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# The synthesis and crystallographic characterization of 4-methylbenzenesulfonamide derivatives

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ABSTRACT

The sulfonamide moiety is present among a variety of biologically significant compounds. A facile synthesis is necessary to produce a variety of sulfonamides with the potential to improve human health. Herein, we report a facile methodology for the synthesis of 4-methylbenzenesulfonamides, amenable to a broad range of nitrogen nucleophiles. Implementing a semi-miscible biphasic solvent system resulted in higher yields, decreased reaction times, and a simplified workup over preliminary methods. Additionally, the crystal structures of five novel sulfonamide compounds and two polymorphs, have been determined by X-ray diffraction. Results obtained through spectroscopic characterization support the successful formation of the desired 4-methylbenzenesulfonamides.

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## 1. Introduction

Sulfonamides, commonly referred to as sulfa drugs, are biologically significant compounds with diverse biological properties that continue to show promise in modern-day therapeutics. The discovery of sulfonamide agents began with the synthesis of sulfanilamide in 1908 by Gelmo *et al.* [1]. A prodrug of sulfanilamide, Prontosil, synthesized by Domagk *et al.* in 1935, became the first effective antibacterial agent [2]. These findings led to the production of numerous sulfonamide drugs. In 1937, the synthesis of sulfapyridine, better known as M&B 693, became the first known treatment for pneumonia [3,4]. In the years preceding, sulfonamides have exhibited antibacterial, antiviral, antimalarial, antifungal, anticancer, and antidepressant properties, among others [5-9]. Improved synthetic techniques are necessary to create novel sulfonamide structures and advance drug discovery. A review of the literature suggests the amination of either sulfonyl halides or activated sulfonic acids as a means of effectively producing sulfonamides [10,11]. A general reaction showing sulfonamide formation via the treatment of a sulfonyl chloride with an amine can be found in Figure 1. Tosylation of an amine has been thought to follow an analogous nucleophilic acyl substitution mechanism [12]. An HCl scavenger is necessary to establish an equilibrium that favors product formation.

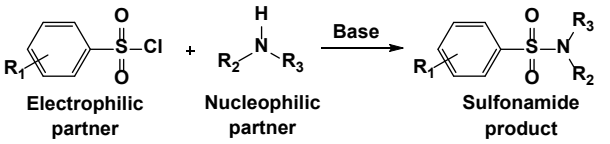


**Figure 1.** General reaction for the formation of sulfonamides from sulfonyl chloride and an amine.

Proper characterization of novel sulfonamide structures gives insight into their biological applications. Reports show that conformational effects play an essential role in the biological activity of sulfonamides [13,14]. Obtaining a reliable structure for interpretation can be done by X-ray diffraction. The information revealed upon characterization is necessary for determining the conformational preferences and structure-property relationships of sulfonamide derivatives. With the ongoing discovery of sulfa drugs, optimizing methodology for the synthesis of sulfonamides becomes increasingly essential.



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An effective recrystallization method must be implemented to produce products of high purity fit for X-ray diffraction. Herein, we report improved methodology towards the synthesis of 4-methylbenzenesulfonamide derivatives and characterization of the resulting crystal structures.

## 2. Experimental

### *2.1. Synthesis*

The reagents used in the synthesis of 4-methylbenzene sulfonamides were obtained from commercial sources and used without further purification. Thin-layer chromatography (TLC) was used to track reaction progress and obtain $R_f$ values for the reactions. Results were analyzed, and figures were created with the use of MestReNova [15].

#### *2.1.1. General procedure for the preparation of sulfonamides synthesized in the presence of pyridine (1-10)*

An amine (5.90 mmol) was added to a flask containing 10 mL of $CH_2Cl_2$. This was followed by the addition of pyridine (0.48 mL, 5.90 mmol). The solution was stirred at room temperate for 10 minutes under $N_2$ atmosphere. 4-Methyl benzenesulfonyl chloride (1.00 g, 5.25 mmol) was then added dropwise to the solution. The mixture was stirred at room temperate for 24 hours under $N_2$ atmosphere. Reaction completion was verified by TLC analysis. After the mixture was acidified with 5 M HCl and diluted with $CH_2Cl_2$, the organic layer was washed three times with $H_2O$. The aqueous layer was back extracted with $CH_2Cl_2$, and the organic layers were combined and dried over anhydrous $Na_2SO_4$. After solvent evaporation, the residue was purified using either recrystallization in ethanol, or trituration with petroleum ether or diethyl ether. The recrystallized product was isolated via vacuum filtration to afford the product in good purity and yield.

*N-Benzyl-N,4-dimethylbenzenesulfonamide* (**1**): Transparent crystals. M.p.: 101-103 °C. $R_f$ = 0.64 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.72 (d, *J* = 8.2 Hz, 2H), 7.38-7.22 (m, 7H), 4.11 (s, 2H), 2.57 (s, 3H), 2.45 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.59, 135.78, 134.33, 129.87, 128.74, 128.49, 127.99, 127.64, 54.24, 34.44, 21.66.

*4-Tosylmorpholine* (**2**): Transparent, needle-like crystals. M.p.: 157-160 °C. $R_f$ = 0.31 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.62 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 3.79-3.66 (m, 4H), 2.96 (t, *J* = 4.8 Hz, 4H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 144.07, 132.05, 129.85, 128.00, 66.19, 46.08, 21.66.

*1-Tosylpyrrolidine* (**3**): White, needle-like crystals. M.p.: 132-134 °C. $R_f$ = 0.35 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.74-7.67 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.26-3.16 (m, 4H), 2.42 (s, 3H), 1.79-1.67 (m, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.39, 133.94, 129.70, 127.67, 48.00, 25.29, 21.63.

*N-Butyl-4-methylbenzenesulfonamide* (**4**): Transparent crystals. M.p.: 51-53 °C. $R_f$ = 0.33 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.74 (d, *J* = 8.2 Hz, 2H), 7.33-7.23 (m, 2H), 4.46 (d, *J* = 8.4 Hz, 1H), 2.91 (q, *J* = 6.8 Hz, 2H), 2.41 (s, 3H), 1.42 (qd, *J* = 7.3, 5.9 Hz, 2H), 1.28 (dt, *J* = 14.8, 7.3 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.44, 137.01, 129.79, 127.20, 43.02, 31.66, 21.63, 19.78, 13.63.

*1-Tosylpiperidine* (**5**): Transparent crystals. M.p.: 104-106 °C. $R_f$ = 0.52 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.65-7.60 (d, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.00-2.89 (m, 4H), 2.42 (s, 3H), 1.68-1.58 (m, 4H), 1.44-1.35 (m, 2H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.39, 133.29, 129.64, 127.83, 47.03, 25.24, 23.61, 21.63.

*N,N-Dibenzyl-4-methylbenzenesulfonamide* (**6**): White crystalline sheets. M.p.: 83-87 °C. $R_f$ = 0.62 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.72 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23-7.16 (m, 6H), 7.07-6.99 (m, 4H), 4.29 (s, 4H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.39, 137.77, 135.76, 129.81, 128.67, 128.50, 127.72, 127.35, 58.59, 50.54, 21.65, 18.53.

*N-Allyl-4-methylbenzenesulfonamide* (**7**): Transparent crystals. M.p.: 67-71 °C. $R_f$ = 0.52 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.75 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.65-5.78 (m, 1H), 5.05-5.19 (m, 2H), 4.37 (s, 1H), 3.55-3.61 (m, 2H), 2.41 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.66, 136.98, 133.06, 129.85, 127.25, 117.87, 45.90, 21.65.

*4-Methyl-N-(4-methylbenzyl)benzenesulfonamide* (**8**): White crystals. M.p.: 103-105 °C. $R_f$ = 0.35 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.74 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 4H), 4.72-4.61 (m, 1H), 4.05 (d, *J* = 6.1 Hz, 2H), 2.43 (s, 3H), 2.29 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.60, 137.80, 136.90, 133.28, 129.84, 129.46, 127.97, 127.31, 47.15, 21.66, 21.19.

*4-Methyl-N-phenylbenzenesulfonamide* (**9**): Pale-pink crystals. M.p.: 110-114 °C. $R_f$ = 0.36 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.63 (d, J = 8.00 Hz, 2H), 7.18-7.27 (m, 4H), 7.01-7.12 (m, 3H), 6.63 (s, 1H), 2.38 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 144.01, 136.61, 136.07, 129.76, 129.41, 127.38, 125.40, 121.62, 21.65.

*4-Methyl-N-propylbenzenesulfonamide* (**10**): Transparent crystals. M.p.: 61.5-63 °C. $R_f$ = 0.52 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.75 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.39 (s, 1H), 2.89 (q, J = 6.8 Hz, 2H), 2.41 (s, 3H), 1.40-1.51 (m, 2H), 0.95 (t, J = 6.0 Hz, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.46, 137.07, 129.80, 127.19, 45.05, 23.04, 21.63, 11.20.

#### *2.1.2. General procedure for the preparation of sulfonamides synthesized in the presence of potassium carbonate (1-13)*

4-Methylbenzenesulfonyl chloride (1.00 g, 5.25 mmol) was added to a flask containing 10 mL of tetrahydrofuran. An amine (5.90 mmol) was added dropwise to the stirring solution, followed by the dropwise addition of 0.59 M aqueous potassium carbonate (10 mL, 5.90 mmol). The flask was sealed and left to react to completion at room temperature. Reaction completion was verified by TLC analysis. The mixture was then concentrated to half its volume, acidified with 5 M HCl, and chilled. The resulting precipitate is isolated via vacuum filtration and recrystallized from ethanol to afford the product in good purity and yield.

*N, N-Bis(2-hydroxyethyl)-4-methylbenzenesulfonamide* (**11**): White crystals. M.p.: 85-87 °C. $R_f$ = 0.11 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.68 (d, J = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.84 (t, *J* = 5.0 Hz, 4H), 3.73 (s, 1H), 3.27-3.20 (t, J = 4.8 Hz, 4H), 2.41 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.89, 135.29, 129.97, 127.41, 62.46, 53.06, 21.64.

*4-Methyl-N-(2, 4, 4-trimethylpentan-2-yl)benzenesulfonamide* (**12**): White crystals. M.p.: 142-145 °C. $R_f$ = 0.60 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.79-7.71 (m, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 2.39 (s, 3H), 1.51 (s, 2H), 1.22 (s, 6H), 0.96 (s, 9H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 142.82, 140.90, 129.51, 127.12, 58.57, 55.66, 31.70, 29.45, 21.59.

*4-Methyl-N-(1-phenylethyl)benzenesulfonamide* (**13**): Red, slightly transparent crystals. M.p.: 85-90 °C. $R_f$ = 0.54 ($CH_2Cl_2$). $^1$H NMR (400 MHz, Chloroform-*d*, δ, ppm): 7.64-7.58 (m, 2H), 7.18 (qt, *J* = 4.3, 2.6 Hz, 5H), 7.13-7.05 (m, 2H), 4.66 (s, 1H), 4.44 (d, *J* = 6.4 Hz, 1H), 2.38 (s, 3H), 1.41 (dd, *J* = 7.4, 2.9 Hz, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*, δ, ppm): 143.18, 142.23, 137.71, 129.53, 128.58, 127.46, 127.19, 126.24, 53.75, 23.68, 21.59.

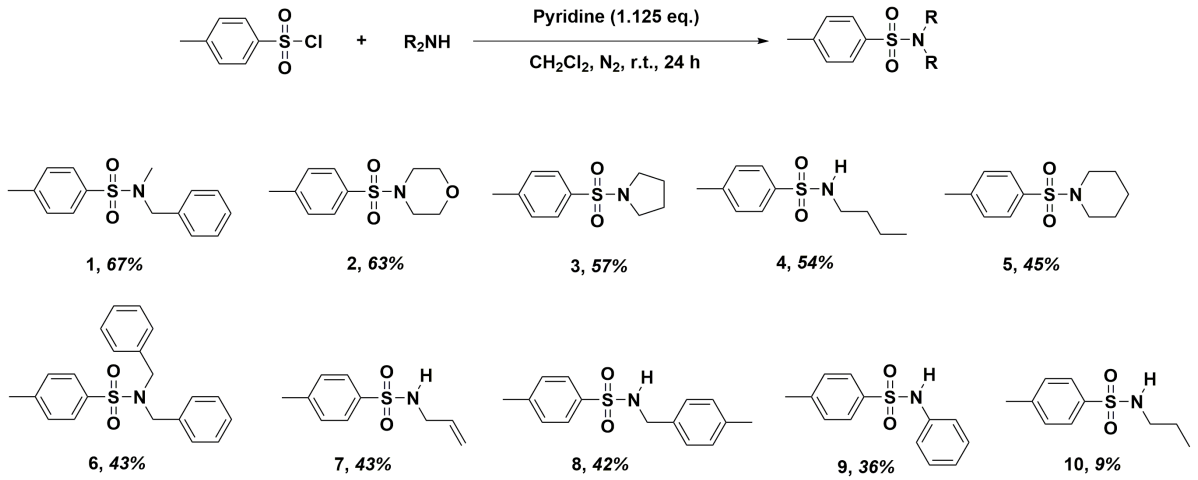



**Figure 2.** Compounds **1-10**, synthesized by the reaction of 4-methylbenzenesulfonyl chloride and an amine, in the presence of pyridine and dichloromethane. Reaction conditions: 4-methylbenzenesulfonyl chloride (5.25 mmol, 1.0 eq) was dissolved in 10 mL of dichloromethane, followed by the dropwise addition of the amine (5.90 mmol, 1.125 eq) and pyridine (5.90 mmol, 1.125 eq). Reactions were run at room temperature for 24 hours, under a nitrogen atmosphere.

#### *2.1.3. General procedure for the preparation of sulfonamides synthesized in the presence of sodium hydroxide (2-4, 8-10)*

4-Methylbenzenesulfonyl chloride (1.00 g, 5.25 mmol) was added to a flask containing 10 mL of tetrahydrofuran. An amine (5.90 mmol) was added dropwise to the stirring solution, followed by the dropwise addition of 0.59 M aqueous sodium hydroxide (10 mL, 5.90 mmol). The flask was sealed and left to react to completion at room temperature. Reaction completion was verified by TLC analysis. The mixture was then concentrated to half its volume, acidified with 5 M HCl, and chilled. The resulting precipitate is isolated via vacuum filtration and recrystallized from ethanol to afford the product in good purity and yield.

### *2.2. Crystallographic characterization*

The software used for data collection is as follows: data collection, APEX2 [16]; cell refinement and data reduction, SAINT [17]; program used to refine structure, SHELXL [18]; program used to solve the structure, SHELXS [19]; molecular graphics and publication material, OLEX2 [20,21]; program used to generate figures, Mercury [22-26]; absorbance correction, SADABS [27]. Hydrogen atoms were refined as riding: C-H = 0.95-1.00 Å with $U_{iso}$(H) = 1.5$U_{eq}$(C) for methyl groups, and $U_{iso}$(H) = 1.2$U_{eq}$(C) for methylene groups and aromatic hydrogen atoms. Hydrogen atom parameters were constrained.

### *2.3. Instrumentation*

$^{1}$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a JEOL ECZ400 spectrometer using a DMSO-$d_6$ or Chloroform-*d* solvent. Chemical shifts are reported in parts per million (ppm, δ) relative to the residual solvent peak, and coupling constants (J) are reported in Hertz (Hz). X-ray diffraction was carried out on a Bruker APEXII CCD diffractometer with Mo*K*α radiation.

## 3. Results and discussion

### *3.1. Tosylation of amines*

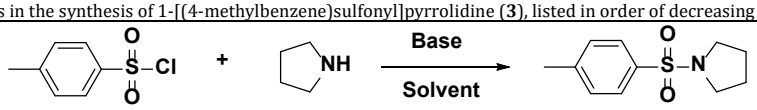
Preliminary experimentation involved the amination of 4-methylbenzenesulfonyl chloride or tosyl chloride in the presence of dichloromethane and pyridine. A variety of primary, secondary, and heterocyclic amines were used in the synthesis of sulfonamides. These amines were selected based on their similarity in structural features to existing sulfonamide drugs. The resulting products and corresponding yields are summarized in Figure 2.

Optimization of reaction conditions led to the development of a miscible biphasic solvent system amenable to various reagents. These changes led to decreased reaction times, improved yields, and ease of workup. In most cases, high purity products could be isolated directly from the reaction mixture after acidification without further purification. A variety of reagents and solvent combinations were implemented in the synthesis of 1-[(4-methylbenzene)sulfonyl]pyrrolidine (**3**; Table 1). Entries 5 and 6 show the effect of solvent change without the presence of an acid scavenger. A comparison of entries 5 and 6 lends credence to conditions that favor tetrahydrofuran over dichloromethane. A comparison of entries 3 and 4, carried out in the presence of pyridine, lends support to the same conclusion. The use of potassium carbonate and sodium hydroxide aqueous bases proved advantageous over the previous method with yields of 91%. Entry 1 resulted in a reaction time of 6 hours using potassium carbonate. The use of sodium hydroxide resulted in a reaction time of only 3 hours for entry 2, without sacrificing yield. This occurrence may be due to the increased basicity of sodium hydroxide. Methods involving the use of aqueous base and tetrahydrofuran proved most effective. Furthermore, the use of less toxic solvents and reagents lends credence to an environmentally benign synthesis of sulfonamides.

Reactions involving pyridine were conducted under an inert atmosphere due to concerns regarding the hydrolysis of the N-tosylpyridinium salt intermediate. Previously reported work provides mechanistic insight into the formation of *N*-tosylpyridinium in the context of sulfonates [28]. However, after achieving higher yields in the presence of aqueous pyridine and tetrahydrofuran it was concluded that the rate of hydrolysis is insignificant compared to the solvent and base combination chosen.

Having the optimized conditions in hand, the scope of the reaction of amines with 4-methylbenzenesulfonyl chloride was explored, utilizing potassium carbonate and sodium hydroxide (Figure 3). Yield increases are noted for either solvent combination, though the potassium carbonate base showed the best results. Reactions in which sodium hydroxide was used exhibited the shortest reaction times.

**Table 1.** Base and solvent effects in the synthesis of 1-[(4-methylbenzene)sulfonyl]pyrrolidine (**3**), listed in order of decreasing yield [a].




| Entry | Base | Solvent | Reaction time | Yield (%) |
|---|---|---|---|---|
| 1 | 0.59 M aq. $K_2CO_3$ | THF | 6 h | 91 |
| 2 | 0.59 M aq. NaOH | THF | 3 h | 91 |
| 3 | 0.59 M aq. Pyridine | THF | 24 h | 74 |
| 4 [b] | Pyridine | DCM | 24 h | 57 |
| 5 | - | THF | 24 h | 55 |
| 6 [b] | - | DCM | 24 h | 26 |

[a] Reaction condition: 4-methylbenzenesulfonyl chloride (5.25 mmol, 1.0 eq.) was dissolved in 10 mL of solvent, followed by the dropwise addition of both pyrrolidine (5.90 mmol, 1.125 eq.) and a base (5.90 mmol, 1.125 eq.). Reactions were run at room temperature.
[b] Reaction run under nitrogen atmosphere.

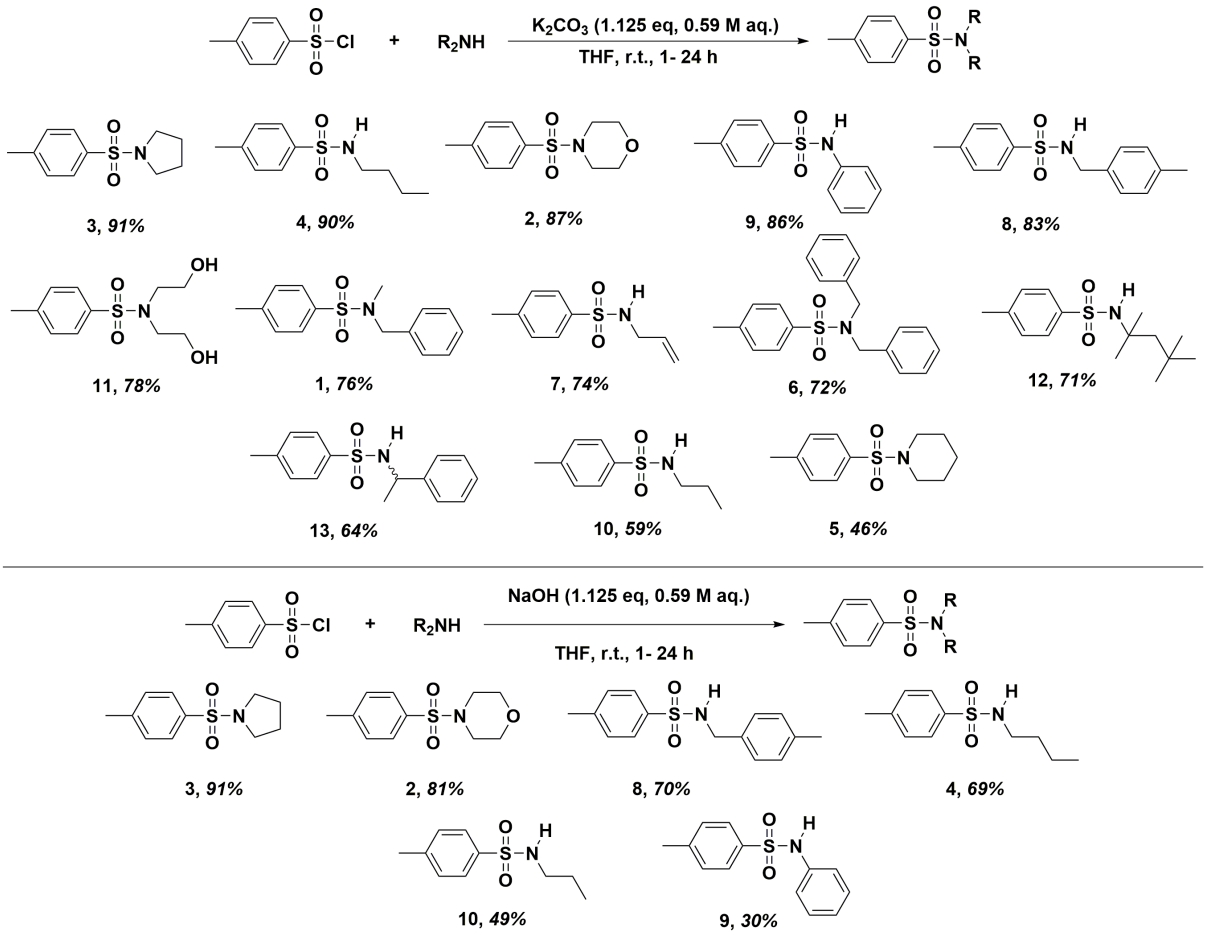



**Figure 3.** Compounds **1**-**13**, synthesized by the reaction of 4-methylbenzenesulfonyl chloride and an amine, in the presence of aqueous base and tetrahydrofuran. Reaction conditions: 4-methylbenzenesulfonyl chloride (5.25 mmol, 1.0 eq) was dissolved in 10 mL of tetrahydrofuran, followed by the dropwise addition of the amine (5.90 mmol, 1.125 eq) and 0.59 M aqueous base (5.90 mmol, 1.125 eq). Reactions were run at room temperature, reaction completion verified by TLC.

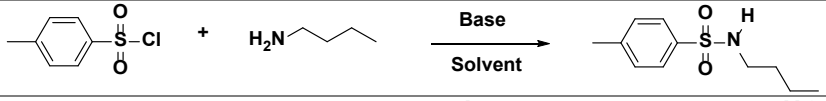
The base and solvent effects were investigated in the synthesis of *N*-butyl-4-methylbenzenesulfonamide (**4**; Table 2). Entry 6 in Table 2 represents the preliminary method, with the lowest yield of 54%. Entries 1, 2, and 3 in Table 2 with yields of 90, 82, and 80%, respectively, represent the effect of changing the solvent alone. The use of acetone and ethanol results in lower-yielding reactions than that of tetrahydrofuran. A comparison of entries 1 and 4 shows dramatic decreases in yield from 90 to 77% by doubling the base's molarity. It was concluded from the results that methods involving the use of tetrahydrofuran and 0.59 M aqueous potassium carbonate offered the best combination of yield and reaction time while amenable to a wide range of amines.

Upon further analysis of the results, no significant trend relating substrate and product yield was noted, suggesting steric and electronic effects were not the only factors involved. The results are, to some extent, dependent on differences in product solubility and methods of isolation/recrystallization, which could explain the absence of any trend.

### *3.2. Isolation and recrystallization*

Methods of isolation varied depending on the starting materials and conditions used. All methods described herein were carried out after acidification of the reaction mixture. Primary amine derived sulfonamides or sulfonamides synthesized in the presence of dichloromethane and pyridine underwent extraction with dichloromethane to afford the crude product.

**Table 2.** Base and solvent effects in the synthesis of *N*-butyl-4-methylbenzenesulfonamide [a] (**4**). Entries are presented in order of decreasing yield.




| Entry | Base | Solvent | Yield (%) |
|---|---|---|---|
| 1 [c] | 0.59 M aq. $K_2CO_3$ | THF | 90 |
| 2 [c] | 0.59 M aq. $K_2CO_3$ | Acetone | 82 |
| 3 [c] | 0.59 M aq. $K_2CO_3$ | Ethanol | 80 |
| 4 [d] | 1.2 M aq. $K_2CO_3$ | THF | 77 |
| 5 [c] | 0.59 M aq. NaOH | THF | 69 |
| 6 [b] | Pyridine | DCM | 54 |

[a] Reaction conditions: Reaction conditions: 4-methylbenzenesulfonyl chloride (5.25 mmol, 1.0 eq) was dissolved in solvent, followed by the dropwise addition of butylamine (5.90 mmol, 1.125 eq) and base (5.90 mmol, 1.125 eq). Reactions were run at room temperature for 24 hours.
[b] Reaction run under nitrogen atmosphere; 10 mL of solvent.
[c] 10 mL of aqueous base; 10 mL of solvent.
[d] 5 mL of aqueous base; 5 mL of solvent.

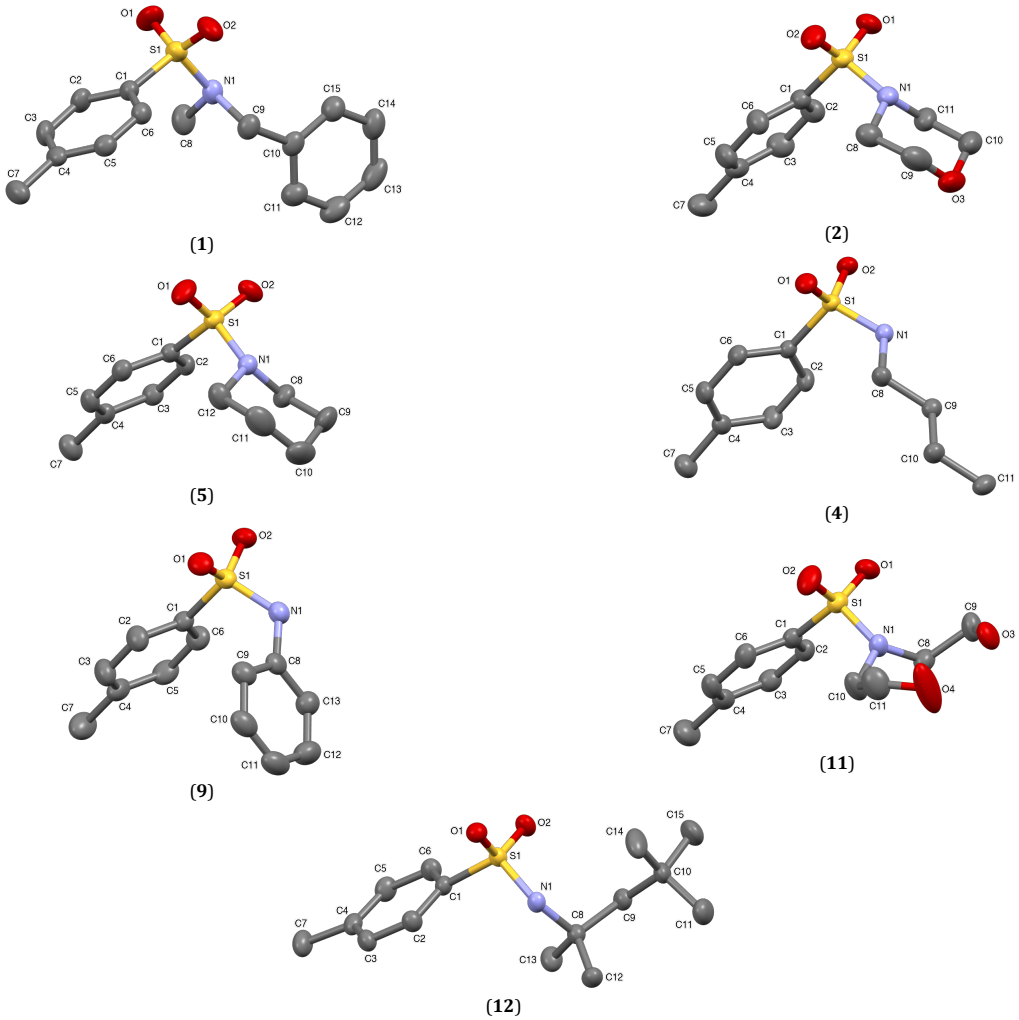



**Figure 4.** The structure of *N*-benzyl-*N*,4-dimethylbenzenesulfonamide (**1**), 4-[(4-methylbenzene)sulfonyl]morpholine (**2**), *N*-butyl-4-methylbenzenesulfonamide (**4**), 1-[(4-methylbenzene)sulfonyl]piperidine (**5**), 4-methyl-*N*-phenylbenzenesulfonamide (**9**), *N*,*N*-bis(2-hydroxyethyl)-4-methylbenzenesulfonamide (**11**) and 4-methyl-*N*-(2,4,4-trimethylpentan-2-yl)benzenesulfonamide (**12**) elucidated by X-ray diffraction at 173 K with atom labeling schemes. Displacement of ellipsoids is shown at the 50% probability level. Hydrogen atoms have been omitted for clarity.

Secondary or heterocyclic amine derived sulfonamides synthesized in a biphasic system were isolated directly from the reaction mixture. Primary amine derived sulfonamides gave crude products as liquids or amorphous solids. Solid crude products were regularly obtained with the use of secondary or heterocyclic amines. The crude products underwent different methods of recrystallization depending on their state. Liquid and amorphous solid products were dried under vacuum and triturated with either chilled diethyl ether, hexanes, or petroleum ether to give a solid. The solid products were then recrystallized in ethanol and chilled at 0 °C to afford highly pure products. The dropwise addition of chilled petroleum ether or hexane was occasionally employed to speed up recrystallization.

### *3.3. Crystallographic characterization*

The crystal structures of five novel compounds, and two packing polymorphs of existing structures were obtained through single-crystal X-ray diffraction experiments (Figure 4).

**Table 3.** Data parameters for the crystal lattices of the investigated sulfonamide derivatives.

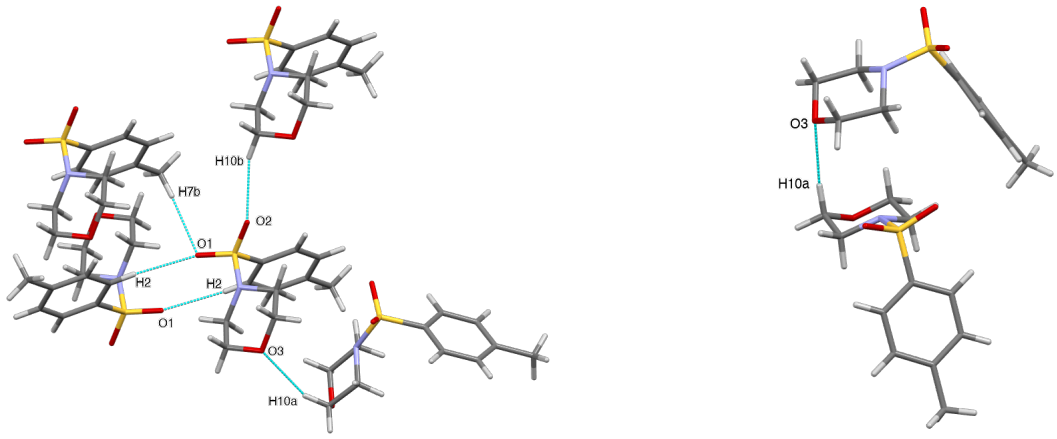
| **Compound** | **1** | **2** | **4** | **9** |
|---|---|---|---|---|
| Molecular formula | $C_{15}H_{17}NO_2S$ | $C_{11}H_{15}NO_3S$ | $C_{11}H_{17}NO_2S$ | $C_{13}H_{13}NO_2S$ |
| Crystal system | Monoclinic | Monoclinic | Monoclinic | Monoclinic |
| Space group | $P2_1/c$ | $P2_1/c$ | $P2_1/c$ | $P2_1/c$ |
| $M_r$ | 275.37 | 241.31 | 227.31 | 247.32 |
| $a$ (Å) | 15.0517(2) | 8.0852(10) | 7.85980(10) | 8.6674(1) |
| $b$ (Å) | 8.2817(1) | 17.913(2) | 15.3377(2) | 9.6925(1) |
| $c$ (Å) | 11.8484(2) | 8.7501(11) | 10.23190(10) | 15.1001(2) |
| $\beta$ (°) | 107.1101(9) | 111.2125(14) | 106.5662(8) | 98.8679(7) |
| Volume (Å$^3$) | 1411.58(4) | 1181.4(3) | 1182.27(2) | 1253.38(3) |
| Crystal size (mm) | 0.354 × 0.232 × 0.188 | 0.275 × 0.164 × 0.118 | 0.478 × 0.293 × 0.15 | 0.431 × 0.425 × 0.322 |
| Radiation type | Cu $K\alpha$ | Mo $K\alpha$ | Cu $K\alpha$ | Cu $K\alpha$ |
| T (K) | 173 K | 173 K | 173 K | 173 K |
| $\mu$ (mm$^{-1}$) | 2.015 | 0.266 | 2.284 | 2.211 |
| $D_x$ (Mg m$^{-3}$) | 1.296 | 1.357 | 1.277 | 1.311 |
| $Z$ | 4 | 4 | 4 | 4 |
| ***Data collection*** | | | | |
| $T_{min}$ | 0.663 | 0.688 | 0.658 | 0.647 |
| $T_{max}$ | 0.753 | 0.745 | 0.754 | 0.754 |
| Measured reflections | 12252 | 9976 | 13296 | 19721 |
| Independent reflections | 2631 | 2330 | 2324 | 2457 |
| Reflections with $I > 2\sigma(I)$ | 2219 | 1829 | 2104 | 2380 |
| $R_{int}$ | 0.038 | 0.038 | 0.029 | 0.032 |
| $\theta_{max}$ (°) | 70.2 | 26.1 | 72.1 | 72.1 |
| $\theta_{min}$ (°) | 3.1 | 2.3 | 5.4 | 5.4 |
| ***Refinement*** | | | | |
| Reflections | 2631 | 2330 | 2324 | 2457 |
| Parameters | 174 | 146 | 142 | 159 |
| $wR(F^2)$ | 0.120 | 0.127 | 0.104 | 0.099 |
| $R[F^2 > 2\sigma(F^2)]$ | 0.0412 | 0.045 | 0.037 | 0.037 |
| $S$ | 1.04 | 1.02 | 1.05 | 1.08 |
| $\Delta\rho_{max}$ (e Å$^{-3}$) | 0.34 | 0.31 | 0.24 | 0.21 |
| $\Delta\rho_{min}$ (e Å$^{-3}$) | −0.40 | −0.29 | −0.49 | −0.47 |
| **Compound** | **5** | **11** | **12** | |
| Molecular formula | $C_{12}H_{17}NO_2S$ | $C_{11}H_{15}NO_4S$ | $C_{15}H_{25}NO_2S$ | |
| Crystal system | Orthorhombic | Orthorhombic | Triclinic | |
| Space group | $P2_12_12_1$ | $Pbca$ | $P$-1 | |
| $M_r$ | 247.32 | 259.33 | 283.44 | |
| $a$ (Å) | 6.15583(9) | 17.8575(15) | 8.4584(15) | |
| $b$ (Å) | 12.13534(18) | 7.1268(6) | 8.7842(16) | |
| $c$ (Å) | 16.3142(2) | 19.8012(17) | 11.251(2) | |
| $\alpha$ (°) | 90 | 90 | 98.6996(18) | |
| $\beta$ (°) | 90 | 90 | 102.7748(18) | |
| $\gamma$ (°) | 90 | 90 | 103.0230(18) | |
| Volume (Å$^3$) | 1218.72(3) | 2520.0(4) | 776.3(2) | |
| Crystal size (mm) | 0.288 × 0.247 × 0.235 | 0.31 × 0.281 × 0.172 | 0.199 × 0.174 × 0.159 | |
| Radiation type | Cu $K\alpha$ | Mo $K\alpha$ | Mo $K\alpha$ | |
| T (K) | 173 | 173 | 173 | |
| $\mu$ (mm$^{-1}$) | 2.246 | 0.260 | 0.207 | |
| $D_x$ (Mg m$^{-3}$) | 1.304 | 1.367 | 1.213 | |
| $Z$ | 4 | 8 | 2 | |
| ***Data collection*** | | | | |
| $T_{min}$ | 0.695 | 0.683 | 0.691 | |
| $T_{max}$ | 0.754 | 0.745 | 0.745 | |
| Measured reflections | 11732 | 18825 | 13646 | |
| Independent reflections | 2411 | 2307 | 3166 | |
| Reflections with $I > 2\sigma(I)$ | 2355 | 1942 | 2692 | |
| $R_{int}$ | 0.027 | 0.036 | 0.030 | |
| $\theta_{max}$ (°) | 72.1 | 25.4 | 26.4 | |
| $\theta_{min}$ (°) | 4.5 | 2.1 | 1.9 | |
| ***Refinement*** | | | | |
| Reflections | 2411 | 1942 | 2692 | |
| Parameters | 146 | 163 | 182 | |
| $wR(F^2)$ | 0.0931 | 0.1380 | 0.1106 | |
| $R[F^2 > 2\sigma(F^2)]$ | 0.0352 | 0.0480 | 0.0399 | |
| $S$ | 1.09 | 1.07 | 1.07 | |
| $\Delta\rho_{max}$ (e Å$^{-3}$) | 0.17 | 0.64 | 0.27 | |
| $\Delta\rho_{min}$ (e Å$^{-3}$) | −0.46 | −0.53 | −0.39 | |

A comparison of the resulting parameters can be found in Table 3. In addition to those mentioned below, the structures of 1-[(4-methylbenzene)sulfonyl]pyrrolidine (**3**), 4-methyl-*N*-(4-met-hylbenzyl)benzenesulfonamide (**8**), and 4-methyl-*N*-propylbenzenesulfonamide (**10**) were previously reported using the conditions aforementioned [29-31].

The structures of 4-[(4-methylbenzene)sulfonyl] morpholine (**2**), 4-methyl-*N*-phenylbenzenesulfonamide (**9**), *N*-benzyl-*N*,4-dimethylbenzenesulfonamide (**1**), and *N*-butyl-4-methyl benzenesulfonamide (**4**) exhibited monoclinic systems ($P2_1/c$ space group) both with one screw axis (2-fold) and one glide plane geometry and an inversion center. 1-[(4-Methylbenzene) sulfonyl]piperidine (**5**) showed an orthorhombic system ($P2_12_12_1$ space group) and had both one screw axis (2-fold) and one glide plane geometry but lacked an inversion center. 4-Methyl-*N*-(2, 4, 4-trimethylpentan-2-yl) benzenesulfonamide (**12**) revealed a triclinic system ($P$-1 space group) with only an inversion center.

**Table 4.** C1-S1-N1-C torsion angles (°) of sulfonamide crystal structures. Atoms numbering follows scheme in Figure 3.

| Compound | Torsion | Angle (°) |
|---|---|---|
| *N*-Benzyl-*N*,4-dimethylbenzenesulfonamide (**1**) | C1-S1-N1-C8 | 63.1(2) |
| | C1-S1-N1-C9 | -71.6(2) |
| 4-[(4-Methylbenzene)sulfonyl]morpholine (**2**) | C1-S1-N1-C8 | -65.2(2) |
| | C1-S1-N1-C11 | 68.8(2) |
| *N*-Butyl-4-methylbenzenesulfonamide (**4**) | C1-S1-N1-C8 | -61.1(1) |
| 1-[(4-Methylbenzene)sulfonyl]piperidine (**5**) | C1-S1-N1-C8 | 67.8(1) |
| | C1-S1-N1-C12 | -70.7(1) |
| 4-Methyl-*N*-phenylbenzenesulfonamide (**9**) | C1-S1-N1-C8 | -50.6(1) |
| *N*,*N*-Bis(2-hydroxyethyl)-4-methylbenzenesulfonamide (**11**) | C1-S1-N1-C8 | 86.4(2) |
| | C1-S1-N1-C10 | -62.9(2) |
| 4-Methyl-*N*-(2,4,4-trimethylpentan-2-yl)benzenesulfonamide (**12**) | C1-S1-N1-C8 | 78.3(2) |




**(A)** **(B)**

**Figure 5.** Depiction of hydrogen bond contacts (**A**) and the O3-H10a hydrogen bond contact (**B**) present in the crystal structure of 4-[(4-methylbenzene)sulfonyl]morpholine (**2**).

*N,N-Bis*(2-hydroxyethyl)-4-methylbenzene sulfonamide (**11**) exhibited an orthorhombic system (*Pbca* space group) with three-screw axis (2-fold) and three glide plane geometries as well as an inversion center. All structures were oriented gauche about the S1-N1 bond with C1-S1-N1-C torsion angles reported in Table 4. *N,N-Bis*(2-hydroxyethyl)-4-methylbenzene sulfonamide (**11**) showed the 2-hydroxyethyl and aryl group oriented at a relatively high C1-S1-N1-C8 torsional angle of 86.4(2)°. This may be due to the orientation of the 2-hydroxyethyl groups, which are connected through an intramolecular hydrogen bond. In agreement with known values, the S1=O1 and S1=O2 bond lengths for all structures fell within the range of 1.4251(18)-1.4428(11) Å. The C1-S1-N1 bond angles are as follows: 106.84(8)°, *N*-benzyl-*N*,4-dimethyl benzenesulfonamide (**1**); 106.51(9)°, 4-[(4-methylbenzene) sulfonyl]morpholine (**2**); 107.74(7)°, *N*-butyl-4-methylbenzene sulfonamide (**4**); 106.66(7)°, 1-[(4-methyl benzene)sulfonyl] piperidine (**5**); 106.57(7)°, 4-methyl-*N*-phenylbenzenesulfon amide (**9**); 106.57(10)°, *N,N*-bis(2-hydroxyethyl)-4-methyl benzenesulfonamide (**11**); 110.29(7)°, 4-methyl-*N*-(2,4,4-tri methylpentan-2-yl)benzenesulfonamide (**12**). The central sulfur atom, S1, exhibits a slightly distorted tetrahedron geometry in all structures according to the $\tau_4$ descriptor for four-fold coordination [32].

Two of the compounds, 4-[(4-methylbenzene)sulfonyl] morpholine (**2**) and 4-methyl-*N*-phenylbenzenesulfonamide (**9**), have previously reported crystal structures. The packing polymorph of 4-methyl-*N*-phenylbenzenesulfonamide has been reported at a temperature of 299 K [33]. The new structure had a cell measurement temperature of 178 K. The two lattices' $\beta$ unit cell angles differ significantly. The previously reported structure showed a $\beta$ angle of 113.200 (2)°, while the newly reported structure shows $\beta$ = 98.8679 (7)°. Additionally, the lengths of the previously reported lattice unit cell were $a$ = 8.770 (2) Å, $b$ = 9.768 (2) Å, and $c$ = 16.234 (5) Å. The newly reported structure had lengths of $a$ = 8.6674 (1) Å, $b$ = 9.6925(1) Å, and $c$ = 15.1001 (2) Å. While both structures are oriented gauche about the S1-N1 bond, the C8-N1-S1-C1 torsional angle differed slightly. The previously reported structure revealed a C8-N1-S1-C1 torsional angle of -51.6 (3)°, whereas the newly obtained structure exhibited the same torsional angle as -50.6 (1)°. Similarly, a polymorph of 4-[(4-methylbenzene)sulfonyl] morpholine (**2**) has been previously reported at a temperature of 210 K [34]. The new structure had a cell measurement temperature of 173 K. The previously reported structure had unit cell lengths of $a$ = 8.068 (2) Å, $b$ = 18.294 (3) Å, and $c$ = 8.815 (2) Å with a $\beta$ angle of 111.694 (2)°. The new structure had unit cell lengths of $a$ = 8.0852 (10) Å, $b$ = 17.931 (2) Å, and $c$ = 8.7501 (11) Å with a $\beta$ angle of 111.2125 (14)°. A notable difference in the hydrogen bond contact involving morpholines heteroatoms was noted. The previous structure reported a O3-H10a hydrogen bond contact length of 2.794 Å, whereas the new structure reported a length of 2.702 Å for the same contact (Figure 5). Differences in temperature offer a suitable explanation for the conformational differences observed in the polymorphs. Therefore, the exhibited polymorphism is most likely a result of temperature dependence.

## 4. Conclusion

In this work, methods for the tosylation of nitrogen nucleophiles using various base and solvent combinations were proposed. The use of aqueous potassium carbonate and tetrahydrofuran gave the best combination of yield and reaction time. The methods were useful in producing a broad range of sulfonamides from primary, secondary, and hetero-cyclic amines. The ability to support a wide range of nitrogen nucleophiles allows for producing a variety of biologically significant compounds. The new synthetic method resulted in

good yields with decreased environmental impact, reaction time, and work-up over the previous method. This facile method produced highly pure sulfonamide products and has the potential to create a variety of biologically significant compounds for therapeutic use. Furthermore, crystallographic characterization of the resulting structures revealed data for five novel structures and two polymorphs of previously reported structures. This data will be useful in determining the conformational preferences of sulfonamide derivatives and predicting their structure-property relationships.

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## Supporting information

CCDC-2054873 (**1**), 2054874 (**2**), 2054875 (**4**), 2054876 (**5**), 2054877 (**9**), 2081811 (**11**) and 2081812 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

## Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Sample of the compounds are available from the author.

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