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# Synthesis and Mechanism of Formation of 5-Benzylidene-2-thioxo-2,3-dihydro-(1*H*,5*H*)-pyrimidine-4,6-diones Difluoromethoxy Derivatives

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**Abstract**—Reactions of 5-benzylidene-2-thioxo-2,3-dihydro-(1*H*,5*H*)-pyrimidine-4,6-diones with a singlet difluorocarbene afford difluoromethoxy derivatives in 20–34% yield. The quantum-chemical analysis of the reaction mechanism showed that *N,N*-dimethylformamide is involved into the formation of difluoromethoxy derivatives.

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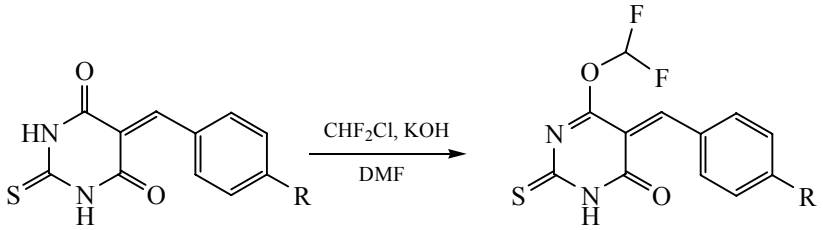
Difluoromethoxy group is known [1] to favor the occurrence of the pharmacological activity. Also the physiological activity of the thiobarbituric acid and its derivatives has been widely studied [2]. Therefore difluoromethylation of thiobarbituric acid arylidene derivatives, synthesized previously [3], is an actual task.

In this work we studied difluoromethylation of 5-benzylidene- (**I**), 5-(4-methylbenzylidene)- (**II**), 5-(4-methoxybenzylidene)- (**III**) and 5-(4-fluorobenzylidene)-2-thioxo-2,3-dihydro-(1*H*,5*H*)-pyrimidine-4,6-diones (**IV**) with singlet difluorocarbene generated *in situ* by the reaction of difluoro(chloro)methane (Freon-22, **V**) with *tert*-BuOK or KOH in anhydrous DMF.

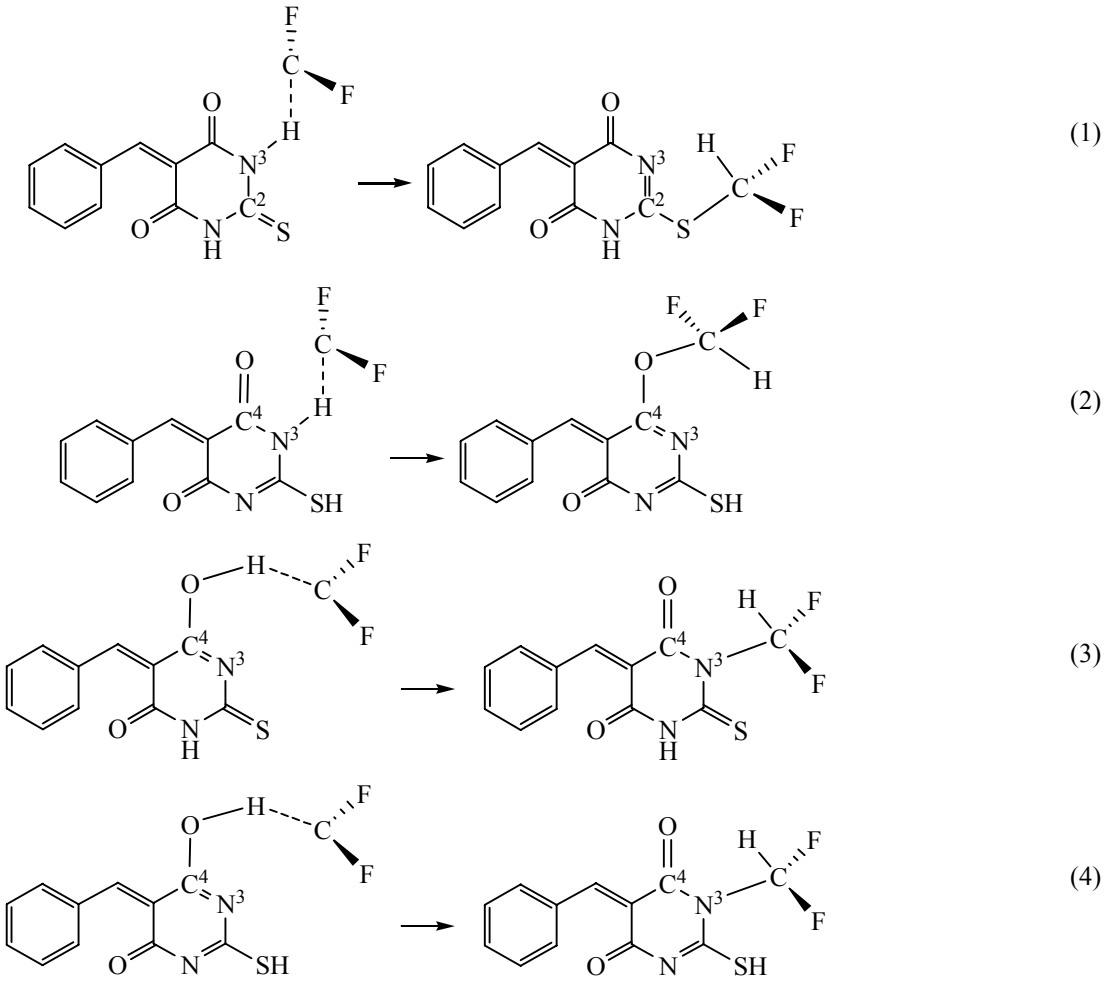



**I–IV** **VI–IX**

The yield of difluoromethylation products is 20–34% relative to the consumed compounds **I–IV**.

The quantum-chemical analysis of the proposed mechanisms of the formation of difluoromethyl derivatives of different structure shows that the reaction can proceed by the paths (1)–(4).

The attack of difluorocarbene on the $N^3$–H bond of the starting reagent [path (1)] can result in eliminating the hydrogen atoms from $N^3$ atom of pyrimidine ring followed by its adding to difluorocarbene. As the valence of difluorocarbene carbon with attached hydrogen must be saturated, this particle tries to form a bond with either the free $N^3$ atom, or with the oxygen atom attached to the carbon $C^4$ of pyrimidine ring, or with the sulfur atom attached to the carbon $C^2$ of pyrimidine. Other tautomeric forms are also capable to react with difluorocarbene to afford different products of difluoromethylation of the 5-benzylidene-2-thioxo-2,3-dihydro-(1*H*,5*H*)-pyrimidine-4,6-dione. The nature



(1)

(2)

(3)

(4)

of these reactions was studied using quantum-chemical simulation of the reaction mechanism shown on the schemes (1)–(4).

All calculations were performed in an approach of isolated molecules in the gas phase by the quantum-chemical semi-empirical method AM1 [4]. The latter was parameterized for the best representation of hydrogen bonds. This method is preferable to other semi-empirical quantum-chemical methods (MNDO, CNDO, PM3) for calculating the structure of complexes with associative interactions. Since the search for an optimal mechanism, where the reactions are characterized by the lowest energy barrier, requires large calculations, the use of the non-empirical method is not advantageous even with the modern high performance computers.

The studied reaction directions can be characterized in the context of one common mechanism, namely the difluorocarbene attack on the hydrogen atom. To simulate this stage one reaction coordinate C–H was chosen. The reaction path was created as the sequential decrease in the length $R_{C–H}$. Geometric and electronic structure of the molecular system was calculated by optimizing all parameters save the reaction coordinate, which remains a constant during the optimization. Step of change in the reaction coordinate was 0.01 Å.

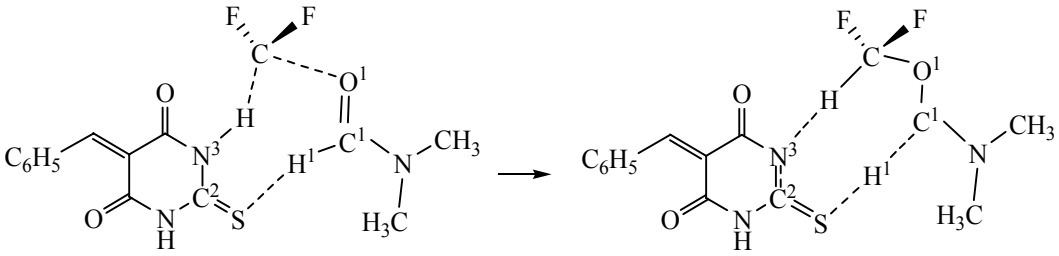
When difluorocarbene is brought closer to the hydrogen atom [path (1)], the charge on the atoms of the reagents is redistributed. The positive charge on the carbene carbon atom increases, while simultaneously increases the positive charge on the hydrogen atom. The negative charge on the nitrogen atom is significantly reduced, i.e., the largest restructuring of electronic shells of atoms occurs on the carbon atom of difluorocarbene and $N^3$ atom of the pyrimidine ring. The transformation of electronic shells at the atom $N^3$ initiates the localization of more negative charge on

the sulfur and oxygen atoms. A significant lengthening of the bonds C–N, C=S, or C=O was not observed. Since the sulfur is characterized by a larger electronic orbitals, in the initial step of reagents rapprochement the difluorocarbene changes its orientation from the oxygen direction to the sulfur. The increase in the positive charge on the carbon atom of difluorocarbene and the more negative charge on the sulfur atom contribute to the Coulomb attraction between them. Further rapprochement of the difluorocarbene and the hydrogen atom leads to the covalent bonding of difluorocarbene carbon with sulfur atom at the carbon $C^2$ in the pyrimidine ring. At the same time, pyrimidine ring undergoes restructuring to form a single C–S bond and a double C=N bond. Finally, the hydrogen atom is detached from pyrimidine ring and attached to difluorocarbene.

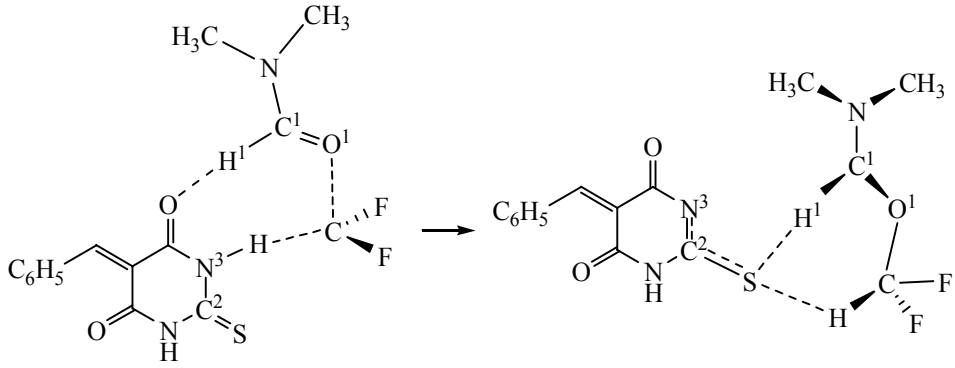
Similarly, the singlet difluorocarbene reacts with thiol form [path (2)]. In this case the difluoromethylation occurs at the oxygen atom bound to the carbon $C^4$ of pyrimidine ring, since sulfur is blocked. The interaction of singlet difluorocarbene with enol form [path (3)], as well as with the structure containing simultaneously SH and OH groups [path (4)], proceeds by the same mechanism, i.e., the attack of difluorocarbene at the O–H bond leads to difluoromethylation of $N^3$ atom of pyrimidine ring. The geometric and electronic structure of the transition state for each of these reactions is characterized by the formation of five-membered ring by the atoms directly involved into the reaction.

As can be seen from Fig. 1, the addition of singlet difluorocarbene to various tautomeric forms of derivative **I** occurs with overcoming the energy barrier. The minimum barrier is 4 kcal $mol^{-1}$ and corresponds to the *S*-difluoromethylation of the derivative **I**. The remaining tautomeric forms of **I** participating in reactions (2)–(4) are significantly disadvantageous in compareson with those involved in to the path (1). This is consistent with the results of *S*-difluoromethylation, described in [5]. In the case of a reaction in DMF the *S*-difluoromethylation does not occur that can be ascribed to the participation of DMF in complexation with difluorocarbene and derivative **I**.

The quantum-chemical analysis of the reaction of singlet difluorocarbene with derivative **I** in DMF solution shows that two mechanisms can exist, with different orientation of the polar hydrogen atom of DMF: toward sulfur [Eq. (5)] or oxygen atoms [Eq. (6)].



(5)



(6)

The participation of DMF molecule [Eqs. (5), (6)] does not promote the *S*-difluoromethylation reaction. Since the path (5) includes blocking the *S*-reaction center with polar hydrogen atom $H^1$ to form a stable ion structure (Fig. 2, curve *1*), the total negative charge at the atoms $N^3$ and S is close to –1. The largest

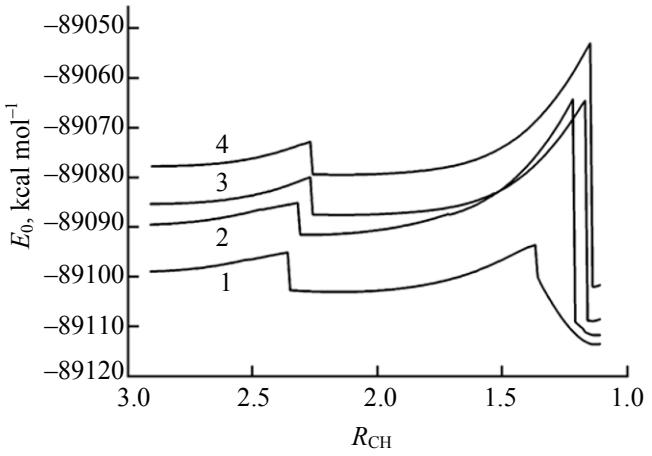



**Fig. 1.** Changes in the total reaction energy [paths (1)–(4)].

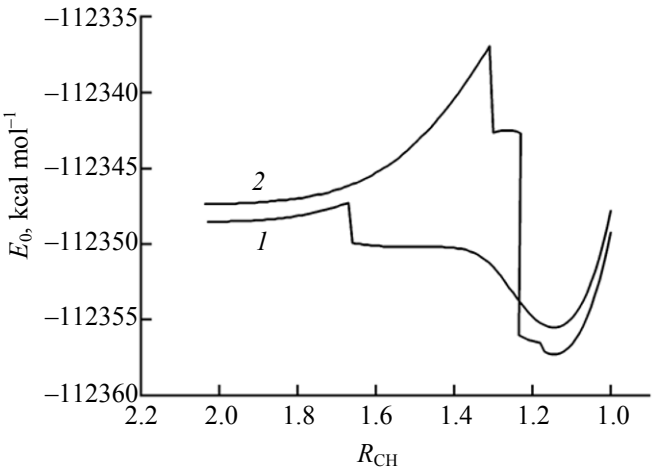



**Fig. 2.** Changes in the total energy of the reaction between a singlet difluorocarbene with **I** in the presence of DMF oriented by the polar hydrogen atom toward (*1*) sulfur or (*2*) oxygen.

positive charge focuses on the atoms $H^1$, $C^1$, and the difluorocarbene carbon atom. In the case of path (6) a stable ionic structure is also formed (Fig. 2, curve *2*).

From a comparison of the reaction barrier (Fig. 2) follows that the path (5) dominates. The ion formed can transform into the reaction product with $CF_2$ group at the oxygen atom (there is an obvious opportunity of the attack by the carbon atom of the $CF_2$ group on the oxygen). The observed by us direction of *O*-difluoromethylation of derivatives **I–IV** and data [5] are due to this opportunity.

## EXPERIMENTAL

The $H^1$ NMR spectra were registered on a Varian Mercury 300BB instrument with internal HMDS, in DMSO-$d_6$. Melting points were measured on a MelTemp 3.0 instrument, heating at 10 deg min$^{-1}$.

**5-Benzylidene-6-difluoromethoxy-2-thioxo-2,3-dihydro-(5*H*)-pyrimidin-4-one (VI).** To a solution of 1.5 g (6.4 mmol) of **I** in anhydrous DMF (15 ml) was added 1.8 g (32 mmol) of finely powdered KOH and 5-fold excess of difluorocarbene source at room temperature under vigorous stirring. The reaction temperature rises to 34°C. The stirring was continued at this temperature for 15 min, then the temperature was increased up to 50–60°C, and the reaction mixture was stirred at this temperature for 60 min. The mixture was cooled to room temperature, filtered, concentrated, and diluted with water to pH 7. The precipitate formed was filtered off and recrystallized from an ethanol–hexane mixture (2:1). Yield 0.36 g (20%). Orange crystals, mp 128–130°C. IR spectrum (vaseline oil, KBr), ν, cm$^{-1}$: 1072 (C–F), 1240 (C=S), 1570 (C=C), 1624 (C=O), 2848 (NH). $^1$H NMR spectrum, δ, ppm: 5.96 s (1H, CH), 6.97–7.56 m (5H, $C_6H_5$), 7.94 t (1H, $CHF_2$, *J* 57 Hz), 11.57 s (1H, NH). Found, %: N 10.10. $C_{11}H_{10}FN_2O_2S$. Calculated, %: N 9.90.

**5-(4-Methylbenzylidene)-6-difluoromethoxy-2-thioxo-2,3-dihydro-(5*H*)-pyrimidin-4-one (VII)** was prepared similarly from 0.74 g (3 mmol) of **II** and 0.88 g (15 mmol) of KOH. Yield 0.30 g (34%). Orange crystals, mp 145–147°C. IR spectrum, ν, cm$^{-1}$: 1172 (C–F), 1204 (C=S), 1582 (C=C), 1630 (C=O), 2854 (NH). $^1$H NMR spectrum, δ, ppm: 2.18 s (3H, $CH_3$), 5.93 s (1H, CH), 7.2–7.6 m (4H, $C_6H_4$), 8.06 t (1H, $CHF_2$, *J* 55 Hz), 12.3 s (1H, NH). Found, %: N 10.0. $C_{12}H_9F_2N2O_2S$. Calculated, %: N 9.45.

**5-(4-Methoxybenzylidene)-6-difluoromethoxy-2-thioxo-2,3-dihydro-(5*H*)-pyrimidin-4-one (VIII)** was prepared similarly from 1.5 g (5.7 mmol) of **III** and 1.6 g (28.6 mmol) of KOH. Yield 0.45 g (25%). Pale orange crystals, mp 120–122°C. IR spectrum, ν, cm$^{-1}$: 1066 (C–F), 1258 (C=S), 1564 (C=C), 1630 (C=O), 2920 (NH). $^1$H NMR spectrum, δ, ppm: 2.48 s (3H, $CH_3$), 5.88 s (1H, CH), 6.82–7.6 m (4H, $C_6H_4$), 7.31 t (1H, $CHF_2$, *J* 59 Hz), 11.54 s (1H, NH). Found, %: N 9.28. $C_{12}H_{12}FN_2O_3S$. Calculated, %: N 8.97.

**5-(4-Fluorobenzylidene)-6-difluoromethoxy-2-thioxo-2,3-dihydro-(5*H*)-pyrimidin-4-one (IX)** was prepared similarly from 1.2 g (4.2 mmol) of **IV** and 1.17 g (20 mmol) of KOH. Yield 0.56 g (31%). Yellow crystals, mp 150–152°C. IR spectrum, ν, $cm^{-1}$: 1078 (C–F), 1222 (C=S), 1546 (C=C), 1624 (C=O), 2920 (NH). $^1$H NMR spectrum, δ, ppm: 5.03 s (1H, CH), 7.94 t (1H, $CHF_2$, *J* 55 Hz), 6.94–7.73 m (4H, $C_6H_4$), 12.3 s (1H, NH). Found, %: N 10.20. $C_{11}H_{10}F_2N_2OS$. Calculated, %: N 9.33.

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