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HETARENESULFENYL(SELENYL) CHLORINATION OF (+)-CAMPHENE

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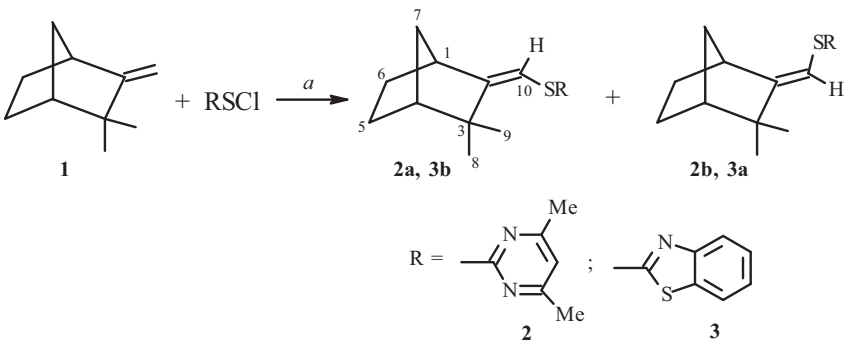
Novel S- *and* Se-*containing terpenoids were prepared by reacting (+)-camphene with* N-*heterocyclic selenyl- and sulfenyl chlorides.*

Keywords: (+)-camphene, hetarenesulfenyl chlorination, hetareneselenyl chlorination.

In continuation of research on hetarenesulfenyl(selenyl) chlorination of monoterpenes [1, 2], we studied the synthetic potential of camphene with *N*-heterocyclic reagents such as 4,6-dimethyl-2-pyrimidine-, 2-benzothiazole-, and 3-methoxycarbonyl-2-pyridinesulfenyl chlorides in addition to 2-pyridineselenyl chloride. Products of formal substitution resulting from Markovnikov addition of highly reactive sulfenylating reagents (sulfenyl chlorides, alkenesulfenamides, etc.) to camphene followed by elimination of HCl were obtained earlier [3–5]. Information on selenyl chlorination of camphene has not been published.

Equimolar amounts of (+)-camphene (**1**) and 4,6-dimethyl-2-pyrimidine- or 2-benzothiazolesulfenyl chlorides were reacted at room temperature in CH_2Cl_2. The reaction was finished after 5–10 d and formed **2** and **3**, respectively. The completion of the reaction was signaled by the disappearance of the camphene double-bond proton resonance in the PMR spectrum of the reaction mixture.



1 **2a, 3b** **2b, 3a** **2** **3**

a. CH_2Cl_2, 25°C

PMR, ^{13}C NMR, and ^{1}H–^{13}C HETCOR spectroscopy found that the reaction of (+)-camphene and 4,6-dimethyl-2-pyrimidinesulfenyl chloride produced **2**, which was a mixture of the *Z*- (**2a**) and *E*-isomers (**2b**) in an ~9:1 ratio. Resonances in the PMR spectra were assigned to geometric isomers **2a** and **2b** based on the literature, from which it was known that the double-bond proton in the *E*-isomer of *ω*-monosubstituted camphenes resonated at stronger fields as a result of its shielding by methyls [6, 7].

The predominant *Z*-isomer (**2a**) gave broad singlets for the bridgehead methine protons (1.91 and 2.84 ppm) and a singlet for the olefinic proton (6.68 ppm). Analogous singlets for protons of the minor *E*-isomer (**2b**) resonated at 1.95, 3.05, and 6.34 ppm, respectively. Resonances for double bond C^{10}–H appeared in the 2D ^{1}H–^{13}C HETCOR NMR spectrum as two

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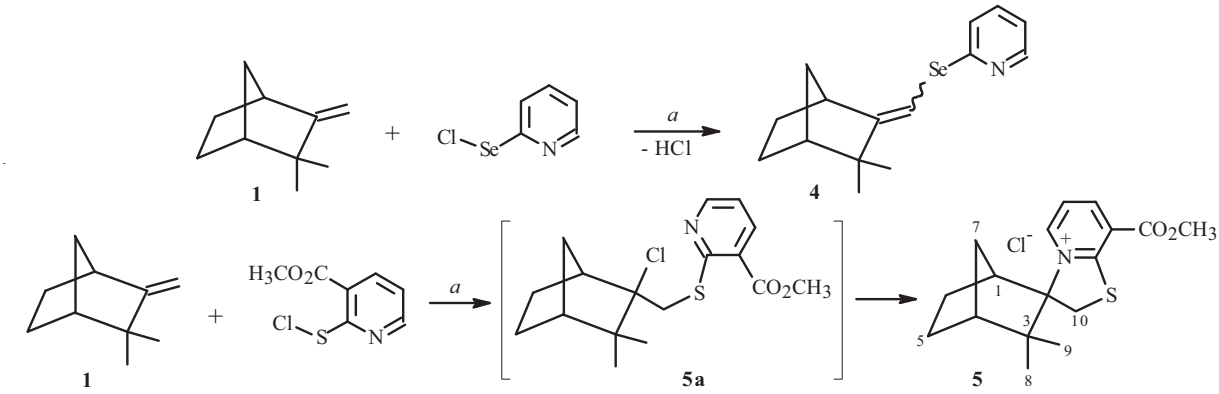
cross peaks 6.34/115.8 (**2b**) and 6.68/115.8 (**2a**) from the two stereoisomers. Cross peaks 1.28/37.1 and 1.82/37.1 were due to C^7–H correlations.

In contrast with the aforementioned reaction, (+)-camphene (**1**) reacted with bulkier 2-benzothiazolesulfenyl chloride to form primarily the *E*-isomer (**3a**). The ratio of *Z*- (**3b**) and *E*-isomers (**3a**) was ~1:5.

In continuation of research on the reactivity of camphene toward *N*-containing heterocyclic compounds, 2-pyridineselenyl chloride [8] was reacted under the conditions described above to give **4** as the only product.



a. CH_2Cl_2, 25°C

The PMR spectrum of **4** was missing a resonance for an –Se–CH_2– fragment although there was a resonance for an olefinic proton at 6.23 ppm. Thus, it was concluded that an addition–elimination reaction occurred, like for sulfenyl chlorination. A cross peak for an olefinic proton (6.23/120.1) in the ^{1}H–^{13}C HETCOR NMR spectrum provided evidence for this. The presence in the PMR spectrum of **4** of only one olefinic proton, unlike those of structurally analogous **2** and **3**, argued in favor of the formation of a single geometric isomer. However, it was impossible at this stage to assign unambiguously the *Z*- or *E*-configuration to the product because of a lack of literature data on the proton chemical shifts of the *E*- and *Z*-isomers in selenyl-containing camphenes. It could be assumed based on steric considerations that **4** was the sterically more favorable *E*-isomer. However, data for series of reactions of camphene with *Se*-containing reagents needed to be compiled in order to confirm this.

Intramolecular cyclization product **5** was formed exclusively by the reaction of (+)-camphene with 3-methoxycarbonyl-2-pyridinesulfenyl chloride. The similar products were characteristic of this sulfenyl chloride. In particular, we obtained the analogous cyclization product from the reaction of (–)-β-pinene with 3-methoxycarbonyl-2-pyridinesulfenyl chloride [2].

Formation of the intramolecular cyclization product was confirmed by the chemical shifts of the heterocyclic protons, which were observed in the PMR spectrum of **5** as singlets at 8.21, 8.73, and 9.79 ppm. If the reaction of camphene had stopped at the formation of adduct **5a**, the pyridine proton resonances would be observed at stronger (by almost 1 ppm) fields compared with the analogous resonances of cyclization product **5**.

The literature data and our results for the reaction of (–)-β-pinene and this sulfenyl chloride identified the cyclization product and the normal addition product analogous to hypothetical **5a**. The resonances of these protons typically experience such weak-field shifts in the cyclization products and could attest to the formation of the corresponding quaternary salts [2, 9].

The ^{1}H–^{13}C HETCOR NMR spectrum of **5** contained two cross peaks 3.70/38.8 and 4.07/38.8 for the methylene on the S atom. The PMR spectrum of **5** also featured a significant increase of the magnetic non-equivalency of the two singlets for the *gem*-dimethyl fragment (0.53 and 1.46 ppm). This could be explained by changes of the dihedral angles occurring after the intramolecular cyclization.

Compound **5** was exceptionally promising for studying antifungal activity because we found earlier that the product from the reaction of β-pinene and 3-methoxycarbonyl-2-pyridinesulfenyl chloride exhibited highly selective activity against *Candida parapsilosis* [10]. Apparently, the cyclization product from the reaction with β-pinene, which was a quaternary salt, played a significant role because quaternary ammonium salts are known to exhibit high antifungal activity.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 and Sorbfil plates (detector EtOH–H_2SO_4–anisaldehyde, 90:5:5). Preparative chromatography used KSKG silica gel (fr. 0.10–0.16, Ekofarm). Solvents were purified and dried by the usual methods [11]. (+)-Camphene was purchased from Acros Organics.

PMR and ^{13}C NMR spectra were recorded with HMDS internal standard on Bruker Avance 400 (operating frequency 400 and 100 MHz for ^1H and ^{13}C) and Varian Unity-300 (operating frequency 300 MHz for ^1H) spectrometers. Chemical shifts were measured relative to residual nuclei in the deuterated solvent.

GC-MS used a DFS Thermo Electron Corp. (USA) instrument with electron-impact ionization. The ionizing-electron energy was 70 eV; ion-source temperature, 280°C. We used an Agilent DB-5MS capillary column (30 m × 0.254 mm) and He carrier gas at flow rate 1 mL/min. Mass spectral data were processed using the Xcalibur program. Samples were diluted before injection into the instrument in chromatography-grade benzene to a concentration of ~10^{-6} mol/μL. The sample volume was 1 μL.

General Method for Synthesizing Sulfenyl Chlorides from Disulfides [2]. Disulfide (1 mmol) in CH_2Cl_2 (5 mL) was treated with a solution of sulfuryl chloride (1 mmol) in CH_2Cl_2 (5 mL) at 25–30°C and stirred for 2–5 min. The solvent was evaporated. The sulfenyl chlorides were used in the reactions with (+)-camphene.

General Method for Reacting (+)-Camphene with Sulfenyl Chlorides. Freshly prepared sulfenyl chloride (2 mmol) in CH_2Cl_2 (4 mL) at room temperature was stirred, treated with the terpene (**1**, 2 mmol) dissolved in CH_2Cl_2 (4 mL, reagent ratio 1:1), and stirred in a flask on a magnetic stirrer. The course of the reaction was monitored by TLC. When the reaction was finished (5–10 d), the solvent was evaporated (water aspirator). The reaction products were isolated by column chromatography over silica gel (*n*-hexane–CH_2Cl_2, 60:40) and were yellowish odorless oils. Product yields (%): 40 (**2**), 70 (**3**), 87 (**5**).

2-{[(*Z*)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)methyl]thio}-4,6-dimethylpyrimidine (2a). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.23, 1.27 (each 3H, s, H-8, 9), 1.91, 2.85 (each 1H, br.s, H-1, 4), 1.17–1.82 (6H, m, H-5, 6, 7), 2.42 (6H, s, $2CH_3$-Ar), 6.68 (1H, s, H-10), 6.75 (1H, s, Ar-H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.5 (C-8), 23.7, 23.8 ($2CH_3$-Ar), 23.9 (C-9), 24.5 (C-5), 28.9 (C-6), 37.1 (C-7), 42.5 (C-3), 49.0 (C-4), 50.0 (C-1), 104.4 (C-2), 115.8 (C-10), 156.2 (C-13), 167.0 (C-12, 14), 169.5 (C-11).

2-{[(*E*)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)methyl]thio}-4,6-dimethylpyrimidine (2b). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.23, 1.25 (each 3H, s, H-8, 9), 1.95, 3.05 (each 1H, br.s, H-1, 4), 1.17–1.82 (6H, m, H-5, 6, 7), 2.42 (6H, s, $2CH_3$-Ar), 6.34 (1H, s, H-10), 6.75 (1H, s, Ar-H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.5 (C-8), 23.7, 23.8 ($2CH_3$-Ar), 23.9 (C-9), 24.5 (C-5), 28.9 (C-6), 37.1 (C-7), 43.9 (C-3), 48.2 (C-4), 50.0 (C-1), 104.4 (C-2), 115.8 (C-10), 156.2 (C-13), 167.0 (C-12, 14), 169.5 (C-11).

2-{[(*E*)-(3,3-Dimethylbicyclo[2.2.1]hept-2-en-2-yl)methyl]thio}-1,3-benzothiazole (3a). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.14, 1.26 (each 3H, s, H-8, 9), 2.08, 3.36 (each 1H, br.s, H-1, 4), 1.17–1.77 (6H, m, H-5, 6, 7), 6.03 (1H, s, H-10), 7.32, 7.44, 7.79, 7.91 (each 1H, s, Ar-H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.4 (C-8), 23.6, 23.7 ($2CH_3$-Ar), 25.5 (C-9), 27.7 (C-5), 28.6 (C-6), 37.3 (C-7), 44.1 (C-3), 44.2 (C-4), 48.3 (C-1), 102.4 (C-2), 162.1 (C-10), 120.8, 121.6, 123.9, 126.0, 135.1, 154.2, 172.7 (7C-Ar). Mass spectrum, *m/z* (I_{rel}, %): 301 [M^+] (48), 286 (18), 268 (15), 258 (26), 232 (80), 218 (30), 205 (48), 167 (37), 135 (42), 119 (28), 107 (63), 91 (100), 77 (56), 67 (47), 65 (30), 53 (27).

2-{[(*Z*)-(3,3-Dimethylbicyclo[2.2.1]hept-2-en-2-yl)methyl]thio}-1,3-benzothiazole (3b). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.14, 1.26 (each 3H, s, H-8, 9), 1.96, 3.04 (each 1H, br.s, H-1, 4), 1.17–1.77 (6H, m, H-5, 6, 7), 6.32 (1H, s, H-10), 7.32, 7.44, 7.79, 7.91 (each 1H, s, Ar-H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.6 (C-8), 25.6 (C-9), 27.7 (C-5), 28.6 (C-6), 37.0 (C-7), 44.1 (C-3), 50.0 (C-4), 53.5 (C-1), 102.8 (C-2), 162.1 (C-10), 120.9, 121.6, 124.0, 126.0, 135.1, 154.2, 172.7 (7C-Ar). Mass spectrum, *m/z* (I_{rel}, %): 301 [M^+] (48), 286 (18), 268 (15), 258 (26), 232 (80), 218 (30), 205 (48), 167 (37), 135 (42), 119 (28), 107 (63), 91 (100), 77 (56), 67 (47), 65 (30), 53 (27).

8′-(Methoxycarbonyl)-3,3-dimethylspiro[bicyclo[2.2.1]heptane-2,3′-[1,3]thiazolo[3,2-*a*]pyridin[4]ium] Chloride (5). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20, 1.28 (each 3H, s, H-8, 9), 1.17–1.85 (6H, m, H-5, 6, 7), 3.26 (2H, br.s, H-1, 4), 3.88–4.07 (2H, m, SCH_2), 3.98 (3H, s, OCH_3), 8.21, 8.73, 9.79 (each 1H, s, Ar-H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 22.7 (C-8), 24.4 (C-9), 26.3 (C-5), 26.3 (C-6), 37.5 (C-7), 35.9 (C-2), 44.4 (C-3), 48.5 (C-4), 49.6 (C-1), 50.2 (C-10), 54.0 (OCH_3), 90.8 (CO), 124.4, 145.2, 147.6, 162.8, 163.1 (5C-Ar). Mass spectrum, *m/z* (I_{rel}, %): 304

[M^+ – HCl] (12), 303 (30), 288 (10), 260 (18), 234 (100), 220 (30), 207 (80), 168 (14), 138 (27), 119 (12), 105 (29), 91 (70), 79 (47), 67 (31), 53 (18).

Reaction of (+)-Camphene with 2-Pyridineselenyl Chloride. Crystalline 2-pyridineselenyl chloride (2 mmol) in CH_2Cl_2 (4 mL) at room temperature was stirred, treated with the terpene (**1**, 2 mmol) dissolved in CH_2Cl_2 (4 mL), and stirred for 10 d. When the reaction was finished, unreacted selenyl chloride was filtered off. The solvent was evaporated (water aspirator). The product was isolated by column chromatography over silica gel (*n*-hexane–CH_2Cl_2, 60:40). Compound **4** was a yellowish odorless oil. Yield 0.379 g (65%).

2-{[(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)methyl]seleno}pyridine (4). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.19, 1.20 (each 3H, s, H-8, 9), 2.08, 3.14 (each 1H, br.s, H-1, 4), 1.17–1.79 (6H, m, H-5, 6, 7), 6.23 (1H, br.s, H-10), 7.08, 7.32, 7.53, 8.48 (each 1H, s, Ar-H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.7 (C-8), 25.9 (C-9), 27.6 (C-5), 29.0 (C-6), 37.3 (C-7), 42.5 (C-3), 45.7 (C-4), 48.5 (C-1), 100.5 (C-2), 112.1 (C-10), 123.9, 136.5, 149.7, 158.1, 176.3 (5C-Ar).

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