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Volume 1 | Number 1 | Jan 2013 | Pages 1–100

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COMMUNICATION

Preparation of Asymmetrical Polyynes by a Solid-Supported Glaser-Hay Reaction

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Polyynes exhibit both unique photophysical properties and biological activities, obviating the necessity for efficient syntheses towards these core structures. A novel methodology for the construction of highly conjugated asymmetrical polyynes has been developed in a chemoselective fashion utilizing a solid-support. The synthesis has been applied to prepare a small library of polyynes in good to moderate yield. Moreover, their interesting fluorescence properties have been investigated, demonstrating the ability to tune fluorescence through selection of appropriate synthetic building blocks.

Polyynes, or molecules containing an acetylenic scaffold, are known core structures in various natural products, polymers, and other supramolecular materials. [1-3] Over one thousand of these naturally occurring molecules have been isolated from organisms such as plants, fungi, and coral.[2] These structures exhibit numerous biological activities including antibacterial, antifungal, anti-HIV, and anticancer properties.[3, 4] Moreover, they provide a structural rigidity of a highly conjugated π-system acting as molecular wires with unique optical and conductive properties.[5]

In 1869, synthesis of these polyyne core structures was developed by Glaser utilizing the oxidative dimerization of copper (I) phenylacetylide upon exposure to air to yield the diyne.[6] This reaction has since found wider applicability within the field of synthetic organic chemistry. Moreover, the Glaser coupling is ideal for combinatorial chemistry due to the extensive functional group tolerance and a wide availability of acetylenic precursors. To further enhance the Glaser

reaction, others have optimized this methodology.[7] Specifically, Hay employed catalytic amounts of copper (I) chloride in the presence of tetramethylenediamine (TMEDA) and oxygen, leading to decreased reaction times and improved yields.[8] This variant reaction is known as the Glaser-Hay reaction, and provides synthesis of symmetric polyyne molecules in an efficient fashion and in relatively high yields.

Unfortunately, the Glaser-Hay reaction conditions do not exhibit chemoselectivity when performed with different terminal alkynes. This reaction, under standard conditions, can yield three different polyyne products: two homodimers and a heterodimer (Scheme 1A). Consequently, to acquire the asymmetric heterodimer using this reaction, the reaction can at best yield only 33% of the desired product based on statistical couplings of the two alkynes. Moreover, further purification is necessary resulting in even lower reaction yields. While some solution phase asymmetrical syntheses have been accomplished, homodimer is still formed and additional purification of excess alkyne is required.[9]

Using a polystyrene resin as a solid support, we have previously addressed the associated chemoselectivity issues with the standard Glaser-Hay reaction, as well as the elimination of post-reaction workup and further purification.[10] Solid-supported synthesis confers several key advantages including pseudo-high dilution conditions, the ability to easily wash away excess reagents, and structural rigidity. Thus, by exploiting the advantages of a solid support with the Glaser-Hay reaction we were able to create a library of asymmetrical diynes in yields of 40-99% (Scheme 1B).[10] This represented a significant advantage as the homologous control reactions in the solution phase

resulted in low yields (~30% asymmetrical product) as all three potential diynes were observed.[10]
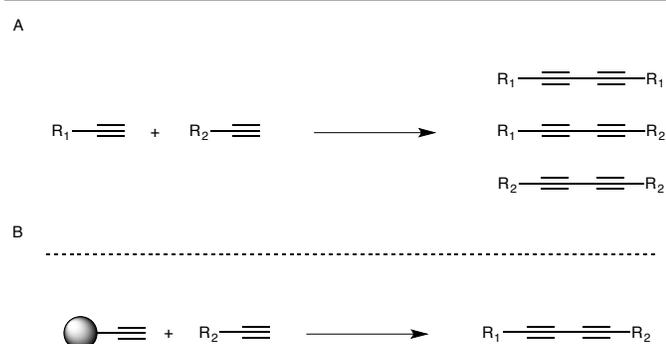
Scheme 1. Chemoselectivity of Glaser-Hay Reactions in Solution and on a Solid Support

To further extend the benefits of the solid-supported Glaser-Hay reaction, we set forth to develop solid-supported methodologies to diversify the previously reported diyne array to include asymmetrical and symmetrical triynes, tetraynes, and pentaynes. A solid-supported preparation of diynes has already been investigated utilizing a Cadiot-Chodkiewicz reaction that achieves chemoselectivity by immobilizing a haloalkyne and attaching a terminal alkyne partner;[11] however, the utilization of the Glaser-Hay coupling is advantageous as it does not first require the synthesis of an acetylenic halide. Another advantage of this approach is the shorter reaction time associated with the Glaser-Hay reaction. Solid-supported Cadiot-Chodkiewicz reactions occurred over two days and also required an additional two days of workup, compared to the 16 hour Glaser-Hay reaction with minimum workup and purification.[11] Although modifications may be made to the classic Cadiot-Chodkiewicz reaction to shorten reaction time, they have been demonstrated to decrease the overall yield, and similar conditions may not transfer to the solid support.[12] Asymmetrical polyynes have also been prepared using a solution phase Cadiot-Chodkiewicz reaction;[13] however, immobilization on a solid support has the potential to confer several advantages as purification after each synthetic step is not required, and excesses of reagents can be employed to drive reactions to completion. Furthermore, another method utilizing desilylation and a copper catalyst system to afford polyynes has previously been reported. However, this methodology reports low yields and affords only symmetrical polyynes.[14]

Building on the previously established methodology, we envisioned the ability to perform Glaser-Hay couplings with an immobilized alkyne and trimethylsilylacetylene (TMS acetylene), followed by silyl deprotection with tetra-*n*-butylammonium fluoride (TBAF) to regenerate a terminal alkyne for another cycle of TMS acetylene coupling or capping with an alternate alkyne (Scheme 2). This iterative synthesis facilitates the preparation of differentially conjugated polyynes based on the number of cycles. Due to the versatility of the solid support, excess of reagents could be employed to drive reactions to completion and minimal purification is required at each cycle.
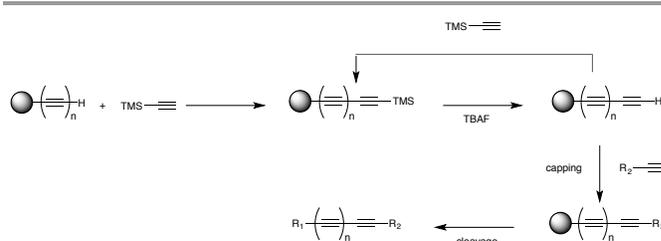
Scheme 2. Synthetic Route to Asymmetrical Polyynes

To ascertain the feasibility of this approach initial efforts required the immobilization of a terminal alkyne. Based on previous work, the linker strategy and alkyne loading was found to be crucial to the preparation of asymmetrical diynes, as alkyne loadings above 0.7 mmol/g resulted in the undesired dimerization on the resin surface. However, when loadings were maintained below this threshold no undesired dimerization was observed.[10] Due to the iterative nature of this synthesis only 2 terminal alkynes, propargyl alcohol (**1**) and 4-ethynylbenzyl alcohol (**2**) were selected for proof-of-principle study (Scheme 3). A 1% cross-linked tritylchloride derivatized polystyrene resin was swelled in dichloromethane followed by the addition of the alkyne (1 eq.) and triethylamine (0.2 eq.) and stirred at room temperature for 16 h. The resin was then washed with repeated DCM/MeOH cycles, and a small amount was cleaved with 2% trifluoroacetic acid (TFA) to validate alkyne loading via TLC, mass difference, and GC/MS. Both **1** and **2** were found to be immobilized at loadings of 0.4-0.7 mmol/g as resins **3** and **4** respectively.
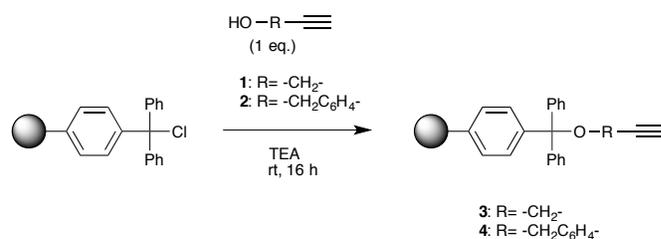
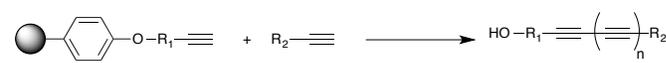**Scheme 3.** Resin Immobilization with Alkynes

Reaction optimization was performed with resin **3** and TMS acetylene (15 eq.) in the presence of a copper catalyst system (CuI (0.5 eq.) and TMEDA (0.5 eq.)) in THF for 16 h at 60 °C. The resin was then washed with cycles of DCM/MeOH (5 x 5 mL each) and a portion was cleaved to ensure TMS acetylene coupling. The resin was then subjected to treatment with a TBAF solution in DCM (1 M) for 1 h at room temperature and again washed using the standard procedure. At this stage the resin was partitioned and Glaser-Hay conditions were repeated with either 4-ethynylanisole (**5**) to cap the reaction as a triyne or another TMS acetylene to continue the polyyne chain. **5** was selected for preliminary studies due to its unique NMR spectrum and UV activity for TLC analysis. Upon preparation of the triyne (**7**), it was cleaved from the resin using 2% TFA in DCM for 1 h at room temperature, and the product was analyzed by TLC, ^{1}H NMR, and GC/MS to confirm the presence of triyne product. Gratifyingly, **7** was obtained in good yield (68%) and purity using the previously optimized conditions. The remaining resin was then subjected to TMS acetylene coupling/TBAF deprotection either one or two more times
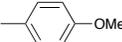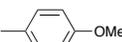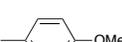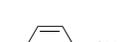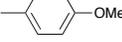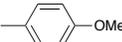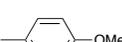
to afford the tetrayne or pentayne respectively after capping with **5**. All products were obtained in good to moderate yield when considering the number of synthetic manipulations, and were characterized by TLC, ^{1}H NMR, and GC/MS.

Having successfully obtained the desired polyynes with the synthetic route, the scope of the reaction was examined using a variety of commercially available terminal alkynes to prepare a small library of compounds (Table 1). Eliminating the coupling of the TMS acetylene step and initial capping led to the preparation of diynes in relatively high yields (99-45%). As previously observed, coupling with basic terminal alkynes (e.g. propargylamine and pyridyl) results in a dramatic lowering of the yields, potentially due to undesirable coordination to the copper catalyst system. Overall yields somewhat decreased with each additional alkyne unit, most likely due to an increased number of synthetic steps (up to 8 in the case of pentaynes). Moreover, unreacted or partially reacted products required removal via a rapid purification with a silica plug. It does appear that the yield-determining step is based on the capping event and relative to the tolerance of the reaction to that specific alkyne, as yields from each series of capping alkyne remain very similar. However, this methodology was able to efficiently prepare several series of asymmetric polyynes over a period of days and the iterative nature of the synthesis contributed to the expedient preparation of the compounds and alleviated the necessity for tedious purification after each reaction.

Due to the significant degree of conjugation in these compounds and their linear nature, we next analyzed them for their fluorescent properties. Absorbance and fluorescence spectra were acquired for each derivative, and the different compounds were found to exhibit unique optical properties both within a series of alkynes, and between derivatives containing different terminal substituents. Excitation at 330 nm of the triynes yielded differential fluorescence emission spectra based on the capping alkyne (Figure 1). Not surprisingly polyynes capped with a terminal alkyne that extended the conjugation exhibited stronger fluorescent properties (pyridyl **27**, phenyl **15**, and anisole **7**). Moreover, even further extended conjugation in **7** through the oxygen afforded a shift in λ_{max} of approximately 20 nm. Similar trends were observed with the tetraynes and pentaynes (Supporting Information).

Table 1. Synthesis of a Polyyne Library

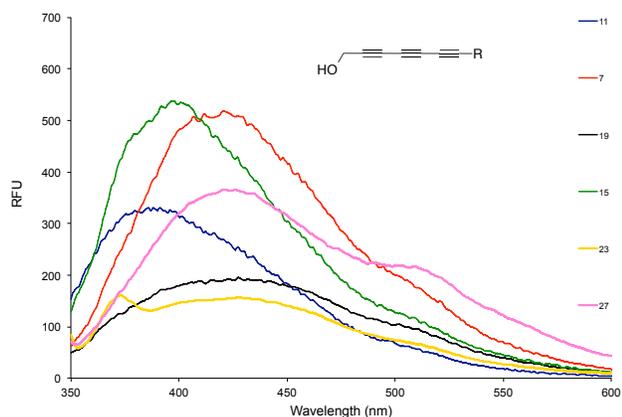| Entry	R$_1$	R$_2$	n	Cmpd	Yield
1	-CH$_2$-	phenyl-OMe	1	**6**	99%
2	-CH$_2$-	phenyl-OMe	2	**7**	68%
3	-CH$_2$-	phenyl-OMe	3	**8**	67%
4	-CH$_2$-	phenyl-OMe	4	**9**	44%
5	-CH$_2$-	CH$_2$NH$_2$	1	**10**	45%
6	-CH$_2$-	CH$_2$NH$_2$	2	**11**	46%
7	-CH$_2$-	CH$_2$NH$_2$	3	**12**	46%
8	-CH$_2$-	CH$_2$NH$_2$	4	**13**	48%
9	-CH$_2$-	Ph	1	**14**	95%
10	-CH$_2$-	Ph	2	**15**	63%
11	-CH$_2$-	Ph	3	**16**	63%
12	-CH$_2$-	Ph	4	**17**	56%
13	-CH$_2$-	CH$_2$CH$_2$CH$_2$CH$_3$	1	**18**	84%
14	-CH$_2$-	CH$_2$CH$_2$CH$_2$CH$_3$	2	**19**	53%
15	-CH$_2$-	CH$_2$CH$_2$CH$_2$CH$_3$	3	**20**	38%
16	-CH$_2$-	CH$_2$CH$_2$CH$_2$CH$_3$	4	**21**	41%
17	-CH$_2$-	CH$_2$OH	1	**22**	99%
18	-CH$_2$-	CH$_2$OH	2	**23**	82%
19	-CH$_2$-	CH$_2$OH	3	**24**	57%
20	-CH$_2$-	CH$_2$OH	4	**25**	49%
21	-CH$_2$-	pyridyl (N)	1	**26**	55%
22	-CH$_2$-	pyridyl (N)	2	**27**	34%
23	-CH$_2$-	pyridyl (N)	3	**28**	30%
24	-CH$_2$-	pyridyl (N)	4	**29**	27%
25	-CH$_2$C$_6$H$_4$-	phenyl-OMe	1	**30**	73%
26	-CH$_2$C$_6$H$_4$-	phenyl-OMe	2	**31**	56%
27	-CH$_2$C$_6$H$_4$-	phenyl-OMe	3	**32**	52%
28	-CH$_2$C$_6$H$_4$-	phenyl-OMe	4	**33**	55%

Figure 1. Fluorescence spectra of the triyne series **7**, **11**, **15**, **19**, **23**, and **27**.

As a result of the extended conjugation in the series resulting from resin **4**, the fluorescence properties were also examined. Previous literature has demonstrated that spectral shifts are difficult to predict, and this was further illustrated by the fluorescence spectra of this series.[15] Minor shifts (both red and blue) were observed upon the addition of each alkyne unit for the diyne, triyne and tetrayne; however, the pentayne exhibited a dramatic blue shift. This may be due to the transition of the compound into a more polymeric state exhibiting complex packing and interactions of the conjugated π-systems (Figure 2). The spectra of other series harbouring the same capping alkyne also displayed similar unpredictable trends (Supporting Information); however, these results do demonstrate the ability to tune the optical properties of the molecules via both selection of capping alkyne and by modulation of the number of alkyne units.
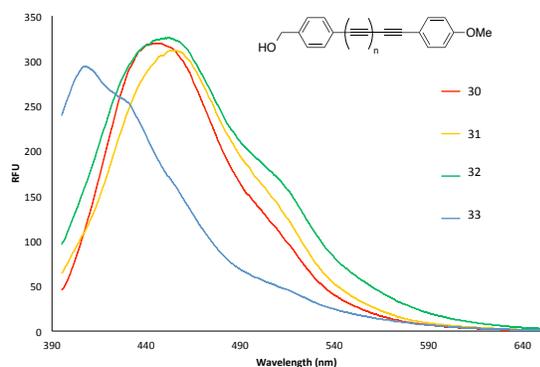

Figure 2. Fluorescence spectra of the 4-ethynylbenzyl alcohol resin series **22**-**25**.

Conclusions

In conclusion, a novel methodology has been developed for the rapid preparation of asymmetrical polyynes utilizing a series of solid-supported Glaser-Hay reactions. This methodology has the potential for widespread use in both materials chemistry and medicinal

chemistry due to the unique optical/electrical and biological activity of polyynes. Current investigations are being conducted to further characterize the optical and conducting properties of the prepared compounds, and to extend the technology to more complex and useful alkynes towards the preparation of biologically active natural product derivatives.

Notes and references

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