Just Click It: Undergraduate Procedures for the Copper(I)-Catalyzed Formation of 1,2,3-Triazoles from Azides and Terminal Acetylenes

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William D. Sharpless*,†
Department of Chemistry, Grinnell College, Grinnell, IA 50112; Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037; *notsharp@mit.edu

Peng Wu and Trond Vidar Hansen††
Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037

James G. Lindberg
Department of Chemistry, Grinnell College, Grinnell, IA 50112

Proposed by Sharpless et al. in 2001 *(1),* click chemistry presents an exciting opportunity for undergraduate chemistry students to work at the forefront of modern organic synthesis. Defined as a fast, modular, process-driven approach to molecular discovery, the term "click", like the snapping of a lock, is an apt description of the rapid, irreversible connections of the substrates involved in click reactions. Click chemistry uses only the most reliable reactions to build complex molecules from olefins, electrophiles, and heteroatom linkers. Many of the qualities of click reactions are those of greatest importance in undergraduate laboratories of the 21st century: readily available modular substrates; benign solvents; high yields; inoffensive byproducts easily removed by nonchromatographic methods; insensitivity to air and water; and regio- and stereospecificity. Examples of reactions meeting these criteria are many of the pericyclic reactions including 1,3-dipolar cycloadditions and hetero Diels–Alder reactions, especially those using imines and oxime ethers as dienophile; nucleophilic ring openings of epoxides and aziridines; and the epoxidations and dihydroxylations of alkenes.

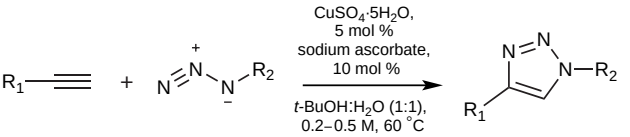
The copper(I)-catalyzed azide–alkyne ligation is currently the premier example of a click reaction *(2).* A variation on Huisgen's azide–alkyne 1,2,3-triazole synthesis *(3),* the addition of the copper(I) catalyst strongly activates terminal acetylenes toward the 1,3-dipole in organic azides, exclusively forming the 1,4-disubstituted regioisomer (Scheme I). 1,2,3-Triazoles have demonstrated diverse biological function *(4)* and recent applications of this reaction include cell surface engineering *(5),* in vivo activity based protein profiling *(6),* dendrimer synthesis *(7),* carbohydrate microarrays *(8),* and syntheses of lead discovery libraries *(9).*

This copper-catalyzed reaction is high-yielding, requires no chromatography, is easily monitored by TLC, and displays distinct signals in ^{1}H-NMR spectroscopy. Virtually all products precipitate, and with just a few different starting blocks every student, or pair of lab partners, can produce a unique, "clicked" compound. Below are two procedures for copper(I)-catalyzed triazole formation in the undergraduate laboratory.

General Procedures

Procedure A

The reaction between benzyl azide and various terminal alkynes is intended specifically for introductory organic students to produce the corresponding triazoles (Scheme II). The reagents are commercially available and the reactions go to completion within two hours and give analytically pure products after filtration. Sodium ascorbate reduces the copper(II) sulfate pentahydrate to copper(I), the active catalyst in this reaction. The presence of copper often results in intensely colored reaction mixtures, but a few drops of aqueous ammonia draws the residual copper into the aqueous solution. The series of digital images in Figure 1 demonstrate the procedure's ease and economy, as well as its final reward.



Scheme I. Copper(I)-catalyzed triazole formation.

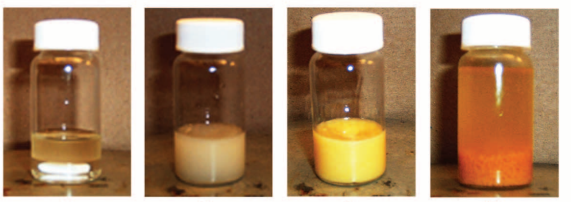
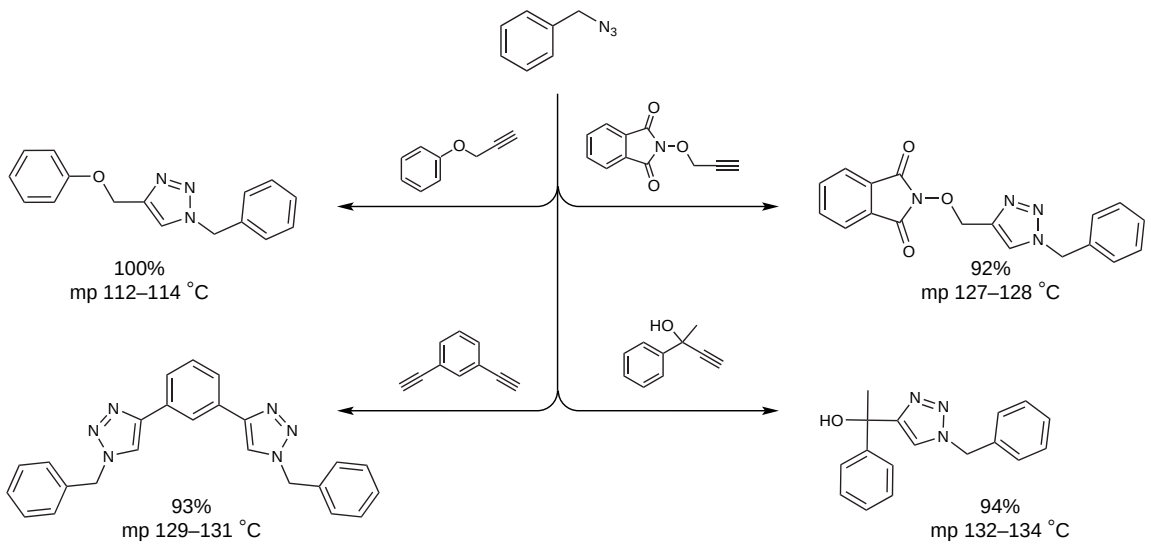


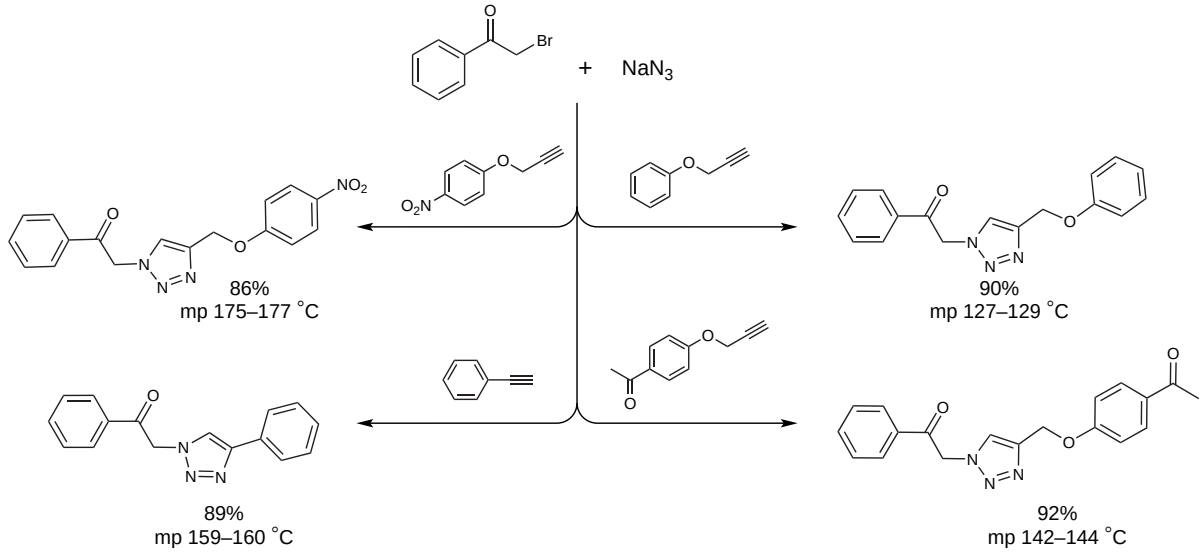
Figure 1. Reaction progress of benzyl azide and phenyl propargyl ether: (A) before addition of $CuSO_4$, (B) 30 min, (C) 120 min, and (D) after dilution with water and addition of aqueous ammonia. (A color version of this figure is in the table of contents on p 1747.)

†Current address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 20141.

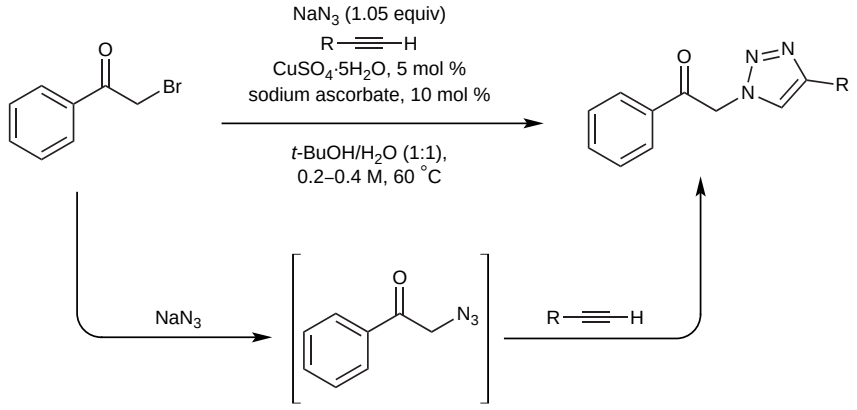
††Current address: Department of Chemistry, University of Oslo, Blindern, N-0316 Oslo, Norway.



Scheme II. Procedure A: Copper(I)-catalyzed triazole formation from benzyl azide and various acetylenes. Reaction conditions: $CuSO_4$ (5 mol %), sodium ascorbate (10 mol %), H_2O/^{t}BuOH (1:1), 0.3 M, 60 °C, 2 h.



Scheme III. Procedure B: Triazoles formed from acetylenes and in situ-generated azides. Conditions: $CuSO_4$ (5 mol %), sodium ascorbate (10 mol %), H_2O/^{t}BuOH (1:1), 0.3 M, 60 °C, 2–3 h.



Scheme IV. Copper(I)-catalyzed triazole formation from in situ-generated azide.

All reactions are easily monitored by TLC using various standard hexane–ethyl acetate solvent systems. Benzyl azide has a distinct azide peak at 2092 cm^{-1} in the IR, and the disappearance of this signal can be used to determine reaction progress or completion. The triazole products do not have characteristic IR peaks; however, the filtered products give clean ^{1}H-NMR spectra with distinct, easily assignable signals (Figure 2). The triazole proton "e" is always a singlet between 8.5–7.5 ppm and the methylene signal "d", formed when benzyl azide is the substrate, is a singlet between 6.0–5.5 ppm (The equivalent methylene signal in the products shown in Scheme III is found between 6.5–6.0 ppm).

Procedures B and C

Simple procedures and high yields make click reactions ideal for creative undergraduate laboratory investigations. Rather than purchase the above mentioned alkynes, students can take advantage of simple procedures for in situ azide formation (procedure B) and phenol propargylation (procedure C) to develop their own unique blocks for the copper-catalyzed triazole formation reaction (Scheme III). Significantly, by forming and reacting the azide in one pot *(10),* the potentially dangerous organic azide is never isolated (Scheme IV). The propargylation procedure is general and high-yielding for many commercially available phenols (Scheme V).

The applications of this reaction are far broader than the specific procedures presented here, which are limited to easily obtainable substrates giving solid products in 2–3 hours. However, with a slightly more advanced group of students (comfortable with aqueous workups and able to run reactions overnight at room temperature), the possibilities for experimentation and discovery are greatly enhanced.

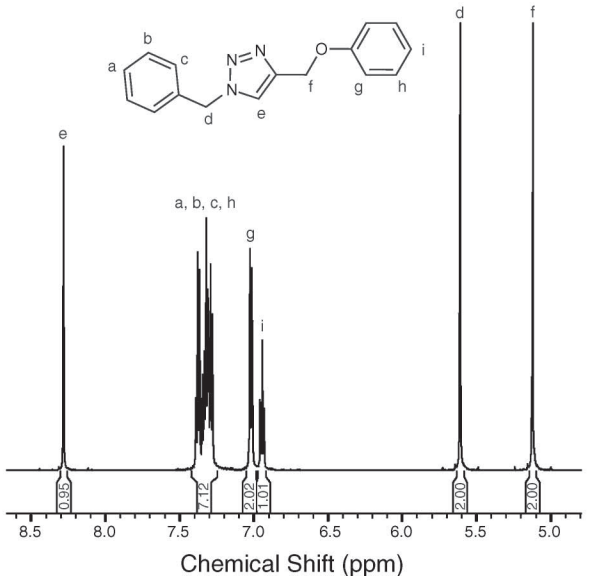
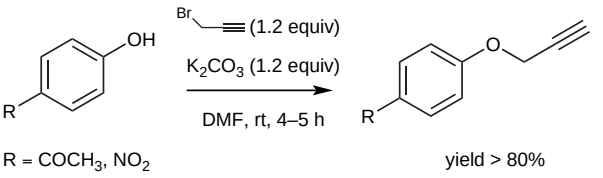


Figure 2. ^{1}H-NMR spectra of the indicated triazole product.



Scheme V. Procedure C: General procedure for phenol propargylation.

Hazards

Sodium azide is a rapidly acting, potentially deadly chemical. When mixed with acid, sodium azide changes rapidly to hydrazoic acid, a toxic gas with a pungent (sharp) odor. The mixing of sodium azide with any acidic solution must be avoided at all times. Any azide-containing waste solutions should be handled separately from other chemical wastes. Phenylacetylene and benzyl azide are flammable and should be kept away from flames. Phenylacetylene is a cancer-suspect agent and proper handling in a fume hood is necessary. The scintillation vial caps do not need to be fully sealed. Goggles, lab coat, and gloves should be worn throughout this experiment.

[W]Supplemental Material

Experimental details for procedures A, B, and C; notes for the instructor; and ^{1}H-NMR spectra for all isolated compounds are available in this issue of *JCE Online*.

Acknowledgements

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