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# NOVEL REGIOSELECTIVE SYNTHESIS OF 4-ISOTHIOCYANATOBUTAN-2-ONE BY A STAUDINGER REACTION. PREPARATION OF 6-UNSUBSTITUTED 4-HYDROXYHEXAHYDROPYRIMIDINE-2-THIONES

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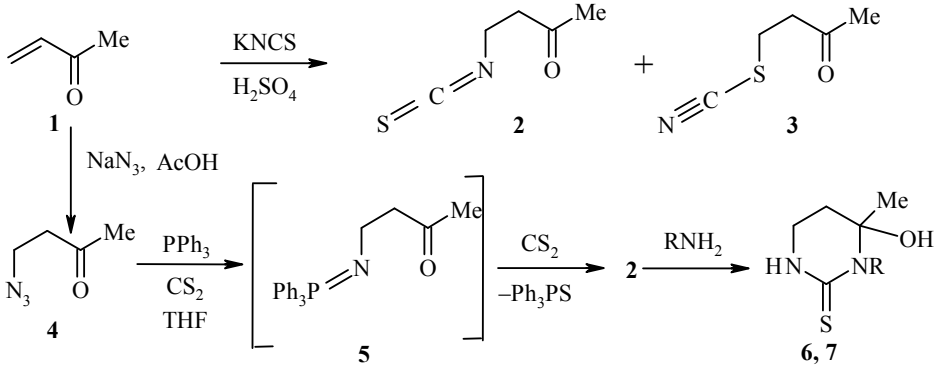
β-Isothiocyanato aldehydes and ketones are valuable starting materials in the syntheses of various nitrogen-containing acyclic and heterocyclic compounds (for reviews, see [1, 2]). The main method for preparing isothiocyanates consists of the addition of thiocyanic acid to the corresponding α,β-unsaturated aldehydes and ketones [1-6]. However, when compounds not having a substituent in the β-position are used, up to 50% of β-thiocyanatocarbonyl side products are formed in this reaction [5, 6]. Hence reaction of vinyl methyl ketone **1** with KNCS in water in the presence of $H_2SO_4$ gives a 50:50 mixture of the 4-isothio-cyanatobutan-2-one (**2**) and 4-thiocyanatobutan-2-one (**3**) [6].




**6** R = H, **7** R = Me

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Due to the close physical properties of the β-isothiocyanato- and β-thiocyanatocarbonyl compounds, it should be noted that their separation presents a complex problem. This obstacle lowers, to a certain extent, the preparative value of the use of β-unsubstituted β-isothiocyanato aldehydes and ketones in the syntheses of heterocyclic compounds.

In this communication, we report a directed synthesis of β-unsubstituted β-isothiocyanato ketones from readily available β-azido ketones in the case of preparing pure 4-isothiocyanatobutan-2-one (**2**) and also conversion of the latter to 4-hydroxyhexahydropyrimidine-2-thiones.

The key starting material we used was 4-azidobutan-2-one (**4**), which was synthesized in 60% yield by method [7] by treating the vinyl methyl ketone **1** with hydrazoic acid. The azide **4** separated from the reaction mixture could be used in the following stage without purification.

The conversion of the azido group of compound **4** to an isothiocyanate group was carried out by a Staudinger reaction (for reviews, see [8, 9]). For this purpose the azide **4** was treated with an equivalent amount of triphenylphosphine in dry THF at 20ºC. Formation of the iminophosphorane **5** occurred with evolution of nitrogen, which was converted to the target isothiocyanato ketone **2** by addition of carbon disulfide to the reaction mixture. A method, where the synthesis of phosphorane **5** and its subsequent reaction with carbon disulfide were combined, had preparative value and, for this, a solution of compound **4** in a mixture of THF and carbon disulfide was treated with triphenylphosphine. After the evolution of gas had ceased the reaction mass was held for several hours at room temperature and evaporated to dryness. The residue was treated with a mixture of diethyl ether and petroleum ether (1:1), the triphenylphosphine sulfide was filtered off, and the solution was again evaporated. We have found that the yield of compound **2** can be increased if, after the end of the nitrogen evolution, the mixture is refluxed for 1-1.5 h. Under optimal conditions the yield of the oily compound **2** from azide **4** is 64%.

The isothiocyanate **2** obtained as reported above was sufficiently pure for its subsequent use in the synthesis of heterocycles. This was shown by us in the conversion of this compound to the hydroxypyrimidine **6** by treatment of a solution of isothiocyanate **2** in acetonitrile at 20ºC for 1 h with aqueous ammonia (1.5 eq.), subsequent evaporation of the reaction mixture, and treatment of the solid residue with diethyl ether. The yield of chromatographically and spectroscopically pure pyrimidine **6** was 59% based on azide **4**. Compound **6** was also prepared under the same conditions in 78% yield using a pure sample of isothiocyanate **2** obtained by vacuum distillation. The reaction of purified isothiocyanate **2** with aqueous methylamine in acetonitrile (20ºC, 1.5 h) gave the N-methyl-substituted hydroxypyrimidine **7** in 82% yield. It should be noted that the yields of pyrimidines **6, 7** reported in the literature [10-13] are markedly below those obtained in our work.

IR spectra were recorded on a Bruker Vector 22 Fourier spectrometer as a thin layer (compound **2**) or as a suspension in vaseline oil (compounds **6** and **7**). $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX 300 spectrometer (300 and 75 MHz respectively) using $CDCl_3$ (compound **2**) or DMSO-$d_6$ (compounds **6** and **7**). The central signals of the residual protons or carbons of the solvent were used as internal standards (δ 2.50 for DMSO-$d_6$ and 7.25 for $CDCl_3$ in the $^1$H NMR spectra and 39.50 for DMSO-$d_6$ and 77.00 ppm for $CDCl_3$ in the $^{13}$C NMR spectra respectively).

**4-Isothiocyanatobutan-2-one (2)**. Yield 53.3% (after distillation); bp 88-90ºC (0.1 mm Hg), $n_D^{20}$ 1.5193. IR spectrum, ν, cm$^{-1}$: 2196 s, 2121 vs (NCS), 1719 s (C=O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.73 (2H, t, $^3J$ = 6.5, $CH_2N$); 2.81 (2H, t, $^3J$ = 6.5, $CH_2C$=O); 2.17 (3H, s, $CH_3$). $^{13}$C NMR spectrum, δ, ppm: 204.24 (C=O), 130.80 (N=C=S), 42.59 ($\underline{C}H_2C$=O); 39.34 ($CH_2N$); 29.97 ($CH_3$). Found, %: C 46.31; H 5.63; N 10.57. $C_5H_7NOS$. Calculated, %: C 46.49; H 5.46; N 10.84.

**4-Hydroxy-4-methylhexahydropyrimidine-2-thione (6)**. Yield 77.9%; mp ~ 111ºC (with decomp., foaming; from acetone, rate of heating 1ºC over 3 sec); at a slower heating rate TLC indicates that the substance decomposes without melting and then melts with decomposition at 147.5-148ºC (mp 151-152ºC [10]). IR spectrum, ν, cm$^{-1}$: 3357 s, 3219 s (NH, OH), 1565 s, 1534 s (thioamide II). $^1$H NMR spectrum, δ, ppm: 8.22 (1H, br. s, 3-NH); 8.13 (1H, unresolved d, 1-NH); 5.60 (1H, s, OH); 3.18-3.29 (1H, m, H-6*a*); 3.00-3.09 (1H, m,

H-6*e*); 1.66-1.75 (1H, m, H-5e), 1.47-1.59 (1H, m, H-5*a*); 1.35 (3H, s, 4-$CH_3$). $^{13}$C NMR spectrum, δ, ppm: 175.33 (C-2), 76.73 (C-4), 36.57 (C-6); 32.61 (C-5), 28.41 (4-$CH_3$).

**4-Hydroxy-3,4-dimethylhexahydropyrimidine-2-thione (7)**. Yield 81.9%; mp 91-91.5ºC (acetone) (mp 85-86ºC [11]). IR spectrum, ν, $cm^{-1}$: 3346 s, 3182 s (NH, OH), 1534 s, 1501 s (thioamide II). $^1$H NMR spectrum, δ, ppm: 8.11 (1H, br. s, 1-NH); 6.05 (1H, s, OH); 3.17 (3H, s, $NCH_3$); 2.97-3.19 (2H, m, H-6); 1.82-1.96 (2H, m, H-5); 1.38 (3H, s, 4-$CH_3$). $^{13}$C NMR spectrum, δ, ppm: 177.56 (C-2), 81.74 (C-4), 36.23, 35.32 (C-5,6), 33.17 (N-$CH_3$); 26.46 (4-$CH_3$).

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