Click Chemistry

**Required Pre-Lab Readings:** McMurry, Section 8.8

**Techniques you must be prepared to perform:** Microscale reaction,vacuum filtration, melting point.

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**Introduction**

The concept of “click chemistry” was proposed by K. Barry Sharpless and his co-workers in 2001, the same year where he was awarded the Chemistry Nobel Prize. Click chemistry is a set of highly selective, exothermic reactions which occur under mild conditions. 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. Examples of such reactions include 1,3-dipolar cycloadditions and hetero Diels–Alder reactions, especially those using imines and oxime ethers as the dienophile; nucleophilic ring openings of epoxides and aziridines; and the epoxidations and dihydroxylations of alkenes.

In this experiment you will perform an azide-alkyne 1,3-dipolar cycloaddition to yield a 1,2,3-triazole (Eq 1). These compounds have diverse biological functions and recent applications of this reaction include cell surface engineering, *in vivo* activity based protein profiling*,* dendrimer synthesis*,* carbohydrate microarrays*,* and syntheses of lead discovery libraries*.* The mechanism is similar to formation of the molozonide intermediate formed during an ozonolysis reaction (Eq 2).

|  |  |
| --- | --- |
|  | Eq 1 |
|  |  |
|  | Eq 2 |

**Procedure**

Into a microwave reaction vial (Standard Wheaton® glass vials 13-425, 15x46 mm, Type I borosilicate glass) add 70 µL **benzyl azide**, 50 µL **phenyl acetylene** and 2 mL tBuOH/water (1:1) reaction solvent. Add 10 mg sodium ascorbate and 25 µL 1 M copper (II) sulfate pentahydrate sequentially. Use the **capping tool** to carefully put a microwave reaction seal (polytetrafluoroethylene, PTFE) onto your vial. The capping tool will ensure the seals lines up properly with the vial to avoid seal damage. Put a microwave reaction cap (polyether ether ketone, PEEK) on the vial and screw it finger tight. Place it in a transport box. Once the whole class finish preparing the samples, all the vials will be placed in microwave reactor. There are four black silicon carbide (SiC) plates in the microwave and each of them may hold up to 24 vials. Evenly distribute the vials on the plates for even irradiation. The click reaction will be assisted by microwave irradiation at 120 oC for 10 min.

Once the microwave irradiation is finished, the instructor will remove the vials from the microwave return them to the transport box. Chill the sealed reaction vial in an ice/water bath for several minutes. Open the caps and seals with caution and return the caps and seals to the designated containers on the instructor’s desk. Transfer the reaction mixture to a small beaker and dilute with 5 mL ice water, followed by the 1 mL 10% aqueous ammonia (What is the purpose of this step?). After stirring for another 5 min, the solid precipitate is vacuum filtered and air-dried. Allow the product to air dry until next week and obtain the weight and mp. The literature melting point for the product, 1-benzyl-4-phenyl-1,2,3-trazine, is 128 – 130 °C.

**Cautions and Reminders**

1. This reaction generates a gas (which one?), so it is necessary to chill the vial before you open it.
2. This is a microscale reaction. The scale is only 1 mmol (~ 0.1g). Handle the product with care to avoid loss, especially for the recrystallization. Do not use too much solvent to transfer or wash the crystals.
3. A stirring bar is not necessary for very small volume under microwave irradiation.
4. The reaction vessel is expensive! The microwave reaction caps ($40 each) and seals ($4 each) are specially designed for microwave reactor and will be reused. Return them to the designated containers once you open your vials. The microwave reaction vials are disposable. Please put them in the designated beaker once you are done with your reaction.

**Hazards**

Benzyl azide is toxic if swallowed and has a risk of explosion by shock, friction or fire above 100 °C. Phenyl acetylene is harmful if swallowed, inhaled, or absorbed through skin. Vapor or mist is irritating to the eyes, mucous membranes and upper respiratory tract. Cupric sulfate pentahydrate is harmful if swallowed, dust or mist are mucous membrane irritants and a skin sensitizer.

**Literature Cited**

1. Kolb, H. C., Finn, M.G., and Sharpless, K. B. *Angew. Chem. Int. Ed.*, **2001**, 40, 2004-2021.

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Overall Reaction: (Chemical drawing software)

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| --- | --- | --- | --- | --- |
| vol of benzyl azide: |  |  | Theo mmol 1,2,3-triazole: |  |
|  |  |  |  |  |
| mmol of benzyl azide: |  |  | Theo mass 1,2,3-triazole: |  |
|  |  |  |  |  |
| volume of phenyl acetylene: |  |  | Mass recovered 1,2,3-triazole: |  |
|  |  |  |  |  |
| mmol of phenyl acetylene: |  |  | mmol recovered 1,2,3-triazole: |  |
|  |  |  |  |  |
| mass sodium ascorbate |  |  | % yield of 1,2,3-triazole: |  |
|  |  |  |  |  |
| mmol sodium ascorbate |  |  |  |  |
|  |  |  |  |  |
| mol % ascorbate (relatve to alkyne) |  |  |  |  |
|  |  |  |  |  |
| mmol CuSO4•5H2O |  |  |  |  |
|  |  |  |  |  |
| mol % Cu (relatve to alkyne) |  |  |  |  |

Observed melting point of recovered 1,2,3-triazole:

Show complete calculations: (notebook)

**Post Lab Questions:**

1. What is the role of sodium ascorbate in this reaction? Show the ***balanced chemical equation*** for sodium ascorbate as it is used in this reaction (use chemical drawing software).

2. Use chemical drawing software to complete the following ring forming reactions. Remember that products should include correct stereochemistry and regiochemistry. Racemic mixtures can be indicated by drawing one enantiomer and writing “+ enantiomer.” When diasteriomers are produced both must be drawn.

|  |  |  |
| --- | --- | --- |
| 1) |  |  |
|  |  |  |
| 2) |  |  |
|  |  |  |
| 3) |  |  |
|  |  |  |
| 4) |  |  |