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Synthesis of Unsaturated Ketones from 3-Hydroxy-1-adamantyl Methyl Ketone

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Abstract—The Claisen–Schmidt reaction between 3-hydroxy-1-adamantyl methyl ketone and aromatic aldehydes (benzaldehyde and 2-thiophenecarbaldehyde) in 2-propanol catalyzed by 50% aqueous potassium hydroxide affords 1-(3-hydroxy-1-adamantyl)-3-R-2-propen-1-ones. The reaction of 3-hydroxy-1-adamantyl methyl ketone with ethyl formate and sodium in benzene gives rise to sodium enolate of 1-(3-hydroxy-1-adamantyl)-3-hydroxy-2-propen-1-one. The latter compound treated with amine hydrochlorides in 50% aqueous alcohol furnishes 1-(3-hydroxy-1-adamantyl)-3-NRR'-amino-2-propen-1-ones.

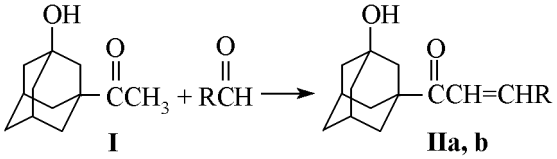
Vinyl ketones and aminovinyl ketones are extensively used in organic synthesis for preparation of linear [1, 2] and heterocyclic [3, 4] compounds. In the literature [5, 6] only syntheses of vinyl ketones and aminovinyl ketones were described proceeding from 1-adamantyl methyl ketone. Yet it is known that introduction of a substituent in the position *3* of adamantane core results in modified biological activity of some heteryladamantanes.

We attempted to introduce a hydroxy group into the molecules of 1-(1-adamantyl)-3-NRR'-amino-2-propen-1-ones whose synthesis had been formerly described [6] by nitration of hydrochlorides of these compounds with nitric acid or its mixtures with acetic acid or acetic anhydride at 0–25°C with subsequent hydrolysis. However we obtained there only the nitrates of enaminoketones, which on treatment with sodium hydroxide recovered the initial bases.

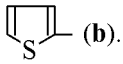
In extension of our investigations [6, 8–10] on the synthesis and chemical properties of adamantane carbonyl derivatives as possible initial compounds for preparation of heterocyclic compounds we carried out the Claisen–Schmidt reaction and performed a synthesis of β-aminovinyl ketones starting with 3-hydroxy-1-adamantyl methyl ketone (**I**). We earlier developed a simple and convenient method of its synthesis [11].

The Claisen–Schmidt reaction between ketone **I** and aromatic aldehydes (benzaldehyde and 2-thiophenecarbaldehyde) in 2-propanol catalyzed by 50% aqueous potassium hydroxide affords 1-(3-hydroxy-1-adamantyl)-3-R-2-propen-1-ones (**II**) (Table 1).

The qualitative comparison of behavior of 1-adamantyl methyl ketone and that of hydroxyketone

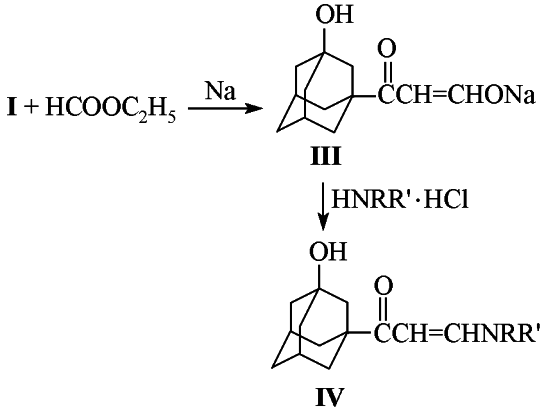


I **IIa, b**

R = CH (**a**),  (**b**).

I shows that the introduction of the hydroxy group in *3* position of the adamantyl core reduces the ketone reactivity. We failed to obtain adamantyl-substituted chalcone analogs under conditions used in [5]. This fact is hardly due to the inductive effect of the hydroxy substituent. We presume that this fact is an additional evidence of the existence of a "cage effect" (electrons delocalization within the adamantane skeleton) [12].

The reaction of 3-hydroxy-1-adamantyl methyl ketone with ethyl formate and sodium in benzene



R = R'= H (**a**), R = H, R' = 1-adamantyl (**b**); R = H, R' = C_6H_5 (**c**); NRR' = piperidino (**d**).

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Table 1. Physical characteristics of chalcones **II** and enaminoketones **IV**

Compd. no.	Yield %	mp, °C	R_f	IR spectrum, ν, CM			Found			Formula	Calcd., %		
				CH_2Ad	C(=O)	NH H OH	C	H	N		C	H	N
II	67	122–123	–	2910, 2860	1695	3300	–	–	–	–	–	–	–
IIb	72	85–86	–	2900, 2850	1680	3300	–		–	–	–	–	–
IVa	46	46–48	0.35[a]	2900, 2850	1650	3200	70.60	8.57	6.25	$C_{13}H_{19}N0_2$	70.61	8.65	6.33
IVb	45	213–214	0.606	2900, 2850	1650	3200	77.81	9.30	4.00	$C_{23}H_{33}NO_2$	77.70	9.36	3.94
IVc	53	143–145	0.616	2910, 2860	1670	3220	76.75	7.84	4.68	$C_{19}H_{23}N_{02}$	76.78	7.80	4.71
IVd	56	133–134	0.296	2900, 2850	1640	3400	74.70	9.53	4.79	$C_{18}H_{27}N_{02}$	74.70	9.40	4.84

[a] Acetone – CC14, 1 : 12; [b] acetone.

Table 2. ^{1}H NMR spectra of chalcones **II** and enaminoketones **IV**, δ, ppm

Compd. no.	CH_2Ad	CHAd	C(=O) CH=	=CHR or =CHN	OH	Other protons
IIa	1.73 d (12H)	2.16 s (2H)	6.98 d (1H, *J* 12.4 Hz)	7.33 d (1H)	9.00 s (1H)	7.42-7.65 m (5H, C_6H_5)
IIb	1.69 d (12H)	2.19 s (2H)	6.92 d (1H, *J* 14.6 Hz)	7.10 d (1H)	9.25 s (1H)	7.46-7.80 m (3H, Thienyl)
IVa	1.60-1.65 d (12H)	1.90 s (2H)	5.55 d (1H, J_{cis} 7 Hz), 6.25 d (1H, J_{trans} 20 Hz)	6.80 q (1H, *cis*-), 7.35 q (1H, *trans)*	9.75 s (1H)	13.15 d (2H, NH2, *J* 14 Hz)
IVb	1.60-1.65 d (24H)	1.85 s (5H)	5.05 d (1H, J_{cis} 8 Hz), 5.39 d (1H, J_{trans} 17 Hz)	7.00 t (1H, *cis*-), 7.48 t (1H, *trans*)	10.20 s (1H)	10.20 d (1H, NH, *J* 16 Hz)
IVc	1.60-1.65 d (12H)	2.00 s (2H)	5.40 d (1H, J_{cis} 8 Hz), 5.85 d (1H, J_{trans} 19 Hz)	7.10 t (1H, *cis*-), 7.88 t (1H, *trans*)	9.55 s (1H) (1H, NH, *J* 16 Hz)	7.20-7.90 m (5H, C_6H_5), 11.75
IVd	1.65-1.75 d (12H)	2.00 s (2H)	5.25 d (1H, *J* 15 Hz),	7.35 d (1H)	9.65 s (1H)	1.40 m (2H, *n*-CH_2, piperidyl), 1.50 m (4H, 2 *m*-CH_2, piperidyl), 2.45 m (4H, 2 *o*-CH_2, *piperidyl)*

afforded sodium enolate of 1-(3-hydroxy-1-adamantyl)-3-hydroxy-2-propen-1-one (**III**). The latter compound treated with amine hydrochlorides in 50% aqueous alcohol furnished 1-(3-hydroxy-1-adamantyl)-3-NRR'-amino-2-propen-1-ones (**IV**).

It is known [2] that the coupling constant of protons at the double bond of N-monosubstituted enaminoketones in cis-isomers amounts to 5–12 Hz, in *trans*-isomers to 13–20Hz, and the N-disubstituted enaminoketones exist nearly exclusively as *trans*-isomers. As seen from Table 2, the synthesized enaminoketones **IVa–c** are mixtures of *cis*-isomers (*J* 7–8 Hz) with *trans*-isomers (*J* 17–20 Hz) with prevalence of the former. The ratio *cis/trans* as evaluated by integral intensity of the signals is equal to 8 : 1 (**IV`**), 21 : 1 (**IVb**), 5 : 1 (**IVc**). Compound **IVd** exists in *trans*-form as indicates the coupling constant of the double bond protons equal to 15 Hz.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker AC-300 (300.13 MHz) and Bruker DS-80 in DMSO and $(CD_3)_2CO$, internal reference HMDS. IR spectra were recorded on spectrophotometer Specord M-80 from KBr pellets. The purity of compounds was tested with TLC on Silufol UV-254 plates, development in iodine vapor.

1-(3-Hydroxy-1-adamantyl)-3-R-2-propen-1-ones (II). In a minimal amount of 2-propanol was dissolved 10 mmol of ketone **I**, 12 mmol of an appropriate freshly distilled aldehyde, and 10 mmol of KOH. The mixture was kept at room temperature for 0.5 h, then diluted with water, the reaction products were extracted into chloroform, the extract was washed with 10% water solution of HCl, then with water till neutral, and dried with calcium chloride. The solvent was distilled off, and the residue was recrystallized from hexane–acetone mixture (1 : 1.5).

Sodium enolate of 1-(3-hydroxy-1-adamantyl)-3-hydroxy-2-propen-1-one (III). In 10 ml of anhydrous benzene was dispersed 0.07 g (2.8 mmol) of sodium at cooling to 0–5°C. To the dispersion was added dropwise at stirring 0.25 ml (3.1 mmol) of ethyl formate, and the mixture was left standing for 30 min. Then at stirring and cooling was added dropwise a solution of 0.25 g (1.3 mmol) of ketone **I** in 10 ml of benzene, the stirring was carried on for 4 h. The separated precipitate was filtered off and washed with cold acetone. Yield 0.29 g (98%), mp 275°C (decomp). IR spectrum (ν, cm^{-1}): 3420 (OÆ), 2910, 2860 (CÆ$_2$ of adamantane), 1620 (C=O).

1-(3-Hydroxy-1-adamantyl)-3-NRR'-amino-2-propen-1-ones (IV). In 15 ml of 50% ethanol was boiled 1 g (4.1 mmol) of freshly prepared sodium enolate **III**, and 4.1 mmol of amine hydrochloride for 4 h. The separated residue was filtered off and recrystallized from ethanol.

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