SYNTHESIS OF CARBOHYDRATE-DERIVED 1,2,3-TRIAZOLES USING 1,3-DIPOLAR CYCLOADDITION ON A SOLUBLE POLYMER SUPPORT

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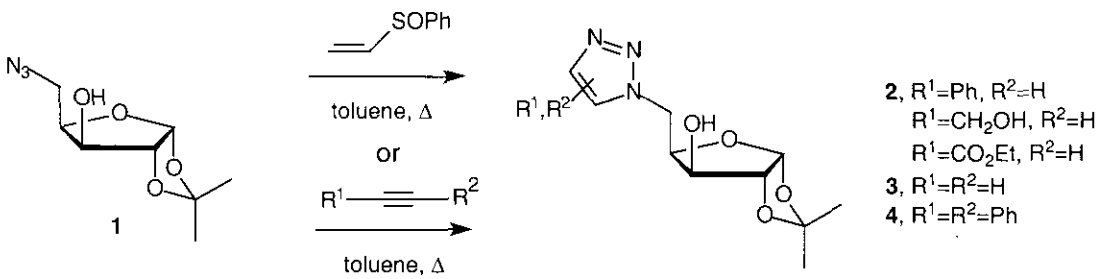
Abstract – 1,3-Dipolar cycloaddition reactions of a soluble polymer-linked D-xylofuranose-derived azide (**5**) with acetylenes have been studied. The utility of the method for the synthesis of reversed-nucleoside triazole analogs is demonstrated.

Triazole derivatives have found use in the synthesis of various agrochemicals and pharmaceuticals[1] and are useful as intermediates *en route* to other heterocycles such as oxazole analogs[2] or as intermediates in the synthesis of oxazole-containing natural products.[3] Dipolar cycloaddition reactions of azides with acetylenes are well-documented and are known to lead to regioisomeric mixtures of triazole products when unsymmetrical alkynes are employed in the cycloaddition.[4] Our current interest lies in the use of simple 1,3-dipolar cycloaddition reactions for the efficient preparation of triazoles which might serve as reversed nucleoside analogs.[5]

We are interested in the application of polymer-supported methods to the efficient synthesis of heterocycles, particularly the use of polymer-supported reagents that are soluble in organic solvents.[6] Not only do such reagents offer the same attractions as insoluble materials, such as the ability to use large excesses of reagents and easy workup, they also have the added advantage that intermediate products can

be readily characterized by solution NMR spectroscopy. Such methodology has found success in the area of oligosaccharide synthesis,[7] as well as in the preparation of small libraries of compounds such as sulfa drug analogs.[8] Herein we describe the use of this support for the synthesis of sugar-derived triazoles.

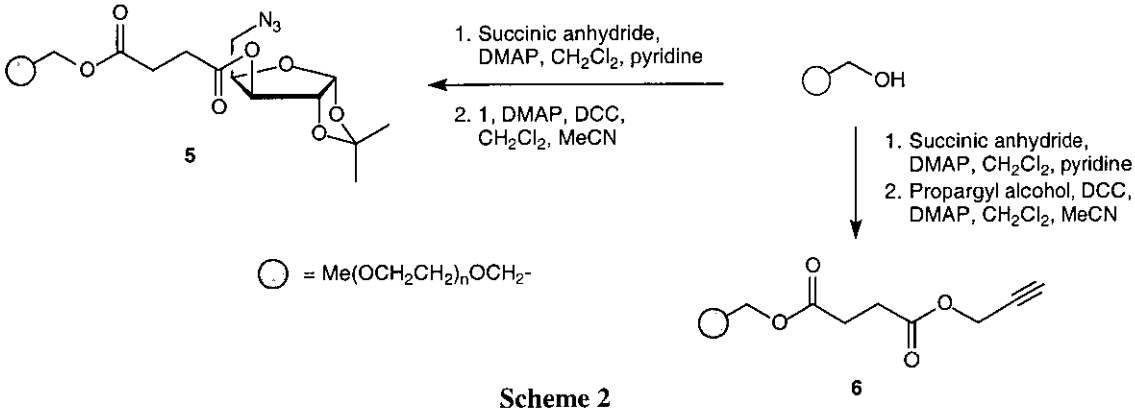
5-Azido-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**1**)[9] has been used previously[5] in solution-phase cycloadditions with phenylacetylene, ethyl propiolate and propargyl alcohol to afford triazoles (**2**) (Scheme 1). We have now extended this method to include the triazoles formed from cycloaddition of **1** with phenyl vinyl sulfoxide and diphenylacetylene (**3** and **4** respectively, Scheme 1).[10]



Scheme 1

We envisioned that using soluble polymer-supported chemistry (so-called "liquid-phase" synthesis[6]) in this area might lead to higher yields of triazoles such as **3** and **4**. Thus, azide (**1**) was attached to the monomethyl ether derivative of polyethylene glycol (MeO-PEG) *via* a succinate ester linkage (**5**, Scheme 2). In similar fashion, propargyl alcohol was linked to MeO-PEG (**6**, Scheme 2), and this material served as a representative polymer-supported dipolarophile.

Polymer-supported azide (**5**) was isolated as a colorless powder (>95%) after first treating MeO-PEG (5000 average molecular weight) with succinic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP), followed by azide (**1**) (1.5 equivalents) in the presence of dicyclohexylcarbodiimide and DMAP. The polymer-supported reagents used throughout this work were generally isolated by cooling the reaction mixture in ice and then precipitating with cold ether. Polymers were further purified by recrystallization from either absolute ethanol or a mixture of ethyl acetate and hexane.



Scheme 2

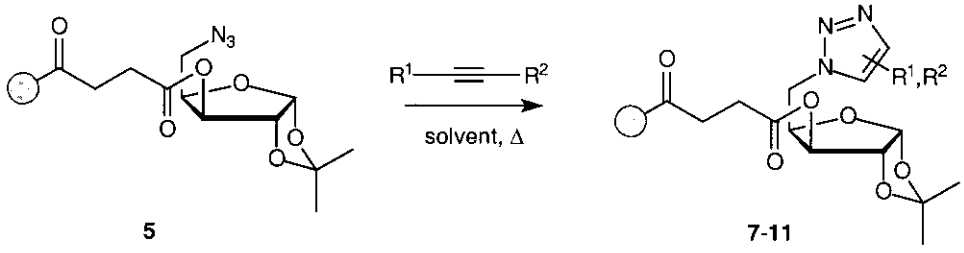
The loading of azide (**1**) onto the polymer support was shown to be >95% by comparing the integration of the signal for H-1 of the xylofuranose ring (5.90 ppm) with that for the methyl group at the end of the polymer chain (3.35 ppm). This material was readily prepared in 10-20 g batches thus allowing for eventual synthesis of 1-4 mmol of triazoles. Likewise, synthesis of dipolarophile (**6**) could be carried out on 10-25 g batches, with this material being isolated in >95% yield with >95% loading of the alkyne as seen from integration of the ^{1}H NMR spectrum. The ^{1}H NMR spectrum of **6** showed a 2 hydrogen doublet at 4.66 ppm for the CH_2 of the propargyl unit and a 1 hydrogen triplet at 2.46 for the alkyne proton. All polymer-supported compounds produced here are stable, low melting (~50 °C) solids that may be stored indefinitely without any appreciable decomposition. One problem that arises occasionally is that the polymers readily absorb moisture from the atmosphere, and additional measures must be taken when handling these reagents under humid conditions.

Cycloaddition on Soluble Polymer Supports

The major advantages envisioned in using reagents such as **5** and **6** in this area included: the ability to use large excesses of reaction partners (acetylenes in the case of **5**, azides in the case of **6**), which could be removed and recovered from reaction mixtures by simply precipitating and filtering the polymer-supported products; reactivity of **5** and **6** similar to that of unsupported reagents since the polymers are soluble; and convenient characterization of products and assessment of product yield and purity by simple

^{1}H NMR spectroscopy in $CDCl_3$ solution.[6]

Thus, treatment of polymer-supported azide (**5**) with the acetylenes detailed in Table 1 afforded the respective triazole(s) after refluxing an excess of the alkyne with the azide in either toluene or o-xylene. As can be seen from Table 1, there are both advantages and disadvantages associated with employing the soluble polymer-supported azide in 1,3-dipolar cycloaddition reactions with acetylenes. In all of the cases highlighted above, the method allows for the use of large excesses of acetylenes (up to 10 equivalents are used here), which can easily be removed from the reaction product by filtration of the polymer without resorting to the use of column chromatography or distillation. In most cases the cycloaddition step is efficient, even up to 100% in the case of ethyl propiolate.



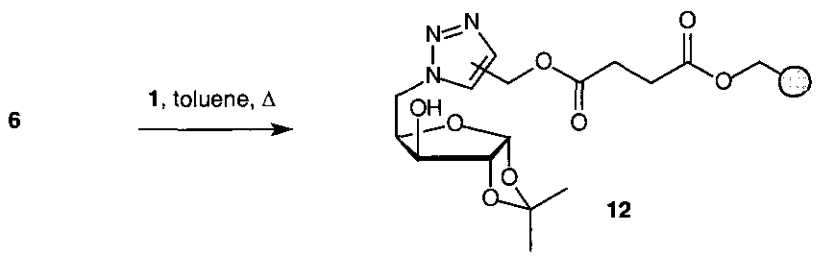
5 **7-11**

Table 1. Yields and regiochemical outcome of cycloadditions of polymer-supported azide (**5**) with alkynes

Acetylene or equivalent	**Triazole(s) formed**	**Polymer Recovery (%)**	**Cycloaddition Efficiency** (from integration of NMR)
Phenylacetylene	**7**, R^1 = Ph, R^2 = H	93	50% (4:1 regioisomers)
Phenyl Vinyl Sulfoxide	**8**, R^1 = H, R^2 = H	97	>95% (only one triazole)
Ethyl Propiolate	**9**, R^1 = CO_2Et, R^2 = H	93	>95% (3:1 regioisomers)
Propargyl Alcohol	**10**, R^1 = CH_2OH, R^2 = H	94	>95% (1.7:1 regioisomers)
Diphenylacetylene	**11**, R^1 = Ph, R^2 = Ph	95	0% (no cycloaddition)

However, the reaction of polymer-supported azide (**5**) with phenylacetylene only goes to 50% completion after 120 hours in boiling toluene. Reaction of **5** with diphenylacetylene, which is sluggish with unsupported azide (**1**), is not detectable even after refluxing **5** for 3 days in o-xylene with an excess of the alkyne. This lack of reactivity is probably due to highly unfavorable interactions between the substituents on the alkyne and the polymer-supported azide as the reagents approach each other.

Additionally, a difference in regioselectivity is observed when the polymer-supported acetylene (**6**) is used as the dipolarophile in cycloaddition. Treatment of **6** with an excess of azide (**1**) in refluxing toluene for 3 days results in almost quantitative isolation of the polymer-supported triazoles (**12**), with the cycloaddition efficiency being >95% as seen from integration of the ^{1}H NMR spectrum of this material.



The regioisomeric outcome of this reaction is, however, somewhat different to that observed in solution. When azide (**1**) reacts with propargyl alcohol in refluxing toluene, a 1:1 mixture of isomeric triazoles is isolated.[5] In the present case of azide (**1**) reacting with acetylene (**6**), a 1.7:1 regioisomer mixture is formed in which the isomer having the CH_2O group at C-4 and the sugar at N-1 of the triazole ring (i.e. the bulky sugar being as far as possible from the polymer) is likely the major product. This type of regiochemical outcome has also been observed when we have employed an oxalate-linked polymer-supported dipolarophile in cycloadditions with sugar-derived azides.[11]

The isolation of the triazoles formed during cycloadditions of azide (**5**) is possible by treating the polymer-supported products with an excess of ammonia in methanol solution, followed by precipitation of the polymer with ether and filtration. The filtrate is evaporated and the heterocycle isolated by passing through a short column of silica gel. For example, the triazole (**3**), which proved difficult to purify using solution chemistry, is isolated in ~94% yield and >95% purity from polymer (**8**) by this method.

Overall, in the present context, polymer-supported dipolar cycloaddition using soluble polymer supports can offer the advantages of high yields and convenient product isolation. However, the method can be limited by several factors. The increased bulk of the polymer-supported reagent may preclude the formation of certain products and regiochemical outcomes may not be the same as those observed using classical solution methods. The use of soluble polymer-supported cycloadditions for the efficient construction of other heterocycles is currently being investigated.

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EXPERIMENTAL

NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer as solutions in $CDCl_3$ with tetramethylsilane (0.0 ppm) as an internal reference. For ^1H NMR spectra of polymer-supported compounds, the polymer methylene signal at 3.62 ppm was suppressed to clarify spectra. All regioisomeric mixtures were determined by integrating the aromatic signals between 7.4 and 8.0 ppm, and polymer loading and cycloaddition efficiency was determined by integrating the ^1H NMR spectrum relative to the polymer CH_3 signal at ~3.35 ppm. Flash chromatography was performed on silica gel 60 (260-400 mesh, Aldrich Chemical Company), and TLC was performed on precoated plates of silica gel 60F-254 (E. Merck). Optical rotations were recorded on a Perkin-Elmer 343 automatic polarimeter.

5-Deoxy-1,2-O-isopropylidene-5-C-(1,2,3-triazol-1-yl)-α-D-xylofuranose (3). Azide (**1**) (300 mg, 1.35 mmol) and phenyl vinyl sulfoxide (0.89 mL, 5.42 mmol) were refluxed in o-xylene (13 mL) for 30 h after which time TLC (hexane-EtOAc 4:1) showed reaction to be complete. The solvent was evaporated and

the residue resolved by flash chromatography to give triazole (**3**) (226 mg, 68%) as a colorless syrup. This material was contaminated with a byproduct, the signals for which showed at 5.9, 6.2 and 7.2-8.0 ppm in the ^{1}H NMR. ^{1}H and ^{13}C NMR data for pure **3** formed on the polymer support are given below.

5-Deoxy-1,2-O-isopropylidene-5-C-(4,5-diphenyl-1,2,3-triazol-1-yl)-α-D-xylofuranose (4). The azide (**1**) (337 mg, 1.52 mmol) and diphenylacetylene (1.1 g, 6.1 mmol) were refluxed in o-xylene (13 mL) for 72 h after which time TLC (hexane-EtOAc 4:1) showed complete reaction. The solvent was evaporated and the residue purified by flash chromatography to give triazole (**4**) (181 mg, 48%) as a colorless solid, mp 227-229 °C: $[\alpha]_D$ –72.7° (*c*, 2.1, CH_2Cl_2); ^{1}H NMR (ppm): 7.27-7.55 (m, 10H, phenyl); 5.95 (d, 1H, *J* = 3.5 Hz, H-1); 4.64 (d, 1H, *J* = 3.6 Hz, H-2); 4.57 (m, 1H, H-5); 4.36 (m, 2H, H-4, H-5'); 4.26 (s, 1H, OH); 3.77 (d, 1H, *J* = 4.0 Hz, H-3). ^{13}C NMR (ppm): 27.3, 28.1, 46.3, 75.7, 80.4, 86.0, 100.8, 106.3, 127.8, 128.0, 129.0, 129.6, 130.6, 130.9, 131.2, 135.6. Exact mass calculated for $C_{22}H_{23}N_3O_4$: 393.1689. Found: 393.1673.

Polymer-supported azide (5). Polyethylene glycol monomethyl ether (MW ~5000, 25 g, 5 mmol) was dissolved in dry CH_2Cl_2 (250 mL) and pyridine (50 mL) and succinic anhydride (10 g, 100 mmol)) and 4-DMAP (1 g) were added. The mixture was stirred at rt for 24 h then evaporated to ~ half volume and the remainder cooled in an ice-water bath. Ice-cold ether (1200 mL) was then added with stirring and the resultant white solid was collected by vacuum filtration and subsequently recrystallized from EtOAc-hexane (~25 g, ~100% yield). ^{1}H NMR (with suppression of polymer methylene signals) showed >95% loading of the succinate linker.[7] This material (5.14 g, ~1.1 mmol) was dissolved in CH_2Cl_2 (25 mL) and MeCN (25 mL) and azide (**1**)[9] (0.44 g, 2 mmol), DMAP (0.24 g) and a solution of dicyclohexyl-carbodiimide (1.5 mL, 1 M in CH_2Cl_2) were added. The mixture was stirred for 24 h at rt after which time the precipitate was filtered and washed with CH_2Cl_2 (~5 mL). The mixture was evaporated back to ~ 50 mL and then cooled in ice-water while ice-cold diethyl ether (250 mL) was added with vigorous stirring. The precipitate was filtered and recrystallized from absolute ethanol (4.90 g, ~98%, mp 50-52

°C): ^{1}H NMR (ppm): 5.95 (d, 1H, J = 3.7 Hz, H-1); 5.22 (d, 1H, J = 3.1 Hz, H-3); 4.55 (d, 1H, J = 3.7 Hz, H-2); 4.40 (m, 1H, H-4); 4.25 (m, 2H, H-5,H-5'); 3.81 (m, 2H, CH_2O, polymer); 3.38 (s, 3H, OCH_3, polymer); 2.68 (m, 4H, CH_2CH_2, linker); 1.54 (s, 3H, CH_3), 1.33 (s, 3H, CH_3).

Polymer-Supported dipolarophile (6). A portion of the succinate-conjugated MeO-PEG from the previous experiment (5 g, 1 mmol) was dissolved in CH_2Cl_2 (25 mL) and MeCN (25 mL) and DMAP (0.1 g), DCC (1.5 mL, 1 M in CH_2Cl_2) and propargyl alcohol (0.5 mL) were added. The mixture was stirred at rt for 24 h then filtered and the solid washed with CH_2Cl_2 (~ 5mL). After evaporation back to ~ 50 mL, the filtrate was cooled in ice-water while ice-cold ether (~ 500 mL) was added with vigorous stirring. After filtration and recrystallization from absolute ethanol, compound (**6**) was isolated as a colorless solid (4.85 g, ~97%, mp 49-51 °C): ^{1}H NMR (ppm): 2.46 (t, 1H, J = 2.4 Hz, C-H alkyne), 2.65 (m, 4H, CH_2CH_2, polymer), 3.35 (s, 3H, OCH_3, polymer), 4.22 (2H, m, CH_2O, polymer), 4.66 (d, 2H, J = 2.4 Hz, CH_2 alkyne).

Cycloaddition of 5 with acetylenes, preparation of triazoles (7-10), attempted preparation of 11. A solution of azide (**5**) (2 g, 0.4 mmol) and the acetylene (10 equivalents) were refluxed in toluene (30 mL) for 48 h. The mixture was cooled in ice-water then ice-cold ether (500 mL) was added with vigorous stirring to induce precipitation. The solid was filtered then recrystallized from absolute ethanol to afford the respective polymer-supported triazoles (**7-10**) in the yields detailed in Table 1. mp for **7** 51-53 °C, mp for **8** 52-54 °C, mp for **9** 48-50 °C, mp for **10** 52-54 °C. No reaction was observed in an attempted analogous reaction between **5** and diphenylacetylene in the hope of forming **11**, even after heating the reactants for 48 hours in boiling xylenes. NMR data for **7-10** is shown in Table 2.

Cycloaddition of 6 with azide (1), preparation of triazoles (12). Alkyne (**6**) (1 g, 0.2 mmol) and azide (**1**) (0.4 g, 1.86 mmol) were refluxed in toluene (15 mL) for 36 h. Ice-cold ether (300 mL) was added with vigorous stirring, and the resultant solid was collected by filtration. The pale-tan solid (1 g, ~100%)

proved to be the mixture of triazoles (**12**) with >95% cycloaddition (1.72 : 1 mixture of regioisomers) as judged from the ^{1}H NMR spectrum. This material could be further purified by recrystallization from absolute ethanol (mp 49-50 °C). ^{1}H NMR (ppm): 1.20-1.42 (4s, total integral 6H, isopropylidene CH_3), 2.62 (m, 4H, succinate CH_2CH_2), 3.35 (s, 3H, CH_3O, polymer), 4.20-5.40 (m, 7H, sugar ring protons, CH_2OCO, polymer), 5.92 (d, 0.37H, J = 3.4 Hz, H-1, minor regioisomer), 5.96 (d, 0.63H, J = 3.6 Hz, H-1, major regioisomer), 7.70 (s, 0.37H, triazole H-4, minor regioisomer), 7.76 (s, 0.63H, triazole H-5, major regioisomer).

Removal of triazoles from the polymer support. Polymer-supported triazole (**8**) (2.51 g, ~0.47 mmol) was dissolved in ice-cold methanol (60 mL) that had been saturated with ammonia. After stirring overnight at rt, the mixture was concentrated to half volume then cold ether (500 mL) was added with stirring. The precipitated polymer was filtered and the filtrate condensed to a syrup which was purified by chromatography using hexane-ethyl acetate (4:1) as eluent. Triazole (**3**) was isolated as a colorless syrup (0.11 g, 0.44 mmol, ~94%), $[\alpha]_D$ –1.6° (*c*, 0.92, CH_2Cl_2). ^{1}H NMR (ppm): 7.73 (s, 1H, triazole H); 7.70 (s, 1H, triazole H); 6.00 (d, 1H, J = 3.7, H-1); 4.82 (dd, 1H, J = 6.6, 14.1, H-5); 4.60 (d, 1H, J = 3.5, H-2); 4.56 (m, 1H, H-5'); 4.45 (m, 1H, H-4); 4.23 (s, 1H, H-3); 1.28 (s, 3H, CH_3); 1.24 (s, 3H, CH_3). ^{13}C NMR (ppm): 27.4, 30.9, 50.1, 75.5, 80.5, 86.5, 106.2, 113.0, 126.1, 134.7. Exact mass calculated for $C_{10}H_{16}N_3O_4$ ($M+H^+$): 242.1141. Found: 242.1147. The NMR spectra of this material were identical to that for **3** formed above, except with the notable absence of byproduct contaminants. Likewise, polymer (**9**) afforded the known amides (**2**) (R^1 = $CONH_2$, R_2 = H)[5] in 85% yield after treatment with ammonia and chromatography using toluene-methanol (3:1) as eluent. Polymer (**10**), upon treatment with ammonia, afforded the known triazoles (**2**) (R^1 = CH_2OH, R^2 = H)[5] in 80% yield after flash chromatography using ethyl acetate as eluent.

Table 2. ^{1}H NMR chemical shifts (ppm) and coupling constants (in Hz) for polymer-supported compounds (**7-10**).[#]

Compound	Triazole H	H-1 (*J*)	H-2 (*J*)	H-3 (*J*)	H-4 (*J*)	H-5 (*J*)	H-5' (*J*)	linker	$C(CH_3)_2$	OCH_3 (polymer)	other
7	7.68 7.95	5.57 d* (3.7 Hz) 5.92 d (3.7 Hz) 5.97 d (3.7 Hz)	Under signal for H-4,H-5, H-5' (~4.5 ppm)	5.16 d* (2.9 Hz) 5.21 d (2.9 Hz) 5.30 d (2.9 Hz)	4.2-5.0 m	4.2-5.0 m	4.2-5.0 m	2.65 m	1.26 s* 1.29 s 1.30 s* 1.42 s 1.45 s 1.50 s	3.38 s	7.2-8.2 m phenyl ring
8	7.68 7.71	5.94 d (3.7 Hz)	4.54 d (3.3 Hz)	5.25 d (2.6 Hz)	4.61 m	4.70 dd (4.0, 14.1 Hz)	4.55 m	2.65 m	1.27 s 1.43 s	3.35 s	
9	8.10 8.24	5.91 d (3.7 Hz) 5.94 d (3.7 Hz)	Under signal for H-4,H-5, H-5' (~4.5 ppm)	5.25 d (3.1 Hz) 5.29 d (2.9 Hz)	4.2-5.0 m	4.2-5.0 m	4.2-5.0 m	2.65 m	1.25 s 1.42 s	3.38 s	1.22 t (7.1 Hz) 1.40 t (7.1 Hz) 4.40 q (7.1 Hz)
10	7.59 7.69	5.91 d (3.5 Hz) 5.92 d (3.5 Hz)	Under signal for H-4,H-5, H-5' (~4.5 ppm)	5.22 d (2.8 Hz) 5.31 d (2.6 Hz)	4.2-5.0 m	4.2-5.0 m	4.2-5.0 m	2.65 m	1.26 s 1.27 s 1.41 s 1.43 s	3.35 s	4.20 m CH_2O

s = singlet, d = doublet, dd = double doublet, m = multiplet

* Signals for unreacted starting material

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10. The reaction with phenyl vinyl sulfoxide affords the parent, unsubstituted, triazole **3** and likely occurs via an initial dipolar cycloaddition followed by an intramolecular elimination of PhSOH from an intermediate triazoline. Similar cycloaddition of phenylvinyl sulfoxide with an adamantyl azide has been reported to yield the aromatic triazole product (T. Sasaki, S. Eguchi, M. Yamaguchi and T. Esaki, *J. Org. Chem.*, 1981, **46**, 1800). The single triazole **3** is isolated in 68% yield after workup and column chromatography, however removal of byproducts proved inefficient and **3** is difficult to purify completely by this method. Cycloaddition of **1** with diphenylacetylene to afford triazole **4** is slow, as might be expected with large substituents on the alkyne, and compound **4** is isolated in only 48% yield after flash column chromatography.
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