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Optimization of the Synthesis of 2-Adamantanecarboxylic Acid

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Abstract

To date, compounds having an adamantane moiety have found wide application in the pharmaceutical industry. Despite the fact that most biologically active adamantyl-bearing derivatives contain substituents in the first position of the adamantane molecule, some derivatives with substituents in the second position have also shown valuable pharmacological properties. While 1-adamantanecarboxylic acid is an inexpensive and commercially available reagent, its 2-substituted analogue is substantially less available, and therefore, the development and optimization of approaches to the synthesis of 2-adamantanecarboxylic acid are of great importance. In this work, a three-stage method for the synthesis of 2-adamantanecarboxylic acid has been optimized, based on the Corey–Chaykovsky reaction of 2-adamantanone with trimethylsulphoxonium iodide in the presence of potassium hydroxide, followed by acid-catalyzed opening of the oxirane ring and oxidation of aldehyde **9** to the target carboxylic acid. The total yield of the target product is 70 %.

Keywords: words: adamantane, biological activity, Corey–Chaykovsky reaction

INTRODUCTION

Adamantane derivatives have currently found broad application in drug design. Compounds containing adamantly substituent exhibit antiviral effect (compounds **1–3**), and also are used as the means to treat type II diabetes (**4**) and to correct Alzheimer's disease (**5**) (Fig. 1) [1].

In spite of the fact that the majority of known biologically active adamantane derivatives contain substituents in the bridgehead position of the molecule, some of its derivatives with substituents in the bridge position also exhibit useful biological properties. For instance, compound **SQ109** (Fig. 2) that has exhibited high activity against mycobacteria [2] is now at the third stage of clinical trials. Moreover, adamantane derivatives with the fragments of some monoterpenes were found to exhibit activity against orthopoxviruses [3] and DNA repair enzyme tyrosyl-DNA-phosphodiesterase 1 (Tdp1) [4], which is a promising target for anticancer therapy. It should be stressed that 2-adamantyl-substituted derivatives **6** and **7** turned out to be more efficient in comparison with their 1-adamantyl-substituted regioisomers **8** and **9**.

It should be noted that, while 1-adamantanecarboxylic acid is a cheap and commercially available reagent, its 2-substituted analogue is substantially less available. The goal of the present work is to optimize the method of obtaining 2-adamantanecarboxylic acid.

EXPERIMENTAL

Materials and methods

The reagents used in the work were adamantane-2-one (98 %, Acros Organics), trimethylsulphoxonium iodide (98 %, Acros Organics), boron

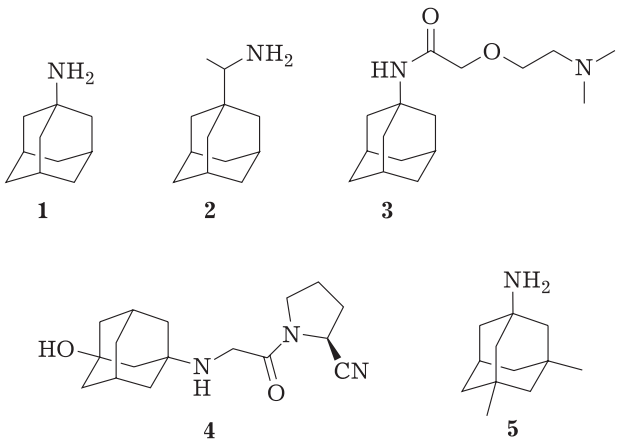


Fig. 1. Biologically active adamantane derivatives.

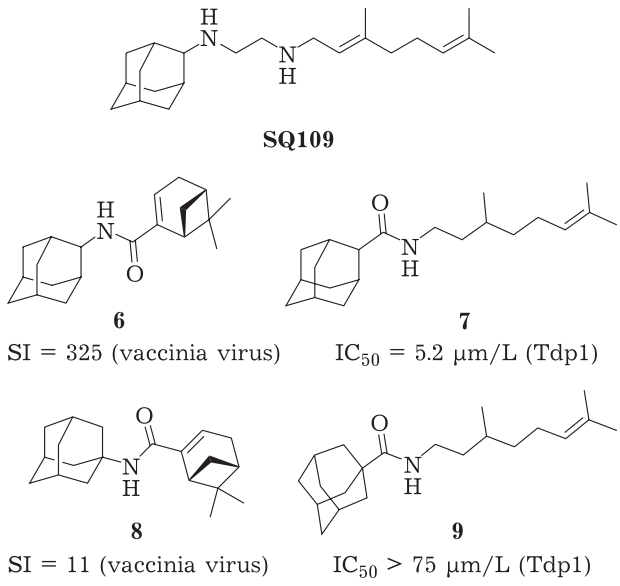


Fig. 2. Comparison of the biological activity of adamantane derivatives substituted at the bridge position. SI – selectivity index, IC_{50} – the concentration of half-maximal inhibition.

trifluoride etherate (Sigma Aldrich), sodium chloride (80 %, Alfa Aesar).

The solvents were distilled before use. Dichloromethane was distilled over anhydrous calcium chloride and stored over molecular sieves 3 Å.

The NMR ^1H spectra were recorded on Bruker AV-400 spectrometer (Germany) in $CDCl_3$ solutions. Gas chromatographic (GC) analysis of reaction mixtures was carried out using gas chromatograph Agilent 7820A (USA) with flame ionization detector and HP-5 column (copolymer diphenyl/dimethoxysiloxane = 5 : 95, length 30 m, inner diameter 0.25 mm, the stationary phase: thickness 0.25 μm, carrier gas He (flow rate 2 mL/min)). Mass spectra were recorded on Agilent 7890A spectrometer (USA) with HP-5 MS column and mass detector Agilent 5975C.

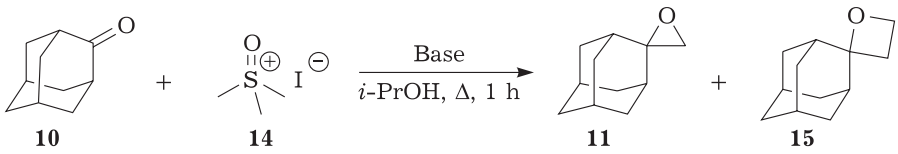
Synthesis procedures

2-Adamantanespirooxyrane (11). Adamantane-2-one (5.0 g, 33 mmol), trimethylsulphoxonium iodide (12.0 g, 55 mmol), potassium hydroxide (3.5 g, 62 mmol) and isopropanol (25 mL) were placed in a found-bottomed flask. The mixture was refluxed for 1 h with stirring. Then water was added (75 mL), which was accompanied by the formation of white precipitate. The product was extracted with hexane (3 × 20 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The drying agent was separated, the solvent was evaporated on a rotary evaporator. The mass of the resulting epoxide was 5.4 g (98 %).

NMR ^1H spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.39 (s, 2H), 1.70–1.92 (m, 12H), 2.63 (s, 2H).

2-Adamantanecarbaldehyde (12). A solution of 2-adamantanespirooxyrane **11** in dichloromethane (2.0 g, 12 mmol in 20 mL) was slowly added while stirring to the solution of boron trifluoride etherate (0.5 mL, 0.4 mmol) in anhydrous dichloromethane (10 mL) cooled to 0 °C. The resulting solution was stirred at this temperature for 5 min, and then water was added. The organic phase was separated, the solvent was evaporated on a rotary evaporator. The residue was used in the next stage without further purification.

2-Adamantanecarboxylic acid (13). The aqueous solution of $NaClO_2$ (1.9 g, 21 mmol in 18 mL of water) was added dropwise to a mixture containing 2-adamantanecarbaldehyde **12**, KH_2PO_4 (0.5 g, 3.6 mmol), 37 % H_2O_2 solution (1.4 mL), MeCN (60 mL) and H_2O (12 mL). The mixture was stirred at room temperature for 6 h, then $Na_2S_2O_3$ (2.2 g, 14 mmol) was added. The organic phase was separated, and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The drying agent was separated, and the solvent was removed under vacuum. The residue was dissolved in 30 mL of diethyl ether, the solution was treated with 30 mL 10 % KOH. The aqueous part was washed with 10 mL of ether. Then concentrated HCl was added to the aqueous phase until a weakly acidic medium. The product was extracted with diethyl ether, the organic phase was washed with brine and dried over anhydrous Na_2SO_4. The yield of the product was 1.7 g (70 %, calculated for three stages).



10 **14** **11** **15**

Scheme 1. Interaction of ketone **10** with trimethylsulphoxonium iodide **14**. Δ – boiling.

NMR ^{1}H spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.62–1.66 (m, 2H), 1.74–1.78 (m, 4H), 1.86–1.94 (m, 6H), 2.34 (s, 2H), 2.66 (s, 1H). NMR ^{13}C spectrum ($CDCl_3$), δ, ppm: 27.2, 27.2, 29.2, 33.4, 37.2, 37.9, 49.3, 181.3. Melting point 142.1–143.6 °C (literature data: 139–142 °C [5]).

RESULTS AND DISCUSSION

We chose to synthesize 2-adamantanecarboxylic acid **13** by obtaining epoxide **11** from adamantane-2-one **10** according to Corey–Chaykovsky reaction, followed by oxirane cycle opening to form aldehyde **12**, and oxidation of the latter to form the corresponding acid.

It is necessary to stress that the yield of 2-adamantanecarboxylic acid in three-stage synthesis according to the literature data was only 28 %. To increase the total yield of the target product, we decided to optimize the conditions for each stage.

The first stage (Scheme 1) was carried out according to the procedure presented in [6], where the yield of product **11** was reported to be 85 %. For this purpose, a mixture containing ketone **10**, trimethylsulphoxonium iodide **14** and NaOH at the molar ratio of 1 : 1.6 : 3.8, respectively, was refluxed in isopropanol for 1 h. According to GC data, the conversion of adamantane-2-one **10** within this time was 80 % (Table 1). Boiling for a longer time did not cause an increase in conversion, so an attempt was made to replace NaOH by KOH with the conservation of the molar ratios of reagents. Under these conditions, the complete conversion is observed as early as within 30 min after the start of reaction; however, along with the target product **11**, the mixture also contained oxetane **15**, so that according to NMR ^{1}H data its content was about 10 mol. %.

With a decrease in the amount of KOH to 1.9 mol, selective reaction progress is observed, and complete conversion of ketone **10** is achieved within 1 h after the start of reaction. The yield of product **11** was 98 %.

The structure of oxetane **15** was confirmed through the analysis of reaction mixture by means of NMR ^{1}H and mass spectrometry. The NMR ^{1}H spectrum contained two triplets with chemical shifts (δ) 4.41 and 2.34 ppm, and spin-spin coupling constants equal to 7.8 Hz, which is in agreement with the data reported in [7]. At the same time, the mass spectrum contains the peak of molecular ion with the highest intensity $[M]^+$ (178), which is consistent with the assumed structure.

Opening of oxirane cycle was carried out according to the procedure described in [6]. For this purpose, boron trifluoride etherate was added to the synthesized epoxide **11** in a benzene solution; then the reaction mixture was stirred intensively for 1 min, and water was added (Scheme 2).

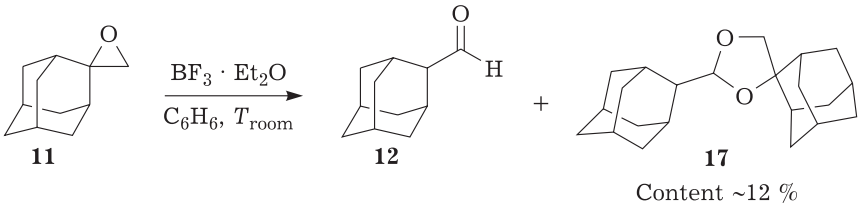
Interestingly, the chromatogram of reaction mixture contained, along with the peak of the target aldehyde, an additional signal related to dioxalane **17**, which is confirmed by NMR ^{1}H spectroscopy. The NMR ^{1}H spectrum of the mixture contained a doublet (δ = 5.18 ppm, spin-spin coupling constant 7.9 Hz), along with two doublets of AB system (δ = 3.82 and 3.68 ppm), with the integral intensities ratio equal to 1 : 1 : 1, which corresponds to the data reported in [8].

The assumed mechanism of the formation of side product **17** involves acid-catalyzed interaction of the aldehyde formed in the reaction mixture with epoxide to form 1,3-dioxalane cycle.

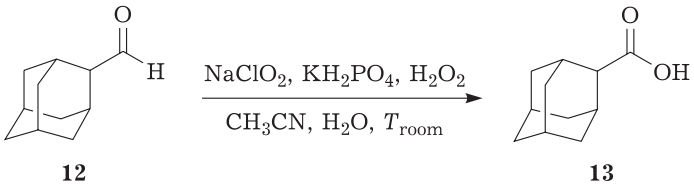
TABLE 1

Optimization of the conditions of ketone **10** interaction with trimethylsulphoxonium iodide **14**

Compound **10**, mol	Compound **14**, mol	Base, mol	Time, h	Ketone conversion, %	Oxetane content, mol. %
1.0	1.6	3.8 (NaOH)	1	80	0
1.0	1.6	3.8 (KOH)	0.5	100	10
1.0	1.6	1.9 (KOH)	1	100	0



Scheme 2. Opening of epoxide **11** in the presence of boron trifluoride etherate according to the procedure described in [6].



Scheme 3. Synthesis of 2-adamantanecarboxylic acid **13**.

Selective interaction of oxirane **11** with boron fluoride is successfully achieved by slow addition of the solution of epoxide **11** in dichloromethane to the solution of boron trifluoride etherate in dichloromethane while cooling to 0 °C. The application of this method leads to the selective formation of the target aldehyde **12**.

In spite of the fact that the only method of aldehyde **12** oxidation described in the literature is the use of Jones reagent, we decided to apply different method because of the high toxicity of Cr(VI). Another convenient method for obtaining carboxylic acids is oxidation of the corresponding aldehydes by sodium chlorite under mild acidic conditions (Pinnick oxidation). This method is widely used in the synthesis of carboxylic acids with diverse structures [9–11]; in particular, it is used for the oxidation of labile substrates, for example monoterpenoids [12, 13]. The transformation of aldehyde **12** into the corresponding carboxylic acid **13** was performed according to this procedure by applying sodium chlorite in the presence of potassium dihydrophosphate and hydrogen peroxide in acetonitrile/water mixture at room temperature (Scheme 3). The completion of the starting material controlled by GC was achieved within 6 h after the start of the reaction. The total yield of the target carboxylic acid in the three stages was equal to 70 %.

CONCLUSION

Thus, optimization of the three-stage synthesis of 2-adamantanecarboxylic acid **13** was carried out based on the Corey–Chaykovsky reaction of adamantane-2-one **10** with trimethylsulphoxonium iodide in the presence of potassium hydroxide, followed by acid-catalyzed opening of the oxirane cycle and aldehyde oxidation to form the target carboxylic acid **13**. The total yield of the target product was 70 %.

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