การเตรียมไดซัลไฟด์จากไทออลโดยใช้ไฮเปอร์วาเลนต์ไอโอดีน (III)

นางสาววทันยา ไกรลาศ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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ปีการศึกษา 2557

PREPARATION OF DISULFIDES FROM THIOLS USING HYPERVALENT IODINE(III)

Miss Watanya Krailat

A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science Program in Petrochemistry and Polymer Science

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Thesis Title	PREPARATION OF DISULFIDES FROM THIOLS USING HYPERVALENT IODINE(III)
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วทันยา ไกรลาศ : การเตรียมไดซัลไฟด์จากไทออลโดยใช้ไฮเปอร์วาเลนต์ไอโอดีน (III) (PREPARATION OF DISULFIDES FROM THIOLS USING HYPERVALENT IODINE(III)) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.สัมฤทธิ์ วัชรสินธุ์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: รศ. ดร.ปรีชา ภูวไพรศิริศาล, 76 หน้า.

ไดซัลไฟด์มีความสำคัญในกระบวนการสังเคราะห์เปปไทด์และยังนำมาใช้ประโยชน์เป็นสารทำให้ยางคงรูปในกระบวนการสังเคราะห์ยางได้ โดยทั่วไปการเตรียมไดซัลไฟด์จะใช้ตัวออกซิแดนท์ที่มีพิษ งานวิจัยนี้ เราจึงพัฒนาการสังเคราะห์ไดซัลไฟด์จากไทออลโดยใช้ไฮเปอร์วาเลนต์ไอโอดีน(III) ซึ่งเป็นตัวออกซิแดนท์ที่สามารถหาซื้อได้ ราคาไม่แพง และมีความเป็นพิษต่ำ เราได้ทำการการศึกษาภาวะที่เหมาะสมของ ชนิดไฮเปอร์วาเลนต์ไอโอดีน (III), ปริมาณของไฮเปอร์วาเลนต์ไอโอดีน (III) และตัวทำละลาย สำหรับปฏิกิริยาออกซิเดชันของไทออล 1a ได้เป็น ไดซัลไฟด์ 2a และทำการตรวจสอบโดยใช้เทคนิคโครมาโทกราฟีของเหลวความดันสูง เราได้ทำการศึกษาหาภาวะที่เหมาะสมโดย โดยการใช้ไดอะเซทอกซีไอโอโดเบนซีนเป็นตัวออกซิแดนท์ เป็นเวลา 5 นาที ในตัวทำละลายไอโซโพรพานอล มาทำการสังเคราะห์ไดซัลไฟด์จากไทออลทั้งหมด 13 ชนิด ได้ร้อยละผลิตภัณฑ์ 75-95 และปฏิกิริยาสามารถทำได้ที่ภาชนะเปิด นอกจากนี้ยังได้เตรียมตัวออกซิแดนท์ คือ ไดอะเซทอกซีไอโอโดเบนซีนบนตัวรองรับพอลิสไตรีน จากปฏิกิริยาไอโอดิเนชันของพอลิสไตรีนจาก ไอโอดีนและไอโอดีนเพนตะออกไซด์ ตามด้วยปฏิกิริยาออกซิเดชัน ทั้งกับแอซิติกแอนไฮไดร์และไฮโดเจนเปอร์ออกไซด์ หรือโซเดียมเปอร์บอเรต โครงสร้างของไดอะเซทอกซีไอโอโดเบนซีนบนตัวรองรับพอลิสไตรีนถูกตรวจสอบเอกลักษณ์โดยเทคนิคฟูเรียร์ทรานส์ฟอร์มอินฟราเรดสเปคโตรสโคปี และได้ทำการหาปริมาณของหมู่ไดอะเซทอกซีไอโอโดฟีนิลที่ติดอยู่บนพอลิเมอร์โดยเทคนิคไอโอโดเมตริกไตเตรชัน ได้ประมาณ 1.26-2.00 มิลลิโมลต่อกรัม และได้นำมาสังเคราะห์ไดซัลไฟด์จากไทออกทั้งหมด 11 ชนิด จากภาวะที่ได้ทำการศึกษา ได้ไดซัลไฟด์ร้อยละผลิตภัณฑ์ 55-100 ซึ่งข้อดีของไดอะเซทอกซีไอโอโดเบนซีนบนตัวรองรับพอลิสไตรีน คือ สามารถนำกลับมาใช้ใหม่ได้โดยปฏิกิริยาออกซิเดชันกับโซเดียมเปอร์บอเรตและนำมาทำปฏิกิริยาออกซิเดชันกับไทออลได้โดยไม่เสียสมรรถนะ

สาขาวิชา ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์ ลายมือชื่อนิสิต .....

ปีการศึกษา 2557 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

5572095323 : MAJOR PETROCHEMISTRY AND POLYMER SCIENCE
KEYWORDS: HYPERVALENT IODINE (III) / (DIACETOXYIODO)BENZENE / POLYSTYRENE-SUPPORTED (DIACETOXYIODO)BENZENE / PS-DIB / DIB / DISULFIDE

WATANYA KRAILAT: PREPARATION OF DISULFIDES FROM THIOLS USING HYPERVALENT IODINE(III). ADVISOR: ASST. PROF. SUMRIT WACHARASINDHU, Ph.D., CO-ADVISOR: ASSOC. PROF. PREECHA PHUWAPRAISIRISAN, Ph.D., 76 pp.

Disulfides are important compounds for peptide synthesis and use as vulcanizing agents for rubber and elastomers. Traditionally, the preparation of disulfides involves the use of toxic oxidizing agents. In this work, we develop the synthesis of disulfide from thiols using hypervalent iodine (III) which is commercially available, inexpensive and less toxic. We screen type of hypervalent iodine (III), amount of hypervalent iodine (III) and solvents for oxidation of thiols 1a to disulfide 2a under monitoring by HPLC. Under the optimized condition which is the use of (diacetoxyiodo)benzene (DIB) in *i*-PrOH for 5 minute at room temperature, 13 thiols are convert into the corresponding disulfides 75-95 %yields. Importantly, the reaction can be performed in an open-flask reaction in undried solvent. In addition, we prepare the polystyrene-supported (diacetoxyiodo)benzene (PS-DIB) from iodination of polystyrene by I_2/I_2O_5 followed by oxidation with either Ac_2O/H_2O_2 or $NaBO_3 \cdot 4H_2O$. Structure of prepared PS-DIB is confirmed by FTIR spectroscopy and the loading of the diacetoxyiodo group on polystyrene is determined by traditional iodometric titration giving value of 1.26-2.00 mmol/g. Under the optimized condition, 11 disulfides are successfully prepared in good to high yields (55-100 %). Moreover, PS-DIB can be regenerated by oxidization with $NaBO_3 \cdot 4H_2O$ and reused for oxidation of thiol without losing its performance.

Field of Study:	Petrochemistry and Polymer Science	Student's Signature .....
		Advisor's Signature .....
Academic Year:	2014	Co-Advisor's Signature .....

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LIST OF ABBREVIATIONS

^{13}C NMR	carbon-13 nuclear magnetic resonance
$CDCl_3$	deuterated chloroform
d	doublet (NMR)
DCE	1,2-dichloroethane
DIB	(diacetoxy)iodo benzene
dd	doublet of doublet
d	doublet (NMR)
equiv.	equivalent (s)
FTIR	Fourier transform infrared spectroscopy
g	gram (s)
GC	Gas chromatography
h	hour (s)
1H	NMR proton nuclear magnetic resonance
Hz	hertz
HPLC	High-performance liquid chromatography
J	coupling comstant (NMR)
kJ	kilojoule (s)
m	multiplet (NMR)
MeOH	methanol
min	minute (s)
mL	milliliter (s)
mmol	milimole (s)
NMR	nuclear magnetic resonance
PS-DIB	polystyrene-supported (diacetoxyiodo)benzene
PS-I	iodopolystyrene
PS	polystyrene
RT	room temperature

s	singlet (NMR)
t	triplet (NMR)
TfOH	trifluoromethanesulfonic acid
TLC	thin layer chromatography
UV	ultra violet
%	percent
$\propto$	alpha
β	beta
δ	chemical shift (NMR)
°C	degree Celsius
μL	microliter (s)
μM	micromolar (s)
%	yield percent yield

CHAPTER I
INTRODUCTTION

1.1 Introduction of Disulfide

Disulfide is a compound containing two linked sulfur atoms. They are important compounds in both biological and chemical processes that involved the peptide synthesis [1], protein stabilization [2], and disulfides have industrial applications as vulcanizing agents [3]. The common methods to synthesize disulfides are oxidation of thiols using various oxidizing agent such as transition metal oxides [4], nitric oxide [5], H_2O_2 [6], $I_2/CeCl_37H_2O$ [7], 2,6-dicarboxy pyridinium chlorochromate [8], $KMnO_4/CuSO_4$ [9], halogens [10], etc. However, there are some disadvantages such as high toxicity, expensive reagent, difficult work-up and long reaction times. Moreover, such strong oxidizing agents can lead to over-oxidized products such as thiosulfinates, thiosulfonates and sulfonic acids. Thus, many new methods for synthesis of disulfide have been developed to clean, mild and efficient oxidative method that produced disulfide in high yield with convenient work-up step. Herein, we reported the use of hypervalent iodine (III) for oxidation of thiols into disulfides which it is a low cost and low toxicity reagent.

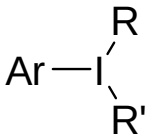
1.2 Introduction to Hypervalent iodine III

The first hypervalent iodine compound reported by the Conrad Willgerodt in 1886 as (dichloroiodo)benzene ($C_6H_5Cl_2I$) [11]. Since then, hypervalent iodine(III) are iodine compounds that have been used extensively in organic synthesis due to the chemical properties have similar to heavy metal reagent such as Hg(III), Pb(IV) or Ti(III) but without toxicity. Moreover, hypervalent iodine reagents are commercial availability, mild and highly selective oxidizing agents [12].

Classes of Hypervalent Iodine (III)

Ligands attached to the iodine atom are used for classification of hypervalent iodine (III). These are general hypervalent iodine (III) compound that have found many applications in organic synthesis.

1. (difluoroiodo)arenes; R, R'= F
2. (dichloroiodo)arenes; R, R'= Cl
3. [bis(acyloxy)iodo]arenes; R, R'= OCOR
4. aryliodine(III) organosulfonates; R= OH R'= OSO_2R



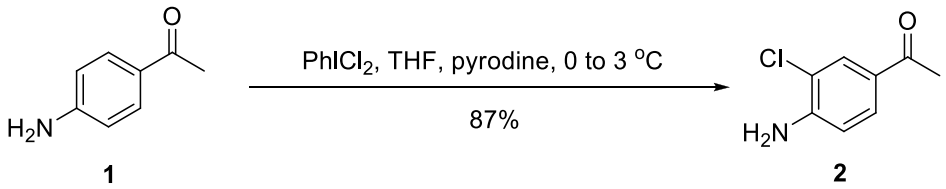
Difluoroiodo)arenes were synthesized from fluorination of iodoarenes with F_2, ClF, CF_3OCl, BrF_5, $C_6F_5BrF_2$, $C_6F_5BrF_4$, XeF_2, XeF_2/BF_3, etc [12]. (Difluoroiodo)benzene and difluoroiodotoluene (**DFIT**) were frequently used as fluorinating agent in organic synthesis. Among (dichloroiodo)arenes, (dichloroiodo)benzene and 4,4'-bis(dichloroiodo)biphenyl were widely used for chlorinating reagents. On the other hand, (bis(trifluoroacetoxy)iodo)benzene (**BTI**) and diacetoxyiodobenzene (**DIB**) are most used reagent in the class of [bis(acyloxy)iodo]arenes for oxygenation and oxidative functionalization of organic substrates. For aryliodine(III) organosulfonates, hydroxy(tosyloxy)iodobenzene (**HTIB**) or Koser's reagent was commonly used as strong oxidizing agent.

1.3 Literature reviews

1.3.1 Literature reviews on hypervalent iodine(III) in organic synthesis

As mention above, hypervalent iodine(III) were used for several synthetic application such as used as halogenation, oxidative transformations of organic substrates [12], in this section we summarized the recent use of such reagent as followed.

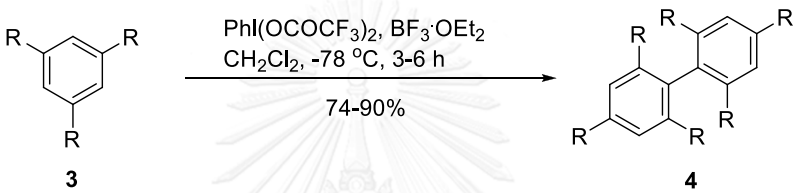
In 1998, Zanka and co-worker [13] described reagents for scaled up chlorination of electron-rich aromatic compounds as shown in scheme 1.1. They used (dichloroiodo)benzene ($PhICl_2$) as chlorinating reagent to synthesize 4-amino-3-chloroacetophenone **2** from aminoacetophenone **1**.



1 **2**

Scheme 1.1 Chlorination of 4-aminoacetophenone

In 2002, Tohma and co-workers [14] developed the use of [bis(trifluoroacetoxy)iodo]benzene (**BTI**) in oxidative coupling reaction of non-phenolic electron-rich aromatic substrate. Alkylbiaryls **4** was occurred from alkylarenes **3** by using a combination of [bis(trifluoroacetoxy)iodo]benzene (**BTI**) and BF_3•OEt_2 as shown in scheme 1.2.

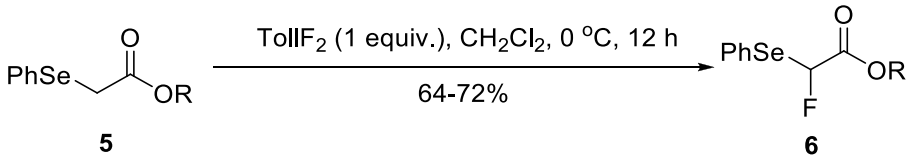


3 **4**

R= Me, Et or I

Scheme 1.2 Oxidative coupling of aromatic substrates Oxidative coupling of aromatic substrates.

In 2005, Maria and co-worker [15] developed the fluorinations of **α**-selanylesters **5** derivatives lead to **α**-fluoro **α**-phenylselanyl esters **6** by using (difluoroiodo)toluene (**TolIF$_2$**) as shown in scheme 1.3. The advantage of this method was avoiding the use of chlorine and fluorine gas. Moreover, the reactions were clean and no further oxidized products under the reaction conditions were detected.



5 **6**

R= Ph, CH_2CH=$CHPh$, CH_2CH=CMe_2, etc.

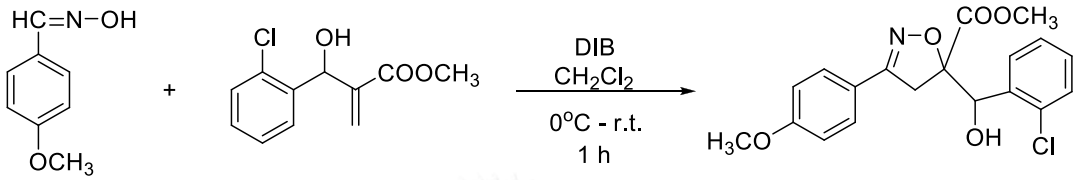
Scheme 1.3 Fluorination of **α**-selanylesters

1.3.2 Literature reviews on (diacetoxyiodo)benzene, (DIB) in organic synthesis

Among hypervalent iodine (III) reagent, (diacetoxyiodo)benzene, (**DIB**) is one of most used reagent in hypervalent iodines (III) family. This is because of wild availability, inexpensive and less toxic in comparison with other hypervalent

iodine(III). Therefore, we summarized the application of **DIB** in organic synthesis as followed.

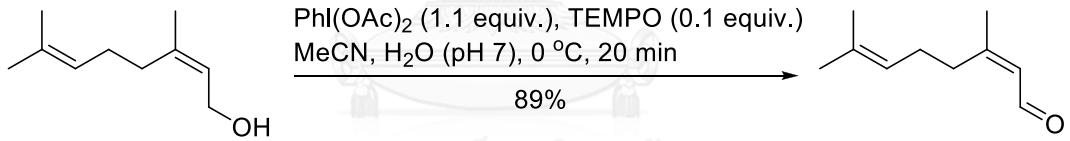
In 2004, Das and co-worker [16] studied the use of (diacetoxyiodo)benzene (**DIB**) for synthesis isoxazolines **9** from aldoximes **7** and Baylis–Hillman adducts **8** as seen in scheme 1.4. This reaction was completed in 60-90 minute at either 0°C or room temperature to give the product in 78-91 % yields.



7 **8** **9**

Scheme 1.4 Synthesis of isoxazolines from aldoximes and Baylis–Hillman adducts.

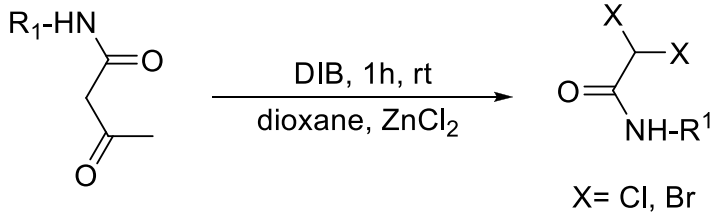
In 2009, Piancatelli and co-workers [17] reported the oxidation of alcohols (nerol **10**) using (diacetoxyiodo)benzene, (**DIB**) in catalytic amounts of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) to nepal **11** as seen in scheme 1.5. Nepal **11** was produced in good yield in aqueous solution.



10 **11**

Scheme 1.5 Oxidative Transformations of nerol to Nepal

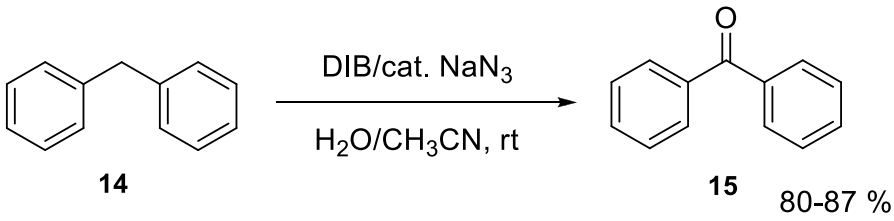
In 2012, Liu and co-worker [18] developed a simple and efficient method for the synthesis of 2,2-dihalo-N-phenylacetamides **13** from 3-oxobutanamides **12** by using (diacetoxyiodo)benzene (**DIB**) and Lewis acids such as $FeCl_3$ $ZnCl_2$ and $CuCl_2$ as seen in scheme 1.6. The advantages of this method are mild condition, various substrate scope and excellent yields.



12 **13**

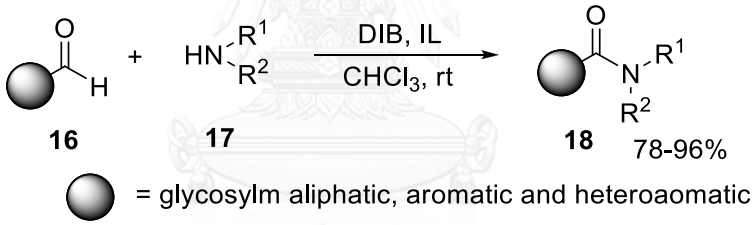
Scheme 1.6 Synthesis of 2,2-dihalo-N-phenylacetamides.

In 2012, Vikas and co-worker [19] developed the oxidation of benzylic C-H **14** to corresponding ketone **15** compounds from (diacetoxyiodo)benzene with a catalytic sodium azide as shown in scheme 1.7. The advantages of this reaction were mild condition and short reaction time.



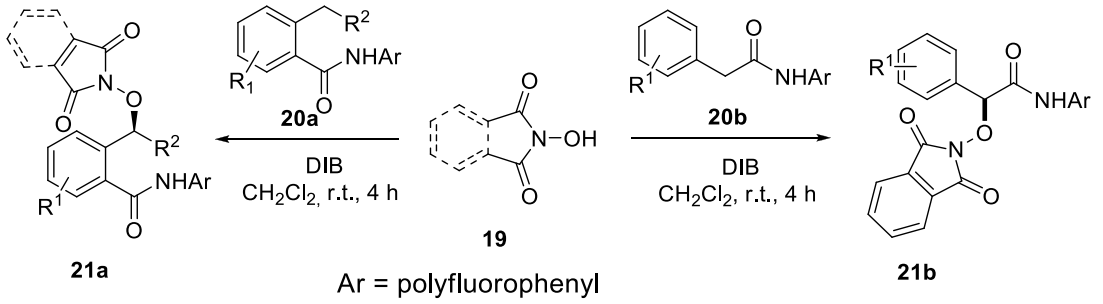
Scheme 1.7 Synthesis of ketone compounds from oxidation of benzylic C-H.

In 2012, Prasad and co-workers [20] developed the one-step oxidative amidation of aldehyde **16** with amine **17** to glycosyl carboxamides **18** under mild conditions using ionic liquid in 78-96 % yields with (diacetoxyiodo)benzene as shown in scheme 1.8.



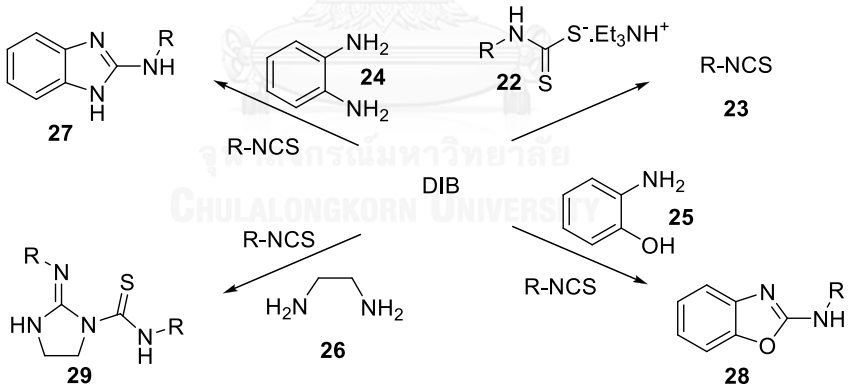
Scheme 1.8 Synthesis of glycosyl carboxamides from aldehyde and amine.

In 2015, Qian and co-worker [21] developed the use of (diacetoxyiodo)benzene for oxygenation of benzylic **19** C(sp^3)–H bonds with benzamides **20a** and 2-arylacetamides **20b** to form C(sp^3)–O bonds in **21a** and **21b** at room temperature as seen in scheme 1.9.



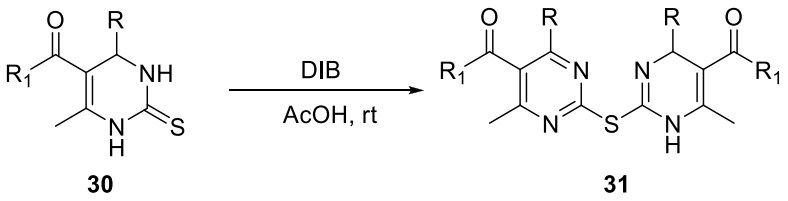
Scheme 1.9 Synthesis of C(sp^3)–O bonds from benzylic C(sp^3)–H bonds and N-hydroxyamides.

In 2008, Ghosh and co-workers [22] used (diacetoxyiodo)benzene for the synthesis of isothiocyanates **23** from the corresponding dithiocarbamate salts **22** in good to excellent yields. After that, they developed one-pot procedure for the synthesis of benzimidazoles **27**, aminobenzoxazoles **28** and imidazolidenecarbothio-amides **29** from o-phenylenediamine **24**, o-aminophenol **25** and 1,2-diamines **26** ,respectively in the presence of **DIB** in good to excellent yield as shown in scheme 1.10. This is the first work reported on the use of hypervalent iodine (III) to activate sulfur atom instead of carbon atom.



Scheme 1.10 Synthesis of benzimidazoles, aminobenzoxazoles and imidazolidenecarbothio-amides from o-phenylenediamine, o-aminophenol and 1,2-diamines.

While we investigated the use of **DIB** to activate thiol, Bhagyashree and co-workers [23] used (diacetoxyiodo)benzene to activate sulfur atom on 4-Aryl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione **30** to produce 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine derivatives **31** in acetic acid in 2013 as shown in scheme 1.11.



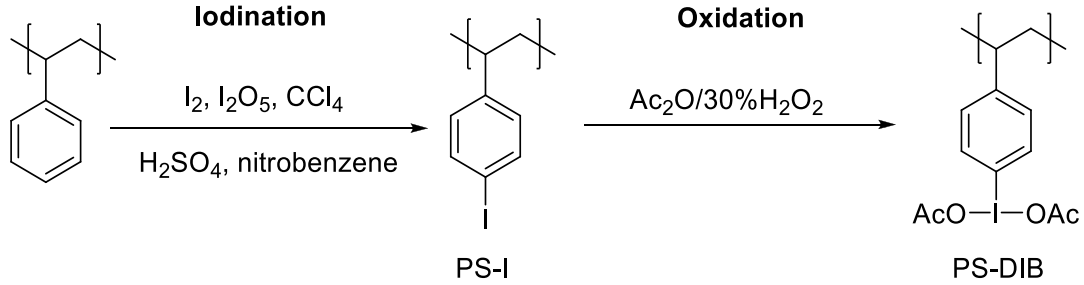
30 **31**

Scheme 1.11 Synthesis of 2-(1,4-dihydropyrimidin-2-ylthio)pyrimidine derivatives from 4-Aryl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione.

Based on above literature reviews, most of hypervalent iodine (III) was used for ether halogenation or oxygenation on carbon atom. However, in recent year, there was reports on activation of sulfur atom on thione derivatives using (diacetoxyiodo)benzene. Therefore in this work, we will investigated the used of (diacetoxyiodo)benzene for activation of sulfur atom on thiol which have never been reported before.

1.3.3 Literature reviews on polymer supported (diacetoxyiodo)benzene, (PS-DIB) in organic synthesis

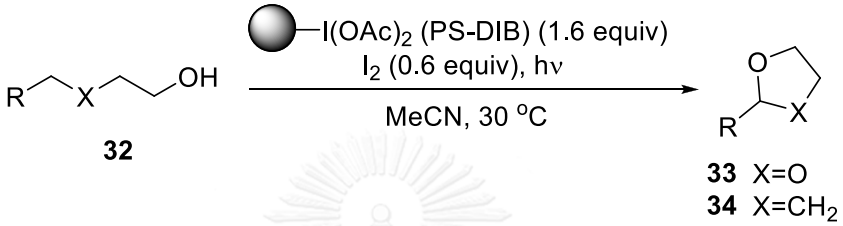
Even though, the (diacetoxyiodo)benzene reagent was extensively used in organic synthesis, the reagent was inconvenient to reuse or recycle and generated toxic byproduct. Those were caused by homogeneous nature of **DIB** and also the iodobenzene byproduct was usually dissolved in reaction mixture. Therefore, several researchers reported the preparation of hypervalent iodine (III) reagent as a form on polymer-supported which were recyclable and reusable reagent. Polymer-supported (diacetoxyiodo)benzene was prepared by iodination on polystyrene lead to iodopolystyrene and was further oxidized by hydrogen peroxide and acetic anhydride as shown in scheme 1.12. Consequently, we summarize the application of polymer-supported (diacetoxyiodo)benzene in organic synthesis as followed.



PS-I PS-DIB

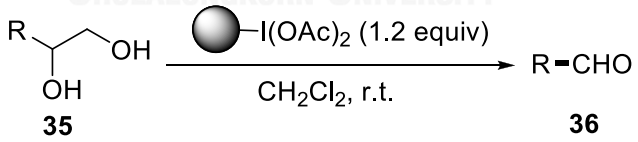
Scheme 1.12 Preparation of polymer-supported (diacetoxyiodo)benzene.

In 2005, Teduka and co-worker [24] used polymer-supported (diacetoxyiodo)benzene (**PS-DIB**) with iodine under irradiation with a tungsten lamp for the preparation of 2-aryl-1,3-dioxolanes **33** and 2-aryl-1,3-tetrahydrofurans **34** from the corresponding alcohols **32** as shown in scheme 1.13. This reaction was used in acetonitrile at 30°C and gave the desired products in 55-76 % yield after flash column chromatography. Moreover, after these reactions, polymer were regenerated and reused for 2 times without losing its efficiency.



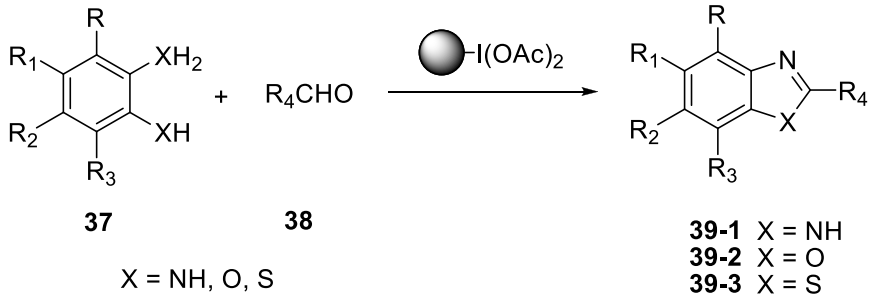
Scheme 1.13 Synthesis of 2-aryl-1,3-dioxolanes 3and 2-aryl-1,3-tetrahydrofurans from alcohols.

In 2006, Chen and co-workers [25] synthesized aldehydes **36** from highly selective oxidative cleavage of vicinal diols **35** by using polymer-supported (diacetoxyiodo)benzene, (**PS-DIB**) in high isolated yield. The advantages of this method are mild conditions, non-toxic and easy reaction work-up by simple filtration to remove the polymer-supported reagent. Moreover, **PS-DIB** can be regenerated and reused for the same reactions with the same efficiency.



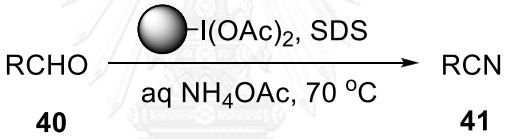
Scheme 1.14 Synthesis of aldehydes from vicinal diols.

In 2009, Kumar and co-workers [26] demonstrated a practical synthetic route to benzimidazoles **39-1**, benzoxazoles **39-2**, and benzothiazoloes **39-3** from reaction between corresponding amines **37** and corresponding aldehydes **38** using polymer-supported (diacetoxyiodo)benzene (**PS-DIB**) as seen in scheme 1.15. The reaction was completed in 5-10 minutes at room temperature in CH_2Cl_2 and gave excellent yields after silica-gel column chromatography. **PS-DIB** can be reused many times without losing the activity.



Scheme 1.15 Synthesis of benzimidazoles, benzoxazoles, and benzothiazoloes from amine and aldehyde.

In 2010, Zhu and co-workers [27] developed a one pot synthesis of nitriles **40** from aldehydes **41** using polymer-supported (diacetoxyiodo)benzene (**PS-DIB**) in excellent yield based on GC analysis as seen in scheme 1.16. The reactions proceed in water at 70 °C in the presence of catalytic amounts of sodium dodecylsulfate (**SDS**) using NH_4OAc as the nitrogen source. Moreover, **PS-DIB** was successfully regenerated and reused three times with the same activity in excellent yield.

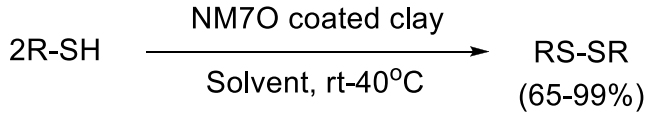


Scheme 1.16 Synthesis of nitriles from aldehydes.

1.3.4 Literature reviews on disulfides from thiols

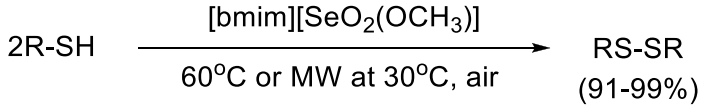
Recent development for synthesis of thiols from disulfides has been focused on the use of new reagent which was mild and efficient as followed.

In 2009, Gondi and co-workers [28] developed the use of a nanophase manganese(VII) oxide coated clay (NM7O coated clay) catalyst for the synthesis of disulfides from thiols as seen in scheme 1.17. Moreover, NM7O coated clay catalyst can be recycled and reused.



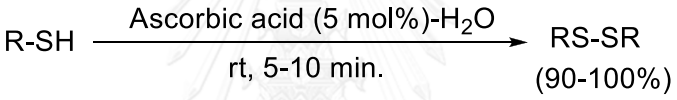
Scheme 1.17 Synthesis of disulfides from thiols using nanophase manganese(VII) oxide coated clay.

In 2010, Thurow and co-workers [29] successfully synthesized disulfides via thiols using 1-n-butyl-3-methylimidazolium methylselenite, [bmim][$SeO_2(OCH_3)$] as shown in scheme 1.18. Such reagent is ionic liquid that used both as solvent and catalyst and easily reuse for further oxidation reactions. The reaction was completed in conventional heating 3-18 hour at 60 ^{o}C or under microwave irradiation in 15 min at 30 ^{o}C.



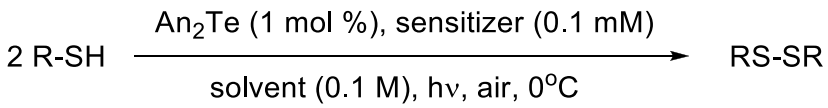
Scheme 1.18 Synthesis of disulfides from thiols using [bmim][SeO2(OCH3)].

In 2010, Attri and co-workers [30] developed the use of ascorbic acid (vitamin C) for the synthesis of disulfides from thiols in short reaction time and excellent yields as shown in scheme 1.19. Ascorbic acid (vitamin C) has several advantages such as inexpensive and environmentally benign catalyst in organic synthesis.



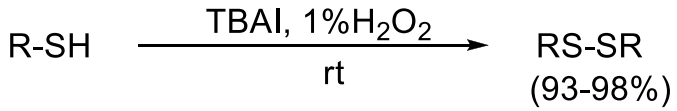
Scheme 1.19 Synthesis of disulfides from thiols using ascorbic acid (vitamin C).

In 2011, Oba and co-workers [31] reported the synthesis of disulfides from aerobic oxidation of thiols using diaryl tellurides such as bis(4-methoxyphenyl) telluride under photosensitized conditions in good to excellent yields as shown in scheme 1.20.



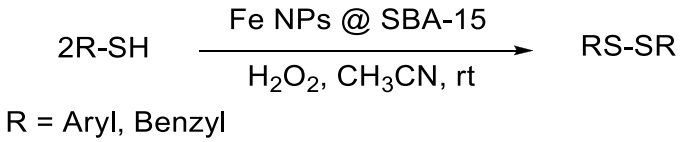
Scheme 1.20 Synthesis of disulfides from thiols using bis(4-methoxyphenyl) telluride.

In 2012, He and co-workers [32] synthesized corresponding disulfides from corresponding thiols using 1% hydrogen peroxide catalyzed tetrabutylammonium iodide (TBAI) without solvent at room temperature as shown in scheme 1.21. In this reaction the desired disulfides was obtained in 93-98 % yields in short reaction time.



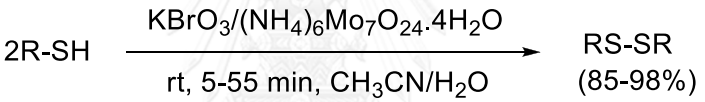
Scheme 1.21 Synthesis of disulfides from thiols using 1%H_2O_2 catalyzed TBAI.

In 2013, Rajabi and co-workers [33] studied the use of supported iron oxide nanoparticles ,Fe NPs @ SBA-15 as environmentally friendly and reusable catalysts with H_2O_2 as a green oxidant for synthesizing disulfides from thiols at room temperature in excellent yields as shown in scheme 1.22. The utilized catalyst was successfully reusable under the reaction conditions in 5 times with the same activity.



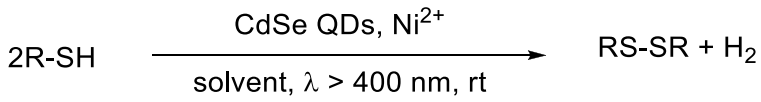
Scheme 1.22 Synthesis of disulfides from thiols using Fe NPs @ SBA-15 with H_2O_2.

In 2013, Bayraq and co-workers [34] synthesized disulfides from thiols using ammonium molybdate, $(NH_4)_6Mo_7O_{24}•4H_2O$ as a cheap, safe and stable catalyst in high yield as shown in scheme 1.23. Moreover, this catalyst can be recovered and reused in the same condition with the same activity.



Scheme 1.23 Synthesis of disulfides from thiols using $(NH_4)_6Mo_7O_{24}•4H_2O$.

In 2015, li and co-worker [35] developed the use of visible-light irradiation of CdSe quantum dots (CdSe QDs) to coupling of a variety of thiols lead to disulfides and H_2 without reagents in good yield and the reaction was added the small amounts of nickel(II) salts to rapidly improve of conversion as shown in 1.24. In addition, CdSe QDs can be regenerated and reused and gave a loss of activity of only approximately 5% between the first and last runs.



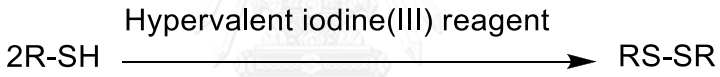
Scheme 1.24 Synthesis of disulfides from thiols using visible-light irradiation of CdSe QDs.

Among the method mentioned in literature reviews, they have still some disadvantages for synthesis of disulfide including the use of transition metal which are toxic and expensive. Moreover, some conditions were difficult for work-up and required long reaction time. In addition, the reaction generated over-oxidized

byproducts such as thiosulfinates, thiosulfonates and sulfonic acids. Based on the advantages of hypervalent iodine (III) reagents such as commercial availability, mild and highly selective oxidizing agents, we will use such reagent for oxidation of thiol into disulfide.

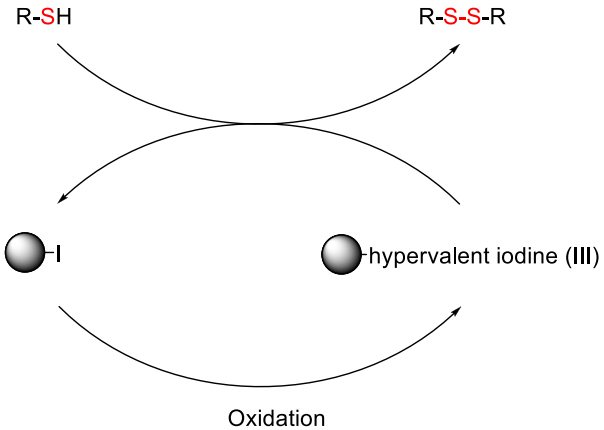
1.4 Objectives of this research

According to the reviews, hypervalent iondine (III) has been widely used as oxidizing agents for organic synthesis but there is no report on the use for oxidizing thiols into disulfide. The advantages of hypervalent iondine (III) are low cost, mild and highly selective properties, environmental friendly character and commercial availability. In this work we will 1) investigate the use of hypervalent iodine (III) to synthesize disulfides from thiols as shown in scheme 1.25. Optimization of the reaction conditions based on the types of hypervalent iodine (III), solvent, and equivalent of hypervalent iodine (III) will be examined.



Scheme 1.25 Utilization hypervalent iodine (III) to synthesized disulfides.

In addition, we will 2) develop polymer-supported hypervalent iodine (III) as reusable reagents for oxidizing thiols as shown in scheme 1.26 and study the reaction optimization including solvent, equivalent of polymer-supported hypervalent iodine (III) and reaction time of reaction.



Scheme 1.26 Utilization of Polymer-supported hypervalent iodine (III) reagent for preparation of disulfide.  = polymer

CHAPTER II
EXPERIMENTAL

2.1 General information

Starting materials were purchased from commercial suppliers and used without further purification. All solvent were used without drying from Sigma-Aldrich. Analytical thin-layer chromatography (TLC) was performed on Kieselgel F-254 pre-coated plastic TLC plates from EM Science and visualized under 254 nm ultraviolet lamp. Column chromatography was carried out with ICN Silitech silica gel 60 (70–230 mesh). MS (ESI) and HRMS (ESI) were obtained with a micro TOF Bruker mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz and Bruker 400 MHz in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C NMR were reported in ppm (δ) and referenced to $CHCl_3$ (δ 7.26 for ^{1}H, δ 77.00 for ^{13}C). Coupling constant (*J*) were reported in Hertz (Hz). Fourier transform infrared spectra were obtained on Nicolet 6700 FT-IR spectrometer furnished with a mercury-cadminum telluride (MCT) detector (Nicolet, USA). The gas chromatography (GC) was completed using Agilent CP 8741 gas chromatography instrument equipped with a flame ionization detector (FID) with N_2 as a carrier gas using 30m long CP sil5 (0.25 mm outer diameter, 0.25 μm film thickness). High performance liquid chromatography (HPLC) analysis was carried out on a HPLC system including a plum (Water 1525 with column heater), auto sampler (Waters 2707) and detector (Waters2489 UV detector). Chromatographic separation was performed on sunfire 5 μm C18 4.6x150 mm using mobile phases was an isocratic system of methanol/water (80:20) at a flow rate of 0.5 mL/min. The system was monitored at 254 of UV-dectector.

2.2 Using hypervalent iodine(III) for preparation of disulfides from thiols

2.2.1 Optimization of the reaction conditions

Table 3.1 Hypervalent iodine(III) screening: 4-chlorothiophenol (**1a**) 20.0 mg (1.0 equiv) and hypervalent iodine (III) (1.0 equiv) were mixed with 4 mL of *i*-PrOH in

round bottom flask with magnetic stir bar to give 1,2-Bis(4-chlorophenyl)disulfane (**2a**). The mixture was stirred at ambient temperature. The solvent was removed by rotary evaporation and the crude product was purified by silica gel chromatography.

Table 3.2 Effect of DIB amount: 4-chlorothiophenol (**1a**) 20.0 mg (1.0 equiv) and (diacetoxyiodo)benzene, **DIB** were mixed with 4 mL of *i*-PrOH in round bottom flask with magnetic stir bar. The mixture was stirred at ambient temperature for 5 minute to give 1,2-Bis(4-chlorophenyl)disulfane (**2a**). The solvent was removed by rotary evaporation and the crude product was purified by silica gel chromatography.

Table 3. Effect of solvent: 4-chlorothiophenol (1a) 20.0 mg (1.0 equiv) and (diacetoxyiodo)benzene, **DIB** (1.0 equiv) were mixed with 4 mL of solvents in round bottom flask with magnetic stir bar. The mixture was stirred at ambient temperature for 5 minute to give 1,2-Bis(4-chlorophenyl)disulfane (**2a**). The solvent was removed by rotary evaporation and the crude product was monitored by HPLC

2.2.2 Screening of thiols

General procedure for synthesis of disulfides 2a–m from thiol 1a-m using (diactoxyiodo)benzene as reagent: thiols **1a-m** (1.0 equiv) and **DIB** (1.0 equiv) were mixed with *i*-PrOH as solvent with magnetic stir bar. The mixture was stirred at ambient temperature for 5 minute to give disulfides (**2a-m**). The solvent was removed by rotary evaporation and the crude product was purified by silica gel chromatography.

1,2-Bis(4-chlorophenyl)disulfane (2a) : synthesized according to general procedure from 4-chlorothiophenol **1a** (100 mg, 0.691 mmol) and **DIB** (222 mg, 0.691 mmol) dissolved in *i*-PrOH (4 mL) to afford **2a** (86.6 mg, 0.346 mmol, 87%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 (d, *J* = 8.7 Hz, 4 H), 7.27 (d, *J* = 8.7 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.2, 133.7, 129.4, 129.3 ppm. IR (neat): $\tilde{\nu}$ = 3079, 2925, 1470, 1385 cm^{-1}.

6,6-Disulfanediyldihexan-1-ol (2b): [CAS: 80901-86-6]: synthesized according to general procedure from 6-mercapto-1-hexanol **1b** (101 μL, 0.745 mmol) and **DIB** (240 mg, 0.745 mmol) dissolved in *i*-PrOH (4 mL) to afford **2b** (87.0 mg, 0.373 mmol, 87%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.66 (t, *J* = 6.6 Hz, 4 H), 2.77–

2.62 (m, 4 H), 1.71 (m, 4 H), 1.59 (m, 4 H), 1.51–1.34 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ** = 62.8, 39.1, 32.6, 29.1, 28.2, 25.4 ppm. IR (neat): $\tilde{\nu}$ = 3346, 2934, 2859, 1465, 1053 cm^{-1}.

1,2-Dioctyldisulfane (2c) : [CAS: 822-27-5]: synthesized according to general procedure from 1-octanethiol **1c** (118 μL, 0.684 mmol) and **DIB** (220 mg, 0.684 mmol) dissolved in *i*-PrOH (4 mL) to afford **2b** (89.0 mg, 0.342 mmol, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ** = 3.30 (m, 4 H), 2.70 (m, 4 H), 1.69 (t, *J* = 7.5 Hz, 4 H), 1.30 (d, *J* = 2.7 Hz, 16 H), 0.9 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ** = 39.2, 31.8, 29.2, 28.6, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3056, 2928, 2859, 1268, 1131 cm^{-1}.

1,2-Dicyclohexyldisulfane (2d): [CAS: 2550-40-5]: synthesized according to general procedure from cyclohexanethiol **1d** (101 μL 0.860 mmol) and, **DIB** (277 mg, 0.860 mmol) dissolved in *i*-PrOH (4 mL) to afford **2d** (79.7 mg, 0.430 mmol, 80%) as white crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ**= 2.65 (m, 2 H), 2.01 (s, 4 H), 1.77 (s, 4 H), 1.60 (t, *J* = 6 Hz, 2 H), 1.25 (m, 10 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): **δ** = 50.0, 32.9, 26.1, 25.7 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2853, 1450, 1340, 1262 cm^{-1}.

1,2-DIBenzyldisulfane (2e): [CAS: 150-60-7]: synthesized according to general procedure from benzyl mercaptan **1e** (94.0 μL, 0.804 mmol) and **DIB** (277 mg, 0.804 mmol) dissolved in *i*-PrOH (4 mL) to afford **2e** (85.7 mg, 0.402 mmol, 86%) as pink crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ**= 7.37–7.29 (m, 10 H), 3.65 (s, 4 H) ppm. ^{13}C NMR (CDCl3, 100 MHz): **δ** = 137.4, 129.4, 128.5, 127.4, 43.4 ppm. IR (neat): $\tilde{\nu}$ = 3052, 3029, 2914, 2857, 1497, 1456, 1405 cm^{-1}.

2,2 -Disulfanediyldianiline (2f): [CAS: 1141-88-4]: synthesized according to general procedure from 2-aminothiophenol **1f** (85.0 μL, 0.799 mmol) and **DIB** (257 mg, 0.799 mmol) dissolved in *i*-PrOH (4 mL) to afford **2f** (74.6 mg, 0.399 mmol, 75%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ**= 7.18 (t, *J* = 11.0 Hz, 4 H), 6.74 (m, 2 H), 6.62 (m, 2 H), 4.19 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ** = 148.6, 136.8, 131.6, 118.8, 115.3 ppm. IR (neat): $\tilde{\nu}$ = 3377, 3294, 3067, 2925, 2852, 1606, 1580, 1470, 1441 cm^{-1}.

1,2-Di-p-tolyldisulfane (2g): [CAS: 103-19-5]: synthesized according to general procedure from 4-methyl thiophenol **1g** (100 mg, 0.804 mmol) and **DIB** (259 mg, 0.804 mmol) dissolved in *i*-PrOH (4 mL) to afford **2g** (94.4, 0.402 mmol, 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ**= 7.30 (d, *J* = 8.4 Hz, 4 H), 7.03 (d, *J* = 8.4 Hz, 4 H), 2.24 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ**= 137.5, 133.9, 129.8, 128.6, 21.0 ppm. IR (neat): ν^{-}= 3020, 2914, 2852, 1488, 1397 cm–1.

1,2-Di(pyridine-2-yl)disulfane (2h): [CAS: 2127-03-9]: synthesized according to general procedure from 2-mercaptopyridine **1h** (50.0 mg, 0.450 mmol), **DIB** (159 mg, 0.495 mmol) dissolved in *i*-PrOH (4 mL) to afford **2h** (44.4 mg, 0.202 mmol, 90%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ** = 8.40 (d, *J* = 8.1 Hz, 2 H), 7.60–7.49 (m, 4 H), 7.04 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 149.6, 137.4, 121.1, 119.7 ppm. IR (neat): ν^{-} = 3046, 2987, 1574, 1556, 1444, 1414 cm–1.

1,2-Di(pyridin-4-yl)disulfane (2i): [CAS: 2645-22-9]: synthesized according to general procedure from 4-mercaptopyridine **1i** (50.0 mg, 0.450 mmol) and **DIB** (159 mg, 0.495 mmol) dissolved in *i*-PrOH (4 mL) to afford **2i** (42.6 mg, 0.194 mmol, 86%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ** = 8.42 (d, *J* = 5.5 Hz, 4 H), 7.29 (d, *J* = 5.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.9, 145.3, 119.0 ppm. IR (neat): ν^{-} = 3032, 3002, 2922, 1568, 1544, 1479, 1405 cm^{-1}.

1,2-Bis(5-bromopyridin-2-yl)disulfane (2J): [CAS: 872273-36-4]: synthesized according to general procedure from 5-bromopyridine-2- thiol **1J** (100 mg, 0.526 mmol) and **DIB** (169 mg, 0.526 mmol) dissolved in *i*-PrOH (4 mL) to afford **2J** (81.5 mg, 0.263 mmol, 82%) as yellow crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.45 (d, *J* = 2.4 Hz, 2 H), 7.66 (dd, *J* = 8.5, 2.4 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ** = 157.2, 150.6, 139.9, 121.1, 118.3 ppm. IR (neat): ν^{-} = 3099, 3058, 2922, 1550, 1438, 1343 cm^{-1}.

1,2-Di(pyrimidin-2-yl)disulfane (2k): [CAS: 15718-46-4]: synthesized according to general procedure from 2-mercaptopyrimidine **1k** (100.00 mg, 0.89 mmol) and **DIB** (287.31 mg, 0.89 mmol) dissolved in *i*-PrOH (4.0 mL) to afford **2k** (74.00 mg, 0.45 mmol, 75%) as yellow crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.52 (d, *J* = 4.8 Hz, 4 H), 7.02 (t, *J* = 4.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ** = 169.8,

157.9, 118.1, 29.7 ppm. IR (neat): $\bar{\nu}$ = 3114, 3067, 2919, 2846, 1550, 1426, 1364, 1264 cm^{-1}.

1,2-Bis(benzo[*d*]thiazol-2-yl)disulfane (2l): [CAS: 120-78-5]: synthesized according to general procedure from 2-mercaptobenzothiazole **1l** (100 mg, 0.599 mmol), **DIB** (192 mg, 0.599 mmol) in *i*-PrOH (4 mL) to afford **2l** (85.9 mg, 0.299 mmol, 89%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ** = 7.87 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz, 2 H), 7.29 (t, *J* = 7.2 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ** = 167.8, 154.5, 136.2, 126.6, 125.3, 122.7, 121.3 ppm. IR (neat): $\bar{\nu}$ = 3058, 2978, 2928, 2869, 1464, 1423, 1317, 1237 cm^{-1}.

1,2-Di(quinolin-2-yl)disulfane (2m): [CAS: 2889-13-6]: synthesized according to general procedure from quinoline-2-thiol **1m** (100 mg, 0.620 mmol) and **DIB** (199 mg, 0.620 mmol) dissolved in *i*-PrOH (4 mL) to afford **2m** (90.4 mg, 0.310 mmol, 91%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): **δ** = 7.95 (m, 4 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 7.65 (m, 4 H), 7.42 (t, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): **δ** = 158.3, 146.9, 136.5, 129.4, 127.3, 126.7, 125.4, 124.4, 116.3 ppm. IR (neat): $\bar{\nu}$ = 3058, 2922, 2849, 1612, 1585, 1556, 1491, 1447, 1423 cm^{-1}.

2.3 Polystyrene-supported (diacetoxyiodo)benzene for oxidation of thiols into disulfides.

2.3.1 Synthesis of polystyrene-supported (diacetoxyiodo)benzene PS-DIB and characterization

Synthesis of poly (4-iodostyrene) (PS-I) [36]**:** To a mixture of nitrobenzene (50 mL), carbon tetrachloride (10 mL) and sulfuric acid (50%, 9 mL) were added commercially available polystyrene (MW=35,000) (4 g, 38.25 mmol), iodine (4.5 g, (17.75 mmol), and iodine pentaoxide (1.79 g, 5.36 mmol) at room temperature and the reaction was stirred under reflux at 90^{o}C for 72 h. After that, methanol 400 mL was added into the reaction mixture and the precipitate was collected by filtration and washed with methanol and dried to give strong yellowish solid (8.79 g, 93 % yield).

Synthesis of polystyrene-supported (diacetoxyiodo)benzene (PS-DIB):

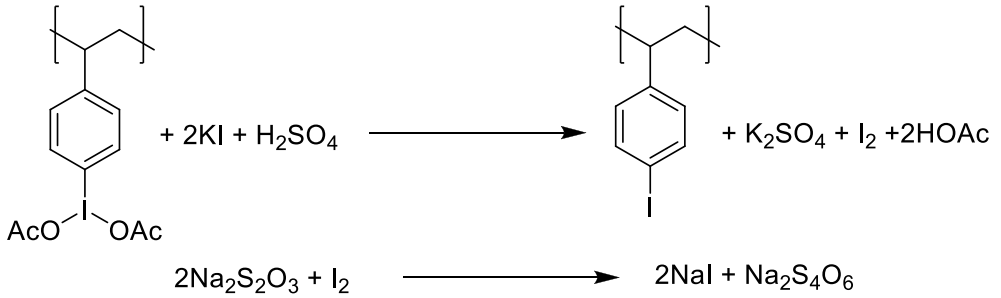
Method A [36] A solution of poly (4-iodostyrene) (5.2 g, 22.61 mmol), acitic acid (113 mL), 1,2 dichloroethane (7 mL), and trifluoromethanesulfonic acid (12 mL, 135.66 mmol) was stirred at 40°C. Then, sodium perborate tetrahydrate (20.88 g, 135.66 mmol) was added slowly within 2 hour. After the reaction that, solvents were evaporated by rotary evaporation and water 40 mL was added into the reaction. The precipitate was filtered, washed with methanol and dried to give yellow powder (5.89 g, 69 % yield).

Method B [25] A solution of 30% hydrogen peroxide (27 mL, 895.01 mmol) was added dropwise into acetic anhydride (97 mL, 1030.91 mmol) and stirred at 40 °C for 4 hour. Then, poly(4-iodostyrene) (5.2 g) was added into the reaction mixture and stirred overnight. Diethyl ether 100 mL was then added into the reaction. The precipitate was filtrated, washed with methanol and dried under vacuum to give yellow powder (4.64 g, 54 % yield).

2.3.2 Determination of loading of (diacetoxyiodo)phenyl group on PS-DIB

Iodometric titration

The loading of the reagent was determined by iodometric titration [37]. A mixture of polystyrene-supported (diacetoxyiodo)benzene (0.031 g), potassium iodide (0.250 g), deionized water (12.5 mL), sulfuric acid (6 N, 1.25 mL), and chloroform (1.25 mL) were added in 50 mL flask and stirred for 4 hour. The reaction mixture was titrated with 0.1 N sodium thiosulfate using starch solution as indicator based on scheme 2.1. The polymer loading of (diacetoxyiodo)phenyl group could be calculated as 27% form the equation shown below:



Scheme 2.1 Iodometric titration.

$$\text{The polymer loading of (diacetoxyiodo)phenyl group} = \frac{1/2 \times N \times V}{\text{Gram of } \mathbf{PS\text{-}DIB}}$$

(Equation 2.1)

2.3.3 Utilization of PS-DIB for oxidization of thiols

2.2.3.1 Optimization of the reaction conditions

Table 3.6 Effect of PS-DIB amount: 4-chlorothiophenol (**1a**) 20.0 mg (1.0 equiv) and polystyrene-supported (diacetoxyiodo)benzene **PS-DIB** were mixed with 5 mL of *i*-PrOH in round bottom flask with magnetic stir bar. The mixture was stirred at ambient temperature for 60 min to give 1,2-Bis(4-chlorophenyl)disulfane (**2a**). The precipitate was filtrated, washed with methanol and solvent was removed by rotary evaporation. The % yield of disulfide **2a** was received from GC analysis based on internal standard using biphenyl.

Table 3.7 Effect of time: 4-chlorothiophenol (**1a**) 20.0 mg (1.0 equiv) and polystyrene-supported (diacetoxyiodo)benzene **PS-DIB** (0.7 equiv) were mixed with 5 mL of *i*-PrOH in round bottom flask with magnetic stir bar. The mixture was stirred at ambient temperature to give 1,2-Bis(4-chlorophenyl)disulfane (**2a**). The precipitate was filtrated, washed with methanol and solvent was removed by rotary evaporation. The % yield of disulfide **2a** was received from GC analysis based on internal standard using biphenyl.

Table 3.8 Effect of solvent: 4-chlorothiophenol (**1a**) 20.0 mg (1.0 equiv) and polystyrene-supported (diacetoxyiodo)benzene **PS-DIB** (0.7 equiv) were mixed with 5 mL of solvent in round bottom flask with magnetic stir bar. The mixture was stirred at ambient temperature for 60 minute to give 1,2-Bis(4-chlorophenyl)disulfane (**2a**). The precipitate was filtrated, washed with methanol and solvent was removed by rotary evaporation. The % yield of disulfide **2a** was received from GC analysis based on internal standard using biphenyl.

2.3.3.2 Screening of thiols

General procedure for synthesis of disulfides **2a–J** and **m** from thiol **1a-J**, **m** using polystyrene-supported (diacetoxyiodo)benzene **PS-DIB** as reagent: thiols **1a-J**,

m (1.0 equiv) and **DIB** (0.7 equiv) were mixed with *i*-PrOH as solvent with magnetic stir bar. The mixture was stirred at ambient temperature for 60 minute to give disulfides (**2a-J**, **m**). The solvent was removed by rotary evaporation and the crude product was purified by silica gel chromatography.

1,2-Bis(4-chlorophenyl)disulfane (2a) : synthesized according to general procedure from 4-chlorothiophenol **1a** (50 mg, 0.346 mmol) and **PS-DIB** 0.7 equiv. (192 mg, 0.242 mmol, 1.26mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2a** (44.0 mg, 0.173 mmol, 89%) as a yellow solid.

6,6-Disulfanediyldihexan-1-ol (2b): [CAS: 80901-86-6]: synthesized according to general procedure from 6-mercapto-1-hexanol **1b** (50.76 μL, 0.372 mmol) and **PS-DIB** 2.5 equiv. (669 mg, 0.930 mmol, 1.39 mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2b** (51.2 mg, 0.186 mmol, 103%) as a yellow solid.

1,2-Dioctyldisulfane (2c) : [CAS: 822-27-5]: synthesized according to general procedure from 1-octanethiol **1c** (59.4 μL, 0.342 mmol) and **PS-DIB** 1.0 equiv. (120 mg, 0.171 mmol, 2.0 mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2c** (45.4 mg, 0.171 mmol, 91%) as a colorless oil.

1,2-Dicyclohexyldisulfane (2d): [CAS: 2550-40-5]: synthesized according to general procedure from cyclohexanethiol **1d** (50.5 μL 0.426 mmol) and, **PS-DIB** 1.0 equiv. (338 mg, 0.426 mmol, 1.26mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2d** (46.8 mg, 0.213 mmol,95%) as white crystals.

1,2-DIBenzyldisulfane (2e): [CAS: 150-60-7]: synthesized according to general procedure from benzyl mercaptan **1e** (47.26 μL, 0.0.402 mmol) and **PS-DIB** 1.0 equiv. (201 mg, 0.402 mmol, 2.0 mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2e** (46.6 mg, 0.201 mmol, 94%) as pink crystals.

2,2 -Disulfanediyldianiline (2f): [CAS: 1141-88-4]: synthesized according to general procedure from 2-aminothiophenol **1f** (42.74 μL, 0.399 mmol) and **PS-DIB** 2.0 equiv. (574 mg, 0.799 mmol, 1.39 mmol/g) dissolved in i-PrOH (5mL) to afford **2f** (80.0 mg, 0.200 mmol, 81%) as a yellow solid.

1,2-Di-p-tolyldisulfane (2g): [CAS: 103-19-5]: synthesized according to general procedure from 4-methyl thiophenol **1g** (50 mg, 0.403 mmol) and **PS-DIB** 0.7 equiv.

(224 mg, 0.282 mmol, 1.26mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2g** (43.3, 0.201 mmol, 97%) as a yellow oil.

1,2-Di(pyridine-2-yl)disulfane (2h): [CAS: 2127-03-9]: synthesized according to general procedure from 2-mercaptopyridine **1h** (50.0 mg, 0.450 mmol), **PS-DIB** 0.7 equiv. (250 mg, 0.315 mmol, 1.26mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2h** (41.3 mg, 0.225 mmol, 83%) as a white solid.

1,2-Di(pyridin-4-yl)disulfane (2i): [CAS: 2645-22-9]: synthesized according to general procedure from 4-mercaptopyridine **1i** (50.0 mg, 0.450 mmol) and **PS-DIB** 1.5 equiv. (486 mg, 0.675 mmol, 1.39mmol/g) dissolved in *i*-PrOH (5 mL)] to afford **2i** (34.6 mg, 0.225 mmol, 70%) as a white solid.

1,2-Bis(5-bromopyridin-2-yl)disulfane (2J): [CAS: 872273-36-4]: synthesized according to general procedure from 5-bromopyridine-2-thiol 1J (50 mg, 0.263 mmol) and **PS-DIB** 1.5 equiv. (284 mg, 0.395 mmol, 1.39 mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2J** (27.4 mg, 0.132 mmol, 55%) as yellow crystals.

1,2-Di(quinolin-2-yl)disulfane (2m): [CAS: 2889-13-6]: synthesized according to general procedure from quinoline-2-thiol **1m** (50 mg, 0.446 mmol) and **PS-DIB** 0.7 equiv. (156 mg, 0.312 mmol, 2.0 mmol/g) dissolved in *i*-PrOH (5 mL) to afford **2m** (48.2 mg, 0.223 mmol, 97%) as a yellow solid.

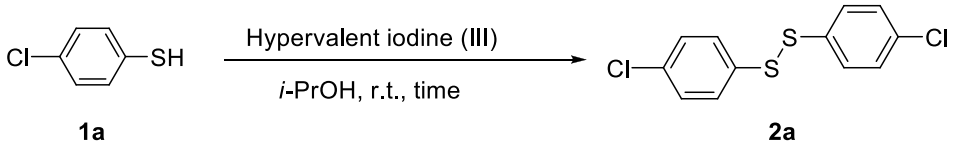
CHAPTER III
RESULTS AND DISCUSSION

3.1 Using hypervalent iodine(III) for preparation of disulfides from thiols

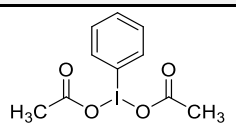
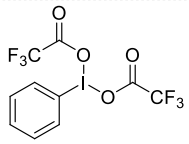
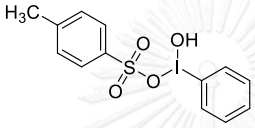
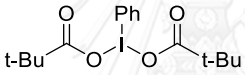
3.1.1 Optimization study

In this work, we plan to develop the method for synthesize of disulfides via thiol using hypervalent iodine(III) reagents. First, 4 types of hypervalent iodine(III) such as (diacetoxyiodo)benzene (**3a**), [bis(trifluoroacetoxy)iodo]benzene (**3b**), [hydroxy(tosyloxy)-iodo]benzene (**3c**) and bis(tert-butylcarbonyloxy)iodobenzene) (**3d**) were treated with 4-chlorothiophenol in *i*-PrOH at room temperature in open flask to provide 1,2-bis(4-chlorophenyl)disulfane. The results were summarized in Table 3.1. Hypervalent iodine(III) reagents **(3b-d)** gave disulfide **(2a)** in moderate yields (55-72%, entry 2-4) while **3a** was able to convert thiol into disulfide (**2a**) 87% yield within 5 min. We hypothesized that hypervalent reagents (III) **3b-3d** were sensitive to oxygen and moisture which could decompose under our reaction condition. (Diacetoxyiodo)benzene not only gave the best yield for synthesize of disulfide but it is also wildly available and inexpensive price comparing to other tested hypervalent iodines (III). Therefore, we selected (diacetoxyiodo)benzene (**3a**) as the oxidizing agent for further investigation.

Table 3.1 Hypervalent iodine (III) screening



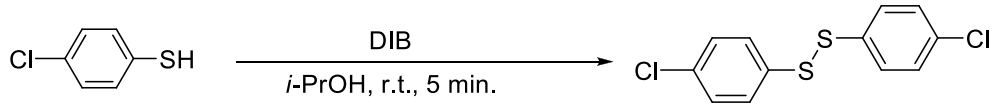
1a **2a**

Entry[a]	Reagent	Time	Yeld (%)[b]
1	 **(3a)** (Diacetoxyiodo)benzene	5 min.	87
2	 **(3b)** [Bis(trifluoroacetoxy)iodo]benzene	3hr.	55
3	 **(3c)** [Hydroxy(tosyloxy)-iodo]benzene	10 min.	54
4	 **(3d)** Bis(tert-butylcarbonyloxy)iodobenzene	45 min.	72

[a] Reaction conditions: 4-chlorothiophenol (1.0 equiv.), hypervalent iodine (1.0 equiv.), *i*-PrOH, r.t., open air. [b] Isolated yield after silica gel chromatography.

Next, we varied amount of (diacetoxyiodo)benzene (**DIB**) from 0.3-1.0 equivalent in the oxidation of 4-chlorothiophenol, and the yields of disulfide **2a** were reported in table 3.2. The reactions were carried out in *i*-PrOH at room temperature and were monitored by HPLC after 5 min. At 0.3 equivalent of **DIB**, only 84% conversion of **1a** to **2a** was observed (Table 3.2, entry 1). We found that the oxidation reaction was completed when used **DIB** at least 0.5 equiv. of **DIB** in the reaction (Table 3.2, entry 2-4). However, in order to ensure the completeness of the oxidation reaction, we decided to use 1 equivalent of **DIB** for further study.

Table 3.2 Effect of amount of **DIB** (**3a**) on the yield of **2a**



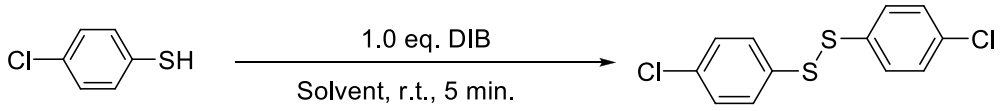
1a **2a**

Entry[a]	Equivalent of **DIB** (mmol)	Conversion (%)[b]
1	0.3	84
2	0.5	100
3	0.7	100
4	1.0	100

[a] Reaction conditions: 4-chlorothiophenol (1.0 equiv.), **DIB**, *i*-PrOH, r.t., under air, 5 min. [b] Determined by HPLC analysis.

For the next optimization study, a number of solvents were tested for the oxidation of 4-chlorothiophenol with 1.0 equivalent of (diacetoxyiodo)benzene (**DIB**) at room temperature in open air conditions. Eight different solvents were tested and the results were presented in Table 3.3. 100% conversion to disulfide (**2a**) was received from all tested solvents based on HPLC monitoring. As an example, the chromatogram of crude reaction (Table 3.1, entry 4) was shown in figure 3.1. Under our HPLC condition, retentions time of standards **1a** and **2a** were 4.4 and 28.4 minute, respectively. Other chromatograms were displayed in Appendix. In *i*-PrOH as solvent, the chromatogram of crude reaction showed only product to **2a** without any remaining starting **1a**. These results indicated a high solvent compatibility of the reaction that can be applied to every solvent system. Based on solvent guideline from Astra Zeneca, GSK and Pfizer, *i*-PrOH was selected as a solvent of choice for drug manufacturing due to its less toxicity. Therefore, we choose *i*-PrOH as solvent for disulfide synthesis for further studies.

Table 3.3 Effect of solvent



1a **2a**

Entry[a]	Solvent	Conversion (%)[b]
1	EtoAc	100
2	Toluene	100
3	Xylene	100
4	Isopropyl alcohol	100
5	n-butanol	100
6	Dicloromethane	100
7	Hexane	100
8	DMSO	100

[a] Reaction conditions: 4-chlorothiophenol (1.0 equiv.), **DIB** (1.0 equiv.), *i*-PrOH, r.t., under air, 5 min. [b] Determined by HPLC analysis.

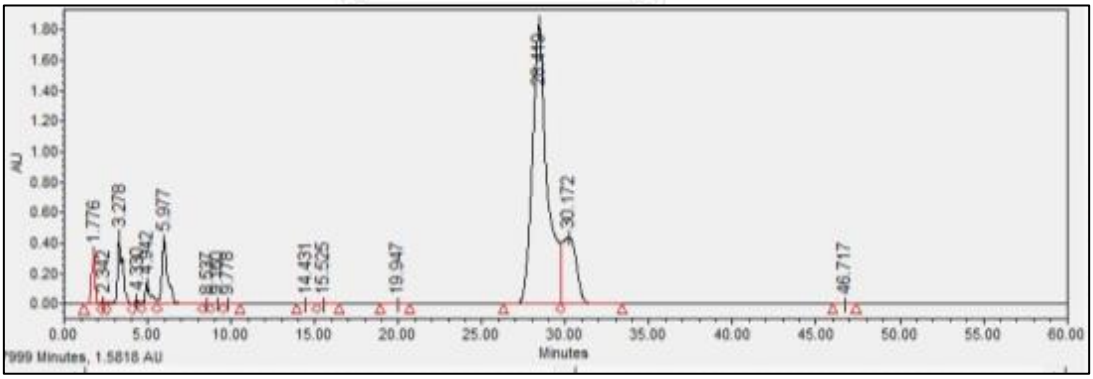


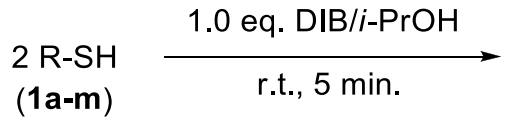
Figure 3.1 HPLC chromatogram of oxidation of 4-chlorothiophenol in *i*-PrOH reaction.

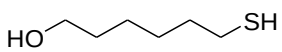
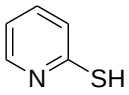
3.1.2 Substrate screening

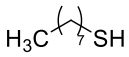
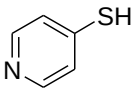
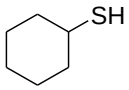
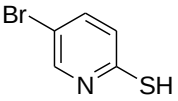
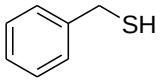
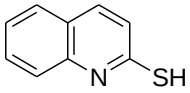
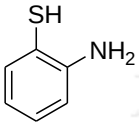
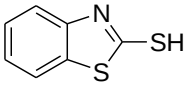
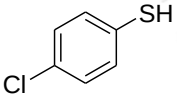
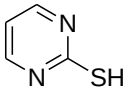
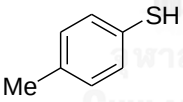
Based on above results, the optimization reaction for disulfide synthesis was the use of 1.0 equivalent of (diacetoxyiodo)benzene in *i*-PrOH at room temperature in open air conditions. This method was simple, mild and convenient reaction. With the optimized conditions in hand, the present reaction was further expanded to

explore the generality and scope of this reaction by using a variety of thiols including aliphatic, cyclic aromatic, and heterocyclic substrates as shown in Table 3.4. Aliphatic thiols (**1b**,**1c**, entries **1** and **2**) and cyclic thiol (**1d**, entry 3) were oxidized under optimized condition to give the corresponding disulfides in very good yields and the desired disulfides **2b-2d** were isolated in 87, 89 and 80% yields, respectively, after column chromatography. For thiol **1b**, both hydroxyl and thiol functional groups were presented in the same substrate but **DIB** selectively reacted with thiol only. Moreover, benzyl mercaptan **1e** was oxidized into disulfide in 86% yield (Table 3.4, entry 4). Aromatic thiols such as 2-aminothiophenol **1f** and 4-methyl thiophenol **1g** containing electron-donating group were successfully transformed into the desired disulfides **2f** and **2g** in fair to excellent yields (Table 3.4, entries 5 and 7). In addition, aromatic thiol having chloro substituent (**1a**) was converted into the corresponding disulfides **2a** in excellent yield (87%) (Table 3.4, entry 6). The nitrogen-containing heteroaromatic thiols such as **1h-j** were oxidized into the corresponding disulfides **2h-j** (Table 3.4, entries 8-10) with yields ranging between 77-90%. In some cases, disulfides were isolated in moderated yields (Table 3.4, Entries 5, 9 and 13), even though, there were no remaining stating thiols in crude reaction. These observations were caused, by strong binding between silica gel and N heteroatom in disulfide in purification step. Moreover, bicyclic aromatic thiol (**1k**) and heterocyclic thiols containing two heteroatoms (**1l-m**) could be converted to disulfides in excellent yields (Table 3.4, entry 12 and 13).

Table 3.4 Synthesis of disulfides from thiols



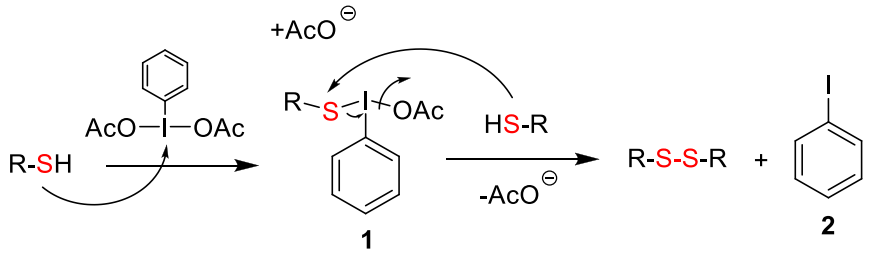
Entry	Substrate	Yield (%)[a]	Entry	Substrate	Yield (%)[a]
1	 **1b**	87	8	 **1h**	90

2	 **1c**	89	9	 **1i**	77
3	 **1d**	80	10	 **1j**	82
4	 **1e**	86	11	 **1k**	91
5	 **1f**	75	12	 **1l**	89
6	 **1a**	87	13	 **1m**	75
7	 **1g**	95			

[a] Isolated yield after silica gel chromatography

3.1.3 Proposed mechanism

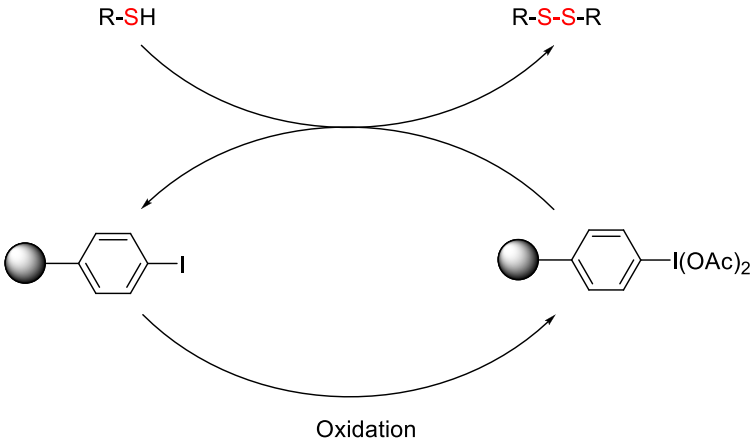
For plausible mechanism of disulfide formation, we hypothesized that sulfur atom of thiol attacks iodine in **DIB** leading to the formation of sulfenyl iodide intermediate (**1**) and acetate ion as shown in Scheme 3.1. Then, another molecule of thiol undergoes nucleophilic substitution with sulfur atom in (**1**). Ligand disengages from **1** to produce the isolated disulfide product along with iodobenzene (**2**) as by-product.



Scheme 3.1 Proposed mechanism of disulfide formation.

3.2 Polystyrene-supported (diacetoxyiodo)benzene for oxidation of thiols into disulfides.

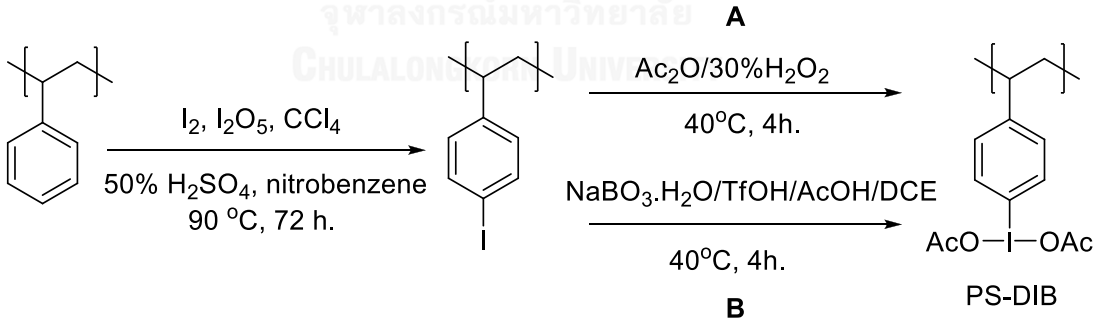
According to the preparation of disulfides from thiols using hypervalent iodine (III), the reaction produced iodobenzene as by-product. The disadvantages of this process are 1) the difficulty in removing disulfide from reaction mixture and 2) **DIB** reagent cannot be recyclable. To overcome these problems, we decided to synthesize hypervalent iodine bounded to a polymeric support (Scheme 3.2). After the use of such reagent, it should be able to convert thiols into disulfides and the iodobenzene will remain on the polymeric support. Furthermore, the disulfide product could be isolated by simple filtration, thus simplifying the isolation step. Moreover, the iodobenzene attached to supported-polymer will be able to recover into hypervalent iodine on polymer. This will allow the polymer to be recyclable in the reaction process [24].



Scheme 3.2 Utilization of polymer-supported (diacetoxyiodo)benzene reagent for preparation of disulfide. ● = polymer

3.2.1 Synthesis of polystyrene-supported (diacetoxyiodo)benzene PS-DIB and characterization

For the polymer support selection, we decided to use polystyrene for several reasons. The structure of polystyrene has a long chain hydrocarbon wherein alternating carbon centers are attached to benzene ring which alike (diacetoxyiodo)benzene structure. In addition, polystyrene is inexpensive and widely available. Therefore, we planned to synthesize polystyrene-supported (diacetoxyiodo)benzene (**PS-DIB**) from polystyrene. Initially, **PS-DIB** was prepared from iodopolystyrene (**PS-I**) by iodination of commercially available polystyrene (MW=35,000) and I_2/I_2O_5 in the mixture of CCl_4/nitrobenzene solution under acidic condition as presented in Scheme 3.3. The appearance of iodopolystyrene (**PS-I**) was showed in Figure 3.2 (middle) as strong yellowish solid. Then, **PS-DIB** was successfully prepared from **PS-I** by two different oxidation methods **A** and **B**. The method **A** used Ac_2O/H_2O_2 as the oxidizing reagent [25] while method **B** utilized $NaBO_3.H_2O$ as oxidizing reagent in acetic acid/1,2-dichloroethane as solvent and triflic acid as additive [36]. After the reaction was completed, the resulting **PS-DIB** products from both methods were isolated by filtration to give yellow powder as shown in Figure 3.2 (right).



Scheme 3.3 Synthesis of **PS-DIB** from method A and B.

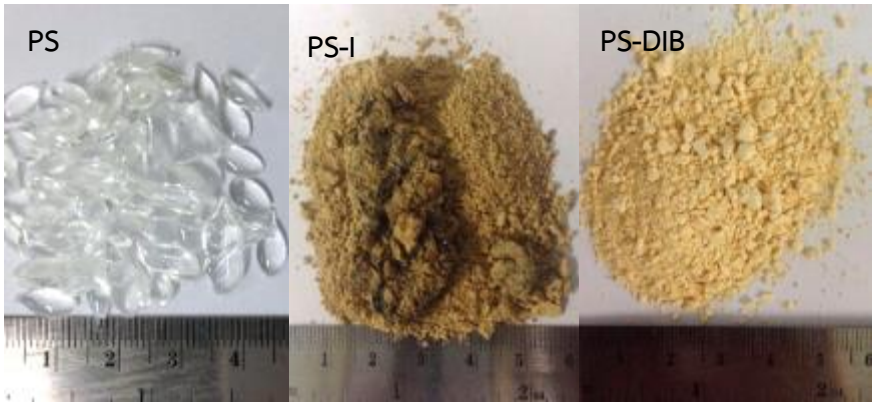


Figure 3.2 Color appearance of **PS** (left), **PS-I** (middle) and **PS-DIB** (right).

The structure of **PS-DIB** was confirmed by FTIR spectroscopy as shown in Figure 3.3. The spectra showed commercially available polystyrene (**PS**), iodopolystyrene (**PS-I**) and polystyrene-supported (diacetoxyiodo)benzene (**PS-DIB**). The **PS-I** showed the reduction of C-H (aromatic) stretching peak at 3020 cm^{-1}, indicating the successful iodination of the benzene ring in polystyrene. In addition, the structure of polystyrene-supported (diacetoxyiodo) benzene (**PS-DIB**) was confirmed by the existence of C=O stretching peaks in the diacetoxy group at 1636 and 1724 cm^{-1}

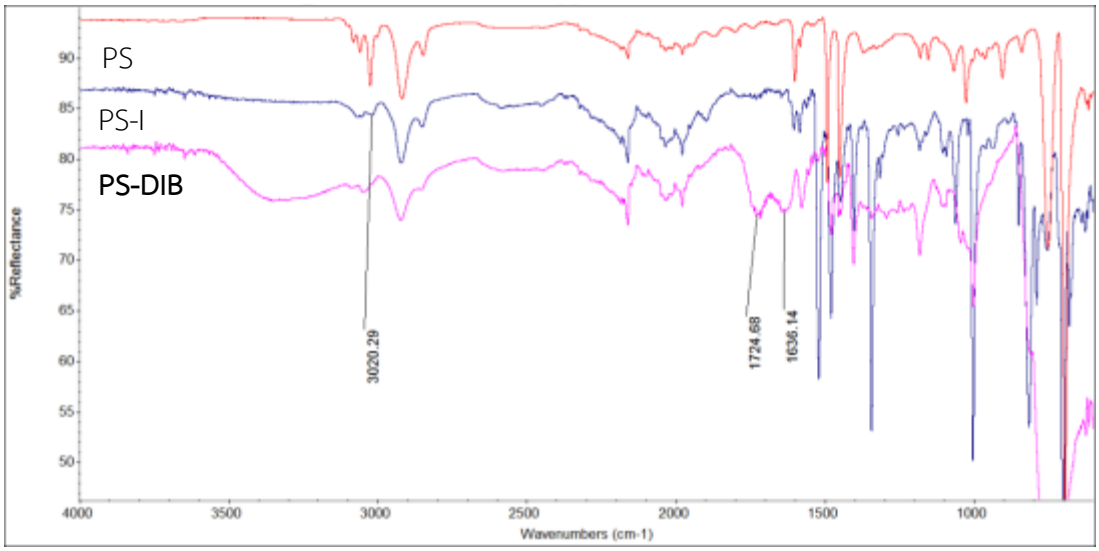
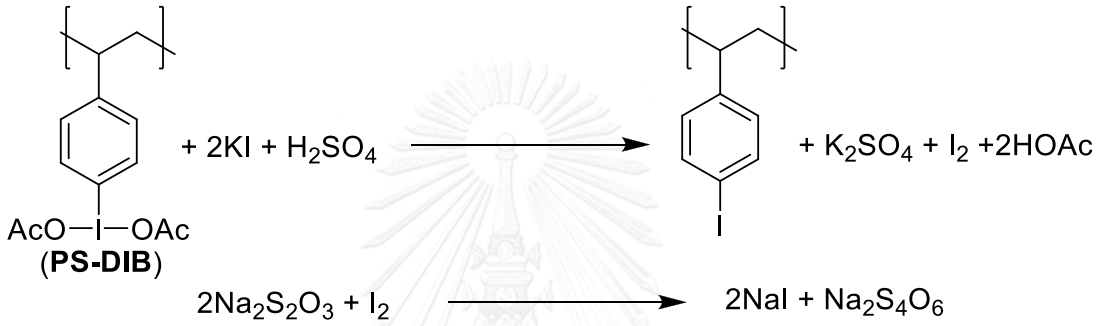


Figure 3.3 FT-IR spectra of **PS**, **PS-I** and **PS-DIB**.

3.2.2 Determination of loading of (diacetoxyiodo)phenyl group on PS-DIB

The loading of the diacetoxyiodo group on polystyrene was determined by traditional iodometric titration [37]. The reaction for the iodometric titration using our prepared **PS-DIB** were demonstrated in Scheme 3.4. The reaction is based on the oxidation of KI by **PS-DIB** to generate I_2 which further react with $Na_2S_2O_3$. Therefore, the amount of $Na_2S_2O_3$ used in the reaction is proportional to (diacetoxyiodo)phenyl group on **PS-DIB.**



Scheme 3.4 Iodometric titration.

First, **PS-DIB** and KI were dissolved in mixed chloroform/sulfuric acid for 4 hour to produce I_2 via oxidation reaction showing the brown solution as seen in figure 3.4**A**. After that the reaction mixture was titrated with $Na_2S_2O_3$ for 0.3-0.5 mL and starch solution was added to the mixture producing blue color (Figure 3.4**B**). Then, $Na_2S_2O_3$ was further titrated until the end point giving the colorless solution (Figure 3.4**C**). The iodometric titration results from **PS-DIBs** prepared from methods A and B were depicted in Table 3.5. In each **PS-DIB**, it was washed by MeOH, dried and titrated in each cycles to evaluate the loading of diacetoxyiodo group in **PS-DIB**.

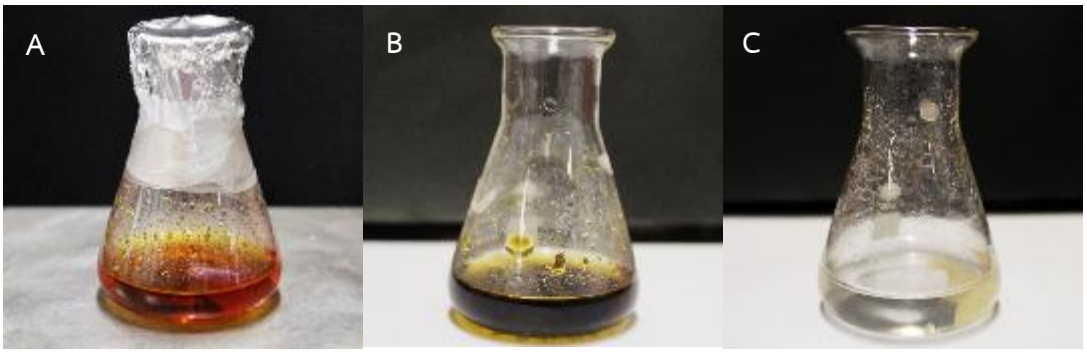


Figure 3.4 Color appearance of solution of **PS-DIB**, KI, H_2SO_4 in chloroform/water for titration. A) before addition of starch solution B) after addition of starch solution C) after titrated with $Na_2S_2O_3$.

The result from method A indicated that the loading of the (diacetoxyiodo)phenyl group on the polystyrene decreased continually after washing with MeOH while **PS-DIB** obtained from method B remained constant after the third wash. We hypothesized that **PS-DIB** prepared from method A contained unreacted H_2O_2 which was washed away after by MeOH. Therefore, we observed the decrease in loading of the (diacetoxyiodo)phenyl group. On the other hands, the consistency from method B may result from remaining oxidizing agent, $NaBO_3.H_2O$. According to the result, we therefore choose the oxidizing agent, $NaBO_3.H_2O$ (method B) to use as a standard method for the preparation of **PS-DIB** throughout this work and it was freshly titrated prior to use.

Table 3.5 The loading of functional group

Washed time	Loading of diacetoxyiodo group (mmol) in **PS-DIB**	
	Method A	Method B
1st	2.13	1.87
2nd	2.28	1.61
3rd	2.36	1.19
4th	1.90	1.19
5th	1.41	1.19

3.2.3 Utilization of PS-DIB for oxidization of thiols

3.2.3.1 Optimization study

PS-DIBs were synthesized by method B, giving the loading of the (diacetoxyiodo)phenyl group on the polystyrene in the range of 1.26-2.00 mmol/g. To investigate the oxidizing ability of our prepared **PS-DIB**, we selected the 4-chlorothiophenol as model for optimization study. 4-Chlorothiophenol (**1a**) was converted to 1,2-bis(4-chlorophenyl)disulfane (**2a**) using **PS-DIB.** The reactions were monitored by gas chromatography and several factors including amount of **PS-DIB**, time and types of solvent were also investigated.

In this study, the %yields were received from GC analysis based on internal standard using biphenyl. The example of chromatogram of crude product in the present of biphenyl was shown in figure 3.5. The retentions time at 4.5 and 6.1 and 10.4 minute corresponded to starting **1a**, internal standard biphenyl and **2a**, respectively. Other chromatograms were displayed in figure A 55 to A 68 Appendix.

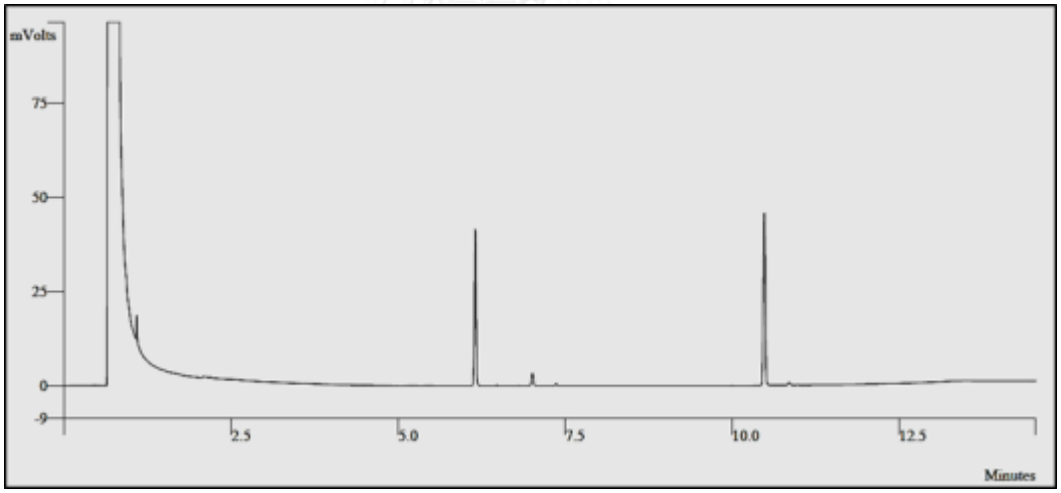
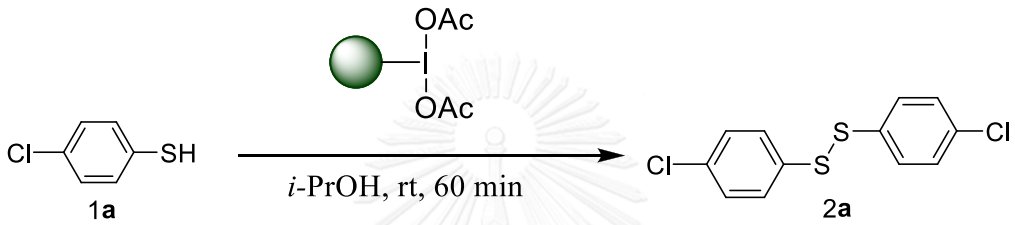


Figure 3.5 GC chromatogram of oxidation of 4-chlorothiophenol in i-PrOH reaction

Initially, we screened the amount of **PS-DIB** by increasing amount of polymer-supported (diacetoxyiodo)benzene (**PS-DIB**) from 0.7 to 2.0 equivalent and yields of disulfide **2a** were summarized in Table 3.6. All reactions were implemented in *i*-PrOH at room temperature and monitored by GC chromatography after 60 min. The oxidation reaction was completed when using 0.7 equiv. of **PS-DIB** in the reaction and gave quantitative yield of disulfide **2a** (Table 3.6, entry 1). When increasing

amount of **PS-DIB** from 0.7 to 1.1, 1.5, and 2.0 equiv. (Table 3.6, entry 2-4), yields of disulfide **2a** were dropped to 80, 80, 68%, respectively. We assumed that low yields of product **2a** were resulted from the generation of unidentified byproduct when **PS-DIB** were used excessively. We observed unidentified peak in GC chromatogram at retention time of 6.1 minute (Appendix figure A 55 to A 58). We therefore decided to use 0.7 equivalent of **PS-DIB** as optimal condition.

Table 3.6 Amount of **PS-DIB**

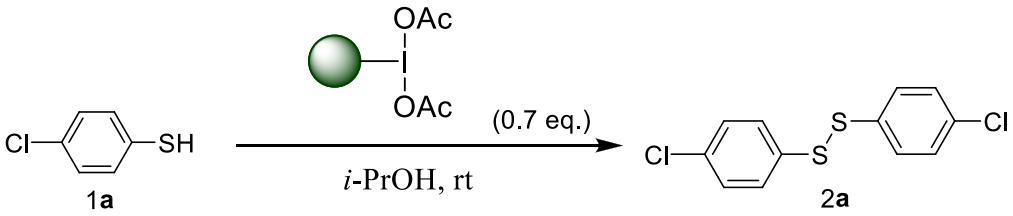


Entry[a]	Equivalent of **PS-DIB** (mmol)	Yields (%)[b]	Product : Unknown
1	0.7	quantitative	92.8 : 7.2
2	1.1	80	86.4 : 13.6
3	1.5	80	88.2 : 11.8
4	2.0	68	84.0 : 16.0

[a] Reaction conditions: 4-chlorothiophenol (1.0 equiv.), **PS-DIB**, *i*-PrOH, r.t., under air, 60 min. [b] Determined by GC analysis.

Then, we optimized reaction time from 5 minutes to overnight using 0.7 equiv. of **PS-DIB** in *i*-PrOH at room temperature and monitored by GC chromatography as shown in Table 3.7. The results indicated that the reaction times at 5 and 30 minutes are insufficient, causing incomplete conversion of starting material as shown in table 3.7, entries 1 and 2. The oxidation reaction was completed after 60 minute as shown in entry 3 with quantitative yield of product **2a**. (Appendix figure A 59 to A 62). Therefore, we decided to use 60 minutes as optimized reaction time in the presence of 0.7 equivalent of **PS-DIB** for further investigation.

Table 3.7 Effect of time

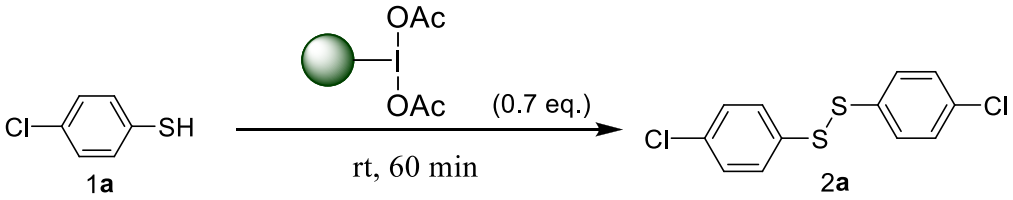


Entry[a]	Time	Yield of **2a** (%)[b]	Remaining **1a** (%)[b]	Product : unknown
1	5 min	86	8	93.7 : 6.3
2	30 min	87	7	93.2 : 6.8
3	60 min	quantitative	-	92.8 : 7.2
4	overnight	quantitative	-	92.4 : 7.6

[a] Reaction conditions: 4-chlorothiophenol (1.0 equiv.), **PS-DIB** (0.7 equiv.), *i*-PrOH, r.t., under air. [b] Determined by GC analysis.

Next, the effect of solvents was investigated by reaction of 4-chlorothiophenol with 0.7 equivalent of **PS-DIB** at room temperature in open air conditions with seven different solvents and the results were presented in Table 3.8. When reactions were carried out in EtOAc, toluene, dimethyl carbonate, *n*-butanol and *i*-PrOH/H_2O (1:1) as solvents, starting material **1a** was recovered around 5-13% and produced target **2a** in good yield (Table 3.8 entryies 1-3 and 5-6). In addition, the use of DMSO as solvent gave complete conversion but product **2a** was observed in 89 %yield (Table 8, entry 7). The highest yield of disulfide **2a** was received when the reaction was performed in *i*-PrOH. Notably, *i*-PrOH was selected as a solvent of choice from Astra Zeneca, GSK and Pfizer solvent guideline [38] as one of the best green solvent. Based on above optimization study, we concluded that the optimal condition for conversion of **1a** to **2a** is performing the reaction with 0.7 eq. of **PS-DIB** in *i*-PrOH at room temperature for 60 minutes.

Table 3.8 Solvent effect



Entry[a]	Solvents	Yield of **2a** (%)[b]	Remaining **1a** (%)[b]
1	Ethyl acetate	67	5
2	Toluene	71	11
3	Dimethyl carbonate	80	9
4	Isopropyl alcohol	quantitative	0
5	n-butanol	81	5
6	*i*-PrOH/H_2O (1:1)	89	13
7	DMSO	89	0

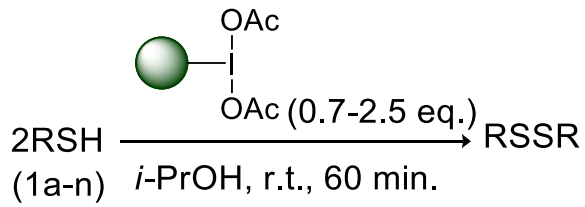
[a] Reaction conditions: 4-chlorothiophenol (1.0 equiv.), **PS-DIB** (0.7 equiv.), r.t., under air 60 min. [b] Determined by GC analysis.

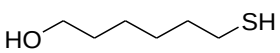
3.3.3.2 Substrate scope

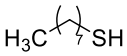
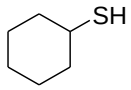
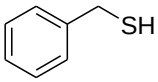
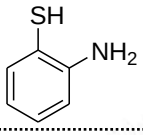
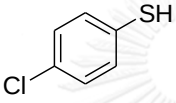
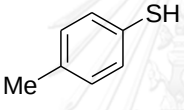
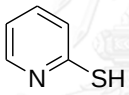
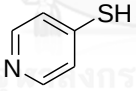
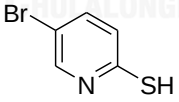
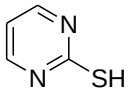
To extend the generality and scope of this work, we synthesized disulfides from a variety of thiols including aliphatic, cyclic aromatic, and heterocyclic substrates under the optimized reaction as shown in Table 3.9. The optimization reaction for disulfide synthesis was the use of 0.7 equivalent of polymer-supported (diacetoxyiodo)benzene for 60 minutes in *i*-PrOH at room temperature in open air conditions. Aromatic thiols **1a** and **1g** containing chloro and methyl substituents, respectively were subjected to the optimization condition to give the responding disulfide **2a** and **2g** in excellent yields after column chromatography (Table 3.9, entry

6-7). The oxidation of aliphatic thiols **1c**, **1e** and cyclic thiol **1d** were synthesized under optimization condition and gave incomplete reactions. However, the reactions were completed when amount of **PS-DIB** was increased up to 1.0 equivalent. These reactions gave the desired disulfides **2c**, **2d** and **2e** in 91, 95 and 94 %yields, respectively (Table 3.9, entry 2-4). To test the selectivity of oxidization using **PS-DIB**, we selected thiols **1b** and **1f** (Table 3.9, entry 1 and 5) having hydroxy and amino functional groups, respectively. However, those substrates were partially oxidized and starting materials remained in the reaction mixture. Therefore, we increased the **PS-DIB** reagent up to 2-2.5 equivalents and there was no remaining starting material, giving the products **1b** and **1f** in quantitative yields (Table 3.9, entry 1 and 5). Those results demonstrated that our **PS-DIB** oxidation is selective to oxidize thiol group without touching other sensitive functional group such as hydroxy and amino groups to oxidize. We hypothesized that hydroxy and amino groups on thiols **1b** and **1f** may interact with **PS-DIB** resulting in the loss of its reactivity. The nitrogen-containing heteroaromatic thiols such as **1h-j** were converted to disulfides **2h-j** in moderate yields in the range between 55–83% (Table 3.9, entry 8-10). Influence of the strong binding group between N heteroatom in thiols and **PS-DIB** had effect on yield. We believe that some N heteroatoms in thiols were oxidized via **PS-DIB**. Therefore, a large amount of **PS-DIB** was necessary. Moreover, heterocyclic thiols **1m** containing two heteroatoms could be converted to disulfides **2m** in excellent yields (Table 3.4, entry 11).

Table 3.9 Synthesis of disulfides from thiols



Entry[a]	Substrate	Equivalent of **PS-DIB**	Yield (%)
1	**1b** 	2.5	quantitative

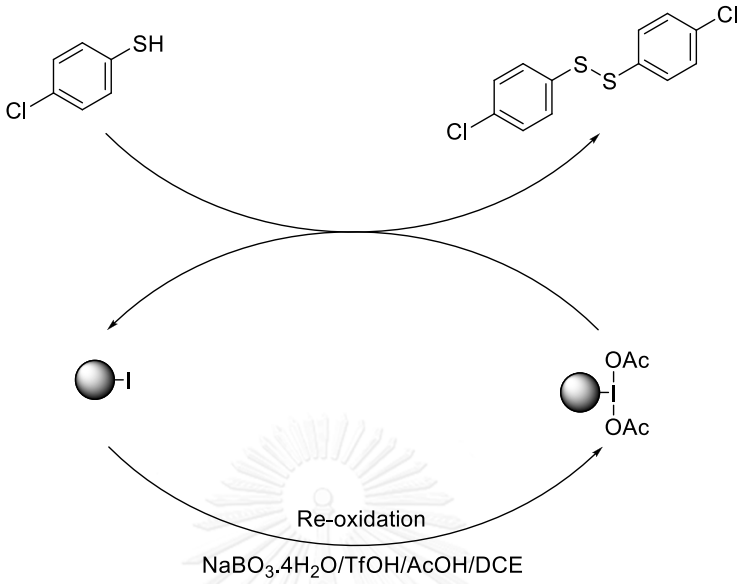
2	**1c** 	1.0	91
3	**1d** 	1.0	95
4	**1e** 	1.0	94
5	**1f** 	2.0	81
6	**1a** 	0.7	89
7	**1g** 	0.7	97
8	**1h** 	0.7	83
9	**1i** 	1.5	70
10	**1j** 	1.5	55
11	**1m** 	0.7	97

[a] Isolated yield after silica gel chromatography

3.2.4 Regeneration and reuse of PS-DIB

After oxidization of thiol into the disulfide using **DIB**, it will generate PS-I as byproduct as shown in scheme 3.5. The solid iodopolystyrene (PS-I) could be removed from the reaction mixture and re-oxidized with sodium perborate. The

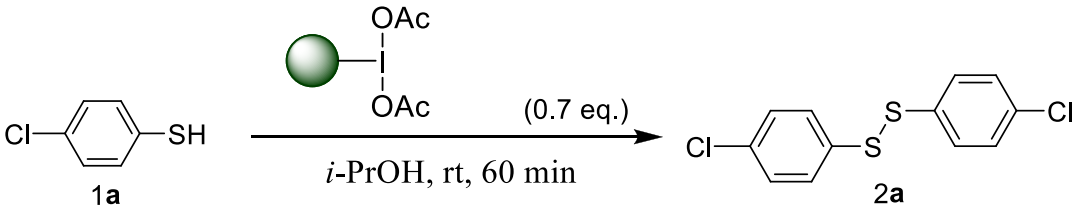
loading of (diacetoxyiodo)phenyl group could be analyzed again by iodometry titration before the reuse in oxidation of thiol.



Scheme 3.5 Utilization of Polystyrene-supported (diacetoxyiodo)benzene reagent for preparation of disulfide. ● = polystyrene

Therefore, we used **PS-DIB** for oxidation of thiol and then reused for 2 times as shown in table 3.10. The freshly prepared **PS-DIB** was able to convert thiol **1a** to disulfide **2a** in 83% yield in 60 minutes without the remaining starting materiel (table 10, entry 1). After filtration and washed by MeOH, iodopolystyrene was re-oxidized by sodium perborate, giving the loading of (diacetoxyiodo)phenyl group in 2.0 mmol/g (Table 10, entry 2). The reused **PS-DIB** was able to oxidize thiol **1a** to disulfide **2a** in 78 %yield under the same condition. This suggested that the **PS-DIB** can be regenerated and reused for oxidation of thiol without losing its efficientcy.

Table 3.10 Regeneration and reuse of **PS-DIB** for oxidation of **1a**



Entry	Cycles[a]	(Diacetoxyiodo)phenyl group loading on polymer	%yield[b]	Time (min)
1	1st	1.67	83	60
2	2nd	2.00	78	60

[a] Reaction conditions: 4-chlorothiophenol (1.0 equiv.), **PS-DIB** (0.7 equiv.), *i*-PrOH, r.t., under air 60 min. [b] Isolated yield after silica gel chromatography

CHAPTER IV
CONCLUSION

In summary, we developed a simple and efficient method for oxidation of thiols to disulfides using cheap and less toxic (diacetoxyiodo)benzene (**DIB**) reagent. The optimization study showed that 1.0 equivalent of (diacetoxyiodo)benzene in *i*-PrOH at room temperature for 5 minute was able to convert a variety of thiols containing aliphatic, aliphatic cyclic, aromatic and heterocyclic substituent to the corresponding disulfides in excellent yields. Moreover, we successfully synthesized polystyrene-supported (diacetoxyiodo)benzene (**PS-DIB**) from iodination of polystyrene followed by the oxidation with $NaBO_3 \cdot 4H_2O$. The loading of (diacetoxyiodo)phenyl group was determined by iodometry titration and found to be 1.26-2.00 mmol/g. The prepared **PS-DIB** was able to convert thiols to the corresponding disulfide in fair to good yields in 60 minute. Importantly, byproduct iodopolystyrene could be separated from the reaction mixtures by simple filtration and regenerated into **PS-DIB** by oxidation with $NaBO_3 \cdot 4H_2O$. The **PS-DIB** was able to reuse for disulfide synthesis with no loss of activity. The key advantages of this reaction were lower toxicity, low cost of **DIB** reagent, recycle of **PS-DIB** and mild reaction conditions (room temperature, undried solvents and open flask).

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APPENDIX

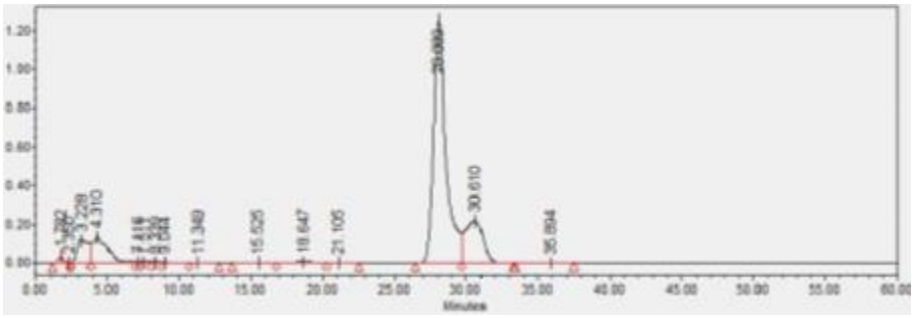

Figure A1 HPLC chromatogram of **2a** (Table 3.2, entry 1)

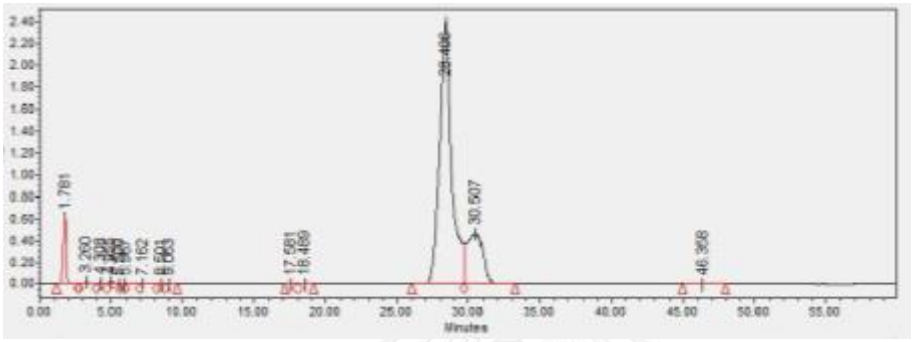

Figure A2 HPLC chromatogram of **2a** (Table 3.2, entry 2)

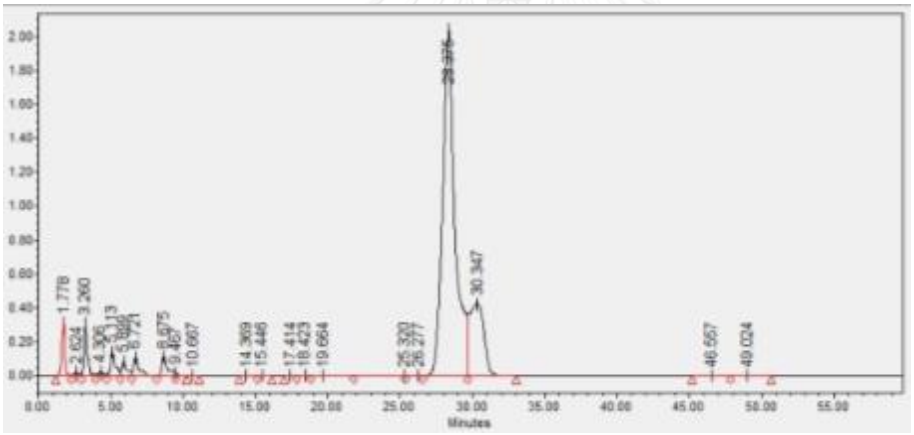

Figure A3 HPLC chromatogram of **2a** (Table 3.2, entry 3)

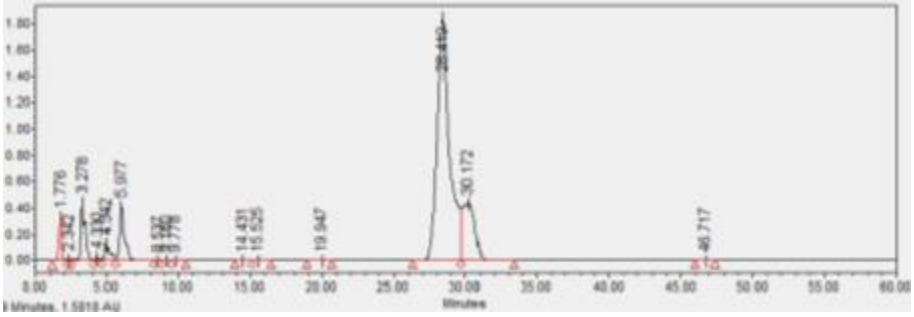

Figure A4 HPLC chromatogram of **2a** (Table 3.2, entry 4)

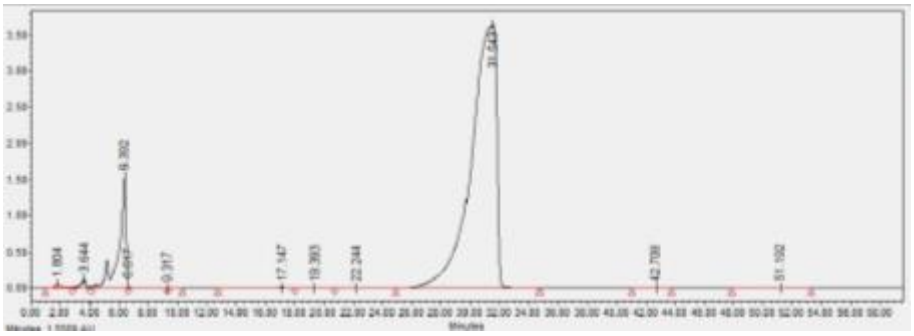

Figure A5 HPLC chromatogram of **2a** (Table 3.3, entry 1)

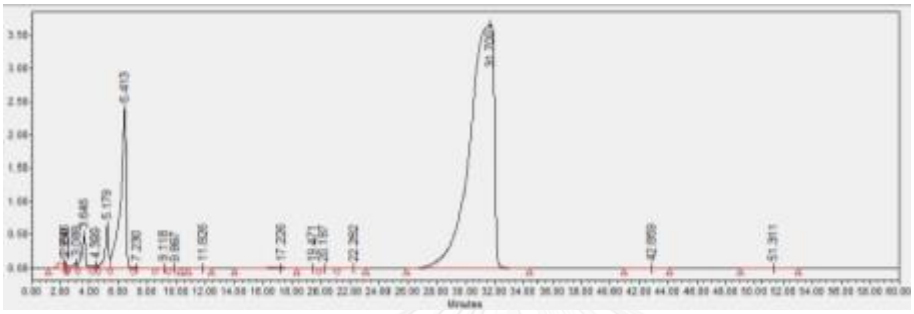

Figure A6 HPLC chromatogram of **2a** (Table 3, entry 2)

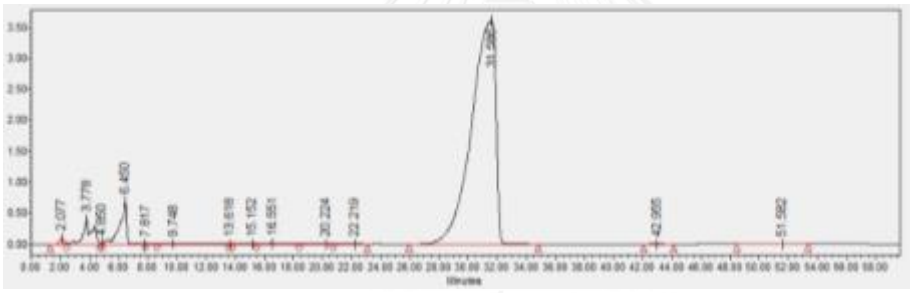

Figure A7 HPLC chromatogram of **2a** (Table 3.3, entry 3)

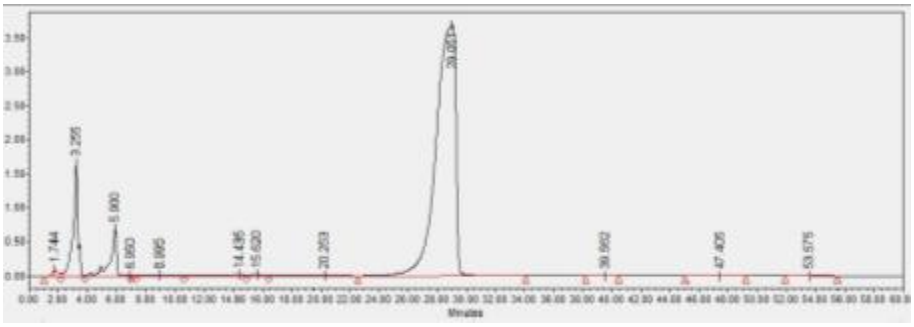

Figure A8 HPLC chromatogram of **2a** (Table 3.3, entry 4)

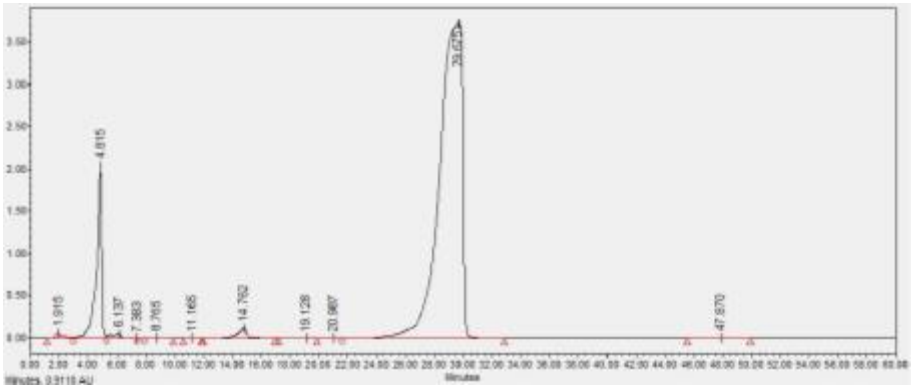

Figure A9 HPLC chromatogram of **2a** (Table 3.3, entry 5)

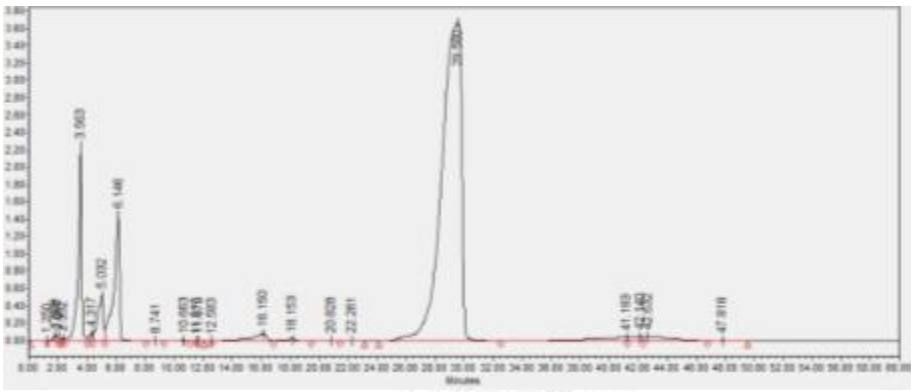

Figure A10 HPLC chromatogram of **2a** (Table 3.3, entry 6)

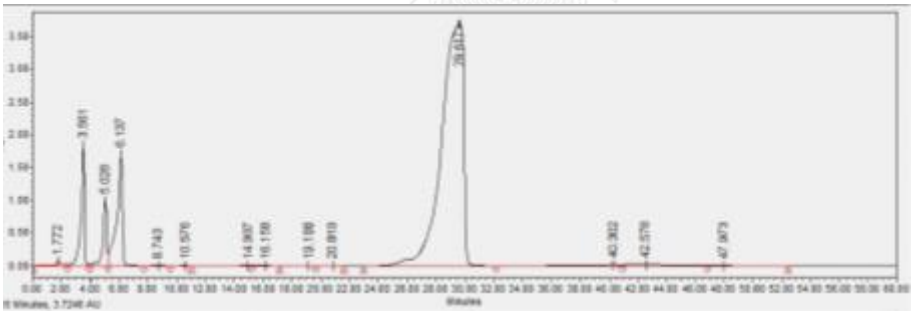

Figure A11 HPLC chromatogram of **2a** (Table 3.3, entry 7)

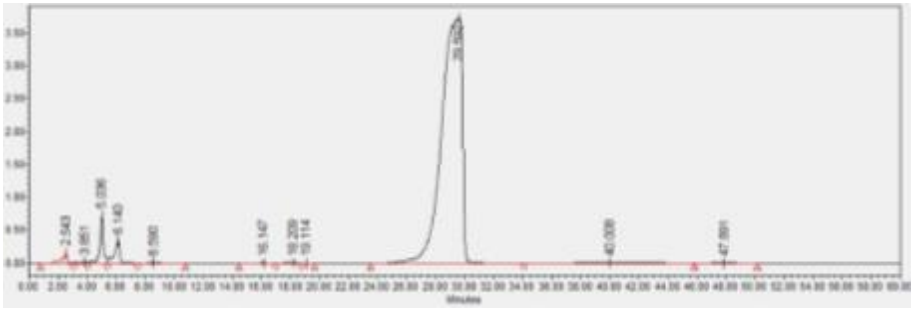

Figure A12 HPLC chromatogram of **2a** (Table 3.3, entry 8)

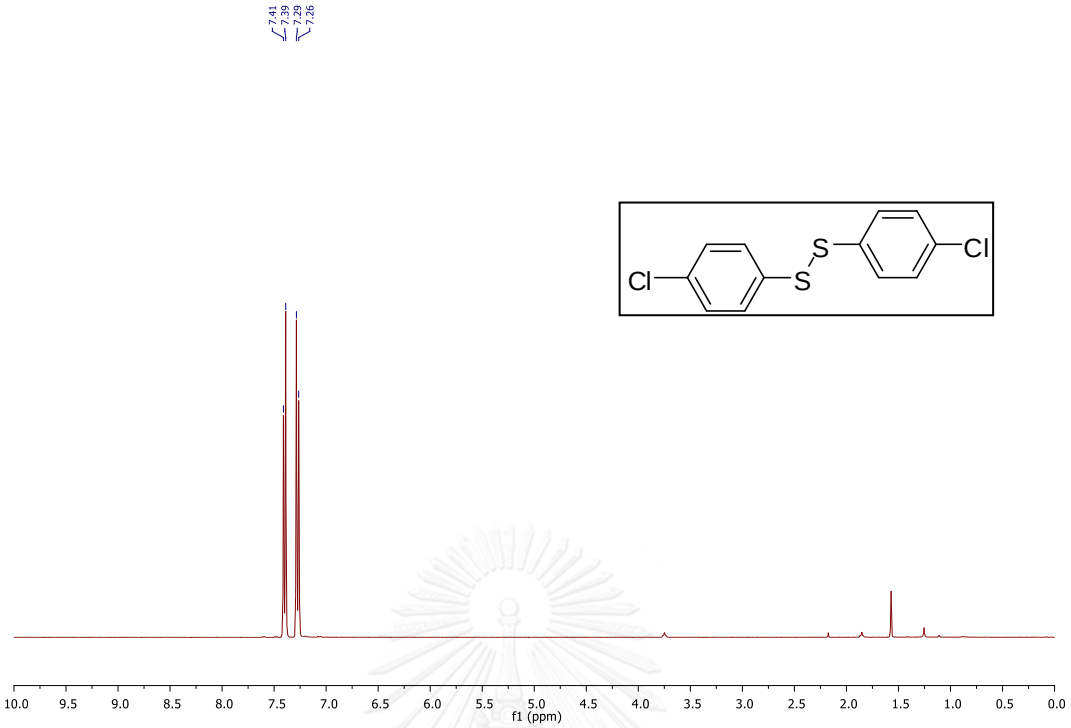

Figure A13 ^{1}H NMR spectrum of **2a** ($CDCl_3$)

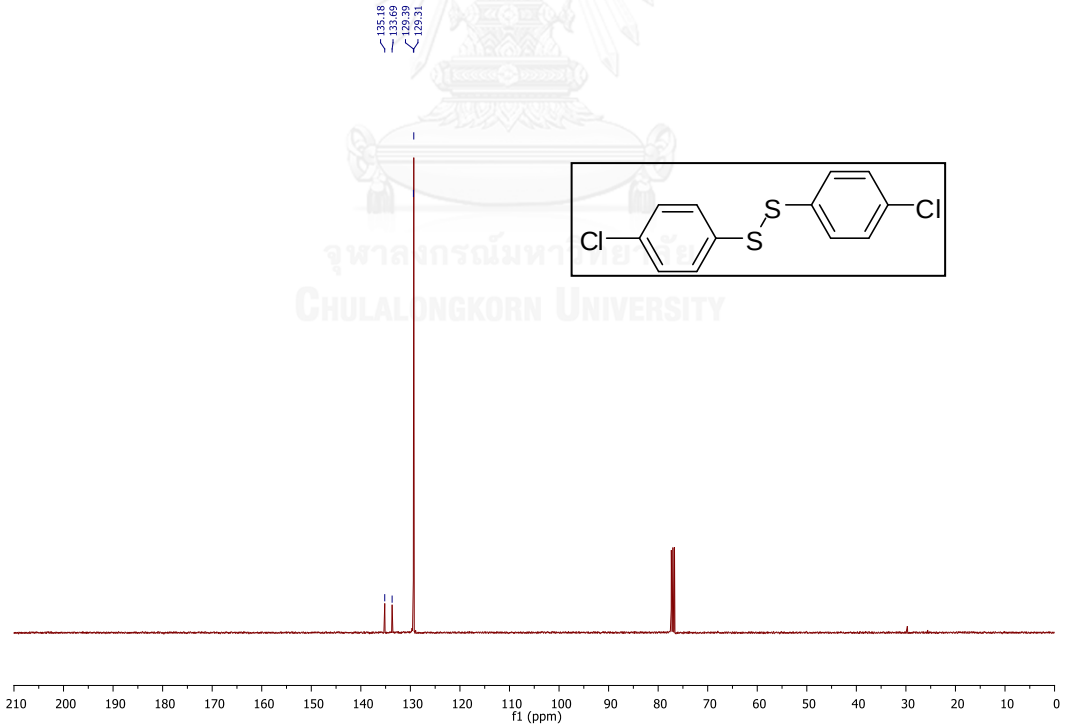

Figure A14 ^{13}C NMR spectrum of **2a** ($CDCl_3$)

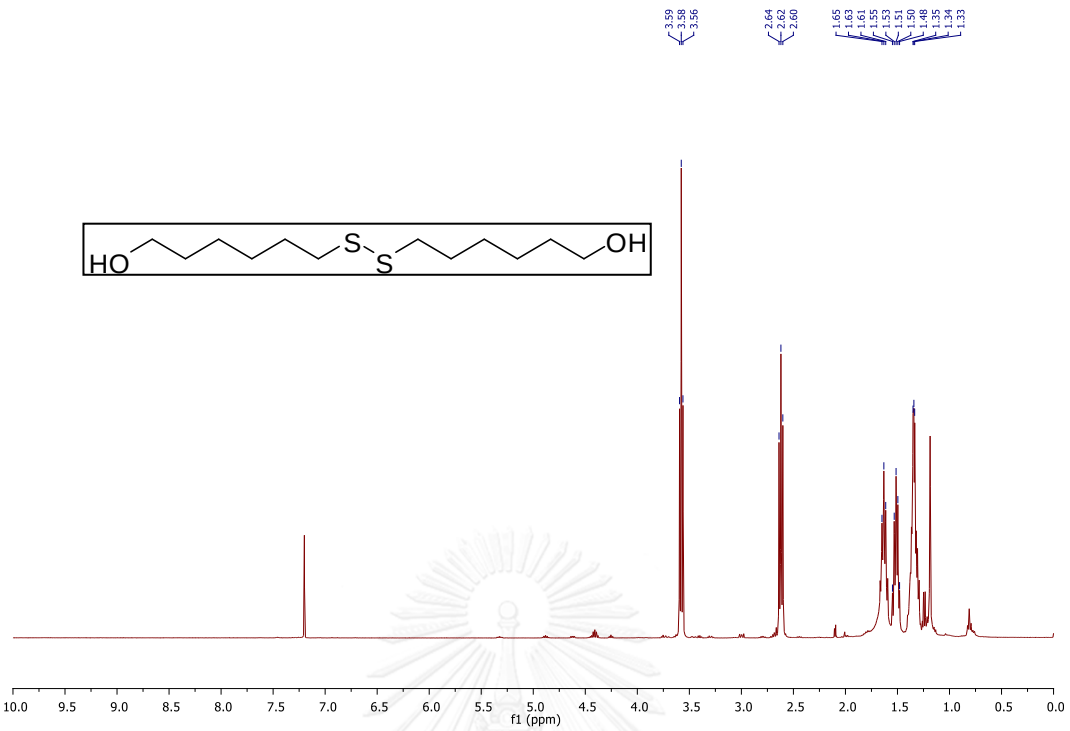

Figure A15 ^{1}H NMR spectrum of **2b** ($CDCl_3$)

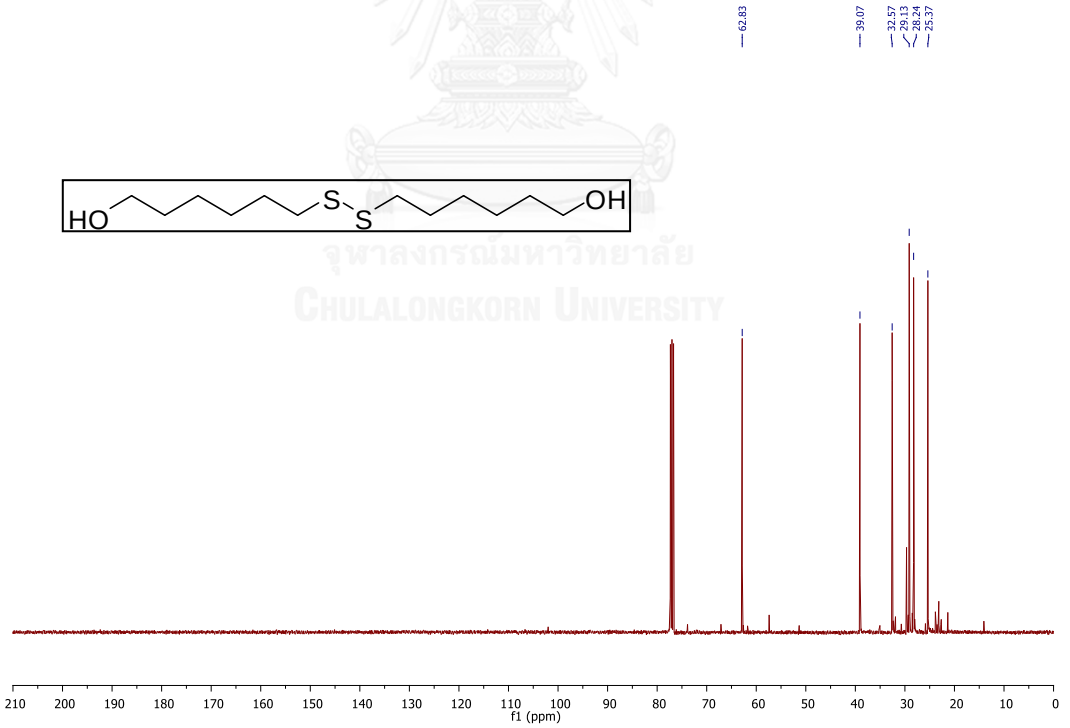

Figure A16 ^{13}C NMR spectrum of **2b** ($CDCl_3$)

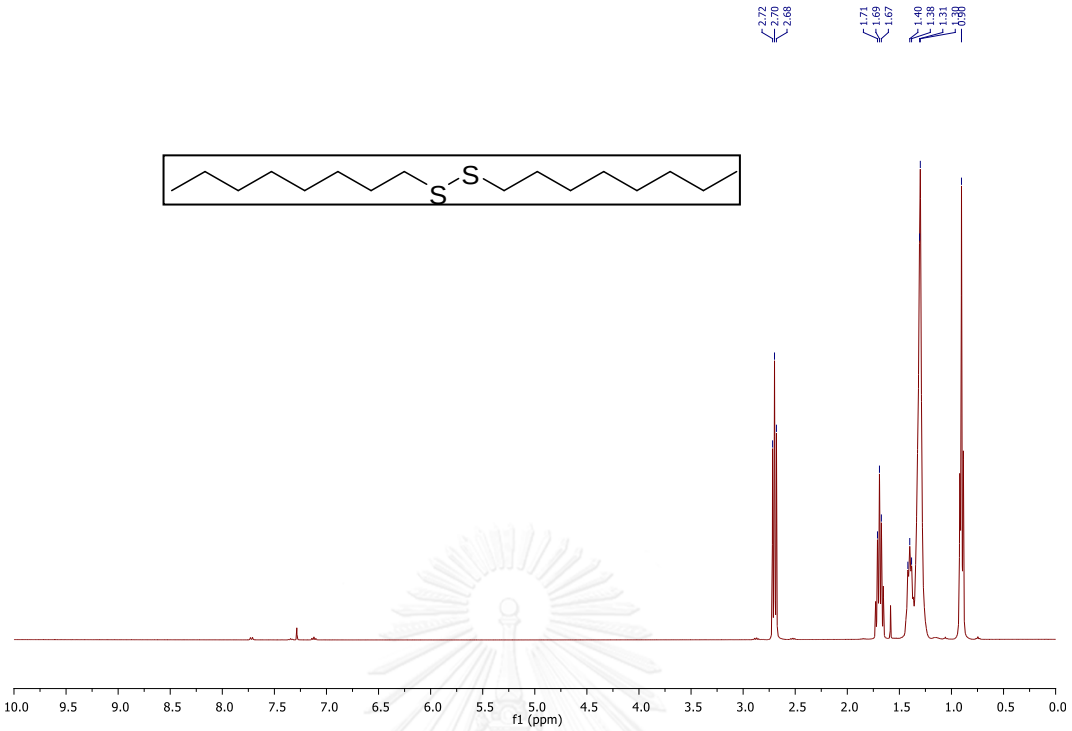

Figure A17 ^{1}H NMR spectrum of **2c** ($CDCl_3$)

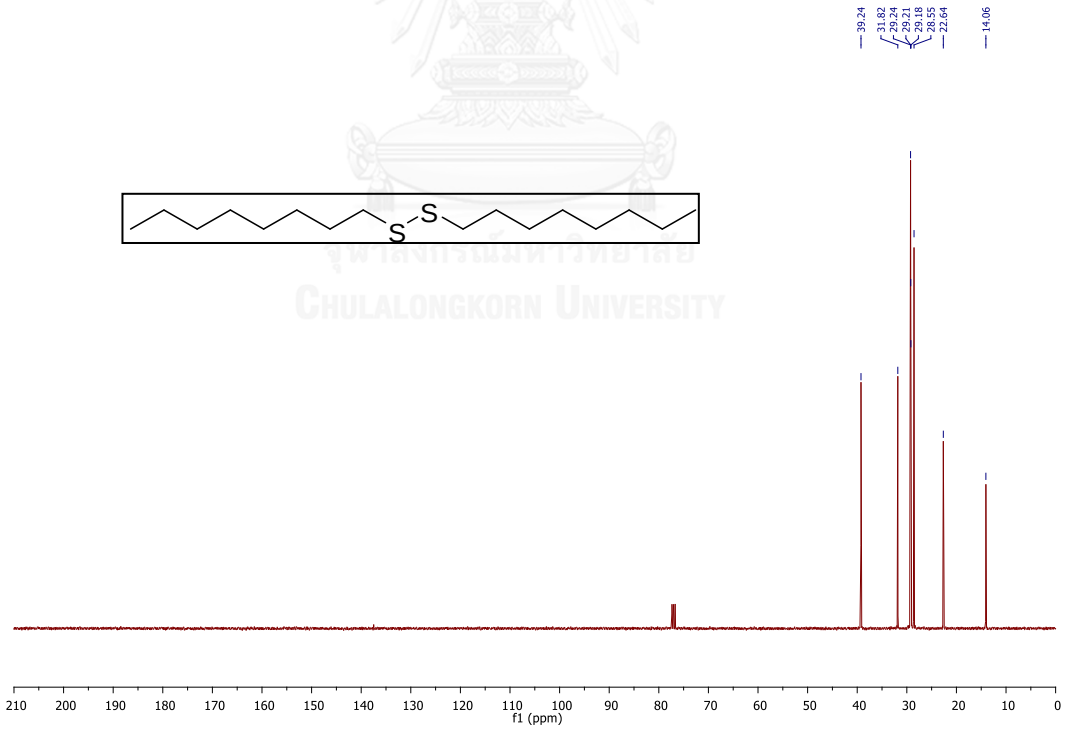

Figure A18 ^{13}C NMR spectrum of **2c** ($CDCl_3$)

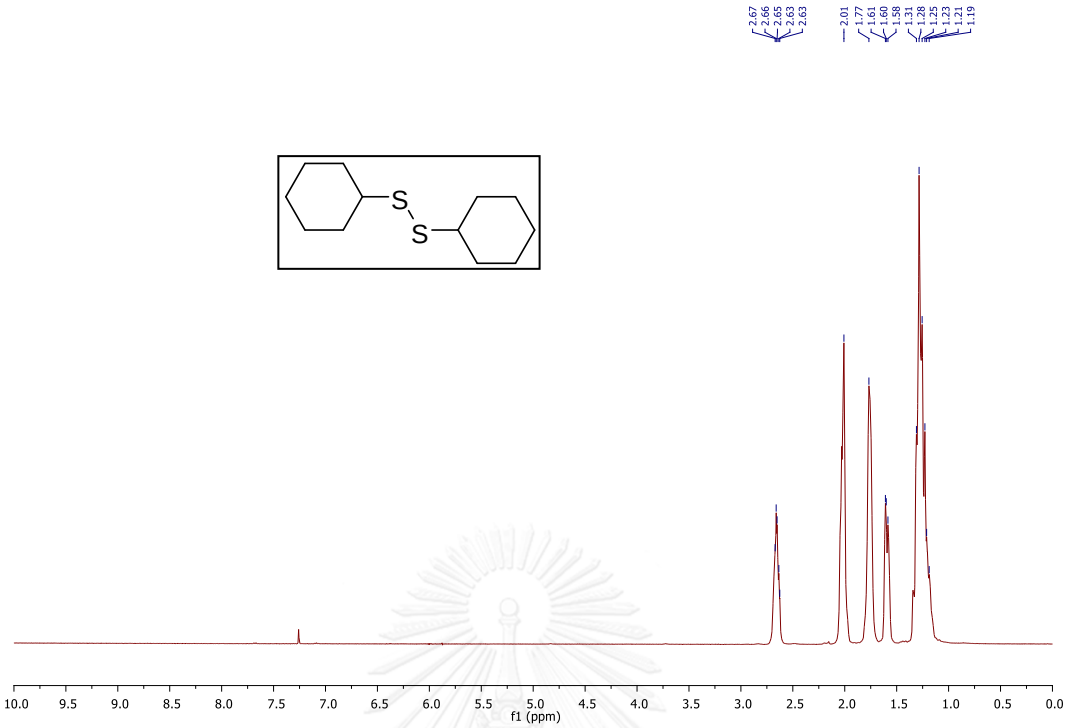

Figure A19 ^{1}H NMR spectrum of **2d** ($CDCl_3$)

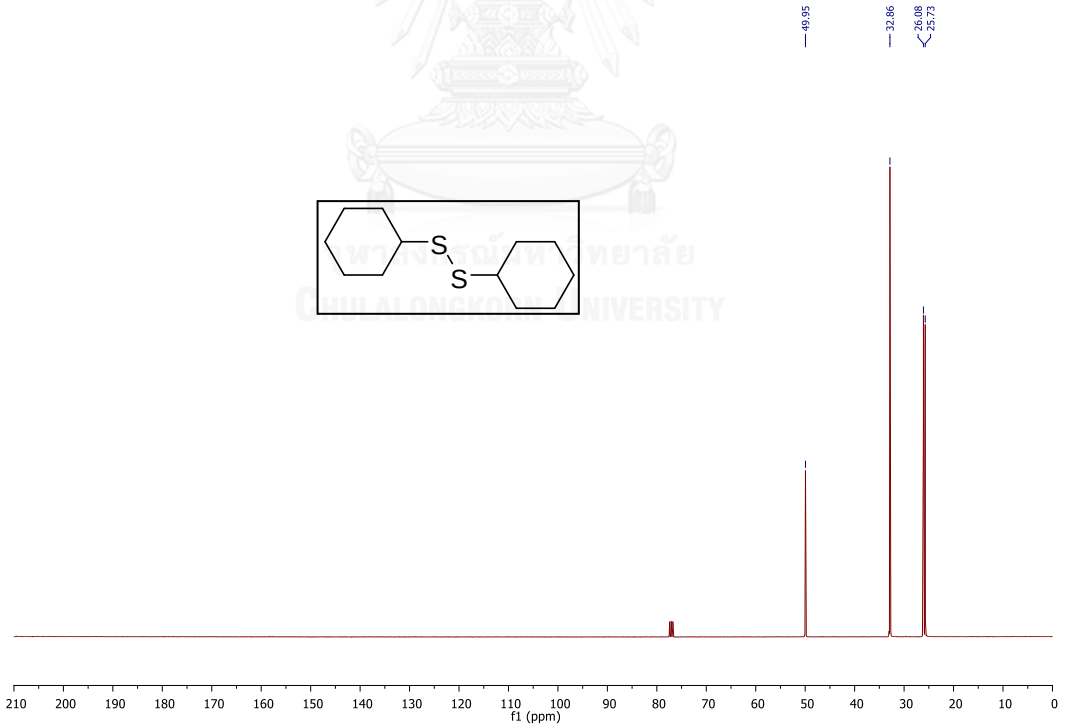

Figure A20 ^{13}C NMR spectrum of **2d** ($CDCl_3$)

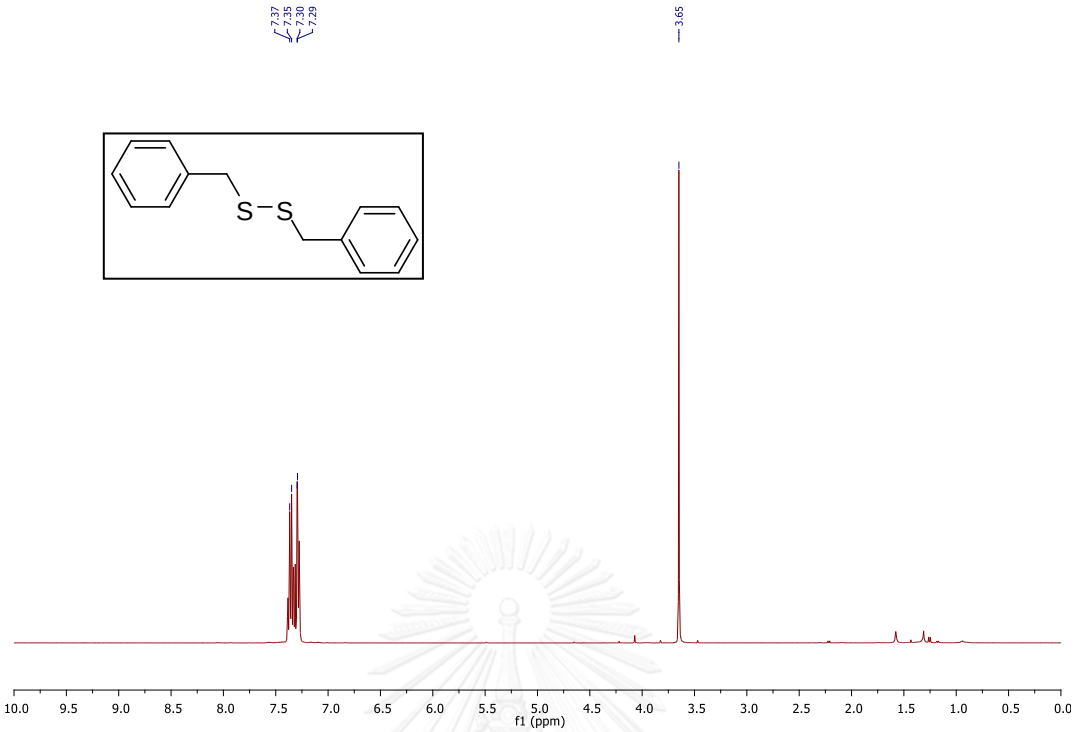

Figure A21 ^{1}H NMR spectrum of **2e** ($CDCl_3$)

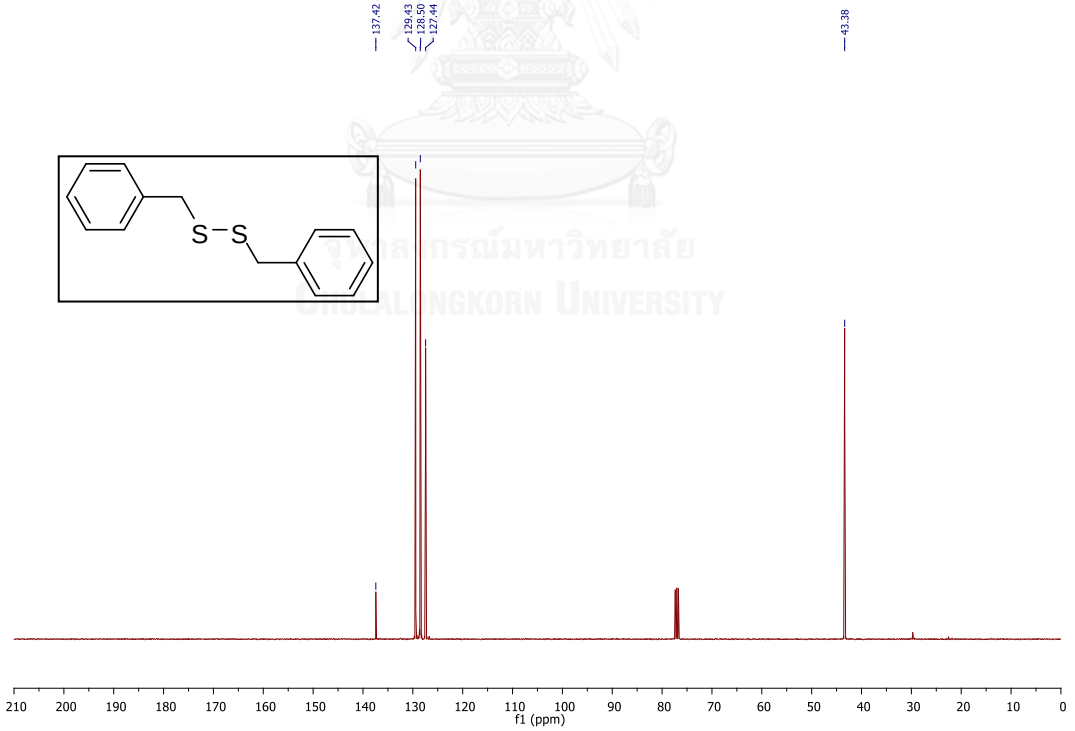

Figure A22 ^{13}C NMR spectrum of **2e** ($CDCl_3$)

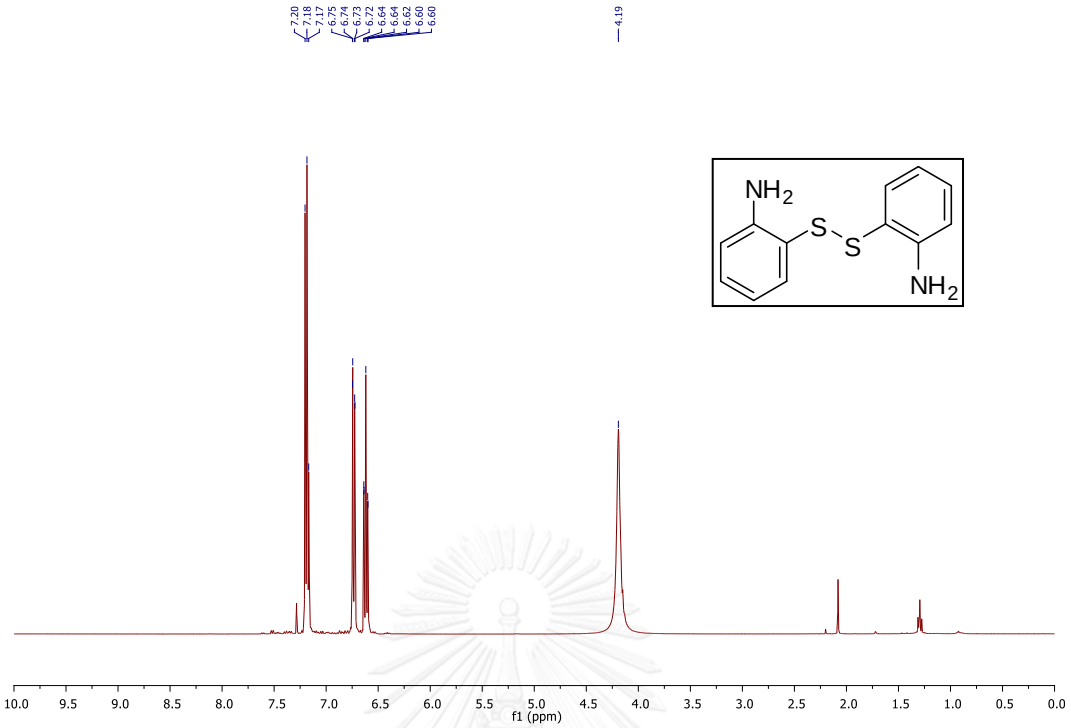

Figure A23 ^{1}H NMR spectrum of **2f** ($CDCl_3$)

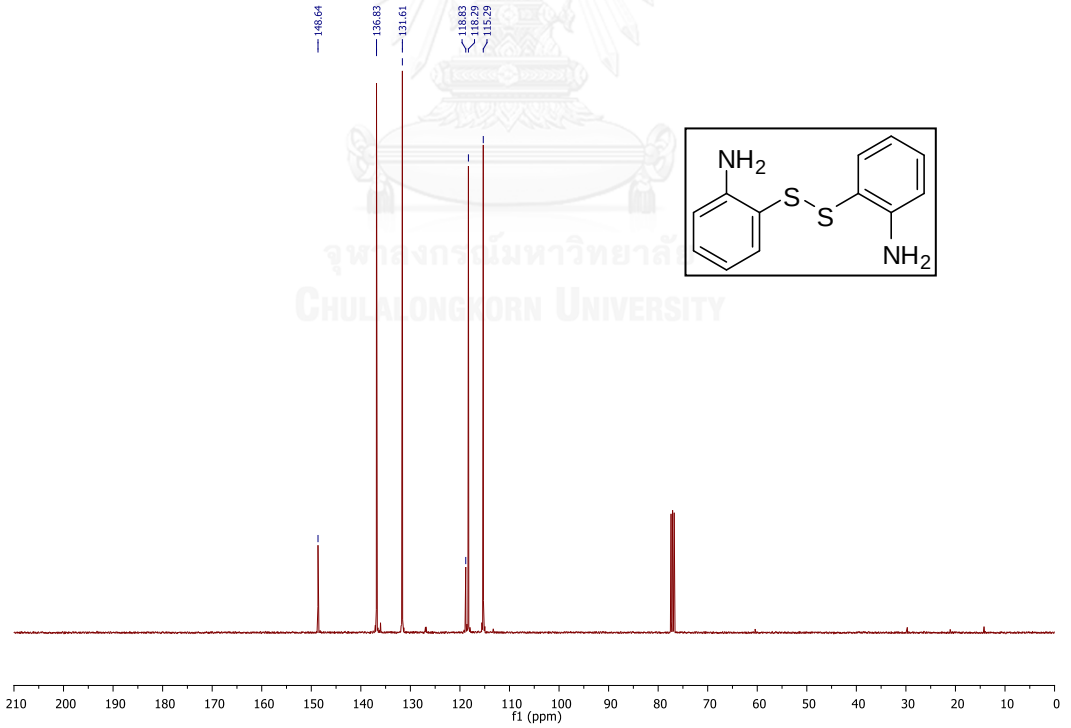

Figure A24 ^{13}C NMR spectrum of **2f** ($CDCl_3$)

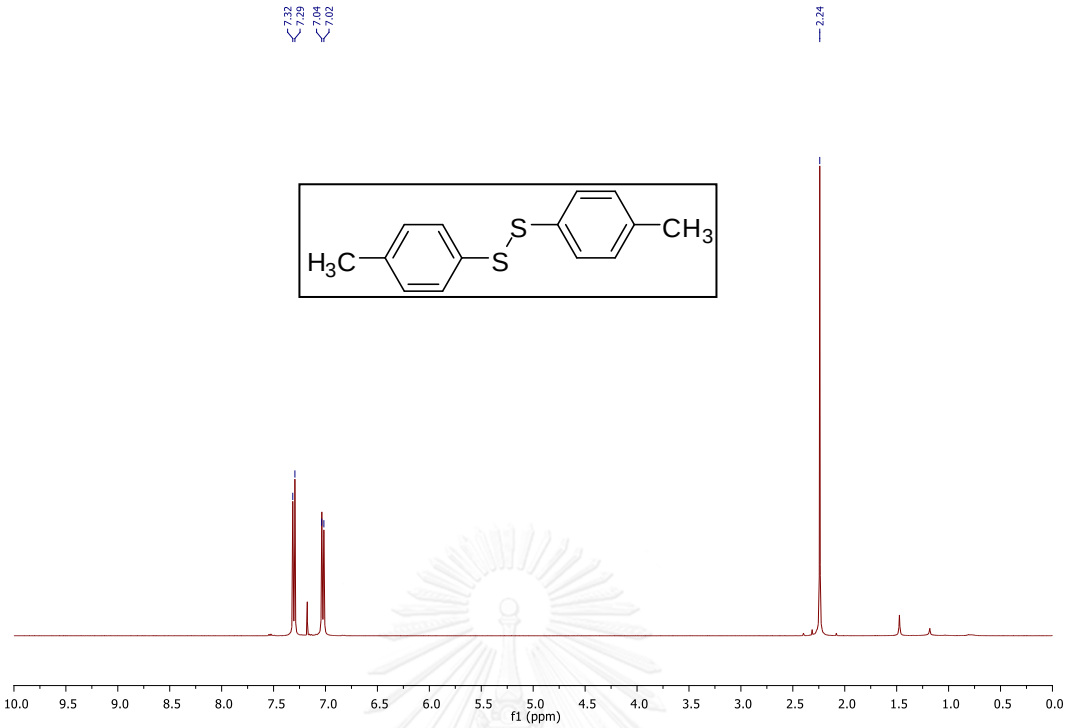

Figure A25 ^{1}H NMR spectrum of **2g** ($CDCl_3$)

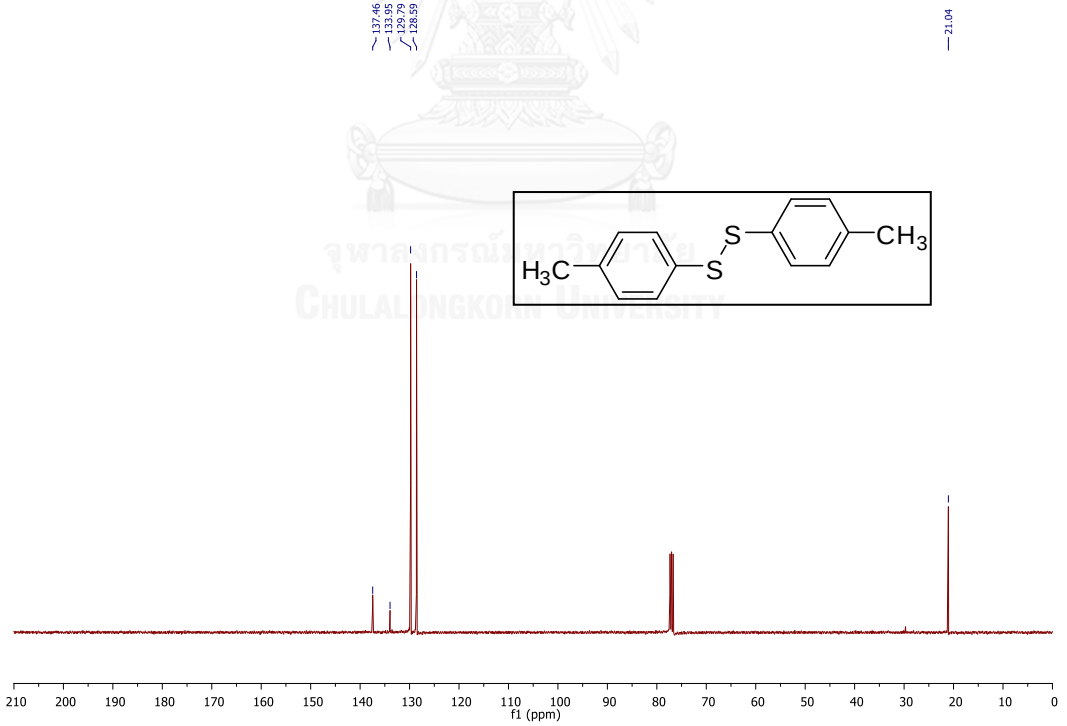

Figure A26 ^{13}C NMR spectrum of **2g** ($CDCl_3$)

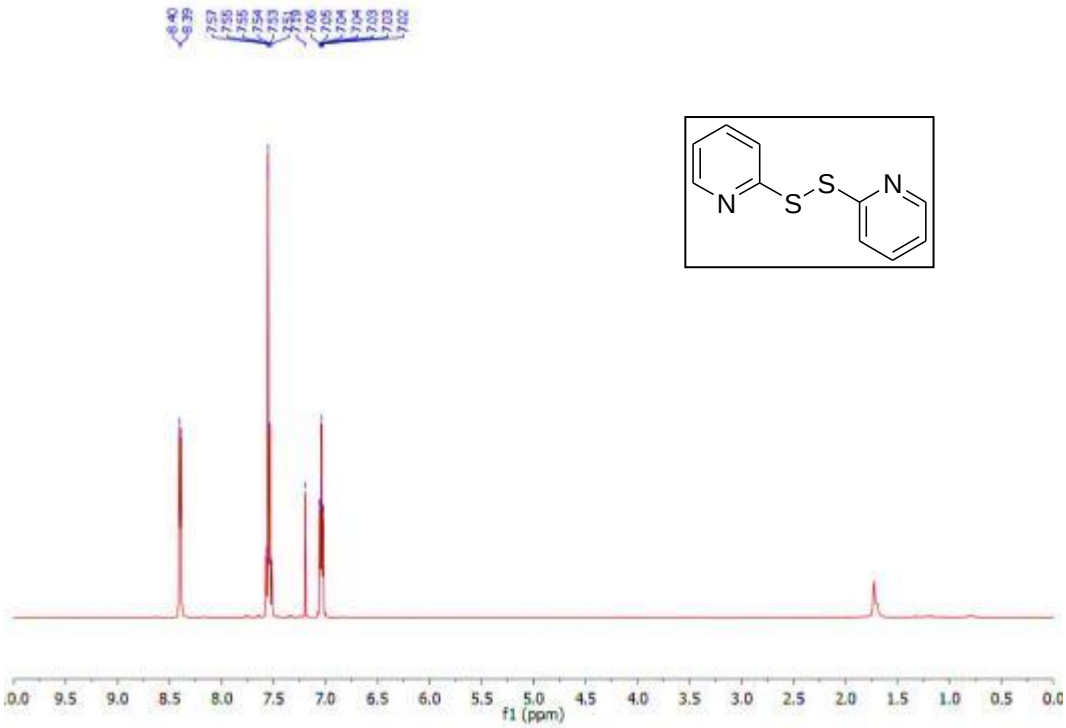

Figure A27 ^{1}H NMR spectrum of **2h** (CDCl3)

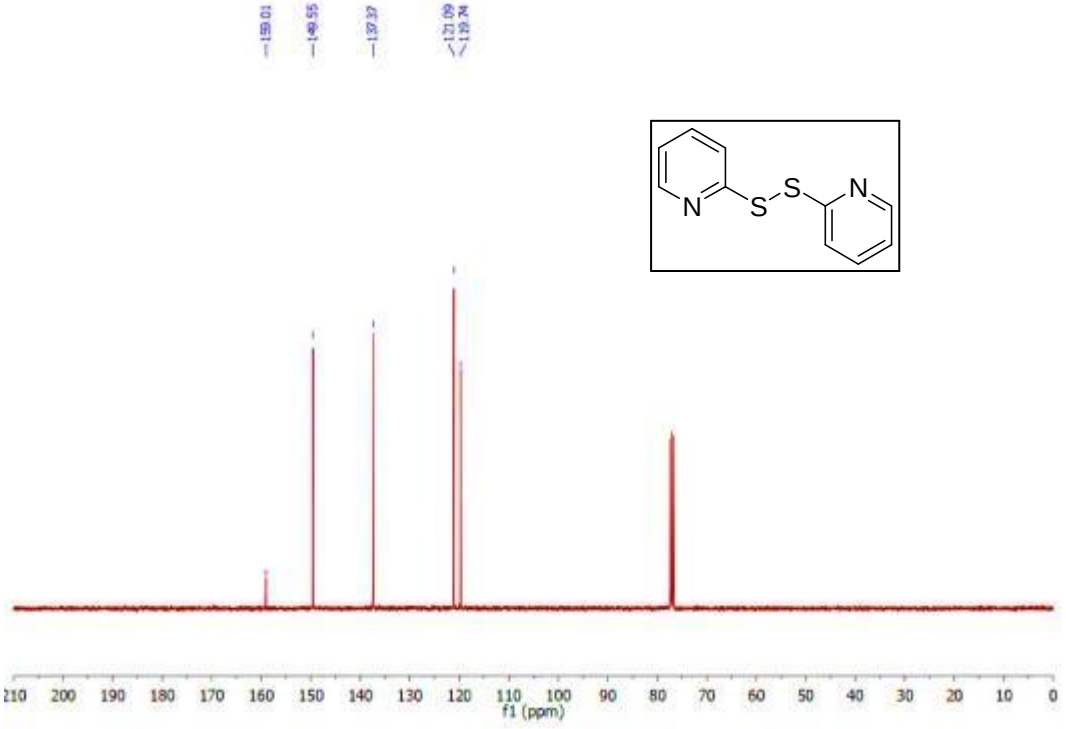

Figure A28 ^{13}C NMR spectrum of **2h** ($CDCl_3$)

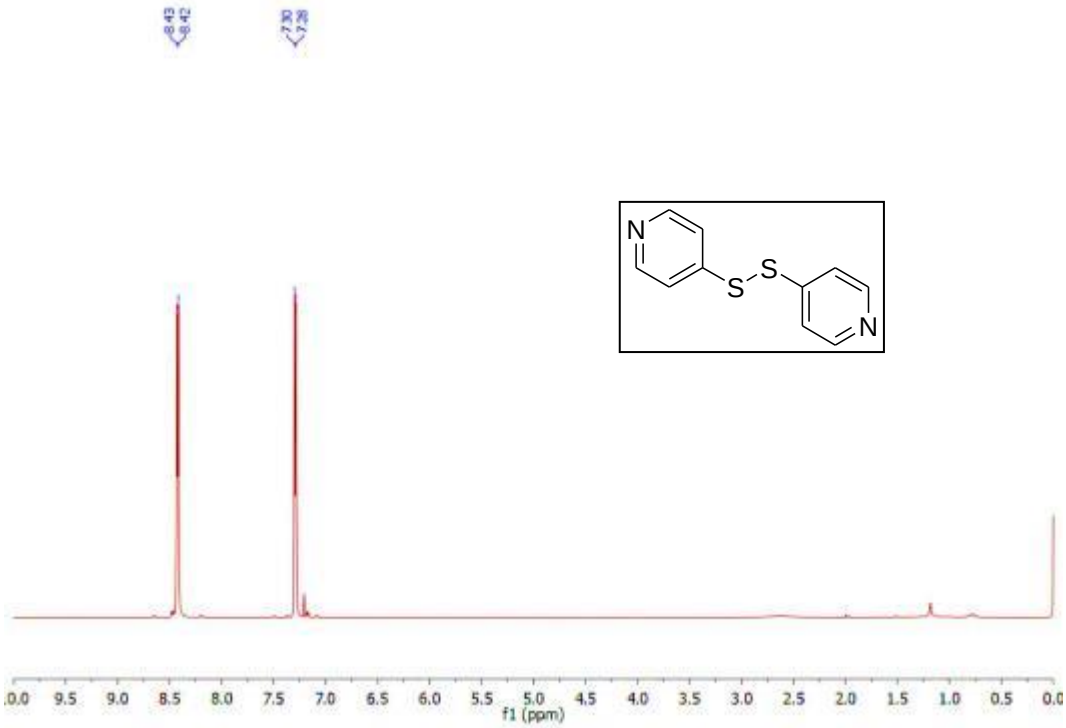

Figure A29 ^{1}H NMR spectrum of **2i** ($CDCl_3$)

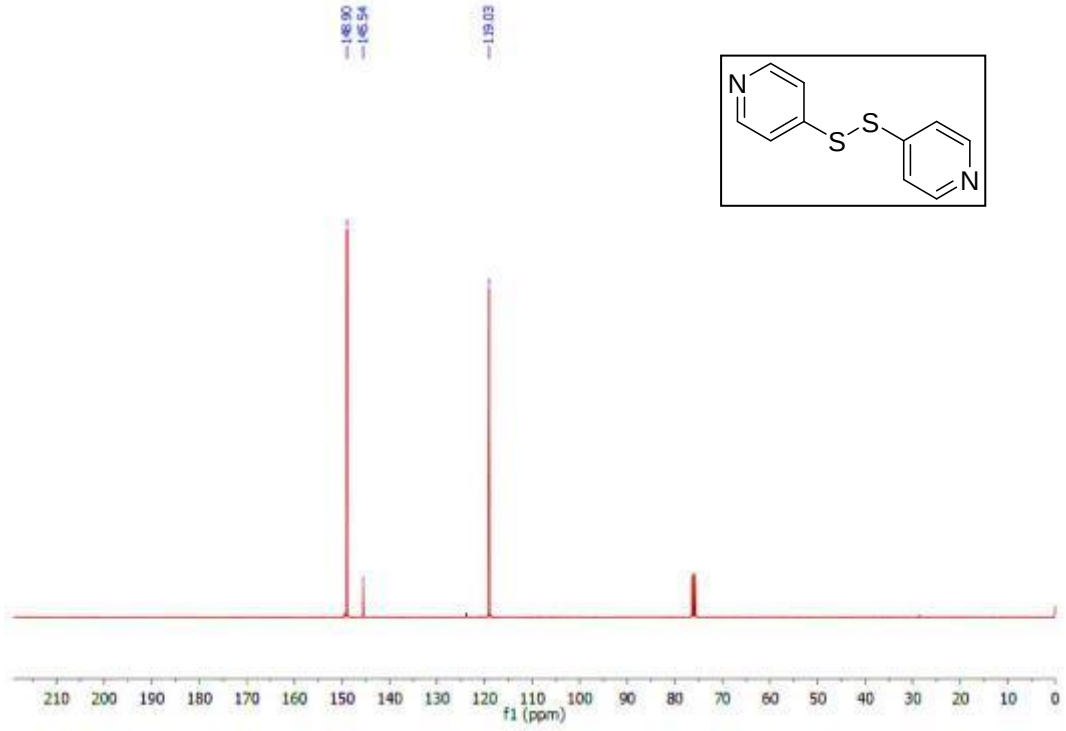

Figure A30 ^{13}C NMR spectrum of **2i** ($CDCl_3$)

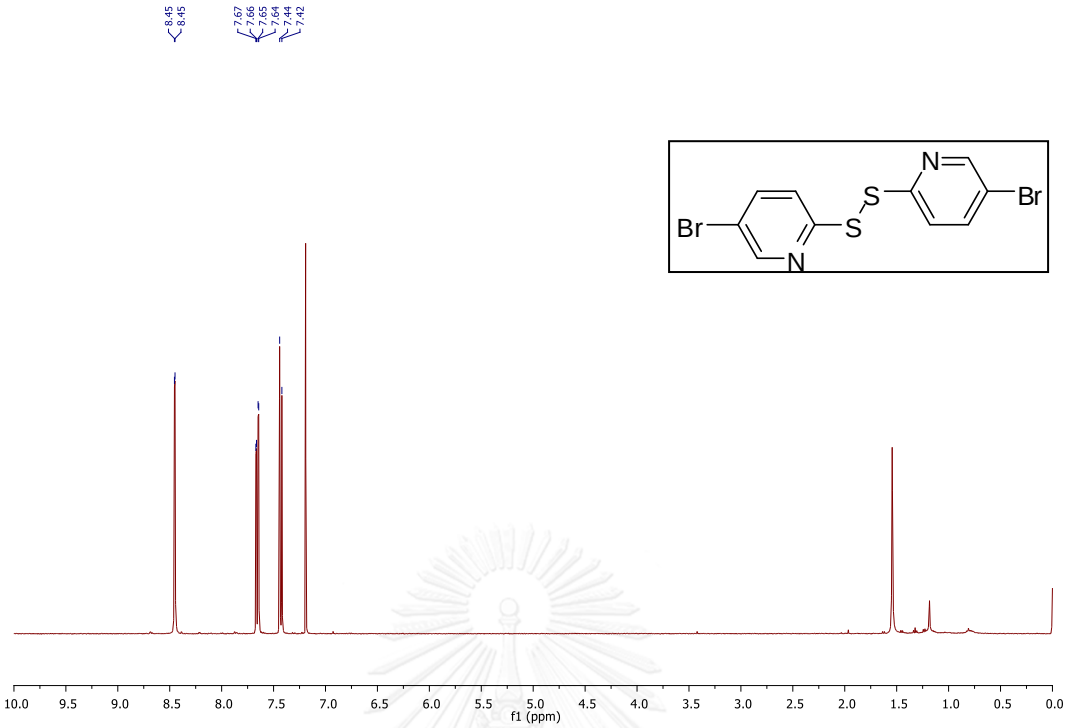

Figure A31 ^{1}H NMR spectrum of **2j** ($CDCl_3$)

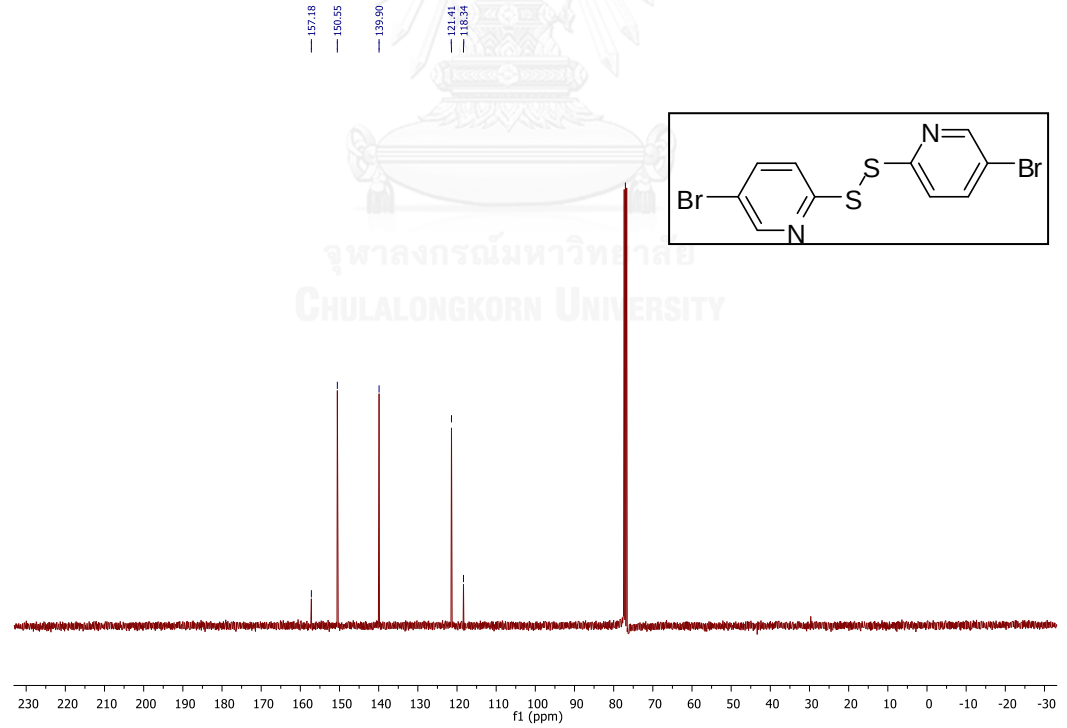

Figure A32 ^{13}C NMR spectrum of **2j** ($CDCl_3$)

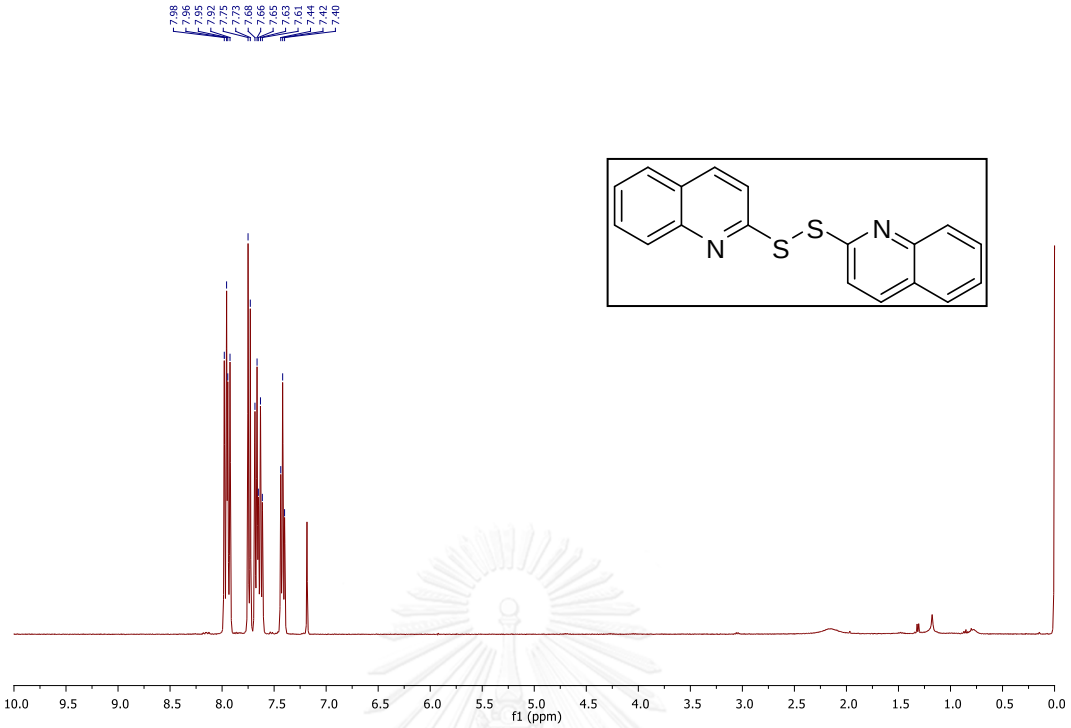

Figure A33 ^{1}H NMR spectrum of **2k** ($CDCl_3$)

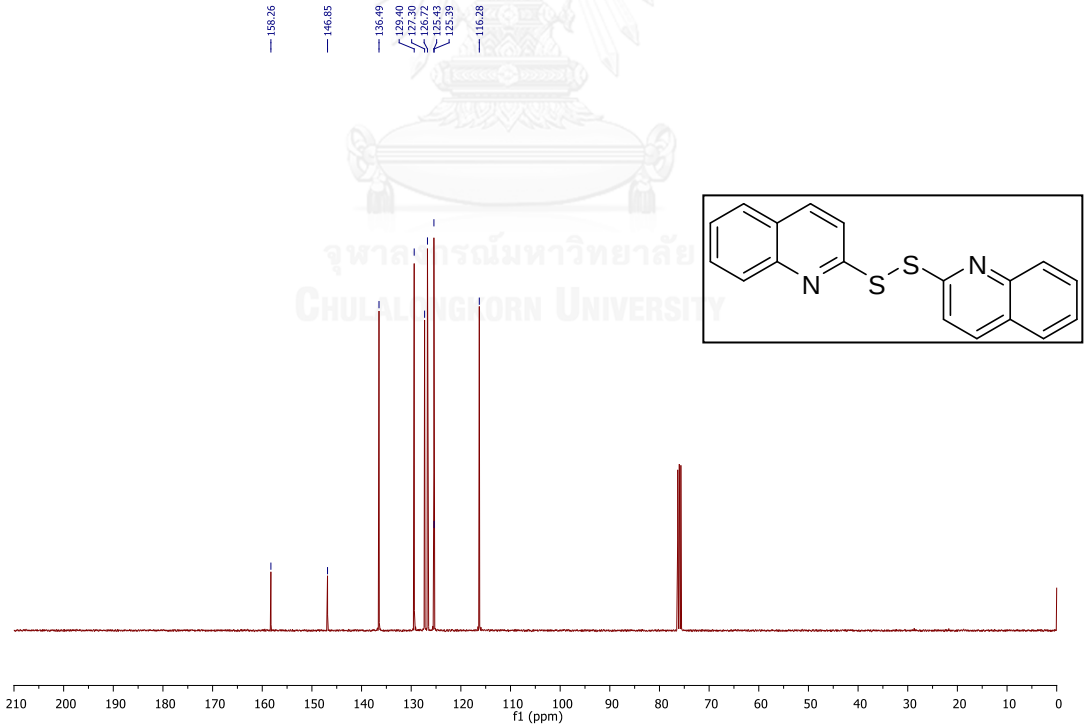

Figure A34 ^{13}C NMR spectrum of **2k** ($CDCl_3$)

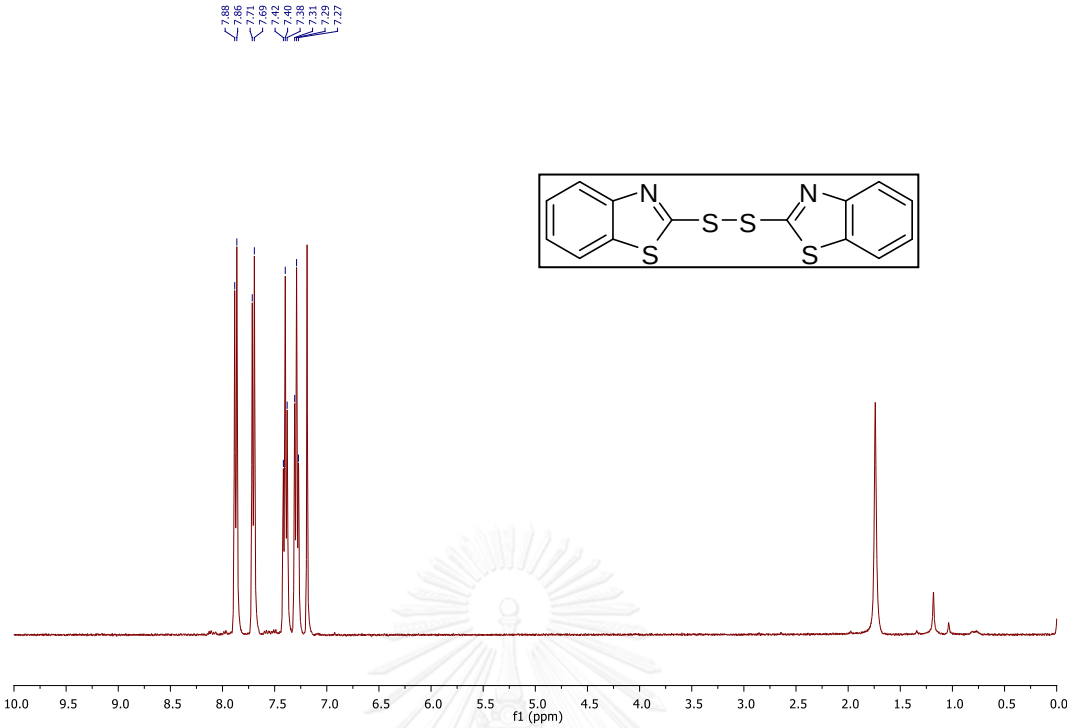

Figure A35 ^{1}H NMR spectrum of **2l** ($CDCl_3$)

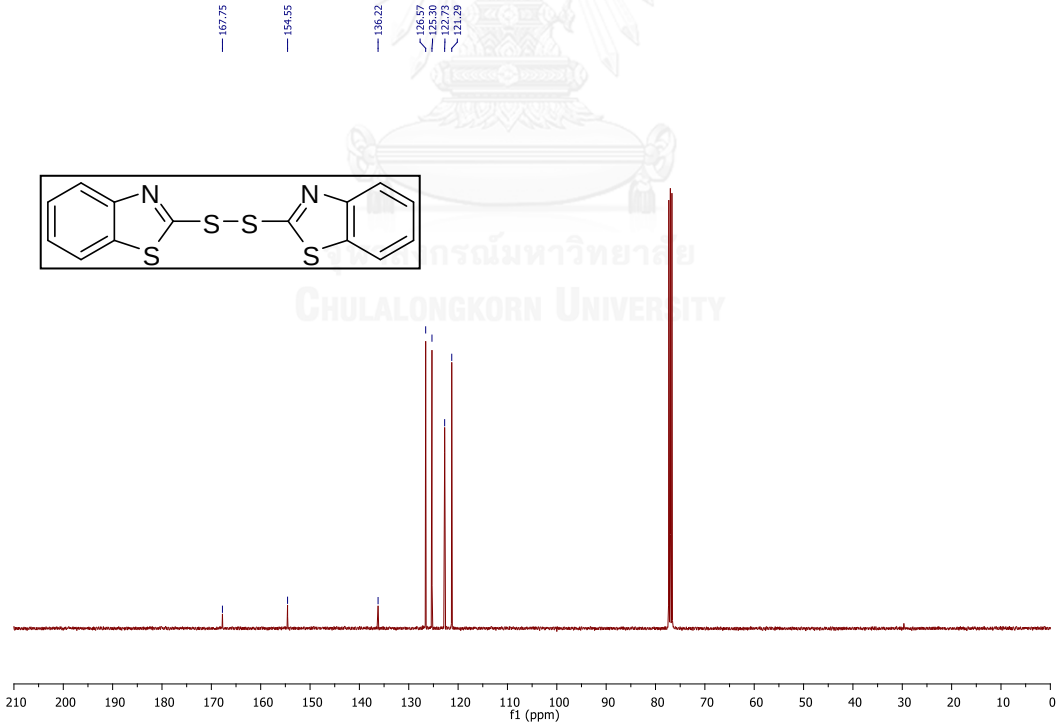

Figure A36 ^{13}C NMR spectrum of **2l** ($CDCl_3$)

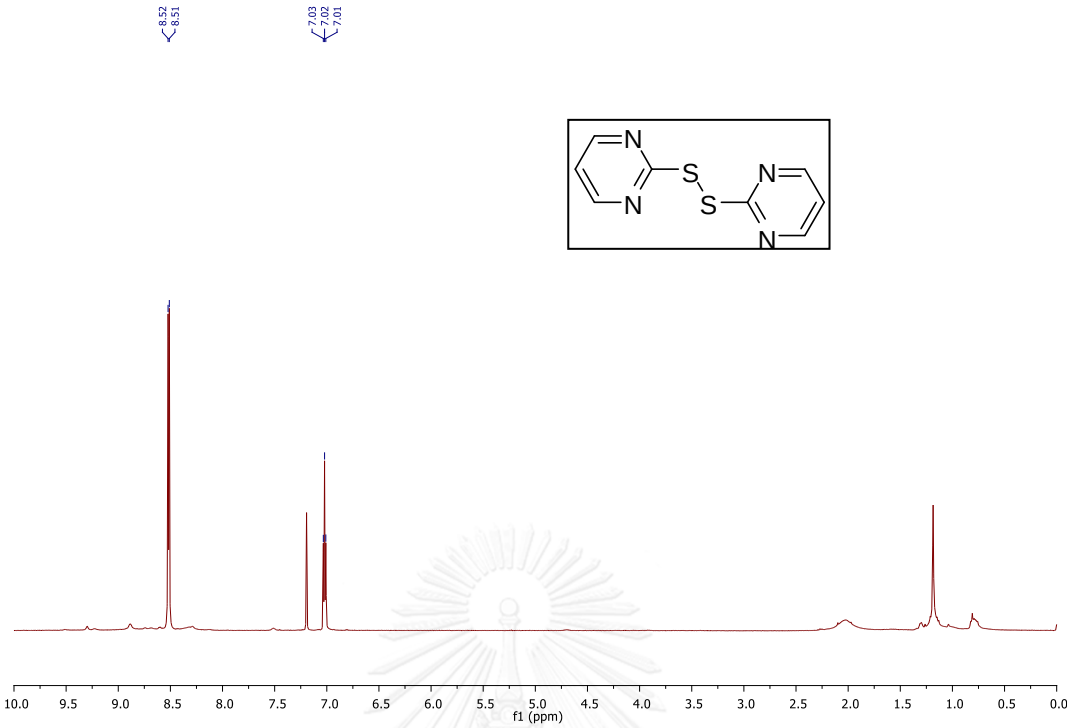

Figure A37 ^{1}H NMR spectrum of **2m** ($CDCl_3$)

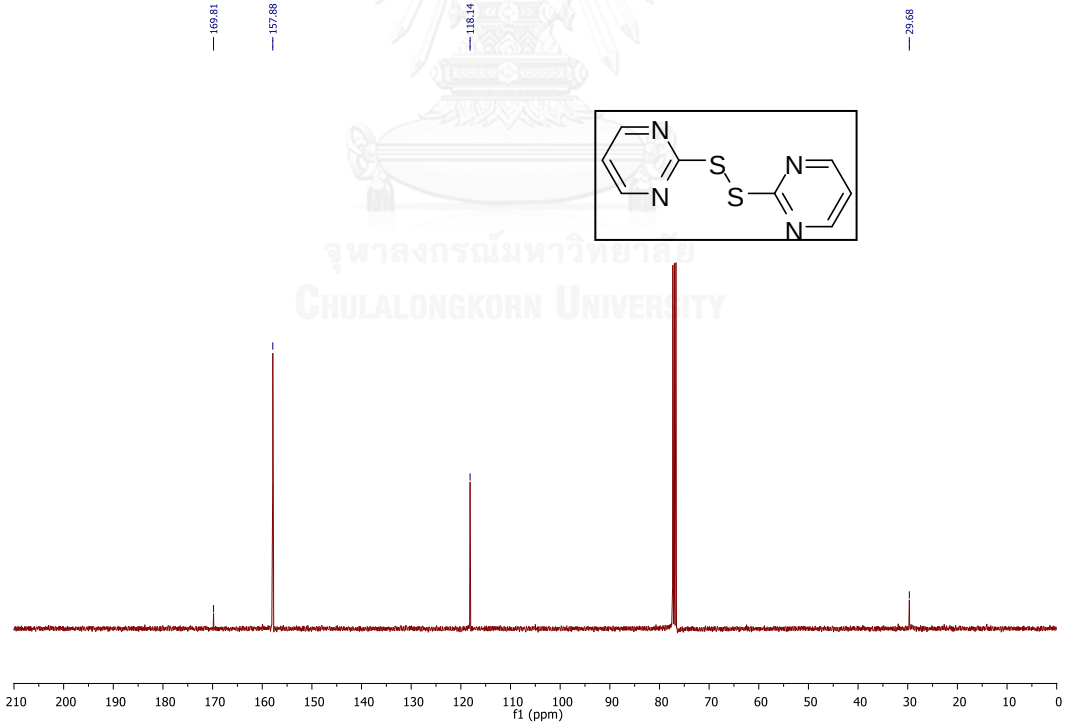

Figure A38 ^{13}C NMR spectrum of **2m** ($CDCl_3$)

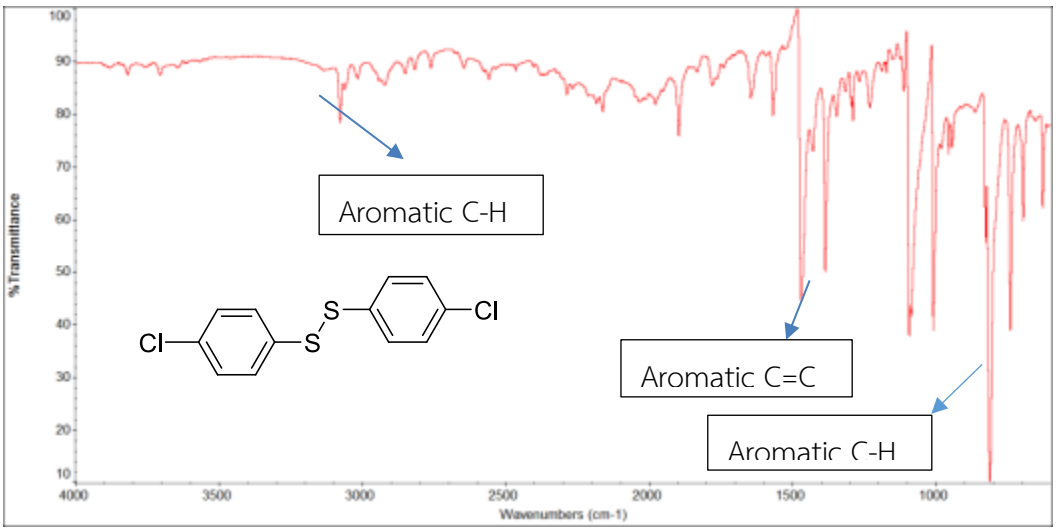

Figure A39 FT-IR spectrum of **2a**

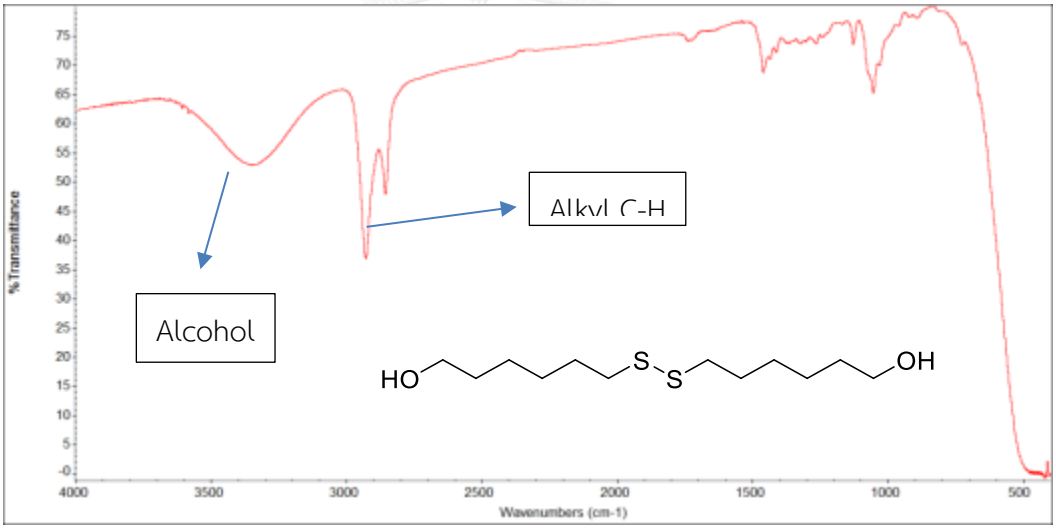

Figure A40 FT-IR spectrum of **2b**

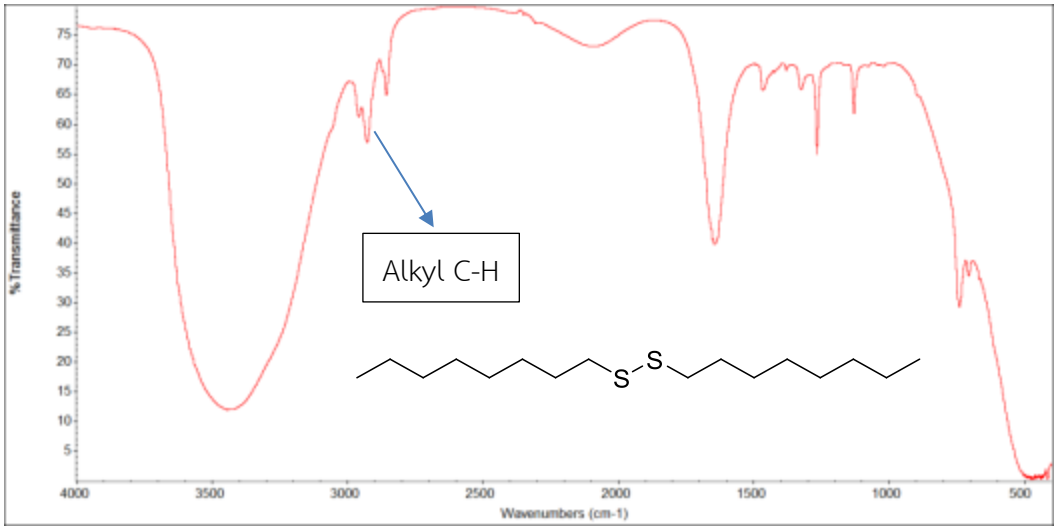

Figure A41 FT-IR spectrum of **2c**

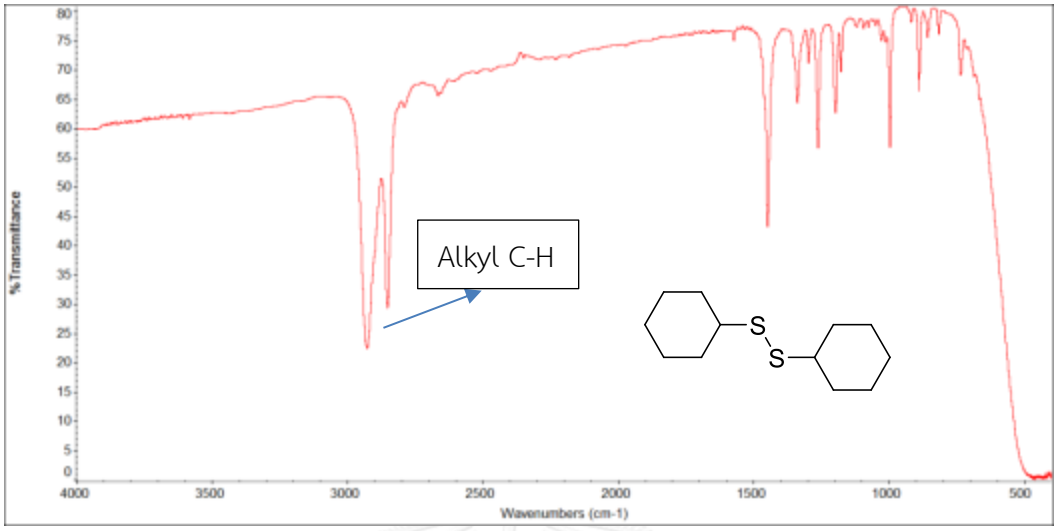

Figure A42 FT-IR spectrum of **2d**

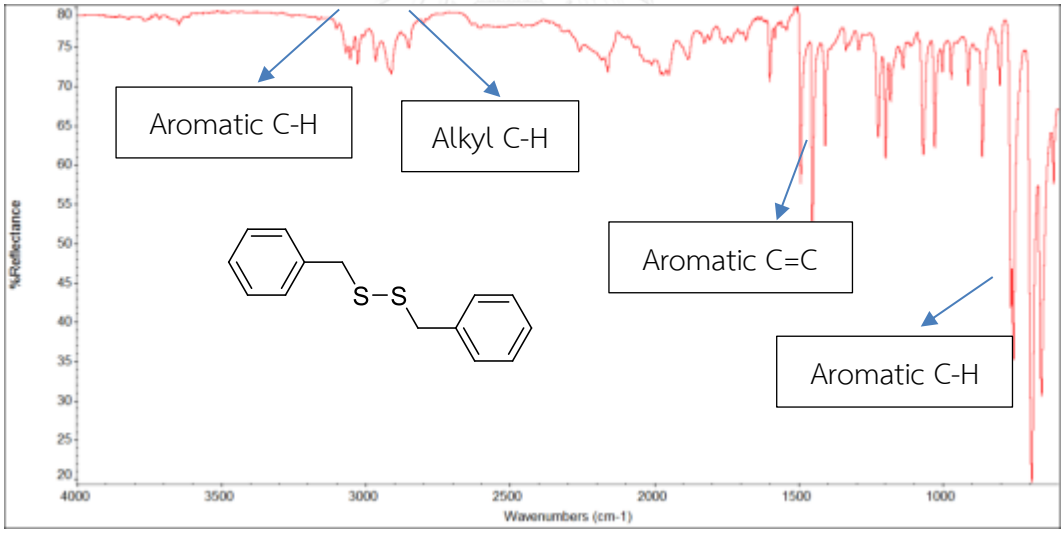

Figure A43 FT-IR spectrum of **2e**

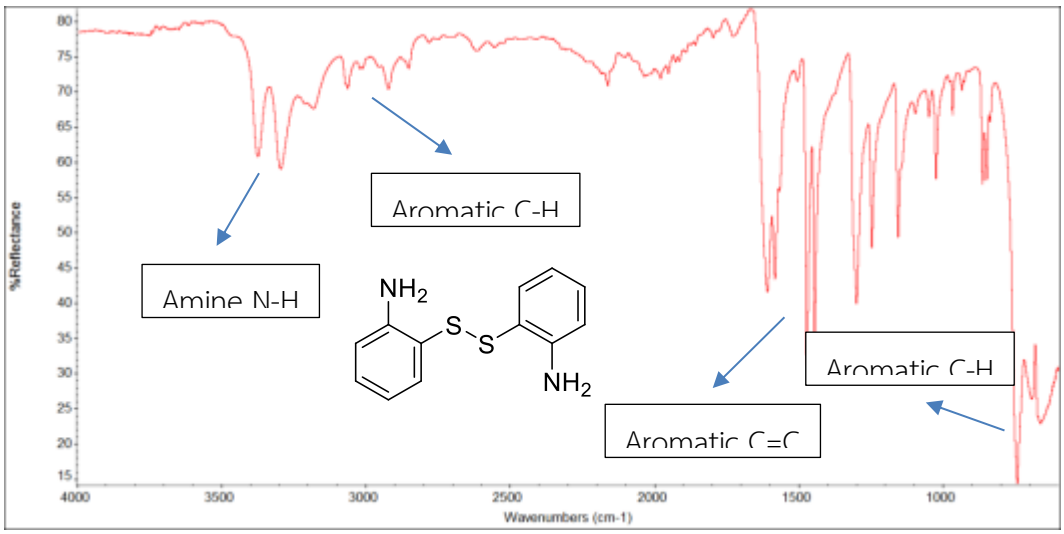

Figure A44 FT-IR spectrum of **2f**

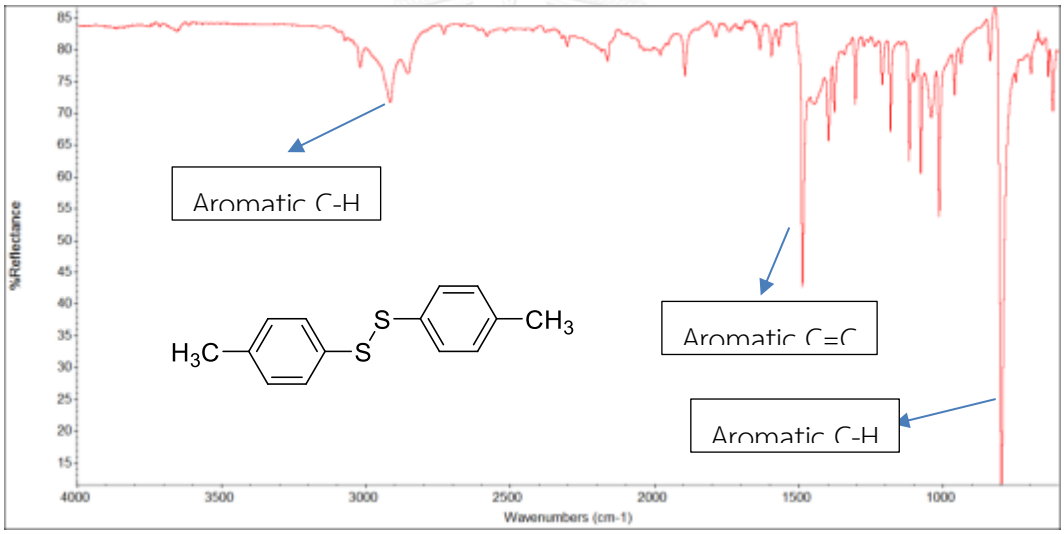

Figure A45 FT-IR spectrum of **2g**

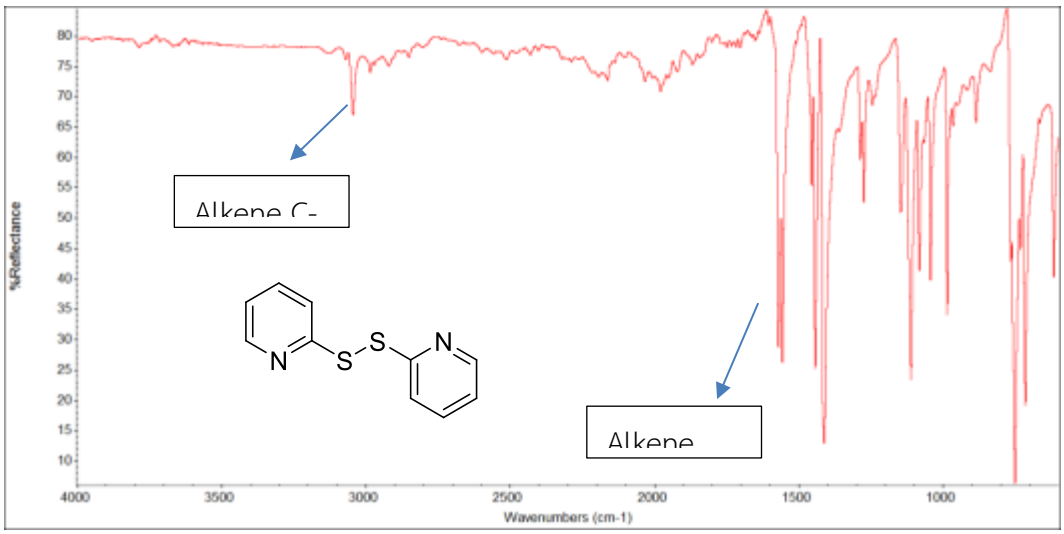

Figure A46 FT-IR spectrum of **2h**

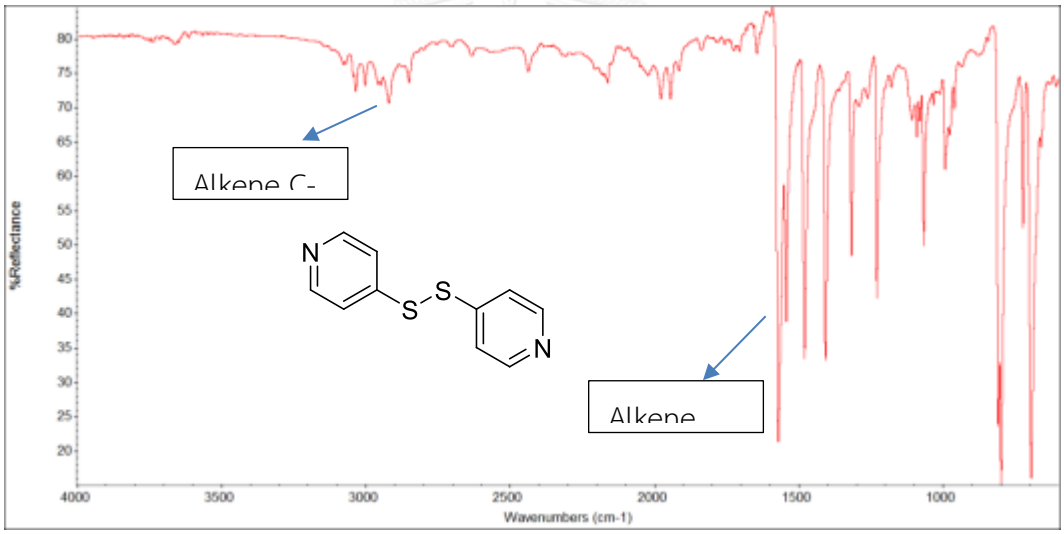

Figure A47 FT-IR spectrum of **2i**

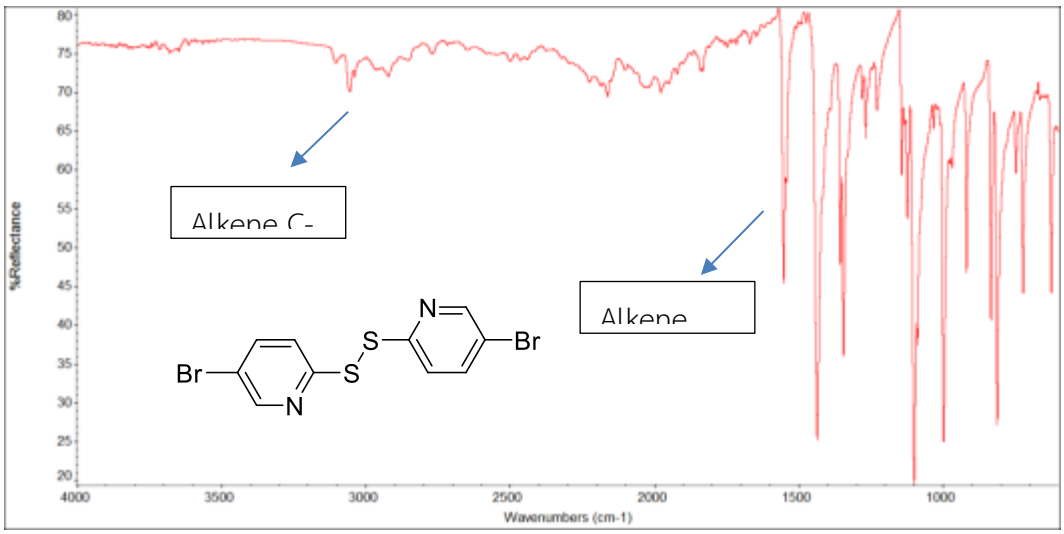

Figure A48 FT-IR spectrum of **2j**

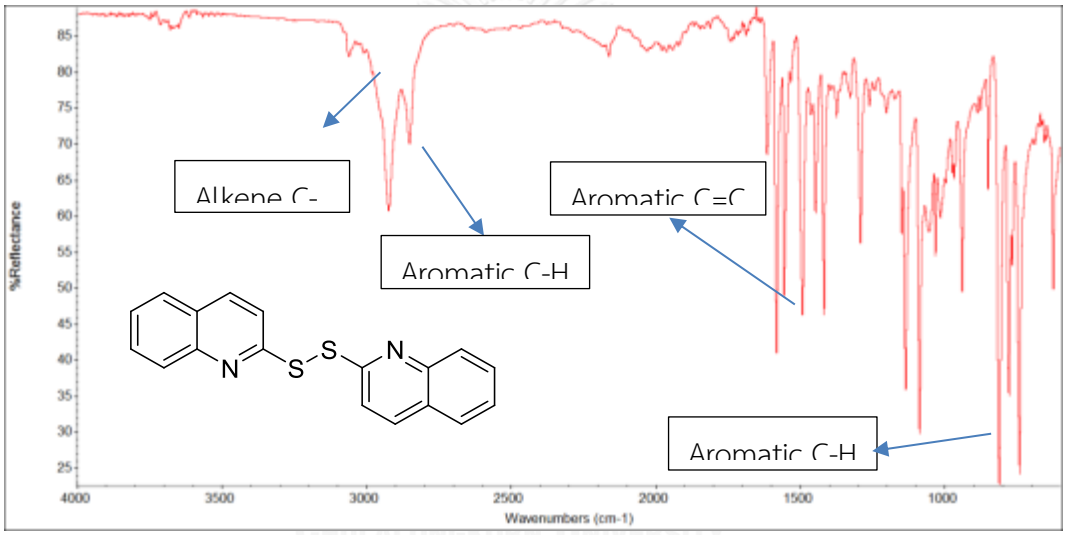

Figure A49 FT-IR spectrum of **2k**

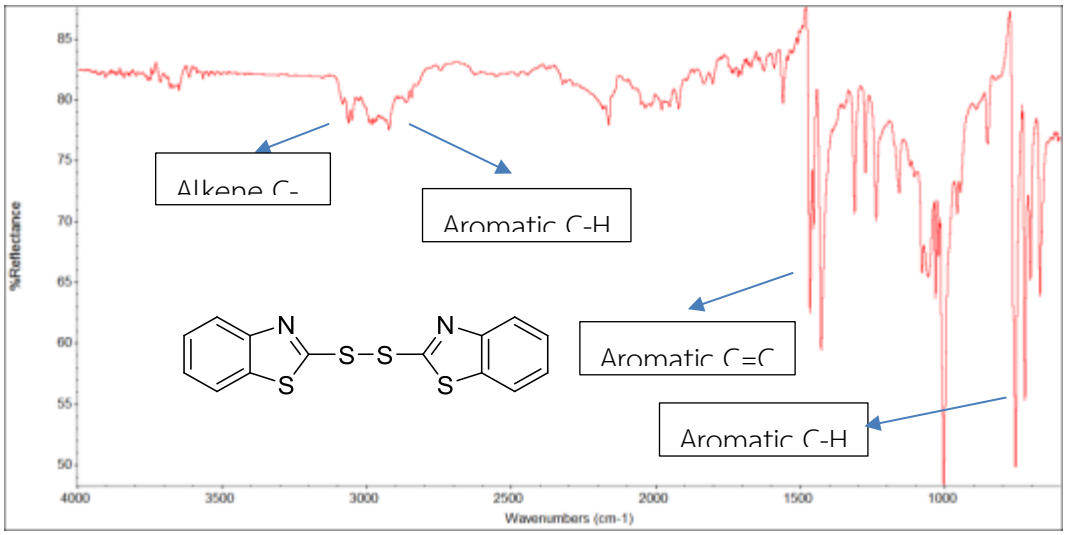

Figure A50 FT-IR spectrum of **2l**

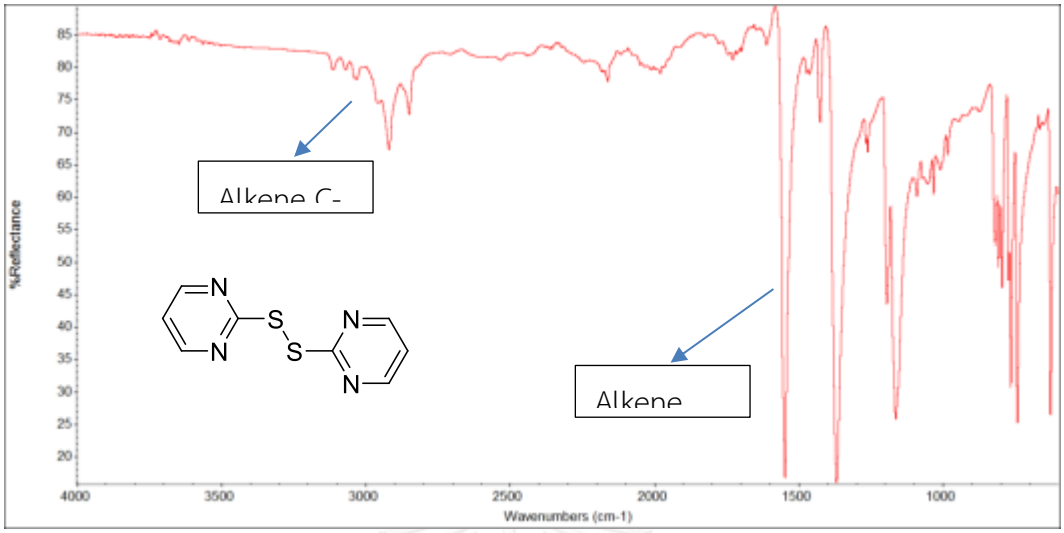

Figure A51 FT-IR spectrum of **2m**

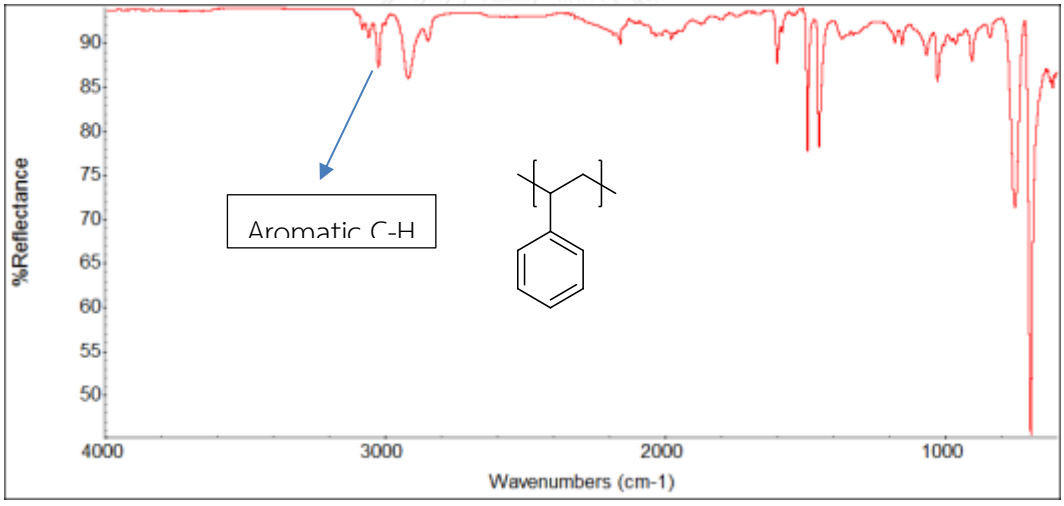

Figure A52 FT-IR spectrum of polystyrene (**PS**)

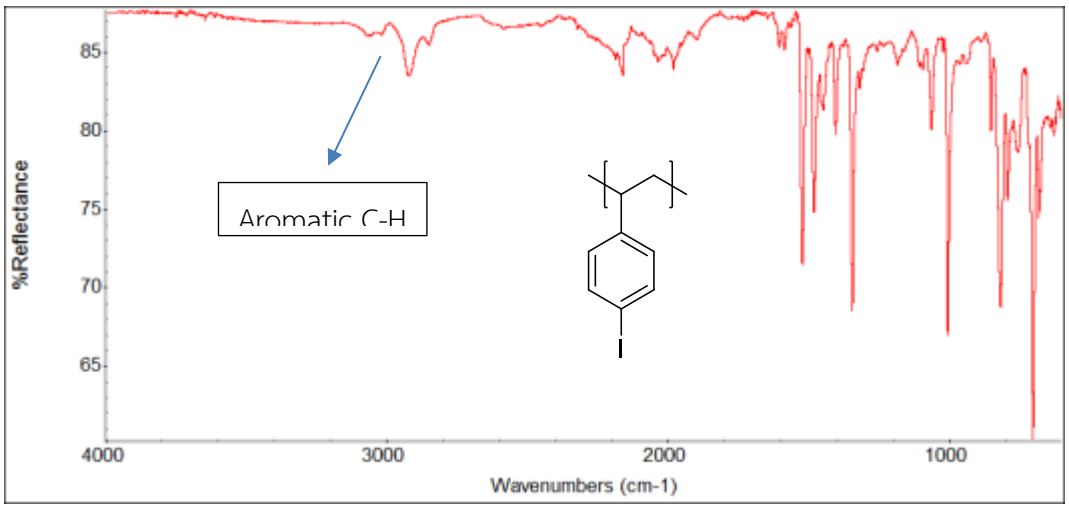

Figure A53 FT-IR spectrum of **PS-I**

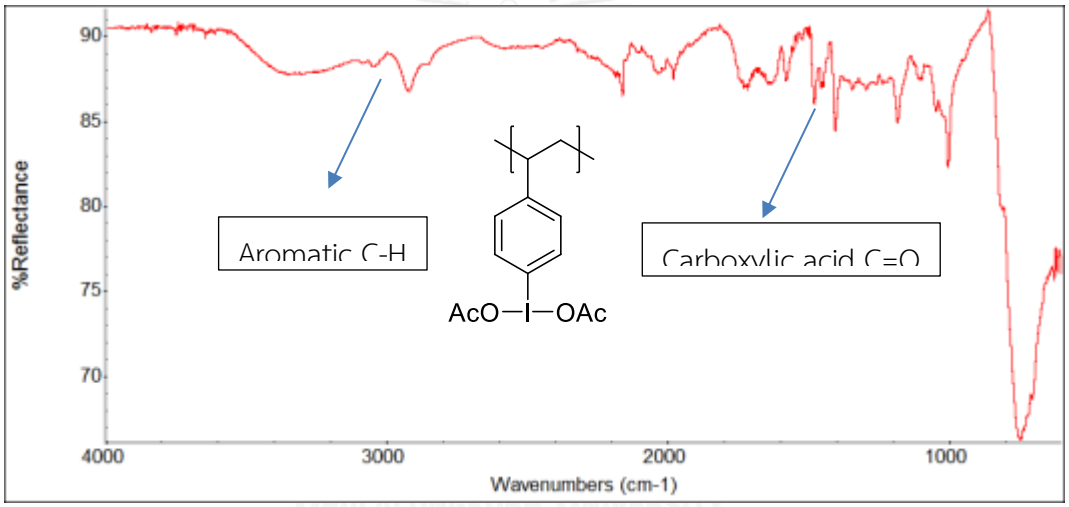

Figure A54 FT-IR spectrum of **PS-DIB**

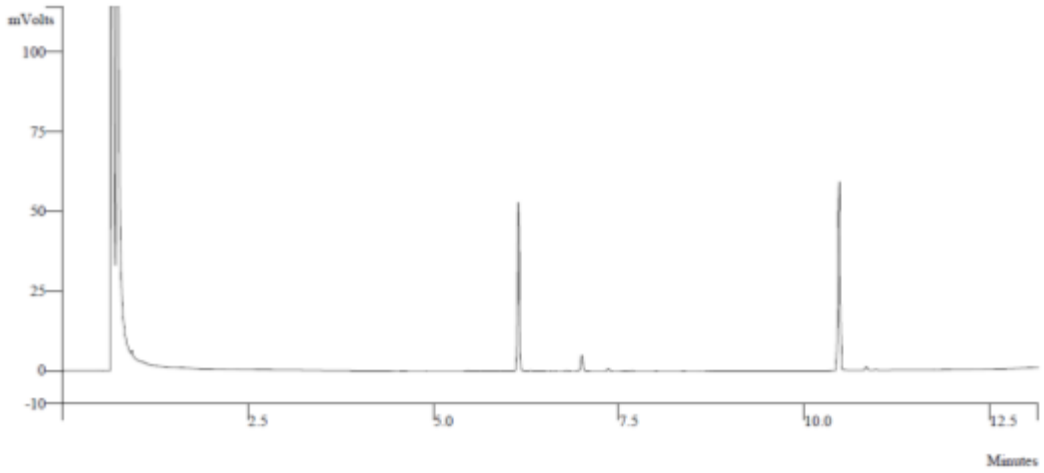

Figure A55 GC chromatogram of **2a** (Table 3.6, entry 1)

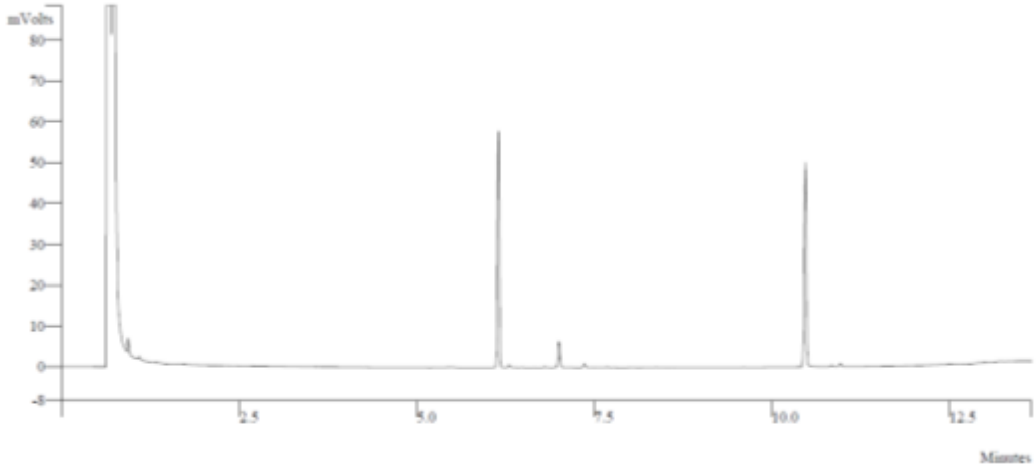

Figure A56 GC chromatogram of **2a** (Table 3.6, entry 2)

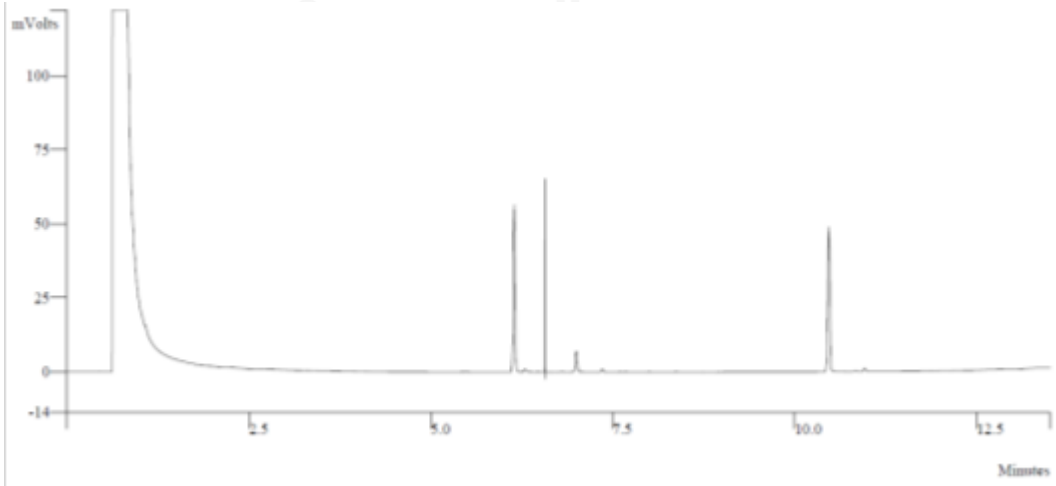

Figure A57 HPLC chromatogram of **2a** (Table 3.6, entry 3)

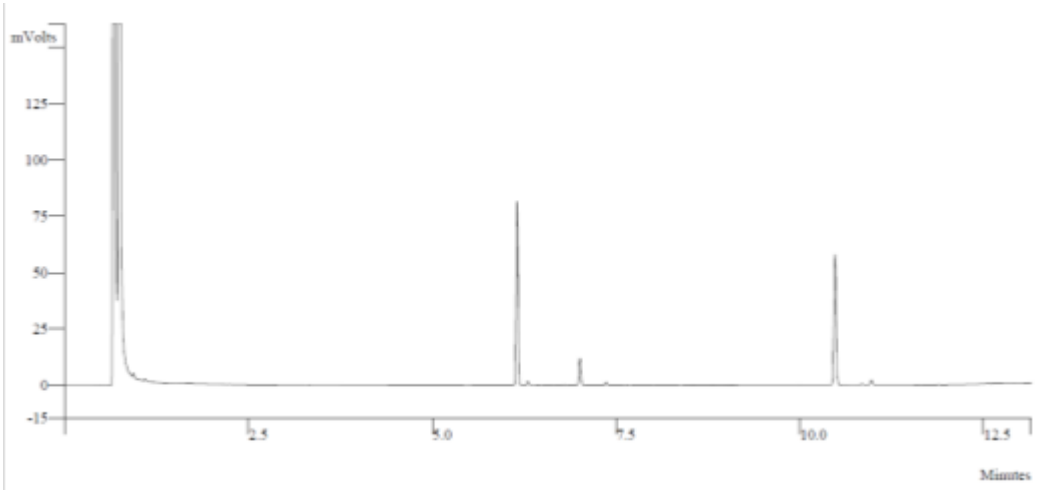

Figure A58 HPLC chromatogram of **2a** (Table 3.6, entry 4)

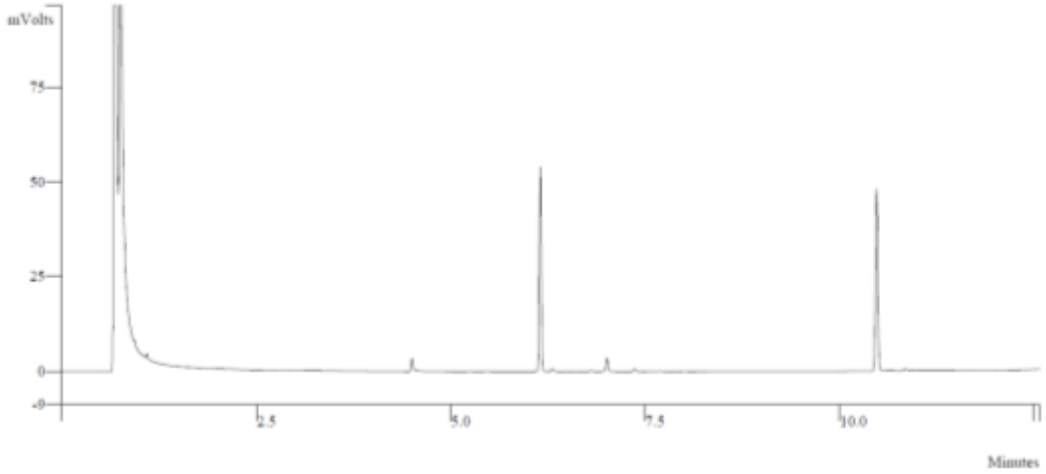

Figure A59 HPLC chromatogram of **2a** (Table 3.7, entry 1)

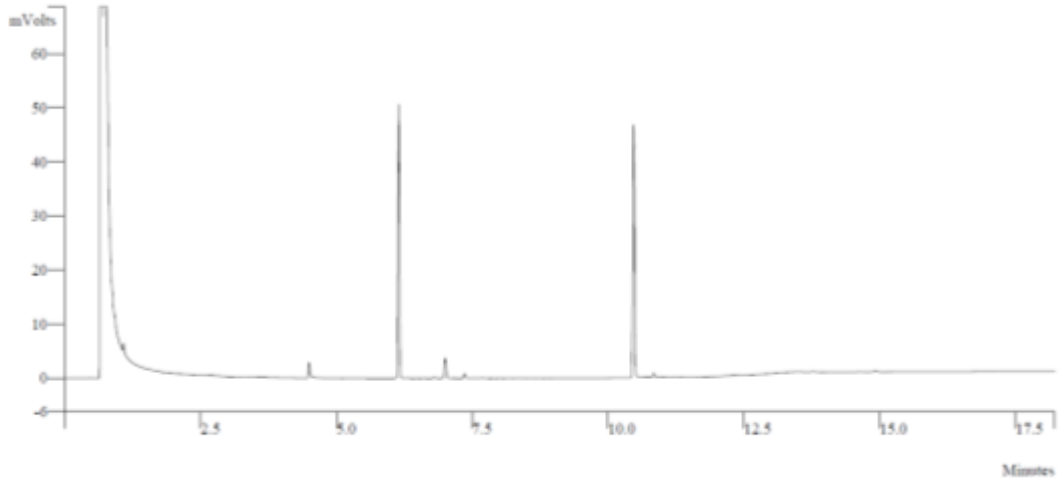

Figure A60 HPLC chromatogram of **2a** (Table 3.7, entry 2)

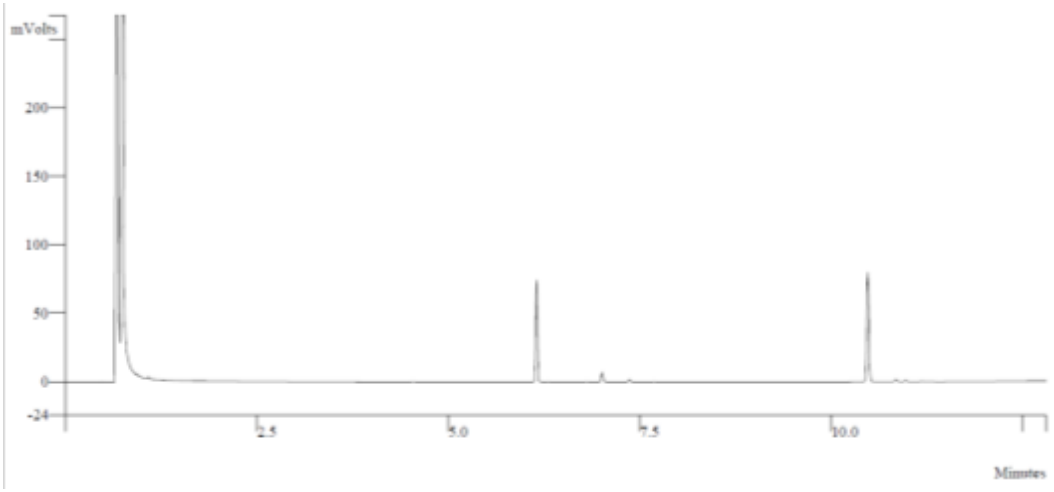

Figure A61 GC chromatogram of **2a** (Table 3.7, entry 3)

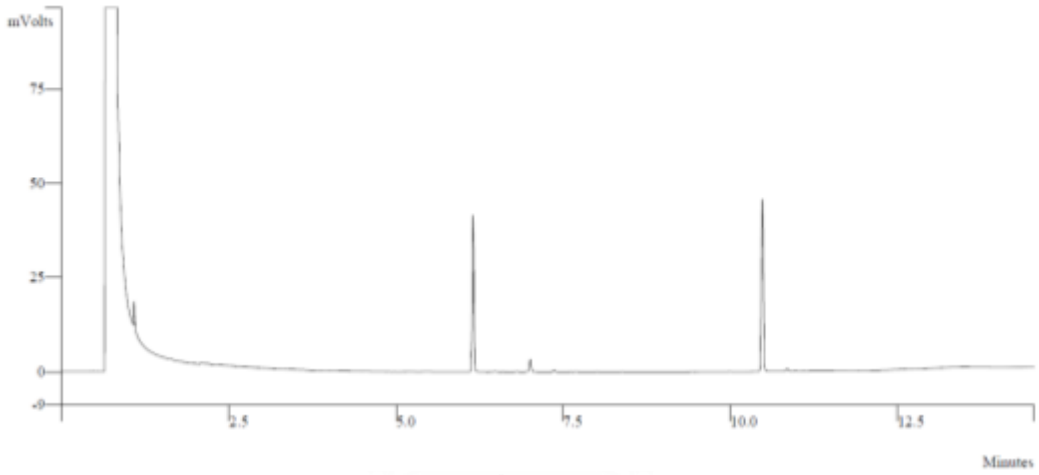

Figure A62 GC chromatogram of **2a** (Table 3.7, entry 4)

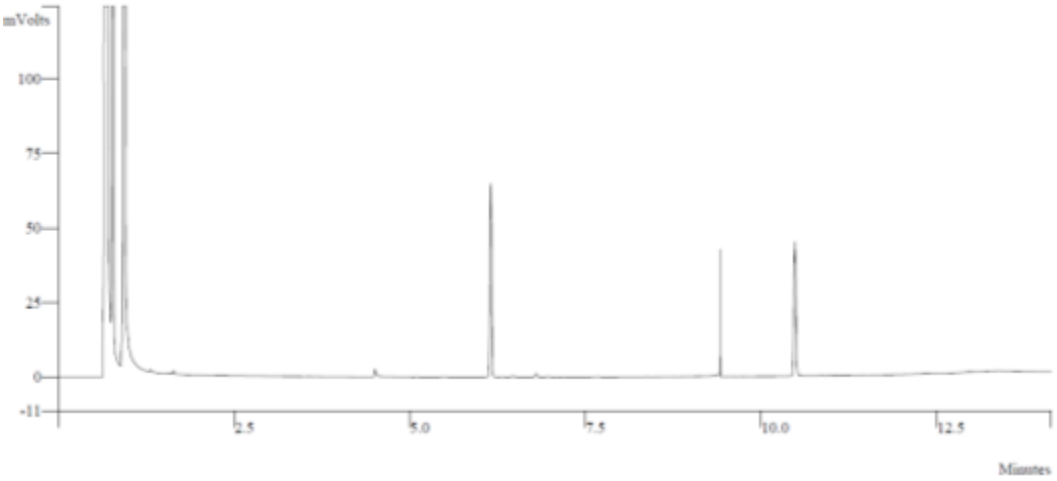

Figure A63 GC chromatogram of **2a** (Table 3.8, entry 1)

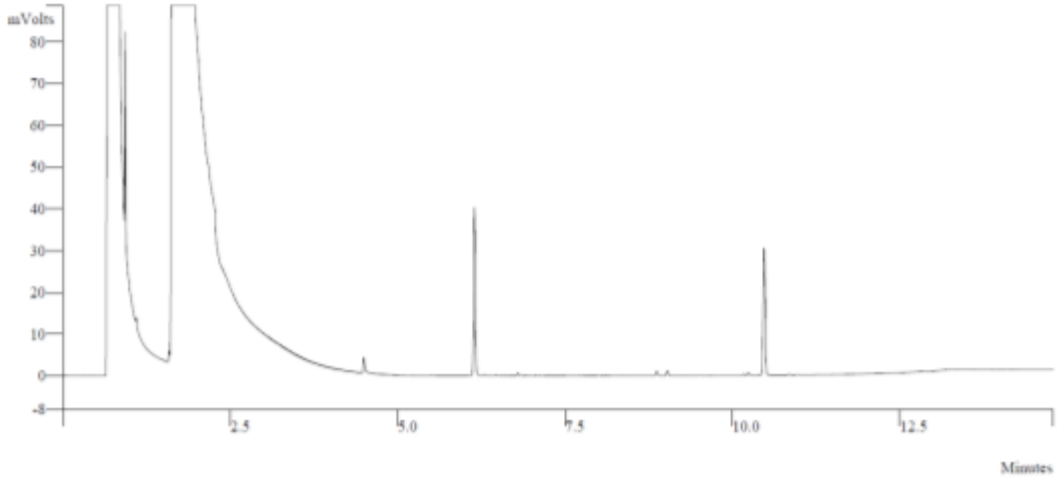

Figure A64 GC chromatogram of **2a** (Table 3.8, entry 2)

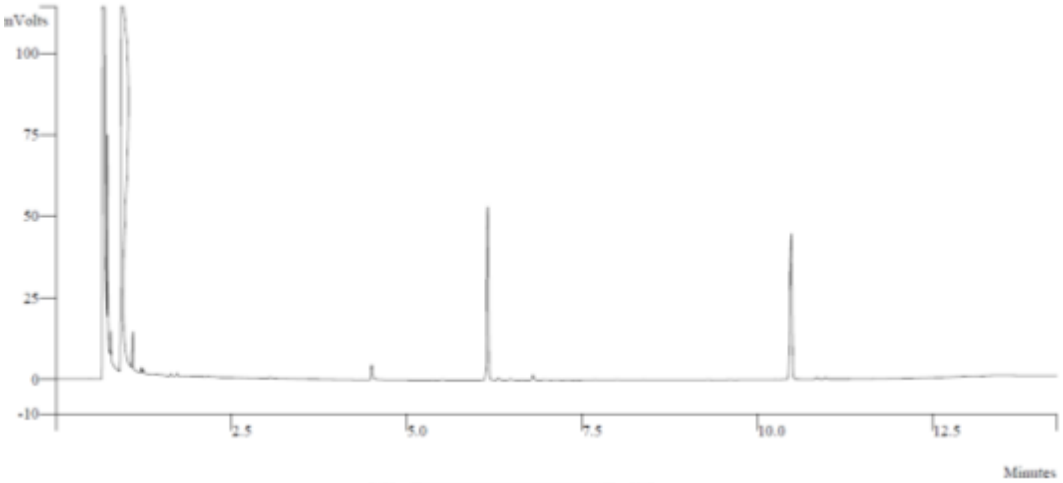

Figure A65 GC chromatogram of **2a** (Table 3.8, entry 3)

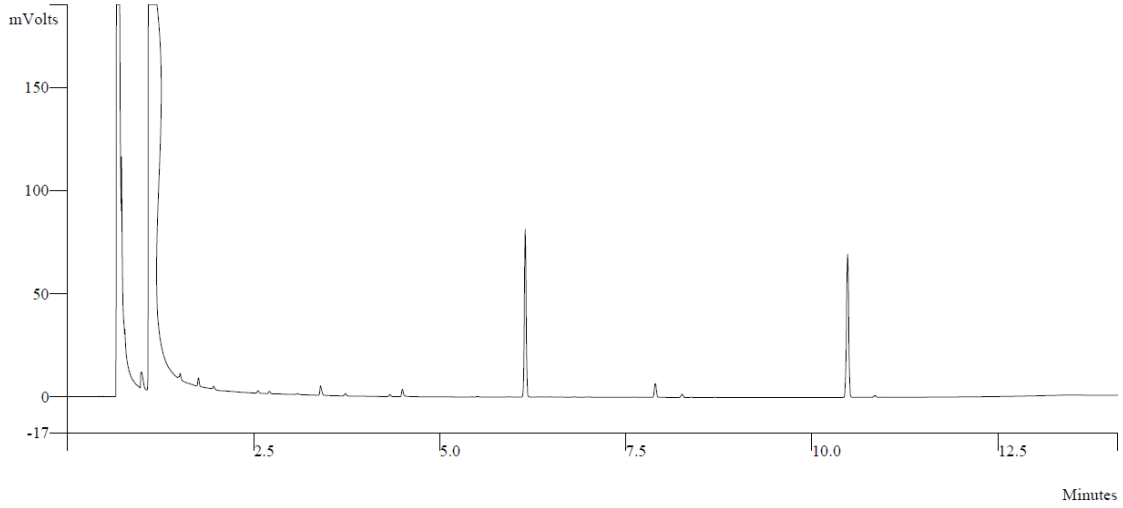

Figure A66 GC chromatogram of **2a** (Table 3.8, entry 5)

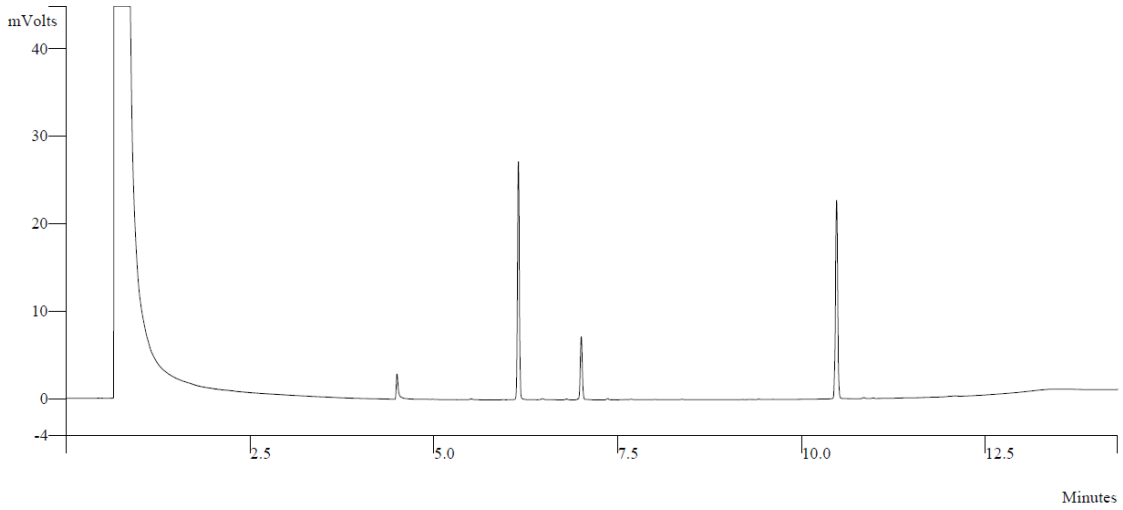

Figure A67 GC chromatogram of **2a** (Table 3.8, entry 6)

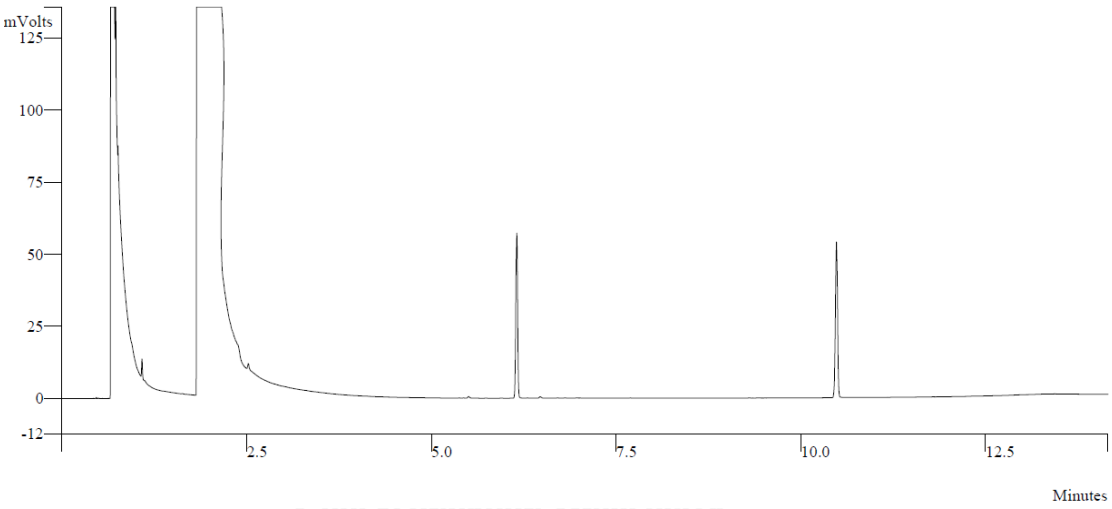

Figure A68 GC chromatogram of **2a** (Table 3.8, entry 7)

VITA

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