

SHORT  
COMMUNICATIONS

## Difluoromethylation of 6-Methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one with Chlorodifluoromethane

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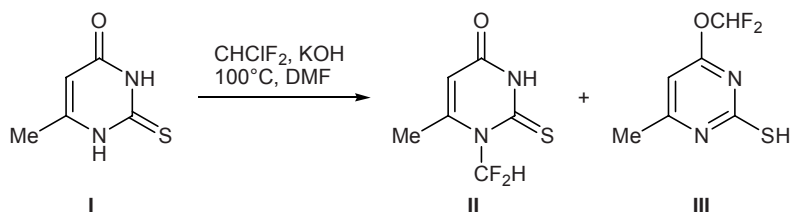
It is known [1, 2] that difluoromethylation of 6-methyluracil and 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (**I**) with chlorodifluoromethane (Freon 22) leads to the formation of the corresponding 2,4-difluoromethoxy derivatives. These reactions were carried out in aqueous dioxane at 60–70°C, and they occurred as nucleophilic replacement with participation of sulfur- and oxygen-centered nucleophiles.

In the present work, difluoromethylation of compound **I** was performed in anhydrous dimethylformamide in the presence of powdered potassium hydroxide, i.e., according to the procedure described in [3, 4]. Under these conditions, the reaction takes two pathways leading to the formation of a mixture of 1-difluoromethyl-6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (**II**) and 4-difluoromethoxy-6-methylpyrimidine-2-thiol (**III**).

The structure of compound **II** was confirmed by the <sup>1</sup>H NMR spectrum which was very consistent with the expected one. It contained singlets from protons in the pyrimidine ring at δ 8.4 (2-H) and 5.5 ppm (5-H) and a signal at δ 7.8 ppm from proton in the F<sub>2</sub>CH group; the latter was split into a triplet as a result of spin–spin coupling with fluorine nuclei. The singlet at δ 1.9 ppm was assigned to protons in the 6-methyl group. Attack by electrophilic difluorocarbene at the nitrogen atom in position 1 of the pyrimidine ring is likely to be favored

by electron-donor effect of the 6-methyl group. The reaction path leading to compound **III** is consistent with the ability of carbenes to react at hydroxy groups in nitrogen-containing heterocyclic compounds. The assumed structure of **III** conforms to its <sup>1</sup>H NMR spectrum: the 2-SH proton resonated as a singlet at δ 2.9 ppm, signal from the 6-methyl group was located at δ 2.1 ppm, the 5-H proton gave a singlet at δ 6.3 ppm, and the 4-OCHF<sub>2</sub> signal appeared as a triplet at δ 7.8 ppm.

A mixture of 1.42 g (0.01 mol) of compound **I** and 15 ml of distilled DMF was heated to 50°C under continuous stirring, while bubbling chlorodifluoromethane over a period of 10 min (1.6 mol). Finely powdered potassium hydroxide, 10 g, was added, and the mixture spontaneously warmed up to 100–110°C. Chlorodifluoromethane was bubbled through the mixture for 20 min more (3.2 mol), the temperature decreased to 50°C, and the reaction mixture turned bright pink. The mixture was cooled, the unreacted initial compound (as potassium salt) was filtered off, the filtrate was poured into 100 ml of water and neutralized with 30% acetic acid to pH 7, and the precipitate of compound **III** was filtered off and recrystallized from ethanol. The mother liquor was evaporated, and the residue (compound **II**) was dissolved in ethanol–heptane (1 : 1). The yellow oily substance was separated by decanting, left to stand



for 12 h until it crystallized, and recrystallized from ethanol–heptane (1:2).

**1-Difluoromethyl-6-methyl-2-thioxo-2,3-dihydro-4(1H)-one (II).** Yield 0.6 g (31%), colorless crystals, mp 200–202°C,  $R_f$  0.6.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.9 s (3H,  $\text{CH}_3$ ), 5.48 s (1H, CH), 7.79 t (1H,  $\text{CHF}_2$ ), 8.42 s (1H, NH). Found, %: N 13.7.  $\text{C}_6\text{H}_6\text{F}_2\text{N}_2\text{OS}$ . Calculated, %: N 14.58.

**4-Difluoromethoxy-6-methylpyrimidine-2-thiol (III).** Yield 0.4 g (21%), colorless crystals very poorly soluble in water, mp 62°C,  $R_f$  0.64.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.16 s (3H,  $\text{CH}_3$ ), 2.97 s (1H, SH), 6.32 s (1H, CH), 7.88 t (1H,  $\text{CHF}_2$ ). Found, %: N 15.2.  $\text{C}_6\text{H}_6\text{F}_2\text{N}_2\text{OS}$ . Calculated, %: N 14.58.

The  $^1\text{H}$  NMR spectra were measured from solutions in  $\text{DMSO}-d_6$  on a Varian Mercury 300BB spectrometer (300 MHz) using hexamethyldisiloxane as internal

reference. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates using diethyl ether–ethanol (20:1) as eluent; spots were visualized by treatment with iodine vapor. The melting points were determined by the capillary technique [5].

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