

Experiment 6

Copper-Catalyzed Three Component Reaction

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1. PURPOSE OF THE EXPERIMENT

- Perform a state of the art transition metal-catalyzed reaction with alkynes, sulfonyl azides, and water to obtain an amide.
- Perform a reaction that has been developed by KAIST chemists.
- Analyze the product by NMR spectroscopy.
- Develop a chemistry literature searching skill.

2. BACKGROUND INFORMATION

The amide group is a key motif in chemistry and biology. Although traditional chemical methods for amide synthesis rely heavily on an interconversion strategy between carbonyl groups or their equivalent reactive compounds, the lability of those functional groups often restricts their ubiquitous applications. Hence, the development of alternative routes has been challenging to synthetic chemists.

The Chang group at KAIST has previously reported the highly efficient Cu-catalyzed three-component reactions of terminal alkynes, sulfonyl azides, and amines or alcohols to afford amidines or imidates.¹ It is believed that the reaction proceeds via a common ketenimine intermediate, which is generated from the copper-mediated intermolecular cycloaddition of azides and alkynes followed by the release of N₂.² On the basis of this postulate, a novel non-conventional amide synthesis could be realized by allowing the plausible ketenimine intermediates, generated in situ under the reaction conditions, to react with water.³

This present procedure describes a convenient approach for the preparation of *N*-sulfonylamides from the reaction of terminal alkynes, sulfonyl azides, and water in the presence of a Cu(I) catalyst. It should be mentioned that water is employed in this case as both a solvent and reagent.

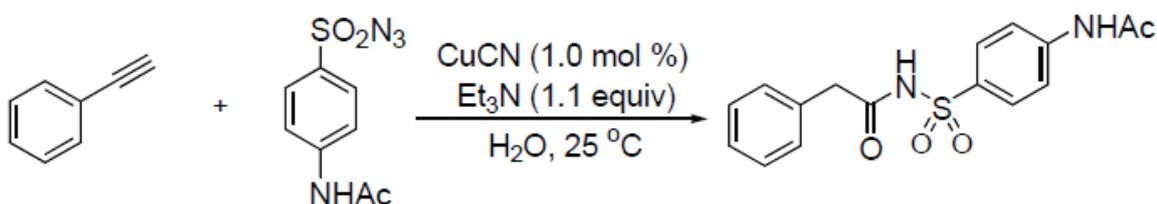
The reaction proceeds smoothly at room temperature within a few hours and generates molecular nitrogen as a sole byproduct. A broad range of both terminal alkynes and sulfonyl azides are readily employed under the reaction conditions. In addition, a range of copper(I) reagents can be readily used as the catalyst with a similar efficiency. For example, product yields were not significantly changed upon using either CuI or CuCN catalyst, although the latter displayed a slightly faster reaction rate.

References

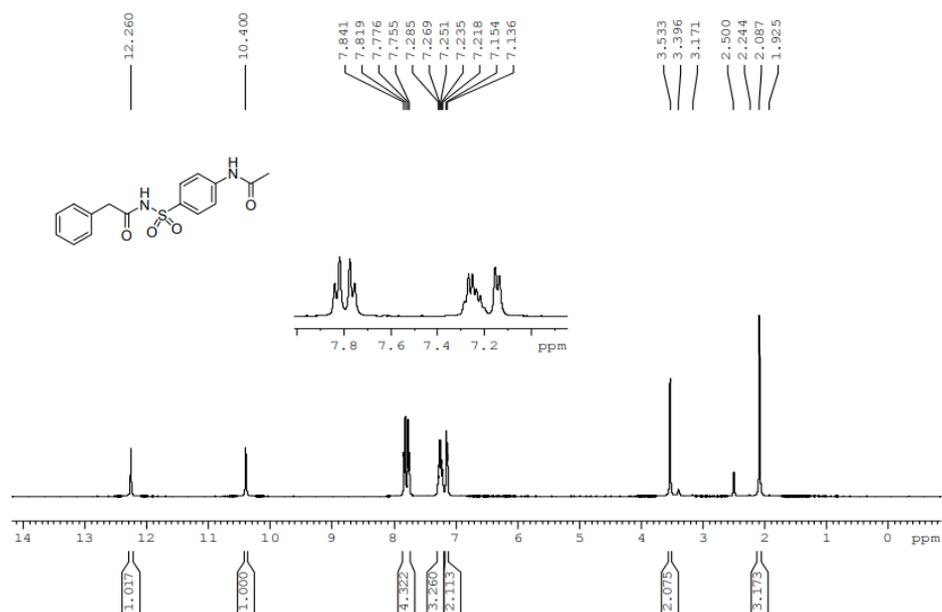
1. (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.*, **2005**, *127*, 2038-2039. (b) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347-1350.
2. Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730-1733.
3. (a) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046-16047. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154-3157. (c) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897-1900.

Overall Reaction

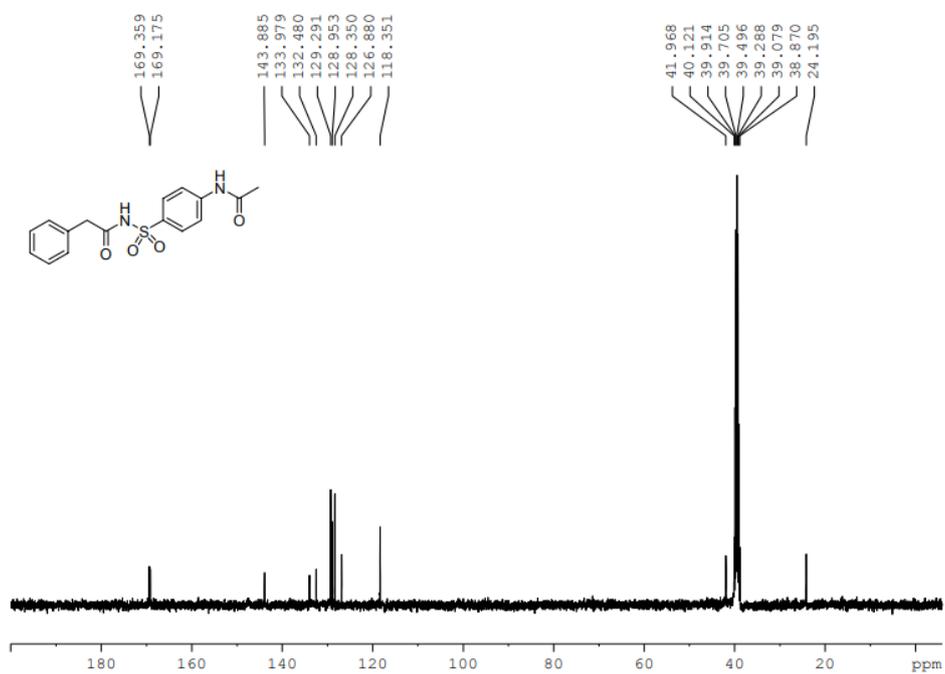
The following figure is the scheme of the amide formation reaction.



The product exhibits the following physicochemical properties: R_f = 0.25 (6.25% methanol in dichloromethane); mp 225-226 °C (decomp); ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.09 (s, 3 H), 3.53 (s, 2 H), 7.14-7.15 (d, J = 7.2 Hz, 2 H), 7.22-7.29 (m, 3 H), 7.76-7.84 (m, 4 H), 10.40 (s, 1 H), 12.26 (s, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 24.2, 42.0, 118.4, 126.9, 128.4, 129.0, 129.3, 132.5, 134.0, 143.9, 169.2, 169.4; IR (neat): 3371, 3241, 3175, 3132, 2970, 1738, 1653, 1590, 1455, 1366, 1167 cm⁻¹. Elemental analysis; Calcd. for C₁₆H₁₆N₂O₄S: C, 57.82; H, 4.85; S, 9.65; N, 8.43; Found: C, 57.77; H, 4.75; S, 9.62; N, 8.43.



Proton NMR of the product



Carbon NMR of the product

3. MATERIALS USED

25 mL round-bottom flask

Magnetic stirring bar

10 mL syringe

Column equipped with Celite

Buchner funnel (Hirsch funnel can be replaced)

4. REAGENTS AND PROPERTIES

Reagents	Molecular weight (g/mol)	Density (g/cm ³)	quantity	equivalent
Copper(I) cyanide	89.563	2.92	4.5 mg	
4-acetamidobenzenesulfonyl azide	240.24		1.2 g	
phenylacetylene	102.133	0.93	0.6 mL	
Triethylamine	101.193	-	0.77 mL	-
Ammonium chloride (saturated aqueous solution)	53.49	-	-	-
Methanol				
1N HCl solution				
Diethyl ether				
Isopropyl alcohol				

5. PROCEDURE

- A single-necked, 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with [copper\(I\) cyanide](#) (4.5 mg, 0.05 mmol) and [4-acetamidobenzenesulfonyl azide](#) (1.2 g, 5.0 mmol).
- Distilled water (10 mL) was added to the flask, and then [phenylacetylene](#) (0.6 mL, 5.5 mmol) was added via syringe at room temperature. To this stirred mixture, [triethylamine](#) (0.77 mL, 5.5 mmol) was slowly added via syringe over one min at room temperature ([Note 1](#)).
- The reaction mixture was then vigorously stirred while open to air for 4 h at room temperature ([Note 2](#)).
- The reaction was quenched by the addition of a saturated aqueous ammonium chloride solution (2 mL) via syringe at room temperature. [Methanol](#) (5 mL) ([Note 7](#)) was added, and then the mixture was stirred for an additional 20 min at the same temperature.
- The resulting mixture was filtered through a Celite pad (0.7 g) ([Note 8](#)), and the pad was washed with [methanol](#) (5 × 5 mL). The filtrate was concentrated to half volume using

a rotary evaporator (20 mmHg, water bath temperature 28 °C), and then the remaining solution was treated with 1N HCl (5 mL) at room temperature to make it slightly acidic (Note 3).

f. The solution was concentrated using a rotary evaporator (20 mmHg, water bath temperature 28 °C) (Note 4), and then the resulting solid was collected by suction filtration with the aid of distilled water (Note 5). The solid was washed with a pre-cooled (0 °C) mixture of diethyl ether and isopropyl alcohol (20:1, 5 mL) followed by diethyl ether (5 mL).

g. The remaining solid was transferred to a pre-weighed 25-mL round-bottomed flask and then was dried under vacuum at room temperature to yield a light yellowish solid.

h. Record the mass of your product.

Caution: Make sure that you should dry your product as much as possible before weighing.

i. Calculate the % yield.

j. Obtain the NMR spectrum and assign peaks.

Notes

1. During the addition of triethylamine, the original heterogeneous reaction mixture turned to a yellowish solution.

2. The internal temperature of the reaction mixture increases to 36 °C over 2 h, and the color becomes dark red. The progress of the reaction was monitored by TLC until complete conversion was observed, and during this time the internal temperature returned to room temperature. For TLC analysis, EMD Chemicals, Inc. silica gel 60 F₂₅₄ TLC plates were used. 4-Acetamidobenzenesulfonyl azide and *N*-(4-acetamidophenyl sulfonyl)-2-phenylacetamide have R_f values of 0.52 and 0.25, respectively (dichloromethane/methanol, 15:1).

3. When the 1 N HCl solution was poured into the mixture, a slight exotherm was observed (internal temperature: 29.3 °C) and a white slurry formed. The solution was measured to have a pH of 3.

4. As the solution was concentrated, solid began to precipitate in the bottom of the round-bottomed flask.

5. A 60-mL glass filter with a medium porosity fritted disc was used. Solid that adhered to the flask was transferred using distilled water (two 35-mL portions).

6. POST-LABORATORY QUESTIONS

1. Calculate the percent yield of your product.

2. Assign the peaks in the ^1H NMR and explain them.
3. List at least 2 other ways to synthesize the amide.
4. What is the proposed mechanism of this transformation?
5. What is the role of the copper catalyst in this transformation?

7. PRE-LABORATORY QUESTIONS

1. Summarize all the MSDS of chemicals used in the experiment.
2. Delineate the potential danger (hazard) of organic azide.
3. Find at least 3 literature precedents that utilized this reaction (Hint: Search papers that cited the original papers (reference 3))