# Development of Solid-Supported Glaser−Hay Couplings

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S *Supporting Information*

ABSTRACT: While the Glaser−Hay coupling of terminal alkynes is a useful reaction, several issues associated with chemoselectivity preclude its widespread application in synthetic chemistry. To address these issues, a solid-supported Glaser−Hay methodology was developed to afford only asymmetric diyne products. This methodology was then applied to a series of immobilized alkynes with a diverse set of soluble alkynes to generate an array of heterocoupled products in high yields and purities.

KEYWORDS: *solid-phase synthesis, Glaser−Hay coupling, chemoselectivity, polyynes*
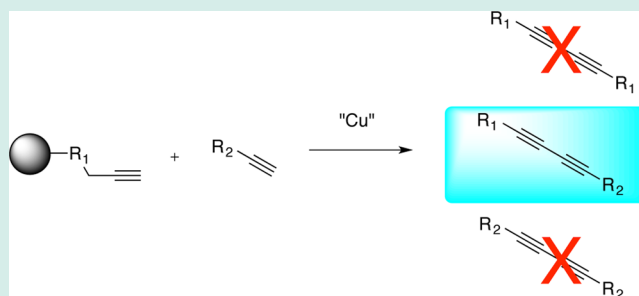
Acetylenic scaffolds, or diynes, are observed as core structures in various natural products, many polymers, and other supramolecular materials.[1−3] To date, over one thousand naturally occurring polyynes have been isolated and found to exhibit a range of biological activities; including antifungal, anticancer, anti-HIV, and antibacterial properties.[3] Within polymer structures, acetylenic cores provide a versatile linear structural moiety, giving rise to unique optical properties. For example, when coupled with transition metals, these organometallic materials display various novel properties, such as luminescence, conductivity, and photovoltaic behavior.[2] Glaser first described the synthesis of the unique polyyne core structure in 1869, after the oxidative dimerization of copper(I) phenylacetylide upon exposure to air.[4] Because of the functional group tolerance and wide availability of acyetelinic precursors, this reaction is optimal for combinatorial chemistry, potentially yielding large libraries of polyynes. Various modifications and enhancements have been developed to optimize the traditional Glaser coupling.[5] One such variant developed by Hay, requires dissolving catalytic amounts of copper(I) chloride in the presence of bidentate tetramethylenediamine (TMEDA) and oxygen; forming the reactive intermediate in situ, and thereby drastically decreasing the reaction time and improving yield.[6] Known as the Glaser−Hay coupling, this reaction provides an efficient procedure for generating symmetric diyne compounds in relatively high yields. However, one major drawback of these reaction conditions is the lack of chemoselectivity with regards to asymmetric coupling. When two different terminal alkynes are coupled by a Glaser−Hay reaction, three potential polyyne compounds are generated (Scheme 1). As a result, further purification steps are required in order to isolate the desired asymmetric dimer, and yields are often low because of the formation of multiple products. While asymmetric conditions have previously been reported in relatively high yields with either a Cu(OAc)$_2$ or NiCl$_2$ catalyst system, substrate scope is limited to alkynes that afford diynes that are isolable from homodi-

Scheme 1. Chemoselectivity Issues Associated with the Glaser−Hay Coupling
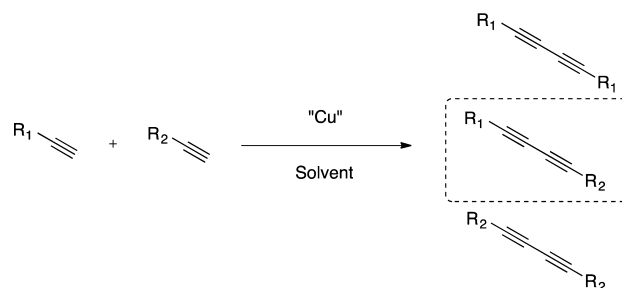
merized product. Moreover, excess of one alkyne is required and significant purification is necessary to remove both excess diyne and undesirable homocoupled product.[7]

To specifically address the problem of chemoselectivity for heterocouplings, one of the terminal alkynes can be immobilized on a polystyrene solid support.[8] After immobilization, the standard Glaser−Hay conditions can be utilized with higher levels of chemoselectivity, yielding a specific heterodimer. Furthermore, the incorporation of a solid support eliminates the need for tedious separations and workups. A similar approach has been taken with the Cadiot−Chodkiewicz reaction,[9] which relies on a terminal alkyne and a haloalkyne to achieve chemoselectivity. The rigidity and pseudo-high dilution conditions offered by the solid support eliminated the self-coupling that was typically observed with the corresponding solution phase Cadiot−Chodkiewicz reactions.[10] By immobilizing the haloalkyne partner, the reaction proceeded in higher yield without the generation of undesired homocoupled products.

Applying this approach to the Glaser−Hay reaction is even more advantageous as there is no requisite for a haloalkyne to aid in the directing of chemoselectivity, and asymmetric diynes can be accessed directly from terminal alkyne precursors. One previous Glaser−Hay coupling has been attempted on the solid support; however, its aim was to provide homocoupling of the immobilized alkyne, and not to address chemoselectivity issues.[11]

Because of the abundance of Glaser−Hay reaction conditions present in the literature, reaction conditions were examined in solution prior to optimization on the solid support. Homocoupling of phenylacetylene (6) was performed with different catalytic systems based on literature precedence.[12] The most promising catalyst systems included CuCl/TMEDA, CuI/TMEDA, and CuI/DIEPA/N-bromosuccinimide, and all were examined toward the solution phase Glaser−Hay coupling of 6. Overall, the CuI/TMEDA catalyst (12 h, rt) led to the highest yields of the phenylacetylene homodimer, and was employed in further couplings.

With optimized solution-phase conditions established, we transitioned the optimization to the solid support. In order to assess the feasibility of the approach, various immobilization strategies of propargyl alcohol (2) were investigated with carboxy, trityl chloride, and bromo Wang resins; however, ultimately a trityl chloride derivatized resin was selected because of the mild immobilization/cleavage conditions and the reproducibility of propargyl alcohol loading. Initially 2 (10 equiv) was reacted at room temperature with trityl choloride resin in the presence of triethylamine (10 equiv) for 16 h to afford propargyl alcohol immobilized resin (1). The coupling conditions were then optimized via the reaction of 1 with phenylacetylene (6), varying solvent, temperature, and resin loading.

Because of the hydrophobic nature of the polystyrene core, solvent selection is important to reaction optimization due to the resin's propensity to swell or contract as a result of solvent polarity. Consequently, we investigated toluene, THF, DCM, and acetonitrile as viable solvents for the solid-supported reaction. Overall, THF consistently generated the highest yields of coupled alkyne products, while significant amounts of unreacted 2 remained in other solvents after 12 h at room temperature.

While THF afforded the highest yields, some starting material still remained, indicating the necessity for further optimization. Consequently, temperature was varied, to elucidate optimal conditions. A range of temperatures was examined, including 30, 60, and 80 °C, with the 60 °C conditions yielding the most promising results. The reactions at 30 °C still contained unreacted starting material, indicating that the temperature was not sufficient to drive the reaction to completion. Meanwhile, the reactions stirred at 80 °C demonstrated complete conversion, but afforded lower yields. This noticeable decrease in the formation of diyne product most likely resulted from the overheating and destruction of some of the polystyrene resin. Some of the copper catalyst was also found to decompose within the reaction vessel, suggesting that the temperature may inactivate the catalyst, thereby reducing the efficiency of the reaction. Reaction of 1 with 6 for 12 h at 60 °C afforded the ideal conditions for virtually quantitative conversion of propargyl alcohol precursor.

Upon further investigation, it was discovered that despite complete conversion, there was also dimerization of the immobilized alkyne, to afford an undesired homodimer product (12). The occurrence of the starting material and homodimer are

especially unfortunate, as they negatively impact the yield of desired product and require further purification steps. This is especially problematic as the use of the solid support in these coupling reactions was intended to eliminate both of these issues. As such, we sought to further optimize the reaction conditions to successfully drive the reaction to completion without the production of the homodimer impurities.

It was speculated that decreasing the initial loading of 2 on the solid support could efficiently prevent the undesirable dimerization on the functionalized resin. Our initial preparation of 1 consisted of swelling the resin in CH_2Cl_2 for 15 min, followed by the addition of propargyl alcohol (10 equiv) and triethylamine (10 equiv). The reaction was stirred for 16 h at room temperature to achieve maximum loading of the starting material. After the discovery of the cross-linked homodimer product, we attempted to generate lower loaded resins by decreasing the amount of reagents and immobilization time employed in the immobilization protocol.
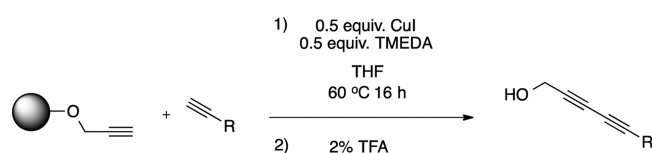
To assess the effects of resin loading on the reaction, several resins were prepared. Trityl chloride resin was again reacted with 10 equiv of propargyl alcohol in the presence of 10 equiv of triethylamine. The reaction was then stirred at 40 °C for 16 h, with the aim of achieving a higher loaded resin, ∼1.8 mmol/g. An identical reaction was set up but heated to 40 °C for only 2 h to generate a medium loaded resin, ∼1.0 mmol/g. Additionally, the amount of propargyl alcohol was decresed to afford even lower loaded resin ∼0.6 mmol/g. Similar immobilizations were also performed on a 2% DVB cross-linked resins to afford similarly loaded resins that provided an increased degree of resin rigidity to discourage interactions of immobilized alkynes. After a sufficient work up, a portion of each version of the resin was cleaved in 2% TFA and analysis of loading by GC/MS and mass recovery of propargyl alcohol.
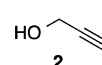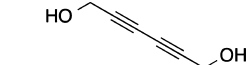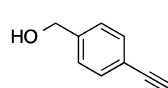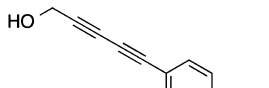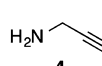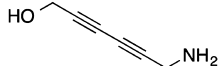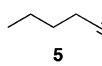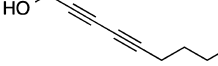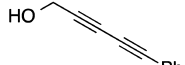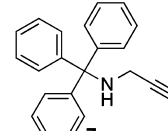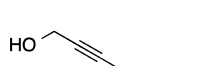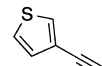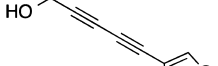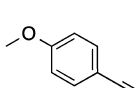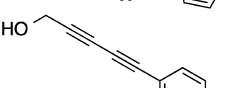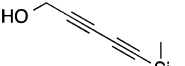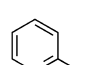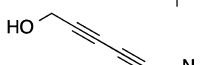
The resins were then subjected to coupling conditions with 6 at 60 °C for 16 h. The level of cross-linked DVB within the resin, 1% or 2%, showed little effect on the suppression of homodimer. This result indicates that the concentration of loading plays a larger role in the formation of homodimer than resin rigidity. After the necessary work up conditions, it was established that resin loaded above 0.7 mmol/g of propargyl alcohol forms undesired homodimer during the reaction conditions. Resin loaded at a concentration less than 0.7 mmol/g successfully eliminates homodimer formation while still generating desired heterocoupled products.

Having elucidated optimized solid-supported Glaser−Hay conditions, the scope of the methodology was assessed via the preparation of a diverse library of diynes. Toward this end, two additional alkynes, 3 and 4, were immobilized on the tritylchloride resin at loadings of ∼0.6 mmol/g. These were then reacted in THF with a CuI/TMEDA catalyst and a diverse set of soluble alkynes to assemble a small library of conjugated diynes. After 16 h of stirring at 60 °C, the resin reaction was filtered then washed with alternating volumes of CH_2Cl_2 and MeOH to remove unreacted reagents and other impurities. The resin was then cleaved with 2% TFA, the solvent was removed in vacuo, and the product was analyzed by TLC, ^1H NMR, and GC/MS (Table 1).

The solid supported Glaser−Hay coupling tolerated a variety of functionalities, including aromatic rings, silyl groups, free amines, alcohols, and alkyl chains. Moreover, the reaction with both 5 and 6 was scaled up 10-fold (500 mg of resin) with comparable yields, suggesting that larger quantities of product could be obtained if desired. Reactions not proceeding to

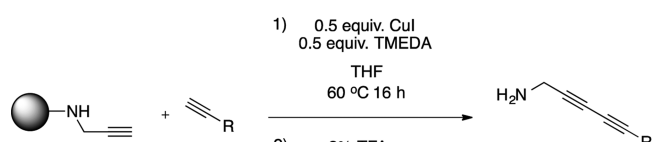**Table 1. Glaser–Hay Couplings with Immobilized Propargyl Alcohol**

Alkyne	Product	% Yield
2	12	99%
3	13	56%
4	14	40%
5	15	84%
6	16	95%
7	14	91%
8	17	45%
9	18	99%
10	19	80%
11	20	55%
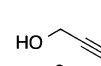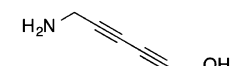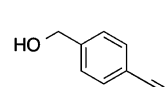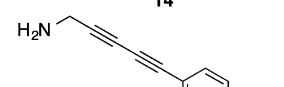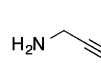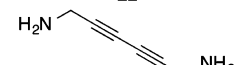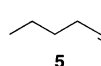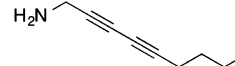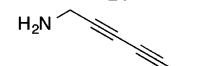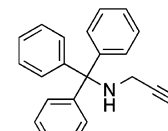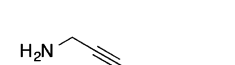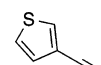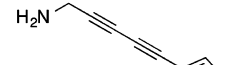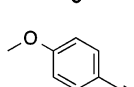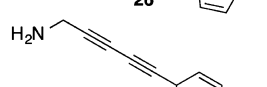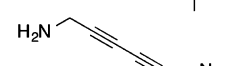
completion under these conditions were quickly purified from starting material via a silica plug. While the reaction conditions were favorable for most alkynes, alkynes containing nucleophilic residues, such as 2, 3, 4, 8, and 11, often resulted in lower yields. To alleviate this, a trityl-protected version, 7, was employed and gave significantly higher yields of the desired product than the unprotected amine 4. Conveniently, the 2% TFA cleavage conditions also removed the trityl protecting group on the amine, thereby yielding the same product as reaction with the free amine. We hypothesize that the free amine functionality may have coordinated with the copper catalyst, reducing its activity within the reaction. This trend continued when analyzing the yields associated with other nucleophilic moieties. While the anisole-based 9 reacted well under the idealized conditions, the

similar benzyl alcohol, 3, had relatively lower yields. Moreover, the 3-ethynylthiophene reactant, 8, also afforded lower yields likely due interaction with the copper catalyst.

Utilizing a propargyl amine derivatized resin, 21, with the optimized coupling conditions we expanded the diyne library (Table 2). Less homodimer formation was observed with this

Table 2. Glaser–Hay Couplings with Immobilized Propargyl Amine

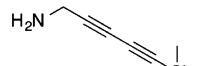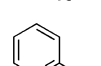| Alkyne	Product	% Yield
2	14	86%
3	22	76%
4	23	87%
5	24	71%
6	25	92%
7	23	98%
8	26	48%
9	27	79%
10	28	84%
11	29	41%

resin, even at higher loadings (0.9 mmol/g), indicating a lower reactivity than that observed with propargyl alcohol loaded resin. The library was further expanded via the immobilization and reaction of 3 to yield 30 at loadings of 0.7 mmol/g. This resin exhibited similar reactivity as the propargyl alcohol immobilized resin (Table 3).

Table 3. Glaser−Hay Couplings with Immobilized Ethynylbenzyl Alcohol

Alkyne	Product	% Yield
2	13	45%
3	31	99%
4	22	96%
5	32	98%
6	33	96%
7	22	99%
8	34	42%
9	35	73%
10	36	87%
11	37	53%

Overall, a novel methodology has been developed that affords a direct route to asymmetrical diynes, solving chemoselectivity issues. The solid-supported Glaser−Hay reaction tolerates a wide range of chemical functionalities and has afforded the construction of a small library of asymmetric diynes. It is important to note, however, that careful attention must be paid to the loading of immobilized alkyne in order to prevent undesired homodimerization. With the optimized conditions in hand, the methodology is currently being employed with more complex alkynes to generate biologically relevant diynes and natural product derivatives. Moreover, the ability to easily prepare asymmetrical polyynes has far reaching applications into the fields of materials and organometallic chemistry.

■ ASSOCIATED CONTENT

S Supporting Information

Experimental protocols and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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