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New possibilities of the functionalization of 6-hydrazino-1,3-dimethyluracils: one-pot synthesis of 5,7-dimethylpyrazolopyrimidine-4,6-dione and 1,3-dimethyl-5-arylidenebarbituric acid derivatives

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Abstract

3-aryl-5,7-dimethylpyrazolopyrimidine-4,6-diones and 5-benzylidene-1,3-dimethylpyrimidine-2,4,6-triones were obtained by heating hydrazones of 1,3-dimethyl-6 -hydrazinouraciles in trifluoroacetic acid (TFA). The same compounds were also obtained by heating the hydrazones of 1,3-dimethyl-6-hydrazinouraciles in aqueous ethanol in the presence of hydrochloric acid.

Keywords

1,3-dimethyl-6-hydrazinouracil hydrazones
pyrazolopyrimidine-6,8-diones
1,3-dimethylbarbituric acid

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1. Introduction

Derivatives of pyrimidine (uracil, cytosine, thymine) are part of nucleic acids, which are carriers of hereditary traits in living organisms and are involved in the synthesis of proteins. The pyrimidine core is a component of bicyclic systems such as purine and pteridine. It is known that pyrazolopyrimidine derivatives have a wide spectrum of biological activity, including antimicrobial[1, 2, 3], antiviral[4, 5], anti-inflammatory and etc. [6, 7, 8].

As a result of the cyclization of hydrazinouracils with the corresponding reagents, derivatives of pyrimidodiazoles and pyrimidotriazines were obtained [9]. 5,7-dimethyl-3-phenylpyrazolopyrimidine-4,6-dione was obtained by heating 6-arylidenehydrazine-1,3-dimethyluracils with thionyl chloride in dry benzene from a mixture of reaction products [10]. As a result of boiling the derivatives of 1,3-dimethyl-6-hydrazinouracil with an equimolar amount of N-bromosuccinimide in acetic acid, the derivatives of the corresponding pyrimidoazoles were isolated [11]. The hydrazone of 3-methyl-5-nitro-6-hydrazinouracil was cyclized on heating in DMF to form 3-arylpyrazolopyrimidine-4,6-dione; The same compound was obtained by nitration of hydrazones of 3-methyl-6-hydrazinouracil [12].

Analysis of the literature showed that pyrimidopyrazoles were obtained in the presence of an easily leaving group in the hydrazinouracil molecule, which undergoes *ipso*-substitution followed by annulation of the pyrazole ring.

In this work, we have studied the transformations of 6-hydrazino-1,3-dimethyluracil to find ways to synthesize new potentially biologically active compounds, as well as to improve the methods for preparing known compounds.

2. Experimental

Unless otherwise indicated, all common reagents and solvents were used from commercial suppliers without further purification.

The reaction progress and purity of the obtained compounds were controlled by TLC method on Sorbfil UV-254 plates, using visualization under UV light. Melting points were determined on a Stuart SMP10 melting point apparatus. ^{1}H, ^{13}C and ^{19}F NMR spectra were acquired on Bruker Bruker AVANCE-400 spectrometer in DMSO-d_6 solutions, using TMS as internal reference for ^{1}H and ^{13}C NMR or $CFCl_3$ for ^{19}F NMR. Mass-spectra (EI, 70 eV) were recorded on MicrOTOF-Q instrument (Bruker Daltonics) at 250 °C. Elemental analysis was performed using a Perkin-Elmer 2400 Series II CHNS/O analyzer.

1,3-Dimethyl-6-hydrazinopyrimidine-2,4-dione 1 was obtained according to the method described in [13].

The general method for the synthesis of hydrazones ***2a-c***

1.0 mmol of hydrazine 1 was dissolved in a mixture of 3 ml of water and 3 ml of alcohol, 1.0 mmol of aldehyde dissolved in 5 ml of alcohol was added to the resulting solution, and the mixture was heated for 1-2 minutes. The formed precipitate was filtered off, washed with 1 ml of alcohol.

6-(2-benzylidenehydrazinyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione 2a. Yield 85 %, m.p. 260-261 °C. (Ref. 261 °C [12]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.18 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 5.51 (s, 1H, CH), 7.38-7.41 (m, 3H, CH_{ar}), 7,70 (d, J = 6.4 Hz, 1H, CH_{ar}), 8.34 (s, 1H, CH_{ar}), 10.38 (s, 1H, NH). Mass spectrum (EI, 70 eV), *m/z* (%): 258 (100) $[M]^+$, 142 (35), 104 (38), 90 (49). Found (%): C, 60.51; H, 5.52; N, 21.71. Calculated for $C_{13}H_{14}N_4O_2$ (%): C, 60.45; H, 5.46; N, 21.69.

6-(2-(4-(dimethylamino)benzylidene)hydrazinyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione 2b. Yield 80 %, m.p. 251-252 °C. (Ref. 252 °C [14]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.02 (s, 6H, $2CH_3$), 3.16 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 5.44 (s, 1H, CH), 6.67 (d, J = 8.8 Hz, 2H, CH), 7.50 (d, J = 8.8 Hz, 2H, CH), 8.17 (s, 1H, CH), 10.00 (s, 1H, NH). Mass spectrum (EI, 70 eV), *m/z* (%): 301 (18) $[M]^+$, 284 (2), 132 (48), 55 (100). Found (%): C, 59.81; H, 6.40; N, 23.22. Calculated for $C_{15}H_{19}N_5O_2$ (%): C, 59.79; H, 6.36; N, 23.24

1,3-dimethyl-6-(2-(4-nitrobenzylidene)hydrazinyl)pyrimidine-2,4(1*H*,3*H*)-dione 2c. Yield 85 %, m.p. 285-286 °C. (Ref. 285 °C [14]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.18 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 5.56 (s, 1H, CH), 7.98 (d, J = 8.8 Hz, 2H, CH), 8.25 (d, J 8.8 Hz, 2H, CH), 8.43 (s, 1H, CH), 10.74 (s, 1H, NH). Mass spectrum (EI, 70 eV), *m/z* (%): 303 (18) $[M]^+$, 256 (2), 218 (12), 142 (32). Found (%): C, 51.52; H, 4.27; N, 23.13. Calculated for $C_{13}H_{13}N_5O_4$ (%): C, 51.48; H, 4.32; N, 23.09.

Reactions of hydrazones ***2a-c*** *with TFA*

0.5 mmol of hydrazone **2** was heated in 1.5 ml of TFA in a closed vessel at 110 ° C for 85-90 hours. The solvent was removed in vacuo. The solid residue was treated with 3 ml of ethanol. The resulting precipitate of product **4** was filtered off. The alcoholic mother liquor was treated with 1-2 ml of water, the precipitate that formed was filtered off to obtain product **3**.

5,7-dimethyl-3-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione 3a. Yield 20 %, m.p. 256-257 °C. (Ref. 257 °C [11]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.30 (s,3H, CH_3), 3.49 (s, 3H, CH_3), 7.46-7.50 (m, 3H, CH_{ar}), 8.14-8.16 (m, 2H, CHar), 13.64 (br.s, 1H, NH). Mass spectrum (EI, 70 eV), *m/z* (%): 256 (92) $[M]^+$, 199 (38), 171 (100). Found (%): C, 60.96; H, 4.75; N, 21.83. Calculated for $C_{13}H_{12}N_4O_2$ (%): C, 60.93; H, 4.72; N, 21.86.

3-(4-(dimethylamino)phenyl)-5,7-dimethyl-1H-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione 3b. Yield 18 %, m.p. 272-273 °C. (Ref. 273 °C [12]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.05 (s, 6H, $2CH_3$), 3.29 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 6.74 (d, J = 8.8 Hz, 1H, CH_{ar}), 8.07 (d, J = 8.8 Hz, 1H, CH), 13.2 (br.s, 1H, NH). Mass spectrum (EI, 70 eV), *m/z* (%): 299 (100) $[M]^+$, 242 (14), 134 (17). Found (%): C, 60.24; H, 5.75; N, 23.42. Calculated for $C_{15}H_{17}N_5O_2$ (%): C, 60.19; H, 5.72; N, 23.40.

5,7-dimethyl-3-(4-nitrophenyl)-1*H*-pyrazolo[3,4-d]pyrimidine-4,6(5*H*,7*H*)-dione 3c. Yield .45 % m.p. >300 °C. (Ref. >300 °C [11]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.31 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 8.34 (d, J = 8.8 Hz, 2H, CH), 8.47 (d, J = 8.8 Hz, 2H, CH), 14.08 (s, 1H, NH). Mass spectrum (EI, 70 eV), *m/z* (%): 301 (100) $[M]^+$, 244 (26), 216 (12), 142 (69). Found (%): C, 51.86; H, 3.71; N, 23.28. Calculated for $C_{13}H_{11}N_5O_4$ (%): C, 51.83; H, 3.68; N, 23.25.

5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4a. Yield 25 %, m.p. 159-160 °C. (Ref. 160 °C [15]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.25 (s, 3H, CH_3), 3.29(s, 3H, CH_3), 7.45-7.53 (m, 3H, $3CH_{ar}$), 8.05-8.07 (d, 2H, $2CH_{ar}$), 8.38 (s, 1H, CH). Mass spectrum (EI, 70 eV), *m/z* (%): 243 (100) $[M-1]^+$, 186 (35), 130 (40), 102 (60). Found (%): C, 63.96; H, 4.99; N, 11.53. Calculated for $C_{13}H_{12}N_2O_3$ (%): C, 63.93; H, 4.95; N, 11.47.

5-(4-(dimethylamino)benzylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4b. Yield 25% m.p. 240-242 °C. (Ref. 241 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.19 (s, 6H, $2CH_3$), 3.28 (s, 6H, $2CH_3$), 6.74-6.77 (d, 2H, $2CH_{ar}$), 8.39-8.41 (d, 2H, $2CH_{ar}$), 8.24 (s, 1H, CH). Mass spectrum (EI, 70 eV), *m/z* (%): 287 (100) $[M]^+$, 286(70), 144 (18). **Found (%):** C, 62.21; H, 5.99; N, 14.67. Calculated for $C_{15}H_{17}N_3O_3$ (%): C, 62.17; H, 5.96; N, 14.63.

1,3-dimethyl-5-(4-nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4c. Yield 17%, m.p. >300 °C. (Ref. >300 °C [16]). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.31 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 8.18 (s, 1H, CH), 8.34 (d, J = 9.2 Hz, 2H, CH_{ar}), 8.49 (d, J = 9.2 Hz, 2H, CH_{ar}). Mass spectrum (EI, 70 eV), *m/z* (%): 288 (87) $[M]^+$, 288 (100), 272 (64), 242 (58), 156 (55). Found (%): C, 54.01; H, 3.85; N, 14.64. Calculated for $C_{13}H_{11}N_3O_5$ (%): C, 53.98; H, 3.83; N, 14.53.

Conversions of hydrazones ***2a-c*** *in ethanol in the presence of acid.*

0.02 Mmol of the corresponding compound **2** in 3 ml of ethanol and the presence of 0.25 ml of concentrated hydrochloric acid was kept at reflux for 2.5-3 hours. The reaction mixture was cooled, precipitate **4** was filtered off.

The melting points and spectral characteristics of the obtained compounds **4a-c** were similar to those obtained earlier.

5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4a. Yield 48%.

5-(4-(dimethylamino)benzylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4b. Yield 53%.

1,3-dimethyl-5-(4-nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4c. Yield 54%.

Reaction of 1,3-dimethylbarbituric acid with aldehydes.

0.05 mmol of barbituric acid **5** was heated in 5.0 ml of ethanol with 0.05 mmol of the corresponding aldehyde in the presence of 0.25 ml of HCl for 25-30 minutes. The reaction mixture was cooled, the precipitate of the corresponding product **4** was filtered off.

The melting points and spectral characteristics of the obtained compounds **4a-c** were similar to those obtained earlier.

5-benzylidene-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4a. Yield 60%.

5-(4-(dimethylamino)benzylidene)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4b. Yield 54%.

1,3-dimethyl-5-(4-nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 4c. Yield 70%.

3. Results and Discussion

We used hydrazones **2a-c**, as objects of study, obtained by short-term heating of 1,3-dimethyl-6-hydrazinouracil **1** in aqueous-alcoholic solutions with the corresponding aldehydes in the presence of HCl (Scheme 1).

We found that heating hydrazones **2a-c** in TFA gave 5,7-dimethylpyrazolopyrimidine-4,6-diones **3a-c** and 5-benzylidene-1,3-dimethylpyrimidine-2,4,6-trione derivatives **4a-c**. Considering the literature data, it can be assumed that the formation of pyrazolopyrimidines **3a-c** occurs through the 5-trifluoroacyl intermediate **A**. The formation of intermediate **A** occurs as a result of acylation of the starting hydrazones **2a-c** of TFA. During this process, water is released and the process of cleavage of hydrazones with the formation of compounds **4a-c** is started.

To confirm the proposed reaction mechanism, we investigated the transformations of hydrazones **2** upon heating in aqueous ethanol in the presence of hydrochloric acid. As a result of the reactions, derivatives of barbituric acid **4a-c** were obtained (Scheme 2).

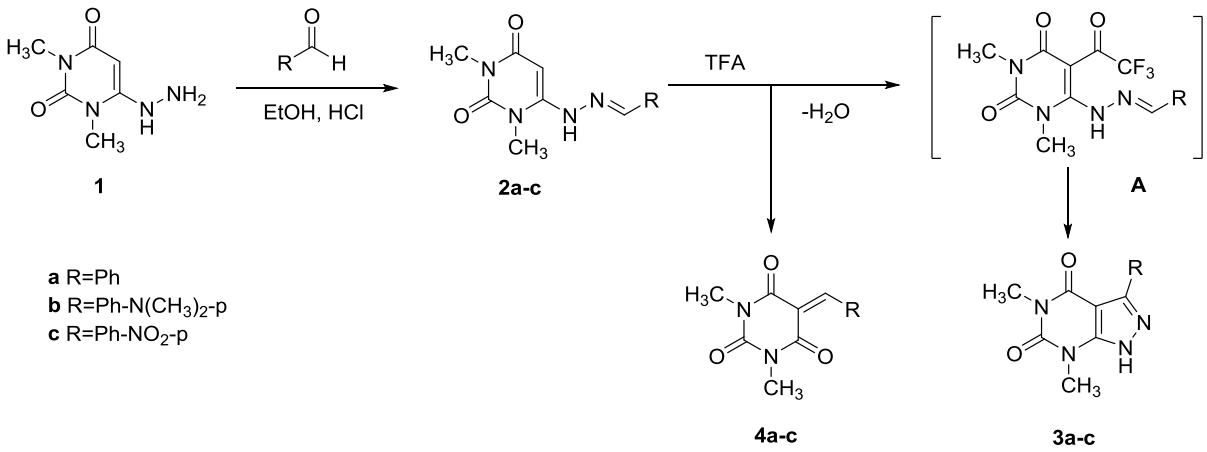
The formation of arylidene derivatives apparently occurred as a result of the transfer of the aldehyde group from the hydrazine fragment to the 5-position of the pyrimidine nucleus with the formation of intermediate A. Then, acid hydrolysis of the hydrazino group of intermediate **A** took place, giving derivatives of barbituric acid **4**.

Products **4a-c** were also obtained by heating 1,3-dimethylbarbituric acid **6** with the corresponding aldehydes.

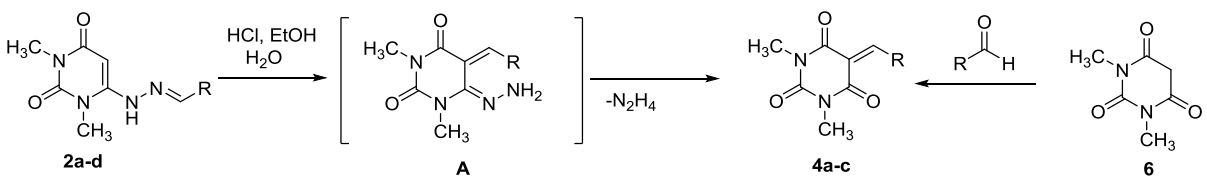
4. Conclusions

Thus, as a result of the conducted studies, a new one-pot method for the synthesis of derivatives of 5,7-dimethylpyrazolopyrimidine-4,6-dione and 5-benzylidene-1,3-dimethylpyrimidine-2,4,6-trione was discovered.

Scheme 1:



Scheme 2:



a R=Ph; b R=Ph-N(CH$_3$)$_2$-p; c R=Ph-NO$_2$-p

References

1. Rashad AE, Shamroukh AH, Ali HS, Abdel-Megeid FME. Some New Pyrazole and Pyrazolopyrimidines: Synthesis and Antimicrobial Evaluation. J Heterocycl Chem. 2013;50:758-65. doi:10.1002/jhet.1550
2. Eweas AF, Swelam SA, Fathalla OA. Synthesis, anti-microbial evaluation, and molecular modeling of new pyrazolo[3,4-d]pyrimidine derivatives. Med Chem Res. 2012;21:3848-57. doi:10.1007/s00044-011-9911-y
3. Aggarwal R, Sumran G, Garg N, Aggarwal AA. A regioselective synthesis of some new pyrazol-1′-ylpyrazolo[1,5-*a*]pyrimidines in aqueous medium and their evaluation as antimicrobial agents. Eur J Med Chem. 2011;46:3038-46. doi:10.1016/j.ejmech.2011.04.041
4. Rashad AE, Shamroukh AH, Abdel-Megeid RE, Ali SH. Synthesis and Isomerization of Some Novel Pyrazolopyrimidine and Pyrazolotriazolopyrimidine Derivatives. Molecules. 2014;19:5459-69. doi:10.3390/molecules19055459
5. Gudmundsson KS, Johns BA, Weatherhead AA. Pyrazolopyrimidines and pyrazolotriazines with potent activity against herpesviruses. J Bioorg Med Chem Lett. 2009;19:5689-92. doi:10.1016/j.bmcl.2009.08.009
6. Yewale SB, Ganorkar SB, Baheti KG, Shelke RU. Novel 3-substituted-1-aryl-5-phenyl-6-anilinopyrazolo[3,4-d]pyrimidin-4-ones: Docking, synthesis and pharmacological evaluation as a potential anti-inflammatory agents. Bioorg Med Chem Lett. 2012;22:6616-20. doi:10.1016/j.bmcl.2012.08.119
7. El-Tombany AA. Synthesis, anti-inflammatory, and Ulcerogenicity studies of novel substituted and fused pyrazolo[3,4-d]pyrimidin-4-ones. Sci Pharm. 2013;81:393-422. doi:10.3797/scipharm.1211-21
8. Alcaro S, Artese A, Botta M, Zizzari AT, Orallo F, Ortuso F, Schenone S, Brullo C, Yáñez M. Hit Identification and Biological Evaluation of Anticancer Pyrazolopyrimidines Endowed with Anti-inflammatory Activity. Chem Med Chem. 2010;5:1242-6. doi:10.1002/cmdc.201000165
9. Hurst DT. An introduction to the chemistry and biochemistry of pyrimidines, purines and pteridines. New York: Wiley&Sons, 1980, 266 p. doi:10.1016/0307-4412(80)90067-9
10. Ichiba M, Senga K. Reaction of 6-arylidenehydrazino-1,3-dimethyluracils with thionyl chloride leading to purine, thiazolo[4,5-d]pyrimidine, pyrimido[4,5-e][1,3,4]thiadiazine, pyrazolo[3,4-d]pyrimidine, and [1,2,3]thiadiazolo[4,5-d]pyrimidine derivativese. J Het Chem. 1985;22:381-6. doi:10.1002/jhet.5570220233
11. Kanazawa H, Nishigaki S, Senga K. N-bromosuccinimide in heterocyclic synthesis. Synthesis of pyrazolo[3,4-d]pyrimidines, Pyrimido[5,4-e]-as-triazines, and pyrimido[4,5-c]pyridazines from 6-arylidenehydrazino-1,3-dimethyluracil derivatives. J Het Chem. 1984;21:969-73. doi:10.1002/jhet.5570210408
12. Yoneda F, Nagamatsu T. The Thermolysis and Photolysis of 6-(Benzylidenehydrazino)uracils. New Syntheses of Pyrazolo[3,4-d]pyrimidines. A Method to Convert Aldehydes to Nitriles. Bull Chem Soc Jap. 1975;48:1484-9. doi:10.1246/bcsj.48.1484
13. Pfleiderer W, Schuendenhuette KH. Untersuchungen in der Pyrimidinreihe IV. Umsetzungen mit 1,3-dimethyl-4-chloruracil. J Lieb Ann Chem. 1958;612:1. doi:10.1002/jlac.19586120117
14. Pfleaderer W, Blankenhorn G. Eine neue pyrimido-[5,4-e]-astriazin synthesis. Tetr Lett. 1969;53:4699-702.
15. Deb ML, Bhuyan PJ. Uncatalysed Knoevenagel condensation in aqueous medium at room temperature. Tetr Let. 2005;46:6453-6. doi:10.1016/j.tetlet.2005.07.111
16. Shi D, Shi J, Rong S. A Facile and Clean Synthesis of Pyrimidine Derivatives via Three-component Reaction in Aqueous Media. Chin J Chem. 2010;28:791-6. doi:10.1002/cjoc.201090148