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Synthesis of New Functionally Substituted Bicyclo[4.2.1]nona-2,4,7-trienes by Co(I)-Catalyzed [6π + 2π] Cycloaddition of 1-Benzoylcycloheptatriene †

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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 [6π + 2π] cycloaddition of hexyn-1 and 4-pentynenitrile to 1-benzoylcycloheptatriene under the action of the three-component catalytic system $Co(acac)_2$(dppe)/Zn/ZnI_2.

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

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1. Introduction

Bicyclo[4.2.1]nonatrienes are of undoubted 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.

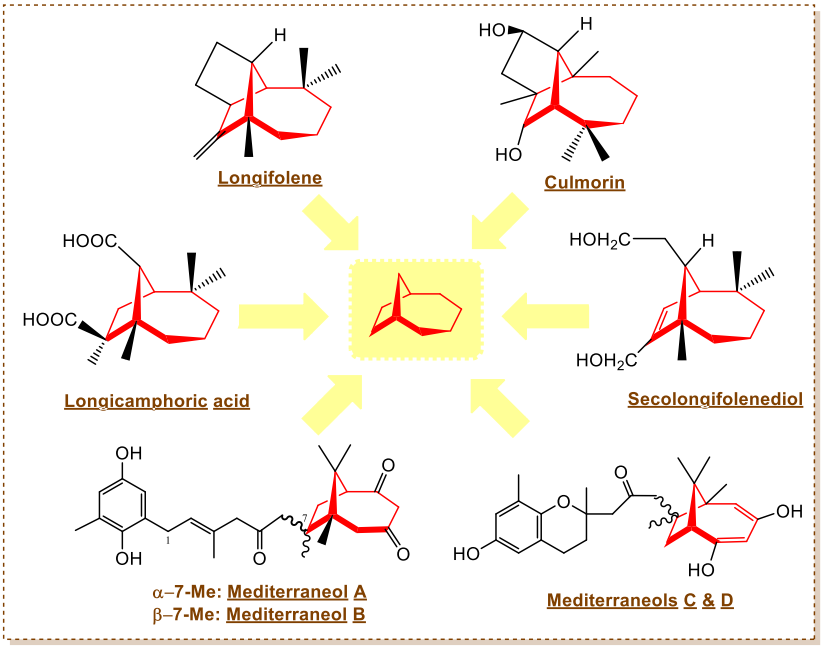


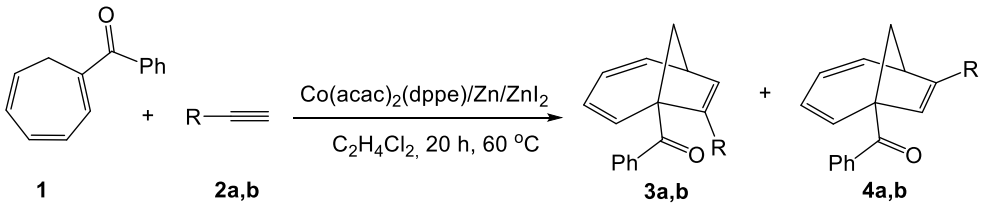
Figure 1. Natural products with the bicyclo[4.2.1]nonane core.

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 [6π + 2π] cycloaddition of terminal alkynes to 1-benzoylcycloheptatriene to obtain new bicyclo[4.2.1]nona-2,4,7-trienes.

2. Results and Discussion

We found that [6π + 2π] cycloaddition of terminal alkynes—hexyne-1 **2a** and 4-pentynenitrile **2b** to 1-benzoylcycloheptatriene **1** under the action of the three-component catalytic system $Co(acac)_2(dppe)/Zn/ZnI_2$ [8–13] under the developed conditions (10 mol% $Co(acac)_2(dppe)$, 30 mol% Zn, 20 mol% ZnI_2, 1,2-dichloroethane ($C_2H_4Cl_2$), 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 [6π + 2π]-cycloaddition of 1-benzoylcycloheptatriene (**1**) with alkynes (**2**) [1].



Alkyne	R	3a,b:4a,b [2]	Yield [3] (%)
2a	Bu	1:1	84
2b	$(CH_2)_2CN$	1:1	80 [4]

[1] Reaction conditions: **1** (1 mmol), **2** (1.3 mmol), $Co(acac)_2(dppe)$ (0.10 mmol), Zn (0.3 mmol), ZnI_2 (0.20 mmol), $C_2H_4Cl_2$ (3 mL), 60 °C, 20 h. [2] Ratio determined by ^1H NMR. [3] Yields of products isolated by column chromatography. [4] CF_3CH_2OH 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 1). It was found that cycloadducts **3**,**4a**,**b** exhibit antitumor activity and the values of inhibitory concentration are in the range IC_{50} = 0.021 ± 0.002–0.048 ± 0.004 μM.

Table 1. Cytotoxic activities IC_{50} 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
3a	0.028 ± 0.002	0.022 ± 0.003	0.031 ± 0.003	0.025 ± 0.002	0.154 ± 0.018
4a	0.024 ± 0.002	0.030 ± 0.003	0.027 ± 0.002	0.021 ± 0.002	0.150 ± 0.016
3b	0.033 ± 0.003	0.048 ± 0.004	0.029 ± 0.002	0.035 ± 0.002	0.194 ± 0.022
4b	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 $Co(acac)_2$(dppe)/Zn/ZnI_2 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

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 a 8 °C/min rate). Flash column chromatography was performed over silica gel 0.060–0.200 mm, 60 A. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 125 MHz for ^{13}C and 500 MHz for ^1H. The chemical shifts are reported as δ values in parts per million relative to the internal standard Me_4Si. The coupling constants (*J*) are reported in hertz.

High-resolution mass spectra (HRMS) were measured on a 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 maximum abundance of fragment peaks. A syringe injection was used for solutions in MeCN/H_2O, 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 under a dry argon atmosphere. **1,2-Dichloroethane** was dried and freshly distilled before use. 1-Hexyne, 4-pentynenitrile, $Co(acac)_2$, 1,2-bis(diphenylphosphino)ethane were purchased from commercial sources. $Co(acac)_2$(dppe), **1-benzoylcycloheptatriene** were synthesized according to procedures described in literature [14,15].

Cycloaddition of alkynes to 1-benzoylcycloheptatriene (general procedure). Zn powder (30 mol%) was added to a solution of $Co(acac)_2$(dppe) (10 mol%) in $C_2H_4Cl_2$ (1.5 mL) for **2a** (in CF_3CH_2OH for **2b**) in a Schlenk tube under 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 $C_2H_4Cl_2$ (1.5 mL) for **2a** (in CF_3CH_2OH for **2b**) and dry ZnI_2 (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 vacuum. Chromatographic purification over SiO_2 (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_f = 0.40 (petroleum ether/ethyl acetate 30:1). ^{1}H NMR (500 MHz, $CDCl_3$): 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. ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{20}H_{22}ONa$ [M + Na]$^+$ 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}H NMR (500 MHz, $CDCl_3$): δ 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}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{20}H_{22}ONa$ [M + 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}H NMR (500 MHz, $CDCl_3$): δ 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}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{19}H_{17}NONa$ [M + 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}H NMR (500 MHz, $CDCl_3$): δ 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}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{19}H_{17}NONa$ [M + Na]$^+$ 298.1208, found 298.1206.

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

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