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Synthesis and properties of CF_2X-substituted 4-methyl-2-hydroxy(chloro)pyrimidines

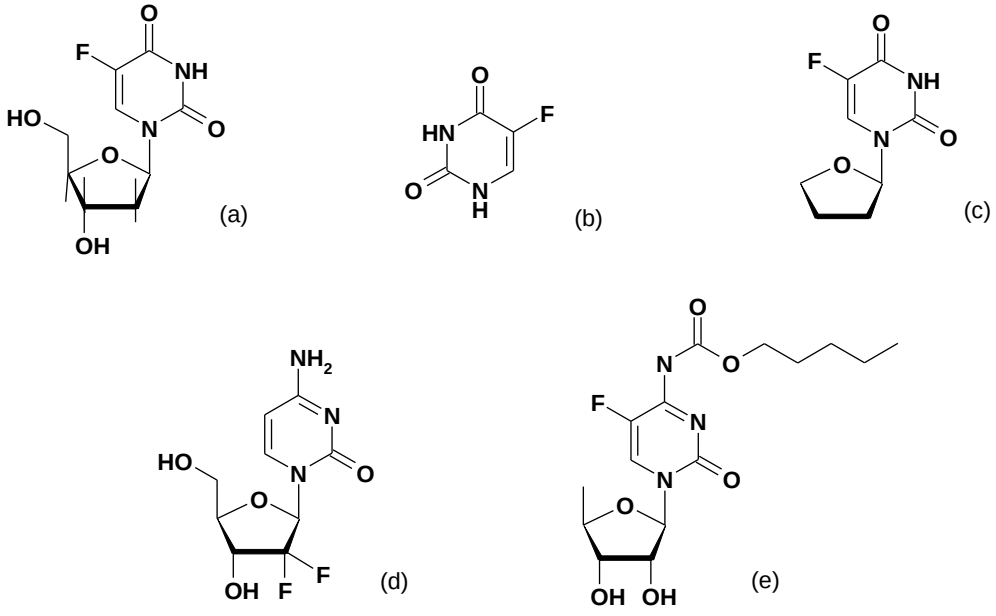
*V. **I. Dyachenko***

A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, V-334, GSP-1, 119991 Moscow, Russia
e-mail: vic-d.60@mail.ru

Abstract: *4-Trifluoromethyl-6-methylpyrimidine-2-ol (3a) and 4-difluoromethyl-6-methylpyrimidine-2-ol (3b) were synthesized by the condensation of 1,1,1-trifluoropentane-2,4-dione (1a) and 1,1-difluoropentane-2,4-dione (1b) correspondently with urea (2) in CH_3CO_2H under reflux in high yields. 2-Chloro-4-trifluoromethyl-6-methylpyrimidine (4a) and 2-chloro-4-difluoromethyl-6-methylpyrimidine (4b) were obtained by the reaction of (3a) and (3b) correspondently with $POCl_3$.*

Keywords:*1,1,1-trifluoropentane-2,4-dione, 1,1-difluoropentane-2,4-dione, 4-trifluoromethyl-6-methylpyrimidine-2-ol, 4-difluoromethyl-6-methylpyrimidine-2-ol, 2-chloro-4-methyl-6-trifluoromethyl-pyrimidine, 2-chloro-4-difluoromethyl-6-methylpyrimidine.*

Pyrimidine bases, which are included in DNA composition, along with purines, are universal chemical base for recording, holding and transferring of information about living organisms construction [1]. Scientists found out the way how to influence the speed of processes occurring in cells by partially changing nucleotides structure without its mispairing. «Masking effect», connected with atoms H and F proportions, is the most frequently used method for that purpose [15].
Floxuridine, 5-fluorouracil, tegafur, gemcitabine and capecitabine able to integrate into the structure of DNA and RNA replacing natural nucleotides slow down the activity and division of cancer cells and thus found application in medical practice. (Pic.1).



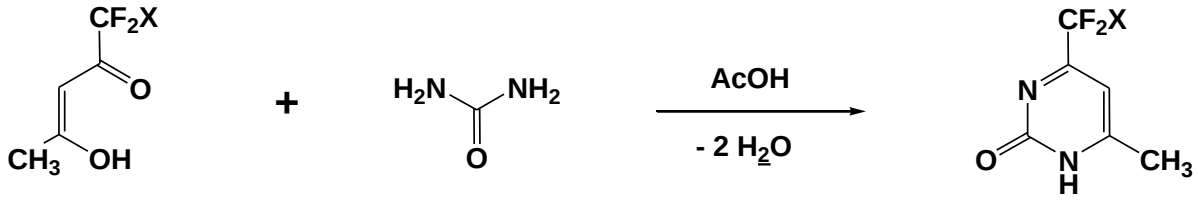
Pic.1. Synthetic fluorine-containing pyrimidines: floxuridine (a), fluorouracil (b), tegafur (c), gemcitabine (d) and capecitabine (e)

CF_3-Substituted pyrimidines are also important for sell metabolism. 4-Trifluoromethyl-6-methylpyrimidine-2-ol (**3a**) derivatives are chemokine receptor antagonists [2]. Vinylpyrimidones obtained on its base exhibit antiviral activity [3]. Chiral 4-trifluoromethyl-6-methylpyrimidine 2-phenoxypropionates are suggested as

herbicides [4]. Other its analogues are effective fungicides [5]. Substituted piperazines containing the structure of 4-trifluoromethyl-6-methylpyrimidine are patented as modulators of X-receptors of liver [6], and 1,2,5-oxadiazepam derivatives are used for treatment of depression, dementia and also Alzheimer’s disease [7].

The goal of this study is a search of effective methods for the preparation of 4-tri(di)fluoromethyl-6-methylpyrimidine-2-oles **3a,b** and the synthesis of its 2-chlorine-containing analogues **4a,b** (Scheme 1). 4-Trifluoromethyl-6-methylpurimidine-2-ol **3a** was obtained for the first time in 1941 by refluxing of 1,1,1-trifluoropentane-2,4-dione **1a** and urea **2** in ethanol in the presence of H_2SO_4 for 24-48 hours with the yield of 87% [8, 9].

Scheme 1.



1a,b **2** **3a,b**

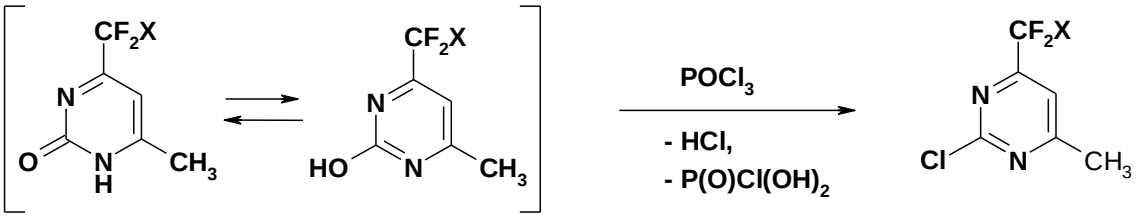
X = F (1a, 3a); H (1b, 3b)

Later it was stated that in these conditions the authors [2, 3] succeed in preparation of pyrimidine **3a** only in 15 and 20% yield correspondingly. Pyrimidine’s **3a** yield also was not higher than 19% by the reaction of pentandione **1a** with cyanamide [10]. According to the literature data [11, 13], condensation of urea with other 1,3-diketones containing one fluorinated substituent by refluxing for 20 hours in ethanol in the presence of concentrated HCl, leads to the pyrimidine-2-ol with the yield only of 34%.

We found out that diketone **1a** reacts with urea **2** at "green chemistry" conditions – under reflux in glacial acetic acid for 1-1,5 hours. Spectroscopically pure **3a** was obtained by crystallization from water with the yield higher than 90%. In the same conditions, using the condensation of 1,1-difluoropentane-2,4-dione **1b** and urea, we obtained 4-difluoromethyl-6-methylpyrimidine-2-ol **3b** for the first time in 83% yield . (Scheme 1). The results obtained show that low yields of pyrimidine **3a** published earlier was due to the reaction temperature which was not high enough. In fact, instead of boiling in acetic acid offered by us (boiling temperature 118ºC), in all previous studies [2, 3, 11-13] condensation of diketone **1a** and urea **2** was held in ethanol (boiling temperature 78ºC). Dispensing with the temperature influence on the reaction rate, the authors emphasized the acid catalysis (H_2SO_4, HCl, p-CH_3-C_6H_4-SO_3H), which, as it seems, is not the most important in these transformations. We found that **3a** formation occurs with comparable speed and with the same yield by refluxing of **1a** and **2** in ethylene glycol monomethyl ether (its boiling temperature 124ºC, that is near to bp of acetic acid), as in acetic acid, while ethylene glycol monomethyl ether is not an acid.

In order to expand the synthetic capabilities of pyrimidines containing CF2X-function, we studied nucleophilic substitution of the the OH-group for chlorine in **3a,b**. Earlier it was noted [2] that when refluxing **3a** with $POCl_3$ the maximum yield of chloropyrimidine **4a** was 37%. The same result [14] was obtained in the reaction **3a** with phosphorus oxide in the presence of DMAP at 95ºC.

Scheme 2.



3a,b **4a,b**

X = F (3a, 4a); H (3b, 4b)

We have shown that when refluxing with $POCl_3$ for 11 hours **3a** turns into the corresponding 2-chlorinated derivative **4a** with a high conversion (Scheme 2). After isolation of the product from the reaction mixture and vacuum distillation, 2-chloro-4-methyl-6-trifluoromethylpyrimidine **4a** was obtained in a yield of 76.5%. According to gas chromatography data its purity was 99%. 2-Chloro-4-difluoromethyl-6-methylpyrimidine **4b** was obtained for the first time from the compound **3b**, using the same method, in 74.4% yield.

Presumably, low yields of chloropyrimidine **4a** obtained earlier [2, 14] was due to the high reaction ability of chlorine in 2-position and peculiarities of its isolation.

Experimental

^1H, ^{19}F NMR spectra were recorded in D_6-DMSO and $CDCl_3$ using «Bruker Avanse 400» spectrometer with operating frequency 400.13 MHz, 376.5 MHz correspondingly. Chemical shifts for ^1H are given according toTMS (internal standard), ^{19}F according to CF_3CO_2H – external standard. Spin-spin interaction constants are given in MHz. Mass-spectrum are recorded on quadrupolar spectrometer *Finnigan MAT INCOS 50* (direct input, ionization energy 70 eV).

4-Trifluoromethyl-6-methylpyrimidine-2-ol (3a) 4.8 g (80 mmol) of urea **2** and 12.8 g (80 mmol) of 1,1,1-trifluoroacetylacetone **1a** during 1 hour were being reflux in 48 ml of glacial acetic acid in a glass bulb equipped with a reflux condenser, dropping funnel and magnetic stirrer**.** The reaction mixture was evaporated on a rotor evaporator and the crude product **3a** was crystallized from water, filtered, dried on air, then in vacuum desiccator over P_2O_5. White crystalline pyrimidine **3a** (13 g) was obtained, melting point 181-182ºC (water). Yield 91%. R_f=0.4 (ethylacetate). ^1H NMR spectra,(*δ*, ppm): 12.76 (br. s., 1H, OH); 6.77 (s, 1H, Het); 2.35 (s, 3H, CH_3). ^{19}F NMR spectra, (*δ*, ppm): 7.85 (s). Mass-spectra, *m*/*z*): 178 $[M]^+$. Found, %: C, 40.33; H, 2.71; F, 31.78. $C_6H_5F_3N_2O$. Calculated, %: C 40.46; H 2.83; F 32.00.

4-Difluoromethyl-6-methylpyrimidine-2-ol (3b) was obtained using the same method as **3a** from 1.2 g (20 mmol) of urea **2** and 3.2 g (20 mmol) of 1,1-difluoroacetylacetone **1b** in 12 ml of glacial acetic acid for 1.5 hour. The solvent was evaporated on a rotor evaporator, and the oil obtained was treated with ether while mixing. The solid residuum was cooled to -15ºC, ground while mixing and filtered. The product was washed with ether and dried on filter, 2.7 g of amorphous substance **3b** were obtained. Yield 83%, melting point 130-131ºC (*tert*-BuOH), R_f=0.5 (acetone-ethyl

acetate=1:3). ^{1}H NMR spectra, (*δ*, ppm; *J,* MHz): 12.36 (br. s, 1H, OH); 6.60 (t, 1H, CF_2H, ^2J=52); 6.53 (s, 1H, Het); 2.30 (s, 3H, CH_3). ^{19}F NMR spectra, (*δ*, ppm; *J,* MHz): –120.00 (d, 2F, CF_2H, ^2J=52). Mass-spectra, *m*/*z*: 160 $[M]^+$. Found, %: C, 45.00; H, 3.63; F, 23.31. $C_6H_6F_2N_2O$. Calculated, %: C, 45.01; H, 3.78; F, 23.73.

2-Chloro-4-methyl-6-trifluoromethylpyrimidine (4a) In a glass bulb equipped with a reflux condenser and magnetic stirrer with heating 14.2 g (0.08 mmol) of **3a** and 90 g of $POCl_3$ were refluxed for 11 hours. The reflux condenser was changed to descending condenser and the excess of $POCl_3$ was distilled at a normal pressure. After this, from the stillage residue chloropyrimidine **4a** and other volatile compounds were distilled with water jet pump (15 mm Hg). For **4a** purification crude chloropyrimidine **4a** with $POCl_3$ admixture was added drop by drop in a 1 l glass with. 200 ml of cold water. At the same time concentrated soda solution was added in the reaction mixture. **4a** was extracted from the reaction mixture with benzene (50 ml x 3 times), organic solution was dried with calcium chloride and filtered through silica gel. After removing of the solvent 14 g of thin oil were obtained. By its distillation with Wurtz cap 12 g (76.5%) of chloropyrimidine **4a** was obtained, boiling temperature 69-70°C/11 mm Hg, n_D^{20} 1.4450. Its purity is 99%. ^{1}H NMR spectra, (*δ*, ppm): 7.46 (s, 1H, Het); 2.67 (s, 3H, CH_3). ^{19}F NMR spectra, (*δ*, ppm): –6.78 (s, 3F, CF_3). Mass-spectra, *m*/*z*: 196 $[M]^+$. Found, %: C, 36.38; H, 2.15; F, 28.69. $C_6H_4ClF_3N_2$. Calculated, %: C, 36.66; H, 2.05; F, 29.00.

2-Chloro-4-difluoromethyl-6-methylpyrimidine (4b) was obtained using the same method as **4a** by refluxing 14.4 g (0.09 mmol) of **3b** and 105 g of $POCl_3$ for 12 hours. After the crude product distillation under vacuum with Wurtz cap 11.9 g of **4b** was obtained in the form of transparent oil liquid with the boiling point 84-85°C/11 mm Hg. Yield 74.4 %. n^{20}_D = 1.4800. ^{1}H NMR spectra, (*δ*, ppm; *J,* MHz): 7.42 (s, 1H, Het); 6.48 (t, 1H, CF_2H, *J*=52); 2.63 (s, 3H, CH_3). ^{19}F NMR spectra, (*δ*, ppm; *J,* MHz): -120.00 (d, 2F, CF_2H, ^2J=52). Mass-spectra, *m*/*z*: 178 $[M]^+$. Found, %: C, 39.99; H, 3.01; F, 20.98. $C_6H_5ClF_2N_2$. Calculated, %: C, 40,36; H, 2.82; F, 21.28.

Conclusion

Eco-friendly, low energy-consuming method of 4-CF_2X-substituted 6-methylpyrimidine-2-ol **3a,b** preparation was found. Using this method, 4-difluoromethyl-6-methylpyrimidine-2-ol **3b** was obtained for the first time.

2-chloro-4-methyl-6-trifluoromethylpyrimidine **4a** and 2-chloro-4-difluoromethyl-6-methylpyrimidine **4b** were obtained with the yields higher than 74% for the first time by refluxing of pyrimidine-2-ol **3a,b** with phosphorus chlorooxide.

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Literature

1. A. Kornberg, T. A. Baker. Chapter 15: The replication mechanisms and operations // DNA replication. — Sausalito, Calif.: University Science Books, **2005**.
2. C. G. Kenneth, R. Prakash, S. Francois. Y. Qing, G. Shomir, *WO 2006071875,* **2006**.

3. A. Missio, T. Herget, A. Aschenbrenner, B. Kramer, J. Leban, K. Wolf, *WO 2004016271,* **2004**.
4. T. Haiyang, H. Tonghui, Z. Aidong, H. Changjian, *Patent China № 101613322,* **2009**.
5. L. Long, L. Qiang, T. Qinghong, L. Xinting, D. Ming, L. Shimeng, S. Juan, *Patent China № 103965117,* ***2014****.*
6. D. A. Claremon, C. Dong, Y. Fan, K. Leftheris, S. D. Lotesta, S. B. Singh, C. M. Tice, W. Zhao, Y. Zheng, L. Zhuang, *WO 2016022521,* **2016.**
7. T. Kamei, Y. Arikawa, T. Ohashi, T. Imaeda, I. Fujimori, T. Miki, J. Yonemori, Y. Oguro, T. Sugimoto, M. Seto, G. Nishida, M. Kamata, H. Imoto, *WO 201617124*, **2016**.
8. J. J. Donleavy, M. A. Kise*, Org. Synth.* 1, **1941**.
9. J. C. Sloop, C. L. Bumgardner, W. D. Loehle, *J. Fluor. Chem.,* **2002**, 118-135.
10. A. Miller, *J. Org. Chem.,* 1984, 49, 21, 4072, DOI:10.1021/jo00195a043.
11. A. Kreutzberger, U. H. Tesch, *Chem. Ber.,* **1976**, 109, 10, 3255.
12. S. Dilli,. K. Robards, *Austral. J. Chem.,* **1978**, 31, 8, 1833.
13. Ya. V. Burgart, O. S. Kuzueva, M. V. Pryadeina, C. O. Kappe and V. I. Saloutin, *Russ. J. Org. Chem.*, **2001**, 37, 6, 869. (*Zh. Org. Khim.,* **2001**, 37, 6, 915).
14. H. Tu, T. Huang, A. Zhang, C. Hou, *Patent China № 101613322,* **2009**.
15. H-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637, DOI: 10.1002/cbic.200301023.

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