



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

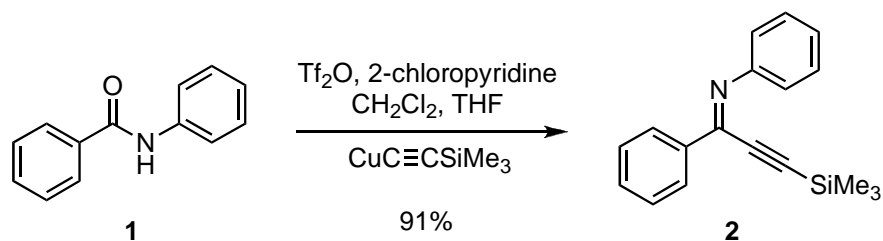
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

**SINGLE-STEP SYNTHESIS OF ALKYNYL IMINES FROM
N-VINYL AND N-ARYL AMIDES.
SYNTHESIS OF N-[1-PHENYL-3-(TRIMETHYLSILYL)-2-
PROPYNYLIDENE]-BENZENAMINE.**



Submitted by Mohammad Movassaghi and Matthew D. Hill.¹
Checked by Rie Motoki and Masakatsu Shibasaki.

1. Procedure

N-[1-phenyl-3-(trimethylsilyl)-prop-2-ynylidene]-benzenamine. A flame-dried, 200-mL, single-necked, round-bottomed flask is equipped with a 2.5-cm football-shaped stir bar, sealed with a rubber septum under an argon atmosphere, and fitted with an argon-filled balloon through a syringe needle. The flask is charged with anhydrous tetrahydrofuran (80 mL, Note 1) and cooled to 0 °C (external temperature) in an ice-bath. Vigorous stirring is commenced and (trimethylsilyl)acetylene (13.3 mL, 9.41 g, 95.8 mmol, 2.70 equiv, Note 2) is added to the flask via syringe. Butyllithium (40.6 mL, 95.8 mmol, 2.36 M, 2.70 equiv, Note 3) is added to the THF solution of (trimethylsilyl)acetylene over 10 min via syringe as the mixture was kept at 0 °C. After 5 min, the colorless solution of the lithium (trimethylsilyl)acetylide is removed from the ice-bath and allowed to warm to ambient temperature and kept at this temperature for an additional 40 min. During this time, another flame-dried, 300-mL, single-neck round-bottomed flask is equipped with a 2.5-cm football-shaped stir bar, charged with solid copper(I) bromide–dimethyl sulfide complex (19.71 g, 95.84 mmol, 2.700 equiv, Note 2), sealed with a rubber septum under an argon atmosphere, and fitted with an argon-filled balloon through a syringe needle. The flask containing copper bromide is charged with tetrahydrofuran (80 mL, Note 1)

and the mixture is cooled in a dry ice-acetone bath ($-78\text{ }^{\circ}\text{C}$, external temperature). The lithium (trimethylsilyl)acetylide solution at ambient temperature is slowly transferred via cannula over 5 min to the cold ($-78\text{ }^{\circ}\text{C}$, external temperature) flask containing copper bromide. The bright-yellow solution is maintained at $-78\text{ }^{\circ}\text{C}$ for an additional 5 min. The flask containing the yellow copper acetylide solution is moved from the dry ice-acetone bath to an ice-water bath and maintained for 20 min prior to use.

A flame-dried, 500-mL single-necked, round-bottomed flask equipped with a 2.5-cm stir bar is charged with benzanilide (**1**, 7.00 g, 35.5 mmol, 1 equiv, Note 2), sealed with a rubber septum under an argon atmosphere, and fitted with an argon-filled balloon through a syringe needle. Anhydrous dichloromethane (71 mL, Note 1) followed by 2-chloropyridine (13.4 mL, 16.1 g, 142 mmol, 4.00 equiv, Note 4) are added via syringe and the heterogeneous mixture is vigorously stirred and cooled by placement in a dry ice-acetone bath ($-78\text{ }^{\circ}\text{C}$, external temperature). After 10 min, trifluoromethanesulfonic anhydride (Tf_2O , 7.03 mL, 12.0 g, 42.6 mmol, 1.20 equiv, Note 2) is added via syringe over 2 min. After five min, the reaction flask is moved to an ice-water bath for a period of five min, and then returned to the dry ice-acetone bath. After five min, the copper (trimethylsilyl)acetylide solution prepared above is transferred via cannula over 5 min to the cold ($-78\text{ }^{\circ}\text{C}$) solution of the activated amide and the reaction mixture is kept in a dry ice-acetone bath (Note 5). After five min, the reaction flask is moved from the dry ice-acetone bath to an ice-water bath. After five min, the cold bath is removed and the reaction mixture is allowed to warm to ambient temperature. After 20 min, the reaction mixture is filtered through Celite into a 500-mL, side-armed Erlenmeyer flask with vacuum filtration (Note 6). The combined filtrate is transferred to a 500-mL round-bottomed flask and concentrated with a rotary evaporator ($30\text{ }^{\circ}\text{C}$, 70 mmHg). The remaining brown oil is purified by flash column chromatography (Note 7) to afford 8.99 g (91%) (Note 8) of imine **2** as a bright yellow oil (Note 9).

2. Notes

1. Submitters purchased tetrahydrofuran and dichloromethane from J.T. Baker (CycletainerTM), which was dried by the method of Grubbs et al. under positive argon pressure.² Checkers purchased dehydrated

tetrahydrofuran and dichloromethane from Kanto Chemical Co., Inc. and used without further purification.

2. Trimethylsilylacetylene (98%), copper(I) bromide-dimethyl sulfide complex (98%), benzanilide (98%), and trifluoromethanesulfonic anhydride (99+%) were purchased from Aldrich Chemical Company, Inc. and were used as received.

3. Butyllithium (2.36 M) in hexanes was purchased from Aldrich Chemical Company, Inc. and the molarity was determined by titration using diphenylacetic acid as an indicator (average of three determinations).³

4. 2-Chloropyridine (Aldrich Chemical Company, Inc.) was distilled from calcium hydride and stored under an argon atmosphere. The yield of the desired product dropped when less 2-chloropyridine was used (see the Supporting Information in reference 7). Prudent experimental practices should be followed in handling 2-chloropyridine and any inhalation, ingestion, skin contact, or eye contact should be avoided.

5. The reaction mixture turned brown as the acetylide was added and gradually regained a bright yellow color upon completion of the addition.

6. At ambient temperature, the yellow solution became heterogeneous and turned dark brown as white salts precipitated. The solids were removed by vacuum filtration (20 mmHg) through a plug of Celite (50 g) in a sintered glass funnel (9 cm diameter). The Celite was rinsed thoroughly with dichloromethane (100 mL). The combined filtrates were concentrated under reduced atmosphere (75 mmHg, 30 °C), at which time additional salts precipitated. This crude residue was purified by flash column chromatography.

7. Flash column chromatography (7 cm diameter, 16 cm height) was performed using silica gel (60-Å pore size, 32–63 μm, standard grade, Sorbent Technologies). Hexanes (300 mL) were used as the first eluent to remove the bis(trimethylsilylacetylene) ($R_f = 0.75$, hexane/ethyl acetate, 9:1, visualized by KMnO_4 stain). The eluent was changed to hexane/ethyl acetate, 13:1 until alkynylimine **2** ($R_f = 0.50$, hexane/ethyl acetate, 9:1, visualized by UV and KMnO_4 stain) was passed through the column (fractions 27–61 collected, ~20-mL fractions) and the combined fractions were concentrated under reduced pressure (30 °C, 75 mmHg). Any residual 2-chloropyridine ($R_f = 0.33$, hexane/ethyl acetate, 9:1, visualized by UV) can be readily removed from the imine **2** with a second flash column chromatography on silica gel (7 cm diameter, 16 cm height and hexane/ethyl

acetate, 29:1 as eluent). TLC was performed on EMD Silica Gel 60F plates. Checkers used Merck silica gel 60 (0.040-0.063 mm, for column chromatography). Checkers used TLC plates purchased from Merck.

8. Submitters obtained the product in 91–98 % yield. Checkers obtained the product in 96% yield on a half-scale reaction.

9. The analytical data for imine **2** is as follows: ^1H NMR (500 MHz, CDCl_3) δ : 0.14 (s, 9 H), 7.11-7.14 (m, 2 H), 7.17 (tt, 1 H, $J = 7.5, 1.1$ Hz), 7.36-7.40 (m, 2 H), 7.45-7.51 (m, 3 H), 8.18-8.21 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ : -0.5, 97.5, 105.4, 120.9, 125.0, 128.3, 128.5, 128.6, 131.4, 137.0, 150.1, 151.7; IR (neat): 3062, 3030, 2960, 2152, 1587, 1563, 1251, 844, 748, 690 cm^{-1} ; EI-HRMS calcd for $\text{C}_{18}\text{H}_{19}\text{NSi}^+$ (M^+): 277.1281, found 277.1281; Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NSi}$: C, 77.93; H, 6.90; N, 5.05. Found: C, 78.23; H, 6.79; N, 5.06. Imine **2** is air stable at ambient temperature for weeks. For prolonged storage (several months) samples of **2** were sealed under an argon atmosphere.

Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

Azaheterocycles are present in natural products, pharmaceuticals, and functional materials.⁴ The cycloisomerization of readily assembled acyclic precursors offers an attractive strategy for the synthesis of heterocycles.^{5,6} We reported⁷ a two-step procedure for the preparation of pyridine and quinoline derivatives that takes advantage of readily available *N*-vinyl⁸ and *N*-aryl amides as starting materials. This methodology required the development of the herein discussed convergent and mild synthesis of alkynyl imines, versatile precursors for a variety of azaheterocycles.^{9,10} The unique activation of amides with trifluoromethanesulfonic anhydride¹¹ in the presence of 2-chloropyridine¹² as an acid scavenger enables the single-step synthesis of a wide range of alkynyl imines (Table 1), including sensitive *N*-vinyl and *N*-heterocyclic imines. For comparison, application of existing multi-step methods toward the synthesis of the highly sensitive *N*-2-thienyl and *N*-dihydropyranyl alkynyl imines shown in Table 1 (entries 12 and 14)

gave none and <10% yield of the desired imines, respectively. Importantly, these imines were obtained using the herein described single-step procedure.

TABLE 1

Entry	Amides	Alkynyl Imines	Yield (%) ^a	Entry	Amides	Alkynyl Imines	Yield (%) ^a
				9			78
1	R = H R' = H R'' = OMe		89	10	Ar = 1-naphthyl		86
2	R = OMe R' = H R'' = H		96	11	Ar = 3,4-dimethoxyphenyl		92
3	R = H R' = CF3 R'' = H		73	12			63 ^b
				13			98
4	R = ^t C ₆ H ₁₁		85	14			99
5	R = ^t Bu		83	15			82
6	R = N(CH ₂ CH ₂) ₂ O		80				
7			81				
8			75				

a. Isolated yields: all entries are average of two experiments. Optimum conditions used uniformly. b. No warming prior to isolation.

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, E-mail: movassag@mit.edu
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12. For a related discussion of amide activation using this reagent combination, see: Movassaghi, M.; Hill, M. *J. Am. Chem. Soc.* **2006**, *128*, 14254-14255.

Appendix

Chemical Abstracts Nomenclature; (Registry Number)

N-Phenylbenzenecarboxamide (benzanilide); (93-98-1)

2-Chloropyridine; (109-09-1)

Trifluoromethanesulfonic acid anhydride; (358-23-6)

1-(Trimethylsilyl)acetylene; (1066-54-2)

N-[1-Phenyl-3-(trimethylsilyl)-2-propyn-1-ylidene]-benzeneamine; (77123-64-9)



Mohammad Movassaghi carried out his undergraduate research with Professor Paul A. Bartlett at U.C. Berkeley, where he received his BS degree in chemistry in 1995. Mo then joined Professor Andrew G. Myers' group for his graduate studies and was a Roche Predoctoral Fellow at Harvard University. In 2001, Mo joined Professor Eric N. Jacobsen's group at Harvard University as a Damon Runyon-Walter Winchell Cancer Research Foundation postdoctoral fellow. In 2003, he joined the chemistry faculty at MIT where his research program has focused on the total synthesis of alkaloids in concert with the discovery and development of new reactions for organic synthesis.

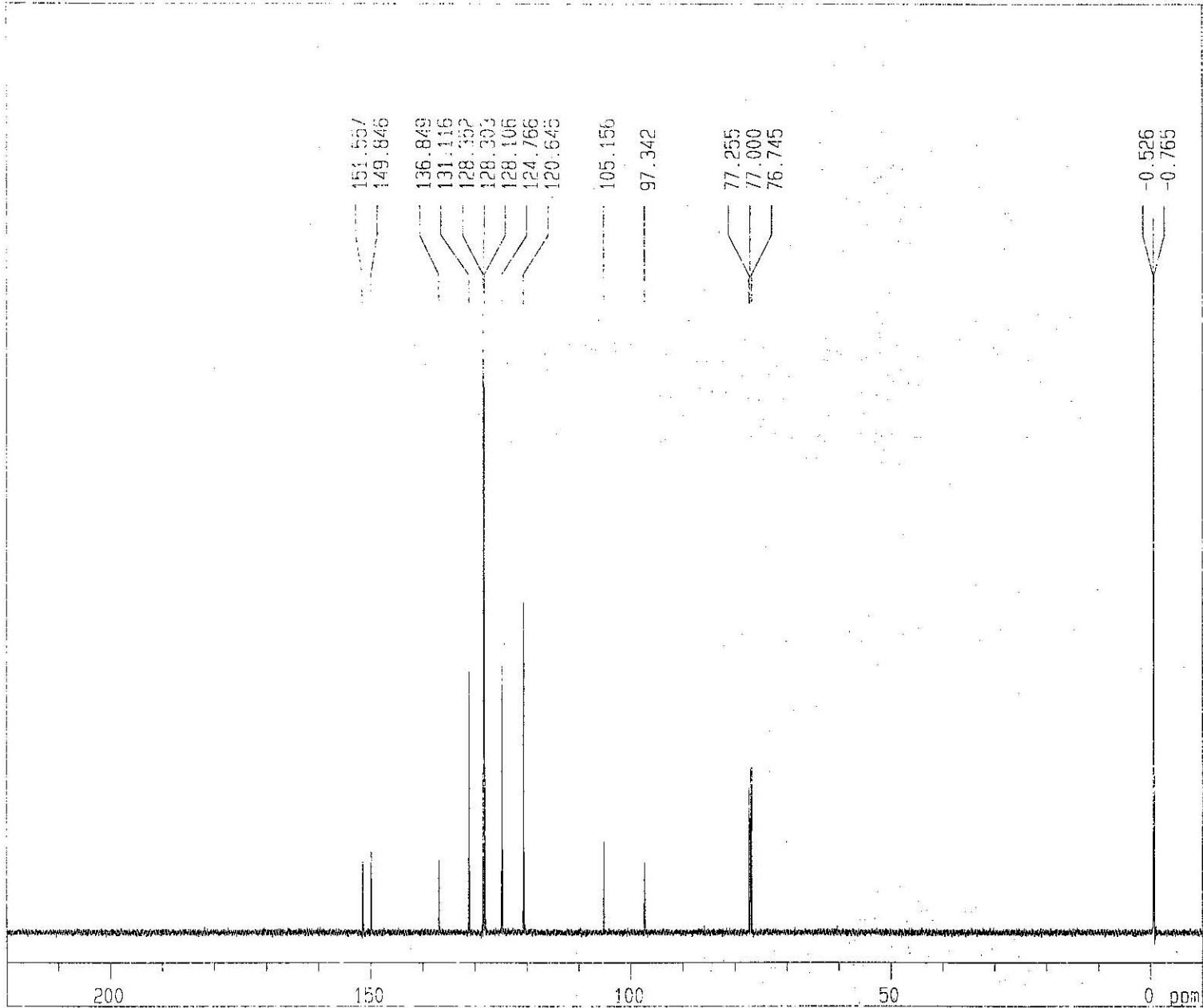


Matthew D. Hill was born in 1980 and grew up in Cleveland, Ohio. Matthew pursued his undergraduate degrees at Ohio University where he studied biochemistry, molecular biology, and legal communication. While an undergraduate he worked in the labs of Professor Mark McMills at Ohio University and Professor Koji Nakanishi at Columbia University. In 2003, Matthew joined Professor Movassaghi's group at MIT where his research has focused on development of new methodologies for azaheterocycle synthesis. In his spare time, Matthew enjoys fishing, boating, volleyball, and most other outdoor recreational activities.



Rie Motoki was born in 1981 in Tokushima, Japan. She graduated in 2004 and received her M.S. degree in 2006 from the University of Tokyo under the direction of Professor Masakatsu Shibasaki. The same year she started her Ph.D. study under the supervision of Professor Shibasaki. Her research interest is design and synthesis of biologically active compounds.

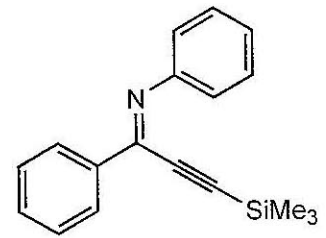
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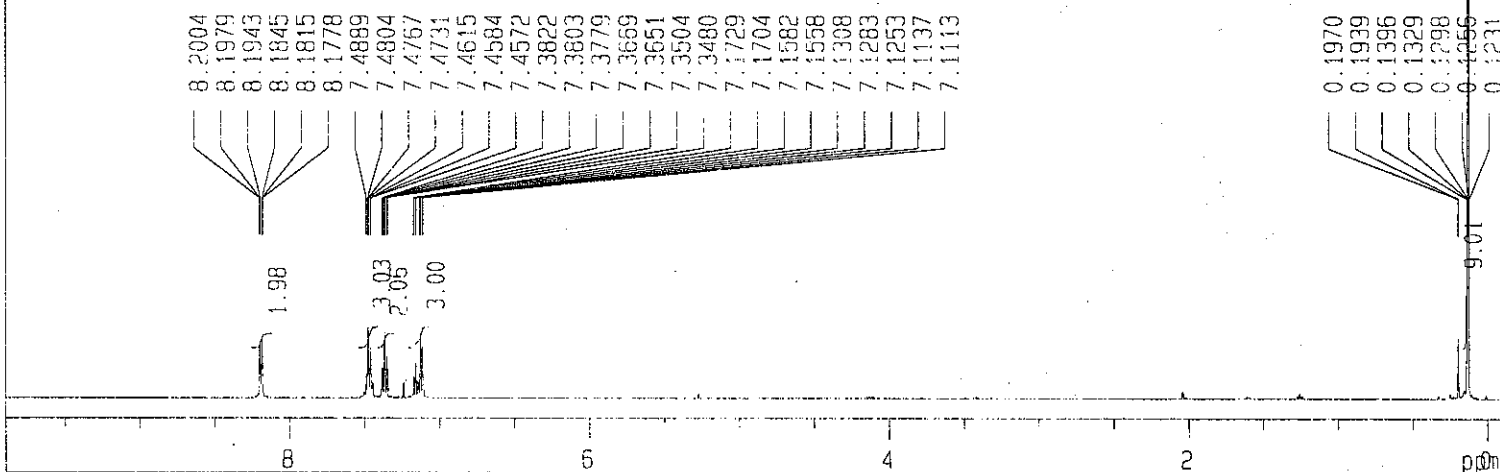
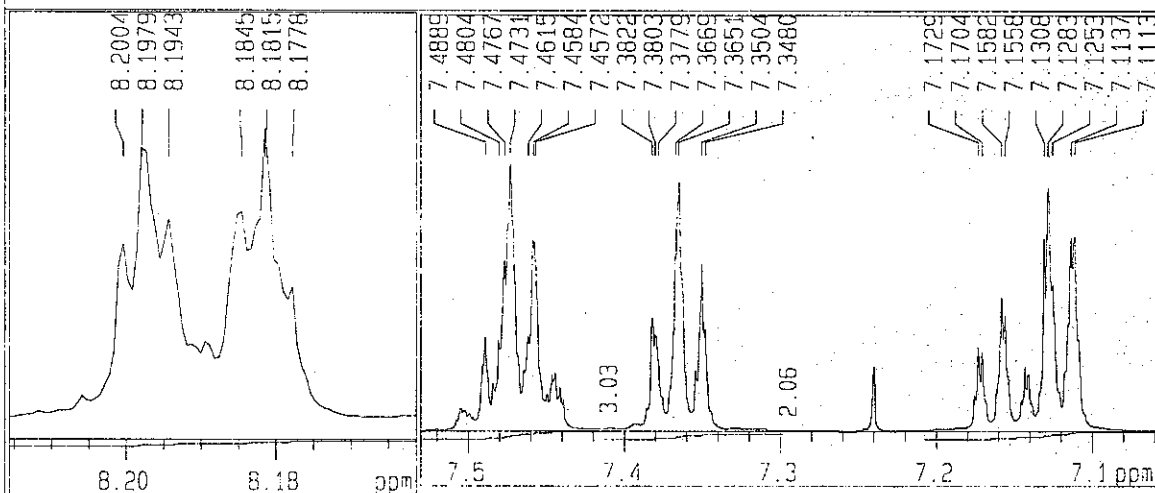
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