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Synthesis of Novel Aryl-Substituted Acetylenic Monoterpene Analogues by Sonogashira Coupling †

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Abstract: The synthesis of new aryl-substituted acetylenic monoterpene derivatives was carried out by the Sonogashira reaction. The reactions proceed in the presence of $PdCl_2(PPh_3)_2$, CuI and Et_3N and provide aryl-substituted acetylenic monoterpenes with the isolated yield of 70–82%.

Keywords: monoterpenes; camphor; carvone; alkylation; reduction; Sonogashira reaction

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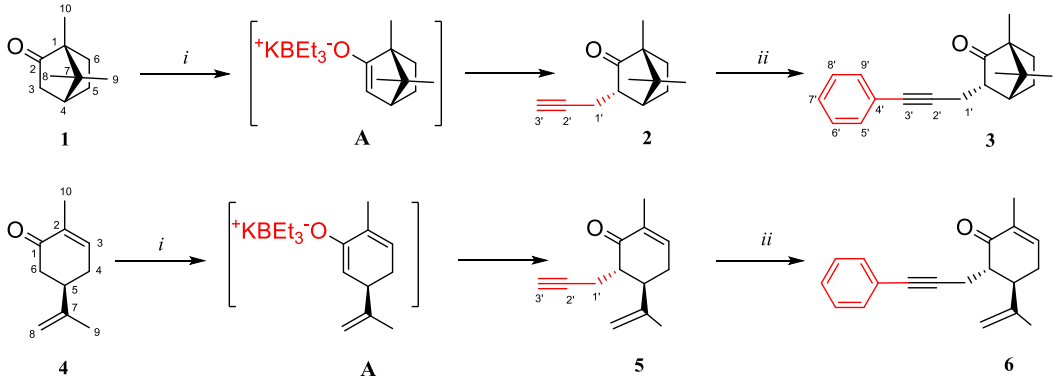
1. Introduction

Terpenes and terpenoids are naturally occurring secondary metabolites isolated from plants, which exhibit broad spectrum of biological activity and provide a large library of basic structures for medicinal chemistry [1–4]. Among this class of substances, camphor and carvone have long been used as starting compounds for the synthesis of new drug candidates [5–12]. Since natural compounds typically have a complex structure, differing in the hydrocarbon framework and/or the number and position of functional groups, the search for chemo-, stereo- and regioselective methods of native molecule transformation to obtain promising pharmacologically significant analogues is of great importance. To date, numerous derivatives of camphor and carvone have been synthesized, which showed various biological effects [13–15]. The present work is aimed at the synthesis of new aryl-substituted propynyl analogues of camphor and carvone as promising building blocks.

2. Results and Discussion

First, alkylation of camphor and carvone with propargyl bromide in the presence of base $KN(SiMe_3)_2$–Et_3B in 1,2-dimethoxyethane (DME) at room temperature provides 2-propargyl- substituted camphor and carvone derivatives with a yield of 69% and 47%, respectively [16]. Second, the synthesis of aryl-substituted acetylenic monoterpene derivatives with the yield of 70-82% was carried out by the Sonogashira reaction in the presence of $PdCl_2(PPh_3)_2$, CuI and Et_3N (Scheme 1).



Reaction conditions: *i.* $KN(SiMe_3)_2$-Et_3B, C_3H_3Br, DME, 20-22 °C, 1-2 h;
ii. $PdCl_2(PPh_3)_2$, CuI and Et_3N, 20-22 °C, 1-3 h.

Scheme 1. Synthesis of aryl-substituted acetylenic monoterpenes.

The structure of the obtained compounds was confirmed by 1D (^1H, ^{13}C) NMR experiments. Thus, in the ^{13}C NMR spectrum of compound **3**, a shift in the signals of the acetylene bond carbon atoms C-2′ and C-3′ to a downfield (to the region of 88.5, 81.3 ppm, respectively) compared to the corresponding signals of carbon atoms of the terminal acetylene bond was observed. In addition to the characteristic signals of camphor, four new signals of carbon atoms appeared in the spectrum at 123.7, 127.8, 128.2 and 131.6 ppm, which were assigned to the atoms of the phenyl ring. In the ^1H NMR spectrum, the signal of the H-3′ proton at 2.00 ppm was absent and new signals of the aromatic ring were observed in the region of 7.42-7.41 and 7.30-7.29 which were assigned to H-6′-8′, H-5′ and 9′ respectively.

3. Conclusions

Thus, we have obtained new camphor and carvone analogues containing a phenyl-substituted acetylene bond via Sonogashira coupling, catalyzed with $PdCl_2(PPh_3)_2$ and copper (I) iodide. At present, a systematic study of this reaction is being carried out with the aim of involving a wide range of aryl iodides to obtain a set of promising structural blocks for the synthesis of new biologically active compounds.

4. Experimental Part

Camphor, carvone, BEt_3, $KN(SiMe_3)_2$ (1 M solution in THF), propargyl bromide, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, DME (dimethoxyethane) were purchased from Sigma-Aldrich (Acros) and used without any further purification. Reactions alkylation of compounds were carried out under dried argon atmosphere. Compounds **2** and **5** were prepared according to the known procedure [16]. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance–500 instrument (500.13 (^1H) and 125.78 MHz (^{13}C)) in $CDCl_3$ with Me_4Si as the internal standard. High-resolution mass spectra (HRMS) of compounds were obtained on a spectrometer MaXis impact (Bruker) using a mass analyzer (TOF) with electrospray ionization (ESI). TLC was carried out on Sorbfil plates (Sorbpolimer, Krasnodar, Russia) in hexane–EtOAc (from 50:1 to 10:1); spots were visualized with anisaldehyde. Silica gel L (KSKG grade, 50–160 μm) was employed for column chromatography.

General procedure for the synthesis of aryl-substituted acetylenic monoterpene 3 and 6 via Sonogashira coupling reaction

A mixture of corresponding terpenoid (0.6 mmol), iodobenzene (0.5 mmol) and Et_3N (0.75 mL, 5.4 mmol) were dissolved in DMF (4.5 mL). Then CuI (11 mg, 0.06 mmol) and $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol) were added to the mixture simultaneously and the resulting mixture was stirred at room temperature for 1–3 h under an argon atmosphere. The completion of reaction was monitored by TLC analysis. The reaction was quenched

by addition of water and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on SiO_2 with hexane/EtOAc (from 100:1 to 1:10) as an eluent to afford pure products **3** and **6**.

1,7,7-trimethyl-3-(3-phenylprop-2-yn-1-yl)bicyclo[2.2.1]heptan-2-one (3). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, s, H-8),0.93 (3H, s, H-10),0.97 (3H, s, H-9),1.48-1.43 (1H, m, H^b-5),1.57-1.51 (1H, m, H^b-6),1.71-1.67 (1H, m, H^a-6),2.08-2.05 (1H, m, H^a-5),2.22 (1H, dd, *J* = 4.5 Hz, *J* = 11 Hz, H-4),2.29 (1H, m, H-3),2.39 (1H, dd, *J* = 12 Hz, *J* = 17 Hz, H^a-1′),2.98 (1H, dd, *J* = 4 Hz, *J* = 17 Hz, H^b-1′),7.30-7.29 (3H, m, H-6′-8′),7.42-7.41 (2H, m, H-5′ and 9′). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 219.2 (C-2), 131.6 (C-6′, C-8′), 128.2 (C-5′, C-9′), 127.8 (C-7′), 123.7 (C-4′), 88.6 (C-2′), 81.3 (C-3′), 57.9 (C-1), 53.6 (C-3), 46.8 (C-7), 46.6 (C-4), 29.3 (C-5), 29.2 (C-6), 21.6 (C-8), 21.3 (C-1′), 20.5 (C-9), 9.5 (C-10). HRMS: *m*/*z* $[M+Na]^+$, calcd for $C_{19}H_{22}O$: 289.1568 found 289.1583. Found (%): C 85.42; H 8.31**.** Calcd for $C_{19}H_{22}O$ (%): C 85.67; H 8.32.

2-methyl-6-(3-phenylprop-2-yn-1-yl)-5-(prop-1-en-2-yl)cyclohex-2-en-1-one (6). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.81 (s, 3H, H-9), 1.83 (s, 3H, H-10), 2.41-2.36 (m, 1H, H^a-4), 2.5-2.47 (m, 1H, H^b-4), 2.59-2.53 (m, 2H, H-5, H-6), 3.07-3.03 (m, 2H, H^a-1′, H^b-1′), 4.95 (s, 1H, H^a-8), 4.99 (s, 1H, H^b-8), 6.75-6.74 (m, 1H, H-3), 7.27-2.76 (m, 3H, H-6′-8′), 7.37-7.36 (m, 2H, H-5′ and 9′). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.7 (C-1), 144.8 (C-7), 143.8 (C-3), 135.2 (C-2), 131.6 (C-6′, C-8′), 128.1 (C-5′, C-9′), 127.5 (C-7′), 124.0 (C-4′), 114.1 (C-8), 87.8 (C-2′), 81.5 (C-3′), 48.4 (C-6), 46.8 (C-5), 30.8 (C-4), 18.9 (C-9), 17.6 (C-10), 16.1 (C-1′).HRMS: *m*/*z* $[M+Na]^+$, calcd for $C_{19}H_{20}O$: 287.1412 found 287.1430. Found (%): C 86.35; H 7.64**.** Calcd for $C_{19}H_{20}O$ (%): C 86.32; H 7.63.

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