Tosylation of *N*-Phthaloyl-Chitosan without Drying of Solvents and Purging of Water Vapor

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ABSTRACT

Tosylation of N-phthaloyl-chitosan, without pretreatment of solvent drying and without treatment of water vapor purging during the reaction has been studied. N-phthaloyl-chitosan was tosylated using excess tosyl chloride in dimethyl acetamide/LiCl as solvent and triethyl amine as catalyst at temperature < 10°C for 12 h. As comparison, the tosylation reaction was also performed using phthaloyl-chitosan (protection of chitosan by phthaloyl group was not chemoselective at amine groups only) as a raw material. The solvents were not dried prior to use and all subsequence reactions were not performed under nitrogen atmosphere. The result showed that by using phthaloyl-chitosan as a raw material, there is no product of tosylation can be isolated. The FTIR spectrum showed that 6-O-tosyl-N-phthaloyl-chitosan could be formed using CPNPC as raw material. It indicated that the success of tosylation can be influenced by selectivity of phthaloyl group protection on chitosan. These results showed that a tosylated-chitosan can also be prepared without pretreatment of solvent drying and treatment of water vapor purging during the reaction.

Keywords: tosyl, tosylation, phthaloyl, phthaloylation, chitosan.

INTRODUCTION

Cellulose and chitin as biopolymers are the most abundant organic compounds in Nature and estimated to be at levels approaching 1011 tons annually. Chitin has been a major structural component of animal exoskeleton since the Cambrian Period, more than 550 million years ago. The total amount of chitin harvestable without imbalancing the marine ecosystem is estimated to be 1.5.108 kg/year, mostly from the shells of crustaceans such as crab, shrimp and krill. Chitin is structurally similar to cellulose, but it is an amino polysaccharide having acetamide groups at the C-2 positions instead of hydroxyl groups. In addition to its unique polysaccharide architecture, the presence of a little amino groups (5-15%) in chitin is highly advantageous for providing distinctive biological functions and for conducting modification reactions. Chitosan is the *N*-deacetylated derivative of chitin. Actually, the names chitin and chitosan correspond to a family of polymers varying in the acetyl content. Therefore, the degree of acetylation (DA) determines whether the biopolymer is chitin or chitosan. Chitosan is the term used for the considerably deacetylated chitin that is soluble in dilute acetic acid (degree of deacetylation, DD 70%) (Zohuriaan-Mehr, 2005). Chitin and chitosan thus expected to have much higher potential than cellulose in many fields. It is a specialty biopolymer having specific properties including biodegradability, biocompatibility, and bioactivity, and it is therefore interesting not only as an abundant resource but also as a novel type of functional material (Kurita, 2001).

In spite of potential applications of chitin and chitosan, it is necessary to establish efficient appropriate modifications to explore fully the high potential of these biomacromolecules. Chemical modifications of chitin are generally difficult owing to the lack of solubility, and the reactions under heterogeneous conditions are accompanied by various problems such as the poor extent of reaction, difficulty in selective substitution, structural ambiguity of the products, and partial degradation due to severe reaction conditions.

Therefore, with regard to developing advanced functions, much attention had been paid to modification of chitosan rather than chitin (Zohuriaan-Mehr, 2005).

In order to prepare derivatives with well-defined structures and to prepare advanced functional material from chitosan, it is crucial to manipulate reactions in a well-controlled manner. Since the *p*-toluenesulfonyl (tosyl) group is bulky and the ester (tosylate) is highly reactive, it is another candidate for a substituent to prepare a soluble precursor that would enable controlled modification in solution (Kurita, 2001).

As the tosyl group is a good leaving group, many reports about tosyl-chitin and their properties have been reported (Kurita *et al*, 1992, Morita *et al*, 1994, Morita *et al*, 1999; Zou and Khor, 2005; Shimizu et al, 2007; Pourjavadi et al, 2007). There are few reports with chitosan (Nishimura et al, 1990; Jančiauskaitė and Makuška, 2008). Prior to tosylation, free amino groups of chitosan were selectively protected with phthaloyl groups to give a N-protected precursor that is soluble in organic solvent such pyridine, dimethyl acetamide (DMAc), and dimethyl sulfoxide (DMSO). Tosylation reaction was usually performed with excess *p*-toluene sulphonyl chloride (in comparison with chitin or phthaloyl-chitosan).

Although some methods of tosylation of chitin were reported using dried solvents and flowing nitrogen to purge water vapor during reaction (Morita *et al*, 1994, Morita *et al*, 1999, Zou and Khor, 2005), but the others were reported using aqueous sodium hydroxide (Kurita *et al*, 1992, Shimizu et al, 2007; Pourjavadi et al, 2007). However, tosylation of phthaloyl-chitosan were not reported clearly whether performed using dried solvent and flowing nitrogen, or without pretreatment of drying of solvents and/or without treatment of flowing nitrogen to purge of water vapor. Considering that tosylation of chitin can be performed in aqueous sodium hydroxide, it is interesting to try tosylation of protected N-phthaloyl-chitosan using without pretreatment of drying of solvents and without flowing nitrogen to purge of water vapor during reaction process and the result would be reported in this paper.

2. MATERIALS AND METHODS

2.1. Materials

Chitosan was obtained from deacetylated chitin that isolated from shrimp sells. *N*,*N*-dimethyl formamide (DMF), phthalic anhydride, *N*,*N*-dimethyl acetamide (DMAc), lithium chloride, tosyl chloride, and triethyl amine (TEA) were obtained from Merck (Germany). All reagents and solvents were of analytical grade and used without further purification. The preparation of N-phthaloyl-chitosan was performed using excess phthalic anhydride in DMF as solvent according to procedure of Nurmasari *et al* (2011).

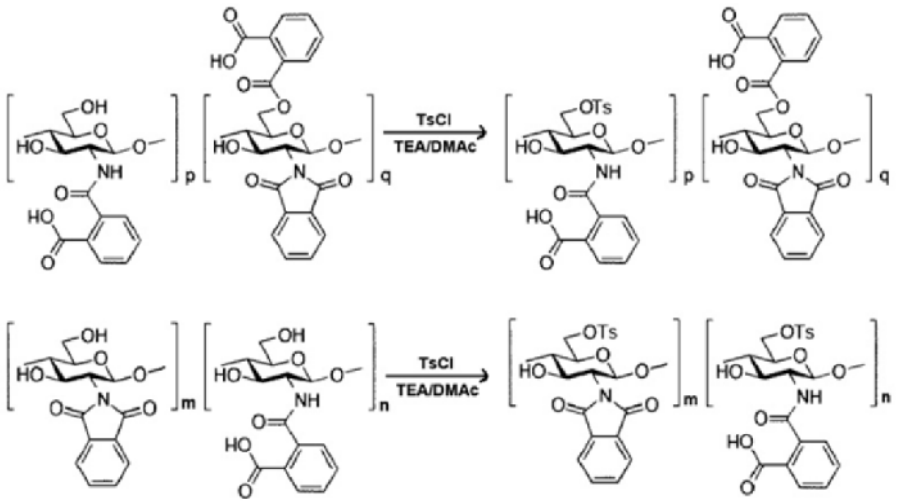
2.2. Preparation of 6-*O*-tosyl-*N*-phthaloyl chitosan

Triethylamine (9.5 ml, 68 mmol) and toluene-4-sulfonyl chloride (3.6 g, 18.8 mmol) dissolved in 20 ml DMAc were gradually added to a cooled to 4–8 °C solution of *N*-phthaloylchitosan (0.5 g, 1.88 mmol) in DMAc/LiCl (50 ml), and the mixture was stirred at 8 °C for 12 h. The precipitate obtained by pouring the solution into ice water was collected by filtration, washed with chloroform, and dried to give the product. As comparison, the tosylation reaction was also carried out in the same way but with phthaloyl-chitosan (protection of chitosan by phthaloyl group was not chemoselective) as a raw material. The product was characterized by recording the FTIR spectrum on a Shimadzu FTIR (IRPrestige-21).

3. RESULTS AND DISCUSSION

The higher reactivity of amino groups present in the main backbone of chitosan requires protection to limit their participation in reactions under tosylation of chitosan. This was done by the use of phthalic anhydride in non-dried DMF (Scheme 1) according to the procedure reported elsewhere (Nurmasari et al, 2011). Introduction of bulky phthaloyl groups prevents formation of intra- and intermolecular hydrogen bonds and consequently improves the solubility of chitosan in organic solvents such as DMF and DMAc/LiCl. Solubilization of *N*-phthaloyl chitosan in DMAc/LiCl is of the last importance for the further derivatization of chitosan in homogeneous conditions. Besides, phthaloyl groups could be removed easily regenerating free amino groups in the derivatized chitosan.

Interestingly, there is no product of tosylation can be isolated if phthaloyl-chitosan (protection of chitosan by phthaloyl group was not chemoselective) was used as a raw material. It could be occurred probably because partial O-phthaloylation of chitosan was at C-6 position. As known, a bulky tosyl groups preferentially react at the least hindered C-6 position of chitosan (Scheme 1). Although some hydroxyl groups at C-6 position were free (not phthaloylated) and could be tosylated, the degree of substitution would be relatively low. Kurita et al (1992) have shown that the resulting tosyl-chitin with a substitution degree less than 0.3 was highly hydrophilic and partially soluble in water. However, the product with a substitution degree above 0.4 become hydrophobic and was soluble in common polar organic solvents such as DMAc. These phenomenon were observed on the resulting tosyl-phthaloyl-chitosan that formed a suspended colloid at bottom part after pouring in ice water, but it could not be isolated by filtration or centrifugation. On the other hand, product of tosylation of N-phthaloyl-chitosan formed a precipitate that can be isolated easily by filtration.



Scheme 1

Formation of 6-*O*-tosyl-*N*-phthaloyl chitosan was proved by FTIR spectra. The IR spectrum of 6-*O*-tosyl-*N*-phthaloyl chitosan showed a characteristic absorption at 1188 cm^{-1} due to tosyl groups (SO_2), absorption at 818 cm^{-1} is characteristic of C-O-S, and 1643 cm^{-1} is typical of peak of aromatic C=C arising from the tosyl group (Fig. 1, bottom). Absorption at 1713 and 1774 cm^{-1} are characteristic of carbonyl in phthalimide and absorption at about 700 cm^{-1} is characteristic of aromatic arising from phthaloyl group. The bands at 1389 cm^{-1} can be attributed to $-CH_2$ bending modes.

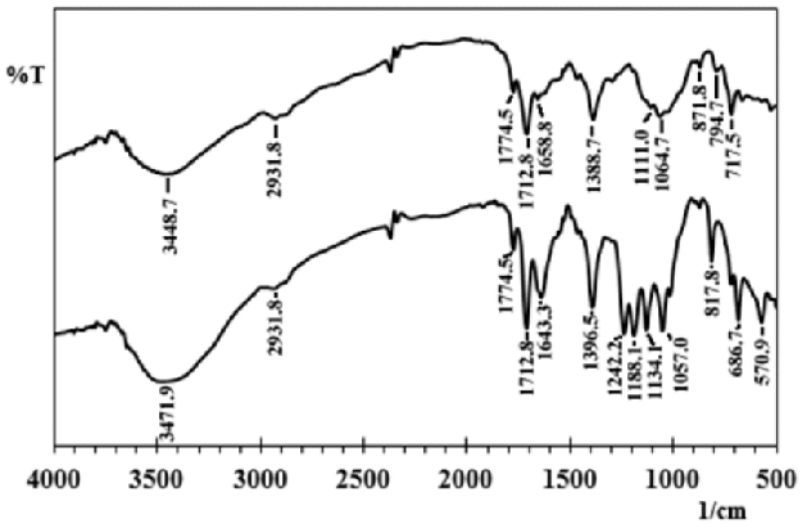


Fig. 1. FTIR spectra of N-phthaloyl-chitosan before (top) and after (bottom) were tosylated. Tosylation was carried out without pretreatment of drying of solvent and without purging of water vapor during reaction process.

The (*p*-tolylsulfonyl)oxy group is one of the most effective leaving groups widely used in carbohydrate chemistry. Since primary hydroxyl groups are more reactive than secondary ones, the regioselective reaction is expected and proved in many cases. Treatment of *N*-phthaloyl chitosan with a 10-fold excess of tosyl chloride and triethylamine in DMAc afforded 6-*O*-tosyl-*N*-phthaloyl chitosan with a very high degree of tosylation. It was proved that primary hydroxyl groups of glucosamine unit could be completely changed to tosyl groups. The use of triethylamine in the tosylation of chitosan was essential for the neutralisation of hydrogen chloride generated during tosylation (Jančiauskaitė and Makuška, 2008).

CONCLUSIONS

Activated chitosan, 6-*O*-tosyl-*N*-phthaloyl-chitosan, could be prepared successfully in one-step using N-phthaloyl-chitosan as raw material, DMAc/LiCl as a solvent, and TEA as catalyst without pretreatment of drying of solvents and without flowing nitrogen to purge of water vapor during reaction process. The simple procedure established here enables facile preparation of 6-*O*-tosyl-*N*-phthaloyl-chitosan, a convenient precursor for the construction of sophisticated molecular architectures based on the specialty biopolymer chitosan.

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