Facile removal of tosyl chloride from tosylates using cellulosic materials, e. g., filter paper

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ABSTRACT

Excess tosyl chloride used in the tosylation of alcohols is quickly and easily removed by reacting it with cellulosic materials, e. g., filter paper, and filtering.

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1. Introduction

Tosylation of hydroxyl-functionalized substrates with tosyl chloride is a popular method of preparing substrates for nucleophilic substitution.¹ There are several reasons that tosylation is preferable to analogous halogenation reactions. Beyond simply avoiding the use of halogenated substrates, tosylation facilitates purification by adding significant molecular weight to the product (155 Daltons). Tosylation is a simple and fast reaction compatible with several types of hydroxyl-functionalized substrates. Traditionally, the reaction is run in solution with a weak base such as pyridine or triethylamine. A popular method in our lab is tosylation using solid potassium carbonate and no solvent as described by Kazemi et al.² Tosyl chloride is usually used in excess compared to the hydroxyl-containing substrate, particularly if the substrate is precious. Thus, the resulting reaction mixtures contain excess tosyl chloride, which must be removed during purification. Most methods of removal of tosyl chloride have some kind of drawback. Tosyl chloride is soluble in hexanes; thus, it can be extracted by washing with hexanes, but this method is limited to products that are immiscible with hexanes. Chromatography is widely used, but it is slow and costly in terms of materials and time. Tosyl chloride can also be removed by its reaction with primary or secondary amines.² In this case the tosyl amides must be removed from solution. Finally tosyl chloride can be removed from solution by its reaction with a second excess hydroxyl source in the presence of a base. The second alcohol is tosylated and then removed from the solution. This last method is simple and straightforward; however, it may require the use of a strong base, such as potassium hydroxide. Thus, it is unsuitable for use with substrates that are sensitive to strong bases. However, this last method of removal was interesting to us as it demonstrated that tosyl chloride could be reacted to completion using a second removable hydroxyl source.

An early paper shows that tosyl chloride will react with cellulose under mild conditions in the presence of a base.³ There are many papers dealing with the tosylation of cellulose in solution. Tosylated cellulose has been used to generate many substituted cellulosic polymers.⁴⁻⁷ Similar to other reactions of cellulose, the tosylation reaction is never entirely complete, and a concern of those working with such derivatives is the degree of substitution that can be achieved.⁸ There are also reactions such as the nitration of cellulose which occur on the undissolved cellulose substrate.^{3,9} Tosylation can also be accomplished on undissolved cellulose, and thus the excess reagent from tosylation reactions can be immobilized and subsequently removed from solution. Therefore, we undertook this work to determine if tosyl chloride could be removed from reaction mixtures by reaction with an insoluble cellulose support and then mechanically removed by filtration. Initial experiments demonstrated that tosyl chloride easily reacts with untreated filter paper under proper conditions. Subsequent experiments determined that multiple sources of cellulose were useful in this method. And finally a series of different hydroxyl-functionalized substrates, both alcohols and phenols, were tosylated and purified using this method to demonstrate its effectiveness and utility.

2. Results & Discussion

2.1. Effect of Stoichiometry of Cellulose and Pyridine

The preliminary experiments for this work hinged upon finding the proper conditions for removal of tosyl chloride from solution using cellulose and a weak base. Pyridine was chosen as the base due to its nearly ubiquitous use in tosylation reactions. The cellulose source was standard qualitative grade laboratory filter paper, which is universally available in the wet chemistry lab. A stock solution (100 mM) of tosyl chloride was made in dichloromethane with anthracene (10 mM) as an internal standard. Aliquots of the stock solution were treated with variable amounts of pyridine and cellulose. The initial experiments were done with

filter paper cut into small pieces. In an effort to hasten the purification reaction, the aliquots were placed in an ultrasonic cleaning bath for one hour. Ultrasonic radiation has been shown to facilitate the interaction of solutions and solid surfaces.¹⁰⁻¹¹ After sonication, the samples were washed with aqueous hydrochloric acid and characterized by ¹H NMR. The residual amount of tosyl chloride was determined by comparing the integrated peak area of its doublet at 7.90 ppm to the area of the anthracene doublet of doublets at 7.99 ppm. The results of these experiments are shown in Tables 1 and 2.

Table 1 shows that the amount of pyridine used in the tosyl chloride removal process is important. It has been shown in previous papers that there should be a large excess of pyridine present during tosylation reactions. Here we show that more than 5 and preferably 10 equivalents of pyridine, compared to tosyl chloride, are required for the complete reaction. In Table 2 an excess of pyridine was used and the amount of cellulose was varied. In all of the solutions, tosyl chloride was essentially completely removed. The cellulose polymer chain, comprised of anhydroglucose units, contains three hydroxyl moieties per repeat unit: a single primary, which is more reactive, and two secondary moieties that are also reactive under these conditions. The results of Table 2 show that with a proper excess of pyridine present, as little as 320 grams (two moles) of cellulose per mole of tosyl chloride (191 g) will essentially completely remove the latter from solution. Figure 1 shows stacked ¹H NMR spectra from before and after the reaction with pyridine and cellulose.

Table 1. Effect of pyridine concentration on reaction of TsCl with filter paper for one hour under sonication.

Equiv. Filter Paper ^a	Equiv. ^a Pyridine	% Residual TsCl
13	2.2	41
13	4.5	4.3
13	9	0.16
13	13	0.16

^aRelative to TsCl. Initial concentrations of TsCl and anthracene: 100 and 10.0 mM in CH₂Cl₂, respectively.

Table 2. Effect of amount of filter paper on residual TsCl after one hour of sonication.

Equiv. Filter Paper ^a	Equiv. ^a Pyridine	% Residual TsCl
2	21	0.19
5.2	21	0.12
10	21	0.16
21	21	0.12

^aRelative to TsCl. Initial concentrations of TsCl and anthracene: 100 and 10.0 mM in CH₂Cl₂, respectively.

Table 3. Effect of cellulose type on removal of TsCl after eight hours of shaking in CH₂Cl₂.

Source (2 equiv. ^a)	Equiv. ^a Pyridine	% Residual TsCl
Filter paper	2.2	63
Cellulose powder	2.2	70
Starch	2.2	59
Cotton	2.2	96

^aRelative to TsCl. Initial concentrations of TsCl and anthracene: 100 and 10.0 mM, respectively.

Figure 1. Partial 500 MHz ¹H NMR spectra (CDCl₃): top) a 1:10 molar mixture of anthracene and tosyl chloride and bottom) the mixture after sonication with pyridine and filter paper, showing the nearly complete removal of tosyl chloride from anthracene.

2.2. Effect of the nature of cellulose

In a second set of experiments, different types of cellulose were tested to optimize the purification method. In this study, only two equivalents of pyridine were used so that the relative amounts of tosyl chloride removed from solution could more easily be determined. Four different cellulosic materials were tested: filter paper, semi-crystalline cellulose powder, cotton and starch. Solutions were shaken with the cellulosic material for eight hours, and then washed with aqueous hydrochloric acid before being characterized by ¹H NMR. The results of these experiments are given in Table 3. The efficiencies were: starch > filter paper > powder >> cotton. We initially predicted that the cellulose powder would give the best results, but this was not the case, probably due to its semi-crystalline nature. With nearly no change in the tosyl chloride concentration after purification with cotton fibers this material is not suitable for this purpose, probably due to its high level of crystallinity. The low cost of starch and filter paper makes them ideal for this application. However, starch tends to form a gel like substance and stick to glassware during filtering.

2.3. Application to tosylation reactions

Finally, a series of tosylation reactions were run, and the resulting reaction mixtures were purified using the sonication method. Both primary and secondary alcohols were used, as well as phenols. The tosylation employed grinding the alcohol or phenol with 1.5 equivalents of tosyl chloride in the presence of potassium carbonate. For secondary alcohols, potassium hydroxide was also added. This method of Kazemi et al.² is fast and efficient; we found that the use of a hot mortar and pestle caused the reaction to proceed nicely. After tosylation the reaction mixtures were treated with pyridine and filter paper, and then sonicated for one hour. After aqueous acidic workup, the compounds were characterized by ¹H NMR to determine their purity.

Additionally all tosylations were done in a solution of dichloromethane with an excess of pyridine. This allowed the simple addition of filter paper and sonication to precede the aqueous workup steps and streamline the process. This method is also more widely applicable than the grinding method as it does not depend on the melting of a mixture of alcohol and

tosylchloride. The yields by the two methods were very similar. Table 4 contains the results from the solution method.

Table 4. Yields of solution preparation of tosylates purified by the filter paper method.

Reactant	Product	% Yield	TsCl in NMR?
CH ₃ O(CH ₂ CH ₂ O) ₃ H	CH ₃ O(CH ₂ CH ₂ O) ₃ Ts	89	No
CH ₃ (C ₂ H ₅)CHOH	CH ₃ (C ₂ H ₅)CHOTs	87	No
C ₆ H ₅ OH	C ₆ H ₅ OTs	90	No
<i>p</i> -CH ₃ OC ₆ H ₄ OH	<i>p</i> -CH ₃ OC ₆ H ₄ OTs	85	No
<i>p</i> -CH ₃ OOCC ₆ H ₄ OH	<i>p</i> -CH ₃ OOCC ₆ H ₄ OTs	86	No

3. Conclusions

Treatment of tosylation reaction mixtures with pyridine and cellulose, in the form of filter paper, is a gentle, efficient and economical method for the removal of excess tosyl chloride. The method can be accelerated by the use of sonication.

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6. References and notes

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Graphical Abstract

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