*Russian Journal of Organic Chemistry, Vol. 37, No. 9, 2001, pp. 1225–1227. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 9, 2001, pp. 1292–1295.*


# Synthesis and Ritter Reaction of 2-Ethynyladamantan-2-ol

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Received November 24, 1999

**Abstract**—The reaction of adamantan-2-one with lithium acetylide gave 2-ethynyladamantan-2-ol. The latter reacted with acetonitrile in the presence of sulfuric acid through formation of an intermediate classical carbocation, leading to 2-acetylamino-2-ethynyladamantane and 1-acetylamino-2-acetyladamantane at a ratio of 20 : 1.

Adamantane derivatives are among the most widely studied cage-like compounds. Interest in these substances was stimulated by their specific chemical behavior originating from the presence of a highly symmetrical tricyclic fragment, as well as by their practically important (primarily biological) properties [1, 2]. There are extensive published data on the transformations of adamantane derivatives under conditions of the Ritter reaction [3–7]; the resulting amides are the nearest precursors of biologically active amines. Nevertheless, it remains unclear whether intermediate adamantyl cations formed in this reaction are classical or multicenter (nonclassical), as those formed from other cage-like compounds. A nonclassical structure of adamantyl cation was presumed in [8], although the data on the rate of solvolysis of adamantyl halides (which were given in the same publication) contradict such assumption.

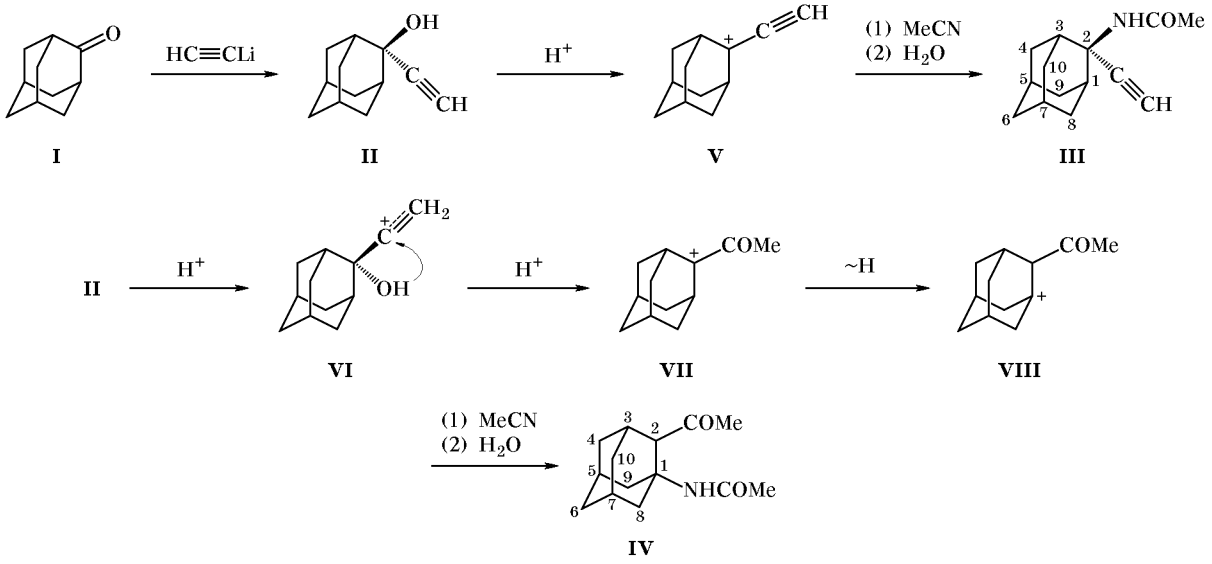
We previously [9] studied the Ritter reaction of ethynyl alcohols of the bicyclo[2.2.1]heptane series, for which the formation of nonclassical cations under conditions of acid catalysis is beyond doubt. When the position of the ethynyl group does not exclude its conjugation with nonclassical cationic center, the first reaction stage is protonation of the terminal carbon atom of the ethynyl group with formation of a cation in which the positive charge is delocalized over three atoms of the bicyclo[2.2.1]heptane skeleton and the $C{=}CH_2$ group. Migration to the latter of the hydroxy group gives rise to acetylbicyclo[2.2.1]-heptyl cation whose further transformations yield the corresponding acetamides. When the steric structure of the reaction center rules out the possibility for conjugation with the ethynyl group, the latter does not change during the process, and the major product is amide containing a $C{\equiv}CH$ group.

In the present work by reaction of adamantan-2-one (**I**) with lithium acetylide we have synthesized 2-ethynyladamantan-2-ol (**II**) and studied its transformations in the Ritter reaction. Insofar as the carbon skeleton of molecule **II** has a symmetrical structure, both potential reaction centers (the hydroxy and ethynyl groups) are stereochemically equivalent. It was reasonable to presume that the reaction should follow two concurrent pathways provided that nonclassical carbocation is formed as intermediate. Elimination of the hydroxy group should result in formation of ethynyladamantyl cation which is then converted into ethynylamide. Protonation of the ethynyl group should yield amide with acetyl group in the adamantane ring. Taking into account that previously [9] we observed no appreciable difference in the rates of these two reactions, in the case of intermediate formation of nonclassical cations the corresponding products should be formed in comparable amounts.

However, the reaction of 2-ethynyladamantan-2-ol (**II**) with acetonitrile in the presence of sulfuric acid gave a mixture of products, the major one being ethynyl-substituted amide [2-acetylamino-2-ethynyl-adamantane (**III**); yield >95%]. The minor product was 2-acetyl-1-acetylaminoadamantane (**IV**). The structure of compounds **III** and **IV** was assigned on the basis of their IR, NMR, and mass spectra. In the IR spectrum of ethynylamide **III** we observed a band at 3310 $cm^{-1}$ which belongs to vibrations of the terminal acetylenic C–H bond, a band at 2120 $cm^{-1}$ corresponding to stretching vibrations of the triple

1070-4280/01/3709-1225 $25.00 

**Scheme 1.**




bond, and also bands at 3400, 1650, and 1550 $cm^{-1}$ which are typical of amide group vibrations. The mass spectrum of **III** contained the molecular ion peak with *m*/*z* 217 ($I_{rel}$ 15%). The signal of the terminal ethynyl proton appears in the $^1H$ NMR spectrum of **III** as a singlet at δ 2.45 ppm, the acetyl group gives a three-proton singlet at δ 1.99 ppm, and a broadened singlet at δ 5.48 ppm was assigned to the NH proton. The presence of a two-proton signal at δ 2.39 ppm, corresponding to the adamantane ring, indicates that the molecule contains two equivalent bridgehead moieties ($C^1H$ and $C^3H$), i.e., it has the structure of unrearranged ethynylamide. The other signal is located at δ 2.27 ppm (1H, broadened singlet); obviously, it belongs to proton in the third bridgehead position ($C^7H$), which suffers deshielding effect of the acetylamino group.

The IR spectrum of 2-acetyl-1-acetylaminoadamantane (**IV**) contains two carbonyl absorption bands at 1725 $cm^{-1}$ (ketone) and 1660 $cm^{-1}$ (amide). Also, the amide group gives rise to absorption at 3360 (ν NH) and 1560 $cm^{-1}$. The molecular ion peak in the mass spectrum of **IV** has an *m*/*z* value of 235 ($I_{rel}$ 17%). Compound **IV** shows in the $^1H$ NMR spectrum two three-proton singlets at δ 2.16 and 2.00 ppm, which belong, respectively, to the 2-acetyl and *N*-acetyl groups. The NH proton signal is located at δ 5.62 ppm (br.s). The structure of **IV** as rearranged 1,2-disubstituted adamantane derivative follows from the presence of signals at δ 2.32 ppm (CH group in the α-position with respect to carbonyl) and 2.06 ppm (br.s, 1H); the latter belongs to the $C^3H$ proton which appears in the vicinity of the acetyl group. The positions of signals from the other adamantane ring protons are also well consistent with the assumed structure (see Experimental).

Presumably, compounds **III** and **IV** are formed as a result of the following transformations. Elimination of the hydroxy group from 2-ethynyladamantan-2-ol (**II**) by the action of acid gives ethynyladamantyl cation (**V**) which takes up acetonitrile molecule. The subsequent hydration leads to formation of unrearranged amide **III** (Scheme 1). The minor product is formed via protonation of the ethynyl group, leading to ion **VI**. Migration of the hydroxy group in **VI** to the cationic center yields acetyladamantyl cation **VII**. The absence of products with geminal acetylamino and acetyl groups may be explained by a large size of the latter, which hinders addition of acetonitrile molecule to the same carbon atom. In this case, hydride shift in **VII** to give cation **VIII** seems to be more favorable. Nucleophile addition to **VIII** results in formation of 1,2-disubstituted adamantane **IV**. It should be noted that the Ritter reaction of unsubstituted adamantan-2-ol is also accompanied by partial isomerization; one of the products is 1-acetylaminoadamantane [6]. By contrast, Schleyer *et al.* [10] asserted that orbital symmetry of the adamantane ring excludes hydride shift and isomerization of 2-adamantyl cation into 1-adamantyl cation.

Thus, the Ritter reaction of 2-ethynyladamantan-2-ol affords mainly unrearranged product **III**. The low yield of ketoamide **IV** suggests that the probability of intermediate formation of nonclassical carbocation in this reaction is not high. An analogous ketoamide–ethynylamide ratio was observed by us previously

while studying the Ritter reaction of 2-ethynylisoborneol [9] in which the stereochemistry of the reaction center prevents conjugation between the ethynyl group and nonclassical cationic center. Therefore, intramolecular hydration of the triple bond therein proceeds as a low rate.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Tesla BS-567 spectrometer (100 MHz) in $CDCl_3$. The IR spectra were measured on a Specord 75IR spectrophotometer. The mass spectra were run on a Chrommas GC/MS Hewlett–Packard 5890/5972 instrument (HP-5MS column; 70 eV).

**2-Ethynyladamantan-2-ol (II).** To a solution of 180 mmol of lithium acetylide (which was prepared by passing acetylene through a solution of butyllithium in THF, following the procedure reported in [9]) we added 18 g (120 mmol) of adamantan-2-one. The mixture was stirred for 4 h at 0–5°C, allowed to gradually warm up to room temperature, and left overnight. It was decomposed by pouring in small portions into water. When acetylene no longer evolved, the organic phase was separated, the aqueous phase was extracted with two portions of diethyl ether, and the combined extracts were dried with a large amount of $CaCl_2$, for tetrahydrofuran contained a lot of water. The solvent was removed on a rotary evaporator, and the product was recrystallized from hexane. Yield 18.8 g (89%), mp 108–109°C. IR spectrum, $\nu$, cm$^{-1}$: 3500, 3390 (OH); 3330 (≡C–H); 3200 (OH); 2940, 2920, 2870 (C–H); 2090 w (C≡C). $^1$H NMR spectrum, δ, ppm: 2.52 s (1H, ≡CH), 2.22 br.s (1H), 2.10 br.s (2H), 1.95 br.s (3H), 1.76 br.s (2H), 1.64 br.s (4H), 1.57 br.s (2H), 1.48 br.s (1H). Mass spectrum, *m*/*z*: 176 (2%) $[M]^+$, 158 $[M-H_2O]^+$, 148 $[M-2CH_2]^+$ (100%), 133 $[M-H_2O-C\equiv CH]^+$, 129, 119, 116, 91, 79, 67, 55, 53, 43.

**Ritter reaction of 2-ethynyladamantan-2-ol (II) with acetonitrile.** The reaction was carried out by the procedure described in [9]. After removal of the solvent, amides **III** and **IV** were obtained in an overall yield of 2.12 g (80%). The ratio of the products in the reaction mixture was determined on the basis of the GC–MS data.

**2-Acetylamino-2-ethynyladamantane (III)** was isolated by recrystallization of the product mixture from ethanol. mp 138–139°C. IR spectrum, $\nu$, cm$^{-1}$: 3400 (NH); 3310 (≡C–H); 3070 (NH); 2920, 2870 (C–H); 2120 (C≡C); 1650 (C=O, amide I), 1550 (δ NH, amide II). $^1$H NMR spectrum, δ, ppm: 5.48 br.s (NH), 2.45 s (1H, ≡CH), 2.39 br.s (2H, 1-H and 3-H), 2.27 br.s (1H, 7-H), 1.99 s (3H, $NCOCH_3$), 1.90–1.55 m (11H). Mass spectrum, *m*/*z* ($I_{rel}$): 217 (15%), $[M]^+$, 202 $[M-CH_3]^+$, 189 $[M-2CH_2]^+$, 176 $[M-CH_3-C\equiv CH]^+$, 174 $[M-COCH_3]^+$, 158 $[M-CH_3CONH_2]^+$, 148 $[M-CH_3CO-HC\equiv CH]^+$, 137, 117, 115, 91, 77, 65, 52, 43 (100%).

**2-Acetyl-1-acetylaminoadamantane (IV)** (minor product) was isolated by repeated crystallization from acetone–diethyl ether of the residue obtained after separation of the main part of the major product. mp 132–133°C. IR spectrum, $\nu$, cm$^{-1}$: 3260 (NH); 2950, 2920, 1875 (C–H); 1725 (C=O, ketone); 1660 (C=O, amide I), 1560 (NH, amide II). $^1$H NMR spectrum, δ, ppm: 5.62 br.s (1H, NH), 2.32 br.s (1H, $CH_3COC\mathbf{H}$), 2.16 s (3H, $COCH_3$), 2.06 br.s (1H, 3-H), 2.00 s (3H, $NCOCH_3$), 1.94 br.s [4H, $CH_3CONHC(C\mathbf{H}_2)_2$], 1.88 br.s (2H), 1.77 br.s (4H), 1.66 br.s (2H). Mass spectrum, *m*/*z* ($I_{rel}$): 235 (17%) $[M]^+$, 220 $[M-CH_3]^+$, 192 $[M-COCH_3]^+$, 177 $[M-COCH_3-CH_3]^+$, 149 $[M-2COCH_3]^+$, 135 $[M-COCH_3-NCOCH_3]^+$, 122, 107, 93, 91, 77, 65, 43 (100%).

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