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Synthesis and Reactivity of 3-R-1-Adamantyl Methyl Ketones

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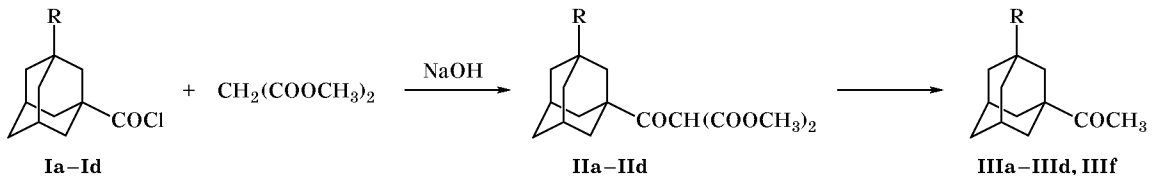
Abstract—A general procedure was proposed for synthesizing 3-R-1-adamantyl methyl ketones from the corresponding adamantanecarbonyl chlorides and dimethyl malonate in toluene (benzene) in the presence of sodium hydroxide. Intermediate dimethyl (3-R-1-adamantylcarbonyl)malonates can also be isolated. The resulting ketones were brought into reactions with hydroxylamine and formamide in the presence of formic acid to obtain the corresponding oximes and 1-(3-R-1-adamantyl)ethylamines. Dimethyl (3-R-1-adamantylcarbonyl)malonates reacted with phenylhydrazine to give adamantyl-substituted 4,5-dihydropyrazol-5-one derivatives.

We previously reported [1] on the synthesis of (3-hydroxy-1-adamantyl) methyl ketone by the action of dimethyl malonate and NaOH on 3-bromo- and 3-chloro-1-adamantanecarbonyl chlorides in toluene and subsequent hydrolysis. We also succeeded in isolating intermediate dimethyl (3-bromo- and 3-chloro-1-adamantylcarbonyl)malonates. With the goal of extending the above procedure to the synthesis of the other 3-R-1-adamantyl methyl ketones and revealing the dependence of the reaction direction on the dissociation constant of 1-adamantanecarboxylic acids, in the present work we studied the reactions of 3-chloro-, 3-ethyl-, 3-phenyl-, and 3-amino-1-adamantanecarbonyl chlorides **Ia**–**Id** and also of 1-adamantylacetyl chloride (**Ie**) with dimethyl malonate in toluene (benzene) in the presence of sodium hydroxide (Scheme 1). As a result, we isolated dimethyl (3-R-1-adamantylcarbonyl)malonates **IIa**–**IId** which were characterized by IR and ^{1}H NMR spectroscopy. The reaction with (1-adamantyl)acetyl chloride failed to occur, and the only isolated product was (1-adamantyl)acetic acid. The applicability of sodium hydroxide for the synthesis of ketones from acyl chlorides and dialkyl malonates is limited because of possible hydrolysis of the initial acyl chloride. Comparison of the dissociation constants of 3-substituted 1-adamantanecarboxylic acids ($pK_a \times 10^7$: 3-Cl-1-AdCOOH, 7.13; 3-Br-1-AdCOOH, 6.46; 3-HO-1-AdCOOH, 4.86; 3-Ph-1-AdCOOH, 1.71) [2] with those of aliphatic and aromatic acids [$pK_a \times 10^5$: PhCOOH, 6.6; $CH_3(CH_2)_5COOH$, 1.28; CH_3COOH, 1.75] [3] led us to presume that just the difference in the acidity is the main factor determining different behavior of acids **Ia**–**Id** and **Ie** in the above reaction.

Hydrolysis of ketodiesters **IIb**–**IId** in a mixture of acetic acid with water and sulfuric acid (CH_3COOH–H_2O–H_2SO_4 ratio 10 : 3 : 1) afforded the corresponding 3-R-1-adamantyl methyl ketones **IIIb**–**IIId**. The hydrolysis of compound **IIa** in 6 h gave 3-hydroxy-1-adamantyl methyl ketone (**IIIf**). By shortening of

Scheme 1.



Ia–Id **IIa–IId** **IIIa–IIId, IIIf**

R = Cl (**a**), C_2H_5 (**b**), C_6H_5 (**c**), NH_2 (**d**), OH (**f**).

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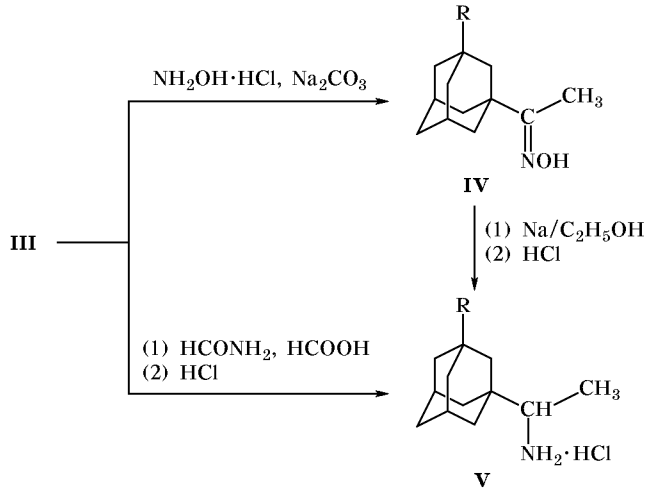
the hydrolysis time to 1 h we succeeded in isolating 66% of 3-chloro-1-adamantyl methyl ketone (**IIIa**). In addition, 4% of ketone **IIIf** was isolated by fractional recrystallization.

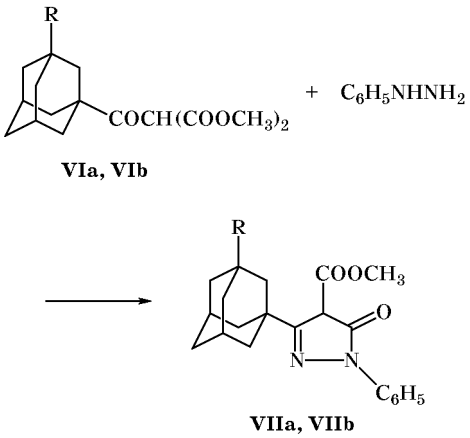
Ketones **IIIa**–**IIIc** and **IIIf** reacted with hydroxylamine hydrochloride in 50% aqueous alcohol in the presence of Na_2CO_3 to give oximes **IVa**–**IVc** and **IVf** in high yields. The reduction of **IVa**–**IVc** and **IVf** with metallic sodium in boiling anhydrous ethanol, followed by treatment with gaseous hydrogen chloride afforded 20–29% of amine hydrochlorides **Va**–**Vc** and **Vf** (Scheme 2). The same products (compounds **Va**, **Vb**, and **Vf**) were obtained in 15–32% yield by direct reductive amination of ketones **IIIa**, **IIIb**, and **IIIf** with formamide in the presence of formic acid and subsequent treatment with gaseous HCl (Scheme 2).

Scheme 2.



We also examined the possibility of using previously synthesized ketodiesters of the adamantane series [1] to prepare heterocyclic compounds. For this purpose, dimethyl (1-adamantylcarbonyl)malonate (**VIa**) and dimethyl (3-bromo-1-adamantylcarbonyl)-malonate (**VIb**) were treated with phenylhydrazine in acetic acid at room temperature. The reaction yielded methyl 3-(3-R-1-adamantyl)-1-phenyl-5-oxo-4,5-dihydropyrazole-4-carboxylates **VIIa** and **VIIb**, respectively (Scheme 3).

Scheme 3.



R = H (**a**), Br (**b**).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer (300.13 MHz) in DMSO using HMDS as internal reference. The IR spectra were measured on a Specord M-80 instrument in KBr. The purity of the products was checked by TLC on Silufol UV-254 plates. Tables 1 and 2 contain yields, physical properties, and spectral parameters of the prepared adamantyl ketones and their derivatives.

Dimethyl (3-R-1-adamantylcarbonyl)malonates IIa–IId. A mixture of 1.08 g (27 mmol) of sodium hydroxide, 12 ml of toluene (or benzene), and 2.5 ml (21.6 mmol) of dimethyl malonate was vigorously stirred for 30–40 min at 25°C, and a solution of 10.8 mmol of 1-adamantylcarbonyl chloride **Ia**–**Id** in 12 ml of toluene (or benzene) was added to the resulting suspension. The mixture was stirred for 1 h at room temperature and was poured into 50 ml of 10% sulfuric acid. The organic phase was separated, washed with 2×50 ml of water, 50 ml of a 10% solution of sodium carbonate, and again with 2×50 ml of water, dried, and distilled under reduced pressure. Dimethyl malonate **IIc** was a thick oily material which decomposed on distillation in high vacuum. Crystalline products **IIa**, **IIb**, and **IId** were recrystallized from alcohol.

3-R-1-Adamantyl methyl ketones IIIa–IIId and IIIf. A mixture of 6.1 mmol of ketodiester **II**, 20 ml of acetic acid, 6 ml of water, and 2 ml of concentrated sulfuric acid was refluxed for 2–4 h. It was then cooled and poured into ice water. Ketones **IIIa** and **IIId** were filtered off and recrystallized from hexane. Products **IIIb**, **IIIc**, and **IIIf** were isolated by extraction with chloroform. Compounds **IIIb** and **IIIc** were purified by vacuum distillation.

3-R-1-Adamantyl methyl ketone oximes IVa–IVc and IVf. A solution of 0.77 g (11 mmol) of hydroxylamine hydrochloride and 0.53 g (5 mmol) of sodium carbonate in 5 ml of water was added to a solution of 10 mmol of ketone **III** in 15 ml of ethanol. The

Table 1. Yields, melting points, TLC data, and IR spectra of compounds **II**–**V** and **VII**

Comp. no.	Yield, %	mp, °C	R_f (eluent)	IR spectrum, ν, cm^{-1}
IIb	67	49–51	0.86 (CCl_4–Me_2CO, 6:1)	2920, 2860 (CH_2, Ad); 1750, 1720 ($COOCH_3$, C=O)
IIc	60	[a]	0.33 (hexane–Me_2CO, 3:1)	2920, 2860 (CH_2, Ad); 1750, 1720 ($COOCH_3$, C=O)
IId	41	74–76	0.25 (CCl_4)	3450 (NH_2); 2920, 2860 (CH_2, Ad); 1765, 1720 ($COOCH_3$, C=O)
IIIa	66	53–55	0.74 (CCl_4–Me_2CO, 6:1)	2920, 2860 (CH_2, Ad); 1710 (C=O)
IIIb	51	[b]	0.60 (CCl_4)	2920, 2860 (CH_2, Ad); 1720 (C=O)
IIIc	62	[c]	0.42 (CCl_4)	2920, 2860 (CH_2, Ad); 1720 (C=O)
IIId	64	101–103	0.55 (CCl_4–Me_2CO, 6:1)	3450 (NH_2); 2920, 2860 (CH_2, Ad); 1710 (C=O)
IVa	84	154–156	0.53 (CCl_4–Me_2CO, 6:1)	3250 (OH); 2910, 2860 (CH_2, Ad); 1665 (C=N)
IVb	84	133–134	0.91 (CCl_4–Me_2CO, 6:1)	3260 (OH); 2920, 2850 (CH_2, Ad); 1660 (C=N)
IVc	81	148–149.5	0.48 (CCl_4)	3220 (OH); 2920, 2860 (CH_2, Ad); 1670 (C=N)
IVf	60	179.5–181.5	0.20 (CCl_4–Me_2CO, 2:1)	3300 (OH); 2900, 2850 (CH_2, Ad); 1620 (C=N)
Va	15	296–297 (decomp.)	–	3000 (NH_3^+); 2910, 2860 (CH_2, Ad)
Vb	20	233–235	–	3020 (NH_3^+); 2920, 2860 (CH_2, Ad)
Vc	21	242–244	–	3000 (NH_3^+); 2920, 2860 (CH_2, Ad)
Vf	32	300–301 (decomp.)	–	3280 (OH); 3000 (NH_3^+); 2920, 2860 (CH_2, Ad)
VIIa	82	128–130	0.48 (CCl_4–Me_2CO, 2:1)	2910, 2860 (CH_2, Ad); 1765, 1750 ($COOCH_3$, C=O); 1650 (C=N)
VIIb	51	65–67	0.76 (Me_2CO)	2900, 2850 (CH_2, Ad), 1730, 1720 ($COOCH_3$, C=O); 1620 (C=N)

[a] Decomposes on attempted distillation.
[b] bp 101–109°C (2 mm); n_D^{20} 1.4996.
[c] bp 112–119°C (2 mm); n_D^{25} 1.5606.

mixture was stirred for 1 h, and the precipitate was filtered off and recrystallized from alcohol.

1-(3-R-1-Adamantyl)ethylamine hydrochlorides Va–Vc and Vf. *a.* A mixture of 10 mmol of ketone **III**, 2 ml (50 mmol) of formamide, and 4 ml (100 mmol) of formic acid was refluxed for 3 h. It was then cooled, 20 ml of 20% hydrochloric acid was added, and the mixture was refluxed for 2 h, cooled, and made alkaline (pH 11–12). The products were extracted into diethyl ether, the extract was dried over potassium carbonate and saturated with hydrogen chloride. The precipitate was filtered off, washed with anhydrous acetone, and recrystallized from ethanol.

b. A solution of 2.2 mmol of oxime **IV** in 25 ml of anhydrous alcohol was heated to the boiling point, 2.6 g (11.3 mmol) of metallic sodium was slowly added through the reflux condenser, and the mixture was heated until it became homogeneous. Water, 25 ml, was added, the solvent was distilled off under reduced pressure, and the residue was extracted with ether. The extract was dried over potassium hydroxide and saturated with hydrogen chloride. The precipitate

Table 2. ^{1}H NMR spectra (δ, ppm) of compounds **II**–**V** and **VII**

Comp. no.	CH_2, CH (Ad)	Other protons
IIb	1.40–2.05 m (14H)	0.78 t (3H, $CH_2C\mathbf{H}_3$), 1.12 q (2H, $C\mathbf{H}_2CH_3$), 3.68 s (6H, $2CH_3OOC$), 5.48 s (1H, CH)
IIc	1.85–2.06 m (14H)	3.65 s (6H, $2CH_3OOC$), 5.24 s (1H, CH), 7.17–7.30 m (5H, C_6H_5)
IId	1.65–2.06 m (14H)	3.15 br.s (2H, NH_2), 3.66 s (6H, $2CH_3OOC$), 5.22 s (1H, CH)
IIIa	1.65–2.02 m (14H)	2.17 s (3H, CH_3CO)
IIIb	1.38–1.95 m (14H)	0.75 t (3H, $CH_2C\mathbf{H}_3$), 1.07 q (2H, $C\mathbf{H}_2CH_3$), 2.10 s (3H, CH_3CO)
IIIc	1.80–2.02 m (14H)	2.15 s (3H, CH_3CO), 7.20–7.30 m (5H, C_6H_5)
IIId	1.64–2.02 m (14H)	2.16 s (3H, CH_3CO), 3.24 br.s (2H, NH_2)
IVa	1.65–2.01 m (14H)	2.15 s (3H, CH_3CO), 9.50 s (1H, NOH)
IVb	1.37–1.95 m (14H)	0.79 t (3H, $CH_2C\mathbf{H}_3$), 1.09 q (2H, $C\mathbf{H}_2CH_3$), 2.10 s (3H, CH_3CO), 9.30 s (1H, NOH)
IVc	1.73–2.00 m (14H)	2.11 s (3H, CH_3), 7.15–7.30 m (5H, C_6H_5), 9.38 s (1H, NOH)
IVf	1.53–1.68 m (14H)	2.12 s (3H, CH_3CO), 4.38 s (1H, OH), 12.50 s (1H, NOH)
Va	1.50–2.05 m (14H)	1.18 d (3H, CH_3), 2.84 m (1H, CH), 8.05 br.s (2H, NH_2)
Vb	1.65–2.10 m (14H)	0.80 t (3H, $CH_2C\mathbf{H}_3$), 1.15 d (3H, CH_3), 1.35 q (2H, $C\mathbf{H}_2CH_3$), 2.95 m (1H, CH), 8.3 br.s (2H, NH_2)
Vc	1.50–2.10 m (14H)	1.40 d (3H, CH_3), 2.80 m (1H, CH), 4.35 s (1H, OH), 8.12 br.s (2H, NH_2)
VIIa	1.65–2.00 m (15H)	2.25 s (3H, CH_3OOC), 4.85 s (1H, CH, pyrazole), 6.80–7.50 m (5H, C_6H_5)
VIIb	1.60–1.95 m (14H)	2.15 s (3H, CH_3OOC), 4.62 s (1H, CH, pyrazole), 6.75–7.40 m (5H, C_6H_5)

was filtered off, washed with anhydrous acetone, dried, and recrystallized from ethanol.

Methyl 3-(3-R-1-adamantyl)-5-oxo-1-phenyl-4,5-dihydropyrazole-4-carboxylates VIIa and VIIb. A mixture of 1.7 mmol of ketodiester **VIa** or **VIb**, 1.7 mmol of phenylhydrazine, and 5 ml of glacial acetic acid was stirred for 54 h at room temperature. The precipitate of compound **VIIa** or **VIIb** was filtered off and recrystallized from alcohol.

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