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\(^2,5\)]Dec-7-enes †

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Abstract: The catalytic \([4\pi + 2\pi]\)-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: \([4\pi + 2\pi]\)-cycloaddition; 1,3,5-cyclooctatriene; 1,2-dienes; tricyclo[4.2.2.0\(^2,5\)]dec-7-enes; cobalt(II) acetylacetonate; antitumor activity

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-dienes to COT to obtain previously undescribed tricyclo[4.2.2.0\(^2,5\)]dec-7,9-dienes [9]. In the development of these studies, for the first time, we carried out the Co(I)-catalyzed \([4\pi + 2\pi]\) 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\(_2\)H\(_4\)Cl\(_2\)), 20 h, 60 °C), \([4\pi + 2\pi]\)-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-diienes 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.

![Scheme 1. Cycloaddition of 1,2-dienes with COT.](image)

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.

| 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-diienes 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. 1H and 13C NMR spectra were recorded in CDCl₃ at 125 MHz for 13C and 500 MHz for 1H. The chemical shifts are reported as δ values in parts per million relative to the internal standard Me₄Si. 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/H₂O, 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 C₂H₄Cl₂ (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 C₂H₄Cl₂ (1.5 mL) and dry ZnI₂ (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 SiO₂ (petroleum ether → petroleum ether / ethyl acetate 30:1 as eluent) afforded the target products 4a,b.

exo-2-(((E)-5-(Tricyclo[4.2.2.0²⁵]dec-9-en-7-ylidene)pentyl)oxy)tetrahydro-2H-pyran (4a): Yield 74% (0.223 g), colorless oil, R₂ = 0.48 (petroleum ether / ethyl acetate 30:1). ¹H NMR (500 MHz, CDCl₃): 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. ¹³C NMR (125 MHz, CDCl₃): 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 C₂₀H₂₀O₂Na [M + Na]⁺ 325.2143, found 325.2141.

exo-9-(Diphenylmethylene)tricyclo[4.2.2.0²⁵]dec-7-ene (4b): Yield 80% (0.238 g), colorless oil, R₂ = 0.44 (petroleum ether / ethyl acetate 30:1). ¹H NMR (500 MHz, CDCl₃): 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. ¹³C NMR (125 MHz, CDCl₃): 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 C₂₃H₂₂Na [M + Na]⁺ 321.1619, found 321.1615.

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References
1. Petasis, N.A.; Patane, M.A. The Synthesis of Carbocyclic Eight-Membered Rings. Tetrahedron 1992, 48, 5757–5821. [CrossRef]
2. D’yakonov, V.A.; Kadikova, G.N.; Dzemilev, U.M. Transition Metal Complex-Mediated Chemistry of 1,3,5-Cycloheptatrienes. Russ. Chem. Rev. 2018, 87, 797–820. [CrossRef]
3. Yu, Z.X.; Wang, Y.; Wang, Y. Transition-metal-catalyzed cycloadditions for the synthesis of eight-membered carbocycles. Chem. Asian J. 2010, 5, 1072–1088. [CrossRef] [PubMed]
4. Fruhauf, H. Metal-assisted cycloaddition reactions in organotransition metal chemistry. Chem. Rev. 1997, 97, 523–596. [CrossRef] [PubMed]
5. Lautens, M.; Klute, W.; Tam, W. Transition metal-mediated cycloaddition reactions. Chem. Rev. 1996, 96, 49–92. [CrossRef] [PubMed]
6. Anand, A.; Singh, P.; Kumar, V.; Bhargava, G. Transition metal catalyzed [6 + 2] cycloadditions. RSC Adv. 2019, 9, 25554–25568. [CrossRef]
7. Schmidt, T. Molybdenum-catalysed and -mediated cycloaddition reactions: Efficient synthesis of complex products from 1-oxa-1,3-dienes and cyclotriynes or -tetaenes. *Chem. Ber.* 1997, 130, 453–461. [CrossRef]

8. Achard, M.; Mosrin, M.; Tenaglia, A.; Buono, G. Cobalt(I)-Catalyzed [6 + 2] Cycloadditions of Cyclooctatetra(tri)ene with Alkynes. *J. Org. Chem.* 2006, 71, 2907–2910. [CrossRef] [PubMed]

9. Dyakonov, V.A.; Kadikova, G.N.; Nasretdinov, R.N.; Dzhemilev, U.M. Cobalt(I)-catalyzed [4π + 2π] cycloaddition reactions of 1,3-diynes with 1,3,5-cyclooctatriene. *Tetrahedron Lett.* 2017, 58, 1839–1841. [CrossRef]

10. Dyakonov, V.A.; Kadikova, G.N.; Dzhemileva, L.U.; Gazzizullina, G.F.; Ramazanov, I.R.; Dzhemilev, U.M. Cobalt-Catalyzed [6 + 2] Cycloaddition of Alkynes with 1,3,5,7-Cyclooctatetraene as a Key Element in the Direct Construction of Substituted Bicyclo[4.3.1]decanes. *J. Org. Chem.* 2017, 82, 471–480. [CrossRef] [PubMed]

11. D’yakonov, V.A.; Kadikova, G.N.; Gazzizullina, G.F.; Dzhemilev, U.M. Cobalt(I)-Catalyzed Cycloaddition of Functionally Substituted Alkynes and 1,3-Diynes to 1,3,5,7-Cyclooctatetraene in the Synthesis of Bicyclo[4.2.2]deca-2,4,7,9-tetraenes. *ChemistrySelect.* 2018, 3, 6221–6223. [CrossRef]

12. D’yakonov, V.A.; Kadikova, G.N.; Nasretdinov, R.N.; Dzhemilev, L.U.; Dzhemilev, U.M. The Synthesis of Bicyclo[4.2.1]nona-2,4,7-trienes by [6π+2π]-Cycloaddition of 1-Substituted 1,3,5-Cycloheptatrienes Catalyzed by Titanium and Cobalt Complexes. *J. Org. Chem.* 2019, 84, 9058–9066. [CrossRef] [PubMed]

13. D’yakonov, V.A.; Kadikova, G.N.; Nasretdinov, R.N.; Dzhemilev, L.U.; Dzhemilev, U.M. Targeted Synthesis of 9-Azabicyclo[4.2.1]nona-2,4,7-trienes by Cobalt(I)-Catalyzed [6σ + 2σ]-Cycloaddition of Alkynes to N-Substituted Azepines and Their Antitumor Activity. *Eur. J. Org. Chem.* 2020, 623–626. [CrossRef] [PubMed]

14. Kadikova, G.N.; Dzhemileva, L.U.; D’yakonov, V.A.; Dzhemilev, U.M. Synthesis of Functionally Substituted Bicyclo[4.2.1]nona-2,4-diynes and Bicyclo[4.2.1]nona-2,4,7-trienes by Cobalt(I)-catalyzed [6σ + 2σ] Cycloaddition of 2-Tropylcyclohexanone. *ACS Omega* 2020, 5, 31440–31449. [CrossRef] [PubMed]

15. Kadikova, G.N.; D’yakonov, V.A.; Dzhemilev, U.M. Synthesis of New Functionally Substituted 9-Azabicyclo[4.2.1]nona-2,4,7-trienes by Cobalt(I)-Catalyzed [6 + 2]-Cycloaddition of N-Carbocholesteroxyazepine to Alkynes. *Molecules* 2021, 26, 2932. [CrossRef] [PubMed]

16. Cope, A.C.; Haven, A.C.; Ramp, F.L.; Trumbull, E.R. Cyclic Polyolefins. XXIII. Valence Tautomerism of 1,3,5-Cyclooctatriene and Bicyclo[4.2.0]octa-2,4-diene. *J. Am. Chem. Soc.* 1952, 74, 4867–4871. [CrossRef]

17. D’yakonov, V.A.; Kadikova, G.N.; Dzhemileva, L.U.; Gazzizullina, G.F.; Yunusbaeva, M.M.; Dzhemilev, U.M. Oxidative skeletal rearrangement of bicyclo[4.2.2]deca-2,4,7,9-tetraenes to bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols and study of the antitumor activity of the products in vitro. *Tetrahedron* 2018, 74, 4071–4077. [CrossRef]

18. Cotton, F.A.; Faut, O.D.; Goodgame, M.L.; Holm, R.H. Magnetic Investigations of Spin-free Cobaltous Complexes. VI. Complexes Containing Phosphines and the Position of Phosphines in the Spectrochemical Series. *J. Am. Chem. Soc.* 1961, 83, 1780–1785. [CrossRef]

19. Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*; Elsevier Academic Press: Bilthoven, The Netherlands, 2004; pp. 229–234.

20. Oda, M.; Kawase, T.; Kurata, H. 1,3,5-Cyclooctatriene. *Org. Synth.* 1996, 73, 240.