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

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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-allyl-N-benzyl-4-methylbenzenesulfonamides 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 Pnma 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 = 17.35 K, μ(MoKα) = 0.206 mm⁻¹, Dcalc = 1.251 g/cm³, 14455 reflections measured (4.56° ≤ 2θ ≤ 54.96°), 3619 unique (I > 2σ(I)) and 3550 reflexions with I > 2σ(I) used in all calculations. The final R₁ = 0.0428 (I > 2σ(I)) and wR₂ = 0.1079 (all data). Molecules are linked through C-H···N hydrogen bonds and C-H···π interactions.

1. Introduction

The N-benzylbenzenesulfonamide moiety is found in a variety of biologically significant compounds. In particular, 2-(N-benzyl-N-phenylsulfonylamido)alkyl amide derivatives [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 [Aβ], which 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 superfamly [6]. GR is activated by endogenous and synthetic glucocorticoids [7]. In recent years, synthetic glucocorticoids are most commonly used as anti-inflammatory agents [8].
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 Rf values for the reactions. 1H NMR spectra (400 MHz) were recorded on a JEOL ECSZ400 spectrometer using a chloroform-δ solvent. Chemical shifts are reported in parts per million (ppm, δ) relative to the residual solvent peak, using a chloroform-δ (400 MHz) as internal standard.

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

4-Methylenesulfonyl 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.: 69.91 °C. (ESI): calcd. for C_{17}H_{19}NNaO_{2}S [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 MoKa 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 Uiso(H) = 1.2Ueq(C) for all methylene groups and aromatic hydrogens (C-H = 0.95-1.00 Å) and Uiso(H) = 1.5Ueq(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 methods. 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 yield.

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 SiI-like reactions. Scheme 1 shows the application of this method regarding the synthesis of N-allyl-N-benzyl-4-methylbenzenesulfonamide (2a).
Table 1. Crystal data, data collection, and refinement details for the crystallographic characterization of N-allyl-N-benzyl-4-methylbenzenesulfonamide.

| Crystal data       |       |
|--------------------|-------|
| C₂₁H₂₃NO₅S        | Dₐ = 1.251 Mg m⁻³ |
| Mₘ = 301.412       | Mo Kα radiation, λ = 0.71073 Å |
| Orthorhombic, Pna₂₁| Cell parameters from 5268 reflections |
| α = 18.6919(18) Å  | β = 10.5612(10) Å |
| β = 10.5612(10) Å  | γ = 11.8059(11) Å |
| V = 1600.3(3) Å³   | Z = 4 |
| F(000) = 640.8     | 0.316 × 0.273 × 0.152 mm |

| Data collection    |       |
|--------------------|-------|
| Bruker APEXII CCD diffractometer | 14455 measured reflections |
| ϕ and ω scans      | 2960 reflections with | |
| Absorption correction: multi-scan | I > 2σ(I) |
| SADABS-2014/5 was used for absorption correction | wR₂(int) was |
| 0.0662 before and 0.0575 after correction | 0.043 |
| The ratio of minimum to maximum transmission is 0.9025 | |
| T = 173 K          | wR₂(max) = 0.044 |
| T(000) = 0.673, T(sym) = 0.746 | |

| Refinement         |       |
|--------------------|-------|
| H atom treatment: constrained | w = 1/[rms²(F²) + (0.0564P)² + 0.1062P] |
| Least-squares matrix: full | where P = (F² + 2 F₂)/3 |
| R[F²] = 0.0114      | (Δ/σ)max = 0.001 |
| S = 1.07           | Δρmax = 0.32 e Å⁻³ |
| 3619 reflections   | Δρmin = -0.24 e Å⁻³ |
| 191 parameters     | Absolute structure: Flack x determined using 2140 quotients |
| 1 restraint        | [+]½-[(+)-(+)]=[(+)+(--)]=21 |
| Hydrogen site location: mixed | Absolute structure parameter: 0.03(9) |

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 Sₓ₁-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 Sₓ₁-like mechanism (Scheme 2). The use of benzyl bromide (1b) adequately generates the highly stable benzyl carbocation which readily reacts with the weakly nucleophilic sulfonamide (2b). The benzylated sulfonamide 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 benzylated 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-methylbenzene sulfonamide (3b) exhibits 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, Pna₂₁ space group. According to the 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, 1.471, 1.763, and 1.636 Å, respectively. The N₁-S₁-O₂ bond angle was 109.6 (10)°. The molecules are linked through C-H···N hydrogen bonds and C-H···C interactions. Table 5 summarizes the hydrogen bond geometries which result from efficient packing. The structure geometries which result from efficient packing. The structure reveals an orthorhombic system, Pna₂₁ space group. According to the 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, 1.471, 1.763, and 1.636 Å, respectively. The N₁-S₁-O₂ bond angle was 109.6 (10)°. The molecules are linked through C-H···N hydrogen bonds and C-H···C interactions. Table 5 summarizes the hydrogen bond geometries which result from efficient packing.
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-C12    | 1.385(4)     |
| C1-C2    | 1.394(3)     | C12-C17    | 1.375(4)     |
| 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 | 120.3(3)  |
| N1-S1-O1 | 107.46(10)| C7-C4-C5 | 120.9(3)  |
| N1-S1-O2 | 106.77(10)| C6-C5-C4 | 121.8(3)  |
| 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 | 119.06(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 | 110.2(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 | -8.7(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 | 179.2(2) |
| N1-S1-C1-C6 | 98.1(2) | C17-C12-C13-C14 | -0.5(4) |
| S1-N1-C8-C9 | 93.1(2) | C12-C13-C17-C16 | 179.8(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-C1-C2-C4 | 0.2(5) | C14-C5-C6-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. Atoms 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   | 2.660         | 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 (Pna2_1 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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Supplementary 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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