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Practical use of NH_4X salts for difunctional oxyethylene-based intermediates

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Abstract—A series of tosyl functionalized oxyethylene-based organic compounds were selected to analyze the scope and efficiency of a general substitution method for conversion to difunctional, soluble oxyethylene based intermediates using readily available ammonium salts, glycols and commercially modified ethoxy-ethanols. Straightforward preparation, product purification and low cost reagents are particularly advantageous for compounds incorporating halides, thiocyanates and methoxy groups.
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Numerous short-chain oxyethylene compounds with a variety of halogen and pseudohalogen terminal functional groups have been synthesized from corresponding precursor alcohols, olefins and halides by various methods and functionalizing reagents that include $SOCl_2$,[1] PBr_3,[2] ClBr,[3] NaI[4] and KSCN.[5] A majority of the research is driven by the utility of these compounds as reagents in classical crown ether chemistry.[6] These compounds are also useful reagents for the preparation of bioadhesion resistant surface treatments,[7] for the pendant functionalization of rigid rod macromolecules into processible molecular composites,[8] and for transforming large dye chromophores into intrinsic liquids.[9] Remarkably, to our knowledge there has not been a general substitution study for conversion to difunctional intermediates utilizing a single, efficient method for a set of ethylene oxide oligomers.

Recent interest in both water-soluble gold nanoclusters stabilized by ligands containing short ethylene oxide oligomers[10] and difunctional solubilizing tether agents for monomer/polymer synthesis via Williamson coupling[11] required analysis of convenient routes towards several related compounds. Coupled with our current research involving tetrabutylammonium cyanide as a catalyst for thioacetate deprotection,[12] the availability of common ammonium salts, and a modification of the conversion of tosylate groups by fluoride substitution using tetrabutylammonium fluoride,[13] this expanded method provided a reliable synthetic pathway for numerous difunctional synthetic pieces.

Originally, tetrabutylammonium fluoride was employed for the nucleophilic displacement of tosylate (*p*-toluenesulfonate) functional groups as a procedure for the convenient access of ^{18}F-labeled octanoic acid derivatives. It was discovered in our hands that an analogous reaction utilizing tetrabutylammonium bromide in refluxing tetrahydrofuran converted a di-tosylated oxyethylene tri-oligomer in high yield. Unfortunately, alkylammonium salts are limited commercially, relatively expensive and remained present as byproducts following workup of the reaction mixture.

Comparatively, simple ammonium salts of the general type NH_4X are commercially abundant, relatively inexpensive and are easily removed following aqueous workup of the reaction mixture. Although the ammonium salts available were not soluble in tetrahydrofuran compared to their alkylammonium analogues, they were soluble in polar organic solvents such as dimethyl sulfoxide and *N*,*N*-dimethyl formamide and subsequent experiments were performed accordingly. These solvents were particularly useful since they did not require the rigorous drying and purification procedures typical for tetrahydrofuran and for their generally broad solubility. Limited kinetic studies were formerly reported using dipolar aprotic solvent hexamethylphosphoric triamide, for nucleophilic substitution between ethyl tosylate and chloride and bromide ions.[14]

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Initially, a commercial glycol and two modified ethoxyethanols, tri(ethylene glycol), 2-(2-methoxyethoxy)ethanol and 2-[2-(2-chloroethoxy)-ethoxy]ethanol, were chosen for further experimentation.[15] The alcohols were converted to their respective tosylates by reaction with tosyl chloride in a pyridine-dichloromethane mixture in moderate yield.[16]

Ammonium chloride, bromide, iodide and thiocyanate salts were originally selected as nucleophilic reagents for reaction with three model tosylates (see Table 1). It was determined by solubility tests that ammonium iodide was more suitable in *N*,*N*-dimethyl formamide, whereas chloride, bromide and thiocyanate dissolved readily in dimethyl sulfoxide. It was also noted that reaction temperatures greater than 65 °C were required for complete conversion of the tosylate to the halide or thiocyanate for samples stirring for a minimum of 4 h. Selective conversion reactions were typically heated to 70 °C overnight, whereas non-competitive reactions were performed at slightly elevated temperatures of 80–85 °C for 4–5 h.[17,18]

Yields greater than 50% were obtained under these conditions for experiments **1**–**12** (Table 1). Selective conversion for samples **5**, **8** and **11** were achieved using 1.2 M equiv of ammonium salt at 70–75 °C for 16 h. It was discovered that a slight ammonium reagent excess did not produce a mixture of products by competitive reaction with the chlorine, although higher molar equivalencies (>1.3) revealed mono- and disubstituted products. These results are particularly advantageous for further chemoselective reactions. For non-competitive experiments **1**–**4**, **6**, **7**, **9**, **10** and **12**, an excess of ammonium reagent was utilized for efficient conversion and shorter reaction times. For **10a** and **10b**, appropriate choice of solvent improved yields from 52% with DMSO to 76% with DMF.

Attempts to employ more common solvents in place of the aprotic solvents were not successful. Methanol and acetone were investigated, but starting material was recovered for each attempt. Generally, poor solubility of the tosylated reactant in methanol and poor solubility of the ammonium salt in acetone were attributing factors.

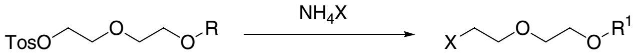
Attempts to employ ammonium fluoride as a reagent for reaction with the three tosylated compounds in dimethyl sulfoxide, *N*,*N*-dimethyl formamide and methanol were unsuccessful. Despite varying conditions and workup, neither product nor starting material was ever recovered. Substitution of fluoride for a tosyl group at the end of an alkane chain has been reported using tetrabutylammonium fluoride in tetrahydrofuran at room temperature.[13] These conditions have also been successful on a tosylate terminated oxyethylene chain.[19]

Yields were generally equivalent or superior to alternate published procedures. For instance, experiment **8** reveals more than double the yield found from the conversion of 1,8-dichloro-3,6-dioxaoctane and sodium iodide in refluxing acetone and an identical yield for experiment **7** under similar conditions.[4a] The liquids possessed similar physical properties identical with those reported.[18]

Tetra(ethylene glycol)di(*p*-toluenesulfonate)[20] underwent nucleophilic substitution with ammonium iodide in *N*,*N*-dimethyl formamide at 80 °C for 5 h to form 1,11-diiodo-3,6,9-trioxaundecane (Fig. 1). Compared to the previously reported 4 day conversion required from 1,11-dichloro-3,6,9-trioxaundecane with sodium iodide/acetone in 67% yield,[21] results were encouraging. Our method required a short reaction time for complete conversion and resulted in a higher yield. The diiodide product represented in Figure 1 is one oxyethylene unit longer than the product in Table 1, entry 7. Our isolated yield decreased from 85% to 75% as a result of this one unit extension in chain length. It is our opinion that this lower yield is a consequence of purification difficulty due to increasing chain length rather than terminal group reactivity differences.[22]

We see two key advantages in the preparation of the tosylate intermediate: (1) this route appears to avoid side reactions that generate inseparable byproducts at short oxyethylene chain lengths previously observed in earlier

Table 1. Nucleophilic substitution of tosylated model compounds



	R	X	R^1	Conditions	Yield (%)
1	C_2H_4–OTos	Cl	C_2H_4–Cl	4 equiv, DMSO 85 °C, 5 h	71
2	C_2H_4–Cl	Cl	C_2H_4–Cl	1.2 equiv, DMSO 70 °C, 16 h	64
3	CH_3	Cl	CH_3	2 equiv, DMSO 80 °C, 5 h	51
4	C_2H_4–OTos	SCN	C_2H_4–SCN	4 equiv, DMSO 80 °C, 5 h	86
5	C_2H_4–Cl	SCN	C_2H_4–Cl	1.2 equiv, DMSO 75 °C, 16 h	71
6	CH_3	SCN	CH_3	2 equiv, DMSO 80 °C, 5 h	83
7	C_2H_4–OTos	I	C_2H_4–I	4 equiv, DMF 80 °C, 5 h	85
8	C_2H_4–Cl	I	C_2H_4–Cl	1.2 equiv, DMF 70 °C, 16 h	70
9	CH_3	I	CH_3	2 equiv, DMF 80 °C, 4 h	76
10a	C_2H_4–OTos	Br	C_2H_4–Br	4 equiv, DMSO 85 °C, 5 h	52
10b	C_2H_4–OTos	Br	C_2H_4–Br	4 equiv, DMF 85 °C, 5 h	76
11	C_2H_4–Cl	Br	C_2H_4–Cl	1.2 equiv, DMSO 70 °C, 16 h	53
12	CH_3	Br	CH_3	2 equiv, DMSO 85 °C, 4 h	63

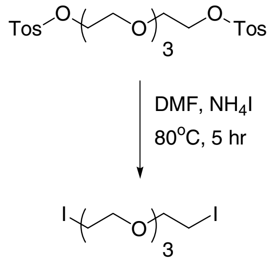


Figure 1. Tetra(ethylene glycol) di(*p*-toluenesulfonate) reacts with ammonium iodide in 75% yield.

research[2] and (2) as a result of solubility differences, mono-tosylated intermediates are separable from oligo ethylene glycol reactant and disubstituted tosylated byproduct. This distinction is particularly important for the preparation of unsymmetrically terminated oxyethylene chain molecules.

In conclusion, the chloride, bromide, iodide or thiocyanate ion in a series of ammonium salts nucleophilically displace the tosylate group at the end of an oxyethylene chain in dimethyl sulfoxide or *N*,*N*-dimethyl formamide solvents. High yields were obtained with three tosylate terminated oxyethylene substrates. This general substitution study has implications towards chemoselective intermediates of varying halogenated ends and lengths.

Acknowledgements

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17. All synthetic procedures were performed under an inert nitrogen atmosphere with oven-dried glassware. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance-300 instrument. Chemical shifts were referenced to the residual chloroform peak at 7.26 and 77.0 ppm, respectively. Proton and carbon NMR spectra of reacted species were compared to published material and analyzed for side products, conversion and yields.
18. *Representative experimental procedure for the synthesis of 1,8-diiodo-3,6-dioxaoctane* **7**: Under an atmosphere of nitrogen, *N*,*N*-dimethyl formamide (5 mL) was added to tri(ethylene glycol)di(*p*-toluenesulfonate) (0.20 g, 0.44 mmol) and ammonium iodide (0.65 g, 1.7 mmol). After stirring for 5 h at 80 °C, the reaction mixture was poured directly into a separatory funnel containing distilled water (20 mL) and diethyl ether (20 mL). The aqueous phase was extracted with diethyl ether (2 × 20 mL) and the organic layers were combined, washed with distilled water (2 × 20 mL), dried with $MgSO_4$, filtered, passed through an activated plug of alumina (Bodman Neutral-Super I) and concentrated in vacuo to reveal an analytically pure product.
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