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# Ultrasound-promoted tosylation of oligo(ethylene glycols)

Pierre-Edouard Danjou, Damien Wallyn, Francine Cazier-Dennin and François Delattre\*

Univ. Lille Nord de France, F-5900 Lille, France

ULCO, UCEIV, F-59140 Dunkerque, France

E-mail address: delattre@univ-littoral.fr (F. Delattre).

## Abstract

A series of oligo(ethylene glycols) was efficiently tosylated by ultrasound procedure within dichloro- methane in the presence of triethylamine. Results show that sonochemical synthesis of oligo(ethylene glycol) ditosylates has a double advantage since it does not use catalysts and it drastically reduces the reaction time. This straightforward method represents an eco-friendly alternative to the traditional tosylation by pyridine synthesis.

## 1. Introduction

Large range molecular weight oligo(ethylene glycols) H-[OCH<sub>2</sub>CH<sub>2</sub>]<sub>n</sub>-OH and their anionic or nonionic derivatives are synthetic amphiphilic polyethers soluble in water as well as in many organic solvents. Due to their non-toxicity, these polymers are used in pharmaceutical and cosmetic formulations [1], bioblock copolymer [2] and drug delivery [3]. They also found widespread applications as synthons for the synthesis of crown-ether deriva- tives [4] or surface functionalization [5]. Usually, only few oligo(ethylene glycols) with a well-defined number of ethylene oxy units are commercially available in high purity ( $n \geq 12$ ) and only small compounds ( $n < 5$ ) are cheap while larger polymer could be more expensive. Poly(ethylene glycols) (PEGs) are also found as polydispersed mixtures due to formation of by-products during “triplication” reaction and require laborious purification proce- dures [6,7]. However despite the versatility of PEGs, the modifica- tion of these compounds is not cost-effective due to a long reaction time and it uses toxic materials like pyridine.

Among the common building blocks based on PEG derivatives, mono- or di-*p*-toluenesulfonylation (tosylation) of oligo(ethylene glycols) terminal alcohol groups are frequently used to achieve functionalization [8–11]. Tosylates compounds have clear advanta- ges compared to halide analogs. On the one hand, their crystalline forms allow an easy recrystallization/purification to obtain highly pure solids. On the other hand, the insolubility of the by-product alkali tosylate salts can be eliminated by a simple filtration.

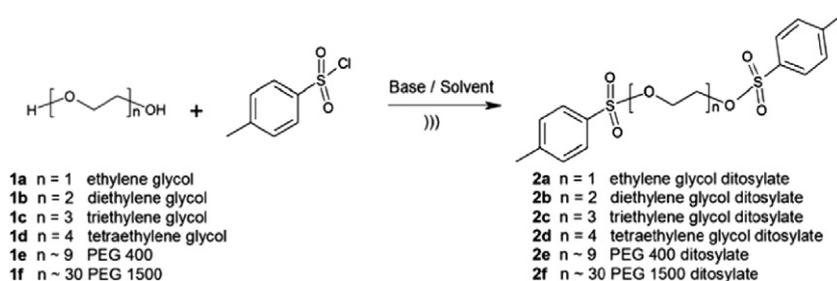
Historically, to prepare tosylated alcohol derivatives, the standard procedures require pyridine as the base/solvent [7,12,13] despite several drawbacks such as (i) total elimination of pyridine requires numerous neutralizations with aqueous hydrochloric acid or purifi- cation by chromatography; (ii) the reaction time can be between a few hours and several days; (iii) undesirable conversion of the tosy- lates into their chloride derivatives occurs during tosylation when TsCl/pyridine is used and (iv) molar excess of bases or base adducts of sulfonyls induce significant amounts of by-products such as total dissolved salts.

In this context, many thermal tosylation procedures of oligo(ethylene glycols) were carried out with various solvents or mixture of solvents associated to bases or catalytic species allow- ing to access mild operating conditions [9,14–16]. Otherwise, to the best of our knowledge, the ultrasound promoted tosylation has only been successfully applied twice for alcohol derivatives with on the one hand a sonochemical application of the traditional pyridine method [17] and on the other hand for a selective tosylation of a cyclic oligosaccharide [18]. So, this context prompted us to explore a new way to synthesize a series of oligo(ethylene glycol) ditosylates by ultrasound irradiations (Scheme 1) with the input of thermal optimized existing alternative methods (other than pyridine method) which moreover could be generalized to the synthesis of various primary alcohols.

## 2. Material and methods

### 2.1. Apparatus

All oligo(ethylene glycols) were purchased from Sigma–Aldrich and were dried under vacuum overnight at room temperature



Scheme 1. Synthesis of ethylene glycol ditosylates 2a–f.

prior to use. Compounds 2a–2d are pure oligo(ethylene glycols) while 2e and 2f correspond to polydisperse mixtures centered around 414 and 1339 g/mol respectively (Fig. 1). Solvents were purchased from Fischer Scientific in the highest grade available and were used as received without further purification.

Ultrasonic experiments were performed with a Branson sonifier 450 (13 mm diameter horn, 20 kHz) from Branson ultrasonic Corporation (Danbury, Connecticut, CT 06810). The instrument, which can furnish a power of 400 W, was used with an output control of 5 and a duty cycle of 80% (0.8 s pulses on and 0.2 s pulses off). The ultrasound probe was immersed 1 cm in the solution and during the sonication, the temperature was monitored with a thermocouple immersed in the solution.  $^1\text{H}$  NMR spectra were recorded in deuterated chloroform containing TMS as internal standard on a Bruker DPX 250 spectrometer operating at 250 MHz. Mass spectra were measured using a Platform II Micromass Apparatus with positive electrospray ionization and a cone voltage of 40 V.

## 2.2. General procedure for the synthesis of glycol di-*p*-toluene sulphonates 2a–f

In a three-necked round bottom flask equipped with a thermocouple and a sonotrode, under argon bubbling, a mixture of glycol 1a–f (20 mmol) and triethylamine (80 mmol) was dissolved in dichloromethane (40 mL). *p*-toluene sulphonyl chloride (60 mmol) was then added at once and the mixture was irradiated under ultrasound for 30 min. A white precipitate of triethylamine hydrochloride was filtered off and the filtrate was concentrated under reduced pressure to afford a crude oil. The purification procedure depends on the nature of products (solid or oil). Pure tosylates

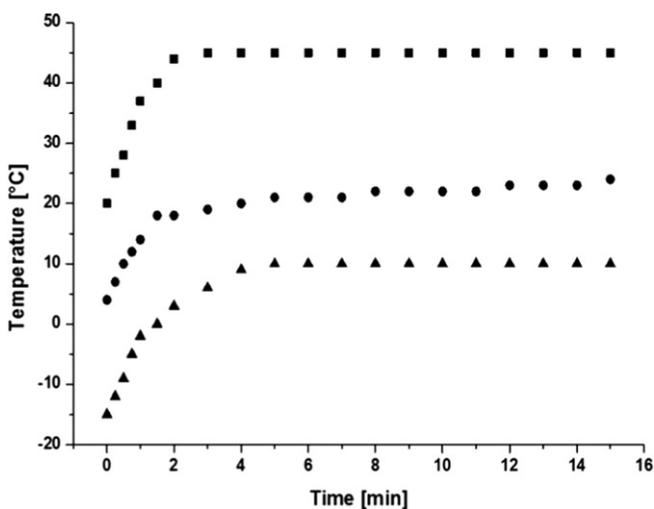


Fig. 1. Evolution of temperature in binary  $\text{Et}_3\text{N}$ /dichloromethane system during sonication experiment.

2a–c were obtained by twice crystallization in MeOH with yields of 94%, 93% and 95% respectively. The crude oily products 2d–f were dissolved in dichloromethane and was then washed three times with 1 N HCl solution, three time with saturated  $\text{NaHCO}_3$  solution and finally with brine. Finally, the organic phase was dried under  $\text{MgSO}_4$  and the solvent was removed under reduced pressure to afford an oil which gave 80% and 78% yields for 2e and 2f, respectively, while further purification of 2d was achieved by column chromatography (silica, dichloromethane) to afford 94% yield.

Ethylene glycol di *p*-toluene sulphonate 2a, white crystalline solid, m.p. 88.0–89.1 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 7.72 (d, 4H,  $J = 8.1$  Hz) 7.27 (d, 4H,  $J = 8.1$  Hz), 4.18 (s, 4H), 2.45 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 145.37, 132.23, 130.02, 127.98, 66.79, 21.72. M/z ESI ( $\text{M}^+$ ): 393 [ $\text{M}+\text{Na}^+$ ] (100%), 409 [ $\text{M}+\text{K}^+$ ] (14%). Yield: 94%.

Diethylene glycol di *p*-toluene sulphonate 2b, white crystalline solid, m.p. 87.0–87.8 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 7.79 (d, 4H,  $J = 8.1$  Hz), 7.35 (d, 4H,  $J = 8.1$  Hz), 4.09 (t, 4H,  $J = 4.6$  Hz), 3.60 (t, 4H,  $J = 4.6$  Hz), 2.45 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 145.12, 132.86, 130.03, 128.07, 69.17, 68.85, 21.80. M/z ESI ( $\text{M}^+$ ): 437 [ $\text{M}+\text{Na}^+$ ] (100%), 453 [ $\text{M}+\text{K}^+$ ] (17%). Yield: 93%.

Triethylene glycol di *p*-toluene sulphonate 2c, white crystalline solid, m.p. 80.0–81.0 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 7.79 (d, 4H,  $J = 8.1$  Hz), 7.34 (d, 4H,  $J = 8.1$  Hz), 4.14 (t, 4H,  $J = 4.7$  Hz), 3.65 (t, 4H,  $J = 4.7$  Hz), 3.53 (s, 4H), 2.45 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 144.98, 132.95, 129.94, 128.02, 70.74, 69.31, 68.79, 21.73. M/z ESI ( $\text{M}^+$ ): 481 [ $\text{M}+\text{Na}^+$ ] (100%), 497 [ $\text{M}+\text{K}^+$ ] (12%). Yield: 95%.

Tetraethylene glycol di *p*-toluene sulphonate 2d, Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 7.78 (d, 4H,  $J = 8.1$  Hz), 7.33 (d, 4H,  $J = 8.1$  Hz), 4.14 (t, 4H,  $J = 4.7$  Hz), 3.66 (t, 4H,  $J = 4.7$  Hz), 3.55 (s, 8H), 2.43 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 144.87, 132.94, 129.86, 127.97, 70.72, 70.54, 69.30, 68.68, 21.65. M/z ESI ( $\text{M}^+$ ): 525 [ $\text{M}+\text{Na}^+$ ] (100%), 541 [ $\text{M}+\text{K}^+$ ] (21%). Yield: 94%.

Polyethylene glycol 400 di *p*-toluene sulphonate 2e, Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 7.77 (d, 4H,  $J = 8.1$  Hz), 7.33 (d, 4H,  $J = 8.1$  Hz), 4.14 (t, 4H,  $J = 4.7$  Hz), 3.68–3.55 (m, 36H), 2.49 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 144.72, 132.78, 129.74, 127.82, 70.55, 70.40 (broad), 69.21, 68.48, 21.52. M/z ESI ( $\text{M}^+$ ) (Supplementary content, left).

Polyethylene glycol 1500 di *p*-toluene sulphonate 2f, Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 7.77 (d, 4H,  $J = 8.2$  Hz), 7.33 (d, 4H,  $J = 8.2$  Hz), 4.13 (t, 4H,  $J = 4.7$  Hz), 3.70–3.55 (m, 116H), 2.43 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $d_{\text{ppm}}$ : 144.71, 132.86, 129.76, 127.88, 72.72, 70.47 (broad), 69.19, 68.56, 68.23, 21.58. M/z ESI ( $\text{M}^+$ ) (Supplementary content, right).

## 3. Results and discussion

To achieve suitable conditions for the synthesis of oligo(ethylene glycol) ditosylates (Scheme 1) by ultrasonic irradiations, triethylene glycol was selected as model compounds in tosylation reaction with *p*-toluene sulphonyl chloride. So first, various procedures have

Table 1

Sonochemical tosylation of triethylene glycol 1c in different mixtures with an irradiation time fixed at 30 min.

Entry	Base (+catalyst)/solvent	Literature		Sonochemistry
		Time (min)	Yield (%)	Yield (%)
1	NaOH/THF-H <sub>2</sub> O [14]	240	65	77 <sup>d</sup>
2	Et <sub>3</sub> N (+0.1 eq. Me <sub>3</sub> N.HCl)/CH <sub>2</sub> Cl <sub>2</sub> [16]	60	83 <sup>a</sup>	89 <sup>d</sup>
3	Et <sub>3</sub> N (+0.05 eq. DMAP)/CH <sub>2</sub> Cl <sub>2</sub> [15]	240	70 <sup>b</sup>	88 <sup>d</sup>
4	Et <sub>3</sub> N/CH <sub>2</sub> Cl <sub>2</sub>	-	-	95 <sup>d</sup>
5	KOH/CH <sub>2</sub> Cl <sub>2</sub> [9]	180	95 <sup>c</sup>	90 <sup>d</sup>

<sup>a</sup> Monotosylation of 3-octanol.

<sup>b</sup> Monotosylation of diethylene glycol.

<sup>c</sup> Ditosylation without purification.

<sup>d</sup> Pure compounds obtained by twice crystallization in MeOH.

Table 2

Ultrasound-assisted synthesis of 2c in Et<sub>3</sub>N/dichloromethane.

Entry	Temperature (°C)	Yield (%) at 15 min	Yield (%) at 30 min	Yield (%) at 60 min
1 <sup>a</sup>	10	54	70	72
2 <sup>a</sup>	21	65	86	85
3 <sup>a</sup>	45	72	95	93

<sup>a</sup> Pure compounds obtained by twice crystallization in MeOH.

been extracted from literature and applied to the synthesis of our model without temperature control and with an arbitrary sonication time fixed to 30 min (Table 1). Moreover, in order to compare results, the ditosylation of triethylene glycol was achieved with four equivalents of base and three equivalents of tosyl chloride in all experiments.

As shown in Table 1, THF-water solvent with sodium hydroxide as base provides only 77% yield (entry 1) while a binary system dichloromethane/base can reach better yields (entries 2–5). Compared to classical methods, the use of catalysts like trimethylamine hydrochloride or 4-dimethylaminopyridine [15,16] does not affect positively the yield of the reaction indicating an inoperative role of these additives in ultrasound procedure. Thus, due to a better yield of Et<sub>3</sub>N compared to KOH, the triethylamine/dichloromethane couple was selected for the continuation of the study.

All authors show that temperature used in all experiments is below 5 °C since a raised temperature would harm the efficiency of the reaction. As it is well-known that sonication increases the medium temperature as a function of solvent and in order to control the reaction, we have monitored the temperature during ultrasound irradiation experiments in Et<sub>3</sub>N/dichloromethane mixture (Fig. 1) for three starting temperatures (16, +4 and 20 °C, respectively).

Over the first five minutes and whatever the departure requirements, a stable level of temperature is reached (Fig. 1). Consequently, in order to evaluate the influence of sonication time on the temperature, we have carried out an ultrasound irradiation of triethylene glycol 1c with *p*-toluene sulphonyl chloride at 10, 21 and 45 °C during 15, 30 and 60 min, respectively (Table 2).

The experimental data show that the efficiency of the tosylation after 15 min at 45 °C is equivalent to those obtained in 1 h at 10 °C. So, tosylation of triethylene glycol 1c is more efficient when the temperature is increased (45 °C is the maximum temperature obtainable with the Et<sub>3</sub>N/dichloromethane system). This ascertainment is contrary to all previous experiments advocating a low temperature between 0 and 5 °C to maintain high yield of tosylation. We assume that phenomenon is due to a positive effect of ultrasound in this nucleophilic substitution reaction, which promotes

Table 3

Synthesis of oligo(ethylene glycol) ditosylates under ultrasonic irradiation in 30 min.

Entry	Compound	Yield (%)	Yield (%) from literature 1
1	2a	94 <sup>a</sup>	65 [14]
2	2b	93 <sup>a</sup>	79 [14]
3	2c	95 <sup>a</sup>	95 [14]
4	2d	94 <sup>b</sup>	83 [14]
5	2e	80 <sup>c</sup>	95 [9]
6	2f	78 <sup>c</sup>	50 [20]

<sup>a</sup> Pure compounds obtained by twice crystallization in MeOH.

<sup>b</sup> Pure compounds obtained by column chromatography (silica, dichloromethane).

<sup>c</sup> Colorless oil obtained successive washes.

the addition–elimination mechanism in aprotic solvent [19]. This assumption is supported by a further experiment for which the ultrasound-assisted synthesis was checked by running a silent handling at 45 °C during 30 min to afford only 61% yield. Accordingly, the sonochemical tosylation of triethylene glycol appears to be effective and could be extended to other ethylene glycols as reported in Scheme 1.

Finally, we have extended the optimum protocol of synthesis (Section 2.2) to a series of oligo(ethylene glycols) from ethylene glycol, di- to tetraethylene glycols and PEG400 then PEG1500 (Scheme 1) and results have been compiled in Table 3.

For entries 1, 2, 4 and 6, we obtained a higher yield compared to the literature with a reaction time divided by 8–10 while for entry 3 the same result has been reached. Only entry 5 shows a lower yield compared to literature since they used a pure PEG while we have carried out experiments with a commercial polydisperse PEG.

#### 4. Conclusion

In conclusion, ultrasonic irradiation was found to be a highly competitive method for the synthesis of oligo(ethylene glycol) ditosylates that was superior to the traditional methods with respect to yields, reaction times, simplicity and safety. This straightforward method represents a very interesting alternative to the traditional pyridine synthesis. Beyond this work, we think that ultrasonic assisted synthesis can be applied and generalized to the whole chemistry of PEG.

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