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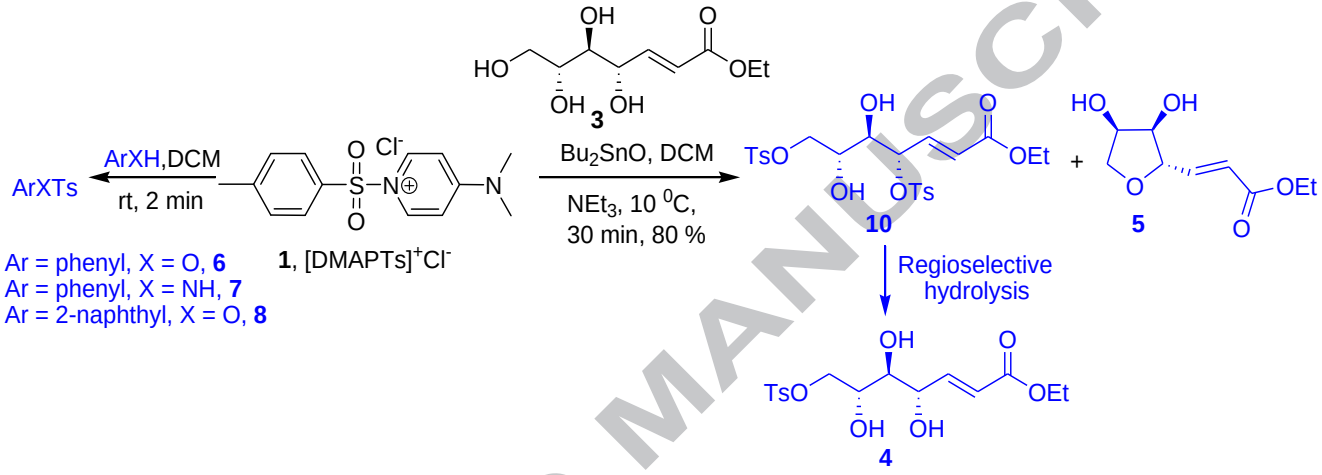

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Unprecedented Regioselective Tosylation Studies of 2-ene 4,5,6,7-polyol Derived from D-Ribose

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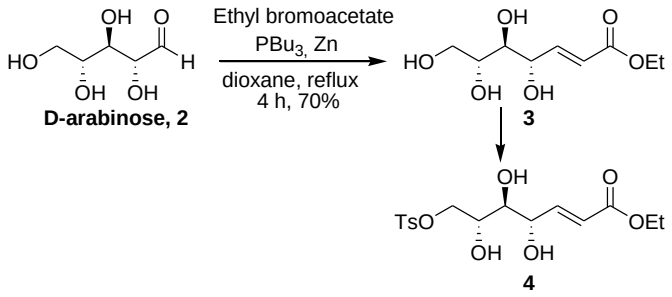
ABSTRACT

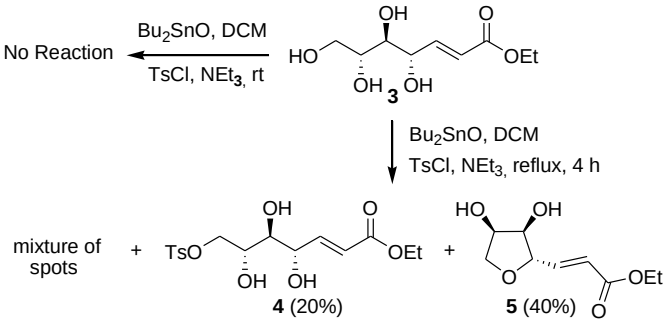
Employing $[DMAPTs]^+Cl^-$ a new facile unprecedented regioselective tosylation procedure for 2-ene 4,5,6,7-polyol derived from D-ribose involving chemoselective ditosylation and regioselective allylic tosyl hydrolysis upon work up with sat. NaCl (brine) solution in a single operation by minimizing the side products obtained under classical regioselective tosylation. The same reagent was also employed for rapid quantitative base free tosylation of aniline, phenol and 2-naphthol. A tentative mechanism for the afore said regioselective tosylation was also proposed.

1. Introduction

Regioselective monoderivatization, in particular tosylation, of polyols has been a challenging task in total synthesis and simultaneously provided ample opportunities for organic chemists to develop new methodologies.[1-7] For selective primary alcohol functionalization of 1,2-glycols, though many methods are available with few exceptions, the dibutyl stannylene derivative of vicinal diol is the method of choice as evident by its superior regio and stereoselective mono functionalization over other existing methods.[8-9] For the regioselective mono functionalization of triols, tetrols and other polyols limited literature reports are available.[10-12] Nkamble *et al*. studied the regioselective tosylation of 1,2,4-triols using dibutyl stannylene acetals and concluded that the regioselectivity depends on the relative stereochemistry of 2,4-hydroxy moieties of 1,2,4-triol.[13] Though both 2,4-*syn* and 2,4-*anti* diastereomers undergo selective primary tosylation, the 2,4-*syn* isomer undergoes faster intramolecular S_N2 displacement through 5-*exo* tet cyclization relative to the 2,4-*anti* isomer through the intermediary of more stable six membered stannylene complex to produce furan derivatives.



Scheme 1: Regioselective tosylation of ene polyol **3**



Scheme 2: Tosylation studies on **2**

2. Results and Discussion

As a part of our ongoing DST project, the transformation **3** to **4** shown in scheme 1 is a prerequisite for the pivotal conversion into the main scaffold. For the afore said purpose, initially compound **3** was prepared by two carbon homologation of D-ribose, **2** which was treated successively with ethyl bromoacetate, zinc, and tri n-butyl phosphine in dioxane and refluxing the reaction mixture for 4 h to produce ene polyol **3** in 70% yield.[14] Then to check the regioselective tosylation on **3**, we adopted standard selective tosylation procedure by employing dibutyl stannylene acetals for 1,2-diols, but it was a failure as the

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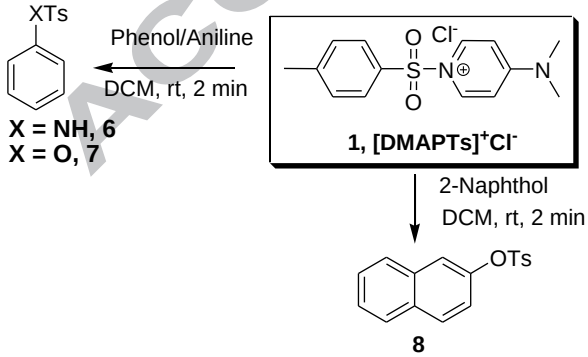
Table 1: Various reaction conditions for tosylation of **3** with TsCl

run	Tin comp.[a]	Base[b]	Solvent	Cat.	Temp.	% of 4[c]
1	Bu_2SnO	NEt_3	DCM	-	rt	No
2	Bu_2SnO	NEt_3	DCM	-	reflux, 4 h	20
3	**Bu_2SnO**	**NEt_3**	**DCM**	**DMAP**	**reflux, 4 h**	**30**
4	Bu_2SnCl_2	NEt_3	DCM	-	reflux, 4 h	20
5	Bu_2SnCl_2	NEt_3	DCM	DMAP	reflux, 4 h	25
6	Bu_2SnO	K_2CO_3	DCM	-	reflux, 3.5 h	12
7	Bu_2SnO	$NaHCO_3$	THF	-	50 ^{0}C, 5 h	15
8	Bu_2SnO	K_2CO_3	THF	-	50 ^{0}C, 3.5 h	17
9	Bu_2SnCl_2	K_2CO_3	THF	-	50 ^{0}C, 3.5 h	15
10	Bu_2SnCl_2	$NaHCO_3$	THF	-	50 ^{0}C, 4 h	10
11	Bu_2SnO	Na_2CO_3	THF	-	50 ^{0}C, 3.5 h	17
12	Bu_2SnCl_2	Na_2CO_3	THF	-	50 ^{0}C, 4 h	15

a = 5 mol% of Bu_2SnO was used
b = 1.1 eq. of base was used
c = Refers to isolated yield of the product

reaction was very sluggish at rt. Later we tried the procedure developed by Nkamble *et al.*[13] for the sulfonylation of 1,2,4-triols but the results were quite disappointing as only 20% of the desired product and the cyclized furan product **5** (40%) were formed along with many unidentifiable spots (Scheme 2). Continuing the reaction for longer times furan product **5** was formed as the major product. The yield of the desired product was improved about 10% by the addition of catalytic amount of DMAP (entry 3 in table 1). Changing different tin reagents and different bases in various solvents at altered temperatures led more or less to the same results as shown in table 1.

Henceforth we have no option but to develop a new methodology for the regioselective tosylation of ene polyol **3** as, to the best of our knowledge, mono functionalization study, in particular, tosylation, on 1,2,3,4-tetrols was unprecedented. In this letter, we wish to report our results of regioselective tosylation studies on ene polyol **3** with reagent **1**.



Scheme 3: Base Free tosylation reactions of $[DMAPTs]^+Cl^-$, **1**

In this direction our journey began with the identification of a suitable tosylating reagent for the afore said purpose and we identified, based on the mechanism of the DMAP catalyzed tosylation, reagent **$[DMAPTs]^+Cl^-$**, **1** (Scheme 3), could be useful for selective transformation of **3** to **4.**

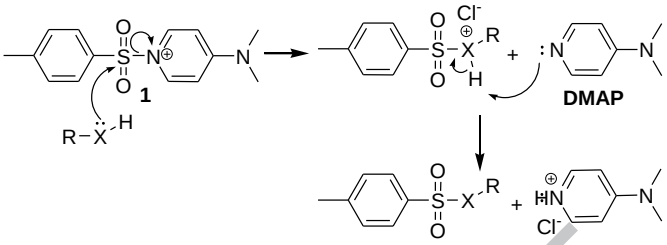
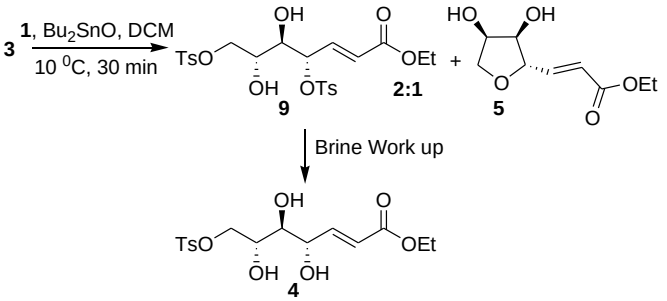


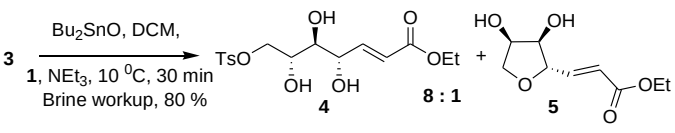
Figure 1: Proposed mechanism of tosylation by reagent **1**

Previously this reagent was used for the tosylation of tyrosine residue in proteins by Wakselman *et al.*[15] and it was also used for the preparation of some aromatic sulfonyl derivatives[16] and it was directly never used for tosylation of either alcohols or for amines. surprisingly, when 1.1 eq. of reagent **1** was treated with aniline in DCM at rt, the reaction was completed within 2 min and N-tosyl aniline **6** was obtained in quantitative yield. Probably this is the fastest tosylation reaction condition of all[17-19] under essentially neutral reaction conditions (no additional base is required as in situ generated DMAP is sufficient to scavenge the HCl, figure 1). The Spectral data of **6** is in total match with the reported data.[20] Later phenol and β-naphthol were treated with 1.1 eq. of **1** in DCM within 2 min both the reactions were completed and the products **7** and **8** were produced quantitatively. These reactions clearly exemplified the rapid tosylating capabilities of reagent **1** which inspired us for further tosylation reactions. Recovery of 80-90% DMAP after workup upon treatment of aqueous phase with base is one of the important advantages of this reagent. Having confirmed that the reagent **1** is a good base free tosylating reagent, next we wished for the tosylation of ene polyol **3** with reagent **1**.



Scheme 4: Base free tosylation of ene polyol **3** with $[DMAPTs]^+Cl^-$, **1**

In this direction when the ene polyol **3** was treated with 1.1 eq. of **1** in DCM at 10 ^{0}C, the results were quite promising as this reaction furnished a major product **9** which was characterized by its ^{1}H NMR based on the presence of a deshielded allylic proton at δ 5.3 as ddd (J = 7.0, 2.7, 1.1 Hz) and it was not matching with the spot obtained under normal tosylation condition, along with minor furan product **5** in 2:1 ratio along with recovery of starting material **3** (Scheme 4). Gratifyingly, to our surprise, the product **9**, on work up with brine solution, was converted into the desired product **4**, by regioselective hydrolysis of allylic tosyl group whose ^{1}H NMR clearly indicated the absence of a peak at δ 5.3 and presence of two deshielded distinct diastereotopic protons due to primary tosyl methylene protons at 4.13 (ddd, J = 10.7, 5.3, 0.7 Hz, 1H) and 4.20 (ddd, J = 10.7, 4.3, 0.7 Hz, 1H).



Scheme 5: Optimized reaction conditions for regioselective tosylation.

Table 2: Optimization of tosylation conditions with reagent **1**

run	Tin catalyst[a]	Base[b]	Solvent	% of 4[c]
1	**Bu_2SnO**	**NEt_3**	**DCM**	**72**
2	Bu_2SnCl_2	NEt_3	DCM	60
3	Bu_2SnO	K_2CO_3	THF	45
4	Bu_2SnO	K_2CO_3	dioxane	45
5	Bu_2SnCl_2	K_2CO_3	THF	40
6	Bu_2SnO	DIPEA	DCM	45
7	Bu_2SnO	$NaHCO_3$	THF	50
8	Bu_2SnCl_2	$NaHCO_3$	THF	40
9	Bu_2SnO	K_2CO_3	DMF	45

a = 5 mol% of Bu_2SnO was employed
b = 1.1 eq. of base was used
c = refers to Isolated yield of primary tosyl compound **4**

The hydrolysis of allylic tosyl group was also affected under acidic conditions. We could stop the hydrolysis, at least for a certain period of time, when we do work up with normal water to get the ditosyl product **9**. These results propelled us for further fine tuning of reaction conditions. Having the desired product, with moderate selectivity and yield, in our hand we further optimized the reaction conditions (table 2) for better selectivity and yield. we thought, based on the literature reports, that addition of a base could enhance not only the rate of the reaction but also the product selectivity.[7]

In this direction the reagent **1** was treated with various tin catalysts with different bases in a range of solvents and the best results were obtained when ene polyol **3** was treated with 2.1 eq. of **1** and 1.1 eq. of NEt_3 in DCM at 10 ^{0}C for 30 min to furnish the product **4**, after brine work up, in 72% yield (entry 1 in table 2) along with the minor furan derivative **5** (9%) in 8:1 ratio. This clearly demonstrates the utility of NEt_3 in maximum product turnover with minimal formation of furan product (Scheme 5). All other reaction conditions employing different tin catalysts and bases in various solvents produced lesser yields of the desired product **4**. we propose a tentative mechanism as depicted in figure **2** (though the exact mechanism, at this juncture, is not known for which further studies with other ene polyols are progress in our lab) in which treatment of ene polyol **3** with Bu_2SnO in DCM would selectively produce dibutyl stannylene acetal **3a** of terminal diol of 2-ene 4,5,6,7-polyol which underwent regioselective tosylation at primary hydroxyl to produce primary tosyl derivative **3b** still as a tin complex. This tin complex **3b** would be transformed into stannylene derivative **3c** through intramolecular 6-*exo* tet cyclization at the tin. There are two competing pathways for complex **3c** for further reaction. In a major pathway **3c** undergo regioselective allylic hydroxyl tosylation to furnish ditosyl derivative **9**. In a minor pathway **3c** undergo intramolecular S_N2 displacement of primary tosyl group

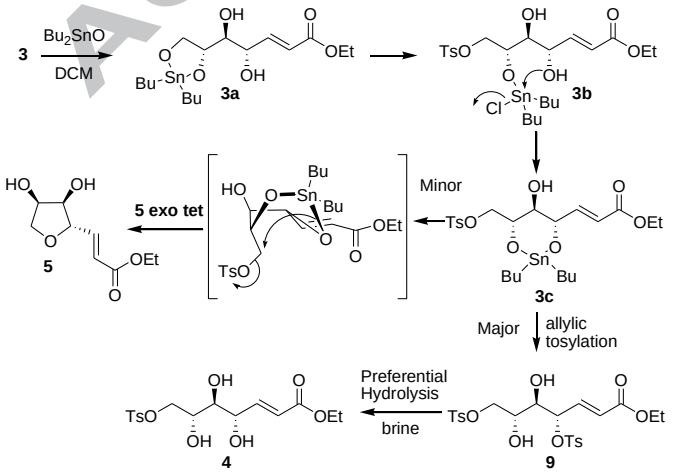


Figure 2: Rationale for the tosylation of **3** with the reagent **1.**

through 5-*exo* tet cyclization involving high energetic boat conformation **3e**. The results obtained were in consistent with the proposed mechanism. Further mechanistic investigations on ene polyols prepared from other pentoses are in progress in our lab.

Conclusions:

In conclusion, for the first time the reagent $[DMAPTs]^+Cl^-$, **1** was successfully used for rapid quantitative tosylation of aniline, phenol and 2-naphthol under essentially neutral (**base free**) reaction conditions. This method would be more useful for the tosylation of complex natural products under neutral reaction conditions. **1** was also employed for the unprecedented regioselective tosylation of ene polyol **3** derived from D-ribose, involving chemoselective difunctionalization followed by regioselective allylic tosyl hydrolysis. The main advantages of our strategy lies in minimization of furan product **5** (which was the major product under the normal tosylation conditions) and recovery of DMAP (80-90%) upon base work up. Further mechanistic investigations were actively progressing in our lab.

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Highlights

- Base free tosylation of phenols/aniline was developed using $[DMAPTs]^{+}Cl^{-}$
- **Intramolecular tin-chelates** favors Monotosylation of ene-tetrol via chemoselective ditosylation
- Preferential allylic tosyl hydrolysis by brine workup was established
- Transformations of tin-chelates is essential for chemoselective ditosylation