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Convenient and Efficient Tosylation of Oligoethylene Glycols and the Related Alcohols in Tetrahydrofuran–Water in the Presence of Sodium Hydroxide

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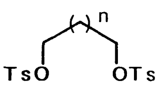
Synopsis. Oligoethylene glycols and some related alcohols were efficiently tosylated with *p*-toluenesulfonyl chloride in a tetrahydrofuran–water (1:1) mixture in the presence of excess sodium hydroxide. This method is advantageous over the conventional tosylation in pyridine both regarding the work-up procedure, the yield, and the purity of the product, and may be potentially useful for the tosylation of certain acid-labile alcohols.

Recently, a wide variety of crown ethers and the related ligands possessing oxyethylene units have been synthesized.[1] As starting materials, appropriate oligoethylene glycol ditosylates have frequently been employed. According to the conventional tosylation procedures for aliphatic alcohols,[2] the ditosylates have been prepared in pyridine,[3] except for a couple of cases.[4,5] However, when the tosylate, thus prepared, is oil, a thorough elimination of the pyridine from the final product requires either repeated neutralization with aqueous hydrochloric acid (10 times) or purification by column chromatography. In our crown ether syntheses using oily tetraethylene glycol ditosylate, it was shown that even a trace amount of the remaining pyridine severely diminishes the product yield or, in some cases, ruins the synthesis completely.[6]

We, therefore, developed an alternative method to prepare oily oligoethylene glycol ditosylates absolutely free from pyridine. In the new method a 1:1 mixture of tetrahydrofuran (THF) and water was used as a solvent, and sodium hydroxide was used as a base. This tosylation method, using inexpensive and less-toxic materials, turned out to be applicable not only to the oligoethylene glycols that give oily ditosylates, but also to a fairly wide variety of mono- and diols without any apparent decrease in product yield or purity, as compared with the corresponding syntheses in pyridine.

	n
1a	1
b	2
c	3
d	4
e	5
f	6
g	7

	R	n
2a	Me	1
b		2
c		3
d		4
e		5
f	n-Bu	1
g	t-Bu	1



	n
3a	1
b	2

Results and Discussion

Oligoethylene Glycols. In method A, mono- to heptaethylene glycol ditosylates **1a**—**g** were synthesized by reactions of the respective oligoethylene glycols with *p*-toluenesulfonyl (tosyl) chloride in THF/water in the presence of sodium hydroxide at 0—5 °C. Caution should be exercised to maintain the temperature of the reaction mixture below 5 °C and to avoid a prolonged reaction period after completion of the addition of tosyl chloride; a raised temperature and/or prolonged reaction period often seriously diminished the yields.

For a comparison, some of the same tosylations were carried out in pyridine according to the conventional procedure (method B).[3] The yields obtained by these two methods are listed in Table 1, along with those reported in the literature.[7–11,15] In general, method A afforded more or less higher yields and purities than those of method B. Hence, the ditosylates **1b**—**g** obtained by method A have widely been used without further purification in the syntheses of various crown ethers to give satisfactory yields.[12]

Other solvents were also surveyed to some extent. 1,4-Dioxane/water mixture has been used as a solvent in the syntheses of **1b** and **1e**, only to give moderate yields of 51—70%.[4,5] We repeated the same procedure in dioxane/water (1:1) at ca. 5 °C (method C). Although the yield of **1d** was satisfactory (93%), the mixture of dioxane (mp 12 °C) and water showed a strong tendency to solidify in the reaction vessel upon cooling on an ice-bath. This requires quite careful temperature control. A less expensive acetone/water mixture has also been employed in the syntheses of the tosylates of some phenols and acidic alcohols.[13] However, in the present case, the use of this solvent mixture resulted in total failure, especially with oily tosylates, since organic extracts from the reaction mixture were heavily contaminated with carbonyl compound, probably produced in the aldol condensation of acetone catalyzed by the base.

Oligoethylene Glycol Monomethyl Ethers. The oily tosylates of a series of oligoethylene glycol monoalkyl ethers **2a**—**g** were similarly prepared in

Table 1. Isolated Yields (%) of Various Mono- and Ditosylates Prepared from the Corresponding Mono- and Diols under Some Different Reaction Conditions[a]

Tosylate	Mp/°C	Reaction Conditions		
		NaOH,THF-H_2O (Method A)	Pyridine (Method B)	NaOH,Dioxane-H_2O (Method C)
1a	124—127 (124—127)[b]	65[c]	64[b]	
1b	87.0—87.5 (86—87)[d]	79[c]	77,[c] 83,[b] 70[e]	51[d]
1c	80—81 (80.5—81.5)[b]	89[c]	70,[c] 77,[b] 75[e]	
1d	f)	94 (83)[g]	56,[f] 67[e]	93[f]
1e	f)	98 (83)[g]	75[f]	70[d]
1f	f)	97	86,[d] 91[h]	
1g	f)	90	63[i]	
2a	f)	88	82[j]	
2b	f)	95		
2c	f)	95		
2d	f)	96		
2e	f)	95		
2f	f)	87	92[j]	
2g	f)	90		
3a	89—92 (91—92)[k]	65[c]	65,[k] 55[l]	
3b	65—68 (67.5—69.5)[m]	41[c]	67[c]	

a) This work, unless stated otherwise. b) Ref.7. c) Recrystallized from methanol. d) Ref.4. e) Ref.3. f) Oily product without further purification. g) Further purified by column chromatography. h) Ref.15. i) Ref.8. j) Ref.11. k) Ref.9. l) Ref.10. m) Ref.19.

excellent yields by method A. The product purities were satisfactorily high, as judged from their ^{1}H NMR spectra, and the tosylates **2** were used without further purification in the syntheses of 16-crown-5 lariats[12c] and longer oligoglymes.[14]

Alkanediols. The same procedure (method A) was extended to the preparation of some higher homologues of ethylene glycol, i.e. 1,3-propanediol and 1,4-butanediol. The isolated yields of **3a** and **3b**, though lower than those for **1** and **2**, were well comparable to those obtained by method B (Table 1).

In conclusion, this improved method of tosylation, which employs THF/water as a solvent and sodium hydroxide as a base, is an attractive alternative to the conventional tosylation in pyridine, especially for oily tosylates, in view of its convenience, efficiency, and use of an inexpensive reagent/solvent. Finally, we wish to mention a marginal benefit of this method. Since no acidic conditions are encountered throughout the reaction and work-up procedures, this method may be potentially useful for the tosylation of certain acid-labile substrates carrying, for example, a tetrahydropyranyl-protective group.

Experimental

General. Infrared spectra were obtained on a JASCO A-100 spectrometer. Melting points were measured with a YANACO Micro Melting Point apparatus and were uncorrected. Mass spectra were measured by electron impact at 70 eV using the RMU-6E instrument. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ on a JEOL GX-400 spectrometer.

Materials. Penta-, hexa-, and heptaethylene glycols were synthesized according to the reported method.[15,16] Other reagents used in this study were commercially available and were used without further purification.

Synthesis. Method A. Sodium hydroxide (80 g, 2.0 mol) dissolved in water (400 mL) and oligoethylene glycol (0.70 mol) or its monoalkyl ether (1.4 mol) in THF (400 mL) were placed in a flask and the mixture was cooled on an ice-bath with magnetic stirring. To the mixture was added dropwise *p*-toluenesulfonyl chloride (243 g, 1.3 mol) in THF (400 mL) over 2 h with continuous stirring and cooling of the mixture below 5 °C. The solution was stirred at 0—5 °C for an additional 2 h, and then poured into ice-water (1 L). The tosylate, if solidified (**1b**,**c**), was filtered, washed thoroughly with water, dried, and then recrystallized twice from methanol to give a pure specimen in the yield shown in Table 1.

The other tosylates, which were oily (**1d**—**g** and **2**) or only partially solidified (**1a** and **3**), were isolated in a different manner. After being poured into ice-water, the mixture was extracted twice with dichloromethane; chloroform or benzene may be used.[17] The combined organic extracts were washed twice with water and once with saturated aqueous sodium chloride solution, and then dried over anhydrous magnesium sulfate.[18] Upon evaporation of the solvent, the tosylate of satisfactory purity was obtained in the yield shown in Table 1. Further purification, if needed, may be achieved by column chromatography over silica gel with dichloromethane eluent for the oily tosylates, or by recrystallization from methanol for the solid tosylates.

Method B. The oligoethylene glycol ditosylates **1b**—**e** and butanediol ditosylate **3b** were synthesized in pyridine according to the conventional procedure reported.[3]

Method C. Tetraethylene glycol ditosylate **1d** was synthesized in a 1 : 1 mixture of dioxane and water at ca. 5 °C. The reagents and the procedures were identical to those employed for method A.

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