One-Pot Synthesis of Sulfonamides from Primary and Secondary Amine Derived Sulfonate Salts Using Cyanuric Chloride

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Abstract: A convenient, mild and efficient one-pot synthesis of new sulfonamides is described. The reaction of primary or secondary amine derived sulfonate salts in the presence of cyanuric chloride, triethylamine as base, and anhydrous acetonitrile as solvent at room temperature gives the corresponding sulfonamides in good to excellent yields.

Key words: one-pot reaction, sulfonamides, amine–sulfonate salt, cyanuric chloride, triethylamine

Sulfonamides (sulfa drugs) were the first drugs largely employed and systematically used as preventive and chemotherapeutic agents against various diseases.1 They are utilized as antihypertensive,2a antiglaucoma,2b antibacterial,2c antiviral,2d antiprotozoal,2e antifungal,2f antitumor,2g antinflammatory2l and anticonvulsant agents.2h They are also effective for the treatment of urinary, intestine and ophthalmic infections,2i scalds,2i ulcerative colitis,2i rheumatoid arthritis,2j male erectile dysfunction 2k and obesity.2l The synthesis of sulfonamides also represents a useful strategy for the protection of primary and secondary amines.3 Furthermore, sulfonamides are employed as herbicides,4a plaguicides,4b pesticides4c,d and surfactants.4c,d Traditionally, sulfonamides are prepared by reaction of ammonia or an amine (primary or secondary) with a sulfonic chloride in an organic or aqueous solvent.3 Another method for the synthesis of sulfonamides involves reaction of a sulfonic acid salt with an electrophilic source of nitrogen such as hydroxylamine-O-sulfonic acid6 or bis(2,2,2-trichloroethyl)azodicarboxylate.7 Additionally, sulfonamides are synthesized by reaction of sulfonic acids with isocyanates in the presence of water,8 via direct reaction of amines with sulfur dioxide,9 by reaction of sulfonic acids with amines using trichloroacetoni-triphenylphosphine,10 and from a sulfonic acid and triphenylphosphine ditriflate.11 Furthermore, arylsulfonamides have been prepared by reduction of arylsulfonyl azides.12 However, several of these methods suffer from disadvantages including the use of reagents that are toxic, corrosive, expensive and difficult to access, problems in handling sulfonil chlorides and amines, bis-sulfonylation, harsh reaction conditions, long reaction times, tedious work-ups and low yields of products. Hence, there is still demand for establishing novel straightforward methods for accessing sulfonamides under mild reaction conditions.

Cyanuric chloride [2,4,6-trichloro-1,3,5-triazine (TCT)] is a stable, non-volatile, inexpensive and safe reagent which has been used in various organic transformations and in synthesis.13 For example, cyanuric chloride and its derivatives have been employed for the dehydration of amides to nitriles,14 deoxygenation of sulfoxides,15 Swern-type oxidation,16 lactonization of hydroxycarboxylic acids,17 conversion of carboxylic acids into acyl chlorides,18a acyl azides18b amides,18a,19 ketones,20 Weinreb amides, hydroxamates,21 diazoketones22 and alcohols.23 It has also been used for the conversion of sulfonic acids into sulfonyl chlorides,24 formamides into isonitriles,25 ketoimino acids into amides (Beckmann rearrangement),26 and for the preparation of β-chlorohydrins from epoxides (in water),27 and the conversion of alcohols into alkyl chlorides28a and formate esters.28b Cyanuric chloride has also been used as an in situ source of hydrochloric acid in aqueous conditions for catalyzing various conversions.29

Recently, De Luca and Giacomelli reported a two-step microwave-assisted synthesis of sulfonamides from sulfonic acids or their sodium salts and various amines using cyanuric chloride.30 Their procedure involved exposure of a mixture of the sulfonic acid (1 equiv), cyanuric chloride (1 equiv) and triethylamine (1 equiv) in acetonitrile of a sealed tube to microwave irradiation at 80 °C for 20 minutes. The resulting precipitate was removed by filtration and the filtrate added to an aqueous solution of sodium hydroxide in tetrahydrofuran. Addition of the amine (1 equiv) followed by further microwave irradiation in a sealed tube at 50 °C for ten minutes gave the desired product. The drawbacks of this method are the harsh reaction conditions and somewhat cumbersome procedure.

Herein, we report a one-pot, mild and highly efficient method for the preparation of sulfonamides from various primary and secondary derived amine sulfonate salts (R’SO3NH2R2R3) using cyanuric chloride in the presence of triethylamine as base and acetonitrile as solvent at room temperature (Scheme 1).

Our studies on the one-pot synthesis of sulfonamides were influenced by the method of Blotny,24 who prepared sulfo-
nyl chlorides from sulfonic acids using cyanuric chloride. In this context, we conducted the reaction of \( p \)-toluene-sulfonic acid (3 equiv), pyrrolidine (3 equiv), triethylamine (3 equiv) and cyanuric chloride (1 equiv) in anhydrous acetone at both room temperature and at reflux. However, none of the corresponding sulfonamide was obtained. The \( p \)-toluenesulfonic acid remained unchanged, and instead, pyrrolidine reacted with cyanuric chloride to afford a pyrrolidine–cyanuric chloride adduct (Scheme 2). Using equimolar amounts of all the reagents, and replacing \( p \)-toluenesulfonic acid with its cesium or potassium salt, accompanied by addition of a catalytic amount of 18-crown-6 or tetrabutylammonium bromide (TBAB) had no significant effect on the outcome of the reaction.

Thus, we decided to use the \( p \)-toluenesulfonate salt of pyrrolidine instead of \( p \)-toluenesulfonic acid and pyrrolidine, in order to enhance the nucleophilicity of the sulfonic acid and to prevent the amine reacting with cyanuric chloride. Initially, cyanuric chloride (1 equiv) was added to the \( p \)-toluenesulfonate salt of pyrrolidine (3 equiv) in anhydrous acetonitrile and the reaction was allowed to stir at room temperature for 30 minutes. During this time, the consumption of cyanuric chloride and formation of \( p \)-toluenesulfonyl chloride and a \( p \)-toluenesulfonic acid–cyanuric chloride adduct were observed (as indicated by TLC monitoring). Subsequently, a solution of anhydrous triethylamine (3 equiv) in anhydrous acetonitrile was added to the reaction mixture which was then stirred at ambient temperature for one hour. Gratifyingly, 1-[(4-methylphenyl)sulfonyl]pyrrolidine was obtained (Scheme 3), the structure of which was confirmed by IR, NMR and mass spectroscopic analysis. Encouraged by this result, we next investigated the influence of various aprotic solvents and bases on this reaction (Table 1). Of the examined solvents, anhydrous acetonitrile (Table 1, entry 1) afforded

\[
\begin{align*}
\text{R}^1 \text{SO}_3^+ + \text{Et}_3\text{N} + \text{TCT} &\rightarrow \text{R}^1 \text{SO}_2 \text{Cl} + \text{Et}_3\text{NH} + \text{TCT} \\
\frac{1}{2} \text{H}_2\text{N} + \text{R}^1 \text{SO}_2 \text{Cl} &\rightarrow \text{R}^1 \text{SO}_2 \text{NHN} - \text{Et}_3\text{N} + \text{TCT}\end{align*}
\]

Scheme 2  An attempted one-pot synthesis of 1-[(4-methylphenyl)sulfonyl]pyrrolidine

\[
\begin{align*}
\text{R}^1 \text{SO}_3^+ + \text{H}_2\text{N} + \text{TCT} &\rightarrow \text{R}^1 \text{SO}_2 \text{Cl} + \text{Et}_3\text{N} + \text{TCT} \\
\frac{1}{2} \text{H}_2\text{N} + \text{R}^1 \text{SO}_2 \text{Cl} &\rightarrow \text{R}^1 \text{SO}_2 \text{NHN} - \text{Et}_3\text{N} + \text{TCT}\end{align*}
\]

Scheme 3  One-pot synthesis of 1-[(4-methylphenyl)sulfonyl]pyrrolidine

Table 1  Effect of Various Solvents and Bases on the Conversion of the \( p \)-Toluenesulfonate Salt of Pyrrolidine into 1-[(4-Methylphenyl)sulfonyl]pyrrolidine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN(^b)</td>
<td>Et(_3)N</td>
<td>1.5</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>(Me(_2)CO(^b))</td>
<td>Et(_3)N</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>HMPA</td>
<td>Et(_3)N</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>CHCl(_3)</td>
<td>Et(_3)N</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)Cl(_2)</td>
<td>Et(_3)N</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>DMF(^b)</td>
<td>Et(_3)N</td>
<td>6</td>
<td>NR(^c)</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>Et(_3)N</td>
<td>6</td>
<td>NR(^c)</td>
</tr>
<tr>
<td>8</td>
<td>MeCN(^b)</td>
<td>K(_2)CO(_3)</td>
<td>1.5</td>
<td>40</td>
</tr>
<tr>
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<td>6</td>
<td>55</td>
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<td>11</td>
<td>MeCN(^b)</td>
<td>DABCO</td>
<td>6</td>
<td>NR(^c)</td>
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<tr>
<td>12</td>
<td>MeCN(^b)</td>
<td>MgO</td>
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<td>10</td>
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<tr>
<td>13</td>
<td>MeCN(^b)</td>
<td>Al(_2)O(_3)(^d)</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^a\) Yield of isolated product.
\(^b\) Anhydrous solvent used.
\(^c\) No reaction.
\(^d\) Basic alumina.
the highest yield of product and was the solvent of choice for all further reactions.

The effect of various organic and inorganic bases on the reaction was also studied (Table 1). Triethylamine (Table 1, entry 1) proved to be the most satisfactory base in terms of yield. In general, heterogeneous inorganic bases (Table 1, entries 8, 12 and 13) afforded lower yields of 1-[(4-methylphenyl)sulfonyl]pyrrolidine while other organic bases were not as efficient as triethylamine.

We next investigated the versatility and scope of this method (Table 2). Primary and secondary amines gave excellent yields of the corresponding sulfonamides in short reaction times. Allylamine (Table 2, entry 1), alkyl amines (Table 2, entries 2, 3 and 8–11), benzylamine (Table 2, entry 4), cyclic amines (Table 2, entries 12, 13, 15 and 18) and 1,2-diamines (Table 2, entries 7, 14, 16 and 17) were efficiently converted into their correspond-

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfonamide b</th>
<th>Time (h)</th>
<th>Mp (°C)</th>
<th>Yield (%) c</th>
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<tr>
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<td>204</td>
<td>82</td>
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<td>113</td>
<td>80</td>
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<td>83</td>
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<td>6</td>
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<td>oil</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>[image]</td>
<td>2</td>
<td>oil</td>
<td>81</td>
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<tr>
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<td>88</td>
</tr>
<tr>
<td>9</td>
<td>[image]</td>
<td>1</td>
<td>79</td>
<td>85</td>
</tr>
</tbody>
</table>

a Reagents and conditions: TCT (0.33 equiv), Et3N (1 equiv), MeCN (40 mL), r.t.

b All products were characterized by 1H and 13C NMR, IR, CHN and MS analysis.

c Yield of isolated product.
ing sulfonamides. This synthetic method also worked well with hydrazine derivatives (Table 2, entries 5 and 6) and is also applicable to aliphatic sulfonic acid salts such as amino salts of methanesulfonic acid (Table 2, entries 16–18).

Mechanistically, this reaction proceeds via an initial S$_N$Ar-type reaction between the sulfonate anion and cyanic chloride. Next, the released chloride ion attacks the sulfur atom of the sulfonate–cyanuric chloride adduct to afford the corresponding sulfonfyl chloride. The primary or secondary amine (liberated from its ammonium salt by triethylamine) then reacts with the sulfonfyl chloride to give the sulfonamide product. However, in contrast to the observation of Blotny, the sulfonyl chloride was not the sole intermediate. High-performance liquid chromatography indicated that the formation of the 2-mono-, 2,4-di- and 2,4,6-trisulfonate–cyanuric chloride adducts could also have occurred. Unfortunately, attempts to separate the sulfonate–cyanic chloride adducts by conventional column chromatography failed due to their decomposition. The use of semi-empirical (AM1 and PM3) and ab initio (Hartree–Fock, 6-31G) quantum mechanical calculations revealed that among the three possible sulfonate–cyanuric chloride adducts, formation of the 2,4,6-trisulfonate–cyanuric chloride adduct requires much lower energy (ΔH$_f$) and hence is the most likely to form.

In summary, we have developed a mild, one-pot synthetic method for the preparation of alkyl and aryl sulfonamides from primary and secondary amine derived sulfonate salts using readily available cyanuric chloride and triethylamine in anhydrous acetonitrile. This method proved to be useful for the conversion of structurally diverse amines into sulfonamides in good to excellent yields. Furthermore, the use of amine–sulfonate salts as substrates overcomes the problems usually associated with handling toxic and corrosive amines and sulfonic acids or their halide derivatives.

All chemicals were purchased from commercial sources. The amine–sulfonate salts were freshly prepared according to the described procedure. Solvents were purified and dried using reported methods and stored over 3 Å molecular sieves. The reaction progress was monitored by TLC using SILG/UV 254 silica gel plates. Column chromatography was carried out on silica gel 60, (0.063–0.200 mm, 70–230 mesh, ASTM). IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. $^1$H NMR (250 MHz) and $^{13}$C NMR (62.5 MHz) were recorded using a Bruker Avance DPX-250, FT-NMR spectrometer with chemical shift values reported in ppm, and coupling constants (J) in Hz. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin–Elmer 240–B microanalyzer. Melting points were recorded on a Büchi 510 apparatus in open capillary tubes and are uncorrected. Full analytical data are provided for novel products and references are given for known compounds (see Table 2).

**Sulfonamide Preparation; General Procedure**

To a soln of freshly prepared primary or secondary amine derived sulfonate salt (0.01 mol) in anhyd MeCN (40 mL) was added TCT (0.0033 mol) and the reaction mixture was stirred at r.t. for 30 min. Next, Et$_3$N (0.012 mol) was added and the soln stirred for a further 30–90 min (until TLC indicated completion of the reaction). The reaction mixture was concd under vacuum and the residue was dissolved in CHCl$_3$ (100 mL). The organic layer was washed with water (2 × 100 mL), dried over anhyd Na$_2$SO$_4$ and evaporated in vacuo. The residue was purified by short column chromatography on silica gel eluting with a mixture of PE–EtOAc.

**N-Butyl-4-methylbenzenesulfonamide (Table 2, Entry 3)**

IR (film): 3292, 3010, 2970, 1573, 1296, 1157 cm$^{-1}$.

$^1$H NMR (250 MHz, CDCl$_3$): δ = 0.72 (t, 3 H, J = 7.0 Hz, CH$_3$CH$_2$), 1.15–1.29 (m, 2 H, CH$_2$CH$_3$), 1.32–1.41 (m, 2 H, NCH$_2$CH$_2$), 2.34 (s, 3 H, ArCH$_3$), 2.79 (t, 2 H, J = 5.4 Hz, NCH$_2$), 4.91 (br s, 1 H, NH, exchangeable with D$_2$O), 7.29 (d, 2 H, J = 7.0 Hz, ArH), 7.67 (d, 2 H, J = 7.0 Hz, ArH).

$^{13}$C NMR (62.5 MHz, CDCl$_3$): δ = 13.5, 19.7, 21.5, 31.5, 42.7, 127.1, 129.6, 136.9, 143.2.

MS (EI): m/z (%) = 227.1 (16) [M$^+$.]

Anal. Calcd for C$_{12}$H$_{19}$N$_3$O$_2$S: C, 53.51; H, 7.11; N, 15.60; S, 11.90. Found: C, 53.55; H, 7.08; N, 15.64; S, 11.92.

**4-Methyl-N-morpholin-4-ylbenzenesulfonamide (Table 2, Entry 5)**

IR (film): 3433, 2962, 1620, 1442, 1180 cm$^{-1}$.

$^1$H NMR (250 MHz, DMSO-d$_6$): δ = 2.25 (s, 3 H, CH$_3$), 3.70–4.30 (m, 9 H, 2 NCH$_2$CH$_2$O, NH), 6.71 (d, 2 H, J = 7.4 Hz, ArH), 7.63 (d, 2 H, J = 7.4 Hz, ArH).

$^{13}$C NMR (62.5 MHz, DMSO-d$_6$): δ = 24.3, 55.1, 63.9, 127.2, 129.4, 136.7, 141.6.

MS (EI): m/z (%) = 256.1 (17) [M$^+$.]

Anal. Calcd for C$_{11}$H$_{16}$N$_2$O$_3$S: C, 51.54; H, 6.29; N, 10.93; S, 12.51. Found: C, 51.59; H, 6.27; N, 10.99; S, 12.46.

**4-Methyl-N-(4-methylpiperazin-1-yl)benzenesulfonamide (Table 2, Entry 6)**

IR (film): 3440, 2980, 1615, 1447, 1180 cm$^{-1}$.

$^1$H NMR (250 MHz, DMSO-d$_6$): δ = 2.27 (s, 3 H, CH$_3$), 2.51 (s, 3 H, NCH$_3$), 2.69 [t, 4 H, J = 5.3 Hz, MeN(CH$_2$)$_2$], 2.84 [t, 4 H, J = 5.3 Hz, NN(CH$_2$)$_2$], 3.67 (br s, 1 H, NH, exchangeable with D$_2$O), 7.17 (d, 2 H, J = 7.5 Hz, ArH), 7.42 (d, 2 H, J = 7.5 Hz, ArH).

$^{13}$C NMR (62.5 MHz, DMSO-d$_6$): δ = 20.2, 21.4, 31.1, 42.7, 127.3, 129.6, 137.0, 143.1.

MS (EI): m/z (%) = 269.1 (25) [M$^+$.]

Anal. Calcd for C$_{15}$H$_{24}$N$_4$O$_2$S: C, 53.51; H, 7.11; N, 15.60; S, 11.90. Found: C, 53.55; H, 7.08; N, 15.64; S, 11.92.

**N-(2-Diisopropylamino)ethyl-4-methylbenzenesulfonamide (Table 2, Entry 7)**

IR (film): 3450, 2985, 1620, 1456, 1185 cm$^{-1}$.

$^1$H NMR (250 MHz, DMSO-d$_6$): δ = 0.97 (d, 12 H, J = 4.4 Hz, 4 CH$_2$), 2.25 (s, 3 H, CH$_3$), 2.34 (t, 2 H, J = 5.6 Hz, NCH$_2$), 2.76–2.79 (m, 2 H, 2 NCH$_2$), 3.33 (t, 2 H, J = 5.6 Hz, SNCH$_2$), 3.77 (s, 1 H, NH, exchangeable with D$_2$O), 7.17 (d, 2 H, J = 7.5 Hz, ArH), 7.51 (d, 2 H, J = 7.5 Hz, ArH).

$^{13}$C NMR (62.5 MHz, DMSO-d$_6$): δ = 20.7, 20.9, 41.7, 45.6, 49.2, 125.5, 128.8, 138.1, 144.1.

MS (EI): m/z (%) = 298.2 (32) [M$^+$.]

Anal. Calcd for C$_{15}$H$_{26}$N$_4$O$_2$S: C, 56.37; H, 8.78; N, 9.39; S, 10.74. Found: C, 56.42; H, 8.81; N, 9.37; S, 10.77.
N,N-Diisopropyl-4-methylbenzenesulfonamide (Table 2, Entry 8)
IR (KBr): 2939, 2854, 1458, 1334, 1157 cm⁻¹.
²¹H NMR (250 MHz, CDCl₃): δ = 1.02 (s, 6 H, 2 CH₃), 1.62–1.68 (m, 4 H, 2 CH₂), 2.34 (s, 3 H, ArCH₃), 2.33–2.39 (t, 4 H, J = 5.6 Hz, 2 NCH₂), 5.33 (d, 2 H, J = 7.5 Hz, ArH), 7.17 (d, 2 H, J = 7.5 Hz, ArH).
¹³C NMR (62.5 MHz, CDCl₃): δ = 21.5, 25.1, 47.9, 127.5, 129.6, 133.7, 143.3.
MS (EI): m/z (%) = 225.1 (26) [M⁺].
Anal. Calcld for C₁₆H₂₄NO₂S: C, 65.70; H, 7.66; N, 5.12; S, 15.52.
Found: C, 65.58; H, 7.65; N, 5.14; S, 15.38.

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References
(g) Lavoie, R.; Bouchain, G.; Frechette, S.; Woa, S. H.; Khalil, E. A.; Leit, S.; Fourmel, M.; Yan, P. T.; Trachy-

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(32) The ab initio (6-31G) quantum mechanic calculations were run using Gaussian 98, version 9.2. The semi-empirical Austin Model 1 (AM1) and Parameterized Model 3 (PM3) calculations were run on MOPAC in CS Chem 3D Ultra 8 (2004 Cambridge Soft) and Hyperchem (Hypercube Inc., version 7). The heat of formation (AH°) is a parameter used to estimate the stability of molecules in comparison with other related isomers or molecules. The molecule with the lowest AH° value is the most stable.

(33) The amine–sulfonate salts are prepared as follows: to a soln of amine (1 equiv) in a minimum amount of H2O–MeOH (60:40) was added the sulfonic acid (1 equiv). The reaction was stirred at r.t. for 15 min and the reaction was judged to be complete when pH paper indicated that the soln was neutral. The soln was evaporated under vacuum and the remaining solid was crystallized from hot MeOH. The crystals were dried in a vacuum oven for 24 h at 50 °C and then stored in a desiccator.