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Azide-alkyne cycloaddition (click) reaction in biomass-derived solvent Cyrene^{TM} under one-pot conditions

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Abstract

It was demonstrated that Cyrene^{TM} as a biomass-originated polar aprotic solvent could be utilized as an alternative reaction medium for copper(I)-catalyzed azide-alkyne cycloaddition (click or CuAAC) reaction, for the synthesis of various 1,2,3-triazoles under mild conditions. Nineteen products involving *N*-substituted-4-phenyl-1*H*-1,2,3- and 1-allyl-4-substituted-1*H*-1,2,3-triazoles were synthesized under one-pot conditions and isolated with good to excellent yields (50–96%) and purity (>98%). The observed results represent an example that proves that biomass-derived safer solvents can be introduced into a synthetically important transformation exhibiting higher chemical and environmental safety.

Keywords

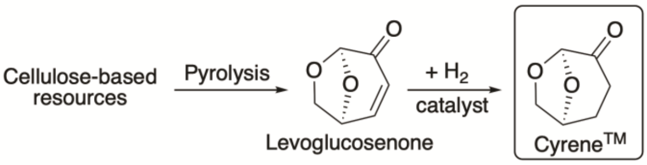
Cyrene; click chemistry; cycloaddition; alternative solvent, 1,2,3-triazols

Introduction

In the past few decades, the transition-metal-catalyzed coupling and addition reaction have represented one of the most powerful and atom-economical strategies for efficiently assembling new carbon-carbon [1,2,3] and carbon-heteroatom [4,5,6] bonds. Thus, it has become the most attractive and facile methodology for creating various complex organic molecular structures from laboratory to industrial scale. Among these methods, the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, the so-called click reaction [7], has received substantial attention for the selective synthesis of various 1,2-3-triazoles that are of utmost importance in the synthesis of biologically active compounds such as active pharmaceutical ingredients (APIs) [8–12] and pesticides [13], or metabolic labeling molecules in plant science [14], to name a few important applications. The CuAAC reactions can be easily carried out under mild reaction conditions and exhibit excellent functional group tolerance [7].

While water has been characterized as an ideal solvent for click reactions, the limited solubility of the substrate(s) could limit its application. Thus, the transformations of either water-insoluble or solid compounds require a solvent to establish high reaction performance, *i.e*. homogeneous solutions with low viscosity. Accordingly, the CuAAC reactions are usually performed in fossil-based common organic reaction media that have high vapor pressure, toxicity, flammability, *etc.*, which could result in several serious environmental concerns. According to the FDA guideline [15], the typical common aprotic polar organic solvents of click reactions such as DCM [16], DCE [17], toluene [17], THF [18,19], DMF [20,21], NMP [22], DMSO [18,20,23], or MeCN [24] are classified into Class 1 and 2, of which applications should be strictly limited, particularly in the pharmaceutical industry. To develop an environmentally benign alternative to this useful method, the identification of an alternative reaction medium is highly desired.

Among the recently characterized biomass-based potential solvents dihydrolevoglucosenone (1R,5S)-7,8-Dioxabicyclo-[3.2.1]octan-2-one, CAS: 53716-82-8) or Cyrene^{TM} (Scheme 1) has received increasing interests for last few years. It can be produced from cellulose-containing feedstocks, including pyrolysis and a selective hydrogenation of levoglucosenone (Scheme 1). Regarding the market position, the Circa Group announced the production of Cyrene^{TM} of 1 ton/year in 2020, signifying the large-scale production of this new biobased molecule [25]. Cyrene^{TM} is a non-toxic substance with $LD_{50,oral}$ > 2000 mg/kg (OECD No. 423, acute toxicity method). $E(L)C_{50}$ > 100 mg/L (daphnia and algae), and it is negative in the Ames test [26]. Recently, we determined key physicochemical properties of Cyrene^{TM} and showed that it has a negligible vapor pressure (<9.6 kPa) and low viscosity (<6.8 mPa ・s) at typical transition metal-catalyzed reactions' temperatures (30–140 °C) [27].



Scheme 1: Synthesis of Cyrene^{TM} (dihydrolevoglucosenone) from cellulose-based feeds *via* levoglucosenone (LG).

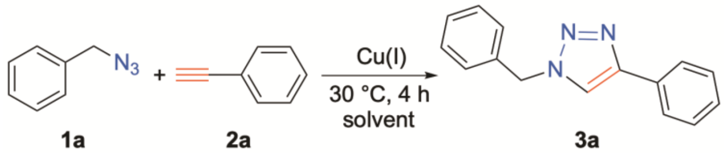
Cyrene^{TM} has been successfully introduced into homogeneous [27–30] and heterogeneous [31–32] carbon-carbon and carbon-heteroatom bond-forming protocols. Although its reactive carbonyl group can limit its application when a strong base (aldol condensation [30]) or amines (potential Schiff-base formation) are present, a wide range of organic reactions *e.g.* urea and amide formation [33,34], amide coupling [35], aldol condensation [36], C–H difluoro-methylation [37], aromatic substitution [38], and MOFs synthesis [39] was demonstrated in Cyrene^{TM}.

Although the CuAAC reaction is a well-studied transformation, it has not been carried out in biomass-based solvents. Consequently, preparing various 1,2-3-triazoles in a less toxic medium could further control and reduce the environmental impacts of this synthetically very important transformation.

Herein, we report a study on the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction in Cyrene^{TM} under mild conditions.

Results and Discussion

We recently demonstrated that Pd-catalyzed Heck reactions could be performed in Cyrene^{TM} [27]. To extend its applicability, first, the typical conventional organic media, selected biomass-originated *i.e.* levulinic acid and γ-valerolactone-based solvents, and Cyrene^{TM} were compared in the transformation of 1.15 mmol benzyl azide (**1a**) and 1 mmol phenylacetylene (**2a**) in the presence of 0.01 mmol CuI and 0.1 mmol Et_3N as a model reaction (Scheme 2) under typically used “click conditions” [7].



Scheme 2: Copper-catalyzed azide-alkyne cycloaddition of benzyl azide (**1a**) and phenylacetylene (**2a**) in various solvents.

In common organic solvents, the yields of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**3a**) were moderate (DCM, 1,4-dioxane) or low (DMF, NMP, DMSO) (Figure 1). While low conversion was still detected in biomass-originated 2-MeTHF, MeLev and EtLev established better performance. When their corresponding 4-alkoxy derivatives (Me-4MeOV and Et-4EtOV) were applied, slightly lower conversions could be observed.

Significantly higher efficiencies were detected in GVL and Cyrene, which clearly verify that both solvents are appropriate for click chemistry.

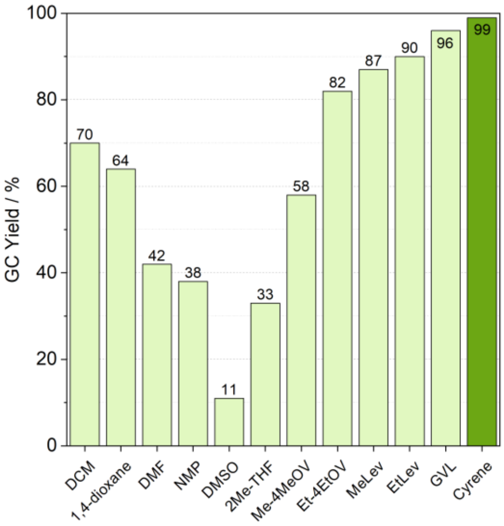


Figure 1: Comparison of various solvents used in CuAAC reaction. Reaction conditions: 1.15 mmol benzyl azide, 1 mmol phenylacetylene, 2.5 mL solvent, 0.01 mmol CuI, *T* = 30 °C, *t* = 4 h. DCM: dichloromethane, DMF: N,N-dimethylformamide, NMP: N-methylpyrrolidone, DMSO: dimethyl sulfoxide, 2Me-THF: 2-methlytetrahydrofurane, Me-4MeOV: methyl 4-methoxyvalerate, Et-4EtOV: ethyl 4-ethoxyvalerate, MeLev: methyl levulinate, EtLev: ethyl levulinate, GVL: γ-valerolactone.

The source of copper could also have a significant effect on the reaction's performance [40]. Accordingly, both Cu(I) and Cu(II) salts were tested in the conversion of 1.15 mmol benzyl azide (**1a**) and 1 mmol (phenylacetylene) **2a** in 2.5 mL Cyrene in the presence of 1 mol% Cu at 30 °C. All the selected Cu salts catalyzed the cycloaddition; however, Cu chlorides and oxides resulted in unexpectedly low product yields for 0.5 h. Copper(I) bromide, thiocyanate, and acetate also gave low yields; however, CuI afforded almost complete conversion of **1a** under identical conditions (Figure 2). The results are in accordance with results obtained for Cu sources in different solvent systems [40, 41].

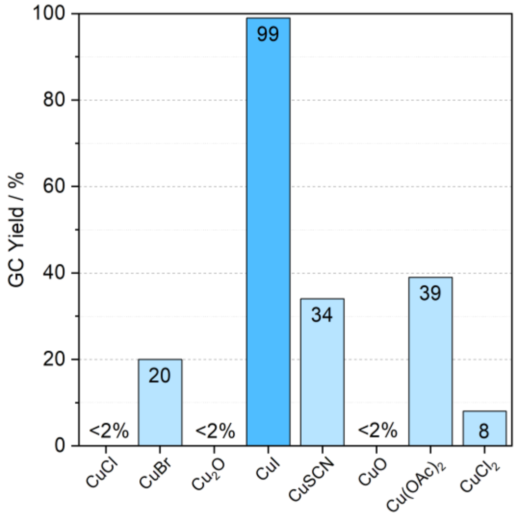


Figure 2: Effect of Cu source used in the click reaction of benzyl azide (**1a**) (1.15 mmol) and phenylacetylene (**2a**) (1 mmol). Reaction conditions: 2.5 mL Cyrene, 1 mol% catalyst precursor, *T* = 30 °C, *t* = 0.5 h.

Although CuAAC reaction can be efficiently performed in water, the moisture content of the organic reaction environment could have a significant effect on the efficiency of a transition metal-catalyzed reaction. Because Cyrene^{TM} is fully miscible in water, investigating the possible effect of the water content on the reaction was highly desired. We found that a slight decrease in formation **3a** was detected when the moisture content was varied between 0.05 and 3.0 wt% (Table 1). Higher moisture content reduces product formation; thus, keeping water content below 1% is necessary to maintain high reaction efficiency.

Table 1: Effect of water content on CuAAC reaction of benzyl azide (**1a**) and phenylacetylene (**2a**).[a]

Entry	Water content / wt%	Yield **3a**[b] / %
1	<0.05	>99
2	1.0	88
3	2.0	86
4	3.0	70
5	4.0	47
6	5.0	29

[a]Reaction conditions: 1.15 mmol benzyl azide (**1a**), 1 mmol phenylacetylene (**2a**), 2.5 mL Cyrene^{TM}, 1 mol% CuI, *T* = 30 °C, *t* = 1 h. [b] GC yield

Hereafter, the readily available CuI was selected as a catalyst precursor to facilitate click reactions involving benzyl azide (**1a**) and various acetylenes (**2b–h**) in Cyrene^{TM} at 30 °C for 12 h (Figure 3). With the exception of 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)pentan-3-ol (**3g**), the isolated 1,2,3-triazole derivatives were generally furnished with good to excellent yields (89–96%). Expectedly, excellent functional group tolerance was verified. Both electron-withdrawing (fluoro (**3b**) or trifluoromethyl (**3c**)) and electron-donating (methoxy, phenoxy, and alkyl, (**3d–h**)) groups were tolerated on the acetylene reaction partner species. It should be noted that no Cu-catalyzed Glaser-coupling [42] of acetylenes was observed, indicating further the applicability of the present synthetic method.

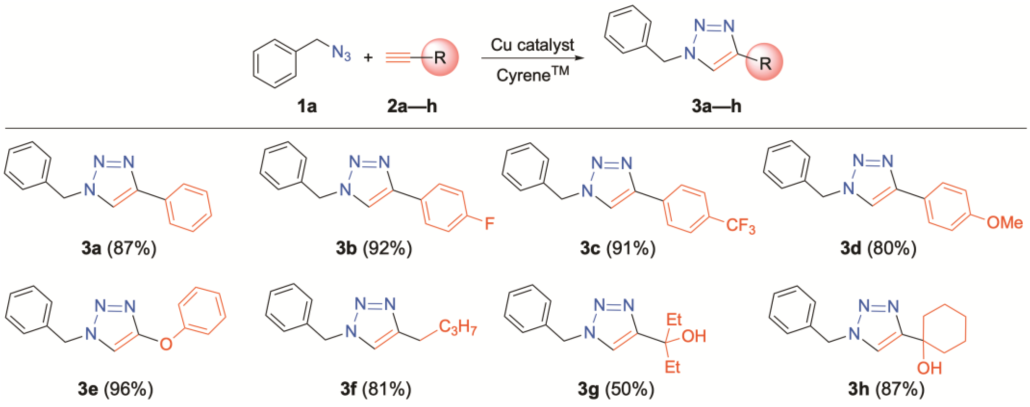


Figure 3: Copper-catalyzed azide-alkyne cycloaddition of benzyl azide (**1a**) and various acetylenes (**2a–h**) in Cyrene^{TM}. Reaction conditions: 1.15 mmol **1a**, 1 mmol **2a–h**, 0.1 mmol Et_3N, 0.01 mmol CuI, 2.5 mL Cyrene^{TM}, T = 30 °C, t = 12 h; Isolated yields based on **2a–h** are given in brackets.

Due to the excellent solvating power of Cyrene^{TM}, the “one-pot” synthesis of 1,2,3-triazoles could be proposed to eliminate the preparation and isolation steps of azide components, which could open an even more green and facile protocol for CuAAC reactions. To demonstrate the one-pot smooth synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**3a)**, 1.23 mmol benzyl bromide (**4a**), 1.57 mmol NaN_3, 1.06 mmol phenylacetylene (**2a**), 0.011 mmol CuI and 0.1 mmol Et_3N were dissolved in 2.5 mL solvent and stirred at 85 °C. After 24 h, GC analysis verified a 90% yield of **3a**, which proves that the CuAAC reaction was completed in Cyrene^{TM} under one-pot conditions. After the workup procedure, a satisfactory 84% yield of **3a** was obtained. When the one-pot reaction was sequenced first to the synthesis of benzyl azide (**1a)** using 1.17 mmol benzyl bromide (**4a**) and 1.31 mmol NaN_3 at 30 °C. After 24 h, 1.06 mmol phenylacetylene (**2a**), 0.01 mmol CuI, and 0.1 mmol Et_3N were added to initiate the click reaction. The mixture was stirred at 30 °C for 24 h. The GC analysis showed complete conversion, and after the workup procedure, 88% **3a** was isolated with 98.5% purity. It is important to note that there are no differences between the isolated yields (*cf.* Figure 3 and 4 for **3a**). According to the observation that the consecutive synthesis could be more efficient, the scope of the method was extended first to synthesizing various *N*-substituted-4-phenyl-1*H*-1,2,3-triazoles in Cyrene^{TM} (Figure 4). It was shown that the protocol resulted in the formation of products **3a** and **5b–f** with yields of 57–91% depending on the structure of bromide derivatives.

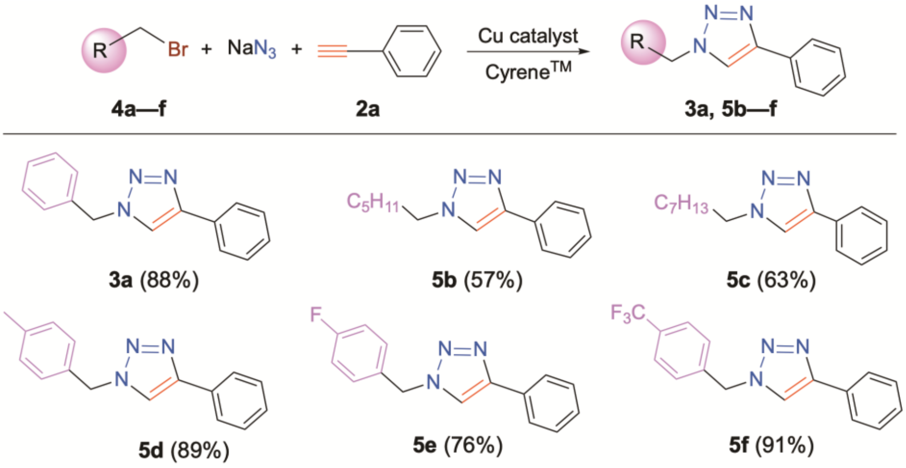


Figure 4: Consecutive synthesis of various *N*-substituted-4-phenyl-1*H*-1,2,3-triazoles in Cyrene^{TM}. Reaction conditions: 1st step: 1.15 mmol **4a–e**, and 1.3 mmol NaN_3, 2.5 mL Cyrene^{TM}, $T = 85$ °C, $t = 8$ h. 2nd step: 1 mmol **2a**, 0.1 mmol Et_3N, 0.01 mmol CuI, $T = 30$ °C, $t = 12$ h; Isolated yields based on phenylacetylene (**2a**) are given in brackets.

The presence of a terminal carbon-carbon double bond in a certain molecular structure could establish efficient subsequent functionalization *via*, for example, an addition reaction, opening possibilities for building even more complex molecular skeletons involving 1,2,3-triazol units. Using allyl bromide in the reaction sequence results in the formation of 1-allyl-4-substituted-1*H*-1,2,3-triazoles bearing a terminal C,C-double bond moiety. Thus, we attempt to prepare a series of 1-allyl-4-substituted-1*H*-1,2,3-triazoles (Figure 5, **6a–f**) from allyl bromide (**4g**) and selected acetylenes (**2a–f**). Similarly to the formation of *N*-substituted-4-phenyl-1*H*-1,2,3-triazoles, the method exhibits good functional tolerance and gives corresponding products (**6a–f**) with moderate and/or good isolated yields (52–83%)

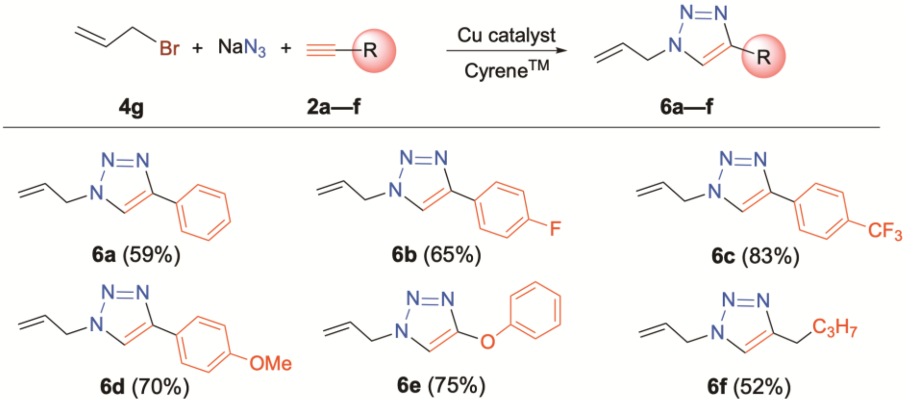


Figure 5: "One-pot" synthesis of various 1-allyl-4-substituted-1*H*-1,2,3-triazoles in Cyrene™. Reaction conditions: 1st step: 1.15 mmol **4g**, 1.3 mmol NaN_3, 2.5 mL Cyrene™, *T* = 75 °C, *t* = 24 h. 2nd step: 1 mmol **2a–f** 0.01 mmol CuI, 0.1 mmol Et_3N, *T* = 30 °C, *t* = 12 h; Isolated yields based on corresponding acetylene derivatives are given in brackets.

Conclusion

In conclusion, we have demonstrated that biomass-originated Cyrene™ can be utilized as an alternative reaction media for copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction of various acetylenes and azides. Due to the strong solvating power of Cyrene™, a sequenced one-pot synthesis of triazoles was successfully demonstrated. The protocol was tested for a wide range of substrates, and successful synthesis and isolation of nineteen 1,2,3-triazole derivatives (**3a**–**h**, **5b**–

f, **6a–f**) with moderate to excellent isolated yields (50–96%) and purity (>98%) was shown.

Experimental

The sources of chemicals are listed in the Supporting Information. ^{1}H, ^{13}C, and ^{19}F NMR spectra were collected on a Bruker Avance 300 MHz or Bruker Avance-III 500 MHz instrument and processed by MestReNova v. 14.3.1-31739 (2022) MestreLab Research S. L.

GC analyses were performed on an HP 5890 N Series II instrument with Restek RTX®-50 capillary column (15 m x 0.25 mm x 0.25 µm) using H_2 as a carrier gas. For the analysis, 10 µL of the reaction mixture was dissolved in 1 mL of ethyl-acetate, followed by adding 10 µL toluene as the internal standard. Heating Profile of GC-FID Analysis: The initial temperature was 100 °C, and was hold for 0.5 min. Heating rate: 40 °C/min up to the final temperature of 270 °C. The final temperature was held for 4.25 min.

The water content Cyrene™ was measured on a Methrom 684 KF Coulometer at Balint Analitika Ltd, Budapest, Hungary.

The Cyrene™ was purchased from Sigma-Aldrich Kft. Budapest, Hungary. Its purification was performed by vacuum distillation (18–20 mmHg, 114–116 °C) and stored under argon before subsequent use. The purity (>99.99 %) was checked by ^{1}H and ^{13}C NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$ with TMS, ppm): δ= 5.10 (s, 1H, CH), 4.71 (s, 1H, CH), 4.05 (d, J=7.3 Hz, 1H, CH), 3.96 (t, J=6.3 Hz, 1H, CH), 2.73–2.02 (m, 4H, CH2). ^{13}C NMR (75 MHz, $CDCl_3$, with TMS, ppm): δ=200.3 (CO), 101.5 (CH), 73.1 (CH), 67.6 (CH2), 31.1 (CH2), 29.9 (CH2). The NMR data correspond to the published result.

Methyl 4-methoxyvalerate and ethyl 4-ethoxyvalerate were prepared using the published method [43].

The synthesis of benzyl azide, detailed experimental procedures, and characterization of prepared compounds are reported in Supporting Information.

General Procedure for Click Reaction in Cyrene^{TM}

In a 4 mL screw-cap vial, 1.15 mmol of benzyl azide (**1a**), 1 mmol corresponding acetylene, 0.1 eq. Et_3N, 0.01 mmol CuI, were dissolved in 2.5 mL Cyrene^{TM}. The reaction mixture was stirred overnight at a given temperature. After the reaction, 20 mL of cold distilled water was added, followed by intensive stirring. The solid product was filtered and washed with distilled water (3 × 5 mL) and dried until constant weight under the fume hood. The detailed experimental procedure, as well as the characterization of isolated compounds, are provided in the Supporting Information.

General Procedure for Click Reaction in Cyrene^{TM} under one-pot conditions

In a 4 mL screw-cap vial, 1.15 mmol of corresponding bromine and 1.3 mmol NaN_3 were dissolved in 2.5 mL Cyrene^{TM} and stirred at a given temperature. After a given reaction time, 1 mmol corresponding acetylene compound, 0.1 mmol Et_3N, and 0.01 mmol CuI were added to the reaction mixture and reacted for a given time at a given temperature. The workup procedure is similar to the one given above. The detailed experimental procedure, as well as the characterization of isolated compounds, are provided in the Supporting Information.

Supporting Information

The source of chemicals, the detailed experimental procedure, and the characterization of isolated compounds.

Supporting Information File 1:

File Name: Medgyesi Mika SI

File Format: pdf

Title: Supporting Information for Azide-alkyne cycloaddition (click) reaction in biomass-derived solvent CyreneTM under one-pot conditions.

Acknowledgments

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