# An iterative route to "decorated" ethylene glycol-based linkers†

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*Received (in Austin, TX, USA) 20th December 2005, Accepted 13th February 2006*
*First published as an Advance Article on the web 7th March 2006*
**DOI: 10.1039/b518061a**



**Iterative copper-catalyzed cycloadditions of azides to alkynes were used to join functionalized triethylene glycol molecules to give "linkers" of defined lengths equipped with several different end-group functionalities.**

Oligomeric compounds of a perfectly defined length, polydispersity 1.0, are highly desirable for a variety of applications. We were interested in using them to link peptidomimetics providing bi- and multivalent molecules that might potentially bind with protein targets.[1] We needed linkers with some intrinsic water solubility, that did not have charged functional groups, but that were able to span dimensions from about 10 Å to around 50 Å. They might also incorporate heterocyclic functionality that could interact with the protein in some positive way. Further, they should be functionalized with end groups that allow pharmacophores or other groups of interest to be attached.

The literature reveals only a few potential leads to the linker types described above. Purified polyethylene glycols are unsuitable because they are mixtures of compounds having different molecular masses. Oligoethylene glycol units of defined length can be made,[2–4] but even the best methods require long reaction times and several chromatographic separations. In fact, routes that feature iterative $S_N2$ ether-bond-forming steps are vulnerable to formation of vinyl ether side-products *via* competing elimination reactions. If these were not removed then acid treatment would give products with only one ethylene glycol unit less. Accumulation of these deletion products would be hard to separate after multiple steps, hence chromatography was required after every iteration. Oligomers that incorporate guanidine and ethylene glycol fragments also have been made,[5] but these may be too polar for some applications.

Fig. 1 outlines the central concept for this communication. A functionalized azidoethylene glycol unit **A** is reacted with a propargylated ethylene glycol tosylate **B** *via* a copper-catalyzed 2 + 3 cycloaddition.[6–8] Displacement of the tosylate with azide and reaction with another equivalent of monomer **B** allows for controlled, stepwise chain-growth. Finally, the chain is capped by addition of an appropriate end-group. This is a novel approach to linkers of a defined length. A conceptually similar iterative approach to expanding dendrimers was published while this work was in progress.[9]

A phthalyl-triethylene glycol **1**[10] was selected to prepare linker with protected amine functionalities (corresponds to unit **A** in the Fig. 1). It was made from a commercially available chloroalcohol

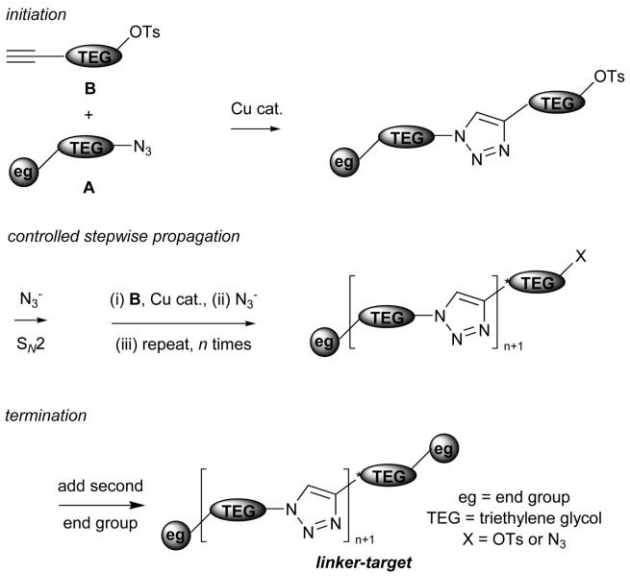
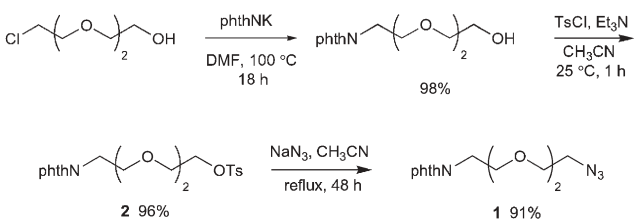



**Fig. 1** Approach to functionalized oligomers of defined length.

(Aldrich), *via* the tosylate **2** in the three steps shown below (Scheme 1). Others using this methodology would probably modify the end-group structure according to their specific needs.

Molecules **B** (Fig. 1) are used repeatedly in the propagation steps, hence clean, concise, synthetic access to this fragment was highly desirable. The alkyne-tosylate **3** was selected as this pivotal intermediate. It was formed by tosylation of the corresponding alcohol **4**. Previous syntheses of alcohol **4** involved monosilation, alkylation, and desilation steps,[11] but here it was realized that selective monoalkylation of triethylene glycol was possible, under conditions that do not involve toxic or expensive reagents. Thus the approach to the alkyne-tosylate **3** in Scheme 2 is direct and convenient.

Scheme 3 outlines the iterative sequence used to prepare the linkers. In these experiments, a slight excess of the core synthon **3** was used, and the yields shown were based on the azide components after chromatographic purification following each




**Scheme 1** Synthesis of the end-group unit **1**.

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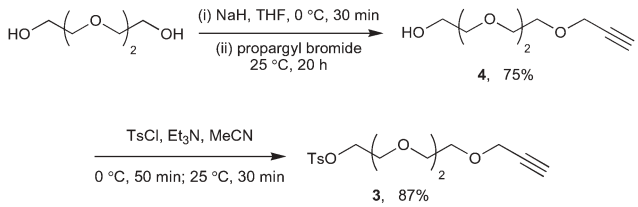
† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b518061a

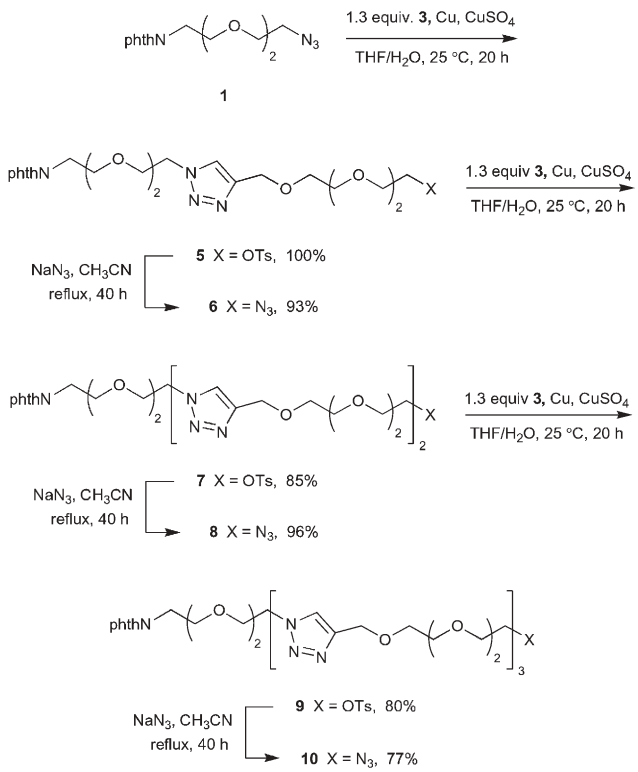



**Scheme 2** Synthesis of the key component for iterative chain elongation.

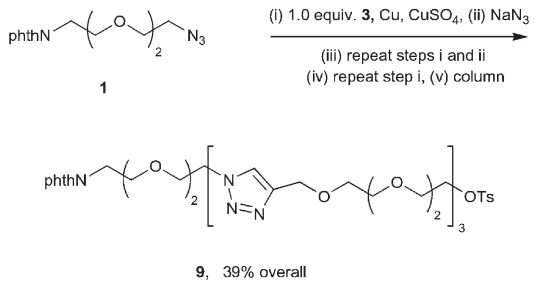
cycloaddition. HPLC analyses gave no indication of elimination by-products in the azide displacement steps, and the chromatographic separations were straightforward.

It was desirable to prove that multiple chromatographic separations were not essential in the sequence above. Columns were performed to obtain material for characterization, but the reactions are relatively clean. Consequently, it was decided to attempt the whole process using just one chromatographic separation in the closing stage (Scheme 4). In this case stoichiometric amounts of the azide **1** and the alkyne **3** were used. Water was added after each reaction, and the desired materials were extracted back into dichloromethane. Finally, the tosylate **9** was easily purified *via* flash chromatography, and pure material was obtained in 39% overall yield.

Both the tosylate and azide intermediates in the linker syntheses could be functionalized to give many different types of linkers. We were most interested in mono-protected diamines and protected-amino acids. Consequently, three reactions were performed (Fig. 2). In the first (Fig. 2a), the tosylate **5** was reacted with Boc-protected piperazine to give the differentially protected diamine **11**. Azide intermediates in the linker syntheses are




**Scheme 3** Iterative chain-elongation.




**Scheme 4** Synthesis of an oligomer without purification of intermediates.

particularly useful since almost any functionalized terminal alkyne can be added *via* copper-catalyzed cycloadditions. Thus, Fig. 2b features combination of the alkyne-ester **12** (from alkylation of alcohol **4** with *tert*-butyl bromoacetate) and the azide **6** to give the system **13**. The latter reaction is more convergent than the first because it introduces another triethylene glycol unit with the

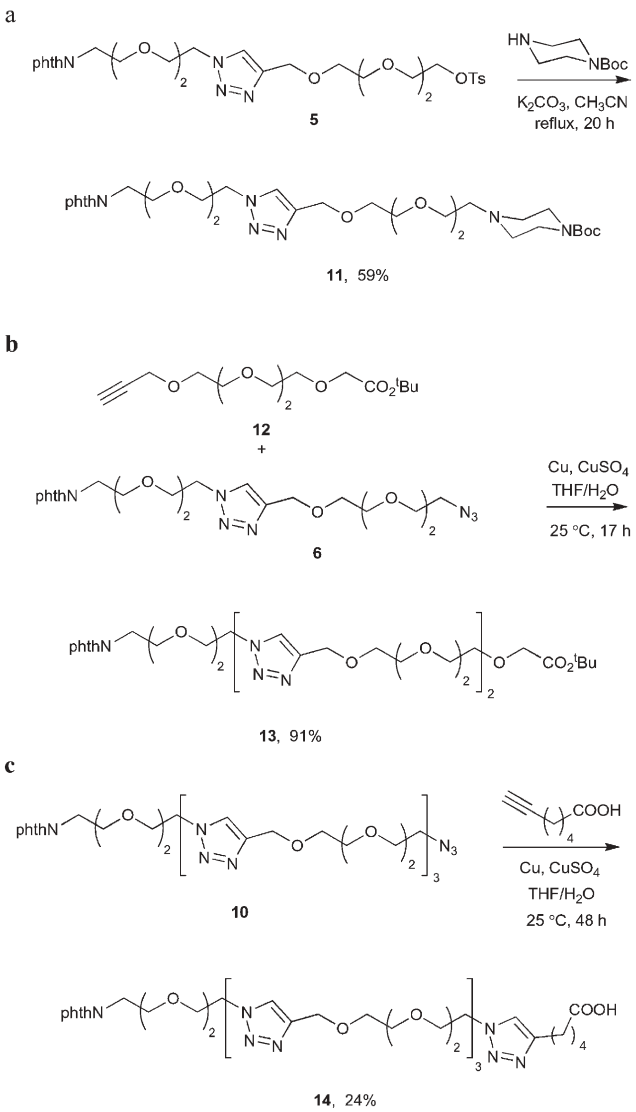



**Fig. 2** Elaboration of the core linker fragments *via*: **a** reaction of a tosylate; **b** "click" reaction of another triethylene glycol-derived alkyne; and, **c** combination with a different terminal alkyne.

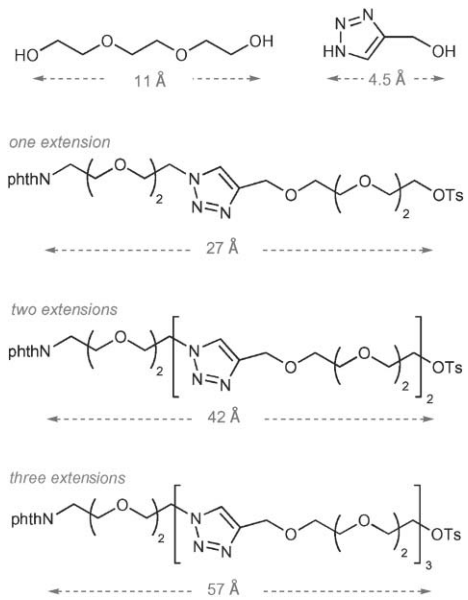



**Fig. 3** Lengths of various linker molecules in completely extended conformations.

second end-group. Finally, azide **10** was joined with 1-heptynoic acid (Fig. 2c).

Illustrative linker molecules in completely extended conformations were modeled to visualize their relative lengths (Fig. 3). On this basis, terminal *O*-atoms in triethylene glycol are separated by approximately 11 Å. Insertion of a triazole-methylene fragment into a chain seems to elongate it by around 4.5 Å, though this is approximate since the completely extended conformation is not linear like it is for a hydrocarbon. Nevertheless the maximum span of the linkers may be estimated using these dimensions of the building blocks.

Described here is a means to form linear oligoethylene glycol-based linkers of perfectly defined lengths. They were functionalized by several end-groups, and it is clear that many others could be used to design oligomers for other purposes. There is also scope for variation of the oligoethylene glycol units; indeed, we have already made similar systems based on hexaethylene glycol.[12] The linkers are easily made in an iterative process. We suspect it might be possible to automate the steps in the synthesis leading to the chromatographic separation, since the work-up at each stage only involves organic/aqueous separations. The triazole units incorporated into these linkers differentiate them from oligo- or polyethylene glycols. They do not make the systems significantly basic (the p$K_a$ of the protonated form of 1-*N*-methyltriazole is less than 2.0),[13] but they may have some characteristics that might be exploited. For instance, it seems likely that they might be able to form non-covalent interactions with proteins. It also would be intriguing to ascertain how they might complex with metals, both in a controlled environment and under physiological conditions. Finally, potential pharmaceuticals developed using linkers of perfectly defined length tend to be easier to steer through the regulatory process surrounding clinical trials and government approval than similar, but non-homogeneous, systems; this could be a major advantage of the linkers described here.

Financial support for this project was provided by the National Institutes of Health (CA82642 and GM076261), and the Robert A. Welch Foundation. TAMU/LBMS-Applications Laboratory headed by Dr Shane Tichy provided mass spectrometric support. The NMR instrumentation in the Biomolecular NMR Laboratory at Texas A&M University was supported by a grant from the National Science Foundation (DBI-9970232) and the Texas A&M University System.

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