2.44 The ^{1}H-NMR spectrum of phenethyl pivalate

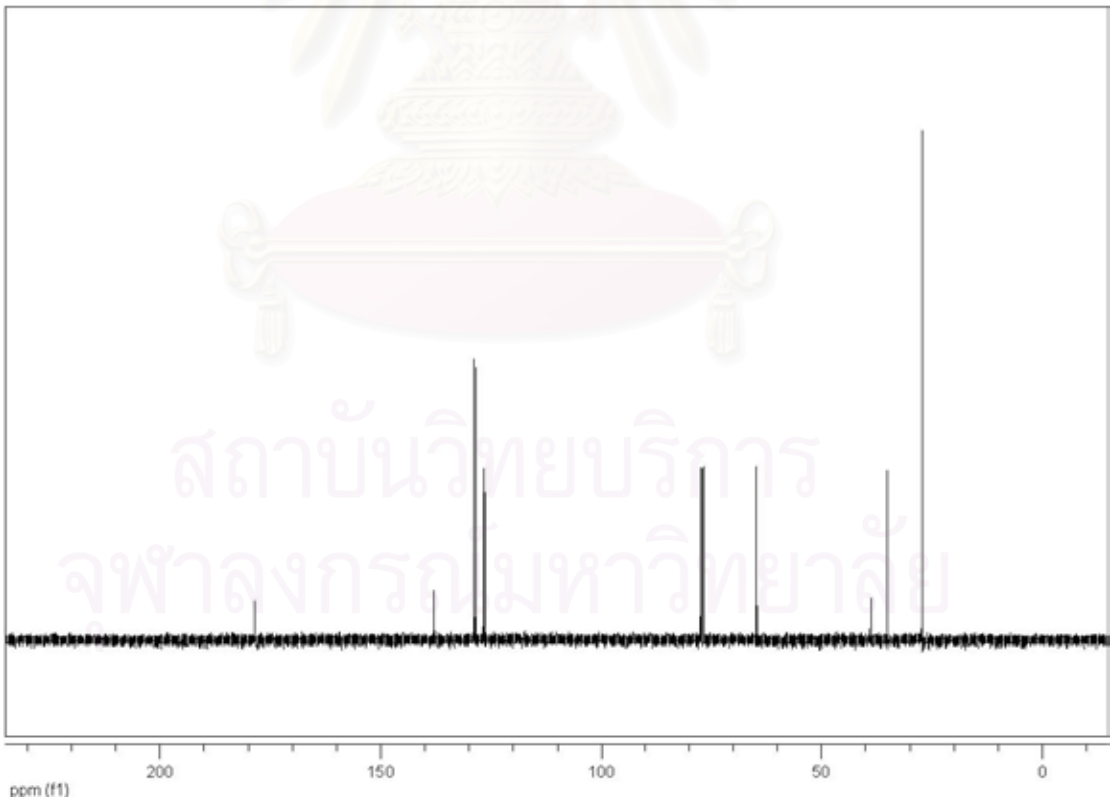


Figure 2.45 The ^{13}C-NMR spectrum of phenethyl pivalate

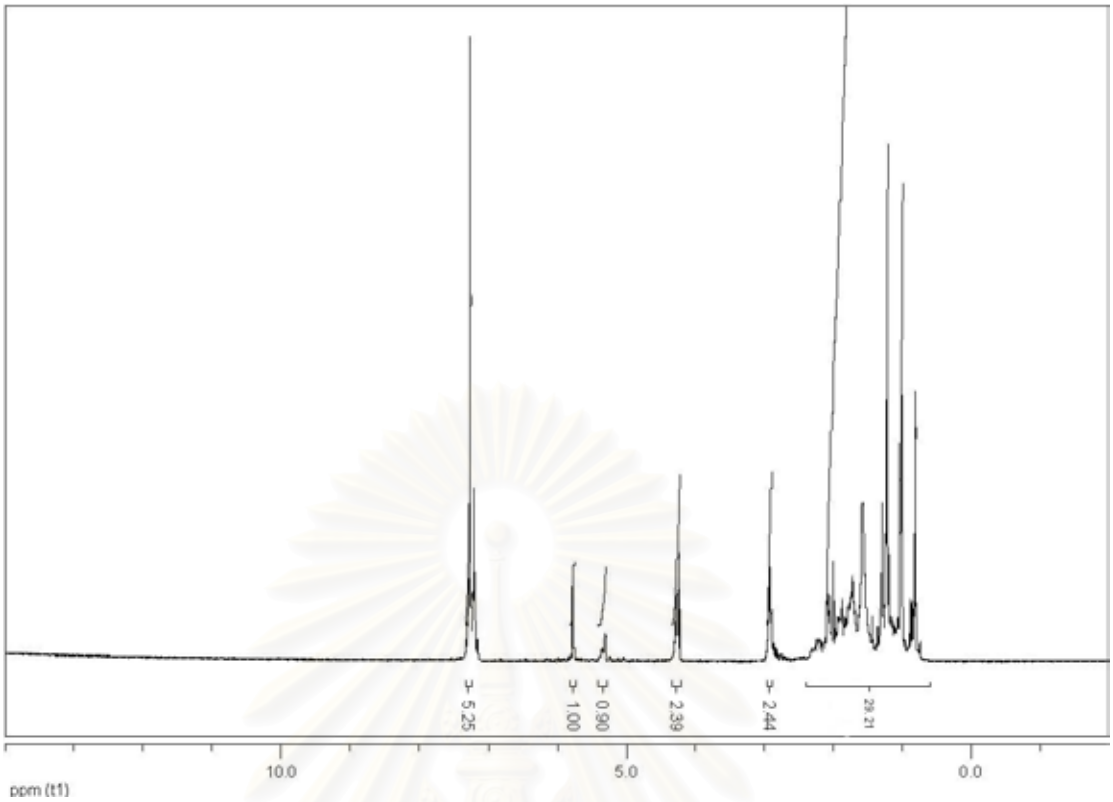


Figure 2.46 The ^{1}H-NMR spectrum of phenethyl abietate

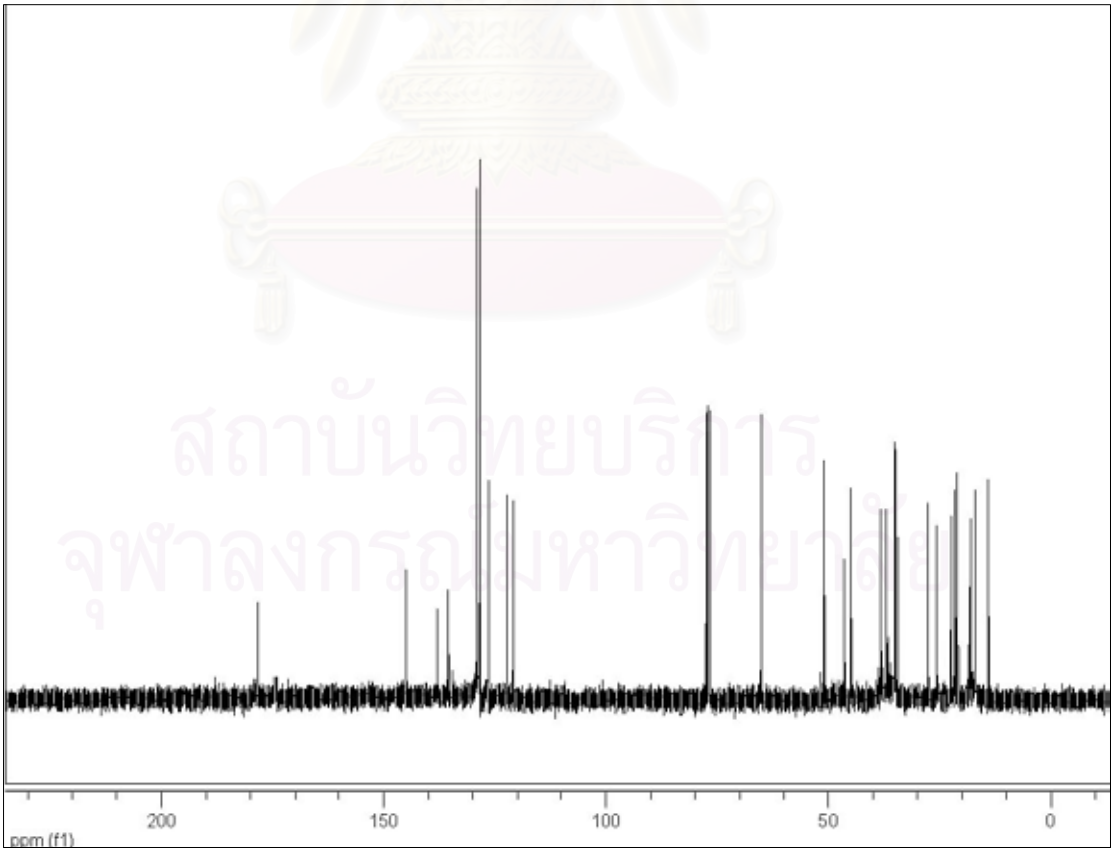


Figure 2.47 The ^{13}C-NMR spectrum of phenethyl abietate

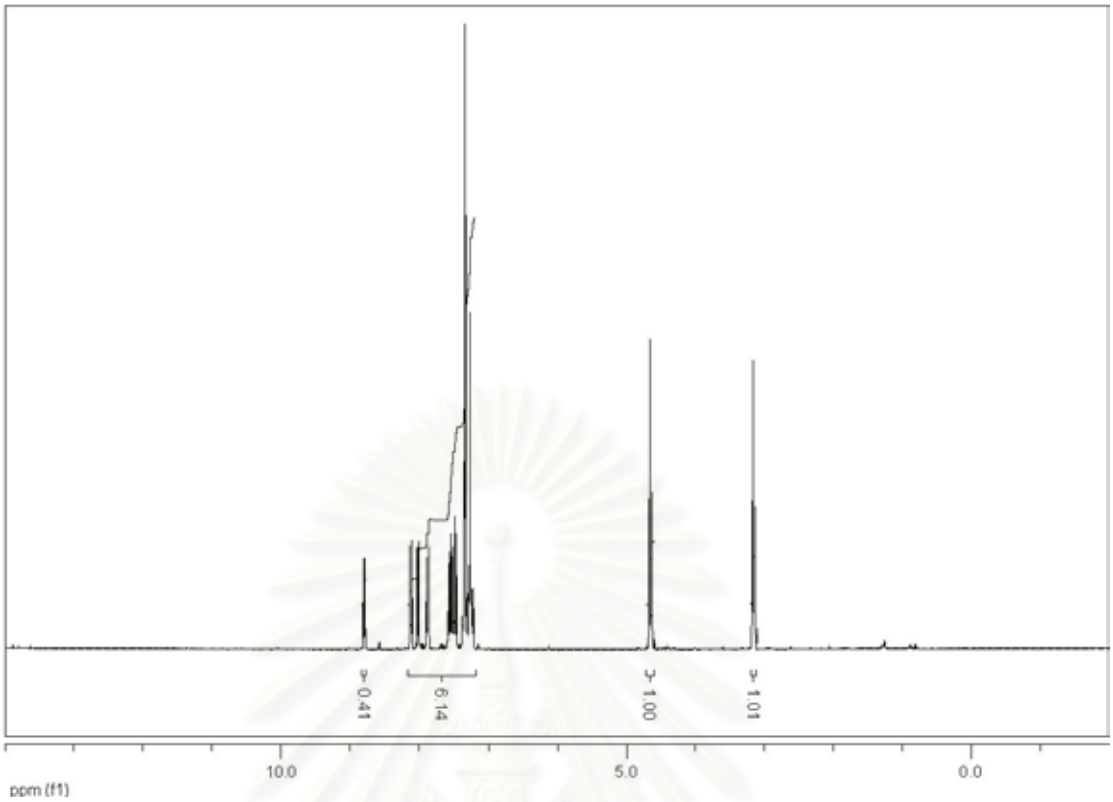


Figure 2.48 The ^{1}H-NMR spectrum of phenethyl 1-naphthoate

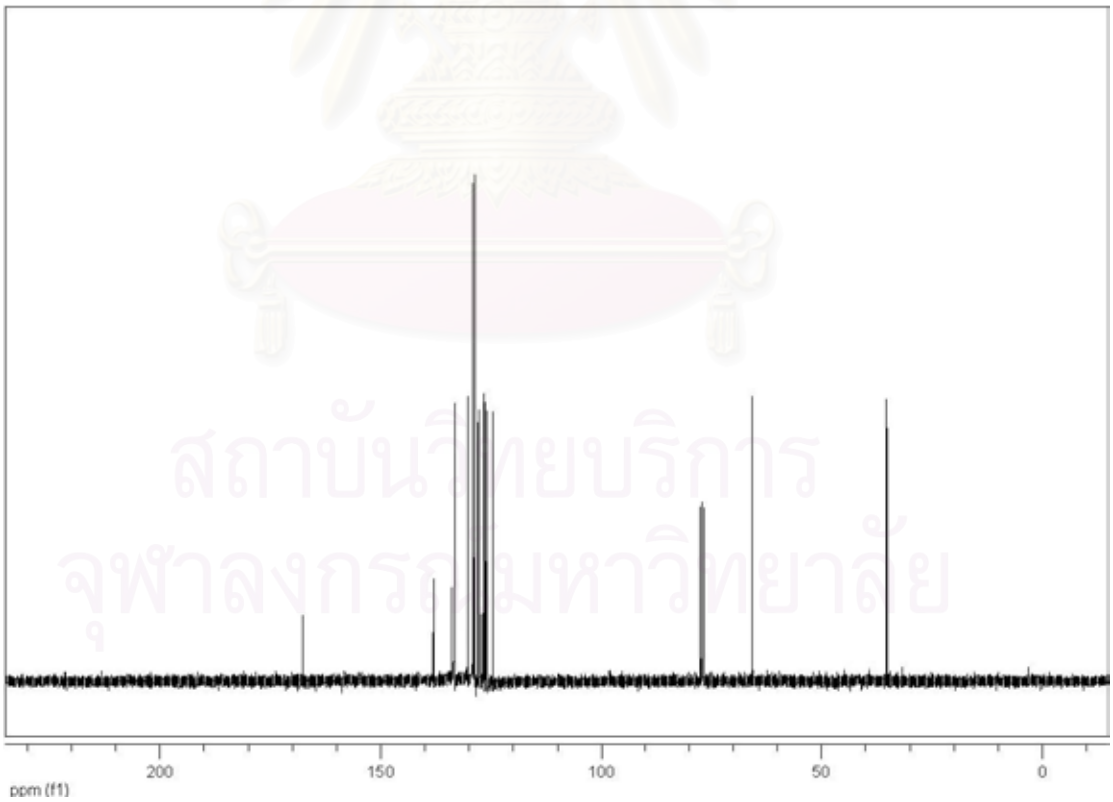


Figure 2.49 The ^{13}C-NMR spectrum of phenethyl 1-naphthoate

2.4 Mechanistic Studies

Identification of the intermediates in this reaction was a major objective of studying the reaction mechanisms. IR, ^{1}H- and ^{13}C-NMR spectroscopy were selected to confirm the presence of acyl chloride under these particular conditions. Cl_3CCN was selected to replace Cl_3CCONH_2 to avoid the shade from C=O peak.

2.4.1 Using IR Spectroscopy

The reaction conditions employed to examine the presence of acyl chloride was similar to the general procedure: 1 mmol of benzoic acid, 2 mmol of Cl_3CCN and 2 mmol of PPh_3 were carried out in CH_2Cl_2 at reflux temperature for 1 h. The reaction was ceased by evaporating all reaction mixture *in vacuo*. PPh_3 and $O{=}PPh_3$ were separated from the reaction mixture by filtration through celite eluting with *n*-hexane. The mother liquor was evaporated *in vacuo* and the crude mixture was then characterized by spectroscopic methods.

The IR spectrum of benzoic acid displayed the strong C=O stretching vibration at 1691 cm^{-1} (Fig 2.50 (a)). The strong stretching absorption peak of the C=O was shifted to 1772 cm^{-1} in the case of the reaction mixture derived from the reaction performed (Fig 2.50 (b)). This strong peak was well-corresponded to that of commercially available benzoyl chloride in Fig 2.50(c).

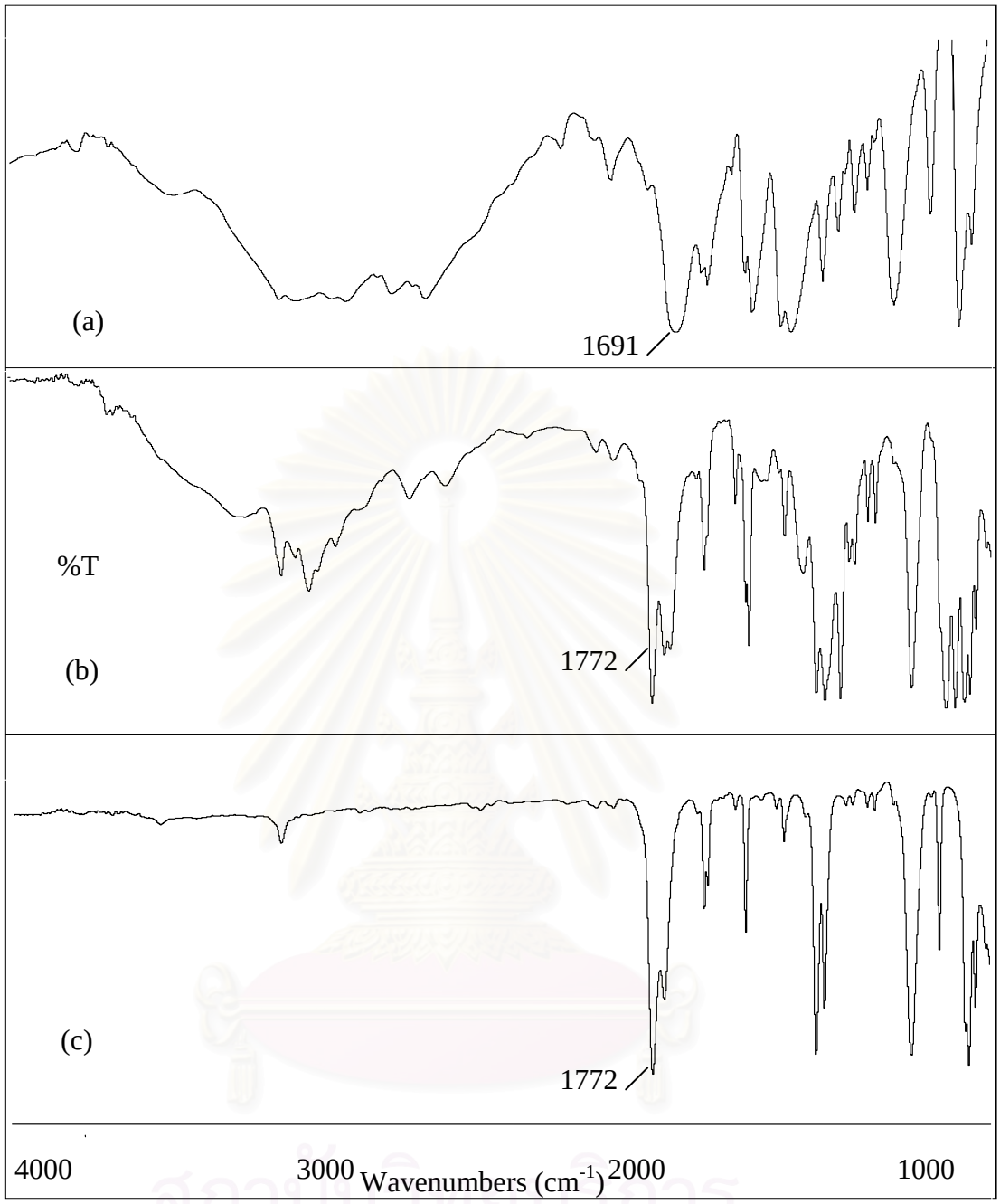


Figure 2.50 The IR spectra of (a) benzoic acid (b) the reaction mixture of benzoic acid, Cl_3CCN and PPh_3 (c) commercial benzoyl chloride

2.4.2 Using ^{13}C-NMR Spectroscopy

The same reaction mixture conducted in 2.4.1 was further examined using ^{13}C-NMR spectroscopy.

The ^{13}C-NMR spectrum of the reaction mixture in Fig 2.51(b) revealed a signal of carbonyl carbon at δ_C 168.4 which was well-coincided with that of benzoyl chloride in Fig 2.51(c) whereas the carbon signal of benzoic acid was detected at δ_C 172.3 (Fig 2.51(a)).

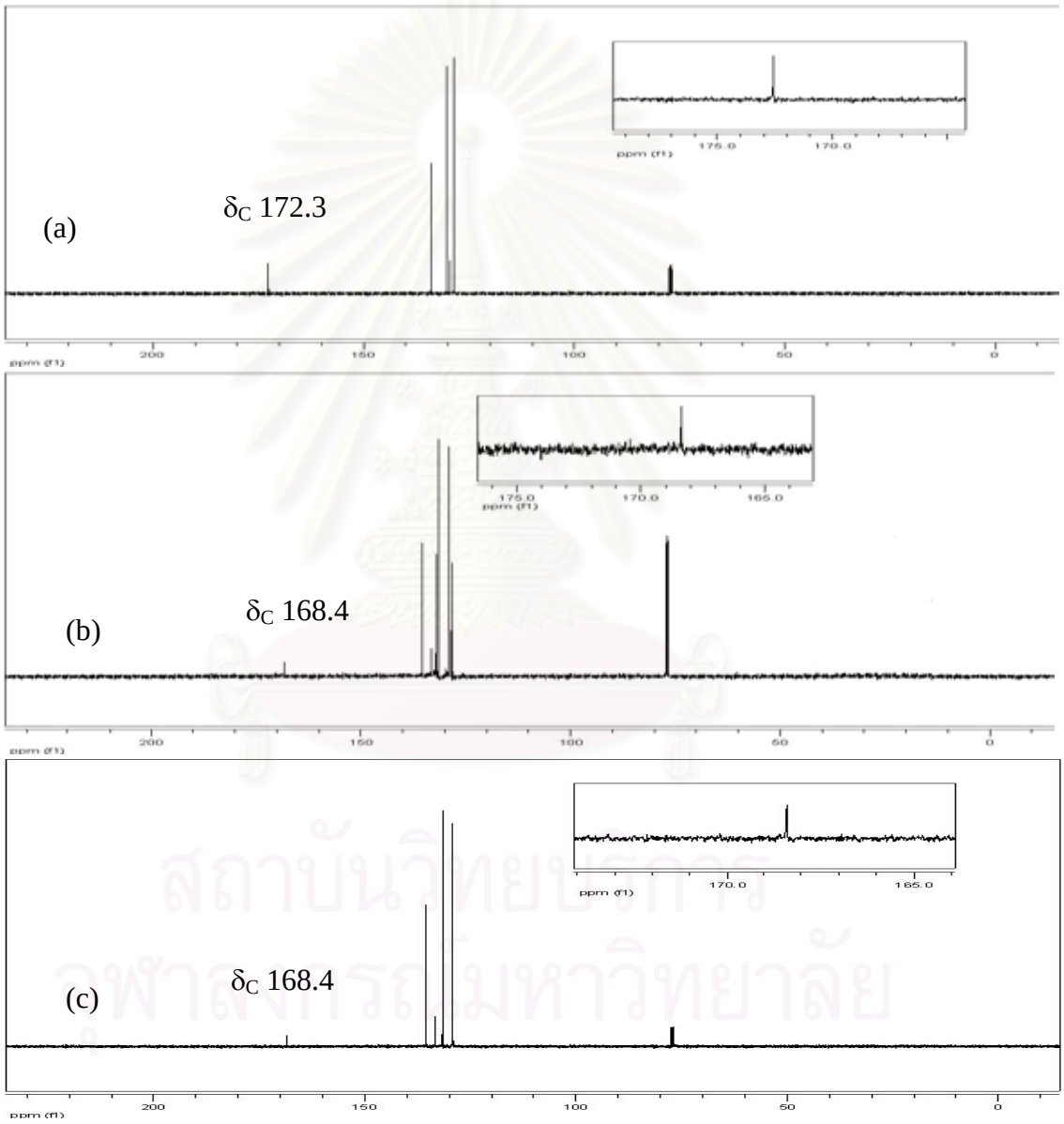


Figure 2.51 The ^{13}C-NMR spectrum (a) benzoic acid (b) the reaction mixture of benzoic acid, Cl_3CCN and PPh_3 (c) commercial benzoyl chloride

2.4.3 Using ^{1}H-NMR Spectroscopy

4-Chlorophenylacetic acid was selected as a model compound. After treating with Cl_3CCONH_2/PPh_3 at room temperature for 20 min, the reaction mixture was brought in the ^{1}H-NMR experiments. The shift of a singlet methylene signal of 4-chlorophenylacetic acid and its chloride were manifestly observed and % yield was determined from ^{1}H-NMR technique by utilizing toluene as an internal standard. The results are summarized in Table 2.4.

Table 2.4 Effect of the ratio of Cl_3CCONH_2 and PPh_3

Entry	Cl_3CCONH_2 (equiv)	PPh_3 (equiv)	%Acyl chloride	%Recovered acid
1	2	0	0	100
2	1	1	11	66
3	2	2	72	14
4	3	3	57	29

Reaction condition: 4-chlorophenylacetic acid 0.25 mmol

From Table 2.4, in the absence of PPh_3, all starting material was recovered (entry 1) due to a singlet methylene signal at δ_H 3.50 was only displayed (Fig 2.52(b)). On the other hand, when PPh_3 was employed to couple with Cl_3CCONH_2, the reaction proceeded to offer the corresponding acid chloride (entry 2), monitoring by the new peak occurred at δ_H 4.18 (Figs 2.52(a-c and f)). These results suggested that PPh_3 was involved to the formation of the desired acid chloride. The signal of acid chloride was truly confirmed from the presence of the singlet methylene signal of phenylacetyl chloride at δ_H 4.18 (Fig 2.52(f)) which attained from the reaction of phenylacetic acid and $SOCl_2$. In addition, the reaction was examined using several ratios of Cl_3CCONH_2 and PPh_3 to compare yields of acid and its acid chloride. When the ratio of Cl_3CCONH_2 and PPh_3 was increased from 1/1 to 2/2, the yield of the corresponding acid chloride increased (entries 2 and 3). In contrast, the yield of the desired product decreased when the ratio of Cl_3CCONH_2 and PPh_3 increased to 3/3 (entry 4).

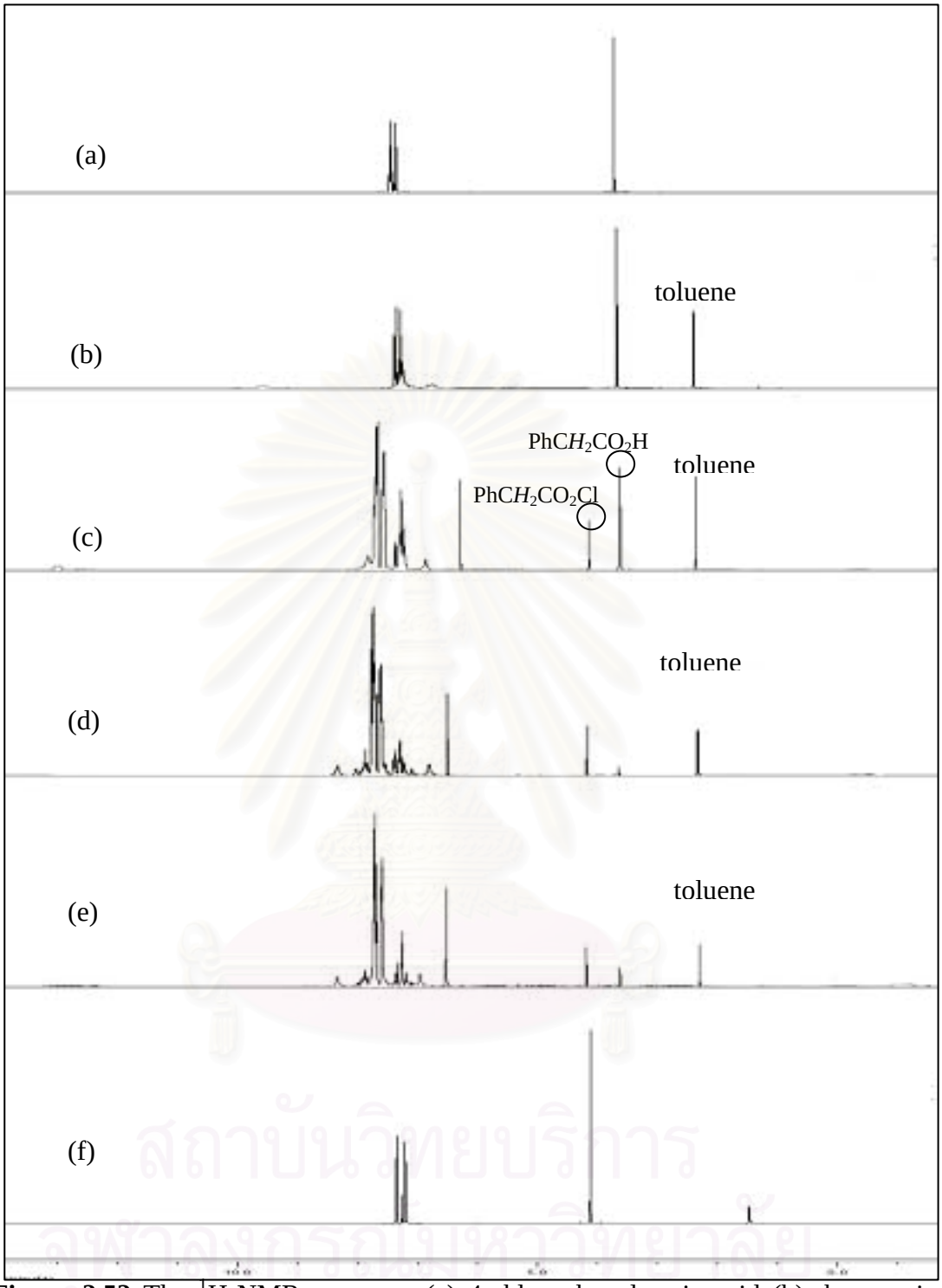


Figure 2.52 The ^{1}H-NMR spectrum (a) 4-chlorophenylacetic acid (b) the reaction mixture of 4-chlorophenylacetic acid 1 equiv and Cl_3CCONH_2 1 equiv (c) the reaction mixture of 4-chlorophenylacetic acid 1 equiv, Cl_3CCONH_2 1 equiv and PPh_3 1 equiv (d) the reaction mixture of 4-chlorophenylacetic acid 1 equiv, Cl_3CCONH_2 2 equiv and PPh_3 2 equiv (e) The reaction mixture of 4-chlorophenylacetic acid 1 equiv, Cl_3CCONH_2 3 equiv and PPh_3 3 equiv (f) 4-chlorophenylacetyl chloride

From IR, ^{13}C-NMR and ^{1}H-NMR studies it could strongly conclude that the combination of halogenated reagent and PPh_3 with carboxylic acid generated acid chloride as the reactive intermediate.

CHAPTER III

APPLICATION OF Cl_3CCN/PPh_3 FOR THE SYNTHESIS OF SULFONAMIDES

3.1 Introduction

Sulfonamide is an organic sulfur compound containing the $-SO_2NR_2$ (the amides of sulfonic acids). Its molecular structure is similar to *p*-aminobenzoic acid (PABA) which is needed in bacteria organisms as a substrate of the enzyme dihydropteroate synthetase for the synthesis of tetrahydrofolic acid. Sulfonamides, derived chiefly from sulfanilamide, are capable of interfering with the metabolic processes in bacteria that require PABA. They act as antimicrobial agents by inhibiting bacterial growth and activity and called sulfa drugs. They are used in the prevention and treatment of bacterial infections, diabetes mellitus, edema, hypertension, and gout. Furthermore, some of them have proved to be useful as herbicides [43] and plaguicides [44]. In addition, arylsulfonyl substituents have been used as protecting groups for oxygen and nitrogen functionalities [45]. Sulfonamide derivatives of azo dyes have been reported to achievely improve light stability, and fixation to fiber [46]. These aforementioned activities have increased the interest in the synthesis of sulfonamides.

3.1.1 Classical methods for the synthesis of sulfonamides

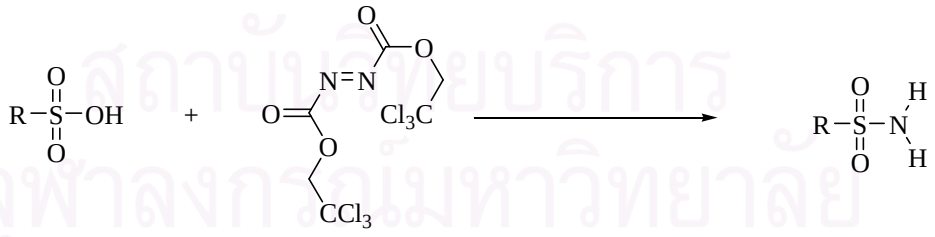
The most commonly used synthetic methods to manipulate sulfonamides involve nucleophilic attack by ammonia, or primary or secondary amines, with sulfonyl halides in the presence of base. Although this method is efficient, it requires the availability of sulfonyl halide. Some of which are hard to prepare and difficult to store or handle. Side reactions are also possible due to the presence of base or liberated chloride nucleophile, particularly under harsh conditions with relatively nonnucleophilic substrates. Moreover, the corresponding disulfonimide is stated to be a by product in a reaction of sulfonyl halides with primary amines or ammonia.

3.1.2 Literature Review on Other Approaches for the Synthesis of Sulfonamides

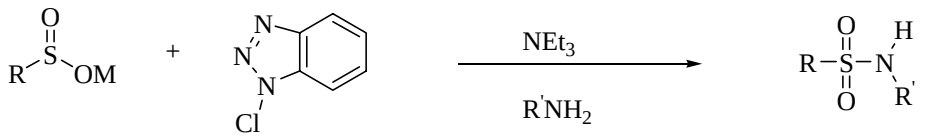
A wide variety of methods have been reported for the preparation of sulfonamides. For example, by the reaction of sulfinic acid and its salts: Graham and Scholz [47] in 1986 addressed that primary sulfonamides could be obtained by reacting sulfinic acid salts with an electrophilic nitrogen source as hydroxylamine-*O*-sulfonic acid. This reaction proceeded in good yields using acetate-buffered water as the solvent. Moreover, this process avoids the preparation of frequently labile sulfonyl halides and obviates the troublesome formation of disulfonamides that occasionally occurs during the ammonolysis of sulfonyl halides.

This method is not common and this reagent is water-soluble and sparingly soluble in organic solvents, resulting in a major drawback for hydrophobic compounds.

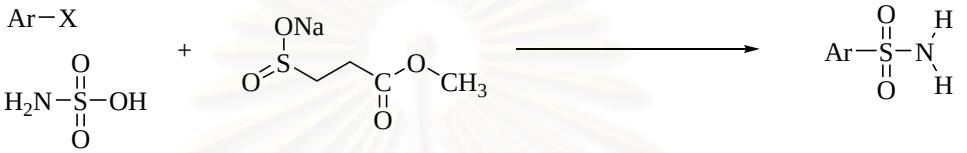
Chan and Berthelette [48] in 2002 developed the formation of sulfonamides from the corresponding sulfinates using *bis*(2,2,2-trichloroethyl)-azodicarboxylate as electrophilic nitrogen source. The intermediate sulfonylhydrazides were obtained in good yield and were cleaved under reductive conditions to deliver the desired sulfonamides in a two-step sequence.



Katritzky, Garcia and Nair [49] in 2004 reported an one-pot reaction of sulfinic acid salts with *N*-chlorobenzotriazole yielding the corresponding *N*-alkane-, *N*-arene-, and *N*-heteroenesulfonylbenzotriazoles in 41-93% yields. These reagents could proceed to react at 20-80 ^{o}C with various primary and secondary aliphatic amines to yield the corresponding sulfonamides in 64-100% yields.



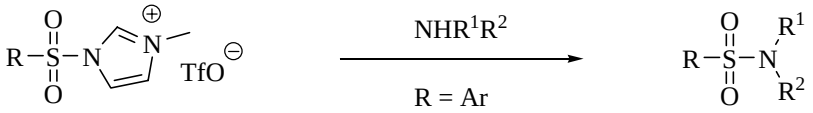
Baskin and Wang [50] in 2002 reported a general, mild and convenient strategy for the synthesis of various alkyl and aryl sulfinic acid salts and sulfonamides from the corresponding halides by means of sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS). This reagent can be served as a donor for the sulfinate moiety directly to the substrate.



Reactions of sulfinic acid and its salts are particularly attractive due to the mildness of the reaction conditions and the possibility to introduce the sulfonamide group at the later stage of a multistep synthesis. However, the success of the process relies on the availability of the required sulfinic acid salt. The existing synthetic approaches of sulfinic acid salts either involve the use of organolithium or Grignard reagents, which are incompatible with a host of functional groups, or involve tedious multi-step syntheses. Furthermore, the purity of the sulfinates is not sufficiently high due to an inability to isolate the hygroscopic salt.

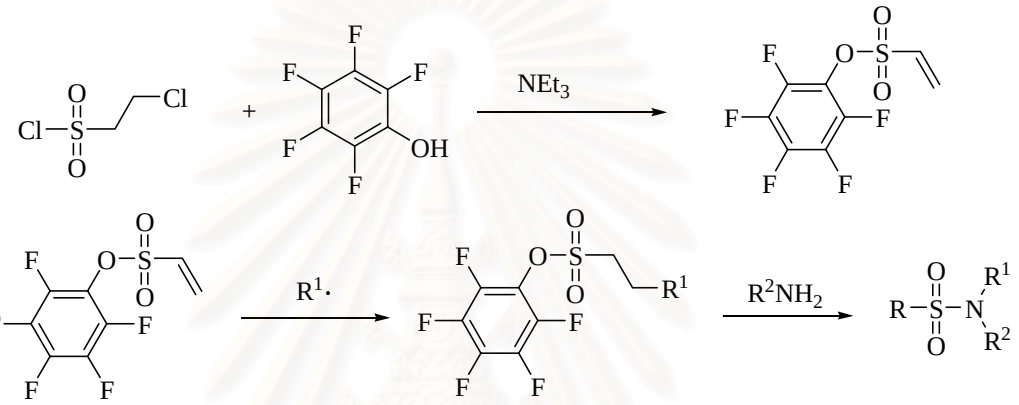
According to the mentioned literature reviews, it has clearly been seen the evidence of the development of several alternative protocols for sulfonamide synthesis. However, sulfonamides could also be prepared from other manners. For example, Tsunoda and co-workers in 1996 [51] reported the use of cyanomethylenetributylphosphorane (CMBP) under Mitsunobu conditions to furnish N-substituted sulfonamides in excellent yields.

O´Connell and Rapoport in 2002 [45] synthesized arylsulfonamides from arylsulfonylimidazoles, prepared from sulfonyl halides and 1*H*-imidazoles or 1-trimethylsilylimidazole.

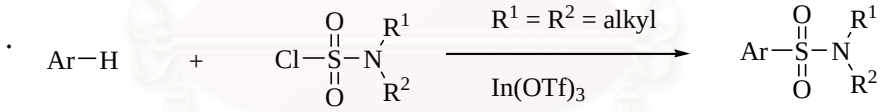


However, the imidazole ring requires activation as its 3-methylimidazolium triflate to act as a leaving group in its reaction with *N*- and *O*-nucleophiles.

Caddick and co-workers in 2002 [52] prepared sulfonamides by the intermolecular radical addition of organohalides to pentafluorophenyl vinylsulfonate follwed by substitution of pentafluorophenyl moiety with amines.



Frost, Hartley and Griffin [53] in 2002 presented the synthesis of aryl sulfonamides using an indium catalyzed sulfamoylation process.



Although several synthetic methods for sulfonamides have been developed, there remains a need for straightforward and general methods towards accessing sulfonamides. It would be highly desirable to have a method that would react under mild conditions in the absence of a strong base or competing nucleophile. Therefore, this research aimed at developing the methodology for the synthesis of sulfonamides using halogenated reagent and PPh_3.

3.2 Experimental

3.2.1 Instruments and Equipment

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminium

sheets pre-coated with silica gel (Merck's, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck's silica gel 60 G Art 7734 (70-230 mesh)).

The IR spectra were recorded on Nicolet model Impact 410 FT/IR spectrophotometer. Solid samples were incorporated into a pellet of potassium bromide. Liquid samples were dropped on sodium chloride plates. The ^{1}H- and ^{13}C-NMR spectra were performed in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference on Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H and 100.54 MHz for ^{13}C nuclei. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

3.2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology. The reagents used for synthesis were purchased from Fluka chemical company or otherwise stated and were used without further purification.

3.2.3 General Procedure for the Synthesis of Sulfonamides

Step 1: PPh_3 3 eq (3 mmol, 0.79 g) in CH_2Cl_2 3 mL was added to a mixture of sulfonic acid 1 eq (1 mmol) and selected halogenated reagent 3 eq (3 mmol) in CH_2Cl_2 3 mL at reflux temperature. The mixture was stirred for approximately 1 h.

Step 2: A mixture of amine 3 eq (3 mmol) and selected base 9 eq (9 mmol) was added to the above mixture. The reaction was continued stirring for another 1 h or followed by TLC at room temperature. When the reaction was completed, the organic layer was extracted with 1 N HCl and saturated aq $NaHCO_3$, respectively, dried over anh Na_2SO_4 and evaporated *in vacuo*. The mixture was separated with silica gel column chromatography eluting with 9:1 hexane/EtOAc. Purification by recrystallization with a mixture of CH_2Cl_2 and hexane or another appropriate solvent was conducted to achieve the desired sulfonamide products.

3.2.4 Conditions Optimization for the Synthesis of Sulfonamides

3.2.4.1 Effect of Type and Amount of Halogenated Reagent

The synthesis of *N*-cyclohexylbenzenesulfonamide was carried out using the reaction conditions described in the general procedure (base: *4*-picoline), but using

four different halogenated reagents: trichloroacetonitrile (Cl_3CCN), ethyl trichloroacetate (Cl_3CCO_2Et), trichloroacetamide (Cl_3CCONH_2) and ethyl tribromoacetate (Br_3CCO_2Et).

3.2.4.2 Effect of Base

According to the general procedure (halogenated reagent: Cl_3CCN), a base was altered from *4*-picoline to Et_3N, DMAP, imidazole, quinaldine, pyridine and quinoline.

3.2.4.3 Effect of Sovent System

Solvents for the synthesis of *N*-cyclohexylbenzenesulfonamide according to the general procedure (halogenated reagent: Cl_3CCN, base: *4*-picoline) were varied from CH_2Cl_2 to chloroform, acetonitrile, THF, EtOAc and 1,2-dichloroethane.

3.2.4.4 Variation of Amine

The general procedure using Cl_3CCN, *4*-picoline and CH_2Cl_2 as halogenated reagent, base and solvent, respectively at reflux temperature for 1 h was carried out. Different amines: *n*-butylamine, *iso*-butylamine, phenethylamine, diethylamine, aniline and methyl alanine ester were employed instead of cyclohexylamine.

3.2.4.5 Variation of Sulfonic Acid

The reaction was carried out using reaction conditions described in 3.2.4.4, but different sulfonic acids: methanesulfonic acid, *4*-toluenesulfonic acid monohydrate, trifluoromethanesulfonic acid and camphor-10-sulfonic acid were employed instead of benzenesulfonic acid.

3.2.5 Synthesis of Target Molecules

***N*-Cyclohexylbenzenesulfonamide:** [54] yellow liquid (quant), R_f 0.57 (50% EtOAc/hexane). IR (neat): 3276, 3058, 1587, 1439, 1318 and 1150 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm):1.13-1.74 (10H, m, alkyl group), 3.13 (1H, quin, *J* = 4.00 Hz, NHC*H*), 4.83 (1H, d, *J* = 7.60 Hz, N*H*) and 7.24-7.75 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.6, 25.1, 33.8 and 52.7.

***N*-Butylbenzenesulfonamide:** [55] yellow liquid (83%), R_f 0.48 (50% EtOAc/hexane). IR (neat): 3291, 3068, 2959, 2861, 1445, 1325, 1162 and 1086 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.84 (3H, t, *J* = 7.36 Hz, C*H*$_3$), 1.27 (2H, sex, *J* = 7.60 Hz, C*H*$_2$CH$_3$), 1.43 (2H, quin, *J* = 7.60 Hz, C*H*$_2$CH$_2$CH$_3$), 2.94 (2H, q, *J* = 6.80 Hz, NHC*H*), 4.61 (1H, br s, N*H*) and 7.40-8.00 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.5, 19.6, 31.5, 42.9, 127.0, 129.0, 132.6 and 139.9.

***N*-*iso*-Butylbenzenesulfonamide:** yellow liquid (71%), R_f 0.48 (50% EtOAc/hexane). IR (neat): 3286, 3068, 2954, 2867, 1445, 1320 and 1157 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (6H, d, *J* = 6.80 Hz, C*H*$_3$), 1.71 (1H, m, C*H*$(CH_3)_2$), 2.76 (2H, t, *J* = 6.80 Hz, NHC*H*$_2$), 4.65 (1H, br s, N*H*) and 7.40-8.00 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 19.8, 28.4, 50.54, 126.0, 129.0, 132.5 and 140.0.

***N*-Phenethylbenzenesulfonamide:** [54, 56] white solid (87%), m.p. ^oC CH_2Cl_2-hexane), R_f 0.43 (50% EtOAc/hexane). IR (KBr): 2956, 1446, 1321 and 1155 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.76 (2H, t, *J* = 6.80 Hz C*H*$_2$Ar), 3.22 (2H, q, *J* = 6.80 Hz, NHC*H*$_2$), 4.53 (1H, br s, N*H*) and 7.00-8.00 (10H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 35.8, 44.3, 126.8, 127.0, 128.7, 128.8, 129.1, 133.7, 137.6 and 139.8.

***N*,*N*-Diethylbenzenesulfonamide:** [57] yellow liquid (74%), R_f 0.58 (50% EtOAc/hexane). IR (neat): 3063, 2976, 2932, 1446, 1331, 1157 and 1020 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.12 (6H, t, *J* = 7.20 Hz, C*H*$_3$), 3.23 (4H, q, *J* = 7.20 Hz, NHC*H*$_2$) and 7.47-7.81 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 42.0, 126.9, 129.0, 132.3 and 140.2.

***N*-Phenylbenzenesulfonamide:** [58] yellow liquid (93%), R_f 0.46 (50% EtOAc/hexane). IR (neat): 3259, 3063, 1587, 1407, 1216 and 1086 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.85 (1H, br s, N*H*) and 7.00-7.90 (10H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 121.6, 125.3, 129.0, 129.3, 133.0, 136.4 and 138.9.

***N*-Benzenesulfonylamino-propionic acid methyl ester:** [56] yellow liquid (46%), R_f (50% EtOAc/hexane). IR (neat): 3276, 2945, 1443, 1337, 1162 and 1096 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.38 (3H, d, *J* = 7.20 Hz, CH_2C*H*$_3$), 3.50 (3H, s, OC*H*$_3$), 3.97 (1H, quin, *J* = 7.20 Hz, NHC*H*), 5.25 (1H, d, *J* = 8.80 Hz, N*H*) and 7.45-7.85 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 19.9, 51.5, 52.6, 127.2, 129.1, 132.8, 139.7 and 172.5.

***N*-Phenethylmethanesulfonamide:** [59] yellow liquid (89%), R_f 0.31 (50% EtOAc/hexane). IR (neat): 3023, 2387, 2925, 1423, 1310, 1143 and 1096 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.83 (3H, s, C*H*$_3SO_2$), 2.88 (2H, t, *J* = 6.80 Hz C*H*$_2$Ar), 3.41 (2H, q, *J* = 6.40 Hz, NHC*H*$_2$), 4.53 (1H, br s, N*H*) and 7.20-7.44 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 36.4, 40.2, 44.5, 126.9, 128.8, 128.9 and 137.9.

***N*-Phenethyl-toluene-4-sulfonamide:** [54, 60] yellow liquid (96%), R_f 0.43 (50% EtOAc/hexane). IR (neat): 3275, 3025, 2932, 2861, 1598, 1429, 1320 and 1157

cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.43 (3H, s, C*H*$_3$ArSO$_2$), 2.76 (2H, t, *J* = 6.80 Hz, C*H*$_2$Ar), 3.21 (2H, q, *J* = 6.80 Hz, NHC*H*$_2$), 4.38 (1H, br s, N*H*) and 7.00-7.80 (9H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.53, 35.8, 44.2, 126.8, 127.1, 128.7, 129.7, 136.8, 137.7 and 143.4.

***N*-Phenethyl-10-camphorsulfonamide:** yellow liquid (77%), R_f 0.52 (50% EtOAc/hexane). IR (neat): 3295, 2956, 1598, 1431, 1326, 1143 and 1065 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.80-3.40 (17H, m, camphor group), 2.93 (2H, m, C*H*$_2$Ar), 3.44 (2H, m, NHC*H*$_2$), 5.04 (1H, br s, N*H*) and 7.20-7.40 (5H, m, Ar*H*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 19.5, 19.9, 26.2, 26.9, 36.5, 42.7, 42.9, 44.8, 48.7, 49.3, 58.9, 126.7, 128.7, 128.9 and 138.1. LC-MS (EI) m/e (relative intensity, assignment) 336.2 (41.0, M^+), 212.3 (100, $C_{10}H_{16}SO_2^+$).

3.3 Results and Discussion

The efficient synthesis of sulfonamides using the combination of halogenated reagent and PPh_3 was demonstrated as a novel and facile method. The general equation can be simplified as shown below.

$$RSO_3H \xrightarrow[2)\ RNH_2,\ base]{1)\ \text{halogenated reagents, } PPh_3} RSO_2NHR$$

3.3.1 Conditions Optimization for the Synthesis of Sulfonamides

In order to extend the scope of the utilization of Cl_3CCN for the synthesis of a variety of acid derivatives, the first reaction conditions tried was imitated to those described by Chaysripongkul [11]. That system was consisted of Cl_3CCONH_2 as a halogenated reagent coupled with PPh_3. Nonetheless, the yield of the desired sulfonamides was not appreciable (13%). The improved method was thus needed for the manipulation of sulfonamides. The optimization of the reaction conditions for the formation of sulfonamides including type of halogenated reagent, amount of reagents, type of bases and solvent system was therefore cautiously investigated.

3.3.1.1 Effect of Type and Amount of Halogenated Reagent

For optimizing the reaction conditions, benzenesulfonic acid and cyclohexylamine were used as model substrates. When the former was treated with selected halogenated reagents and PPh_3 in CH_2Cl_2 at refluxing temperature, and then followed by treating with the latter in the presence of *4*-picoline as a base, *N*-

cyclohexylbenzenesulfonamide was obtained as the desired product. The effect of type and amount of halogenated reagents was investigated and the results are accumulated in Table 3.1.

Table 3.1 Effect of type and amount of halogenated reagents on the formation of *N*-cyclohexylbenzenesulfonamide

Entry	Halogenated reagent		PPh_3 (mmol)	% Isolated yield
	Type	Amount (mmol)		
1	Cl_3CCN	1	1	21
2		2	2	67
3		3	3	quant
4		6	6	23
5	Cl_3CCO_2Et	3	3	14
6		6	3	23
7	Cl_3CCONH_2	3	3	20
8		6	6	trace
9		6	3	43
10	Br_3CCO_2Et	3	3	4

reaction conditions: benzenesulfonic acid (1 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol), *4*-picoline (9 mmol)

reaction time: step I at reflux for1 h, step II at room temparature for 1 h.

It was found that only 3 mmol of Cl_3CCN with 3 mmol of PPh_3 were required to convert benzenesulfonic acid to the corresponding sulfonamides quantitatively (entry 3). Indeed when the ratio of Cl_3CCN and PPh_3 was reduced to 1/1, the yield of sulfonamide decreased (entries 1-2). In contrast, the yield of the desired product decreased when the ratio of Cl_3CCN and PPh_3 were increased to 6/6 (entry 4). This may be because the excess of PPh_3 could react with product and led to the formation of unwanted products.

Furthermore, other halogenated reagents were tried in place of Cl_3CCN such as Cl_3CCO_2Et, Cl_3CCONH_2 and Br_3CCO_2Et, the desired sulfonamide was achieved in only a poor yield (entries 5-10). This may be because the nitrile group as an electron-withdrawing group was of much more affinity than ester and amide groups of α-

haloesters and α-haloamides, respectively. Therefore, the most reactive of halogenated reagent was Cl_3CCN.

N-cyclohexylbenzenesulfonamide as the target molecule was fully characterized its identity by IR, ^1H and ^{13}C-NMR spectra. IR spectrum (Fig 3.1) showed the appearance of two strong bands at 1318 and 1150 cm^{-1} due to asymmetric and symmetric stretching vibrations of the SO_2 group respectively. Secondary sulfonamide displayed an N-H stretching band at 3276 cm^{-1}. The presence of aromatic ring was inferred from the presence of the absorption bands at 3058, 1587 and 1439 cm^{-1}. The ^1H-NMR spectrum (Fig 3.2) displayed a doublet signal (J = 7.60 Hz) at δ_H 4.83 indicated the presence of N-H proton. A multiplet aromatic signal at δ_H 7.45-7.80 were assigned for five aromatic protons. A multiplet signal and a quintet signal at δ_H 1.00-2.00 and 3.13 were ascribed to eleven protons of cyclohexyl group. The ^{13}C-NMR spectrum (Fig 3.3) contained six aliphatic carbons at δ_C 24.6, 25.1, 33.8 and 52.7. In addition, the six signals of aromatic carbons at δ_C 126.1, 128.5, 132.9 and 141.4 were observed.

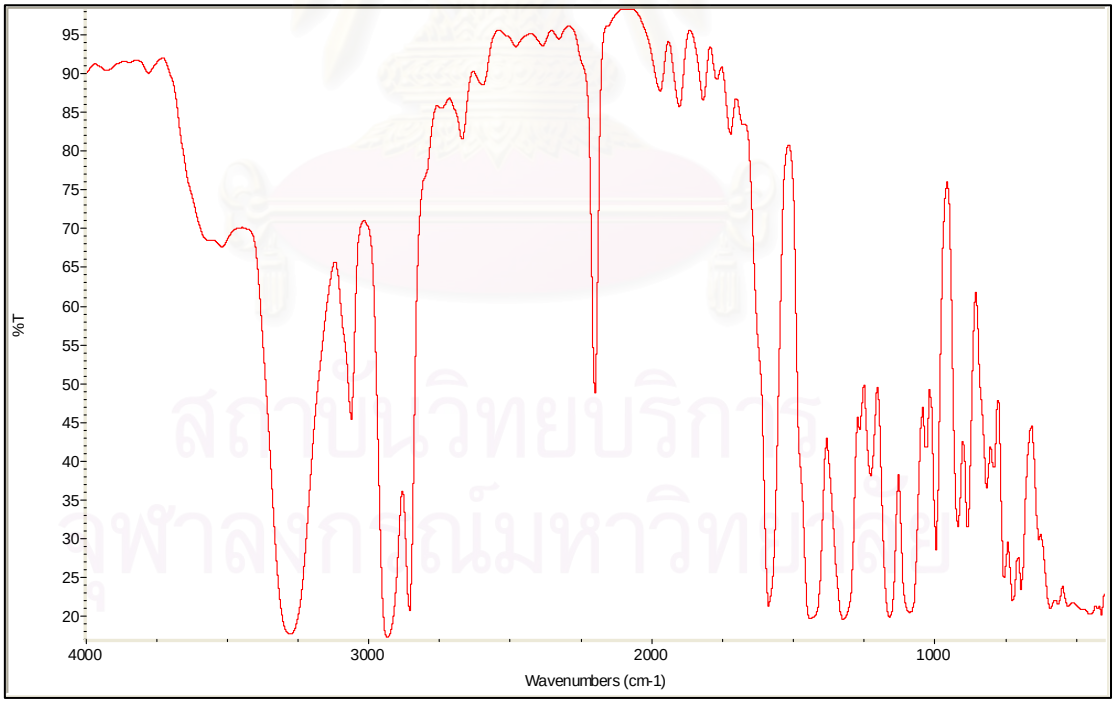


Figure 3.1 The IR spectrum of *N*-cyclohexylbenzenesulfonamide

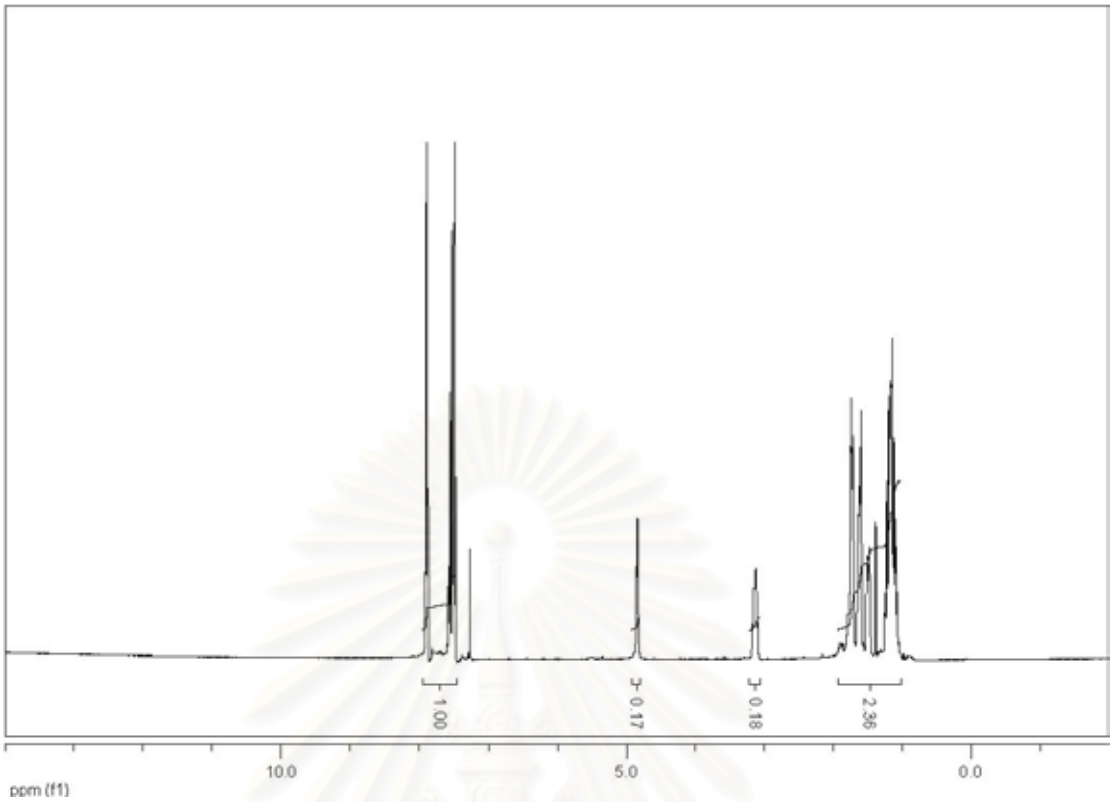


Figure 3.2 The ^{1}H-NMR spectrum of *N*-cyclohexylbenzenesulfonamide

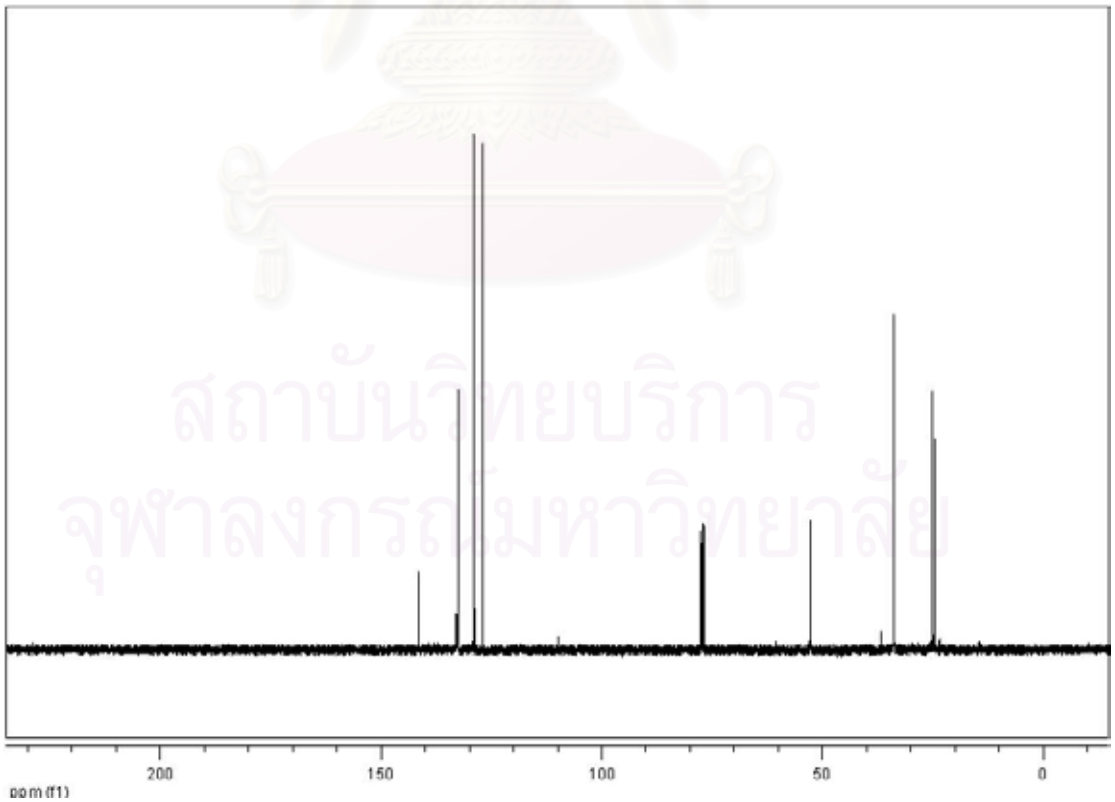


Figure 3.3 The ^{13}C- NMR spectrum of *N*-cyclohexylbenzenesulfonamide

3.3.1.2 Effect of Base

The objective in selecting bases for this reaction is to eliminate chloride ion which was taken place from the substitution of sulfonyl chloride [49]. A variety of commercially available bases were then tested to optimize the yield of *N*-cyclohexylbenzenesulfonamide. The results are listed in Table 3.2

Table 3.2 Effect of bases on the formation of *N*-cyclohexylbenzenesulfonamide

Entry	Base	%Isolated yield
1	none	25
2	triethylamine	5
3	DMAP	51
4	*4*-picoline	67
5	imidazole	66
6	quinaldine	52
7	pyridine	72
8	quinoline	60
reaction conditions:	benzenesulfonic acid (1 mmol), Cl_3CCN (2 mmol) PPh_3 (2 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol) base (9 mmol), room temparature (28-30 ^oC).	
reaction time:	step I 1 h, step II 1 h.	

It was revealed that when DMAP, *4*-picoline, imidazole, quinaldine, pyridine and quinoline were used, the corresponding sulfonamide was isolated in moderate to high yields (51-72 %, entries 3-8). In the absence of base, however, only 25% yield of sulfonamide was obtained (entry 1). In addition, when Et_3N which was used in the synthesis of amides and symmetrical acid anhydrides [22, 25, 61] was employed, the desired sulfonamide was attained in low yield (entry 2). Thus, 4-picoline was selected in this study.

3.3.1.3 Effect of Solvent System

Most organic reactions are performed in solution. It is therefore important to recognize some of the ways in which solvent can affect the rate of reactions. Some of common solvents were selected as in Table 3.3 on the basis of their dielectic constants and boiling points. The results are demonstrated in Table 3.3.

Table 3.3 Effect of solvent on the formation of *N*-cyclohexylbenzenesulfonamide

Entry	Solvent	% Isolated yield
1	CH_2Cl_2	quant
2	$CHCl_3$	48
3	CH_3CN	48
4	THF	44
5	EtOAc	20
6	$ClCH_2CH_2Cl$	59
reaction conditions:	benzenesulfonic acid (1 mmol), Cl_3CCN (3 mmol) PPh_3 (3 mmol), solvent (6 mL), cyclohexylamine (3 mmol) base (9 mmol), reflux temperature.	
reaction time:	step I 1 h, step II 1 h.	

Six common solvents including CH_2Cl_2, $CHCl_3$, CH_3CN, THF, EtOAc and $ClCH_2CH_2Cl$ were examined whether they could use to replace CH_2Cl_2 in this reaction. It was found that when CH_2Cl_2 was used, the corresponding sulfonamide was obtained in quantitative yield (entry 1). The yield of product fell to 44-59% when $CHCl_3$, CH_3CN, THF and $ClCH_2CH_2Cl$ were used (entries 2-4 and 6). Moreover, when EtOAc was used in this reaction, the solubility of most reagents in this solvent is poor and led to the formation of the resultant sulfonamide in low yield (20%, entry 5). After screening a number of solvents, CH_2Cl_2 was found to suit the need for this reaction.

3.3.2 Mechanistic Study of Sulfonamide Formation

The absorption of S=O stretching vibrations of sulfonyl chloride was primarily used to confirm the mechanism for the combination of sulfonic acid, Cl_3CCN and PPh_3. Mechanistic studies were investigated with the aids of IR spectroscopy as illustrated in Fig 3.4.

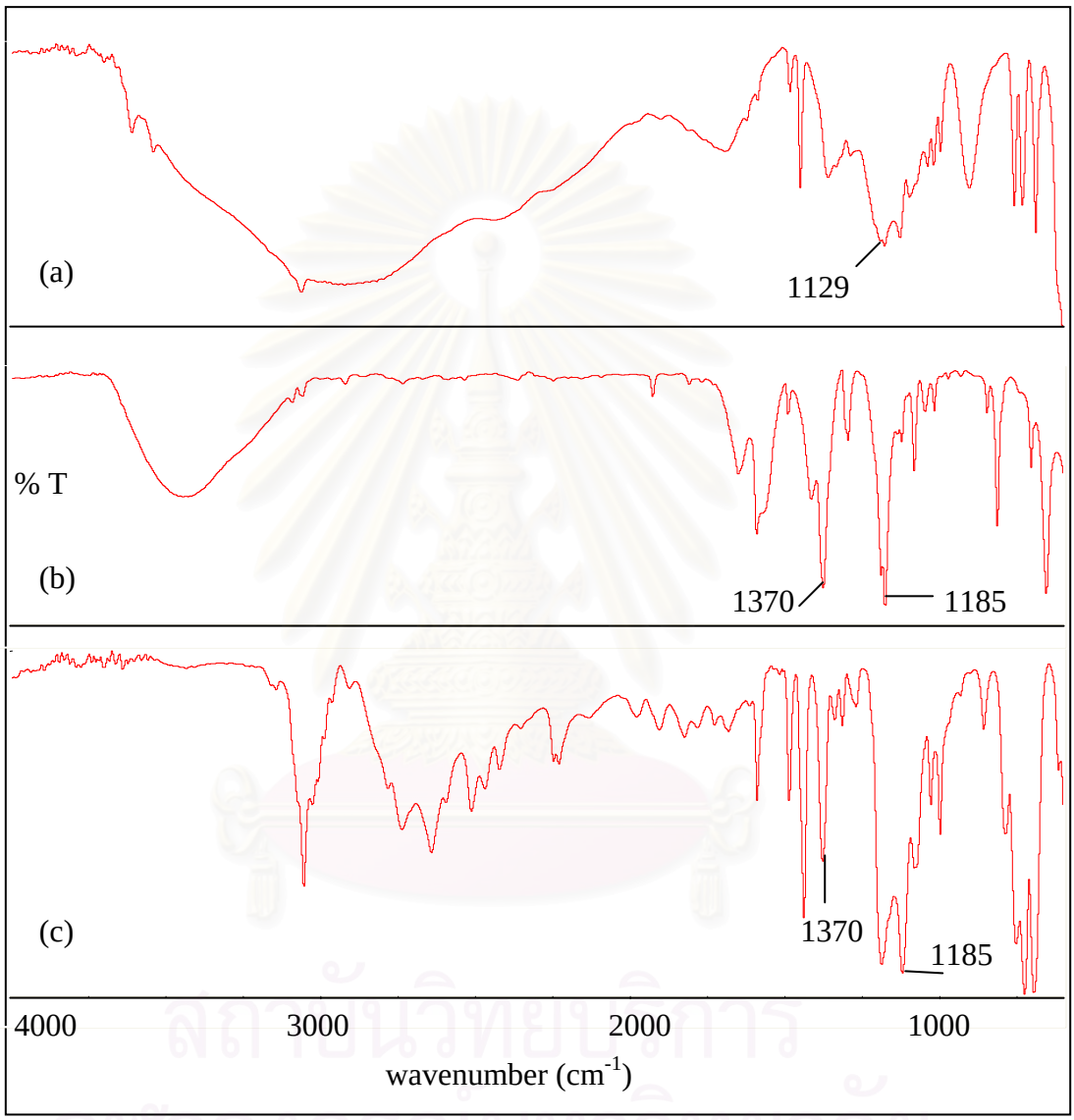


Figure 3.4 The IR spectra of (a) benzenesulfonic acid (b) benzenesulfonyl chloride (c) The reaction mixture of benzenesulfonic acid, PPh_3 and Cl_3CCN

Compared the IR spectra of benzenesulfonyl chloride in Fig 3.4 (b) with that of the reaction mixture in Fig 3.4 (c), both IR spectra displayed two strong bands at 1370 and 1185 owing to S=O stretching vibrations of sulfonyl chloride. The IR spectrum of benzenesulfonic acid revealed the strong absorption band at 1129 cm^{-1} assigned for S=O stretching vibrations.

From these attained results, the combination of sulfonic acid, Cl_3CCN and PPh_3 provided the occurrence of sulfonyl chloride as reactive intermediate.

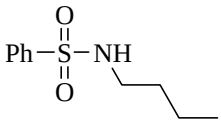
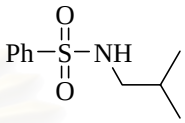
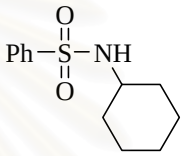
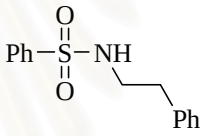
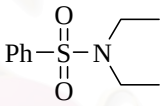
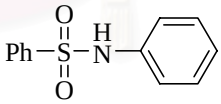
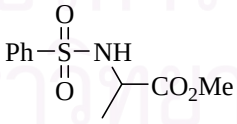
3.3.3 Application of Developed Procedures for the Synthesis of Target Molecules

To investigate the generality and scope of this method, the reaction was carried out with various structurally diverse carboxylic acids and amines.

3.3.3.1 Effect of Amines

To test the generality of this method, the range of amines were utilized in this developed procedure. These results are outlined in Table 3.4.

Table 3.4 Effect of amines on the synthesis of sulfonamides

Entry	Starting amine	Product	% Isolated Yield
1	*n*-butylamine		83
2	*iso*-butylamine		71
3	cyclohexylamine		quant
4	phenethylamine		87
5	diethylamine		74
6	aniline		93
7	methyl alanine ester		46

As presented in Table 3.4, primary and secondary, alkyl, and aryl amines all readily gave excellent yields of sulfonamides. Alkyl amine such as *n*-butylamine, *iso*-butylamine and phenethylamine were readily reacted to give the corresponding sulfonamides in high yields (71-87%, entries 1-2 and 4). The reaction of secondary amine such as diethylamine proceeded to the corresponding sulfonamide in 74% yield

(entry 5). In the case of arylamine such as aniline, the corresponding sulfonamide was isolated in 93% yield (entry 6). Gratifyingly, it was observed that there was no limit for simple amine substrates, and also applicable with amino acid derivatives (entry 7). In the case of alanine, the desired product was not observed possibly due to the solubility of this substrate is particularly poor in organic solvents. From these obtained results, the reaction generally worked well in the case of alkyl primary, alkyl secondary and aryl amine substrates.

All benzenesulfonamides could be characterized their identity by ^{1}H- and ^{13}C-NMR.

The ^{1}H-NMR spectrum of *N*-butylbenzenesulfonamide (Fig 3.5) showed a triplet signal (*J*= 7.36 Hz) of methyl group at δ_H 0.84. A sextet signal (*J*= 7.60 Hz) at δ_H 1.27 was belonged to two protons on a carbon connecting with methyl group. The presence of a quintet (*J*= 7.60 Hz) and a quartet (*J*= 6.80 Hz) signals at δ_H 1.43 and 2.94, indicating for other two methylene protons and those adjacent to amino group, respectively. A broad singlet signal at δ_H 4.61 and a multiplet signal were ascribed to a proton of N-H and five protons of aromatic. The ^{13}C-NMR spectrum of this compound (Fig 3.6) contained four peaks at δ_C 13.5, 19.6, 31.5 and 42.9 of four carbons of butyl group. The four peaks at δ_C 127.0, 129.0, 132.6 and 139.9 were assigned to six aromatic carbons.

The ^{1}H-NMR spectrum of *N-iso*-butylbenzenesulfonamide (Fig. 3.7) presented a doublet signal (*J*= 6.80 Hz) at δ_H 0.86 belonging to the signal of two methyl groups. The multiplet and triplet (*J*= 6.80 Hz) signals at δ_H 1.71 and 2.76 were assigned to a proton and two protons on a carbon connecting to methyl group and amino group, respectively. The broad singlet at δ_H 4.65 was assigned to a proton of N-H. The multiplet signal around δ_H 7.40-8.00 with five protons integration were assigned to five aromatic protons. The ^{13}C-NMR spectrum of this compound (Fig 3.8) displayed three peaks at δ_C 19.8, 28.4 and 50.5 of four aliphatic carbons. The presences of six aromatic carbons were inferred from the detection of four signals at δ_C 126.0, 129.0, 132.5 and 140.0.

The ^{1}H-NMR spectrum of *N*-phenethylbenzenesulfonamide (Fig 3.9) showed a triplet signal (*J*= 6.80 Hz) and a quartet signal (*J*= 6.80 Hz) at δ_H 2.76 and 3.22 of two ethyl groups. The broad singlet at δ_H 4.53 was assigned for N-H proton. The ^{13}C-NMR spectrum of this compound (Fig 3.10) displayed two peaks at δ_C 35.8 and 44.3

of two aliphatic carbons. The presence of twelve aromatic carbons were inferred from the detection of eight signals at δ_C 126.8, 127.0, 128.7, 128.8, 129.1, 133.7, 137.6 and 139.8.

The ^{1}H-NMR spectrum of *N*,*N*-diethylbenzenesulfonamide (Fig 3.11) presented a triplet (*J*= 6.80 Hz) at δ_H 1.12 and a quartet (*J*= 7.20 Hz) at δ_H 3.23 of two methyl and two methylene groups, respectively. A multiplet signal at δ_H 7.47-7.81 was due to five aromatic protons. The ^{13}C-NMR spectrum of this compound (Fig 3.12) displayed two peaks at δ_C 14.1 and 42.0, indicating the presence of two aliphatic carbons. The presence of six aromatic carbons was inferred from the presence of four peaks at δ_C 126.9, 129.0, 132.3 and 140.2.

The ^{1}H-NMR spectrum of *N*,*N*-phenylbenzenesulfonamide (Fig 3.13) exhibited a broad singlet at δ_H 6.85 which could be assigned to a proton of N-H. A multiplet signal at δ_H 7.00-7.90 was due to ten aromatic protons. The ^{13}C-NMR spectrum of this compound (Fig 3.14) displayed seven peaks at δ_C 121.6, 125.3, 129.0, 129.3, 133.0, 136.4 and 138.9, indicating the presence of twelve aromatic carbons.

The ^{1}H-NMR spectrum of *N*-benzenesulfonylamino-propinoic acid methyl ester (Fig 3.15) presented two doublet signals at δ_H 1.38 (*J*= 7.20 Hz) and δ_H 5.25 (*J*= 8.80 Hz) of methyl group and N-H proton, respectively. A singlet signal at δ_H 3.50 was inferred to three protons of methoxy group. A quintet signal (*J*= 7.20 Hz) at δ_H 3.97 was due to a proton on a carbon connecting with an amino group. A multiplet at δ_H 7.45-7.85 was ascribed to five protons of aromatic ring. The ^{13}C-NMR spectrum (Fig 3.16) of this compound contained three peaks at δ_C 19.9, 40.2 and 44.5, indicated three carbons of alkyl group. The four signals of six aromatic carbons were observed at δ_C 127.2, 129.1, 132.8 and 139.7. The peak at δ_C 172.5 appropriated for a carbonyl carbon was observed.

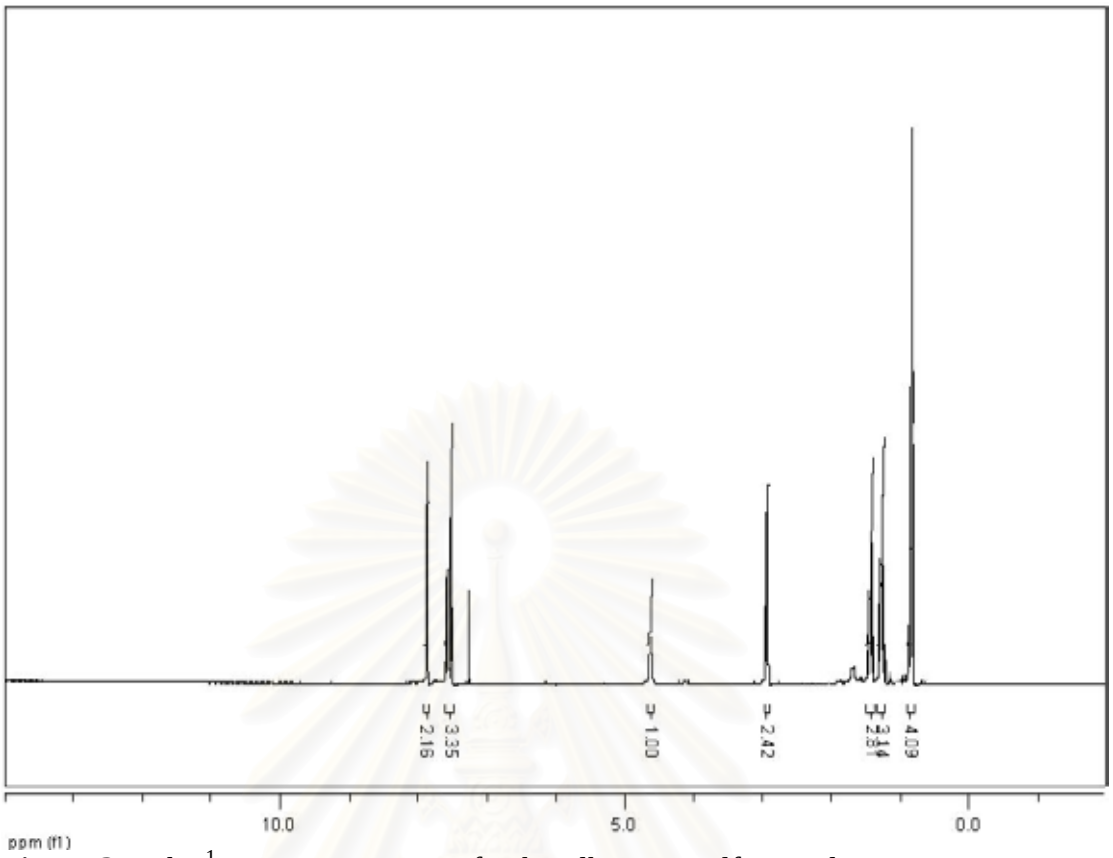


Figure 3.5 The ^{1}H-NMR spectrum of *N*-butylbenzenesulfonamide

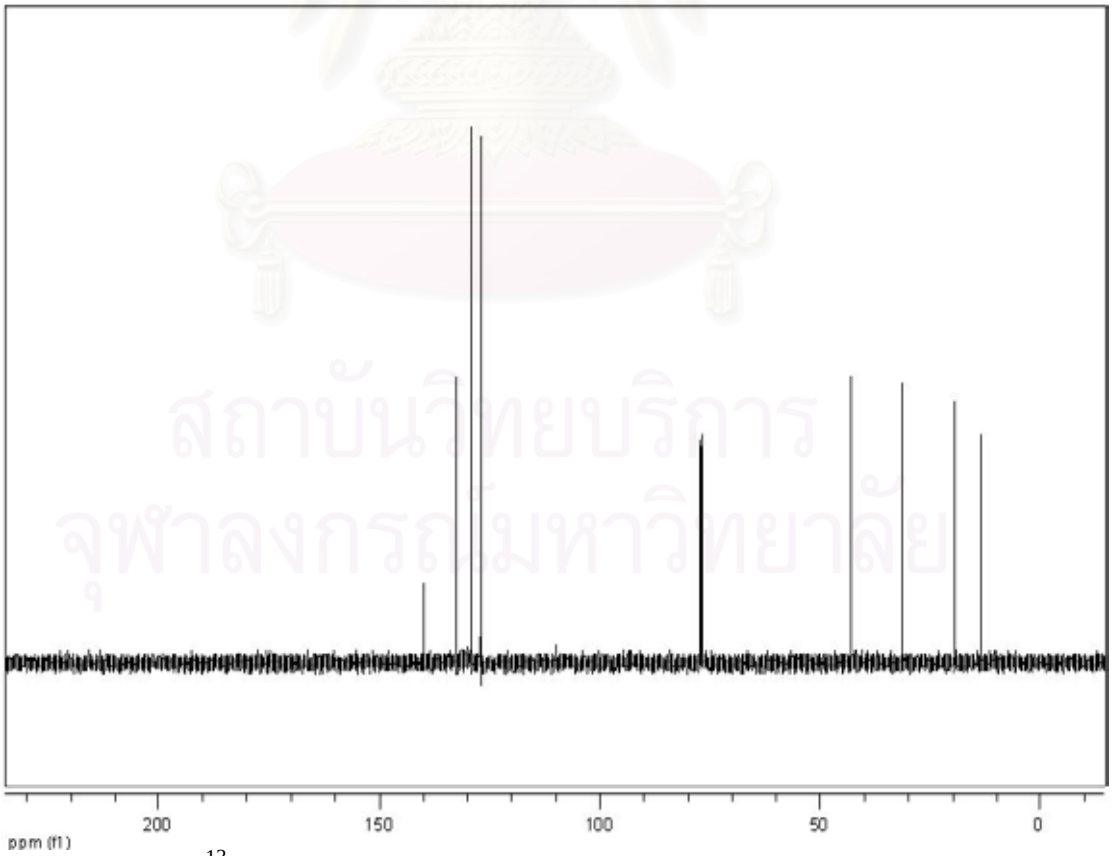


Figure 3.6 The ^{13}C-NMR spectrum of *N*-butylbenzenesulfonamide

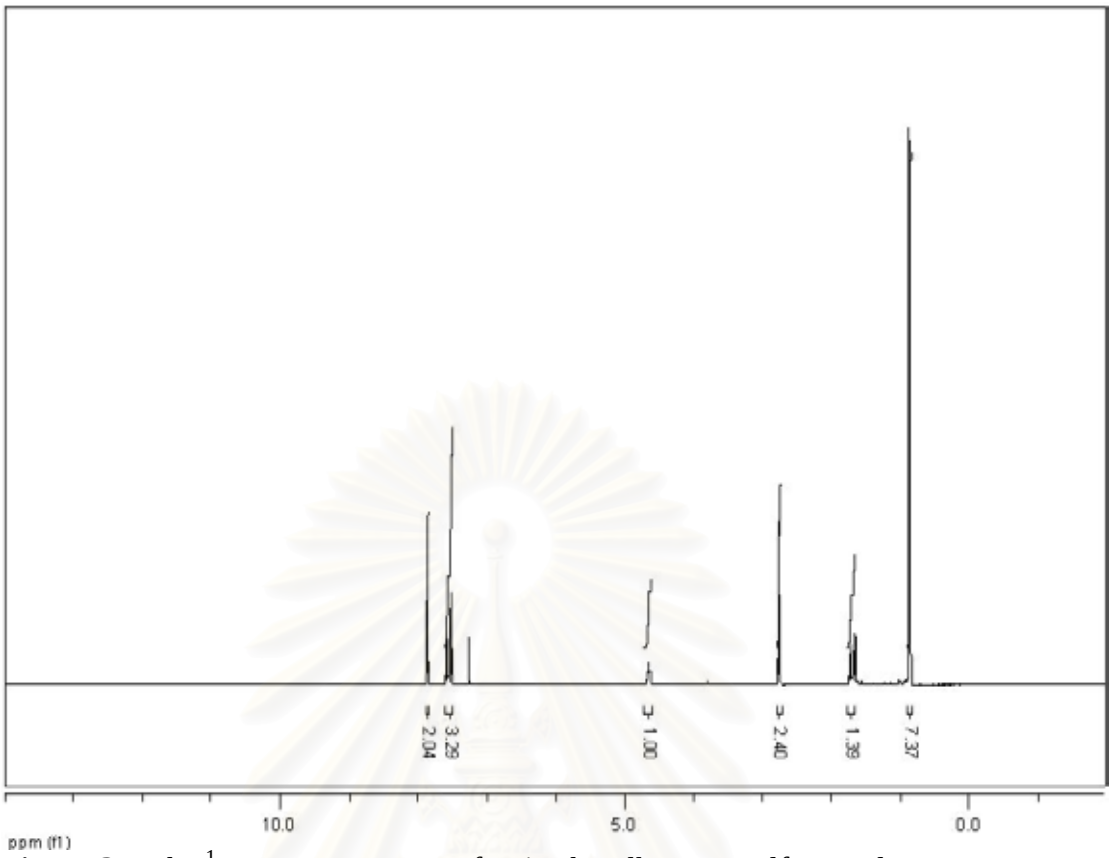


Figure 3.7 The [1]H-NMR spectrum of *N-iso*-butylbenzenesulfonamide

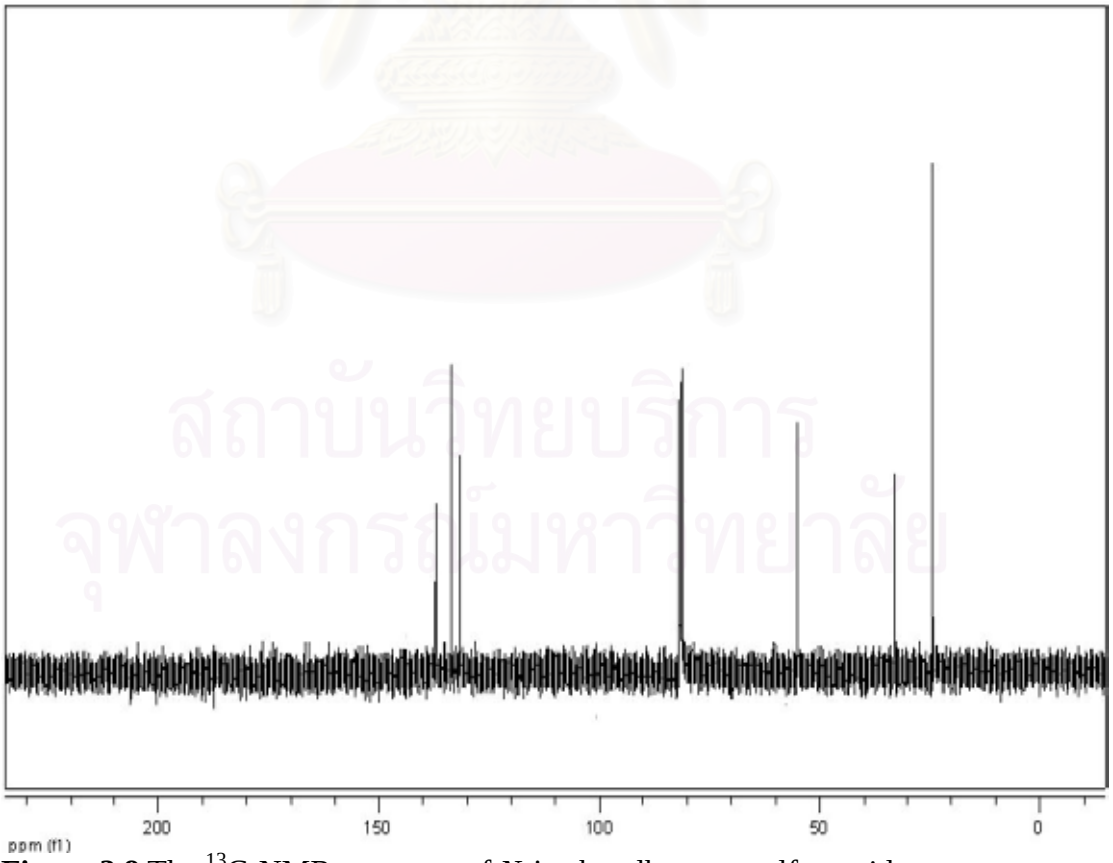


Figure 3.8 The [13]C-NMR spectrum of *N-iso*-butylbenzenesulfonamide

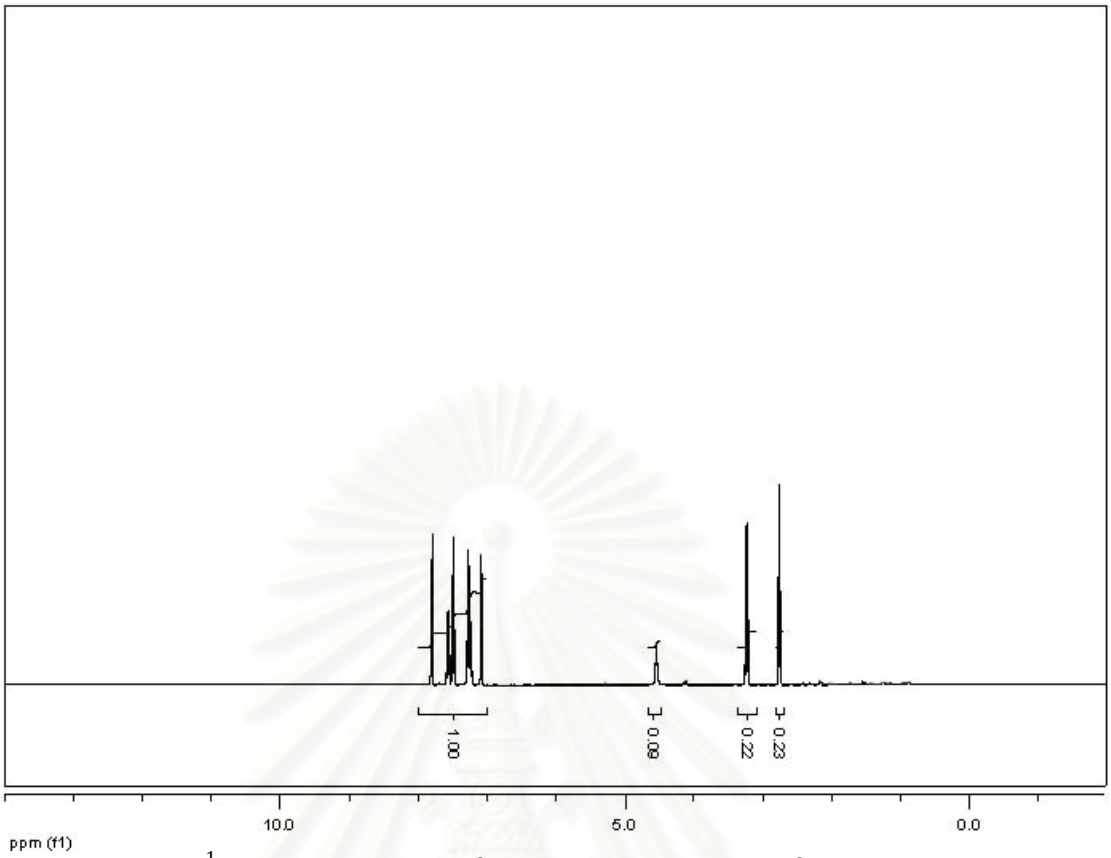


Figure 3.9 The ^{1}H-NMR spectrum of *N*-phenethylbenzenesulfonamide

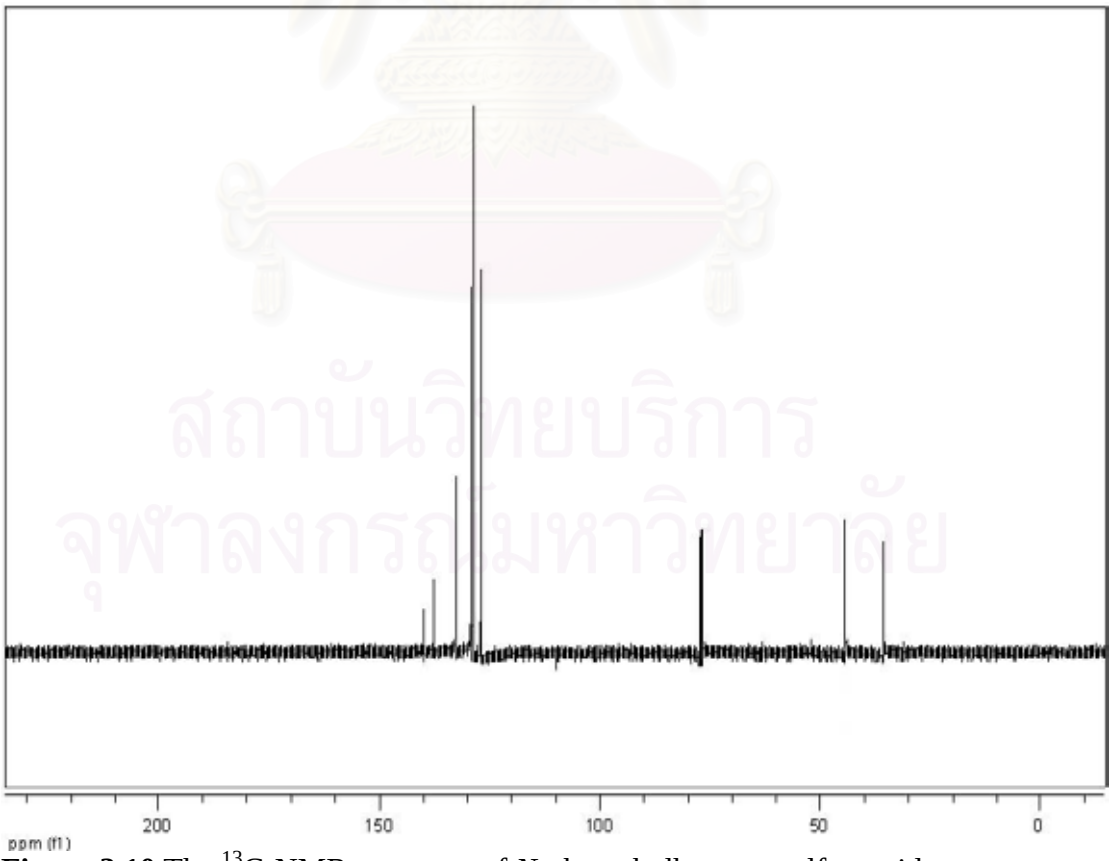


Figure 3.10 The ^{13}C-NMR spectrum of *N*-phenethylbenzenesulfonamide

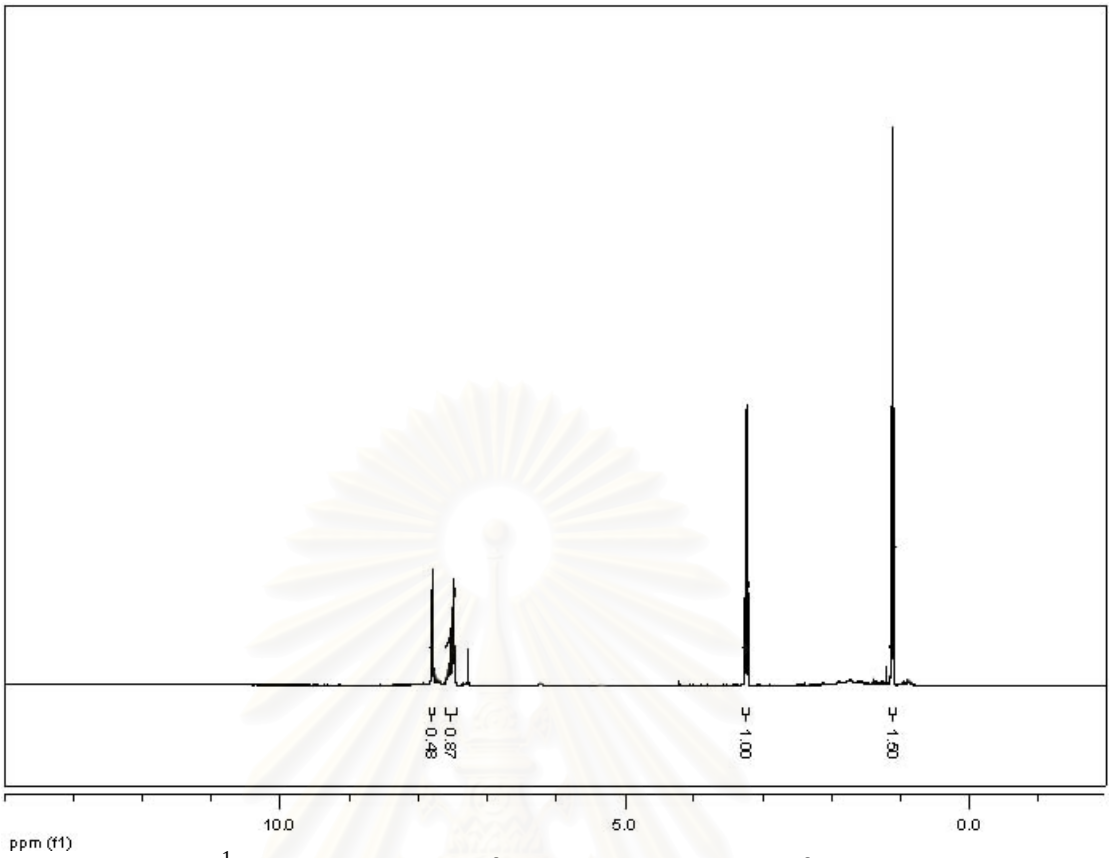


Figure 3.11 The ^{1}H-NMR spectrum of *N*,*N*-diethylbenzenesulfonamide

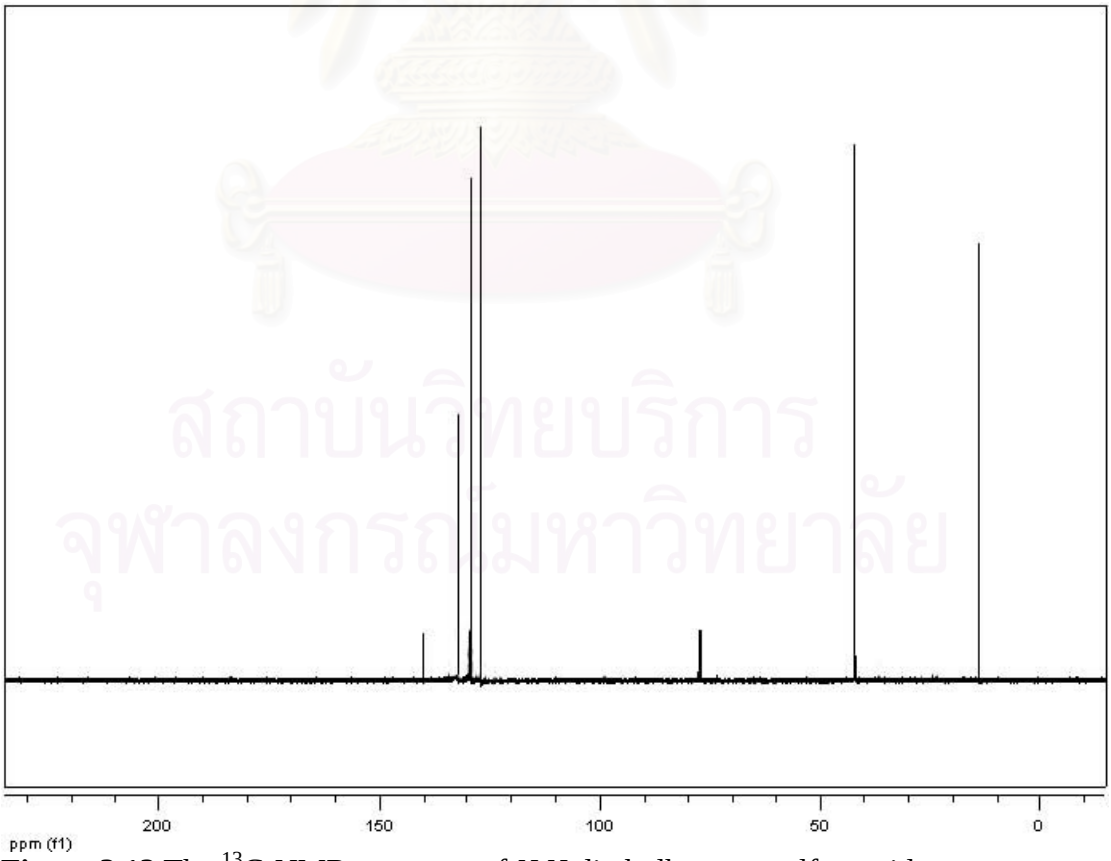


Figure 3.12 The ^{13}C-NMR spectrum of *N*,*N*-diethylbenzenesulfonamide

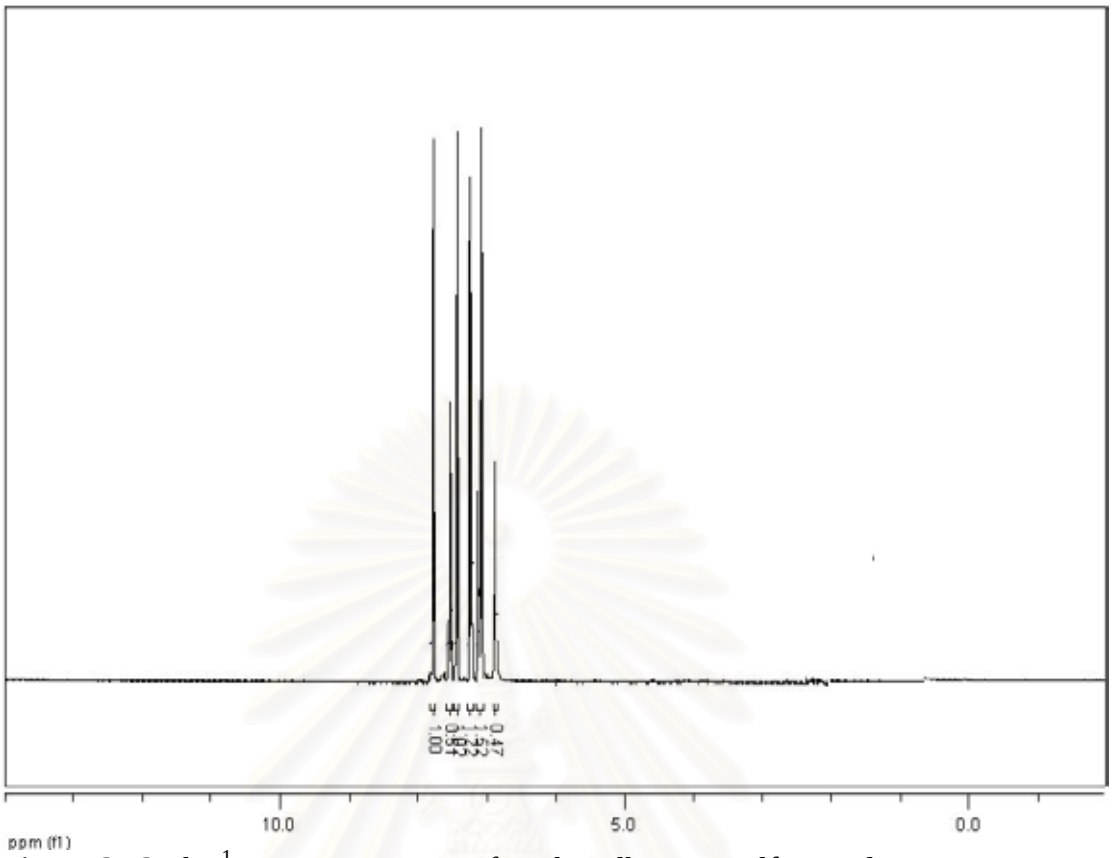


Figure 3.13 The ^{1}H-NMR spectrum of *N*-phenylbenzenesulfonamide

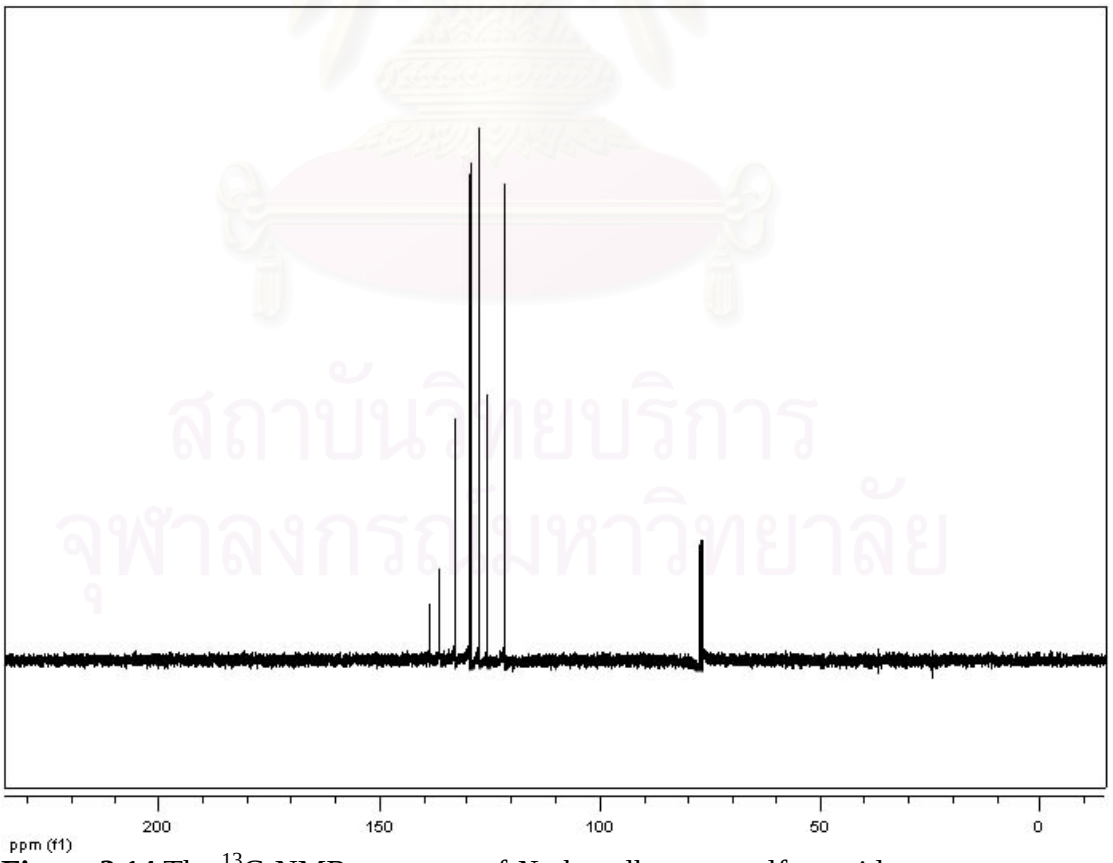


Figure 3.14 The ^{13}C-NMR spectrum of *N*-phenylbenzenesulfonamide

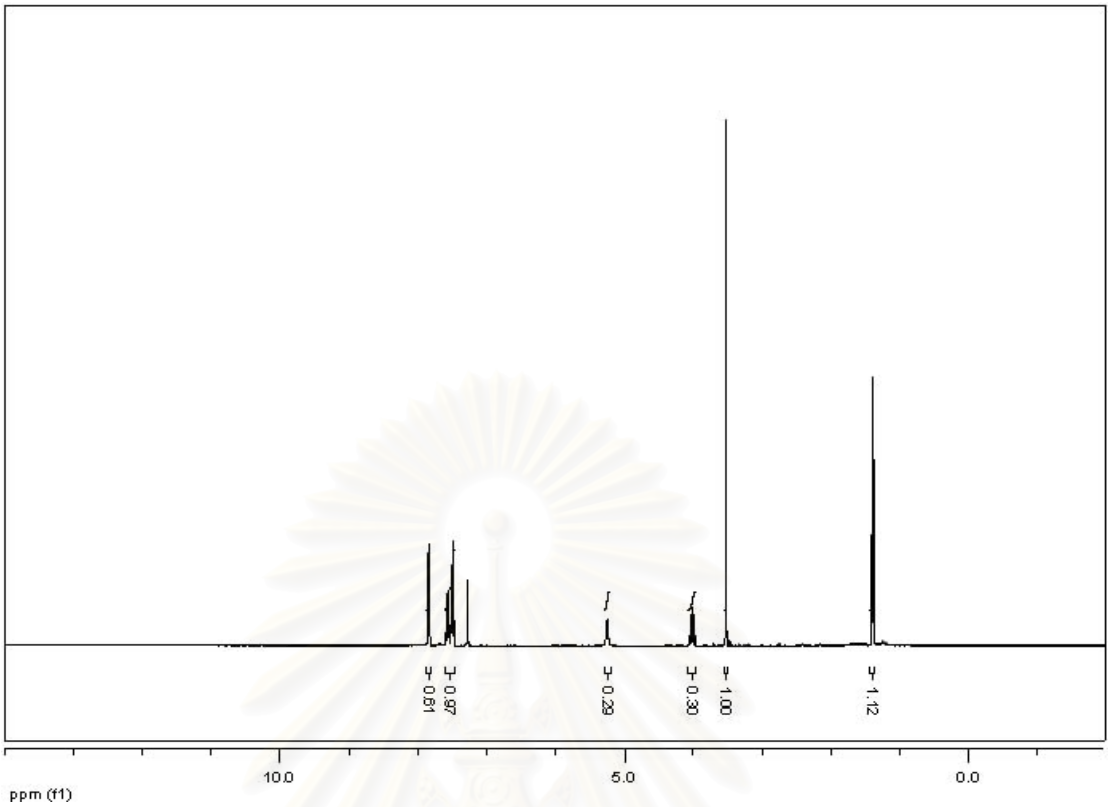


Figure 3.15 The ^{1}H-NMR spectrum of *N*-benzenesulfonylamino-propionic acid methyl ester

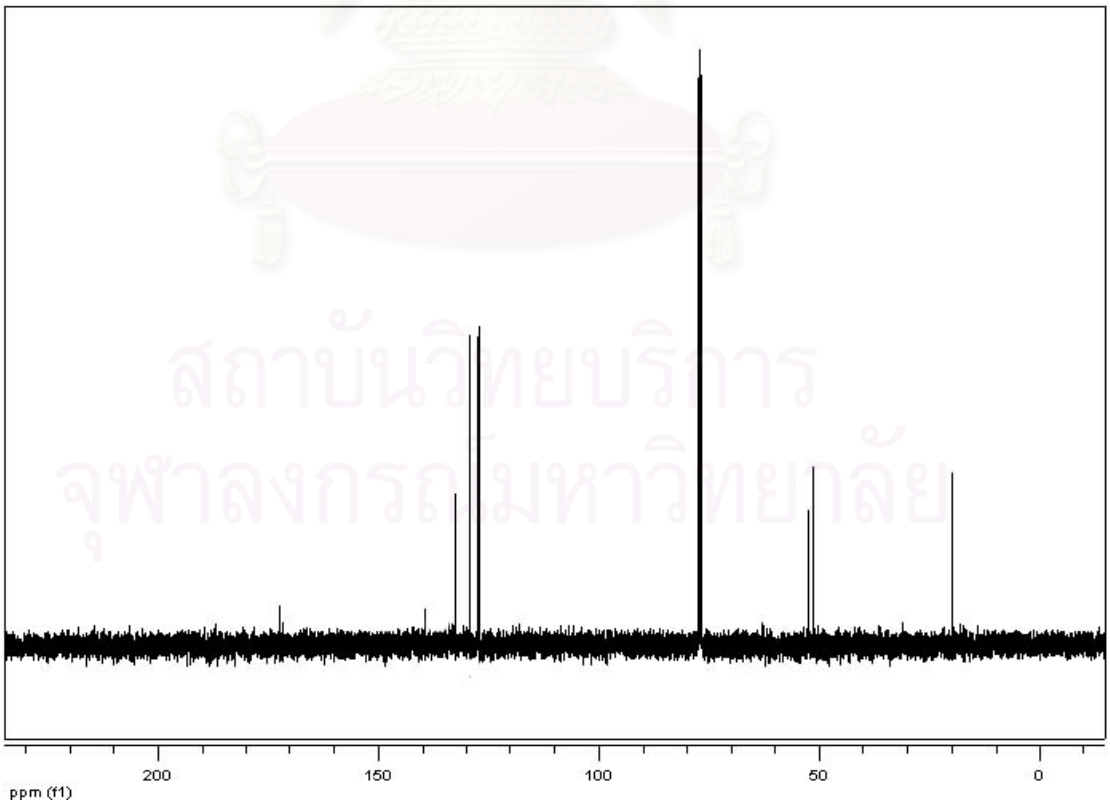
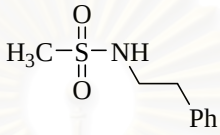
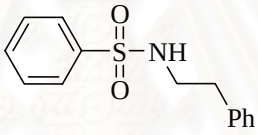
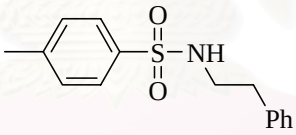
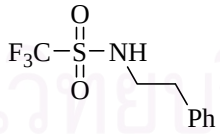
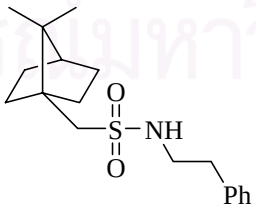


Figure 3.16 The ^{13}C-NMR spectrum of *N*-benzenesulfonylamino-propionic acid methyl ester

3.3.3.2 Effect of Sulfonic Acids

The diverse ranges of sulfonic acid were then tested for this developed reaction. Phenethylamine was selected in this reaction with a number of common sulfonic acid. The results of these reactions are summarized in Table 3.5.

Table 3.5 Effect of sulfonic acid on the synthesis of sulfonamides

Entry	Starting sulfonic acid	Sulfonamide product	Time at reflux temperature(h)	% Isolated yield
1	methanesulfonic acid		1	51
2			3	75
3			8	89
4	benzenesulfonic acid		1	87
5	*4*-toluenesulfonic acid monohydrate		1	33
6			3	96[a]
7	trifluoromethane sulfonic acid		1	0
8	camphor-10-sulfonic acid		1	77

[a] PPh_3 6 mmol

From the results in Table 3.5, it was observed that the reaction is not limited to a number of sulfonic acid. The reaction condition could be altered to improve the yield of desired sulfonamide. It was found that increasing time at refluxing temperature in step I (the reaction of methanesulfonic acid) from 1 h to 3 and 8 h offering the corresponding sulfonamide in 51, 75 and 89 % respectively (entries 1-3). For the reaction of *4*-toluenesulfonic acid monohydrate, the hydrate in this complex may react with PPh_3. Thus the amount of PPh_3 may not be enough for the reaction to react with Cl_3CCN furnishing 33% yield of sulfonamide. However, when the amount of PPh_3 increased from 3 to 6 mmol and reaction time in step I was increased from 1 to 3 h, the yield of the desired sulfonamide gained was almost quantitative (entries 5 and 6). For CF_3SO_3H, none of the desired sulfonamide was obtained (entry 7). This may be specurated that the nucleophilicity of trifluoromethansulfonate anion was not good resulting in the reaction cannot proceed to give the desired product. Nevertheless, the method introduced here has proven to be very useful for the molecule with steric hindrance group such as camphor-10-sulfonic acid, the desired sulfonamide was gained in 77% (entry 8).

Sulfonamides were well confirmed their identity by ^{1}H- and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum of *N*-phenethylmethansulfonamide (Fig 3.17) clearly displayed a singlet signal at δ_H 2.83, indicating the presence of methyl group connected to sulfonyl group. A triplet signal at δ_H 2.88 (J= 6.80 Hz) and a quartet at δ_H 3.41 (J= 6.40 Hz) belonged to two ethyl groups. The broad singlet at δ_H 4.53 was assigned to a proton of N-H. The multiplet signal around δ_H 7.20-7.44 with five protons integration were assigned to five aromatic protons. The ^{13}C-NMR spectrum of this compound (Fig 3.18) displayed three peaks at δ_C 36.4, 40.2 and 44.5 of three aliphatic carbons. The four peaks at δ_C 126.9, 128.8, 128.9 and 137.9 were assigned to six aromatic carbons.

The ^{1}H-NMR spectrum of *N*-phenethyl-toluene-4-sulfonamide (Fig 3.19) exhibited a singlet signal at δ_H 2.43, pointing out the presence of a methyl group substituted on an aromatic ring. A triplet signal at δ_H 2.76 (J= 6.80 Hz) and quartet at δ_H 3.21 (J= 6.80 Hz) were ascribed to ten protons of two ethyl groups. The broad singlet signal at δ_H 4.38 could be assigned for N-H proton. The signals around δ_H 7.00-7.80 were typical of nine aromatic protons. The ^{13}C-NMR spectrum of this compound (Fig 3.20) displayed three peaks at δ_C 21.5, 35.8 and 44.2 of three aliphatic

carbons. The presence of twelve aromatic carbons were inferred from the detection of seven signals at δ_C 126.8, 127.1, 128.7, 129.7, 136.8, 137.7 and 143.4.

The ^{1}H-NMR spectrum of *N*-phenethyl-10-camphorsulfonamide (Fig 3.21) showed two multiplet signal around δ_H 0.80-3.40 and 7.45-7.85 which could be ascribed to fifteen camphor protons and five aromatic protons, respectively. The broad singlet at δ_H 5.04 was assigned to a proton of N-H. The two multiplet signals at δ_H 2.93 and 3.44 were assigned to ten protons of two ethyl groups. The ^{13}C-NMR spectrum of this compound (Fig 3.22) displayed peaks at δ_C 19.5-58.9, indicating the presence of twelve aliphatic carbons. The presence of five aromatic carbons was inferred from the detection of signals at δ_C 126.7-138.1.

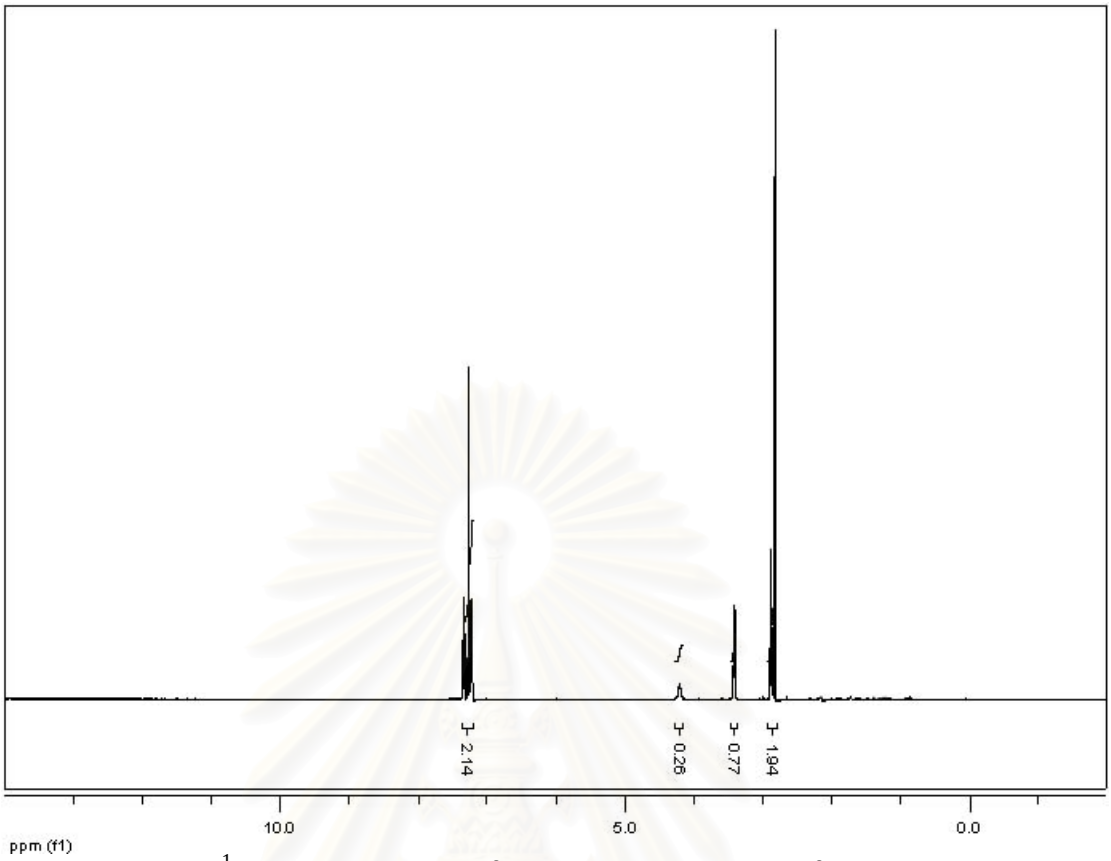


Figure 3.17 The ^{1}H-NMR spectrum of *N*-phenethylmethanesulfonamide

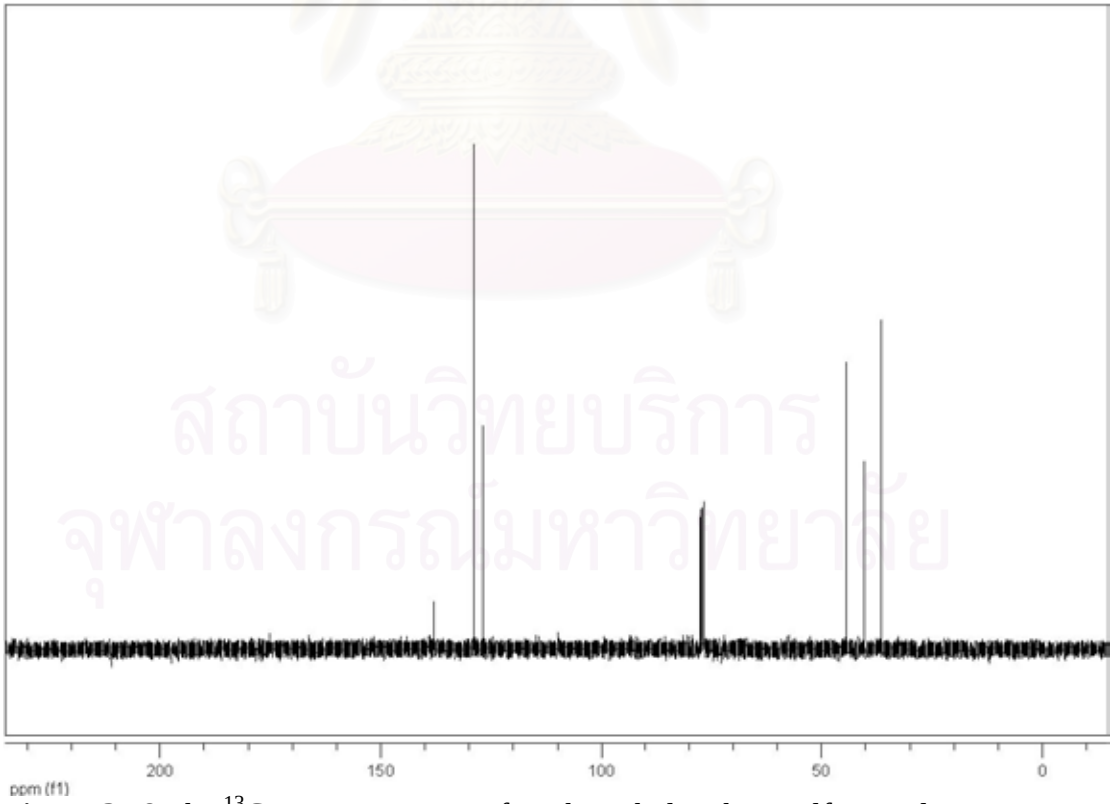


Figure 3.18 The ^{13}C-NMR spectrum of *N*-phenethylmethanesulfonamide

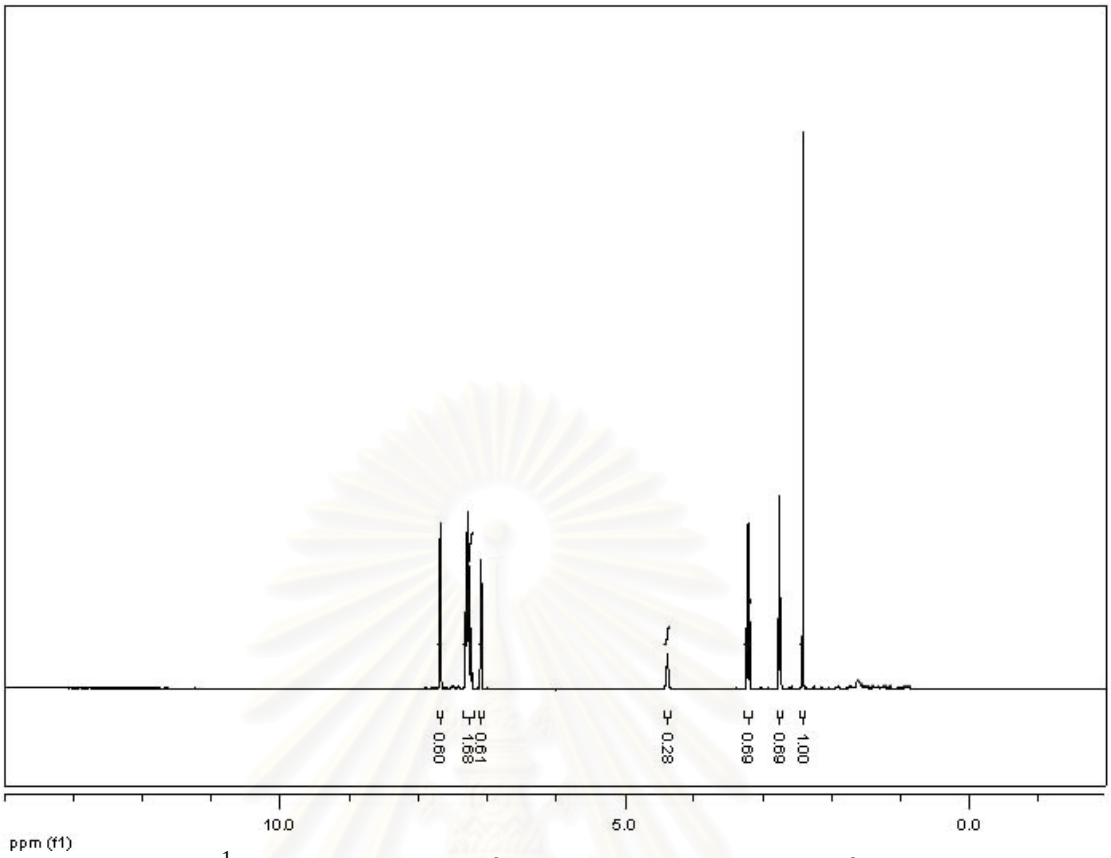


Figure 3.19 The [1]H-NMR spectrum of *N*-phenethyl-toluene-4-sulfonamide

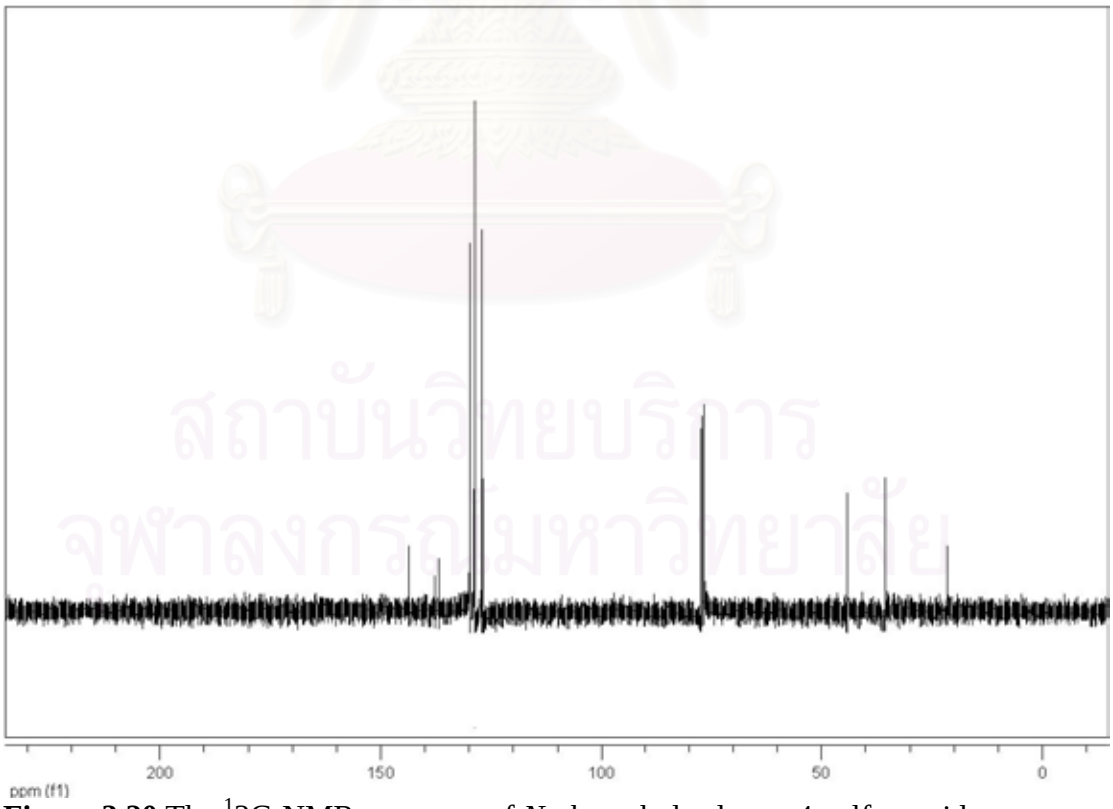


Figure 3.20 The [1]3C-NMR spectrum of *N*-phenethyl-toluene-4-sulfonamide

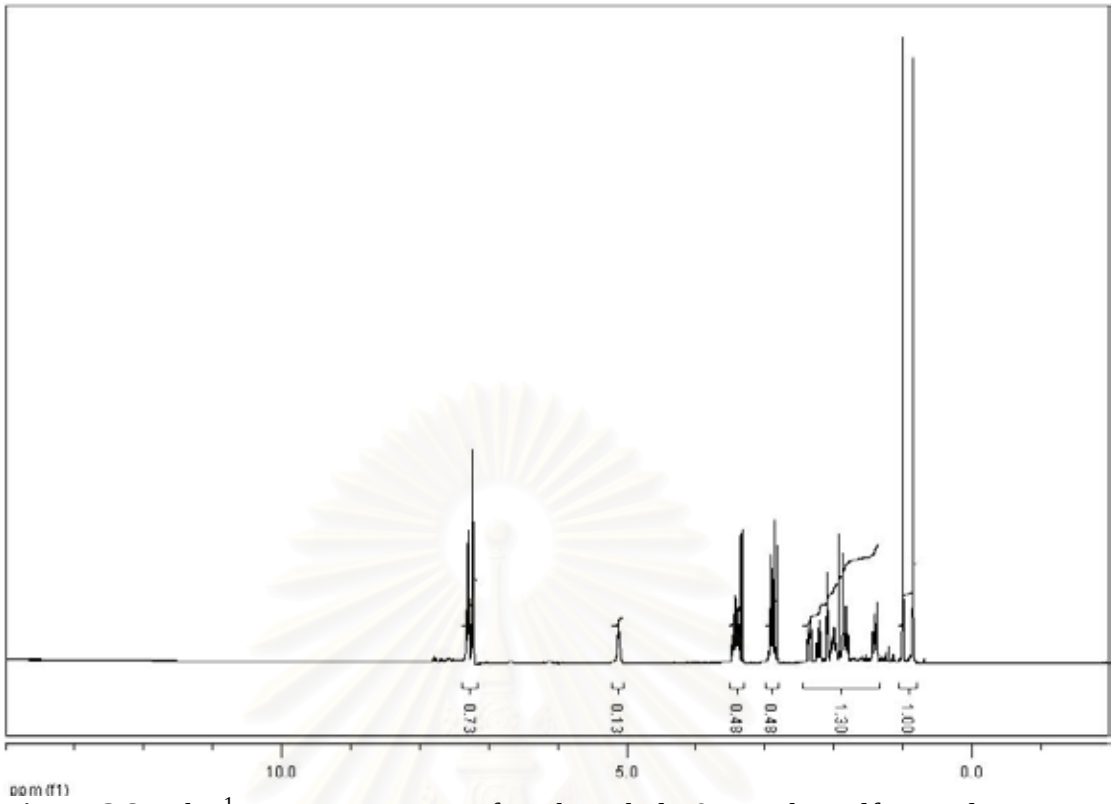


Figure 3.21 The ^{1}H-NMR spectrum of *N*-phenethyl-10-camphorsulfonamide

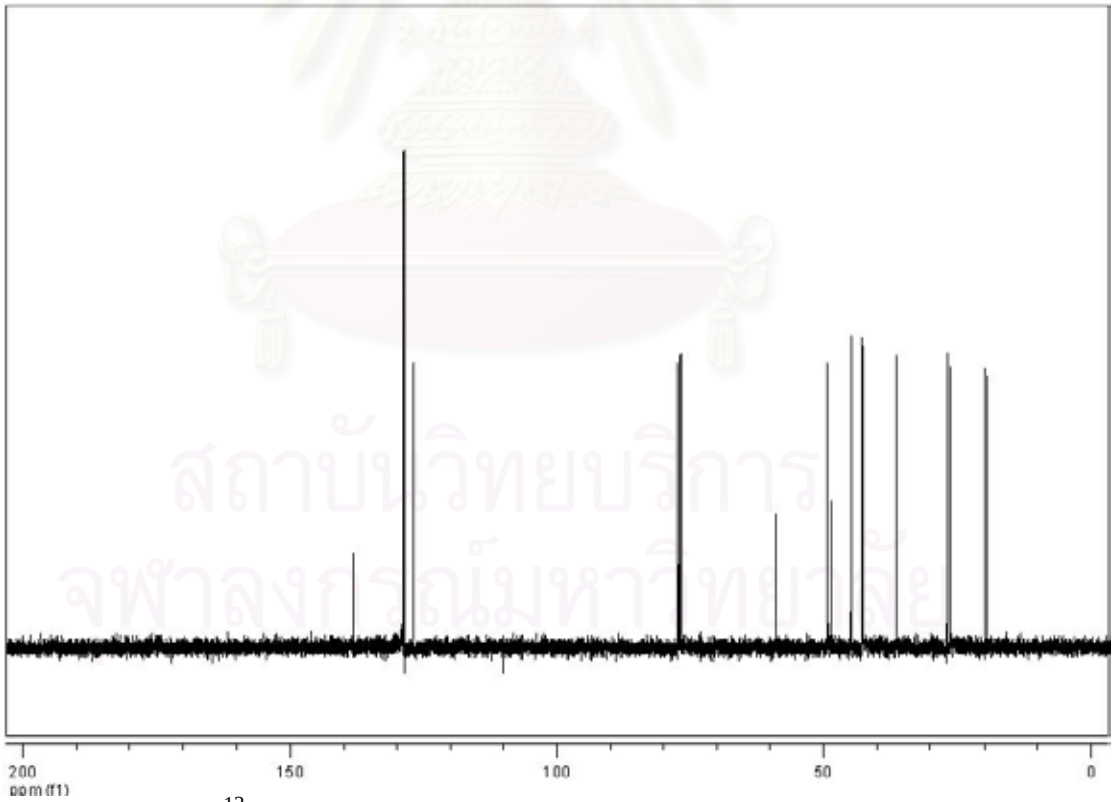


Figure 3.22 The ^{13}C-NMR spectrum of *N*-phenethyl-10-camphorsulfonamide

3.3.4 Applications for the Synthesis of Bioactive Sulfonamides

Particularly noteworthy is the success of this methodology in the formation of sulfonamides, which demonstrate the applicability of this approach toward introduction of bioactive sulfonamides.

Sulfonamides have been shown to possess a wide spectrum of therapeutic applications [62]. Their potential use as therapeutic drugs for the treatment of Alzheimer's disease has been reported [63].

Alzheimer's disease (AD) is the most common progressive dementia associated with aging, with β-amyloid plaques, neurofibrillary tangles, and synaptic loss being the major neuropathological hallmarks of the disease. The cholinergic system is the earliest and most profoundly affected neurotransmitter system in AD, with substantial losses in the forebrain, cortex, and hippocampus [64]. This neurotransmitter together with these brain regions are critical in the acquisition, processing, and storage of memories and have supported the use of chlinomimetics in the treatment of AD. Thus far, the agents that have demonstrated the greatest activity in AD therapy are cholinesterase inhibitors [65]. Two forms of cholinesterase coexist ubiquitously throughout the body, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE).

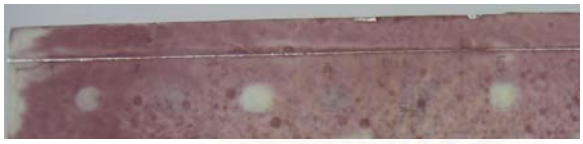
The role of BChE in normal, aging, and diseased brain remains largely unknown, and there has been minimal interest in the design, synthesis, and development of selective inhibitors of BChE, expect in the agricultural industry where toxic irreversible BChE inhibitors have long been used as insecticides.

Interestingly, recent research has shown that over expression of BChE occurs in neuritic Aβ plaques in the AD brain and, furthermore, that the presence of BChE with dramatically amplifies the toxicity of Aβ *in vitro*. Additionally, BChE is now known to be elevated in the AD brain, and a specific mutation in the gene. These facts suggest that inappropriate BChE activity increase the risk and/or progression of AD. It is hence possible that well-tolerated inhibitors of BChE may have utility in the treatment of AD.

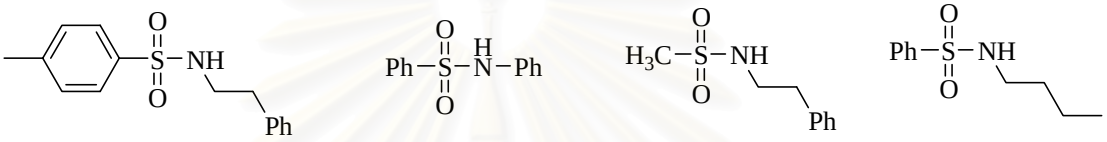
According to the synthesis and development of novel inhibitors of BChE to obtain an idea of drug for the treatment of AD was promoted. Thus, this research demonstrated qualitative structure-activity study of sulfonamides.

3.3.4.1 Qualitative Analysis of Anticholinesterase Activity

The action of four sulfonamides; *N*-phenethyl-toluene-4-sulfonamide**,** *N*-phenylbenzenesulfonamide, *N*-phenethylmethanesulfonamide and *N*-butylbenzenesulfonamide to inhibit BChE was kindly tested by Ms. Nisa Changwong. The adjustment of the color from purple to white on a paper test was called that positive test due to BchE was inhibited [66]. The results are shown in Fig 3.23.



(S1) **(S2)** **(S3)** **(S4)**



(S1) **(S2)** **(S3)** **(S4)**

Figure 3.23 Preliminary results of BChE of sulfonamide; *N*-phenethyl-toluene-4-sulfonamide **(S1)**, *N*-phenylbenzenesulfonamide **(S2)**, *N*-phenethylmethanesulfonamide **(S3)** and *N*-butylbenzenesulfonamide **(S4)**

From Fig 3.23, when *N*-phenethyl-toluene-4-sulfonamide **(S1)**, *N*-phenylbenzenesulfonamide **(S2)** and *N*-butylbenzenesulfonamide **(S4)** were tested, S1**,** S2 and S4 could inhibit BChE activity. This may be because the connection of the phenyl ring on a sulfur atom of sulfonyl group resulted in an active effect on the interaction with this enzyme. In contrast, replacement of a phenyl group by a methyl group at the sulfur atom of sulfonyl group resulted in **(S3)**, EChE was not inhibited.

This analysis was preliminary study. Therefore, the quantitative analysis will be evaluated for further study.

CHAPTER IV

CONCLUSION

The combination of halogenated reagent and PPh_3 was prompted to synthesize amides, esters and sulfonamides. Cl_3CCONH_2/PPh_3 was disclosed as an efficient coupling reagent for conversion of carboxylic acids to amides and esters. The utilization of this reagent could be fruitfully applied for the preparation of bioactive benzamides and investigated of the scope for the synthesis of esters. The mechanistic studies were fully explored for intermediate, deriving from the reaction of carboxylic acids with Cl_3CCONH_2/PPh_3. In addition, this new methodology could be employed for sulfonamides synthesis.

From this research, Cl_3CCONH_2/PPh_3 was used to prepare bioactive benzamides. *N*,*N*-Diethyl-m-toluamide (DEET^{TM}), are insect repellant, was selected as a model compound for the synthesis their derivatives. Nine benzamide compounds were synthesized from various benzoic acids. This protocol was an efficient method for aromatic carboxylic acids with the presence of electron-withdrawing or electron-donating groups at *meta* position on aromatic ring. The presence of the substituents at *para* position can be prepared using this protocol. Unfortunately, the developed method could not convert aromatic carboxylic acids bearing either one or two substituents at *ortho* position to the desired benzamides.

To investigate the scope of the synthesis of esters, various carboxylic acids and alcohols were examined to establish the limitation of this protocol. The study on the effect of alcohols can be summarized that primary and secondary alcohols could only smoothly proceed to obtain the corresponding benzoate esters whereas tertiary alcohol did not under this condition. From the variation of alcohol, the yields of the isolated esters were insignificantly depended on type of alcohol. The study on the effect of carboxylic acids, tertiary carboxylic acid could be efficiently reacted under this reaction. The IR, ^{1}H-, ^{13}C-NMR spectra can confirm the intermediate of this reaction that this reaction truly occur *via* acid chloride.

The explosion of halogenated reagents for the synthesis of sulfonamide was also examined. The optimum conditions were relied: the suitable halogenated reagent

is Cl_3CCN. The ratio of sulfonic acid, Cl_3CCN and PPh_3 is 1:3:3 and the reaction was carried out under refluxing CH_2Cl_2 for approximately 1 h or followed by TLC.

For the synthesis of sulfonamides, various sulfonic acids and amines were studied. This method was suitable for alkyl primary, alkyl secondary and aryl amine substrates.

Furthermore, qualitative study of butyrylcholinesterase (BChE) activity of sulfonamides, prepared from this method, was carried out. Sulfonamides, whose aromatic ring connected with S=O group revealed BChE inhibition while the presence of aliphatic moiety did not express good inhibition of BChE.

Proposed for the further work

This research relates to the application of Cl_3CCONH_2/PPh_3 for the synthesis of amides and esters and Cl_3CCN/PPh_3 for the synthesis of sulfonamides. The outcome opened many possibilities to deal with further exploration. The methodology for the synthesis of acetate esters should be performed due to these compounds synthesized via either acetyl chloride or acetic anhydride. These compounds are interesting to synthesize for the new methodology. The methodology of the synthesis of acid derivatives using halogenated reagents and PPh_3 should be in addition preformed.

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