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New in the catalytic synthesis of practically important eight- and nine-membered carbocycles by cycloaddition reactions with the participation of 1,3,5-cycloheptatrienes and 1,3,5,7-cyclooctatetraenes †

Gulnara N. Kadikova,* Usein M. Dzhemilev

Institute of Petrochemistry and Catalysis of Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russian Federation; Dzhemilev@anrb.ru (U.M.D.)
* Correspondence: Kad.Gulnara@gmail.com; Tel. +791-7481-8495
† Presented at the title, place, and date.

Abstract: The data obtained by the authors in the field of chemistry of 1,3,5-cycloheptatrienes and 1,3,5,7-cyclooctatetraenes with the participation of complexes of transition metals are summarized. The reactions of cyclocodimerization of 1,3,5-cycloheptatrienes and 1,3,5,7-cyclooctatetraenes with alkenes, dienes and alkynes in the presence of transition metal complexes, carried out by the type of [$6\pi + 2\pi$]- and [$4\pi + 2\pi$]-cycloaddition, are considered. Special attention is paid to the application of these reactions in the synthesis of practically important bi-, tri- and polycyclic strained compounds, as well as in the development of stereoselective methods for the synthesis of natural compounds.

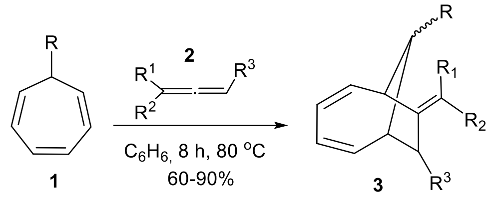
Keywords: cycloaddition; 1,3,5-cycloheptatrienes; 1,3,5,7-cyclooctatetraenes; alkenes; dienes; alkynes; transition metal complexes; eight- and nine-membered carbocycles

1. Introduction

Among the large number of possible ways of constructing medium cycles, the most preferred are those based on cycloaddition reactions using metal complex catalysis methods [1-3]. The development of reactions of catalytic cycloaddition with obtaining medium cycles is one of the most urgent and demanded areas of modern organic synthesis, in view of the high prevalence of these compounds in the composition of a large number of biologically active substances and drugs [1]. According to the analysis of the world literature, one of the promising directions in the synthesis of medium cycles is directed catalytic conversions of available cyclic polyunsaturated monomers - 1,3,5-cycloheptatrienes (CHT) and 1,3,5,7-cyclooctatetraene (COTT) [3]. In the literature, there are preferably publications devoted to the study of reactions of thermally and photochemically induced cycloaddition of alkenes, 1,2-, 1,3-dienes and alkynes to Fe-, Ru- and Cr-containing carbonyl complexes CHT [4-8]. The catalytic variants of these transformations are represented by Ti-, Co-, Cr-, Mo- and Rh-catalyzed cyclodimerization of CHT [9-15].

2. Results and discussion

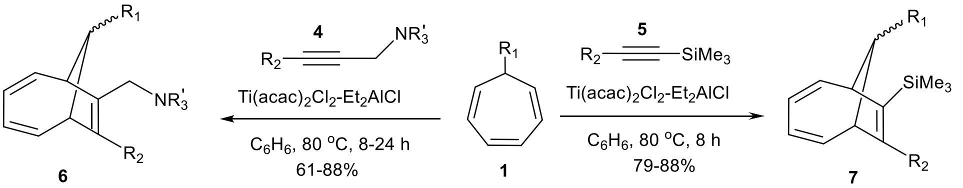
To date, we have accumulated significant experience in the development of effective one-pot methods for the synthesis of various classes of previously undescribed bi-, tri- and polycyclic compounds based on cycloaddition reactions CHTs and COTT catalyzed by complexes of transition metals [3]. As a result of research carried out over the past 5-10 years, we have proposed effective preparative methods for the synthesis of a wide range of substituted bicyclo[4.2.1]nona-2,4-dienes and bicyclo[4.2.1]nona-2,4,7-trienes based on reactions of titanium- and cobalt-catalyzed cycloaddition of 1,2-dienes and alkynes to CHT and its derivatives. So, in 2013, we developed a two-component catalytic system TiX_2Cl_2-Et_2AlCl (X = Cl, acac, *i*-PrO), which was used for the first time in the [6π+2π] cycloaddition of 1,2-dienes **2** to CHT and 7-alkyl(phenyl,allyl)-1,3,5-cycloheptatrienes **1** to form substituted bicyclo[4.2.1]nona-2,4-dienes **3** as a single regioisomer [16] (Scheme 1).



Kat. = TiX_2Cl_2-Et_2AlCl, X = Cl, acac, *i*-PrO; R = H, alkyl, Ph, allyl
1) R_1 = H, CH_3, Ph; R_2 = alkyl, Ph, Bn, -$(CH_2)_5$-; R_3 = H;
2) R_1 = R_3 = -$(CH_2)_6$-, R_2 = H

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

In the development of research on the synthesis of new bicyclo[4.2.1]nonanes, as well as in order to expand the scope of application of the developed titanium-containing catalytic system, we carried out the cyclocodimerization of CHTs with alkynes [17]. It was found that [6π+2π] cycloaddition of nitrogen- **4** and silicon-containing alkynes **5** to CHTs **1** under the action of the $Ti(acac)_2Cl_2$-Et_2AlCl catalytic system in benzene for 8-24 h at 80 °C leads to the formation of bicyclo[4.2.1]nona-2,4,7-trienes **6** (61-88%) and **7** (79-88%) (Scheme 2):

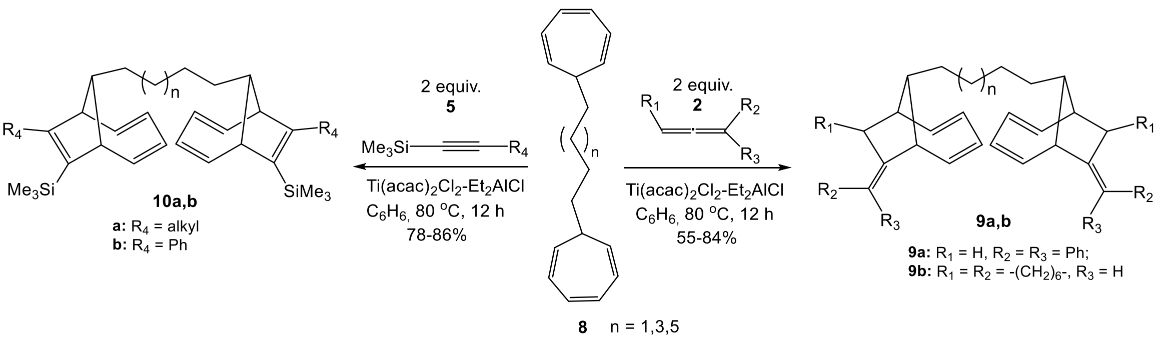


R_1 = H, alkyl, Ph
R_2 = alkyl, Ph
R_3 = -$(CH_2)_5$-, -$(CH_3)_2$

R_1 = H, alkyl, Ph, allyl
R_2 = alkyl, Ph

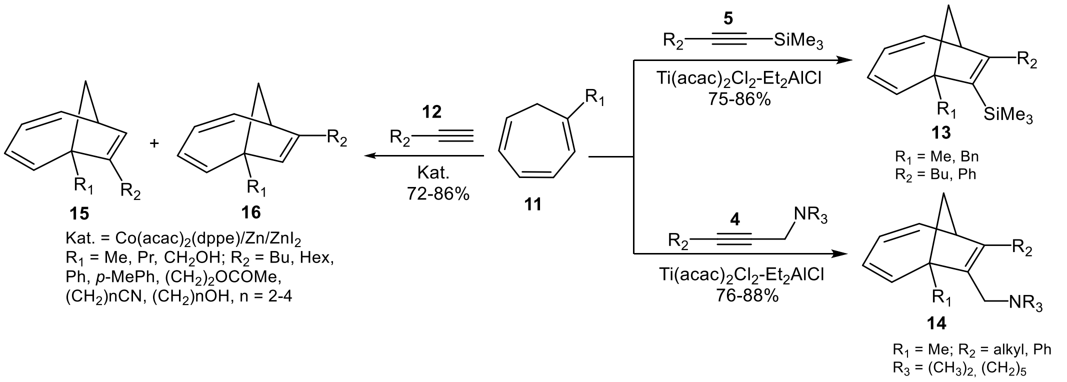
Scheme 2. Cycloaddition of alkynes with CHTs.

Of particular interest are the works [18,19] on the reactions of cyclocodimerization of *bis*(1,3,5-cycloheptatriene-7-yl)alkanes - monomers containing in their structure simultaneously two cycloheptatriene fragments, which means two reaction centers. We found that as a result of the interaction of *bis*(1,3,5-cycloheptatriene-7-yl)alkanes **8** with a two-fold excess of 1,2-dienes **2** or Si-containing alkynes **5** under the action of the catalytic system $Ti(acac)_2Cl_2$-Et_2AlCl (benzene, 12 hours , 80 °C) the corresponding [6π+2π] cycloadducts are formed - *bis*(bicyclo[4.2.1]nona-2,4-diene)alkanes **9a,b** and *bis*(bicyclo[4.2.1]nona-2,4,7-triene)alkanes **10a,b** [18,19] (Scheme 3):



Scheme 3. Cycloaddition of alkynes and 1,2-dienes with *bis*(1,3,5-cycloheptatriene-7-yl)alkanes.

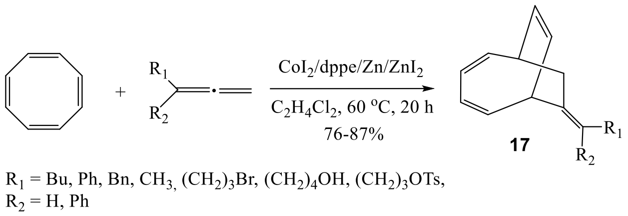
In 2019, we studied the cyclocodimerization reactions of 1-substituted CHTs [20]. We found 1-methyl(benzyl)-1,3,5-cycloheptatrienes **11** enter into a [6π+2π]-cycloaddition reaction with Si-containing alkynes **5** under the action of the catalytic system $Ti(acac)_2Cl_2$-Et_2AlCl (5 mol% $Ti(acac)_2Cl_2$, Ti/Al = 1:20, C_6H_6, 80 °C, 8 h) to form substituted bicyclo[4.2.1]nona-2,4,7-trienes **13** as a single regioisomer. Similarly, under the developed conditions (15 mol% $Ti(acac)_2Cl_2$, Ti/Al = 1:20, C_6H_6, 80 °C, 8 h), we managed to carry out the cyclodimerization of 1-methylcycloheptatriene **11** with propargylamines **4** to obtain nitrogen-containing bicyclo[4.2.1]nona-2,4,7-trienes **14** in high yields (76-88%) [20] (Sheme 4).



Scheme 4. Cycloaddition of alkynes with CHTs.

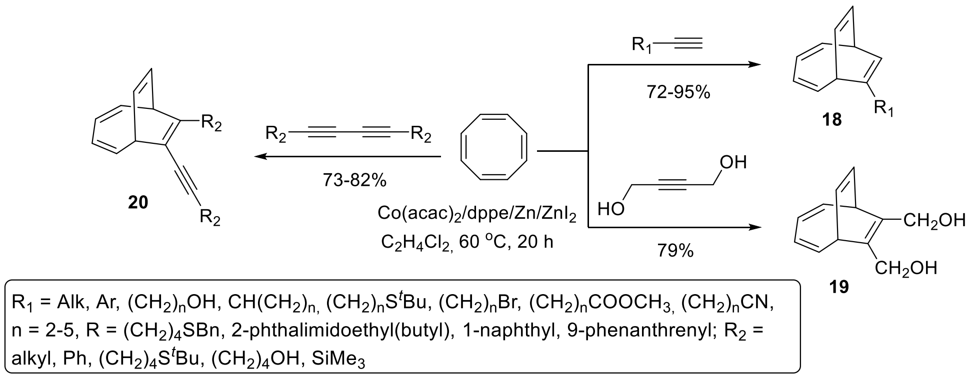
The reaction of 1-substituted CHTs **11** with terminal alkynes **12** takes place in the presence of a three-component cobalt-containing catalytic system $Co(acac)_2(dppe)/Zn/ZnI_2$ with the formation of functionally substituted bicyclo[4.2.1]nona-2,4,7-trienes **15, 16** as two regioisomers (72-86%) (Scheme 4).

In the development of ongoing studies on the synthesis of middle cycles based on cyclocodimerization of cyclic polyenes with unsaturated compounds of various structures, as well as with the aim of developing effective preparative methods for the synthesis of new classes of bicyclo[4.2.2]decatri(tetra)enes, we paid attention to COTT. In 2015, for the first time, we carried out the [6π+2π]-cycloaddition of 1,2-dienes to COTT in the presence of a four-component catalytic system CoI_2/dppe/Zn/ZnI_2 with the formation of substituted (*E*)-bicyclo[4.2.2]deca-2,4,7-trienes **17** in high yields (76-87%) [21] (Scheme 5).



Scheme 5. Cycloaddition of 1,2-dienes with COTT.

It should be emphasized that [6π+2π]-cycloadducts of COTT with alkynes - bicyclo[4.2.2]deca-2,4,7,9-tetraenes are widely used as key synthons in the preparation of practically valuable natural and synthetic biologically active compounds [22-25]. For this reason, the creation of highly efficient methods for the synthesis of bicyclo[4.2.2]deca-2,4,7,9-tetraenes is especially urgent and in demand. To accomplish this task, we have developed an effective catalytic system - $Co(acac)_2$/dppe/Zn/ZnI_2, using which we have synthesized a wide range of functionally substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes **18-20** based on the reaction of [6π+2π]-cycloaddition of alkynes and 1,3-diynes to COTT [22,26] (Scheme 6):



R_1 = Alk, Ar, $(CH_2)_nOH$, $CH(CH_2)_n$, $(CH_2)_nS^tBu$, $(CH_2)_nBr$, $(CH_2)_nCOOCH_3$, $(CH_2)_nCN$, n = 2-5, R = $(CH_2)_4SBn$, 2-phthalimidoethyl(butyl), 1-naphthyl, 9-phenanthrenyl; R_2 = alkyl, Ph, $(CH_2)_4S^tBu$, $(CH_2)_4OH$, $SiMe_3$

Scheme 6. Cycloaddition of alkynes with COTT.

3. Conclusions

Thus, in the course of our studies, we have developed effective one-pot methods for the synthesis of a large assortment of previously undescribed and hard-to-reach functionally substituted bicyclo[4.2.1]nonadi(tri)enes and bicyclo[4.2.2]decatri(tetra)enes, which can act in as key precursors in the synthesis of modern drugs and valuable biologically active compounds.

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