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A New Approach to 7-Amino-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carbonitriles †

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Abstract: S-alkyl derivatives of thiobarbituric acid easily react with arylmethylene malononitriles in the presence of base to give new 7-amino-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carbonitriles. The structure of products and the mechanism of formation are discussed.

Keywords: thiobarbituric acid; malononitrile; 2-amino-4H-pyran-3-carbonitriles; michael addition; heterocycliaztion

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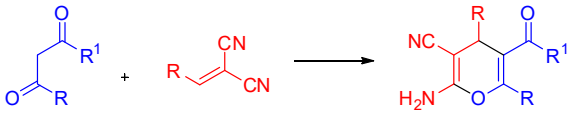
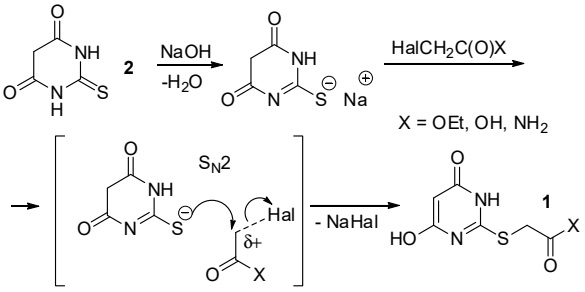
1. Introduction

2-Amino-4H-Pyran-3-carbonitriles and related chromenes are of practical interest due to their wide range of biological activity and complexing capability [1–3]. One of the most useful methods to prepare these compounds is the reaction of 1,3-dicarbonyl compounds with arylmethylene malononitriles (Scheme 1).



Scheme 1. General approach to 2-amino-4H-pyrans.

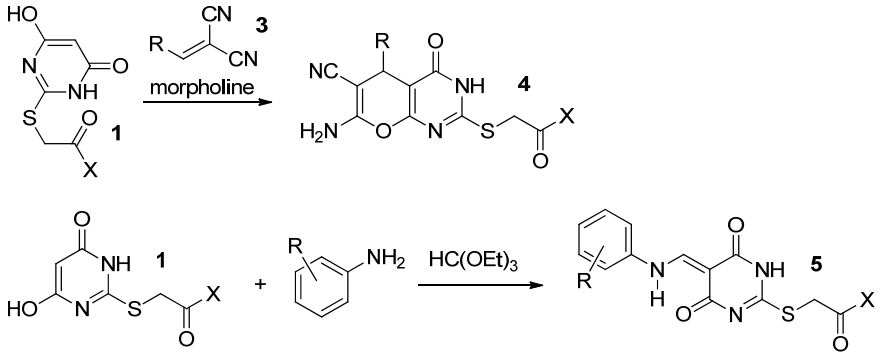
Easily accessible S-alkyl derivatives of thiobarbitic acids **1** [4] have not been used in the reaction prior to our studies. Compounds **1** can be easily prepared by treating thiobarbitic acid **2** with 2-haloacetic acid derivatives in an aqueous dioxane or aqueous alcohol solution in the presence of bases (Na_2CO_3, NaOH) (Scheme 2).



Scheme 2. The preparation of compounds **1**.

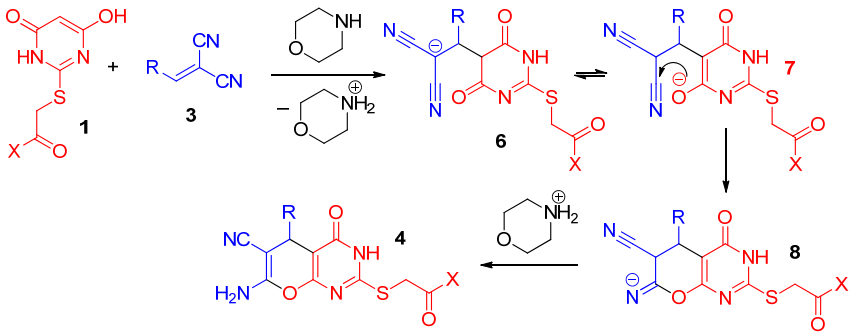
2. Results and Discussion

When active methylene pyrimidines **1** react with dinitriles **3** in boiling EtOH in the presence of catalytic amounts of base, previously undescribed 7-amino-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidine-6-carbonitriles **4** were isolated. The latter can be also prepared by multicomponent approach, using aldehydes, malononitrile and pyrimidines **1** as the starting reagents. This approach allows one to use aliphatic aldehydes since corresponding alkylidene malononitriles are hardly available. However, in this case the yields of target products **4** are low, probably due to the side reactions of aldol condensation with aliphatic aldehydes occurred in the presence of base. Compounds **1** are capable to react with anilines and triethyl orthoformate to form compounds **5** that were not described in the literature previously (Scheme 3).



Scheme 3. The preparation of compounds **4** and **5**.

The mechanism of the reaction is shown in the Scheme 4. On the first stage, thiobarbitic acid derivatives **1** undergo a Michael reaction with activated alkenes **3** in boiling ethanol in the presence of morpholine to form non-isolable Michael adducts **6**. The resulting Michael adducts under reaction conditions are easily isomerized to give anions **7**. The latter undergo heterocyclization, leading to the formation of pyran six-membered ring. Finally, intermediate **8** after protonation afforded the target products **4**.



Scheme 4. The plausible mechanism for the formation of bicyclic core of 4.

The structures of the key compounds were confirmed by X-ray studies (Figures 1 and 2).

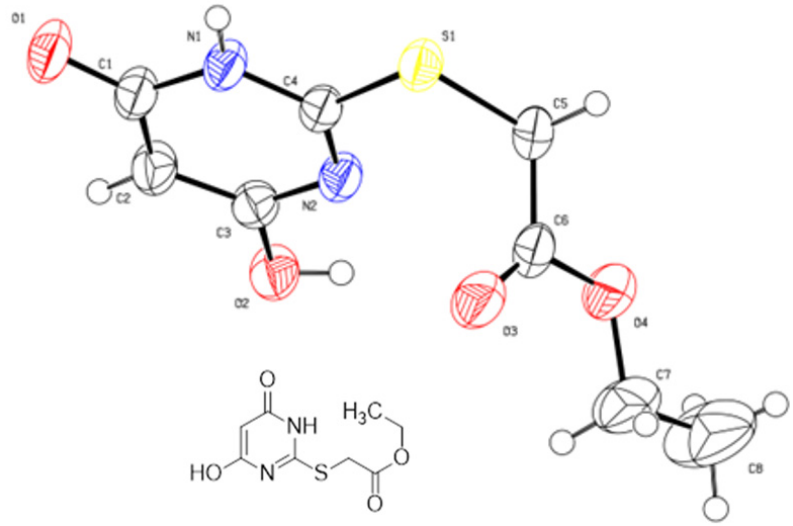


Figure 1. The structure of compound **1** (X = OEt).

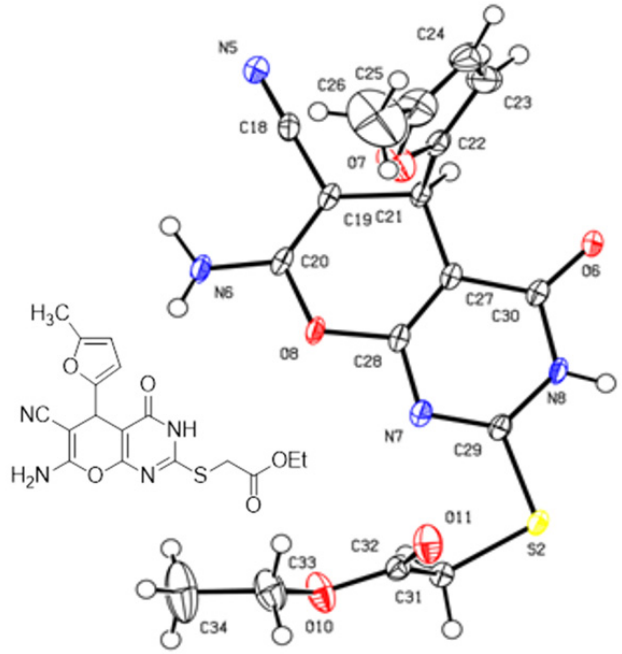
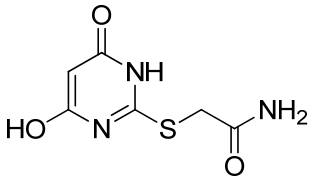


Figure 2. The structure of compound **4** (X = OEt, R = 5-methylfur-2-yl).

3. Experimental

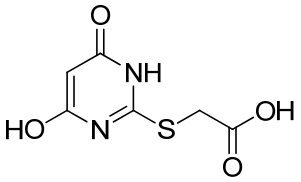
2-[(4-Hydroxy-6-oxo-1H-pyrimidin-2-yl)sulfanyl]acetamide (1, X = NH_2)



The compound was prepared according to a modified method reported in [5] as follows: 2.88 g (0.02 mol) of thiobarbituric acid **2**, 0.8 g (0.02 mol) of sodium hydroxide and 30 mL of water were mixed together. The resulting cloudy orange solution was filtered through a paper filter. Then, 1.88 g (0.02 mol) of α-chloroacetamide was added to the clear filtrate. The solution was vigorously stirred for 30 min at a constant temperature

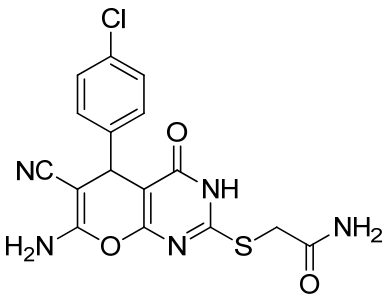
of 50 °C and left to stand for three days. The precipitate formed was filtered off and washed with water and dried to constant weight. The resulting product **1** is a pale pink powder. The substance is insoluble in water, EtOH, AcOH, ethyl acetate, and well soluble in DMF when heated. The yield was 62%.

2-[(4-Hydroxy-6-oxo-1H-pyrimidin-2-yl)sulfanyl]acetic acid (**1**, X = OH)



The compound was prepared according to a modified method reported in [5] as follows: 0.96 g (0.024 mol) of sodium hydroxide and 3.46 g (0.024 mol) of thiobarbituric acid **2** were dissolved in 100 mL of water. The resulted solution had a pH value of 8. Furthermore, 0.96 g (0.024 mol) of sodium hydroxide was dissolved in 100 mL of water, then 2.27 g (0.024 mol) of monochloroacetic acid was added. To the prepared aqueous solution of sodium chloroacetate, sodium thiobarbiturate solution was added dropwise through a paper filter. The reaction mixture was stirred for 15 min at a constant temperature of 50 °C, and left overnight. Then, diluted hydrochloric acid (10 mL of HCl + 20 mL of dist. H_2O) was added dropwise to the reaction mixture to adjust pH to 2. The precipitate was filtered off and dried to constant weight. The product was a colorless fine crystalline powder. The compound is poorly soluble in water and EtOH, but well soluble in DMF upon heating. The yield was 30%.

2-[(7-Amino-5-(4-chlorophenyl)-6-cyano-4-oxo-4,5-dihydro-3H-pyrano[2,3-d]pyrimidin-2-yl)thio]acetamide (**4**, R = 4-ClC_6H_4, X = NH_2)



A round-bottom flask was charged with 15 mL of EtOH, 0.28 g (0.002 mol) of 4-chlorobenzaldehyde, 0.13 g (0.002 mol) of malononitrile and one drop of base (triethylamine or morpholine). The mixture was stirred until completion of the reaction and the formation of a white precipitate of dinitrile **3**. To the resulting suspension 2-[(4-hydroxy-6-oxo-1H-pyrimidin-2-yl)sulfanyl]acetamide **1** (0.2 g, 0.001 mol) and 3 drops of morpholine were added. The reaction mixture was heated under reflux until the reaction was completed (control by TLC, precipitation). The formed precipitate was filtered off and dried to a constant weight. The product **4** is light yellow powder. The substance is insoluble in water and EtOH, but well soluble in DMF when heated. The yield was 23%.

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References

1. Shestopalov, A.M.; Emelyanova, Y.M. *Synthesis and Biological Activity of Substituted 2-amino-4H-Pyrans/Selected Methods of Synthesis and Modification of Heterocycles*; Springer Nature: Basingstoke, UK; 2003; Volume 2.
2. Litvinov, Y.M.; Shestopalov, A.M. Synthesis, structure, chemical reactivity and practical significance of 2-amino-4H-pyrans. *Adv. Heterocycl. Chem.* **2011**, *103*, 175–260.
3. Sharanin, Y.A.; Goncharenko, M.P.; Litvinov, V.P. Reactions of carbonyl compounds with α, β-unsaturated nitriles as a convenient pathway to carbo-and heterocycles. *Russ. Chem. Rev.* **1998**, *67*, 393–422.
4. Moskvin, A.V.; Reznikova, N.R.; Ivin, B.A. Condensation of hydroxypyrimidines with carbonyl compounds. I. Barbituric acids. *Russ. J. Org. Chem.* **2002**, *4*, 487–498.
5. Fedorova, E.V.; Meshcheryakov, M.P.; Ganina, M.B.; Moskvin, A.V.; Ivin, B.A. Azoles and Azines: CXIX. Alkylation of 5,5′-(4-nitrobenzylidene)bis(2-thiobarbituric) acid and 5-(4-nitrophenyl)-2,8-dithioxo-5,7,8,9-tetrahydro-2H-pyrano[2,3-d:6,5-d′]dipyrimidine-4,6(1H,3H)-dione with haloacetic acids and their esters. *Russ. J. Gen. Chem.* **2004**, *74*, 128–133.