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Reaction of Singlet Difluorocarbene with 6-Methylpyrimidin-4(3*H*)-one Derivatives

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Abstract—Regularities of regioselective *O*-difluoromethylation of 6-methylpyrimidin-4(3*H*)-one derivatives with difluorocarbene generated in situ were studied.

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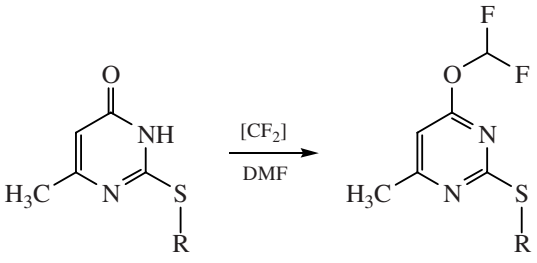
Proceeding with our previously initiated research on difluoromethylation of 6-mehyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one with singlet difluorocarbene [1], we extended this reaction on various derivatives of 6-methylpyrimidin-4(3*H*)-one, containing alkylsulfanyl and aralkylsulfanyl groups in the 2 position of the pyrimidine heteroring.

Difluorocarbene was generated in situ via the reaction of chlorodifluoromethane (Freon 22) (**I**) with *t*-BuOK or KOH in anhydrous DMF.

It was found that 2-(methylsulfanyl)- (**II**), 2-(ethylsulfanyl)- (**III**), 2-(benzylsulfanyl)- (**IV**), and 2-[(3-phenoxybenzyl)sulfanyl]-6-methylpyrimidin-4-(3*H*)-ones (**V**) are difluoromethylated regioselectively by the exocyclic oxygen atom.



II–**V** **VII**–**X**

Attempted reaction of 5,6-dimethyl-2-(methylsulfanylpyrimidin-)-4(3*H*)-one (**VI**) under the same conditions failed.

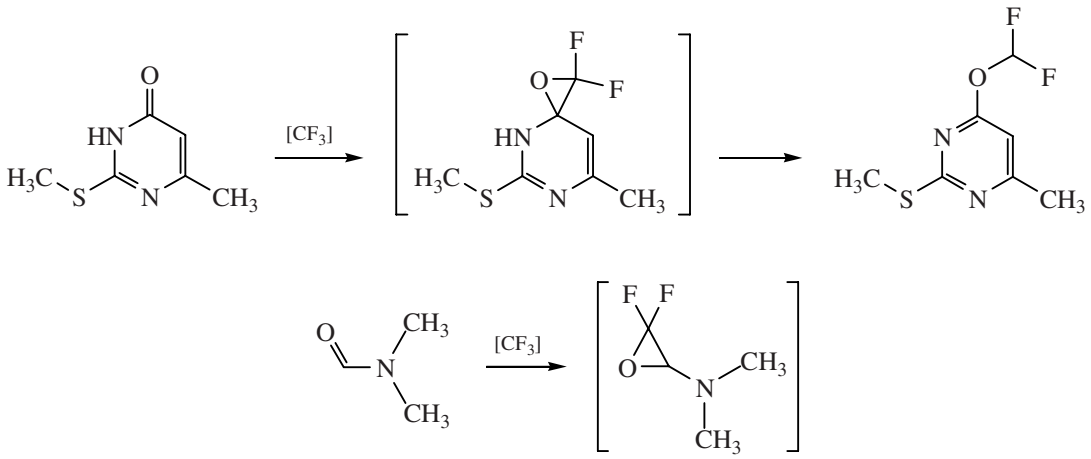
Our data suggest that the possibility of the reaction and its direction are controlled by a steric factor. Hence in derivatives **II–V** the least shielded and most susceptible to the attack of difluorocarbene is the oxygen atom, whereas in derivative **VI** the 5-Me group creates additional steric hindrances to difluorocarbene attack and prevents *O*-difluoromethylation.

Hypothetically, the reaction involves incorporation of difluorocarbene and intermediate formation of a 2,2-difluoro-7-methyl-1-oxa-4,6-diazaspiro[2.5]octa-5,7-diene derivative that further rearranges to form the target product.

The low yields of the target products are explained by incomplete conversion of starting compounds **II–V**. This phenomenon is associated with a high reactivity of difluorocarbene, as well as its tendency for dimerization (to form tetrafluoroethylene) and reaction with the solvent.

2,2-Difluro-3-(dimethylamino)oxirane formed by this reaction is in itself an unstable compound and undergoes immediate oligo- and polymerization.

The reaction yield is also strongly dependent on the strength of the base: With *t*-BuOK instead of KOH, the yield of diflurocarbene is higher, which affects the yield of the target product. Furthermore, with *t*-BuOK, the side reaction product is *t*-BuOH and with KOH, water. *tert*-Butanol is much less mobile, contains a stronger shielded proton, and is more inert in the reaction with diflurocarbene, yielding *t*-BuOCHF$_2$. By



contrast, water formed in the case of KOH can actively react with difluorocarbene to form F_2CHOH and $(F_2CH)_2O$.

In summary it should be noted that the yields of the target products can be improved by performing the reaction in the presence of a base able to irreversibly deprotonate the starting chlorodifluromethane (for example, NaH). Furthermore, a positive effect can be reached by using a large excess of the base and compound **I**.

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Varian Mercury 300BB instrument in CDCl3, internal reference HMDS. The melting points were determined on a MelTemp 3.0 device, heating rate 10 deg min^{-1}.

2-(Ethylsulfanyl)-4-(diflurомethoxy)-6-methylpyrimidine. Chlorodifluoromethane was introduced into a stirred solution of 5.6 g of KOH in 15 ml of anhydrous DMF until the reagent was no longer absorbed; therewith, the reaction mixture was maintained at a temperature of no higher than 22°C. Compound **III**, 3.4 g, was then added, and the mixture was stirred for 30 min at 40–50°C, filtered, and evaporated in a vacuum. Ethyl ether was added to the residue, and the mixture was filtered, evaporated, and the residue was distilled at reduced pressure. Yield 1.25 g (28%), bp 78–80°C (3.5 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, SCH_2CH_3, *J* 7.5 Hz), 2.15 s (3H, CH_3), 3.02–3.09 q (2H, SCH_2), 6.68 s (1H, CH), 7.71 t (1H, CHF_2, *J* 72 Hz). Found, %: N 12.73. $C_8H_{10}F_2N_2OS$. Calculated, %: N 13.80.

4-(Difluoromethoxy)-6-methyl-2-(methylsulfanyl)pyrimidine was prepared in a similar way. Yield 0.4 g (11%), mp 42–45°C. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 6.72 s (1H, CH), 7.74 t (1H, CHF_2, *J* 72 Hz). Found, %: N 13.83. $C_7H_8F_2N_2OS$. Calculated, %: N 13.59.

2-(Benzylsulfanyl)-4-(difluoromethoxy)-6-methylpyrimidine. Chlorodifluoromethane was introduced into a stirred solution of 2.8 g of *t*-BuOK in 15 ml of anhydrous DMF until the reagent was no longer absorbed; therewith, the reaction mixture was maintained at a temperature of no higher than 22°C. Compound **III**, 1.16 ml, was added, and the mixture was stirred for 30 min at 40–50°C, filtered, evaporated in a vacuum, and the residue was crystallized from aqueous EtOH. Yield 0.28 g (20%), mp 193–195°C. ^{1}H NMR spectrum, δ , ppm: 1.82 s (3H, CH_3), 4.36 s (2H, SCH_2), 6.74 s (1H, CH), 7.10–7.35 m (5H, H_{arom}), 7.76 t (1H, CHF_2, *J* 72 Hz). Found, %: N 10.12. $C_{13}H_{12}F_2N_2OS$. Calculated, %: N 9.93.

4-(Difluoromethoxy)-6-methyl-2-[(3-phenoxybenzyl)sulfanyl]pyrimidine was prepared in a similar way. Yield 0.3 g (24%), mp 145–147°C. ^{1}H NMR spectrum, δ, ppm: 2.03 s (3H, CH_3), 4.28 s (2H, SCH_2), 5.91 s (1H, CH), 6.84–7.34 m (10H, H_{arom}). Found, %: N 8.64. $C_{19}H_{16}F_2N_2OS$. Calculated, %: N 7.49.

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