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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis of 6-Methyluracil-5-sulfonyl Chloride

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Abstract—Sulfochlorination of 6-methyluracil with chlorosulfonic acid in the presence of thionyl chloride was studied. The lactam–lactim tautomerism of 6-methyluracil was considered. Ways to increase the yield of the sulfonyl chloride were suggested. The mechanism of the effect exerted by thionyl chloride additions was discussed.

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Sulfochlorination reactions are widely used in organic (in particular, pharmaceutical) chemistry. Sulfonyl chlorides are intermediates in syntheses of active and dispersible dyes, herbicides, and fungicides [1]. Among six-membered heterocyclic compounds containing two nitrogen atoms, a prominent place is occupied by pyrimidine derivatives used as drugs (sulfamide drugs such as Sulfadimethoxine, Sulfamonomethoxine; antitumor agent Fluorouracil; antibiotic Amecytin, etc.) [2, 3].

Of particular interest in this respect is readily available methyluracil, which is used in syntheses of sulfonamides, sulfonyldiureides, sulfonylhydrazides, and sulfonates; some of these compounds showed biological activity.

Data on sulfochlorination of 6-methyluracil are relatively few. As shown in [4–6], uracil and 6-methyluracil 1 react with a tenfold excess of chlorosulfonic acid to form uracil-6-sulfonyl chloride and 6-methyluracil-5-sulfonyl chloride 2 in a low yield ($\leq 22\%$).

To develop a more efficient procedure for preparing 6-methyluracilsulfonyl chloride, we examined the effect of various factors on the sulfochlorination of 1 [7, 8].

At 30°C, compound 1 does not noticeably react with chlorosulfonic acid; the reaction starts only at 35° C, and the yield of 2 under these conditions does not exceed 15%. With increasing temperature, the reaction rate and sulfonyl chloride yield increase, but even after the sulfochlorination for 7 h at 75°C the yield of 2 does not exceed 28% (see figure). When the reaction mixture is poured onto ice to isolate the product, a considerable part of 2 undergoes hydrolysis and transforms into 6-methyluracilsulfonic acid, which was isolated from the solution by salting-out with NaCl. Thus, the desired sulfonyl chloride is unstable and is readily hydrolyzed in aqueous solution. To suppress the hydrolysis, the reaction mixture was poured onto a 1:1 mixture of ice and acetic acid.

It was found in [9, 10] that the use of chlorosulfonic acid in combination with thionyl chloride (volume ratio 1.5:1) considerably increases the rate of formation and yield of **2** (see figure). In contrast to SOCl₂, addition of SO₂Cl₂ or POCl₃ does not noticeably af-



Yield of 6-methyluracilsulfonyl chloride W vs. time t (1-4) in the absence and (5-9) in the presence of thionyl chloride. T, °C: (1, 5) 45, (2, 6) 55, (3, 7) 65, (4, 8) 75, and (9) 85.

fect the sulfochlorination rate and yield of the target product. Sulfochlorination of 6-methyluracil follows the scheme



As seen from the figure, addition of $SOCl_2$ results in that the rate of formation of **2** increases by a factor of 3–4 even at 45°C, with the yield of **2** reaching 40%. Similar relationships are observed at higher temperatures.

The highest yield of **2** (82%) was obtained after heating at 85°C for 5 h. Further increase in the temperature decreases the yield of the target product because of formation of the sulfone (see figure, curve 9).

The favorable effect of thionyl chloride on the rate of formation and yield of sulfonyl chlorides is apparently due to the presence of a lone electron pair at the S(IV) atom. The S atoms in SO_2Cl_2 and $SOCl_2$ differ

in the electronic structure and affect the substrate differently. In contrast to the S atom in chlorosulfonic acid and sulfuryl chloride, in which all the valence electrons are fully involved in formation of six covalent bonds, in thionyl chloride a lone *p*-electron pair remains on the sulfur atom, and it may compensate the electron density deficiency on the O atom in the 4-position of methyluracil, facilitating electrophilic substitution of the H atom by the SO₂Cl group:



The ready incorporation of the SO₂Cl group in the 5-position of methyluracil is due to its lactam–lactim tautomerism. 6-Methyluracil can exist in the form of five tautomers, four of which contain one or two hydroxy groups. Nonaqueous titration shows that 1 mol of sodium methylate is spent per mole of methyluracil, suggesting the presence of only one OH group (structures **4**, **5**):



As shown by quantum-chemical calculations, ¹H NMR spectra, and certain chemical transformations, structure **5** is the most favorable energetically. In this structure, the 5-position will be the most reactive owing to the concerted effect of CH_3 and OH groups. Sulfochlorination occurs at a higher rate via intermediate **3** (see above).

Experiments showed that methyluracil reacts with sodium methylate to form monosodium derivative 7, which reacts with methyl iodide CH_3I to form compound 8:



The structures of **7** and **8** were confirmed by IR and NMR spectra and by elemental analysis.

EXPERIMENTAL

The ¹H NMR spectra were recorded in CDCl₃ on a Tesla BS-487c spectrometer operating at 80 MHz. The chemical shifts (δ , ppm) are given relative to TMS. The IR spectra were measured on a UR-20 spectrometer (KBr pellets).

6-Methyluracil-5-sulfonyl chloride 2. A fournecked flask equipped with a power-driven stirrer, a thermometer, a reflux condenser, and a dropping funnel was charged with 7.6 g (0.054 mol) of 6-methyluracil 1 dried in an oven at $110-115^{\circ}$ C for 3-4 h. The flask was placed on a water bath, and 10 ml (16.5 g, 0.138 mol) of freshly distilled thionyl chloride was added with vigorous stirring. The contents were stirred for 20–30 min, after which 16 ml (28.6 g, 0.265 mol) of freshly distilled chlorosulfonic acid was added dropwise at such a rate that the reaction mixture temperature did not exceed $30-35^{\circ}$ C. The reflux condenser was connected through a CaCl₂ tube with a beaker absorbing the released gases.

The mixture was heated to $60-65^{\circ}$ C and kept at this temperature with vigorous stirring for 4.5–5 h, after which it was heated to 75–80°C and kept for an additional 5.5–6 h. The reaction progress was monitored chromatographically on Silufol UV-254 plates, eluent ethyl acetate. After the reaction completion, the mixture was cooled to 0–5°C and poured with vigorous stirring onto a mixture of 50 g of crushed ice and 35 ml of glacial acetic acid, keeping the temperature in the range from –5 to 0°C. 6-Methyluracil-5-sulfonyl chloride precipitated as a white crystalline substance; it was filtered off and washed several times with ice-cold water and acetic acid. Yield 9.95 g (82%). White needle-like crystals, mp 269–270°C (from glacial acetic acid).

Found, %: C 26.91, H 2.61, N 12.40, Cl 15.94, S 14.48. $C_5H_5ClN_2O_4S.$

Calculated, %: C 26.74, H 2.69, N 12.47, Cl 15.78, S 14.27.

IR spectrum, cm⁻¹: 985, 1030 ($\omega_{C=C}$); 1305 (C=N–); 1675, 1730 ($\nu_{C=O, =N-C=O}$); 3275 (ν_{NH}); 1355, 1380 ($\nu_{S(CH_3)}$). ¹H NMR spectrum, δ , ppm (CDCl₃): 2.45 s (3H, C⁶–CH₃); 11.68 d (1H, N¹–H), 5.85 s (1H, C⁴–OH).

4-Methoxy-6-methyluracil. Sodium metal (1.25 g, 0.054 mol) was dissolved in 50 ml of absolute methanol, and 6.25 g (0.050 mol) of methyluracil was added. The mixture was heated at 65°C for 45 min with stirring. To the resulting colorless solution, 3.7 ml (0.060 mol) of methyl iodide was added, and the mixture was heated with weak refluxing for 4-5 h until the methyluracil spot disappeared from the chromatogram (Silufol UV-254, eluent ethyl acetate). On cooling, colorless needle-like crystals precipitated. The precipitate was filtered off, washed with water, and dried. Yield of 4-methoxy-6-methyluracil 6.31 g (89.9%), mp 192–193°C.

Found, %: C 51.63, H 5.71, N 19.86.

 $C_6H_8N_2O_2$.

Calculated, %: C 51.42, H 5.75, N 19.99.

IR spectrum, cm⁻¹: 1020 ($\omega_{C=C}$); 1025 ($v_{S(=C-O-C)}$); 1245 ($v_{as(=C-O-C)}$); 1055–1275 (C=N–); 1685, 1745 ($v_{C=O, =N-C=O}$); 1380 ($v_{S(CH_3)}$); 2825 (OCH₃); 2850 ($v_{S(OCH_3)}$); 2870 ($v_{S(CH_3)}$); 2965 ($v_{as(CH_3)}$). ¹H NMR spectrum, δ , ppm (CDCl₃): 2.11 s (3H, C⁶–CH₃), 4.92 d (1H, C⁵–H), 4.01 s (3H, C⁴–OCH₃), 11.92 s (1H, N¹–H).

CONCLUSIONS

(1) Sulfonation of 6-methyluracil with a mixture of chlorosulfonic acid and thionyl chloride allows the rate of formation and yield of 6-methyluracil-5-sulfo-nyl chloride to be appreciably increased, with the yield reaching 82%.

(2) In solution, 6-methyluracil mainly occurs in the lactim form (4-hydroxy-6-methyl-1,2-dihydro-pyrimidin-2-one).

(3) The favorable effect of thionyl chloride on the sulfochlorination rate and yield of sulfonyl chloride is due to the fact that the lone electron pair of the S atom of thionyl chloride eliminates the electron density deficiency on the oxygen atom, thus facilitating the electrophilic substitution of hydrogen by the SO_2Cl group.

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