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-mercaptopyrimidine 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 Na₂CO₃ 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.
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$_2$CO$_3$ (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, $\nu$, cm$^{-1}$: 2910 and 2860 (CH$_2$ in Ad), 1630 (C=N). $^1$H NMR spectrum, $\delta$, 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.