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Catalytic Cyclocodimerization of Silicon-Containing 1,2-Dienes with 1,3,5-Cycloheptatriene in the Synthesis of Biologically Active Bicyclo[4.2.1]Nona-2,4-Dienes †

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Abstract: The [6+2] cycloaddition of (2-butyl-2,3-butadienyl)(trimethyl)silane and 2,3-butadienyl(trimethyl)silane to 1,3,5-cycloheptatriene was studied using titanium- and cobalt-containing multicomponent catalytic systems: R_2TiCl_2-R'_nAlCl_{3-n} (R = acac, Pr^iO, Bu^tO, Cl; R′ = Et, Bu^i, n = 2, 3) and $CoX_2(Y)/Z/ZnI_2$ (X = acac, Br, I, Cl, OAc; Y = dppe, dppm, dppp, dppb, Ph_3P, $P(OPr^i)_3$, $P(OPh)_3$; Z = Zn, Mg, In, Bu_4NBH_4). The work investigated the influence of the nature of the central atom of the catalyst, the ligand environment of the catalyst, the nature of the organoaluminum cocatalyst, the reducing agent, the effect of temperature, as well as the nature of the solvent on the yield and stereoselectivity of the formation of cycloadducts. Catalytic cyclocodimerization occurs with the formation of silicon-containing bicyclo[4.2.1]nona-2,4-dienes, which are of interest as promising precursor compounds in the synthesis of new drugs. It is known that many bridged carbo- and heterocarbocyclic compounds containing silicon atoms in the structure have diverse biological activities and are valuable drugs. Based on this, the work for the first time carried out a comprehensive study of the antitumor activity of synthesized silicon-containing bicyclo[4.2.1]nona-2,4-dienes in vitro using various tumor cell lines (U937, K562, Jurkat, HL60) and normal fibroblasts.

Keywords: cycloaddition; catalysis; 1,3,5-cycloheptatriene; Si-containing 1,2-dienes; bridged carbocycles; antitumor activity

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1. Introduction

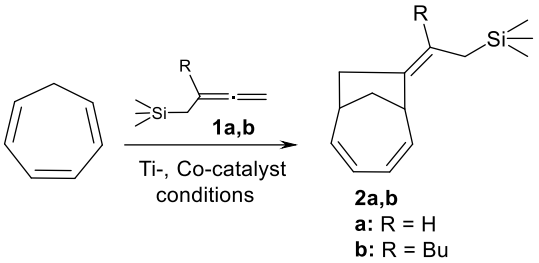
Catalytic cyclodimerization reactions involving 1,3,5-cycloheptatrienes (CHT) are an effective tool for obtaining a wide variety of bridged polycycles [1,2], many of which are used in the targeted synthesis of new bioactive and medicinal compounds [1,3,4]. For example, compounds such as taxol, ingenol and phorbol, which have high physiological activity, were obtained based on bicyclic adducts of CHT [3,4]. Therefore, studies on the synthesis of previously unknown polycycles based on CHTs are a relevant and promising direction in the field of modern organic synthesis. Previously, we developed effective catalytic systems that allow cycloaddition reactions of CHT and its substituted derivatives to be carried out with various classes of unsaturated compounds [5–7]. As a result of the implementation of these transformations, new classes of bi- and polycyclic carbocycles were obtained, and their antitumor activity in vitro was studied [7].

It is known that the presence of a silicon atom in a molecule increases the lipophilicity of a compound, and as a result, its cytotoxic effect is enhanced [8]. For example, it has been proven that the silyl protecting group plays an important role in enhancing the cytotoxic activity of the molecule [9,10]. Therefore, the development of effective approaches to the synthesis of new silicon-containing carbo- and heterocarbocycles is of particular interest in the targeted search for new antitumor compounds. In the present work, we studied the [6+2] cycloaddition of (2-butyl-2,3-butadienyl)(trimethyl)silane and 2,3-

butadienyl(trimethyl)silane to CHT using multicomponent catalytic systems based on titanium and cobalt in order to obtain silicon-containing bicyclo[4.2.1]nona-2,4-dienes, and also studied the in vitro antitumor properties of the synthesized adducts.

2. Results and Discussion

Initially, we studied the cyclodimerization reactions of Si-containing 1,2-dienes with CHT under the action of titanium-based catalytic systems in combination with organoaluminum reducing agents. It was found that [6+2] cycloaddition of 2,3-butadienyl(trimethyl)silane **1a** and (2-butyl-2,3-butadienyl)(trimethyl)silane **1b** to CHT under the action of the R_2TiCl_2-R'_nAlCl_{3-n} (R = acac, Pr^iO, Bu^tO, Cl; R′ = Et, Bu^i, n = 2, 3) catalytic system leads to the formation of bicyclo[4.2.1]nona-2,4-dienes **2a,b** in 19–89% yields as an equimolar mixture of *Z*- and *E*-isomers (Scheme 1, Table 1).



Scheme 1. Catalytic cycloaddition of Si-containing 1,2-dienes with CHT.

Table 1. Effect of the nature of the catalyst, reducing agent, solvent, temperature and reaction time on the yield of cycloadducts **2a,b**.

Entry	Ti-Catalyst	Conditions	Yield 2a,b (%)
1	$Ti(acac)_2Cl_2$-Et_2AlCl	benzene, 80 °C, 8 h	**a:** 82; **b:** 85
2	$Ti(acac)_2Cl_2$-Et_2AlCl	toluene, 80 °C, 8 h	**a:** 76; **b:** 78
3	$Ti(acac)_2Cl_2$-Et_2AlCl	1,2-dichlorobenzene, 80 °C, 8 h	**a:** 71; **b:** 70
4	$Ti(acac)_2Cl_2$-Et_2AlCl	cyclohexane, 80 °C, 8 h	**a:** 51; **b:** 53
5	$Ti(acac)_2Cl_2$-Et_2AlCl	hexane, 80 °C, 8 h	**a:** 65; **b:** 70
6	$Ti(acac)_2Cl_2$-Et_2AlCl	THF, 80 °C, 8 h	-
7	$Ti(acac)_2Cl_2$-Et_2AlCl	benzene, 40 °C, 8 h	**a:** 20; **b:** 19
8	$Ti(acac)_2Cl_2$-Et_2AlCl	benzene, 60 °C, 8 h	**a:** 41; **b:** 44
9	$Ti(acac)_2Cl_2$-Et_2AlCl	benzene, 80 °C, 5 h	**a:** 68; **b:** 70
10	$Ti(acac)_2Cl_2$-Et_2AlCl	benzene, 80 °C, 11 h	**a:** 82; **b:** 84
11	$Ti(acac)_2Cl_2$-Et_3Al	benzene, 80 °C, 8 h	**a:** 80; **b:** 82
12	$Ti(acac)_2Cl_2$-Bu^i_2AlCl	benzene, 80 °C, 8 h	**a:** 82; **b:** 86
13	$Ti(acac)_2Cl_2$-Bu^i_3Al	benzene, 80 °C, 8 h	**a:** 85; **b:** 89
14	$TiCl_4$-Et_2AlCl	benzene, 80 °C, 8 h	**a:** 79; **b:** 77
15	$Ti(OPr^i)_2Cl_2$-Et_2AlCl	benzene, 80 °C, 8 h	**a:** 80; **b:** 79
16	$Ti(OBu^t)_2Cl_2$-Et_2AlCl	benzene, 80 °C, 8 h	**a:** 74; **b:** 76

$Ti(acac)_2Cl_2$, $TiCl_4$, $Ti(OPr^i)_2Cl_2$ and $Ti(OBu^t)_2Cl_2$ (entries 1, 14–16) can be successfully used as catalysts without significant changes in the yield of cycloadducts. Equally effective are the following reducing agents: Et_2AlCl, Et_3Al, Bu^i_2AlCl and Bu^i_3Al (entries 1, 11–13). Codimerization occurs most effectively in benzene and toluene; it is also possible to use 1,2-dichlorobenzene, cyclohexane and hexane as solvents (entries 1–5). The reaction does not occur in THF (entry 6). It was found that the yield of codimers is affected by the

temperature and duration of the experiment. The most optimal condition is a reaction temperature of 80 °C and an experiment duration of 8 h (entries 1–5, 11–16) (Table 1).

As a result of further studies, it was established that the [6+2] cycloaddition of 2,3-butadienyl(trimethyl)silane **1a** and (2-butyl-2,3-butadienyl)(trimethyl)silane **1b** to CHT using a three-component catalytic system based on cobalt complexes $CoX_2(Y)/Z/ZnI_2$ (X = acac, Br, I, Cl, OAc; Y = dppe, dppm, dppp, dppb, Ph_3P, $P(OPr^i)_3$, $P(OPh)_3$; Z = Zn, Mg, In, Bu_4NBH_4) leads to the formation of bicyclo[4.2.1]nona-2,4-dienes **2a,b** in yields of 7–88% as the *E*-isomer (the *Z*-isomer was detected in trace amounts not exceeding 5%) (Scheme 1, Table 2).

Table 2. Effect of the nature of the catalytic system, temperature and reaction time on the yield of cycloadducts **2a,b**.

Entry	Co-Catalyst	Conditions	Yield 2a,b (%)
1	$Co(acac)_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 85; **b:** 88
2	$CoBr_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 75; **b:** 79
3	$CoCl_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 54; **b:** 49
4	$CoI_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 80; **b:** 83
5	$Co(OAc)_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 78; **b:** 74
6	$Co(acac)_2(dppm)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 35; **b:** 36
7	$Co(acac)_2(dppp)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 20; **b:** 18
8	$Co(acac)_2(dppb)/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	-
9	$Co(acac)_2/Ph_3P/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 10; **b:** 7
10	$Co(acac)_2/P(OPh)_3/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	-
11	$Co(acac)_2/P(OPr^i)_3/Zn/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	-
12	$Co(acac)_2(dppe)/Zn$	$C_2H_4Cl_2$, 60 °C, 5 ч	-
13	$Co(acac)_2(dppe)/Mg/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 78; **b:** 80
14	$Co(acac)_2(dppe)/In/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 77; **b:** 79
15	$Co(acac)_2(dppe)/Bu_4NBH_4/ZnI_2$	$C_2H_4Cl_2$, 60 °C, 5 ч	**a:** 83; **b:** 85
16	$Co(acac)_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 25 °C, 72 ч	**a:** <6; **b:** <5
17	$Co(acac)_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 40 °C, 5 ч	**a:** 28; **b:** 30
18	$Co(acac)_2(dppe)/Zn/ZnI_2$	$C_2H_4Cl_2$, 40 °C, 20 ч	**a:** 82; **b:** 85

The experiments showed that the reaction is catalyzed by such cobalt(II) salts as $Co(acac)_2$, $CoBr_2$, $CoCl_2$, CoI_2, and $Co(OAc)_2$ (entries 1–5). The most effective ligand was dppe (entries 1–5, 13–15), while the use of dppm, dppp, and Ph_3P resulted in a sharp decrease in the yield of the target cycloadduct (entries 6, 7, and 9). Zn, Mg, In, and Bu_4NBH_4 (entries 1–5, 13–15) can be successfully used as reducing agents. In the absence of the Lewis acid ZnI_2, the codimerization reaction does not occur (entry 12). The maximum yield of the product is achieved at a temperature of 60 °C and an experiment duration of 5 h (entry 1), while at a lower temperature the yield of the product decreases noticeably (entries 16, 17) (Table 2).

It is known that many silicon-containing bi- and polycyclic compounds exhibit pronounced biological activity and are medicinal products [7–10]. Therefore, in this work, we studied for the first time the antitumor activity of the synthesized silicon-containing bicyclo[4.2.1]nona-2,4-dienes **2a,b** in vitro using tumor cell lines U937, K562, Jurkat, HL60 and normal fibroblasts (Table 3). It was found that cycloadducts **2a,b** exhibit an antitumor effect on the studied cell lines and the inhibitory concentration values are in the range of IC50 = 0.012 ± 0.001–0.034 ± 0.003 μM.

Table 3. Cytotoxic activities IC_{50} in vitro of bicyclo[4.2.1]nona-2,4-dienes **2a,b** measured on tumor cell cultures (Jurkat, K562, U937, HL60) and normal fibroblasts (μM).

Compound	IC_{50} (μM)				
	Jurkat	**K562**	**U937**	**HL60**	**Fibroblasts**
2a	0.025 ± 0.002	0.019 ± 0.002	0.034 ± 0.003	0.015 ± 0.001	0.157 ± 0.019
2b	0.020 ± 0.002	0.017 ± 0.002	0.028 ± 0.002	0.012 ± 0.001	0.160 ± 0.020

3. Conclusions

The [6+2] cycloaddition of (2-butyl-2,3-butadienyl)(trimethyl)silane and 2,3-butadienyl(trimethyl)silane to CHT under the action of titanium- and cobalt-containing multicomponent catalytic systems was studied for the first time, leading to the selective formation of Si-containing bicyclo[4.2.1]nona-2,4-dienes. The synthesized carbocycles exhibited antitumor properties, which makes these compounds promising objects of study in the field of creating modern anticancer drugs.

4. Experimental Part

All solvents were dried and freshly distilled before use. All reactions were carried out under a dry argon atmosphere. Analytical data for compounds **2a,b** (^1H NMR, ^{13}C NMR, elemental analysis, mass spectral analysis) are reported in the literature [5].

Titanium catalyzed cycloaddition of 1,3,5-cycloheptatriene and Si-containing 1,2-dienes (general procedure). A glass ampoule, at ~0 °C under a dry argon atmosphere, was charged with 1,3,5-cycloheptatriene (1 mmol), Si-containing 1,2-diene (1.2 mmol), 0.03 mmol $Ti(acac)_2Cl_2$ (or $TiCl_4$, $Ti(OBu^t)_2Cl_2$, $Ti(OPr^i)_2Cl_2$) and anhydrous benzene (3 mL). The ampoule was cooled in liquid nitrogen, charged with Et_2AlCl (or Et_3Al, Bu^i_2AlCl, Bu^i_3Al) (0.4 mmol in 1 mL of benzene) and sealed. After heating at 80 °C for 8 h the ampoule was opened, its contents poured into C_2H_5OH (2 mL). Volatile solvents were removed under vacuum. Chromatographic purification on SiO_2 (100% petroleum ether as eluent) afforded the target products **2a,b**.

Cobalt catalyzed cycloaddition of 1,3,5-cycloheptatriene and Si-containing 1,2-dienes (general procedure). Zn powder (30 mol%) (or Mg, In, Bu_4NBH_4) was added to a solution of $Co(acac)_2$(dppe) (10 mol%) (or $CoBr_2$(dppe), $CoCl_2$(dppe), CoI_2(dppe), $Co(OAc)_2$(dppe)) in $C_2H_4Cl_2$ (1.5 mL) in a glass ampoule under a dry argon atmosphere, and the mixture was stirred at room temperature for 2 min. Next, 1,3,5-cycloheptatriene (1.0 mmol), Si-containing 1,2-diene (1.2 mmol) in $C_2H_4Cl_2$ (1.5 mL) and ZnI_2 (20 mol%) were added successively. The ampoule was sealed and after heating at 60 °C for 5 h, the ampoule was opened and 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 as eluent) afforded the target products **2a,b**.

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