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An unexpected product of the reaction between *N*-hydroxy-6-methyluracil-5-carboximidoyl chloride and thioureas

Inna B. Chernikova,*[a] Alexander N. Lobov,[a] Ekaterina S. Meshcheryakova,[b] Leonard M. Khalilov[b] and Marat S. Yunusov[a]

[a] *Ufa Institute of Chemistry, Ufa Federal Research Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. E-mail: inna.b.chernikova@yandex.ru*

[b] *Institute of Petrochemistry and Catalysis, Ufa Federal Research Centre of the Russian Academy of Sciences, 450071 Ufa, Russian Federation*

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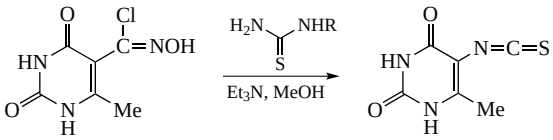
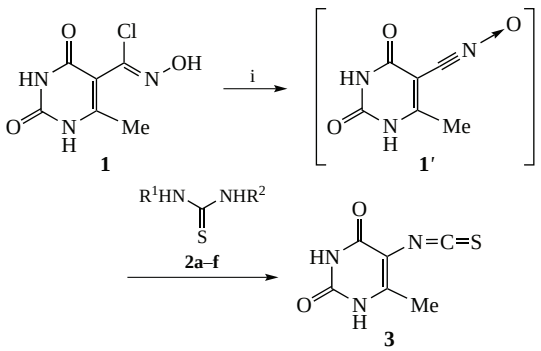
5-Isothiocyanato-6-methylpyrimidine-2,4(1*H*,3*H*)-dione was formed in the course of the reaction between *N*-hydroxy-6-methyluracil-5-carboximidoyl chloride and a series of thioureas in MeOH in the presence of Et_3N. The transformation follows the Hoffman rearrangement mechanism, with the nitrile *N*-oxide being the key intermediate.



Keywords: 6-methyluracil, *N*-hydroxy-6-methyluracil-5-carboximidoyl chloride, nitrile *N*-oxides, thioureas, isothiocyanates.

As a heterocyclic base, uracil is an important component of nucleic acids.[1] Uracil derivatives are used in medical practice as drugs with proven efficiency, including the treatment of SARS-CoV-2 (COVID-19)[2] and cancer treatment.[3] Synthetic chemists pay special attention to hybrid structures containing two or more pharmacophore groups. Thus, uracil modification is a promising approach to the synthesis of xenobiotics that can be involved in RNA synthesis or affect the activity of enzymes involved in the synthesis of nucleic acids by disrupting the pyrimidine exchange.

We have previously shown that in the presence of Et_3N, hydroxamic acid chloride **1** (Scheme 1) was converted to nitrile *N*-oxide **1′** that reacted with amines, alcohols and unsaturated compounds.[4–6] In continuation of this work, we performed the reaction of **1** with allylthiourea **2a** in MeOH in the presence of Et_3N at room temperature for 1 h, expecting to obtain 2-isoxazoline derivative with a thiourea residue in the side chain. Unexpectedly, another product **3** was isolated in 63% yield (see Scheme 1). Prolongation of the reaction to 3 h did not improve the product yield, while performing the reaction at 0 °C for 1 h increased its yield to 77%. The reaction performed at –10 °C gave nearly the same yield.



a $R^1 = CH_2{=}CHCH_2$, $R^2 = H$
b $R^1 = R^2 = H$
c $R^1 = Ac$, $R^2 = H$
d $R^1 = Ph$, $R^2 = H$
e $R^1 = 2\text{-}MeC_6H_4$, $R^2 = H$
f $R^1 = R^2 = 2\text{-}MeC_6H_4$

Scheme 1 *Reagents and conditions*: i, Et_3N, MeOH, –10 to 25 °C.

Elemental analysis data correspond to the molecular formula $C_6H_5N_3O_2S$, which is confirmed by the presence of the ion peak with the maximum intensity at *m/z* 182.0022 in the negative ion mass-spectrum due to the $[M-1]^-$ ion with $C_6H_4N_3O_2S$ composition. The ^1H and ^{13}C NMR spectra of the product manifest all signals of the C^6-methyluracil moiety. Taking into account the elemental composition of the product and the presence of 6-methyluracil moiety in it, we proposed the presence of the NCS grouping which can be either isothiocyanate or thiocyanate.

The structure of compound **3** and the assignments of the ^1H, ^{13}C and ^{15}N NMR signals were determined using two-dimensional {^1H, ^{13}C} and {^1H, ^{15}N} HSQC and HMBC correlation spectra in DMSO-d_6 solution (Figure 1). The positions of all carbon signals of the 6-methyluracil nucleus were determined from the {^1H, ^{13}C} HMBC cross-peaks. The position of the signal at δ_C 144.94 in the substituent at C^5 and its weak intensity due to quadrupole broadening at ^{14}N should correspond to isothiocyanate group.[7,8] It is known that the

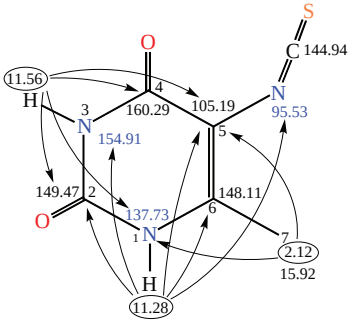


Figure 1 Diagram of HMBC interactions; assignments of ^1H, ^{13}C and ^{15}N signals for compound **3** in DMSO-d_6 solution.

Table 1 Dependence of isothiocyanate **3** yield on the reaction conditions.[a]

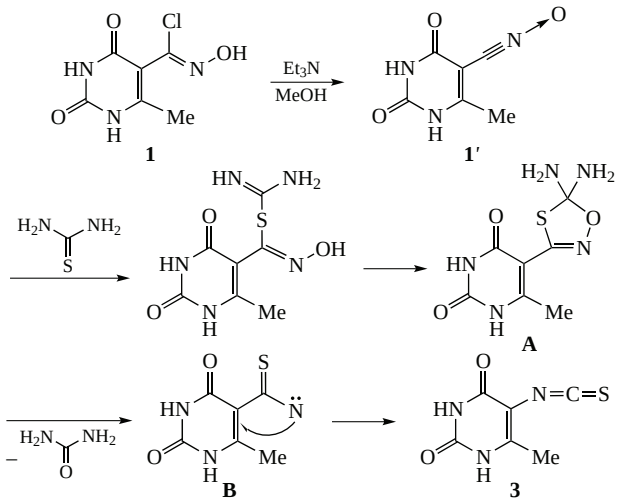
Entry	Reagent	*T*/°C	Yield of **3** (%)
1	**2a**	25	63[b]
2	**2a**	0	77
3	**2a**	–10	78
4	**2b**	25	65
5	**2b**	0	78
6	**2c**	25	58
7	**2c**	0	74
8	**2c**	–10	76
9	**2d**	25	56
10	**2d**	0	72
11	**2e**	25	59
12	**2e**	0	75
13	**2f**	0	73

[a] Reaction time 1 h. [b] Reaction time 1–3 h.

^{15}N signals for isothiocyanates are located in the 90–120 ppm region while those for thiocyanate, within 270–290 ppm, which allows them to be unambiguously distinguish. The {^{1}H, ^{15}N} HMBC and HSQC spectrum manifests, along with the amide proton cross-peaks at N^1 and N^3, also a weak H^1 cross-peak (δ_H 11.28) with a nitrogen signal at δ_N 95.53 (see Online Supplementary Materials, Figure S1) which is of tertiary nature according to the INEPT spectrum. Thus, the chemical shifts δ_C 144.94 and δ_N 95.53 would evidence for isothiocyanate group.[9,10]

Similar reactions with thiourea **2b** and its derivatives **2c–f** gave the same product **3** in good yields (see Scheme 1, Table 1). From the diversity of the thiourea derivatives used in the reaction and the fact that the same product with the composition $C_6H_5N_3O_2S$ is formed in all cases it follows that only the S atom passes from thiourea into the resulting product.

The transformation **1** → **3** is likely to occur by the mechanism shown in Scheme 2. In the first step, *N*-nitrile oxide **1′** is formed which would further react with reagents **2a–f**. The unstable intermediate **A** eliminates urea to give thioxo nitrene **B**, which undergoes isomerization into the isothiocyanate, similarly to the reactions used for the synthesis of amines from acid derivatives (Hoffmann, Curtius, Lossen rearrangements).[11] Preparative reactions of nitrile oxides to afford isothiocyanates with the C–C bond cleavage on treatment with thiourea[12,13] and other sulfur-containing reactants[14] were documented. The formation of isothiocyanates from nitrile oxides, along with other products, on treatment with sulfur-containing reactants was noted[15,16] where the [3 + 2]-cycloaddition mechanism was



Scheme 2

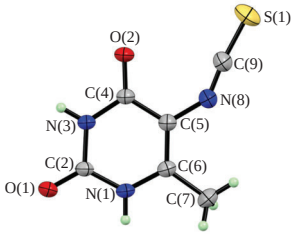


Figure 2 Molecular structure of compound **3**. Non-hydrogen atoms are presented as ellipsoids of thermal vibrations (p = 50%).

assumed. So, our results are in agreement with the literature data.

The single-crystal X-ray analysis ultimately confirms the presence of isothiocyanate group in compound **3** (Figure 2).† The bond lengths and bond angles in the uracil moiety, except for the C(4)–C(5) and C(5)=C(6) bonds, are similar to those in 6-methyluracil,[19] which is probably due to the effect of the isothiocyanate group on the uracil ring. The SCNC group is bent (non-linear); the C(5)–N(8)–C(9) and N(8)–C(9)–S(1) angles are 141.66(13) and 173.51(13)°, respectively. It should be noted that a similar spatial structure of the isothiocyanate group is typical of structures where keto and SCNC groups are arranged alternately.[20] The N(8)=C(9) and C(9)=S(1) bond lengths are 1.1853(18) and 1.5666(15) Å, respectively. In contrast to the N(8)=C(9) and C(9)=S(1) bonds, the C(5)–N(8) bond length in the isothiocyanate group depends on the nature of the moiety to which it is bound: in this case, it is 1.3807(16) Å, which is typical of C–N bonds of isothiocyanate groups bound to moieties of aromatic nature.[21] The molecules of compound **3** form transparent lamellar crystals with triclinic crystal lattice, spatial group $P\bar{1}$. The independent part of the unit cell includes one molecule (Z = 2, Z' = 1). Two paired N–H···O hydrogen bonds [N(1)···O(1) = 2.7836(13) Å and N(3)···O(2) = 2.8080(14) Å] arranged around the symmetry centers bind the molecules together into chains (1D motif, see Online Supplementary Materials, Figure S2).

It should be noted that compound **3** does not react with urea, guanidine, thiosemicarbazide, and cytisin-12-thiocarbamide under the reported conditions.[22] It should also be noted that the isothiocyanate group does not exhibit its characteristic properties in compound **3**. In fact, refluxing 5-isothiocyanate-6-methyluracil in acetic acid or in acetic anhydride for 36 h did not result in the corresponding acetamide, and the initial substrate was recovered. A similar picture is observed in the reaction of 5-isothiocyanate-6-methyluracil with Zn/HCl and with excess benzylamine in toluene.

† *Crystal data for* **3**. $C_6H_5N_3O_2S$ (M = 183.19), triclinic, space group $P1$, a = 4.7912(2), b = 7.2561(4) and c = 12.1180(6) Å, α = 98.484(5), β = 90.493(4) and γ = 106.926(5)°, V = 398.04(4) Å^3, Z = 2, d_{calc} = 1.528 g cm^{-3}, μ(MoKα) = 0.366 mm^{-1}, F(000) = 188.0. Total of 15221 reflections were collected (3283 independent reflections, R_{int} = 0.0408) and used in the refinement, which converged to wR_2 = 0.1484, GOOF 1.034 for all independent reflections [R_1 = 0.0488 was calculated for 3283 reflections with $I > 2\sigma(I)$]. The X-ray diffraction analysis were performed on an Agilent XCalibur automatic four-circle diffractometer (Gemini, Eos, graphite monochromator, MoKα radiation, ω-scan mode, $2\theta_{max}$ 62°) at 293 K. The structures were solved by direct methods and refined using the SHELX program package.[17,18] The structure was refined by a full-matrix least-square technique using anisotropic thermal parameters for non-hydrogen atoms. All hydrogen atoms were generated using the proper HFIX command and refined isotropically using the riding model.

CCDC 2243154 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

A method for synthesizing isothiocyanate **3** from 5-aminouracil by a direct reaction with $CSCl_2$ is reported.[23] We are the first to synthesize 5-isothiocyanato-6-methyluracil by the reaction of *N*-hydroxy-6-methyluracil-5-carboximidoyl chloride with a series of thioureas in MeOH in the presence of Et_3N.

This work was performed within the scope of the state assignment of the Ministry of Education and Science of the Russian Federation on the subject no. 122031400260-7. Spectral studies were carried out using the equipment of the 'Chemistry' User Service Center of the Ufa Institute of Chemistry of the Ufa Federal Research Centre of the Russian Academy of Sciences (UFRC RAS). The X-ray diffraction study was carried out using Agilent XCalibur equipment belonging to 'Agidel' Regional Center for Collective Use at the Institute of Petrochemistry and Catalysis of the UFRC RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.039.

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