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The Use of Copper Flow Reactor Technology for the Continuous Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

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Abstract: A library of 1,4-disubstituted 1,2,3-triazoles was synthesized using a copper flow reactor. Organic azides, generated *in situ* from alkyl halides and sodium azide, were reacted with acetylenes using the copper-catalyzed Huisgen 1,3-dipolar cycloaddition. This process eliminates both the handling of organic azides and the need for additional copper catalyst and permits the facile preparation of numerous triazoles in a continuous flow process.

Keywords: click chemistry; flow chemistry; heterogeneous catalysis; high-throughput screening; high-throughput synthesis; microreactors

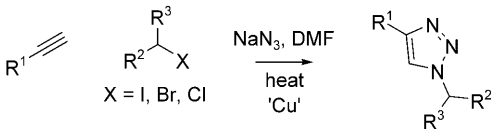
The click reaction between organic azides and acetylenes has gained a considerable amount of attention since its discovery in 2001.[1] The resulting 1,2,3-triazoles are an interesting class of heterocycles, as they have found use in many biological applications, antifungal agents, as well as dyes.[2] Chemists are attracted to click chemistry in drug discovery due to its high dependability, its appeal to combinatorial chemistry, and its compatibility with biological systems.[3]

Whilst acetylenes can be readily prepared using high-yielding methodologies such as the Sonogashira coupling, azide preparation is more problematic. Azides are a class of compounds known to readily decompose[4] and as such their preparation and isolation must be handled with care, particularly on scale.

Eliminating the need to isolate azides would be a significant advantage and while reports have shown that alkyl azides can be generated *in situ* prior to the copper-catalyzed cycloaddition, these methodologies have either been slow or relied on microwave technology.[5]

Flow chemistry is an important, emerging field that pushes the boundaries of organic synthesis by accessing so-called 'forbidden chemistries' through unparalleled reaction control.[6] The numerous advantages of running reactions in flow are often attributed to the large surface area-to-volume ratios.[6c] Small dimensions lead to good mixing[7] and the superb heat transfer within these systems enables excellent control of exotherms, limiting the impact of runaway reactions.[6b] Back-pressure regulation technology enables solvent boiling suppression and reaction kinetics can be substantially increased.[8] In addition, scale-up becomes a facile process compared with batch systems and output is measured as a function of time rather than batch size.[9]

Realizing the benefits of flow chemistry we sought to explore a one-pot click methodology (Scheme 1).



Scheme 1. The one-pot click reaction.

Organic azides could be generated in small volumes from their corresponding alkyl halides at high temperatures and immediately reacted with acetylenes. By adopting this approach we hoped to overcome the safety and supply issues of azides and dramatically increase the monomers available to us, enabling a greater number of triazoles to be synthesized.

We report herein the rapid synthesis of a 1,4-disubstituted 1,2,3-triazole library in a flow reactor using this one-pot click methodology. A copper flow reactor has been developed to catalyze the reaction, enabling triazoles to be synthesized from simple starting materials without the need for additional catalyst. The

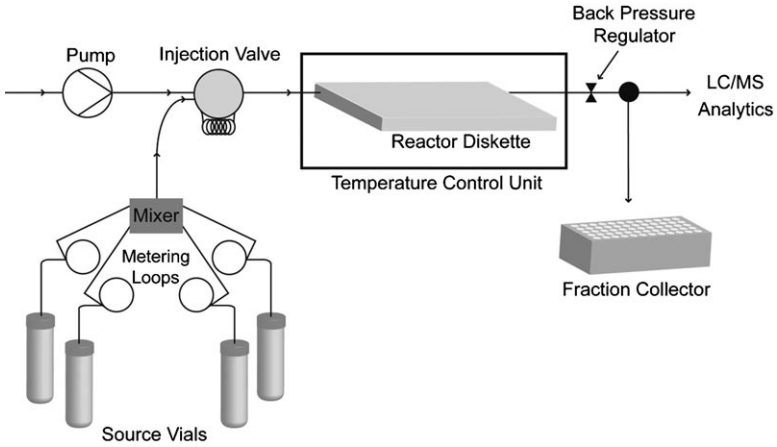


Figure 1. Conjure flow reactor, schematic drawing.

facile scale-up of one triazole is also demonstrated, and the application of this technology to drug discovery is discussed.

The Conjure flow reactor (Figure 1) was designed to operate on a scale suitable for both medicinal chemistry and process research. The instrument adopts a segmented flow approach versus a continuous stream approach in order to minimize material consumption and limit reaction size. Reaction segments are separated by an immiscible fluorous spacer, perfluoromethyldecalin, that prevents segment diffusion and reaction trailing.[10,11] Using this approach, multiple segments can flow through the reactor at any one time, maximizing the system's efficiency and permitting rapid library development (medicinal chemistry) or reaction optimization (process research).

The reactor diskette consists of a reaction coil made of copper, Hastelloy or PTFE tubing placed between two copper plates (Figure 2). Multiple segments can be passed through the system sequentially since the internal volume of the reactor diskette ranges from 2–10 mL and reaction segments are on the order of 400 μL.

Heterogeneous catalysis has been used extensively in flow systems and has proven to be highly recyclable and selective.[12] Realizing that even Cu(0) sources such as copper wire[1b] and copper metal turnings[5a] had been effectively used as catalysts for the click reaction, we had a reactor diskette prepared from copper. Using this method, we envisioned that no additional copper catalyst would be necessary, removing a level of complexity from the system. Indeed, when reaction segments containing sodium azide, an alkyl halide, and acetylene in DMF were passed through the copper flow reactor, high conversions were obtained within 5 min.[13] Replacing the copper reactor with a Hastelloy reactor diskette prohibited the reaction, confirming the necessity of the copper and proving the triazole formation was not occurring under thermal conditions.[14] The copper reactor was used to catalyze hundreds of reactions, never showing a loss of catalytic activity[15] and was also shown to effectively catalyze other copper-mediated reactions such as the Sonogashira and Ullman couplings.

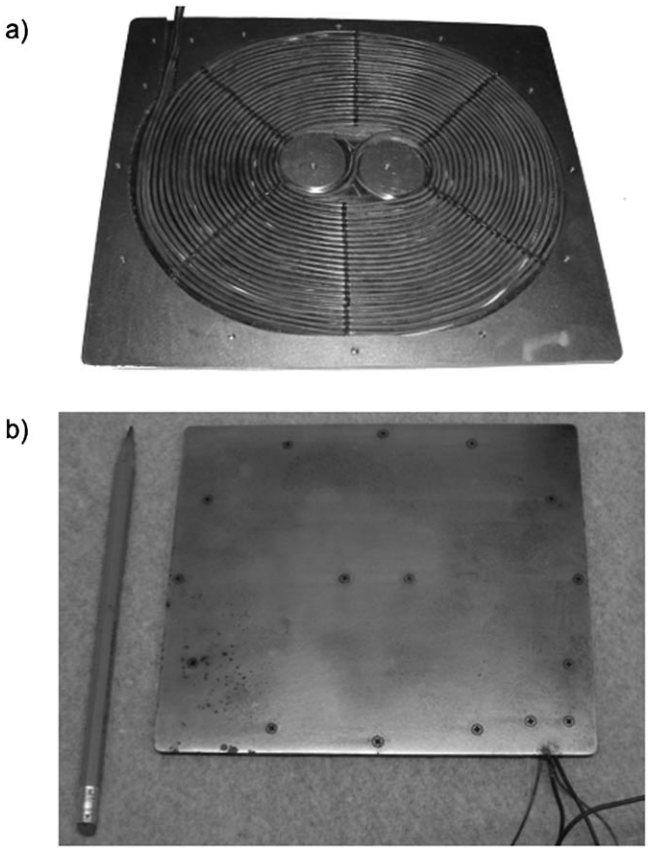
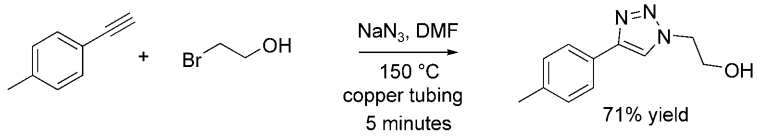


Figure 2. a) A reactor diskette with the top copper plate removed, exposing the copper tubing within (0.75 mm i.d.). **b**) An assembled reactor diskette for the flow reactor (145 mm × 165 mm × 5 mm).



Scheme 2. The optimized one-pot click reaction using 4-ethynyltoluene and 2-bromoethanol.

We optimized the one-pot click methodology using 4-ethynyltoluene, 2-bromoethanol and sodium azide in DMF (Scheme 2).[16] By varying the residence time, reactor temperature, and equivalents of alkyl azide, we were able to rapidly obtain optimal reaction conditions using minimal amounts of material.[17] By linking the instrument's analytical output to DOE software such as Design Expert®, reports are generated after the optimization, dictating the optimal reaction conditions for this transformation (see Supporting Information).

Using these conditions, a library was prepared using six different acetylenes, six different alkyl halides, and sodium azide (Figure 3). It should be noted

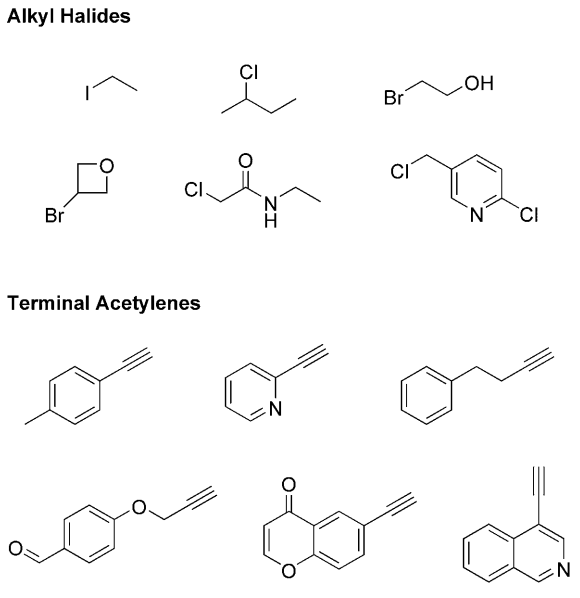


Figure 3. Alkyl halides and terminal acetylenes used for the triazole library.

that the preparation of six acetylene source vials (0.25 M in DMF), six alkyl halide source vials (0.5 M in DMF) and a sodium azide source vial (0.5 M in DMF/H_2O 4:1 v/v) *was the only chemical handling necessary to run the library synthesis.* Using the optimized conditions for the flow click methodology, thirty triazoles were synthesized in a matter of hours in modest to excellent yield (Figure 4).[18] For reactions resulting in low yields, an optimization could be carried out in order to increase the yield. In this proof of concept work, the optimization conditions from the DOE between 4-ethynyltoluene and 2-bromoethanol were the only conditions used. The click methodology worked for aliphatic and aromatic acetylenes, as well as primary and secondary alkyl halides. Low molecular weight azides such as azidoethane and 3-azidooxetane were also used safely in the Conjure flow reactor.

The batch scale-up of processes involving energetic intermediates such as organic azides can be dangerous as high concentrations can accumulate, thus creating an explosion hazard. Such reactions can require extensive process safety investigation and costly custom engineered facilities. In flow this danger is significantly reduced as scale-up is a function of time and flow rate and the volume of active chemistry remains small. Through this principle, processes developed using flow technology on a small scale can subsequently be used to prepare larger scale batches as compounds move through development, minimizing process development and capital equipment costs.

To demonstrate the preparative capability of the Conjure flow reactor, the click reaction between 4-ethynyltoluene and *N*-ethylchloroacetamide was scaled-up (Table 1). The stoichiometry was adjusted such that only 1 equivalent of alkyl azide was generated, thus limiting excess azide (either organic or inorganic) in the output stream. After 12 min, 115 mg (60%) of triazole **5** were isolated after the simple work-up of aqueous precipitation and filtration. If run continuously, this output extrapolates to generating 575 mg of product per hour, or 13.8 g of product per day (Table 1).

In summary, we have developed a one-pot click reaction using a copper flow reactor that permits the *in situ* generation of organic azides and facile preparation of triazole libraries. The use of a custom engineered copper reactor serves as the catalyst to facilitate the cycloaddition. Reactions are readily scaled up with fewer safety concerns than the corresponding batch processes. The high-throughput, automated nature of the instrument greatly adds to the appeal of this process and this technology is currently being employed in the drug discovery process to rapidly synthesize vast numbers of compounds towards flow discovery.[10a]

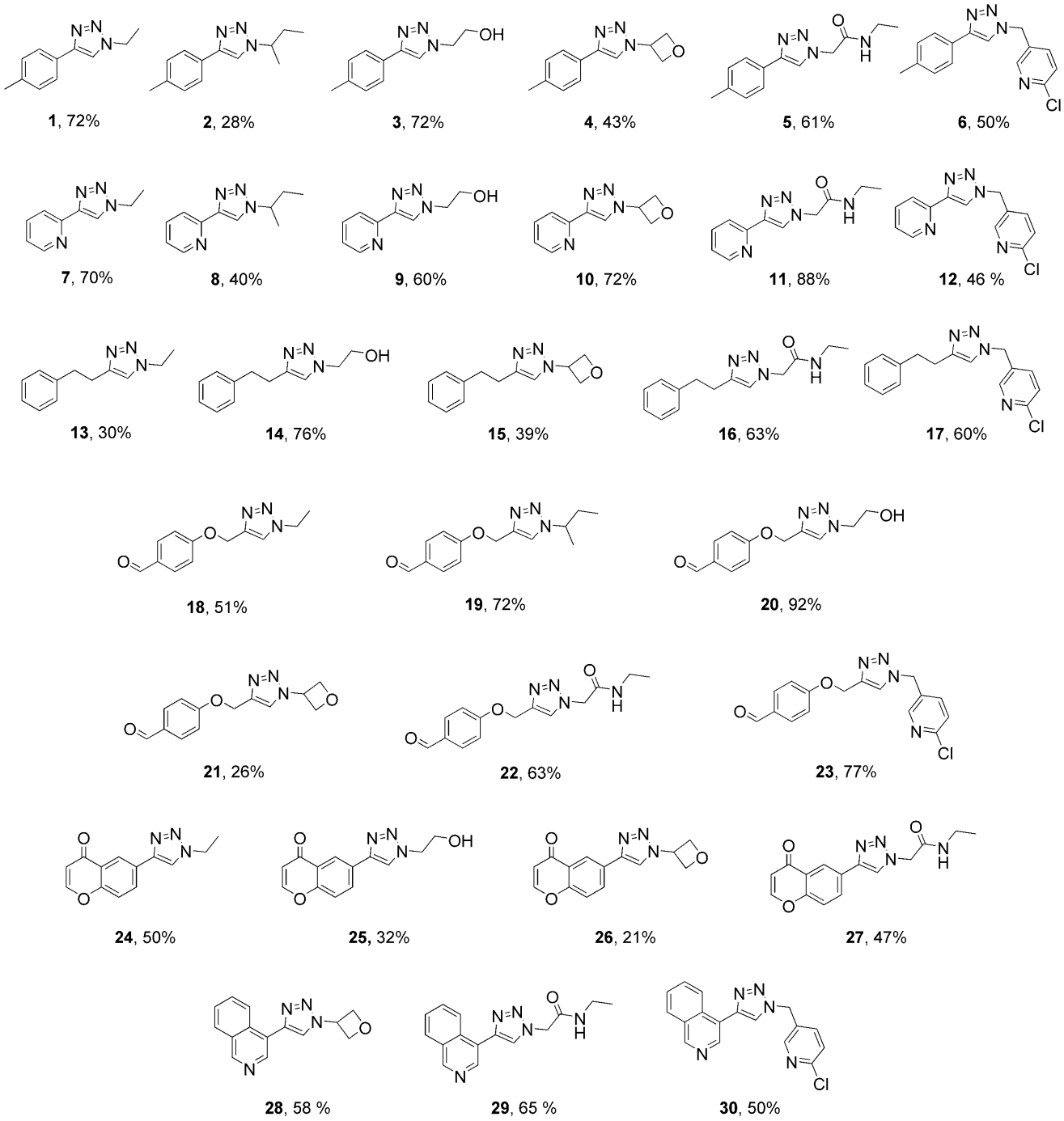


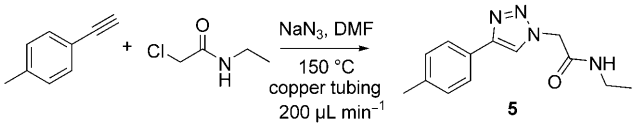
Figure 4. The 1,4-disubstituted 1,2,3-triazoles synthesized using the Conjure flow reactor. Yields determined by ^{1}H NMR using an internal standard.

Experimental Section

General Remarks

All reagents and solvents were used as received. ^{1}H NMR analysis was carried out using a capillary NMR probe (Protasis MRM Division, Savoy, IL) on a Varian Inova spectrometer with a Larmor frequency of 499.667 MHz. The capillary NMR probe consisted of a 5 μL flow cell (active volume 2.5 μL) double-tuned to ^{1}H and ^{13}C with a deuterium lock channel and *z*-gradient (Protasis MRM Division, Savoy, IL). The spectrometer was equipped with a CTC HTC-PAL autosampler (Leap Technologies, Carrboro, NC). Samples were prepared using DMSO-d_6 spiked with the internal standard 2,5-dimethylfuran. Peaks were referenced to 2,5-dimethylfuran (5.8 ppm for ^{1}H). LC/MS analyses were carried out using an Agilent Technologies HPLC (Agilent Technologies 1200 Series diode array detector, Agilent Technologies 1200 Series column heater, Agilent 1100 Series

Table 1. Triazole synthesis scale-up.



Time	Triazole Output
12 min	115 mg[a]
1 hour	575 mg
1 day	13.8 g

[a] Isolated yield.

fraction collector, Agilent 1100 Series pump, and Agilent 1100 Series degasser) interfaced with an Agilent Technologies 6120 Quadrupole LC/MS. Elemental analysis was carried out by QTI Analytical.

Typical Experimental Procedure for Triazole Library Synthesis

4-Ethynyltoluene (133.3 μL, 0.25 M in DMF, 0.033 mmol, 1.0 equiv.), ethyl iodide (133.3 μL, 0.5 M in DMF, 0.066 mmol, 2.0 equiv.), and NaN_3 (133.3 μL, 0.5 M in DMF/H_2O 4:1 v/v, 0.066 mmol, 2.0 equiv.) were aspirated from their respective source vials, mixed through a PFA mixing tube (0.2 mm i. d.), loaded into an injection loop and injected into the flow reactor set at 150 °C at a rate of 400 μL min^{-1} (5 min residence time). Reaction segments were collected in a 96-well plate containing QuadraPure TU copper-scavenging resin. Segments were filtered, concentrated, and analyzed using ^{1}H NMR.

Experimental Procedure for Scaled-Up Triazole Synthesis

4-Ethynyltoluene (133.3 μL, 1.0 M in DMF, 0.1333 mmol, 1.0 equiv.), *N*-ethylchloroacetamide (133.3 μL, 1.0 M in DMF, 0.1333 mmol, 1.0 equiv.), and NaN_3 (133.3 μL, 1.0 M in DMF/H_2O 4:1 v/v, 0.1333 mmol, 1.0 equiv.) were aspirated from their respective source vials, mixed through a PFA mixing tube (0.2 mm i. d.), and loaded into an injection loop. Six reaction segments were injected into the flow reactor set at 150 °C, passed through the reactor at 200 μL min^{-1} (10 min residence time) and collected in a reaction vial containing heptane and water. The yellow precipitate was collected by filtration, washed with water (2×), heptane (2×) and dried under vacuum to afford triazole **5**; yield: 115 mg (60%).

Supporting Information

Experimental procedures, DOE data, and compound characterization data are available in the Supporting Information.

Acknowledgements

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[13] Depending on the solvent used for this reaction, the rate of copper leaching from the reactor diskette greatly varied. When EtOH was used as the reaction solvent at 150 °C, elemental analysis showed a copper concentration of 78 ppm. However, as EtOH proved to be a poor solvent for the triazole products, precipitation ultimately lead to blockages in the channels. When DMF was chosen as the reaction solvent, elemental analysis showed a copper concentration in the order of 300 ppm. The addition of QuadraPure TU scavenging resin reduced the copper concentration to <5 ppm, effectively removing all copper from the system.

[14] The Husigen [3+2] thermal addition of organic azides to acetylenes is a slow process that requires extensive heating. This thermal cycloaddition also yields a mixture of isomers, whereas the copper-catalyzed cycloaddition preferentially generates the 1,4-triazole. There were no traces of the 1,5-disubstitued isomers by LC/MS and NMR.

[15] The reactor was frequently washed with 1 M aqueous NH_3, 1 M HCl, and again with 1 M aqueous NH_3 to ensure there was not a build-up of dangerous copper azide within the reactor.

[16] The reaction was optimized in terms of reactor output to demonstrate the high-throughput synthetic capabilities of the flow reactor.

[17] Equivalents of alkyl azide are defined as the equivalents of alkyl halide, coupled with equivalents of sodium azide. For instance, 1 equiv. alkyl halide and 1 equiv. sodium azide are assumed to be 1 equiv. alkyl azide.

[18] LC traces of reaction segments were very clean, showing the presence of products, unreacted acetylene starting materials, as well as trace amounts of the free triazole (formed from the reaction of the terminal acetylene with sodium azide).

