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IJIEMR Transactions, online available on 25th Feb 2021. Link :http://www.ijiemr.org/downloads.php?vol=Volume-10/ISSUE-02

DOI: 10.48047/IJIEMR/V10/I02/21

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Volume 10, Issue 02, Pages: 106-110

Paper Authors

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Practical synthesis of Sulfonates and Sulfonamides by employing a New Sulphonation Reagent $[DMAPSO_2Ph]^+Cl^-$

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Abstract

N-benzenesulphonyl-4-N,N-dimethylaminopyridinium chloride ($[DMAPSO_2Ph]^+Cl^-$) has been investigated for base-free, catalyst-free, and chromatography-free synthesis of sulfonate esters from phenols and sulfonamides from amines. Regardless of the electronic nature of their substitutes, the majority of phenols and amines or their derivatives underwent benzene sulfonylation at roughly the same rate with an average yield of 95%. Recovery of DMAP and recycling it for reagent preparation is an added advantage of our protocol.

Keywords: ($[DMAPSO_2Ph]^+Cl^-$, Benzenesulphonation, Sulphonamides, Sulphonates

Introduction

Oscar Hinsberg originally described the Hinsberg reactions in 1890.[1-2] The preparation of sulfonamide and sulfonate ester moieties, which serve as the building blocks of significant physiologically active chemicals, is the outcome of sulfonylation of heteroatoms.[3-10] Vast majority of sulfonamides and sulfonates are generally prepared in the presence of a base in an aprotic solvent, or through similar transformations, wherein a sulfonyl/sulfuryl chloride interacts with primary or secondary amines, phenols, or phenol derivatives.[11-13] The synthesis of sulfonamide utilising aryl primary amine and aryl sulfonyl chloride using pyridine as a base at 0 to 25 °C was described by Youn et al [14]. When aniline is considered as a primary amine and benzene sulfonyl chloride or 4-nitrobenzyl sulfonyl chloride is used as a sulfonylation agent, they have obtained in 100% yield.

There is still a need to find an easy and effective way to synthesise novel sulfonamides under favourable circumstances [15,16]. Out of all methods, the preferable way is to employ sulfonyl chlorides and amines as the starting ingredients [17], and finally scavenging HCl using organic solvents and organic amine bases .[18, 19] Another procedure referred as the modified Schott-Baumann procedure uses a two-phase system of organic solvents and a basic aqueous solution (Na_2CO_3 or NaOH) [20-21]. Under these circumstances, sulfonyl chloride hydrolyzes, necessitating the use of more

reagent to ensure a full reaction. Due to safety and environmental concerns, water has recently been employed as a green solvent for a number of chemical processes [22,23].

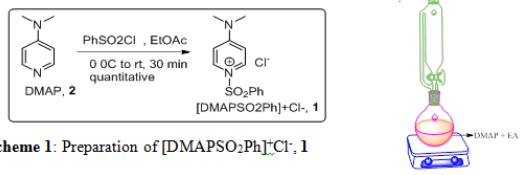
One of them is the conversion of amines into sulfonamides and phenols and alcohols into their respective sulfonate esters. Sulfonamides (privileged structures) have such a high pharmacological profile, including anti-inflammatory, anti-cancer, anti-viral, HIV protease inhibitors, anticonvulsant[24,25], etc. converted them into commercially available medications including bosentan [28], amprenavir[26], a phosphodiesterase inhibitor, sildenafil[27], an inhibitor of the HIV protease, and others.

Sulfonic esters exhibit significant pharmacological activity, just like sulfonamides. [29]Additionally, despite the reality that these benzenesulfonyl derivatives have multiple synthetic uses, the synthesis of sulfonamides and sulfonic esters has drawn the attention of many synthetic chemists all over the world due to their ability to mask a variety of functional groups[30] and act as alkylating agents in SN [31]reactions.[32] The traditional benezenesulfonyl method[33], which calls for treating a substrate with benzenesulfonyl chloride and Py/NEt_3 in DCM, has drawbacks due to its prolonged reaction times, which can result in undesirable reactions like the formation of disulfonamides and, in some cases, functional group compatibility.[34] All methods discussed above demand chromatographic purification to separate the pure product or a base/catalyst to enhance benzene sulfonylation. Therefore, a need for a safe technique that overcomes aforementioned drawbacks is still required.

A green method of benzenesulfonylation of phenols and amines that does not require the use of a base or chromatographic purification employing $[DMAPSO_2Ph]^+Cl^-$ is presented in this communication.

Results and Discussions

Preparation and Structure determination of $[DMAPSO_2Ph]^+Cl^-$, 1



Scheme 1: Preparation of $[DMAPSO_2Ph]^+Cl^-$, **1**

Our journey began with the preparation and characterization of $[DMAPSO_2Ph]^+Cl^-$ When a solution of DMAP in ethylacetate was treated with a solution of benzenesulphonyl chloride at 0 ^{0}C followed by raising the reaction temperature to rt the desired product **1** was formed in quantitative yields. The structure of **1** was thoroughly established from ^{1}H NMR, ^{13}C NMR, IR and Mass spectra. To test the reactivity of reagent 1 we selected phenol, **3** as a model substrate. Fortunately sulphonate ester 4 was obtained in very good yields (98%) when **3** was treated with reagent **1** in DCM in just 2 min. The product structure was assigned based on the NMR and IR spectral data. This clearly indicated about the rapid reactivity of reagent **1**.

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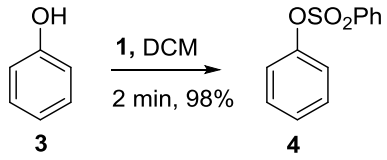


Scheme 2: Benzenesulfonylation of phenol (**3**) with **1**.

Benzenesulfonylation of phenols

These results further driven us to check the generality of benzenesulphonation of reagent **1** under base free conditions. A total of 10 phenols were tested as given in table 1 which produced corresponding sulphonate esters in excellent yields in shorter reaction times (2-15 min).

Table 1: benzenesulphonylation of phenols with $[DMAPSO_2Ph]^+Cl^-$, **1**

SN	Phenols	Time	Solvent	Yield(%)
1	Phenol, **3**	2 min	DCM	98
2	4-Chloro phenol, **5**	2 min	DCM	97
3	7-Hydroxy 4-methyl coumarin, **7**	2 min	DCM	97
4	8-Hydroxy quinoline, **9**	5 min	DCM	95
5	4-Methyl coumarin, **11**	10 min	DCM	93
6	o-Nitro phenol, **13**	8 min	DCM	92
7	p-cresol, **15**	15 min	DCM	96
8	p-Nitro phenol, **17**	10 min	DCM	85
9	Salicilic acid, **19**	10 min	DCM	92
10	Vanillin, **21**	15 min	DCM	93

a) Reagents and conditions : substrate (1.0 mmol), $[DMAPSO_2ph]^+Cl^-$(1.1mmol), DCM(5ml), rt

Benzenesulfonylation of amines

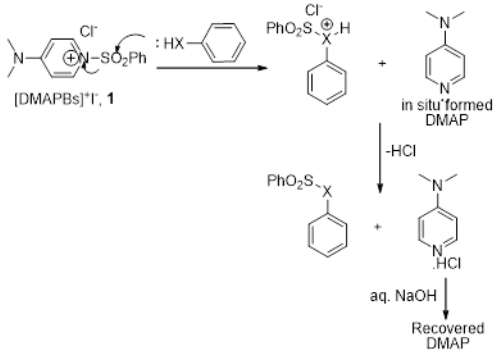
After the successful studies on phenols, we also wished for benzenesulphonylation of different amines mentioned in table 2. Gratifyingly all the tested amines were preferentially converted in to their monosulphonamide derivatives in good yields within 10 min.

Table 2: Sulphonamide formation of various amines employing **1**

SN	Amines	Time	Solvent	Yield (%)
1	Aniline,**23**	2 min	DCM	97
2	4-Chloro aniline, **25**	5 min	DCM	92
3	p-toluidine, **27**	2 min	DCM	95
4	Pepperdine, **29**	3 min	DCM	96
5	o-Toluidine, **31**	5 min	DCM	97
6	N-Methyl aniline, **33**	5 min	DCM	95
7	Benzylamine, **35**	2 min	DCM	96
8	p-Methoxy benzylamine, **37**	2 min	DCM	97
9	Isopropylamine, **39**	10 min	DCM	85
10	p-Anisidine, **41**	5 min	DCM	97

a) Reagents and conditions : substrate (1.0 mmol), $[DMAPSO_2ph]^+Cl^-$ (1.1mmol), DCM (5ml), rt

Plausible Mechanism:



Conclusions:

In conclusion a novel benzenesulphonylation reagent has been discovered and is synthesized on multigram scale. The structure of the new reagent was unambiguously assigned based on spectral data. The reagent is successfully used for monobenzenesulphonylation of 10 phenols and 10 amines in excellent yields within short reaction times. All the solid products were isolated without chromatographic purification. DMAP was recovered from the reaction mixture upon basification of aqueous layer.

Acknowledgements
We thank Osmania University and Palamuru University for providing infrastructural facilities and IICT, UoH for spectral data assistance.

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