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[3+2] click chemistry approach to tetrazine containing polymers†

David E. Chavez,^a Bryce C. Tappan,^{id}^a Valerie A. Kuehl,^{id}^{*a} Andrew M. Schmalzer,^a Philip W. Leonard,^a Ruilian Wu,^a Greg H. Imler^{id}^b and Damon A. Parrish^b

We report a [3+2] cycloaddition using 3,6-bis-propargyloxy-1,2,4,5-tetrazine and azides to synthesize energetic polymers containing 1,2,4,5-tetrazine within the scaffold. This work also includes [3+2] cycloaddition to crosslink azide containing glycidyl azide polymer (GAP). These reactions provide pathways for incorporation of 1,2,4,5-tetrazine into novel energetic materials using click-chemistry and provide an alternative polymer curing approach.

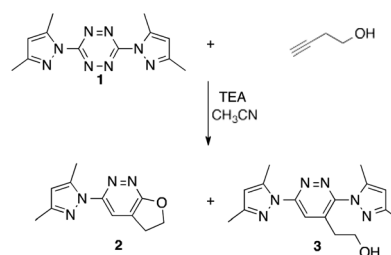
Due to their versatility and unique chemical and physical properties, tetrazines have found utility in organic solar cells,^{1,2} sensors,^{3,4} on/off fluorescence^{5–8} and energetic materials applications.^{9,10} A significant increase in 1,2,4,5-tetrazine chemistry synthesis has also occurred over the past several years.^{11–14} A number of investigations have focused in large part on bio-orthogonal, inverse electron demand hetero-Diels–Alder reactions with 1,2,4,5-tetrazines for numerous applications, such as *in situ* synthesis of fluorogenic probes for live cell imaging, and near infrared fluorogenic probes.⁸ Unfortunately, the inverse electron demand hetero-Diels–Alder reaction of 1,2,4,5-tetrazines is not a promising pathway in energetic materials chemistry as a concomitant reduction in the inherent energy of the molecule results during these types of transformations due to the loss of N₂. Thus alternative pathways for the incorporation of 1,2,4,5-tetrazine into novel energetic materials are warranted.

One very interesting possibility for the preparation of new energetics is to employ a [3+2] cycloaddition (click-chemistry) strategy. In this case, a Huisgen 1,3-dipolar cycloaddition between 1,3-dipoles such as azides, and 1,2-dipolarophiles such as acetylenes could be incorporated onto the tetrazine ring system at the 3 and 6 positions either directly or through linkers of varying length. The challenge presented with this approach is the possibility for the 1,2,4,5-tetrazine system to undergo competitive inverse electron demand [4+2] hetero-Diels–Alder chemistry with acetylene functional groups. Indeed, Rusinov and co-workers found that the reaction of but-3-yn-1-ol with 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**1**) in the presence of triethylamine in acetonitrile led to the two products **2**

and **3** (5 : 1) as shown in Scheme 1.¹⁵ These two products both are a result of inverse electron demand hetero-Diels–Alder processes. Changing the leaving group from 3,5-dimethylpyrazole to imidazole led to the exclusive isolation of the bicyclic product **2**.

While these literature results were not encouraging, we decided to pursue the synthesis of 3,6-bispropargyloxy-1,2,4,5-tetrazine (**4**). We found that shortening the distance between the alcohol group and the acetylene moiety allowed for nucleophilic addition to proceed exclusively with no evidence of inter- or intramolecular hetero-Diels–Alder cyclization occurring. Thus propargyl alcohol reacted with **1** in the presence of potassium carbonate to provide **4** in excellent yield (Scheme 2). Ultimately, we were able to perform the reaction neat, using propargyl alcohol as the solvent, although only in minimal amounts.

To confirm the structure of **4**, X-ray quality crystals were obtained from slow diffusion of diethyl ether into a solution of **4** in acetone. The compound was found to have the monoclinic crystal system with a *P2₁/c* space group.⁷ It displayed a density of 1.46 g cm^{−3} at 293 K (see ESI†). The Ortep representation of the crystal structure is displayed in Fig. 1. Overall, the transformation resulting in **4** is unprecedented and allowed for a “click” chemical approach to make energetic, tetrazine containing polymers.



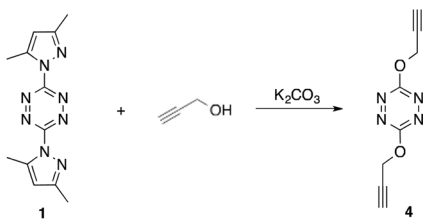
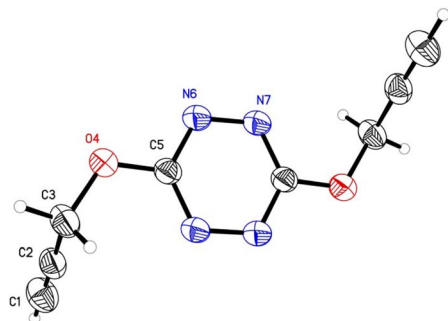
Scheme 1 But-3-yn-1-ol reaction with **1** in the presence of TEA

^aQ Division, Los Alamos National Laboratory, Los Alamos 87545, NM, USA. E-mail: vkuehl@lanl.gov

^bNaval Research Laboratory, DC 20735, Washington, USA

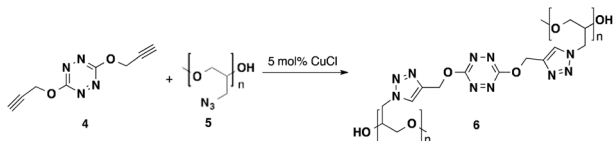
† Electronic supplementary information (ESI) available: For experimental details, including characterization, X-ray crystallographic and rheometry data. CCDC 1846069. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2ra05339j>



Scheme 2 The synthesis of **4**.Fig. 1 Molecular conformation of **4**, nonhydrogen atoms are shown as 50% probability displacement ellipsoids. Ellipsoids of **4** shown at 50% probability.

With **4** in hand, we attempted to perform the Huisgen cycloaddition reaction with azide containing materials employing the Cu(I)-catalyzed azide/alkyne cycloaddition approach (CuAAC) to accomplish prepolymer curing, polymerization and self-polymerization.⁸ We first investigated a [3+2] cross-linking strategy using **4** as a curing agent for azide containing prepolymers, such as the glycidyl azide (GAP) prepolymer. A similar approach has been described with other polyacetylene compounds.⁹ Typically GAP is cured using a urethane crosslinking approach, but this method presents challenges, such as sensitivity to moisture and the use of reactive isocyanates. A [3+2] curing approach with a high energy cross linker could provide higher energy GAP polymers. Initial results found that 5 wt% **4** was successful at curing the GAP prepolymer (**5**) in the presence of a catalytic amount of CuCl, to produce polymer **6** (Scheme 3).

These results were expanded on to include a curing study of GAP (**5**) and GAP plasticizer (GAPP, **5p**) with varying weight percentages of **4** in the presence of a copper halide species to produce polymer **6** and **6p**, respectively. The GAP (also called GAP 5527-Polyol) is a high molecular weight prepolymer with a hydroxyl equivalent between 2.5–3 used in urethane cures,



Scheme 3 Curing of glycidyl azide prepolymer.

while the GAPP is a lower viscosity prepolymer with an average MW of 700, and a hydroxyl equivalent close to 1. As the click-chemistry cure for these GAP pre-polymers is independent of hydroxyl terminal group content, the two materials were utilized to evaluate rheological properties over the course of reaction. Rheometry measurements were conducted on samples containing 3% of **4** for both polymers (see ESI†). The transition from liquid to solid, or gel point, for **6** occurred at roughly 83 minutes compared to **6p** at about 4 hours.

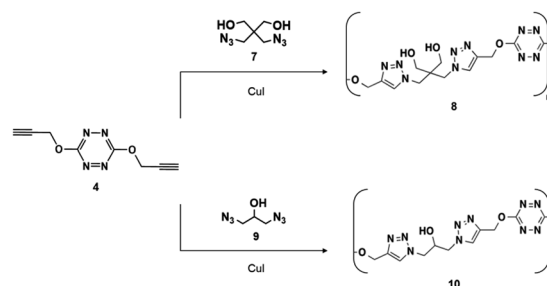
After demonstrating that **4** could be used to cure GAP, we turned our attention to polymerization studies of **4** with diazide compounds. One such material was 2,2-bisazidomethyl-1,3-propanediol (**7**).¹⁶ Since **7** is a liquid, we performed the cycloaddition neat by thoroughly mixing **4**, **7** with a catalytic amount of a copper halide (CuCl or CuI). Heating for several hours at 60 °C led to the polymerized product (**8**) (Scheme 4). Similarly, when **4** was reacted with 2-hydroxy-1,3-diazidopropane (**9**)^{17,18} in the presence of a catalytic amount of CuCl, the desired polymerization product (**10**) was observed (Scheme 4).

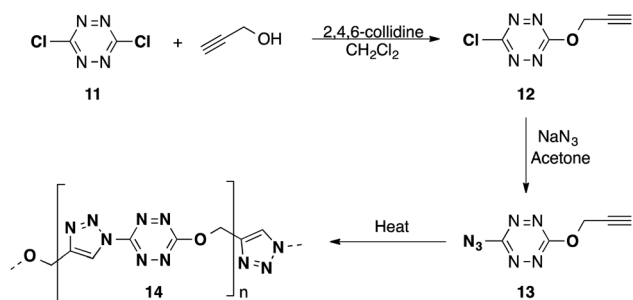
Polymers **8** and **10** were found to have molecular weights of $3602 \pm 136.71 \text{ g mol}^{-1}$ and $6796 \pm 132.17 \text{ g mol}^{-1}$, respectively. As expected, Fourier transform infrared spectroscopy (FT-IR) comparisons of **4** to both polymers showed significant reduction in the intensity of the terminal acetylene stretch at 3261 cm^{-1} (C–H) and 2126 cm^{-1} ($\text{C}\equiv\text{C}$) (see ESI†).

Further studies for single compound self-polymerization were explored by incorporation of the azide group and an acetylene group on the same tetrazine ring. We began with the reaction of propargyl alcohol with 3,6-dichloro-1,2,4,5-tetrazine (**11**) in the presence of 2,4,6-collidine, using *tert*-butyl methyl ether as a solvent. This provided **12** in good yield (Scheme 5). Subsequent treatment of **12** with sodium azide in acetone provided the 3-azido-6-propargyloxy-1,2,4,5-tetrazine (**13**).¹⁰ This material melts at 50 °C and begins to polymerize if left in the melt for several hours to provide polymer **14**. Unfortunately, the extreme sensitivity of **13** precluded further studies on the properties of the resultant polymer.

Calculations for compounds **4**, **7**, and **9** are provided in Table 1, and include: theoretical maximum density (ρ), heat of formation (ΔH_f), and oxygen balance (OB).^{19–21}

Additionally, sensitivity measurements were conducted on compounds **6**, **6p**, **8**, **9**, **10** and are compared to pentaerythritol tetranitrate (PETN) in Table 2. Measurements include: impact

Scheme 4 Polymerization of **4** with diazides.



Scheme 5 Synthesis of **13** and subsequent thermal polymerization to **14**.

Table 1 Theoretical calculations

	4	7	9
ρ (g cm ⁻³)	1.40	1.39	1.40
ΔH_f (kcal mol ⁻¹)	128.04	44.91	87.87
OB (%)	-143	-155.7	-90.1

Table 2 Sensitivity measurements

	IS ^a [cm]	FS ^b [N]	ESD ^c [J]
4	20.7	225	0.0625
6	177	>360	0.0625
6p	194	>360	0.0625
8	79.4	>360	0.125
9	21.5	>360	0.125
10	>320	>360	0.125
PETN	12.9	58	0.0625

^a LANL type 12, 50% drop height, 2.5 kg weight. ^b 50% load Neyer d-optimal method. ^c ABL spark, 3.4% threshold initiation level (TIL).

sensitivity (IS), friction sensitivity (FS), and electrostatic discharge (ESD).

Illustrated in Table 2 polymers **6**, **6p**, **8**, and **10** all have impact sensitivities less than PETN. However, **6** and **6p** both are comparable to PETN with respect to spark sensitivities.

In conclusion, propargyl alcohol and **1** reacted to give the unprecedented product **4** which maintained the 1,2,4,5-tetrazine ring system intact. With this result in hand, we implemented a [3+2] cycloaddition strategy using alkyne and azide moieties to accomplish prepolymer curing, polymerization and self-polymerization reactions. The resultant energetic polymers contain the 1,2,4,5-tetrazine within the polymer scaffolds. All polymers presented here display explosive sensitivity properties either less than or equal to PETN. Further work on studying these energetic polymers and developing new energetic materials are currently being pursued.

Experimental section

General methods

Unless otherwise noted, all ¹H- and ¹³C-NMR spectra were recorded in DMSO-d₆ at ambient temperature using a Bruker

Avance 400 spectrometer operating at 400 MHz for ¹H and 100 MHz for ¹³C. Chemical shift values (δ) are reported in ppm, referenced to the residual DMSO solvent signal (¹H: 2.50 ppm & ¹³C: 39.52 ppm). FT-IR spectra were measured with a Thermo-Nicolet iS5 FTIR spectrophotometer using the OMNIC software, and data collection are reported in reciprocal centimeters (cm⁻¹). IR spectra measurements were made using an ATR cell. Elemental Analyses (EA) were performed with a PerkinElmer series II 2400 CHNS/O analyzer. All reagents and solvents were used as received (Sigma-Aldrich, Fluka, Acros Organics and Mach 1 Specialty Chemicals). 2,2-Diazidomethyl-1,3 propanediol (**7**)¹⁶ and 2-hydroxy-1,3-diazido-propane (**9**)^{17,18} were synthesized according to literature procedure.

Caution! The compounds and polymers presented here are highly energetic with sensitivity to various stimuli. While we encountered no issues while working with this material, proper protective measures (Kevlar® gloves, face shield, and grounded equipment) should still be used at all times. The [3+2] cycloaddition between alkyne and azide moieties is highly exothermic and should only be undertaken in small amounts with sufficient heat-dissipation to avoid ignition during reaction.

4. To propargyl alcohol (10 mL) is added freshly powdered K₂ CO₃ (0.40 g, 2.89 mmol). The mixture was stirred at ambient temperature.

3,6-Bis(3,5-dimethyl-pyrazol-1-yl)-1,2,4,5-tetrazine (5.4 g, 20 mmol) was then added. The mixture was heated to 70 °C and the mixture became a solution. The reaction was stirred for 30 min at 70 °C, cooled to ambient temperature and water (50 mL) was added. A red-orange precipitate was formed. The product was filtered, washed with water and air-dried to provide 2.8 g (74% yield) of product. FTIR cm⁻¹ 3260, 2130, and 1320. ¹H NMR (DMSO-d₆, 400 MHz): δ 3.64 (d, J = 2.4 Hz, alkyne CH) and 5.72 (d, J = 2.4 Hz, CH₂). ¹³C NMR (DMSO-d₆, 100 MHz): δ 67.1, 87.3, 176.2, 215.7 ppm. Elemental analysis calcd C, 50.53, H, 3.18, 29.46. Found C, 50.51, H, 3.19, N, 29.448.

8. To 2,2-bisazidomethyl-1,3-propanediol (**7**) (0.093 g, 0.500 mmol) 3,6-bispropargyloxy-1,2,4,5-tetrazine (**4**) (0.086 g, 0.452 mmol) was added, followed by copper iodide (0.002 g, 0.010 mmol). The mixture was stirred for one minute (X2) at ambient temperature. The mixture was slowly heated in increments of 10 °C to 60 °C. The reaction was held at 60 °C for 24 hours. A dark burgundy solid was formed. The product was air-dried to provide 0.078 g of material. FTIR cm⁻¹ 3417, 2102, 1710, and 1419. GPC/SEC 3.602 ± 136.71 g mol⁻¹. DSC onset 115.98 °C, T_g at 15.4 °C.

10. To a vessel containing 3,6-bispropargyloxy-1,2,4,5-tetrazine (**4**) (0.203 g, 1.07 mmol), 2-hydroxy-1,3-diazidopropane (**9**) (0.167 g, 1.17 mmol) was added, followed by copper iodide (0.005 g, 0.026 mmol). The mixture was stirred for one minute (X2) at ambient temperature. The mixture was slowly heated in increments of 10 °C to 60 °C. The reaction was held at 60 °C for 24 hours. A dark burgundy solid was formed. The product was air-dried to provide 0.332 g of material. FTIR cm⁻¹ 3435, 2102, and 1642. GPC/SEC 6.796 ± 132.17 g mol⁻¹. DSC onset 143.67 °C, T_g at 24.7 °C.



Conflicts of interest

The authors have no conflicts to declare.

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