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TWO NEW METHODS TO FORM SUBSTITUTED OLIGOETHYLENE GLYCOLS

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Abstract. 1-Bromo-2-trityloxyethane (**1**) and 1-allyloxymethyl-2-trityloxyethanol (**2**) react readily at room temperature with substituted oligoethylene glycols or the ditosylate derivative of an oligoethylene glycol, respectively, to form the extended, ditrityl-protected, substituted oligoethylene glycols in high yields. The trityl groups are easily removed by acidified methanol in CH_2Cl_2 to give the extended, substituted oligoethylene glycols.

According to *Chemical Abstracts*, there have been more than 3,800 papers and 60 reviews concerning the oligoethylene glycols published in the past 24 years.[1] Unfortunately, only one review summarizes most of the methods for the synthesis of the glycols.[2] The oligoethylene glycols are important compounds because they are used as starting materials for the preparation of macrocyclic ligands,[2,3] peptides,[4] surfactants[5] and ion conducting organic materials.[6]

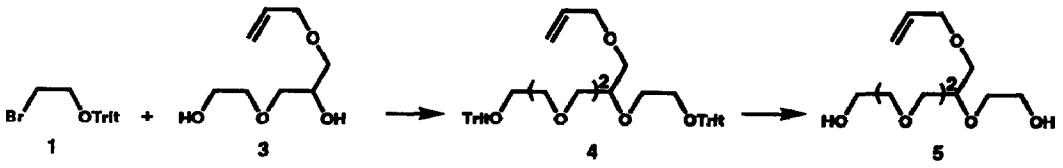
The most widely used synthons for the introduction of a protected or free 2-hydroxyethyl group are ethylene oxide and its derivatives,[7] chloroacetic acid or its ester derivatives,[8] 2-(2-chloroethoxy)tetrahydro-2*H*-pyran,[9] 2-(2-bromoethoxy)-tetrahydro-2*H*-pyran,[10] 2-(2-tosyloxyethoxy)tetrahydro-2*H*-pyran,[11] 2-benzyloxyethanol and its derivatives,[11c,12] and 2-trityloxyethanol.[13] The first three synthons are commercially available but they are not convenient to use. Ethylene oxide is a gas and requires special precautions. Substituted ethylene oxides (such as propylene oxide) react with an alcohol to give a mixture of secondary and primary alcohols by attack of the alkoxide on either the unsubstituted epoxide carbon or the substituted carbon of the epoxide.[7] These two products are very difficult to separate. Chloroacetic acid is useful but its reaction with a glycol in base often gives a mixture of mono- and diacetic acid substitution.[8] Again, these two products are difficult to separate. Even with a successful substitution of two acetic acid units, the product diacid must be reduced to form the final glycol product. 2-(2-Chloro- or 2-bromoethoxy)tetrahydro-2*H*-pyran is useful when treated with primary glycols or alcohols,[9,10] but the yields are often low when treated with secondary alcohols. The other synthons listed above are not readily available and must be prepared from ethylene glycol. In these cases, reaction on only one primary alcohol group is desired which necessitates use of a large excess of the glycol to react with

the relevant protecting group.

Glycols with a variety of side arms are not available. These compounds are very important because substituted macrocyclic ligands are desired materials. Often, ligands substituted with hydroxy, amino or allyl functions are attached to solid inorganic or organic supports for use in separation studies.[14] Long chain-substituted macrocyclic ligands are used for extracting metal ions from water into organic solvents.[15] The above mentioned synthons are not convenient for the preparation of the substituted glycols needed to prepare the substituted macrocyclic ligands. 2-(2-Bromo- or 2-chloroethoxy)tetrahydro-2*H*-pyran is the most used synthon for the substituted glycols but it often reacts with the starting short, substituted glycol to form mono- and disubstituted products even when the starting glycol is used in a large excess.[9a]

We now report the use of trityl-protected 2-bromoethanol (**1**) and trityl-protected allyloxymethyl-substituted ethylene glycol (**2**) to prepare various allyloxymethyl-substituted glycols where the substituent is attached to an internal carbon atom. Synthon **1** (mp 124°C) was prepared by treating 2-bromoethanol with trityl chloride as reported[16a] except CH_2Cl_2 and $(C_2H_5)_3N$ were used as solvent and base. A three-step process from ethylene glycol[16b] for **1** was not useful. Synthon **2** has been reported.[17] We used the reaction of equal amounts of 3-allyloxy-1,2-propanediol with trityl chloride in CH_2Cl_2 using $(C_2H_5)_3N$ as the base to prepare **2** in an 85% yield (mp 75°C, from hexane).

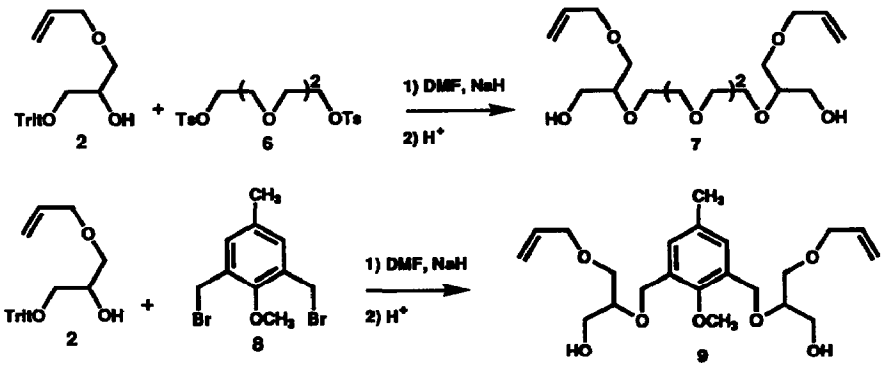
Synthon **1** reacts readily with substituted diethylene, triethylene or tetraethylene glycol at room temperature to form the bistrityl-protected, extended oligoethylene glycols. For example, 1-allyloxymethyl-3-oxa-1,5-



pentanediol (**3**) was treated with 2.05 equivalents of NaH and then with 2.05 equivalents of **1** to give a 90% yield of **4**. Ditrityl-protected **4** was not purified but was treated with HCl/CH_3OH in CH_2Cl_2 to give **5** (90%) which was purified by distillation. **5** was identical in every way to the same product prepared by a different route using chloroacetic acid.[18]

Synthon **2** can be used to introduce two allyloxymethyl substituents on internal carbons of an oligoethylene glycol. Bis(allyloxymethyl)-substituted tetraethylene glycol **7** was prepared as follows. A mixture of 37.4 g (0.1 mol) of **2** and 3 g (0.12 mol) of 95% NaH in 300 mL of DMF was stirred at rt for 15 min. Ditosylate **6** (22.5 g. 0.05 mol) was added to the mixture in portions. The resulting mixture was stirred at rt for 24-36 h. The solvent was then

evaporated under reduced pressure and 100 mL each of water and CH_2Cl_2 were added. The organic layer was separated and the water layer was extracted two times with 50 mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated to give crude ditrityl-protected **7**. This material could be purified by silica gel chromatography using $CH_2Cl_2/CH_3CO_2C_2H_5$: 50/1, 20/1 and then 10/1 as eluants. Glycol **7** was prepared from the crude ditrityl-protected product by treatment with 25 mL of concentrated HCl in 200 mL of CH_3OH and 200 mL of CH_2Cl_2. This mixture was stirred for 24h and then $NaHCO_3$ was added to make the pH = 7-8. The solvents were evaporated under reduced pressure and 300 mL of water was added to the residue. A solid was filtered and the solvent was evaporated under reduced pressure. The residue was mixed with 300 mL of CH_2Cl_2 and filtered. The filtrate was dried ($MgSO_4$) and the product was distilled to give 14 g (74%) of **7**;[19] bp 215-220°C/0.2 mm Hg; ^1H NMR δ 5.9 (m, 2 H), 5.2 (m, 4 H), 4.0 (m, 4 H), 3.65 (m, 24 H). A similar reaction with 3,5-bis(bromomethyl)-4-methoxytoluene (**8**) gave the corresponding bis(allyloxymethyl)-



substituted glycol containing the aromatic ring in a 70% yield.[19]

Synthons **1** and **2** can be reacted together to prepare diethylene glycol with an internal allyloxymethyl substituent in an 80% yield using the same procedure as above. The same compound (2-allyloxymethyl-3-oxa-1,5-pentanediol) was prepared previously in six steps in an overall yield of 20%.[12b]

Synthon **1** could easily be used to prepare large unsubstituted oligoethylene glycols from a smaller glycol. This process would use the available glycols rather than their ditosylate derivatives and the hard-to-prepare monotrityl-protected ethylene glycol as has been reported.[13]

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