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Chemical Transformations of Tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane (1,3-Dehydroadamantane): VII.[1] Reaction of 1,3-Dehydroadamantane with Alkanediols and Amino Alcohols

G. M. Butov[a, b]* and V. M. Mokhov[b]

[a] *Volzhsky Polytechnic Institute (Branch), Volgograd State Technical University, ul. Engel'sa 42a, Volzhsky, Volgograd oblast, 404121 Russia*
**e-mail: butov@volpi.ru*

[b] *Volgograd State Technical University, pr. Lenina 28, Volgograd, 400131 Russia*

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Abstract—The reaction of 1,3-dehydroadamantane with C_2–C_6 α,ω-alkanediols selectively afforded ω-(adamantan-1-yloxy)alkan-1-ols in 87–94% yield. The reaction of 1,3-dehydroadamantane with ω-aminoalkan-1-ols (2-aminoethanol and 3-aminopropan-1-ol) gave mixtures of addition products through the oxygen and nitrogen atoms, which can be readily separated by fractional vacuum distillation or crystallization.

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ω-(Adamantan-1-yloxy)- and ω-(adamantan-1-ylamino)alkan-1-ols are convenient intermediate products for the introduction of an adamantyl fragment and an oxygen-containing spacer into pharmacophoric molecules. In particular, 2-(adamantan-1-yloxy)ethanol was used as precursor to 2-(adamantan-1-yloxy)-5-[hydroxy(tetrahydrofuran-2-yl)amino]isoxazole-3-carboxylate tested as a lipoxygenase inhibitor [2], as well as to synthesize carnitine acyltransferase-1 (CAT-1) inhibitors [3]. The synthesis of tosyloxymethylphosphonic acid esters, key intermediate products for the preparation of nucleoside phosphonate antiviral agents, on the basis of 2-, 3-, and 4-(adamantan-1-yloxy)-alkan-1-ols has been described in [4–6].

n-(Adamantan-1-yloxy)alkan-1-ols were used to synthesize supramolecular compounds, e.g., complexes with β-cyclodextrin (*n* = 2) [7], or novel water soluble rhenium-containing dendrimers as potential radiotherapeutic agents (*n* = 3) [8].

n-(Adamantan-1-yloxy)alkan-1-ols (*n* = 2–4) were previously obtained by reaction of 1-bromoadamantane with the corresponding glycols on heating in an argon atmosphere for 24 h in the presence of an equimolar amount of triethylamine [6, 8, 9], for 5 h at 100°C in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene and triethylamine [6], or for 24 h in diethylene glycol dimethyl ether [10]. 3-(Adamantan-1-yloxy)propan-1-ol was also synthesized by reaction of 1-(allyloxy)adamantane with the BH_3–Me_2S complex in THF, followed by treatment with sodium hydroxide and hydrogen peroxide [10]. Thus, the known methods of synthesis of ω-(adamantan-1-yloxy)alkan-1-ols require elevated temperature (>110°C), long reaction times (5–24 h), and the use of specific reagents.

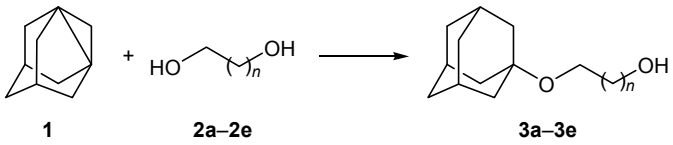
We have developed a selective procedure for the synthesis of C_2–C_6 ω-(adamantan-1-yloxy)alkan-1-ols from 1,3-dehydroadamantane (1,3-DHA, tetracyclo-[3.3.1.1^{3,7}.0^{1,3}]decane) and the corresponding α,ω-alkanediols. As shown previously, 1,3-DHA (**1**) is a highly reactive propellane capable of reacting with activated C–H bonds of various organic compounds [11], as well as with various NH acids [12].

There are a few data on reactions of 1,3-DHA with hydroxy compounds. In particular, reactions of **1** at fairly acidic O–H bonds of carboxy (acetic acid [13] and unsaturated acids [14]) and peroxycarboxy groups [15] have been reported. Propellane **1** readily and selectively reacted with mono- and dihydric phenols [16, 17] to give the corresponding adamantyl phenyl ethers.

1,3-Dehydroadamantane (**1**) reacted with methanol in the presence of a catalyst [18], as well as with peroxy alcohols in which the hydroxy group is activat-

* For communication VI, see [1].

Scheme 1.



1 **2a–2e** **3a–3e**

n = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**), 5 (**e**).

ed due to the effect of alkylperoxy group [19]. However, the use of an acid catalyst is not always appropriate because of the possibility of dehydration of alcohols and reduction of the reaction selectivity. Therefore, in this work the reactions of **1** with diols **2a**–**2e** were carried out in the absence of a catalyst in diethyl ether at 35–40°C (2–3 h), the **1**-to-**2** molar ratio being 1 : (2.7–3.7) (Scheme 1).

When the reaction was complete, compound **3a**–**3e** was separated from excess diol **2a**–**2e** by vacuum distillation. The structure of **3a**–**3e** was confirmed by ^{1}H NMR and mass spectra. Analysis of the reaction mixtures by gas chromatography–mass spectrometry showed high chemoselectivity of the reaction. The properties and spectral characteristics of known compounds were consistent with published data [6, 9, 10]. Thus, the reactions occurred under mild conditions in a shorter time with high selectivity.

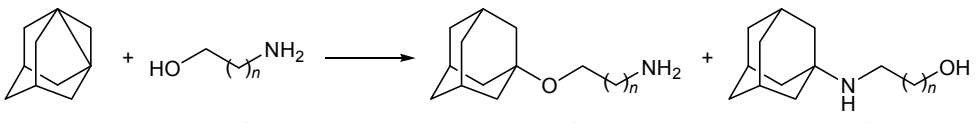
Apart from ω-(adamantan-1-yloxy)alkan-1-ols, important precursors to biologically active adamantane derivatives are ω-(adamantan-1-ylamino)alkan-1-ols and ω-(adamantan-1-yloxy)alkan-1-amines which provide a nitrogen-containing spacer between the adamantane fragment and pharmacophore such as urea or thiourea residue. These compounds were used to obtain soluble epoxide hydrolase (sEH) inhibitors [20, 21], and an influence of the spacer structure on the activity (IC_{50}), solubility in water, and melting point of the inhibitors was revealed.

Like ω-(adamantan-1-yloxy)alkan-1-ols, reactions of 1-haloadamantanes with amino alcohols are widely used to obtain ω-(adamantan-1-ylamino)alkan-1-ols. However, in most cases these reactions are not selective. ω-(Adamantan-1-yloxy)alkan-1-amines can be obtained by reaction of 1-bromoadamantane with ω-aminoalkan-1-ols in the presence of triethylamine (10 h at 120°C), but the yield was low ~13% [22, 23], whereas the major products were ω-(adamantan-1-ylamino)alkan-1-ols (87%) [23]. Another method of synthesis of ω-(adamantan-1-ylamino)alkan-1-ols is based on the reaction of adamantan-1-amine hydrochloride with ω-bromoalkan-1-ols in the presence of sodium hydrogen carbonate on heating [24]. These reactions require elevated temperature and long time.

In order to eliminate the above noted disadvantages and compare the reactivity of O–H and N–H bonds in ω-aminoalkan-1-ols, we studied the reactions of propellane **1** with 2-aminoethan-1-ol (**4a**) and 3-aminopropan-1-ol (**4b**). The reactions were carried out using 10 equiv of the amino alcohol. According to the GC/MS data, the products were mixtures of approximately equal amounts of O- and N-alkylation products **5a**, **5b** and **6a**, **6b**. The product mixtures were readily separated by fractional distillation under reduced pressure. Crystalline amino alcohols **6a** and **6b** were additionally purified by recrystallization.

The formation of mixtures of O- and N-alkylation products in the reaction of 1,3-DHA with ω-aminoalkan-1-ols attracts interest since the OH proton is much more mobile than protons of the amino group, so that predominant or even exclusive addition of propellane to the O–H bond could be expected. Presumably, the reason is strong hydrogen bonding in ω-aminoalkan-1-ol molecules, which equalizes to some extent the reactivities of the O–H and N–H groups. Probably, the attack of 1,3-DHA is directed not at a particular O–H or N–H bond but at associated OH···NH groups. The formation of mixture of O- and N-alkylation products was also observed in the reactions of amino alcohols with 1-bromoadamantane [22].

Scheme 2.



1 **4a**, **4b** **5a**, **5b** **6a**, **6b**

n = 1 (**a**), 2 (**b**).

Thus, on the basis of the reaction of 1,3-dehydroadamantane with α,ω-alkanediols and ω-aminoalkanols we have developed a one-step procedure for chemoselective introduction of an adamantan-1-yl substituent into molecules of difunctional compounds in 87–94% (α,ω-alkanediols) and 39–44% yield (ω-aminoalkanols).

EXPERIMENTAL

The mass spectra were recorded on an Agilent GC 7820/MSD 5975 instrument (HP-5MS quartz capillary column, 30 m; carrier gas helium; oven temperature programming from 80 to 280°C; injector temperature 250°C). The ^{1}H NMR spectra were measured on Bruker DRX 500 (500.13 MHz) and Varian Mercury-300 (300 MHz) spectrometers using DMSO-d_6 as solvent; the ^{1}H chemical shifts are given relative to tetramethylsilane. The elemental analyses were obtained with a Perkin Elmer 2400 Series II analyzer.

2-(Adamantan-1-yloxy)ethanol (3a). A mixture of 2 g (0.015 mol) of 1,3-dehydroadamantane (**1**) and 3 g (0.05 mol) of ethane-1,2-diol (**2a**) in 10 mL of diethyl ether was heated for 1 h at 35°C. The solvent was distilled off, excess diol **2a** was removed under reduced pressure, and the residue was purified by vacuum distillation. Yield 2.7 g (0.014 mol, 93%), viscous liquid which crystallized on storage, mp 38–39°C [9].

Compounds **3b**–**3e** were synthesized in a similar way.

3-(Adamantan-1-yloxy)propan-1-ol (3b) was synthesized from 2 g (0.015 mol) of **1** and 3.8 g (0.05 mol) of **2b**. Yield 2.7 g (0.013 mol, 87%), viscous liquid. Mass spectrum, *m*/*z* (I_{rel}, %): 210.3 (3) $[M]^+$, 179.2 (11), 151.1 (15) [AdO$^+$], 135.2 (100) [Ad$^+$], 117.1 (41), 104.0 (36), 95.1 (99), 79.0 (42), 41.1 (30). The ^{1}H NMR spectrum of **3b** was consistent with that given in [9].

4-(Adamantan-1-yloxy)butan-1-ol (3c) was synthesized from 2 g (0.015 mol) of **1** and 4.5 g (0.05 mol) of **2c**. Yield 3.2 g (0.014 mol, 94%), n_D^{20} = 1.5024; published data [6]: n_D^{20} = 1.5021. Mass spectrum, *m*/*z* (I_{rel}, %): 224 (12) $[M + 2]^+$, 207 (1) $[M - OH]^+$, 135 (100) $[Ad]^+$.

5-(Adamantan-1-yloxy)pentan-1-ol (3d) was synthesized from 2 g (0.015 mol) of **1** and 5.7 g (0.055 mol) of **2d**. Yield 3.3 g (0.014 mol, 92%), viscous liquid. Mass spectrum, *m*/*z* (I_{rel}, %): 238.2 (1) $[M]^+$, 208.2 (5), 163.2 (19), 151.1 (20) $[AdO]^+$, 135.2 (100) $[Ad]^+$, 119.1 (45), 104.0 (40), 95.1 (99), 79.0 (42), 69.1 (63), 41.1 (30). Found, %: C 75.46; H 10.93. $C_{15}H_{26}O_2$. Calculated, %: C 75.58; H 10.98. *M* 238.36.

6-(Adamantan-1-yloxy)hexan-1-ol (3e) was synthesized from 2 g (0.015 mol) of **1** and 5.3 g (0.045 mol) of **2e**. Yield 3.4 g (0.0135 mol, 90%), viscous liquid. Mass spectrum, *m*/*z* (I_{rel}, %): 252.3 (2) $[M]^+$, 196.1 (4), 177.2 (5), 165.2 (4), 151.1 (7) $[AdO]^+$, 135.2 (100) $[Ad]^+$, 117.0 (40), 95.1 (99), 83.1 (61), 55.1 (55), 41.1 (25). Found, %: C 76.40; H 11.23. $C_{16}H_{28}O_2$. Calculated, %: C 76.14; H 11.18. *M* 252.38.

2-(Adamantan-1-yloxy)ethan-1-amine (5a) and 2-(adamantan-1-ylamino)ethan-1-ol (6a). A mixture of 2 g (0.015 mol) of 1,3-DHA and 9.2 g (0.15 mol) of 2-aminoethanol (**4a**) was heated for 1 h at 60–70°C. Excess 2-aminoethanol (**4a**) was distilled off under reduced pressure, and the residue was subjected to vacuum distillation to collect fractions with bp 120–122°C (2 mm) (**5a**) and 139–142°C (2 mm) (**6a**). Yield of **5a** 1.4 g (0.007 mol, 49%), n_D^{20} = 1.4567. Mass spectrum, *m*/*z* (I_{rel}, %): 195.3 (5) $[M]^+$, 164 (75) $[M - CH_2OH]^+$, 135.1 (100) $[Ad]^+$, 107.1 (10), 93.2 (18), 79.0 (20), 44.0 (11). Compound **6a** was purified by recrystallization from benzene. Yield 1.3 g (0.006 mol, 44%), mp 98–99°C; published data [23]: mp 97–99°C.

3-(Adamantan-1-yloxy)propan-1-amine (5b) and 3-(adamantan-1-ylamino)propan-1-ol (6b) were synthesized in a similar way from 2 g (0.015 mol) of **1** and 11.3 g (0.15 mol) of 3-aminopropan-1-ol (**4b**). Yield of **5b** 1.3 g (0.006 mol, 42%). Yield of **6b** 1.2 g (0.0058 mol, 39%), mp 94–95°C; published data [23]: mp 93–95°C.

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