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REACTION OF 5-HYDROXYMETHYL-6-METHYLURACIL WITH TOLUENESULFONYL CHLORIDE OR METHANESULFONYL CHLORIDE AND TERTIARY AMINES

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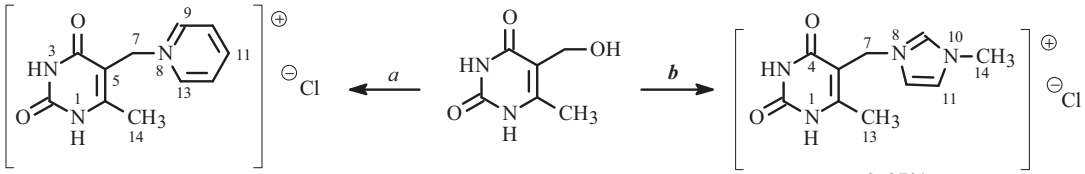
Quaternary ammonium salts were formed or the starting uracil was recovered after the reaction of 5-hydroxymethyl-6-methyluracil with toluenesulfonyl chloride or methanesulfonyl chloride and tertiary amines.

Keywords: 5-hydroxymethyl-6-methyluracil, toluenesulfonyl chloride, methanesulfonyl chloride, tertiary amines, quaternary ammonium salts.

Pyrimidones are the most important diazine derivatives encountered in nature and occur in nucleic acids as a part of the nucleosides. Much synthetic effort has been directed toward discovering antiviral and antitumor drugs among representatives of this class of organic compounds [1–10].

In continuation of chemical studies of uracils and the search for potential drugs among them, we wished to prepare various derivatives using tosyl (Ts) or mesyl (Ms) derivatives of 5-hydroxymethyl-6-methyluracil as starting materials. For this, the known method for preparing tosylates of alcohols in anhydrous Py at 0°C was used [11].

The reaction was carried out in Py with TsCl at room temperature for 5 h. A mixture of **2** and starting alcohol **1** in a 2:1 (determined from the integrated intensity of PMR resonances) ratio was isolated. Replacing TsCl by MsCl led to the production of only **2** (Scheme 1). Carrying out the reaction with MsCl or TsCl at 0°C gave a 3:1 mixture of **2** and **1**. Analogously, 1-[(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]pyridinium chloride (**2**) was produced from **1** in 90% yield by using MsCl and a five-fold excess of Py in DMF as the solvent at room temperature. Compound **3** was obtained in 97% yield by using MsCl and *N*-methylimidazole as the tertiary amine at room temperature (Scheme 1).



2, 98% **1** **3**, 97%

a. MsCl (1.2 equv.), Py, r.t., 5 h; *b*. MsCl (1.2 equv.), N-methylimidazole, r.t., 5 h

Scheme 1

The structures of **2** and **3** were elucidated using standard PMR and ^{13}C NMR spectra in addition to C–H HSQC and HMBC correlation spectra and ^{15}N–^{1}H HMBC and inept spectra.

Resonances of protons and C atoms were assigned based on ^{13}C–^{1}H HSQC and HMBC spectra. ^{15}N–^{1}H HMBC and HSQC spectra were accumulated for a more reliable assignment of proton and ^{13}C resonances and to find the chemical shifts of the N atoms. A study of couplings in the ^{13}C–^{1}H HMBC spectrum of **2** found that the methylene protons gave cross peaks with the resonances of C-5 in addition to C-9, C-6, and C-4. Chemical shifts of N atoms were reliably attributed and the assignments of proton and ^{13}C chemical shifts were confirmed in the ^{15}N–^{1}H HMBC spectrum. Thus, the methyl-proton

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resonance gave a cross peak with the N-1 resonance. The N-8 resonance exhibited coupling with methylene protons, H-9, and H-13. The $^{15}N–^{1}H$ HSQC spectrum showed N-1/H-1 and N-3/H-3 couplings.

Chemical shifts of protons and ^{13}C atoms of the uracil group were easily assigned for **3**. The $^{13}C–^{1}H$ HMBC spectrum confirmed the assignments because the methylene-proton resonance gave couplings with C-5, C-6, C-4, C-9, and C-12. The $^{15}N–^{1}H$ inept spectrum was used to determine the chemical shifts of N and to measure the proton and N spin–spin coupling constants. The methylene protons showed coupling with N-8; C-14 methyl protons, with N-10 in the $^{15}N–^{1}H$ HMBC spectrum.

We studied this reaction with other tertiary amines (dimethylbenzylamine, dimethylaniline, triethylamine, tributylamine, *N*-methylmorpholine, gramine, and 2-bromo- and 3-bromo-substituted Py derivatives) because the formation of the ammonium salt was unexpected for this reaction. Precipitates formed during the course of the reaction, like with Py and *N*-methylimidazole. Their analyses (NMR spectra and elemental analyses) suggested that quaternary ammonium derivatives had formed. However, a detailed study (PMR, ^{13}C and ^{15}N NMR, elemental analyses) showed that the reaction products in these instances were 1:1 mixtures of the starting hydroxymethyl derivative **1** and the tertiary base hydrochloride. Apparently, unstable compounds were formed. This dilemma was explained by the similar spectral data of the quaternary ammonium salt and the corresponding mixture of **1** and the tertiary base hydrochloride. Elemental analyses were also similar and differed by one water molecule.

Correlation spectra (C–H HSQC and HMBC and $^{15}N–^{1}H$ HMBC and inept), i.e., cross peaks of the methylene with uracil and amine atoms, provided the main proof that quaternary ammonium derivatives had formed. Such proof was obtained only if Py and *N*-methylimidazole were used. In all other instances, the corresponding correlations were not observed. In other words, the reaction products were the aforementioned mixtures. This conclusion was confirmed by brief grinding of the reaction products with aqueous Me_2CO (1:4) suspensions of Na_2CO_3 at room temperature and subsequent isolation of starting **1**.

However, treatment with a suspension of Na_2CO_3 also gave 5-hydroxymethyl-6-methyluracil (**1**) in good yield in Py, where the formation of the quaternary ammonium salt was proven. Probably, an anomalously facile hydrolysis of the quaternary ammonium salt into **1** occurred in this instance. The quaternary ammonium salt was returned unchanged after treatment of **3** with a suspension of Na_2CO_3.

The isolation of starting **1** in all cases other than Py and *N*-methylimidazole was indicative of very facile hydrolysis of the tosylates or mesylates of **1** or their corresponding quaternary salts by traces of H_2O at 0–25°C. Such unexpected results for the reactions of **1** with TsCl or MsCl and tertiary amines at 0–25°C in a solution of the amine or DMF indicated that conclusions about the structures of the synthesized compounds based on analyses of the reaction products should be made after detailed analyses of the NMR spectra.

Apparently, the anomalous course of the studied reaction was due to the benzyl nature of the hydroxymethyl group and the specific uracil structure and required further study.

The reaction of 5-hydroxymethyluracil with Py at room temperature for 70 h was reported to give 1-[(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]pyridinium chloride [12]. The reaction product was assigned the corresponding structure based on IR spectra and elemental analyses for N. Also, 1-[(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]pyridinium chloride was produced via convergent synthesis from the corresponding uracil and Py chloromethyl derivative. However, it is noteworthy that in our instance the quaternary ammonium salt of Py formed in high yield after 5 h at 0–25°C, in contrast with the previous work [12], with preference given to MsCl instead of TsCl.

Furthermore, the previous reaction product [12] was characterized only by its IR spectrum and elemental analysis for N. Our studies showed that such characterization could be insufficient to establish the structures of the obtained products. It is also noteworthy that the products (tosylates, mesylates, quaternary ammonium salts) were decomposed unusually easily by traces of H_2O. The conclusion that 1-[(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]pyridinium chloride resulted from convergent synthesis from the corresponding uracil hydrochloride [12] could be erroneous without a detailed study of the NMR spectra of the reaction product and treatment of it at room temperature with a weakly alkaline solution (Na_2CO_3).

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker Avance-III 500 MHz pulsed spectrometer at operating frequency 500.13 MHz for ^{1}H, 125.47 MHz for ^{13}C, and 50.58 MHz for ^{15}N using a 5-mm Z-gradient PABBO probe at constant sample temperature (298 K). Chemical shifts in ^{13}C NMR and PMR spectra were given in ppm with solvent resonances acting as internal standards. Those in ^{15}N NMR spectra were obtained from F_1-projections of $^{1}H–N^{15}$ HMBC spectra on the NH_3-scale. ^{13}C NMR spectra with proton suppression were recorded with spectral window 29.8 kHz, 64,000 points, exciting

pulse (30°) length 3.2 μs, relaxation delay 2 s, and 512–2048 scans. ^{13}C NMR spectra were interpreted based on DEPT-90 and DEPT-135 experiments. 2D spectra were recorded using standard multi-pulse sequences of the instrument software. The gs-COSY spectrum was recorded with 4K matrix size in 512 scans and spectral window 5.0 kHz. A sinusoidal bell-curve weighting function was used to process F_1 and F_2 projections (ssb = 2). The gs-HSQC spectra were recorded with a delay optimized for observing J_{CH} = 145 Hz and J_{NH} = 80 Hz, 2K matrix size, and 256 scans. The gs-HMBC spectra were recorded with a small-constant evolution delay of 71.4 ms for $^{1}H–^{13}C$ and 142.8 ms for $^{1}H–^{15}N$ HMBC, matrix size 2K, and 256 scans.

Elemental analyses were performed on a EURO-3000 instrument. Melting points were determined in glass capillaries.

Synthesis of Quaternary Ammonium Salts (General Method). A mixture of **1** (0.20 g, 1.30 mmol) in Py or *N*-methylimidazole (2 mL) was stirred at room temperature for 5 h and treated with CH_3SO_2Cl (0.12 mL, 1.56 mmol). The resulting precipitate was filtered off, rinsed with Me_2CO, and dried.

1-[(6-Methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]pyridinium Chloride (2). Yield 0.32 g (98%), mp 220–223°C (MeOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.40 (3H, s, CH_3), 5.58 (2H, s, H-7), 8.16 (2H, t, J = 7.7, H-10, 12), 8.64 (1H, t, J = 7.7, H-11), 9.12 (2H, d, J = 7.7, H-9, 13), 11.40 (1H, s, H-1), 11.46 (1H, s, H-3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 16.46 (q, C-14), 55.63 (t, C-7), 101.74 (s, C-5), 127.67 (d, C-10, 12), 144.45 (d, C-9, 13), 145.56 (d, C-11), 150.52 (s, C-2), 155.86 (s, C-6), 163.96 (s, C-4). ^{15}N NMR spectrum (50.58 MHz, DMSO-d_6, δ, ppm, J/Hz): 142.11 (d, ^{1}J = 99.9, N-1), 155.86 (d, ^{1}J = 90.6, N-3), 214.11 (s, N-8). $C_{11}H_{12}ClN_3O_2$.

1-Methyl-3-[(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]-1*H*-imidazolium-3 Chloride (3). Yield 0.32 g (97%), mp 265–267°C (MeOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.30 (3H, s, H-13), 3.86 (3H, s, H-14), 5.07 (2H, s, H-7), 7.73 (1H, d, J = 8.0, H-11), 7.75 (1H, d, J=8.0, H-12), 9.26 (1H, s, H-9), 11.33 (1H, s, H-1), 11.36 (1H, s, H-3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 16.80 (q, C-13), 35.64 (q, C-14), 43.56 (t, C-7), 102.05 (s, C-5), 122.24 (d, C-12), 123.34 (d, C-11), 136.24 (d, C-9), 150.50 (s, C-2), 154.52 (s, C-6), 163.82 (s, C-4). ^{15}N NMR spectrum (50.58 MHz, DMSO-d_6, δ, ppm, J/Hz): 141.7 (d, J = 93.5, N-3), 155.7 (d, J = 90.7, N-1), 171.0 (s, N-10), 182.9 (s, N-8). $C_{10}H_{13}ClN_4O_2$.

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