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One-Pot Assembly of 7-Methylene-6,8-dioxabicyclo[3.2.1]octanes, Congeners of Frontalin, from Ketones and Acetylene

Boris A. Trofimov,*[a] Elena Yu. Schmidt,[a] Igor A. Ushakov,[a] Albina I. Mikhaleva,[a] Nadezhda V. Zorina,[a] Nadezhda I. Protsuk,[a] Elena Yu. Senotrusova,[a] Elena V. Skital'tseva,[a] Olga N. Kazheva,[b] Grigorii G. Alexandrov,[c] and Oleg A. Dyachenko[b]

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A facile, consecutive, self-consisting assembly of two molecules of ketones with two molecules of acetylene to afford 7-methylene-6,8-dioxabicyclo[3.2.1]octanes, which are unknown congeners of widespread insect pheromones, has been discovered. The reaction is realized in a one-pot procedure in a MOH/DMSO system (M = K, Cs) at 80 °C for 1 h under acetylene pressure or under atmospheric pressure; the isolated yields of the bicycles reached 86 %. The new reaction conceptually contributes to the synthesis of insect pheromones as well as to the chemistry of ketones and acetylene.
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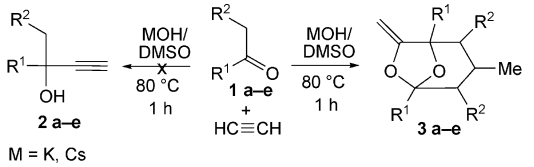
Introduction

It is well known that ketones react with acetylene in the presence of bases to furnish acetylenic alcohols (Favorsky reaction).[1] To our surprise, when conducting the reaction of aromatic and heteroaromatic ketones **1a**–**e** with acetylene in MOH/DMSO (M = K, Cs) at 80 °C for 1 h under acetylene pressure (autoclave, initial acetylene pressure at ambient temperature 12–14 atm), we isolated, instead of the expected acetylenic alcohols **2a**–**e**, 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **3a**–**e** as the only products in up to 86% yield (Scheme 1, Table 1).



Scheme 1. The assembly of 7-methylene-6,8-dioxabicyclo[3.2.1]-octanes **3a**–**e** from ketones **1a**–**e** and acetylene.

Results and Discussion

The 6,8-dioxabicyclo[3.2.1]octane[2] scaffold is an important structural organization (assembly) present in a number of pheromones and natural products such as frontalin, brevicomin, multistriatin, bullerone, and palytoxin.[3] Frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane) is the aggregation pheromone of pine beetles of the *Dendroctonus* family.[4] This pheromone has also been isolated from the bark of several angiosperm trees[5] and from the temporal gland of the male Asian elephant during sexual activity.[6] These compounds are now successfully used to control the progression of pine beetle infestations in forests.[4] Therefore, a great deal of effort is now being spent to develop concise and rational approaches to the synthesis of frontalin and its congeners.[4,7,8] However, most of the proposed strategies are either multistep[9] or require hardly accessible starting materials.[3,10] Our serendipitous discovery of the one-pot assembly of the frontalin scaffold originates a new synthetic concept in this important area.

The structures of compounds **3a**–**e** unambiguously follow from the single-crystal X-ray diffraction of compound **3e** (Figure 1) as a typical representative of this series. Its structure is formed by one crystallographically independent molecule, $C_{18}H_{20}O_2S_2$. In the dioxabicyclooctane fragment, the dihedral angle formed by the O(1)O(2)C(8) and O(1)C(3)O(2) planes equals 153.0°, the dihedral angle between the O(1)O(2)C(8) and O(1)C(7)C(8) planes is 157.4°, and the dihedral angle between the O(1)C(3)O(2) and O(1)C(7)C(8) planes is 132.8°. The dihedral angle between the planes of the thiophene heterocycles equals 98.3°. Torsion angles in the dioxolane heterocycle are O(1)C(7)C(8)O(2) 22.5(1)°,

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[a] A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences
1 Favorsky Str., 664033 Irkutsk, Russia
Fax: +7-3952-419346
E-mail: boris_trofimov@irioch.irk.ru
[b] Institute of Problems of Chemical Physics, Russian Academy of Sciences
Acad. Semenov av. 1, Chernogolovka, Moscow region 142432, Russia
[c] N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences
Leninsky prp. 31, Moscow 119991, Russia

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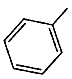
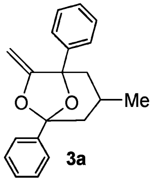
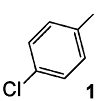
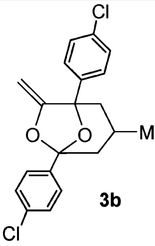
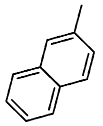
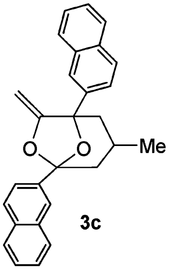
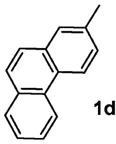
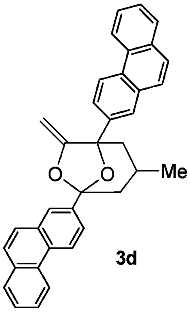
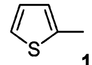
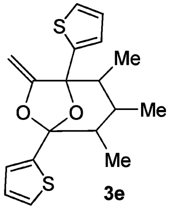
Table 1. 7-Methylene-6,8-dioxa-bicyclo[3.2.1]octanes **3a**–**e** synthesized according to Scheme 1.

R^1, R^2	Product	Yield[a] [%]
 , H **1a**	 **3a**	86 (100)[b]
 , H **1b**	 **3b**	15 (77)[b]
 , H **1c**	 **3c**	41 (100)[b]
 , H **1d**	 **3d**	54 (100)[b]
 , Me **1e**	 **3e**	41 (78)[b]

[a] The products were isolated and purified by column chromatography (basic Al_2O_3; hexane/diethyl ether, 3:1). [b] Conversion of ketones **1** according to ^1H NMR spectroscopy.

C(7)C(8)O(2)C(3) 2.1(1)°, C(8)O(2)C(3)O(1) 27.0(1)°, O(2)C(3)O(1)C(7) 41.7(1)°, and C(3)O(1)C(7)C(8) 38.8(1)°.

The ^1H and ^{13}C NMR spectra are in agreement with the structure of compounds **3a**–**e**. In the ^1H NMR spectra, characteristic signals are the two doublets (^2J = 2.2–2.4 Hz) of the methylene groups (H^a and H^b, 3.5–4.5 ppm). The signals of the H^a and H^b protons were distinguished by using 2D NOESY experiments (Figure 2). The chemical shift difference of these protons ranged from 0.7 to 1.0 ppm. The low-field shift of the H^b proton is due to the *cis*-oxygen atom that is typical for vinyl ethers.[11] The aliphatic CH_2 protons (2- and 4-positions) are represented by multiplets, owing to the spin–spin coupling with the C*H* proton in the 3-position. For all compounds **3a**–**e**, nonequivalency of the aromatic and heteroaromatic protons was observed. The 2D NMR experiments (COSY, NOESY, HSQC, HMBC) in the ^1H and ^{13}C NMR spectra allowed all the resonance signals to be assigned.

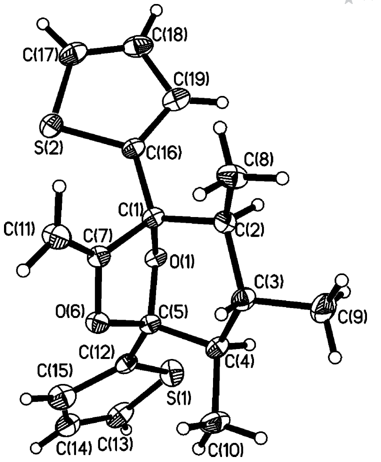


Figure 1. X-ray structure of **3e**.

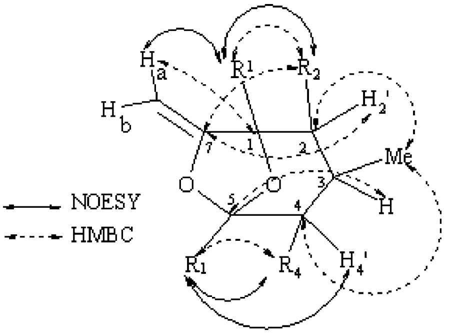
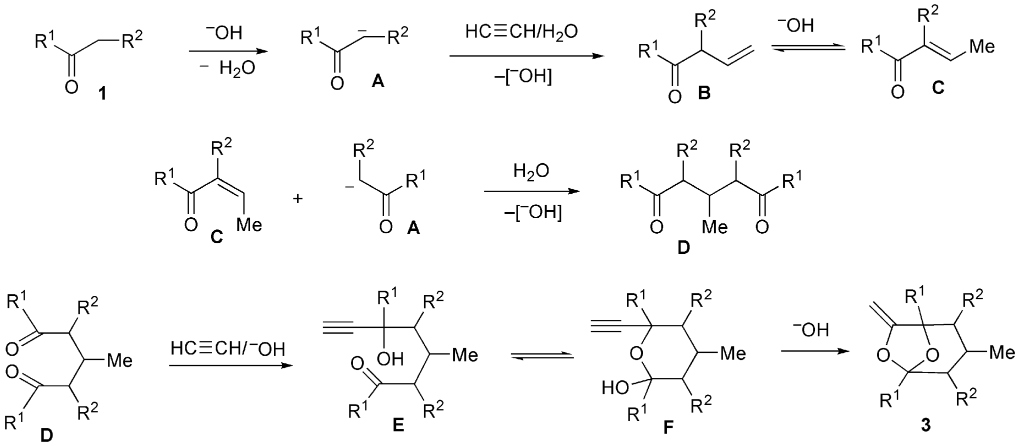


Figure 2. Characteristic NOESY and HMBC correlations of compounds **3a**–**e**.

The NMR spectroscopic data evidence that exclusively one diastereomer is formed in all the cases. Only in the ^1H and ^{13}C NMR spectra of **3e** were weak signals corresponding to other isomers in a total amount of ca. 10% detected. In the ^1H and ^{13}C NMR spectra of other bicycles, no signals of minor isomers were discernible.

The reaction was carried out both in KOH/DMSO and CsOH/DMSO, with nearly equal efficacy, and the ketone/MOH molar ratio was 1:1. According to the ^1H NMR spectra, the crude material contained only bicycles **3a**–**e** and unreacted ketones, though in most cases conversion of the latter was complete (Table 1). The reaction can be also realized under atmospheric pressure (flow reactor), but here higher temperatures and longer reaction times are required. For example, the conversion of ketone **1a** to bicycle **3a** (100 °C, 5 h) was 50% (^1H NMR spectroscopy).



Scheme 2. A tentative sequence for the assembly of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **3** from ketones and acetylene.

An aliphatic ketone (acetone) was also tested in this assembly (KOH/DMSO, 80 °C, 1 h, autoclave, acetylene pressure 14 atm). In the crude material obtained, the expected 1,3,5-trimethyl-7-methylene-6,8-dioxabicyclo[3.2.1]octane was detected (ca. 10%, ^{1}H NMR spectroscopy) among the self-condensation products of acetone that complicated the separation of the components. Obviously, to improve the preparative value of the reaction discovered for aliphatic ketones, a special systematic optimization of both the reaction conditions and the isolation procedures are needed. This will be a target of our further investigations.

As to the preliminary rationalization for the assembly (Scheme 2), we assume that first ketone carbanion **A** adds to acetylene and adduct **B** prototropically isomerizes to α,β-ethylenic ketone **C**, which is further attacked by the same ketone carbanion **A** to give 1,5-diketone **D**. The latter undergoes the Favorsky reaction with a second molecule of acetylene to afford acetylenic alcohol **E**, which then participates in a domino sequence: formation of hemiacetal **F** and intramolecular nucleophilic addition of its hydroxy group at the acetylenic moiety to finalize the assembly.

The suggested reaction sequence is supported by the fact that acetylene is very sensitive towards nucleophilic attack[12] and readily adds diverse nucleophiles in the presence of bases,[12,13] particularly superbases[1b,14] without activation by the transition metals.

Alternatively, intermediate **C** could be formed by aldol condensation of ketone **1** with acetaldehyde, which in turn may originate from acetylene hydration (nucleophilic addition of water to the triple bond). The transformation of intermediate diketone **D** into acetylenic alcohol **E** (addition of deprotonated acetylene to carbonyl group) is in accordance with the easy deprotonation of acetylene in the KOH/DMSO system. According to the experimental data (e.g., see ref.[15]), the pK_a value for acetylenes in DMSO is on the level of 28–29, whereas the basicity function ($H\_$) of the KOH/DMSO system is higher than 30 (e.g., see ref.[16]). Therefore, ionization of acetylenes in such systems exceeds 90%.

Scheme 2 is in keeping with our experimental data that aliphatic ketones undergo the above assembly nonselectively. This might be due to the lower CH acidity of aliphatic ketones (less favorable formation of type **A** carbanion) and the lower electrophilicity of intermediate α,β-ethylenic ketone **C** as well as their higher propensity to undergo self-condensation.

As seen from Table 1, the new reaction allows diverse aromatic, heteroaromatic, and condensed aromatic substituents, as well as the enol ether moiety, to be introduced into the frontalin skeleton, which essentially enriches the frontalin family with hitherto unknown representatives.

Conclusions

A new reaction representing a one-pot assembly of two molecules of aromatic and heteroaromatic ketones (acylarenes and -hetarenes) or acylated condensed aromatics with two molecules of acetylene to deliver densely substituted 7-methylene-6,8-dioxabicyclo[3.2.1]octanes, unknown congeners of insect pheromones of the frontalin series, was discovered. The reaction is highly regio- and stereoselective and proceeds smoothly in simple MOH/DMSO (M = K, Cs) systems at 80 °C for 1 h under elevated or atmospheric pressure; the isolated yields of the assemblies reached 86%. Aliphatic ketones are potentially also valid for this assembly.

Fundamentally, the reaction essentially extends the frontiers of the synthetic applications of simple organic compounds such as ketones and acetylene. Practically, the reaction gives exceptionally facile access to new diversely substituted derivatives of important insect pheromones, which can be prospective building blocks for organic synthesis and precursors of advanced materials.

Supporting Information (see footnote on the first page of this article): Full experimental data and spectroscopic data.

CCDC-736221 (for **3e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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