

Proceeding Paper

# Synthesis of New Functionally Substituted Bicyclo[4.2.1]nona-2,4,7-trienes by Co(I)-Catalyzed $[6\pi + 2\pi]$ Cycloaddition of 1-Benzoylcycloheptatriene <sup>†</sup>

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**Abstract:** Functionally substituted bicyclo[4.2.1]nona-2,4,7-trienes were synthesized for the first time on the basis of the reaction of  $[6\pi + 2\pi]$  cycloaddition of hexyn-1 and 4-pentynenitrile to 1-benzoylcycloheptatriene under the action of the three-component catalytic system  $\text{Co}(\text{acac})_2(\text{dppe})/\text{Zn}/\text{ZnI}_2$ .

**Keywords:**  $[6\pi + 2\pi]$  cycloaddition; 1-benzoylcycloheptatriene; alkynes; bicyclo[4.2.1]nona-2,4,7-trienes; cobalt(II) acetylacetonate; antitumor activity



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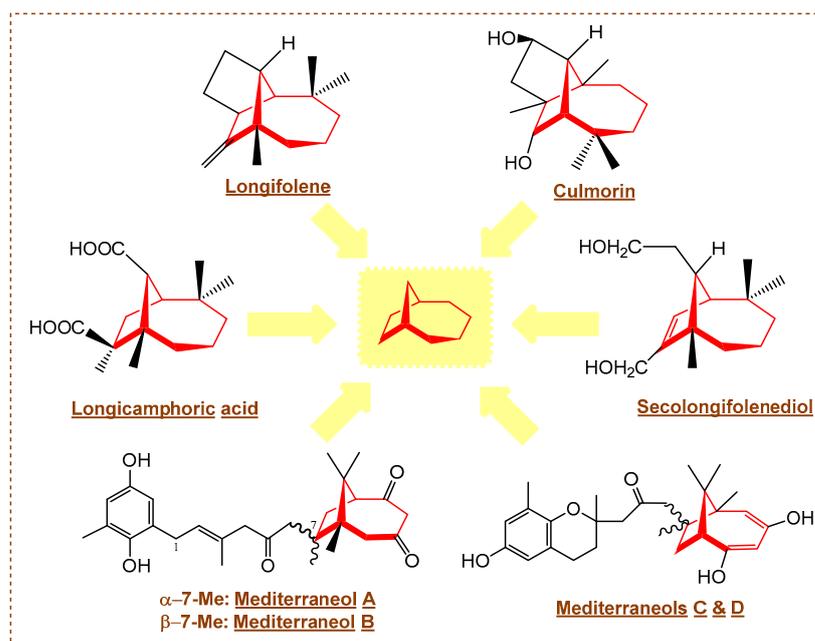


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## 1. Introduction

Bicyclo[4.2.1]nonatrienes are undoubtedly of interest for the development of the chemistry of biologically active and medicinal compounds. The bicyclo[4.2.1]nonane backbone forms a key structural element of some important terpenoids and their metabolites (mediterraneols, longifolene, longicamphoric acid, culmorin, secolongifolenediol), exhibiting pronounced antitumor activity [1–3] (Figure 1). As the analysis of literature data [4] shows, currently one of the effective and available methods for constructing a bicyclo[4.2.1]nonane skeleton is based on the reactions of catalytic cycloaddition of alkynes to 1,3,5-cycloheptatriene and its derivatives. These transformations open access to bicyclo[4.2.1]nonanes containing reactive functional substituents of various nature in the structure, which is an essential condition for their use as precursors in the synthesis of biologically active and other practically important compounds.

Earlier [4–9], we obtained a wide spectrum of bicyclo[4.2.1]nona-2,4,7-trienes using the catalytic cycloaddition reaction of 1- and 7-substituted 1,3,5-cycloheptatrienes. In the development of these studies, we, for the first time, carried out the Co(I)-catalyzed  $[6\pi + 2\pi]$  cycloaddition of terminal alkynes to 1-benzoylcycloheptatriene to obtain new bicyclo[4.2.1]nona-2,4,7-trienes.



**Figure 1.** Natural products with the bicyclo[4.2.1]nonane core.

## 2. Results and Discussion

We found that the  $[6\pi + 2\pi]$  cycloaddition of terminal alkynes—hexyne-1 **2a** and 4-pentynenitrile **2b** to 1-benzoylcycloheptatriene **1**, under the action of the three-component catalytic system  $\text{Co}(\text{acac})_2(\text{dppe})/\text{Zn}/\text{ZnI}_2$  [8–13] under the developed conditions (10 mol%  $\text{Co}(\text{acac})_2(\text{dppe})$ , 30 mol% Zn, 20 mol%  $\text{ZnI}_2$ , 1,2-dichloroethane ( $\text{C}_2\text{H}_4\text{Cl}_2$ ), 20 h, 60 °C) passes with the formation of substituted bicyclo[4.2.1]nona-2,4,7-trienes **3,4a,b** in 80–84% yields. Bicyclo[4.2.1]nona-2,4,7-trienes **3,4a,b** are formed as two regioisomers in a 1:1 ratio. Each of the regioisomers was isolated individually using column chromatography (Table 1).

**Table 1.** Cobalt-catalyzed  $[6\pi + 2\pi]$ -cycloaddition of 1-benzoylcycloheptatriene (**1**) with alkynes (**2**)<sup>1</sup>.

| Alkyne    | R                                 | 3a,b:4a,b <sup>2</sup> | Yield <sup>3</sup> (%) |
|-----------|-----------------------------------|------------------------|------------------------|
| <b>2a</b> | Bu                                | 1:1                    | 84                     |
| <b>2b</b> | ( $\text{CH}_2$ ) <sub>2</sub> CN | 1:1                    | 80 <sup>4</sup>        |

<sup>1</sup> Reaction conditions: **1** (1 mmol), **2** (1.3 mmol),  $\text{Co}(\text{acac})_2(\text{dppe})$  (0.10 mmol), Zn (0.3 mmol),  $\text{ZnI}_2$  (0.20 mmol),  $\text{C}_2\text{H}_4\text{Cl}_2$  (3 mL), 60 °C, 20 h. <sup>2</sup> Ratio determined by <sup>1</sup>H NMR. <sup>3</sup> Yields of products isolated by column chromatography. <sup>4</sup>  $\text{CF}_3\text{CH}_2\text{OH}$  as the solvent.

Earlier [8], we found that substituted bicyclo[4.2.1]nona-2,4,7-trienes have a cytotoxic effect on a number of tumor cell lines. In the development of these studies, we studied the in vitro antitumor activity of bicyclo[4.2.1]nona-2,4,7-trienes **3,4a,b** synthesized in this work against tumor lines Jurkat, K562, U937, and HL60 (Table 2). It was found that cycloadducts **3,4a,b** exhibit antitumor activity, and the values of inhibitory concentration are in the range  $\text{IC}_{50} = 0.021 \pm 0.002$ – $0.048 \pm 0.004$   $\mu\text{M}$ .

**Table 2.** Cytotoxic activities IC<sub>50</sub> in vitro of bicyclo[4.2.1]nona-2,4,7-trienes **3,4a,b** measured on tumor cell cultures (Jurkat, K562, U937, HL60) and normal fibroblasts (μM).

| Compound  | Jurkat        | K562          | U937          | HL60          | Fibroblasts   |
|-----------|---------------|---------------|---------------|---------------|---------------|
| <b>3a</b> | 0.028 ± 0.002 | 0.022 ± 0.003 | 0.031 ± 0.003 | 0.025 ± 0.002 | 0.154 ± 0.018 |
| <b>4a</b> | 0.024 ± 0.002 | 0.030 ± 0.003 | 0.027 ± 0.002 | 0.021 ± 0.002 | 0.150 ± 0.016 |
| <b>3b</b> | 0.033 ± 0.003 | 0.048 ± 0.004 | 0.029 ± 0.002 | 0.035 ± 0.002 | 0.194 ± 0.022 |
| <b>4b</b> | 0.029 ± 0.002 | 0.034 ± 0.003 | 0.031 ± 0.003 | 0.036 ± 0.003 | 0.189 ± 0.020 |

### 3. Conclusions

Thus, we were the first to carry out the reactions of [6π + 2π]-cycloaddition of alkynes to 1-benzoylcycloheptatriene under the action of the three-component catalytic system Co(acac)<sub>2</sub>(dppe)/Zn/ZnI<sub>2</sub> to obtain previously undescribed O-, N-containing bicyclo[4.2.1]nona-2,4,7-trienes in high yields (80–84%). The obtained functionally substituted bicyclic compounds may be of interest as key precursors in the synthesis of important biologically active compounds and drugs.

### 4. Experimental Part

A chromatographic analysis was performed on a chromatograph using a 2000 × 2 mm column (SE-30 (5%) stationary phase on Chromaton N-AW-HMDS (0.125–0.160 mm), helium carrier gas (30 mL/min), and temperature programming from 50 to 300 °C at an 8 °C/min rate). Flash column chromatography was performed over silica gel 0.060–0.200 mm, 60 Å. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> at 125 MHz for <sup>13</sup>C and 500 MHz for <sup>1</sup>H. The chemical shifts are reported as δ values in parts per million, relative to the internal standard Me<sub>4</sub>Si. The coupling constants (*J*) are reported in hertz.

High-resolution mass spectra (HRMS) were measured on an instrument using a time-of-flight mass analyzer (TOF) with electrospray ionization (ESI). In experiments on selective collisional activation, the activation energy was set at a maximum abundance of fragment peaks. A syringe injection was used for solutions in MeCN/H<sub>2</sub>O, 50/50 *v/v* (flow rate 3 mL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C. All reactions were carried out in a dry argon atmosphere. 1,2-Dichloroethane was dried and freshly distilled before use. 1-Hexyne, 4-pentynenitrile, Co(acac)<sub>2</sub>, 1,2-bis(diphenylphosphino)ethane were purchased from commercial sources. Co(acac)<sub>2</sub>(dppe), 1-benzoylcycloheptatriene were synthesized according to procedures described in the literature [14,15].

Cycloaddition of alkynes to 1-benzoylcycloheptatriene (general procedure). Zn powder (30 mol%) was added to a solution of Co(acac)<sub>2</sub>(dppe) (10 mol%) in C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub> (1.5 mL) for **2a** (in CF<sub>3</sub>CH<sub>2</sub>OH for **2b**) in a Schlenk tube in a dry argon atmosphere, and the mixture was stirred at room temperature for 2 min. Next, 1-benzoylcycloheptatriene (1.0 mmol), the alkyne (1.3 mmol) in C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub> (1.5 mL) for **2a** (in CF<sub>3</sub>CH<sub>2</sub>OH for **2b**) and dry ZnI<sub>2</sub> (20 mol%) were added successively. After heating at 60 °C for 20 h, the reaction was stopped by the addition of petroleum ether and stirring in air for 10 min to deactivate the catalyst. After filtration through a short pad of silica, the volatiles were removed under a vacuum. Chromatographic purification over SiO<sub>2</sub> (petroleum ether → petroleum ether/ethyl acetate 30:1 as eluent for **3,4a**, petroleum ether → petroleum ether/ethyl acetate 10:1 → 5:1 → 2:1 as eluent for **3,4b**) afforded the target products **3,4a,b**.

(8-Butylbicyclo[4.2.1]nona-2,4,7-trien-1-yl)(phenyl)methanone (**3a**): Yield 42% (0.117 g), colorless oil, *R*<sub>f</sub> = 0.40 (petroleum ether/ethyl acetate 30:1). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.07–8.10 (m, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 6.66 (d, *J* = 11.1 Hz, 1H), 6.31 (dd, *J* = 10.5 Hz, *J* = 7.3 Hz, 1H), 5.92–6.02 (m, 2H), 5.15 (s, 1H), 3.27 (t, *J* = 6.9 Hz, 1H), 2.60 (dd, *J* = 11.8 Hz, *J* = 7.2 Hz, 1H), 2.04–2.17 (m, 2H), 1.83 (d, *J* = 11.8 Hz, 1H), 1.18–1.42 (m, 4H), 0.83 (t, *J* = 7.3 Hz, 3H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 202.4, 141.0, 139.1, 138.9, 136.5, 132.5, 129.2 (2C), 128.3 (2C), 123.7, 122.5, 117.1, 66.5, 42.4, 37.6, 31.2, 27.1, 22.4, 13.9 ppm. HRMS (ESI-TOF): calcd for C<sub>20</sub>H<sub>22</sub>ONa [M + Na]<sup>+</sup> 301.1568, found 301.1565.

(7-Butylbicyclo[4.2.1]nona-2,4,7-trien-1-yl)(phenyl)methanone (**4a**): Yield 42% (0.117 g), colorless oil,  $R_f = 0.46$  (petroleum ether/ethyl acetate 30:1).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.04 (d,  $J = 7.7$  Hz, 2H), 7.40–7.58 (m, 3H), 6.39 (d,  $J = 10.9$  Hz, 1H), 6.27 (dd,  $J = 10.1$  Hz,  $J = 7.8$  Hz, 1H), 5.92–6.03 (m, 2H), 5.42 (s, 1H), 3.39 (t,  $J = 7.1$  Hz, 1H), 2.38 (dd,  $J = 11.3$  Hz,  $J = 7.1$  Hz, 1H), 2.19 (t,  $J = 7.6$  Hz, 2H), 1.99 (d,  $J = 11.5$  Hz, 1H), 1.26–1.54 (m, 4H), 0.92 (t,  $J = 7.3$  Hz, 3H) ppm.  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.5, 140.0, 138.9, 138.4, 135.7, 132.7, 129.2 (2C), 128.3 (2C), 124.3, 122.1, 120.4, 64.0, 46.7, 37.2, 30.8, 28.4, 22.5, 13.9 ppm. HRMS (ESI-TOF): calcd for  $\text{C}_{20}\text{H}_{22}\text{ONa}$  [ $\text{M} + \text{Na}$ ] $^+$  301.1568, found 301.1564.

3-(6-Benzoylbicyclo[4.2.1]nona-2,4,7-trien-7-yl)propanenitrile (**3b**): Yield 40% (0.110 g), colorless oil,  $R_f = 0.58$  (petroleum ether/ethyl acetate 2:1).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.06 (d,  $J = 7.4$  Hz, 2H), 7.58 (t,  $J = 7.4$  Hz, 1H), 7.46 (t,  $J = 7.7$  Hz, 2H), 6.47 (d,  $J = 11.2$  Hz, 1H), 6.34 (dd,  $J = 10.7$  Hz,  $J = 7.4$  Hz, 1H), 6.07 (dd,  $J = 11.2$  Hz,  $J = 7.2$  Hz, 1H), 6.01 (dd,  $J = 10.9$  Hz,  $J = 7.5$  Hz, 1H), 5.27 (s, 1H), 3.31 (td,  $J = 7.1$  Hz,  $J = 2.3$  Hz, 1H), 2.44–2.64 (m, 5H), 1.95 (d,  $J = 11.7$  Hz, 1H) ppm.  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.03, 139.24, 137.46, 135.78, 135.67, 133.06, 129.19 (2C), 128.51 (2C), 124.09, 123.75, 119.34, 119.29, 66.22, 42.47, 37.66, 23.27, 17.31 ppm. HRMS (ESI-TOF): calcd for  $\text{C}_{19}\text{H}_{17}\text{NONa}$  [ $\text{M} + \text{Na}$ ] $^+$  298.1208, found 298.1204.

3-(1-Benzoylbicyclo[4.2.1]nona-2,4,7-trien-7-yl)propanenitrile (**4b**): Yield 40% (0.110 g), colorless oil,  $R_f = 0.55$  (petroleum ether/ethyl acetate 2:1).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.00–8.04 (m, 2H), 7.54–7.59 (m, 1H), 7.45 (t,  $J = 7.8$  Hz, 2H), 6.37 (d,  $J = 11.1$  Hz, 1H), 6.28 (dd,  $J = 10.4$  Hz,  $J = 7.4$  Hz, 1H), 6.07 (dd,  $J = 11.1$  Hz,  $J = 7.4$  Hz, 1H), 5.97–6.02 (m, 1H), 5.54 (s, 1H), 3.45 (t,  $J = 7.1$  Hz, 1H), 2.50–2.60 (m, 4H), 2.39 (dd,  $J = 11.6$  Hz,  $J = 6.9$  Hz, 1H), 2.03 (d,  $J = 11.6$  Hz, 1H) ppm.  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  201.7, 138.7, 137.9, 135.2, 133.6, 133.1, 129.2 (2C), 128.4 (2C), 125.4, 122.6, 122.4, 119.3, 64.0, 46.4, 37.0, 24.7, 16.8 ppm. HRMS (ESI-TOF): calcd for  $\text{C}_{19}\text{H}_{17}\text{NONa}$  [ $\text{M} + \text{Na}$ ] $^+$  298.1208, found 298.1206.

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