

Proceeding Paper

# Co(I)-Catalyzed $[4\pi+2\pi]$ Cycloaddition of 1,2-Dienes to 1,3,5-Cyclooctatriene in the Synthesis of Previously Undescribed Tricyclo[4.2.2.0<sup>2,5</sup>]Decenes <sup>†</sup>

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**Abstract:** The catalytic  $[4\pi+2\pi]$ -cycloaddition of mono- and disubstituted 1,2-dienes to 1,3,5-cyclooctatriene under the action of  $\text{Co}(\text{acac})_2(\text{dppe})/\text{Zn}/\text{ZnI}_2$  was performed for the first time to give substituted tricyclo[4.2.2.0<sup>2,5</sup>]dec-7-enes.

**Keywords:**  $[4\pi+2\pi]$ -cycloaddition; 1,3,5-cyclooctatriene; 1,2-dienes; tricyclo[4.2.2.0<sup>2,5</sup>]dec-7-enes; cobalt(II) acetylacetonate; antitumor activity

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## 1. Introduction

Over the past decades, bi- and polycyclic, as well as cage hydrocarbons and their functionally substituted derivatives have been the objects of close attention of synthetic chemists due to their wide use as promising precursors for the development of modern drugs, important biologically active compounds and other practically valuable substances [1]. However, on the way to the widespread use of bi- and polycyclic compounds, both in laboratory practice and in industry, there are a number of difficulties associated with the inaccessibility of the feedstock for obtaining polycarbocycles of a given structure, the multistage synthesis for the isolation and purification of target compounds. Therefore, the development of one-pot methods for directed synthesis of previously hard-to-reach carbo- and heterocarbocycles is an important and urgent problem of modern organic chemistry.

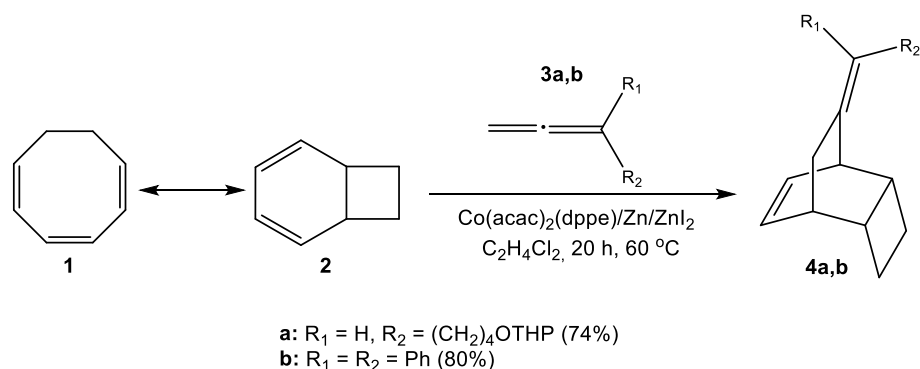
Analysis of the world literature shows that the number of promising and widespread methods for the synthesis of bi- and polycyclic compounds include catalytic cycloaddition reactions with the participation of available cyclic trienes [2–6]. In this area of research, 1,3,5-cyclooctatriene (COT) is of particular interest. However, the reactions of catalytic cycloaddition with the participation of this monomer have hardly been studied, and are represented by works on Mo- and Co-catalyzed cycloaddition of COT [7,8].

Earlier, we developed an efficient cobalt-containing catalytic system based on  $\text{Co}(\text{acac})_2$  [9–15], using which we first carried out the cycloaddition of 1,3-dienes to COT to obtain previously undescribed tricyclo[4.2.2.0<sup>2,5</sup>]deca-7,9-dienes [9]. In the development of these studies, we for the first time carried out the Co(I)-catalyzed  $[4\pi+2\pi]$  cycloaddition of mono- and disubstituted 1,2-dienes to COT.

## 2. Results and Discussion

We found that as a result of the reaction of 1,2-dienes **3a,b** with COT **1** under the action of the three-component catalytic system  $\text{Co}(\text{acac})_2(\text{dppe})/\text{Zn}/\text{ZnI}_2$  [9–15] 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)  $[4\pi+2\pi]$ -cycloadducts are formed—substituted tricyclo[4.2.2.0<sup>2,5</sup>]dec-7-enes **4a,b** in 74–80% yields (Scheme 1). It is known that COT **1** is in tautomeric equilibrium with bicyclo[4.2.0]octa-2,4-diene **2** [16]. Thus, under the above conditions, the valence tautomer COT of bicyclo[4.2.0]octa-2,4-diene **2** enters into the reaction of cyclocodimerization with 1,2-dienes **3a,b**. Along with the main codimer, the formation of a minor  $[6+2]$  cycloadduct COT in an amount not exceeding 5%.



**Scheme 1.** Cycloaddition of 1,2-dienes with COT.

Earlier [10,12,14,17] we found that substituted bicyclo[4.3.1]deca-2,4,8-trienes and bicyclo[4.2.1]nona-2,4,7-trienes have pronounced cytotoxic properties. In the development of these studies, we studied the *in vitro* antitumor activity of the synthesized tricyclo[4.2.2.0<sup>2,5</sup>]dec-7-enes **4a,b** against tumor cell lines Jurkat, K562, U937 and HL60 (Table 1). We found that tricyclic adducts **4a,b** exhibit a cytotoxic effect and the inhibitory concentration values are in the range  $\text{IC}_{50} = 0.019 \pm 0.002$ – $0.045 \pm 0.004$   $\mu\text{M}$ .

**Table 1.** Cytotoxic activities  $\text{IC}_{50}$  *in vitro* of tricyclo[4.2.2.0<sup>2,5</sup>]dec-7-enes **4a,b** measured on tumor cell cultures (Jurkat, K562, U937, HL60) and normal fibroblasts ( $\mu\text{M}$ ).

| Compound  | Jurkat            | K562              | U937              | HL60              | Fibroblasts       |
|-----------|-------------------|-------------------|-------------------|-------------------|-------------------|
| <b>4a</b> | $0.032 \pm 0.003$ | $0.029 \pm 0.002$ | $0.045 \pm 0.004$ | $0.028 \pm 0.002$ | $0.161 \pm 0.020$ |
| <b>4b</b> | $0.026 \pm 0.002$ | $0.023 \pm 0.002$ | $0.031 \pm 0.002$ | $0.019 \pm 0.002$ | $0.158 \pm 0.019$ |

### 3. Conclusions

Thus, we have performed for the first time the reactions of  $[4\pi+2\pi]$ -cycloaddition of 1,2-dienes to COT under the action of the three-component catalytic system  $\text{Co}(\text{acac})_2(\text{dppe})/\text{Zn}/\text{ZnI}_2$  to obtain new tricyclo[4.2.2.0<sup>2,5</sup>]dec-7-enes in high yields (74–80%). The obtained tricyclic adducts exhibited cytotoxic activity, which makes this class of compounds very attractive for further study as potential antitumor drugs.

### 4. Experimental Part

Chromatographic analysis was performed on a chromatograph using a  $2000 \times 2$  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 Å. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  at 125 MHz for  $^{13}\text{C}$  and 500 MHz for  $^1\text{H}$ . The chemical shifts are reported as  $\delta$  values in parts per million relative to the internal standard  $\text{Me}_4\text{Si}$ . 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  $\text{MeCN}/\text{H}_2\text{O}$ , 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 under a dry argon atmosphere. 1,2-Dichloroethane was dried and freshly distilled before use. Co(acac)<sub>2</sub>(dppe), 1,2-dienes, COT were synthesized according to procedures described in literature [18–20].

**Cycloaddition of 1,2-dienes to COT (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) in a Schlenk tube under a dry argon atmosphere, and the mixture was stirred at room temperature for 2 min. Next, COT (1.0 mmol), the 1,2-dienes (1.3 mmol) in C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub> (1.5 mL) 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 vacuum. Chromatographic purification over SiO<sub>2</sub> (petroleum ether → petroleum ether / ethyl acetate 30:1 as eluent) afforded the target products **4a,b**.

**exo-2-(((E)-5-(Tricyclo[4.2.2.0<sup>2,5</sup>]dec-9-en-7-ylidene)pentyl)oxy)tetrahydro-2H-pyran (4a):** Yield 74% (0.223 g), colorless oil, *R*<sub>f</sub> = 0.48 (petroleum ether/ethyl acetate 30:1). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.41 (t, *J* = 4.0 Hz, 2H), 5.10–5.14 (m, 1H), 4.59 (t, *J* = 4.0 Hz, 1H), 3.86–3.90 (m, 1H), 3.72–3.77 (m, 1H), 3.50–3.53 (m, 1H), 3.38–3.41 (m, 1H), 2.87 (t, *J* = 4.0 Hz, 1H), 2.62–2.70 (m, 1H), 2.38–2.51 (m, 2H), 1.83–2.08 (m, 7H), 1.39–1.82 (m, 11H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 139.1, 133.4, 132.5, 119.7, 98.8, 67.6, 62.3, 45.4, 38.9, 38.6, 35.8, 30.8, 30.6, 29.4, 28.1, 26.1, 25.5, 23.0, 22.1, 19.7 ppm. HRMS (ESI-TOF): calcd. for C<sub>20</sub>H<sub>30</sub>O<sub>2</sub>Na [M + Na]<sup>+</sup> 325.2143, found 325.2141.

**exo-9-(Diphenylmethylene)tricyclo[4.2.2.0<sup>2,5</sup>]dec-7-ene (4b):** Yield 80% (0.238 g), colorless oil, *R*<sub>f</sub> = 0.44 (petroleum ether/ethyl acetate 30:1). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.28–7.35 (m, 4H), 7.22–7.26 (m, 2H), 7.16–7.20 (m, 4H), 6.52 (t, *J* = 7.2 Hz, 1H), 6.45 (t, *J* = 7.3 Hz, 1H), 3.35–3.38 (m, 1H), 2.62–2.69 (m, 2H), 2.53–2.59 (m, 1H), 1.95–2.10 (m, 4H), 1.44–1.54 (m, 2H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 143.4, 142.9, 138.6, 134.3, 133.3, 132.2, 129.5 (2C), 129.4 (2C), 128.1 (2C), 128.0 (2C), 126.1, 126.0, 40.5, 38.6, 37.9, 35.8, 33.3, 23.0, 22.2 ppm. HRMS (ESI-TOF): calcd. for C<sub>23</sub>H<sub>22</sub>Na [M + Na]<sup>+</sup> 321.1619, found 321.1615.

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

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