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Synthesis and Thermal Transformations of Allyl Aryl Ethers of Adamantane Series

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Abstract—Allyl aryl ethers of adamantane series were obtained by reacting (*E*)-1-(adamant-1-yl)-3-bromoprop-1-ene with phenol or ethyl salicylate. The features of thermal transformations of allyl aryl ethers containing bulky adamantane scaffold were investigated. It has been found that the composition of the reaction products is largely dependent on temperature, time and nature of the solvent. When a nucleophilic solvent was used, the reaction proceeded via formal substitution of phenoxy fragment with nucleophilic species prevailing in the reaction medium.

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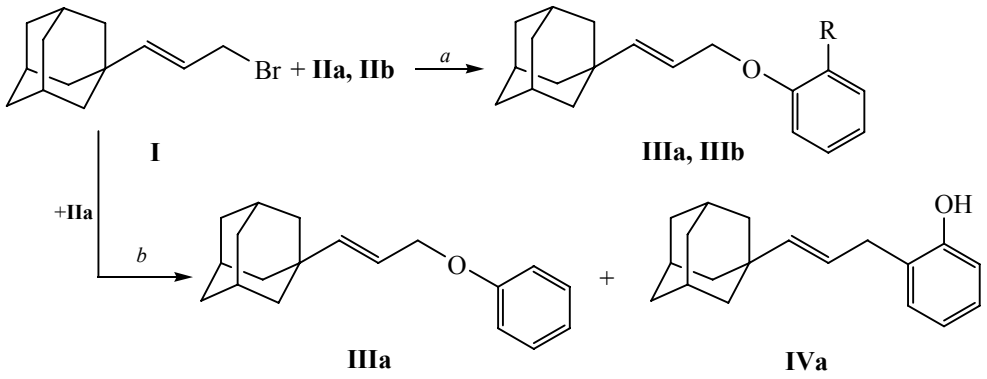
Search for new synthesic approaches to functional derivatives based on transformations of unsaturated substrates of framework structure remains an important area of research in the chemistry of adamantane. Thermal rearrangement of allyl aryl ethers are well known and often used in organic synthesis [1–6]. The presence of bulky framework fragment in the γ-position of the allyl unit opens new possibilities of using thermal transformations in the synthesis of compounds of the adamantane series virtually unavailable by other methods. The investigation of thermal transformation features of allyl aryl ethers containing bulky adamantane scaffold will expand the knowledge on the possible routes of these reactions.

The main method of synthesis of allyl aryl ethers is the alkylation of phenolates with allyl halides. The reaction of (*E*)-1-(adamant-1-yl)-3-bromoprop-1-ene **I** with phenol **IIa** or ethyl salicylate **IIb** in the presence of potassium carbonate in boiling acetone gave the corresponding allyl ethers **IIIa** or **IIIb** (Scheme 1).

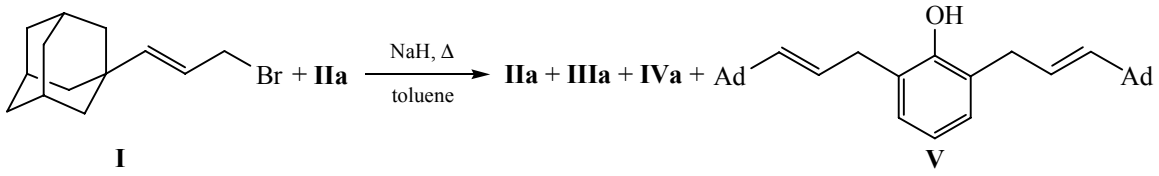
Bromide **I** reacted with phenol in the presence of sodium hydride in toluene under reflux for 2 h to afford a 1 : 1 mixture of two products (by GC-MS): ether **IIIa** and *ortho*-substituted phenol **IVa** as a *C*-allylated product. The resulting mixture was separated by column chromatography on silica gel.

Scheme 1.



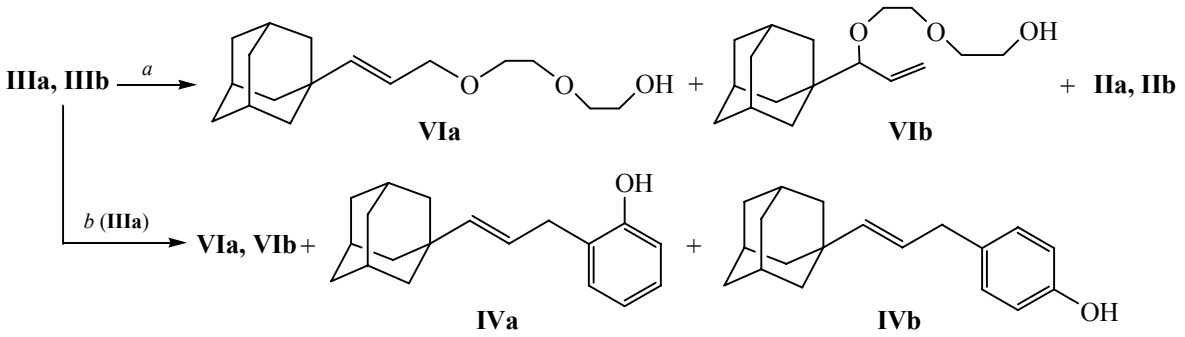
a, K_2CO_3, acetone, 3 h (**IIIa**), 5 h (**IIIb**), Δ; *b*, NaH, toluene, 2 h, heating. R = H (**a**), $COOC_2H_5$ (**b**).

Scheme 2.



Ad = adamant-1-yl.

Scheme 3.



a, diethylene glycol, heating, 0.5 h; *b*, diethylene glycol, heating, 10 h.

2,6-Di-[(*E*)-3-(adamant-1-yl)prop-2-en-1-yl]phenol **V** was obtained along with compounds **IIIa** and **IVa** when the reaction time was 15 h.

In this case, phenol **IIa** was also detected among the reaction products. It is presumable that in the initially formed allyl ether **IIIa** a splitting of the C–O bond occurred followed by the allylation of phenol **IIa** or *ortho*-substituted phenol **IVa** to give the product **V** (Scheme 2).

The formation of 2,6-disubstituted phenols along with the major products of thermal rearrangement has been known [7]. A possibility of ether **IIIa** disproportionation into product **V** and phenol **IIa** is not excluded.

Reaction of bromide **I** with ethyl salicylate under these conditions yields ether **IIIb** as a single product. This is due to deactivating effect of ethoxycarbonyl group on the aromatic ring.

We failed to carry out the thermal Claisen rearrangement of allyl ethers **IIIa** and **IIIb**. The rearrangement products with retention of the structure of the allyl unit were detected, whereas the Claisen rearrangement is a concerted pericyclic process involving [3.3]-sigmatropic shift and should lead to the products with inverted allyl unit [8, 9]. The absence of the intramolecular rearrangement products is probably due to the presence of bulky substituent in the γ-position of the allyl moiety. Some examples of Claisen rearrangement leading to the formation of products with the retention of the structure of the allyl unit have been known [7, 10–12].

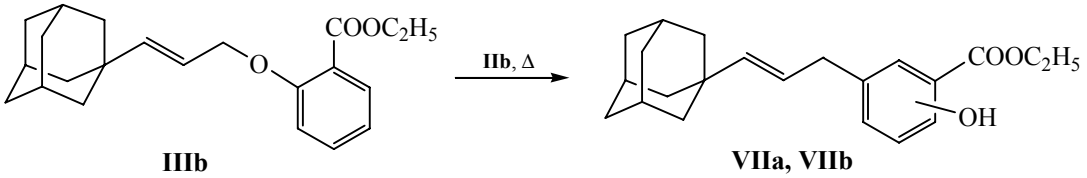
Heating of ethers **IIIa** and **IIIb** in diethylene glycol for 0.5 h resulted in the reallylation products, isomeric alcohols **VIa** and **VIb** in a ratio of 9 : 1 (by GC-MS).

Synthesis of long-chain adamantyloxyalkanols similar to **VIa** is of interest for their use as lipophilic modifiers when creating antiviral drugs [13, 14]. Thus, the data [14, 15] show a considerable influence of the aliphatic chain length and the presence of hinge oxygen atoms on the biological activity of nucleoside phosphonates (Scheme 3).

Heating of ether **IIIa** in diethylene glycol for 10 h gave rise to *ortho*- and *para*-substituted phenols **IVa** and **IVb** (2.5 : 1) as a result of thermal rearrangement, along with compounds **VIa** and **VIb**.

Thermal rearrangement of allyl ether **IIIb** in ethyl salicylate resulted in the products of *ortho*- and *para*-substitution **VIIa** and **VIIb** in a ratio of 1 : 1.2 (according to ^{1}H NMR spectra). The resulting mixture of isomers was separated by column chromatography on silica gel eluting with petroleum ether (Scheme 4).

Scheme 4.



IIIb **VIIa, VIIb**

Study of thermal transformations of allyl aryl ethers of adamantane series showed that the composition of the reaction products is significantly dependent on temperature, time, and nature of the solvent used. When a nucleophilic solvent was used, the reaction proceeded via formal substitution of phenoxy fragment with nucleophilic species prevailing in the reaction medium. The formation of *ortho*- and *para*-substituted phenols with retention of the allyl unit indicates the intermolecular reaction pathway.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra in $CDCl_3$ were recorded on a JEOL JNM ECX-400 instrument operating at 400 MHz. IR spectra (KBr) were registered on a Shimadzu IRAffinity-1 spectrometer. Mass spectra were obtained on a gas chromatograph-mass spectrometer Thermo Finnigan DSQ (capillary column BPX-5, 30 × 0.32, 70 eV). Elemental analysis was performed on an EuroVector EA-3000 EA elemental analyzer using L-cystine as a reference.

(*E*)-3-(Adamant-1-yl)-1-phenoxyprop-2-ene (IIIa). A mixture of 2.2 g (0.023 mol) of phenol, 5.6 g (0.022 mol) of bromide **I**, 3.2 g (0.023 mol) of potassium carbonate in 20 mL of acetone was refluxed for 3 h. The mixture was poured into water and extracted with toluene. The extract was washed with water and dried over sodium sulfate. Toluene was evaporated in a vacuum. Yield 4.95 g (85%), pale yellow oil. IR spectrum, ν, cm^{-1}: 3058, 3031 (CH_{Ar}), 2904, 2846 (CH_{Ad}), 1666 (C=C), 1450 (CH_2), 1380, 1299, 1238, 1218 (C–O–C), 1172, 1029, 968 (CH=CH, *trans*), 752 (CH_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.59–1.91 m (12H, CH_{2Ad}), 2.02–2.12 m (3H, CH_{Ad}), 4.55 d (2H, OCH_2, *J* 7.5), 5.62 d.t (1H, =C<u>H</u>CH$_2$, J_1 16.5, J_2 7.5), 5.75 d (1H, =CH, *J* 16.5), 6.94–7.06 m (3H, CH_{Ar}), 7.29–7.40 m (2H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 28.59, 34.88, 36.88, 42.02, 69.28, 114.81, 119.97, 120.60, 129.35, 146.12, 158.87. Mass spectrum, *m*/*z* (I_{rel}, %): 268 (6) $[M]^+$, 176 (14), 175 (100), 147 (5), 135 (17), 105 (16), 93 (27), 79 (23), 55 (12). Found, %: C 85.2; H 8.94. $C_{19}H_{24}O$. Calculated, %: C 85.03; H 9.01.

Ethyl 2-[(*E*)-3-(adamant-1-yl)prop-2-en-1-yloxy]-benzoate (IIIb) was prepared similarly. Yield 85%, colorless oil. IR spectrum, ν, cm^{-1}: 3024, 2977 (CH_{Ar}), 2900, 2846 (CH_{Ad}), 1731(C=O), 1600 (C=C), 1450 (CH_2), 1303, 1249 (C–O_{st}), 1080 (C–O–C), 968 (CH=CH, *trans*). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 t (3H, CH_3, *J* 7.3), 1.56–1.70 m (12H, CH_{2Ad}), 4.32 q (2H, C<u>H</u>$_2$-CH$_3$, *J* 7.3), 4.52 d (2H, =CHC<u>H</u>$_2$, *J* 5.5), 5.51 d.t (1H, =C<u>H</u>CH$_2$, J_1 16.0, J_2 5.5), 5.68 d (1H, =CH, *J* 16.0), 6.89–6.93 m (2H, CH_{Ar}), 7.33–7.38 m (1H, CH_{Ar}), 7.73–7.75 m (1H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 14.45, 28.45, 34.91, 36.89, 42.05, 60.78, 70.31, 114.02, 119.68, 120.24, 121.18, 131.56, 133.12, 145.84, 158.34, 166.56. Mass spectrum, *m*/*z* (I_{rel}, %): 340 (5) $[M]^+$, 296 (7), 205 (5), 175 (100), 147 (12), 135 (40), 119 (22), 93 (48), 91 (40), 79(37), 55 (16). Found, %: C 77.39; H 8.17. $C_{22}H_{28}O_3$. Calculated, %: C 77.61; H 8.29.

Reaction of (*E*)-1-(adamant-1-yl)-3-bromoprop-1-ene with sodium phenolate. To a mixture of 1.9 g (0.02 mol) of phenol and 0.8 g (0.033 mol) of sodium hydride in 30 mL of toluene was added 5 g (0.02 mol) of bromide **I** in 10 mL of toluene and the reaction mixture was refluxed for 2 h. Then the reaction mixture was poured into water, the organic layer was separated, and the aqueous layer was extracted with toluene. The extracts were combined, washed with water, and dried over sodium sulfate. The solvent was evaporated, and the resulting mixture of **IIIa** and **IVa** was separated by column chromatography on silica gel eluting with petroleum ether. **2-[(*E*)-3-(Adamant-1-yl)-prop-2-en-1-yl]phenol (IVa).** Yield 36%, white crystals, mp 54–56°C. IR spectrum, ν, cm^{-1}: 3282 (OH), 3035 (CH_{Ar}), 2896 (CH_{Ad}), 2846 (CH_{Ad}), 1593 (C=C), 1454 (CH_2), 1388, 1342, 1230 (C–O), 1176 (C–OH), 1095, 1041, 972 (CH=CH, *trans*), 748, 736 (CH_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53–1.86 m (12H, CH_{2Ad}), 1.92–2.11 m (3H, CH_{Ad}), 3.37 d (2H,

=CHC$\underline{H}_2$, *J* 8), 5.29 s (1H, OH), 5.48 d.t (1H, =C$\underline{H}$CH$_2$, J_1 16.0, J_2 8), 5.60 d (1H, =CH, *J* 16.0), 6.80–6.96 m (2H, CH_{Ar}), 7.06–7.22 m (2H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 28.51, 35.02, 35.10, 36.91, 42.35, 116.12, 120.79, 122.71, 125.88, 127.94, 130.26, 144.99, 154.91. Mass spectrum, *m*/*z* (I_{rel}, %): 268 (19) $[M]^+$, 135 (100), 107 (70), 93 (41), 91 (45), 79 (72), 77 (49), 53 (17). Found, %: C 85.2; H 8.94. $C_{19}H_{24}O$. Calculated, %: C 85.03; H 9.01.

2,6-Di[(*E*)-3-(adamant-1-yl)prop-2-en-1-yl]phenol (V) was prepared similarly under reflux for 15 h. The products mixture was separated by column chromatography eluting with petroleum ether. Yield 23%, white crystals, mp 106–108°C. IR spectrum, ν, cm^{-1}: 3471 (OH), 3031 (CH_{Ar}), 2900 (CH_{Ad}), 2846 (CH_{Ad}), 1658, 1589 (C=C), 1458 (CH_2), 1338, 1265, 1207 (C–O), 1103, 1041, 987, 972 (CH=CH, *trans*), 763, 744 (CH_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53–1.76 m (24H, CH_{2Ad}), 1.93–2.03 m (6H, CH_{Ad}), 3.40 d (4H, C$\underline{H}_2$CH=, *J* 5.5), 5.40 br. s (1H, OH), 5.44 d.t (2H, CH_2-C$\underline{H}$=, J_1 16.0, J_2 5.5), 5.51 d (2H, CH=, *J* 16.0), 6.80 t (1H, CH_{Ar}, *J* 7.3), 6.98 d (2H, CH_{Ar}, *J* 7.3). ^{13}C NMR spectrum, δ_C, ppm: 28.56, 34.60, 34.96, 36.97, 42.42, 120.31, 122.83, 126.78, 128.28, 144.34, 153.20. Mass spectrum, *m*/*z* (I_{rel}, %): 442 (5) $[M]^+$, 307 (5), 145 (2), 136 (10), 135 (100), 107 (9), 93 (13), 79 (11), 67 (4). Found, %: C 86.73; H 9.44. $C_{32}H_{42}O$. Calculated, %: C 86.82; H 9.56.

2-{2-[(*E*)-3-(Adamant-1-yl)prop-2-en-1-yloxy]-ethoxy}ethanol (VIa). A mixture of 0.007 mol of ether **IIIa** or **IIIb** and 20 mL of diethylene glycol was heated for 0.5 h, then poured into water and extracted with diethyl ether. The extract was washed with 40% aqueous sodium hydroxide solution, with water, and dried over sodium sulfate. The solvent was evaporated, and the product was purified by column chromatography on silica gel eluting with cyclohexane. Yield 57%, pale yellow oil. IR spectrum, ν, cm^{-1}: 3440 (OH), 2904 (CH_{Ad}), 2846 (CH_{Ad}), 1454 (CH_{2Ad}), 1346, 1118 (C–O), 1073, 972 (CH=CH, *trans*). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.55–1.71 m (12H, CH_{2Ad}), 1.95–2.05 m (3H, CH_{Ad}), 2.72 br. s (1H, OH), 3.55–3.76 m (8H, CH_2O), 3.97 d (2H, =CHC$\underline{H}_2$, *J* 6.4), 5.38 d.t (1H, =C$\underline{H}$CH$_2$, J_1 15.6, J_2 6.4), 5.54 d (1H, =CH, *J* 15.6). ^{13}C NMR spectrum, δ_C, ppm: 28.45, 34.86, 36.90, 42.13, 61.85, 69.08, 70.50, 72.61, 72.64, 120.76, 146.29. Mass spectrum, *m*/*z* (I_{rel}, %): 280 $[M]^+$ (1), 237 (2), 191 (5), 175 (11), 145 (3), 135 (100), 117 (9), 93 (15), 79 (14), 67 (7), 45 (34). Found, %: C 72.67; H 9.94. $C_{17}H_{28}O_3$. Calculated, %: C 72.82; H 10.06.

Thermolysis of ethyl 2-[(*E*)-3-(adamant-1-yl)-prop-2-en-1-yloxy]benzoate (IIIb). A mixture of 2 g (0.007 mol) of **IIIb** and 8 g (0.048 mol) of **IIb** was heated at 200°C for 2 h. Ethyl salicylate was distilled off in a vacuum at 110°C (10 mm Hg). A mixture of *o*- and *p*-isomers **VIIa** and **VIIb** was separated by column chromatography on silica gel eluting with petroleum ether. **Ethyl 3-[(*E*)-3-(adamant-1-yl)prop-2-en-1-yl]-2-hydroxybenzoate (VIIa).** Yield 30%, colorless oil. IR spectrum, ν, cm^{-1}: 3210 (OH), 3097, 2981 (CH_{Ar}), 2904, 2846 (CH_{Ad}), 1670 (C=O), 1612 (C=C), 1450 (CH_2), 1296, 1246 (C–O_{st}), 1087 (C–O–C), 972 (CH=CH, *trans*), 756. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 t (3H, CH_3, *J* 7.1), 1.61–1.79 m (12H, CH_{2Ad}), 1.98–2.06 m (3H, CH_{Ad}), 3.42 d (2H, =CHC$\underline{H}_2$, *J* 5.3), 4.42 q (2H, C$\underline{H}_2$CH$_3$, *J* 7.1), 5.45–5.55 m (2H, CH=CH), 6.84 t (1H, CH_{Ar}, *J* 7.6), 7.35 d.d (1H, CH_{Ar}, J_1 7.6, J_2 1.5), 7.76 d.d (1H, CH_{Ar}, J_1 7.6, J_2 1.5), 11.21 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 14.35, 28.73, 32.66, 34.92, 37.12, 42.61, 61.40, 112.05, 118.61, 122.29, 127.70, 129.95, 135.38, 143.91, 159.85, 170.77. Mass spectrum, *m*/*z* (I_{rel}, %): 340 $[M]^+$ (4), 295 (1), 165 (1), 135 (100), 107 (5), 93 (7), 79 (5). Found, %: C 77.39; H 8.17. $C_{22}H_{28}O_3$. Calculated, %: C 77.61; H 8.29.

Ethyl 5-[(*E*)-3-(adamant-1-yl)prop-2-en-1-yl]-2-hydroxybenzoate (VIIb). Yield 36%, colorless oil. IR spectrum, ν, cm^{-1}: 3197 (OH), 3024 (CH_{Ar}), 2904, 2850 (CH_{Ad}), 1681 (C=O), 1612 (C=C), 1450 (CH_2), 1292, 1253 (C–O_{st}), 1087 (C–O–C), 972 (CH=CH, *trans*), 794, 717. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 t (3H, CH_3, *J* 7.1), 1.56–1.75 m (12H, CH_{2Ad}), 1.94–2.03 m (3H, CH_{Ad}), 3.24 d (2H, =CHC$\underline{H}_2$, *J* 5.3), 4.39 q (2H, C$\underline{H}_2$CH$_3$, *J* 7.1), 5.32–5.43 m (2H, CH=CH), 6.90 d (1H, CH_{Ar}, *J* 8.5), 7.26 d.d (1H, CH_{Ar}, J_1 8.5, J_2 2.3), 7.63 d (1H, CH_{Ar}, *J* 2.3), 10.68 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 14.28, 28.60, 34.86, 37.00, 38.12, 42.53, 61.39, 112.24, 117.50, 123.41, 129.27, 131.92, 136.07, 143.95, 160.02, 170.33. Mass spectrum, *m*/*z* (I_{rel}, %): 340 $[M]^+$ (25), 295 (7), 204 (7), 192 (15), 179 (10), 161 (25), 147 (6), 135 (100), 105 (10), 93 (10), 79 (13). Found, %: C 77.68; H 8.36. $C_{22}H_{28}O_3$. Calculated, %: C 77.61; H 8.29.

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