Synthesis of azolyl-substituted derivatives of 1-adamantanecarboxylic acid

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Abstract

Ligands containing azole rings are interesting as ligands for coordination chemistry, especially as building blocks for metal-organic frameworks. Adamantane can serve as a rigid linker for the construction of multidentate ligands. In this work we describe the synthesis of 3-azolyl-1-adamantanecaroboxylic acid derivatives starting from 3-bromo-1-adamantanecaroboxylic acid and the corresponding azoles (pyrazole, imidazole, 1,2,4-triazole, benzimidazole, 1,2,3-benzotriazole). The structure of products was confirmed by NMR and mass-spectrometry.

Keywords: adamantane, carboxylic acid, pyrazole, imidazole, triazole

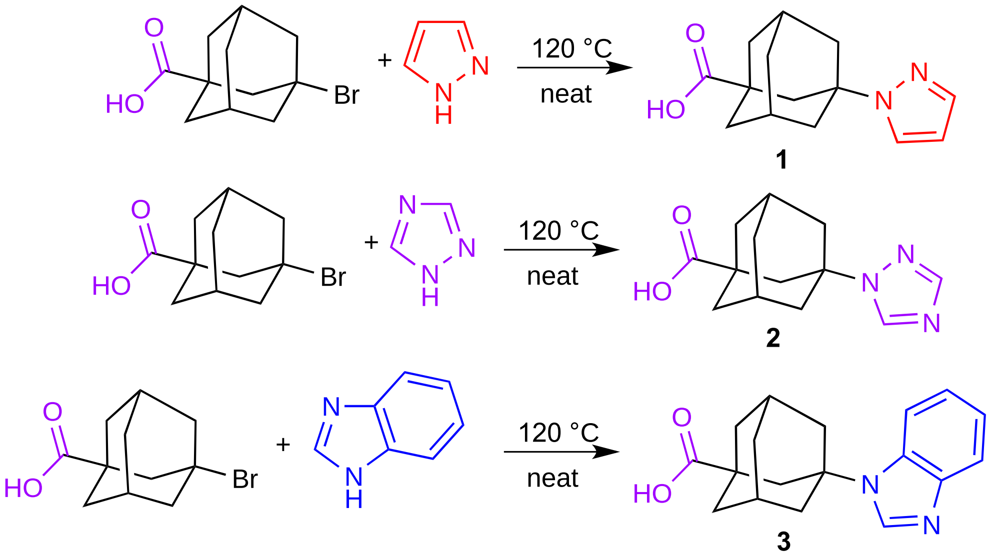
Introduction

Diamondoids are cage hydrocarbons, in which the arrangement of carbon resembles the diamond crystal lattice [1]. Adamantane, being the simplest and the most readily available of them attracts attention for its rigidity, relatively low molecular volume and lipophilicity [2–4]. Functionalized adamantanes find use in pharmaceutical applications [5–7], polymer synthesis [8], design of nanostructured materials [9,10], ionic liquids [11] and coordination chemistry [12,13]. Among pharmaceutical applications, potent antiviral activity of functionalized adamantanes should be noted [14–16]. Some of azolyl-substituted adamantanes resembling rimantadine analogs were evaluated as antiviral agents [17]. In addition, arrangement of azoles around a rigid linker makes azolyladamantanes perfect auxiliary ligands for metal-organic framework design, however, only several examples of such ligands have been reported so far [18–22].

In this contribution synthesis of new azolyl-functionalized adamantane-carboxylic acids is reported.

Results and discussion

3-Azolyl-1-adamantanecarboxylic acids **1**-**3** were prepared by heating the liquid mixture of the corresponding azoles and 3-bromo-1-adamantanecarboxylic acid at 120 °C (Scheme 1).



Scheme 1

The products were identified using GC/MS and NMR methods. GC/MS analysis of products was performed after their derivatization with MeOH / $SOCl_2$ system. Methyl ethers of 3-azolyl-1-adamantanecarboxylic acids gave stable molecular ions in electron impact mass spectra (see Figure 1 as an example). Other characteristic peaks correspond to ions formed abstraction of azole (m/z 193) or COOMe (m/z 202) moieties. Further fragmentation leads to a stable dehydroadamantane cation-radical (Scheme 2).

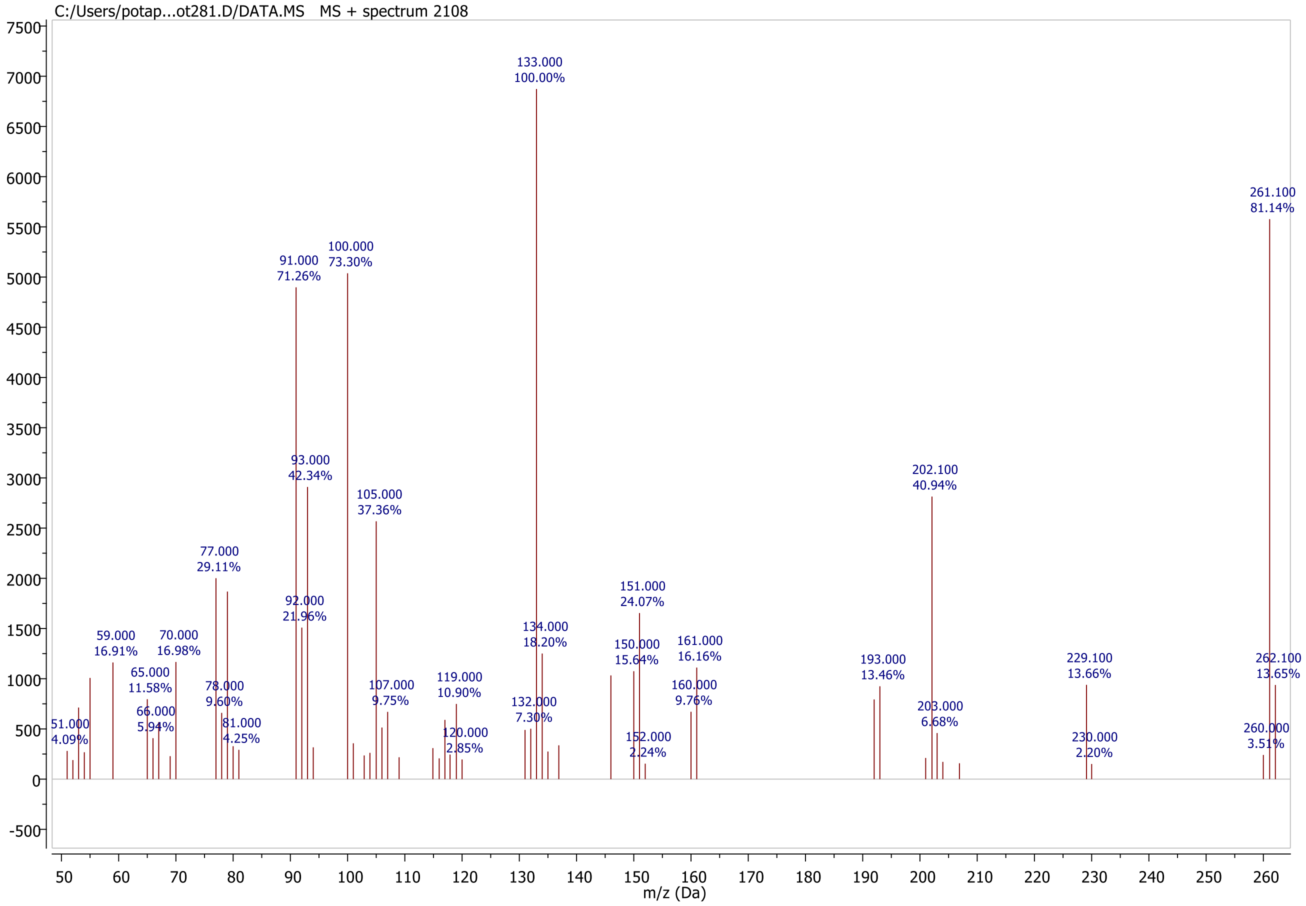
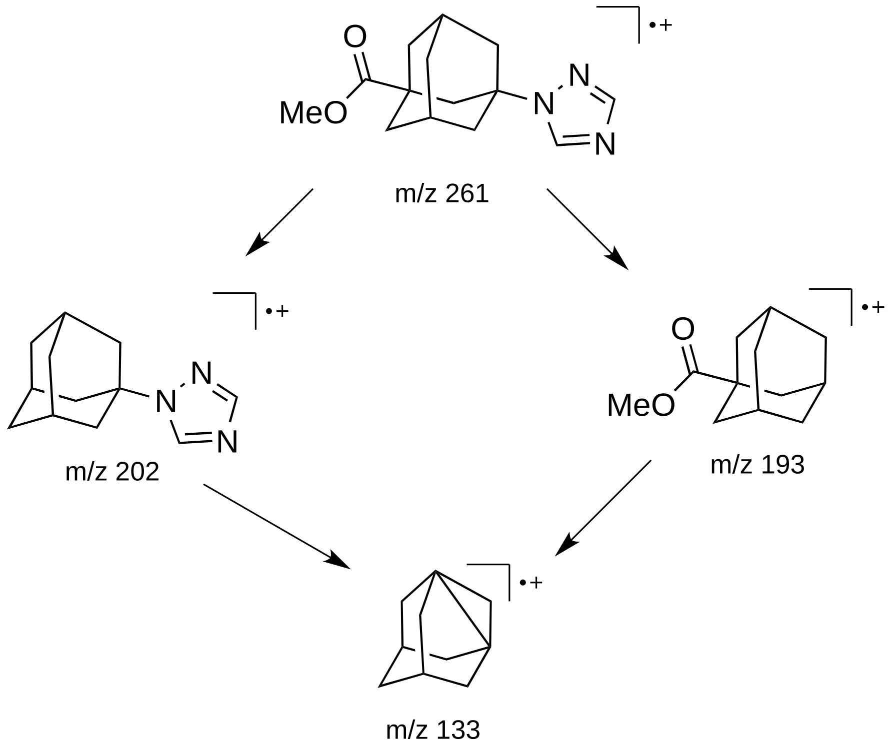
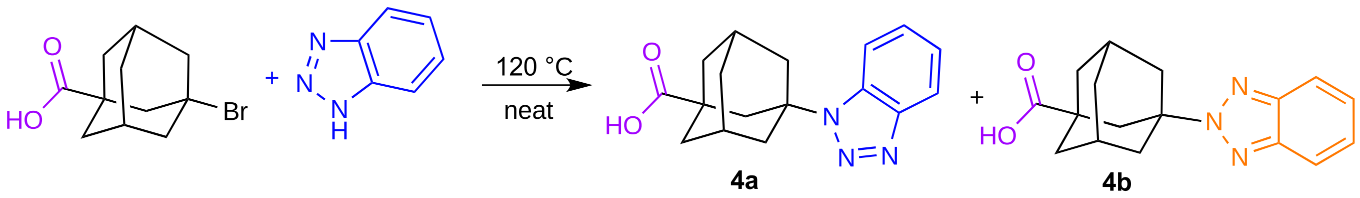


Figure 1. Electron impact mass-spectrum of methyl ether of compound **2**.



Scheme 2

When 1,2,3-benzotriazole was used as a starting azole, a mixture of the corresponding 1- and 2-benzotriazolyl derivatives **4a** and **4b** was isolated (Scheme 3).



Scheme 3

Compounds **4a** and **4b** could be easily discerned by their mass-spectra (Figure 2). 1-Benzotriazolyl derivative **4a** is able to eliminate dinitrogen, thus its molecular ion is unstable and the corresponding peak at m/z 311 was not detected. Instead, the heaviest peak in the mass-spectrum of compound **4a** was at m/z 281 and accounted for [M-N2-2H] particle. On the contrary, mass-spectrum of compound **4b** demonstrated a peak at m/z 310 corresponding to [M-H] ion.

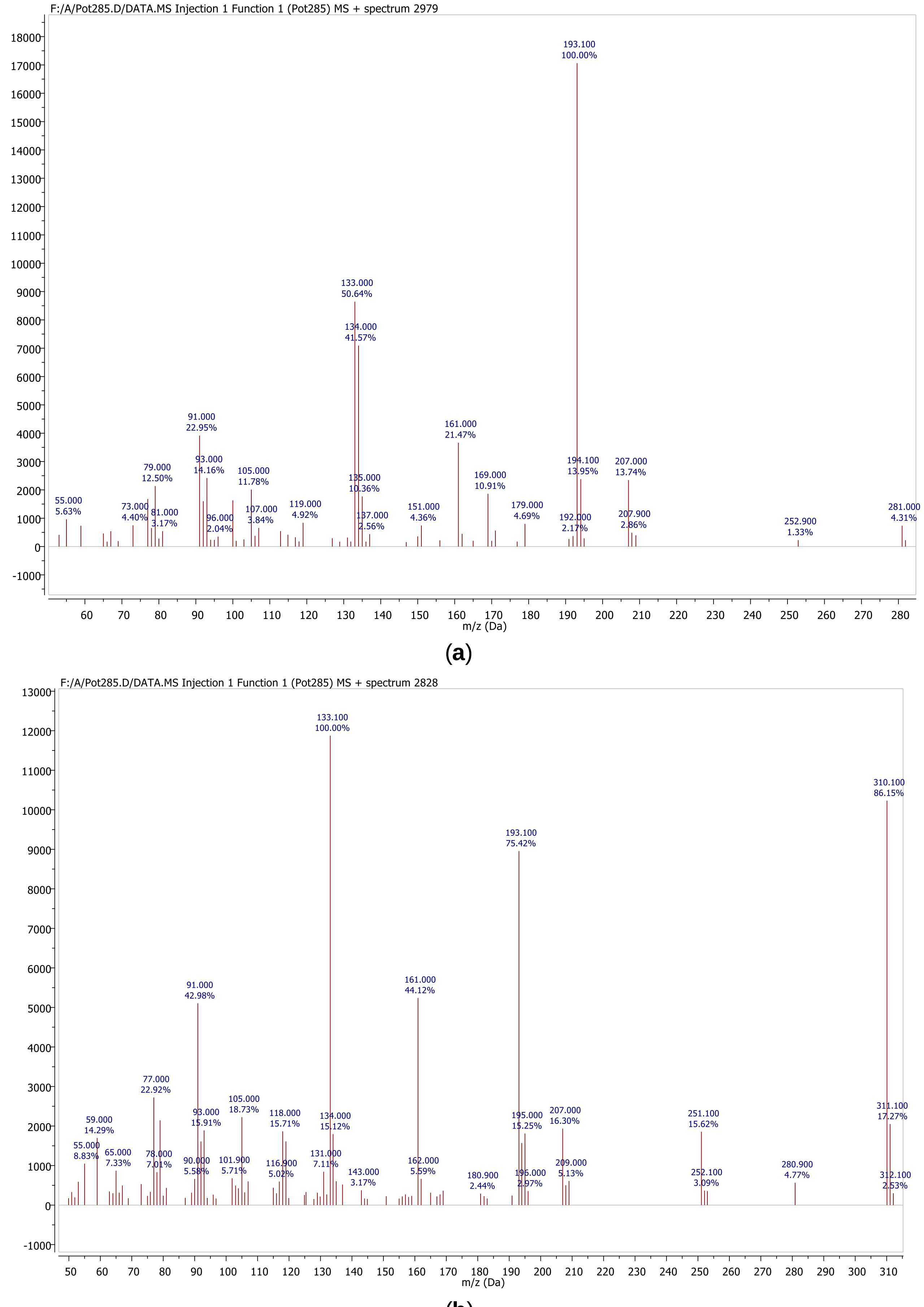


Figure 2. Electron impact mass-spectra of methyl ethers of compounds **4a** (**a**) and **4b** (**b**).

A typical synthetic procedure is given in the experimental part.

Experimental

Gas chromatography-mass spectrometry analysis was performed using Agilent 7890A gas chromatograph equipped with Agilent MSD 5975C mass-selective detector.

NMR spectra were recorded on Bruker AV300 instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C.

3-(Pyrazol-1-yl)-1-adamantane carboxylic acid (**1**). A mixture of 3-bromo-1-adamantanecarboxylic acid (5 mmol) and 1*H*-pyrazole (10 mmol) were heated in a screw-caped glass vial at 120 °C in a dry bath incubator for 24 hours. The glassy residue was then dissolved and DCM (10 ml) and the organic phase was washed several time with water to remove the excess of pyrazole. After removal of the solvent the acid 1 was obtained as a colorless solid. Yield 1.14 g (92 %). NMR ^{1}H, δ, ppm ($CDCl_3$): 1.74-2.79 (14H, Adm), 6.23 (1H, 4-H-Pz), 7.51 (1H, 3-H-Pz), 7.57 (1H, 5-H-Pz), 11.0 (1H, COOH).

Summary

In summary, a simple procedure for the synthesis of new functionalized adamantanes, which are potentially useful ligands for metal-organic frameworks was proposed. The structure of the products was confirmed by NMR and mass-spectrometry.

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