**Azabrendanes IV. Synthesis and characterization of *N*-(alkyl- and benzylsulfonyl)-*exo*-2-hydroxy-4-azatricyclo[4.2.1.0$^{3,7}$]nonanes / Lilija I. Kasyan, Igor N. Tarabara, Andrey O. Kasyan, Sergiy I. Okovytyy, Andrey V. Tokar, Svetlana V. Shishkina, Oleg V. Shishkin** // Tetrahedron **Volume 63, Issue 8, 19 February 2007, Pages 1790-1797**

## Abstract

*exo*- and *endo*-5-Aminomethylbicyclo[2.2.1]hept-2-enes have been obtained from stereoisomeric *exo*- and *endo*-5-cyanobicyclo[2.2.1]hept-2-enes and the corresponding sulfonamides were obtained through reaction of amines with methyl-, *n*-propyl-, *n*-butyl-, benzyl-, and cyclohexylsulfonyl chlorides. From the stereoisomeric sulfonamides with peroxy acids, various products were obtained: *exo*-sulfonamides were transformed into epoxy derivatives, and, in contrast, most of the *endo*-stereoisomers underwent heterocyclization resulting in substituted *exo*-2-hydroxy-4-azatricyclo[4.2.1.0$^{3,7}$]nonanes. The type of the products obtained did not depend on the type of peroxy acid used (peroxyacetic, peroxyphthalic, and *m*-chloroperoxybenzoic one). In contrast to other *endo*-sulfonamides, *N*-(cyclohexylsulfonyl)-*endo*-5-aminomethylbicyclo[2.2.1]hept-2-ene in reaction with peroxyacetic acid did not undergo heterocyclization, probably, due to steric factors. The structure and stereochemical homogeneity of the sulfonamides and the structure of the products of their oxidation with peroxy acids were confirmed by spectroscopic methods. The molecular structure of *N*-(cyclohexylsulfonyl)-*endo*-5-aminomethyl-*exo*-2,3-epoxybicyclo[2.2.1]heptane was determined by X-ray

diffraction analysis. The mechanism of the intramolecular heterocyclization reaction of *N*-substituted *endo*-5-aminomethyl-*exo*-2,3-epoxybicyclo[2.2.1]heptanes was studied at the BHandHLYP/6-31G(d) level of theory.

## Introduction

Azabrendanes **1a** are of interest as potential biologically active systems or as intermediates for the preparation of such compounds.[1] They are easily obtained by epoxidation of the *p*-substituted arylsulfonamides of type **1b** having an *endo*-orientation of the substituent. The ability to heterocyclization decreases when the number of substituents in the benzene ring increases, especially in the case of nitro groups in an *o*-position.[2] Analogous heterocyclization of the ureas **1c** (Ar=$C_6H_5$, *m*-$ClC_6H_4Cl$) under oxidation conditions has been described previously.[3] Ring transformations of this kind are attributed to a favorable location of the substituted nitrogen atom in the vicinity of the loosening $\pi^*$-molecular orbital of the incipient epoxy ring.[4]

On the other hand, a number of cases when the structural analogs of the compounds **1b**, **1c** in reactions with peroxy acids are transformed into epoxy compounds without heterocyclization are well known. For example, the lack of heterocyclization by fluorine-containing sulfonamide **1d**,[5] and by a series of *endo*-carboxamides including methyl, trifluoromethyl, and aryl substituents at nitrogen atom **1e**,[6] has been shown. *N*-Alkyl-substituted azabrendanes **1d** have been obtained in the latter case by chemoselective reduction of epoxy amides **1f** and subsequent cyclization of the epoxy amines (Scheme 1).[6]

The reasons determining the behavior of the substituted *endo*-5-aminomethylbicyclo[2.2.1]hept-2-enes in reactions with peroxy acids and formation of two different types of oxidation products have not been stated until recently. In order to obtain new facts, which would help to

address this issue, we have investigated in the current work the behavior of stereoisomeric alkyl-, benzyl-, and cyclohexylsulfonamides in reactions with peroxy acids.

## Section snippets

### Results and discussion

The required stereoisomeric sulfonamides were synthesized using *exo*- and *endo*-cyanobicyclo[2.2.1]hept-2-enes **2a**, **2b** that were obtained by methods described in the literature.[7] These stereoisomeric nitriles were converted into amines **3a**, **3b** by the action of lithium aluminum hydride.7, 8 In accordance with the literature,[9] the reduction of nitrile **2b** was accompanied by epimerization of the product. An impurity (5–10%) of the corresponding *exo*-stereoisomer was revealed by $^{1}$H NMR spectroscopy. In

### Quantum-chemical calculations

Formation of azabrendanes during the interaction of *endo*-sulfonamides with peroxy acids may proceed with or without formation of an epoxide as an intermediate compound. Recently, we have shown that the oxygen-transfer step for the reaction of olefins with peroxy acids is followed by very fast proton-transfer and epoxy ring closure step.[20] Detailed analysis of the potential energy surface (PES) of *endo*-amine **3b** interaction with peroxyacetic acid at the UBHandHLYP/6-31G(d) level of theory showed

### General

All solvents for reactions were dried and distilled immediately prior to use. Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded on a

Specord 75-IR spectrometer using KBr pellets. $^{1}H$ NMR spectra were recorded at 300 and 400 MHz, and $^{13}C$ NMR spectra were recorded at 100.6 MHz on Varian and Bruker spectrometers. Chemical shifts are reported in parts per million relative to TMS in $CDCl_3$. For thin-layer chromatographic (TLC) analysis, TLC plates