Chemistry of Heterocyclic Compounds, Vol. 37, No. 7, 2001

SYNTHESES OF HETEROCYCLES FROM THE SODIUM SALTS OF 3-(1-ADAMANTYL)-1-HYDROXY-1-PROPEN-3-ONE AND 4-(1-ADAMANTYL)-1-HYDROXY-1-BUTEN-3-ONE

N. V. Makarova, M. N. Zemtsova, and I. K. Moiseev

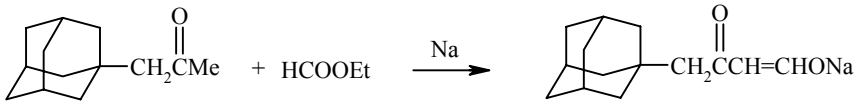
The interaction of the sodium salts of 3-(1-adamantyl)-1-hydroxy-1-propen-3-one and 4-(1-adamantyl)-1-hydroxy-1-buten-3-one with hydroxylamine, hydrazine, and guanidine leads to the synthesis of 5-(1-adamantyl)-5-hydroxy- and 5-(1-adamantylmethyl)-5-hydroxy-Δ^2-isoxazolines, 3-(1-adamantyl)- and 3-(1-adamantylmethyl)pyrazoles, 3-(1-adamantyl)-2-phenylpyrazole, and 4-(1-adamantyl)-2-amino- and 4-(1-adamantylmethyl)-2-aminopyrimidines.

Keywords: (1-adamantyl)acetone, 2-aminopyrimidines, 5-hydroxy-Δ^2-isoxazolines, 3-(1-adamantyl)-1-hydroxy-1-propen-3-one sodium salt, 4-(1-adamantyl)-1-hydroxy-1-buten-3-one sodium salt, pyrazoles, cyclization.

Scores of heterocyclic compounds from simple four-membered rings to the most complex condensed heterocyclic systems have been obtained from β-chloro- and β-aminovinyl ketones. The sodium salts of 3-R-1-hydroxy-1-propen-3-ones are infrequently used in syntheses of heterocycles [1-3]. For example, syntheses of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines [1], furans [2], and 2-pyridones [3] have been described.

The sodium salt of 3-(1-adamantyl)-1-hydroxy-1-propen-3-one (**1**) has been used successfully in the synthesis of 6-(1-adamantyl)-3-cyano-2(1H)-pyridinones, thiones, and selenones [4-8]. This reaction has also been extended to aromatic [9] and unsaturated [10] compounds. The sodium salt **1** was obtained by the interaction of methyl (1-adamantyl) ketone with ethyl formate and sodium in ether [5,6].

Based on this reaction we have synthesized the sodium salt of 4-(1-adamantyl)-1-hydroxy-1-buten-3-one (**3**) from (1-adamantyl)acetone (**2**). Compound **3** is unstable, decomposing in the air in a few days and has a high melting point.



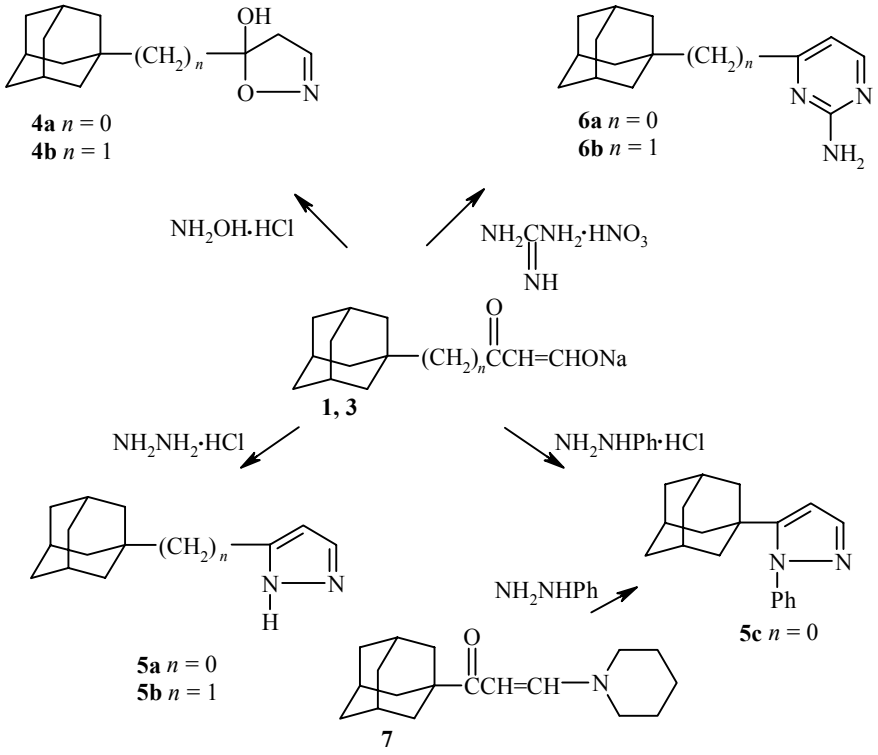
2 **3**

In a continuation of studies on the synthesis of adamantane-containing heterocycles [11,12], the reaction of sodium salts **1** and **3** with the hydrochlorides of hydroxylamine, hydrazine, and phenylhydrazine, and guanidine nitrate by boiling in 50% aqueous ethanol gave 5-(1-adamantyl)-5-hydroxy- (**4a**) and

Samara State Technical University, Samara 443100, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 912-915, July, 2001. Original article submitted August 2, 1999.

 0009-3122/01/3707-0840$25.00

5-(1-adamantylmethyl)-5-hydroxy-Δ^2-isoxazolines (**4b**), 5-(1-adamantyl)- (**5a**) and 5-(1-adamantylmethyl)-pyrazoles (**5b**), 5-(1-adamantyl)-1-phenylpyrazole (**5c**), and 4-(1-adamantyl)-2-amino- (**6a**) and 4-(1-adamantylmethyl)-2-aminopyrimidines (**6b**).



In addition, pyrazole **5c** was obtained from 3-(1-adamantyl)-1-piperidino-1-propen-3-one (**7**) and phenylhydrazine by boiling in acetic acid. The β-aminovinyl ketone **7** was obtained by the reaction of salt **1** with piperidine hydrochloride. The physicochemical characteristics of the synthesized compounds and data of their IR and ^{1}H NMR spectra are given in Tables 1 and 2.

TABLE 1. Physicochemical Characteristics of the Synthesized Heterocycles

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
4a	$C_{13}H_{19}NO_2$	70.61 / 70.56	8.65 / 8.65	6.30 / 6.33	160-162	0.79[a]	41
4b	$C_{14}H_{21}NO_2$	71.50 / 71.46	9.00 / 8.99	6.00 / 5.95	88-89	0.48[a]	42
5a	$C_{13}H_{18}N_2$	77.13 / 77.18	9.00 / 8.97	13.80 / 13.85	128-129	0.86[b]	77
5b	$C_{14}H_{20}N_2$	77.60 / 77.73	9.21 / 9.32	12.93 / 12.95	184-186	0.37[a]	72
5c	$C_{19}H_{22}N_2$	82.00 / 81.97	7.91 / 7.97	10.16 / 10.06	130-132	0.54[c]	59
6a	$C_{14}H_{19}N_3$	73.35 / 73.32	8.40 / 8.35	18.25 / 18.32	45-47	0.70[b]	50
6b	$C_{15}H_{21}N_3$	74.00 / 74.03	8.68 / 8.70	17.20 / 17.27	190-192	0.74[a]	70

* Eluent acetone–CCl_4: a) 1:4; b) 1:2; c) 1:6.

TABLE 2. IR and ^{1}H NMR Spectra of the Synthesized Heterocycles

Compound	IR spectra, ν, cm^{-1}				^{1}H NMR, δ, ppm				
	C=N	$CH_{2\ Ad}$	OH	NH/ NH_2	$6CH_{2\ Ad}$ (12H)	$3CH_{Ad}$ (3H)	$AdCH_2$ (2H)	H_{Het}	other protons
4a	1620	2850, 2900	3330	—	1.70, d	2.00, s	—	3.45 (2H, d, CH_2), 8.25 (1H, t, C=N)	10.10 (1H, s, OH)
4b	1640	2850, 2900	3400	—	1.65, d	1.95, s	2.50, s	3.30 (2H, d, CH_2), 8.40 (1H, t, C=N)	11.20 (1H, s, OH)
5a	1610	2850, 2900	—	3000	1.70, d	1.95, s	—	5.90 (1H, d, H-4), 7.30 (1H, d, H-5)	14.45 (1H, s, NH)
5b	1600	2850, 2900	—	3100	1.70, d	1.95, s	2.45, s	5.90 (1H, d, H-4), 7.30 (1H, d, H-5)	14.45 (1H, s, NH)
5c	1610	2850, 2900	—	—					
6a	1640	2850, 2900	—	3300	1.70, d	1.90, s	—	6.42 (1H, d, H-$5_{pyrimidine}$), 8.08 (1H, d, H-$6_{pyrimidine}$)	6.05 (2H, br. s, NH_2)
6b	1580	2850, 2900	—	3320	1.70, d	1.95, s	2.40, s	6.42 (1H, d, H-$5_{pyrimidine}$), 8.08 (1H, d, H-$6_{pyrimidine}$)	6.05 (2H,br. s, NH_2)

The reaction of the sodium salts of compounds **1** and **3** with hydroxylamine, hydrazine, and guanidine has therefore led to the synthesis of 5-(1-adamantyl)-5-hydroxy- and 5-(1-adamantylmethyl)-5-hydroxy-Δ^3-isoxazolines, 3-(1-adamantyl)- and 3-(1-adamantylmethyl)pyrazoles, 3-(1-adamantyl)-2-phenylpyrazoles, and 4-(1-adamantyl)-2-amino- and 4-(1-adamantylmethyl)-2-aminopyrimidines. In the proposed procedure the use of readily oxidizable bases of nitrogen-containing compounds has been avoided which enables the desired compounds to be obtained in high yield.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AC 300 (300.13 MHz) in DMSO-d_6, internal standard was HMDS. The IR spectra were taken on a Specord M 80 instrument in KBr disks. The purity of compounds was checked by TLC (Silufol UV 254, visualization in iodine vapor).

General Procedure for the Synthesis of Heterocycles (4-6). A solution of sodium salt **1** or **3** (2.2 mmol) and hydroxylamine hydrochloride (hydrazine hydrochloride, guanidine nitrate) (2.2 mmol) in 50% ethyl alcohol (10 ml) was boiled for 4-15 h until precipitation of the desired heterocycle. The solid was filtered off and recrystallized from alcohol.

3-(1-Adamantyl)-1-piperidino-1-propen-3-one (7). A solution of the sodium salt **1** and piperidine hydrochloride (0.27 g, 2.2 mmol) in 50% ethyl alcohol (10 ml) was boiled for 12 h. The precipitated solid was filtered off and recrystallized from alcohol. Yield 91%; mp 168-170°C, R_f 0.31 (acetonitrile). IR spectrum, ν, cm^{-1}: 2860 and 2910 (CH_2 adamant.), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.25 (2H, m, *p*-H piperidyl); 1.55 (4H, m, *m*-H piperidyl); 1.70 (12H, d, CH_2 adamant.); 1.95 (3H, s, CH adamant.); 2.30 (4H, m, *o*-H piperidyl); 4.95 (1H, d, CHN); 7.25 (1H, d, CHCO). Found, %: C 78.86; H 9.64; N 5.23. $C_{18}H_{27}NO$. Calculated, %: C 79.07; H 9.95; N 5.12.

3-(1-Adamantyl)-2-phenylpyrazole (5c). A solution of β-aminovinyl ketone **7** (0.5 g, 1.8 mmol) and phenylhydrazine (0.27 ml, 2.7 mmol) in glacial acetic acid (10 ml) was boiled for 8 h. The reaction mixture was poured onto ice, the solid was filtered off, and recrystallized from alcohol.

REFERENCES

1. R. N. Schut, *Chem. and Ind.*, 1246 (1960).
2. M. Valenta, *Coll. Czech. Chem. Commun.*, **32**, 897 (1967).
3. P. Nantka-Namirski and L. Kaszmarek, *Acta Pol. Pharm.*, **34**, 133 (1977).
4. V. P. Litvinov, E. E. Apenova, and Yu. A. Sharanin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2408 (1984).
5. V. P. Litvinov, E. E. Apenova, and Yu. A. Sharanin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 145 (1986).
6. E. E. Apenova, Yu. A. Sharanin, B. M. Zolotarev, and V. P. Litvinov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 406 (1986).
7. V. P. Litvinov, E. E. Apenova, and Yu. A. Sharanin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 386 (1987).
8. V. Yu. Mortikov, V. P. Litvinov, and A. M. Shestopalov, *Khim.-farm. Zh.*, No. 5, 41 (1991).
9. L. A. Rodinovskaya, V. K. Promonenkov, and Yu. A. Sharanin, *Zh. Org. Khim.*, **21**, 1578 (1985).
10. N. G. Frolova, V. K. Zav'yalova, and V. P. Litvinov, *Zh. Org. Khim.*, **33**, 291 (1997).
11. N. V. Makarova, M. N. Zemtsova, and I. K. Moiseev, *Khim. Geterotsikl. Soedin.*, 1580 (1993).
12. N. V. Makarova, M. N. Zemtsova, and I. K. Moiseev, *Khim. Geterotsikl. Soedin.*, 130 (1995).