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SHORT COMMUNICATIONS

Features of the Synthesis of S-Monobenzyl and S,O-Dibenzyl, Di(*m*-phenoxybenzyl) Derivatives of 6-Methyl-2-thiouracil

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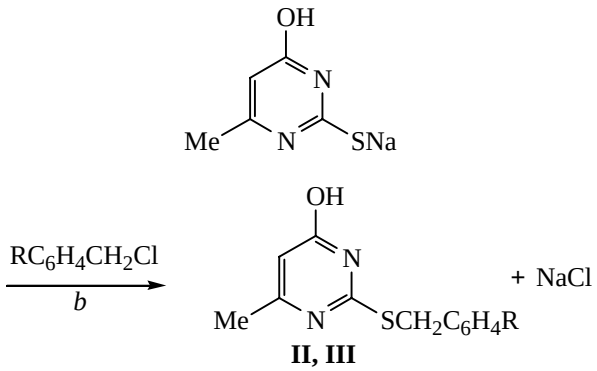
S-Benzyl derivative **II** of 6-methyl-2-thiouracil (**I**) is known [1] to form in reaction of benzyl chloride with compound **I** in DMF in the presence of K_2CO_3 at 75–80°C within 5–6 h in a 56% yield (method *a*).

We studied the synthesis of S-monobenzyl and S,O-dibenzyl, di(*m*-phenoxybenzyl) derivatives of compound **I** by reaction of nucleophilic replacement of chlorine in benzyl chloride and *m*-phenoxybenzyl chloride in a water-dioxane solution in the presence of NaOH (method *b*).

The comparison of the published procedure *a* of S-benzyl derivative **II** preparation with our method consisting in reaction of compound **I** monosodium salt with benzyl chloride in a water-dioxane solution revealed the advantage of the method *b*: The yield of 2-benzylthio-4-hydroxy-6-methylpyrimidine (**II**) was 72 and 96% by methods *a* and *b* respectively. Besides the reaction along procedure *b* occurred at milder conditions (50°C) and within shorter time (40–60 min). The reaction product is sparingly soluble in the reaction medium and separated in the course of the process.

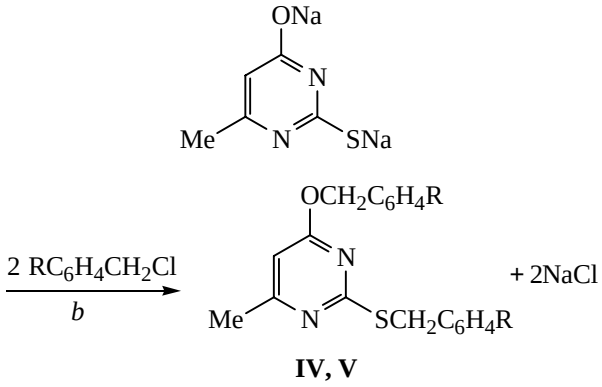


II, III

R = H (**II**), *m*-OPh (**III**).

The introduction of a phenoxy group into the *meta*-position of the ring in the benzyl chloride reduces its reactivity [2]. Under conditions of method *a* the yield of 4-hydroxy-6-methyl-2-(*m*-phenoxy-benzylthio)pyrimidine (**III**) was 62% whereas the reaction carried out by procedure *b* afforded compound **III** in a 94% yield.

Method *a* failed to provide biderivative of compound **I** whereas in the water-dioxane medium compound **I** disodium salt readily reacted furnishing S,O-disubstituted compounds **IV** and **V**.



IV, V

R = H (**IV**), *m*-OPh (**V**).

The yields of 3-benzyloxy-2-benzylthio-6-methylpyrimidine (**IV**) and 6-methyl-2-(*m*-phenoxybenzylthio)-3-(*m*-phenoxybenzyloxy)pyrimidine (**V**) were 90 and 83% respectively. They are well soluble in the water-dioxane mixture and were isolated by evaporating the solvent in a vacuum.

2-Benzylthio-4-hydroxy-6-methylpyrimidine (II). In 5 ml of water was dissolved 0.56 g (14 mmol) of

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sodium hydroxide and 2 g (14 mmol) of 6-methyl-2-thiouracil. To the solution was added 6 ml of dioxane and then dropwise a solution of 1.77 g (14 mmol) of benzyl chloride in 5 ml of dioxane. The mixture was stirred for 1 h at 50°C. On cooling the separated precipitate was filtered off, washed with cold water, dried, and recrystallized from benzene. Yield of colorless crystalline compound **II** 3.93 g (96%), mp 173–174°C (publ: mp 172–173°C [1]), R_f 0.62. ^{1}H NMR spectrum, δ, ppm: 2.2 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.95 s (1H, H^5), 7.05–739 m (5H, Ar–H), 1.2 C (1H, NH).

4-Hydroxy-6-methyl-2-(*m*-phenoxybenzylthio)-pyrimidine (III) was obtained by the same procedure. Yield 94%, colorless crystalline substance, mp 137–139°C, R_f 0.64. ^{1}H NMR spectrum, δ, ppm: 2.0 s (3H, CH_3), 4.25 s (2H, SCH_2), 5.95 s (1H, H^5), 6.75–7.40 m (9H, Ar–H), 12.2 s (1H, NH).

3-Benzyloxy-2-benzylthio-6-methylpyrimidine (IV). In 6 ml of water was dissolved 1.12 g (28 mmol) of sodium hydroxide and 2 g of 6-methyl-2-thiouracil. To the solution was added 6 ml of dioxane and then dropwise a solution of 3.54 g (28 mmol) of benzyl chloride. The mixture was stirred for 3 h at 50°C. On cooling the reaction mixture was filtered, the filtrate was evaporated in a vacuum, the residue was washed with cold water and recrystallized from benzene. Yield of colorless crystalline compound **IV** 3.61 g (90%), mp 59–60°C, R_f 0.73. ^{1}H NMR spectrum, δ, ppm: 1.8 s (3H, CH_3), 4.25 s (2H, SCH_2), 5.5 s (1H, H^5), 7.2–7.7 m (10H, Ar–H).

6-Methyl-2-(*m*-phenoxybenzylthio)-3-(*m*-phenoxybenzyloxy)pyrimidine (V) was obtained by the same procedure.. Yield 83%, colorless crystalline substance, mp 78–79°C, R_f 0.75. ^{1}H NMR spectrum, δ, ppm: 2.0 s (3H, CH_3), 4.3 s (2H, SCH_2), 5.8 s (1H, H^5), 6.20–7.45 m (18H, Ar–H).

^{1}H NMR spectra of compounds in DMSO-d_6 were registered on spectrometer Varian at operating frequency 300 MHz, internal reference HMDS. The homogeneity of compounds obtained was proved by TLC on Silufol UV-254 plates, eluent ethyl ether–ethanol (1:0.05 by volume), development in iodine vapor. Melting points were measured by melting compounds in capillaries.

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