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SUPPORTING INFORMATION

Laboratory Experiment: Synthesis and Characterization of 4-Methyl-*N*-(phenylacetyl)benzenesulfonamide through Cu(I)-Catalysis

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■ Information for an Instructor or a Teaching Assistant

1. Assessment

· Overall Evaluation:
prelab-report (30%) + experimental performance (25%) + postlab-report (45%)
· Evaluation Items on Prelab-report:
– Review of prelab materials[1]
– Prelab Questions
– Experimental Procedure
– MSDS Information on Chemicals
· Evaluation Items on Experimental Performance:
– Safety
– Thin Layer Chromatography
– %yield
– Melting Point
· Evaluation Items on Postlab-report:
– Analysis of Spectra
– Interpretation of Experimental Results including %yield, melting point, and spectra
– Consideration of Plausible Reaction Mechanism, roughly
– There is no special Postlab-Questions.

2. Prelab Report and Prelab Questions

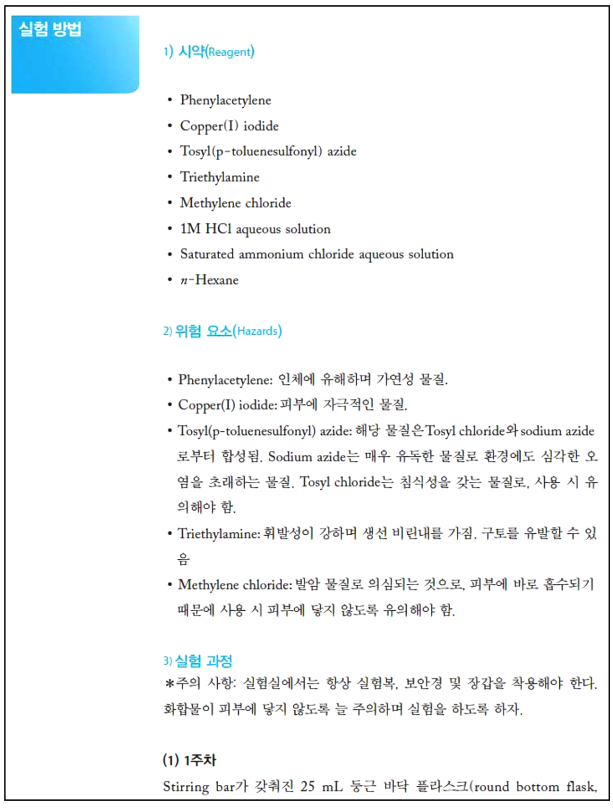
· Experimental Procedure:
The material of experimental procedure was provided to students before a week of the lab class with the following document in page 2. Because all students was Korean, so the material was written in Korean. For the English version of experimental procedure, please see the page 11 in '*2. Experimental Information*'.
· MSDS Information on Chemicals:
The basic information on hazards was given by the prelab material in page 2. But the detailed MSDS information on chemicals should be done by student's own online-search.
· Prelab Questions:
The prelab questions are also given in page 3, Korean. The English version is as follows:

1. What is the recrystallization?
2. There is another purification method for solid-state compounds, sublimation. What are the differences between recrystallization and sublimation?

■ Experimental Information

1. General

Infrared (IR) spectra were recorded on a SHIMADZU IRAFFINITY-1 spectrophotometer, n_{max} in cm^{-1}. The ^1H NMR spectrum was recorded on a Bruker 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26). The ^{13}C NMR spectrum was


실험 방법

1) 시약(Reagent)

- Phenylacetylene
- Copper(I) iodide
- Tosyl(p-toluenesulfonyl) azide
- Triethylamine
- Methylene chloride
- 1M HCl aqueous solution
- Saturated ammonium chloride aqueous solution
- *n*-Hexane

2) 위험 요소(Hazards)

- Phenylacetylene: 인체에 유해하며 가연성 물질.
- Copper(I) iodide: 피부에 자극적인 물질.
- Tosyl(p-toluenesulfonyl) azide: 해당 물질은 Tosyl chloride와 sodium azide로부터 합성됨. Sodium azide는 매우 유독한 물질로 환경에도 심각한 오염을 초래하는 물질. Tosyl chloride는 침식성을 갖는 물질로, 사용 시 유의해야 함.
- Triethylamine: 휘발성이 강하며 생선 비린내를 가짐. 구토를 유발할 수 있음
- Methylene chloride: 발암 물질로 의심되는 것으로, 피부에 바로 흡수되기 때문에 사용 시 피부에 닿지 않도록 유의해야 함.

3) 실험 과정

*주의 사항: 실험실에서는 항상 실험복, 보안경 및 장갑을 착용해야 한다. 화합물이 피부에 닿지 않도록 늘 주의하며 실험을 하도록 하자.

(1) 1주차

Stirring bar가 갖춰진 25 mL 둥근 바닥 플라스크(round bottom flask,

***Figure* S1.** First Page of Prelab Materials.

RBF)에 주사기를 이용해 110 μL의 phenylacetylene과 216 mg의 tosyl azide을 넣는다. 약수저를 이용하여 3.8 mg의 CuI를 측정하여 플라스크에 넣은 후, 2 mL의 증류수를 넣어준다. 0.16 mL의 triethylamine을 주사기를 이용하여 반응 용기에 천천히 넣어준 후, 상온에서 1시간 동안 stirring 해준다(그림 6-3). 1시간 후, 6 mL의 포화된 염화암모늄 수용액을 넣어주고, 4 mL의 CH_2Cl_2를 추가로 반응 용기에 넣어 유기층과 물층을 분리하는 '층분리'를 한다. 15분 정도 stirring을 하여 반응을 충분히 종결시킨 후, 2주차에 생성물을 분리하는 과정을 진행하도록 한다.

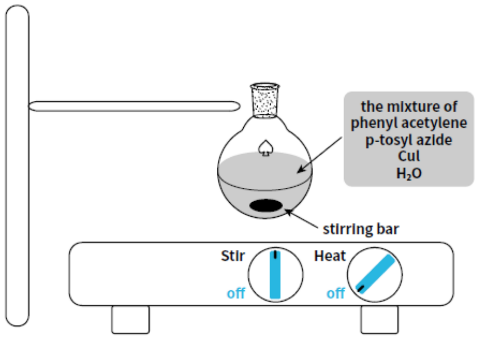


그림 6-3 C-H 활성화 반응 용기

Stirring bar가 갖춰진 25 mL 둥근 바닥 플라스크(round bottom flask, RBF)에 주사기를 이용해 110 μL의 phenylacetylene과 216 mg의 tosyl azide을 넣는다. 약수저를 이용하여 3.8 mg의 CuI를 측정하여 플라스크에 넣은 후, 2 mL의 증류수를 넣어준다. 0.16 mL의 triethylamine을 주사기를 이용하여 반응 용기에 천천히 넣어준 후, 상온에서 1시간 동안 stirring 해준다(그림 6-3). 1시간 후, 6 mL의 포화된 염화암모늄 수용액을 넣어주고, 4 mL의 CH_2Cl_2를 추가로 반응 용기에 넣어 유기층과 물층을 분리하는 '층분리'를 한다. 15분 정도 stirring을 하여 반응을 충분히 종결시킨 후, 2주차에 생성물을 분리하는 과정을 진행하도록 한다.

***Figure* S2.** Second Page of Prelab Materials.

recorded on a Bruker 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16). The melting point was determined by a METTLER-TOLEDO MP50 melting point system.

Experiments were conducted open to the atmosphere. Work-up and purification procedures were carried out with reagent grade solvent (Acetone, CH_2Cl_2, *n*-hexanes; purchased from DUKSAN Company) in air. Distilled water was obtained by a high-purity water producing device, Milli-Q Direct 8.

2. Reagents

Ammonium Chloride was purchased from Junsei Chemical Co., Ltd. and used as received.

Copper(I) iodide was purchased from SIGMA-ALDRICH and used as received.

(2) 2주차

6 mL의 1M 염산 수용액을 넣어주고 분별깔대기를 이용해 유기층을 물층에서 분리해낸다 (그림 6-4).

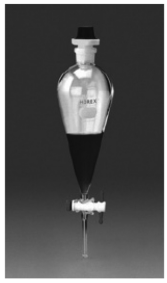


그림 6-4 분별깔대기를 이용한 혼합물의 분리

분별깔대기에 남겨진 물층에 10 mL의 CH_2Cl_2를 넣고 유기층을 분리하는 위의 과정을 2번 정도 반복한다. 각 차례에서 유기층을 빼어낼 때는 처음 유기층을 담아두었던 플라스크를 이용해 받아낸다. 모아진 유기층은 황산나트륨 무수물을 이용해 유기층 내 수분을 제거하고 여과와 rotary evaporator를 이용한 휘발성 용매의 증발을 통해 생성물을 농축시킨다. 농축된 혼합물을 CH_2Cl_2/hexane을 이용한 재결정을 통해 생성물을 분리하고 여과, 건조 후 생성물의 FT-IR, 녹는점 data를 얻도록 한다. 실험 마친 후 조교가 얻은 생성물에 대한 ^1H, ^{13}C NMR 스펙트럼을 통해 화합물의 구조를 분석하도록 한다. 이때, 스펙트럼에서 각 봉우리에 해당하는 탄소 및 수소가 생성물 분자 내에 어떤 탄소 및 수소를 가리키는지 보고서에 나타내야 한다.

***Figure* S3.** Third Page of Prelab Materials.

1M HCl aqueous solution was made by dilution of 35% HCl aqueous solution from MATSUNDEN Chemicals Ltd. with distilled water.

Phenylacetylene was purchased from SIGMA-ALDRICH and used as received.

Sodium azide was purchased from SIGMA-ALDRICH and used as received.

Sodium sulfate anhydrous was purchased form Junsei Chemical Co., Ltd. and used as received.

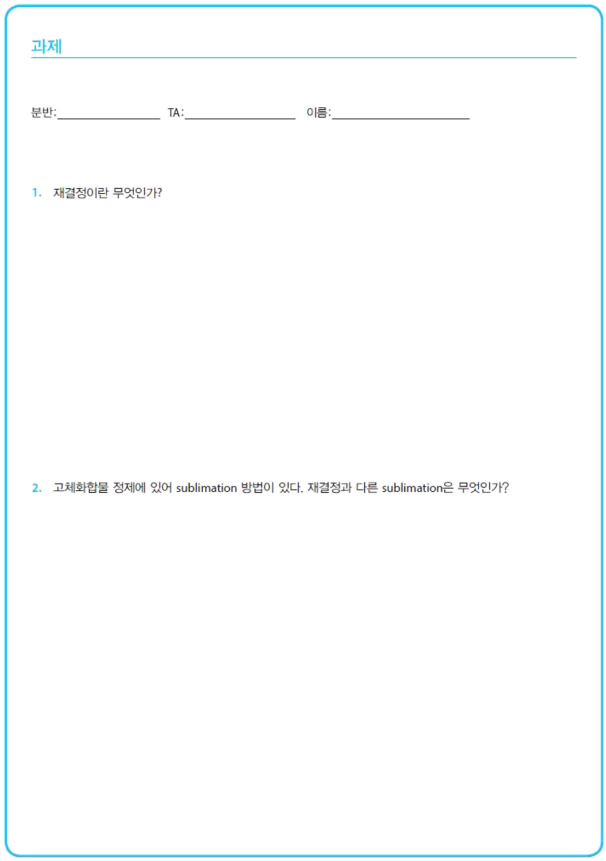
p-Toluensulfonyl azide[2] was prepared by a skilled instructor from *p*-toluenesulfonyl chloride and sodium azide based on established method.

p-Toluensulfonyl chloride was purchased from SIGMA-ALDRICH and used as received.

Triethylamine was purchased from SIGMA-ALDRICH and used as received.

3. Hazards

Students' investigation of MSDS information on chemicals is highly recommended. The reported MSDS information on chemicals are as following. In case of 4-methyl-*N*-(phenylacetyl)benzenesulfonamide (a product), the detailed MSDS information has not been reported. But it should be regarded as a skin and eye irritating toxin.


과제

분반:_____ TA:_____ 이름:_____

1. 재결정이란 무엇인가?

2. 고체화합물 정제에 있어 sublimation 방법이 있다. 재결정과 다른 sublimation은 무엇인가?

***Figure* S4.** Prelab Questions.

3-1. Ammonium chloride (CAS number: 12125-02-9)
· Pictogram:

· Warning: Harmful if swallowed. Causes serious eye irritation.

3-2. Copper (I) iodide (CAS number: 7681-65-4)
· Pictogram:

· Warning: Harmful if swallowed. Causes skin irritation and serious eye damage. May cause respiratory irritation. Very toxic to aquatic life with long lasting effects.

3-3. Dichloromethane (CAS number: 75-09-2)
· Pictogram:

· Warning: Causes skin irritation and serious eye irritation. May cause respiratory irritations and drowsiness or dizziness. Suspected of causing cancer. May cause damage to organs (liver, blood) through prolonged or repeated exposure if swallowed. May cause damage to organs (central nervous system) through prolonged or repeated exposure if inhaled. Do not breathe vapor.

3-4. Hexane (CAS number: 110-54-3)
· Pictogram:

· Warning: Highly flammable liquid and vapor. May be fatal if swallowed and enters airways. Causes skin irritation and serious eye irritation. May cause drowsiness or dizziness. Suspected of damaging fertility. May cause damage to organs through prolonged or repeated exposure. Toxic to aquatic life with long lasting effects. Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking.

3-5. Phenylacetylene (CAS number: 536-74-3)
· Pictogram:

· Warning: Flammable liquid and vapor. May be fatal if swallowed and enters airways. Causes skin irritation and serious eye irritation.

3-6. Triethylamine (CAS number: 121-44-8)
· Pictogram:

· Warning: Highly flammable liquid and vapor. Harmful if swallowed. Toxic in contact with skin or if inhaled. Causes severe skin burns sand eye damage. May cause respiratory irritation. Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking.

3-7. *p*-Toluenesulfonyl azide (CAS number: 941-55-9)
· Warning: Heating may cause an explosion. May cause skin irritation and eye irritation. May be harmful if swallowed.

3-8. Deuterated Chloroform, Chloroform-d (CAS number: 865-49-6)

· Pictogram:

· Warning: Suspected of causing cancer. May cause damage to the lung, the kidneys, the liver and the blood through prolonged or repeated exposure. Harmful if swallowed and irritating to skin.

4. Experimental Procedures

Day one:

In a 25-mL round-bottom flask equipped with a stir bar, students added *p*-toluenesulfonyl azide (*p*-TsN_3, 216 mg, 1.1 mmol), copper iodide (CuI, 3.8 mg, 0.04 mmol), and phenylacetylene (110 μL, 1.0 mmol) sequentially to a reaction flask. The order of chemical additions could be changeable, but the given order is recommendable due to practicality. *p*-Toluenesulfonyl azide would be weighed on a reaction apparatus by a pipette and a bulb, and copper iodide would be measured by a spatula in a weighing paper. Finally, phenylacetylene would be measured by a syringe and a needle. Complete addition of three chemicals made students to dissolved them in water (2 mL) under air (inert gas (N_2 or Ar) or Schlenk line were not necessary). Dropwise addition of triethylamine (Et_3N, 0.16 mL, 1.1 mmol) by a syringe and a needle initiated the progress. After complete addition of Et_3N, the reaction flask was sealed with a polyethylene stopper[3] and the reaction mixture was allowed to stir for 1 hour at ambient temperature. Students terminated a reaction by addition of saturated aqueous NH_4Cl solution (6 mL) and CH_2Cl_2 (4 mL). After stirring for an additional 15 min at ambient temperature, the mixture was treated with 1 M HCl (6 mL) and extracted with CH_2Cl_2 (7 mL × 3). With the combined organic layer, students carried out thin-layer chromatography on SiO_2 plates eluting with 1:5 EtOAc/hexanes to check the presence of remained phenylacetylene and produced 4-Methyl-*N*-(phenylacetyl)benzenesulfonamide. Each group was demanded to report the spot size of remained phenylacetylene qualitatively in a postlab report (no starting material, trace, or significant amount). Students sealed the reaction RBF and stored it in a freezer for second laboratory class.

Day two:

In second 2 h laboratory class, students performed the purification and the characterizations of the obtained product. The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated using a rotary evaporator. Students dissolved the crude in about 3 mL of hot CH_2Cl_2 and added more than 15 mL of *n*-hexane carefully by a pipette and a bulb. The mixture was allowed to cool in an ice bath to give the solid product. Students collected the solid *via* filtration along with 2 times-rinse by cooled *n*-hexanes. After drying the product under air for 40 min, students recorded the weight of what they obtained and conducted an experiment for the determination of melting point. Due to the instrument availability, only two groups in each class carried out to obtain FT-IR spectra. Other groups were provided with copies of the IR spectra. In case of NMR spectra, they were obtained by an instructor and the copies of NMR spectra were given to students for analysis of the structure.

■ **Spectra**

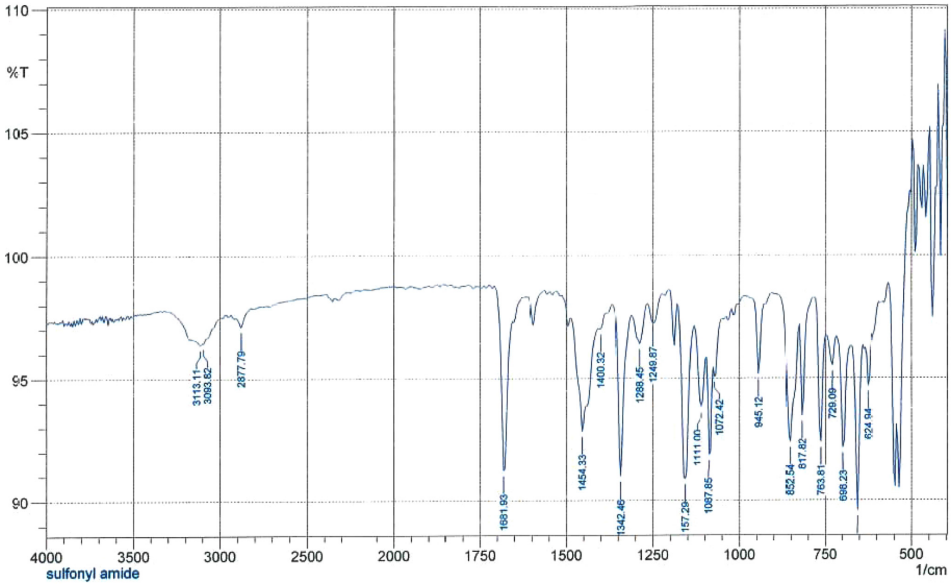


***Figure* S5.** FT-IR spectrum of 4-methyl-*N*-(phenylacetyl)benzenesulfonamide.

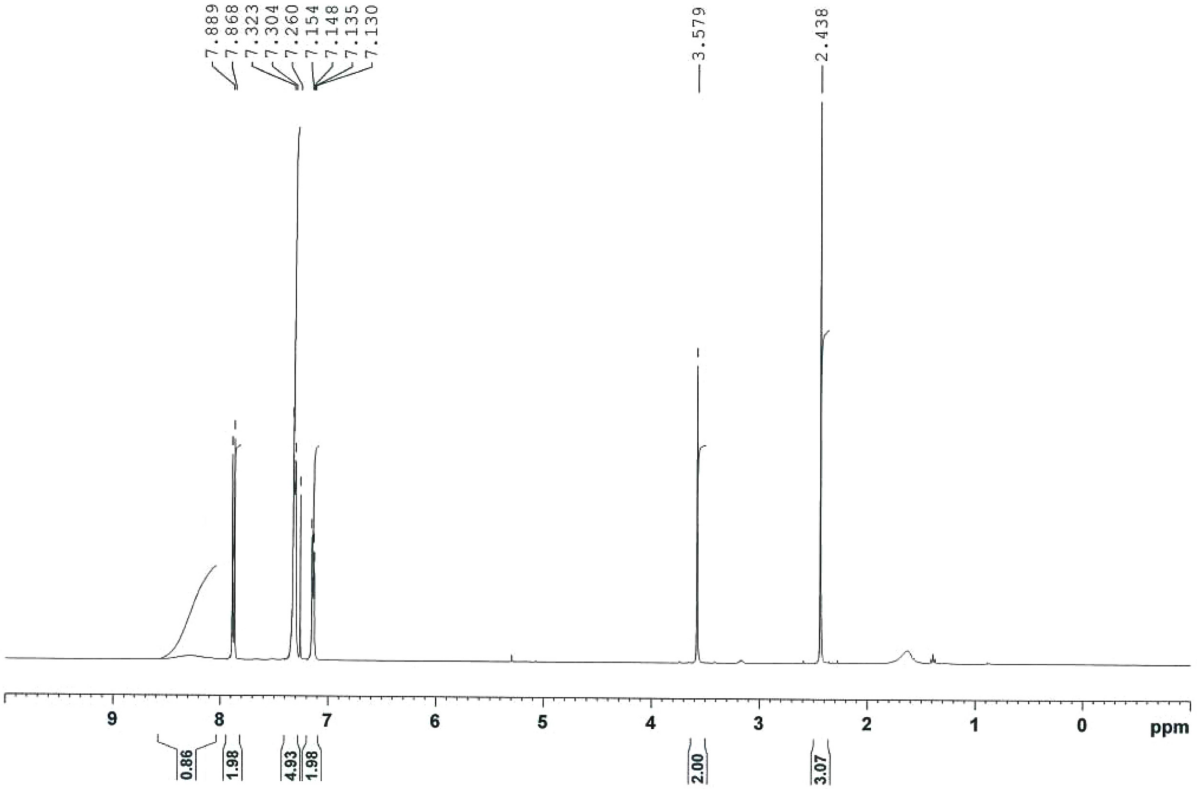


***Figure* S6.** ^{1}H NMR spectrum of 4-methyl-*N*-(phenylacetyl)benzenesulfonamide.

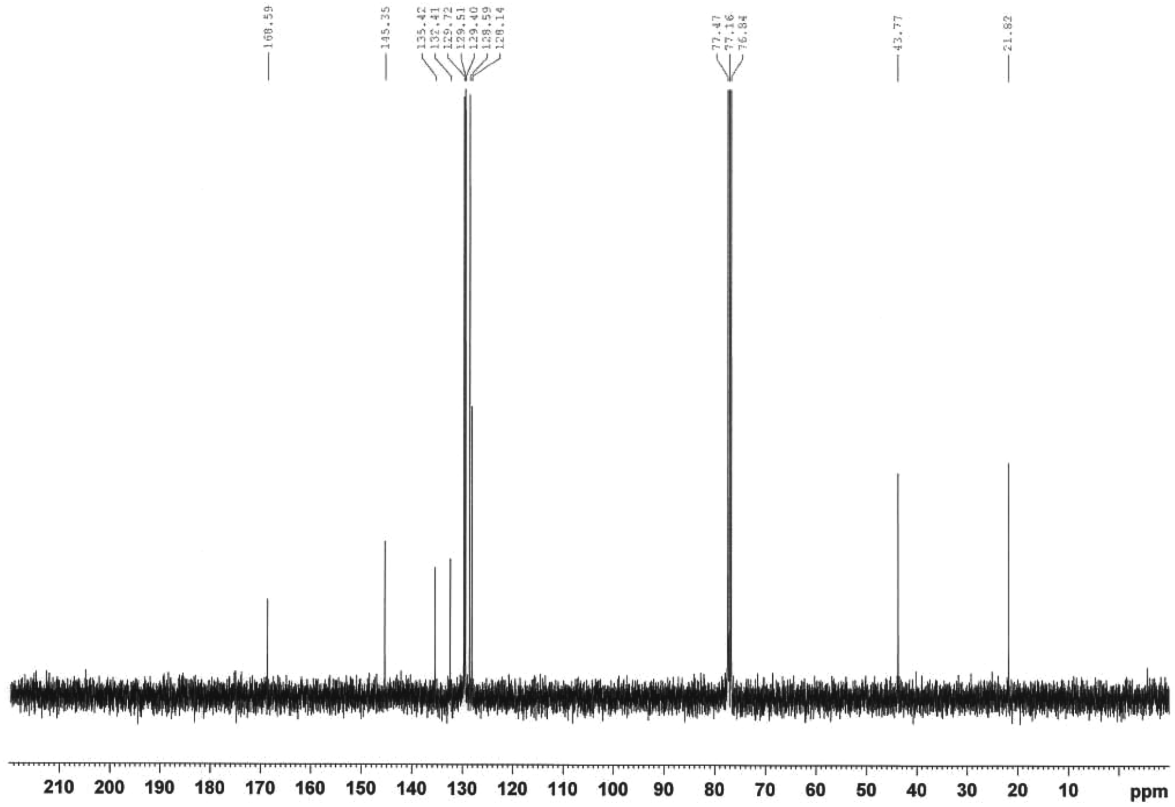


***Figure* S7.** ^{13}C NMR spectrum of 4-methyl-*N*-(phenylacetyl)benzenesulfonamide.

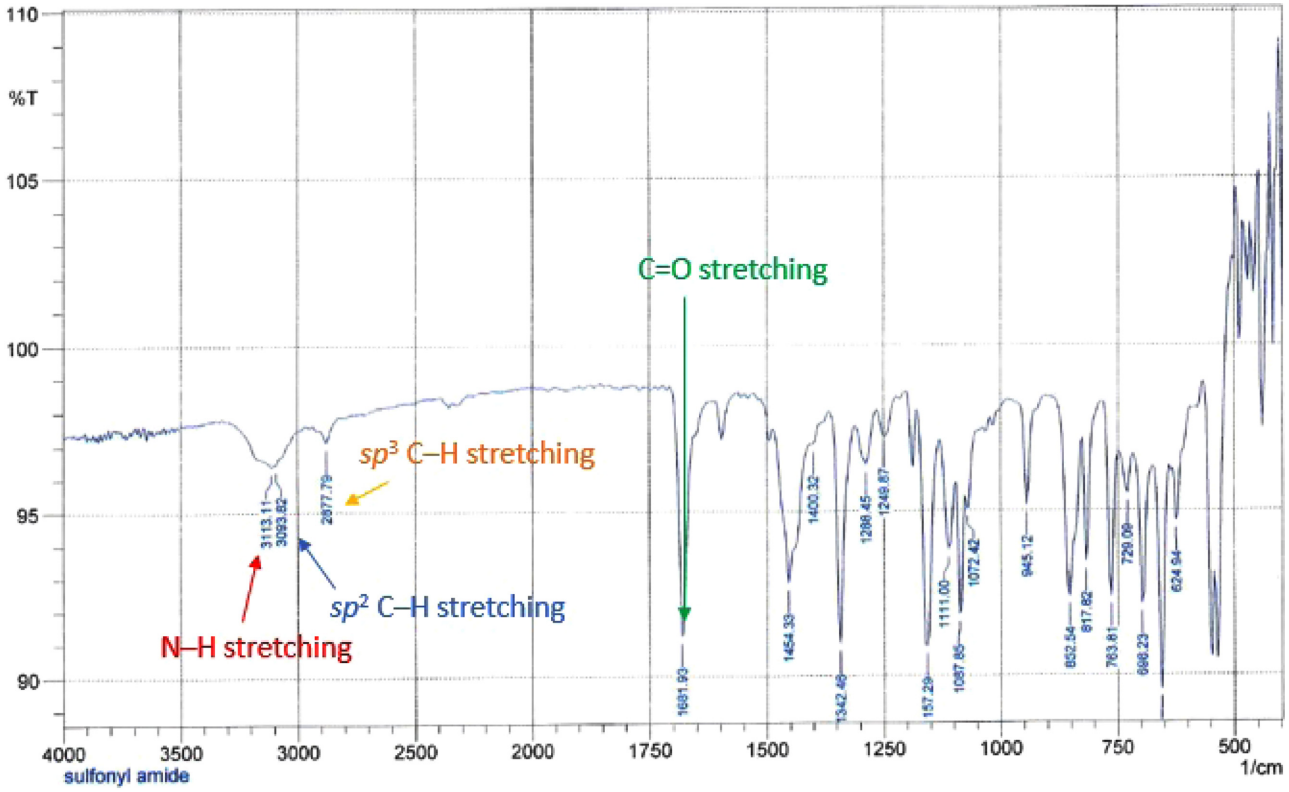


***Figure* S8.** One of IR spectrum analysis by students.

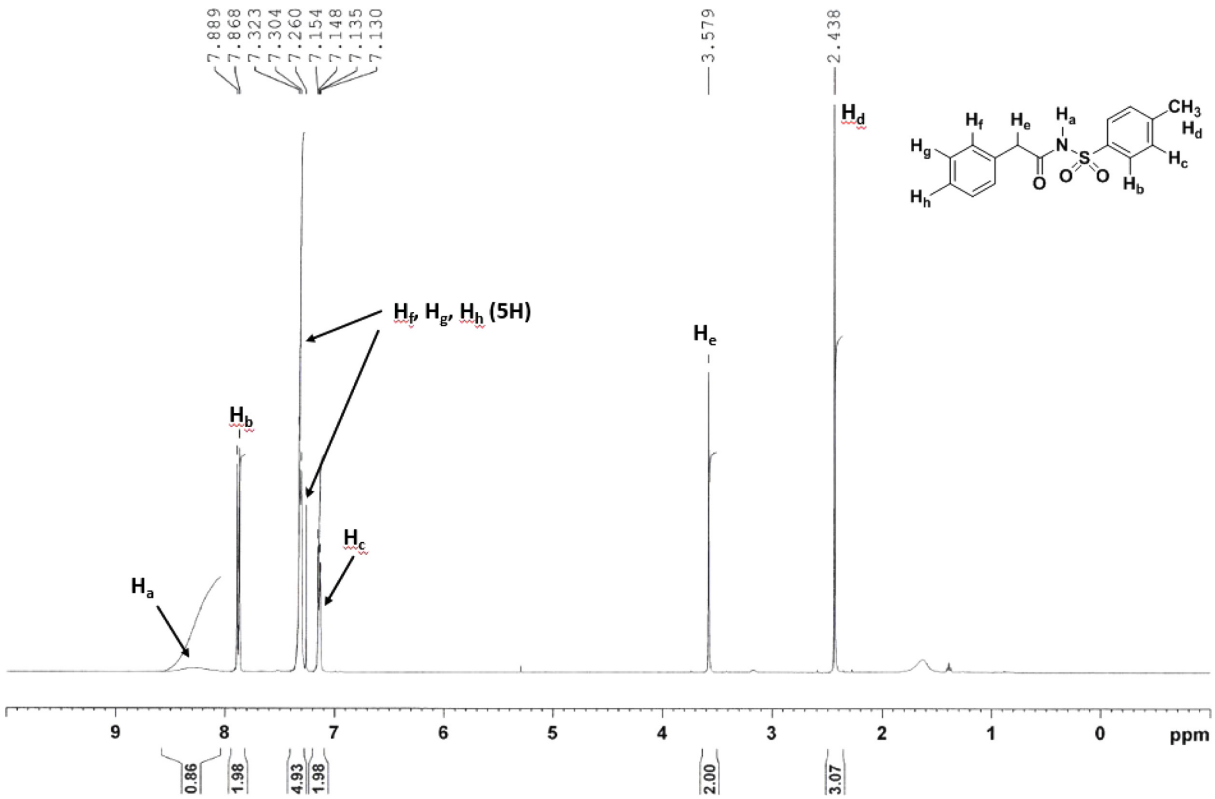


***Figure* S9.** One of ^{1}H NMR spectrum analysis by students.

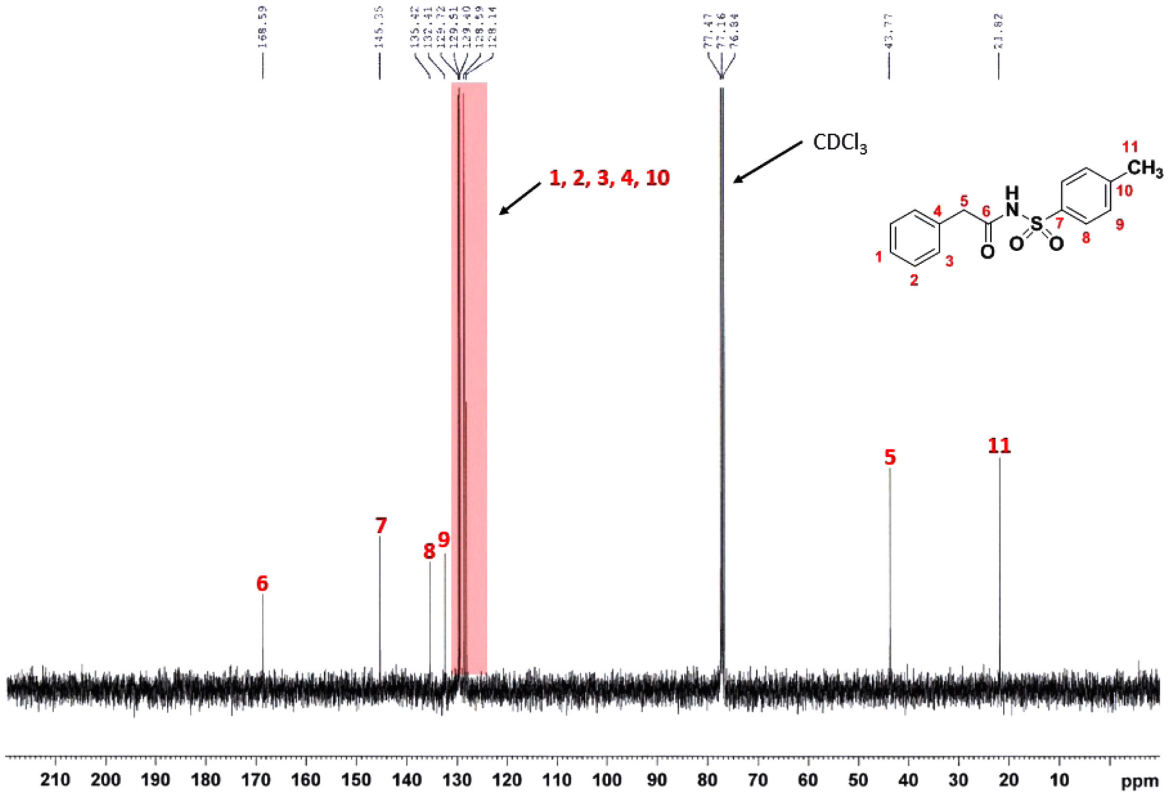


***Figure* S10.** One of ^{13}C NMR spectrum analysis by students.

■ Students Feedback

· Questionnaire in Korean

Questions	Evaluation (1: Disagree → 5: Agree)				
	1	2	3	4	5
A. About Pre-Lab(실험 수업 전 과제, 예비 보고서등에 관해)					
1. 나는 예비보고서 작성을 통해 수업 전, 실험 과정에 대해 충분히 인지하였다.					
2. 나는 과제를 통해 고체 화합물의 정제(purification) 방법에 대해 충분히 이해하였다.					
3. 나는 예비보고서 및 과제를 충분히, 성실히 작성하였다.					
4. 실험서에 설명된 실험 과정은 실제로 실험을 진행하는데 있어 큰 어려움이 없게끔 충분히 설명되었다(안전, 실험 방법 등).					
B. About Lab (실험 수업에 관해)					
1. C–H 활성화 연구에 대해 이해할 수 있도록, Instructor는 충분한 정보를 제공하였다.					
2. Instructor는 실험의 이론적인 부분에 대해 학생들이 이해할 수 있도록 충분한 정보를 제공하였다.					
3. 실험 과정은 학부 2학년에 진행되기 충분한 정도의 난이도였다.					
C. About Post-Lab(실험 수업 후 보고서 등)					
1. 주어진 실험을 통해 같은 학기 이론 수업 내용인 분광학을 통한 화합물 구조 분석 이해에 도움이 되었다.					
2. 주어진 실험을 통해 C–H 활성화 연구를 이해하는데 도움이 되었다.					
3. 실험 준비부터, 실험 진행, 보고서 작성까지 난이도가 적절하였다.					

· Questionnaire in English

Questions	Evaluation (1: Disagree → 5: Agree)				
	1	2	3	4	5
A. About Pre-Lab					
1. I understood whole experiment process by preparing a pre-lab report.					
2. I understood the way to purify solid compounds by a pre-lab assignment.					
3. I prepared a prelab report and a prelab assignment perfectly.					
4. Experimental procedure is good enough to understand and follow.					
B. About Lab					
1. The instructor supported enough information for C–H activations.					
2. The instructor delivered enough theoretical backgrounds of C–H activations.					
3. The level of this experiment is proper.					
C. About Post-Lab					
1. This experiment is helpful for understanding spectroscopy.					
2. This experiment is helpful for understanding C–H activations.					
3. The difficulty of Prelab/Postlab assignments is proper.					

· Results of Students Feedback

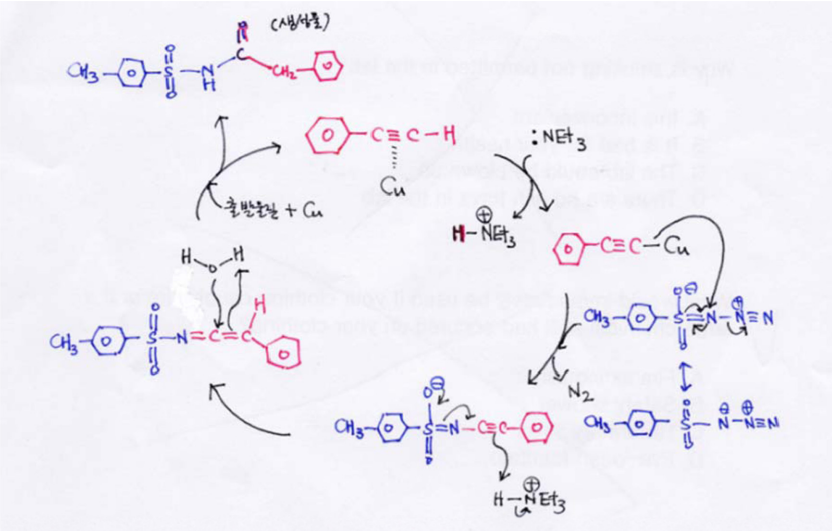
- 28/45 students were participated for this survey.

***Table* 1.** Students Feedback of Questionnaire

Question	Strongly Disagree	Disagree	Neither Agree Or Disagree	Agree	Strongly Agree
B-1	0	2	3	13	10
B-2	0	2	7	11	8
B-3	0	2	7	10	9
C-1	0	1	2	10	15
C-2	0	1	9	7	11
C-3	0	3	4	10	11

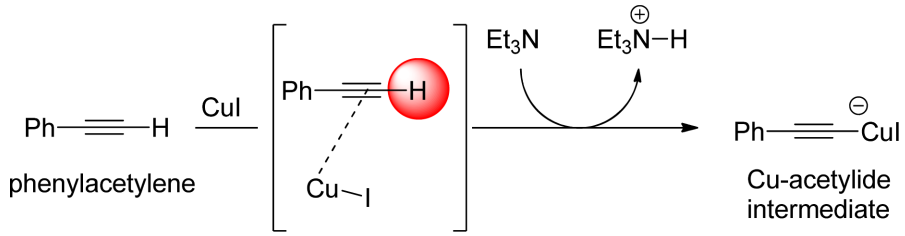
■ Information on Reaction Mechanism

· The prelab material for understanding reaction mechanism[4]



***Scheme* S1.** Catalytic Cycle of Amide Synthesis.

· The prelab material for details of Cu-mediated *sp* C–H activation[5]



***Scheme* S2.** Cu-mediated *sp* C–H activation.

References

1. For the references as prelab materials, see: (a) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. C–H Functionalization in organic synthesis. *Chem. Soc. Rev.*, **2011**, *40*, 1855-1856. (b) Labinger, J. A.; Bercaw, J. E. Understanding and exploiting C–H bond activation. *Nature* **2002**, *417*, 507-514.
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5. The original prelab material of this turned out that it might make misleading. The present version is revised to avoid misleading.