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A practical and efficient method for the preparation of sulfonamides utilizing Cl_3CCN/PPh_3

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Abstract—Cl_3CCN in combination with PPh_3 proved to be a highly reactive reagent for the conversion of sulfonic acids to the corresponding sulfonyl chlorides in refluxing CH_2Cl_2. Upon reaction with amines, the corresponding sulfonamides were obtained in good to excellent yields.

Sulfonamides have long been the subject of pharmaceutical interest as a result of their potent biological activities.[1] They are used in the prevention and treatment of bacterial infections, diabetes mellitus, oedema, hypertension and gout. Some have proved to be useful as herbicides[2] and plaguicides.[3] Arylsulfonyl substituents have been used as protecting groups for oxygen and nitrogen functionalities.[4] Sulfonamide derivatives of azo dyes have been reported to improve light stability and fibre fixation.[5]

The most commonly used synthetic methods to manipulate sulfonamides involve the nucleophilic attack by ammonia, or primary or secondary amines, with sulfonyl chlorides in the presence of a base. Although this method is efficient, it requires the availability of sulfonyl chlorides, some of which are hard to prepare and difficult to store or handle. Side reactions are also possible due to the presence of base or liberated nucleophilic chloride, particularly under harsh conditions with relatively non-nucleophilic substrates. Sulfonyl chlorides are generally prepared from the corresponding sulfonic acids using $SOCl_2$,[6] $POCl_3$[7] or PCl_5.[8] The use of triphosgene,[9] PPh_3/SO_2Cl_2,[10] or SO_2Cl_2[11] has been reported for the preparation of carbohydrate sulfonyl chlorides. A recent transformation of sulfonic acids or their salts into sulfonyl chlorides using cyanuric chloride has also been reported.[12] In addition, there are disadvantages in that these methods necessitate an excess of chlorinating reagent and that highly toxic and corrosive by-products are formed. Alternatively, sulfonamides can be prepared by reacting sulfinic acid salts with an electrophilic nitrogen source such as hydroxylamine-*O*-sulfonic acid[13] or bis-(2,2,2-trichloroethyl)-azodicarboxylate.[14] However, the success of the process lies in the availability of the required sulfinic acid salt. The existing synthetic approaches to sulfinic acid salts either involve the use of organolithium or Grignard reagents, which are incompatible with a host of functional groups, or tedious, multi-step syntheses. Furthermore, the purity of the sulfinates is usually insufficiently high due to the inability to isolate the hygroscopic salt. Although several synthetic methods for sulfonamides have been developed, there remains a need for a straightforward and general methodology towards accessing sulfonamides under mild conditions in the absence of a strong base or competing nucleophile. Recently, it has been reported that the PPh_3/Cl_3CCN[15] system could be used for the conversion of carboxylic acids to acid chlorides, which were subsequently transformed into the corresponding amide, ester or acid anhydride. Herein, we report the utilization of Cl_3CCN and PPh_3 for the efficient synthesis of sulfonamides.

Benzenesulfonic acid and cyclohexylamine were used as model substrates. When the former was treated with selected halogenated reagents and PPh_3 in CH_2Cl_2 at reflux, followed by a treatment with the latter in the presence of 4-picoline as base, *N*-cyclohexylbenzenesulfonamide was obtained. The type and amount of halogenated reagents were investigated and the results are given in Table 1.

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Table 1. Effect of the type and amount of halogenated reagent on the formation of *N*-cyclohexylbenzenesulfonamide

Entry	Halogenated reagent		PPh_3 (mmol)	% Isolated yield
	Type	Amount (mmol)		
1	Cl_3CCN	1	1	21
2		2	2	67
3		3	3	Quant
4		3	3	57[a]
5		6	6	23
6	Cl_3CCO_2Et	3	3	14
7		6	3	23
8	Cl_3CCONH_2	3	3	20
9		6	6	Trace
10		6	3	43
11	Br_3CCO_2Et	3	3	4

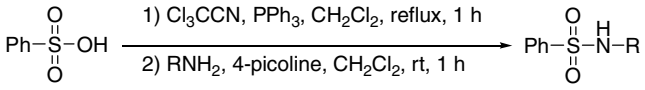
Reaction conditions: benzenesulfonic acid (1 mmol), CH_2Cl_2 (6 mL), cyclohexylamine (3 mmol), 4-picoline (9 mmol).
Reaction time: step I, at reflux for 1 h; step II, at room temperature for 1 h.
[a] Room temperature (28–30 °C) for step I.

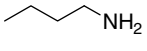
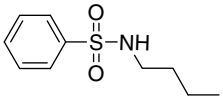
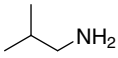
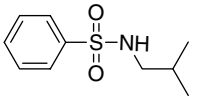
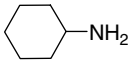
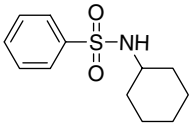
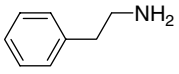
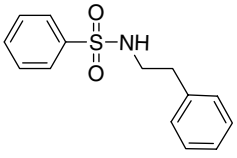
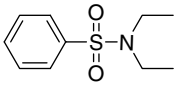
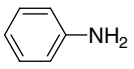
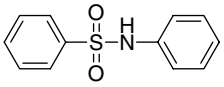
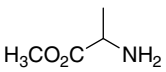
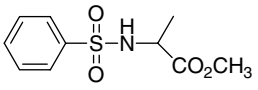
At refluxing temperature, when the ratio of Cl_3CCN:PPh_3:sulfonic acid was 1:1:1 and 2:2:1, the yields of sulfonamide were low to moderate (entries 1 and 2). Increasing the ratio to 3:3:1 gave the corresponding sulfonamide quantitatively (entry 3) whereas the desired sulfonamide was obtained only in moderate yield at room temperature (entry 4). However, when the ratio was increased to 6:6:1, the yield of the desired product was decreased (entry 5). Other halogenated reagents were investigated such as Cl_3CCO_2Et, Cl_3CCONH_2 and Br_3CCO_2Et; however, the desired sulfonamide was obtained in only poor yields (entries 6–11).

The effect of solvent was next examined. The reaction of benzenesulfonic acid and the adduct of Cl_3CCN and PPh_3 in common organic solvents such as $CHCl_3$, CH_3CN, THF, EtOAc and 1,2-DCE gave *N*-cyclohexylbenzenesulfonamide in low to moderate yields. The reaction performed in CH_2Cl_2 was the most efficient yielding the desired sulfonamide in quantitative yield.

The generality and scope of this method was thoroughly investigated (Table 2). All primary and secondary, alkyl and aryl amines gave excellent yields of sulfonamides. Alkyl amines such as *n*-butylamine, *iso*-butylamine and phenethylamine furnished the corresponding sulfonamides in high yields (71–87%, entries 1, 2 and 4). The secondary amine diethylamine was converted into the corresponding sulfonamide in 74% yield (entry 5). In the case of arylamine aniline, the corresponding sulfonamide was isolated in 93% yield (entry 6). Gratifyingly, there was no limit for simple amine substrates, and the

Table 2. Effect of various amines on the synthesis of sulfonamides



Entry	Amine	Sulfonamide	% Isolated yield
1			83
2			71
3			Quant
4			87
5			74
6			93
7			46

reaction also occurred with an amino acid derivative (entry 7).

A diverse range of sulfonic acids were then tested under optimized reaction conditions. Phenethylamine was reacted with a number of common sulfonic acids and the results are summarized in Table 3.

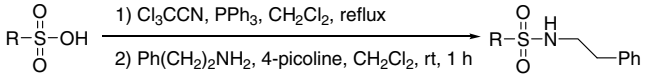
The reaction was not limited by sulfonic acid; however, the reaction conditions needed to be altered to improve the yields of the desired sulfonamides such as increasing the time at reflux in step I (the reaction of methanesulfonic acid) from 1 to 3 h and then to 8 h to provide the corresponding sulfonamide in 51%, 75% and 89% yields, respectively (entries 1–3). In the case of benzenesulfonic acid, the corresponding sulfonamide was obtained in high yield (87%, entry 4). In the reaction of 4-toluenesulfonic acid monohydrate, the hydrate reacted with PPh_3 resulting in only 33% yield of the sulfonamide. However, increasing the amount of PPh_3 from 3 to 6 mmol and the reaction time in step I from 1 to 3 h improved the yield almost quantitatively (entries 5 and 6). Interestingly, this method proved to be very useful even for sterically hindered compounds such as camphor-10-sulfonic acid, the corresponding sulfonamide was obtained in 77% yield (entry 7).[16]

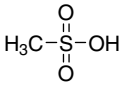
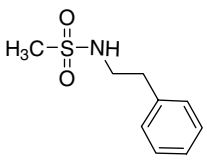
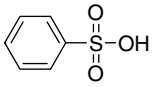
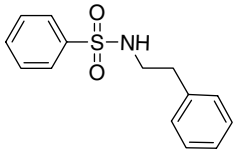
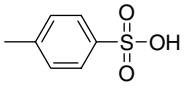
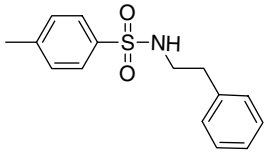
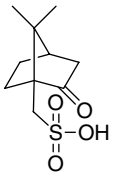
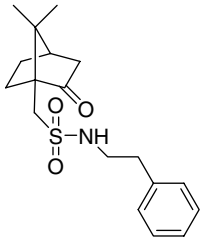
The mechanism for the reaction of sulfonic acid, Cl_3CCN and PPh_3 was studied by IR and sulfonyl chloride was confirmed as the reaction intermediate. The IR spectra of benzenesulfonyl chloride (Fig. 1b) and the reaction mixture (Fig. 1c) both displayed two strong bands at 1370 and 1185 cm^{-1} due to S=O stretching vibrations of sulfonyl chloride. The IR spectrum of benzenesulfonic acid (Fig. 1a) revealed a strong absorption band at 1129 cm^{-1} assigned to S=O stretching vibrations.[17] These results endorsed sulfonyl chloride as a reactive intermediate in the reaction.

In summary, a simple and convenient method for the synthesis of sulfonamides utilizing Cl_3CCN/PPh_3 has been established.

A typical experimental procedure is as follows: PPh_3 (3 mmol, 0.79 g) in CH_2Cl_2 (3 mL) was added to a mixture of sulfonic acid (1 mmol, 0.16 g) and a selected halogenated reagent (3 mmol) in CH_2Cl_2 (3 mL) at reflux. The mixture was stirred for approximately 1 h. A mixture of amine (3 mmol) and 4-picoline (9 mmol, 0.84 g) was added to the above mixture. The reaction mixture was stirred for another 1 h at room temperature and was monitored using TLC. When the reaction was complete, the organic layer was extracted with 1 N HCl and saturated by aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was separated by silica gel column chromatography eluting with hexane/EtOAc (9:1). Further purification by recrystallization from a mixture of CH_2Cl_2 and hexane

Table 3. Effect of various sulfonic acids on the synthesis of sulfonamides



Entry	Sulfonic acid	Sulfonamide	Time for step I	% Isolated yield
1			1	51
2			3	75
3			8	89
4			1	87
5			1	33
6			3	96[a]
7			1	77

[a] 6 equiv of PPh_3 was used.

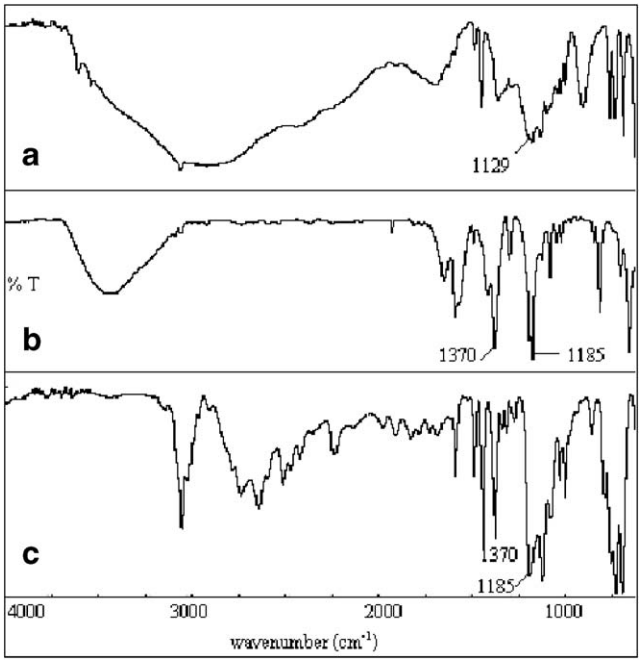


Figure 1. The IR spectra of (a) benzenesulfonic acid, (b) benzenesulfonyl chloride and (c) the reaction mixture of benzenesulfonic acid, PPh_3 and Cl_3CCN.

or another appropriate solvent gave the desired sulfonamide products.

Acknowledgements

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16. *N*-Phenethyl-10-camphorsulfonamide: yellow liquid (77%), R_f 0.52 (50% EtOAc/hexane). IR (neat): 3295, 2956, 1598, 1431, 1326, 1143 and 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.80–3.40 (15H, m, camphor group), 2.93 (2H, m, CH_2Ar), 3.44 (2H, m, $NHCH_2$), 5.04 (1H, br s, N*H*) and 7.20–7.40 (5H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 19.5, 19.9, 26.2, 26.9, 36.5, 42.7, 42.9, 44.8, 48.7, 49.3, 58.9, 126.7, 128.7, 128.9, 138.1 and 216.6. LC–MS (EI) *m*/*z* (relative intensity, assignment) 336.2 (41.0, $[M+H]^+$), 212.3 (100).
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