ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 4, pp. 750–752. © Pleiades Publishing, Ltd., 2020.
Russian Text © The Author(s), 2020, published in Zhurnal Obshchei Khimii, 2020, Vol. 90, No. 4, pp. 642–644.

LETTERS TO THE EDITOR

Some Features of the Reaction of 6-Methyl-2*S*-substituted Pyrimidin-4-ols with the Vilsmeier–Haack Reagent

E. S. Ofitserova[a],*, A. A. Shklyarenko[a], and I. P. Yakovlev[a]

[a] *St. Petersburg Chemical and Pharmaceutical University of the Ministry of Health of Russia, St. Petersburg, 197376 Russia*
**e-mail: OfizerovaES@mail.ru*

Received November 1, 2019; revised November 1, 2019; accepted December 21, 2019

Abstract—Formylation of 6-methyl-2*S*-substituted pyrimidin-4-ols under the conditions of the Vilsmeier–Haack reaction leads to the formation of nucleophilic substitution products of the hydroxyl group. The formation of the expected formylation products does not occur.

Keywords: formylation, Vilsmeier–Haack reagent, 6-methyl-2*S*-substituted pyrimidin-4-ol

DOI: 10.1134/S1070363220040301

The carbonyl group introduced into the organic compound molecule is a convenient tool for constructing annelated heterocyclic structures [1] exhibiting a wide range of pharmacological properties [2]. The most acceptable way to obtain aldehydes is formylation according to Reimer–Tiemann or Vilsmeier–Haack reaction.

The use of the Vilsmeier–Haack reagent ($POCl_3$–DMF) for the formylation of most aromatic and heteroaromatic compounds has been sufficiently studied and described in [3]. Polyoxypyrimidine derivatives occupy a special place as substrates for carrying out the formylation reaction. Thus, during the formation of 2*S*-substituted derivatives of thiobarbituric acids [4, 5], simultaneously with the formation of the target compound, parallel nucleophilic substitution of one or more hydroxy groups of the pyrimidine ring occurs. Compounds synthesized in this way are interesting synthons for obtaining new polyheterocyclic structures [6].

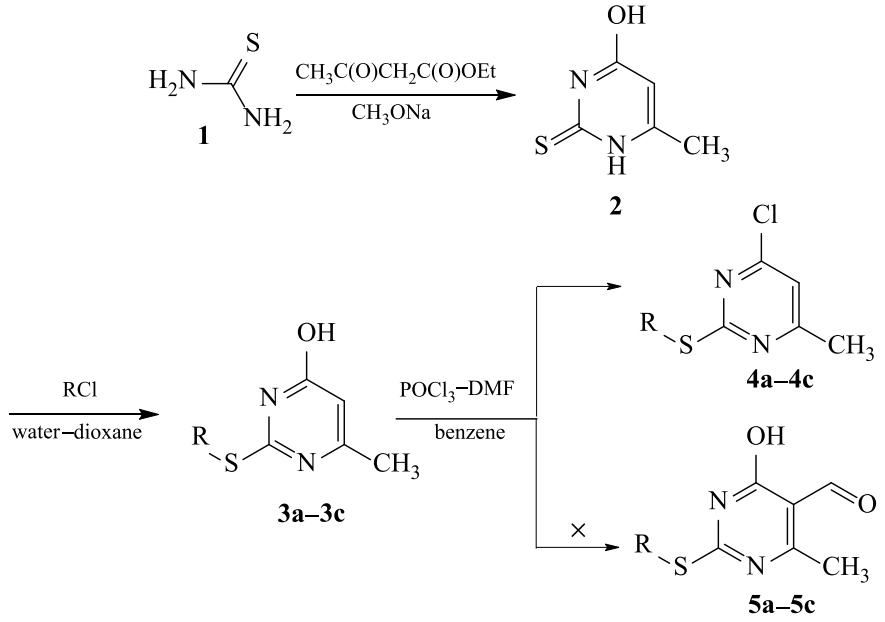
Of particular interest are the 6-methyl-2*S*-substituted pyrimidin-4-oles **3a–3c** obtained by the reaction of thiourea **1** with acetoacetic ester [7] followed by alkylation at the sulfur atom (Scheme 1). As in the case of 2*S*-substituted thiobarbituric acid, the formyl group was introduced under the conditions of the Vilsmeier–Haack reaction with an excess of phosphorus oxychloride [4, 5]. It was found that, regardless of the amount of excess phosphorus oxychloride, only the nucleophilic substitution of the hydroxy group in the molecule of the starting 6-methyl-2*S*-substituted pyrimidin-4-ol **3a–3c** occurs, and the resulting chlorine derivatives **4a–4c** does not enter into the formylation reaction.

General procedure for *S*-alkylation of 4-hydroxy-6-methylpyrimidine-2(1*H*)-thione (2). A mixture of 5.0 g (35.2 mmol) of 4-hydroxy-6-methylpyrimidine-2(1*H*)-thione **2** and 0.8 g (35.2 mmol) of sodium hydroxide dissolved in 10 mL of water was stirred until the precipitate was completely dissolved, then a solution of an alkylating agent (42.24 mmol) in 10 mL of dioxane was added. The resulting emulsion was stirred at room temperature for 12 h. The precipitate was filtered off and dried.

6-Methyl-2-(methylthio)pyrimidine-4-ol (3a). Yield 80%, white powder, mp 180–182°C (subl.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.16 s (3H, CH_3), 2.46 s (3H, SCH_3), 5.96 s (1H, pyrimidine), 12.44 br. s (1H, OH). Found, %: C 46.11; H 5.12; N 17.91; O 10.23. $C_6H_8N_2OS$. Calculated, %: C 46.13; H 5.16; N 17.93; O 10.24.

6-Methyl-2-[(1-naphthylmethyl)thio]pyrimidine-4-ol (3b). Yield 75%, white powder, mp 200–202°C (subl.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.27 s (3H, CH_3), 4.90 s (2H, SCH_2), 6.04 s (1H, pyrimidine), 7.44–7.48 m (1H, H_{Ar}), 7.54–7.62 m (2H, H_{Ar}), 7.67–7.69 m (1H, H_{Ar}), 7.87–7.89 m (1H, H_{Ar}), 7.95–7.97 m (1H, H_{Ar}), 8.13–8.15 m (1H, H_{Ar}), 12.51 br. s (1H, OH). Found, %: C 68.03; H

Scheme 1.



R = Me (**a**), 1-naphthylmethyl (**b**), *n*-Bu (**c**).

5.07; N 9.95; O 5.66. $C_{16}H_{14}N_2OS$. Calculated, %: C 68.06; H 5.00; N 9.92; O 5.67.

2-(Butylthio)-6-methylpyrimidine-4-ol (3c). Yield 67%, white powder, mp 85–86°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.91 t (3H, $CH_2C\underline{H}_3$, J_{HH} = 7.3 Hz), 1.35–1.44 m (2H, CH_2), 1.58–1.66 m (2H, CH_2), 2.16 s (3H, CH_3), 3.11 t (2H, SCH_2, J_{HH} = 7.3 Hz), 5.94 s (1H, pyrimidine), 12.42 br. s (1H, OH). Found, %: C 54.51; H 7.11; N 14.15; O 8.08. $C_9H_{14}N_2OS$. Calculated, %: C 54.52; H 7.12; N14.13; O 8.07.

General procedure for the formylation of 6-methyl-2*S*-substituted pyrimidine-4-thiones 3a–3c. To a suspension of 6-methyl-2*S*-substituted pyrimidine-4-ol **3** (2.5 mmol) in 7.5 mL of benzene, 5 mmol of dimethyl formamide and 7.5 mmol of phosphorus oxychloride were added while cooling. The reaction mixture was kept at 78–80°C for 8 h. After cooling, finely crushed ice (50 g) was added, then the mixture was stirred for 1 h. The precipitate was filtered off and dried.

6-Methyl-2-(methylthio)-4-chloropyrimidine (4a). Yield 80%, white powder, mp. 30–31°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 s (3H, CH_3), 2.55 s (3H, CH_3), 6.86 s (1H, pyrimidine). Found, %: C 41.24; H 4.02; N 16.02. $C_6H_7ClN_2S$. Calculated, %: C 41.26; H 4.04; N 16.04.

6-Methyl-2-[(1-naphthylmethyl)thio]-4-chloropyrimidine (4b). Yield 70%, white powder, mp 110–112°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.46 s (3H, CH_3), 4.92 s (2H, SCH_2), 6.89 s (1H, pyrimidine), 7.40–7.46 m (1H, H_{Ar}), 7.51–7.60 m (2H, H_{Ar}), 7.68–7.69 m (1H, H_{Ar}), 7.81–7.83 m (1H, H_{Ar}), 7.88–7.90 m (1H, H_{Ar}), 8.16–8.18 m (1H, H_{Ar}). Found, %: C 63.88; H 4.37; N 9.29. $C_{16}H_{13}ClN_2S$. Calculated, %: C 63.89; H 4.36; N 9.31.

2-(Butylthio)-6-methyl-4-chloropyrimidine (4c). Yield 70%, pale yellow powder, mp 26–27°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 t (3H, $C\underline{H}_3CH_2$, J_{HH} = 7.3 Hz), 1.40–1.49 m (2H, CH_2CH_2), 1.64–1.71 m (2H, CH_2CH_2), 2.4 s (3H, CH_3), 3.11 t (2H, CH_2S, J_{HH} = 7.3 Hz), 6.81 s (1H, pyrimidine). Found, %: C 49.86; H 6.03; N 12.92. $C_9H_{13}ClN_2S$. Calculated, %: C 49.88; H 6.05; N 12.93.

^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer with an operating frequency of 400 MHz using a solvent signal as a standard.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Ali, T.E., Ibrahim, M.A., El-Gendy, Z.M., and El-Amin, E.M., *Synth. Commun.*, 2013, vol. 43, p. 3329. https://doi.org/10.1080/00397911.2013.783074
2. Schenone, S., Bruno, O., Bondavalli, F., Ranise, A., Mosti, L., Menozzi, G., Fossa, P., Manetti, F., Morbidel-

li, L., Trincavelli, L., Martini, C., and Lucacchini, A., *Eur. J. Med. Chem*., 2004, vol. 39, p. 153. https://doi.org/10.1016/j.ejmech.2003.11.007

3. Rajput, A.P. and Girase, P.D., *Int. J. Pharm. Chem. Biol. Sci*., 2012, vol. 3, p. 25.
4. Ofitserova, E.S., Shklyarenko, A.A., Yakovlev, I.P., and Fedorova, E.V., *Russ. J. Org. Chem*., 2016, vol. 52, p. 1374. https://doi.org/10.1134/S1070428016090256
5. Ofitserova, E.S., Shklyarenko, A.A., and Yakovlev, I.P., *Zh. Registratsii i Razrabotki Lekarstvennykh Sredstv*, 2017, no. 1, p. 112.
6. Vignaroli, G., Mencarelli, M., Sementa, D., Crespan, E., Kissova, M., Maga, G., Schenone, S., Radi, M., and Botta, M., *ACS Comb. Sci*., 2014, vol. 16, p. 168. https://doi.org/10.1021/co500004e
7. Pivazyan, V.A., Ghazaryan, E.A., Shainova, R.S., Tamazyan, R.A., Ayvazyan, A.G., and Yengoyan, A.P., *J. Chem*., 2017, vol. 2017, p. 1. https://doi.org/10.1155/2017/8180913