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Catalytic [6+2] Cycloaddition of *N*-Substituted Azepines as a Key Element in the Direct Construction of 9-azabicyclo[4.2.1]nonanes †

Gulnara N. Kadikova [1,*], Lilya U. Dzhemileva [2] and Usein M. Dzhemilev [2]

[1] Institute of Petrochemistry and Catalysis, Ufa Federal Research Center, Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russian Federation
[2] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospekt, 47, Moscow 119991, Russian Federation; dzhemilev@mail.ru (L.U.D.); dzhemilev@anrb.ru (U.M.D.)
* Correspondence: kad.gulnara@gmail.com; Tel.: +791-7481-8495
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Abstract: The data obtained by the authors in the field of studying catalytic cycloaddition reactions of *N*-substituted azepines are summarized. Cobalt(I)-catalyzed [6π+2π]-cycloaddition of *N*-carbethoxy-, phenoxy-, and cholesteroxyazepines with 1,2-dienes, alkynes, and 1,3-diynes leads to the formation of a practically important class of heterocyclic compounds, 9-azabicyclo[4.2.1]nonadi(tri)enes. Data on the study of the antitumor properties of the synthesized azabi(tri)cycles are presented, among which samples with increased antitumor activity and a high selectivity index were identified.

Keywords: catalytic cycloaddition; azepines; 9-azabicyclo[4.2.1]nonadi(tri)enes; antitumor activity

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1. Introduction

The chemistry of azacycloheptatrienes or azepines is one of the important and demanded areas of research in modern organic chemistry. Seven-membered aza- and diazacycles are an integral part of valuable pharmacologically active substances. Based on azacycloheptatrienes and their derivatives, antipsychotic, analgesic, antiepileptic, anticonvulsant and antihistamine drugs (azapine, azelastine, carbamazepine, clomipramine, nitrazepam, phenazepam, diazepam, elenium, oxazepam) have been developed, which are widely used today in world medicine.

At the same time, cycloaddition reactions leading to the formation of bridged heterocycles, 9-azabicyclo[4.2.1]nonadi(tri)enes, are of particular interest in the field of azepine chemistry [1]. These transformations have long attracted the attention of scientists, since the 9-azabicyclo[4.2.1]nonane backbone is a key structural element of such valuable alkaloids as anatoxin-a [2–6], pinnamine [7,8], bis-homoepibatidine [9,10], UB-165 [11–13], which have a pronounced pharmacological effect. These alkaloids are of interest as potential drugs for the treatment of mental illnesses associated with impaired production of neurotransmitters (depression, schizophrenia, Parkinson's and Alzheimer's diseases) [12,14].

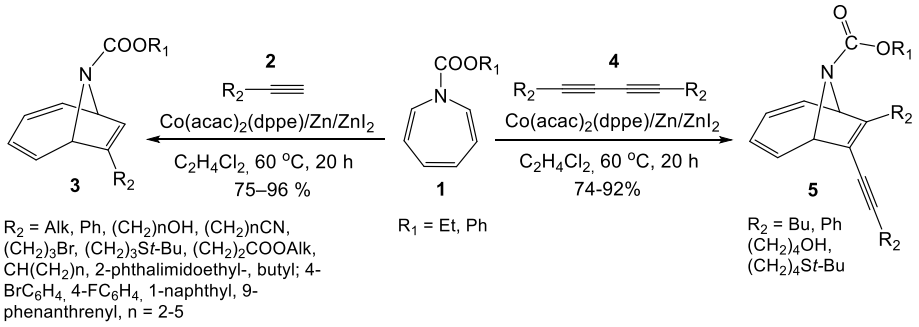
However, cycloaddition reactions involving *N*-substituted azepines have been studied very superficially. There are several publications in the world literature on photoinduced cyclocodimerization of tricarbonyl(η⁶-*N*-carboalkoxyazepine)chromium(0) [15–20] and tricarbonyl(η⁶-*N*-cyanoazepine)chromium(0) [21] with alkenes, 1,3-dienes and alkynes. It should be noted that there is practically no information on the catalytic variants of these transformations, represented by two examples of the Cr(0)-catalyzed

cycloaddition of *N*-carbomethoxyazepine [18] and *N*-carbethoxyazepine [22] to ethyl acrylate.

Based on the foregoing, we planned a research program to study new catalytic cycloaddition reactions of *N*-substituted azepines leading to the formation of 9-azabicyclo[4.2.1]nonadi(tri)enes.

2. Results and Discussion

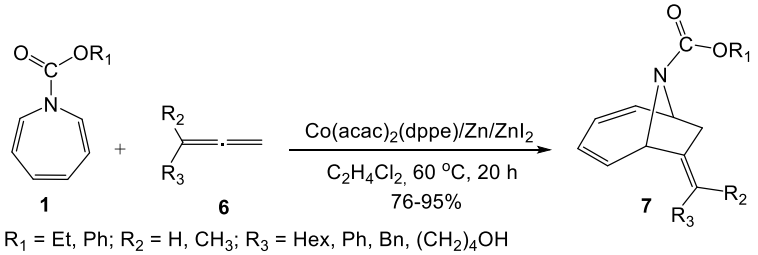
In 2020, we first reported an efficient one-pot method for the synthesis of substituted 9-azabicyclo[4.2.1]nonadi(tri)enes based on the cobalt(I)-catalyzed cycloaddition of alkynes, 1,3-diynes, and allenes to *N*-carbethoxy(phenoxy)azepines [23–25]. As a catalyst, we used the previously developed system based on $Co(acac)_2$, which showed high efficiency in the cyclocodimerization reactions of 1,3,5-cyclooctatriene, 1,3,5,7-cyclooctatetraene and 1-substituted 1,3,5-cycloheptatrienes [26–29]. It was shown that [6π+2π]-cycloaddition of terminal alkynes **2**, 1,3-diynes **4** to *N*-carbethoxyazepine **1** and *N*-carbophenoxyazepine **1** under the action of a three-component catalytic system $Co(acac)_2$(dppe)/Zn/ZnI_2 in the developed conditions (10 mol% $Co(acac)_2$(dppe), 30 mol% Zn, 20 mol% ZnI_2, $C_2H_4Cl_2$, 20 h, 60 °C) proceeds with the formation of substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes **3**, **5** in 74–96% yields [23,25]. The adducts are formed as two N-(CO)OR_1 rotamers, resulting from hindered rotation of substituent about the C-N bond (Scheme 1). In all cases, the ratio of stereoisomers is 1:1 and does not depend on the nature of the starting azepine and alkyne (or 1,3-diyne).



Scheme 1. Cobalt(I)-catalyzed [6+2] cycloaddition of alkynes and 1,3-diynes to azepines.

The reaction is equally successful for alkynes containing chemically different functional groups such as alcohol, ester, sulfide, nitrile, phthalimide, naphthalene, phenanthrene, *p*-halophenyl, cycloalkyl, alkyl, or phenyl.

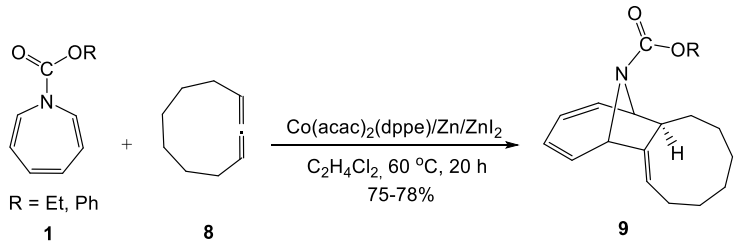
Cobalt(I)-catalyzed cyclocodimerization of *N*-carbethoxyazepine **1** and *N*-carbophenoxyazepine **1** with allenes **6** proceeds under similar conditions to form [6π+2π]-cycloadducts—substituted (*E*)-9-azabicyclo[4.2.1]nona-2,4-dienes **7** as two N-(CO)OR_1 rotamers in a 1:1 ratio in 76–95% yields [24] (Scheme 2).



Scheme 2. Cobalt(I)-catalyzed [6+2] cycloaddition of allenes to azepines.

As a continuation of our studies, we have found that *N*-carbethoxy(phenoxy)azepines **1** interact with the cyclic allene, 1,2-cyclononadiene **8**

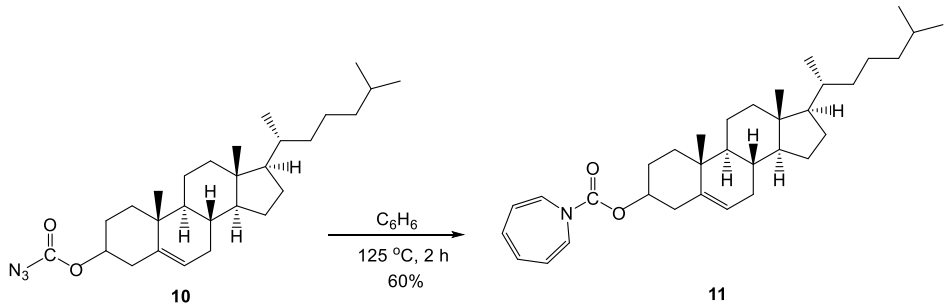
under previously developed conditions (10 mol% $Co(acac)_2(dppe)$, 30 mol% Zn, 20 mol% ZnI_2, $C_2H_4Cl_2$, 20 h, 60 °C) to obtain 16-azatricyclo[9.4.1.$0^{2,10}$]hexadecatrienes **9** as two N-(CO)OR rotamers (1:1) [24] (Scheme 3).



Scheme 3. Cobalt(I)-catalyzed [6+2] cycloaddition of 1,2-cyclononadiene to azepines.

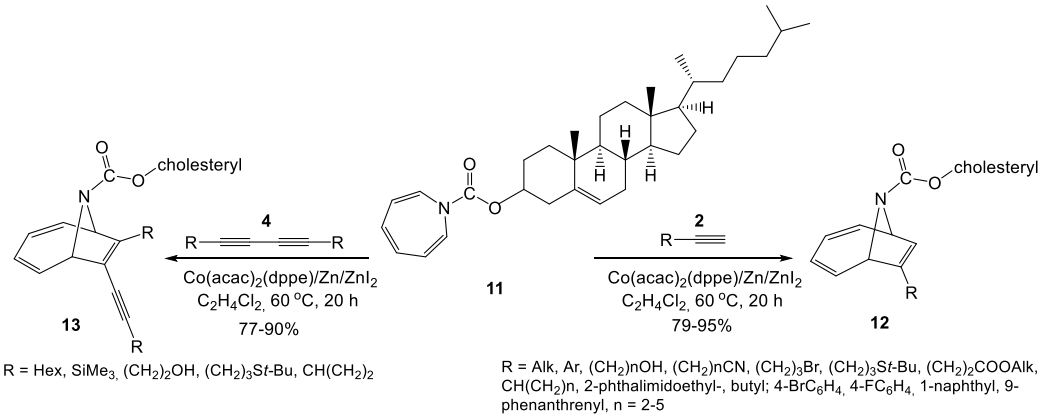
It is important to note that we have found a high *in vitro* antitumor activity of the synthesized 9-azabicyclo[4.2.1]nona-2,4-dienes and 9-azabicyclo[4.2.1]nona-2,4,7-trienes against tumor cell lines Jurkat, K562, U937 and HL60 [23–25].

In order to further develop a promising direction in the synthesis of new biologically active 9-azabicyclo[4.2.1]nonanes, we set ourselves the task of obtaining 9-azabicyclo[4.2.1]nona-2,4,7-trienes covalently bound to a natural metabolite, cholesterol. To implement this idea, the initial monomer, *N*-carbocholesteroxyazepine, was obtained. *N*-Carbocholesteroxyazepine **11** was synthesized by us for the first time by the reaction of thermolysis of cholesteryl azidoformate **10** in benzene at 125 °C (in an autoclave) [30] (Scheme 4).



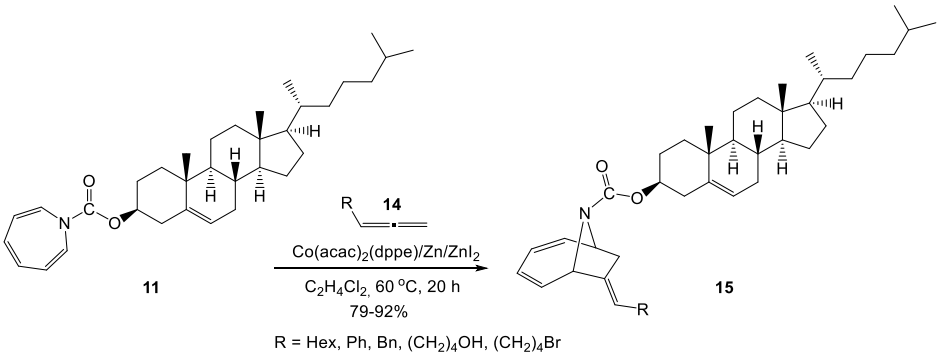
Scheme 4. Synthesis of *N*-carbocholesteroxyazepine.

Having obtained the initial monomer, we carried out cobalt(I)-catalyzed [6π+2π] cycloaddition of terminal alkynes **2** and 1,3-diynes **4** to *N*-carbocholesteroxyazepine **11** under the developed conditions (10 mol% $Co(acac)_2$(dppe), 30 mol% Zn, 20 mol% ZnI_2, $C_2H_4Cl_2$), 20 h, 60 °C) (Scheme 5). Cyclocodimerization proceeds with the formation of substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes **12**, **13** in the form of two N-(CO)O-cholesteryl-rotamers in a ratio of 1:1, resulting from hindered rotation of substituent about the CN bond [30,31] (Scheme 5).



Scheme 5. Cobalt(I)-catalyzed [6π+2π] cycloaddition of alkynes and 1,3-diynes to *N*-carbocholesteroxyazepine.

At the same time, we found that as a result of [6π+2π]-cycloaddition of terminal allenes **14** (including functionally substituted ones) to *N*-carbocholesteroxyazepine **11** in the presence of the Co(acac)2(dppe)/Zn/ZnI2 catalytic system, substituted (*E*) -9-azabicyclo[4.2.1]nona-2,4-dienes **15** as two rotamers (1:1) in 79–92% yields [31] (Scheme 6).



Scheme 6. Cobalt(I)-catalyzed [6π+2π] cycloaddition of allenes to *N*-carbocholesteroxyazepine.

3. Conclusions

Thus, as a result of our studies, effective one-pot methods have been developed for the synthesis of a wide range of previously undescribed and hard-to-reach heterofunctional 9-azabicyclo[4.2.1]nona-2,4-dienes and 9-azabicyclo[4.2.1]nona-2,4, 7-trienes, which can act as key precursors in the synthesis of modern drugs and valuable biologically active compounds.

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