

Dipolar Cycloaddition Reactions on a Soluble Polymer-Supported Dipolarophile: Synthesis of Sugar-derived Triazoles

Martin Moore and Peter Norris*

*Department of Chemistry, Youngstown State University
1 University Plaza, Youngstown, OH 44555 USA*

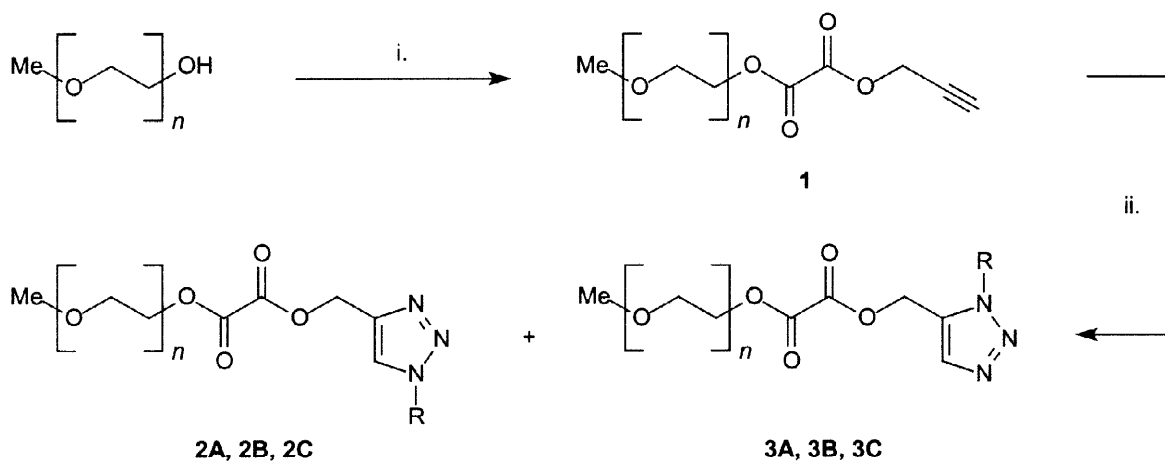
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Abstract: An organic-soluble polymer-supported alkyne has been employed as a dipolarophile in 1,3-dipolar cycloaddition reactions with azides. Several carbohydrate-derived azides react to form mixtures of regioisomeric triazoles in good to high yields, and the thus formed heterocycles are freed from the polymer under mild conditions using NaBH_4 in ethanol. © 1998 Elsevier Science Ltd. All rights reserved.

Dipolar cycloaddition to alkenes and alkynes is a well-established and general method for the synthesis of both aromatic and non-aromatic five-membered ring heterocycles. Solution methods for their preparation are well documented,¹ and several examples of dipolar cycloaddition to *insoluble* polymer-supported dipolarophiles have recently been reported.² These polymer-supported syntheses offer potential in the combinatorial synthesis of small heterocycle libraries since the established advantages of solid phase organic chemistry (for example ease of work up and repeated application of reagents) can be readily applied. General difficulties in solid phase work however include the possibility of lower reactivity at the polymer-solvent interface, and characterization of intermediate products while still attached to the polymer. Some of these problems can be alleviated with the use of a *soluble* polymer support.³ We now wish to report on our preliminary efforts in the area of dipolar cycloaddition chemistry, in which we employ a soluble polymer-supported dipolarophile for the synthesis of triazole heterocycles.

For development of dipolar cycloaddition chemistry we chose to employ the monomethyl ether derivative of polyethylene glycol with an average molecular weight of 5000 (MeO-PEG 5000). Polyethylene glycol derivatives are available in varying average molecular weights and with a variety of end groups attached. MeO-PEG 5000 is attractive as a support since it is soluble in many organic solvents, with the notable exception of ethers (including THF) and hexane, and is a solid at room temperature. Not only does solubility allow for solution reactivity but also intermediate products can easily be adequately characterized by proton NMR. The methyl group at one terminus of the polymer chain serves as an internal standard that can be used to calculate loading efficiency and reaction yield.⁴

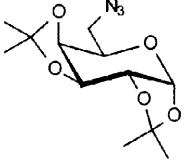
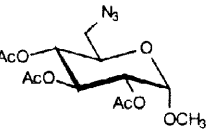
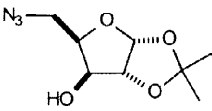
Treatment of MeO-PEG 5000 with oxalyl chloride in CH_2Cl_2 , followed by the addition of propargyl alcohol afforded, upon precipitation with diethyl ether, the polymer supported alkyne **1**. This material, isolated in 95% crude yield, could be purified by recrystallization from absolute ethanol to afford **1** (85%) with 85% loading of the propargyl alcohol.⁵ The polymer-supported alkyne was then treated with several azidodeoxy carbohydrate derivatives to afford regioisomeric mixtures (**2** and **3**) of polymer-supported triazoles *via* 1,3-dipolar cycloaddition (Scheme 1).⁶



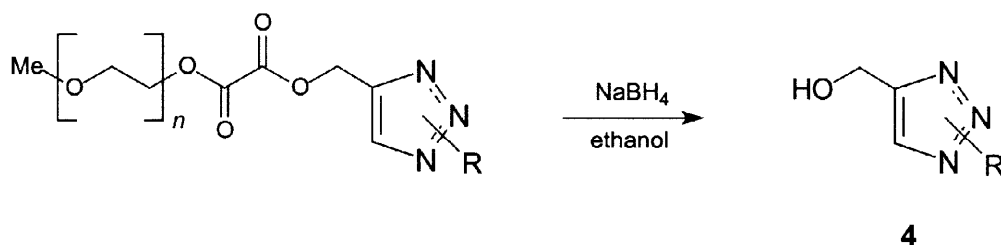
Scheme 1. Reagents and conditions: i. $(\text{CO})_2\text{Cl}_2$, pyridine, CH_2Cl_2 , 0°C , then propargyl alcohol. ii. R-N₃, toluene, reflux.

Table 1 shows results from cycloadditions employing 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**A**), which reacts to afford polymer-supported triazoles **2A** and **3A**, methyl 6-azido-6-deoxy-2,3,4-tri-*O*-acetyl- α -D-glucopyranoside (**B**), which reacts to afford triazoles **2B** and **3B**, and 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (**C**) which affords triazoles **2C** and **3C**. All of the polymer-supported triazoles are readily isolated using a general procedure of polymer precipitation followed by recrystallization. In calculating the regioisomeric distributions in these cycloadditions it is assumed that the major isomer is that which has the carbohydrate and polymer substituents in a head to tail orientation, i.e. **2A**, **2B** and **2C**. This outcome has been observed in previous examples of dipolar cycloaddition using azides,⁸ and the supposition that isomers **2A**, **2B** and **2C** are major is supported by a recent X-ray crystal structure of a carbohydrate-derived triazole.⁹ Interestingly, the cycloaddition with 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose gave a mixture of triazoles in ~2:1 ratio. The same reaction using propargyl alcohol itself was reported to result in an ~1:1 product mixture.⁸ The increased bulk of the polymer-supported dieneophile likely accounts for this difference, with the head to tail triazole being favored.

Table 1: Yields and regioisomeric outcome of cycloadditions with carbohydrate-derived azides.

R-N ₃	Yield of Polymer-bound Triazoles ⁵	2:3 and location of aromatic signals ⁷
A 	86% for cycloaddition step 85% isolated pure polymer	2.04 : 1.00 7.92 and 7.65 ppm
B 	82% for cycloaddition step 89% isolated pure polymer	1.65 : 1.00 7.90 and 7.72 ppm
C 	73% for cycloaddition step 92% isolated pure polymer	2.10 : 1.00 7.92 and 7.65 ppm

Liberation of the triazole products from the polymer is achieved under mild conditions (NaBH₄ in ethanol) in >75% yield. The polymer byproduct is readily removed from the heterocyclic products (**4**) by precipitation and filtration, and the triazoles are isolated as regioisomeric mixtures.⁶



In conclusion, we have demonstrated the feasibility of generating triazoles by means of dipolar cycloaddition of several carbohydrate-derived azides to a soluble polymer-supported dipolarophile. We are now investigating the use of nitrones and nitrile oxides for the generation of heterocycles on soluble polymer supports, and the application of the polymer-supported cycloadducts in multi-step synthesis.

Acknowledgments

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References and Notes

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5. ¹H NMR spectra were collected on a Varian Gemini 2000 instrument at 400 MHz. For polymer-bound material, the polymer methylene signal at ~3.6 ppm was suppressed to clarify spectra and the singlet at ~3.3 ppm for the polymer's terminal methyl group was used as an internal standard for integration when calculating yields. Loading of the propargyl alcohol onto the polymer via the oxalate linker was found to be ~85% by comparing integrals for the propargylic CH₂ signal at 4.8 ppm with the polymer CH₃ signal at ~3.3 ppm. Cycloaddition efficiency was determined from the total integral for the aromatic protons observed (in **2** + **3**) and comparing this with the methyl signal at ~3.3 ppm.
6. Typical procedure for triazole synthesis: The MeO-PEG-bound dipolarophile was prepared by treating an ice-cold mixture of oxalyl chloride (1.1 mmol), pyridine (2.2 mmol) and methylene chloride (10 mL) with a solution of MeO-PEG (MW 5000, 1.0 mmol) in methylene chloride (50 mL). After 2h propargyl alcohol (5 mmol) was added and the mixture refluxed for 12h. After precipitation with ether and recrystallization from absolute ethanol, the dipolarophile (**1**) was isolated as a colorless solid (¹H NMR δ 2.67 [t, alkyne proton], 4.38 [m, 2H, -CH₂-OCOCO], 4.80 [d, propargylic CH₂]). This material (1.0 mmol) was refluxed in toluene (30 mL) with 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (**C**, 2 mmol) for 12 h and the product (**2C** and **3C**) was precipitated with cold ether and recrystallized from absolute ethanol. Treatment of **2C/3C** (0.2 mmol) with NaBH₄ (0.4 mmol) in hot ethanol (50 mL) for 3 h, followed by precipitation with ether and evaporation of the filtrate, afforded the known⁸ regioisomeric triazoles (**4**, R = 1,2-*O*-isopropylidene-D-xylyl) as a colorless syrup (30 mg, 76%, ¹H NMR δ 1.3 [s, 3H], 1.4 [s, 3H], 4.2-4.8 [m, 7H], 5.95 [d, 1H, *J*=3Hz], 7.65 and 7.92 [two singlets, total integral 1H]).
7. Regioisomer ratio is determined by integrating the signals for the triazole protons in the aromatic region of the ¹H NMR spectra of the polymer-supported mixture.
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