chemistry proceedings

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Co(I)-Catalyzed [4π + 2π] Cycloaddition of 1,2-Dienes to 1,3,5-Cyclooctatriene in the Synthesis of Previously Undescribed Tricyclo[4.2.2.0^{2,5}]Decenes †

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† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: The catalytic [4π + 2π]-cycloaddition of monosubstituted and disubstituted 1,2-dienes to 1,3,5-cyclooctatriene under the action of Co(acac)$_2$(dppe)/Zn/ZnI$_2$ was performed for the first time to produce substituted tricyclo[4.2.2.0^{2,5}]dec-7-enes.

Keywords: [4π + 2π]-cycloaddition; 1,3,5-cyclooctatriene; 1,2-dienes; tricyclo[4.2.2.0^{2,5}]dec-7-enes; cobalt(II) acetylacetonate; antitumor activity

Citation: Kadikova, G.N.; Dzhemileva, L.U.; Dzhemilev, U.M. Co(I)-Catalyzed [4π + 2π] Cycloaddition of 1,2-Dienes to 1,3,5-Cyclooctatriene in the Synthesis of Previously Undescribed Tricyclo[4.2.2.0^{2,5}]Decenes. *Chem. Proc.* **2022**, *8*, 47. https://doi.org/10.3390/ecsoc-25-11633

Academic Editor: Julio A. Seijas

Published: 12 November 2021

1. Introduction

Over the past decades, bicyclic and polycyclic and 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 bicyclic 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 carbocycles and heterocarbocycles is an important and urgent problem of modern organic chemistry.

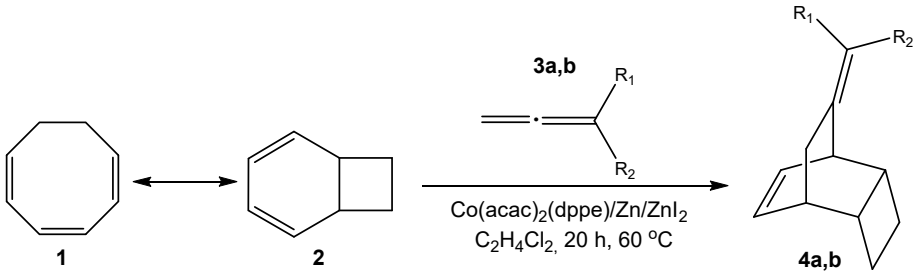
An analysis of the world literature shows that the number of promising and widespread methods for the synthesis of bi- and polycyclic compounds include catalytic cycloaddition reactions with the participation of available cyclic trienes [2–6]. In this area of research, 1,3,5-cyclooctatriene (COT) is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

In a previous study, we developed an efficient cobalt-containing catalytic system based on Co(acac)$_2$ [9–15], in which we first carried out the cycloaddition of 1,3-diines to COT to obtain previously undescribed tricyclo[4.2.2.0^{2,5}]deca-7,9-dienes [9]. In the development of these studies, for the first time, we carried out the Co(I)-catalyzed [4π + 2π] cycloaddition of monosubstituted 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 Co(acac)$_2$(dppe)/Zn/ZnI$_2$ [9–15] 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), [4π + 2π]-cycloadducts formed substituted tricyclo[4.2.2.0^{2,5}]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**. In addition to the main codimer, the formation of a minor [6 + 2] cycloadduct COT in an amount not exceeding 5% was observed.



a: R_1 = H, R_2 = $(CH_2)_4OTHP$ (74%)
b: R_1 = R_2 = Ph (80%)

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

In a previous study [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.$0^{2,5}$]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 of IC_{50} = 0.019 ± 0.002–0.045 ± 0.004 μM.

Table 1. Cytotoxic activities IC_{50} in vitro of tricyclo[4.2.2.$0^{2,5}$]dec-7-enes **4a,b** measured on tumor cell cultures (Jurkat, K562, U937 and HL60) and normal fibroblasts (μM).

Compound	Jurkat	K562	U937	HL60	Fibroblasts
4a	0.032 ± 0.003	0.029 ± 0.002	0.045 ± 0.004	0.028 ± 0.002	0.161 ± 0.020
4b	0.026 ± 0.002	0.023 ± 0.002	0.031 ± 0.002	0.019 ± 0.002	0.158 ± 0.019

3. Conclusions

Thus, we have performed, for the first time, the reactions of [4π + 2π]-cycloaddition of 1,2-dienes to COT under the action of the three-component catalytic system $Co(acac)_2(dppe)/Zn/ZnI_2$ to obtain new tricyclo[4.2.2.$0^{2,5}$]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 × 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 A. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 125 MHz for ^{13}C and 500 MHz for ^{1}H. 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 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 $MeCN/H_2O$, 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. $Co(acac)_2(dppe)$, 1,2-dienes and COT were synthesized according to procedures described in the literature [18–20].

Cycloaddition of 1,2-dienes to COT (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) 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 $C_2H_4Cl_2$ (1.5 mL) 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 a petroleum ether and stirred 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) afforded the target products **4a,b**.

exo-2-(((*E*)-5-(Tricyclo[4.2.2.0^{2,5}]dec-9-en-7-ylidene)pentyl)oxy)tetrahydro-2*H*-pyran (**4a**): Yield 74% (0.223 g), colorless oil, R_f = 0.48 (petroleum ether/ethyl acetate 30:1). ^{1}H NMR (500 MHz, $CDCl_3$): 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. ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{20}H_{30}O_2Na$ $[M + Na]^+$ 325.2143, found 325.2141.

exo-9-(Diphenylmethylene)tricyclo[4.2.2.0^{2,5}]dec-7-ene (**4b**): Yield 80% (0.238 g), colorless oil, R_f = 0.44 (petroleum ether/ethyl acetate 30:1). ^{1}H NMR (500 MHz, $CDCl_3$): 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. ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{23}H_{22}Na$ $[M + Na]^+$ 321.1619, found 321.1615.

Author Contributions: Conceptualization, U.M.D. and G.N.K.; methodology, validation and execution of chemistry experiments, G.N.K. and L.U.D.; manuscript preparation, G.N.K., L.U.D. and U.M.D. All authors have read and agreed to the published version of the manuscript.

Funding: The work was performed within the approved plans for research projects at IPC RAS State Registration No. FMRS-2022-0075 and Grant of Russian Foundation for Basic Research (19-03-00393).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data available on request.

Acknowledgments: The structural studies of the synthesized compounds were performed with the use of Collective Usage Centre "Agidel" at the Institute of Petrochemistry and Catalysis of RAS. The biological studies of bicycles were performed in the Laboratory of Molecular Design and Drug Bioscreening at the Institute of Petrochemistry and Catalysis.

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

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