Synthesis of nitrogen containing heterocycles based on fluorinated building blocks: use of perfluoroketene dithioacetals and γ-ketothioesters

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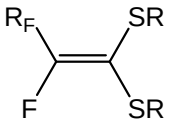
γ-Ketothioesters **2** are versatile building blocks for the synthesis of a wide variety of fluorinated nitrogen-containing heterocycles (pyrroles, furans, pyridazines, …). They were prepared from perfluoroketene dithioacetals **1** using a two-steps sequence: substitution of vinylic fluorine with potassium enolates of ketones – hydrolysis of ketene dithioacetal intermediate under acidic conditions.[1]

Heterocyclisations of compounds **2** with various amines or hydrazines led to the preparation of new pyridazin-3(*2H*)-ones **3** and α,β-unsaturated γ-lactams **4**. The structure of all heterocycles and the reaction mechanisms will be discussed.

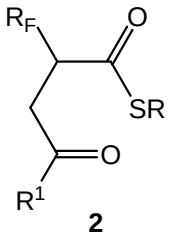
More recently, we have developed a research program[2] dedicated to synthesis of mixed 4-aminoquinoline-γ-lactams **5** in order to discover new drug candidates for malaria treatment. Several derivatives were identified as very potent compounds with *in vitro* activity against *P. falciparum* clones of variable sensitivity (CQ-Sensitive 3D7 and CQ-Resistant W2 strains) in the range 20-50 nM.



1

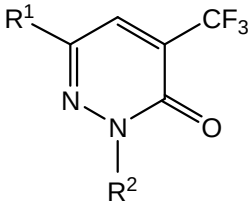
R = Et, Ar

R_F = CF_3, C_2F_5



2

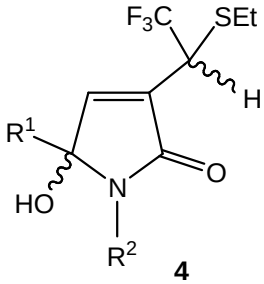
R^1 = Alk, Ar



3

R^1 = Ar

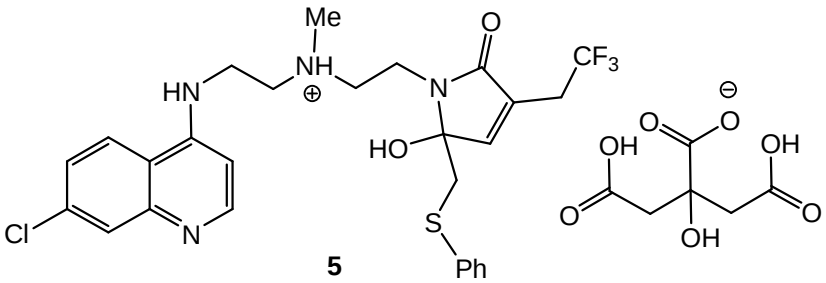
R^2 = H, Me, Ph



4

R^1 = Me, Ar

R^2 = various substituents



5

References:

1. Portella, C.; Bouillon, J.-P. *ACS Symposium Series # 911*, Soloshonok, V. A. Ed., Oxford University Press / American Chemical Society, Washington D.C., **2005**, Chapter 12, 232.
2. Cornut, D.; Lemoine, H.; Kanishchev, O.; Okada, E.; Albrieux, F.; Beavogui, A. H.; Bienvenu, A. -L.; Picot, S.; Bouillon, J.-P.; Médebielle, M. *J. Med. Chem*. **2013**, *56*, 73.