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Competitive formation of cellulose *p*-toluenesulfonate and chlorodeoxycellulose during homogeneous reaction of *p*-toluenesulfonyl chloride with cellulose in *N,N*-dimethylacetamide–lithium chloride

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ABSTRACT

The homogeneous preparation of a cellulose *p*-toluenesulfonate (tosylate) in *N,N*-dimethylacetamide–lithium chloride (DMAc–LiCl) is hampered by solvolysis of the *p*-toluenesulfonyl chloride (tosyl chloride). This Vilsmeier–Haack type reaction results in competitive formation of cellulose *p*-toluenesulfonate and chlorodeoxycellulose. Highly *p*-toluenesulfonylated cellulose may be prepared in DMAc–LiCl with minimal incorporation of chlorine by utilization of either triethylamine or 4-dimethylaminopyridine as base. A mechanism for the competing series of reactions is postulated.

INTRODUCTION

Sulfonic acid esters of various carbohydrates, including cellulose, have been extensively reported in the literature. These represent a technologically important class of materials which have been utilized as intermediates for nucleophilic displacement reactions. The *p*-toluenesulfonate derivative (tosylate) has been the most extensively studied of these intermediates, followed by the methanesulfonate (mesylate) and benzenesulfonate derivatives.

Klein and Snowden, as early as 1958, reported the preparation of a number of sulfonic acid esters of cellulose (both mesylate and tosylate)[1]. The sulfonates were reacted in displacement reactions with potassium halides, potassium phthalimide, *p*-toluenesulfonamide, propylamine, *p*-methylthiophenol, saccharin, potassium thiocyanate, pentabromophenol, bis(2-propyl)dithiophosphoric acid, bis(dibromopropyl) phosphoric acid, nitropropane, and potassium cyanide.

In addition to serving as leaving groups in substitution reactions, *p*-toluenesulfonate (tosylate) substituents serve as valuable hydroxyl protecting groups for carbohydrates[2,3]. Tosylates are stable under a variety of reaction conditions, allowing a broad range of transformations, yet photolytic cleavage is facile. Tosylate-protected hydroxyl groups are reported to withstand treatment with acids and bases, alkylation, hydrogenation, and nitrous acid deamination[3].

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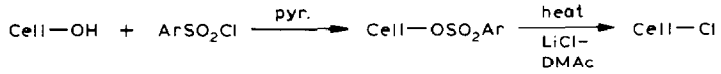
Historically, the *p*-toluenesulfonylation (tosylation) of cellulose has been carried out heterogeneously in pyridine[1,4,5]. Large excesses of the sulfonyl chloride are required. Reaction times of two to four days typically result in d.s. values of 0.08 to 1.36 (ref. 5).

As an extension of previous work in our laboratories on dissolution and derivatization of cellulose in LiCl and *N,N*-dimethylacetamide, including the reactions of cellulose with acid chlorides[6–13], McCormick and Callais reported the *in situ* synthesis and subsequent characterization of chlorodeoxycellulose. This reaction, conducted under homogeneous reaction conditions[13], was presumed to have proceeded through a cellulose tosylate (Scheme 1) intermediate (d.s. = 2.3). Further research in our laboratories, including isolation of intermediates, indicates that our originally proposed sequence shown in Scheme 1 is overly simplified. In this paper, we examine in further



Scheme 1. Reaction pathway previously described for formation of chlorodeoxycellulose[10].

detail the tosylation reaction of cellulose under homogeneous reaction conditions in DMAc–LiCl. From these results, we have determined the conditions necessary for competitive formation of chlorodeoxycellulose previously reported in our laboratories.

EXPERIMENTAL

Materials. — Purified, reagent-grade cellulose was obtained from J.T. Baker Chemical Company (cat. no. 1529). This unfractionated material[14] is microcrystalline with $M_w = 1.5 \times 10^5$. Other reagents were of reagent grade and were used without further purification unless specifically noted.

N.m.r. analysis. — ^{13}C-N.m.r. spectra were recorded on a Bruker AC-300 F.t-n.m.r. instrument at 75.5 MHz. Chemical shifts are reported in δ-units, downfield in p.p.m. relative to tetramethylsilane (TMS), as determined from the internal solvent resonances of *N,N*-dimethylacetamide (DMAc). All spectra were recorded in non-deuterated DMAc using D_2O inserts for a frequency lock.

N,N-*Dimethylacetamide–lithium chloride (DMAc–LiCl) solvent.* — Stock solutions of LiCl in DMAc (9% w/w) were prepared by dissolving LiCl (4.2 g), (Aldrich, Cat. no. 21,323-3) in DMAc (50 mL) (Aldrich, cat. no. 18,588-4) at 80°. To minimize moisture uptake, solvent solutions for each experiment were prepared immediately prior to use.

Cellulose preparation. — To facilitate dissolution, the cellulose was pretreated as follows: Cellulose powder (100 g) was slurried overnight in deionized water (500 mL). The mixture was vacuum filtered through coarse fritted glass. The cellulose was then added to methanol (500 mL), stirred for 1 h, and filtered. This procedure was repeated three times. Five similar repetitions with DMAc (500 mL) completed the process.

The concentration of cellulose per gram of swollen material was determined by drying several samples (1.0 g) in a vacuum over for 48 h at 80°. The average cellulose

content for this material was thus determined to be 0.486 g per 1.0 g of sample.

Cellulose Dissolution. — Fresh DMAc–LiCl solvent was prepared *in situ* in a dry, 100-mL, three-neck flask equipped with dry nitrogen inlet/outlet, heating mantle, thermometer, and magnetic stirrer. Upon removal of the heating mantle, 1.0 g of solvent-exchanged cellulose (0.486 g of actual cellulose weight or 9.0 mmol of hydroxyl functionality) was added to the heated solvent. The mixture was allowed to stir, with nitrogen sparging, while cooling to room temperature. Typical solutions cleared at 40°–50°, or after stirring for approximately 20 min. All subsequent reactions were performed under a nitrogen atmosphere.

Sulfonyl Chlorides. (a) Preparation of Cellulose N,N-*dimethylacetimidate.* — To 50 mL of 1.0% (wt.) cellulose in 9% DMAc–LiCl, pyridine (1.4 mL, 18 mmol) and *p*-toluenesulfonyl chloride (TsCl, 3.4 g, 18 mmol) were added. The reaction was allowed to continue for 12 h at room temperature. After this period, the reaction mixture was orange in color and turbid. The polymer was precipitated into acetone. The product was water-soluble. It was later determined that pyridine was nonessential to the reaction. I.r. data: 1628 (C=N) and 1745 (C=O) cm^{-1}. ^{13}C-n.m.r. data: δ 178.0 (C=N), 176.4 (C=O), 44.1 and 41.8 $N(CH_3)_2$, 17.9 (CH_3CO).

(b) Hydrolysis of cellulose N,N-*dimethylacetimidate:* A sample (0.5 g) of the polymer was dissolved in D_2O ($\sim$1.5 mL) and monitored by ^{13}C-n.m.r. spectroscopy for hydrolysis to the acetate. Upon hydrolysis, the reported iminium peaks at δ 178.0, 44.1, 41.8, and 17.9 disappeared after $\sim$3 h. ^{13}C-n.m.r. data: δ 176.4 (C=O); 37.3 [$(CH_3)_2$] and 23.2 (CH_3CO).

(c) Preparation of cellulose p-*toluenesulfonate.* — To 25 mL of 1.0% (wt.) cellulose in 9% DMAc–LiCl, triethylamine (TEA, 12.2 mL, 88 mmol) was added. The reaction flask was immersed in a cooling bath, and the temperature was lowered to 10°. A solution of *p*-toluenesulfonyl chloride (5.6 g, 29 mmol) in DMAc (10 mL) was added dropwise to the cooled reaction mixture. The reaction was allowed to stir for 24 h at 10°. The TEA salts were filtered, and the polymer was precipitated into ice water. After purification and drying, the yield was found to be 0.9 g (Equiv. to a d.s. = 0.9). The product was soluble in DMAc and in DMF. Decompositon on heating was observed at 150°. I.r. data: 1350 and 1170 (S–O) cm^{-1}. ^{13}C-n.m.r. data: δ 145.3–127.8 (tosylate aromatics), 20.7 (tosylate CH_3) and 105–65 cellulose backbone.

Anal. Found: C, 50.18; H, 5.22; Cl, 0.71; N, 0.58; O, 32.48; S, 10.65. These data indicate a d.s. = 1.1.

(d) Optimization of the preparation of cellulose p-*toluenesulfonate.* — The effects on the reaction of combinations of variables were evaluated. A two-level, multivariable, 8 × 8 Hadamard matrix was prepared according to Diamond[15] (Table I). This provided for eight combinations of six reaction variables. Each trial was carried out as described below with the appropriate incorporation of each variable.

Reactions were conducted by preparing the cellulose solutions using DMAc (25 mL) or 1-methyl-2-pyrrolidinone (25 mL) (NMP) with LiCl (2.1 g). A solution containing the appropriate quantity of TEA or 4-dimethylaminopyridine (DMAP) in the indicated solvent (20 mL) was added to the reaction flask. (This quantity of base was

two or four times the molar concentration of the sulfonyl chloride). The temperature was then adjusted to either 10° or 30°, and the indicated amount of sulfonyl chloride was added in the solvent (5 mL). The concentration of sulfonyl chloride was either two or three times the molar cellulose hydroxyl content. The reaction was then allowed to continue for either 8 or 24 h, as dictated by the matrix.

TABLE I

Hadamard matrix design for cellulose *p*-toluenesulfonyl[a,b]

	Variable[c]	*A*	*B*	*C*	*D*	*E*		*F*	
Trial	0	1	2	3	4	5	6	7	*Highs*[c]
1	+	+	−	−	+	−	+	+	ADF
2	+	+	+	−	−	+	−	+	ABEF
3	+	+	+	+	−	−	+	−	ABC
4	+	−	+	+	+	−	−	+	BCDF
5	+	+	−	+	+	+	−	−	ACDE
6	+	−	+	−	+	+	+	−	BDE
7	+	−	−	+	−	+	+	+	CEF
8	+	−	−	−	−	−	−	−	(1)

[a] See ref. 15 for matrix details. [b] *Conditions.* — Trial No. 1: 24 h, 10°, TsCl (1.7 g, 8.9 mmol), DMAP (4.4 g, 36 mmol), DMAc.
Trial No. 2: 24 h, 30°, TsCl (1.7 h, 8.9 mmol), TEA (2.5 mL, 18 mmol), DMAc.
Trial No. 3: 24 h, 30°, TsCl (2.6 g, 14 mmol), DMAP (3.3 g, 27 mmol), NMP.
Trial No. 4: 8 h, 30°, TsCl (2.6 g, 14 mmol), DMAP (6.6 g, 54 mmol), DMAc.
Trial No. 5: 24 h, 10°, TsCl (2.6 g, 14 mmol) TEA (7.5 mL, 54 mmol), NMP.
Trial No. 6: 8 h, 30°, TsCl (1.7 g, 8.9 mmol), TEA (5.0 mL, 36 mmol), NMP.
Trial No. 7: 8 h, 10°, TsCl (2.6 g, 14 mmol), TEa (3.9 mL, 28 mmol), DMAc.
Trial No. 8: 8 h, TsCl (1.7 g, 8.9 mmol), DMAP (2.2 g, 18 mmol), NMP.

[c] *Variable*	*(+)*	*(−)*
A = Time (h)	24	8
B = Temperature (°)	30	10
C = [sulfonyl][b]	3/1	2/1
D = [base][d]	4/1	2/1
E = base	Triethylamine	4-Dimethylaminopyridine (DMAP)
F = solvent	*N,N*-dimethylacetamide	1-methyl-2-pyrrolidinone

[d] Equivalents of sulfonyl chloride to cellulose hydroxyl groups. [e] Molar ratio of tertiary amine to sulfonyl chloride.

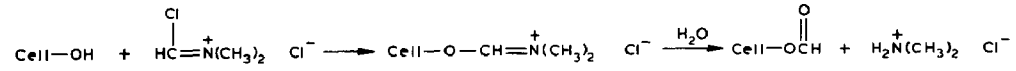
Only trials 2,4, and 5 resulted in soluble products. Product 2 was soluble in hot DMAc, whereas products 4 and 5 were readily soluble in both DMAc and DMF at room temperature. Gravimetric analysis indicated d.s. values of 0.4, 1.2, and 0.8, respectively, for these products. An effort was made to measure the d.s. values using u.v. spectroscopy. A Beer's law plot of methyl *p*-toluenesulfonate (TSA) in 9% DMAc–LiCl was prepared. TSA absorbed at 267 and 273 nm; however, it was found that the cellulose solution produced a broad absorption centered at about 250 nm, which interfered with quantitative analysis. Although the trend showed increasing absorbance per gram of sample ($2 < 5 < 4$) no quantitative values could be extracted.

RESULTS AND DISCUSSION

Our first effort to isolate a cellulose *p*-toluenesulfonate derivative (tosylate) under previously reported synthesis yielded an unexpected water-soluble product. Since no other solvent could be found, it was concluded that the polymer had been converted into an ionic derivative. ^{13}C-n.m.r. analysis of the product in aqueous solution showed two unexpected peaks in the carbonyl region at δ 176.3 and 178.0, indicating that side reactions were involved.

Attempts to obtain a resolvable F.t.-n.m.r. spectrum in water were unsuccessful due to formation of an insoluble product before a sufficient number of scans could be obtained. The polymer solution became visibly more viscous after about 1 h in the n.m.r. tube, eventually phase-separating into a clear, swollen gel.

A literature search of ionic cellulose derivatives capable of hydrolysis reactions was important to our mechanistic considerations. Vigo, Daigle, and Welch[16] had reported the reactions of cellulose with chlorodimethylformiminium chloride in DMF to yield either *N,N*-dimethylformimidate chloride or cellulose formate, depending on the isolation procedure[16]. Two different products were rationalized by those authors as shown in Scheme 2. The intermediate ionic product could be isolated in an anhydrous



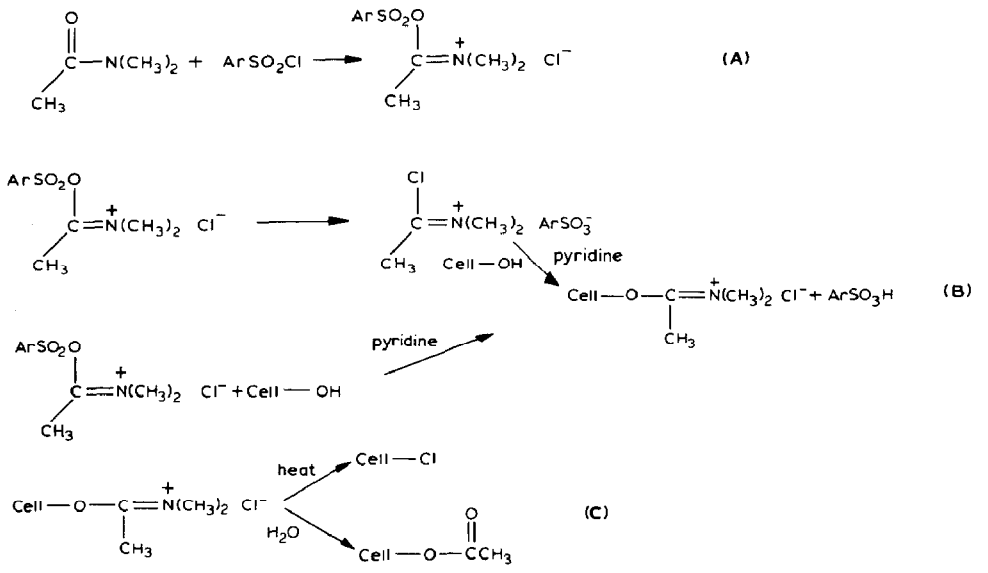
Scheme 2. Reaction pathway for formation of cellulose *N,N*-dimethylformimidinium chloride and cellulose formate[16].

solvent such as benzene; the hydrolysis product, on the other hand, would be the formate. Elevating the temperature led to displacement of DMF by the chloride ion and produced a chlorodeoxycellulose. Consideration of this reaction scheme and the reactions of formamides and acetamides with sulfonyl chlorides to yield iminium salts *via* The Vilsmeier–Haack reaction[17] led to our consideration of the series of reactions shown in Scheme 3.

Step one appears to be the formation of the *O*-(*p*-toluenesulfonyl)-*N,N*-dimethylacetiminium salt. The second step, nucleophilic displacement of the tosylate, has two possible routes [Scheme 3, Eq. (*B*)]. The chloride ion may attack the iminium carbon, displacing the sulfonate, with subsequent displacement of the chloride by cellulose. Alternatively, the cellulose hydroxyl group could attack the tosylated iminium species, directly displacing the tosylate. The chloroiminium cellulose intermediate [Scheme 3, Eq. (*C*)] could then be attacked by the chloride ion to produce chlorodeoxycellulose, or hydrolyzed (as in the case of Vigo *et al.*[16]) to produce cellulose acetate.

Cellulose p-*toluenesulfonate*. — Facile preparation of an easily isolated cellulose *p*-toluenesulfonate (tosylate) under homogeneous reaction conditions continued to be a priority in our research efforts. A key to the successful reaction seemed to be avoiding removal of the tosylate group from the reaction pathway. Our approach was to investigate the effects of base strength and nucleophilicity on reaction products.

Simple substitution of triethylamine for pyridine in the reaction produced the



Scheme 3. Proposed reaction pathways for competitive formation of cellulose *p*-toluenesulfonate (tosylate) and chlorodeoxycellulose in DMAc–LiCl.

desired results. The tosyl ester, a white solid, was prepared in good yield. The ^{13}C-n.m.r. spectrum is shown in Fig. 1. Resonances assigned to the tosylate methyl and aromatic ring carbons are visible at δ 21 and 128–145, respectively. The carbons of the cellulose backbone are seen from δ 65 to 105. Peaks at δ 30, 34, and 162 are DMF from the solvent. Elemental analysis shows minimal incorporation of chlorine. D.S. values for

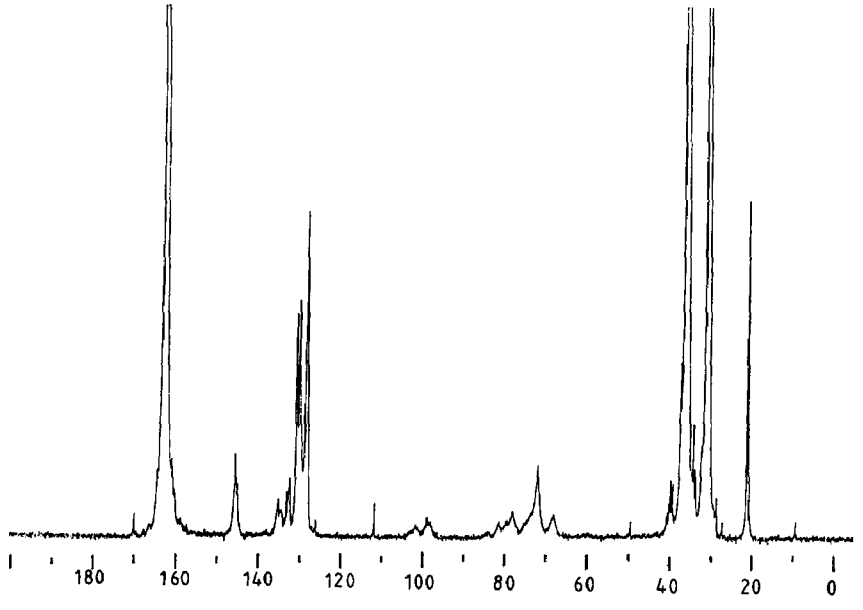
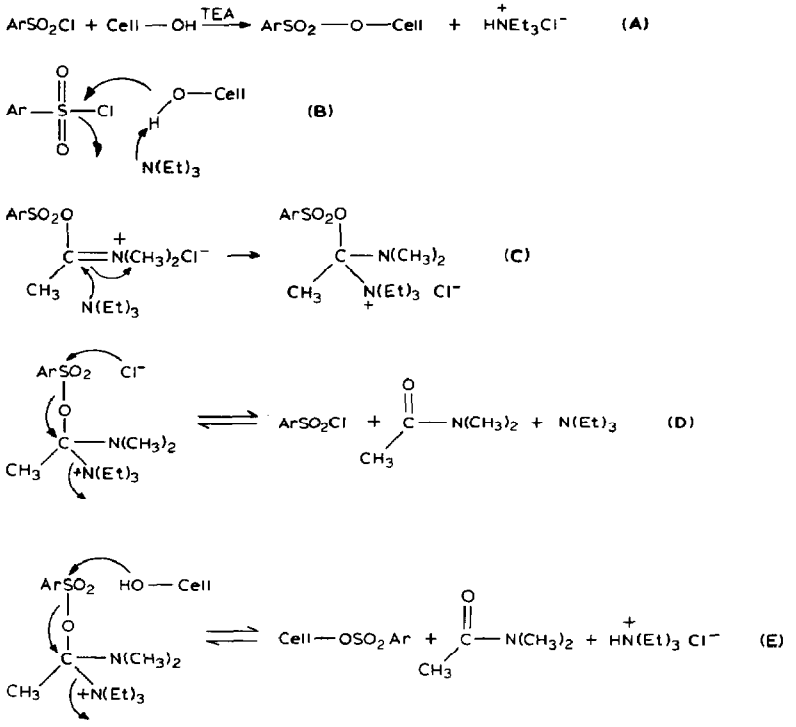


Fig. 1. ^{13}C-N.m.r. spectrum of cellulose *p*-toluenesulfonate (tosylate) in non-deuterated DMAc.

the tosylate from the initial experiment were 1.1, as determined by elemental analysis (see Experimental section).

Obviously TEA, unlike pyridine, favors formation of cellulose tosylate [Scheme 4 Eq. (*A*)] over the cellulose iminium species [Scheme 3, Eq. (*B*)]. To date we have been unable to determine the precise reasons for differential reactivity of the two bases. However, at least two explanations seem reasonable. TEA may simply be more effective as a catalyst or acid scavenger [Scheme 4, Eqs.(*A*) and (*B*)] than pyridine under these reaction conditions. Alternatively, the TEA may react efficiently with a tosylated iminium species [Scheme 4, Eq. (*C*)] to produce a tetragonal species that is less accessible to attack at the central carbon by cellulose. The tosylate could be reactivated by reaction with a chloride anion [Scheme 4, Eq. (*D*)], or a cellulose hydroxyl group could attack the



Scheme 4. Mechanistic pathways for the *p*-toluenesulfonylation (tosylation) of cellulose.

activated tosylate complex as shown in Scheme 4, Eq. (*E*).

Electronic or solvation factors stabilizing similar pyridine complexes may inhibit reactions comparable to Eqs. (*D*) or (*E*) in Scheme 4.

An effort was made to evaluate the variables which most affect the tosylation of cellulose. Such information should help to optimize conditions for derivatizations. This study utilized a fractional factorial experimental design in order to minimize the number of experiments[15,22,22]. The variables considered were time, temperature, concentration of

sulfonyl chloride, concentration of base, type of base (TEA or DMAP), and type of solvent (DMAc or NMP).

From a series of eight experiments (Table I), it was found that only three combinations of these variables produced derivatives soluble in DMAc. The product of experiment 2 (d.s. = 0.4) was marginally soluble in DMAc requiring heat to dissolve the sample. Both experiments 4 (d.s. = 1.2) and 5 (d.s. = 0.8) produced cellulose tosylates which were readily soluble at room temperature in DMAc. It is apparent from these results that the most important elements for successful tosylation in the DMAc–LiCl solvent are concentration of base and concentration of sulfonyl chloride. Both solvents (DMAc and NMP) and both tertiary amines (TEA and DMAP) produced soluble tosylated derivatives when used in the appropriate combination.

CONCLUSIONS

The side reactions of tosyl chlorides in DMAc–LiCl govern subsequent cellulose derivatization. The oxygen atom of the amide carbonyl is easily esterified by sulfonyl chlorides resulting in a dimethyliminium species which can further react with cellulose. Consideration of the mechanism leading to the cellulose iminium species resulted in the discovery that TEA could redirect the reaction. Nucleophilic addition of TEA to the sulfonated iminium intermediate is believed to regenerate the tosyl chloride and prevent production of the chlorodimethyliminium species. It has been shown that by using TEA, cellulose can be readily tosylated in the DMAc–LiCl system, without interference from side reactions. This product should prove to be valuable for subsequent derivatizations.

Elemental analysis indicates that a minimal amount of chlorine is incorporated into the polymer during tosylation. Although further work is required, initial experimental design efforts indicate that the tosylation reaction may be optimized by using a high concentration of sulfonyl chloride and a high concentration of an effective tertiary amine. It was found that substitution of DMAP for TEA produced soluble tosylated derivatives with no evidence of side reactions. Similar results were found in the substitution of NMP for DMAc.

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REFERENCES

1 E. Klein, and J. Snowden, *Ind. and Eng. Chem.*, 50 (1958) 80–82.
2 J. Masnovi, D. Koholic, R. Berki, and R. Binkley, *J. Am. Chem. Soc.*, 109 (1987) 2851–2853.
3 R. Binkley, and T. Flechtner, in W. Horspool (Ed.), *Synthetic Organic Photochemistry*, Plenum Press, New York, NY, 1984, p. 377.

4 E. Heuser, M. Heath, and W. Shockley, *J. Am. Chem. Soc.*, 72 (1950) 670–674.
5 B. Trask, G. Drake Jr., M. Margavio, *J. Appl. Poly. Sci.*, 33 (1987) 2317–2331.
6 C. L. McCormick and D. K. Lichatowich, *J. Polym. Sci., Polym. Lett. Ed.*, 17 (1979) 479–484.
7 C. L. McCormick and T. S. Shen in R. B. Seymour and G. S. Stahl, (Eds.), *Macromolecular Solutions*, Pergamon Press, New York, 1982, pp. 101–107.
8 C. L. McCormick, D. K. Lichatowich, J. A. Pelezo, and K. W. Anderson, in C. E. Carraher (Ed.), *Modification of Natural Polymers*, ACS Symposium Series No. 121, American Chemical Society, Washington, DC, 1980, pp. 371–380.
9 C. L. McCormick, P. A. Callais, *Polym. Prep.*, 27 (1986) 91–92.
10 C. L. McCormick, P. A. Callais, and B. H. Hutchinson, *Macromolecules*, 18 (1985) 2394.
11 C. L. McCormick, U.S. Pat., 4 278 790, (1981).
12 C. L. McCormick, K. W. Anderson, J. A. Pelezo, and D. K. Lichatowich, in D. H. Lewis, (Ed.), *Controlled Release of Pesticides and Pharmaceuticals*, Plenum, New York, NY, 1981, pp. 147–158.
13 C. L. McCormick and P. Callais, *Polymer*, 28 (1987) 2317–2323.
14 P. Callais, Ph. D. Dissertation, University of Southern Mississippi, Hattiesburg, MS, 1986.
15 W. J. Diamond, *Practical Experiment Design for Engineers and Scientists*, Lifetime Learning Publications, Belmont, CA, 1981.
16 T. Vigo, D. Daigle, and C. Welch, *Polym. Letters*, 10 (1972) 397–406.
17 H. Ulery, *J. Org. Chem.*, 30 (1965) 2464–2465.
18 W. Pawlowski, Ph. D. Dissertation, North Carolina State University, Raleigh, NC, 1986.
19 R. Roberts, *J. Am. Chem. Soc.*, 79 (1957) 1175–1178.
20 D. Horton, A. E. Luetzow, and O. Theander, *Carbohydr. Res.*, 27 (1973) 268–272.