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Synthesis and Structure of *N*-(1-(Bromomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)benzenesulfonamide

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Abstract: A new bicyclic sulfonamide derivative, *N*-(1-(bromomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)benzenesulfonamide, was synthesized in the reaction of benzenesulfonamide and camphene in the presence of *N*-bromosuccinimide in acetonitrile. The proposed mechanism of investigated reaction involves the Wagner–Meerwein rearrangement stage. 3-(Bromomethylene)-2,2-dimethylbicyclo[2.2.1]heptane was isolated as a minor product. The products were characterized by IR, NMR spectroscopy, X-ray diffraction analysis, HRMS and elemental analysis data.

Keywords: camphene; benzenesulfonamide; bromosulfonamidation; rearrangement; oxidative reactions

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1. Introduction

The relevance of expanding the library of modified monoterpene compounds is associated with their diverse biological activity. For example, camphene derivatives alleviate oxidative stress, reduce skeletal muscle atrophy [1], and exhibit antibacterial [2], anti-inflammatory [3], antioxidant [4] and antiviral activity [5]. Camphene derivatives show insecticidal properties [6]. Thiosemicarbazide derivatives of camphene significantly increase antifungal activity compared to unsubstituted thiosemicarbazide (Figure 1) [7]. Microorganisms' and viruses' resistance to drugs is a growing concern that poses a challenge for chemists to search for synthesis methods of new biocompatible substances, so the modification of terpenes is an urgent task.

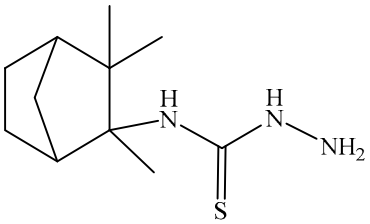
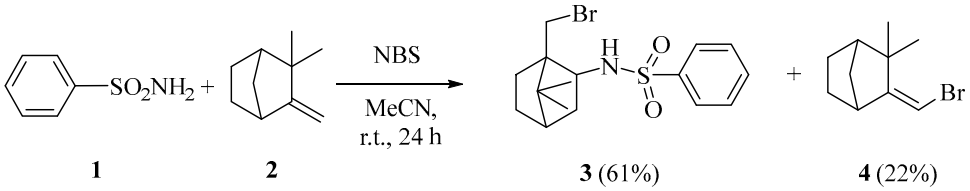


Figure 1. Thiosemicarbazide camphene fungicide.

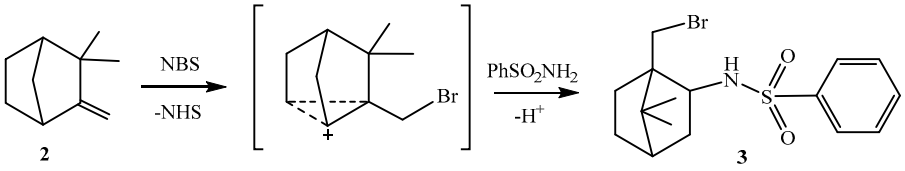
2. Results and Discussion

The reaction of benzenesulfonamide **1** and camphene **2** was carried out in acetonitrile in the presence of *N*-bromosuccinimide at room temperature. The reaction led to the formation of two products: *N*-(1-(bromomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)benzenesulfonamide **3** with good yield and 3-(bromomethylene)-2,2-dimethylbicyclo[2.2.1]heptane **4** as a minor product (Scheme 1).



Scheme 1. Oxidative sulfonamidation of camphene **2**.

The first step of the reaction was the attack of the bromine cation by NBS at the terminal carbon atom of the camphene **1** C=C bond. The next step was accompanied by Wagner–Meerwein rearrangement, followed by the attack of sulfonamide **1** to form the final structure **3** (Scheme 2):



Scheme 2. Proposed reaction mechanism.

The reactions of camphene **2** and similar substrates are sometimes accompanied by Wagner–Meerwein rearrangement processes [8,9].

The structure and composition of the resulting products were established with NMR, IR spectroscopy, high resolution mass spectrometry (HRMS) and elemental analysis data. The ^{1}H NMR spectrum of compound **3** displayed the doublet of the NH group, and CH_2Br doublets at 3.47 and 3.34 ppm with J = 10.5 Hz (Figure S3). The ^{13}C NMR spectrum contained signals of the carbon atom CHN: CH_2Br and CH_3 groups at 59, 38 and 20 ppm, respectively (Figure S4). The IR spectrum of compound **3** showed bands at ν_{NH} = 3289 cm^{-1} and ν_{SO2} = 1322 cm^{-1}. Structure **3** was proved by X-ray analysis (Figure 2, Tables S1 and S2). Compound **4** had the following structure of 3-(bromomethylene)-2,2-dimethylbicyclo[2.2.1]heptane according to the presence in the ^{1}H NMR spectrum of a signal at 5.62 ppm, which had ^{1}H-^{13}C satellites with $^{1}J_{CH}$ = 196.12 Hz, which proved the presence of the =CHBr group (Figures S5 and S6). In reference [6], the preparation of compound **4** under similar conditions in the absence of benzenesulfonamide was described.

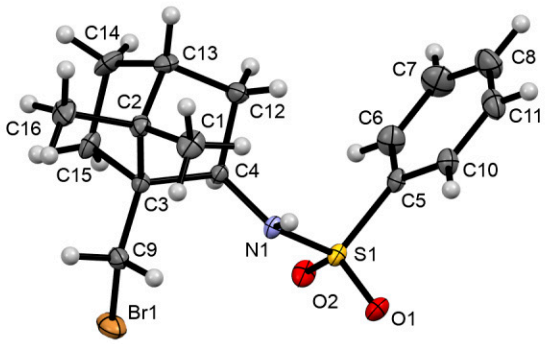


Figure 2. X-ray of compound **3**.

Crystal Structure

The single crystals of compound **3** were obtained through re-crystallization from a chloroform solution. Molecules of compound **3** crystallized in monoclinic space group C2/c in the crystal molecules of **3** connected by intermolecular hydrogen bonds NH···O=S by lengths 2.252 Å (Figure 3).

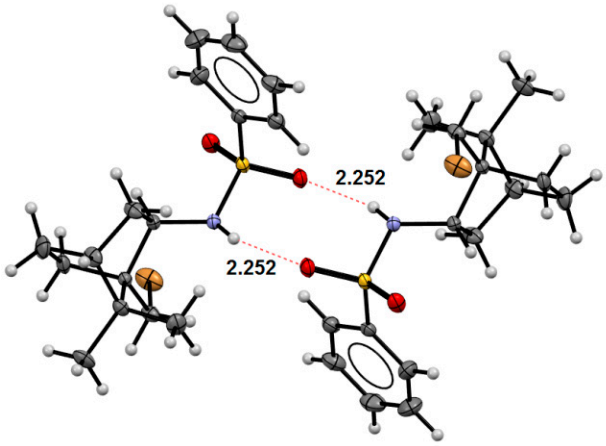


Figure 3. Hydrogen bonds NH···O=S in the crystal of **3**.

3. Materials and Methods

3.1. General Information

All starting materials have been described in the literature. All products were identified using IR, ^{1}H and ^{13}C NMR spectroscopy. IR spectra were taken on a Bruker Vertex 70 spectrophotometer in KBr. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker DPX 400 spectrometer at working frequencies of 400 (^{1}H) and 100 (^{13}C) MHz. All shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ peak (7.27 and 77.1 ppm, ^{1}H and ^{13}C). All coupling constants (*J*) are reported in hertz (Hz). Abbreviations are s, singlet; d, doublet; t, triplet; m, multiplet. High-resolution mass spectra (HRMS) were measured on an Agilent 1200 HPLC chromatograph with Agilent 6210 mass spectrometer (HR-TOF-MS, ESI + ionization in acetonitrile with 0.1% HFBA). Elemental compositions were determined by accurate mass measurement with standard deviation. H_3PO_4 was used as reference compound. Elemental analysis of C, H and N was carried out on an elemental analyzer from Thermo-Finnigan (Milan, Italy) model Flash EA, bromine was determined by Shoniger titration method and sulfur was determined by titration with $Ba(OAc)_2$. Melting points were measured on a Boetius apparatus. Flash chromatography was performed using silica gel, 60 Å, 300 mesh. TLC analysis was carried out on aluminum plates coated with silica gel 60 F_{254}, 0.2 mm thickness. The plates were visualized using a 254 nm UV lamp.

3.2. Synthesis

To a solution of 1 g (6.4 mmol) of benzenesulfonamide **1** and 0.87 g (6.4 mmol) of camphene **2** in 40 mL of acetonitrile was added 1.37 g (7.0 mmol) of NBS and the reaction mixture was stirred in the dark for 24 h. Solvent was removed in a vacuum, then the succinimide was precipitated with diethyl ether, filtered off, and ether removed in a vacuum. The residue was purified by column chromatography (Silicagel, 0.063–0.2 mm, Acros Organics; eluents: hexane:ether = 3:1; ether:hexane = 2:1) to obtain compounds 3 (1.45 g, 61%) and 4 (0.30 g, 22%).

N-(1-(Bromomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)benzenesulfonamide **3**. White crystals, m. p. 146–147 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.91 (d, *J* = 7.3 Hz, 2H, H-6, H-10), 7.59 (tr, *J* = 7.3 Hz, 1H, H-8), 7.53 (d, *J* = 7.3 Hz, 2H, H-7, H-11), 4.67 (d, *J* = 6.4 Hz, 1H, NH), 3.47 (d, 1H, *J* = 10.5 Hz, H-9′), 3.34 (d, *J* = 10.5 Hz, 1H, H-9″), 3.28–3.19 (m, 1H), 1.91–1.81 (m, 2H), 1.77–1.54 (m, 4H), 1.45–1.36 (m, 1H), 1.02 (s, 3H, H-1), 0.88 (s, 3H, H-16). ^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 140.0 (C-5), 132.7 (C-8), 129.0 (C-7), 127.5 (C-6), 59.1 (C-4), 52.8 (C-3), 48.8 (C-2), 46.8 (C-13), 38.9 (C-9), 34.4 (C-12), 33.7 (C-15), 26.3 (C-14), 20.8 (C-1), 20.6 (C-16). IR (KBr): 3289, 2957, 1715, 1460. 1322, 1160, 1095, 1027, 926, 757, 690, 645, 592. Elemental analysis calcd (%) for $C_{16}H_{22}BrNO_2S$: C, 51.62; H, 5.96; N, 3.76; S, 8.61; Br, 21.46; found: C, 51.99; H, 6.00; N; 3.61; S, 8.45; Br, 21.02.

3-(Bromomethylene)-2,2-dimethylbicyclo[2.2.1]heptane **4**. Colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.62 (s, 1H, =CHBr), 3.15 (d, *J* = 3.5 Hz, 1H, CH), 2.08–2.02

(m, 1H, H-1), 1.79–1.65 (m, 3H), 1.49–1.40 (m, 1H), 1.33–1.28 (m, 1H), 1.27–1.24 (m, 1H), 1.08 (s, 3H, CH_3), 1.06 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 160.9 (=C), 94.1 (=CHBr), 49.1 (CH), 45.1 (CH), 44.3 ($C(CH_3)_2$), 36.8 (CH_2), 28.9 (CH_2), 27.0 (CH_2), 25.8 (CH_3), 23.5 (CH_3). IR (KBr): 3067, 2959, 2883, 1641, 1461, 1307, 1241, 950, 887, 770, 696. HRMS (ESI): *m/z* calcd for $C_{10}H_{16}Br^+$: 215,04354 $(M+H)^+$; found: 215.04340.

Supplementary Materials: The following supporting information can be downloaded online: ^{1}H-NMR and ^{13}C-NMR spectra of **3** and **4**, HRMS spectra of **4**; IR and X-ray crystallography data of **3**.

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Conflicts of Interest: The authors declare no conflict of interest.

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