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An efficient practical tosylation of phenols, amines, and alcohols employing mild reagent [DMAPTs]$^{+}$Cl^{-}

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ABSTRACT

Efficient exploration of [DMAPTs]$^{+}$Cl^{-} for base free and chromatography free preparation of sulfonate esters from phenols and alcohols and sulfonamides from amines was achieved in excellent yields. Majority of the phenols irrespective of their substituents electronic nature underwent tosylation nearly at same reaction rate with an average yield of 95%. For amines, ring activating substituents favors rapid sulfonylation while the ring deactivating substituents relatively lowers the rate of tosylation. Furthermore the reagent was employed for Chemoselective sulfonylation as well as solvent free tosylation of phenols and amines.

Introduction

Functional group interconversion (FGI) in Organic Chemistry plays a decisive role for the synthesis of many natural products.[1] One among them is interconversion of phenols and alcohols into respective sulfonate esters and amines into sulfonamides. High biological profile of sulfonamides (privileged structures), such as anti inflammatory, anti cancer, anti viral, HIV protease inhibitors, anticonvulsant, etc.[2,3] evolved them into marketed drugs such as amprenavir[4] as HIV protease inhibitor, sildenafil[5] as phosphodiesterase inhibitor, bosentan[6] as anti hypertensive drug, etc. Like sulfonamides, sulfonic esters also display important pharmacological activities.[7] Besides that, though synthetically these tosyl derivatives serve in different ways, masking of many functional groups[8] and as alkylating agents under SN reactions[9] are a couple of fundamental applications in organic chemistry therefore synthesis of sulfonamides and sulfonic esters have attracted many synthetic chemists across the globe.[10] The classical tosylation procedure,[11] which involves treatment of a substrate with TsCl and Py/NEt_3 in DCM, has some setbacks vowing to its longer reaction times which leads to undesired reactions such as disulfonamide formation and under some circumstances even functional group compatibility.[12] Many methods have been progressed to address these problems. Notably, Tanabe et al. developed several tosylation pyridine free protocols either by employing organic base and its hydrochloride salt as base or by using substituted ethylene diamines as bases for high reaction rates with economic process by minimizing side products.[13] Metal catalyzed tosylation using various metal catalysts, i.e., $Yb(OTf)_3$, Cobalt(II) salts, Bismuth(III) halides, and Ag_2O, etc. solved the problem of base sensitivity but suffered from relatively vigorous reaction conditions with long reaction times leading to lesser yields.[14] Few green protocols by employing water as solvent and certain solvent free tosylations procedures were also developed but has gained little attention as maintenance of pH of the medium and preparation of organic bases required for tosylation limits their applications.[15] Almost all of the aforesaid methodologies require either a base/catalyst to promote tosylation or chromatographic purification to isolate the pure product. Henceforth, an environmentally benign protocol is still needed which overcome both the above mentioned setbacks. Here in we wish to report, in this letter, an eco-friendly tosylation procedure employing [DMAPTs]$^{+}$Cl^{-} as a green reagent which neither uses a base nor requires chromatographic purification for effective tosylation.

Results and discussion

After successful usage of [DMAPTs]$^{+}$Cl^{-}[16] for the regioselective tosylation of ene polyols and for rapid base free quantitative tosylation of aniline, phenol, and 2-naphthol,[17] we inspired for its further exploration on direct tosylation of a diverse class of substrates. In this direction, various phenol derivatives and amines both containing ring activating and deactivating substituents, and alcohols were tested for tosylation with **1**.

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Tosylation of phenols

Gratifyingly, all the compounds were smoothly transformed into sulfonate esters nearly at similar reaction rates with almost quantitative yields (90–98%, Table 1). For example, simple phenols like phenol, **2** 1-naphthol, **3** and 2-naphthol, **4** were tosylated in quantitative yields (Scheme 1). *p*-Cresol, **8** furnished its tosyl derivative **13** in 5 min while *p*-nitro and *o*-nitro phenols **9** and **10** formed their sulfonate esters **14** and **15** with in 8 min and 10 min, respectively (Scheme 2). High reactivity of the hydroxyl groups of resorcinol, **11** leads to bis-sulfonylation, **16** which was best accomplished when the reaction was performed in MeOH instead of DCM which requires longer reaction times due to its meagre solubility.

Further it also affected the tosylation of some natural products like 7-hydroxy 4-methyl coumarin, **18** and Vanillin, **12** within 15 min (Scheme 3). Among the phenols, 8-hydroxy quinoline, **19** was difficult to tosylate as evident by the reaction completion time, which is about 12 h. Nevertheless use of 1.1 equiv of NEt_3 propelled the reaction to complete within 2 min in quantitative yields. These reactions undoubtedly demonstrate the unique base free tosylation ability and functional group compatibility of $[DMAPTs]^+Cl^-$ in comparison to other reported reaction conditions.

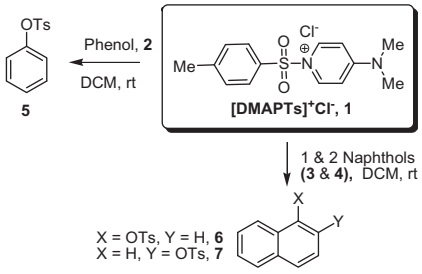
Tosylation of amines

Aniline, **22** on treatment with **1** in DCM furnished *N*-tosyl aniline, **26** in quantitative yield within 2 min. Consequence of electronic effects of ring activating and deactivating substituents were distinctly noticed among substituted anilines.

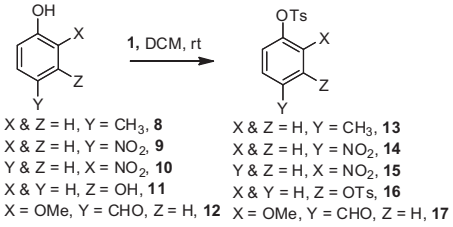
For example, ring activating substituent like Me, **23** the reaction rate was as fast as aniline (Table 2, entry 2). Moderately deactivating substituent like Cl, **24** decreased the rate of tosylation up to 30 min for completion. Refluxing the reaction mixture was necessary when a strong deactivating group like NO_2, **25** is present which took 6 h to form its sulfonamide derivative **29**. Longer reaction times in case of *p*-nitro aniline resulted into the isolation of small quantity of ditosyl derivative **30** (Scheme 4). Reagent **1** transforms even aliphatic amines like benzyl amine, **31** into *N*-benzyl sulfonamide (Scheme 5), **32** relatively faster (15 min, Table 2, entry 8). Isolation of all the sulfonamides in an average yield of 92% from respective amines further supports the tosylation ability of $[DMAPTs]^+Cl^-$.

Tosylation of alcohols

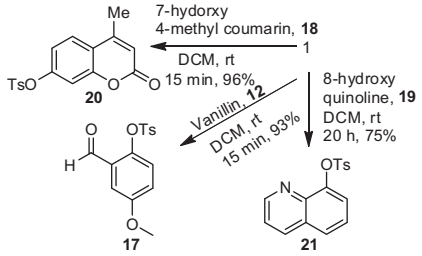
The reactivity of aliphatic alcohols with **1** under base free reaction conditions was slow when compared to phenols and anilines.



Scheme 1. Tosylation of phenol and naphthols with $[DMAPTs]^+Cl^-$.



Scheme 2. Tosylation of phenols with **1**.



Scheme 3. Sulfonylation of important classes of phenols with **1**.

For instance *n*-butyl alcohol **33** and iso-amyl alcohol **35** were converted into corresponding sulfonate esters after 5 h in moderate yields (60%, Scheme 6).

Chemoselective sulfonylation studies

Chemoselective sulfonamide formation, in preference to sulfonate ester formation, was observed in the case of *p*-amino phenol **37**. In IR spectroscopy, presence of a broad peak around 3446 cm^{-1} due to O–H stretch and a single peak around 3249 cm^{-1} corresponding to N–H Stretch and presence of a phenolic OH peak at δ

Table 1
Tosylation of various phenols with reagent **1**

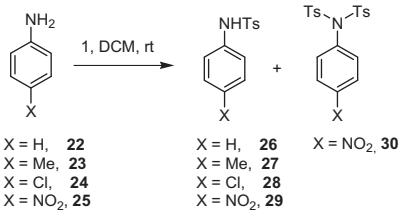
Run	Phenols	Time	Solvent	Yield[b] (%)
1	Phenol	2 min	DCM	98
2	1-Naphthol	2 min	DCM	97
3	2-Naphthol	2 min	DCM	97
4	*p*-Cresol	5 min	DCM	95
5	*o*-Nitro phenol	10 min	DCM	93
6	*p*-Nitro phenol	8 min	DCM	92
7	7-Hydroxy 4-methyl coumarin	15 min	DCM	96
8	8-Hydroxy quinoline	20 h and 2 min	DCM	75 (94[c])
9	Resorcinol	60 min	MeOH	92
10	Vanillin	15 min	DCM	93
11	Vanillyl alcohol	15 min	DCM	90

[a] Reagents and conditions: substrate (1.0 mmol), $[DMAPTs]^+Cl^-$ (1.1 mmol), DCM (5 mL), rt.
[b] Refers to the isolated yield of the product.
[c] 1.1 equiv of NEt_3 in DCM was used.

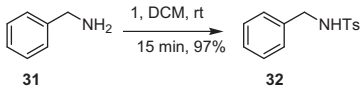
Table 2
Tosylation of various amines with reagent **1**

Run	Amines	Time	Solvent	Yield[b] (%)
1	Aniline	2 min	DCM	98
2	*p*-Toluidine	2 min	DCM	96
3	*p*-Amino phenol	5 min	DCM	93
4	*p*-Chloro aniline	30 min	DCM	95
5	*p*-Nitro aniline	6 h	DCM	87
6	Benzyl amine	15 min	DCM	97

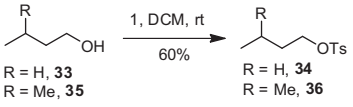
[a] Reagents and conditions: substrate (1.0 mmol), $[DMAPTs]^+Cl^-$ (1.1 mmol), DCM (5 mL), rt.
[b] Refers to the isolated yield of the product.



Scheme 4. Tosylation of substituted anilines with **1**.



Scheme 5. Tosylation of benzyl amine with **1**.



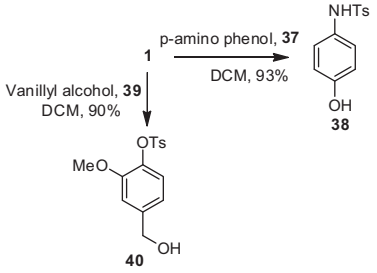
Scheme 6. Tosylation of alcohols with **1**.

9.10 ppm in ^{1}H NMR unambiguously confirmed the structure of **38**. When vanillyl alcohol, **39** was reacted with **1**, sulfonate ester of phenolic hydroxy was preferentially formed over primary benzylic hydroxy group. Efficient chemo selectivity of **1** in comparison to traditional tosylation methodology despite its higher reactivity is one of the attractive features of our methodology (Scheme 7). Intermolecular competitive tosylation studies with **1** clearly revealed the reactivity of various classes of compounds. When 1 mol of **1** was treated with equimolar mixture of benzyl amine and aniline, benzyl amine was preferentially tosylated to the extent of 94% while only 6% aniline was tosylated. Highly selective tosylation (97%) of benzyl amine was observed when equimolar mixture of benzyl amine and phenol were reacted with **1**.

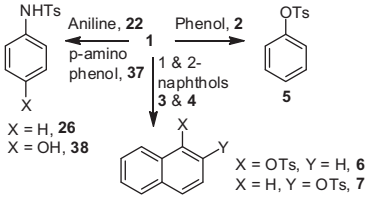
Preferential tosylation of aniline (95%) was achieved when an equimolar mixture of aniline and 2-naphthol were treated with **1**. Further reagent **1** selectively tosylated phenol (98%) when compared to 4-chloro aniline. Aforementioned intermolecular competitive experiments clearly demonstrated the following points. N-tosylation is faster for aliphatic amines compared to anilines owing to its higher nucleophilicity. Among anilines ring activating substituents favor faster tosylation compare to ring deactivating substituents. For structurally similar compounds N-sulfonylation is faster than O-sulfonylation. Phenolic O-tosylation is quite faster than alcoholic O-tosylation.

Solvent free tosylation with 1

Reagent **1** transforms phenols with ring activating groups and ring deactivating groups into corresponding sulfonate esters with comparable reaction rates which hints at substituents insignificant effect on sulfonylation. Above reactions indicated that the general chemo selectivity would be in the order of aliphatic amines > anilines > phenols > alcohols as evident from the time taken to complete. To our fortune, reagent **1** also transformed aniline, *p*-amino phenol, phenol, 1-naphthol, and 2-naphthols (Scheme 8) into corresponding tosyl derivatives under solvent free reaction conditions (Green approach) in very good yields (Table 3). The ^{1}H NMR, ^{13}C NMR, IR, and Mass spectral data of all the compounds are in good agreement with the structure of the products.



Scheme 7. Chemoselective tosylation with **1**.



Scheme 8. Solvent free tosylation of amines and phenols with **1**.

Table 3
Tosylation of various amines with reagent **1**

Run	Amines	Time (min)	Solvent	Yield[b] (%)
1	Aniline	5	Free	95
2	*p*-Amino phenol	8	Free	91
3	Phenol	10	Free	90
4	1-Naphthol	10	Free	87
5	2-Naphthol	10	Free	90

[a] Reagents and conditions: substrate (1.0 mmol), $[DMAPTs]^+Cl^-$ (1.1 mmol), rt.
[b] Refers to the isolated yield of the product.

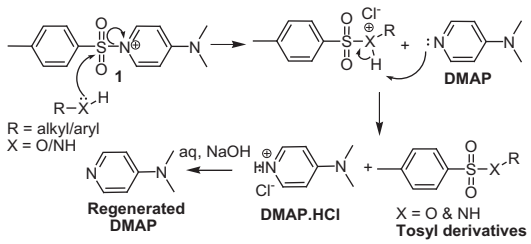


Figure 1. Proposed mechanism for base free tosylation by reagent **1**.

Mechanism of sulfonylation by reagent **1** involves initial nucleophilic substitution at activated sulfur atom followed by abstraction of proton by in situ formed DMAP to produce the tosyl derivatives and DMAP·HCl (Fig. 1). Regeneration of DMAP (95%) upon basification of the aq layer of the reaction mixture further supports the proposed mechanism.

Conclusions

In conclusion, $[DMAPTs]^{+}Cl^{-}$, **1** was successfully used for the first time for base free and chromatography free tosylation of phenols, anilines, amines, and alcohols in an average yield of 92%. Almost all the phenols were converted into their sulfonate esters nearly at same rate while the anilines were not due to distinct electronic factors operating among anilines having ring activating groups in comparison to ring deactivating groups. Therefore this base free tosylation could be more useful for the sulfonylation of base sensitive natural products. Efficient Chemoselective sulfonylation was also achieved. The generality, operational simplicity (direct addition of reagent at rt), recovery of DMAP (95%) upon basification, devoid of chromatographic purification and solvent free sulfonylation of phenols and amines makes this methodology Eco friendly. Further research on tosylation of triols and tetrols derived from carbohydrates and different alcohols including optically active are progressively going on in our lab.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09.010.

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