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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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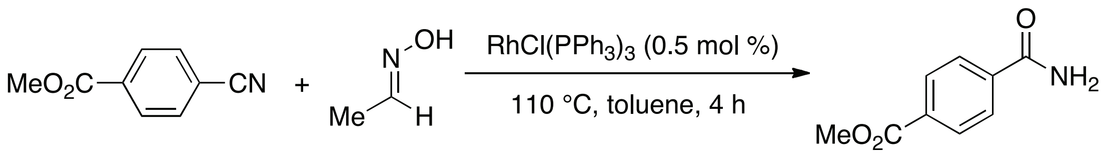
Anhydrous Hydration of Nitriles to Amides: *p*-Carbomethoxybenzamide



Submitted by Dahye Kang, Jinwoo Lee and Hee-Yoon Lee.[1]
Checked by Hiroshi Kumazaki and Tohru Fukuyama.

1. Procedure

A. p-Carbomethoxylbenzamide. A 100-mL single-necked, round-bottomed flask that is equipped with a magnetic stirring bar (round, 5 x 15 mm), a reflux condenser and Argon bubbler is charged with the following order of the reagents: methyl *p*-cyanobenzoate (5.0 g, 31 mmol) (Note 1), toluene (9.5 mL) (Note 2), Wilkinson's catalyst (145 mg, 0.16 mmol, 0.5 mol%) (Note 3), and acetaldoxime (9.2 g, 9.5 mL, 156 mmol, 5.0 equiv) (Notes 4 and 5). The reaction mixture is heated to reflux with an oil bath (bath temperature 130 ºC) for 4 h and then is allowed to cool down to room temperature (Notes 6 and 7). The reaction mixture is concentrated under reduced pressure on rotary evaporator (20–30 mmHg, bath temperature 40–45 ºC). Water (20 mL) is added to the concentrate and the mixture is heated with an oil bath (90~100 °C bath temperature) under air for 1 h and cooled down to room temperature (Note 8). The resulting mixture is filtered through a Büchner funnel. The solid product is washed with water (40 ml). The solid is transferred to a 50-mL round-bottomed flask and dried under vacuum (0.1 mmHg) to afford 5.1 g (92%) of *p*-carbomethoxylbenzamide (Notes 9 and 10) as a white solid.

2. Notes

1. Methyl *p*-cyanobenzoate (99%) was purchased from Aldrich and used as received.
2. The submitters purchased toluene (CHROMASOLV® for HPLC, >99.9%) from Aldrich and it was used as received. The checkers purchased toluene (>99.5%) from Kanto Chemical Company and used it as received.

3. Wilkinson's catalyst ($RhCl(PPh_3)_3$) was purchased from Aldrich and used as received.

4. Acetaldoxime (>99%) was purchased from TCI and used as received.

5. Since acetonitrile produced from the reaction also reacts with acetaldoxime to form acetamide, at least five equivalents of acetaldoxime are required to complete the reaction.

6. As the reaction proceeds, solid begins to appear in the flask.

7. The reaction is monitored by TLC analysis on Merck silica gel 60 F254 plates (hexane/ethyl acetate = 3:2); visualization was accomplished with 254 nm UV light and ethanolic solution of phosphomolybdic acid with heat: R*f* (starting nitrite) = 0.69; R*f* (amide product) = 0.06 .

8. The crude product is heated in water to dissolve all the acetamide.

9. *p*-Carbomethoxylbenzamide exhibits the following physical and spectroscopic properties: mp = 206 °C (lit.[8] 206 °C); IR (neat) cm^{-1}: 3404, 3197, 1724, 1655, 1281, 1116; ^1H NMR (400 MHz, CD_3OD) δ: 3.85 (s, 3 H), 7.96 (d, 2 H), 8.10 (d, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ: 53.0, 129.0, 130.7, 134.3, 139.4, 167.9, 171.4; Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.48; H, 5.08; N, 7.76.

10. Recrystallization of the product can be performed according to the following procedure: A 500-mL, single-necked, round-bottomed flask is charged with *p*-carbomethoxybenzamide (5.1 g, 28 mmol) and ethanol (150 mL). The suspension is heated to reflux with an oil bath (bath temperature 90 ºC) until complete dissolution occurs. Then the oil bath is removed, and the solution is allowed to cool to room temperature overnight. The crystallized product is collected with a Büchner funnel, washed with cooled ethanol (10 mL), and dried *in vacuo* to afford 4.4 g (86%) of pure amide.

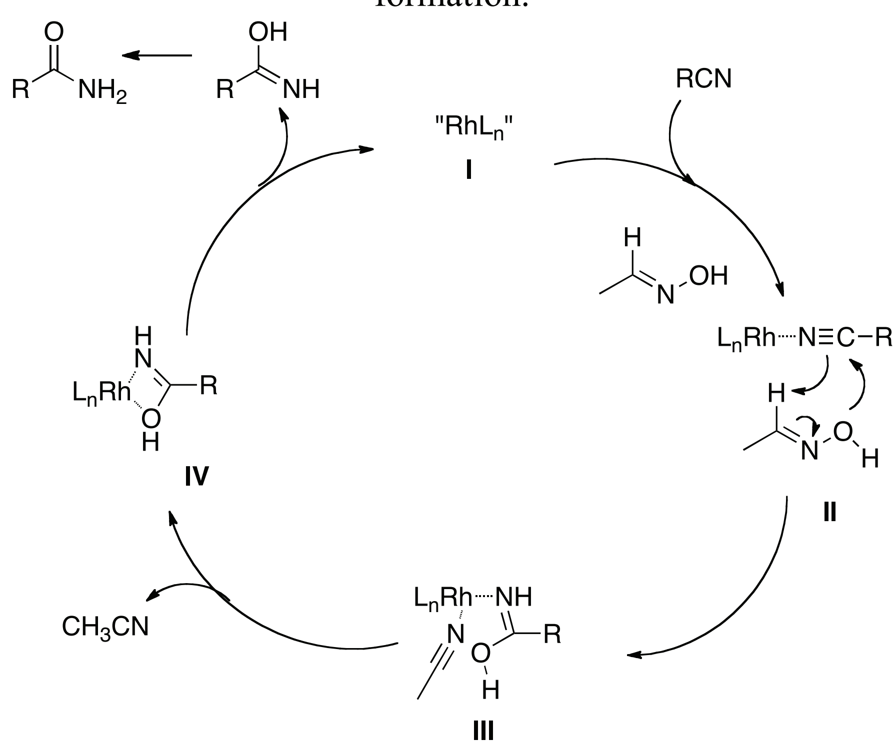
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

3. Discussion

The amide is one of the important functional groups in chemical industry, as well as the pharmaceutical industry,[2] and can be readily prepared from the corresponding nitriles, since they are *isohypsic*.[3] However, hydration of nitriles to amides requires strong acidic or basic conditions, and is accompanied often by the formation of the corresponding carboxylic acids through further hydrolysis.[4] To circumvent side reactions and harsh reaction conditions, transition metal-catalyzed hydrolysis reactions of nitriles or rearrangement reactions of oximes have been developed.[5] During the study of Rh-catalyzed rearrangement of oximes into amides[6] we found out that the transformation not only proceeded through the intermediacy of nitriles, but the reaction was also catalyzed by the same nitrile intermediates. A brief mechanistic study of this transformation strongly indicated that dehydration of oximes into nitriles or hydration of nitriles into amides did not produce or use water molecules. Instead, oxygen and hydrogen atoms of the oximes are delivered directly to the nitriles to convert the nitriles into amides. Thus, the concentration of nitriles stays constant. This nitrile-catalyzed transformation of oximes into amides prompted the development of a new method of hydrolyzing nitriles into amides without using or generating water molecules. (Scheme 1)[7] Acetaldoxime was selected as the reagent along with $RhCl(PPh_3)_3$ as the catalyst for nitrile hydrolysis and the reaction was optimized with five equivalent of acetaldoxime and 0.5 mol% of the catalyst in toluene.[8]

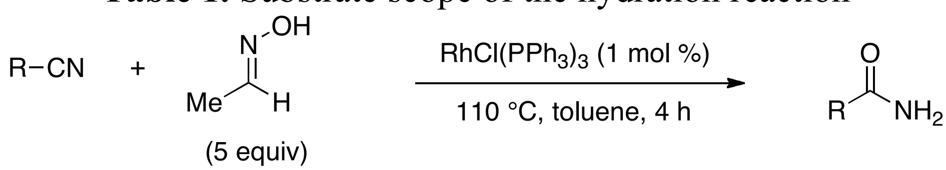
Scheme 1. Mechanistic proposal for the aldoxime promoted amide formation.

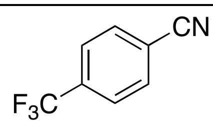
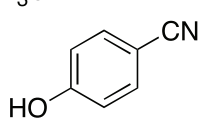
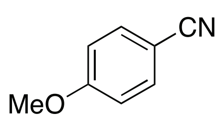
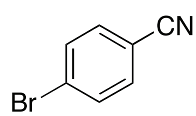
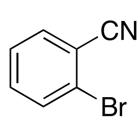
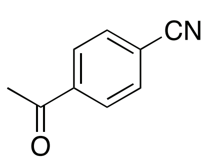
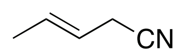
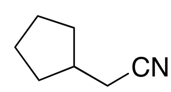
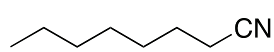
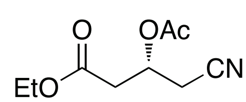
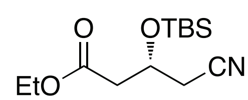
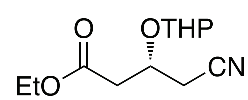
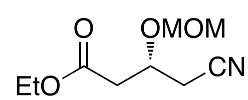


The procedure described here provides not only a mild and practical way of preparation of amides from nitriles, but also provides a method of hydration without utilizing water as the nucleophile during the reaction. The choice of acetaldoxime as the hydrating agent makes all the byproducts from this reagent to be either volatile or soluble in water, and thus simplifies the work-up process and eliminates the purification step of the amide products.

The scope of functional group tolerance is summarized in the Table 1. Aliphatic and aromatic nitriles, regardless of the substitution patterns, are hydrolyzed efficiently. Wide range of functional group tolerability indicates that the reaction is non-nucleophilic as well as neutral, since the hydrolysis of esters, the isomerization of olefins, or the deprotection of protecting group is not observed.

Table 1. Substrate scope of the hydration reaction[a]



Entry	Nitrile	Yield[b]
1		95
2		99
3		79
4		96
5		90
6		87
7		81
8		82
9		92
10		81
11		76
12		75
13		80

[a] 0.5 mmole scale. [b] Isolated yields.

In summary, water-free selective hydrolysis of nitriles into amides using acetaldoxime as the water surrogate with Wilkinson's catalyst is demonstrated as a practical and mild procedure compatible with various functional groups.

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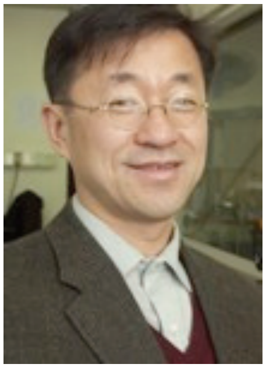
Appendix
Chemical Abstracts Nomenclature; (Registry Number)

p-Carbomethoxylbenzamide: Benzoic acid, 4-(aminocarbonyl)-, methyl ester; (6757-31-9)

Methyl *p*-cyanobenzoate: Benzoic acid, 4-cyano-, methyl ester; (1129-35-7)

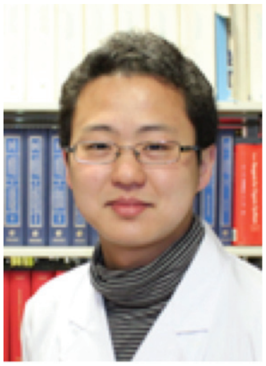
Wilkinson's catalyst: Rhodium, chlorotris(triphenylphosphine)-; (14694-95-2)
Acetaldoxime: Acetaldehyde, oxime; (107-29-9)



Hee-Yoon Lee received his B.S. degree in Chemistry from Seoul National University in 1980, his M.S. 1982 with Eun Lee, and his Ph.D., 1988, in Chemistry from Stanford University with Paul A. Wender. After two years of postdoctoral work at the Department of Chemistry, Columbia University with Gilbert Stork, he worked at Merck Research Laboratories at West Point in 1990 as a senior research chemist. Then, he took up the professorship at KAIST in 1994, where he is focusing on the development of new synthetic strategies and application to total synthesis of natural products.

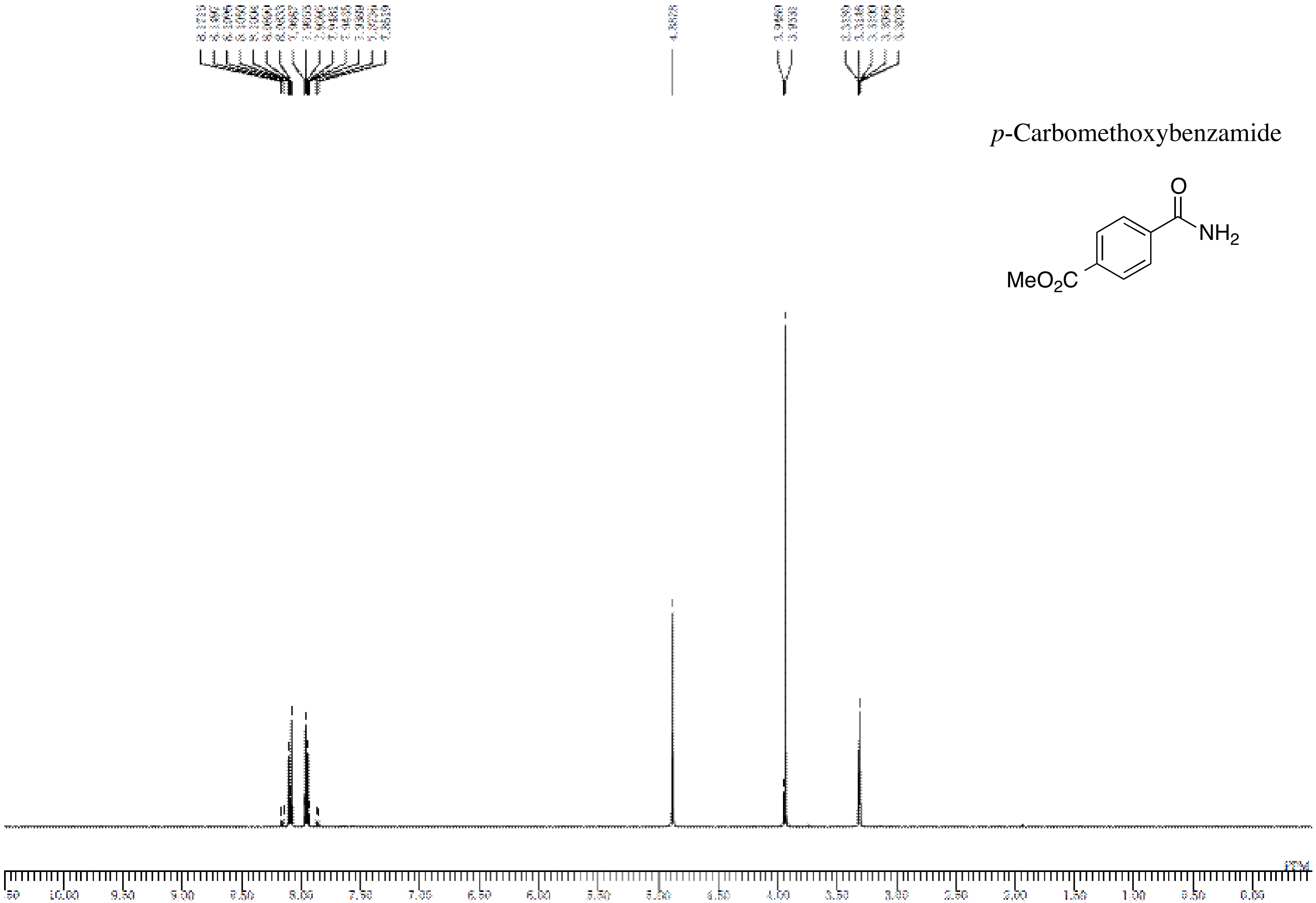
Dahye Kang was born in Incheon, Republic of Korea, in 1991. After graduating from Bupyong Girls High School in 2009 skipping her senior year, she entered KAIST in 2009. She is currently an undergraduate student in the Department of Chemistry at KAIST, studying organic synthesis in the laboratory of Professor Hee-Yoon Lee.

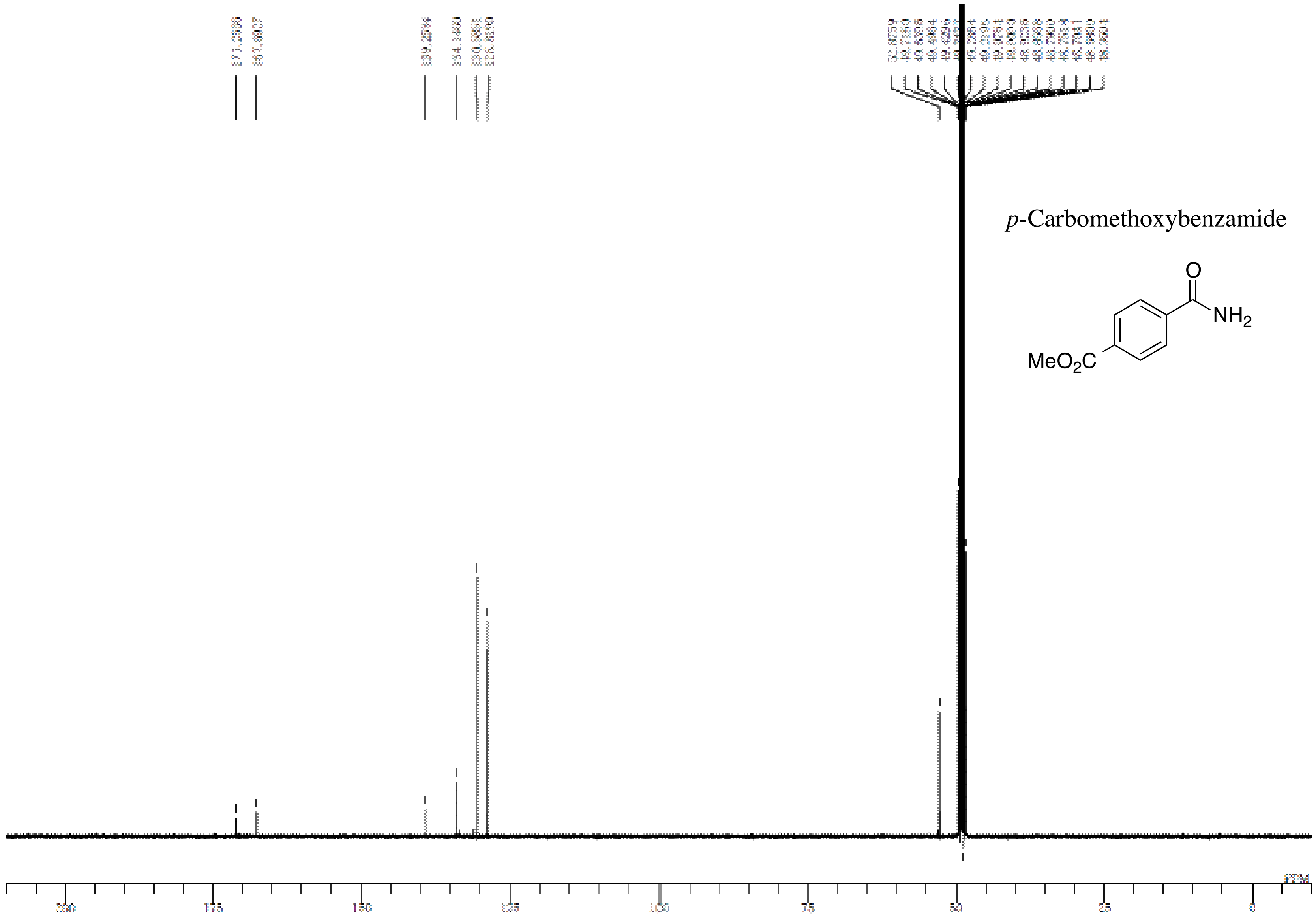
Jinwoo Lee was born in Daegu, Republic of Korea, in 1982. He received B.S. in 2003 from KAIST, Ph.D. in 2010 under the supervision of Hee-Yoon Lee. He is currently postdoctoral research fellow at Tuberculosis Research Section (National Institute of Allergy and Infectious Diseases) at the NIH, where he participates in the design, chemical synthesis and biological evaluation of novel compounds as anti-tubercular agents with Clifton E. Barry, III.



Hiroshi Kumazaki was born in Gifu, Japan in 1988. He received his B.S. in 2010 from the University of Tokyo. In the same year, he began his graduate studies at the Graduate School of Pharmaceutical Sciences, the University of Tokyo, under the direction of Professor Tohru Fukuyama. His current interest is total synthesis of natural products.

p-Carbomethoxybenzamide





p-Carbomethoxybenzamide