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SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM β-AMINOVINYL KETONES OF THE ADAMANTANE SERIES

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3-(1-Adamantyl)isoxazole, 6-(1-adamantyl)-3-carbethoxy-2-pyridone, and 4-(1-adamantyl)-2-mercapto-pyrimidine have been synthesized by the interaction of 3-(1-adamantyl)-1-(methylamino)prop-1-en-3-one with hydroxylamine, ethyl cyanoacetate, and thiourea respectively. The pyrimidine was also synthesized from the sodium salt of 3-(1-adamantyl)-1-hydroxyprop-1-en-3-one with thiourea.

Keywords: β-aminovinyl ketones, isoxazole, 3-carbethoxy-2-pyridone, 2-mercaptopyrimidine, cyclization.

Previously we reported the synthesis of β-aminovinyl ketones from the sodium salt of 3-(1-adamantyl)-1-hydroxyprop-1-en-3-one (**1**) [1]. It is known from the literature that enamino ketones may serve as starting materials for the synthesis of heterocycles [2], specifically isoxazoles [3], pyrazoles [4], pyridines [5], pyrimidines [6], and a series of condensed heterocyclic systems [7-9].

As a continuation of our work on the synthesis of adamantyl-containing heterocycles [10-12] and with the aim of studying the chemical properties of β-aminovinyl ketones of the adamantane series, the cyclization of 3-(1-adamantyl)-1-(methylamino)prop-1-en-3-one (**2**) has been carried out. Reaction of enamino ketone **2** with hydroxylamine hydrochloride in aqueous ethanol in the presence of Na_2CO_3 gave 3-(1-adamantyl)isoxazole (**3**), and the interaction of ketone **2** with ethyl cyanoacetate in methanol leads to 6-(1-adamantyl)-3-carbethoxy-2-pyridone (**4**). The synthesis of 4-(1-adamantyl)-2-mercaptopyrimidine (**5**) was effected in two ways: A) reaction of β-aminovinyl ketone **2** with thiourea in ethyl alcohol in the presence of KOH, B) by the interaction of the sodium salt of hydroxy ketone **1** with thiourea in acetic acid (Scheme 1).

It is possible to offer two variants for the interaction of enamino ketones of type **2** with nitrogen-containing compounds, such as hydroxylamine and also hydrazine and its derivatives studied previously by us in reactions with β-amino ketones [12]. The first stage of the process is addition at the carbonyl group (C) or first transamination of the β-aminovinyl ketone occurs with subsequent cyclization (D). It was shown previously that transamination occurs readily for β-amino ketones of the adamantane series [12]. It is possible that in the case considered by us the synthesis of heterocycles occurs through the analogous process for enamino ketone **2**, i.e. according to route D (Scheme 2).

A series of heterocyclic compounds has therefore been obtained from 3-(1-adamantyl)-1-(methylamino)prop-1-en-3-one (**2**) synthesized previously.

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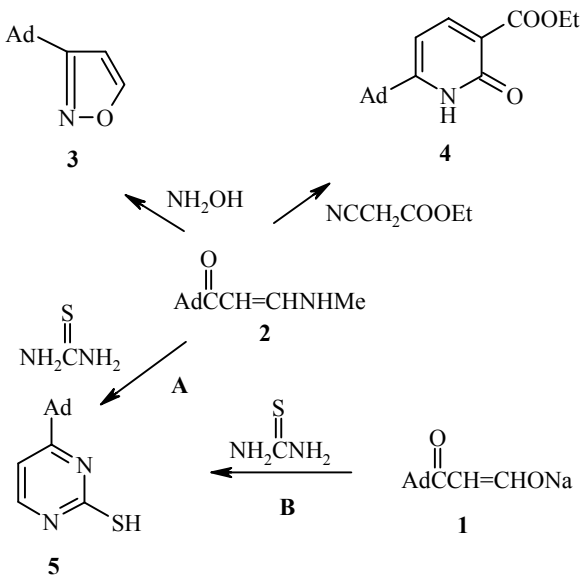
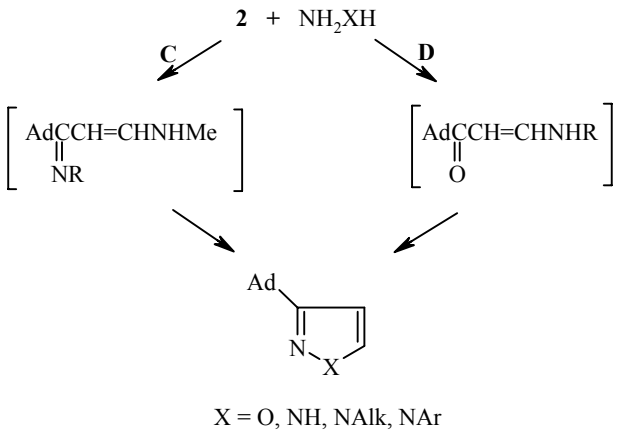
Scheme 1



Scheme 2



X = O, NH, NAlk, NAr

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AC 300 (300 MHz) instrument in DMSO, internal standard was HMDS. The IR spectra were obtained on a Specord M 80 instrument in KBr tablets. The purity of compounds was checked by thin layer chromatography on Silufol UV 254 plates.

3-(1-Adamantyl)isoxazole (3). A solution of Na_2CO_3 (0.17 g, 1.7 mmol) in water (3 ml) was added to enamino ketone **2** (0.5 g, 2.3 mmol) and hydroxylamine hydrochloride (0.19 g, 2.7 mmol) in alcohol (10 ml). The mixture obtained was refluxed for 18 h, then stored in the refrigerator for 24 h. The precipitated fine pale yellow needles of product **3** were filtered off and recrystallized from aqueous alcohol. Yield 0.21 g (45.7%); mp 110-112°C, R_f 0.32 (acetone–CCl_4, 1:1). IR spectrum, ν, cm^{-1}: 2910 and 2860 (CH_2 in Ad), 1630 (C=N). ^{1}H NMR spectrum, δ, ppm, J (Hz): 1.65-1.90 (15H, m, CH_2 and CH in Ad); 6.80 (1H, d, 4-H_{Het}); 7.10 (1H, d, J = 2.35, 3-H_{Het}). Found, %: C 77.00; H 8.50; N 7.88. $C_{13}H_{17}NO$. Calculated, %: C 76.81; H 8.43; N 6.89.

6-(1-Adamantyl)-3-carbethoxy-2-pyridone (4). A mixture of enamino ketone **2** (0.5 g, 2.3 mmol) and ethyl cyanoacetate (0.3 ml, 2.8 mmol) in methanol (10 ml) was refluxed on a water bath for 10 h. After cooling, the precipitated orange crystals of product **4** were filtered off, washed with cold alcohol (3 ml), and dried. Yield 0.22 g (31.9%); mp 199-200°C, R_f 0.31 (acetone–CCl_4, 1:1). IR spectrum, ν, cm^{-1}: 2900 and 2850 (CH_2 in Ad), 1730 (COO), 1700 (C=O), 1650 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.21 (3H, t, $C\underline{H}_3CH_2$); 1.65-1.92 (15H, m, CH_2 and CH in Ad); 3.75 (2H, q, $CH_3C\underline{H}_2$); 7.80-7.95 (2H, m, 4- and 5-H_{Het}); 11.6 (1H, br s, NH). Found, %: C 71.65; H 7.93; N 4.00. $C_{18}H_{23}NO_3$. Calculated, %: C 71.73; H 7.69; N 4.65.

4-(1-Adamantyl)-2-mercaptopyrimidine (5). A. A mixture of enamino ketone **2** (0.5 g, 2.3 mmol), thiourea (0.52 g, 6.9 mmol), and KOH (0.13 g, 2.3 mmol) in absolute ethyl alcohol (10 ml) was refluxed for 6 h. After cooling, the precipitated pale yellow fine needle-like crystals of product **5** were filtered off, and recrystallized from alcohol. Yield 0.4 g (71.4%); mp 190-192°C, R_f 0.19 (acetone–CCl_4, 1:1). IR spectrum, ν, cm^{-1}: 3350 (SH), 2900 and 2850 (CH_2 in Ad), 1620 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.62-1.95 (15H, m, CH_2 and CH in Ad); 7.88-9.01 (2H, m, 5- and 6-H_{Het}). Found, %: C 68.00; H 7.55; N 11.42. $C_{14}H_{18}N_2S$. Calculated, %: C 68.25; H 7.36; N 11.37.

B. A mixture of compound **1** sodium salt (0.5 g, 2.2 mmol), thiourea (0.17 g, 2.2 mmol), and glacial acetic acid (10 ml) was heated at 40°C for 30 h, then cooled, and neutralized with Na_2CO_3 solution. The precipitated solid product **5** was filtered off, washed many times with cold water, and recrystallized from alcohol. Yield 0.35 g (64.8 %); mp 190-192°C.

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