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C- and O-Alkylation with α-Haloketones of the Adamantane Series

A. A. Danilin, P. P. Purygin, N. V. Makarova, M. N. Zemtsova, and I. K. Moiseev

Samara State University, Samara, Russia

Samara State Technical University, ul. Galaktionovskaya 141, Samara, 443010 Russia

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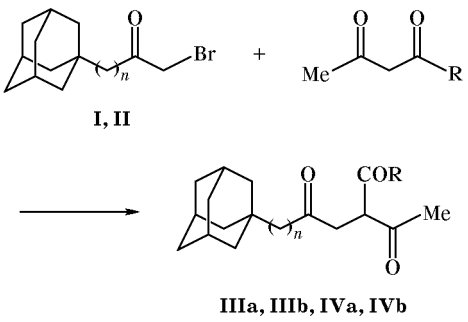
Abstract—Reactions of 1-adamantyl bromomethyl ketone and 1-(1-adamantyl)-3-bromo-2-propanone with acetylacetone and ethyl acetoacetate in a mixture of dry diethyl ether with anhydrous methanol in the presence of sodium methoxide afforded 3-(1-adamantylcarbonylmethyl)-2,4-pentanedione, ethyl 2-(1-adamantylcarbonylmethyl)-3-oxobutanoate, 4-acetyl-1-(1-adamantyl)-2,5-hexanedione, and ethyl 2-acetyl-5-(1-adamantyl)-4-oxopentanoate. The Knoevenagel–Cope reactions of 1-adamantyl bromomethyl ketone and 1-(1-adamantyl)-3-bromo-2-propanone with diethyl malonate yielded, respectively, diethyl 1-(1-adamantyl)-2-bromoethylidenemalonate and diethyl 1-(1-adamantylmethyl)-2-bromoethylidenemalonate. O-Alkylation of ethyl acetoacetate with 1-adamantyl bromomethyl ketone gave ethyl 3-(1-adamantylcarbonylmethoxy)-2-butenoate. Carboxylic acids reacted with 1-adamantyl bromomethyl ketone to form the corresponding 2-(1-adamantyl)-2-oxoethyl carboxylates.

α-Haloketones are widely used in organic synthesis as N-, C-, and O-alkylating agents for preparation of acyclic and heterocyclic compounds. We previously described [1] N-alkylation of amines with 1-adamantyl bromomethyl ketone (**I**), which resulted in formation of α-aminoketones of the adamantane series. The latter were then used for synthesis of a number of heterocyclic compounds [2–6]. C-Alkylation with the same reagent was reported only for ethoxymagnesium diethyl malonate [7]; as a result (after hydrolysis), β-(1-adamantylcarbonyl)propionic acid was obtained. O-Alkylation was studied in reactions with sodium or potassium methoxide, ethoxide, isopropoxide, and *tert*-butoxide as examples [8]. Here, according to GLC data, a mixture of products was isolated: 1-adamantyl hydroxymethyl ketone, its dimethyl acetal, 1-adamantyl methoxymethyl ketone, 1-adamantyl methyl ketone, and 1-adamantanecarboxylic acid.

In the present work we performed a more detailed study of C- and O-alkylation of acetylacetone, ethyl acetoacetate, diethyl malonate, and carboxylic acids with 1-adamantyl bromomethyl ketone (**I**) and homologous 1-(1-adamantyl)-3-bromo-2-propanone (**II**). The reactions of haloketones **I** and **II** with acetylacetone and ethyl acetoacetate were carried out in a mixture of dry diethyl ether with anhydrous methanol using sodium methoxide as base catalyst and in dry diethyl ether in the presence of metallic sodium (Scheme 1).

Scheme 1.



R = Me (**a**), OEt (**b**); **I**, **III**, *n* = 0; **II**, **IV**, *n* = 1.

The products were C-alkylated compounds: 3-(1-adamantylcarbonylmethyl)-2,4-pentanedione (**IIIa**), ethyl 2-(1-adamantylcarbonylmethyl)-3-oxobutanoate (**IVa**), 4-acetyl-1-(1-adamantyl)-2,5-hexanedione (**IIIb**), and ethyl 2-acetyl-5-(1-adamantyl)-4-oxopentanoate (**IVb**). The reaction times and yields, melting points, and analytical and spectral data of the products are collected in Table 1.

For the sake of comparison, haloketones **I** and **II** were brought into Knoevenagel reaction with diethyl

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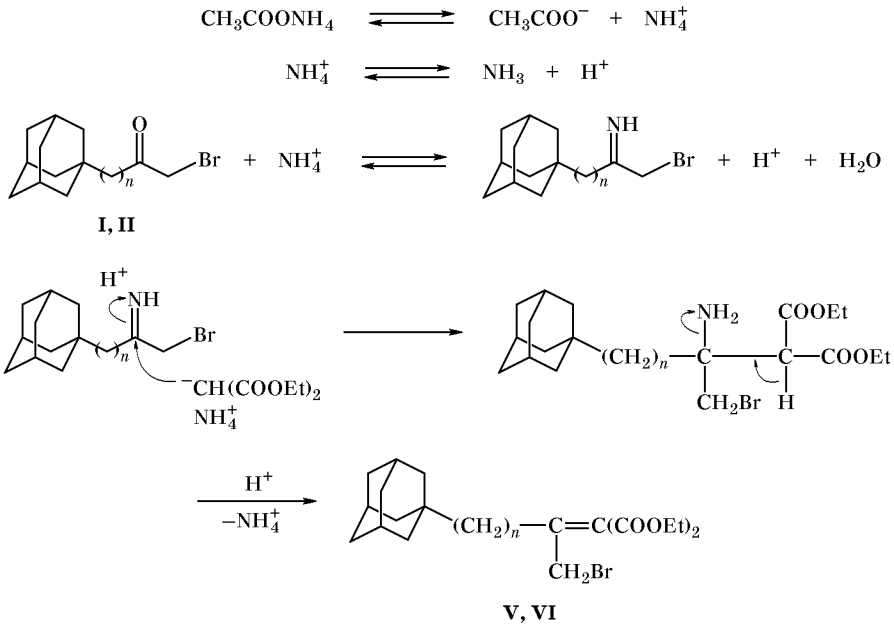
Scheme 2.



I, II

V, VI

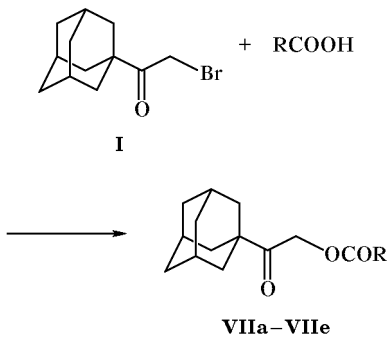
V, n = 0; **VI**, n = 1.

malonate. According to the data of Lehnert [9], the R substituent strongly affects the direction of this process and even the possibility for the Knoevenagel reaction to occur with α-haloketones. It was reported that the condensation of α-haloketones with diethyl malonate leads to formation of α,β-unsaturated dicarboxylic acid esters containing an allylic halogen atom in the γ-position. On the other hand, testosterone failed to react under the same conditions, the reaction with camphor was difficult, and the reactions with 1,2,3,4-tetrahydronaphthalen-1-one and acetophenone followed a different path. Taking into account structural similarity between haloketones **I** and **II** and those described in [10], we tried to effect C-alkylation according to Cope. The procedure is based on the use of catalytic amounts of acetic acid and ammonium acetate. In a number of cases it was found that in the Knoevenagel reactions amines act not only as base catalysts but directly react with carbonyl compounds in the initial stage of the process. Scheme 2 shows a possible mechanism of such reactions.

Table 2 contains yields, melting points, analytical data, and IR and ^{1}H NMR spectra of the resulting unsaturated diesters having an adamantane moiety: diethyl and 1-(1-adamantyl)-2-bromoethylidenemalonate (**V**) and diethyl 1-(1-adamantylmethyl)-2-bromoethylidenemalonate (**VI**).

As a next step, we examined reactions of α-bromoketone **I** with such O-nucleophiles as carboxylic acids, namely formic acid, acetic acid, furan-2-carboxylic acid, 1-adamantanecarboxylic acid, and 1-adamantylacetic acid. According to published data, reactions of α-haloketones with O-nucleophiles follow a conventional bimolecular nucleophilic substitution scheme. From the preparative viewpoint, these reactions are very important; they underlie synthesis of a number of heterocyclic structures, e.g., furan, benzofuran, and their hydrogenated analogs [11–14]. By reactions of **I** with the above carboxylic acids we obtained the corresponding 2-(1-adamantyl)-2-oxoethyl carboxylates **VIIa**–**VIIe** (Scheme 3). The reactions were carried out in acetone in the presence of triethylamine

Scheme 3.



I

VIIa–VIIe

R = H (**a**), Me (**b**), 2-furyl (**c**), 1-adamantyl (**d**), 1-adamantylmethyl (**e**).

Table 1. Yields, melting points, and analytical and spectral data of C-alkylated derivatives **IIIa**, **IIIb**, **IVa**, and **IVb**

Comp. no.	Yield, %	Reaction time, h	mp, °C	R_f[a]	Found, %		Formula	Calculated, %	
					C	H		C	H
IIIa	80	3.5	110–112 (from alcohol)	0.74	74.22	8.52	$C_{17}H_{24}O_3$	73.91	8.70
IVa	69	7.5	61–63 (from alcohol)	0.69	71.00	8.49	$C_{18}H_{26}O_4$	70.59	8.50
IIIb	90	2.5	96–98 (from alcohol)	0.65	74.62	9.14	$C_{18}H_{26}O_3$	74.48	8.97
IVb	73	5	84–87 (from alcohol)	0.46	70.95	9.10	$C_{19}H_{28}O_4$	71.25	8.75

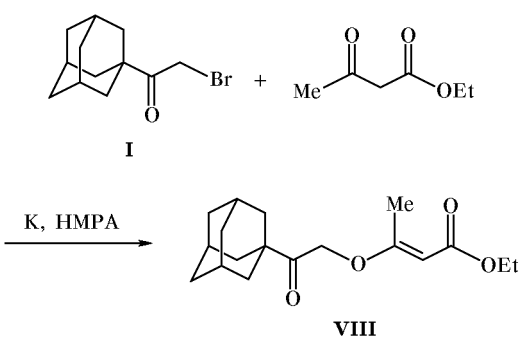
Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm
IIIa	1695, 1710, 1725 (C=O); 2800, 2920 (CH_2 adamantane)	1.75 d (12H, CH_2, adamantane), 1.95 s (3H, CH adamantane), 2.45 s (6H, CH_3), 2.85 d (2H, CH_2), 4.40 t (1H, CH)
IVa	1245 (C–O); 1700 (C=O); 1730 (C=O, ester); 2870, 3000 (CH_2, adamantane)	1.15 t (3H, $CH_2C\mathbf{H}_3$), 1.80 d (12H, CH_2, adamantane), 2.00 s (3H, CH, adamantane), 2.40 s (3H, CH_3), 2.90 d (2H, CH_2), 3.80 m (2H, $C\mathbf{H}_2CH_3$), 4.35 t (1H, CH)
IIIb	1690, 1700, 1715 (C=O); 2800, 2900, 2910 (CH_2, adamantane)	1.70 d (12H, CH_2, adamantane), 1.95 s (3H, CH, adamantane), 2.45 s (6H, CH_3), 2.80 s (2H, Ad$C\mathbf{H}_2$), 2.90 d (2H, CH_2), 4.35 t
IVb	1250 (C–O); 1710 (C=O); 1735 (C=O, ester); 2830, 2900 (CH_2, adamantane)	1.10 t (3H, $C\mathbf{H}_3CH_2$), 1.70 d (12H, CH_2, adamantane), 1.95 s (3H, CH, adamantane), 2.35 s (3H, CH_3), 2.60 s (2H, Ad$C\mathbf{H}_2$), 2.75 d (2H, CH_2), 3.85 m (2H, $C\mathbf{H}_2CH_3$), 4.10 t (1H, CH)

[a] Hexane–chloroform, 1:2.

as a base. Both triethylamine and the acid were taken in a large excess (6- and 9-fold, respectively). Excess acid was then removed by treatment with a 10% aqueous solution of sodium hydroxide. Compound **VIIb** was synthesized previously [15] in 84% yield by reaction of 1-diazo-2-(1-adamantyl)ethanone with acetic acid. Table 3 contains the yields, melting points, and analytical and spectral data of compounds **VIIa**–**VIIe**.

Our attempts to replace the bromine atom in 1-adamantyl bromomethyl ketone (**I**) [8] by hydroxy or alkoxy group using hydroxide or alkoxide ion were unsuccessful. Presumably, these nucleophiles reacted mainly at the carbonyl group and C–H bond rather than at the C–Br bond. As a result, complex mixtures of products were formed (see above). On the other hand, carboxylate ions reacted at the C–Br bond following mainly bimolecular nucleophilic substitution pattern, and the corresponding O-alkylation products were formed in fairly high yields.

Scheme 4.



O-Alkylation of ethyl acetoacetate with bromomethyl ketone **I** was performed in hexamethylphosphoramide in the presence of metallic potassium. We thus obtained ethyl 3-(1-adamantylcarbonylmethyl)-2-butenoate (**VIII**) in ~50% yield (Scheme 4).

Metallic potassium reacts with ethyl acetoacetate to give a chelate-like complex in which the metal ion coordinates to oxygen atoms of the enolate ion. Hexamethylphosphoramide is capable of strongly solvating potassium cations, whereas solvation of the enolate anion is insignificant, and the latter remains highly nucleophilic.

We can conclude that reactions of α-haloketones **I** and **II** with acetylacetone and ethyl acetoacetate in diethyl ether–methanol in the presence of sodium methoxide lead to formation of C-alkylation products, triketones **IIIa** and **IVa** and ethyl diketocarboxylates **IIIb** and **IVb**. The Knoevenagel–Cope reaction of diethyl malonate with ketones **I** and **II** yields

Table 2. Yields, melting points, and analytical and spectral data of Knoevenagel condensation products **V** and **VI**

Comp. no.	Yield, %	Reaction time, h	mp, °C	R_f[a]	Found, %		Formula	Calculated, %	
					C	H		C	H
V	82	5	125–127 (from alcohol)	0.75	57.82	7.07	$C_{19}H_{27}BrO_4$	57.14	6.77
VI	66	7	117–119 (from alcohol)	0.67	58.61	6.80	$C_{20}H_{29}BrO_4$	58.11	7.02

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm
V	650 (C−Br); 1300 (C−O); 1645 (C=C); 1720 (C=O); 2800, 2900, 2950 (CH_2, adamantane)	1.15 t (6H, C**H**$_3$CH$_2$), 1.70 d (12H, CH_2, adamantane), 1.90 s (3H, CH, adamantane), 3.80 s (2H, CH_2Br), 4.00 m (4H, C**H**$_2$CH$_3$)
VI	600 (C−Br); 1280 (C−O); 1645 (C=C); 1725 (C=O); 2850, 2900, 2930 (CH_2, adamantane)	1.15 t (6H, C**H**$_3$CH$_2$), 1.65 d (12H, CH_2, adamantane), 1.85 s (3H, CH, adamantane), 2.35 s (2H, AdCH_2), 3.85 s (2H, CH_2Br), 3.95 m (4H, C**H**$_2$CH$_3$)

[a] Hexane–chloroform, 1:2.

Table 3. Yields, melting points, and analytical and spectral data of compounds **VIIa**–**VIIe** and **VIII**

Comp. no.	Yield, %	mp, °C	R_f	Found, %		Formula	Calculated, %	
				C	H		C	H
VIIa	76	159–161	0.46[a]	70.30	8.25	$C_{13}H_{18}O_3$	70.24	8.16
VIIb	98	56–57[b]	0.25[a]	71.22	8.44	$C_{14}H_{20}O_3$	71.16	8.53
VIIc	63	112–113	0.58[c]	70.94	7.00	$C_{17}H_{20}O_4$	70.81	6.99
VIId	65	154–156	0.74[d]	77.61	8.85	$C_{23}H_{32}O_3$	77.49	9.05
VIIe	35	89–90	0.63[d]	77.80	9.36	$C_{24}H_{34}O_3$	77.80	9.25
VIII	50	80–83	0.37[a]	70.03	8.48	$C_{18}H_{26}O_4$	70.59	8.50

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm
VIIa	1720 (COO); 2850, 2900 (CH_2 adamantane)	
VIIb	1710 (COO); 2850, 2900 (CH_2 adamantane)	
VIIc	1730 (COO); 2850, 2900 (CH_2 adamantane)	1.70–1.75 d (12H, CH_2, adamantane), 1.90 s (3H, CH, adamantane), 5.10 s (CH_2O), 6.55 s (1H, 5-H, furan), 7.25 d (1H, 4-H, furan), 7.85 s (1H, 3-H, furan)
VIId	1740 (COO); 2850, 2900 (CH_2 adamantane)	1.65–1.75 m (24H, CH_2, adamantane), 1.85 s and 1.90 s (6H, CH, adamantane), 4.85 s (CH_2O)
VIIe	1730 (COO); 2850, 2900 (CH_2 adamantane)	1.65–1.75 m (24H, CH_2, adamantane), 1.95 s and 2.05 s (6H, CH, adamantane), 2.1 s (2H, CH_2), 4.80 s (CH_2O)
VIII	1200, 1270 (C–O); 1630 (C=C); 1730, 1765 (C=O); 2850, 2900 (CH_2 adamantane)	1.13 t (3H, C**H**$_3$CH$_2$), 1.75 d (12H, CH_2, adamantane), 1.95 s (3H, CH, adamantane), 2.10 s (3H, CH_3), 3.70 m (2H, C**H**$_2$CH$_3$), 4.30 s (2H, CH_2), 4.80 s (1H, CH)

[a] Acetone–CCl_4, 1:6. [b] Published data [9]: mp 57–59°C. [c] Acetone–CCl_4, 1:4. [d] Acetone–CCl_4, 1:8.

unsaturated diesters **V** and **VI**. O-Alkylation of carboxylic acids with α-haloketone **I** results in formation of 2-(1-adamantyl)-2-oxoethyl carboxylates **VII**, and ethyl acetoacetate reacts with ketone **I** in HMPA in the presence of metallic potassium to give ethyl 3-(1-adamantylcarbonylmethoxy)-2-butenoate (**VIII**).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-300 instrument (300.13 MHz) in DMSO-d_6 with HMDS as internal reference. The IR spectra were measured on a Specord M-80 spectrometer in KBr. The purity of the products was checked by TLC on Silufol UV-254 plates; the chromatograms were developed with iodine vapor.

3-(1-Adamantylcarbonylmethyl)-2,4-pentanedione (IIIa) and 4-acetyl-1-(1-adamantyl)-2,5-hexanedione (IVa). Metallic sodium, 3.9 mmol, was added in small pieces to a mixture of 15 ml of dry diethyl ether and 15 ml of anhydrous methanol, stirred at 20°C. The mixture was stirred for 15 min, and 3.9 mmol of acetylacetone was added dropwise with stirring over a period of 10–15 min. The mixture was stirred for 30 min at 20°C and for 2 h under reflux. It was then cooled to room temperature, a solution of 3.89 mmol of haloketone **I** or **II** in 20 ml of dry diethyl ether was added, and the mixture was stirred for 30 min at 20°C and for 30 min under reflux. The solvent was distilled off, the product was extracted into ether, the extract was washed with a small amount of water, dried over sodium sulfate, and evaporated, and the residue was recrystallized from ethanol.

Ethyl 2-(1-adamantylcarbonylmethyl)-3-oxobutanoate (IIIb) and ethyl 2-acetyl-5-(1-adamantyl)-4-oxopentanoate (IVb). Ethyl acetoacetate, 3.89 mmol, was added with stirring over a period of 30 min to a suspension of 3.9 mmol of metallic sodium in 40 ml of dry diethyl ether, and the mixture was heated for about 3 h until sodium dissolved completely. A solution of 3.89 mmol of haloketone **I** or **II** in 30 ml of dry diethyl ether was then added over a period of 40 min, the mixture was heated for 6–7 h, and 30 ml of water was added on cooling. The organic phase was separated, dried, and evaporated, and the crude product was recrystallized from a small amount of methanol.

Diethyl 1-(1-adamantyl)-2-bromoethylidenemalonate (V) and diethyl 1-(1-adamantylmethyl)-2-bromoethylidenemalonate (VI). A mixture of 0.5 mol of haloketone **I** or **II**, 0.5 mol of diethyl malonate, 0.05 mol of ammonium acetate, and 0.1 mol of glacial acetic acid in 150 ml of benzene was refluxed in a flask equipped with a Dean–Stark trap. When water no longer separated (after 2.5–6 h), the mixture was cooled to room temperature, and the benzene layer was washed with four small portions of a semisaturated solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was recrystallized from ethanol–diethyl ether (5:1).

2-(1-Adamanyl)-2-oxoethyl carboxylates VIIa–VIIe. A mixture of 0.5 g (1.9 mmol) of bromoketone **I**, 18 mmol of carboxylic acid, and 11 mmol of triethylamine in 10 ml of acetone was refluxed for 6–12 h. A colorless solid (triethylamine hydrobromide) separated during the process. The mixture was poured into water, and the precipitate was filtered off, washed with a 10% solution of sodium hydroxide, and recrystallized from hexane.

Ethyl 3-(1-adamantylcarbonylmethoxy)-2-butenoate (VIII). Metallic potassium, 1.15 g (3.9 mmol), was added with stirring to 20 ml of hexamethylphosphoramide. Ethyl acetoacetate was then added dropwise at 20°C. The mixture was stirred for 10 min at room temperature and for 10 h at about 100°C. It was then cooled to 20°C, and a solution of 1 g (3.89 mmol) of bromoketone **I** in 10 ml of HMPA was added with stirring over a period of 20 min. The mixture was stirred for 30 min at 20°C and for 5 h at 100°C, diluted with a tenfold amount of water, and extracted with ether (3×100 ml). The extracts were washed with water and dried over sodium sulfate. The solvent was distilled off to leave a yellow oily substance which crystallized on treatment with methanol.

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