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Thioglycolic acid를 이용한
황-포함 작용기 도입에 관한 연구

2021

성신여자대학교 대학원

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이 논문을 석사학위 논문으로 제출함

2020년 11월

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논문개요

$C_{aryl}-S$ 결합은 유기화합물, 천연물, 의약품 등의 다양한 화합물에서 발견되는 중요한 결합으로 팔라듐, 구리, 니켈 등 전이금속을 촉매로 이용하여 $Ar-S-Ar$ 이나 $Ar-S-alkyl$ 등의 $C-S$ 결합을 효율적으로 합성하는 연구들이 최근에도 지속되고 있다. 그 중 구리 촉매는 값이 싸고 독성이 적다는 장점이 있어 많은 연구자들이 선호하는 촉매 중 하나이다. $C_{aryl}-S$ 결합에 흔히 이용되는 S 제공 시약인 aryl 또는 alkyl thiol은 상업적으로 구입할 수 있는 종류에 제한이 있고 쉽게 산화하는 높은 반응성을 가져 다루기 어렵다. 이를 대체하는 다른 S 제공 시약들이 연구되고 있는데 thioglycolic acid는 현재까지 보고된 적이 없는 S 제공 시약이다. 본 연구에서는 thioglycolic acid를 이용하여 $C_{aryl}-S$ 결합 형성 반응을 개발하였다. 반응의 용매 조건에 따라 biaryl disulfide와 (arylthio)acetic acid가 각각 주생성물로 합성되는 것을 확인하였다.

이와 함께 amine 에 thioformyl 기를 도입하는 데에도 thioglycolic acid 를 이용할 수 있음을 확인하였다. Thioformyl 기는 여러 화합물의 중간체로 다양하게 쓰일 수 있지만 합성하는 방법은 드물게 알려져 있다. 독성이 있는 가스, atom 경제성이 떨어지는 시약 등을 이용해 고온/고압/전하 조건 하에서 합성해야 하고, 이러한 방법들을 이용해도 합성 가능한 thioformamide 의 다양성이 매우 제한적이다. 본 연구는 저렴하고 널리 사용 가능한 시약인

thioglycolic acid 로 전이금속 촉매 없이 1, 2 차 amine 및 aniline 에 thioformyl 기의 도입이 가능한 것을 확인하였다.

Abbreviations

Many abbreviations are used throughout in this dissertation in order to save space. For convenience, a list of most abbreviations is compiled for easy access.

DMSO	Dimethylsulfoxide
DME	Dimethyl Ether
Et ₃ N	Triethylamine
rt	room temperature
^t PrOH	Isopropyl alcohol
PEG-200	polyethylene glycol-200
<i>i</i> -Pr ₂ NEt	<i>N,N</i> -Diisopropylethylamine
DHPB	1,1'-Diheptyl-4,4'-bipyridinium dibromide
LiHMDS	Lithium bis(trimethylsilyl) amide
Ar	Aryl
^t Bu	Tertiary butyl
P ₂ S ₅	Phosphorus pentasulfide

DMF

N,N-dimethylformamide

GC

Gas chromatography

목 차

논문개요

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I. 서 론

C-S 결합은 C-O 결합과 C-N 결합과 마찬가지로 여러 천연 물질에 존재하며 의약품, 농약, 고분자 물질과 같은 다양한 화합물에서 중요하다.¹ 황을 포함한 화합물들은 천식이나 폐질환의 억제제, antifolate 등의 의약품 등이 있다²(Figure 1). 그러므로 C-S 결합형성 반응법 연구 및 개발이 활발히 이루어지고 있다. 그 중 aromatic ring에 aryl thiol 또는 alkyl thiol을 도입하여 Ar-S-Ar 또는 Ar-S-alkyl을 합성하는 방법들은 최근까지도 주목받고 있다.

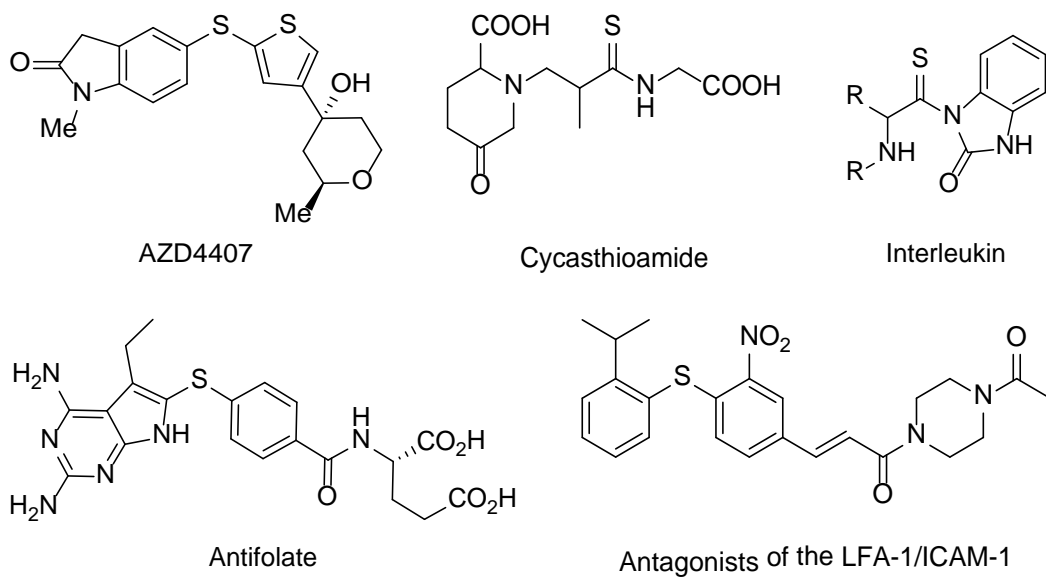


Figure 1. Diverse compounds with C-S bond

C_{aryl}-S 결합 형성 방법으로 최근에 팔라듐,⁴ 구리,⁵ 니켈, 코발트 등⁶ 전이금속 촉매를 이용한 방법들이 많이 연구되었다.³

특히, palladium(팔라듐) 촉매를 이용한 C_{aryl}-S coupling 반응을 통해 황을 포함하는 arylalkyl thioether, vinyl thioether, biaryl thioether 등을 형성하는 다양한 합성방법들이 보고되어 왔다. 1978년 Migita 그룹에서 Pd[PPh₃]₄를 촉매로 이용해 aryl halide와 thiolate anion로부터 biaryl sulfide의 합성을 보고하였다(Scheme 1).⁷ 이후 팔라듐과 다양한 ligand를 이용한 thioether 합성방법들이 보고되었다. 또한, vinyl halide를 이용한 alkenyl sulfide의 *E/Z* 선택적 합성도 보고되었다(Scheme 1).⁸ 2006년 Hartwig 그룹은 팔라듐의 양을 0.01 mol%까지 줄여도 팔라듐 촉매와 강한 coordination을 하여 반응 수율을 높일 수 있는 Josiphos ligand(CyPF-^tBu)를 개발하였고(Scheme 1),⁹ 2019년 Buchwald 그룹에서는 monodentate ligand(^tBuXPhos, ^tBuBrettPhos)를 이용한 반응도 보고하였다¹⁰(Figure 2, Scheme 1). 최근에는 ball-milling에 의한 방법 등의 반응 시스템들도 개발되고 있다.¹¹

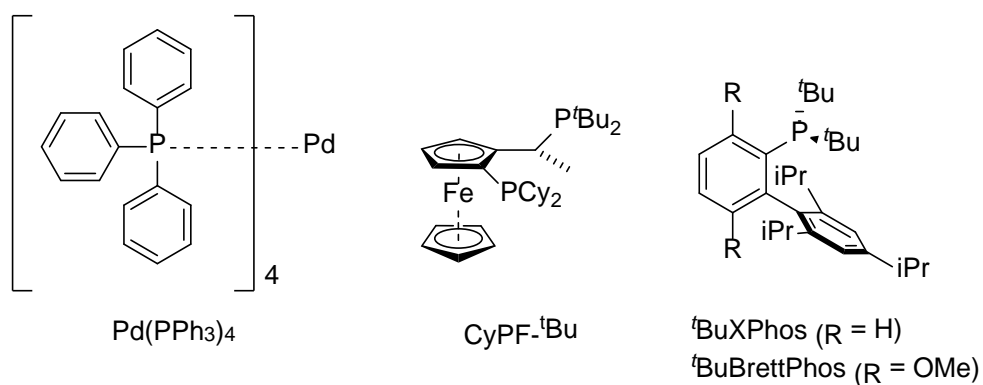
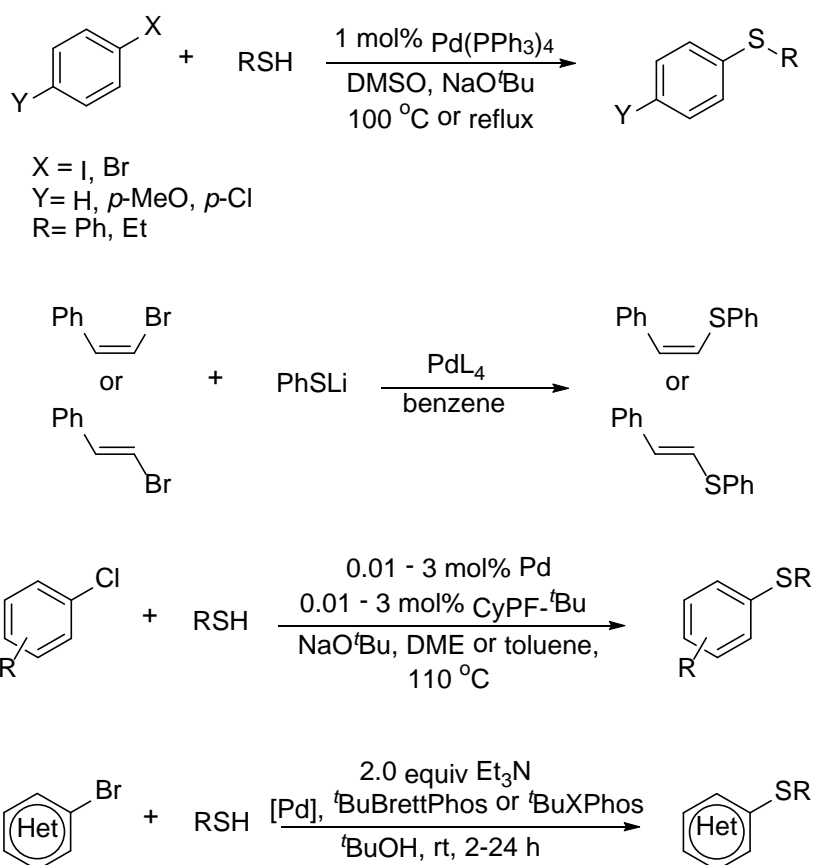


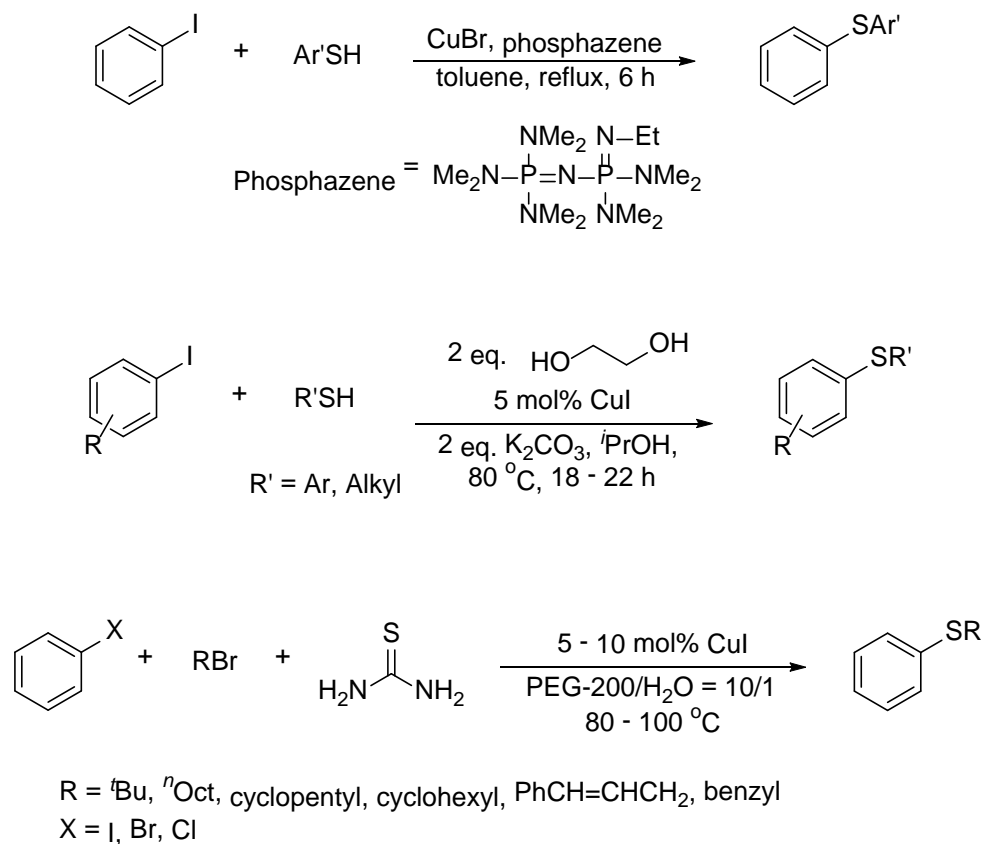
Figure 2. Ligands used in palladium-catalyzed $\text{C}_{\text{aryl}}\text{-S}$ coupling



Scheme 1. 다양한 palladium-catalyzed $\text{C}_{\text{aryl}}\text{-S}$ coupling 반응

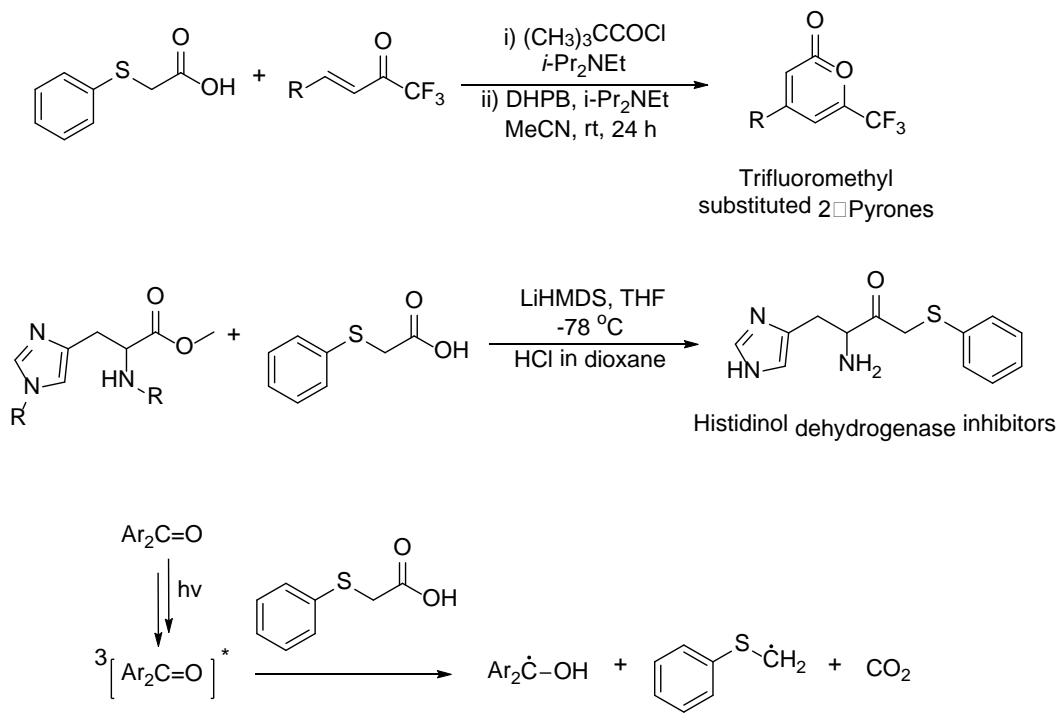
그러나 팔라듐은 가격이 비싸고 독성이 있어 다른 촉매 시스템에 대한 연구들도 많이 이루어졌다. 팔라듐의 대체 촉매로서 구리를 이용하는 연구 또한 많이 보고되었다.^{3,12} 구리는 가격이 저렴하고 독성이 적어 C-S 결합 형성에서 가장 선호되는 촉매 중 하나이다.

고전적으로는 200-300 °C의 높은 온도에서 구리를 당량으로 쓰는 반응들이 보고되었다.¹³ Suzuki 그룹에서 CuI 하에 aryl iodide와 aryl thiolate의 C_{aryl}-S 합성을 보고한 이후,¹⁴ Palomo 그룹이 phosphazene을 base로 이용하여 biaryl sulfide를 합성할 수 있음을 보고하였다(Scheme 2).¹⁵ Buchwald 그룹에서는 ethylene glycol를 리간드로 이용한 aryl iodide와 alkyl/aryl thiol의 실용적인 합성을 보고하였다(Scheme 2).¹⁶ 이외에도 S-coupling partner로서 thiol을 대체할 수 있는 thiourea와 thioimide, disulfide를 이용한 반응들이 연구되는 등 최근까지 꾸준히 다양한 방법들이 보고되고 있다¹⁷(Scheme 2).



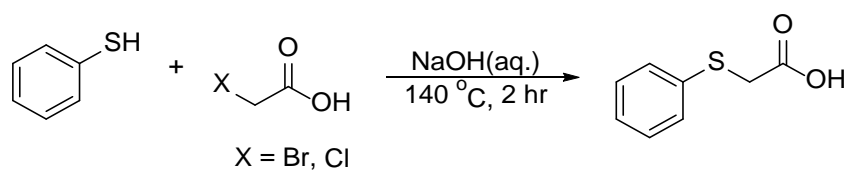
Scheme 2. 다양한 copper-catalyzed $\text{C}_{\text{aryl}}-\text{S}$ coupling 반응

한편, $\text{C}_{\text{aryl}}-\text{S}$ 를 포함한 (aryltio)acetic acid는 다른 화합물의 블록 물질인 2-pyrone합성의 반응물질로 이용하거나¹⁹(Scheme 3), 항결핵성 활성물질 합성에 이용한다²⁰(Scheme 3). 최근에는 photopolymerization반응에서 free-radical quencher로 이용하기도 하고²¹(Scheme 3), 다른 화합물과의 co-crystal 분석에서도 이용한다.²² 이외에도 (aryltio)acetic acid는 arylthio기를 갖는 화합물들의 전구체로 쓰이며,²³ 활성자리를 두 군데 가지고 있어 고리화합물 합성에도 적용 가능하다고 보고되었다.²⁴



Scheme 3. Application of (phenylthio)acetic acid

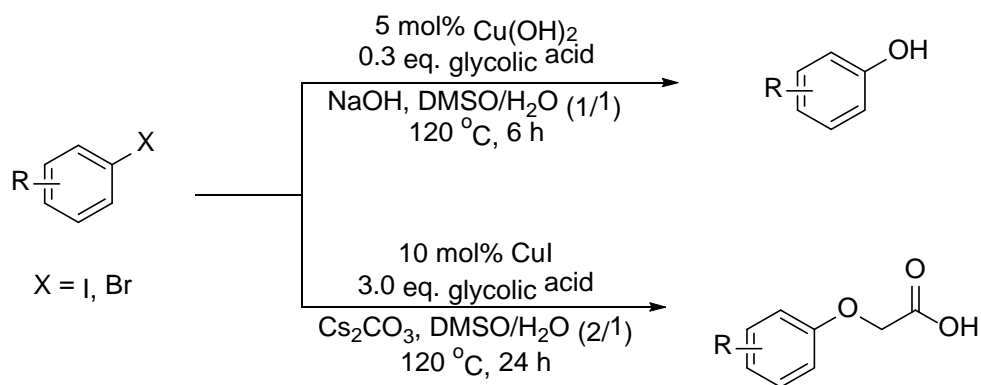
기존에 알려진 (phenylthio)acetic acid를 합성하는 방법에는 bromo-/chloroacetic acid와 thiophenol의 치환반응²⁵을 이용한 것이 있다(Scheme 4). 그러나 thiophenol은 불안정하여 상업적으로 구입 가능한 종류가 제한적이고, 강한 염기의 고온 반응조건으로 aromatic ring에 다양한 치환기를 갖는 (phenylthio)acetic acid를 합성하기에는 상당한 한계점이 있다.



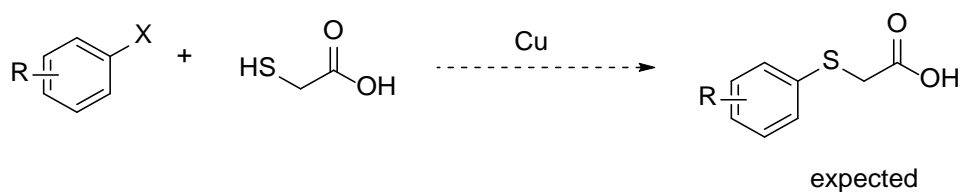
Scheme 4. Bromo-/chloroacetic acid를 이용한 (phenylthio)acetic acid

합성 방법

이전에 본 연구실에서 구리 금속 촉매 하에 aryl halide와 glycolic acid를 coupling partner로 이용해 C_{aryl}-O 결합 형성 연구를 보고한 적이 있다.¹⁸ 반응조건에 따라 glycolic acid가 coupling partner로 반응하여 2-phenoxyacetic acid가 생성되거나, ligand로 사용되어 phenol이 생성되는 결과를 얻었다(Scheme 5). Glycolic acid를 새로운 C-O coupling partner로 쓴 것에서 착안하여 thioglycolic acid를 C-S coupling partner로 이용하면 C_{aryl}-S 결합을 형성할 수 있을 거라고 예상하였고 예비 실험 결과 (arylthio)acetic acid를 합성할 수 있음을 확인하여 연구를 진행하였다(Scheme 6).



Scheme 5. 선행된 $\text{C}_{\text{aryl}}\text{-O}$ 결합 형성 연구



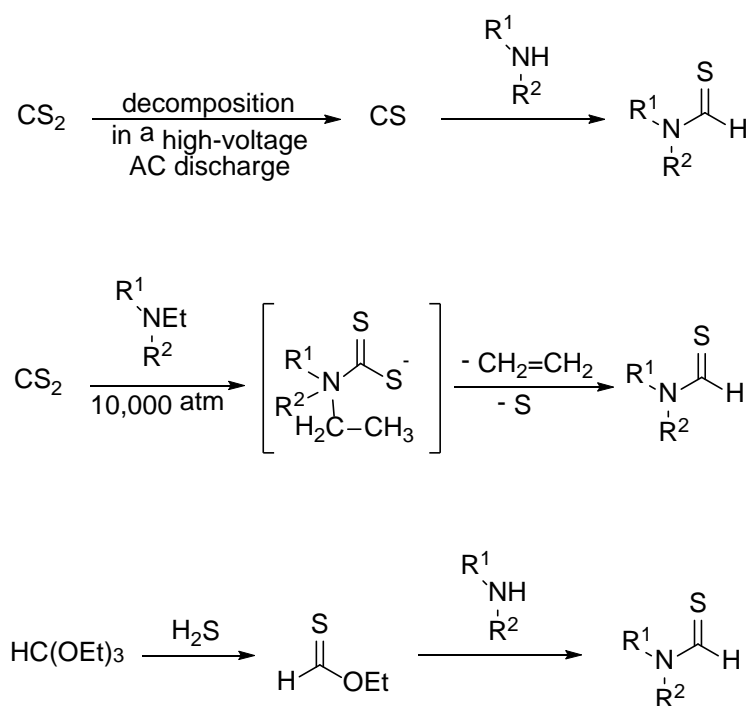
Scheme 6. 예상한 $\text{C}_{\text{aryl}}\text{-S}$ 결합 형성

전이금속 촉매를 이용한 $\text{C}_{\text{aryl}}\text{-S}$ 결합 형성 반응은 위에서 설명한 바와 같이 많이 알려져 있지만 “S”를 갖는 작용기 중 하나인 thioformyl기의 합성 및 도입에 관한 연구는 미미하게 알려져 있다.

Thioformamide는 heterocycle,²⁷ thioamide,²⁸ iminyl sulfide,²⁹ enamine³⁰ 등 다양한 유기물들의 유용한 중간체로 쓰이고, 생물이나 의학분야에서 다양한 물질의 기본 반응물질로 쓰여(Figure 1) 그 쓰임이 다양하지만 thioformamide의 합성 방법에 대한 연구는 미비하다.

기존에 알려진 방법으로는 amine에 직접적으로 thioformylation을 하는

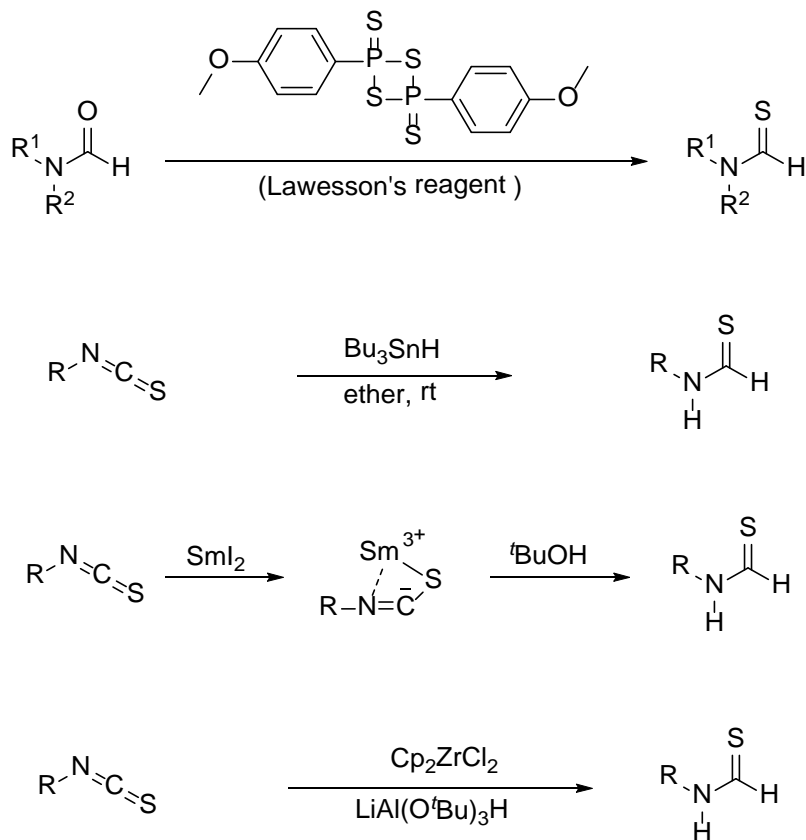
방법이 있다. 이때 사용하는 thioformylating reagent로 CS₂(carbon disulfide),³¹ CS(carbon monosulfide),³² O-ethylthioformate³³ 등이 보고되었으나, 고온/고압/전하 조건 하에 여러 단계를 걸쳐 CS₂ 가스 또는 H₂S 가스를 이용하는 위험한 방법으로 연구실 또는 산업체에서 이용되기 어렵다(Scheme 7).



Scheme 7. Thioformylation of amine

이외에도 Lawesson's reagent를 이용해 oxoformamide의 “O”를 “S”로 바꾸는 방법³⁴과 isothiocyanate(N=C=S)를 reduction하는 방법³⁷⁻³⁹이 보고된 바 있다. Oxoformamide에 “S”를 제공하는 시약으로는 Lawesson's

reagent 외에도 P_2S_5 ,³⁵ S_8 ³⁶이 보고되었는데 atom 경제성이 떨어지고 인화성의 위험과 냄새가 심하게 난다는 단점이 있다. 뿐만 아니라 Lawesson's reagent는 물과 만나면 유독한 H_2S 가스를 분출하는 등의 안전성 문제로 다른 대체재를 찾는 연구들이 지속되고 있다. Isothiocyanate를 환원시키는 방법으로 알려진 reducing agent에는 Bu_3SnH ,³⁷ SmI_2 ³⁸와 $CpZrHCl$ ³⁹이 있지만 substrate scope가 제한적이라 합성 가능한 thioformamide가 매우 한정적이다.



Scheme 8. Reduction of isothiocyanate

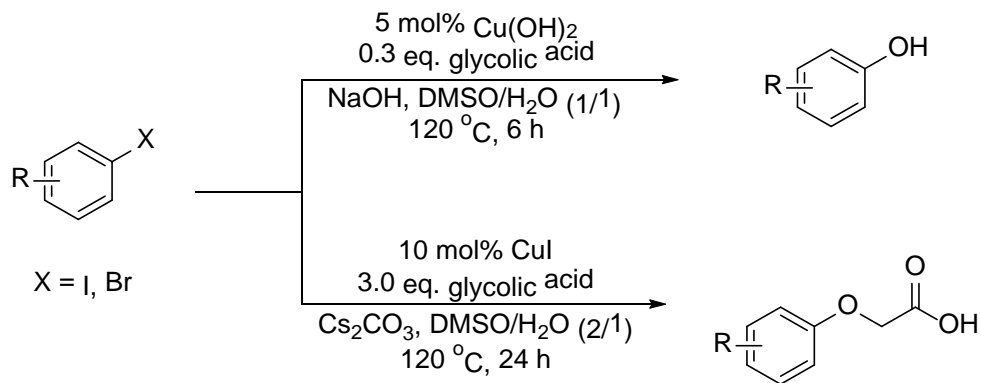
이에 본 연구실은 thioglycolic acid가 S 제공시약으로서 작용하는 점을 고려하여 amine과의 테스트 실험들을 수행했고 그 결과 thioglycolic acid를 이용해 amine에 thioformyl기가 도입됨을 확인하여 이에 대한 연구를 진행하였다.

II. 결과 및 고찰

II-1. Aryliodide와 thioglycolic acid를 이용한 구리 금속 촉매

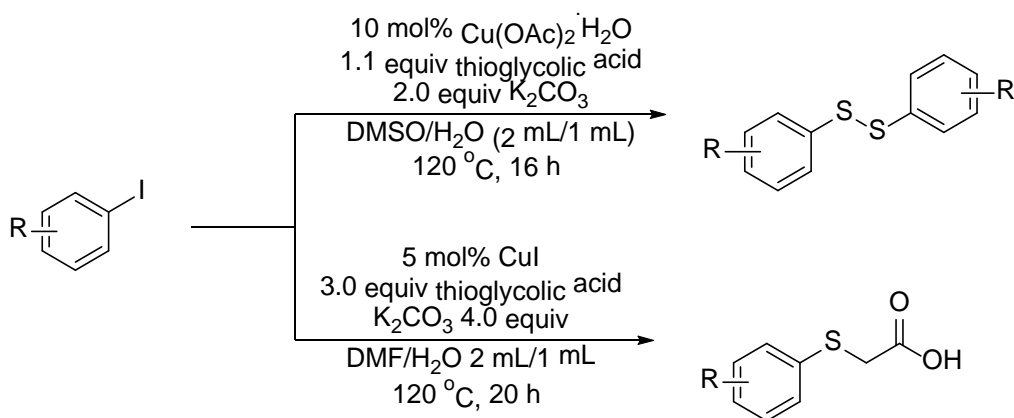
하의 C-S 결합 형성 방법 연구

본 연구실에서는 구리 촉매 하에 glycolic acid를 C_{aryl}-O 결합 형성 반응에서 산소원자 “O”를 coupling partner로 이용하여 2-phenoxyacetic acid의 합성 및 응용 연구를 보고한 바 있다(Scheme 9). 이에 착안하여 본 연구는 glycolic acid의 “O”가 황원자 “S”로 바뀐 thioglycolic acid를 구리 촉매 하에서 “S” coupling partner로 이용하여 (arylthio)acetic acid를 얻어낼 수 있을 것이라고 예상하고 실험을 진행하였다.



Scheme 9. 구리 금속 촉매 하에 glycolic acid를 이용한 C_{aryl}-O 결합 형성 반응

선행 연구 결과,⁴⁰ DMSO/H₂O 조건은 예상한 바와 달리 biaryl disulfide가 형성되었고, 한편 DMF/H₂O 조건에서는 예상한 (phenylthio)acetic acid가 형성된 것을 확인하였다(Scheme 10). 각각의 반응은 최적화 조건 실험을 통해 1) biaryl disulfide : DMSO/H₂O (2 mL/1 mL), Cu(OAc)₂·H₂O 10 mol%, thioglycolic acid 1.1 eq, K₂CO₃ 2.0 eq, 120 °C, 16 hr, 2) (arylthio)acetic acid : DMF/H₂O (2 mL/1 mL), CuI 5 mol%, thioglycolic acid 3 eq, K₂CO₃ 4.0 eq, 120 °C, 20 hr 으로 정립하였다.



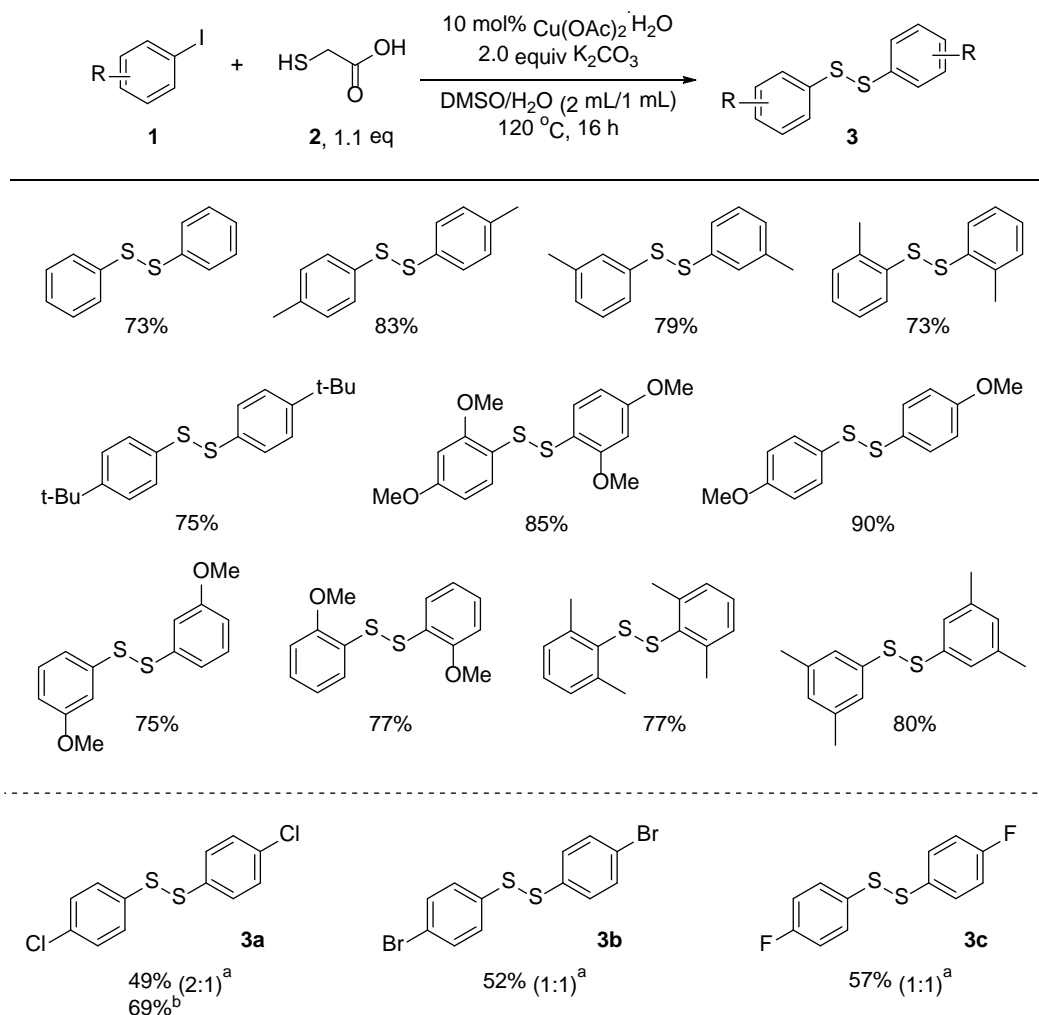
Scheme 10. 선행된 thioglycolic acid를 이용한 C_{aryl}-S 결합 형성 반응 연구

Biaryl disulfide는 분리 및 보관이 어려운 aryl thiol의 동등체로 쓰이는 화합물이다. Biaryl disulfide를 합성하는 방법으로는 S₈이나 thiourea를 이용하는 방법 등이 알려져 있지만 thioglycolic acid를 이용하는 방법은 보고된 적이 없어 선행 연구에서 biaryl disulfide 합성에 대한 연구를 진행하였다.

선행 연구에서 정립한 최적화 실험 조건을 다양한 기능기의 aryl iodide에 적용하여 실험을 진행하였다(Table 1). 실험결과 electron donating group을 가진 경우 70% 이상의 좋은 수율로 화합물을 얻을 수 있었지만 halide기를 갖는 aryl iodide의 경우에는 수율이 낮고 부생성물인 biaryl sulfide의 비율도 높음을 확인하였다. 따라서 halide group을 기능기로 갖는 aryl iodide 기질들에 대한 추가적인 최적화 실험을 진행하였다.

선행 연구에서⁴⁰ thioglycolic acid의 당량에 따른 영향을 확인하기 위해 thioglycolic acid를 1.1 eq에서 3.0 eq까지 당량별 실험을 진행하였다. Thioglycolic acid의 당량이 3.0 eq인 경우에 **3a**이 69%로 수율 향상을 보여 thioglycolic acid 3.0 eq과 K₂CO₃ 4.0 eq을 최적화 조건으로 정립하였다 (Table1).

Table 1. Substrate scope of biaryl disulfide (선행 연구 결과)⁴⁰

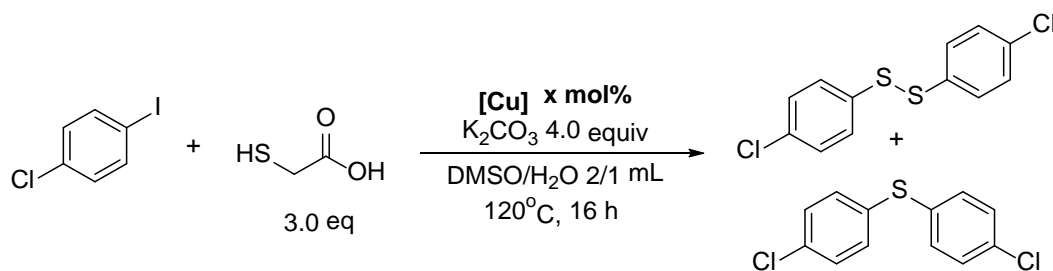


^a total G.C yield of biaryl disulfide and biaryl sulfide, ^b thioglycolic acid 3.0 eq, K₂CO₃ 4.0 eq

정립된 반응 조건으로 biaryl disulfide를 합성 시, 가장 큰 문제점은 biaryl sulfide가 경쟁적으로 생성된다는 점이다. 이러한 문제점은 halide group을 갖고 있는 aryl iodide 기질에서 더욱 두드러졌다. 그리하여 halide group을 갖는 aryl iodide의 최적화 조건 검색에서는 조건별로 biaryl disulfide와 biaryl sulfide 생성 비율을 조사하는 것이 필요했다.

Thioglycolic acid와 염기의 사용 적정량을 구리 촉매 양에 따른 효과를 보기 위해 실험을 진행하였다(Table 2). 실험은 1-iodo-4-chlorobenzene을 반응물질로, dodecane 기준물질로 정해 GC-MS를 이용하여 disulfide와 sulfide의 생성 비율을 살펴보았다. 실험 결과 구리 촉매의 양이 1.0 eq일 때 disulfide의 생성비율이 오히려 줄어드는 것을 볼 수 있었다(Table 2, entry 5). 비록 sulfide의 생성도 같이 증가했지만 disulfide가 가장 많이 생성된 조건인 entry 3의 결과에 따라 구리 촉매의 양을 15 mol%로 고정하였다.

Table 2. Effect of amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ on disulfide bond formation between 1-iodo-4-chlorobenzene and thioglycolic acid



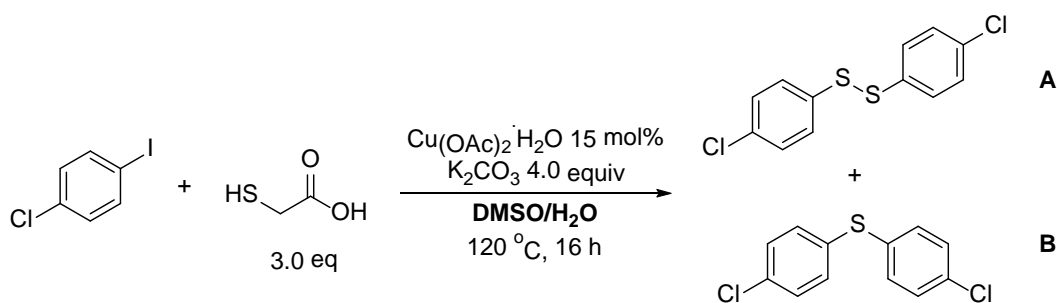
Entry	$[\text{Cu}]$	x mol%	dodecane : disulfide : sulfide ^a
1	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	5 mol%	1 : 0.44 : 0.15
2	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	10 mol%	1 : 0.42 : 0.08
3	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	15 mol%	1 : 0.51 : 0.13
4	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	20 mol%	1 : 0.42 : 0.13
5	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	1 equiv	1 : 0.22 : 0.26

^a molar ratio of GC MS

다음으로 용매 조건의 DMSO와 H_2O 의 비율에 따른 영향을 보기 위한 실험

을 진행하였다(Table 3). 실험 결과 DMSO와 물의 비율이 1:1인 경우 부생성물이 거의 생성되지 않았으며(entry 1) 1.5 : 1인 경우에는 수율이 79%로 증가하였다(entry 3). 그러나 biaryl disulfide와 biaryl sulfide의 분리가 쉽지 않아 용매조건을 biaryl sulfide의 생성이 거의 없는 DMSO/H₂O 1:1로 정하였다.

Table 3. Effect of solvents on disulfide bond and sulfide bond formation from 1-iodo-4-chlorobenzene



Entry	Solvent (1.5 mL)	Ratio	Yield(A) ^a	Yield(B) ^a
1	DMSO/H ₂ O	1 : 1	73%	0%
2	DMSO/H ₂ O	2 : 1	75%	10%
3	DMSO/H ₂ O	1.5 : 1	79%	8%

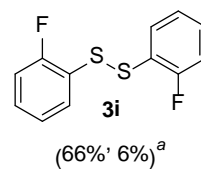
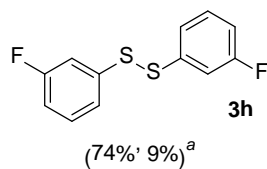
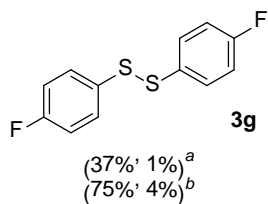
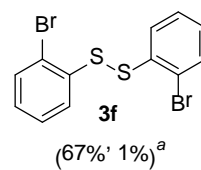
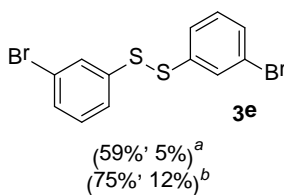
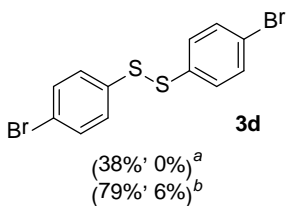
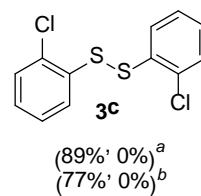
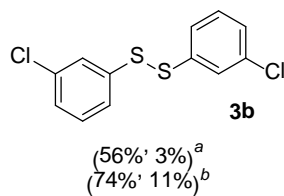
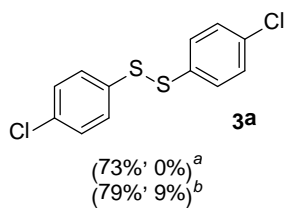
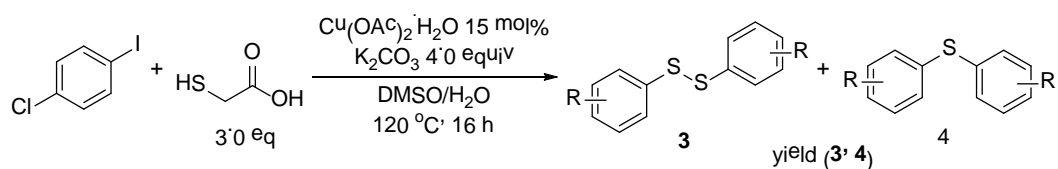
^a isolation yield

Halide group을 가진 biaryl disulfide의 효율적인 합성을 위해서는 기존 조건에 비해 구리 촉매의 양이 5 mol% 더 필요했고 DMSO와 H₂O의 비율은 1:1로 조절하여 부생성물인 sulfide를 최소화할 수 있는 새로운 정립한 조건을 결과로 얻었다; Cu(OAc)₂·H₂O 15 mol%, thioglycolic acid 3.0 equiv,

K₂CO₃ 4.0 eq, DMSO/H₂O 1:1, 120 °C, 16 h.

새로 얻은 결과를 *ortho*-, *meta*-, *para*-에 위치하는 여러 halide group을 가진 aryl iodide에 적용하였다(Table 4). 그 결과 3a, 3e, 3g, 3h, 3i의 경우 대체로 65% 이상의 좋은 수율을 얻었다. 3b, 3c, 3d, 3f는 DMSO/H₂O 1.5:1 비율의 용매 조건에서 70% 이상의 수율로 얻어짐을 확인했다.

Table 4. Synthesis of biaryl disulfide from aryl iodides having halide substituents and thioglycolic acid

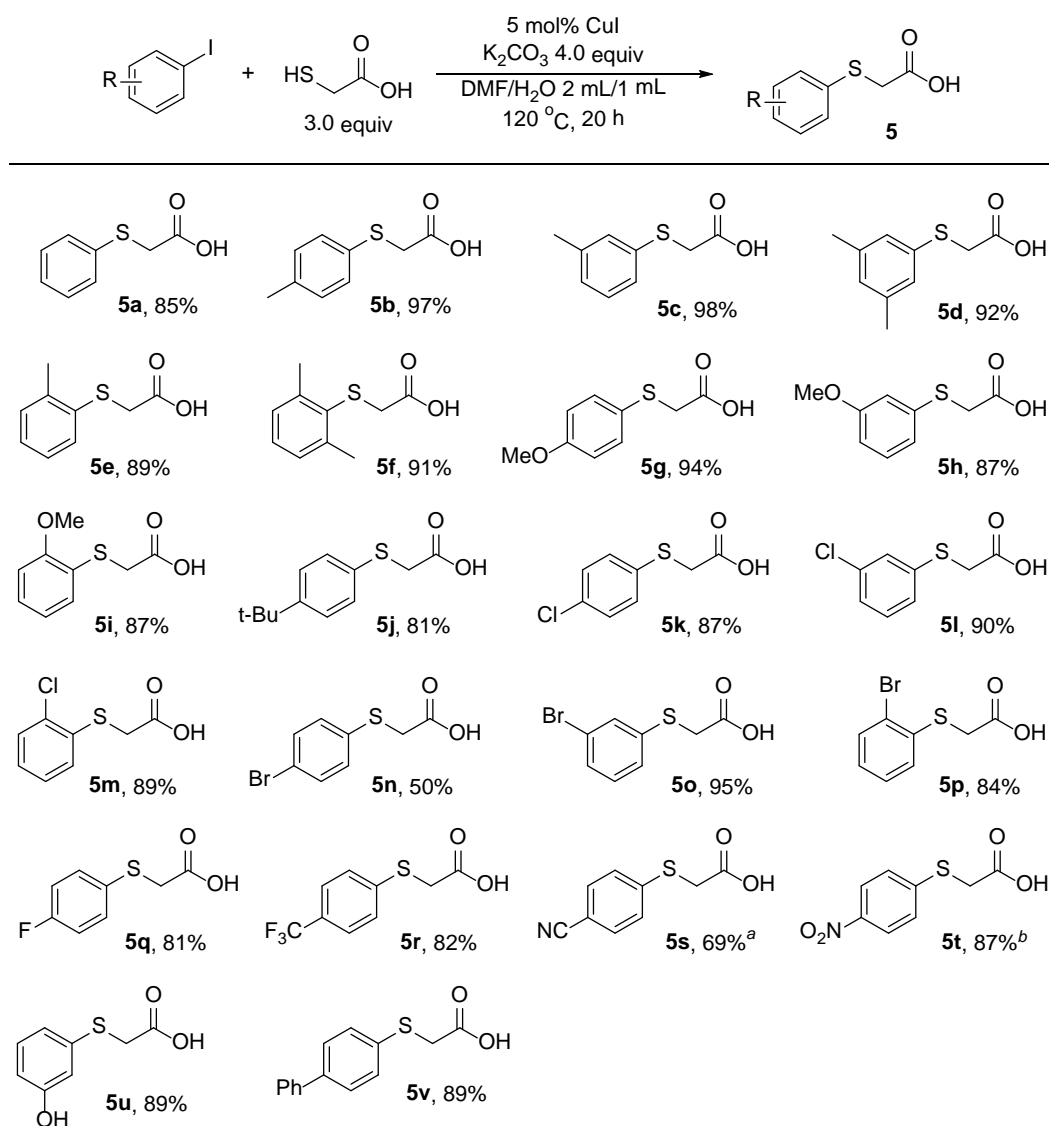


isolation yield: ^a DMSO/H₂O 1:1, ^b DMSO/H₂O 1.5:1

앞서 기술했듯이 선행 연구에서 정립한 DMF/H₂O 2:1, CuI 5 mol%, thioglycolic acid 3 eq, K₂CO₃ 4.0 eq, 120 °C, 20 h 조건으로 반응하는 경우에는 (phenylthio)acetic acid가 주생성물로 얻어진다(Scheme 6). 본 연구에서는 이를 기반으로 다양한 기능기를 가진 aryl iodide에 최적화 조건을 적용하는 실험을 진행했고 그 결과 다양한 기능기의 (arylythio)acetic acid를 합성할 수 있었다(Table 5).

Phenyl기에 많은 범위의 기능기를 포함한 (arylythio)acetic acid를 합성할 수 있었다. Electron donating group 또는 electron withdrawing group을 갖는 aryl iodide들은 모두 비교적 좋은 수율로 (arylythio)acetic acid로 전환되었다. 특히 electron donating group을 가진 경우 81~98%의 높은 수율을 보였고 electron withdrawing group을 가진 경우에는 electron donating group을 가진 경우보다 약간 낮은 수율을 보였다. Phenyl을 기능기로 가진 경우에도 89%의 수율을 보였다(Table 5, **5v**). Electron withdrawing group인 CN 또는 NO₂를 갖는 aryl iodide의 경우 더 낮은 온도에서 반응을 진행하였다(Table 5, **5s**, **5t**). Hydroxyl group을 갖는 aryl iodide는 hydroxyl group의 보호기 없이도 free-OH 상태에서 반응이 진행될 수 있었다(Table 5, **5u**).

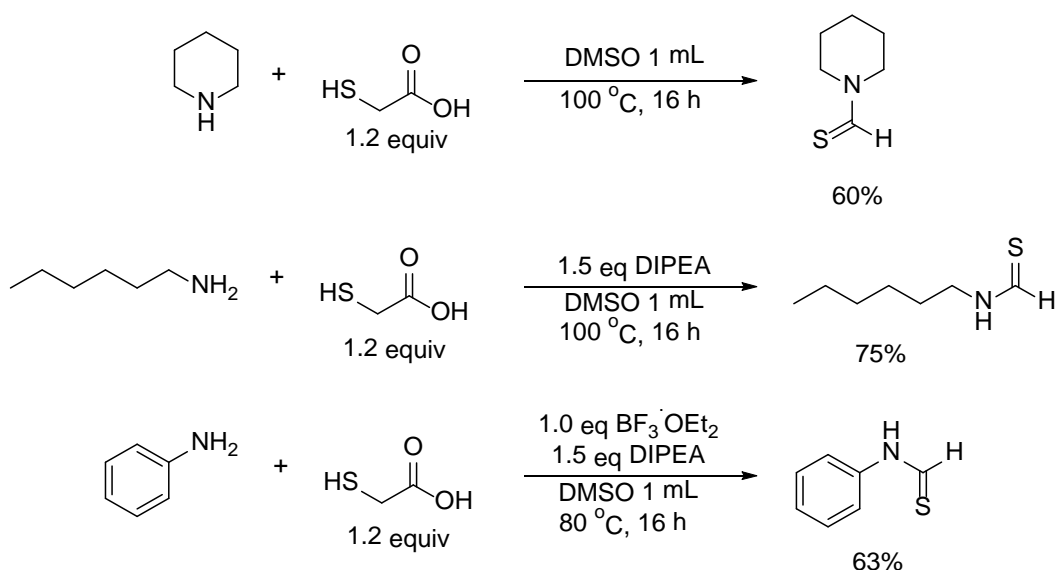
Table 5. Synthesis of various (aryltio)acetic acid from various aryl iodide



^a 70 °C, 20 hr, ^b 70 °C, 3 hr

II -2. Thioglycolic acid를 이용한 무촉매 조건의 thioformamide 합성법 연구

본 연구실에서 촉매 없이 thioglycolic acid를 이용해 amine에 thioformyl기를 도입하여 thioformamide를 합성할 수 있음을 확인하였고 선행 연구⁴⁰에서는 이에 대한 최적화 조건을 찾는 실험을 진행하였다. 그 결과 2차 amine은 thioglycolic acid 1.2 eq, DMSO 1 mL, 100 °C, 16 hr 의 최적화 반응 조건을, 1차 amine은 thioglycolic acid 1.2 eq, *N,N*-diisopropylethylamine(DIPEA) 1.5 eq, DMSO 1 mL, 100 °C, 16 h의 최적화 조건을, aniline은 thioglycolic acid 1.2 eq, DIPEA 1.5 eq, BF₃·OEt₂ 1.0 eq, DMSO 1 mL, 80 °C, 16 hr의 반응 최적화 조건이 정립되었다(Scheme 11).



Scheme 11. 선행된 optimized conditions for synthesis of thioformamide

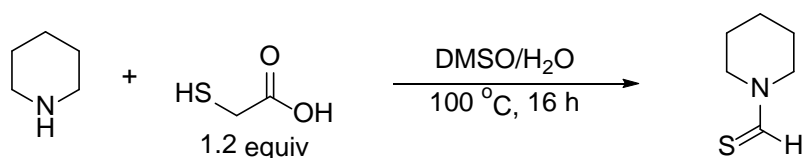
본 연구에서는 1, 2차 amine 및 aniline에 대한 정립된 반응 조건을 다시 한번 세밀하게 최적화하고 최적화 조건을 다양한 amine기질에 적용하여 다양한 thioformamide를 합성하였다.

먼저 반응에 미치는 물의 영향을 알아보기 위해 DMSO에 소량의 물을 첨가하는 실험을 진행하였다(Table 6). 그 결과 DMSO 1 mL 용매 조건보다 DMSO/H₂O의 비율이 0.95/0.05일 때 70%로 수율이 가장 높은 것을 확인하였다. 또한 온도와 시간은 기존 조건인 100 °C와 16 h일 때 가장 효율적인 것을 확인하였다(Table 6, entry 2). 물을 첨가하면 2차 amine은 66%에서 70%로, 1차 amine은 75%에서 92%로 수율이 올랐지만, aniline의 경우에는 오히려 수율이 낮아졌다. 따라서 최종적인 thioformamide 합성 최적화 조건은 amine의 종류에 따라 조금씩 다르며 다음과 같다; 1) 2차 amine:

thioglycolic acid 1.2 eq, DMSO/H₂O 0.95/0.05 mL, 100 °C, 16 h, 2) 1차 amine: thioglycolic acid 1.2 eq, DIPEA 1.5 eq, DMSO/H₂O 0.95/0.05 mL, 100 °C, 16 h, 3) aniline: thioglycolic acid 1.2 eq, DIPEA 1.5 eq, BF₃OEt₂ 1.0 eq, DMSO 1 mL, 80 °C, 16 h.

Table 6. Effect of ratio of DMSO/H₂O on synthesis of

N-thioformylpiperidine



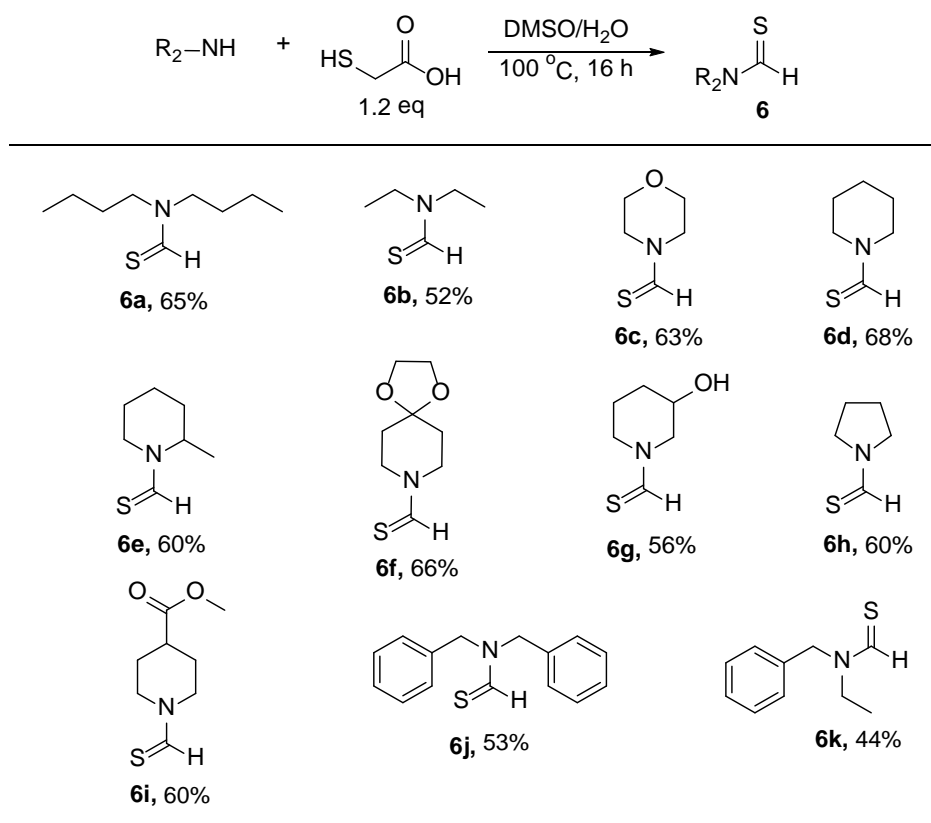
Entry	DMSO/H ₂ O (mL)	Temp	Time	Yield ^a
1	1/0	100 °C	16 h	66%
2	0.95/0.05	100 °C	16 h	70%
3	0.9/0.1	100 °C	16 h	67%
4	0.8/0.2	100 °C	16 h	60%
5	0.6/0.4	100 °C	16 h	55%
6	0.5/0.5	100 °C	16 h	47%
7	0.95/0.05	100 °C	8 h	61%
8	0.95/0.05	100 °C	10 h	63%
9	0.95/0.05	100 °C	14 h	66%
10	0.95/0.05	80 °C	16 h	27%
11	0.95/0.05	60 °C	16 h	0%

^a yield of G.C MS

이에 최종적으로 정립된 조건을 다양한 기능기의 2차-, 1차 amine 및 aniline 각각에 적용하여 다양한 기능기를 가진 thioformamide를 합성하는 실험을 진행했다(Table 7,8,9).

2차 amine은 1차 amine과 aniline에 비해 비교적 낮은 수율로 반응이 진행되었지만 다양한 기능을 가진 2차 amine도 반응에 참여하였다. **6c**나 **6f**처럼 heterocycle 기능을 가진 thioformamide가 합성되었으며, free-OH 기(Table 7, **6g**)나 ester기 (Table 7, **6i**)를 가지고 있어도 해당 기능을 가진 thioformamide가 합성되었다. Table 7의 **6d**와 **6e**를 비교 시, steric hindrance의 영향을 다소 받는 것으로 보인다.

Table 7. Various substrate scope of thioformamide from secondary amine



1 차 amine 의 경우 benzyl amine 을 포함한 다양한 amine 이 thioformamide 로 합성되는 것을 확인하였다. 특히 aromatic ring 에 다양한 치환기를 갖는 benzyl amine 은 전반적으로 좋은 수율의 결과를 얻었으며 heterocycle 을 가진 **7p** 경우에도 합성되었다(Table 8). Free-OH 기를 가진 경우에도 합성되었다(Table 8, **7q**). Alkyl 기를 가진 amine 의 경우에도 **7b**, **7d** 는 85% 이상의 수율을 보였지만 **7c** 의 경우는 예상보다 낮은 40%의 수율을 보였다. Alkyl 기의 말단에 OH 가 달린 경우는 합성이 되지 않았지만 OMe 가 달린 **7e** 는 합성할 수 있었다.

Aniline 구조의 경우 N의 nucleophilicity가 낮아 선행 연구에서 진행된 additive 첨가 실험을 통해 Lewis acid 역할을 하는 BF_3OEt_2 1.0 equiv을 첨가한 반응 조건을 최적화 조건으로 정립하였고, 이를 기반으로 다양한 구조를 가진 aniline substrate를 이용하여 화합물을 얻었다(Table 9). 다양한 기능을 갖는 aniline은 전반적으로 높은 수율의 thioformamide로 전환되었다. **8c**와 **8d** 같은 cyclic alkyl이 aromatic ring에 붙어 있어도 70% 이상의 수율을 보였다. Alkoxy를 갖는 다양한 aniline의 경우에도 좋은 수율로 합성되었다(Table 9, **8e-8i**). Free-OH기를 가진 **8m**의 경우에도 반응이 이루어졌고 pyridine을 포함한 **8o**도 낮은 수율이지만 합성되었다. Acetyl기를 가진 **8t**는 50%의 수율을 얻을 수 있었다. Steric hindrance가 있을 것으로 보이는 **8p**의 경우에도 66%의 수율로 합성되었다.

Table 8. Various substrate scope of thioformamide from primary amine

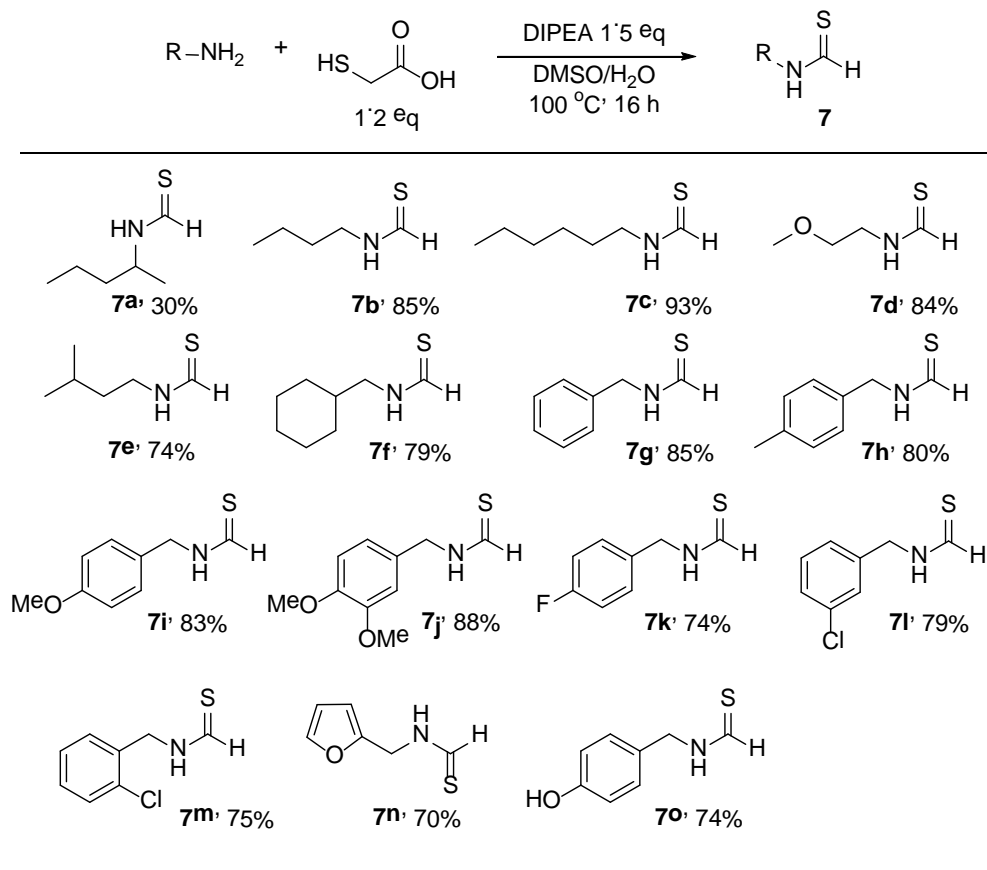
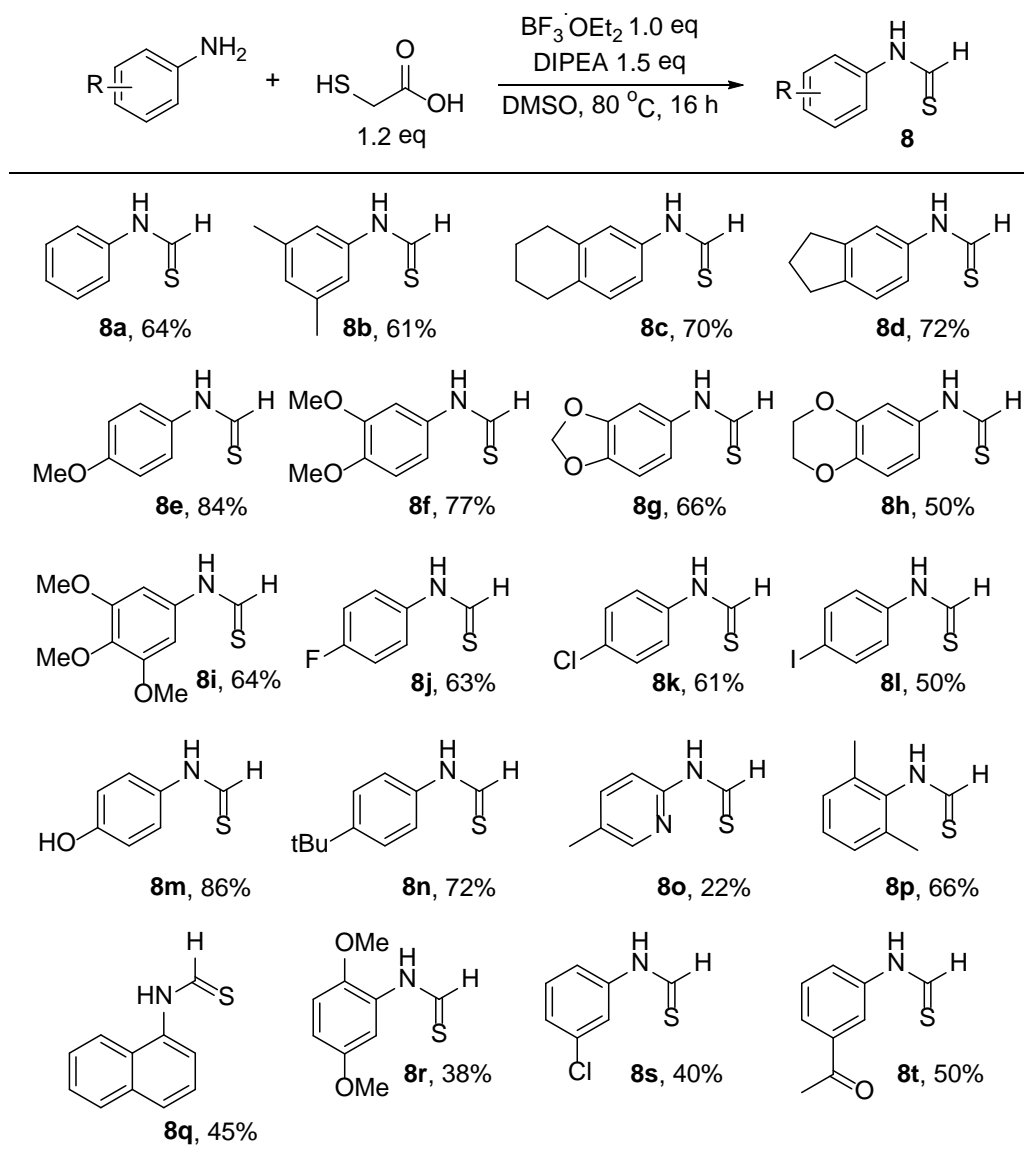


Table 9. Synthesis of various thioformamide from aniline



Ⅲ. 결 론

C-S 결합 및 thioformyl기는 다양한 천연물, 의약품, 생리활성물질에서 흔히 발견되는 구조로 이를 효율적으로 합성하기 위한 연구가 지속되고 있다. 본 연구에서는 thioglycolic acid를 이용하여 황을 포함한 작용기를 효율적으로 도입하는 연구를 진행하였다.

II-1에서는 구리 금속 촉매 하에서 aryl iodide와 thioglycolic acid를 이용해 C_{aryl}-S 결합 화합물들을 합성하기 위한 연구를 진행했다. 기존에 쓰이는 S 제공시약은 thiol이 대표적인데 이는 민감하여 다루기 어렵고 냄새가 좋지 않다는 단점이 있어 biaryl disulfide이나 thiourea 같은 thiol의 대체재를 찾는 연구들이 지속되고 있다. 본 연구는 S 제공시약으로 보고된 적이 없는 thioglycolic acid를 이용하여 다양한 기능기를 가진 biaryl disulfide와 (arylthio)acetic acid를 합성하였다. 이 두 화합물을 결정하는 중요변수는 DMSO와 DMF 같은 용매 조건이었으며 특히 halide group을 가진 biaryl disulfide의 경우 DMSO와 물의 비율이 생성 수율을 결정지었다. Electron withdrawing group을 가진 biaryl bisulfide의 최적화조건은 Cu(OAc)₂·H₂O 15 mol%, thioglycolic acid 3.0 equiv, K₂CO₃ 4.0 eq, DMSO/H₂O 1:1, 120 °C, 16 h이었고 경우에 따라 DMSO/H₂O 1.5:1 조건에서 더 높은 수율을 보

여준 화합물들도 있었다.

(arylthio)acetic acid의 경우 CuI 5 mol%, thioglycolic acid 3 eq, K₂CO₃ 4.0 eq, DMF/H₂O 2:1, 120 °C, 20 h 조건에서 다양한 범위의 기능을 가진 생성물을 높은 수율로 합성할 수 있었다.

II-2에서는 구리 금속 촉매 없이 thioglycolic acid를 이용하여 thioformyl기를 amine에 도입하는 새로운 조건을 연구하였다. Thioformyl기는 다양한 유기반응의 중간체 및 천연물, 생화학적 물질 등에서 주요 구조체로 활용가능한 물질이다. 그러나 그 합성법이 다양하지 않아 연구가 미비하다. 몇몇 알려진 방법들도 유독한 가스 형태인 H₂S를 쓰거나 Lawesson's reagent 및 그 유도체를 이용하는 것 이외에는 알려진 바가 없다. 본 연구에서는 thioglycolic acid를 이용하여 기존에 없던 새로운 합성법을 개발하였다. 금속 촉매 없이 약염기 조건에서 1차, 2차 amine 뿐만 아니라 aniline에도 다음 조건에서 thioformyl기를 도입할 수 있었다; 1) 2차 amine: thioglycolic acid 1.2 eq, DMSO/H₂O 0.95/0.05 mL, 100 °C, 16 h, 2) 1차 amine: thioglycolic acid 1.2 eq, DIPEA 1.5 eq, DMSO/H₂O 0.95/0.05 mL, 100 °C, 16 h, 3) aniline: thioglycolic acid 1.2 eq, DIPEA 1.5 eq, BF₃·OEt₂ 1.0 eq, DMSO 1 mL, 80 °C, 16 h.

각각의 조건들이 amine과 aniline에 있는 N의 nucleophilicity 차이에 따라 달라짐을 확인하였고, 총 47개의 amine substrate들을 22-93%의 수율을 갖는 thioformamide로 전환할 수 있었다.

IV. 실험

1. 실험기기 및 시약

(1) 실험기기

^1H NMR과 ^{13}C NMR 스펙트럼은 Varian-500(500 MHz for ^1H , 126 MHz for ^{13}C)과 ZEOL-500(500 MHz for ^1H , 126 MHz for ^{13}C)분광계로부터 얻었으며, NMR 용매로 CDCl_3 , $\text{DMSO}-d_6$ 를 사용하였다. Chemical shift는 표준물질 tetramethylsilane(TMS)로부터 ppm 단위로 기록하였다. 데이터는 Chemical shift multiplicity (*s*-singlet, *d*-doublet, *t*-triplet, *m*-multiplet, *dd*-doublet of doublet, *dt*-doublet of triplet), coupling constant(Hz), integration의 순서로 기록하였다. Gas chromatography (GC)는 Hewlett Packard Series 6890 모델로 HP-1 capillary column을 사용하였고, MSD로부터 질량분석기(MS)는 ionization 방법으로 electron impact (EI)에 의해 얻어 *m/z*로 기록하였다. Thin layer chromatography(TLC)는 Merck사의 silica gel 60 F₂₅₄가 입혀진 glass plate를 사용하였고 TLC 상에 분리된 물질의 확인을 위해 UV lamp(254 nm)을 사용하거나 KMnO_4 용액에 stain하여 확인하였다.

(2) 시약

반응에 사용된 대부분 시약은 Sigma-Aldrich, Alfa Aesar, TCI에서 구입하여 별도의 정제 없이 사용하였다.

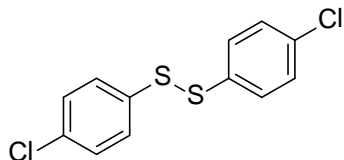
2. 실험방법

1) Biaryl disulfide 화합물의 합성

General procedure A

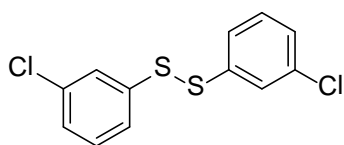
Test tube에 aryl iodide 1.0 mmol, $\text{Cu}_2(\text{OAc})_2 \cdot \text{H}_2\text{O}$ 15 mol%, K_2CO_3 4.0 equiv 를 넣고 argon 치환 한다. 그 다음 DMSO 2.0 mL 와 Argon으로 치환된 H_2O 1.0 mL를 첨가한 후 thioglycolic acid 3.0 equiv를 첨가한다. Sealing 후 120 °C oil bath에 담가 16시간 동안 반응시킨다. 상온에서 식힌 다음 1 M HCl로 quenching한 후 H_2O 와 ethyl acetate로 extraction 한 후 유층을 따로 모아 MgSO_4 로 남은 물을 제거한 후 거른다. 모은 유층을 감압 하에 용매를 제거하고 hexane과 ethyl acetate로 화합물을 분리, 정제한다. 감압 하에 용매를 완전히 제거하여 순수한 화합물을 얻는다.

1,2-bis(4-chlorophenyl)disulfide (**3a**)



General procedure A 방법으로 seal tube에 iodobenzene 0.5 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(무색 액체, 104 mg, 73%)을 얻었다. ^1H NMR (500 MHz, DMSO-D6) δ 7.54–7.51 (m, 2H), 7.44 (tt, $J = 7.1, 2.3$ Hz, 2H). ^{13}C NMR (126 MHz, DMSO-D6) δ 134.5, 132.5, 129.5, 129.2.

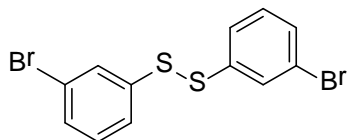
1,2-bis(3-chlorophenyl)disulfide (**3b**)



General procedure A 방법으로 seal tube에 1-iodo-3-chlorobenzene 0.5 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(무색 액체, 76 mg, 53%)을 얻었다. ^1H NMR (500 MHz, DMSO-D6) δ 7.57 (t, $J = 1.7$ Hz, 1H), 7.49 (dt, $J = 8.2, 1.4$ Hz, 1H), 7.43–7.39 (m, 1H), 7.37–7.35 (m, 1H). ^{13}C NMR (126 MHz, DMSO-D6) δ 137.7, 134.1, 131.3, 127.7,

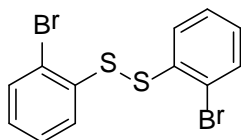
126.2, 125.5.

1,2-bis(3-bromophenyl)disulfide (**3e**)



General procedure A 방법으로 seal tube에 1-iodo-3-bromobenzene 0.5 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(무색 액체, 124 mg, 59%)을 얻었다. ^1H NMR (500 MHz, DMSO- D_6) δ 7.70 (t, $J = 2.0$ Hz, 1H), 7.54–7.49 (m, 2H), 7.35 (t, $J = 8.0$ Hz, 1H). ^{13}C NMR (126 MHz, DMSO- D_6) δ 137.9, 131.5, 130.6, 129.0, 125.9, 122.5.

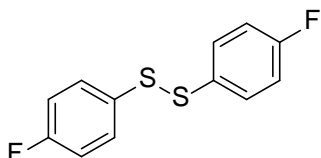
1,2-bis(2-bromophenyl)disulfide (**3f**)



General procedure A 방법으로 seal tube에 1-iodo-2-bromobenzene 0.5 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(흰색 고체, 125 mg, 67%)을 얻었다. ^1H NMR (500 MHz, DMSO- D_6) δ 7.70 (d, $J = 8.0$ Hz, 2H), 7.53 (dd, $J = 8.0, 1.7$ Hz, 2H), 7.45–7.42 (m, 2H), 7.26–7.22 (m, 2H). ^{13}C NMR (126 MHz, DMSO- D_6) δ 134.7, 133.2, 129.1, 129.0,

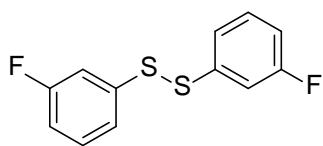
127.1, 120.7.

1,2-bis(4-fluorophenyl) disulfide (**3g**) [CAS]



General procedure A 방법으로 seal tube에 1-iodo-4-fluorobenzene 0.5 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(무색 액체, 47 mg, 38%)을 얻었다. ^1H NMR (500 MHz, DMSO-D6) δ 7.55 (qd, $J = 4.6$, 2.0 Hz, 2H), 7.26–7.21 (m, 2H). ^{13}C NMR (126 MHz, DMSO-D6) δ 162.9, 161.0, 130.9, 130.8, 116.7, 116.5.

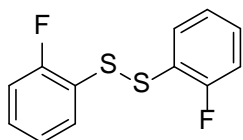
1,2-bis(4-fluorophenyl) disulfide (**3h**)



General procedure A 방법으로 seal tube에 1-iodo-3-fluorobenzene 0.5 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(무색 액체, 94 mg, 74%)을 얻었다. ^1H NMR (500 MHz, DMSO-D6) δ 7.46–7.42 (m, 1H), 7.40–7.36 (m, 2H), 7.20–7.12 (m, 1H). ^{13}C NMR (126 MHz,

DMSO-D6) δ 163.4, 161.4, 137.9, 137.9, 131.5, 131.4, 122.9, 122.9, 114.7, 114.6, 113.7, 113.5, 40.0, 39.8, 39.7, 39.5, 39.3, 39.2, 39.0.

1,2-bis(2-fluorophenyl)disulfide (**3i**)



General procedure A 방법으로 seal tube에 1-iodo-2-fluorobenzene 0.5 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(무색 액체, 84 mg, 66%)을 얻었다. ^1H NMR (500 MHz, DMSO-D6) δ 7.62 (td, $J = 7.7, 1.4$ Hz, 2H), 7.43 (q, $J = 6.5$ Hz, 2H), 7.30 (t, $J = 8.9$ Hz, 2H), 7.24 (t, $J = 7.4$ Hz, 2H). ^{13}C NMR (126 MHz, DMSO-D6) δ 161.1, 159.2, 131.9, 131.2, 131.1, 125.5, 125.5, 125.4, 122.3, 122.2, 116.4, 116.3, 116.2, 116.1.

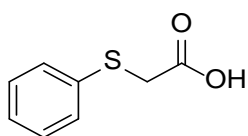
2) (Arylthio)acetic acid 화합물의 합성

General procedure A

Seal tube에 CuI 5 mol%와 aryl iodide 1 mmol, K_2CO_3 4.0 eq을 취해

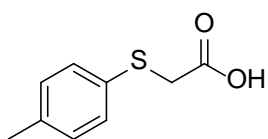
stirring bar를 넣고 Argon 치환한 후 DMSO/H₂O 2.0/1.0 mL에 녹인 다음 thioglycolic acid 3.0 eq을 첨가한다. 반응 혼합물을 120 °C에서 20 h 동안 stirring한 후 상온에서 식힌다. 1M HCl로 quenching해준 후 ethyl acetate로 추출한다. 추출한 다음 MgSO₄로 남아 있는 물을 제거한 후 column chromatography로 hexane과 ethyl acetate를 이용해 분리 정제한다.

(Phenylthio)acetic acid (**5a**) [CAS 103-04-8]



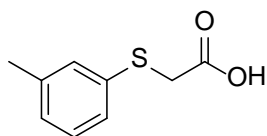
General procedure A 방법으로 seal tube에 iodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 (phenylthio)acetic acid (무색 액체, 143 mg, 85%)을 얻었다. ¹H NMR (500 MHz, CHLOROFORM-D) δ 7.42 (d, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 6.0 Hz, 1H), 3.67 (s, 2H).

4-Methyl phenyl thioacetic acid (**5b**) [CAS 3996-29-0]



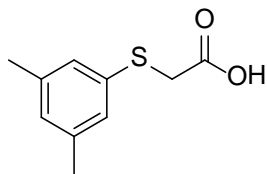
General procedure A 방법으로 seal tube에 4-iodotoluene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 4-methyl phenyl thioacetic acid (흰색 고체, 176 mg, 97%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.38 – 7.29 (m, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 3.62 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.26 (s), 137.68 (s), 131.00 (s), 130.63 (s), 129.95 (s), 37.30 (s), 21.07 (s). MS (EI) $m/z = 182, 164, 151, 137$. FT-IR : 2917, 2688, 1696, 1200, 798 cm^{-1}

2-[(3-Methylphenyl)thio]acetic acid (**5c**) [CAS 3996-30-3]



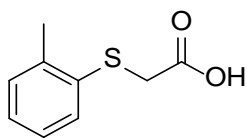
General procedure A 방법으로 seal tube에 3-iodotoluene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(3-methylphenyl)thio]acetic acid (흰색 고체, 179 mg, 98%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.25 – 7.17 (m, 3H), 7.09 – 7.04 (m, 1H), 3.68 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.27 (s), 139.02 (s), 134.13 (s), 130.61 (s), 129.01 (s), 128.12 (s), 126.95 (s), 36.54 (s), 21.30 (s). MS (EI) $m/z = 182, 164, 151, 137$. FT-IR : 2919, 2580, 1696, 1198, 770 cm^{-1}

2-[(3,5-Dimethylphenyl)thio]acetic acid (**5d**) [CAS 253304-13-1]



General procedure A 방법으로 seal tube에 5-iodo-m-xylene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(3,5-dimethylphenyl)thio]acetic acid (흰색 고체, 164mg, 83%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.02 (s, 2H), 6.87 (s, 1H), 3.66 (s, 2H), 2.28 (s, 6H). ^{13}C NMR (126 MHz, cdcl_3) δ 175.54 (s), 138.84 (s), 133.90 (s), 129.11 (s), 127.55 (s), 36.55 (s), 21.18 (s). MS (EI) m/z = 196, 178, 151, 137. FT-IR : 2920, 2853, 1710, 1192, 828 cm^{-1}

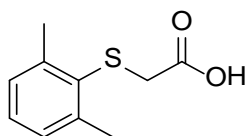
2-[(2-Methylphenyl)thio]acetic acid (**5e**) [CAS 18619-15-3]



General procedure A 방법으로 seal tube에 2-iodotoluene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(2-methylphenyl)thio]acetic acid (흰색 고체, 162mg, 89%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.38 - 7.32 (m, 1H), 7.22 - 7.18 (m, 1H),

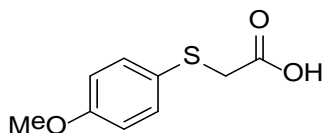
7.16 (s, 2H), 3.66 (s, 2H), 2.42 (d, J = 0.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.55 (s), 138.35 (s), 133.56 (s), 130.39 (s), 129.44 (s), 127.13 (s), 126.76 (s), 35.64 (s), 20.31 (s). MS (EI) m/z = 182, 151, 137, 124. FT-IR : 2913, 2694, 1701, 1193, 888, 745 cm^{-1}

2-[(2,6-Dimethylphenyl)thio]acetic acid (**5f**) [CAS 32133-94-1]



General procedure A 방법으로 seal tube에 2-iodo-m-xylene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(2,6-dimethylphenyl)thio]acetic acid (흰색 고체, 178mg, 91%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.20 - 7.06 (m, 3H), 3.39 (s, 2H), 2.55 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 176.29 (s), 143.35 (s), 131.61 (s), 129.10 (s), 128.33 (s), 36.67 (s), 21.78 (s). MS (EI) m/z = 196, 178, 151, 137. FT-IR : 2920, 2659, 2555, 1697, 1460, 1426, 1399, 1374, 1118, 775 cm^{-1}

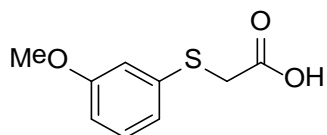
2-[(4-Methoxyphenyl)thio]acetic acid (**5g**) [CAS 3406-77-7]



General procedure A 방법으로 seal tube에 4-iodoanisole 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(4-methoxyphenyl)thio]acetic acid (흰색 고체, 187mg, 94%)을 얻었다. ¹H NMR (500 MHz, CDCl₃) δ 7.48 - 7.41 (m, 2H), 6.89 - 6.83 (m, 2H), 3.80 (s, 3H), 3.55 (d, J = 0.8 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 175.75 (s), 159.84 (s), 134.28 (s), 124.47 (s), 114.79 (s), 55.33 (s), 38.55 (s).

MS (EI) m/z = 198, 183, 167, 153, 139. FT-IR : 2926, 1703, 1285, 12335, 827 cm⁻¹

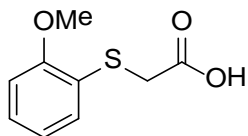
2-[(3-Methoxyphenyl)thio]acetic acid (**5h**) [CAS 3996-32-5]



General procedure A 방법으로 seal tube에 3-iodoanisole 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(3-methoxyphenyl)thio]acetic acid (투명 액체, 172mg, 87%)을 얻었다. ¹H

NMR (500 MHz, cdcl₃) δ 7.22 (t, J = 8.0 Hz, 1H), 6.97 (ddd, J = 7.7, 2.9, 1.4 Hz, 2H), 6.81 – 6.75 (m, 1H), 3.79 (s, 3H), 3.69 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 175.81 (s), 159.89 (s), 135.82 (s), 130.00 (s), 121.75 (s), 114.97 (s), 112.99 (s), 55.30 (s), 36.34 (s), 26.34 (s). MS (EI) m/z = 198, 186, 153, 138. FT-IR : 2936, 2668, 1706, 1588, 856 cm⁻¹

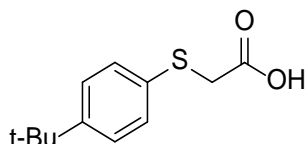
2-[(2-Methoxyphenyl)thio]acetic acid (**5i**) [CAS 18619-21-1]



General procedure A 방법으로 seal tube에 2-iodoanisole 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(2-methoxyphenyl)thio]acetic acid (흰색 고체, 172mg, 87%)을 얻었다. ¹H NMR (500 MHz, CDCl₃) δ 7.41 (dd, J = 7.6, 1.7 Hz, 1H), 7.29 (ddd, J = 8.2, 7.5, 1.7 Hz, 1H), 6.93 (td, J = 7.6, 1.2 Hz, 1H), 6.89 (dd, J = 8.2, 1.2 Hz, 1H), 3.89 (s, 3H), 3.64 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 174.95 (s), 158.15 (s), 132.32 (s), 129.32 (s), 121.77 (s), 121.15 (s), 110.86 (s), 55.70 (s), 35.53 (s). MS (EI) m/z = 198, 186, 167, 157.

FT-IR : 2919, 1698, 1245, 755 cm^{-1}

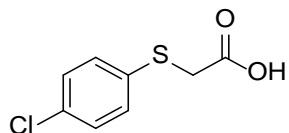
2-[[4-(1,1-Dimethylethyl)phenyl]thio]acetic acid (**5j**) [CAS 4365-63-3]



General procedure A 방법으로 seal tube에 1-tert-butyl-4-iodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[[4-(1,1-dimethylethyl)phenyl]thio]acetic acid (투명 액체, 182mg, 81%)을 얻었다.

^1H NMR (500 MHz, CDCl_3) δ 7.35 (dd, $J = 18.0, 8.7$ Hz, 4H), 3.65 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 176.08 (s), 150.60 (s), 131.00 (s), 130.29 (s), 126.24 (s), 37.04 (s), 34.55 (s), 31.24 (s). MS (EI) $m/z = 224, 209, 191, 181$. FT-IR : 2960, 2868, 1707, 1267, 823 cm^{-1}

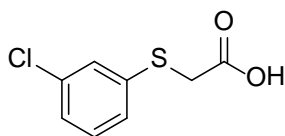
2-[(4-Chlorophenyl)thio]acetic acid (**5k**) [CAS 3405-88-7]



General procedure A 방법으로 seal tube에 1-Chloro-4-iodobenzene 1.0

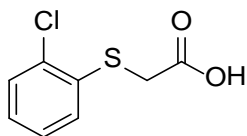
mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(4-chlorophenyl)thio]acetic acid (흰색 고체, 176mg, 87%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.38 – 7.34 (m, 2H), 7.30 – 7.27 (m, 2H), 3.64 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.71 (s), 133.54 (s), 132.87 (s), 131.61 (s), 129.33 (s), 36.66 (s). MS (EI) m/z = 202, 184, 157, 143. FT-IR : 2920, 1691, 1094, 887, 808 cm^{-1}

2-[(3-Chlorophenyl)thio]acetic acid (5l) [CAS 3996-38-1]



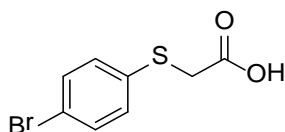
General procedure A 방법으로 seal tube에 3-chloriodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(3-chlorophenyl)thio]acetic acid (엷은 갈색 고체, 90%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.40 (td, J = 1.8, 0.5 Hz, 1H), 7.28 (dt, J = 7.3, 1.8 Hz, 1H), 7.25 – 7.19 (m, 2H), 3.69 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.41 (s), 136.56 (s), 134.85 (s), 130.17 (s), 129.30 (s), 127.61 (s), 127.29 (s), 36.15 (s). MS (EI) m/z = 202, 186, 174, 157, 143. FT-IR : 2919, 2583, 1696, 1425, 893, 774, 678 cm^{-1}

2-[(2-Chlorophenyl)thio]acetic acid (**5m**) [CAS 18619-18-6]



General procedure A 방법으로 seal tube에 1-chloro-2-iodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(2-chlorophenyl)thio]acetic acid (노란 고체, 181mg, 89%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.43 - 7.38 (m, 2H), 7.24 (td, $J = 7.6, 1.6$ Hz, 1H), 7.21 - 7.16 (m, 1H), 3.72 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.88 (s), 134.36 (s), 133.55 (s), 129.98 (d, $J = 14.9$ Hz), 128.00 (s), 127.42 (s), 35.00 (s). MS (EI) $m/z = 202, 184, 157, 143$. FT-IR : 2918, 2852, 1694, 1430, 1200, 750 cm^{-1}

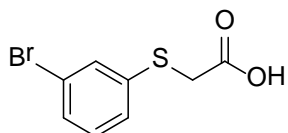
2-[(4-Bromophenyl)thio]acetic acid (**5n**) [CAS 3406-76-6]



General procedure A 방법으로 seal tube에 1-bromo-4-iodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(4-bromophenyl)thio]acetic acid (흰 고체, 124mg, 50%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.38 - 7.34 (m, 2H), 7.30 - 7.27 (m, 2H), 3.64 (s,

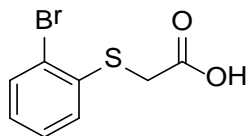
2H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.16 (s), 133.62 (s), 132.25 (s), 131.65 (s), 121.40 (s), 36.50 (s). MS (EI) m/z = 248, 231, 203, 189. FT-IR : 2922, 2851, 1692, 1473, 1195, 808 cm^{-1}

2-[(3-Bromophenyl)thio]acetic acid (**5o**) [CAS 3996-39-2]



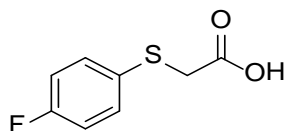
General procedure A 방법으로 seal tube에 3-bromiodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(3-bromophenyl)thio]acetic acid (흰 고체, 95%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.55 (t, J = 1.7 Hz, 1H), 7.40 - 7.35 (m, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 3.69 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.98 (s), 136.86 (s), 132.17 (s), 130.44 (s), 130.19 (s), 128.12 (s), 122.90 (s), 36.19 (s). MS (EI) m/z = 248, 228, 218, 203, 189. FT-IR : 2920, 2852, 2583, 1697, 1553, 1199, 892, 774, 749 cm^{-1}

2-[(2-Bromophenyl)thio]acetic acid (**5p**) [CAS 15939-85-2]



General procedure A 방법으로 seal tube에 2-bromiodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(2-bromophenyl)thio]acetic acid (흰 고체, 84%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 7.57 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.38 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.29 (td, $J = 7.7, 1.3$ Hz, 1H), 7.10 (td, $J = 7.9, 1.5$ Hz, 1H), 3.72 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.63 (s), 135.65 (s), 133.23 (s), 129.54 (s), 128.02 (d, $J = 10.3$ Hz), 124.27 (s), 35.32 (s). MS (EI) $m/z = 248, 228, 216, 203, 189$. FT-IR : 2916, 2852, 1700, 1426, 1197, 746 cm^{-1}

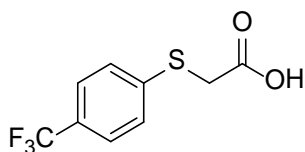
2-[(4-Fluorophenyl)thio]acetic acid (**5q**) [CAS 332-51-4]



General procedure A 방법으로 seal tube에 4-fluoriodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[(4-fluorophenyl)thio]acetic acid (흰 고체, 151mg, 81%)을 얻었다. ^1H NMR

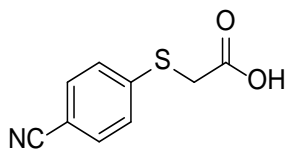
(500 MHz, CDCl₃) δ 7.49 – 7.42 (m, 2H), 7.06 – 6.98 (m, 2H), 3.60 (d, $J = 0.4$ Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 175.7, 163.6, 161.6, 133.7, 133.6, 129.2, 116.5, 116.3, 37.7. MS (EI) $m/z = 186, 167, 157, 141, 127$. FT-IR : 2921, 2608, 1698, 1489, 1430, 1393, 1196, 807 cm⁻¹

2-[[4-(Trifluoromethyl)phenyl]thio]acetic acid (**5r**) [CAS 102582-93-4]



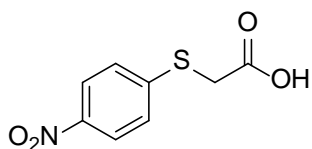
General procedure A 방법으로 seal tube에 4-iodobenzotrifluoride 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 2-[[4-(trifluoromethyl)phenyl]thio]acetic acid (노란 고체, 194mg, 82%)을 얻었다. ¹H NMR (500 MHz, CDCl₃) δ 7.59 – 7.52 (m, 2H), 7.49 – 7.43 (m, 2H), 3.75 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 175.20 (s), 139.88 (s), 128.83 (s), 128.57 (s), 128.22 (s), 125.94 (q, $J = 3.8$ Hz), 125.00 (s), 122.84 (s), 35.16 (s). MS (EI) $m/z = 236, 217, 191, 179$. FT-IR : 2919, 2852, 1695, 1603, 1321, 1096, 821 cm⁻¹

2-[(4-Cyanophenyl)thio]acetic acid (**5s**) [CAS 17893-44-6]



General procedure A 방법으로 seal tube에 4-iodobenzonitrile 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(황토색 고체, 69%)을 얻었다. ^1H NMR (500 MHz, DMSO- d_6) δ 7.78 - 7.72 (m, 2H), 7.49 - 7.42 (m, 2H), 3.98 (s, 2H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 170.46 (s), 144.25 (s), 132.87 (s), 126.93 (s), 119.24 (s), 107.73 (s), 33.92 (s).

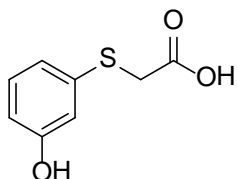
2-[(4-Nitrophenyl)thio]acetic acid (**5t**) [CAS 3406-75-5]



General procedure A 방법으로 seal tube에 1-iodo-4-nitrobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 생성물(황토색 고체, 87%)을 얻었다. ^1H NMR (500 MHz, dms) δ 8.19 - 8.12 (m, 2H), 7.55 - 7.49 (m, 2H), 4.05 (s, 2H). ^{13}C NMR (126 MHz, DMSO- D_6) δ 169.8, 147.4, 144.4, 126.1, 123.8, 34.4. FT-IR : 2920, 2851, 1694, 1312, 1186,

836 cm^{-1}

2-(3-Hydroxyphenyl)sulfanylacetic acid (**5u**)



General procedure A 방법으로 seal tube 에 4-phenyliodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 (흰색 고체, 69%)을 얻었다. ^1H NMR (500 MHz, DMSO-d_6) δ 7.08 (t, $J = 7.9$ Hz, 1H), 6.76 - 6.63 (m, 2H), 6.56 (d, $J = 8.0$ Hz, 1H), 3.71 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.06 (s), 158.15 (s), 137.18 (s), 130.32 (s), 118.53 (s), 114.60 (s), 113.48 (s), 35.31 (s). FT-IR : 3375, 3056, 2922, 1709, 1583, 1180, 894, 771 cm^{-1}

2-(4-phenylphenyl)sulfanylacetic acid (**5v**)



General procedure A 방법으로 seal tube 에 4-phenyliodobenzene 1.0 mmol, thioglycolic acid 3.0 equiv.을 넣고 반응하여 (흰색 고체, 69%)을

얻었다. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.62 (dd, $J = 12.6, 8.0$ Hz, 4H), 7.51 – 7.37 (m, 4H), 7.34 (t, $J = 7.2$ Hz, 1H), 3.83 (s, 2H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 171.05 (s), 139.80 (s), 138.14 (s), 135.51 (s), 129.42 (s), 128.64 (s), 127.64 (s), 126.88 (s), 35.35 (s). FT-IR : 2921, 2694, 2590, 1691, 1599, 1203, 916, 820, 759, 700 cm^{-1}

3) Thioformamide 화합물의 합성

각각의 amine과 aniline마다 합성 방법에 차이가 있다. 화합물을 얻는 방법에 특이한 점이 있다. 시약을 화합물을 만들 때마다 첨가해도 되지만 미리 많은 양의 thioglycolic acid, $\text{DMSO}/\text{H}_2\text{O}$ (혹은 DMSO), 2차 amine과 aniline의 경우 DIPEA를 먼저 60 °C에서 1 h 동안 반응을 돌린 후 각 반응을 보낼 때마다 적절한 양을 취해 사용해도 화합물이 같은 수율로 생성되었다.

뿐만 아니라 1차 amine을 이용해 만든 thioformamide는 conformer가 형성되었다.

General procedure A of secondary amine

Seal tube에 Ar을 치환한 뒤 DMSO와 H₂O 0.95/0.05 mL 넣은 후 thioglycolic acid 1.2 eq을 취해 넣는다. 2차 amine 0.5 mmol을 넣고 100 °C에서 16 h 동안 stirring한 후 상온에서 식힌다. 1M HCl로 quenching해준 후 ethyl acetate로 추출한다. 추출한 다음 Na₂SO₄로 남아 있는 물을 제거한 후 column chromatography로 ethyl acetate와 hexane을 이용해 분리 정제한다.

General procedure B of primary amine

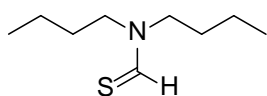
Seal tube에 Ar을 치환한 뒤 DMSO와 H₂O 0.95/0.05 mL 넣은 후 thioglycolic acid 1.2 eq, DIPEA 1.5 eq을 취해 넣은 후 60 °C에서 1 h 먼저 돌린다. 혼합물을 상온에서 식힌 후 1차 amine 0.5 mmol을 넣고 100 °C에서 16 시간동안 stirring한 후 상온에서 식힌다. 1M HCl로 quenching해준 후 ethyl acetate로 추출한다. 추출한 다음 Na₂SO₄로 남아 있는 물을 제거한 후 column chromatography로 ethyl acetate와 hexane을 이용해 분리 정제한다.

General procedure C of aniline

Seal tube에 Ar을 치환한 뒤 DMSO 1 mL 넣은 후 thioglycolic acid 1.2 eq, DIPEA 1.5 eq을 취해 넣은 후 60 °C에서 1 시간 먼저 돌린다. 혼합물을 상온에서 식힌 후 aniline 0.5 mmol과 BF₃OEt₂ 1.0 eq을 넣고 80 °C에서 16 h

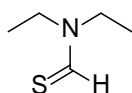
동안 stirring한 후 상온에서 식힌다. 1M HCl로 quenching해준 후 ethyl acetate로 추출한다. 추출한 다음 Na₂SO₄로 남아 있는 물을 제거한 후 column chromatography로 ethyl acetate와 hexane을 이용해 분리 정제한다.

N,N-Dibutylmethanethioamide (**6a**) [CAS 13749-55-8]



General procedure A 방법으로 seal tube에 dibutylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 *N,N*-dibutylmethanethioamide(노란 액체, 56 mg, 65%)을 얻었다. ¹H NMR (500 MHz, CDCl₃) δ 9.21 (s, 1H), 3.78-3.75 (m, 2H), 3.46 (t, J = 7.2 Hz, 2H), 1.68-1.59 (m, 4H), 1.35 (tt, J = 22.1, 7.4 Hz, 4H), 0.96 (td, J = 7.3, 4.8 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 187.5, 56.2, 47.5, 30.6, 28.0, 20.2, 19.7, 13.8, 13.6. MS (EI) m/z = 173, 158, 144, 130. FT-IR : 2957, 2930, 2871, 1671, 1502, 1217, 1168.

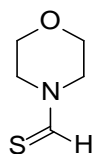
N,N-Diethylmethanethioamide (**6b**) [CAS 13839-14-0]



General procedure A 방법으로 seal tube에 diethylamine 0.5 mmol,

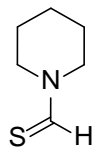
thioglycolic acid 1.2 equiv.을 넣고 반응하여 *N,N*-diethylmethanethioamide (갈색 액체, 30 mg, 52%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.23 (s, 1H), 3.86 (q, $J = 7.3$ Hz, 2H), 3.54 (q, $J = 7.3$ Hz, 2H), 1.27 (dt, $J = 25.8, 7.2$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.8, 50.7, 42.3, 14.4, 11.2. MS (EI) $m/z = 117, 102, 88$. FT-IR : 2974, 2934, 1666, 1636, 1431, 1397, 1380, 1350, 1102 cm^{-1}

4-Morpholinecarbothioaldehyde (**6c**) [CAS 5780-30-3]



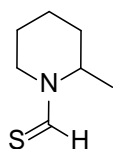
General procedure A 방법으로 seal tube에 morpholine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 4-morpholinecarbothioaldehyde (노란 고체, 41 mg, 63%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.27 (s, 1H), 4.11 (t, $J = 4.9$ Hz, 2H), 3.79-3.76 (m, 4H), 3.68 (t, $J = 4.6$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.8, 66.8, 66.0, 55.0, 45.5. MS (EI) $m/z = 131, 116, 117, 103$. FT-IR : 2965, 2907, 2854, 1637, 1500, 1108, 849 cm^{-1}

1-Piperidinecarbothioaldehyde (**6d**) [CAS 7584-63-6]



General procedure A 방법으로 seal tube에 piperidine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 1-piperidinecarbothioaldehyde (갈색 고체, 44 mg, 68%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D) δ 9.22 (s, 1H), 4.01 (t, $J = 5.7$ Hz, 2H), 3.60 (t, $J = 5.4$ Hz, 2H), 1.75-1.67 (m, 6H). MS (EI) $m/z = 129, 114, 100$.

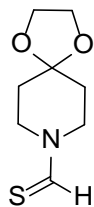
2-methylpiperidine-1-carbothialdehyde (**6e**) [CAS 20278-12-0]



General procedure A 방법으로 seal tube에 2-methylpiperidine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 2-methylpiperidine-1-carbothialdehyde (노란 액체, 43 mg, 60%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D, mixture of conformers) δ (major of conformer) 9.29 (s, 1H), 4.33-4.29 (m, 1H), 3.89-3.85 (m, 1H), 3.84-3.79 (m, 1H), ,

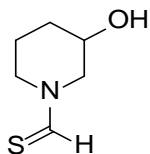
1.86–1.68 (m, 6H), 1.37 (d, $J = 6.9$ Hz, 3H), (minor of conformer) ^1H NMR (500 MHz, CHLOROFORM-D) δ 9.17 (s, 1H), 5.52–5.49 (m, 1H), 3.58 (d, $J = 2.3$ Hz, 1H), 3.56 (q, $J = 2.3$ Hz, 1H), 1.67–1.52 (m, 6H), 1.25 (d, $J = 7.4$ Hz, 3H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 185.6, 184.3, 60.3, 51.8, 48.1, 43.1, 32.5, 29.2, 26.4, 24.9, 20.7, 18.8, 17.8, 14.6. MS (EI) $m/z = 143, 129, 114, 100$. FT-IR : 2936, 2860, 1481, 1441, 1062 cm^{-1}

1,4-Dioxa-8-azaspiro[4.5]decane-8-carbodithioic acid (**6f**)



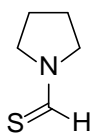
General procedure A 방법으로 seal tube에 4-piperidone ethylene acetal 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 62 mg, 66%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.25 (s, 1H), 4.15 (t, $J = 6.0$ Hz, 2H), 4.04–3.98 (m, 4H), 3.73 (t, $J = 5.7$ Hz, 2H), 1.83–1.78 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.6, 106.5, 64.7, 53.1, 42.5, 35.6, 33.9. MS (EI) $m/z = 187, 171, 158, 144, 128$. FT-IR : 2963, 2894, 1717, 1637, 1505, 1446, 909 cm^{-1}

3-Hydroxypiperidine-1-carbothioaldehyde (**6g**)



General procedure A 방법으로 seal tube에 3-hydroxypiperidine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물 (노란 액체, 38 mg, 53%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.24 (d, $J = 41.8$ Hz, 1H), 4.27 (dd, $J = 12.6, 3.4$ Hz, 1H), 4.06–3.90 (m, 2H), 3.87–3.75 (m, 1H), 3.65–3.49 (m, 2H), 3.01 (s, 1H), 2.03–1.88 (m, 2H), 1.80–1.73 (m, 1H), 1.65–1.57 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.3, 187.2, 66.0, 65.5, 61.6, 55.8, 51.3, 45.3, 32.0, 31.9, 22.7, 20.6 MS (EI) $m/z =$ 145, 128, 116, 102. FT-IR : 3358, 2927, 2859, 1650, 1499, 1440, 1232, 988 cm^{-1}

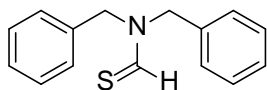
1-Pyrrolidinecarbothioaldehyde (**6h**) [CAS 2474-33-1]



General procedure A 방법으로 seal tube에 pyrrolidine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 1-

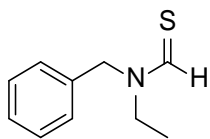
pyrrolidinecarbothioaldehyde (갈색 액체, 35 mg, 60%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.35 (s, 1H), 3.74–3.70 (m, 4H), 2.07–2.01 (m, 4H). FT-IR : 2971, 2876, 1654, 1502, 1420, 1388, 1157 cm^{-1}

N,N-Bis(phenylmethyl)methanethioamide (**6j**) [CAS 25576-20-9]



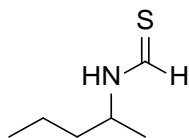
General procedure A 방법으로 seal tube에 dibenzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N,N-bis(phenylmethyl)methanethioamide (노란 고체, 64 mg, 53%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.62 (s, 1H), 7.41–7.32 (m, 6H), 7.30–7.28 (m, 2H), 7.16 (dd, $J = 7.9, 1.3$ Hz, 2H), 5.00 (s, 2H), 4.53 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 189.6, 134.8, 134.1, 129.2, 128.9, 128.7, 128.5, 128.1, 128.0, 58.8, 49.3. MS (EI) $m/z = 241, 165, 150, 123$. FT-IR : 2922, 1658, 1497, 1439, 1193, 751, 696 cm^{-1}

N-Benzyl-N-ethylmethanethioamide (**6k**)



General procedure A 방법으로 seal tube에 N-benzylethylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-benzyl-N-ethylmethanethioamide (갈색 액체, 39 mg, 44%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.43 (d, $J = 20.6$ Hz, 1H), 7.40–7.29 (m, 4H), 7.23–7.21 (m, 1H), 5.12 (s, 1H), 4.65 (s, 1H), 3.79 (q, $J = 7.1$ Hz, 1H), 3.47 (q, $J = 7.3$ Hz, 1H), 1.21 (dt, $J = 33.6, 7.2$ Hz, 3H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 188.4, 188.1, 135.0, 134.5, 129.1, 128.8, 128.6, 128.2, 128.0, 127.8, 59.7, 50.1, 49.8, 42.3, 14.0, 10.8. MS (EI) $m/z = 179, 163, 150, 91$. FT-IR : 3208, 2974, 2932, 1602, 1494, 1430, 1159, 696 cm^{-1}

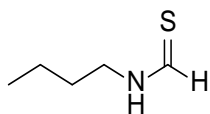
(7a)



General procedure B 방법으로 seal tube에 2-aminopentane 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(갈색 액체, 20 mg, 30%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D , mixture(1:1) of

conformers) δ 9.39 (d, $J = 7.4$ Hz, 1H), 9.17 (d, $J = 15.5$ Hz, 1H), 7.77 (s, 1H), 7.16 (s, 1H), 4.78–4.73 (m, 1H), 3.67 (dt, $J = 15.3, 7.0$ Hz, 1H), 1.63–1.50 (m, 4H), 1.45–1.33 (m, 3H), 1.27 (dd, $J = 16.3, 6.6$ Hz, 6H), 0.96–0.92 (m, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 189.5, 187.8, 56.5, 48.6, 39.2, 37.9, 21.4, 19.3, 19.1, 19.1, 13.9, 13.7. MS (EI) $m/z = 131, 116, 104, 88$.

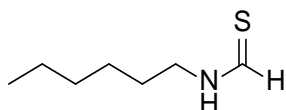
N-Butylmethanethioamide (**7b**) [CAS 60448-30-8]



General procedure B 방법으로 seal tube에 butylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-butylmethanethioamide (갈색 액체, 50 mg, 85%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D , mixture of conformers) δ (major of conformer) 9.43 (d, $J = 6.3$ Hz, 1H), 7.39 (s, 1H), 3.73–3.69 (m, 2H), 1.69–1.57 (m, 3H), 0.96 (q, $J = 7.4$ Hz, 5H); δ (minor of conformer) 9.15 (d, $J = 14.9$ Hz, 1H), 7.81 (s, 1H), 3.45 (q, $J = 6.7$ Hz, 2H), 1.46–1.35 (m, 3H), 0.96 (q, $J = 7.4$ Hz, 5H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 188.9, 49.5, 43.2, 32.1, 29.9, 20.1, 19.5, 13.7, 13.5. MS (EI) $m/z = 117, 102, 88, 75$. FT-IR : 3195,

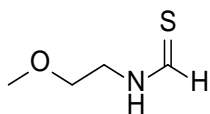
2959, 2930, 2871, 1667, 1529, 1444 cm^{-1}

N-Hexylmethanethioamide (**7c**) [CAS 13989-76-9]



General procedure B 방법으로 seal tube에 hexylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-hexylmethanethioamide (갈색 액체, 68 mg, 93%)을 얻었다. ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 191.0, 188.9, 49.8, 43.5, 31.3, 31.2, 30.1, 27.8, 26.5, 26.0, 22.5, 22.4, 14.0 MS (EI) m/z = 145, 130, 116, 112. FT-IR : 3207, 2926, 2856, 1668, 1527, 1443, 1290. 868, 724 cm^{-1}

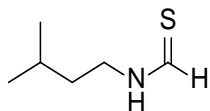
(**7d**) [CAS 2361305-36-2]



General procedure B 방법으로 seal tube에 2-methoxyethylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(갈색 액체, 50 mg, 84%)을 얻었다. ^1H -NMR (500 MHz, CHLOROFORM-D) δ 9.46 (d, J = 6.3 Hz, 1H), 7.75 (s, 1H), 3.91 (q, J = 5.2 Hz, 2H), 3.61 (t, J = 5.2

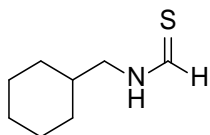
Hz, 3H), 3.39 (d, $J = 3.2$ Hz, 2H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 189.2, 69.3, 59.1, 58.9, 42.9. MS (EI) $m/z = 119, 104, 88, 74$.

N-isoamylthioformamide (**7e**) [CAS 873974-70-0]



General procedure B 방법으로 seal tube에 isoamylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 *N*-isoamylthioformamide (갈색 액체, 49 mg, 74%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D, mixture of conformers) δ (major of conformer) 9.42 (d, $J = 6.0$ Hz, 1H), 7.35 (s, 1H), 3.75-3.70 (m, 2H), 1.54 (qd, $J = 14.2, 7.3$ Hz, 3H), 0.95 (q, $J = 6.1$ Hz, 6H); (minor of conformer) δ 9.15 (d, $J = 14.9$ Hz, 1H), 7.76 (s, 1H), 3.46 (q, $J = 7.1$ Hz, 2H), 1.71-1.64 (m, 3H), 0.95 (q, $J = 6.1$ Hz, 6H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 190.9, 188.8, 48.0, 41.9, 38.8, 36.7, 26.0, 25.2, 22.4, 22.2. MS (EI) $m/z = 131, 116, 102, 90, 75$. FT-IR : 3207, 2955, 2869, 1664, 1527, 1442, 1291, 872.

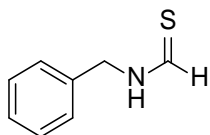
Cyclohexylthioformamide (**7f**) [CAS 2248161-17-1]



General procedure B 방법으로 seal tube에 cyclohexanemethylamine 0.5

mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(갈색액체, 62 mg, 80%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D, mixture of conformers) δ 9.46 (d, $J = 6.3$ Hz, 1H), 7.48 (s, 1H), 3.57 (t, $J = 6.3$ Hz, 2H), 1.77–1.72 (m, 6H), 1.69 (tt, $J = 10.5, 3.8$ Hz, 4H), 0.98–0.90 (m, 1H); (minor of conformer) δ 9.09 (d, $J = 14.9$ Hz, 1H), 7.90 (s, 1H), 3.27 (t, $J = 6.6$ Hz, 2H), 1.58–1.50 (m, 1H), 1.32–1.11 (m, 6H), 1.07–0.99 (m, 4H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 191.4, 189.1, 56.3, 49.6, 38.5, 36.8, 30.9, 30.4, 26.2, 26.1, 25.7, 25.6. MS (EI) $m/z = 157, 142, 124, 114$. FT-IR : 3205, 2920, 2849, 1530, 1445, 1277, 865.

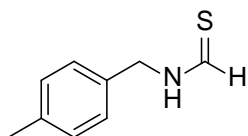
N-Benzylthioformamide (**7g**) [CAS 20278-32-4]



General procedure B 방법으로 seal tube에 benzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-benzylthioformamide (갈색 액체, 64 mg, 80%)을 얻었다. ^1H -NMR (500 MHz, CHLOROFORM-D, mixture of conformers) δ (major of conformer) 9.50 (dd, $J = 6.3, 1.1$ Hz, 1H), 7.55 (s, 1H), 7.40–7.32 (m, 5H), 4.87 (d, $J = 5.2$ Hz, 2H; (minor of conformer) δ 9.25 (d, $J = 14.9$ Hz, 1H), 7.89 (s, 1H), 7.40–7.32 (m,

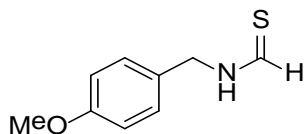
5H), 4.60 (d, J = 5.7 Hz, 1H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 188.8, 135.6, 129.1, 129.0, 128.5, 128.3, 128.3, 127.5, 53.4, 47.6. MS (EI) m/z = 151, 118, 106, 91.

4-methylbenzylthioformamide (**7h**) [CAS]



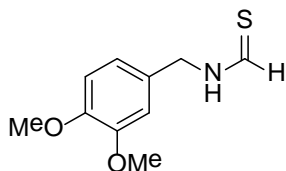
General procedure B 방법으로 seal tube에 4-methylbenzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(갈색 액체, 66 mg, 80%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D, mixture of conformers) (major of conformer) δ 9.49 (dd, J = 6.3, 1.1 Hz, 1H), 7.46 (s, 1H), 7.19–7.12 (m, 4H), 4.82 (d, J = 5.2 Hz, 2H), 2.35 (s, 3H); (minor of conformer) δ 9.25 (d, J = 14.9 Hz, 1H), 7.78 (s, 1H), 7.22 (t, J = 8.9 Hz, 4H), 4.56 (d, J = 5.7 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 191.4, 188.7, 138.1, 132.6, 129.8, 129.7, 128.4, 127.5, 53.3, 47.4, 21.2. MS (EI) m/z = 165, 132, 118, 91.

N-[(4-Methoxyphenyl)methyl]methanethioamide (7i) [CAS
1219505-09-5]



General procedure B 방법으로 seal tube에 4-methoxybenzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-[(4-methoxyphenyl)methyl]methanethioamide (갈색 고체, 75 mg, 83%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.48 (dt, $J = 6.4, 1.1$ Hz, 1H), 7.28–7.27 (m, 2H), 6.91–6.88 (m, 2H), 4.79 (d, $J = 5.7$ Hz, 2H), 3.81 (d, $J = 2.3$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 188.6, 159.6, 129.8, 129.0, 127.7, 114.4, 55.3, 47.2. MS (EI) $m/z = 181, 166, 153, 121$. FT-IR : 3164, 2953, 1668, 1609, 1510, 1242, 870, 682 cm^{-1}

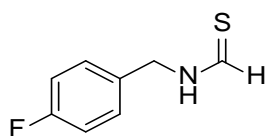
N-(3,4-dimethoxybenzyl)methanethioamide (7j)



General procedure B 방법으로 seal tube에 3,4-dimethoxybenzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-[(3,4-

dimethoxyphenyl)methyl]methanethioamide (갈색 고체, 93 mg, 88%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.50–9.49 (m, 1H), 7.48 (s, 1H), 6.90–6.84 (m, 3H), 4.80 (d, $J = 5.2$ Hz, 2H), 3.88–3.87 (m, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 188.6, 149.3, 149.0, 128.2, 120.9, 111.5, 111.3, 56.0, 47.6. MS (EI) $m/z = 211, 196, 183, 169, 151$. FT-IR : 3312, 2920, 1669, 1608, 1508, 1436, 1233, 1149, 1017.865, 806 cm^{-1}

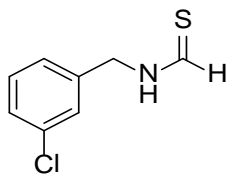
N-[(4-fluorophenyl)methyl]-methanethioamide (**7k**) [CAS 1379249-29-2]



General procedure B 방법으로 seal tube에 4-fluorobenzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-[(4-fluorophenyl)methyl]-methanethioamide (갈색 액체, 63 mg, 74%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D , mixture of conformers) (major of conformer) δ 9.51–9.49 (m, 1H), 7.53 (s, 1H), 7.34–7.31 (m, 2H), 7.07–7.03 (m, 2H), 4.86 (d, $J = 5.7$ Hz, 2H); (minor of conformer) δ 9.27 (d, $J = 14.9$ Hz, 1H), 7.90 (s, 1H), 7.25–7.23 (m, 2H), 7.09 (dd, $J = 9.5, 3.2$ Hz, 2H), 4.59 (d, $J = 5.7$ Hz, 1H). ^{13}C NMR

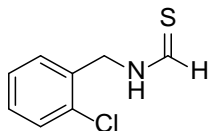
(126 MHz, CHLOROFORM-D) δ 191.6, 189.0, 163.5, 161.6, 131.5, 131.5, 130.2, 130.1, 129.4, 129.4, 116.2, 116.1, 116.0, 115.8, 52.7, 46.7. MS (EI) m/z = 169, 152, 121, 109. FT-IR : 3201, 2964, 1602, 1506, 1440, 1218, 818 cm^{-1}

(71)



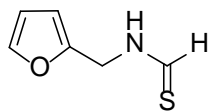
General procedure B 방법으로 seal tube에 3-chlorobenzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(갈색 액체, 73 mg, 79%)을 얻었다. ¹H-NMR (500 MHz, CHLOROFORM-D, mixture of conformers) (major of conformer) δ 9.53–9.52 (m, 1H), 7.57 (s, 1H), 7.34–7.28 (m, 4H), 4.88 (d, J = 5.7 Hz, 2H); (minor of conformer) δ 9.27 (d, J = 14.9 Hz, 1H), 7.89 (s, 1H), 7.25–7.14 (m, 2H), 4.59 (d, J = 6.3 Hz, 2H). ¹³C NMR (126 MHz, CHLOROFORM-D) δ 189.3, 137.6, 134.8, 130.2, 128.4, 128.3, 126.4, 52.7, 46.6 MS (EI) m/z = 185, 155, 140, 125. FT-IR : 3195, 2965, 1516, 1429, 1282, 679.

(7m)



General procedure B 방법으로 seal tube에 2-chlorobenzylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물 (갈색 액체, 70 mg, 75%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D, mixture of conformers) (major of conformer) δ 9.51 (d, $J = 6.3$ Hz, 1H), 7.63 (s, 1H), 7.41 (dd, $J = 7.2, 2.0$ Hz, 1H), 7.31–7.25 (m, 3H), 5.00 (d, $J = 5.7$ Hz, 2H); (minor of conformer) δ 9.30 (d, $J = 14.9$ Hz, 1H), 7.86 (s, 1H), 7.48 (dd, $J = 7.2, 2.6$ Hz, 1H), 7.31–7.25 (m, 3H), 4.70 (d, $J = 6.3$ Hz, 1H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 192.0, 189.0, 134.0, 133.2, 131.3, 130.1, 130.1, 129.8, 129.7, 127.5, 127.2, 51.3, 45.1. MS (EI) $m/z = 185, 150, 125$, FT-IR : 3203, 2960, 1680, 1516, 1439, 747.

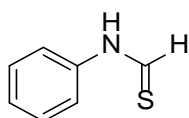
N-(2-Furylmethyl)thioformamide (7n) [CAS 2248161-16-0]



General procedure B 방법으로 seal tube에 furfurylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 N-(2-

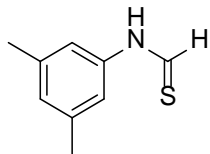
Furylmethyl)thioformamide (갈색 액체, 49 mg, 70%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D, mixture of conformers) (major of conformer) δ 9.48–9.47 (m, 1H), 7.54 (s, 1H), 7.41 (d, $J = 1.1$ Hz, 1H), 6.37 (td, $J = 3.7, 1.7$ Hz, 2H), 4.88 (dd, $J = 5.2, 1.1$ Hz, 2H); (minor of conformer) δ 9.27 (d, $J = 14.9$ Hz, 1H), 7.81 (s, 1H), 7.42 (d, $J = 1.7$ Hz, 1H), 6.32 (d, $J = 2.3$ Hz, 2H), 4.58 (d, $J = 5.7$ Hz, 2H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 191.9, 188.8, 148.6, 143.5, 142.8, 110.7, 109.3, 109.0, 45.9, 40.3. MS (EI) $m/z = 141, 112, 96, 81$. FT-IR : 3195, 2965, 1716, 1517, 1450, 1008, 867, 734.

N-Phenylmethanethioamide (**8a**) [CAS 637-51-4]



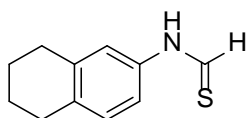
General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 *N*-phenylmethanethioamide (갈색 고체, 44 mg, 64%)을 얻었다. MS (EI) $m/z = 136, 104, 93, 77$.

N-3,5-dimethylphenylmethanethioamide (**8b**)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 50 mg, 61%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.75 (dd, $J = 14.6, 3.2$ Hz, 1H), 9.19 (s, 1H), 6.88 (s, 1H), 6.74 (s, 2H), 2.34–2.32 (m, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.2, 140.0, 138.4, 128.1, 115.3, 21.3. MS (EI) $m/z = 164, 150, 138, 105$. FT-IR : 3206, 3092, 3013, 2913, 1568, 1329, 837.

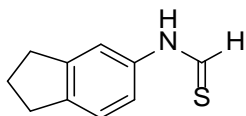
(**8c**)



General procedure C 방법으로 seal tube에 5,6,7,8-tetrahydro-2-naphthylamine 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 (노란 고체, 67 mg, 70%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.71 (d, $J = 14.9$ Hz, 1H), 9.31 (s, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 6.86 (dd, $J = 8.0, 2.3$ Hz, 1H), 6.83 (d, $J = 1.7$ Hz, 1H), 2.75 (t, $J = 6.9$ Hz, 4H), 1.82–

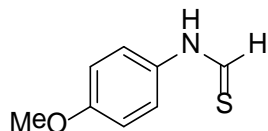
1.77 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.9, 139.1, 136.0, 135.7, 130.5, 118.0, 114.9, 29.5, 28.9, 23.0, 22.8. MS (EI) m/z = 191, 173, 164, 158. 3047, 2926, 1555, 1317, 967, 800.

(8d)



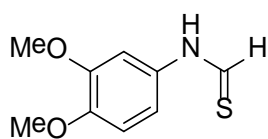
General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(진한 노란 고체, 64 mg, 72%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.72 (d, J = 14.9 Hz, 1H), 9.21–9.41 (1H), 7.21 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 6.89 (dd, J = 7.7, 2.0 Hz, 1H), 2.94–2.88 (m, 4H), 2.15–2.09 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.1, 146.5, 142.9, 137.1, 125.5, 116.0, 113.9, 33.0, 32.4, 25.6. MS (EI) m/z = 177, 161, 150. FT-IR : 3060, 2965, 2587, 2126, 1693, 1600, 1563, 1331, 805.

(8e)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 70 mg, 84%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.71 (s, 0H), 9.64 (d, $J = 14.9$ Hz, 1H), 7.11–7.09 (m, 2H), 6.92–6.90 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.9, 158.2, 132.2, 119.4, 115.1, 55.6. MS (EI) $m/z =$ 167, 151, 140. FT-IR : 3184, 3066, 2932, 2836, 1675, 1506, 816.

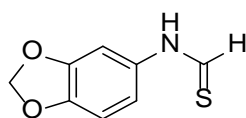
(8f)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 76 mg, 77%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.67 (s, 1H), 6.85 (d, $J = 8.6$ Hz, 1H), 6.73 (dd, $J = 8.6, 2.3$ Hz, 1H), 6.69 (d, $J = 2.3$ Hz, 1H), 3.89 (d, $J = 5.7$

Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.0, 149.9, 147.8, 132.4, 111.8, 110.1, 102.3, 56.2, 56.1. MS (EI) m/z = 197, 180, 170, 155. FT-IR : 3130, 3065, 1602, 1285, 970.

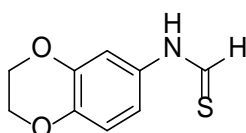
(8g)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(갈색 고체, 60 mg, 66%)을 얻었다.

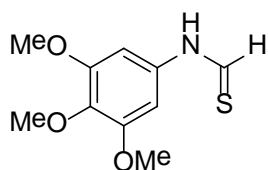
^1H NMR (500 MHz, CDCl_3) δ 9.60 (d, J = 14.9 Hz, 1H), 9.36 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 2.3 Hz, 1H), 6.59 (dd, J = 8.6, 2.3 Hz, 1H), 6.01 (s, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.1, 148.9, 146.3, 133.3, 111.4, 108.8, 101.9, 99.8. MS (EI) m/z = 181, 154, 136, 121. FT-IR : 3147, 3057, 29095, 1680, 1617, 1488, 1250, 793.

(8h)



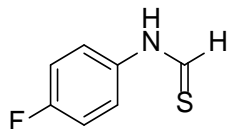
General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(엷은 노란 고체, 49 mg, 50%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.61 (d, $J = 14.9$ Hz, 1H), 9.33 (s, 1H), 6.86 (d, $J = 8.6$ Hz, 1H), 6.68 (d, $J = 2.9$ Hz, 1H), 6.62 (dd, $J = 8.6, 2.9$ Hz, 1H), 4.29–4.26 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.0, 144.3, 142.3, 132.6, 118.3, 111.1, 107.1, 64.5, 64.3. MS (EI) $m/z = 195, 168, 154, 135$. FT-IR : 3057, 2905, 1500, 1250, 793.

(8i)



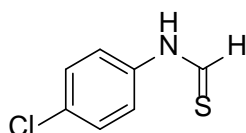
General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(엷은 노란 고체, 73 mg, 64%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.72 (d, $J = 14.3$ Hz, 1H), 9.58–9.67 (1H), 6.37 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.3, 154.3, 136.6, 134.8, 95.6, 61.1, 56.4. MS (EI) $m/z = 227, 212, 200, 185$. FT-IR : 3276, 2925, 1607, 1293, 1121 cm^{-1}

(8j)



General procedure C 방법으로 seal tube에 4-fluoroaniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 49 mg, 63%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.71 (d, $J = 14.3$ Hz, 1H), 9.59 (s, 1H), 7.15–7.08 (m, 4H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.7, 161.8, 159.9, 134.9, 119.5, 119.5, 117.0, 116.8. MS (EI) $m/z = 155, 139, 111, 95$. FT-IR : 3051, 2921, 1503, 822, 507.

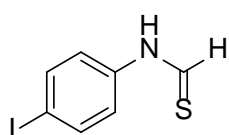
(8k)



General procedure C 방법으로 seal tube에 4-chloroaniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 52 mg, 61%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D) δ 9.77 (d, $J = 14.9$ Hz, 1H), 9.25–9.46 (1H), 7.37 (dd, $J = 6.6, 2.0$ Hz, 2H), 7.09 (dd, $J = 6.9, 2.3$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 187.5, 137.1, 131.8, 130.1,

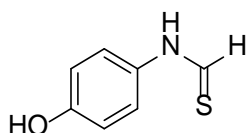
118.7. MS (EI) $m/z = 171, 144, 138$. FT-IR : 3058, 1483, 1313, 943, 819.

(8l)



General procedure C 방법으로 seal tube에 4-iodoaniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 66 mg, 50%)을 얻었다. ^1H NMR (500 MHz, DMSO- D_6) δ 12.22 (d, $J = 13.7$ Hz, 1H), 9.99 (d, $J = 13.7$ Hz, 1H), 7.70 (dd, $J = 6.9, 1.7$ Hz, 2H), 7.22 (dd, $J = 6.6, 2.0$ Hz, 2H). ^{13}C NMR (126 MHz, DMSO- D_6) δ 189.6, 139.9, 138.7, 119.9, 90.1. MS (EI) $m/z = 263, 230, 219, 203$. FT-IR : FT-IR : 3166, 3056, 1548, 1314, 945, 812.

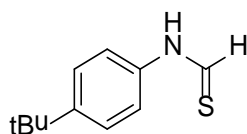
(8m)



General procedure C 방법으로 seal tube에 4-hydroxyaniline 0.5 mmol,

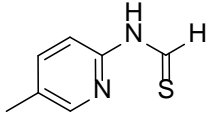
thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 66 mg, 86%)을 얻었다. ^1H NMR (500 MHz, DMSO-D6) δ 12.04 (d, $J = 13.7$ Hz, 1H), 9.71 (dd, $J = 14.3, 4.0$ Hz, 1H), 9.49 (s, 1H), 7.19 (t, $J = 4.6$ Hz, 2H), 6.75–6.73 (m, 2H). ^{13}C NMR (126 MHz, DMSO-D6) δ 187.2, 155.8, 132.4, 123.9, 119.5, 116.4, 115.5. MS (EI) $m/z = 153, 137, 126, 108$. FT-IR : 3197, 3095, 1570, 1213, 945, 823, 509.

(8n)



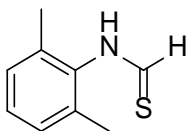
General procedure C 방법으로 seal tube에 4-tert-butyl aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(주황색 고체, 69 mg, 72%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.75 (d, $J = 14.3$ Hz, 1H), 7.40 (d, $J = 8.6$ Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.9, 149.6, 136.3, 126.7, 117.4, 34.5, 31.3, 31.2. MS (EI) $m/z = 193, 178, 166, 151$. FT-IR : 3171, 3107, 3074, 2955, 2856, 1673, 1513, 1306, 972, 817.

(8o)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(엷은 갈색 고체, 17 mg, 22%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 10.29 (d, $J = 13.7$ Hz, 1H), 9.79 (s, 1H), 8.22 (s, 1H), 7.53 (dd, $J = 8.3, 2.0$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 188.6, 149.0, 148.2, 139.5, 130.8, 109.8, 17.9. MS (EI) $m/z = 152, 122, 107, 93$. FT-IR : 3029, 2920, 2850, 1688, 1544, 1304, 820.

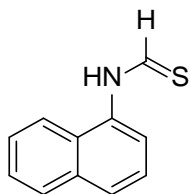
(8p)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(갈색 고체, 55 mg, 66%)을 얻었다. ^1H NMR (500 MHz, CHLOROFORM-D , mixture of conformers) (major of conformer) δ 9.22 (d, $J = 14.9$ Hz, 1H), 8.87 (s, 1H), 7.13 (t, $J = 7.7$ Hz, 3H), 2.31 (s, 6H); (minor of conformer) δ 9.69 (d, $J = 5.7$ Hz, 1H),

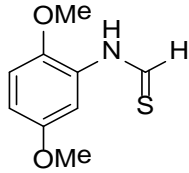
8.39 (s, 1H), 7.23–7.16 (m, 3H), 2.26 (s, 6H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 193.2, 189.1, 136.9, 135.4, 133.9, 128.9, 128.4, 128.2, 18.6, 18.2 MS (EI) m/z = 165, 150, 138. FT-IR : 3319, 3122, 2921, 2851, 2079, 1483, 1236, 777 cm^{-1}

(8q)



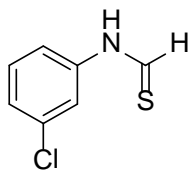
General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 42 mg, 45%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.80 (d, J = 14.3 Hz, 1H), 9.72 (s, 1H), 7.95 (dd, J = 21.2, 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 1H), 7.65–7.58 (m, 2H), 7.49 (t, J = 7.7 Hz, 1H), 7.41–7.40 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 190.6, 134.8, 134.2, 128.7, 127.7, 127.4, 127.1, 125.8, 125.6, 120.6, 117.7. MS (EI) m/z = 187, 177, 160, 154. FT-IR : 3111, 3015, 2954, 1654, 1541, 1334, 962, 767 cm^{-1}

(8r)



General procedure C 방법으로 seal tube에 2,5-dimethoxyaniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 37 mg, 38%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.79 (d, $J = 14.9$ Hz, 1H), 9.45–9.64 (1H), 6.87–6.84 (m, 2H), 6.70 (dd, $J = 8.6, 2.9$ Hz, 1H), 3.86 (d, $J = 6.3$ Hz, 3H), 3.78 (d, $J = 2.3$ Hz, 3H) ^{13}C NMR (126 MHz, CDCl_3) δ 185.8, 154.3, 141.8, 128.3, 112.4, 110.2, 102.4, 56.3, 55.8. MS (EI) $m/z = 197, 181, 166, 155$. FT-IR : 3359, 3246, 2922, 2831, 1659, 1534, 1221, 700.

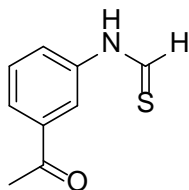
(8s)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(엷은 노란 고체, 34 mg, 40%)을 얻었다. ^1H NMR (500 MHz, CDCl_3) δ 9.80 (d, $J = 14.3$ Hz, 1H), 9.31 (s,

1H), 7.33 (t, J = 8.0 Hz, 1H), 7.23 (dd, J = 8.0, 1.1 Hz, 1H), 7.16 (t, J = 1.9 Hz, 1H), 7.03 (dd, J = 8.0, 1.7 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 187.7, 139.5, 135.8, 131.1, 126.3, 117.6, 115.5. MS (EI) m/z = 170, 142, 138. 127. FT-IR : 3056, 1590, 1472, 1326, 770.

(8t)



General procedure C 방법으로 seal tube에 aniline 0.5 mmol, thioglycolic acid 1.2 equiv.을 넣고 반응하여 생성물(노란 고체, 45 mg, 45%)을 얻었다. ¹H NMR (500 MHz, CDCl₃) δ 9.89 (d, J = 14.3 Hz, 1H), 9.36-9.49 (1H), 7.81 (dd, J = 6.3, 1.1 Hz, 1H), 7.76 (t, J = 2.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.35 (dd, J = 7.7, 2.0 Hz, 1H), 2.64 (s, 3H). ¹³C NMR (126 MHz, DMSO-D₆) δ 198.0, 190.2, 140.5, 138.6, 130.6, 125.3, 122.1, 117.3, 27.4. MS (EI) m/z = 179, 164, 150, 136. FT-IR : 3247, 3071, 2921, 2851, 1673, 1549, 1312, 944, 782 cm⁻¹

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40. 성신여자대학교 화학과 김경미 선생 연구 수행

Abstract

Introduction of sulfur-containing functional group into aryl compounds
using thioglycolic acid

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Sungshin University

C-S bond formation is important for the synthesis of various chemicals such as pharmaceuticals, pesticides, and polymer materials. Several reagents such as H_2S , NaSH , sulfur powder, etc. have been used as sulfur source for the C-S coupling. However, they have some limitations; they are highly reactive and toxic, and have unpleasant odor. Thioglycolic acid can be a complementary sulfur source for copper-catalyzed C-S bond forming reactions and the most important variable in

this reaction is the solvent; polar aprotic solvents such as DMSO or DMF work best. Interestingly, several different C–S bond containing products were obtained depending on the reaction solvents. Each optimized protocol gave biaryl disulfide and 2-(phenylthio)acetic acid, respectively.

Thioglycolic acid can be also used to introduce a thioformyl group into amines. Thioformyl group are often used as an intermediate of various compounds. However, its synthetic methods have been rarely reported. Toxic H₂S gas or reagents of low atom economy are required to prepare thioformamides. Yet, these reagents produce a very limited variety of thioformamide. This study discovered that the introduction of thioformyl group into primary and secondary amines and aniline is possible by using of thioglycolic acid in the absence of a transition metal catalyst.

Appendix

Figure 3. ^1H NMR spectrum of 3a

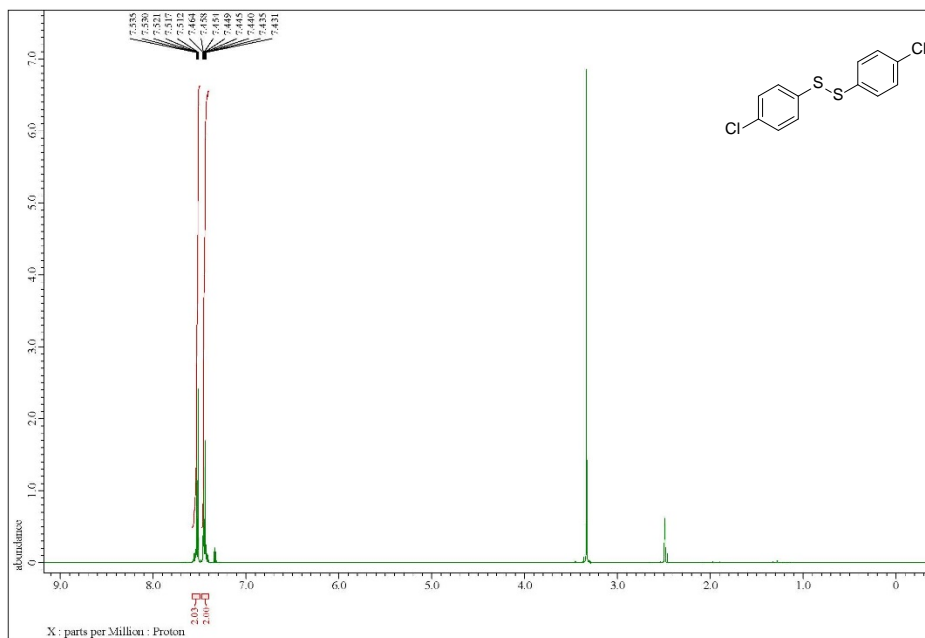


Figure 4 ^{13}C NMR spectrum of 3a

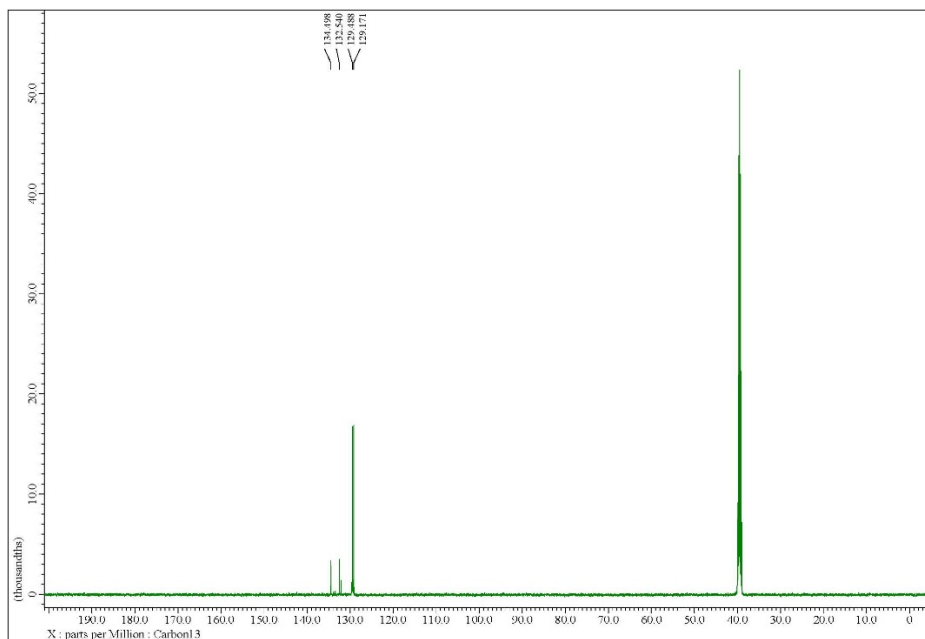


Figure 5. ^1H NMR spectrum of 3b

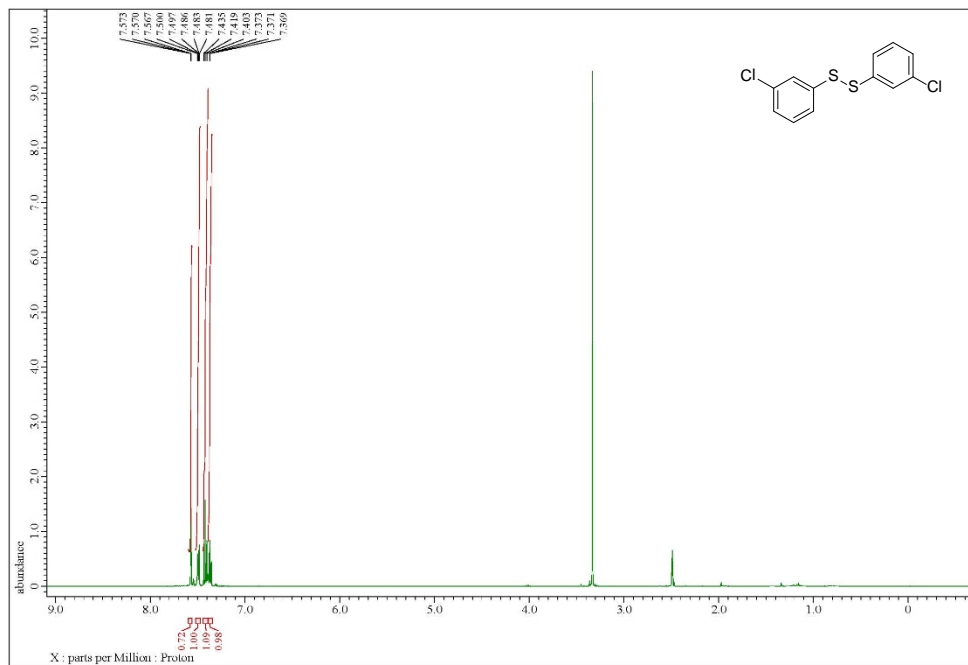


Figure 6. ^{13}C NMR spectrum of 3b

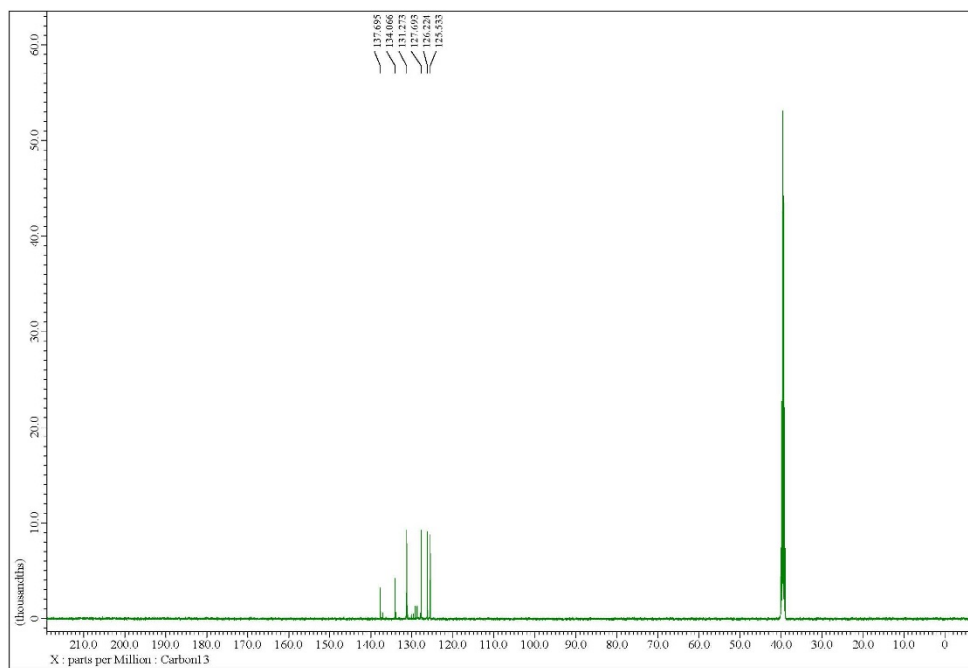


Figure 11. ^1H NMR spectrum of 3e

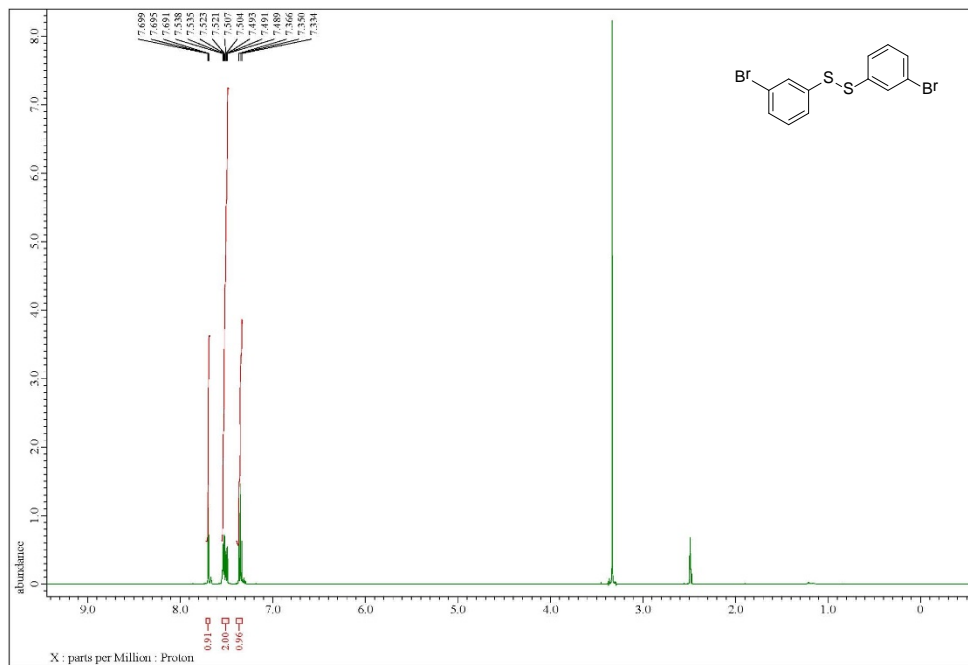


Figure 12. ^{13}C NMR spectrum of 3e

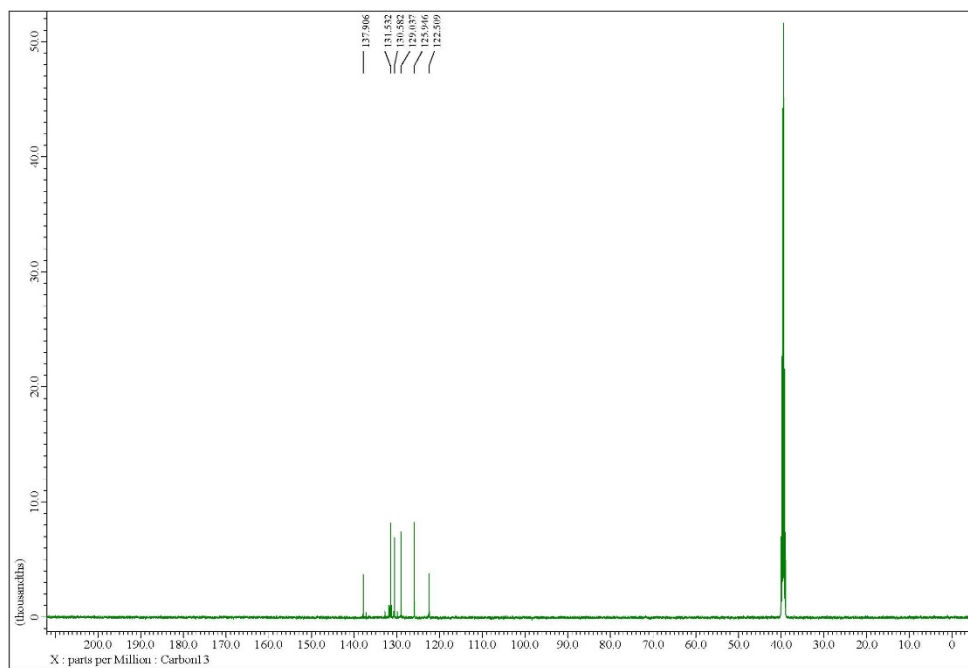


Figure 13. ^1H NMR spectrum of 3f

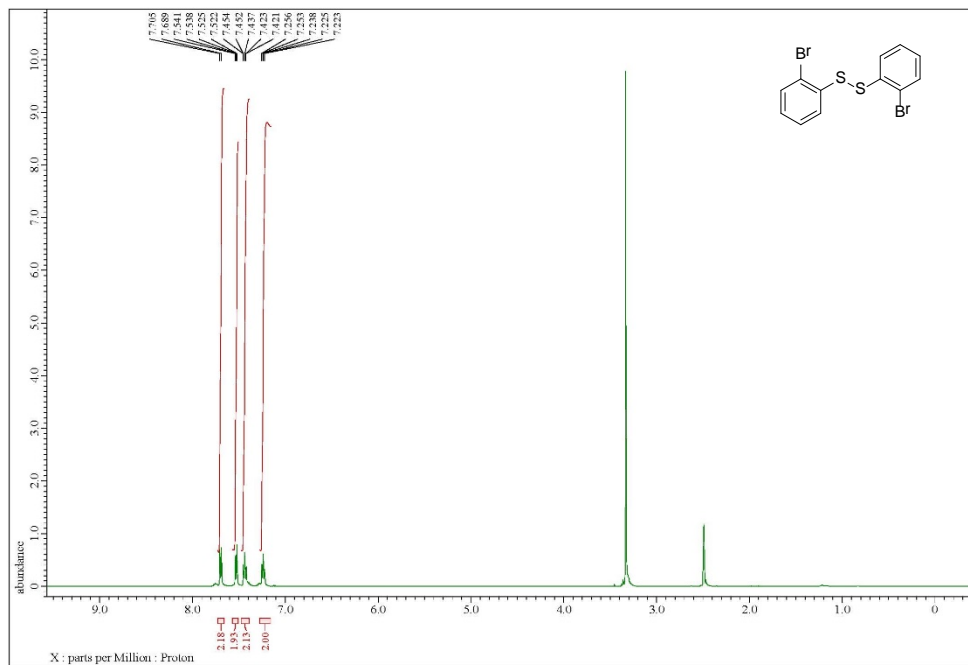


Figure 14. ^{13}C NMR spectrum of 3f

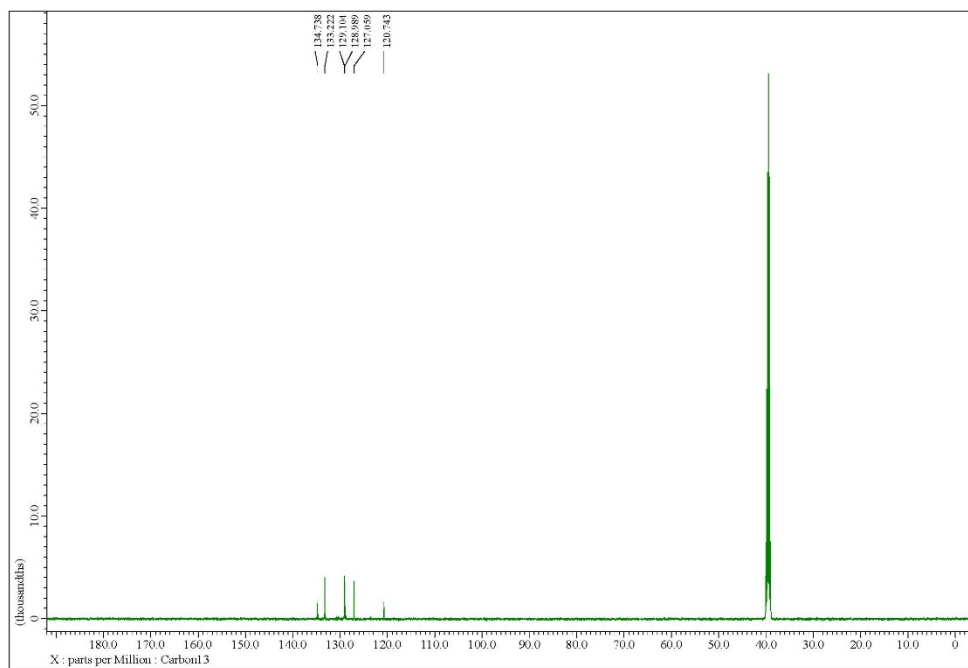


Figure 17. ^1H NMR spectrum of 3h

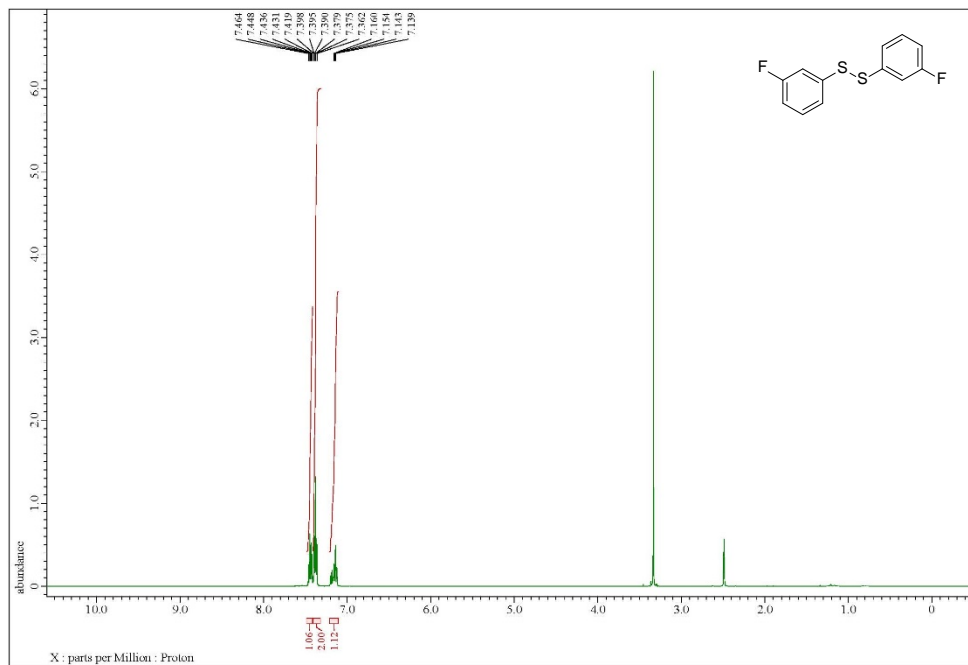


Figure 18. ^{13}C NMR spectrum of 3h

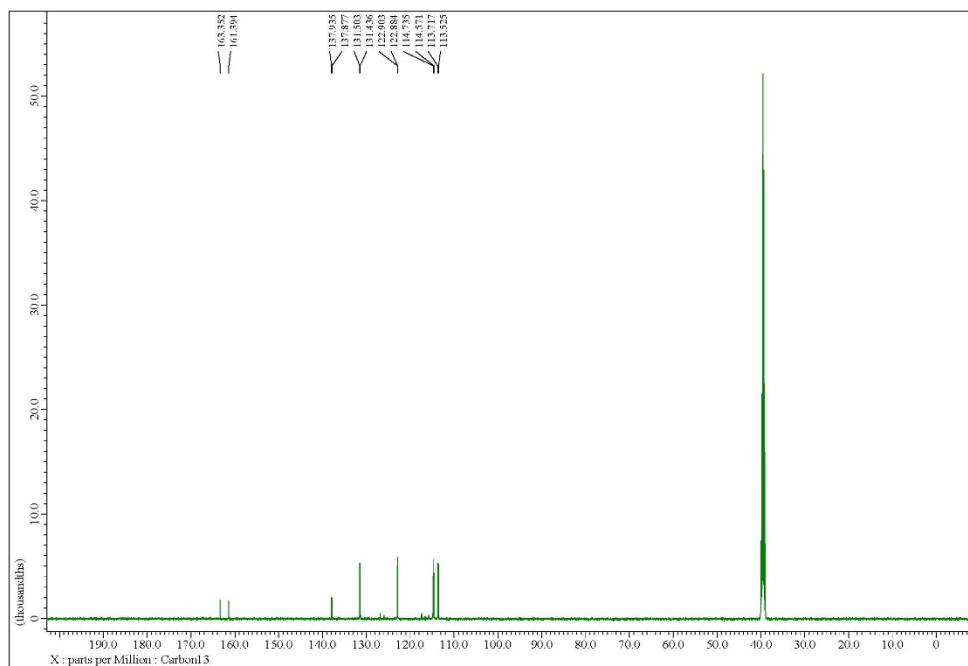


Figure 19. ^1H NMR spectrum of 3i

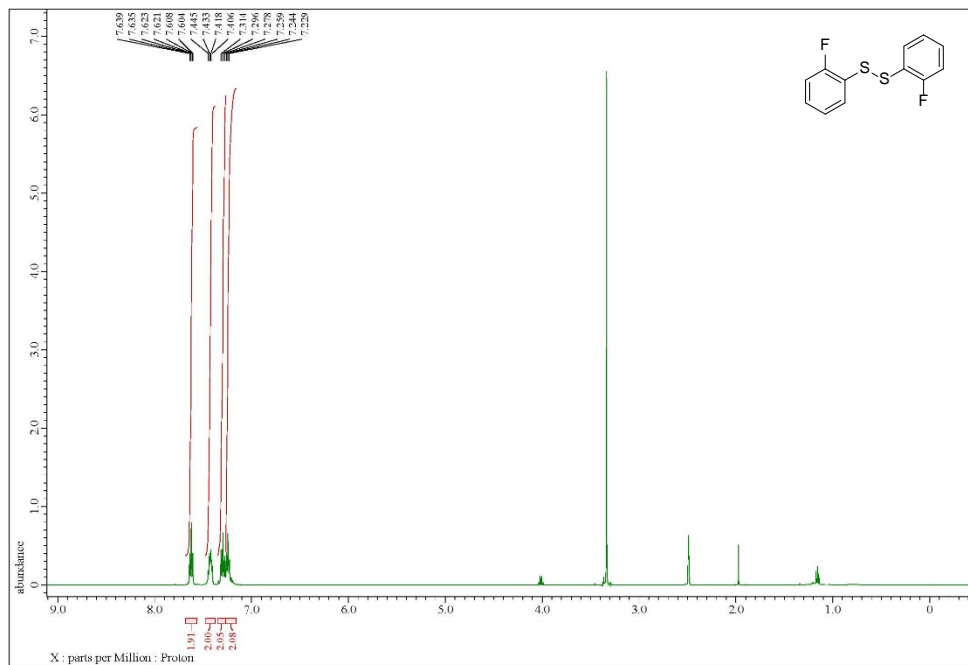


Figure 20. ^{13}C NMR spectrum of 3i

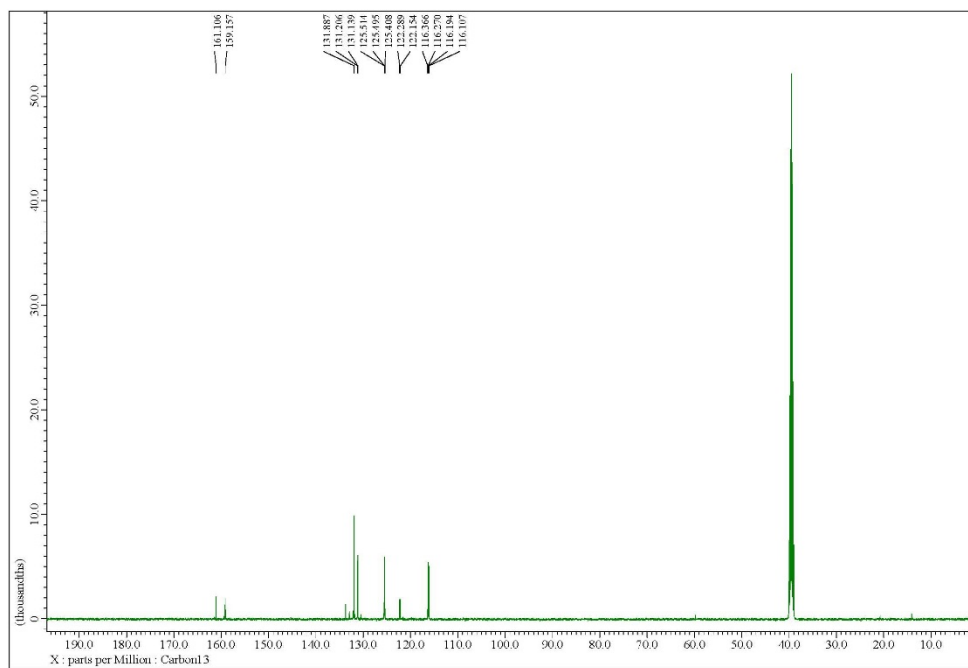


Figure 21. ^1H NMR spectrum of 5a

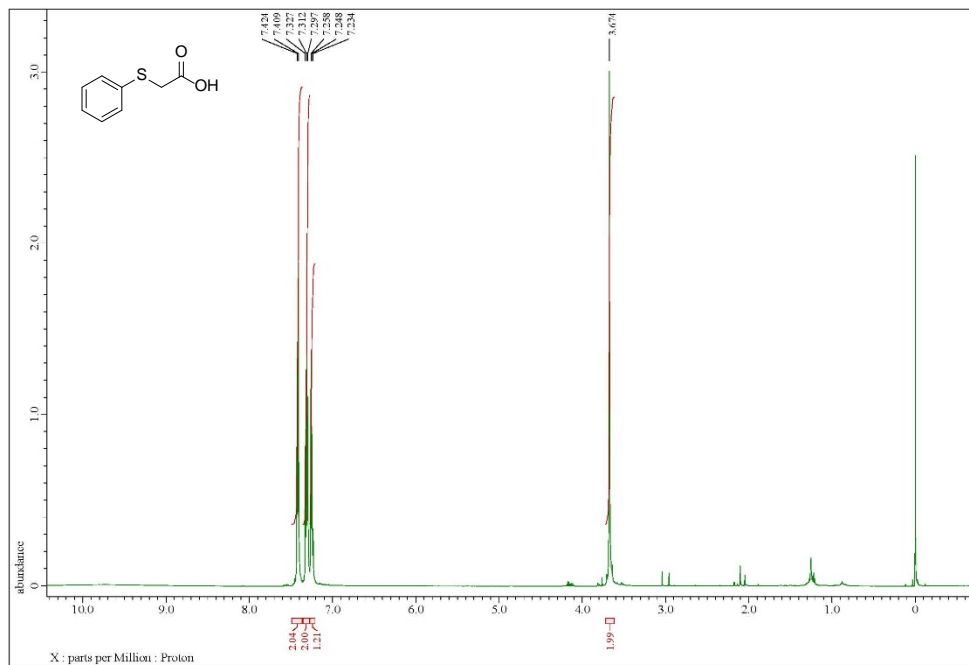


Figure 23. ^1H NMR spectrum of 5b

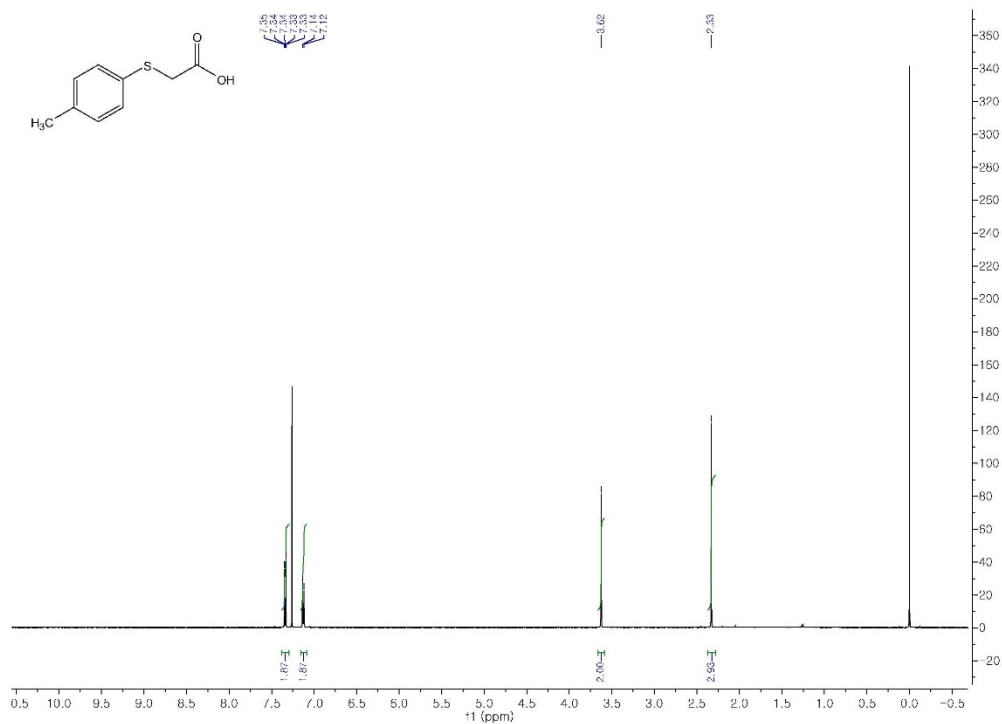


Figure 24. ^{13}C NMR spectrum of 5b

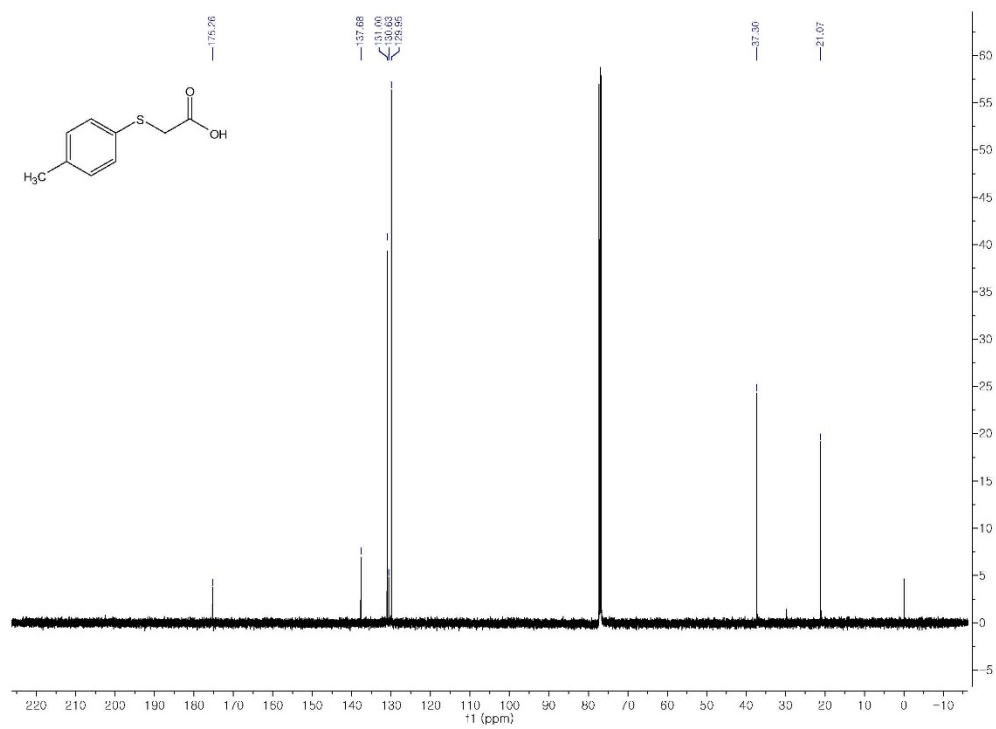


Figure 25. ^1H NMR spectrum of 5c

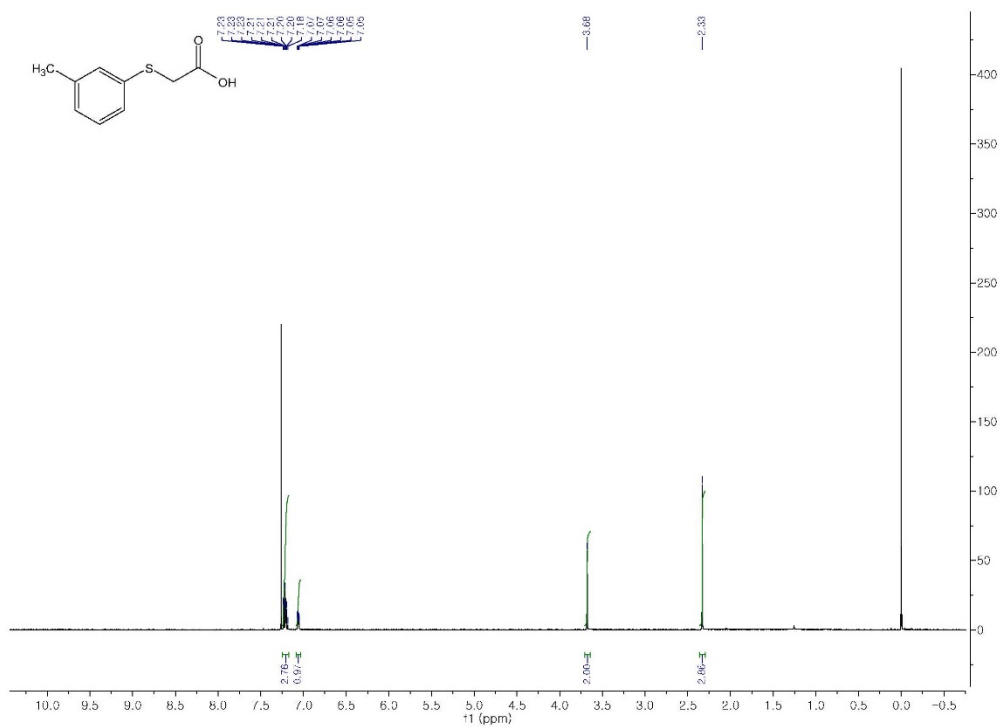


Figure 27. ^1H NMR spectrum of 5d

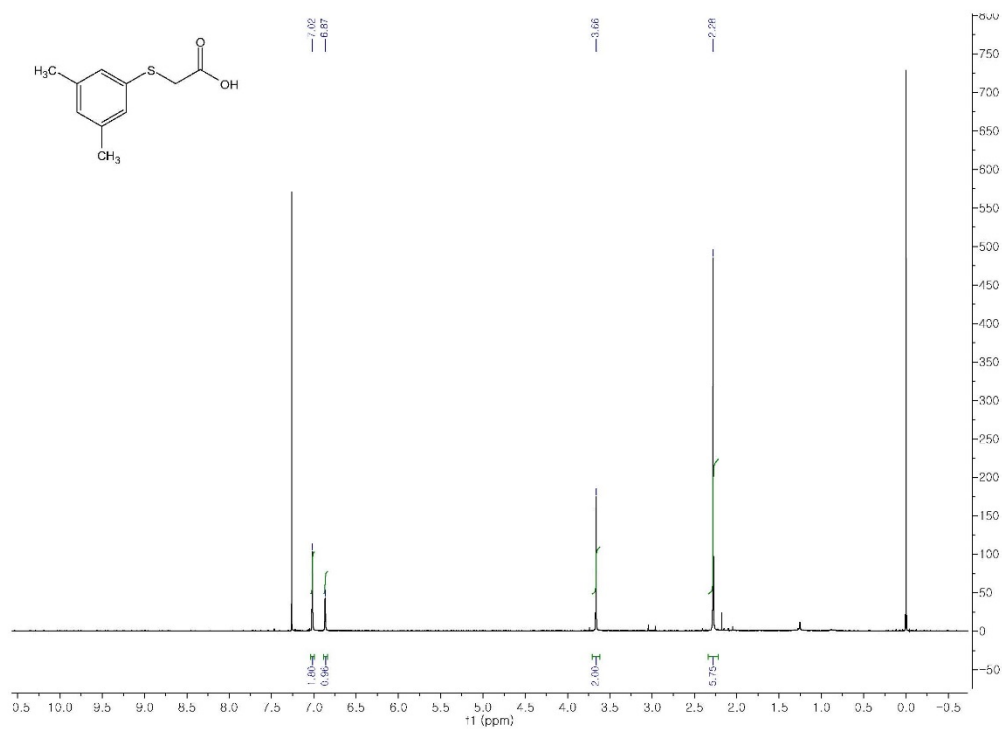


Figure 28. ^{13}C NMR spectrum of 5d

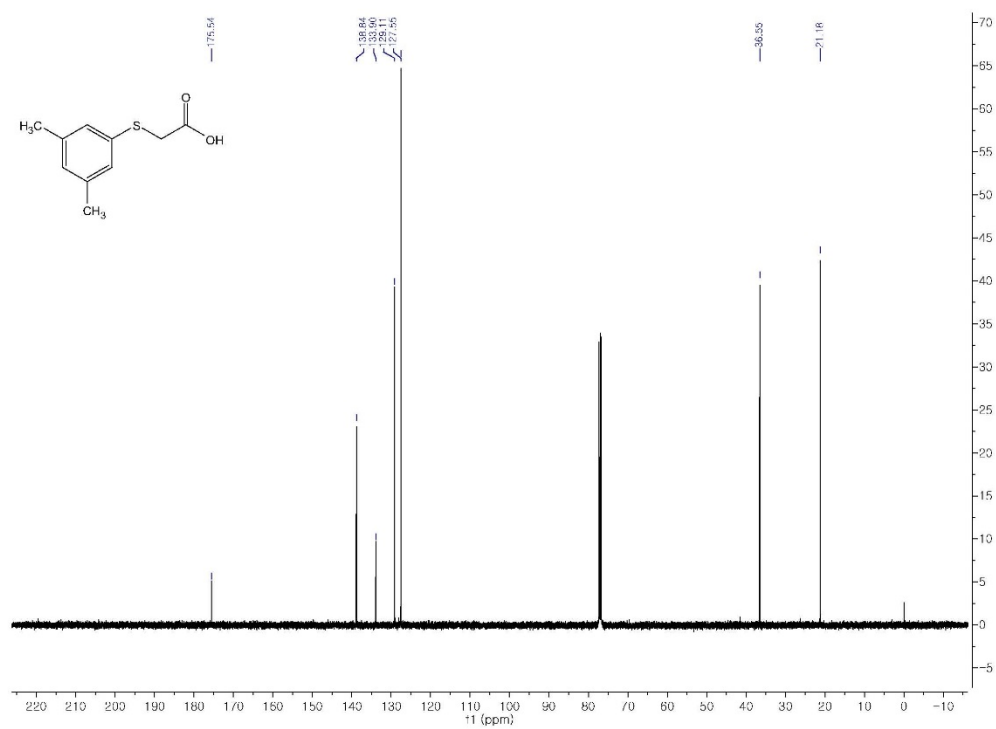


Figure 29. ^1H NMR spectrum of 5e

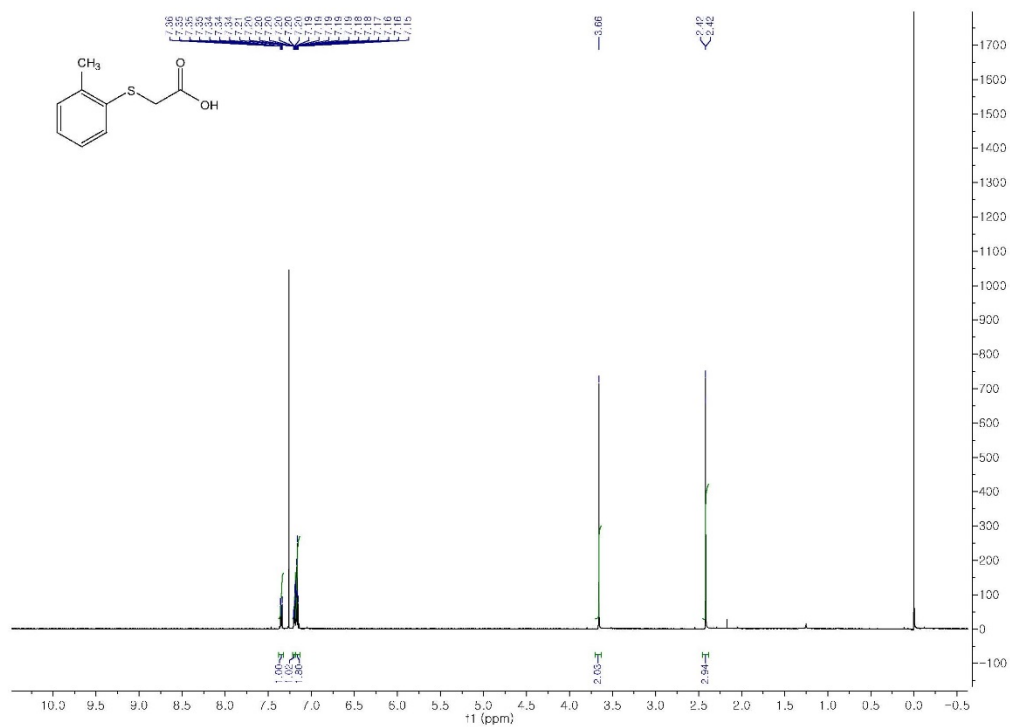


Figure 31. ^1H NMR spectrum of 5f

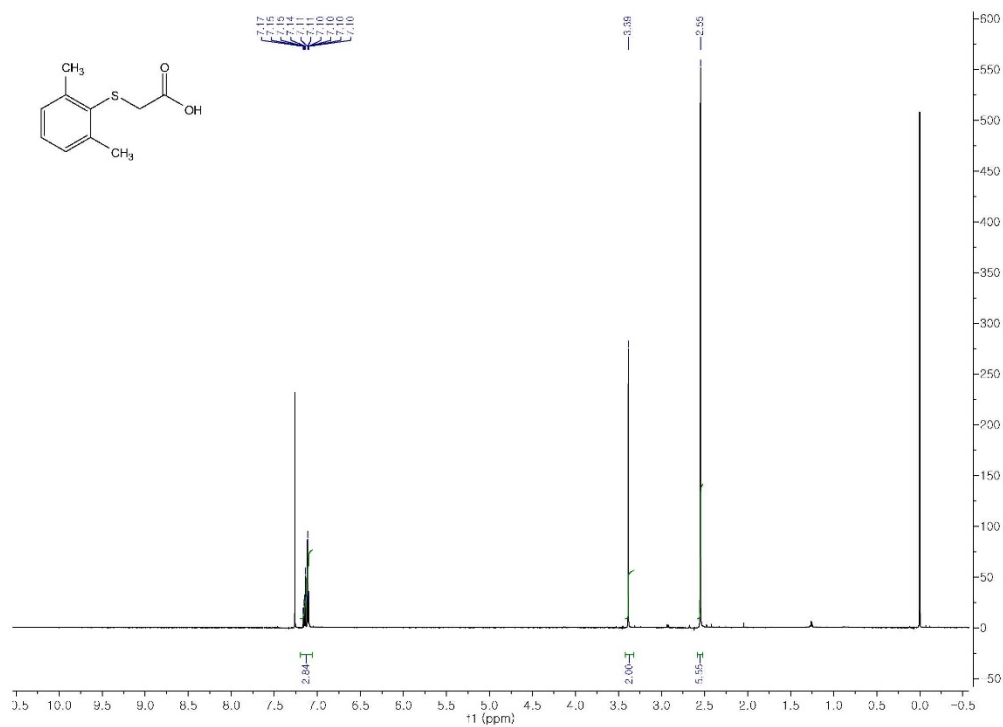


Figure 32. ^{13}C NMR spectrum of 5f

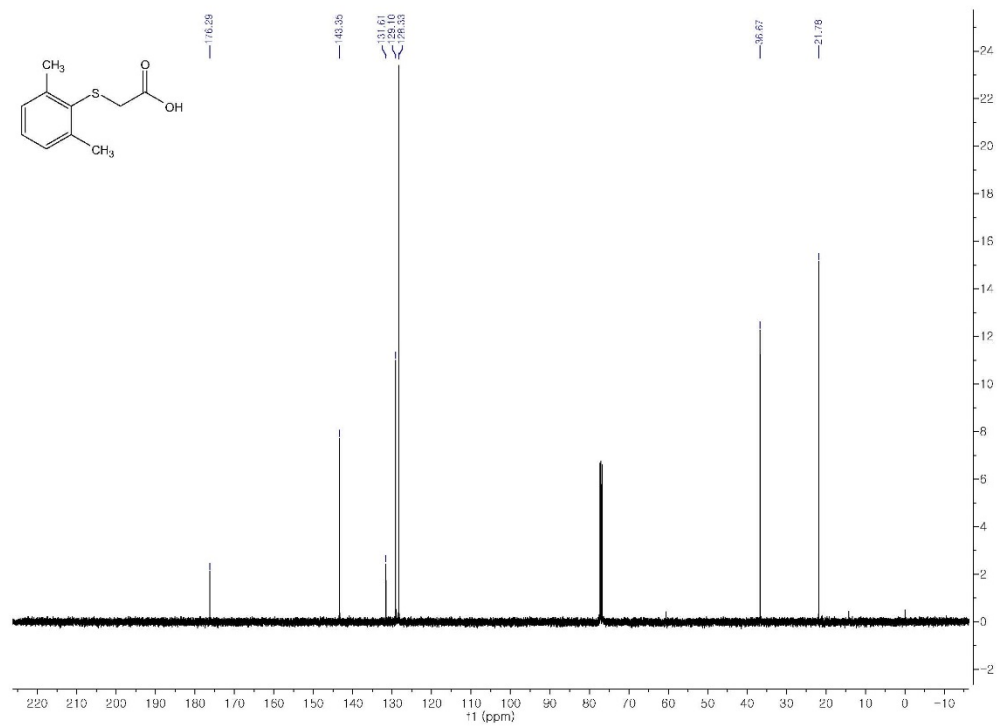


Figure 33. ^1H NMR spectrum of 5g

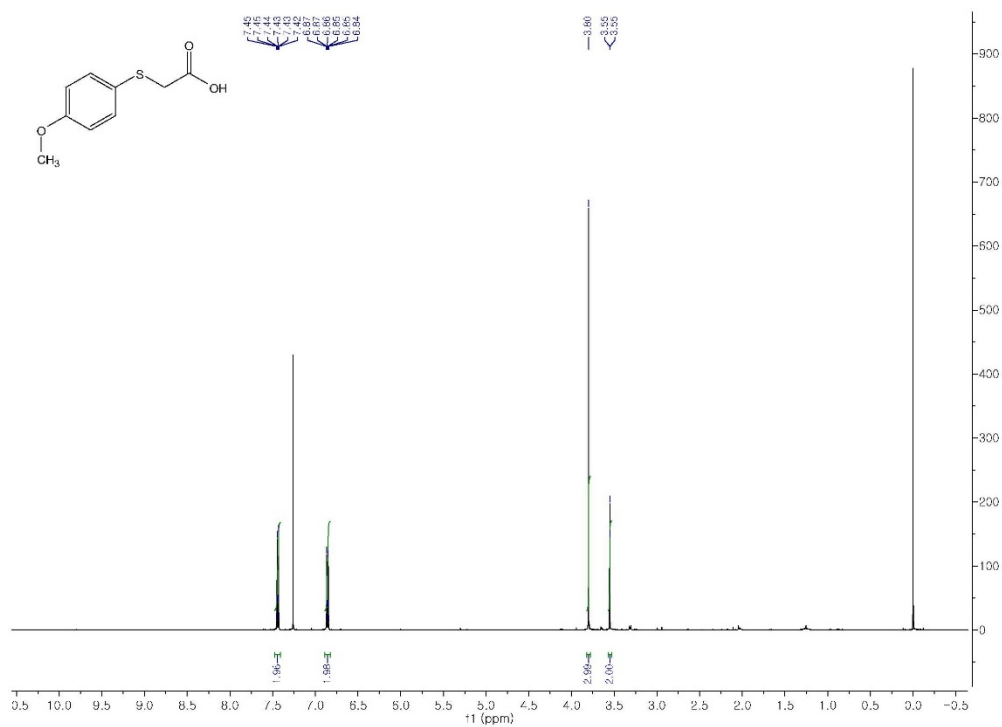


Figure 34. ^{13}C NMR spectrum of 5g

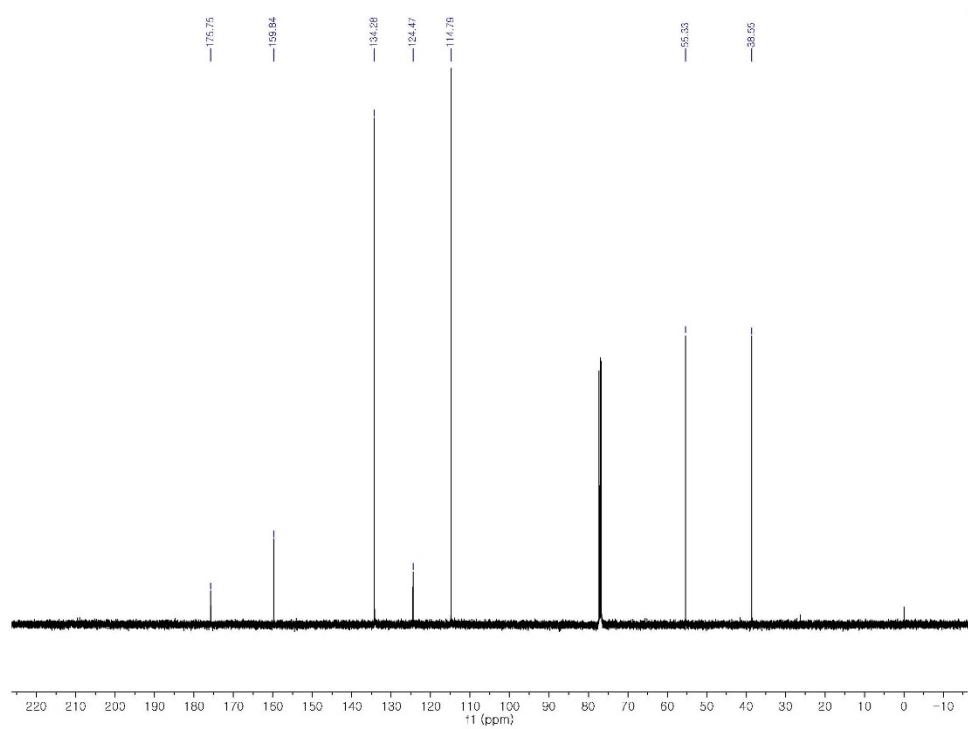


Figure 35. ^1H NMR spectrum of 5h

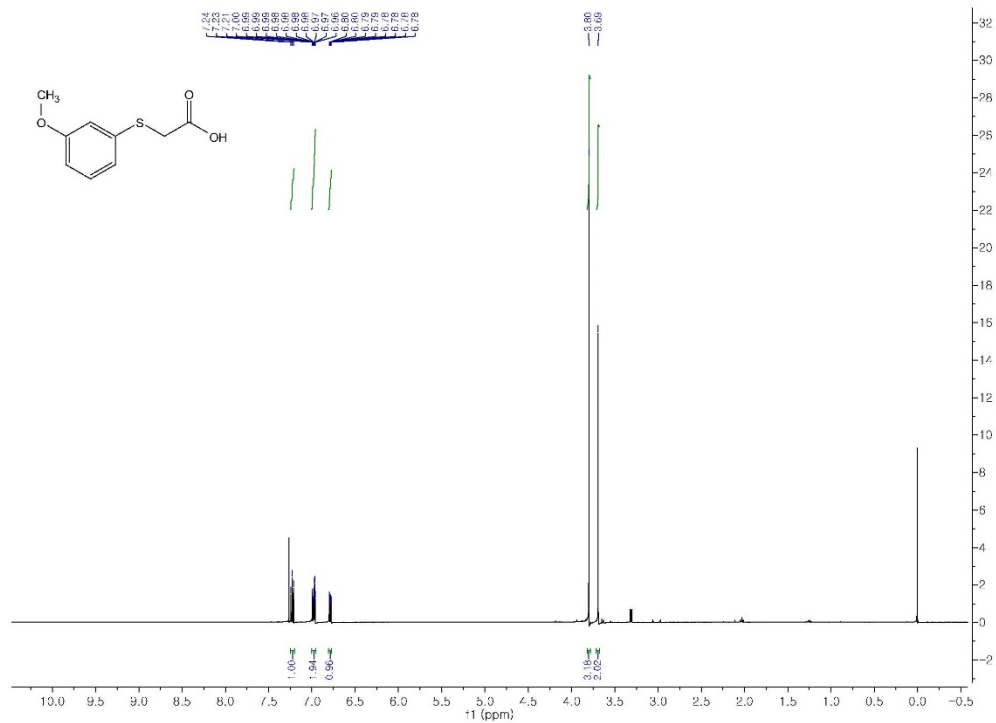


Figure 36. ^{13}C NMR spectrum of 5h

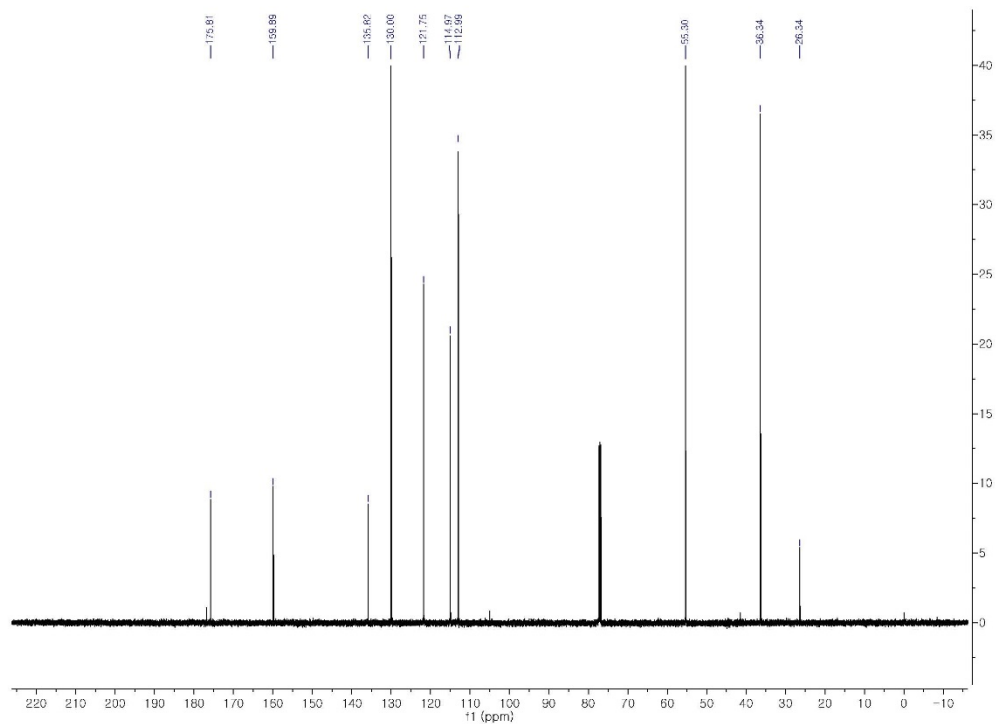


Figure 37. ^1H NMR spectrum of 5i

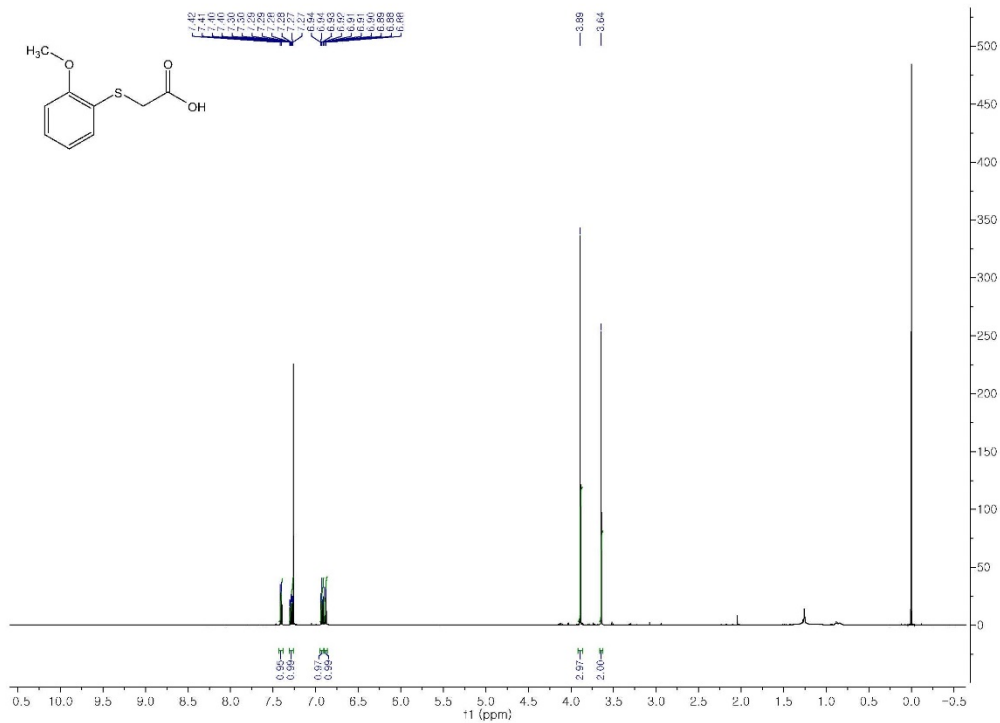


Figure 38. ^{13}C NMR spectrum of 5i

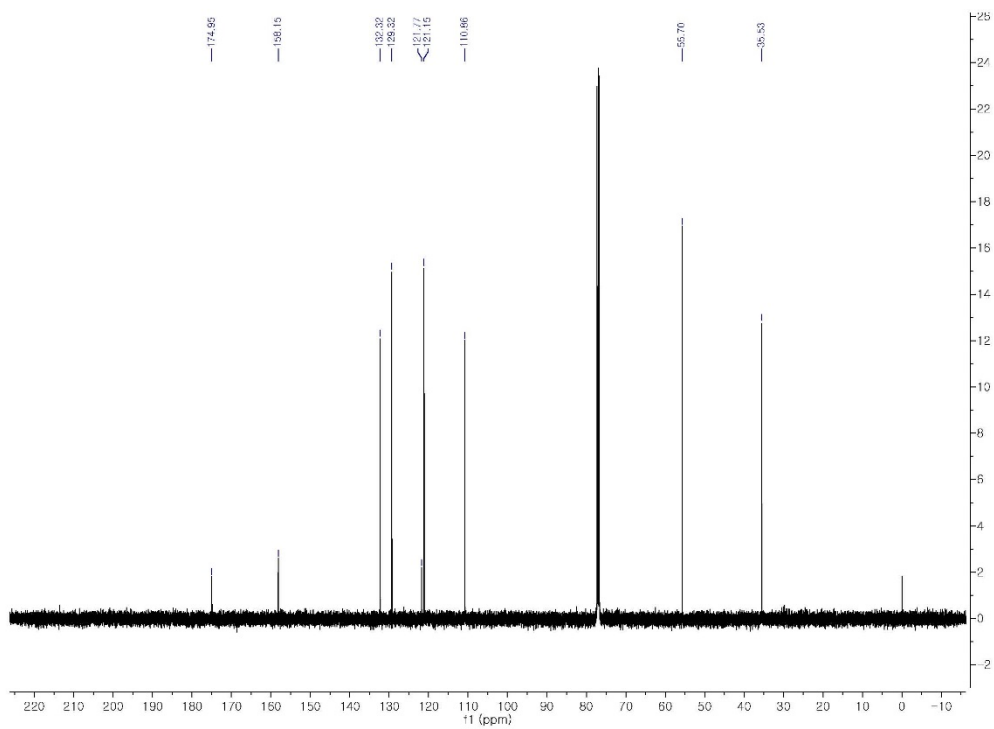


Figure 39. ^1H NMR spectrum of 5j

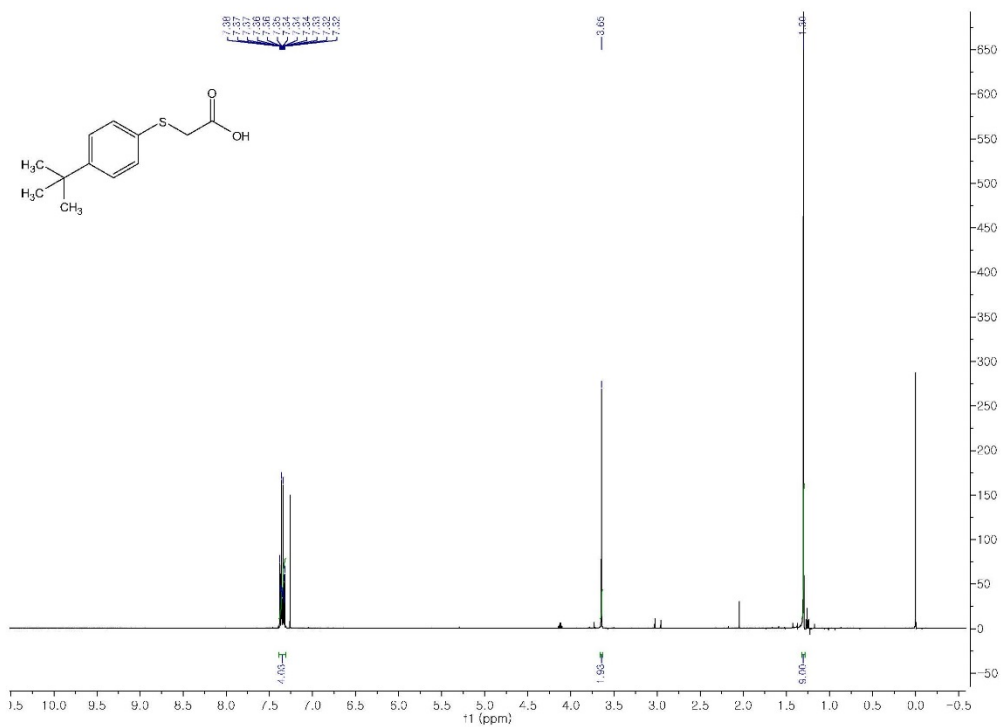


Figure 40. ^{13}C NMR spectrum of 5j

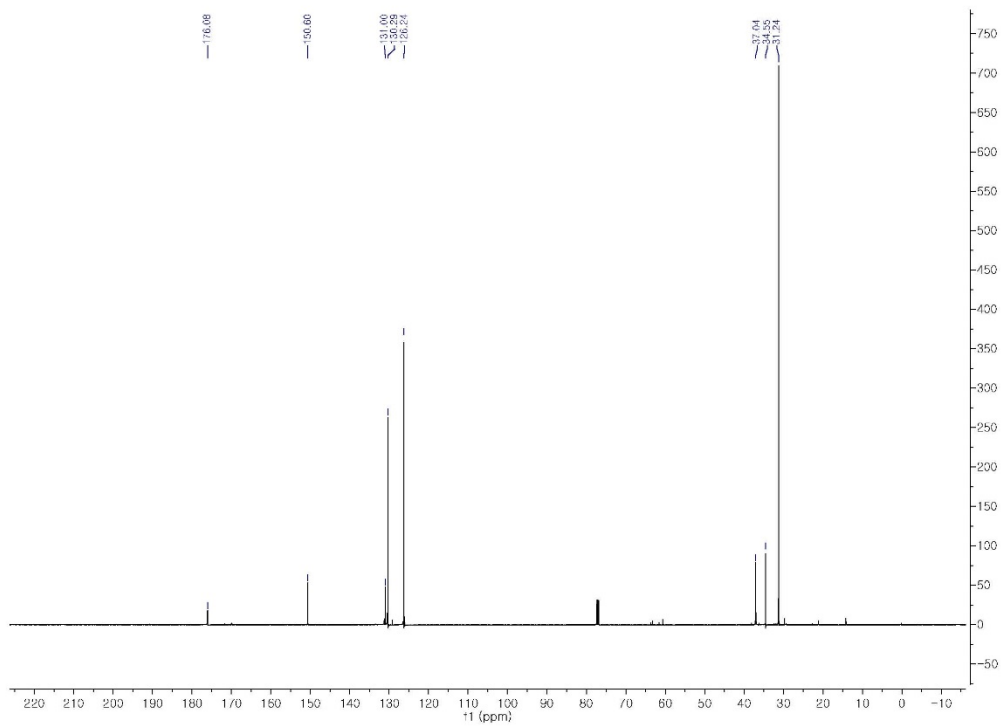


Figure 41. ^1H NMR spectrum of 5k

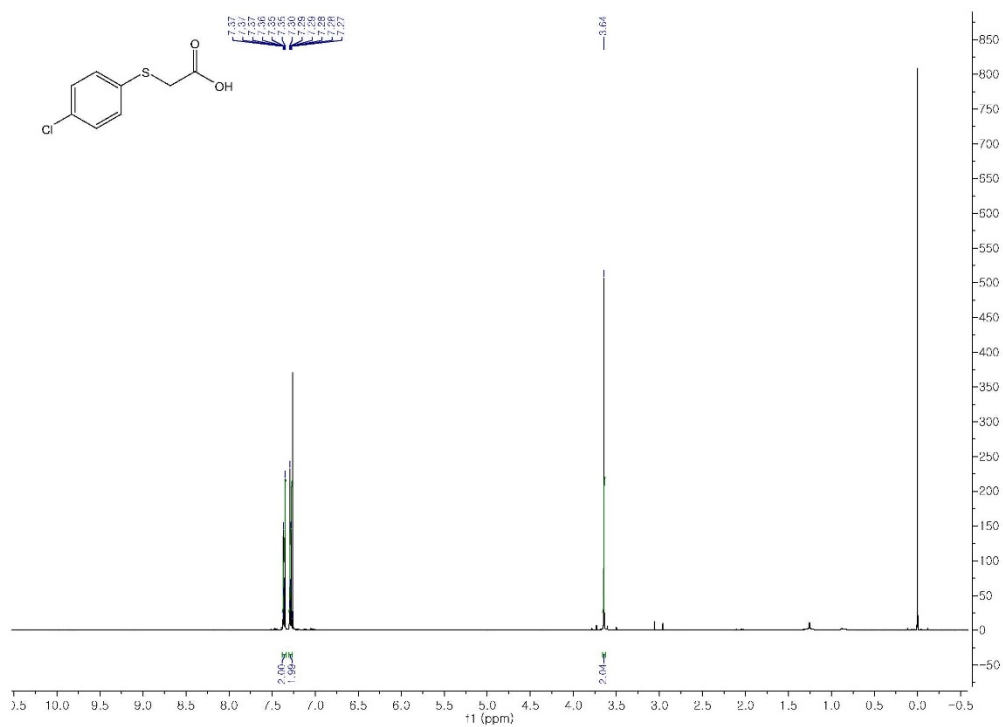


Figure 42. ^{13}C NMR spectrum of 5k

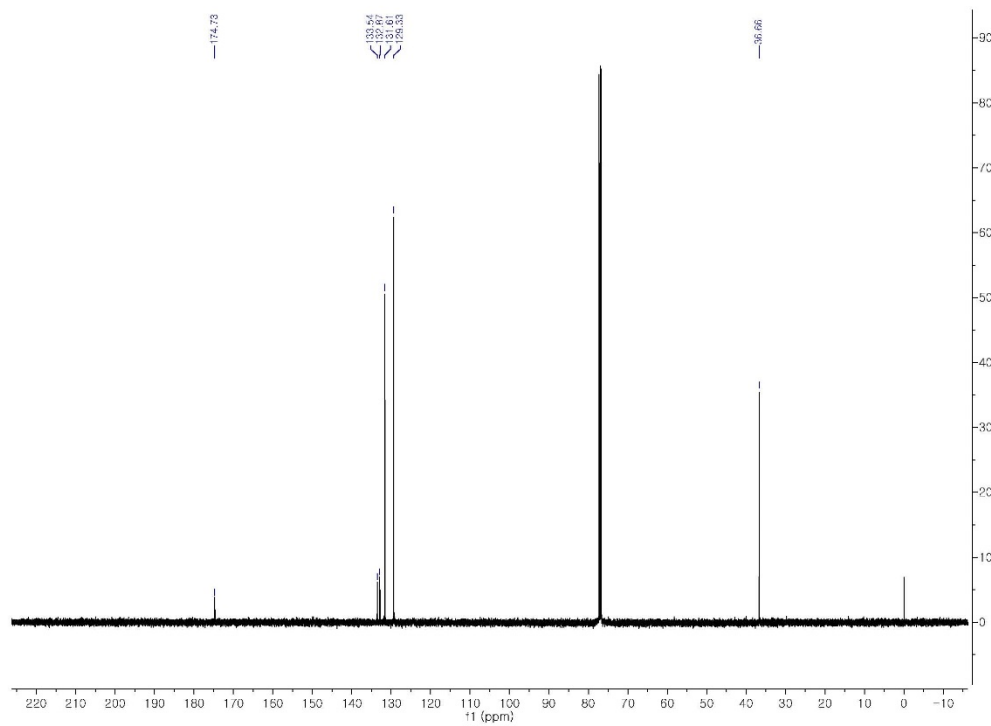


Figure 45. ^1H NMR spectrum of 5m

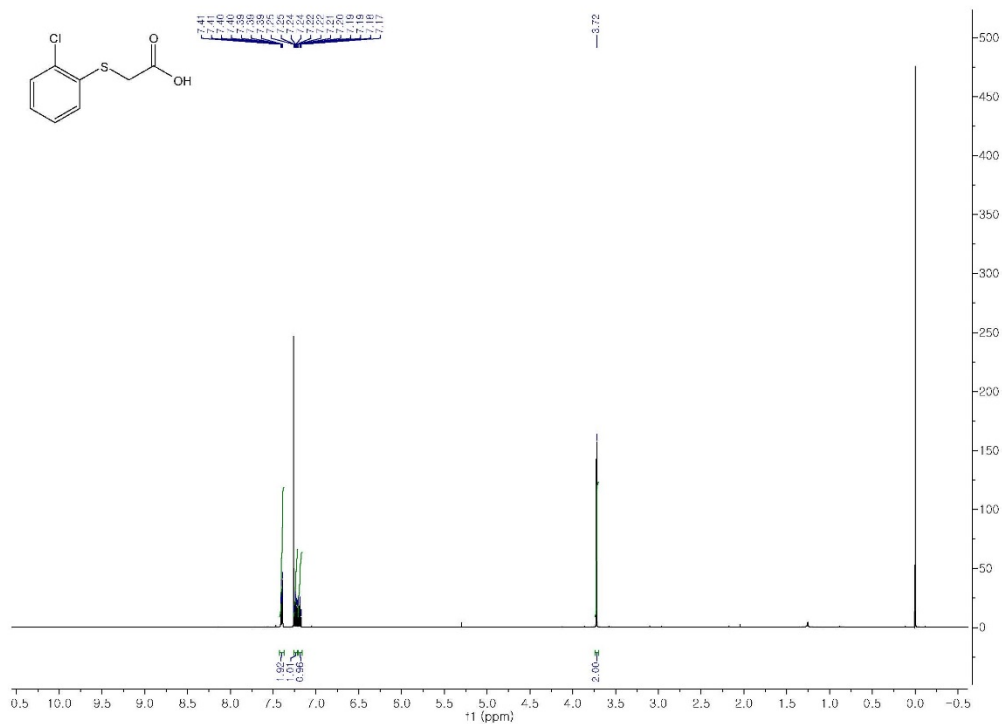


Figure 46. ^{13}C NMR spectrum of 5m

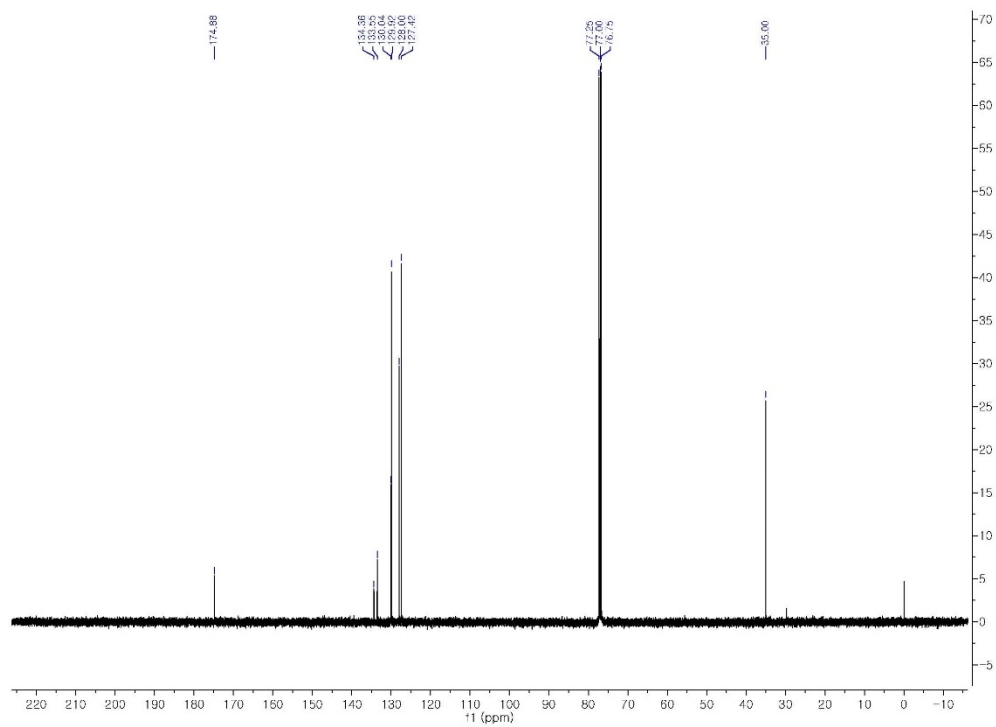


Figure 47. ^1H NMR spectrum of 5n

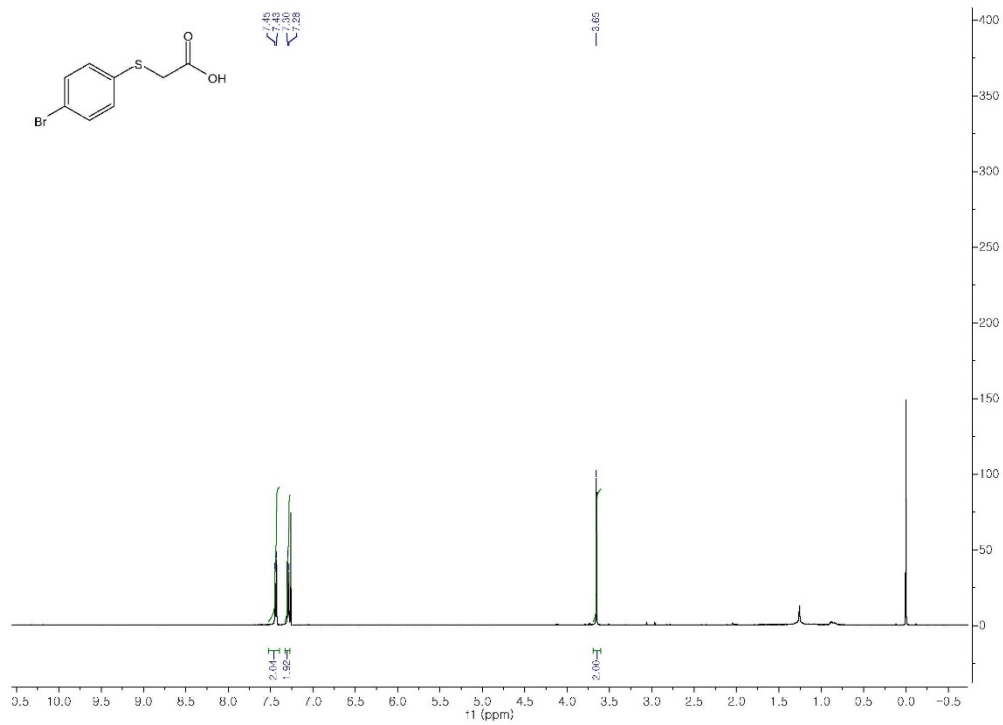


Figure 48. ^{13}C NMR spectrum of 5n

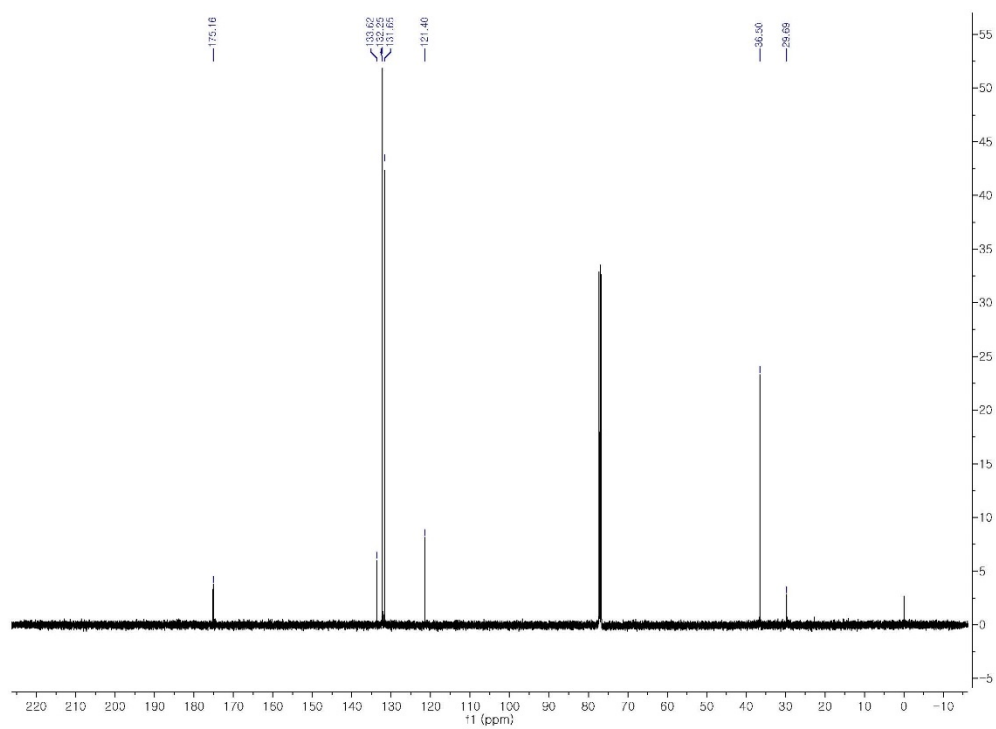


Figure 49. ^1H NMR spectrum of 5o

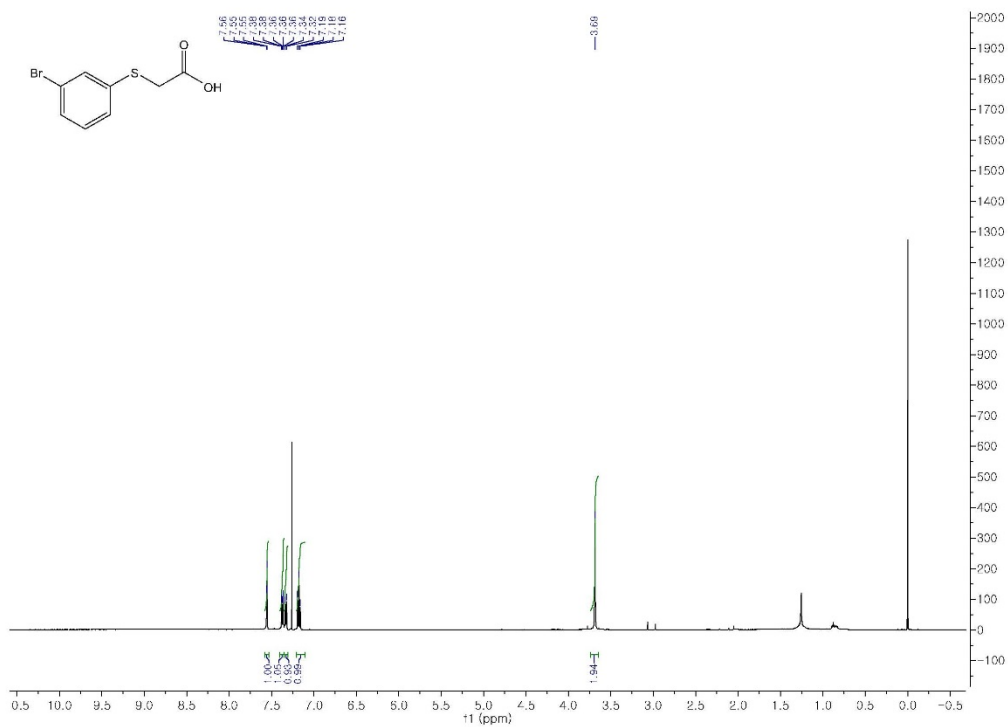


Figure 50. ^{13}C NMR spectrum of 5o

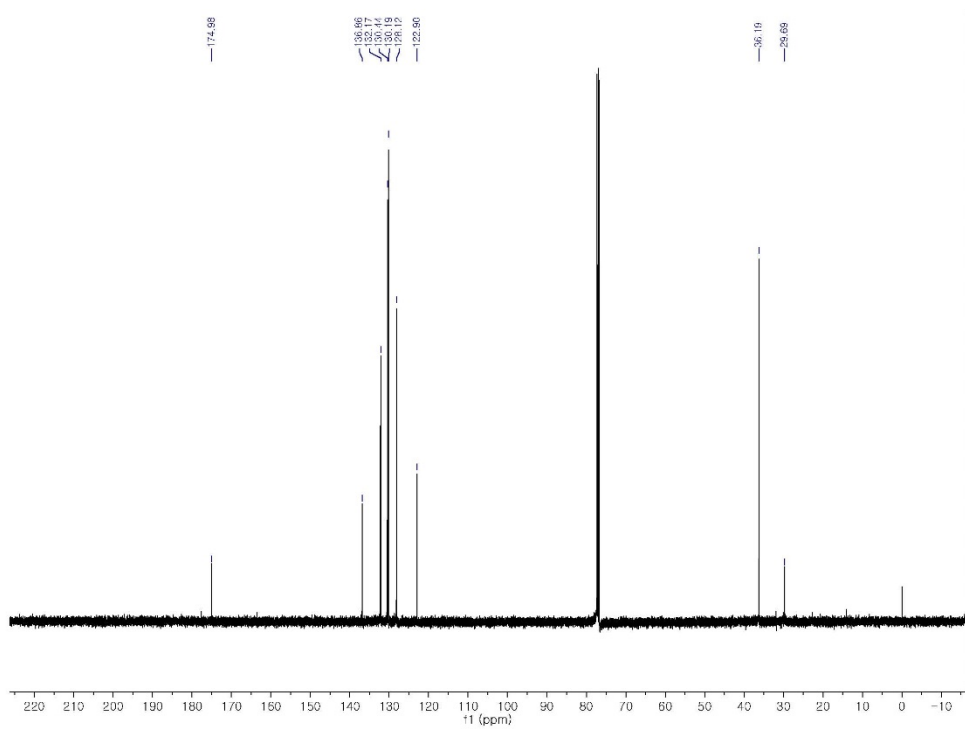


Figure 51. ^1H NMR spectrum of 5p

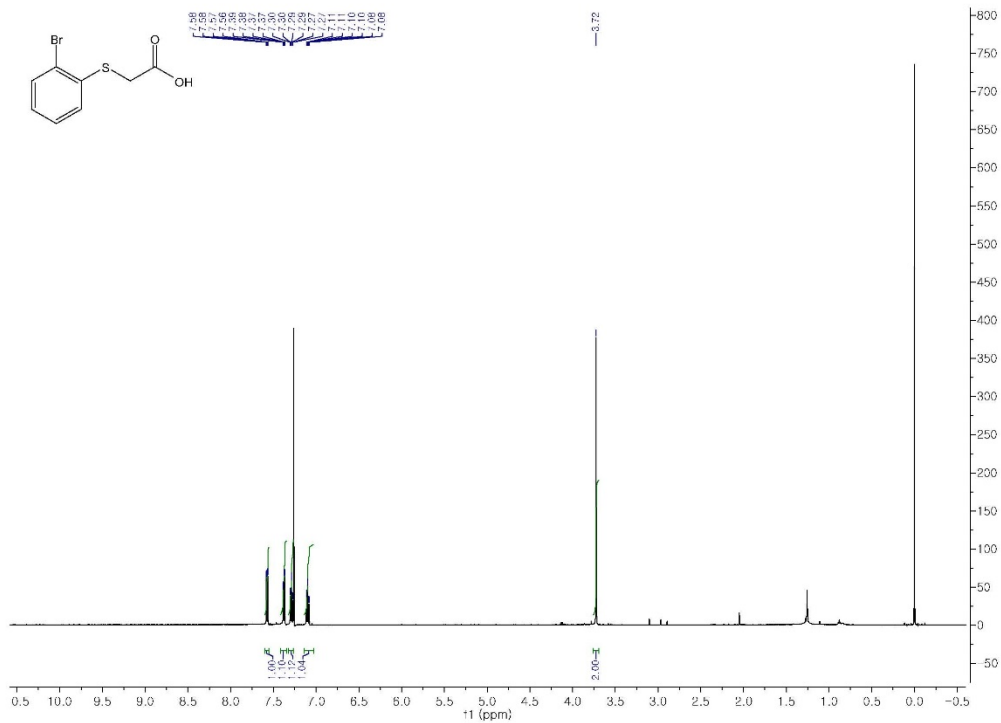


Figure 52. ^{13}C NMR spectrum of 5p

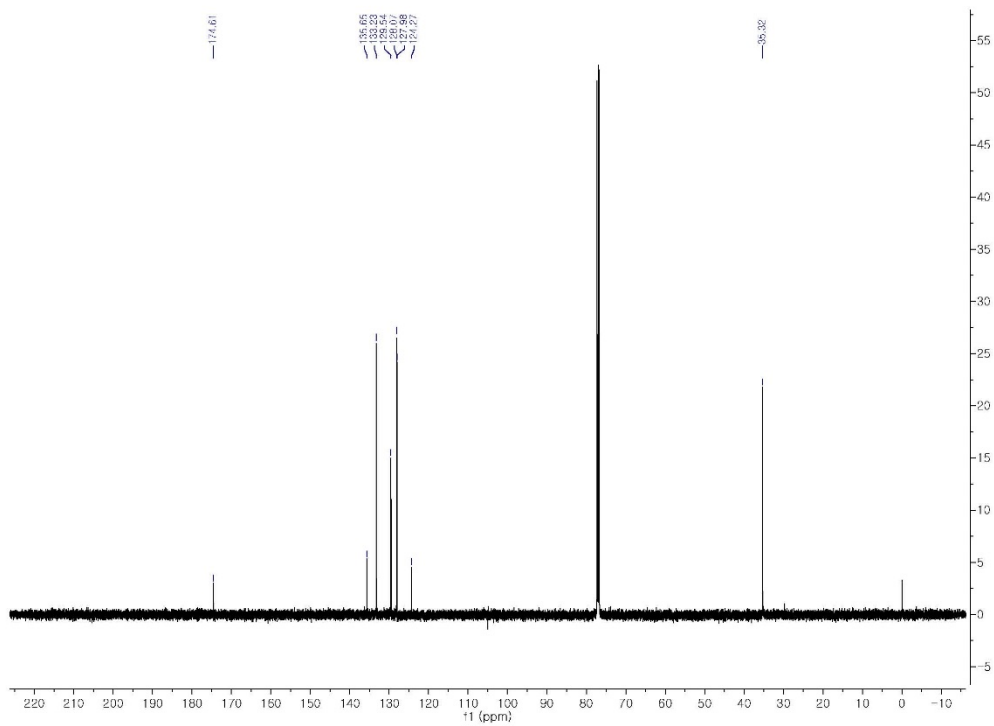


Figure 53. ^1H NMR spectrum of 5q

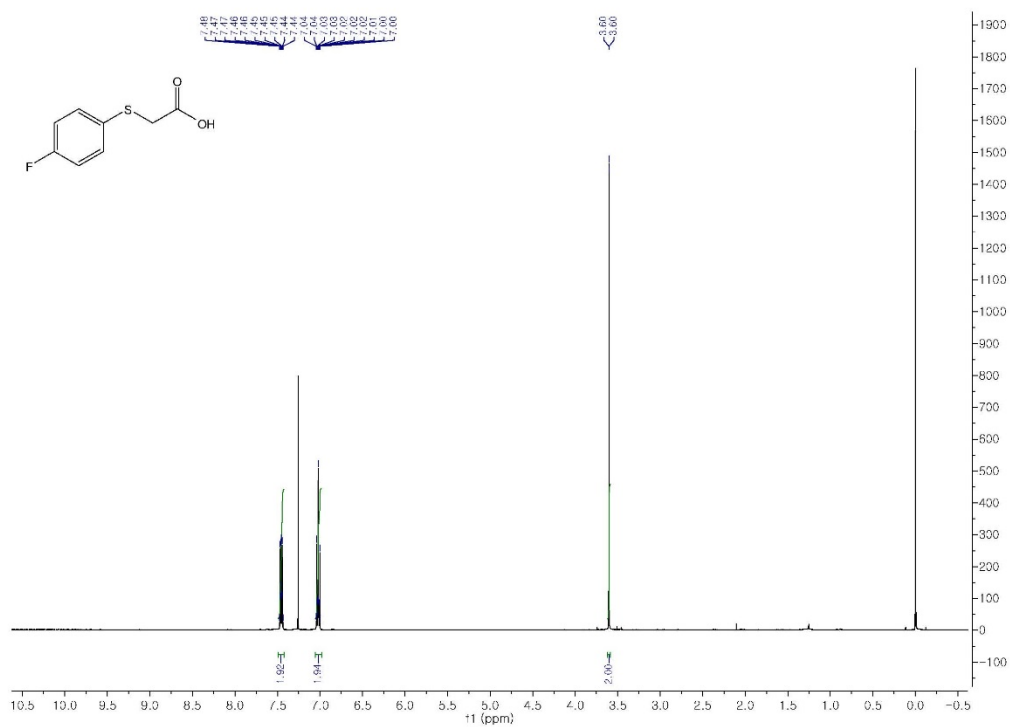


Figure 54. ^{13}C NMR spectrum of 5q

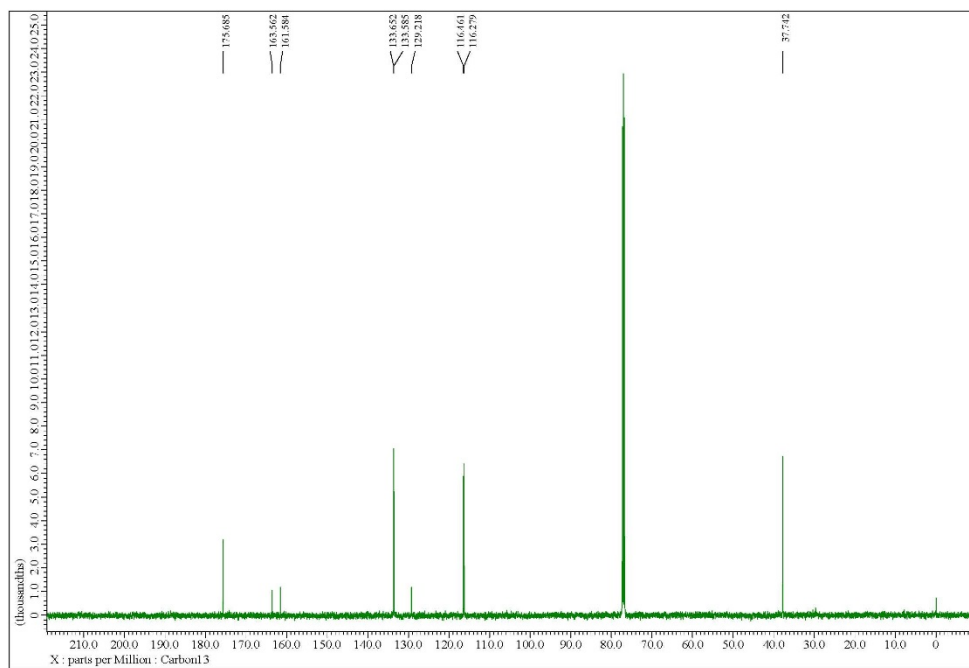


Figure 55. ^1H NMR spectrum of 5r

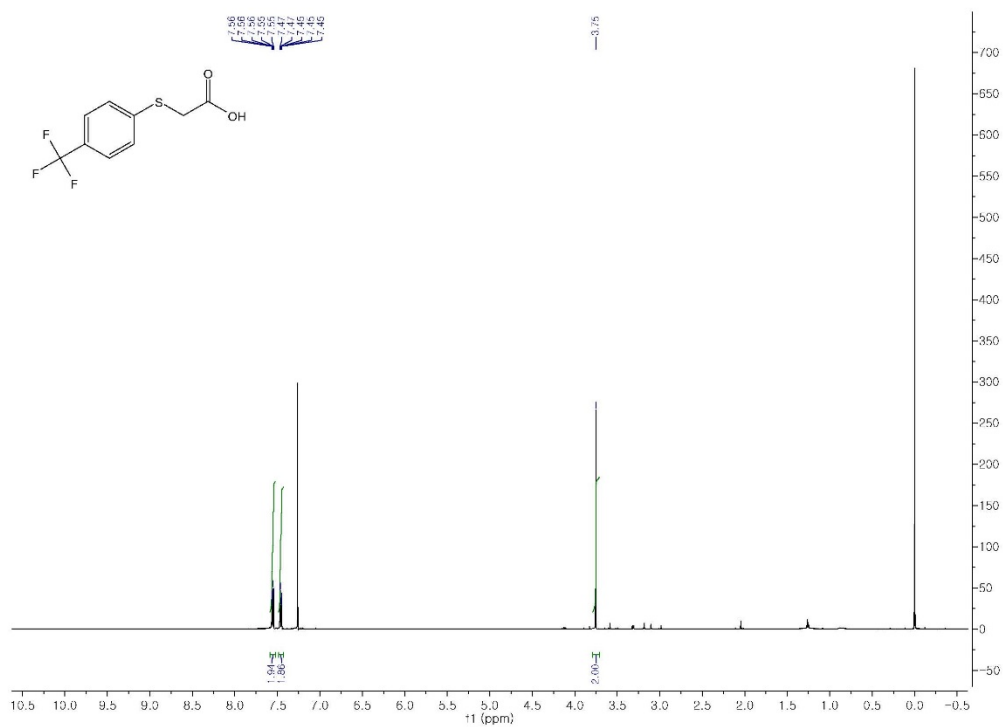


Figure 56. ^{13}C NMR spectrum of 5r

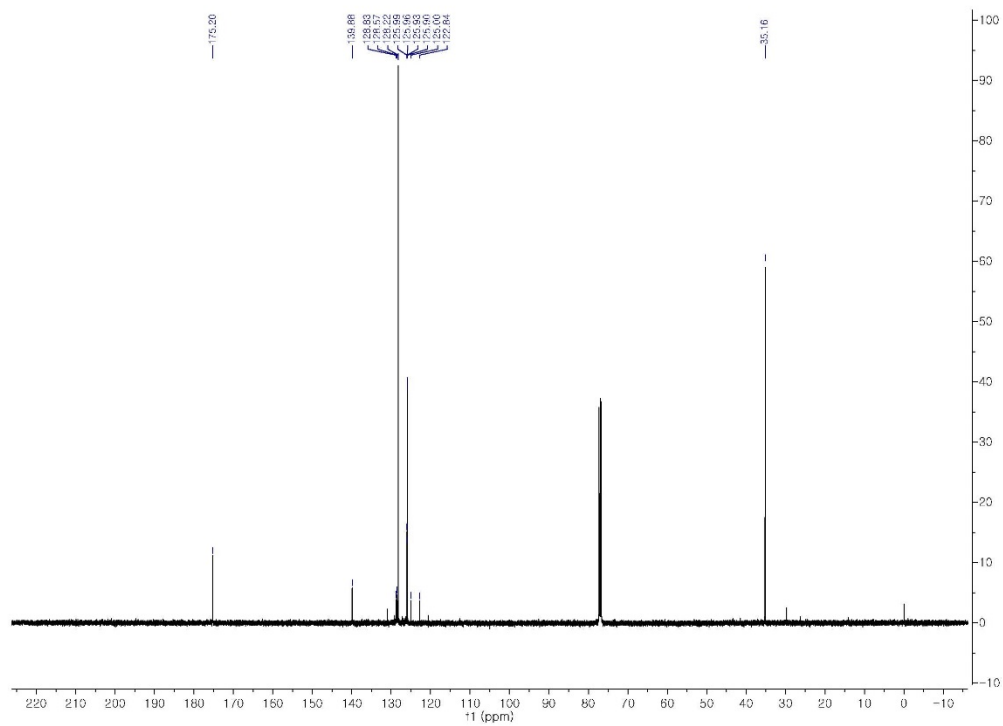


Figure 57. ^1H NMR spectrum of 5s

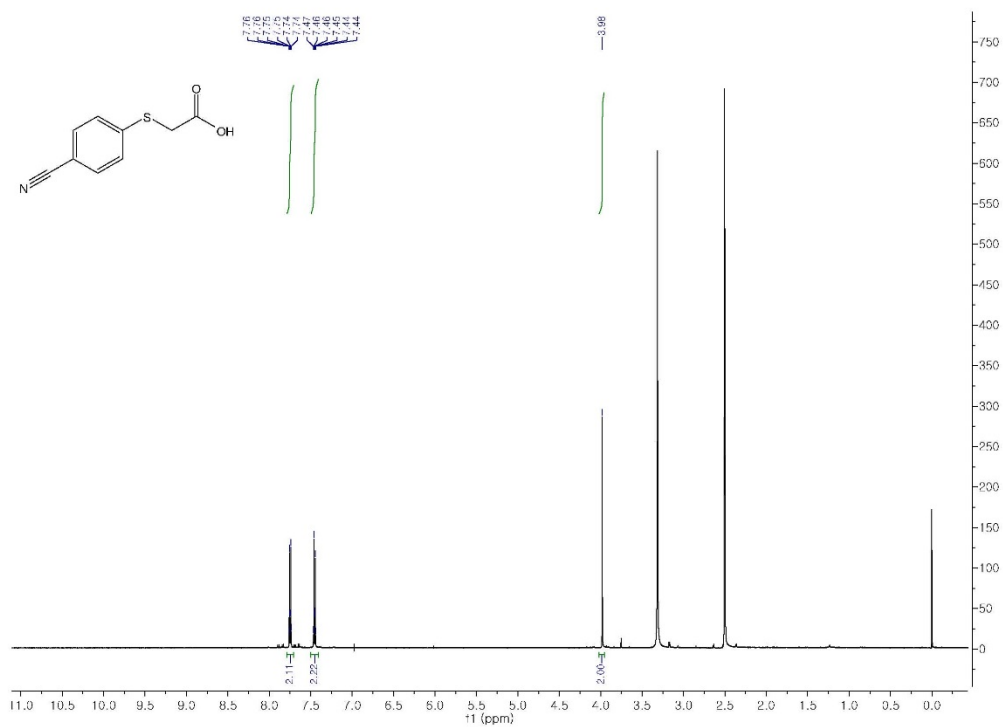


Figure 58. ^{13}C NMR spectrum of 5s

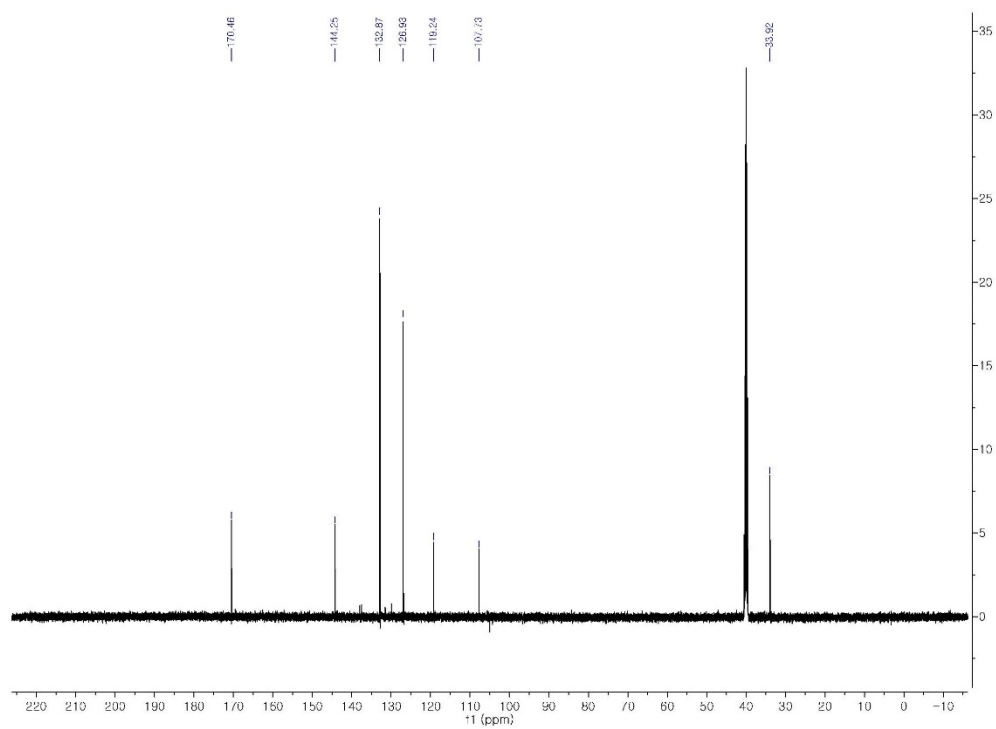


Figure 59. ^1H NMR spectrum of 5t

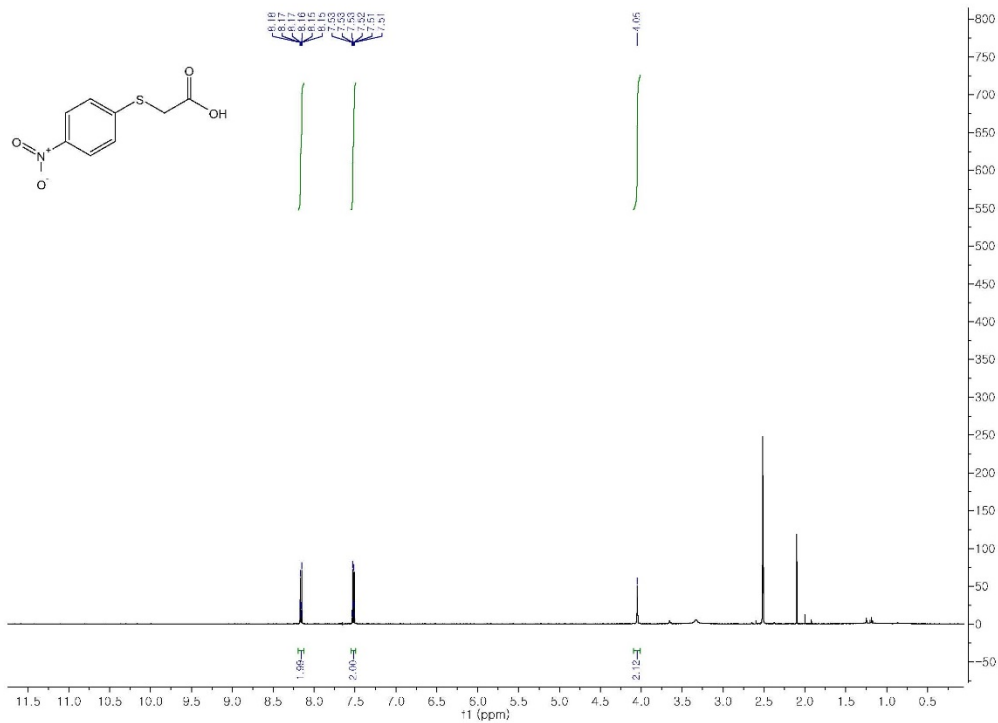


Figure 60. ^{13}C NMR spectrum of 5t

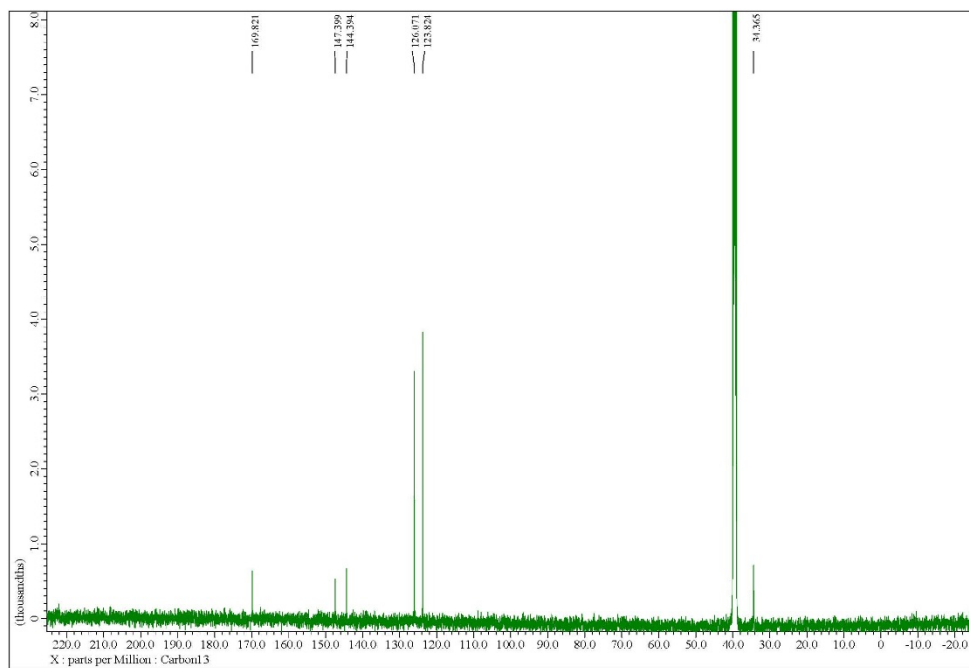


Figure 63. ^1H NMR spectrum of 5v

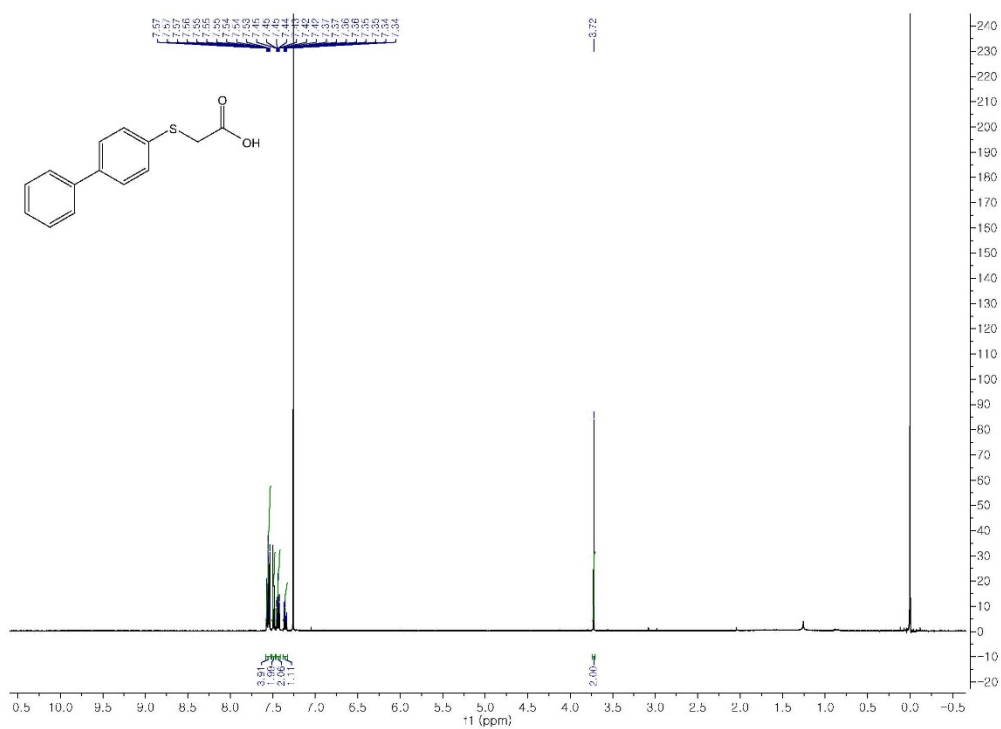


Figure 65. ^1H NMR spectrum of 6a

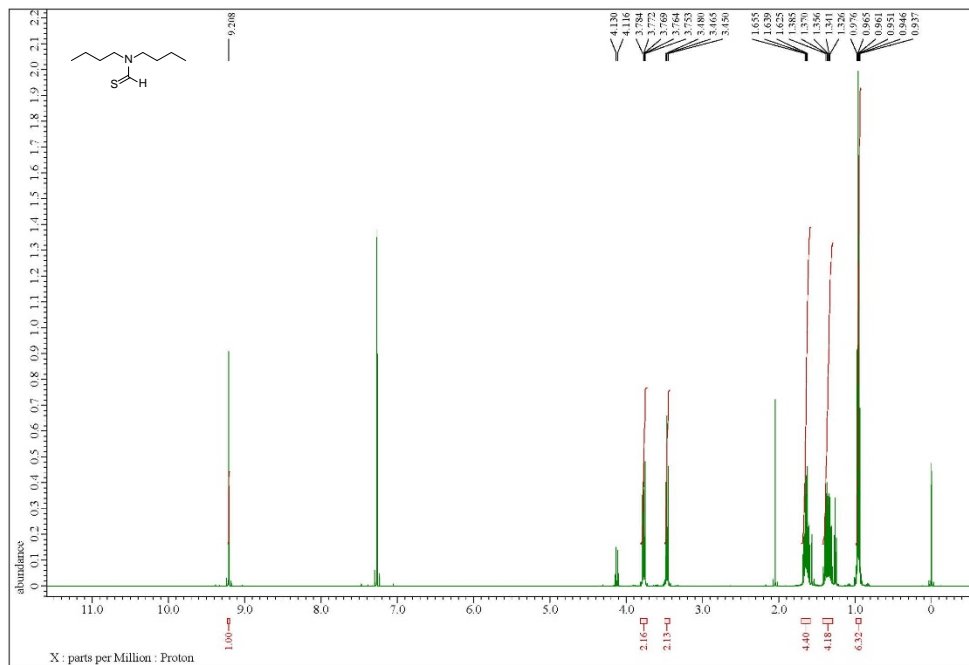


Figure 66. ^{13}C NMR spectrum of 6a

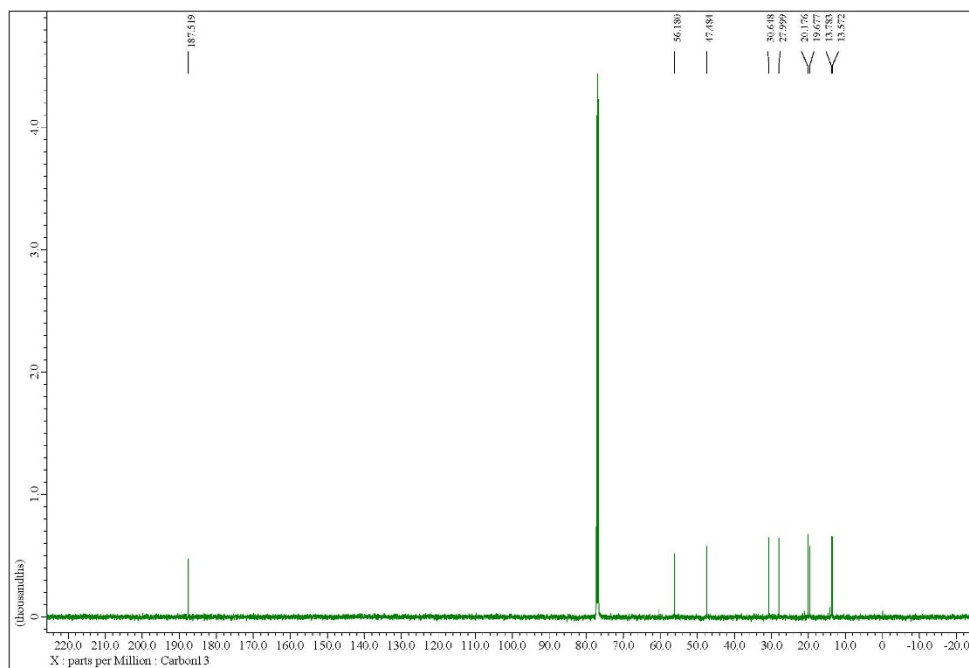


Figure 67. ^1H NMR spectrum of 6b

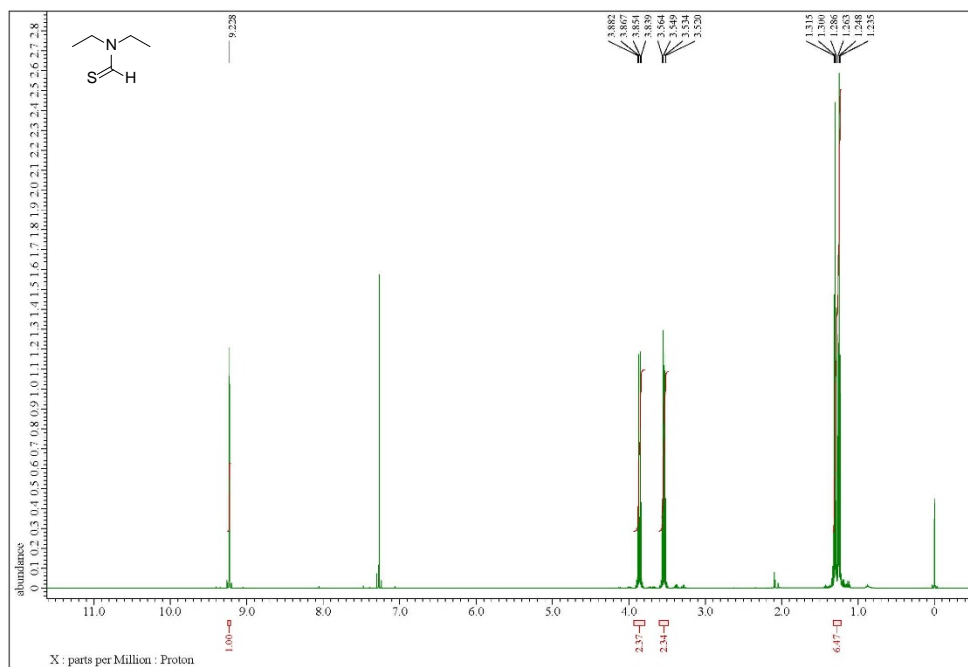


Figure 68. ^{13}C NMR spectrum of 6b

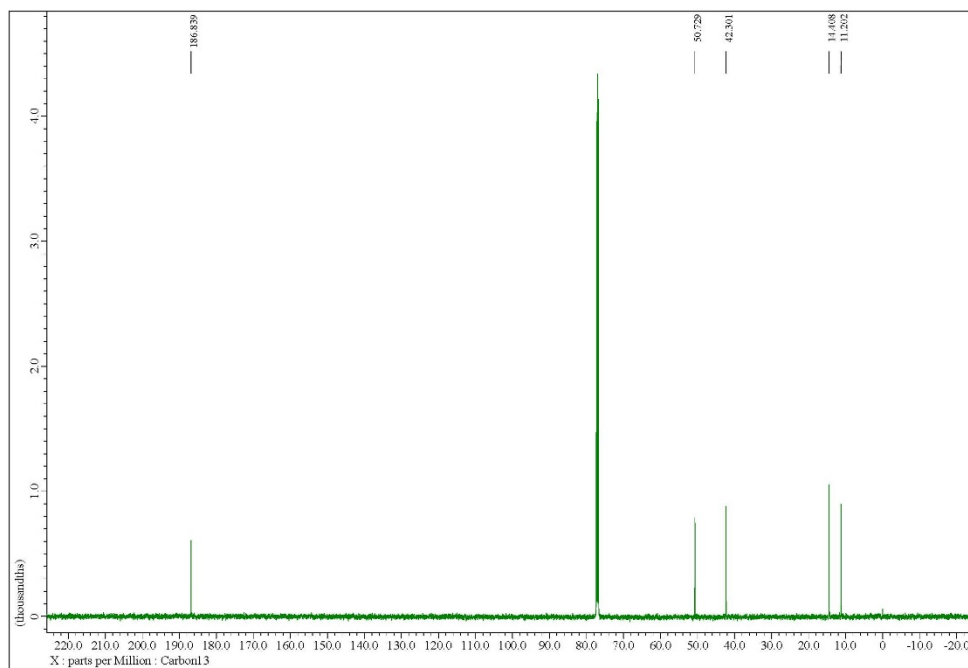


Figure 69. ^1H NMR spectrum of 6c

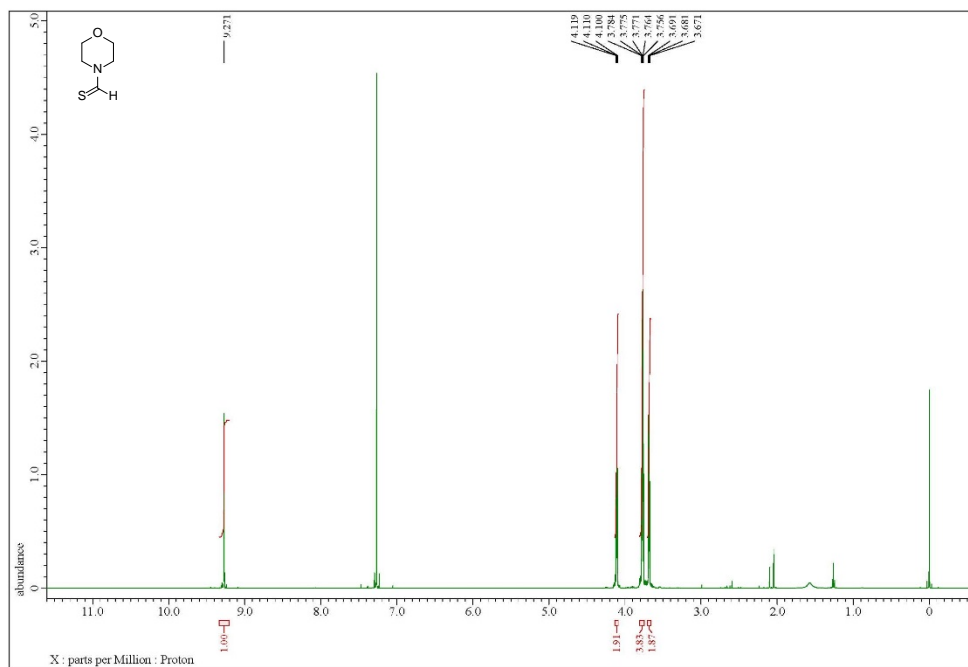


Figure 70. ^{13}C NMR spectrum of 6c

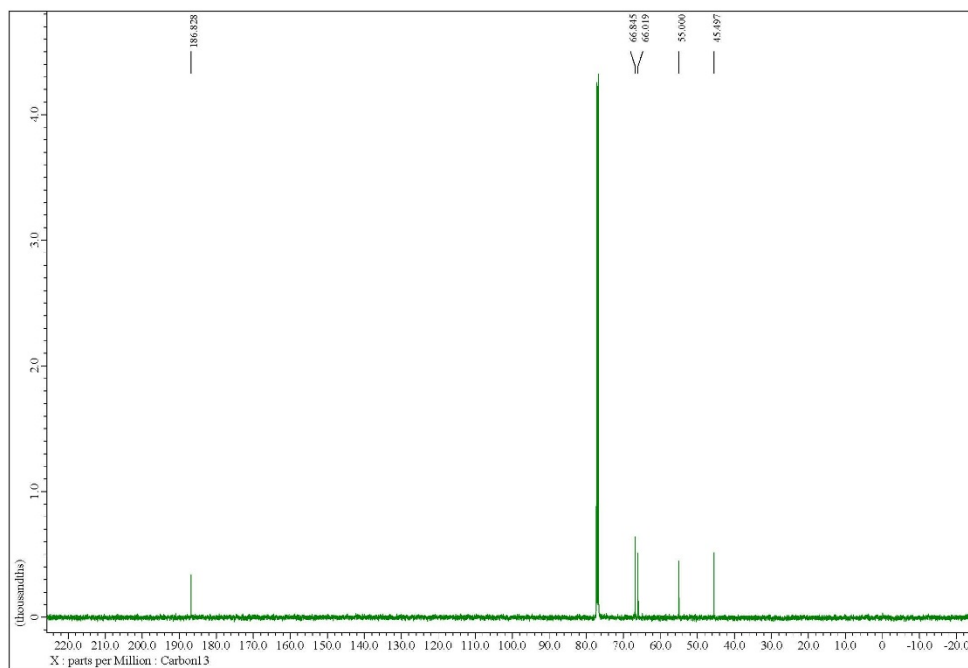


Figure 71. ^1H NMR spectrum of 6d

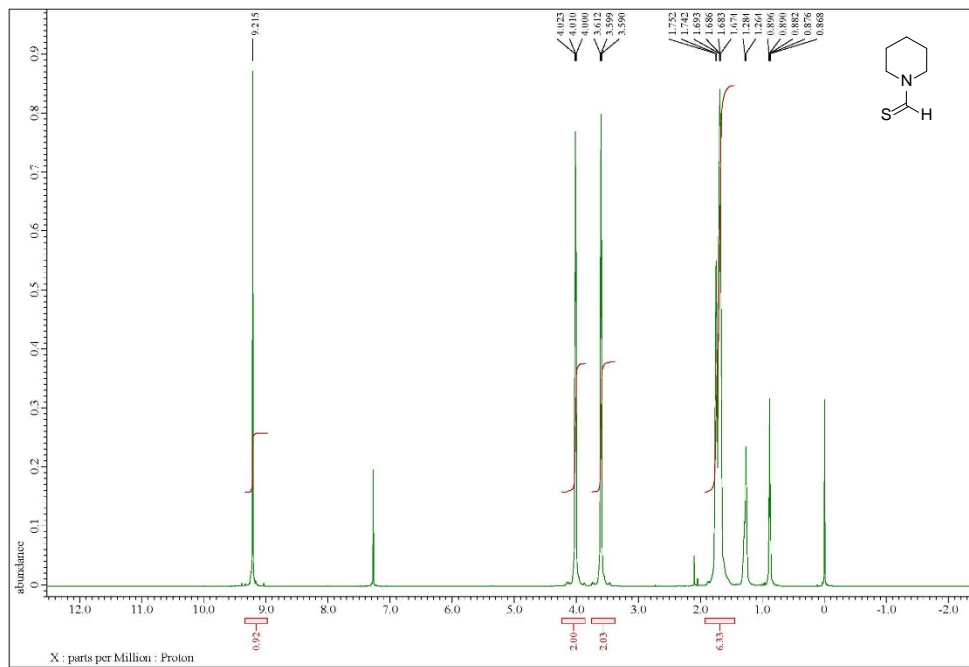


Figure 73. ^1H NMR spectrum of 6e

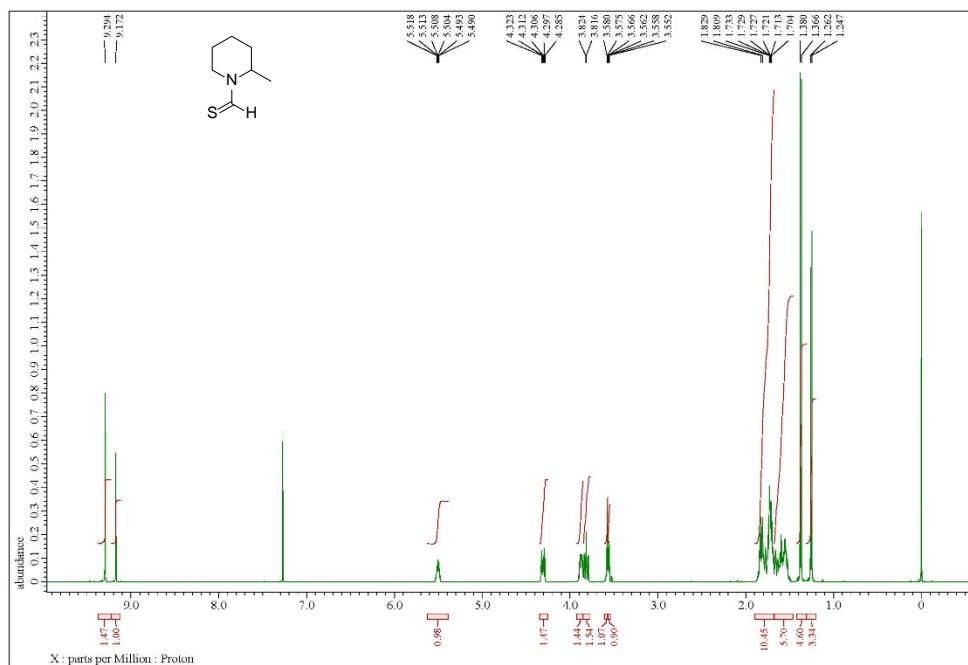


Figure 74. ^{13}C NMR spectrum of 6e

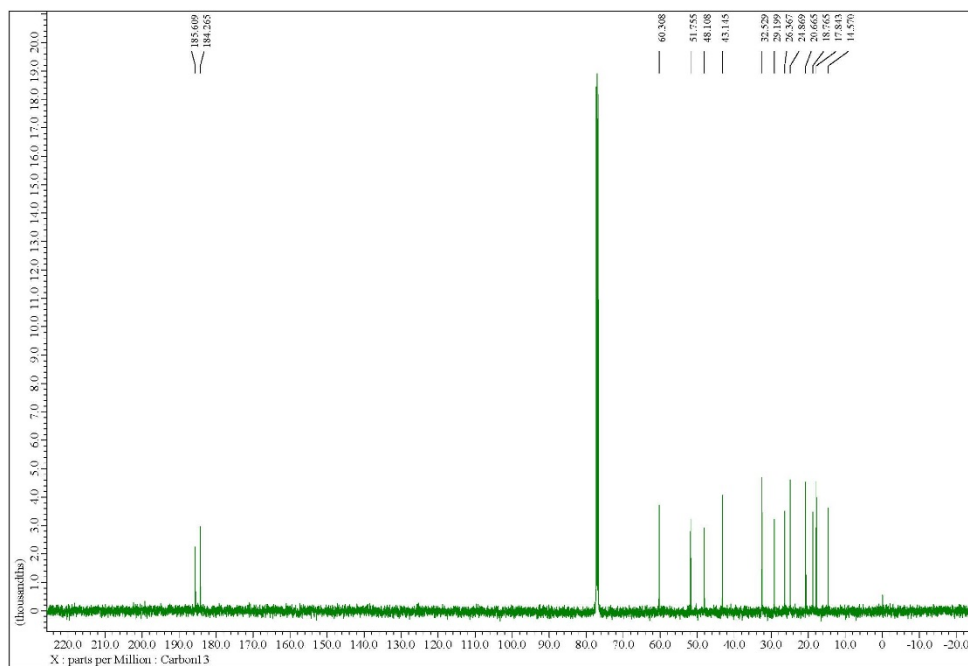


Figure 75. ^1H NMR spectrum of 6f

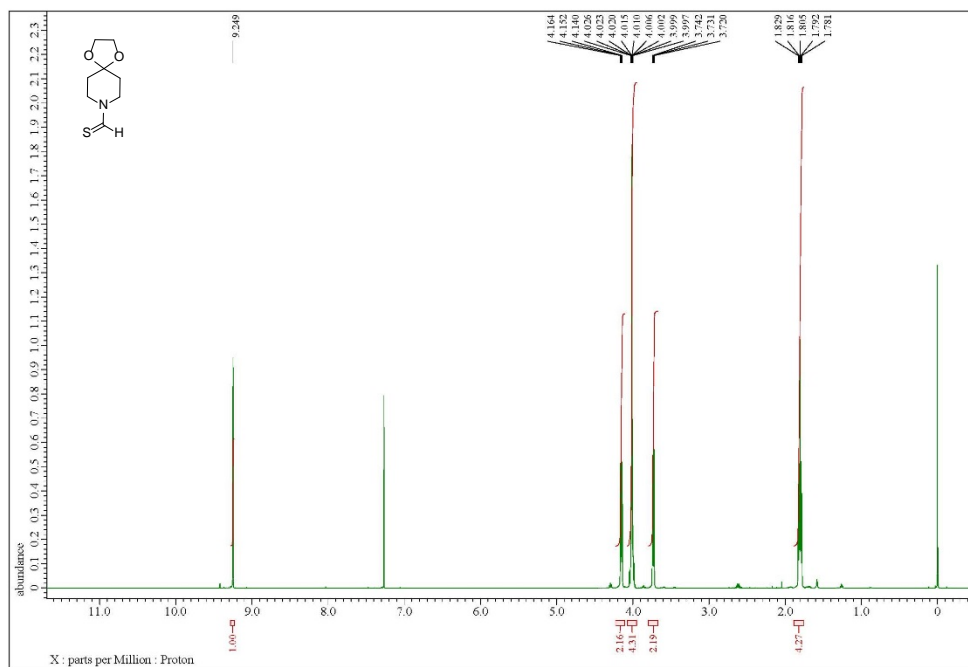


Figure 76. ^{13}C NMR spectrum of 6f

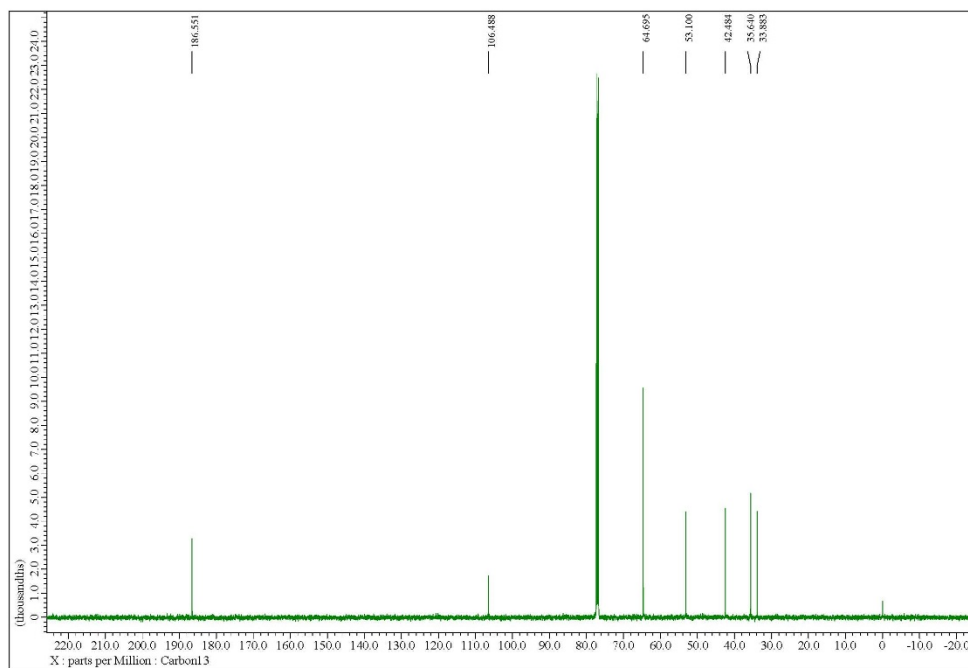


Figure 77. ^1H NMR spectrum of 6g

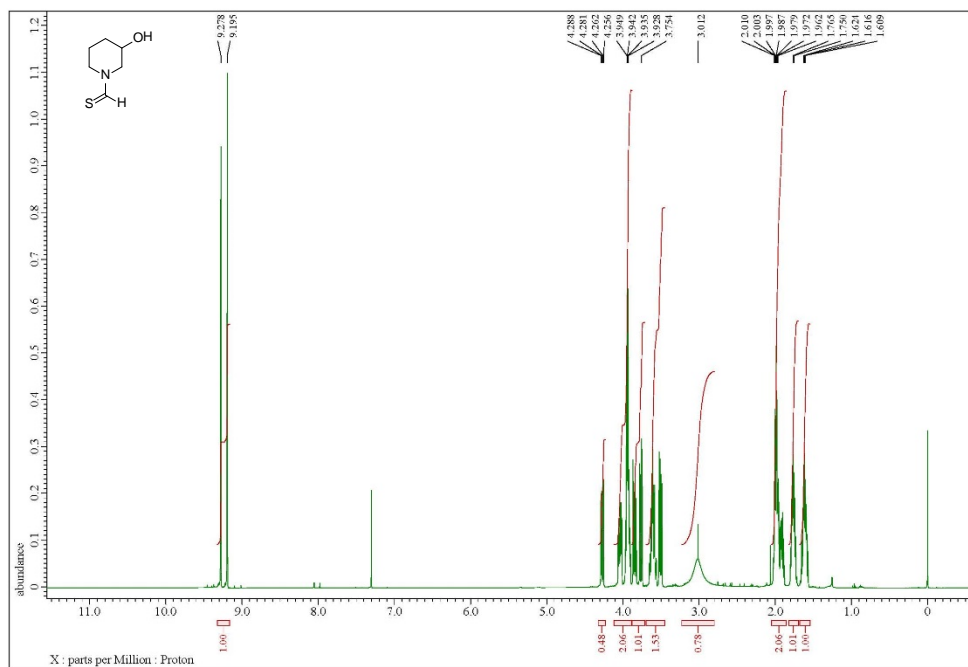


Figure 78. ^{13}C NMR spectrum of 6g

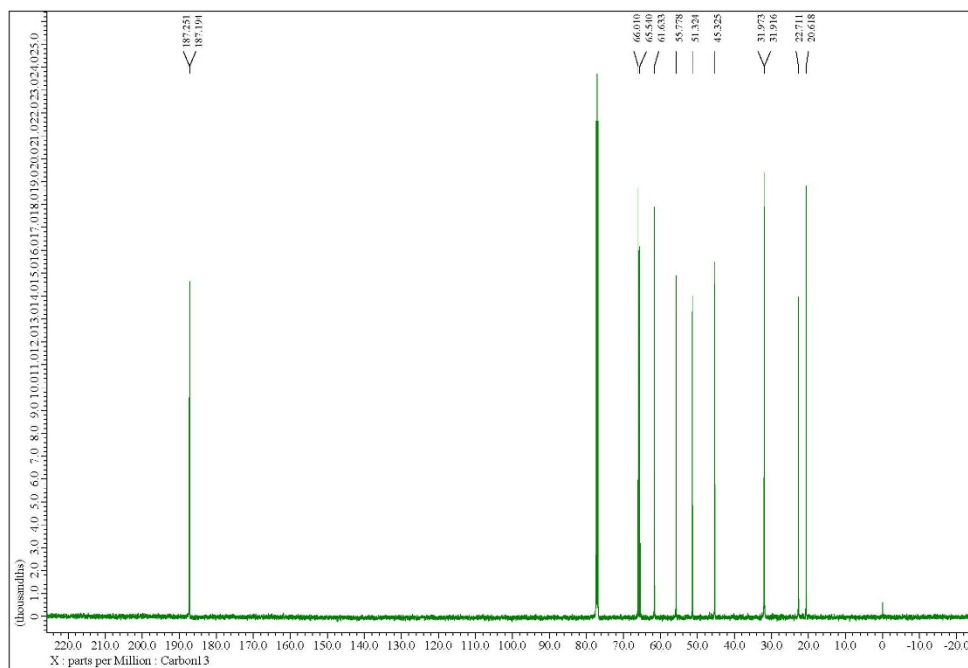


Figure 79. ^1H NMR spectrum of 6h

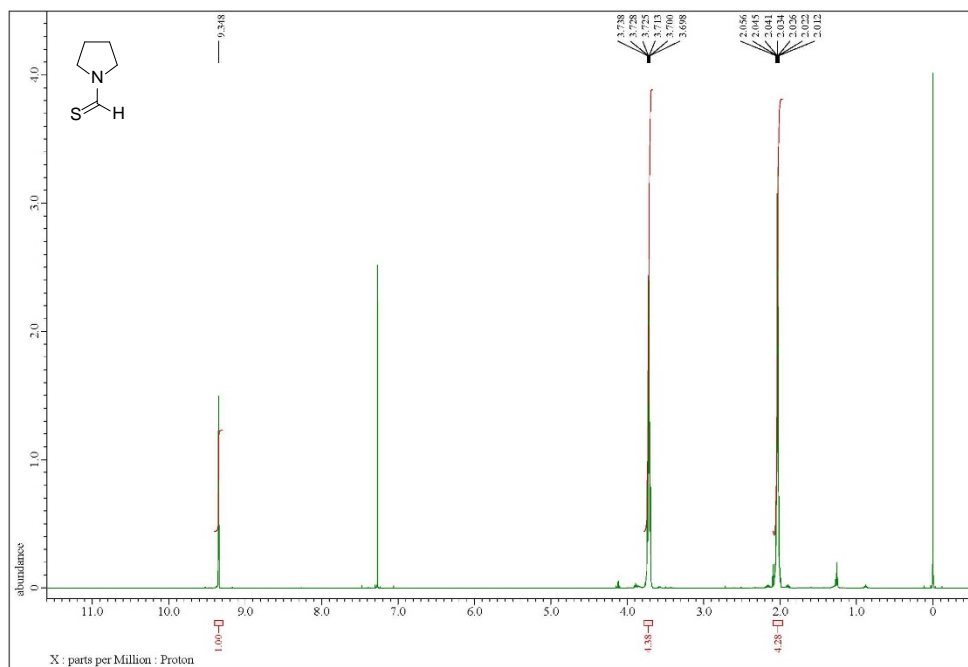


Figure 80. ^{13}C NMR spectrum of 6h

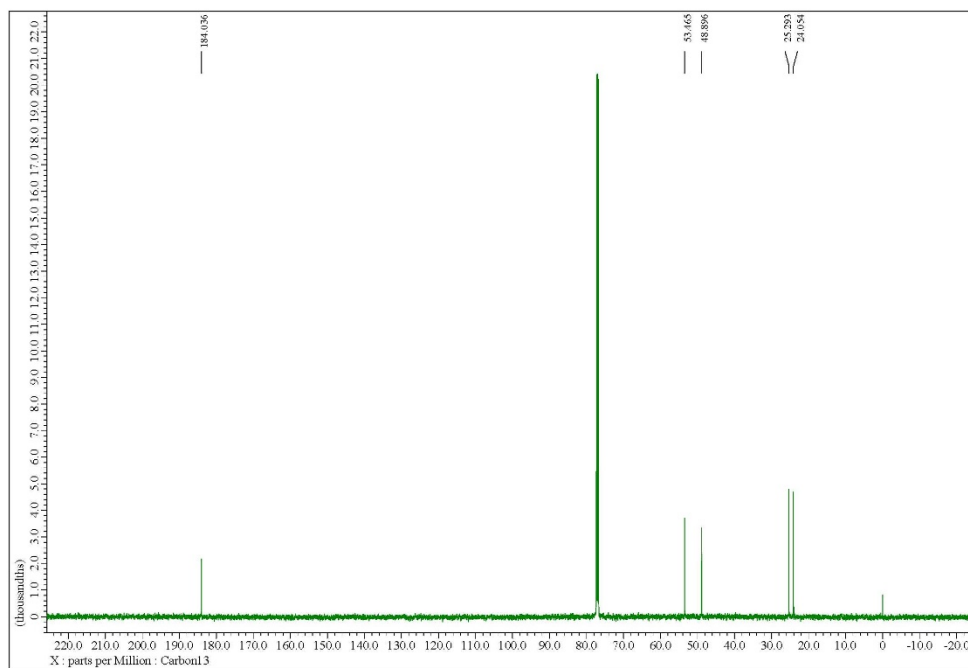


Figure 83. ^1H NMR spectrum of 6j

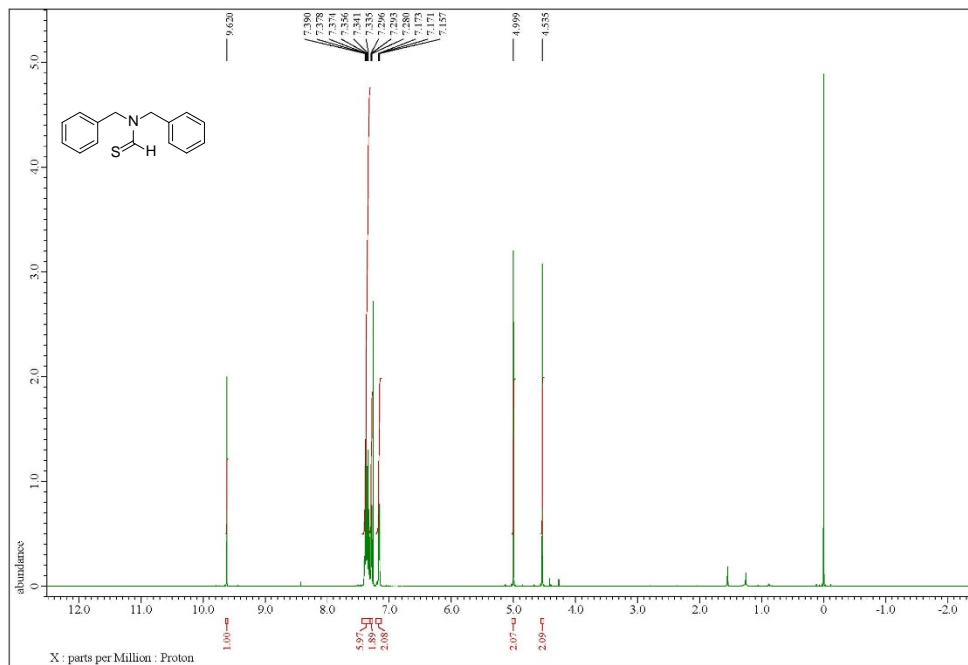


Figure 84. ^{13}C NMR spectrum of 6j

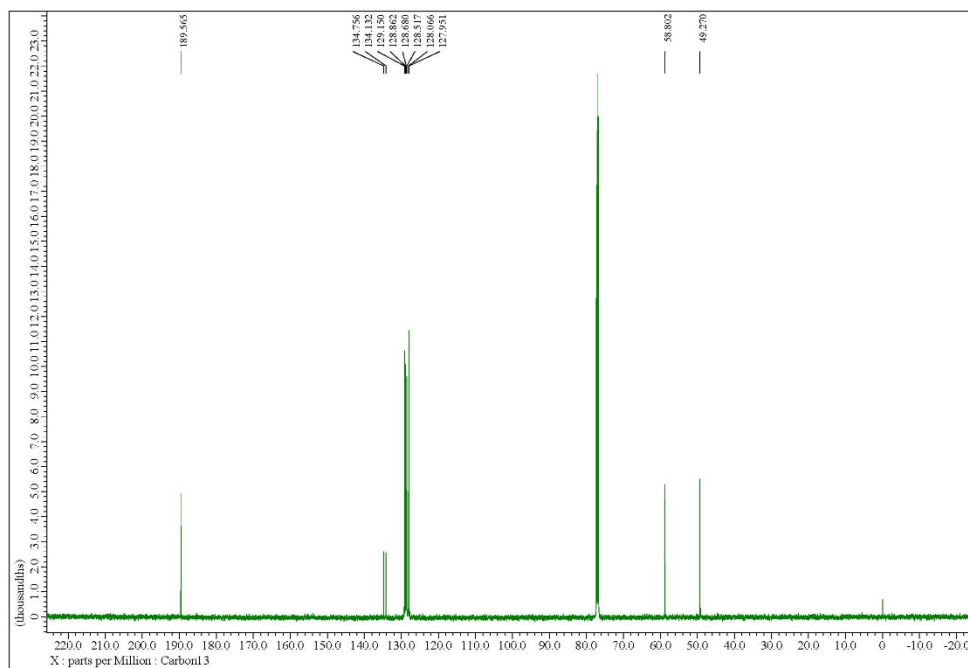


Figure 85. ^1H NMR spectrum of 6k

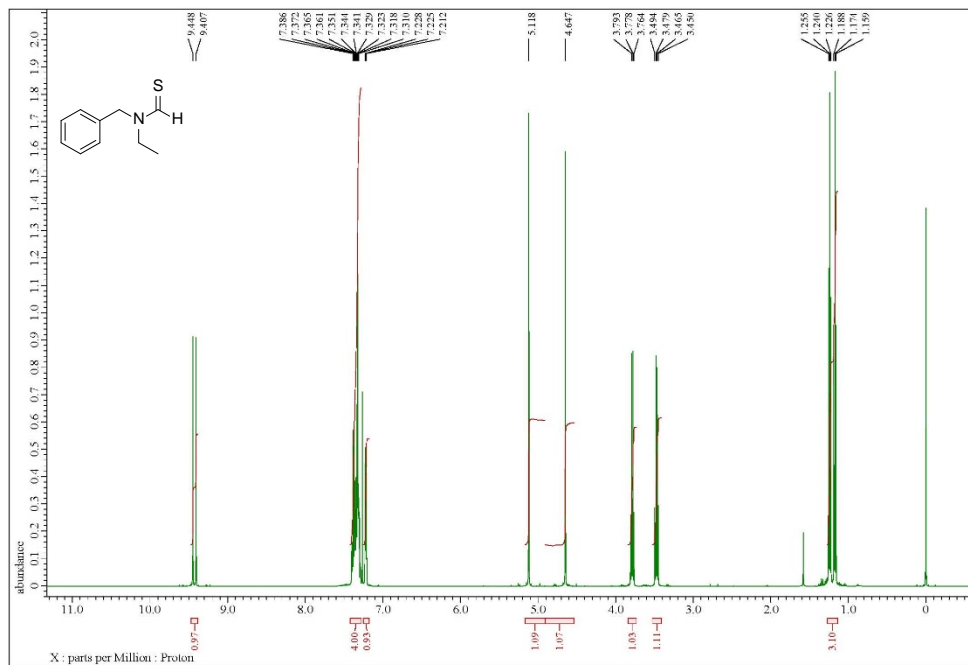


Figure 86. ^{13}C NMR spectrum of 6k

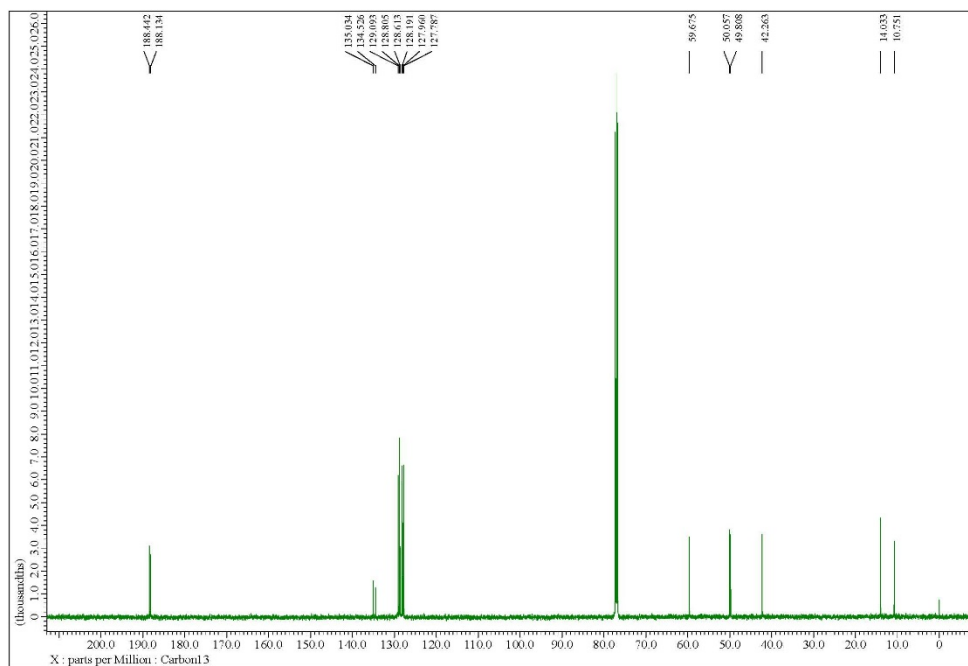


Figure 87. ^1H NMR spectrum of 7a

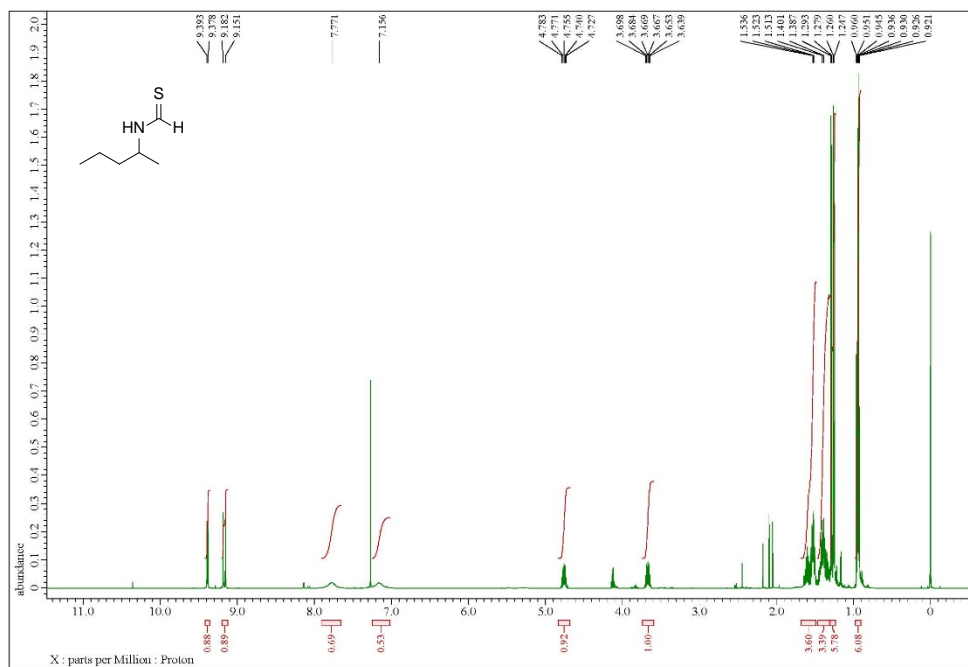


Figure 88. ^{13}C NMR spectrum of 7a

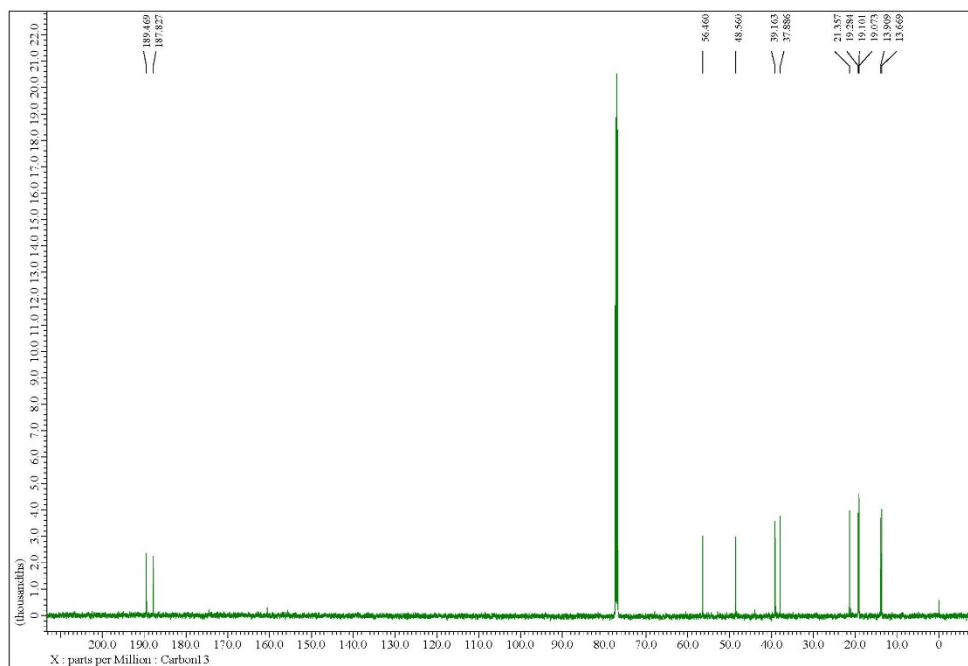


Figure 89. ^1H NMR spectrum of 7b

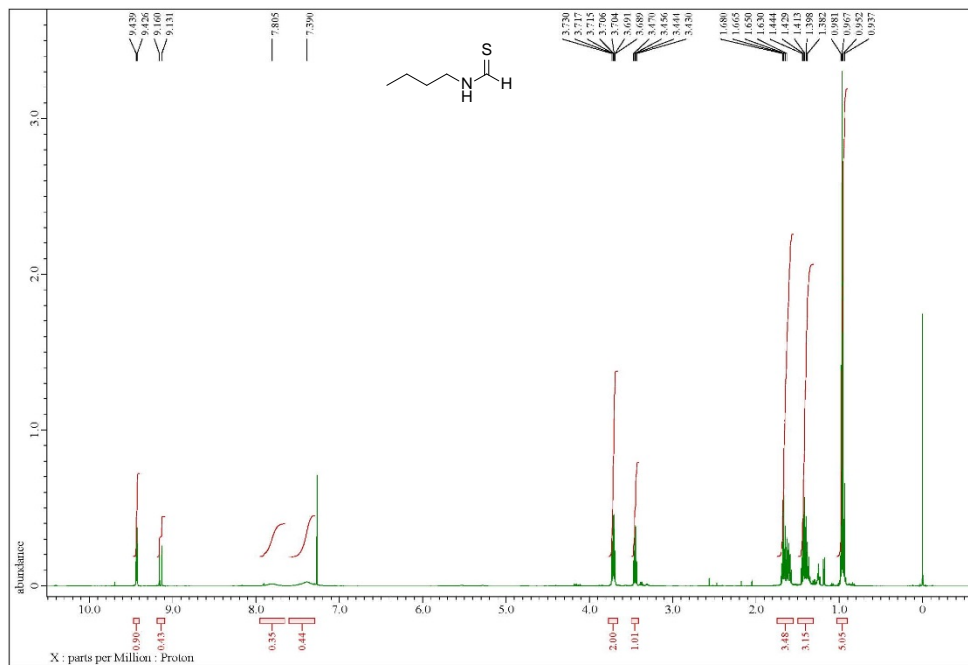


Figure 90. ^{13}C NMR spectrum of 7b

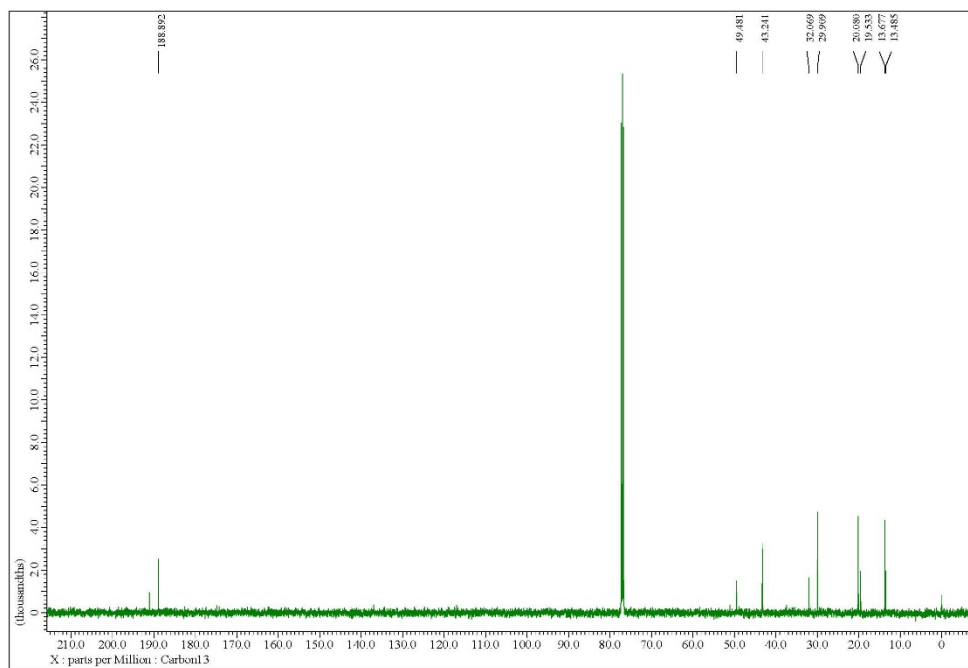


Figure 91. ^1H NMR spectrum of 7c

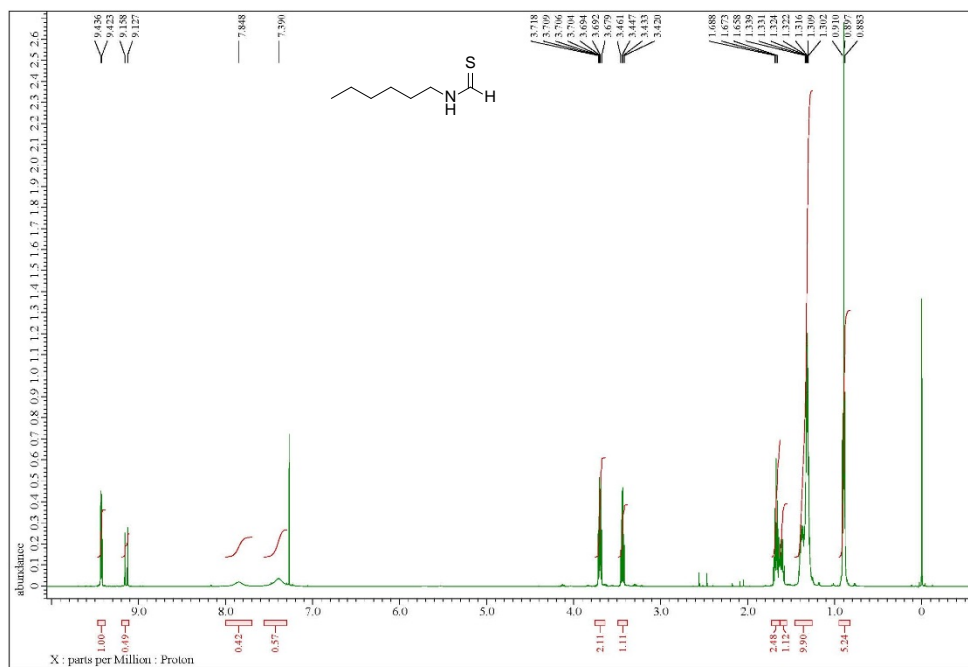


Figure 92. ^{13}C NMR spectrum of 7c

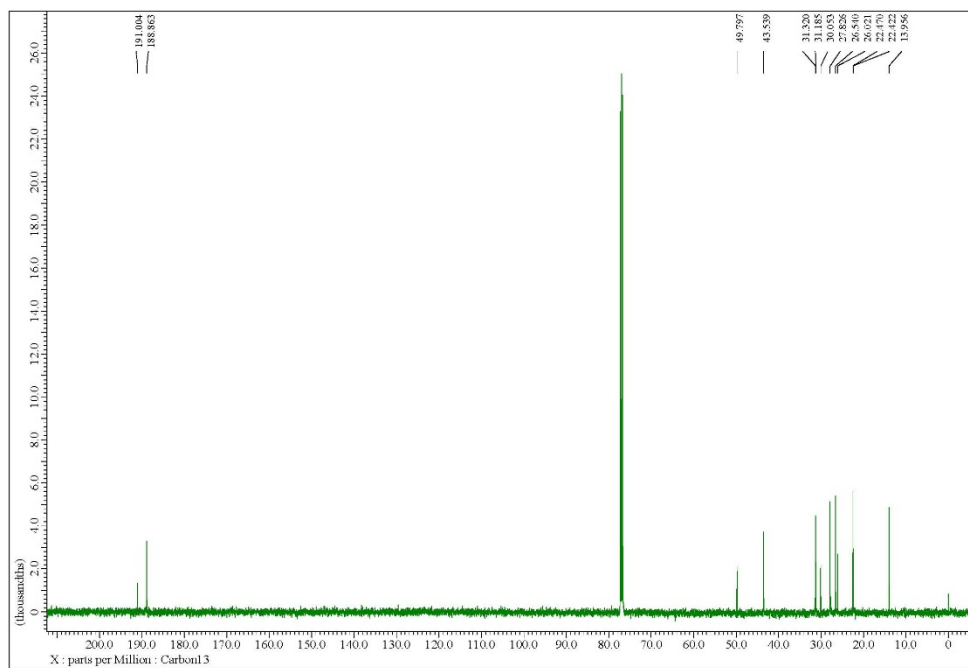


Figure 93. ^1H NMR spectrum of 7d

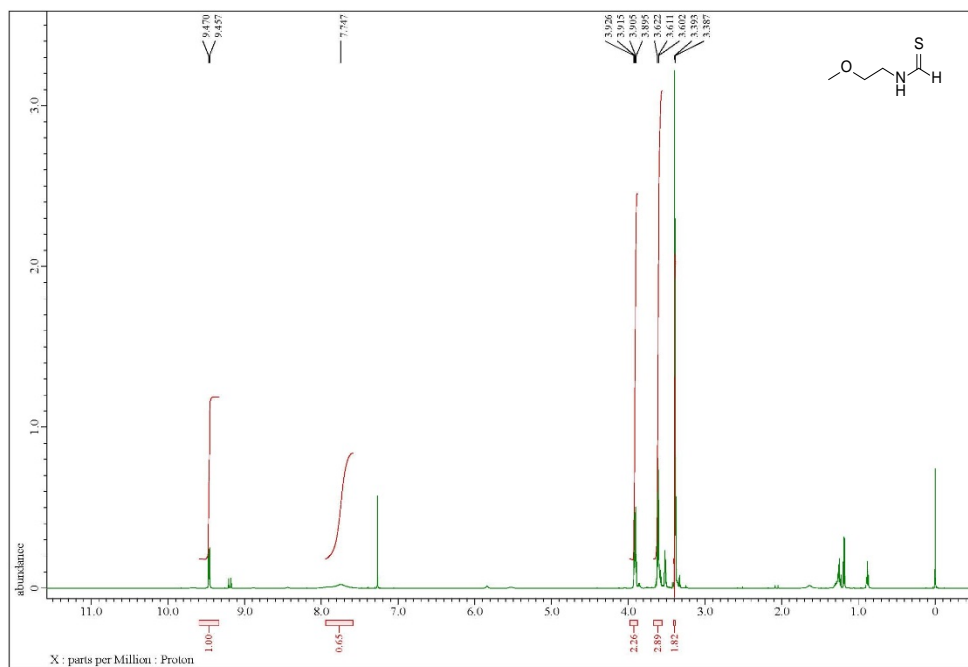


Figure 94. ^{13}C NMR spectrum of 7d

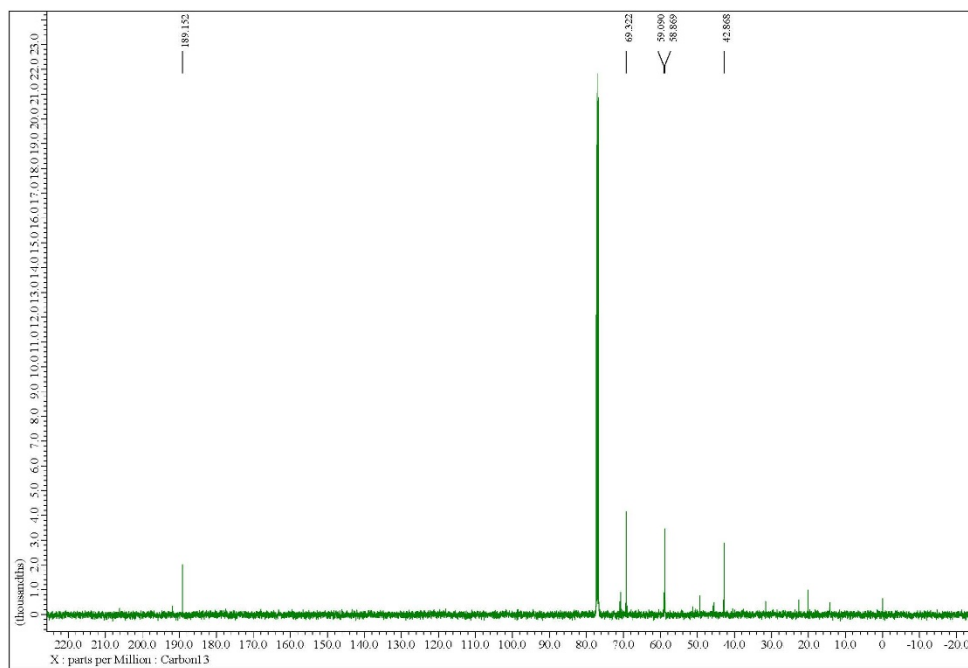


Figure 95. ^1H NMR spectrum of 7e

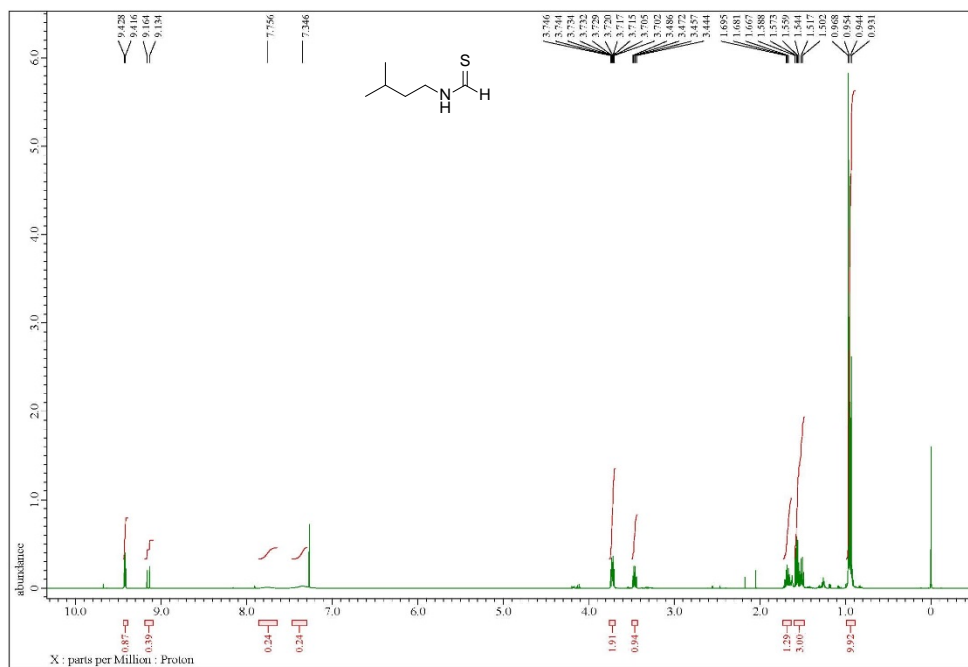


Figure 96. ^{13}C NMR spectrum of 7e

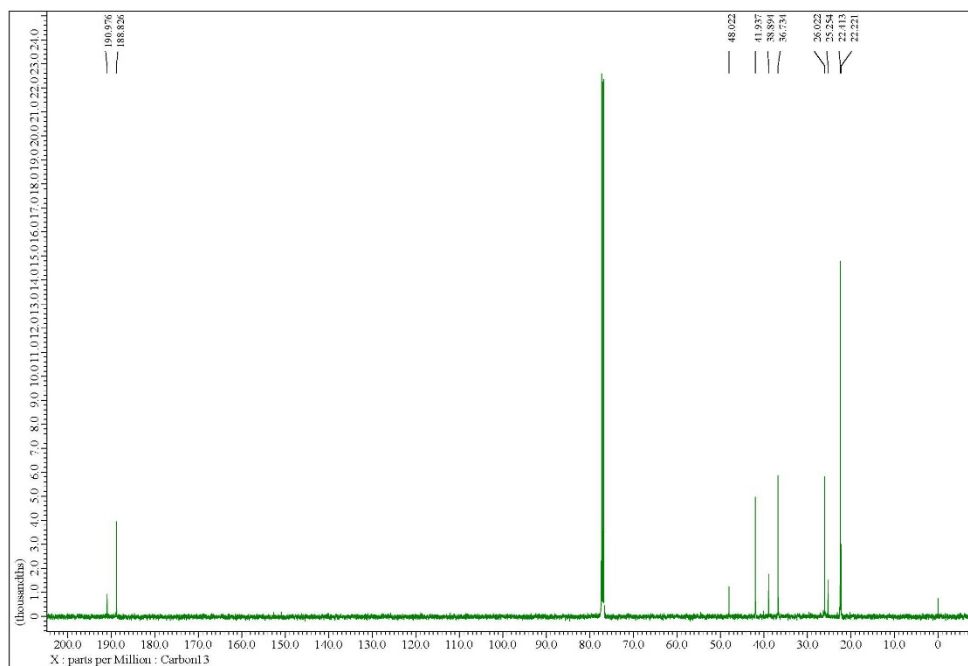


Figure 97. ^1H NMR spectrum of 7f

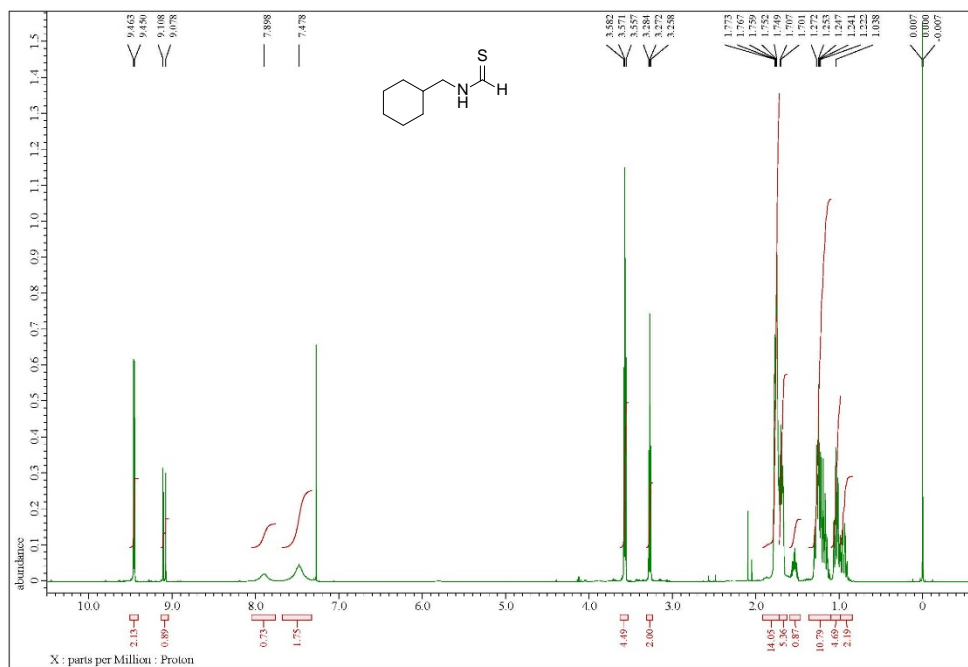


Figure 98. ^{13}C NMR spectrum of 7f

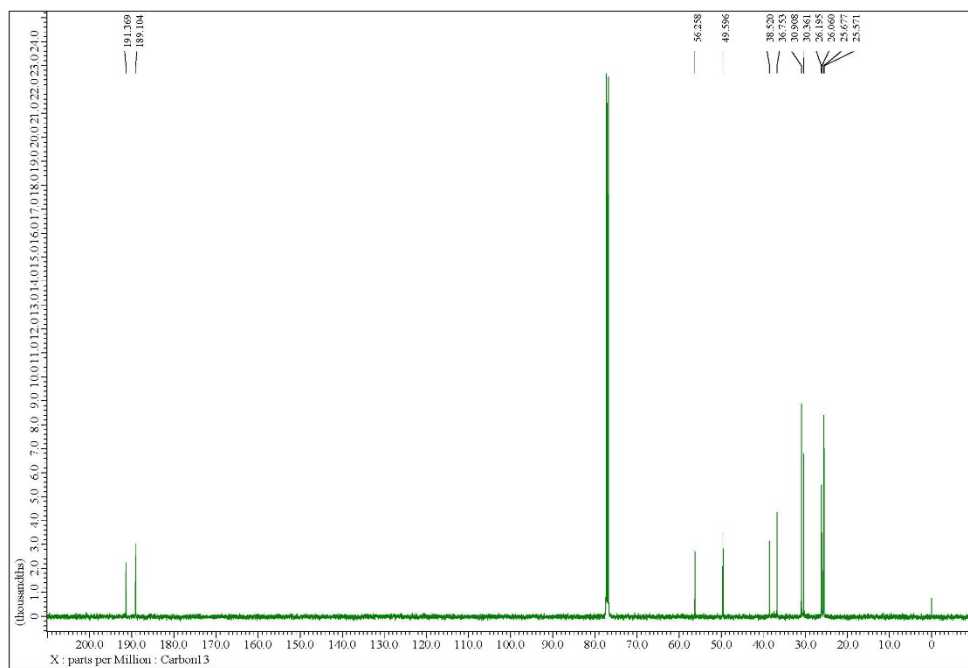


Figure 99. ^1H NMR spectrum of 7g

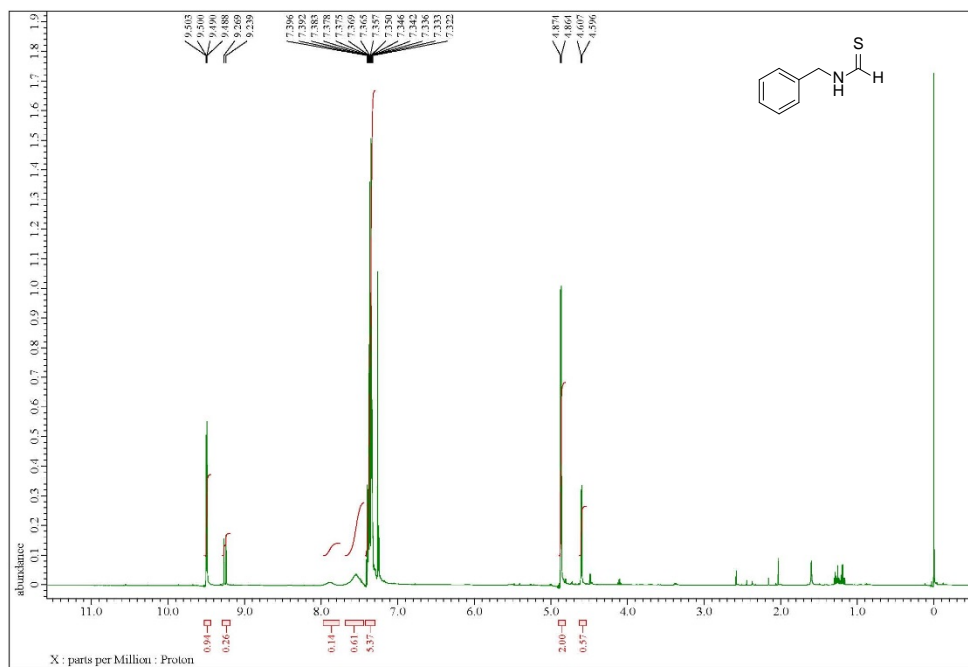


Figure 100. ^{13}C NMR spectrum of 7g

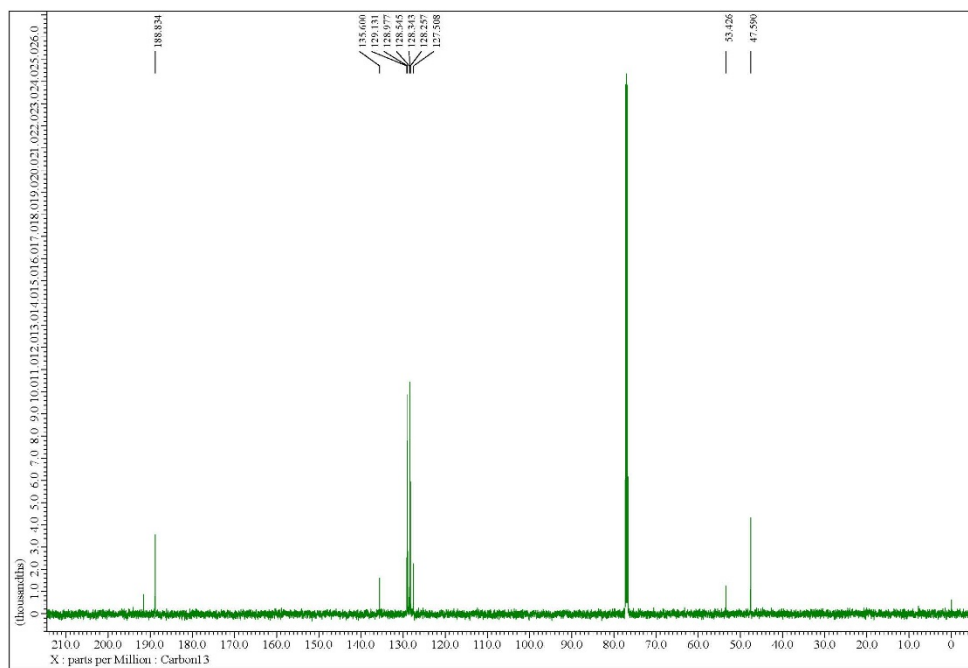


Figure 101. ^1H NMR spectrum of 7h

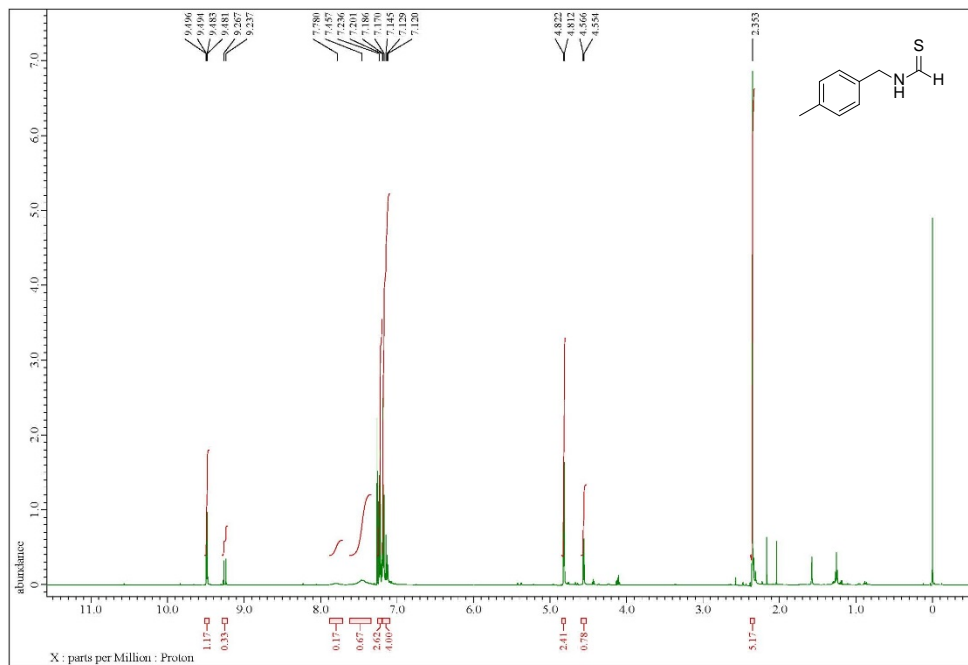


Figure 102. ^{13}C NMR spectrum of 7h

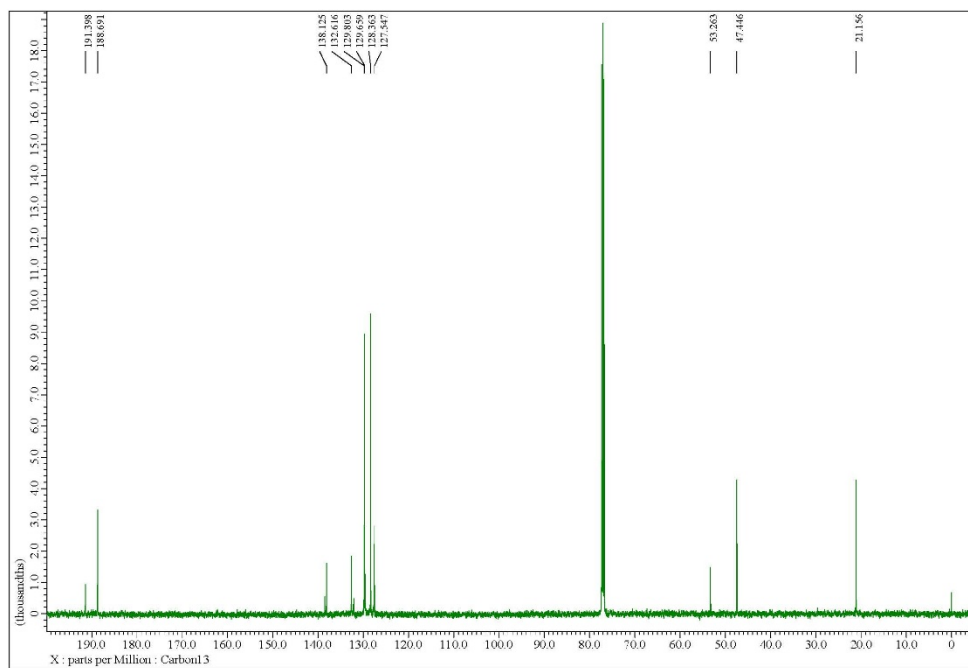


Figure 103. ^1H NMR spectrum of 7i

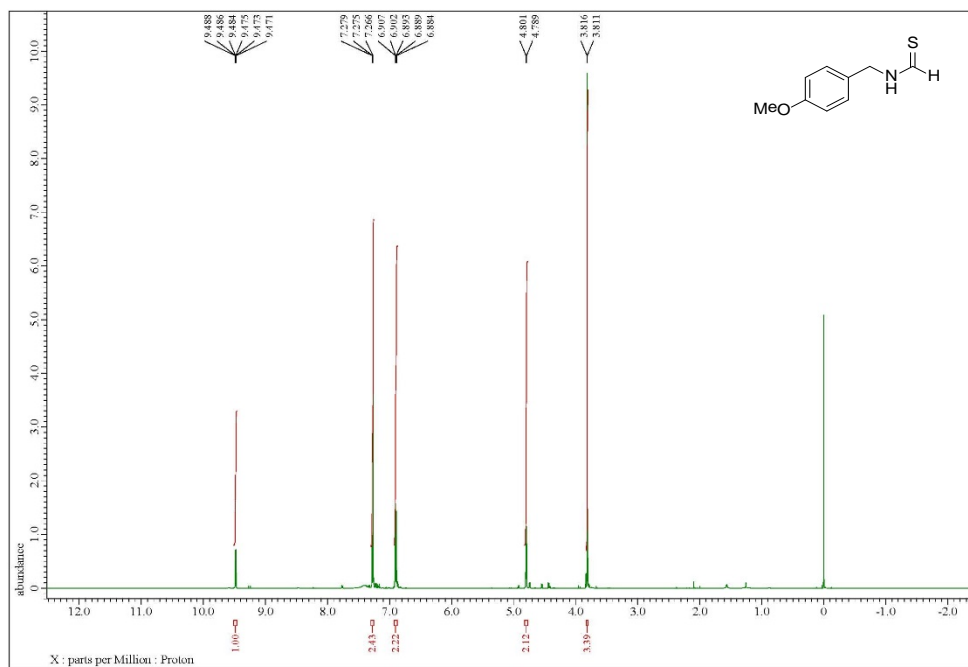


Figure 104. ^{13}C NMR spectrum of 7i

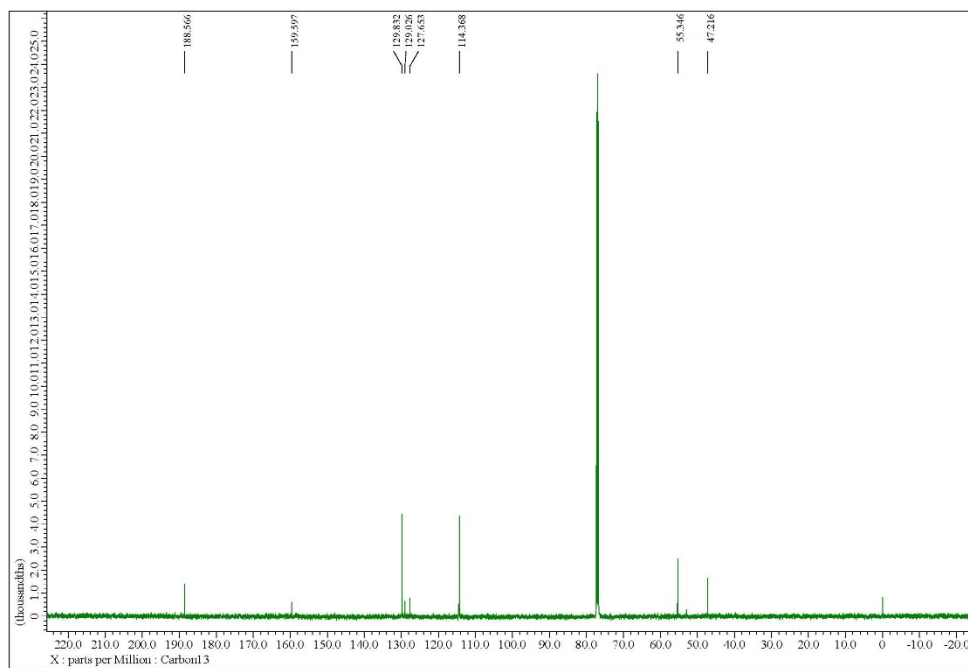


Figure 105. ^1H NMR spectrum of 7j

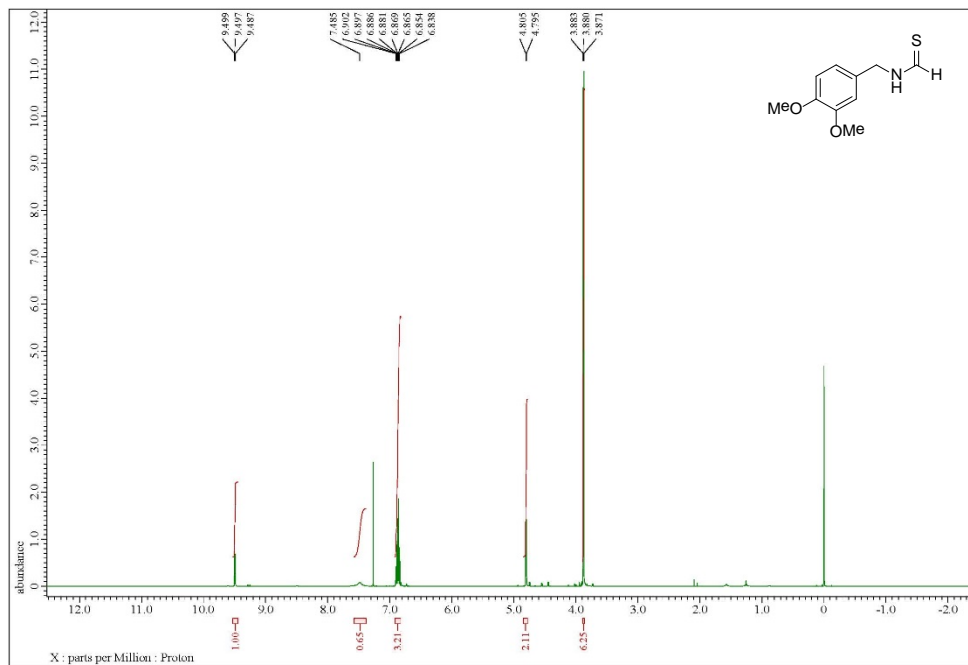


Figure 106. ^{13}C NMR spectrum of 7j

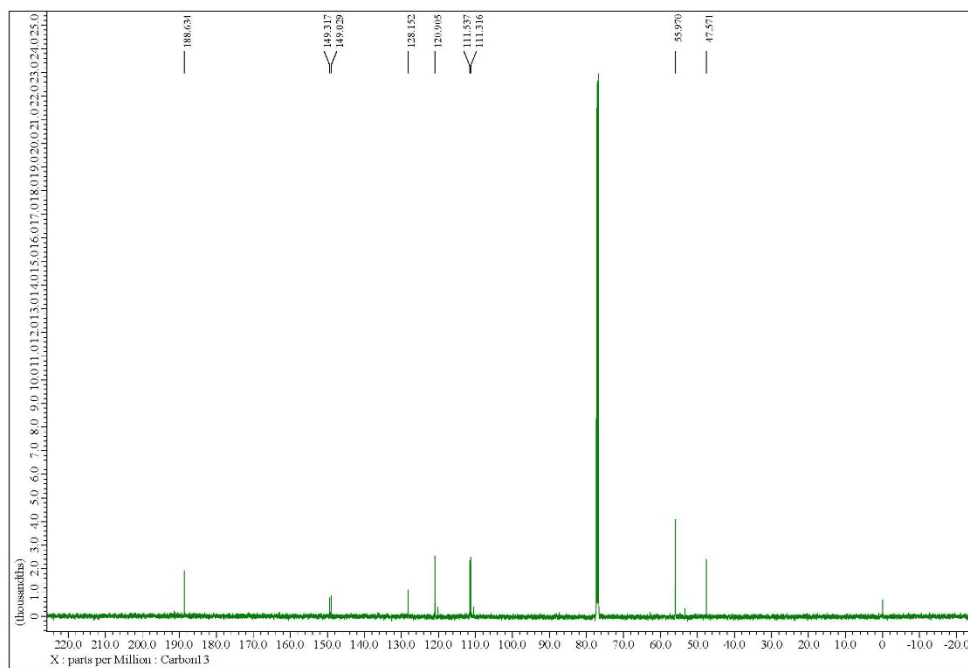


Figure 107. ^1H NMR spectrum of 7k

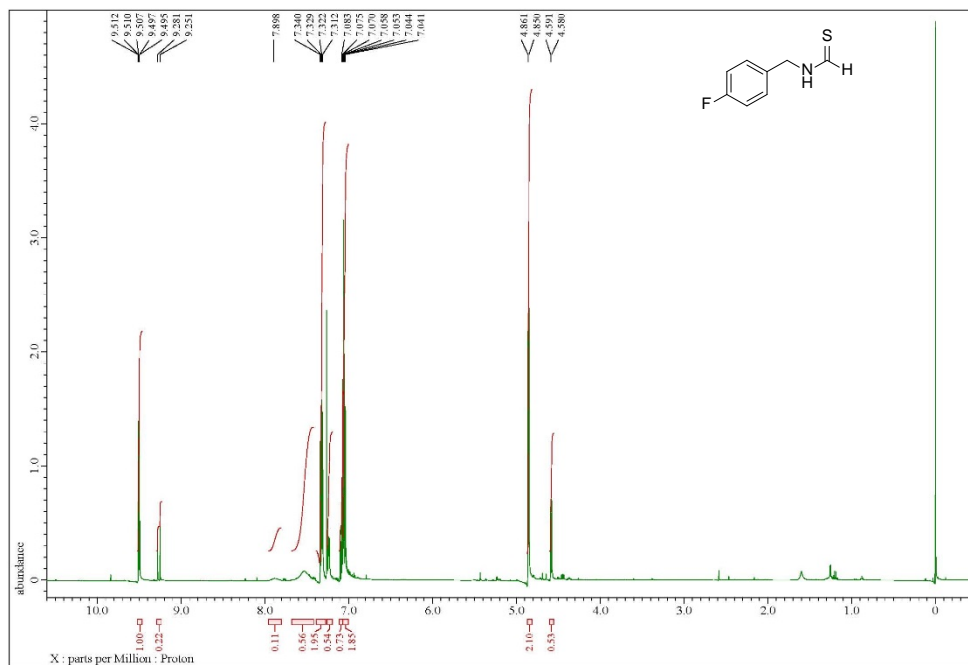


Figure 108. ^{13}C NMR spectrum of 7k

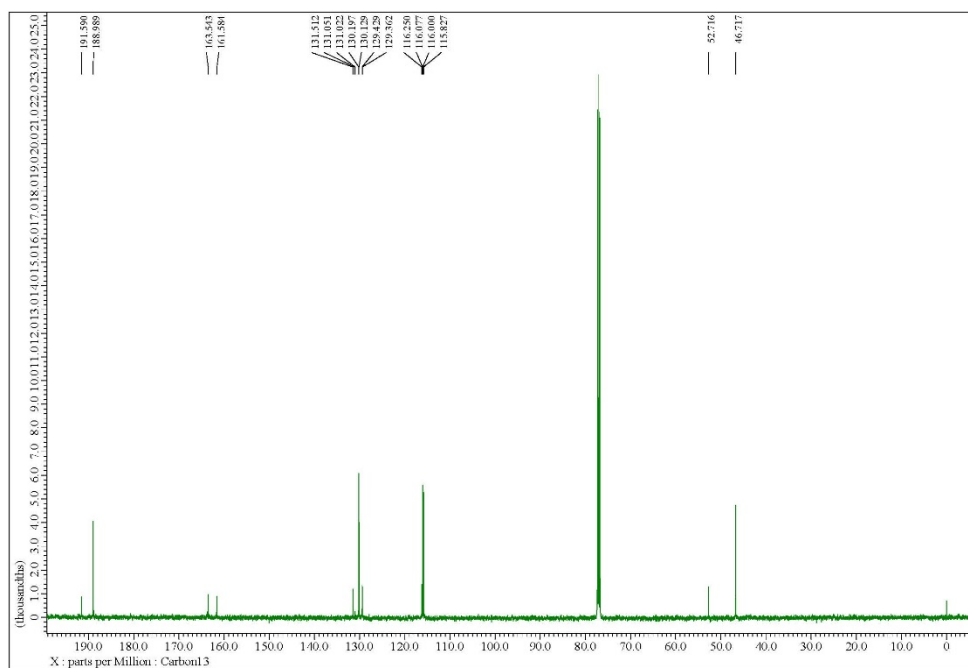


Figure 109. ^1H NMR spectrum of 71

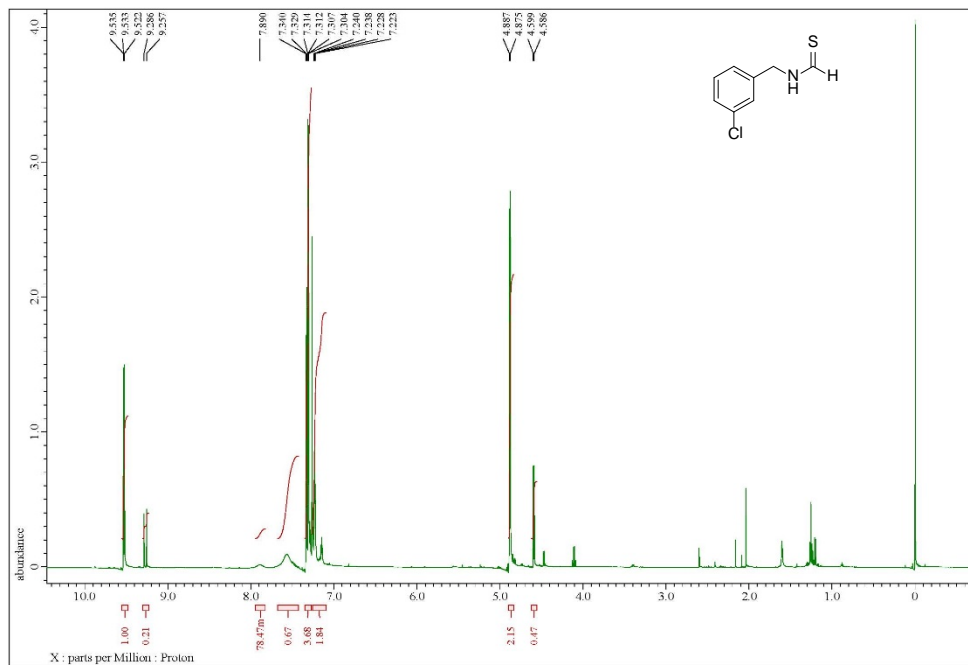


Figure 110. ^{13}C NMR spectrum of 71

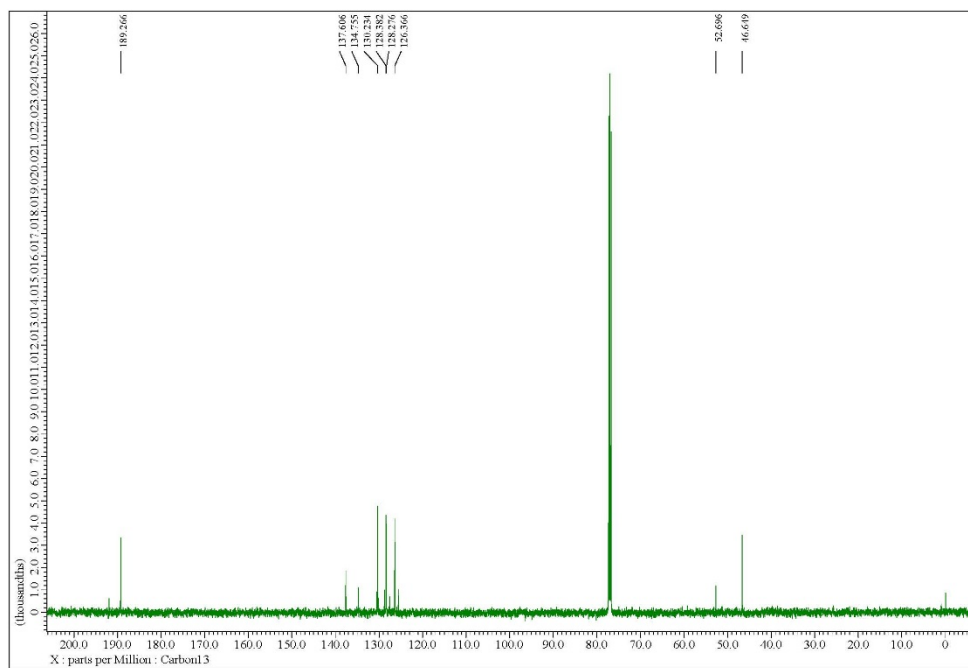


Figure 111. ^1H NMR spectrum of 7m

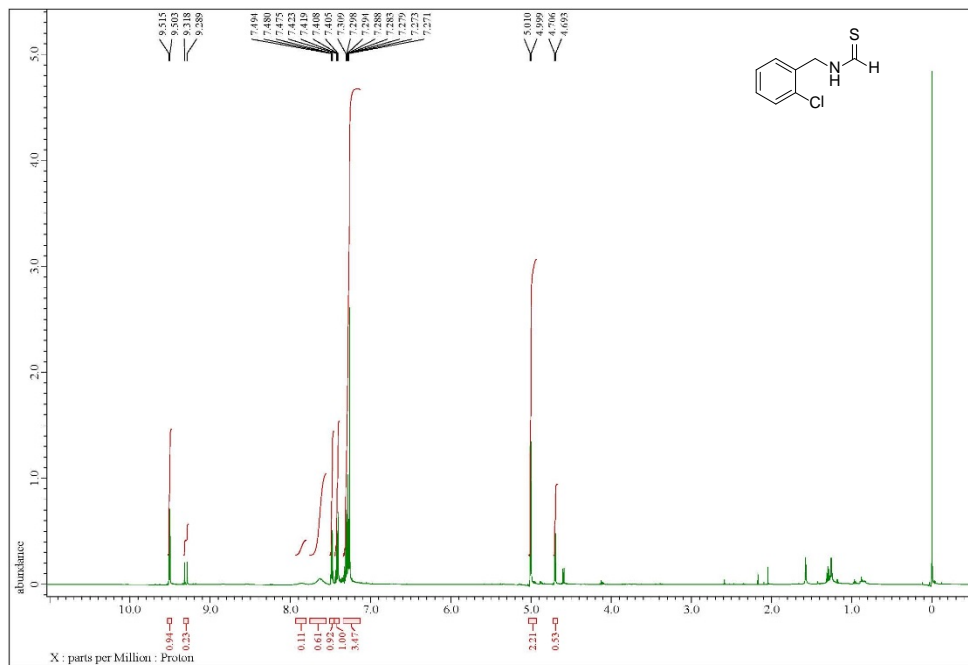


Figure 112. ^{13}C NMR spectrum of 7m

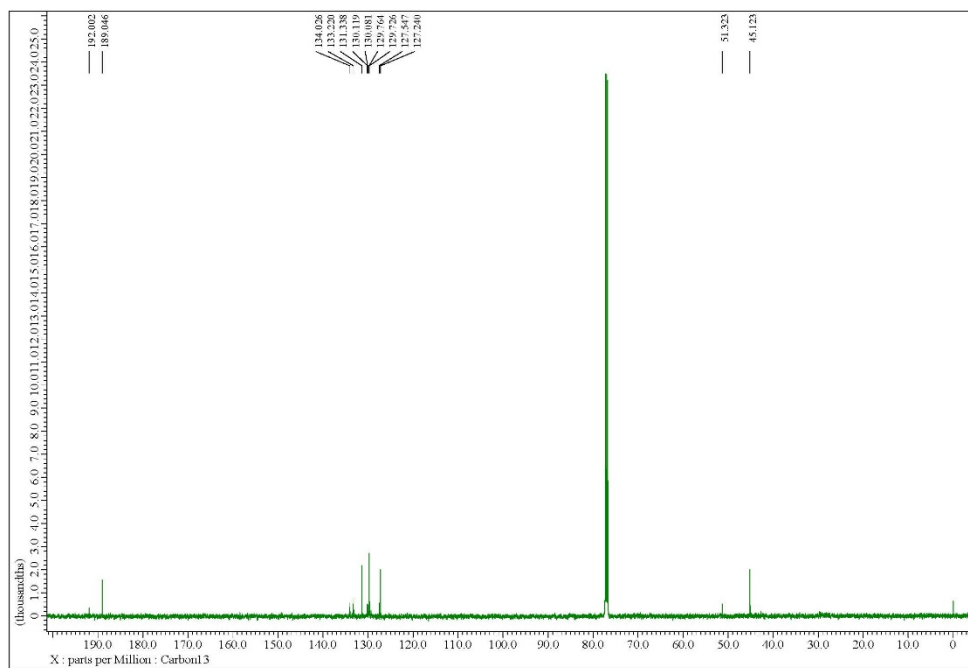


Figure 113. ^1H NMR spectrum of 7n

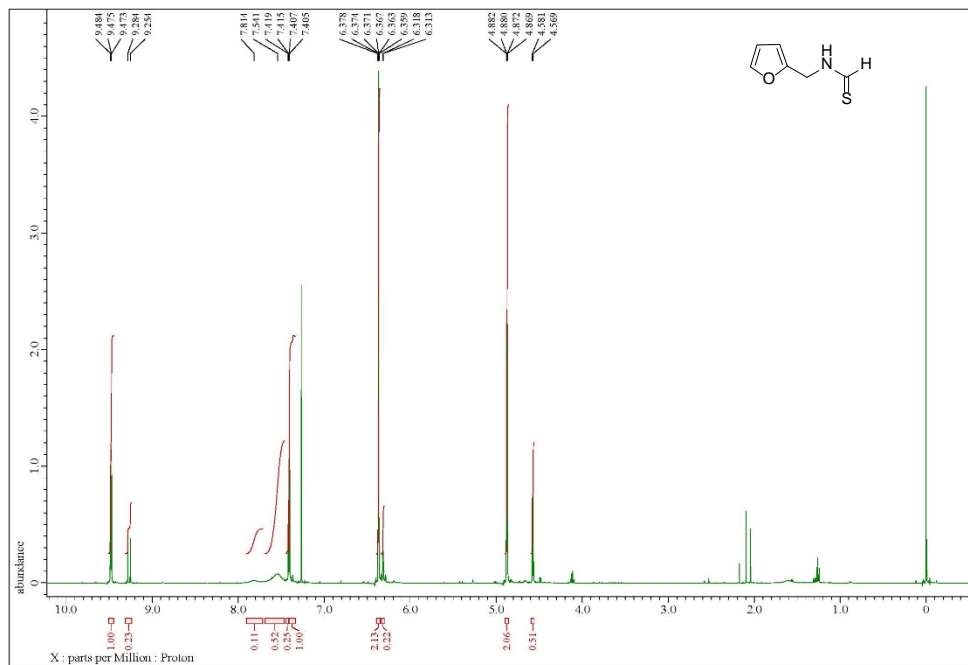


Figure 114. ^{13}C NMR spectrum of 7n

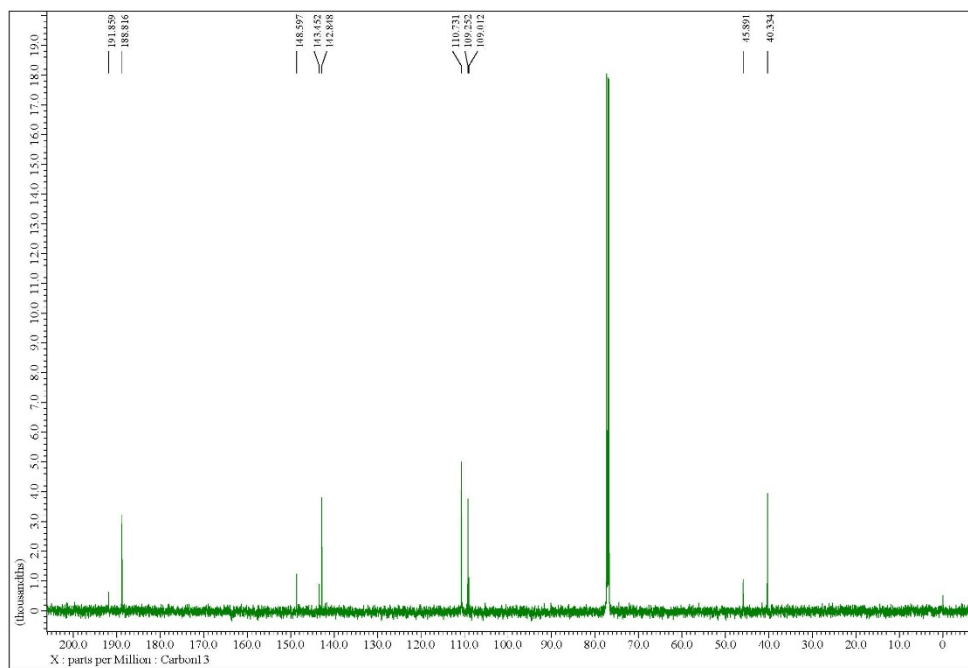


Figure 119. ^1H NMR spectrum of 8b

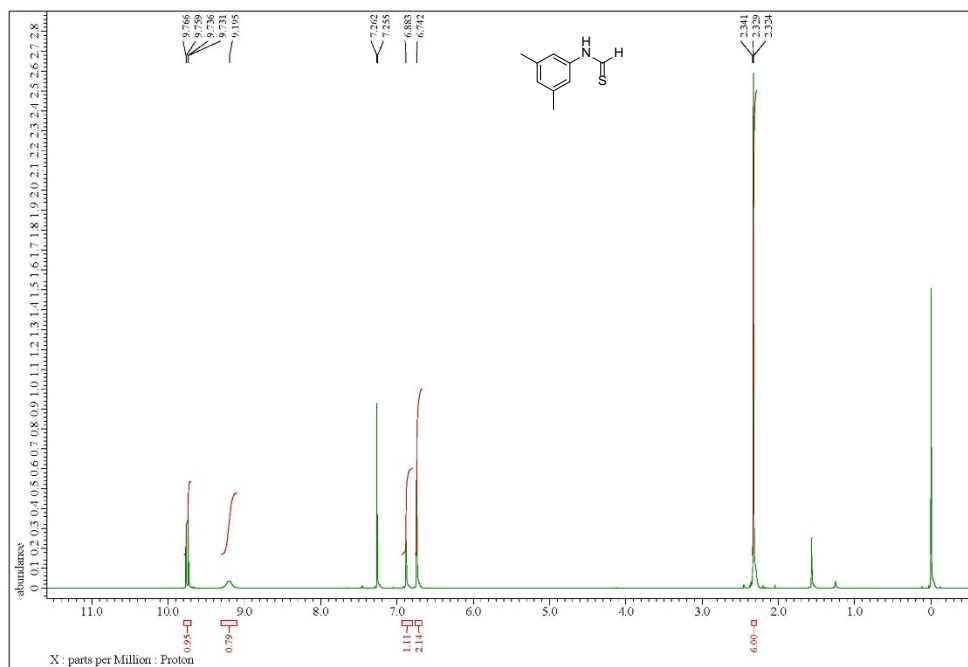


Figure 120. ^{13}C NMR spectrum of 8b

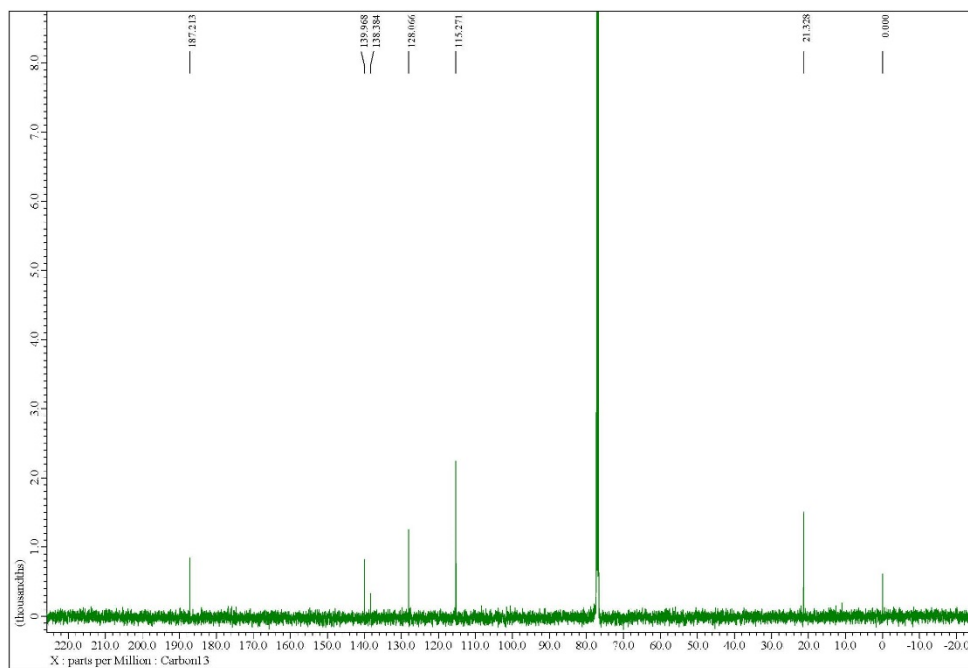


Figure 121. ^1H NMR spectrum of 8c

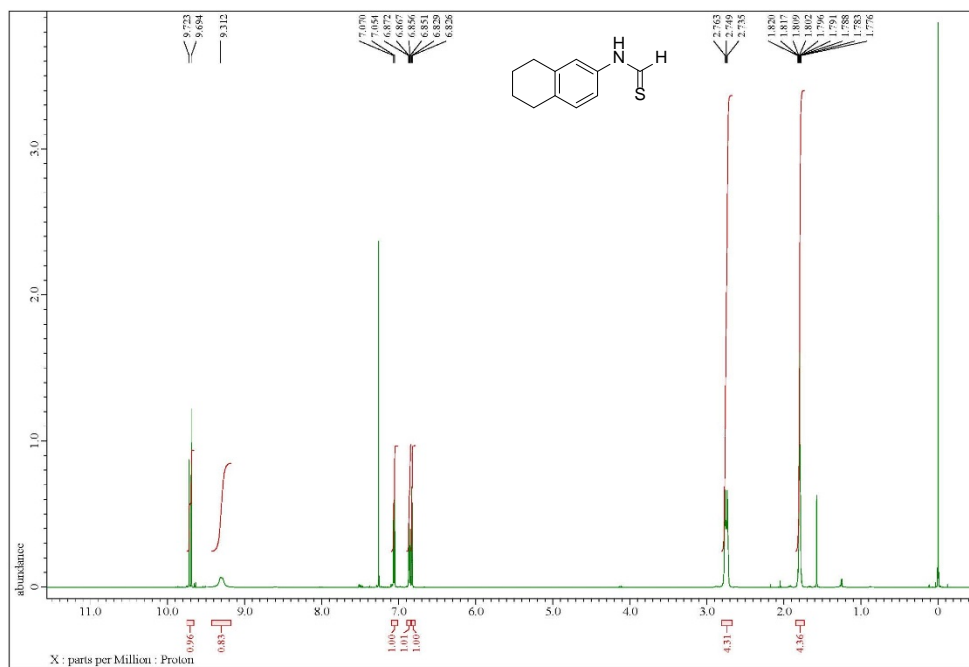


Figure 122. ^{13}C NMR spectrum of 8c

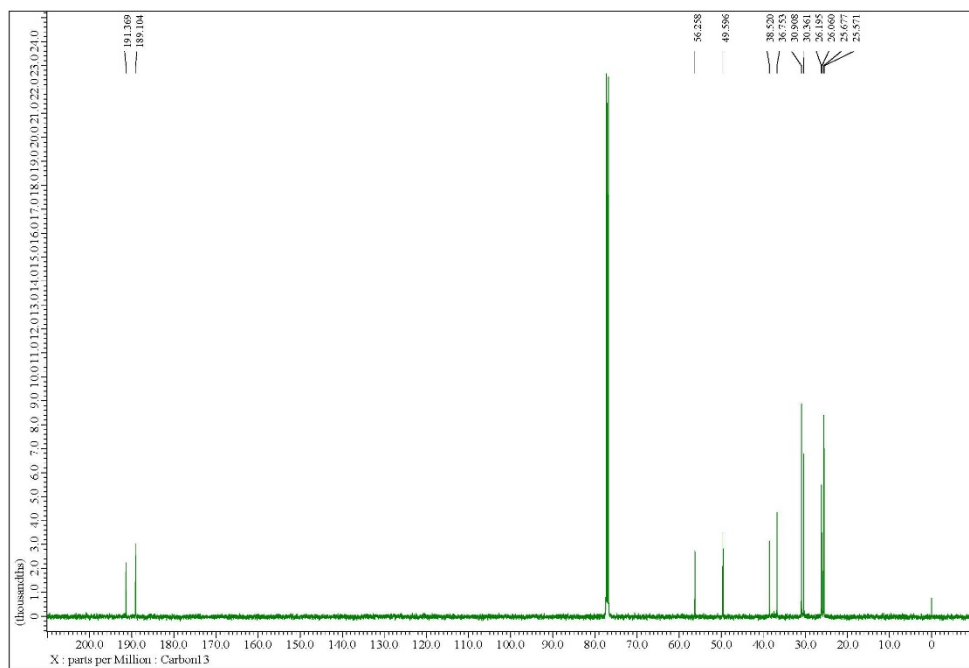


Figure 123. ^1H NMR spectrum of 8d

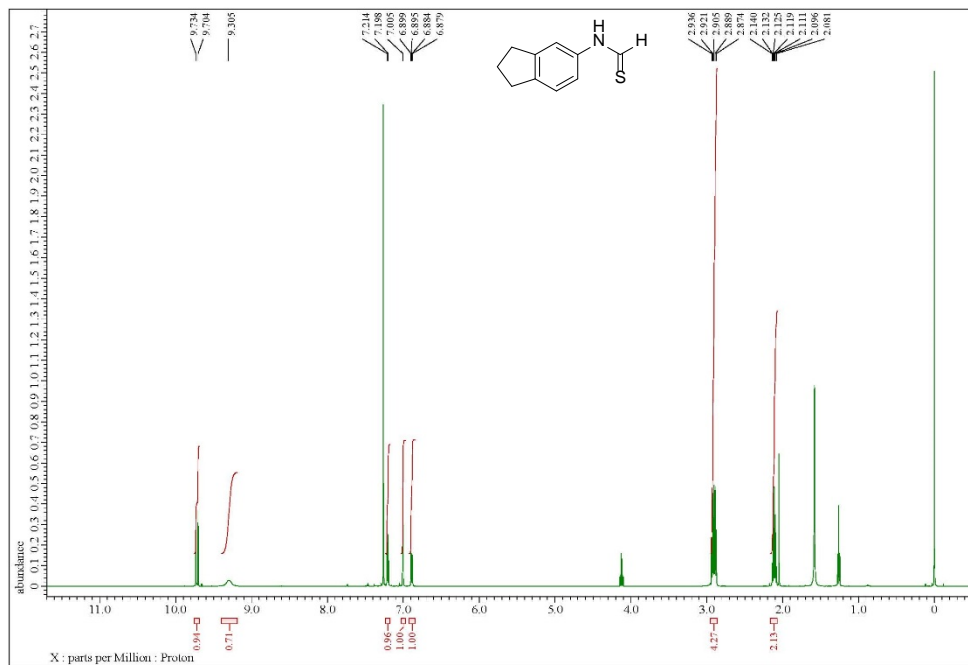


Figure 124. ^{13}C NMR spectrum of 8d

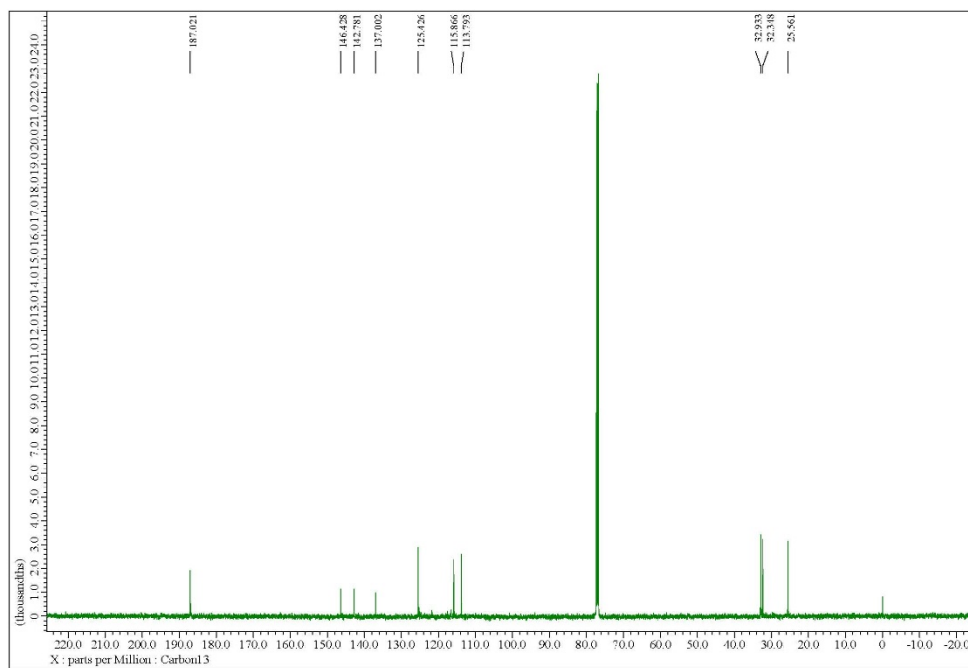


Figure 125. ^1H NMR spectrum of 8e

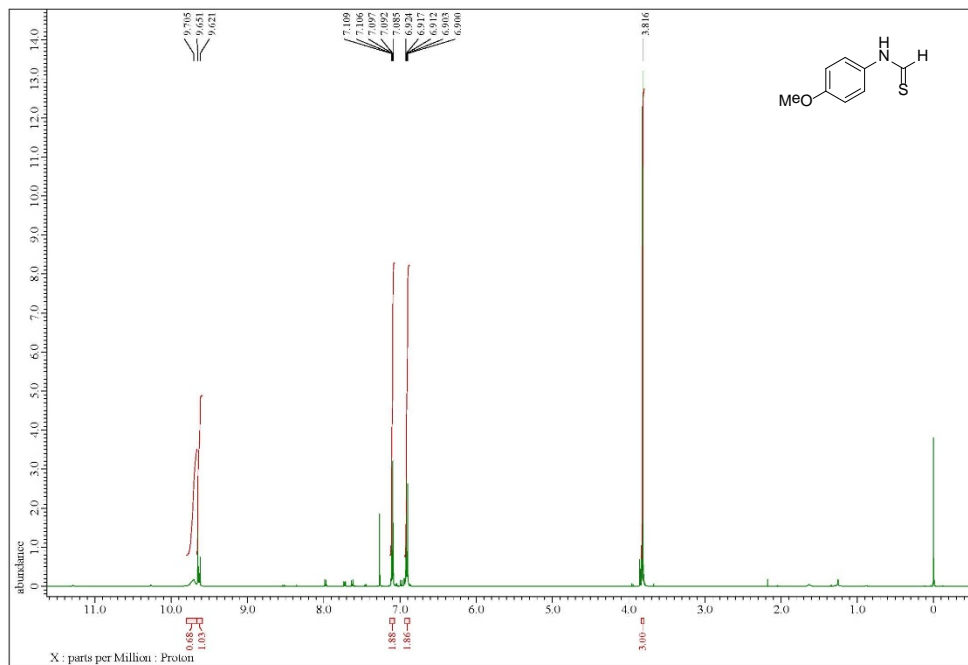


Figure 126. ^{13}C NMR spectrum of 8e

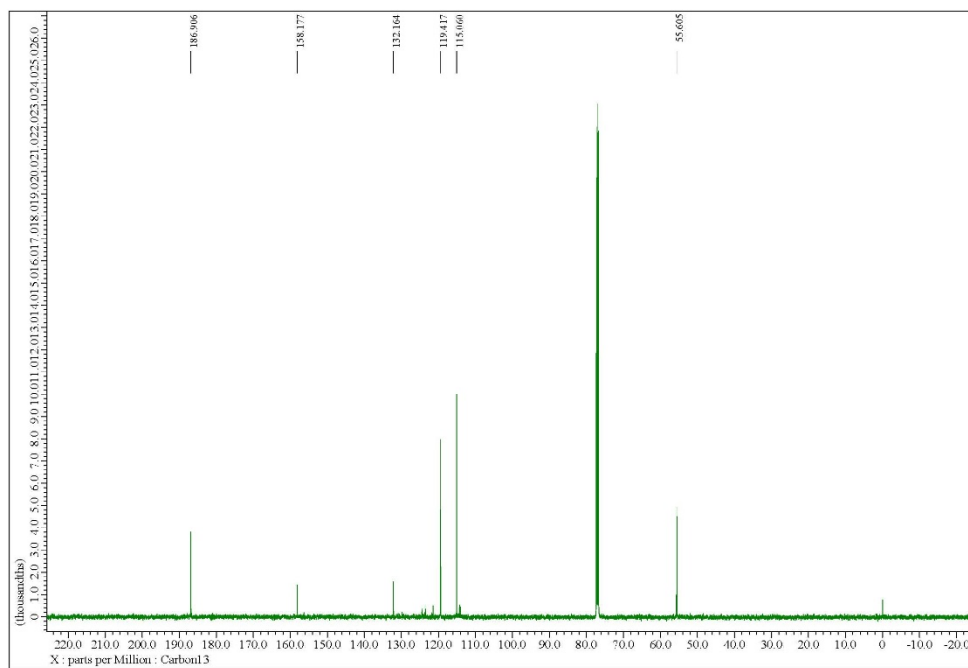


Figure 127. ^1H NMR spectrum of 8f

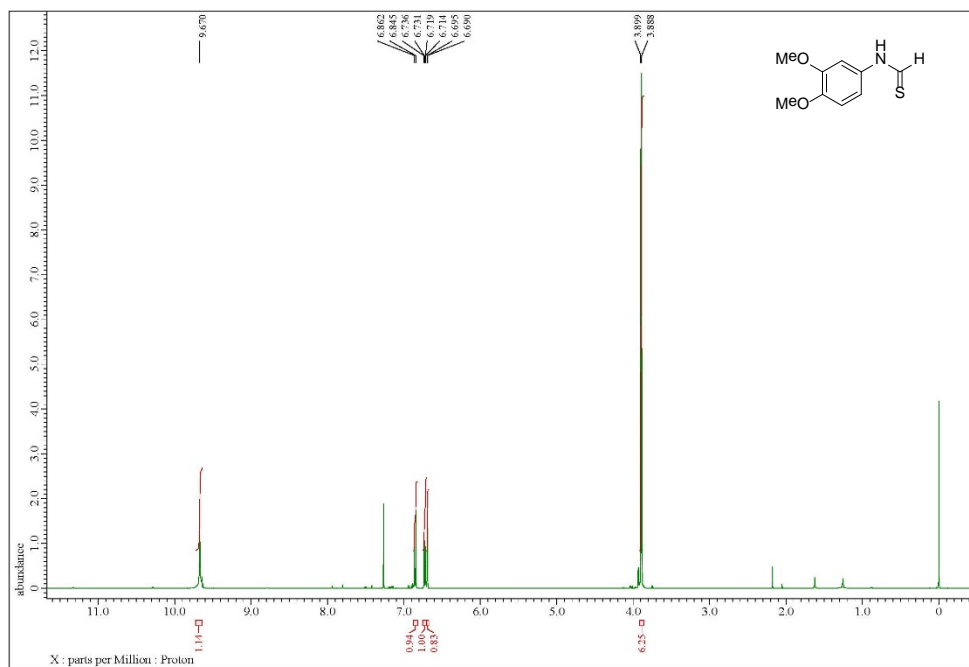


Figure 128. ^{13}C NMR spectrum of 8f

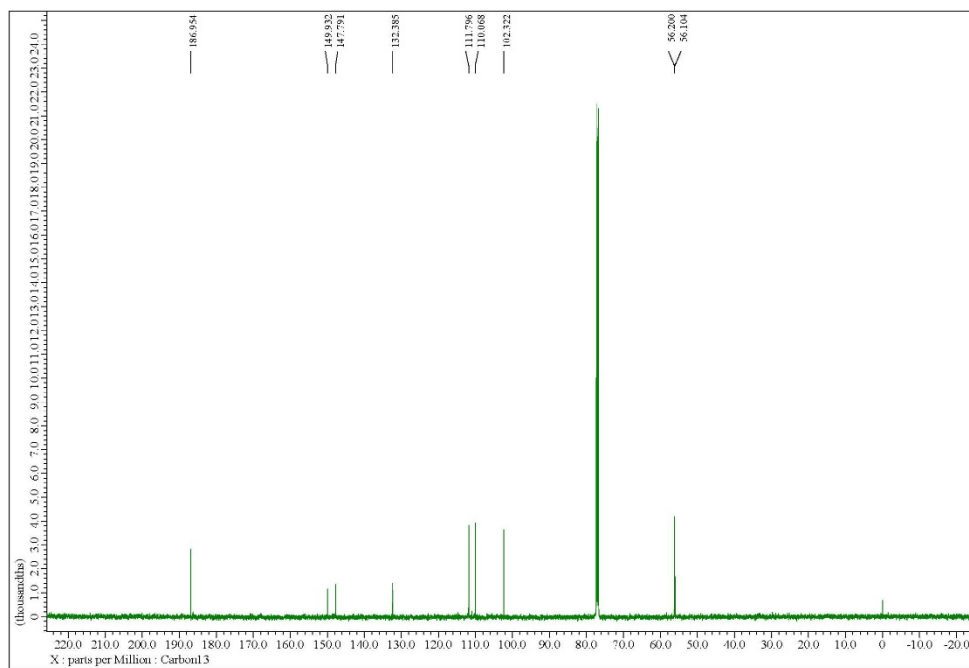


Figure 129. ^1H NMR spectrum of 8g

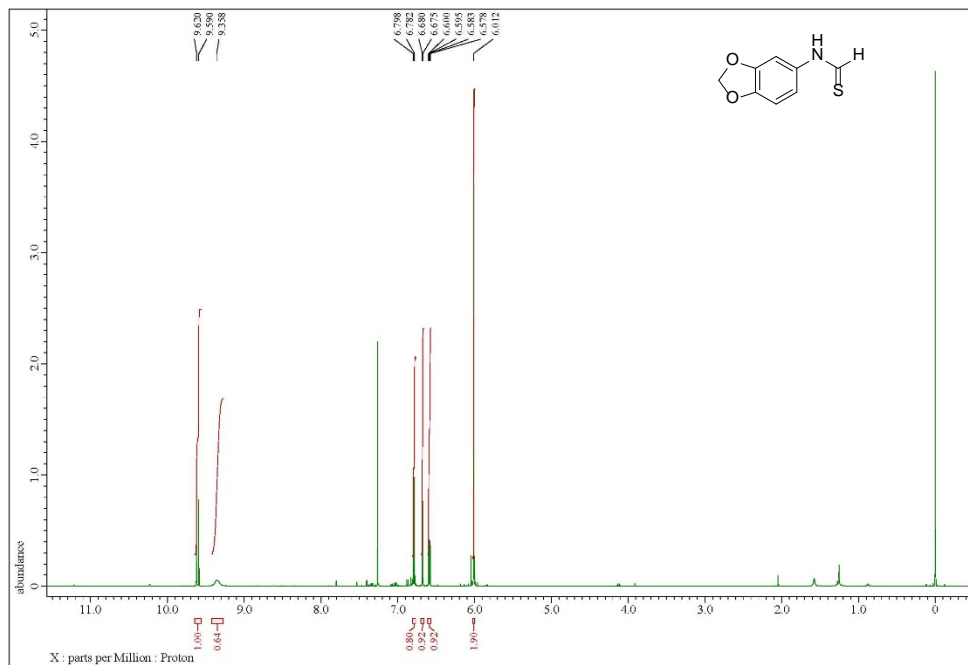


Figure 130. ^{13}C NMR spectrum of 8g

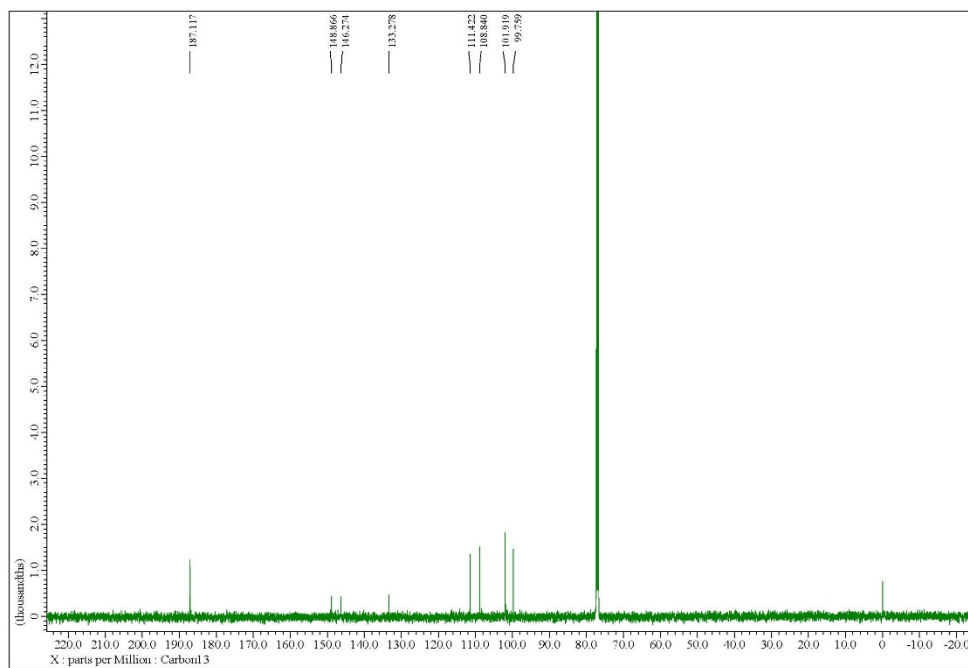


Figure 133. ^1H NMR spectrum of 8i

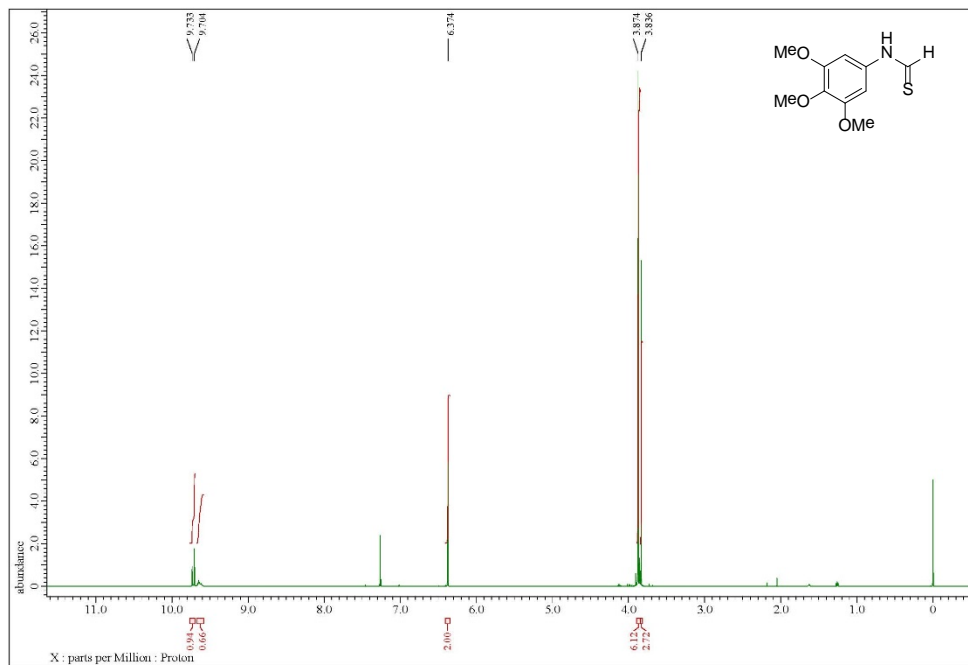


Figure 134. ^{13}C NMR spectrum of 8i

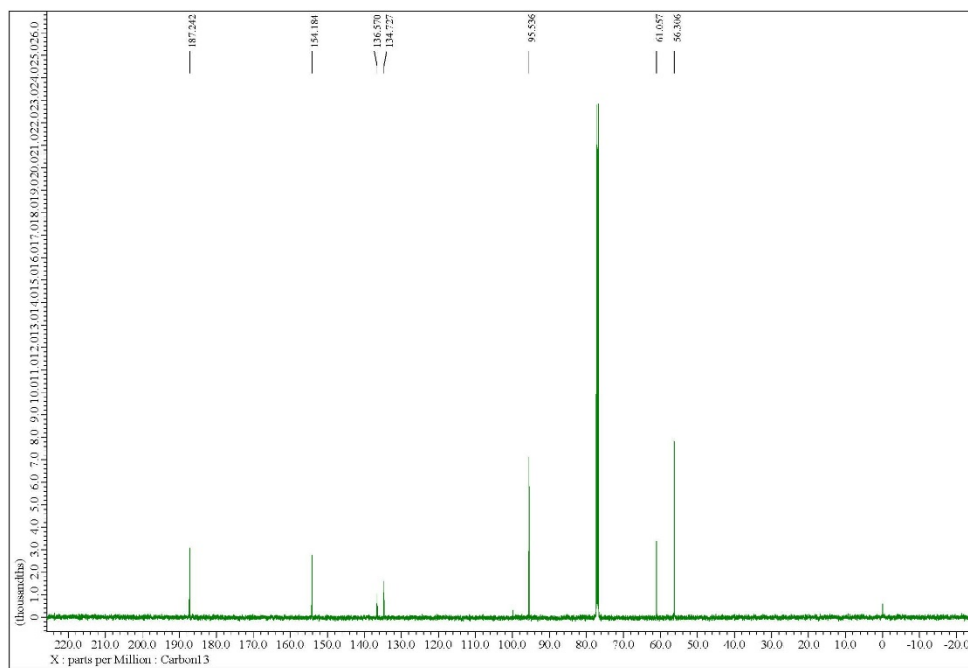


Figure 135. ^1H NMR spectrum of 8j

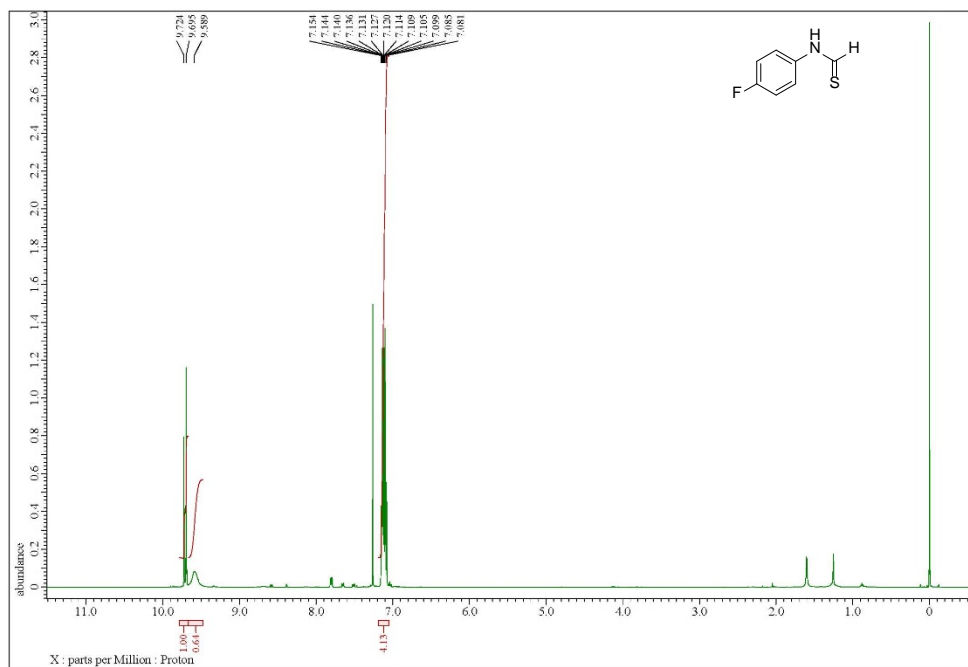


Figure 136. ^{13}C NMR spectrum of 8j

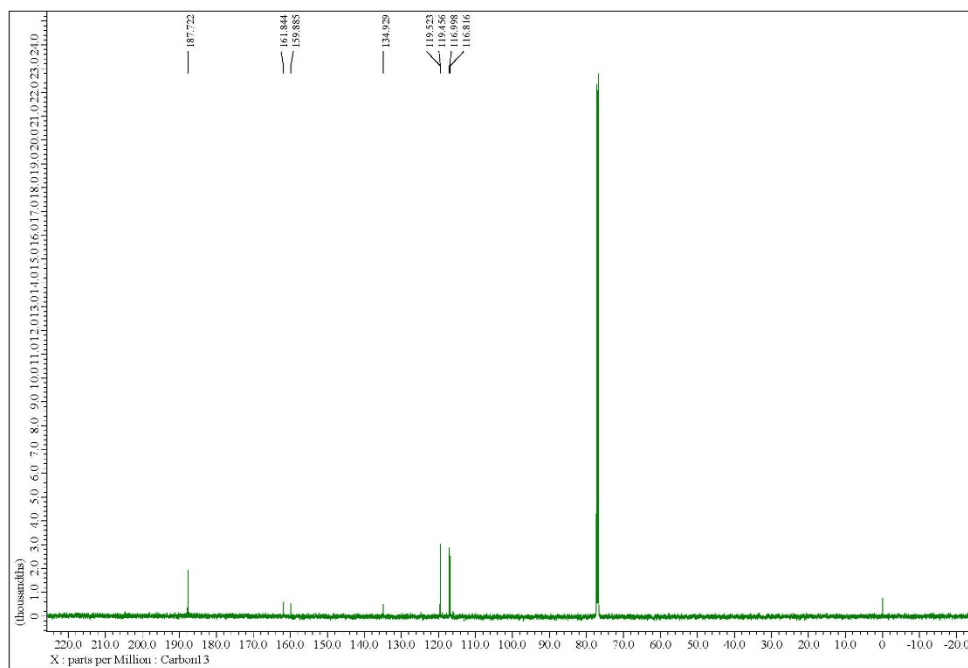


Figure 137. ^1H NMR spectrum of 8k

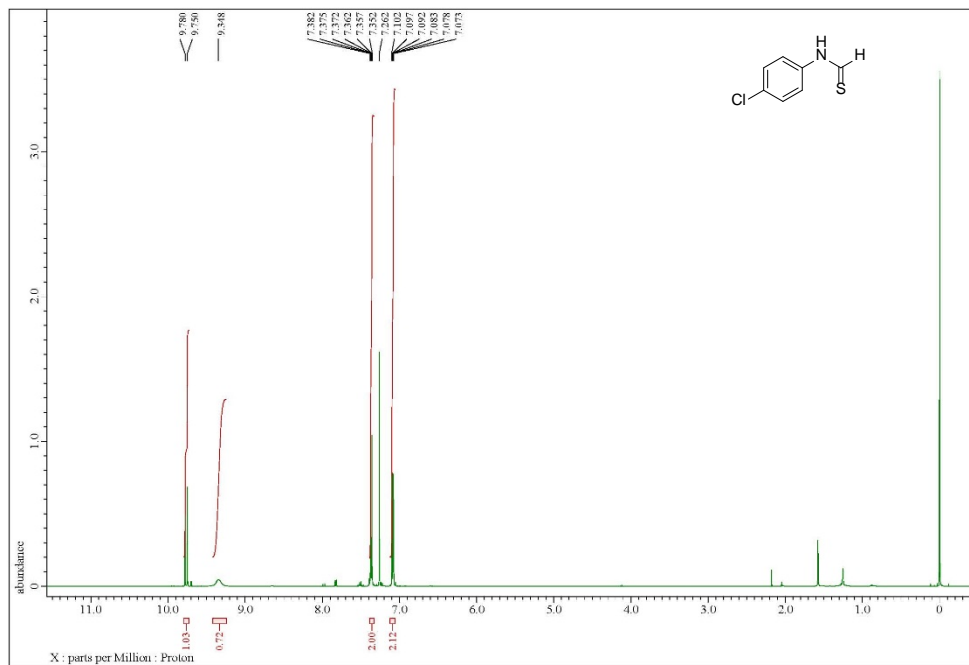


Figure 138. ^{13}C NMR spectrum of 8k

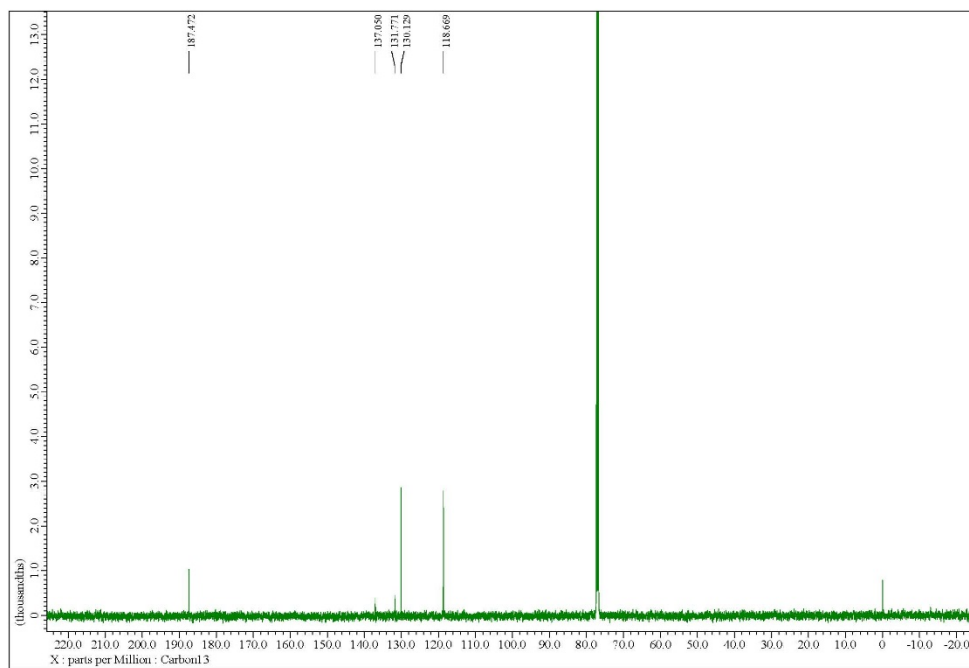


Figure 139. ^1H NMR spectrum of 81

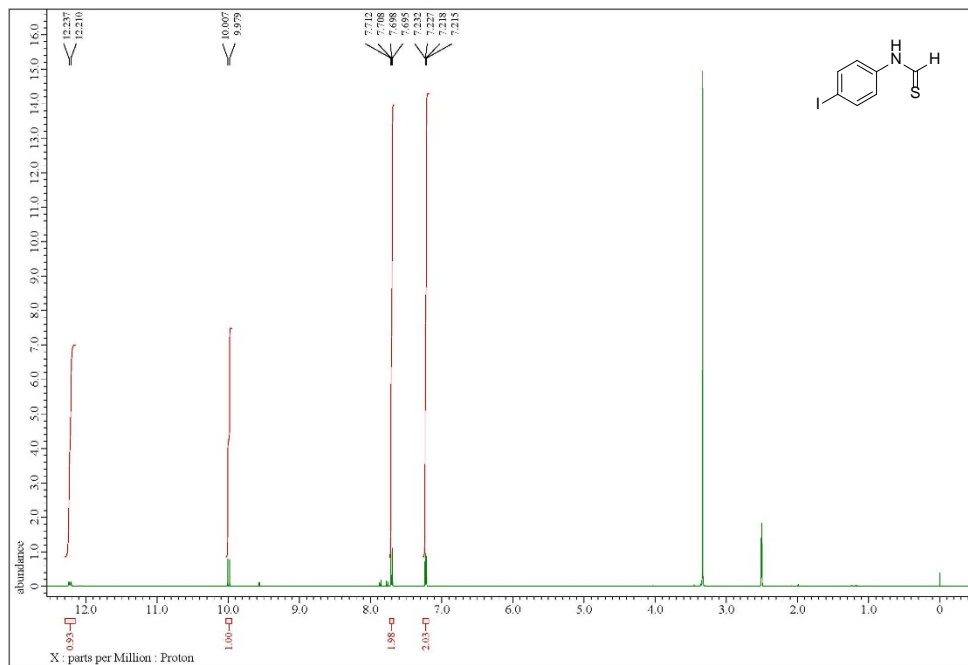


Figure 140. ^{13}C NMR spectrum of 81

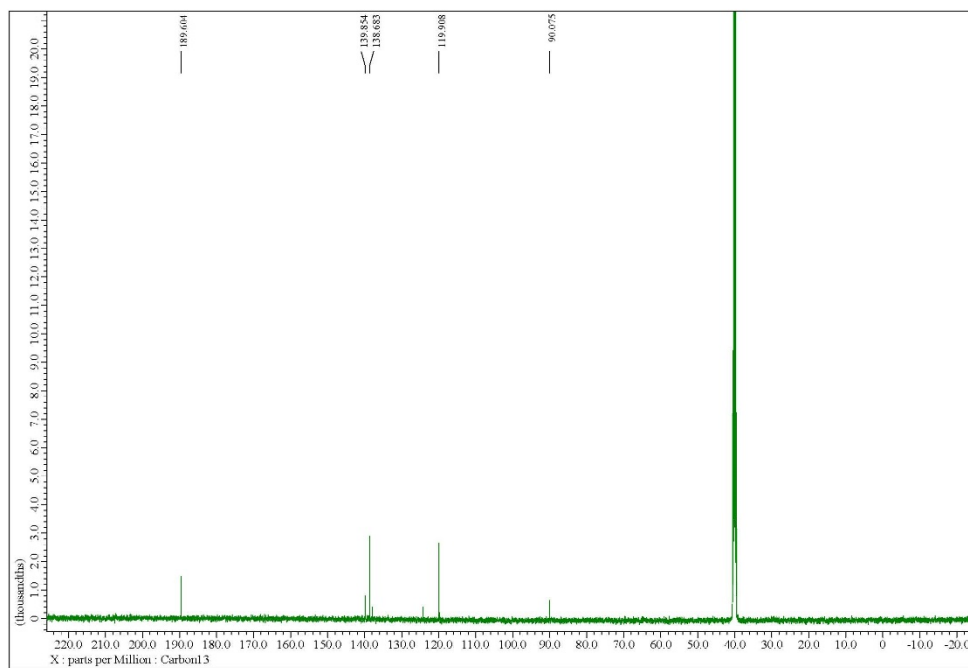


Figure 141. ^1H NMR spectrum of 8m

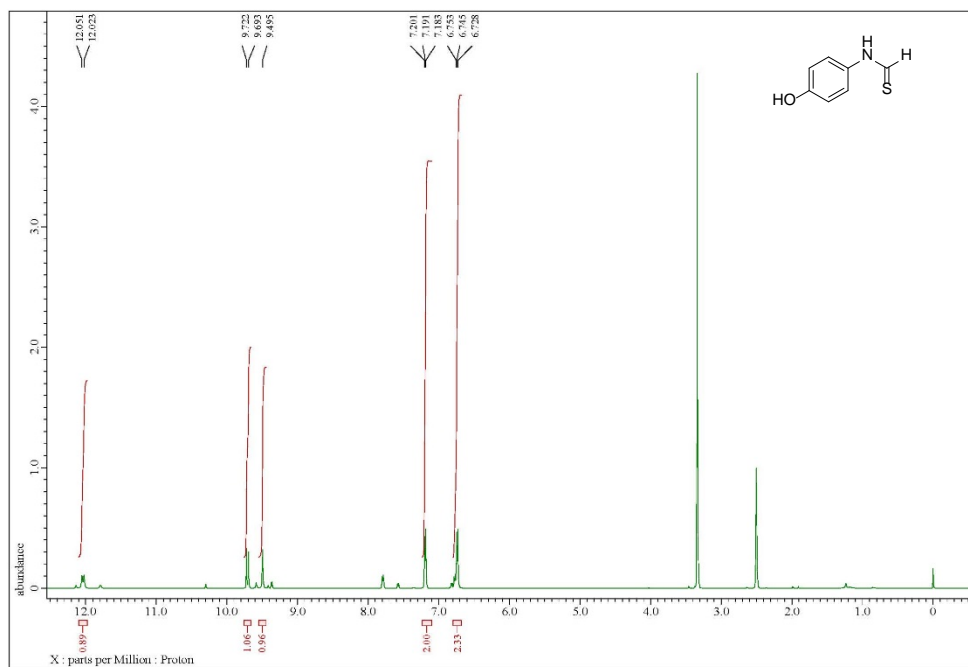


Figure 142. ^{13}C NMR spectrum of 8m

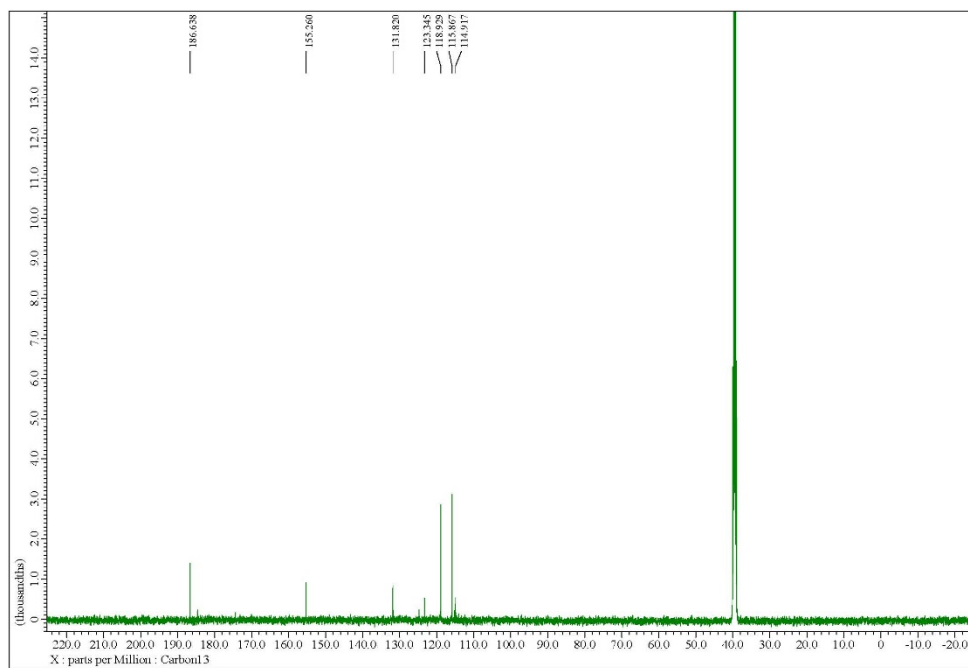


Figure 143. ^1H NMR spectrum of 8n

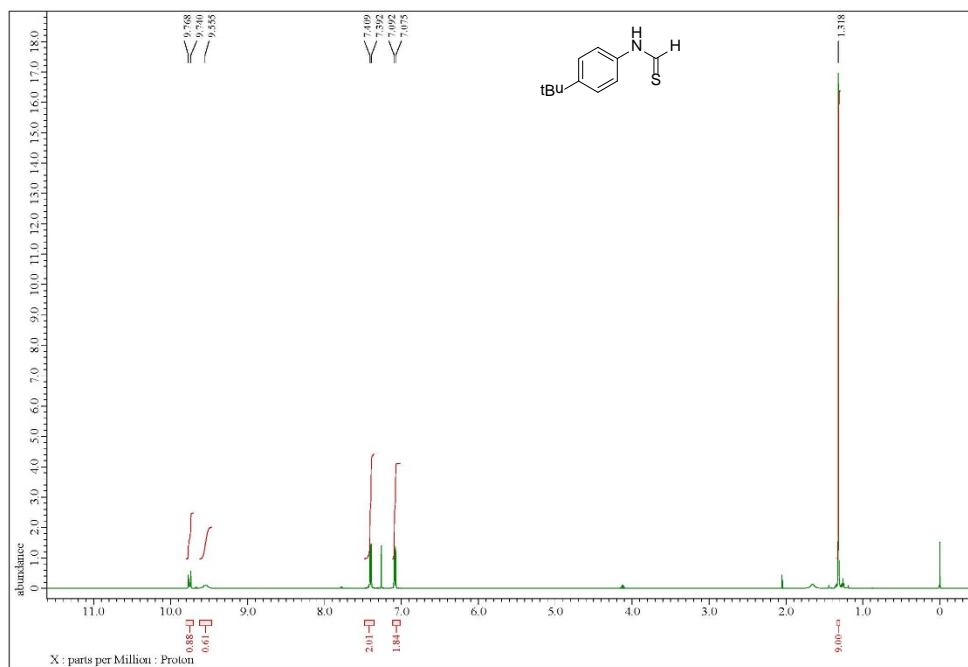


Figure 144. ^{13}C NMR spectrum of 8n

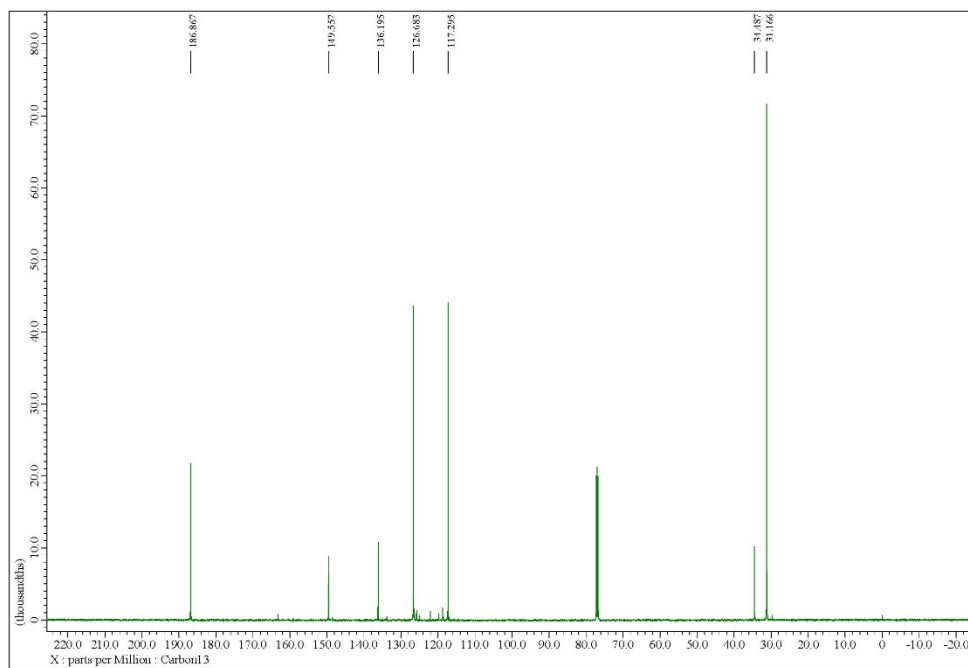


Figure 145. ^1H NMR spectrum of 8o

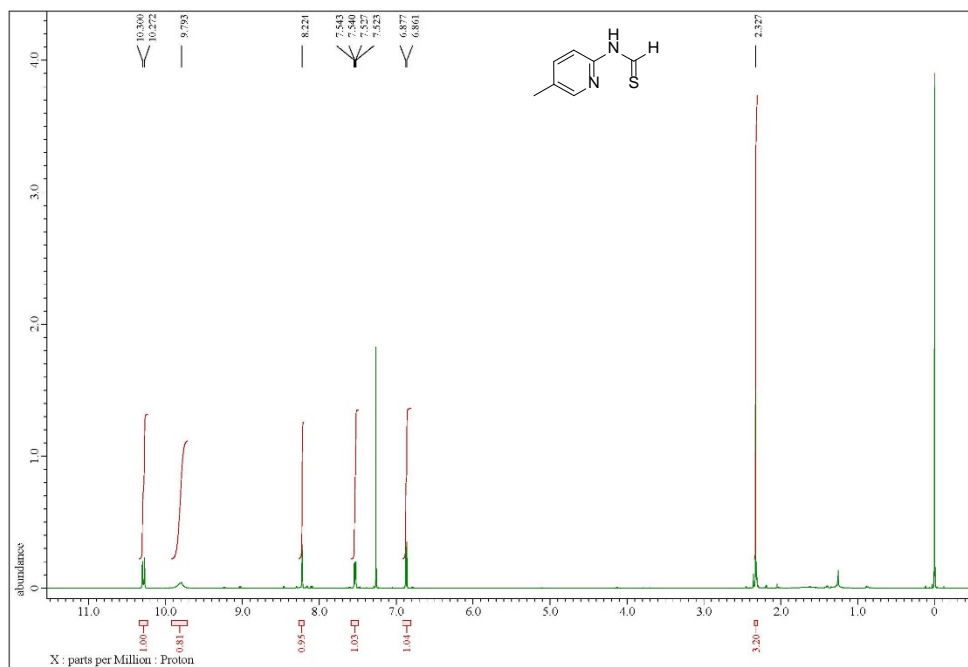


Figure 146. ^{13}C NMR spectrum of 8o

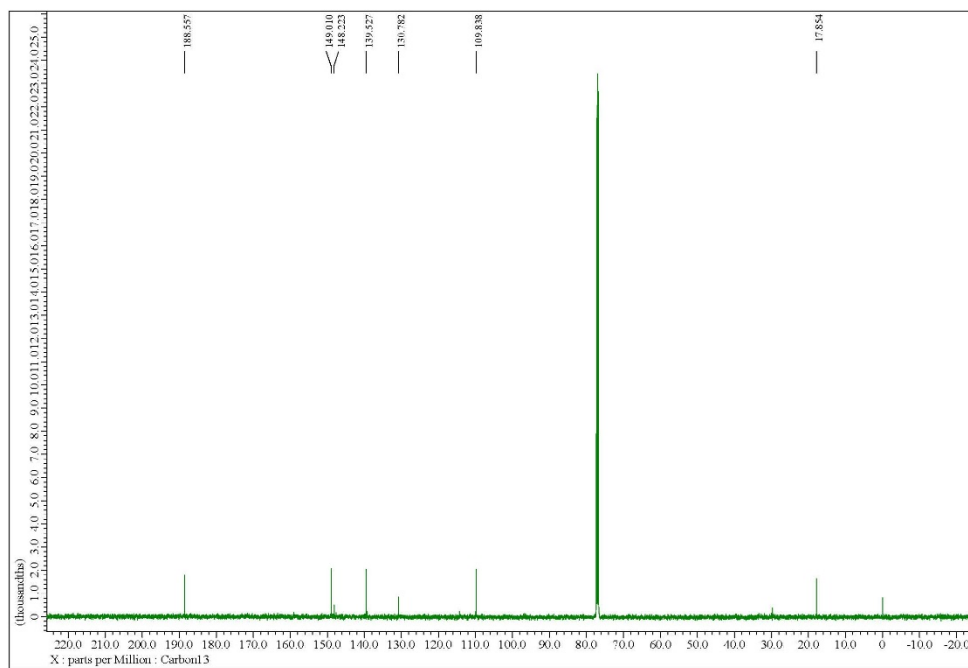


Figure 147. ^1H NMR spectrum of 8p

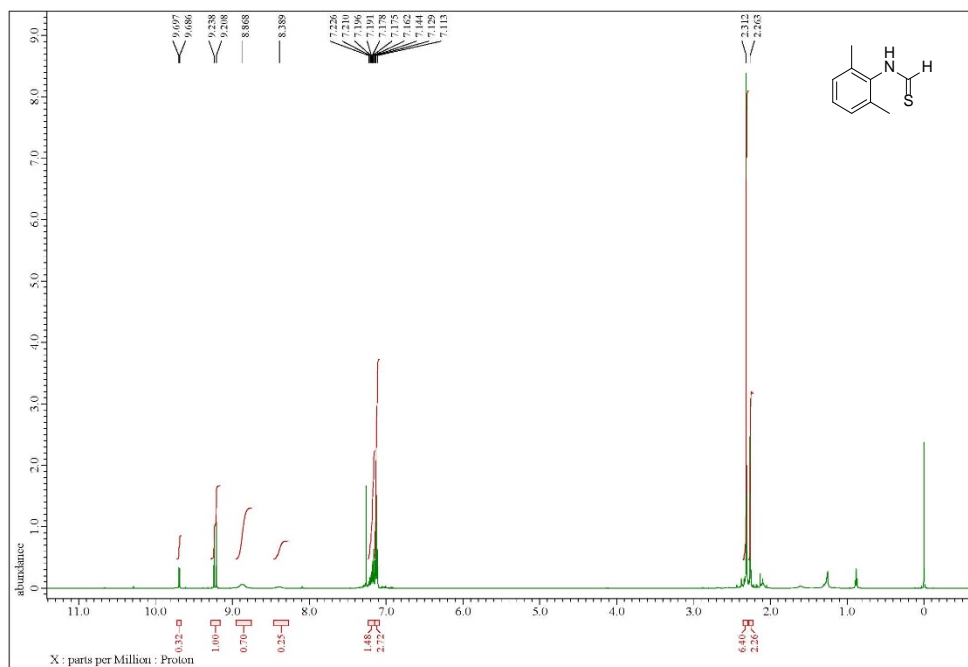


Figure 148. ^{13}C NMR spectrum of 8p

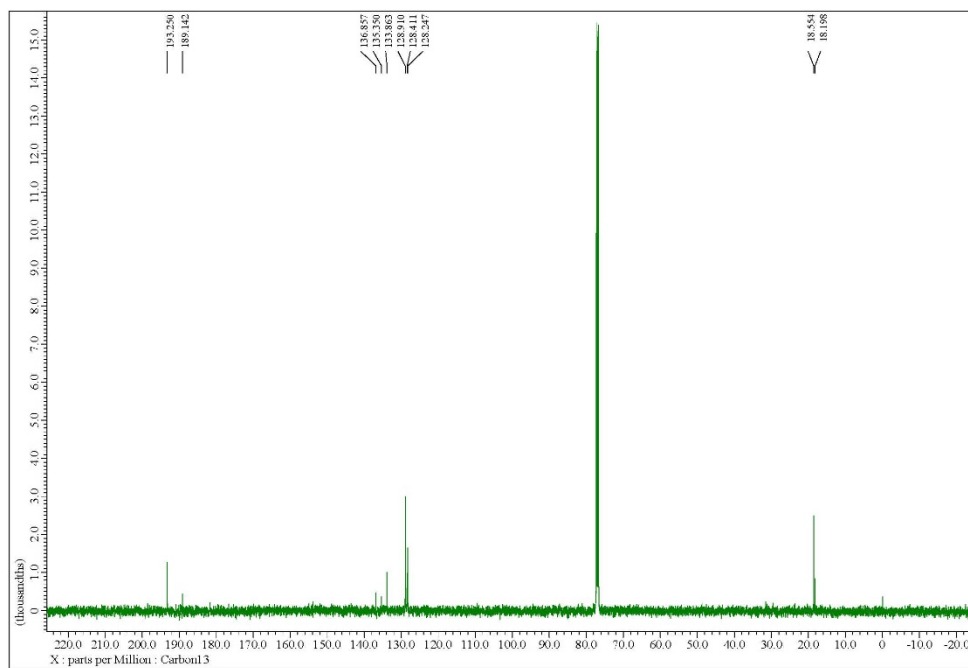


Figure 149. ^1H NMR spectrum of 8q

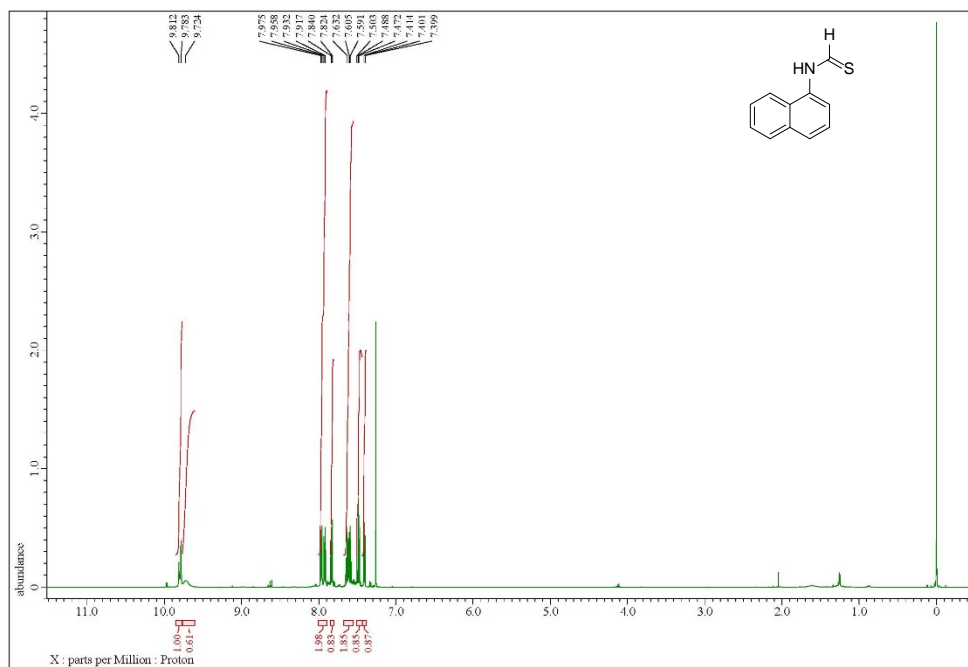


Figure 150. ^{13}C NMR spectrum of 8q

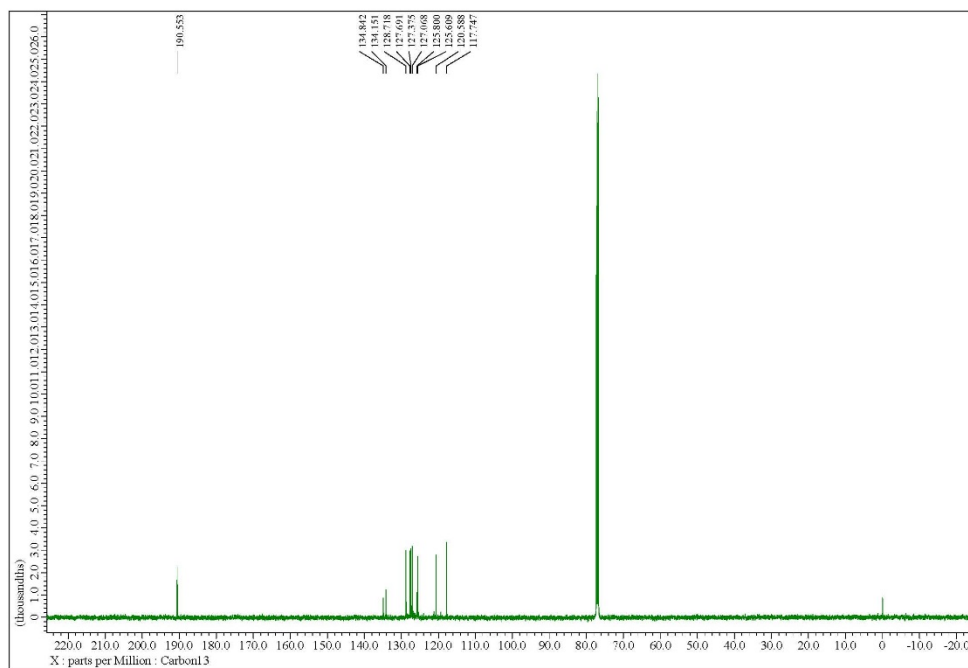


Figure 151. ^1H NMR spectrum of 8r

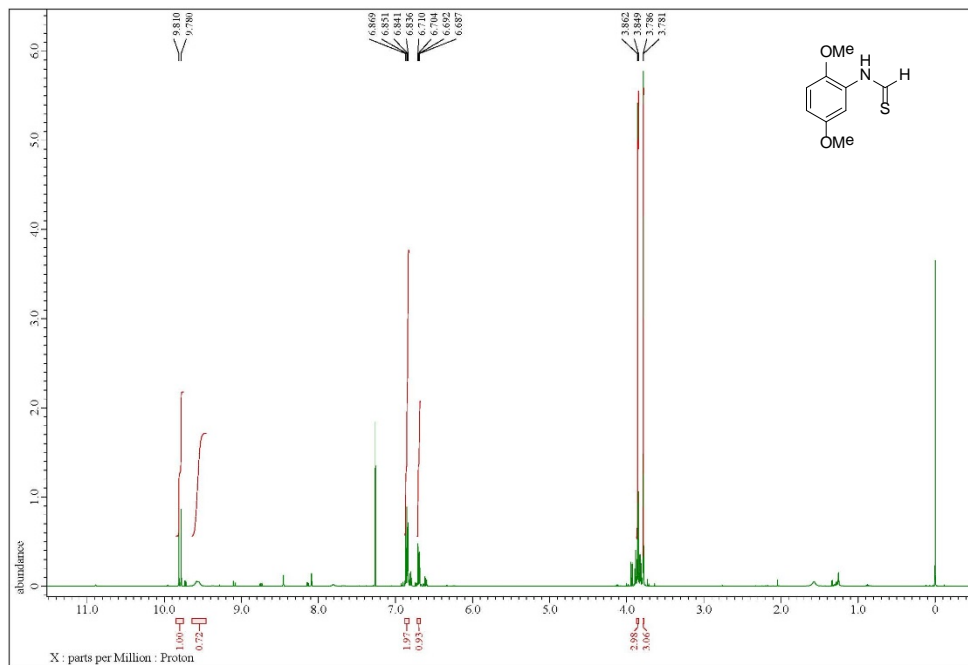


Figure 152. ^{13}C NMR spectrum of 8r

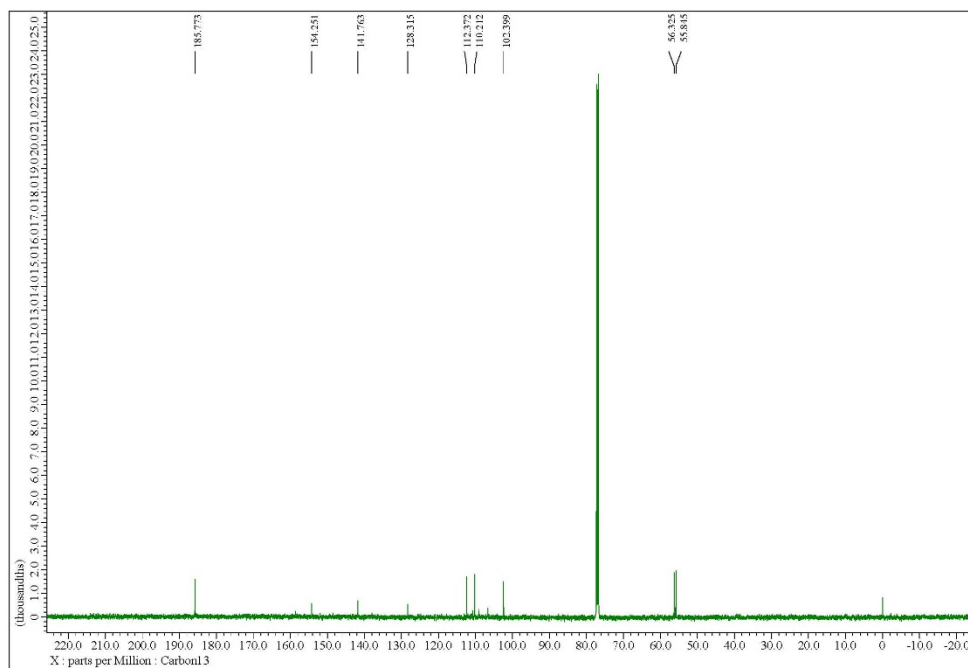


Figure 153. ^1H NMR spectrum of 8s

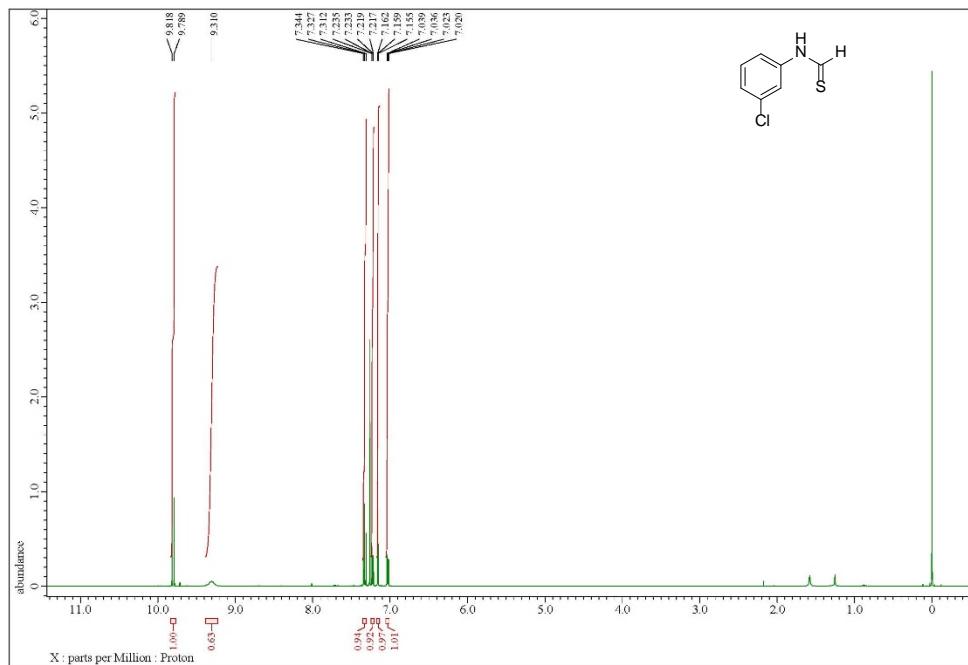


Figure 154. ^{13}C NMR spectrum of 8s

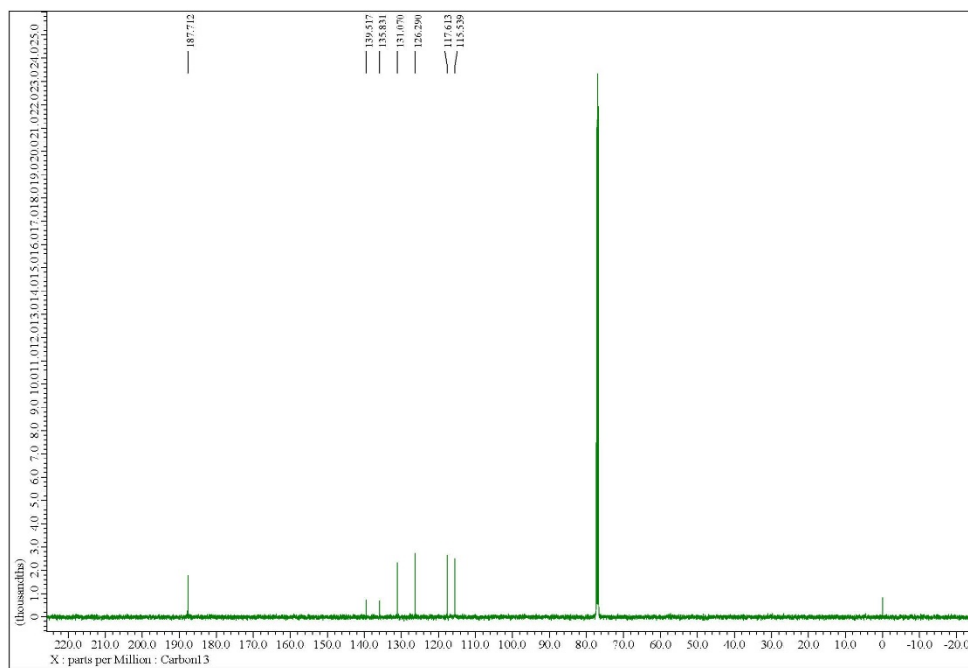


Figure 155. ^1H NMR spectrum of 8t

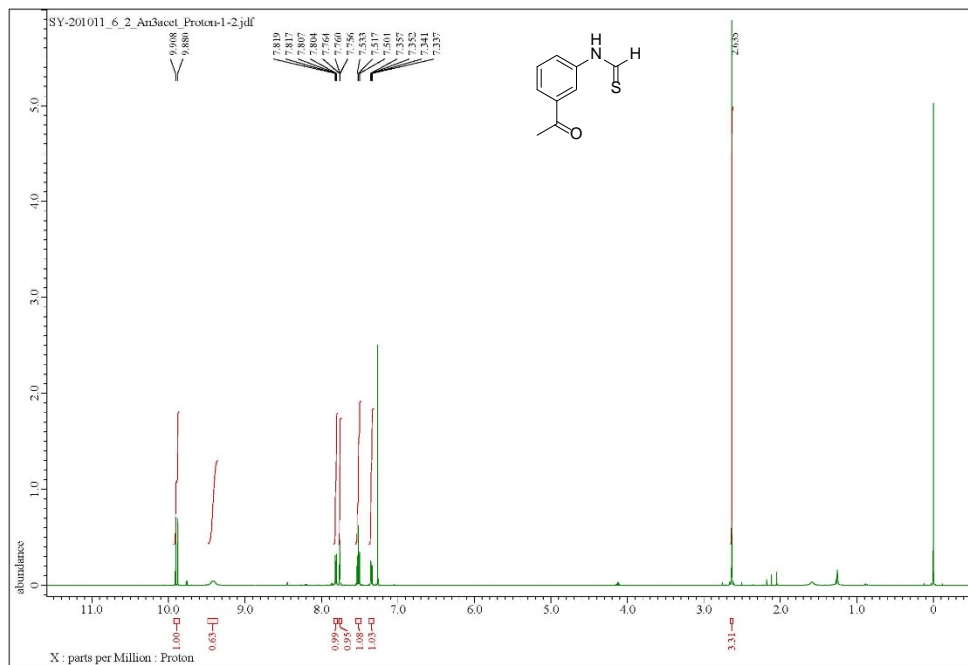


Figure 156. ^{13}C NMR spectrum of 8t

