

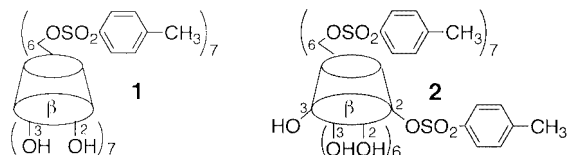
Zinc Bromide-Promoted Tosylation of Alcohols Allows Efficient Temperature-Controlled Primary Hydroxy Sulfonation

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The combination of zinc bromide with tosyl chloride promoted sulfonation, allowing temperature-controlled regioselective sulfonation of carbohydrates which possess both primary and secondary hydroxy groups.

A sulfonate ester is one of the most useful intermediates in organic chemistry and sulfonation of alcohols by use of tosyl chloride is one of the most prevalent reactions. It is possible to selectively tosylate primary over secondary alcohols in pyridine at 0 °C.¹ It is also possible to tosylate nonprotected hydroxy functionalities regioselectively by use of organotin compounds.² However, application of these methods to relatively large molecules possessing a number of primary and secondary hydroxy groups is not always straightforward, as discrimination of the hydroxy groups is difficult. In the case of the preparation of hepta-6-*O*-sulfonated β -cyclodextrin **1** which is considered a suitable intermediate for hepta-6-functionalized derivatives, a significant amount of the 2-*O*-sulfonated derivative **2** (1:2 = 5:3 molar ratio) was also produced.³ In the synthetic study to improve the yield of **1**, we found a unique role of zinc bromide to promote sulfonation and here we will describe the results.



Steric crowding on the primary side of a cyclodextrin during the later stages of sulfonation to prepare the derivative **1** may enable the reaction of the less reactive secondary hydroxy groups before the completion of 6-*O*-sulfonation. The effect of metal halides as additives was studied because either selective activation or protection of hydroxy groups by coordination of metal ion was expected. The results are shown in Figure 1. Metal ions such as Mg^{2+} and Ca^{2+} suppressed the sulfonation reaction. In contrast, zinc halides facilitated the reaction. Among them $ZnBr_2$ showed the highest acceleration effect,^{4,5} although the ratio of the tosylate **1** and the additionally 2-*O*-sulfonated **2** was the same as that observed on a reaction without the additive. The lack of selectivity suggests that $ZnBr_2$ promotes tosylation on both primary and secondary hydroxy groups. A possible role of $ZnBr_2$ is considered to be coordination to an oxygen atom of the sulfonyl moiety making the halogen a better leaving group. Coordination of $ZnBr_2$ to tosyl chloride is suggested by the fact that the solubility of a mixture of $ZnBr_2$ and tosyl chloride, in a mole ratio of 1:1.5, in pyridine is greater than the metal halide itself. Use of a mixture of

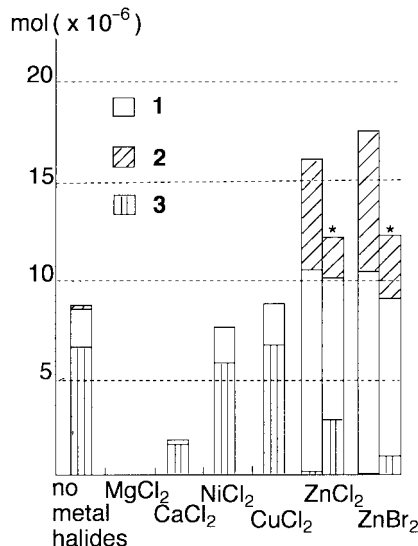
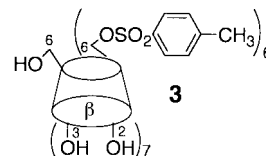


Figure 1. Effect of metal halides on 6-*O*-sulfonation of β -cyclodextrin with tosyl chloride. A mixture of β -cyclodextrin (2.25×10^{-6} mol), TsCl (3.35×10^{-5} mol), and metal halide (2.25×10^{-5} mol) in dry pyridine (1.5 cm³) was reacted at r. t. and the products were analyzed after 90 min (* 30 min) using reverse phase HPLC. The amounts of sulfonates possessing less than six tosyl groups are not shown.



$ZnCl_2$ and KBr in place of $ZnBr_2$ did not give comparable results on sulfonation to those on addition of $ZnBr_2$, suggesting that the greater effect of $ZnBr_2$ may be due to conversion of the sulfonyl chloride to more reactive sulfonyl bromide on the coordination sphere of zinc atom at the first step of the reaction. It is reasonable that zinc bromide might additionally coordinate an oxygen atom of a hydroxy group of cyclodextrin to bring the two reactants close (Figure 2). Dose effect is shown in Figure 3. Addition of $ZnBr_2$ at 10.5 times the concentration

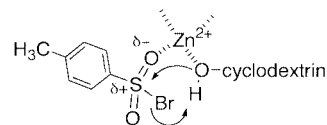


Figure 2. Possible role of $ZnBr_2$ on sulfonation.

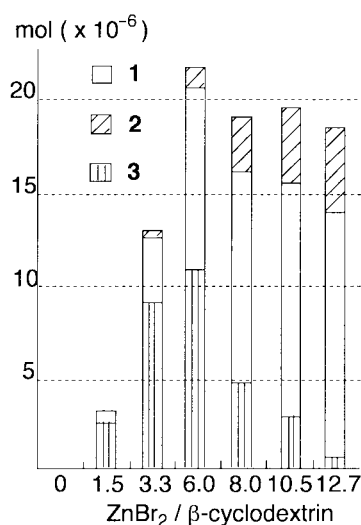


Figure 3. Effect of zinc bromide on 6-*O*-sulfonylation of β -cyclodextrin with tosyl chloride. A mixture of β -cyclodextrin (2.25×10^{-6} mol), TsCl (3.35×10^{-5} mol), and zinc bromide in dry pyridine (1.5 cm^3) was reacted at 0°C and the products were analyzed after 30 min using reverse phase HPLC. The amounts of sulfonates possessing less than six tosyl groups are not shown.

of cyclodextrin (1.5 times the concentration of the glucose residues) reduced the reaction time by a factor of twelve.

While ZnBr_2 promoted the sulfonylation at both primary and secondary hydroxy groups, it was found that low reaction temperature effectively suppressed the undesirable 2-*O*-sulfonylation. On lowering the reaction temperature to below -20°C the yield of the desired product **1** increased to more than 70% in the absence of ZnBr_2 . The HPLC chromatogram was much simpler with fewer peaks. However, the reaction required 25 mole equivalents of tosyl chloride and took more than 30 h to obtain the maximal yield of **1**. Use of ZnBr_2 enabled reaction to be carried out at lower reaction temperature, in a shorter time, and with less sulfonyl chloride, namely at -40°C ,⁶ for 4 h, and in the presence of ZnBr_2 and tosyl chloride, ten and fifteen mole equivalents, respectively, to give the desired product **1** in 84% yield. Through the use of twenty mole equivalents of tosyl chloride at -40°C the tosylate **1** (83%) was obtained within 1 h.

On tosylation of methyl α -D-glucoside in pyridine, similar effects of ZnBr_2 were demonstrated. The sulfonylation at r.t. in the absence of ZnBr_2 using ten mole equivalents of tosyl chloride took 30 min to consume the glucoside affording mono- and ditosylate (57 and 43%, respectively). Reaction at -20°C using

both ZnBr_2 and tosyl chloride (two and three mole equivalents, respectively) converted the glucoside in 20 min to the mono- and disulfonates in the yield of 64 and 36 %, respectively. The latter reaction needed less tosyl chloride to consume the glucoside. Taking into account differences between the two conditions above in reaction temperature, amount of sulfonyl chloride, and reaction time, addition of ZnBr_2 increased the efficiency of conversion of the glucoside to sulfonates by a factor of eighty. Lowering the reaction temperature from r.t. to -20°C resulted in preferential sulfonylation on primary hydroxy group, as observed in the case of cyclodextrin, although the effect of temperature was smaller than that of cyclodextrin. It is probable that macrocyclic structure of the cyclodextrin makes its secondary hydroxy groups more crowded than that of the glucoside, leading to a greater difference in reactivity between the primary and secondary hydroxy groups.

In conclusion, zinc bromide promoted tosylation such that less sulfonyl chloride was required. Further, the additive enabled low temperature reactions, which gave selective reaction on primary hydroxy groups, to be carried out efficiently. Although the use of zinc halides as Lewis acids is known, this is the first example of the influence of zinc bromide on the reactivity of sulfonyl chloride with hydroxy groups, to the best of our knowledge, in the literature. The results suggest the possibility of very rapid ("instant") sulfonylation and the use of much lower temperatures for sulfonylation in an effort to increase specificity. Further studies including the application of this process to other alcohols including carbohydrates and cyclitols such as mannitol, are underway in our laboratory.

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References and Notes

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