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Synthesis of new alkynyl containing 9-azabicyclo[4.2.1]nonatrienes from diynes and azepines

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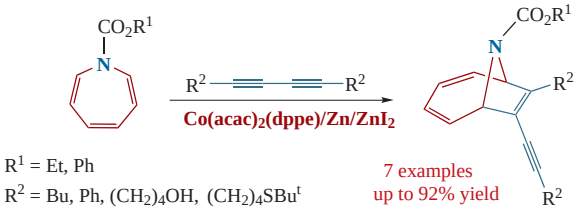
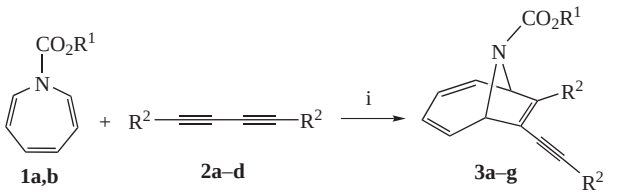
New 7-alkynyl-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylates were obtained upon the Co(acac)$_2$(dppe)/Zn/ZnI$_2$-catalyzed [6π+2π]-cycloaddition of 1,3-diynes to ethyl/phenyl azepine-1-carboxylates. The structures of the obtained azacyclic compounds were established by 1D and 2D NMR spectroscopy. The compounds prepared were tested for antitumor activities *in vitro* against Jurkat, K562, U937 and HL60 cancer cell lines.



Keywords: cycloaddition, catalytic systems, azepine-1-carboxylates, 1,3-diynes, 9-azabicyclo[4.2.1]nona-2,4,7-trienes, cobalt complexes, antitumor activity.

A large number of publications is devoted to metal-promoted homo- and co-dimerization between 1,3,5-cycloheptatrienes and unsaturated compounds.[1] There is virtually no data on the similar reactions with seven-membered hetero-cyclohepta-2,4,6-trienes, for example, azepine-1-carboxylates, which should lead to 9-azabicyclonona(di)trienes. The available published data concern mostly the cycloaddition involving stoichiometric amounts of Ru-, Fe-, and Cr-containing methyl azepine-1-carboxylate carbonyl complexes.[2,3] Only few papers report catalytic reactions of N-substituted azepines, describing Cr^0-catalyzed cycloaddition of ethyl acrylate to alkyl azepine-1-carboxylates.[3(*d*),4]

It is noteworthy that cycloaddition of azepines with diverse unsaturated compounds should give practically valuable 9-azabicyclo[4.2.1]nonanes possessing broad range of biological activities. The homotropane skeleton is the key structural unit of valuable alkaloids such as anatoxin-A,[5] UB-165,[6] pinnamine,[7] and bis-homo-epibatidine.[8] Anatoxin-A and its synthetic analogues reveal high activities towards nicotinic acetylcholine receptors and are used in medicinal studies[9] of diseases associated with decreased production of acetylcholine (the Alzheimer's disease). 9-Azabicyclo[4.2.1]nonane derivatives are of obvious interest as potential pharmaceuticals for the treatment of severe psychiatric disorders associated with neurotransmitter imbalance (mental depression, schizophrenia, the Parkinson's and Alzheimer's diseases).[5,9]



a R^1= Et
b R^1= Ph

a R^2= Bu
b R^2= Ph
c R^2= (CH$_2$)$_4$OH
d R^2= (CH$_2$)$_4$SBu^t

a R^1= Et, R^2= Bu, 92%
b R^1= Et, R^2= Ph, 85%
c R^1= Et, R^2= (CH$_2$)$_4$OH, 76%
d R^1= Et, R^2= (CH$_2$)$_4$SBu^t, 79%
e R^1= Ph, R^2= Bu, 89%
f R^1= Ph, R^2= (CH$_2$)$_4$OH, 74%
g R^1= Ph, R^2= (CH$_2$)$_4$SBu^t, 80%

Scheme 1 *Reagents and conditions*: i, Co(acac)$_2$(dppe) (10 mol%)/Zn (30 mol%)/ZnI$_2$ (20 mol%), ClCH$_2$CH$_2$Cl or CF$_3$CH$_2$OH (for **3c**,**f**), 60 °C, 20 h.

Here, we report an efficient synthesis of substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes based on a catalytic cycloaddition of 1,3-diynes to azepine-1-carboxylates. Earlier,[1(*f*)] we have carried out [6π+2π]-cycloadditions between terminal alkynes and azepine-1-carboxylates in the presence of the three-component catalytic system Co(acac)$_2$(dppe)/Zn/ZnI$_2$.[10] Relying on these results, we studied the possibility of expanding such cycloaddition onto 1,3-diynes. Symmetrical conjugated diynes such as alkyl- and phenyl-substituted 1,3-diynes, including those with functional groups (alcohols, sulfides), were used as investigation objects. We found that the reaction of 1,3-diynes **2a–d** with ethyl or phenyl azepine-1-carboxylates **1a**,**b** catalyzed by Co(acac)$_2$(dppe)/Zn/ZnI$_2$ [Co(acac)$_2$(dppe):Zn:ZnI$_2$ = 1:3:2] gave substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes **3a–g** in 74–92% yields as two N–C(O)OR^1 rotamers (Scheme 1).† These conformers arise due to hindered rotation around the C(O)–N bond.[3(*c*),(*d*)] In all cases, the ratio of rotamers was 1.2:1.0 and did not depend on the nature of the initial diyne or azepine. We have established that the required amount of the catalyst to achieve maximum yields of cycloadducts was 10 mol%, while the application of less Co(acac)$_2$dppe catalyst (5 mol%) reduced the yield of azabicycles by 5–10%.

In our previous studies,[10,11] we found that substituted bicyclo[4.2.1]nona-2,4,7-trienes exhibited antitumor activity against cancer cell lines. Taking into consideration that

† For procedures and characteristics of the products, see Online Supplementary Materials.

Table 1 Cytotoxic activities IC_{50} of 9-azabicyclo[4.2.1]nona-2,4,7-trienes **3a**–**g** measured on tumor cell cultures (Jurkat, K562, U937, HL60) and normal fibroblasts (μM).

Compound	Jurkat	K562	U937	HL60	Fibroblast
3a	0.305 ± 0.029	0.693 ± 0.061	0.611 ± 0.054	0.298 ± 0.024	2.376 ± 0.212
3b	0.014 ± 0.001	0.025 ± 0.004	0.037 ± 0.003	0.013 ± 0.001	0.179 ± 0.016
3c	0.056 ± 0.005	0.311 ± 0.028	0.278 ± 0.026	0.051 ± 0.005	1.064 ± 0.098
3d	1.167 ± 0.097	1.456 ± 0.124	1.964 ± 0.167	1.068 ± 0.092	5.679 ± 0.456
3e	0.007 ± 0.001	0.029 ± 0.003	0.024 ± 0.002	0.006 ± 0.001	0.078 ± 0.007
3f	0.049 ± 0.004	0.148 ± 0.013	0.122 ± 0.011	0.045 ± 0.004	0.566 ± 0.052
3g	1.812 ± 0.163	2.691 ± 0.238	2.478 ± 0.212	1.729 ± 0.164	7.964 ± 0.537

bicyclo[4.2.1]nona-2,4,7-trienes and 9-azabicyclo[4.2.1]nona-2,4,7-trienes have a similar framework, it was of interest to study the cytotoxic activity of the herein obtained cycloadducts. The results of an *in vitro* study of the antitumor activity of substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes **3a**–**g** towards the Jurkat, K562, U937 and HL60 tumor cell lines are given in Table 1.

Dibutyl-substituted 9-azabicyclo[4.2.1]nona-2,4,7-triene **3e** containing a phenoxycarbonyl group at the bridging nitrogen atom has shown the highest cytotoxic activity (IC_{50} = = 0.006±0.001–0.029±0.003 μM). The presence of an additional functional group in the tested compounds had a noticeable effect on the value of the inhibitory concentration. Thus, the cytotoxic activity of azabicyclononatrienes **3c**,**f** bearing the butanol moiety (IC_{50} = 0.045±0.004–0.311±0.028 μM) was higher as compared to that of adducts **3d**,**g** containing in the structure *tert*-butylthio group (IC_{50} = 1.068±0.092–2.691±0.238 μM). In general, 9-azabicyclo[4.2.1]nona-2,4,7-trienes **3d**,**g** showed the lowest antitumor activity in the series.

In conclusion, we have performed the [6π+2π]-cycloaddition of 1,3-diynes to ethyl/phenyl azepine-1-carboxylates catalyzed by the three-component $Co(acac)_2$(dppe)/Zn/ZnI_2 system, which afforded new 9-azabicyclo[4.2.1]nona-2,4,7-trienes in high yields. Some of the synthesized compounds were found to possess high antitumor activities *in vitro* against Jurkat, K562, U937 and HL60 cancer cell lines. The prepared azabicyclic compounds have high potential for applications in pharmaceutical chemistry and can be used as the basis for the development of modern drugs for the treatment of socially significant diseases.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.019.

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