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Synthesis and crystallographic characterization of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide

 Brock Anton Stenfors  and Felix Nyuangem Ngassa *

 Department of Chemistry, Grand Valley State University, 1 Campus Drive, Allendale, MI 49401, USA
stenforb@mail.gvsu.edu (B.A.S.), ngassaf@gvsu.edu (F.N.N.)

 * Corresponding author at: Department of Chemistry, Grand Valley State University, 1 Campus Drive, Allendale, MI 49401, USA.
 e-mail: ngassaf@gvsu.edu (F.N. Ngassa).

RESEARCH ARTICLE



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ABSTRACT

N-Benzyl-4-methylbenzenesulfonamides were prepared via a two-step synthetic process involving the treatment of 4-methylbenzenesulfonyl chloride with a primary amine to give the corresponding 4-methylbenzenesulfonamide. Benzylation of the sulfonamide affords the substituted *N*-benzyl-4-methylbenzenesulfonamides. The similarities between the two steps of synthesis lend credence to the development of a one-pot synthesis of substituted *N*-benzyl-4-methylbenzenesulfonamides from 4-methylbenzenesulfonyl chloride. This method was applied to the synthesis of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide and characterized through spectroscopic and crystallographic means. The crystal structure of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide was obtained by single-crystal X-ray diffraction. The crystal structure reveals an orthorhombic *Pna*2₁ space group with cell parameters $a = 18.6919$ (18) Å, $b = 10.5612$ (10) Å, $c = 8.1065$ (8) Å, $V = 1600.3$ (3) Å³ and $Z = 4$, $T = 173.15$ K, $\mu(\text{MoK}\alpha) = 0.206$ mm⁻¹, $D_{\text{calc}} = 1.251$ g/cm³, 14455 reflections measured ($4.36^\circ \leq 2\theta \leq 54.96^\circ$), 3619 unique ($R_{\text{int}} = 0.0439$, $R_{\text{sigma}} = 0.0429$) which were used in all calculations. The final R_1 was 0.0428 ($I > 2\sigma(I)$) and wR_2 was 0.1079 [all data]. Molecules are linked through C-H...N hydrogen bonds and C-H... π interactions.

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1. Introduction

The *N*-benzylbenzenesulfonamide moiety is found in a variety of biologically significant compounds. In particular, 2-[(*N*-benzyl-*N*-phenylsulfonamido)alkyl] amide derivatives (*R*)-2-[(4-chlorobenzensulfonyl)-(4-methoxybenzyl)amino]-2-hexanolactam and (*R*)-2-[(4-chlorobenzensulfonyl)-(4-methoxybenzyl)amino]-4-methylpentanoic acid amide have been reported to exhibit inhibition against γ -secretase (Figure 1) [1]. γ -Secretase is a four-subunit protein responsible for the cleavage of numerous type-1 transmembrane proteins [2]. Inhibition of this protein leads to the decreased production of the amyloid β -peptide (A β), whose accumulation within the brain is one of the two pathological hallmarks of patients with Alzheimer's disease (AD) [3,4]. γ -Secretase inhibition via sulfonamide compounds lends credence to the prevention or treatment of AD.

The *N*-benzylbenzenesulfonamide moiety is also found in novel nonsteroidal glucocorticoid receptor modulators (Figure 2) [5]. The glucocorticoid receptor (GR) is a ligand-activated transcription factor and a component of the nuclear receptor superfamily [6]. GR is activated by endogenous and synthetic glucocorticoids [7]. In recent years, synthetic glucocorticoids are most commonly used as anti-inflammatory agents [8].

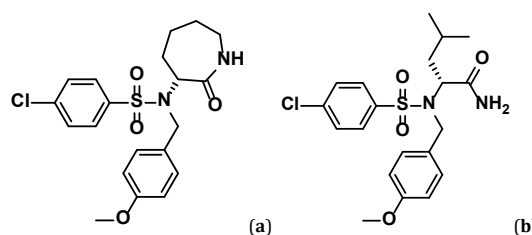


Figure 1. 2-[(*N*-Benzyl-*N*-phenylsulfonamido)alkyl] amide derivatives reported to exhibit inhibition against γ -secretase. The compounds shown are (*R*)-2-[(4-chlorobenzensulfonyl)-(4-methoxybenzyl)amino]-2-hexanolactam (a) and (*R*)-2-[(4-chlorobenzensulfonyl)-(4-methoxybenzyl)amino]-4-methylpentanoic acid amide (b).

A facile synthesis of compounds containing the *N*-benzylbenzenesulfonamide moiety is necessary to produce novel drugs for therapeutic use. Herein, we report an efficient and environmentally benign synthesis of *N*-benzyl-4-methylbenzenesulfonamide derivatives as well as the crystallographic characterization of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide.

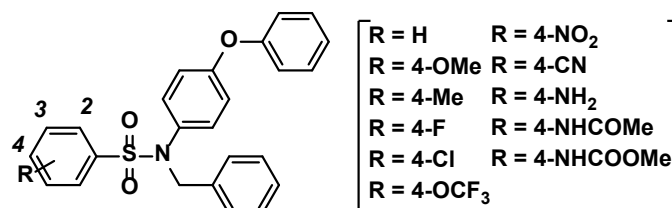


Figure 2. *N*-Benzylbenzenesulfonamide compounds exhibiting GR antagonistic activity.

2. Experimental

The reagents used in the synthesis of *N*-benzyl-4-methylbenzenesulfonamide derivatives 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. ¹H NMR spectra (400 MHz) were recorded on a JEOL ECZ400 spectrometer using a 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). The results were analyzed, and figures were created with the use of MestreNova [9].

2.1. Synthesis of *N*-allyl-4-methylbenzenesulfonamide (2a)

4-Methylbenzenesulfonyl chloride (1.002 g, 5.25 mmol) was dissolved in 10 mL of tetrahydrofuran. Allylamine (0.46 mL, 5.90 mmol) was added dropwise to the stirring mixture, followed by the dropwise addition of 0.59 M aqueous potassium carbonate (10 mL, 5.90 mmol). The reaction mixture was stirred at room temperature for 24 hours. After acidification with 5 M HCl and dilution with 15 mL of dichloromethane, the organic layer was washed three times with water and once with brine. The aqueous layers were back extracted with 10 mL of dichloromethane. The combined organic layers were then dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was recrystallized in ethanol to afford clear crystals, dried under vacuum for 24 hours. M.p.: 69–72 °C. Yield: 0.814 g, 73 %. *R_f* = 0.44 (CH₂Cl₂). ¹H NMR (400 MHz, Chloroform-*d*, δ , ppm): 7.78–7.70 (m, 2H, Ar-H), 7.30 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.71 (ddt, *J* = 17.2, 10.2, 5.8 Hz, 1H, =CH), 5.15 (dq, *J* = 17.1, 1.5 Hz, 1H, =CH_{trans}), 5.09 (dq, *J* = 10.3, 1.3 Hz, 1H, =CH_{cis}), 4.44 (s, 1H, NH), 3.57 (tt, *J* = 6.0, 1.5 Hz, 2H, NCH₂), 2.42 (s, 3H, CH₃). ¹³C NMR (100 MHz, Chloroform-*d*, δ , ppm): 143.66, 136.98, 133.06, 129.85, 127.25, 117.87, 45.90, 21.65. HRMS (ESI): calcd. for C₁₀H₁₃NNaO₂S [M + Na]⁺ 234.2700; Found 234.2690.

2.2. Synthesis of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide (3a)

N-Allyl-4-methylbenzenesulfonamide (0.905 g, 4.28 mmol) was added dropwise to a stirring solution of benzyl bromide (0.51 mL, 4.29 mmol) in 10 mL of tetrahydrofuran. This was followed by the dropwise addition of 0.535 M sodium hydroxide (10 mL, 5.35 mmol) and the mixture was left to stir for 24 hours at room temperature. After 24 hours, a white precipitate was isolated directly from the reaction mixture via vacuum filtration. The crude product was recrystallized in ethanol to afford white crystals, dried under vacuum for 24 hours. M.p.: 44–47 °C. Yield: 0.819 g, 67 %. *R_f* = 0.64 (CH₂Cl₂). ¹H NMR (400 MHz, Chloroform-*d*, δ , ppm): 7.77–7.69 (m, 2H, Ar-H), 7.34–7.20 (m, 7H, Ar-H), 5.45 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, =CH), 5.05 (dq, *J* = 10.1, 1.2 Hz, 1H, =CH_{trans}), 4.98 (dq, *J* = 17.0, 1.4 Hz, 1H, =CH_{cis}), 4.32 (s, 2H, NCH₂), 3.74 (dt, *J* = 6.5, 1.3 Hz, 2H, NCH₂), 2.43 (s, 3H, CH₃). ¹³C NMR (100 MHz, Chloroform-*d*, δ , ppm): 143.42, 137.60, 136.08, 132.25, 129.86, 128.63,

128.57, 127.81, 127.31, 119.52, 50.24, 49.55, 21.65. HRMS (ESI): calcd. for C₁₇H₁₉NNaO₂S [M+Na]⁺ 324.3800; Found 324.3801.

2.3. Single-crystal X-ray diffraction data collection

The data for the crystallographic characterization of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide was collected through φ and ω scans using a Bruker APEXII CCD diffractometer with MoK α radiation (λ = 0.71073 Å) at 173 K. The following programs were used during the crystallographic characterization of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide: Data collection, APEX2 [10]; cell refinement, SAINT [11]; data reduction, SAINT [11]; program used to solve structure, SHELXT [12]; program used to refine structure, OLEX2 [13,14]; program used to generate figures, Mercury [15–19]; Absorbance correction, SADABS [20].

The crystal data, data collection and refinement details are summarized in Table 1. Hydrogen atoms were placed in calculated positions and refined as riding with *U*_{iso}(H) = 1.2*U*_{eq}(C) for all methylene groups and aromatic hydrogens (C-H = 0.95–1.00 Å) and *U*_{iso}(H) = 1.5*U*_{eq}(C) for all methyl groups.

3. Results and discussion

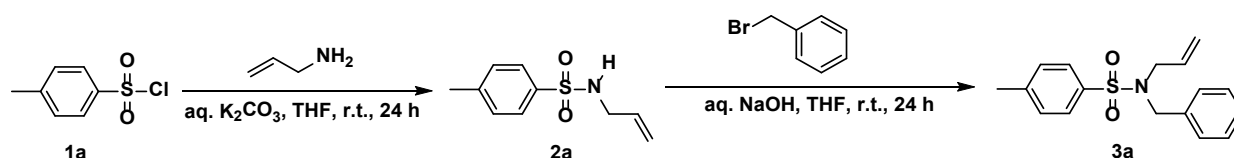
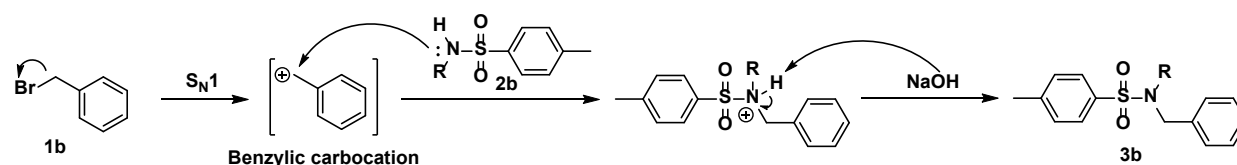
3.1. Synthesis

Preliminary experimentation regarding the synthesis of sulfonamides was done via the treatment of 4-methylbenzenesulfonyl chloride with an amine in the presence of dichloromethane and pyridine. This reaction resulted in low yields, long reaction times, and had a moderate environmental impact due to the carcinogenic properties of dichloromethane. Due to the apparent drawbacks of the reaction, novel methods were developed to produce the sulfonamide compounds more efficiently with less environmental impact over the previous method. In doing so, a single-phase two-solvent system was developed using an aqueous ionic base and tetrahydrofuran. As a result, yields were increased drastically while shorter reaction times were observed. Two ionic bases, sodium hydroxide and potassium carbonate, were used. Potassium carbonate gave the highest yielding reactions, while sodium hydroxide gave the shortest reaction times. It was determined that the use of potassium carbonate allows for high yield reactions without a significant sacrifice in reaction time. The relatively mild nature of the base and solvent used decreases the environmental impact of producing sulfonamides.

The synthesized primary amine derived from 4-methylbenzenesulfonamides is able to undergo benzylation via nucleophilic substitution by acting as weak nucleophiles. Due to the compound's weakly nucleophilic nature, a substitution reaction was created using conditions that support S_N1-like reactions. Scheme 1 shows the application of this method regarding the synthesis of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide (3a).

Table 1. Crystal data, data collection, and refinement details for the crystallographic characterization of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide.

Crystal data	
C ₁₇ H ₁₉ NO ₂ S	$D_x = 1.251 \text{ Mg m}^{-3}$
$M_r = 301.412$	Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$
Orthorhombic, $Pna2_1$	Cell parameters from 5268 reflections
$a = 18.6919(18) \text{ \AA}$	$\theta = 2.2^\circ - 27.5^\circ$
$b = 10.5612(10) \text{ \AA}$	$\mu = 0.206 \text{ mm}^{-1}$
$c = 8.1065(8) \text{ \AA}$	$T = 173 \text{ K}$
$V = 1600.3(3) \text{ \AA}^3$	Plate, colorless
$Z = 4$	$0.316 \times 0.273 \times 0.152 \text{ mm}$
$F(000) = 640.8$	
Data collection	
Bruker APEXII CCD diffractometer	14455 measured reflections
φ and ω scans	2960 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan	3619 independent reflections
SADABS-2014/5 was used for absorption correction. $wR_2(\text{int})$ was 0.0662 before and 0.0575 after correction. The ratio of minimum to maximum transmission is 0.9025. The $\lambda/2$ correction factor is 0.00150.	$R_{\text{int}} = 0.044$
$T_{\text{min}} = 0.673$, $T_{\text{max}} = 0.746$	$\theta_{\text{max}} = 27.5^\circ$, $\theta_{\text{min}} = 2.2^\circ$
	$h = -24 \rightarrow 23$
	$k = -13 \rightarrow 13$
	$l = -10 \rightarrow 10$
Refinement	
Refinement on F^2	H atom treatment: constrained
Least-squares matrix: full	$w = 1/[\sigma^2(F_o^2) + (0.0564P)^2 + 0.1062P]$, where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.043$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$wR(F^2) = 0.114$	$\Delta\rho_{\text{max}} = 0.32 \text{ e \AA}^{-3}$
$S = 1.07$	$\Delta\rho_{\text{min}} = -0.24 \text{ e \AA}^{-3}$
3619 reflections	Absolute structure: Flack x determined using 2140 quotients
191 parameters	$[(I^+)-(I^-)]/[(I^+)+(I^-)]$ [21]
1 restraint	Absolute structure parameter: 0.03(9)
Hydrogen site location: mixed	

**Scheme 1.** Synthesis of *N*-allyl-4-methylbenzenesulfonamide (2a) via the treatment of 4-methylbenzenesulfonyl chloride (1a) with allylamine and the benzylation of compound 2a to form *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide (3a).**Scheme 2.** A proposed S_N1-like mechanism for the benzylation of primary amine derived from 4-methylbenzenesulfonamides.

The benzylation of primary amine derived from 4-methylbenzenesulfonamides most likely follows an S_N1-like mechanism (Scheme 2). The use of benzyl bromide (1b) adequately generates the highly stable benzylic carbocation which readily reacts with the weakly nucleophilic sulfonamide (2b). The benzylation product (3b) is formed following proton transfer.

Though further experimentation is necessary to reach a conclusion, the results lend credence to the possibility of a one-pot synthesis of benzylation primary amine derived 4-methylbenzenesulfonamides from 4-methylbenzenesulfonyl chloride.

3.2. Crystallographic characterization

The crystallographic characterization of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide was carried out through the use of single-crystal X-ray diffraction. Pertinent data such as fractional atomic coordinates, equivalent displacement parameters, and anisotropic displacement parameters can be found in the supporting information. The selected bond lengths (Å), bond angles (°), and torsion angles (°) for the crystal structure of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide can be found

in Tables 2, 3, and 4, respectively. The asymmetric unit of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide (3b) is shown in Figure 3.

The crystal structure of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide (3b) exhibits a two-fold screw axis ($-x, -y, 1/2+z$) and two glide plane ($1/2-x, 1/2+y, 1/2+z$ and $1/2+x, 1/2-y, z$) geometries which result from efficient packing. The structure reveals an orthorhombic system, $Pna2_1$ space group. According to the τ_4 descriptor for four-fold coordination, the sulfur atom, S1, has a slightly distorted tetrahedron geometry [22]. The bond lengths of the carbonyls S1=O1 and S1=O2 are 1.4290 (18) and 1.4342 (18) Å, respectively. These values are in agreement with known values. The aryl groups of the structure are oriented gauche about the S1-N1 bond with a C1-S1-N1-C11 torsion angle of 84.2 (2)°. The N1-C11, N1-C8, S1-C1, and N1-S1 bond lengths were 1.466 (3), 1.471 (3), 1.763 (2) and 1.636 (2) Å, respectively. The N1-S1-O1 bond angle was 107.46 (10)°. The molecules are linked through C-H...N hydrogen bonds and C-H... π interactions. Table 5 summarizes the hydrogen bond contacts present in the structure of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide. A depiction of these can be found in Figure 4.

Table 2. Bond distances (Å) for *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide. Atoms labels follow the atom numbering scheme in Figure 3.

Bond	Distance (Å)	Bond	Distance (Å)
S1-O1	1.4290(18)	C4-C7	1.518(4)
S1-O2	1.4342(18)	C5-C6	1.382(3)
S1-N1	1.636(2)	C8-C9	1.500(4)
S1-C1	1.763(2)	C9-C10	1.302(4)
N1-C8	1.471(3)	C11-C12	1.519(3)
N1-C11	1.466(3)	C12-C13	1.385(4)
C1-C2	1.394(3)	C12-C17	1.378(3)
C1-C6	1.392(3)	C13-C14	1.390(4)
C2-C3	1.381(4)	C14-C15	1.380(4)
C3-C4	1.390(4)	C15-C16	1.367(4)
C4-C5	1.380(4)	C16-C17	1.393(4)

Table 3. Bond angles (°) for *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide. Atoms labels follow the atom numbering scheme in Figure 3.

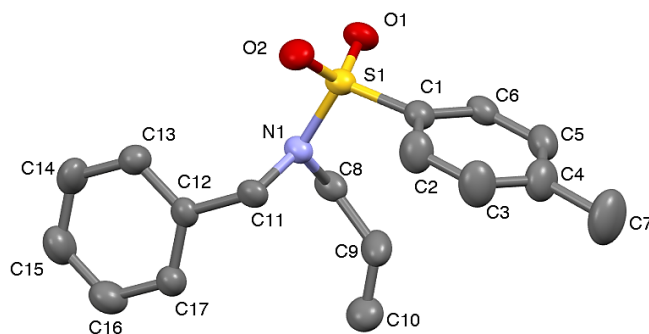
Bond	Angle (°)	Bond	Angle (°)
O2-S1-O1	119.78(12)	C7-C4-C3	120.9(3)
N1-S1-O1	107.46(10)	C7-C4-C5	120.9(3)
N1-S1-O2	106.77(10)	C6-C5-C4	121.8(2)
C1-S1-O1	107.00(11)	C5-C6-C1	119.1(2)
C1-S1-O2	108.12(11)	C9-C8-N1	113.8(2)
C1-S1-N1	107.11(13)	C10-C9-C8	125.3(3)
C8-N1-S1	117.88(15)	C12-C11-N1	110.3(2)
C11-N1-S1	119.73(16)	C13-C12-C11	119.6(2)
C11-N1-C8	116.10(19)	C17-C12-C11	121.1(2)
C2-C1-S1	119.71(18)	C17-C12-C13	119.3(3)
C6-C1-S1	119.86(17)	C14-C13-C12	120.2(2)
C6-C1-C2	120.1(2)	C15-C14-C13	120.0(3)
C3-C2-C1	119.2(2)	C16-C15-C14	120.1(3)
C4-C3-C2	121.5(3)	C17-C16-C15	120.1(3)
C5-C4-C3	118.2(2)	C16-C17-C12	120.4(3)

Table 4. Torsion angles (°) for *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide. Atoms labels follow the atom numbering scheme in Figure 3.

Torsion	Angle (°)	Torsion	Angle (°)
O1-S1-N1-C8	47.8(2)	C2-C3-C4-C7	-178.5(3)
O1-S1-N1-C11	-161.1(2)	C3-C4-C5-C6	-1.2(4)
O2-S1-N1-C8	177.5(2)	S1-C1-C2-C3	173.3(2)
O2-S1-N1-C11	-31.4(2)	C6-C1-C2-C3	-0.0(4)
C1-S1-N1-C8	-66.9(2)	S1-C1-C6-C5	-174.0(2)
C1-S1-N1-C11	84.2(2)	C2-C1-C6-C5	-0.7(4)
O1-S1-C1-C2	169.8(2)	C4-C5-C6-C1	1.3(4)
O1-S1-C1-C6	-16.9(2)	N1-C8-C9-C10	117.4(3)
O2-S1-C1-C2	39.6(2)	N1-C11-C12-C13	-70.0(3)
O2-S1-C1-C6	-147.1(2)	N1-C11-C12-C17	110.4(3)
N1-S1-C1-C2	-75.2(2)	C11-C12-C13-C14	179.9(2)
N1-S1-C1-C6	98.1(2)	C17-C12-C13-C14	-0.5(4)
S1-N1-C8-C9	93.1(2)	C11-C12-C17-C16	179.0(2)
C11-N1-C8-C9	-59.0(3)	C13-C12-C17-C16	-0.6(4)
S1-N1-C11-C12	138.4(2)	C12-C13-C14-C15	0.9(4)
C8-N1-C11-C12	-70.0(2)	C13-C14-C15-C16	-0.3(5)
C1-C2-C3-C4	0.2(5)	C14-C15-C16-C17	-0.9(5)
C2-C3-C4-C5	0.4(5)	C15-C16-C17-C12	1.3(5)

Table 5. Length of hydrogen bond contacts (Å) and corresponding symmetry codes for *N*-Allyl-*N*-benzyl-4-methylbenzenesulfonamide. Atom labels follow the atom numbering scheme in Figure 3.

Bond	Distance (Å)	Symmetry codes
H8a-O2	2.639	x, y, z
H10a-O1	2.652	x, y, z
H17-O2	2.669	x, y, z

**Figure 3.** The molecular structure of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide (**3b**) with atom labeling scheme. Displacements of ellipsoids are shown at the 50% probability level. Hydrogen atoms have been omitted for clarity.

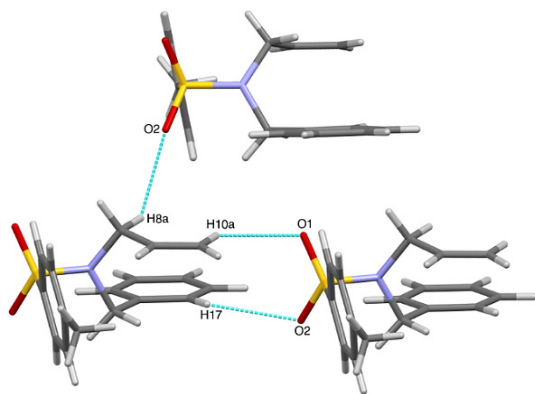


Figure 4. A depiction of the intermolecular hydrogen bonds in the crystal structure of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide shown as capped sticks with standard CPK colors. Hydrogen bond contacts are depicted with cyan dashed lines. Atom labels follow the atom numbering scheme in Figure 3.

4. Conclusion

The tosylation of allylamine resulted in the formation of *N*-allyl-4-methylbenzenesulfonamide. The treatment of *N*-allyl-4-methylbenzenesulfonamide with benzyl bromide afforded the desired product, *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide, as white crystals. The similarity in conditions between the two synthetic steps lends credence to the possibility of a one-pot synthesis. Additionally, the synthetic method is environmentally benign and produces the desired product in good purity and yield. The synthesized product underwent a single-crystal X-ray diffraction process to reveal an orthorhombic system (*Pna*2₁ space group) with screw axis and glide plane geometries. The values for S=O bond length align with known values. A slightly distorted tetrahedron geometry was observed from the four-fold coordination about the S1 atom. The crystallographic results support the successful formation of *N*-allyl-*N*-benzyl-4-methylbenzenesulfonamide.

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Supporting information

CCDC-2022196 contains 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: Samples of the compounds are available from the author.

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ORCID

Brock Anton Stenfors

 <http://orcid.org/0000-0001-8760-5878>

Felix Nyuangem Ngassa

 <http://orcid.org/0000-0001-8246-3639>

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