Cu(I)-azidopyrrolo[3,2-*d*]pyrimidine Catalyzed Glaser−Hay Reaction under Mild Conditions

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ABSTRACT: The limitation of the CuAAC "click" reaction with a 2-azidopyridine substrate, owing to its equilibrium with a tetrazole isomer, is exploited herein for its utility in the Glaser−Hay reaction. A catalytic combination of a 2-azidopyridine analogue, 4-azido-5*H*-pyrrolo[3,2-*d*]pyrimidine, and CuI afforded homocoupled products of terminal alkynes, without any trace of triazole product, under mild conditions with a broad substrate scope. Emphasis on carbohydrate-based substrates appended to a propargylic group led to 1,3-diynes in good to excellent yields.

KEYWORDS: Glaser−Hay reaction, Homocoupling, CuAAC click reaction, 2-Azidopyridine, Pyrrolopyrimidine
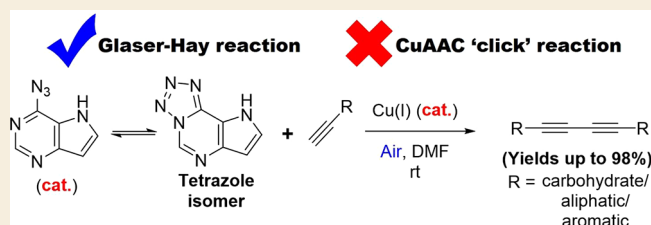
Copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC, Figure 1) is a versatile "click" reaction that affords 1,4-
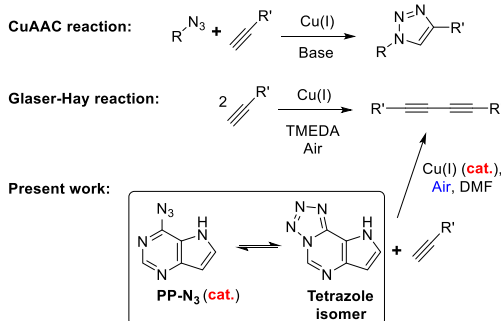
Figure 1. Cu(I)-catalyzed CuAAC reaction, Glaser−Hay reaction, and present work.

disubstituted triazoles with a broad range of applications in the fields of chemistry, biology, and materials science.[1−5] The Glaser−Hay (GH, Figure 1) reaction is another interesting copper(I)-catalyzed reaction in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)/air that converts terminal acetylenes, by homocoupling, to symmetric 1,3-diynes, which exhibit technologically relevant applications in the field of materials science.[6−8] Mechanistically, both CuAAC and GH reactions are truly catalytic that involve an initial π-coordination of alkynes to Cu(I) species, affording electrophilic Cu(I)-acetylides.[1,6]

A report which demonstrates a competition between both CuAAC and GH reactions, conducted by the use of excess alkyne in the presence of azide and CuI, clearly showed an initial consumption of azide to form a CuAAC product and

then the remaining alkyne underwent slower GH reaction.[9] In another report, Bolje et al. reported the observation of a homocoupled 1,3-diyne GH byproduct along with the intended CuAAC reaction with 2-azidopyridine substrate due to prolonged heating in toluene.[10] In both of these reports, the formation of the GH product during an intended CuAAC reaction indicates the commonalities in both reactions. In the later report, the 2-azidopyridine substrate is well-known as an exception to an otherwise versatile CuAAC reaction, with vast functional group tolerance, due to its equilibrium with tetrazolo[1,5-*a*]pyridine at room temperature, particularly in polar solvents.[11,12] However, alteration of the reaction conditions, which can shift the equilibrium to the azido form such as elevated temperature or nonpolar solvents or prolonged reaction times, resulted in triazole formation.[13−15] In other words, a 2-azidopyridine substrate that exists in equilibrium with its tetrazole isomer, in the presence of Cu(I), can form a CuAAC "click" product under harsh conditions but under mild conditions a GH reaction can operate wherein 2-azidopyridine takes the role of a ligand. In the present study, a mild method for a GH reaction catalyzed by a 2-azidopyrimidine analogue, 4-azido-5*H*-pyrrolo[3,2-*d*]-pyrimidine (PP-N$_3$, Figure 1), in the presence of a catalytic CuI is demonstrated.

The GH reaction was given its name from the introduction of a catalytic amount of bidentate ligand TMEDA by Hay in the presence of copper(I) chloride (Figure 1).[16] Ever since, several GH methods were introduced for the synthesis of 1,3-diynes from terminal alkynes catalyzed by copper(I) by the variation of ligands and under ligand-free conditions by the use of base. Recently, a mild method was reported with 1H-benzotriazole as a ligand in the Cu-catalyzed GH reaction in the presence of potassium carbonate; the same group also demonstrated a GH reaction with D-glucosamine as the ligand.[17,18] L-Proline was used as a ligand along with excess pyrrolidine in the GH reaction of a natural product conjugate 9-ethynylnoscapine.[19] A carbazole-based NHC catalyst in combination with CuI in the presence of KOtBu led to a GH reaction.[20] Under ligand-free conditions, the base itself serves as a ligand, albeit monodentate; e.g., DMAP, NBS/DIPEA, and ethyl lactate were reported in catalytic combination with CuI in promoting the GH reaction under aerobic conditions.[21−23] A nonafluorobutanesulfonyl azide was used as a reagent in the presence of a base in the GH reaction that afforded 1,3-diynes with a fast coupling rate.[24] Copper coordination complexes such as $[Cu_2(ophen)_2]$ and $[Cu_4(ophen)_4(tp)]$ and a $Cu_3(BTC)_2$-metal−organic framework were also used as catalysts in GH reactions.[25,26]

The choice of ligand is crucial in GH reactions with certain substrates; e.g., the choice of ligand 4,4′-bis(hydroxymethyl)-2,2′-bipyridine was decisive in biomolecule GH conjugation involving peptides, which further helped in sequestering Cu(II) species that are detrimental to peptides by oxidative damage.[27] To decipher the role of the ligand, the GH reaction was investigated by varying the amines. The use of triethylamine resulted in the precipitation of a Cu-acetylide complex; however, upon addition of TMEDA, the precipitated complex dissolved and the desired GH reaction took place.[28]

There are GH methods that demonstrate the synthesis of 1,3-diynes with carbohydrate substrates appended to terminal alkynes, but expansion of the substrate scope is missing.[17,21,22,29] α-D-Mannopyranosides appended with propargylic and phenylacetylene groups were homocoupled using copper(II)acetate in refluxing pyridine for 48 h.[29] Hence, in the present study, emphasis was given to carbohydrate based substrates to demonstrate the efficiency of the method.

A CuAAC condition with excess CuI and DIPEA that was utilized by our group for the synthesis of a phytosphingosine conjugate of 2-pyrrolidinone triazole product was applied in our initial reaction.[30] In a report, heating a phenylethynylcopper(I) intermediate in DMF at reflux for 24 h resulted in 1,3-diyne;[31] hence, we chose DMF as the solvent but planned our first attempt at 0 °C. Our interest in the area of synthesis of iminosugar derivatives prompted the application of N-propargylated deoxynojirimycin 1′ (Scheme 1) for the GH reaction with PP-N3. In a separate study from our lab, PP-N3 was intended for synthesis of immucillins BCX-1777 and BCX-4430. By following known procedures,[32,33] PP-N3 was derived from 9-deazahypoxanthine (PP) and en route PP-Cl serves as an intermediate (Figure 2). A clean transformation took place in our initial GH reaction, observed over TLC as a polar product, to a homocoupled symmetric 1,3-diyne product 1 in 74% yield (entry 1, Table 1), with no trace of any triazole adduct. The use of the other two pyrrolopyrimidines PP and PP-Cl and the absence of PP-N3 led to a drastic loss in the yield of the reaction (entries 2−4), with substantial amounts of unreacted terminal alkyne; hence, PP-N3 has a major role in

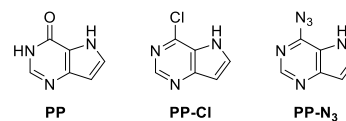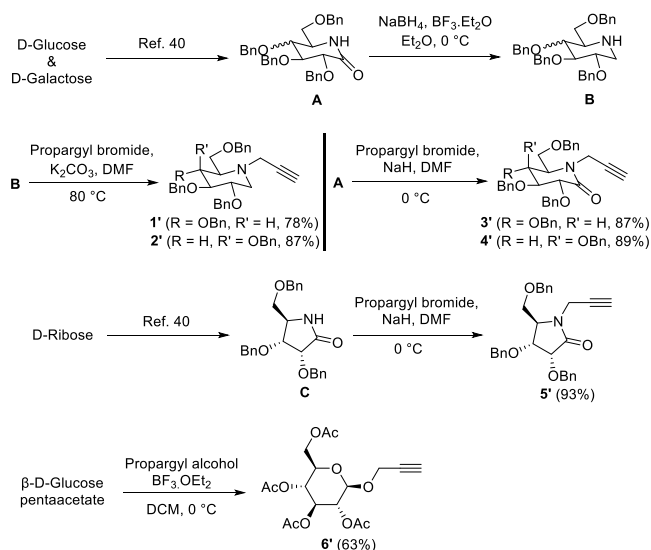**Scheme 1. Synthesis of Propargylated Carbohydrate Based Substrates**

Figure 2. Pyrrolopyrimidines used in the present study.

Table 1. Reaction Optimization[a]

entry	catalyst (equiv)	pyrrolopyrimidine (equiv)	base (equiv)	temp (°C)	yield 1 (%)[f]
1	CuI (2)	PP-N3 (1)	DIPEA (3)	0	74
2	CuI (2)	PP (1)	DIPEA (3)	0	12
3	CuI (2)	PP-Cl (1)	DIPEA (3)	0	11
4	CuI (2)		DIPEA (3)	0	trace
5	CuI (2)	PP-N3 (0.5)	DIPEA (3)	0	79
6	CuI (2)	PP-N3 (0.1)	DIPEA (3)	0	79
7	CuI (2)	PP-N3 (0.1)		0	81
8	CuI (0.2)	PP-N3 (0.1)		0	83
9	CuI (0.2)	PP-N3 (0.1)		rt	86
10	CuI (0.2)	PP-N3 (0.1)		100	85
11[b]	CuI (0.2)	PP-N3 (0.1)		rt	82
12[c]	CuI (0.2)	PP-N3 (0.1)		rt	0
13[d]	CuI (0.2)	PP-N3 (0.1)		rt	0
14[e]	CuI (0.2)	PP-N3 (0.1)		rt	trace

[a]Reaction conditions: To a stirred solution of alkyne 1′ (30−50 mg) in DMF (1 mL), CuI and PP-N3 were added successively and the reaction takes 5−6 h for complete consumption of the starting material. [b]Open air. [c]Solvent: MeOH. [d]Solvent: CH_2Cl_2. [e]Solvent: CH_3CN. [f]Isolated yields.
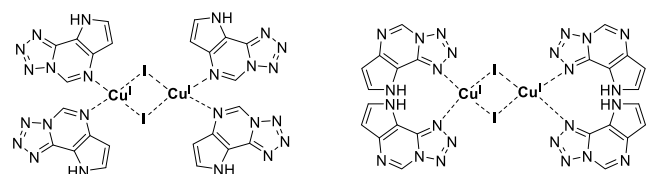
this homocoupling reaction. Reducing the equivalents of PP-N3 to catalytic amounts led to a tad improvement in the yield of compound 1 (entries 5 and 6). Furthermore, in the absence of DIPEA, taking CuI and PP-N3 in catalytic amounts afforded compound 1 in 81−83% yields (entries 7 and 8), and repeating the reaction at room temperature or at 100 °C afforded

compound **1** in 86 and 85% yields, respectively (entries 9 and 10). All the aforementioned reactions were conducted without any stringent measures, i.e., by a mere stoppering of the round-bottom flask (RB) and using undistilled solvents; a reaction conducted under open-air atmosphere afforded compound **1** in 82% yield (entry 11). However, the reaction suffered a setback in the solvents methanol, dichloromethane, and acetonitrile (entries 12−14). Thus, the homocoupling of terminal alkyne **1′** can take place at room temperature in DMF with catalytic amounts of CuI and PP-N$_3$, in the absence of base and under open-air atmosphere, signifying the mildness of the present method (entry 11). Reactions with a further decrease in the mole percentage of catalysts lead to longer reaction times; hence, entry 11 is considered as the optimized reaction condition for demonstrating the feasibility of the reaction with different substrates.

Reaction optimization studies reveal that the GH reaction in the absence of PP-N$_3$ suffers from low yields (entries 2−4), suggesting Cu(I) and PP-N$_3$ complexation, which is the driving force for the GH reaction. The reaction is unaffected by the change from stoichiometric to catalytic PP-N$_3$, thus fulfilling the role of PP-N$_3$ as a ligand like TMEDA, used in standard GH reactions. A successful outcome in DMF against acetonitrile (entry 14), where both solvents have the same coordinating ability with transition metals,[34] prompts the difference in reactivity due to solvation. Acetonitrile exhibits strong solvation of Cu(I) and preferential solvation with cosolvent DMF;[35] hence, acetonitrile inhibits reactivity beyond its solvation shell, especially where CuI is used in catalytic amounts. Having considered the reaction optimization studies, the role of PP-N$_3$ as a ligand in the GH reaction is apparent. As we were unable to detect the triazole product in all of our attempts, we conclude that PP-N$_3$ exists in the tetrazole form in DMF and thus promotes the GH reaction and inhibits the CuAAC reaction. As further evidence, the pyrimidine proton of PP-N$_3$ appeared at δ_H 9.81 ppm in the ^{1}H NMR spectrum (Supporting Information) which matches with analogous tetrazolo[4,5-*c*]pyrimido[5,4-*b*]indole at δ_H 9.80 ppm.[36]

The tetrazole moiety of PP-N$_3$ is 1,5-disubstituted, and through its nitrogen electron-donating atoms it can exist as a multidentate coordinating ligand.[37] Additionally, tetrazole can serve as a base. However, the tetrazole moiety or the pyrimidine nitrogen complexes with copper in a monodentate coordination mode.[38,39] Accordingly, PP-N$_3$, complexes with CuI to yield a dimeric intermediate (Figure 3) proposed by Bohlmann,[6−8] which takes the productive route to 1,3-diyne and regenerates the catalysts.

In order to check the feasibility of the present method with other carbohydrate based substrates, compounds **1′−4′** were prepared from D-glucose and D-galactose, **5′** from D-ribose, and **6′** from β-D-glucose pentaacetate by standard synthetic carbohydrate chemistry methods (Scheme 1).[40,41] Initially, compound **1** was subjected to Pd/C debenzylation reduction

to generate a novel DNJ-dimer **2** (Scheme 2) with an aliphatic linker, which can be of pharmacological relevance. Compound

Scheme 2. Substrate scope
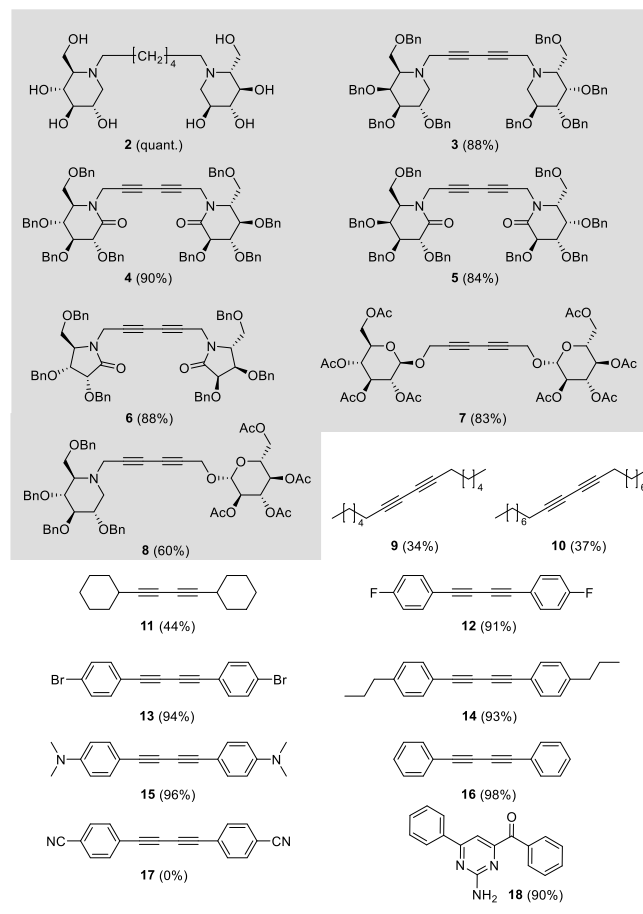
2′ derived from D-galactose underwent homocoupling to afford compound **3** in 88% yield. Homocoupling of the lactams **3′−5′** also proceeded smoothly to afford compounds **4−6** in good yields. 1-*O*-Propargylated glucose pentaacetate **6′** homo-coupled conveniently to afford compound **7** in 83% yield. An attempt to afford unsymmetric 1,3-diynes led to the treatment of compounds **1′** and **6′** in a 1:1 ratio under the reaction conditions which resulted in heterocoupled product **8** in 60% yield. An attempt with terminal alkynes having aliphatic groups produced homocoupled products **9** to **11** in low yields. Terminal alkynes with aromatic groups gave rise to compounds **12−16** in excellent yields, but there was no reaction with the *para*-cyano substituted substrate. Finally, compound **16** was intentionally converted with guanidine in a known reaction[42] to 2-amino pyrimidine **18**, which can be easily converted to azide and results in another pyrimidine-based catalyst that can participate in the GH reaction.

To probe the significance of PP-N$_3$ in GH reaction against reported ligands/bases in GH reactions, attempts were made with carbohydrate based substrates in the present study (Scheme S1, Supporting Information). GH reaction with a benzotriazole ligand for a protected glycosylated alkyne afforded 1,3-diyne in only 15% yield,[17] and the use of benzoriaozle in place of PP-N$_3$ with our carbohydrate substrates led to poor yields indeed. On the other hand, a catalytic system comprising CuI and DMAP in acetonitrile

Figure 3. Probable complexes with CuI and tetrazole isomer of PP-N$_3$.

reported under aerobic conditions with a protected glycosylated alkyne afforded 1,3-diyne in a good yield.[21] Hence, we investigated the feasibility of the GH reaction with DMAP using a deprotected glycosylated alkyne. A globally deacetylated alkyne of compound **6′** was attempted for the GH reaction, in the presence of DMAP, and there was no reaction in either acetonitrile or DMF. Remarkably, with PP-N$_3$, a facile GH reaction took place that afforded 1,3-diyne in 75% yield. Homocoupled glycosylated alkynes under GH reaction conditions using TMEDA are subjected to standard deprotection of acetyl groups under Zemplén conditions;[29] however, PP-N$_3$ provides an advantage of working directly with deprotected carbohydrate substrates. These results suggest a reciprocal relation between PP-N$_3$ and carbohydrate substrates for a fruitful GH reaction, which prompts the application of the present method in glycobiology.

In conclusion, a recalcitrant 2-azidopyridine toward CuAAC "click" reaction owing to its equilibrium with tetrazole isomer is hypothesized for use as a ligand for the Glaser–Hay coupling reaction of terminal alkynes to 1,3-diynes. As a model, 4-azido-5*H*-pyrrolo[3,2-*d*]pyrimidine was studied in the presence of CuI and terminal alkynes, which afforded 1,3-diynes without any trace of triazole "click" product. The present method is an add-on to the repertoire of GH methods and serves as the first report of the use of azidopyrimidine as a ligand in catalytic amounts along with catalytic CuI, without any base, that displays a broad substrate scope. The utility of the reaction in the synthesis of various carbohydrate based dimers prompts further diversification and exploration for biological studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00015.

Experimental procedures and NMR spectral information (PDF)

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Notes

The authors declare no competing financial interest.

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