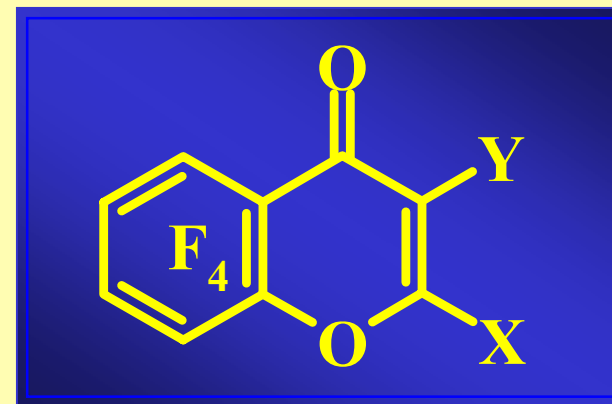


Synthesis and transformations 2(3)-alkoxycarbonyl-5,6,7,8-tetrafluorochromones

Yanina Burgart

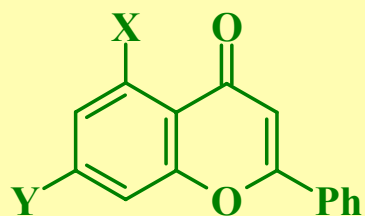
Victor Saloutin

Oleg Chupakhin

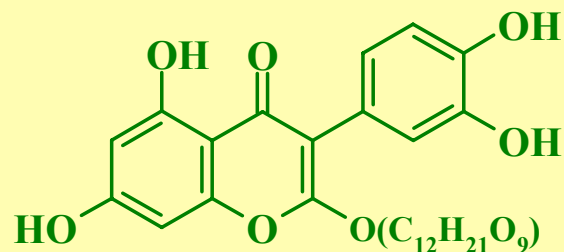


**Institute of Organic Synthesis,
Ural Division of Russian academy of sciences,
Ekaterinburg, Russia**

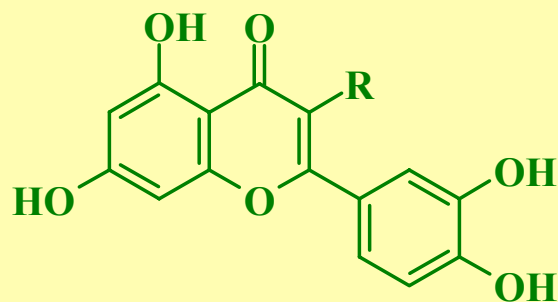




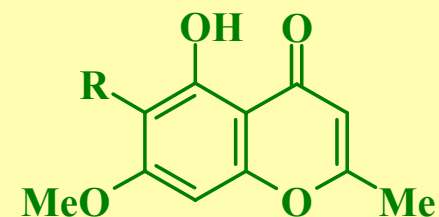
Flavons (in plants)



Vitamin P (bioflavonoids ~ 500 species)



Pigments (in plants)

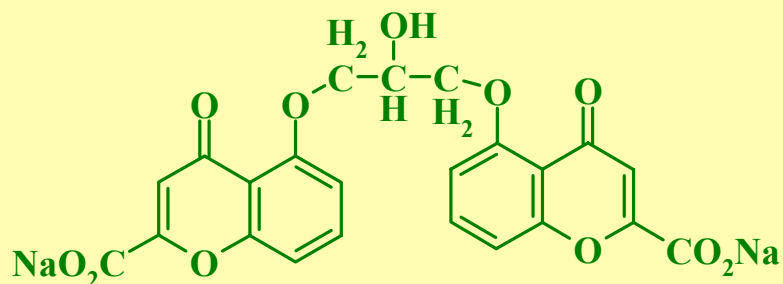


Eugenin (R = H)
Eugenitin (R = Me)
(in clover *Eugenia caryophyllata* L.)



Biological active compounds

3

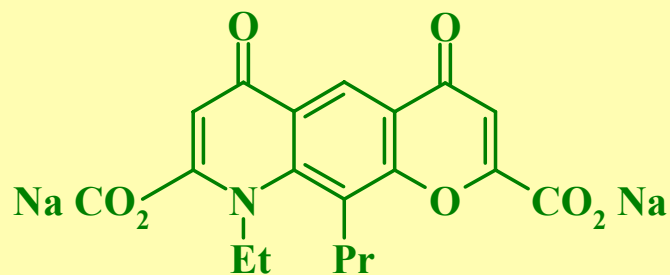


Intal (bronchial asthma)



$\text{R} = \text{OMe}, \text{H}$

Khellinum, Visnagin (spasmolytic)



Nedocromil sodium (antiallergic)

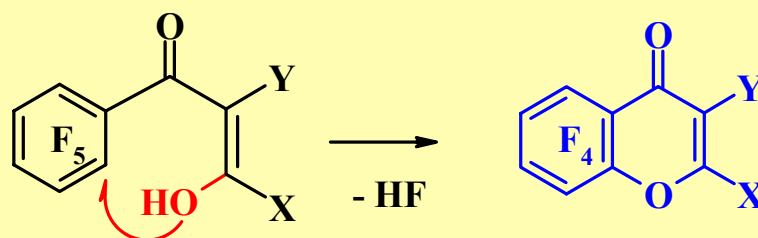
- Chromones make up a substantial class of heterocyclic compounds
- Chromones are to be the starting blocks for the synthesis of various organic compounds
- Derivatives of chromones possess biological activity and are used in the medicine
- Fluorine-containing representatives of chromones are not studied practically



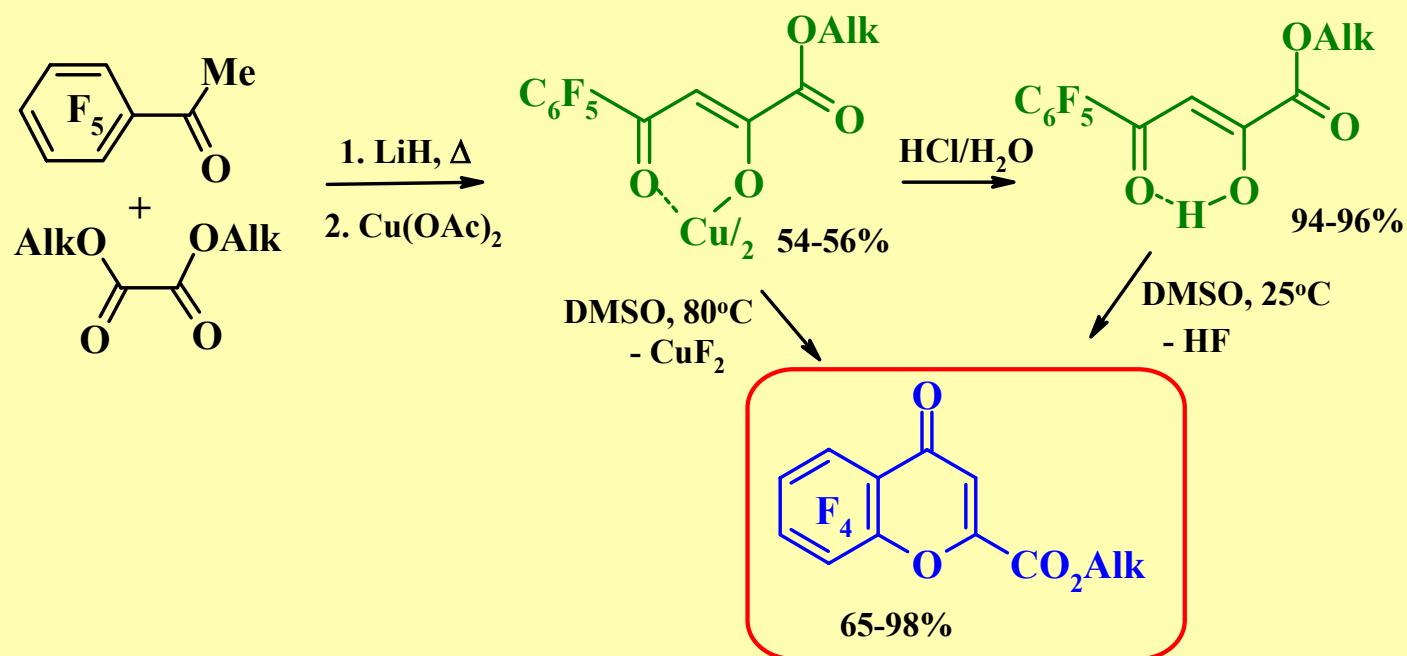
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Synthesis of 5,6,7,8-tetrafluorochromen-4-ones

4



Synthesis of 2-alkoxycarbonyl-5,6,7,8-tetrafluorochromones



ook: Saloutin V.I., Burgart Ya.V., Chupaknin O.N. Fluorine-containing compounds. Preparation,

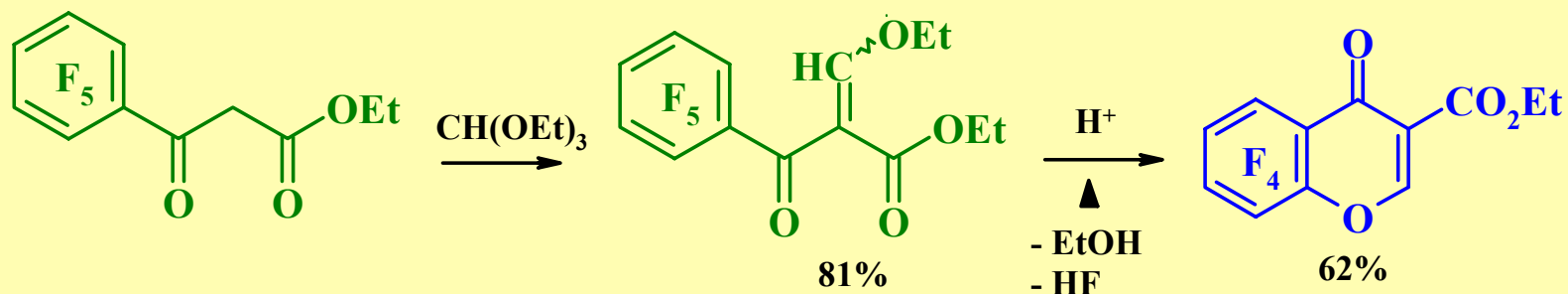
Reviews: Saloutin V.I., Burgart Y.V., Chupakhin O.N. Heterocycles. 2000, 52-(3), 1411-1434.
properties, reactions, synthesis of heterocycles. Ekaterinburg. 2002. 242 p.

erevalov S.G., Burgart Y.V., Saloutin V.I., Chupakhin O.N. Target in Heterocyclic Systems. 2001, 5, 419-439.

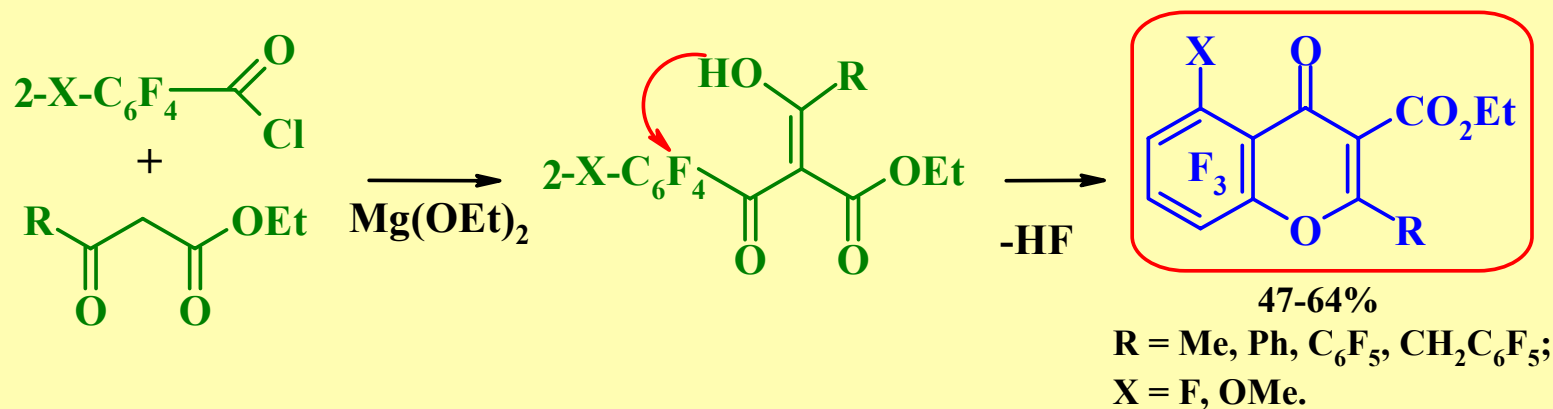
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Synthesis of 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromones

5



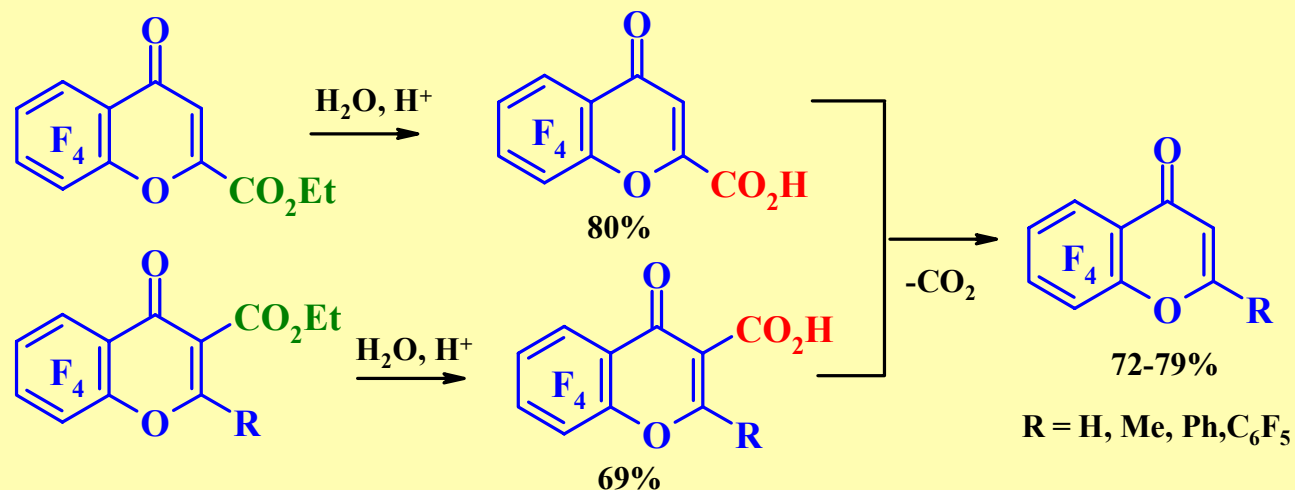
● Cyclization of 2-ethoxymethylidenepentafluorobenzoylacetate affords 3-ethoxycarbonyltetrafluorochromone



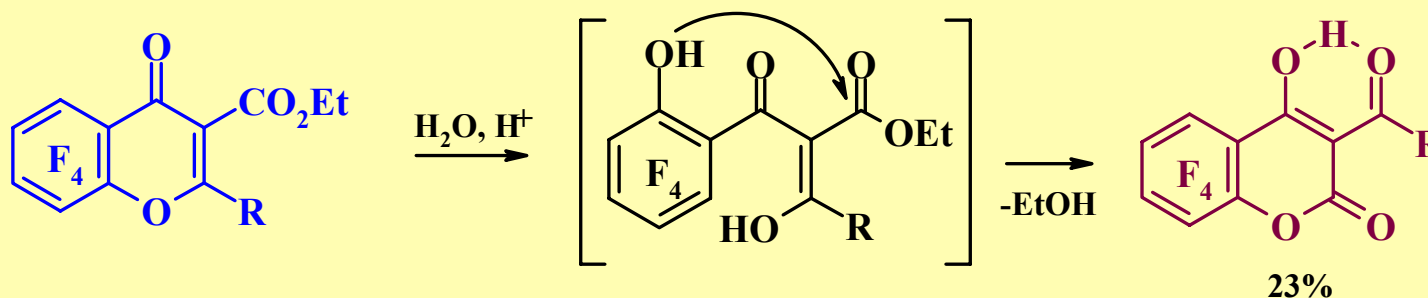
● Acylation of β-oxo esters by polyfluorobenzoyl chlorides are used for synthesis of 3-ethoxycarbonylfluorochromones

Hydrolysis of 2(3)-ethoxycarbonyl-5,6,7,8-tetrafluorochromones

6



Acid hydrolysis of 2(3)-ethoxycarbonylfluorochromones gives series of isomeric carboxylic acids; that is the way to unsubstituted and alkyl or arylsubstituted (tetrafluoro)chromones



3-Acetyl-4-hydroxytetrafluorocoumarin was obtained as a by-product at hydrolysis of 3-ethoxycarbonyl-2-methylchromone in a result of chromone-coumarin rearrangement

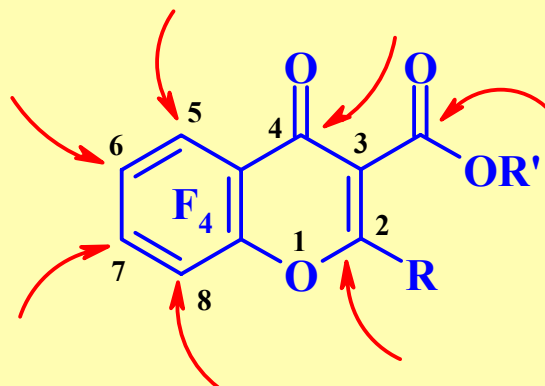
Saloutin V.I., Skryabina Z.E., Bazyl' I.T., Chupakhin O.N. J. Fluorine Chem. 1993, 65 (1), 37-41.

Saloutin V.I., Skryabina Z.E., Bazyl' I.T., Chupakhin O.N. J. Fluorine Chem. 1999, 94 (1), 83-90.

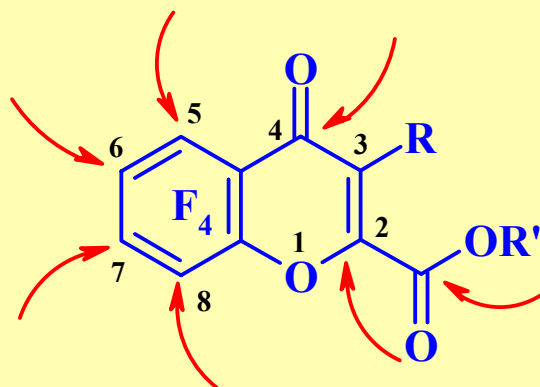
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Reactivity of 2(3)-ethoxycarbonyl-5,6,7,8-tetrafluorochromones

7



● Tetrafluorochromones are multifunctional compounds having hardly predicted reactivity

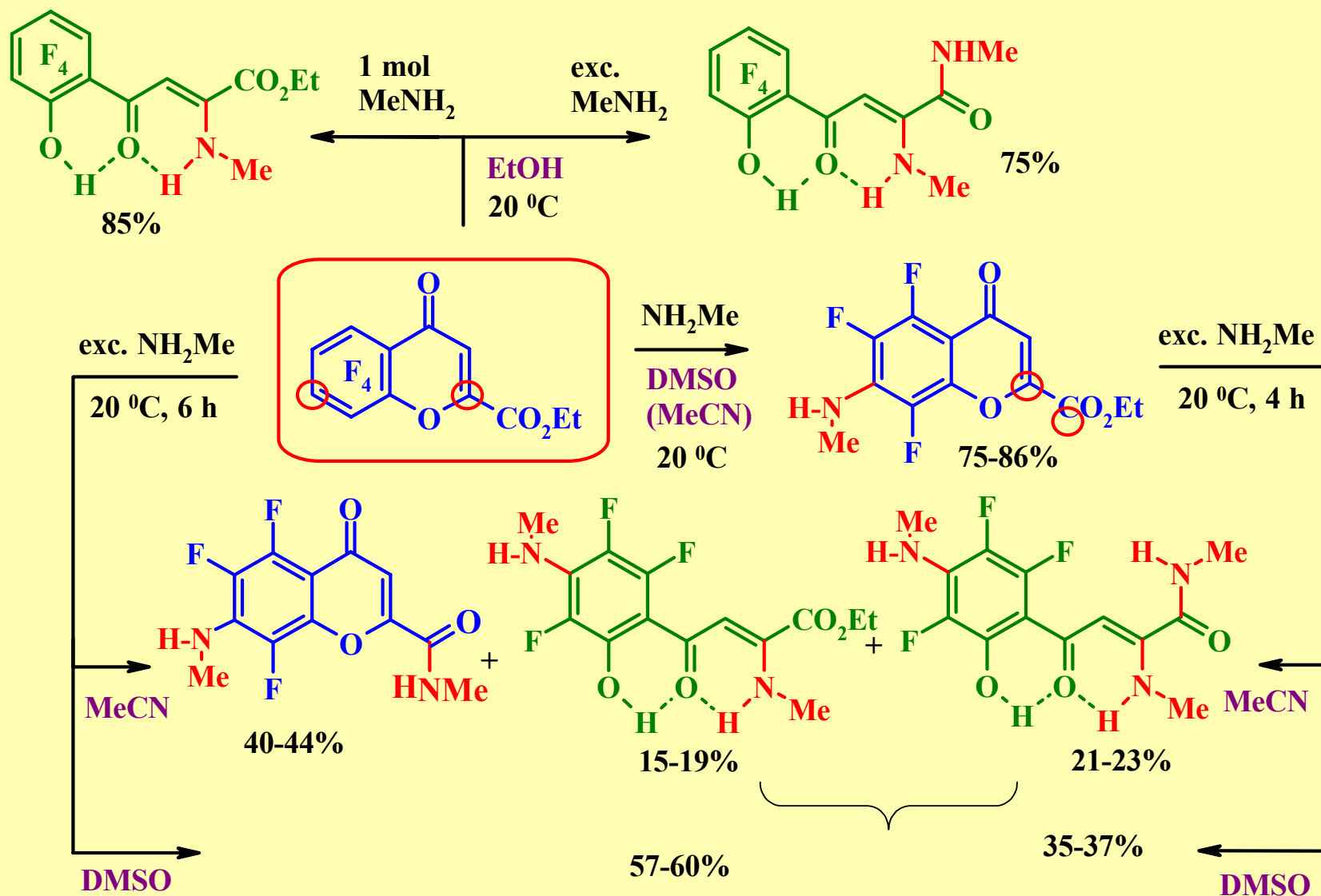


● Direction of nucleophilic attacks



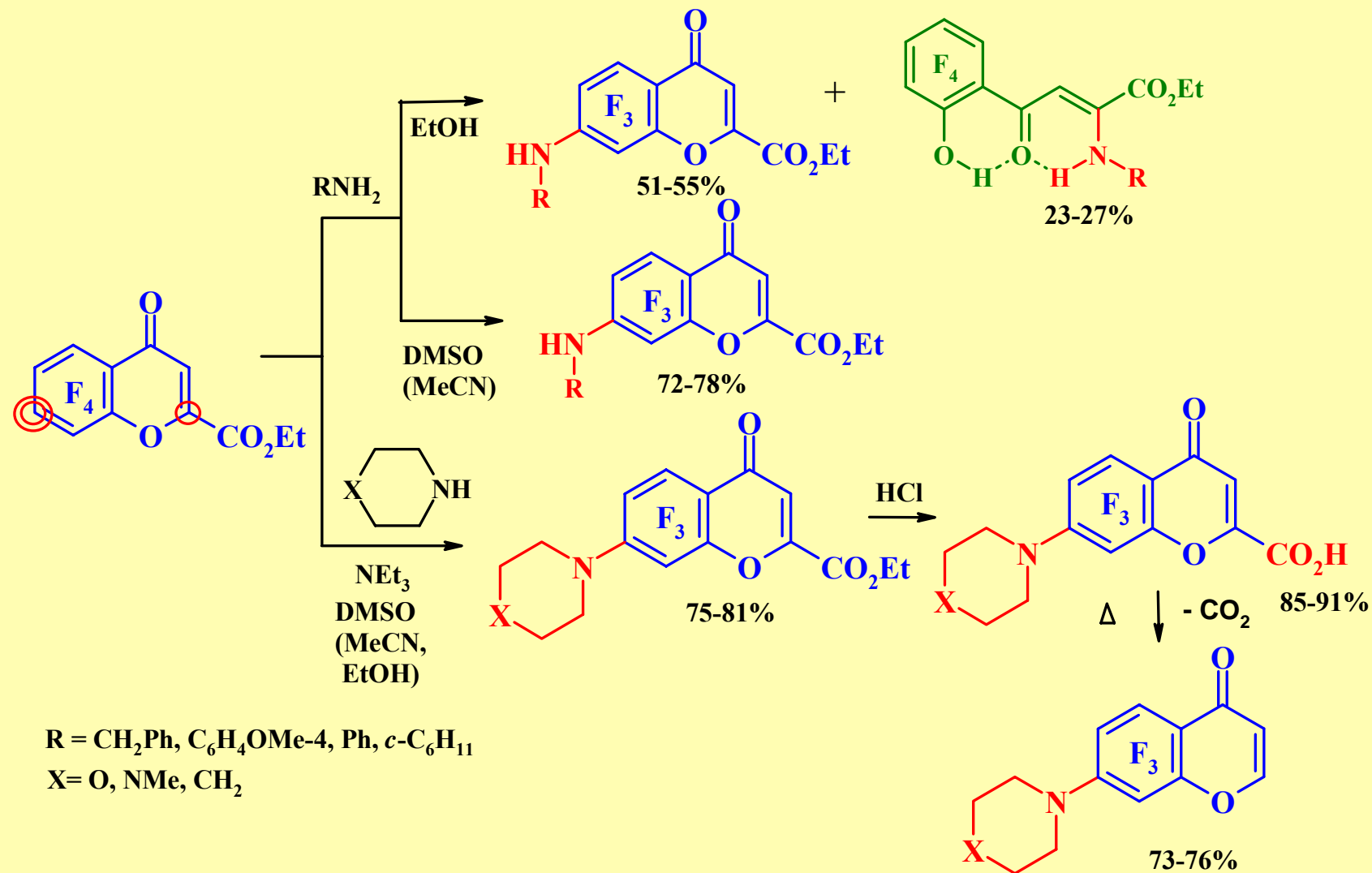
Reactions of 2-ethoxycarbonyltetrafluorochromone with methylamine

8



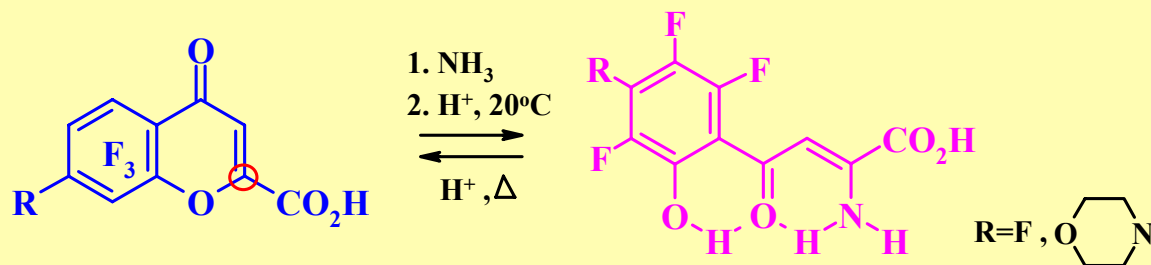
Reactions of 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone with monoamines

9

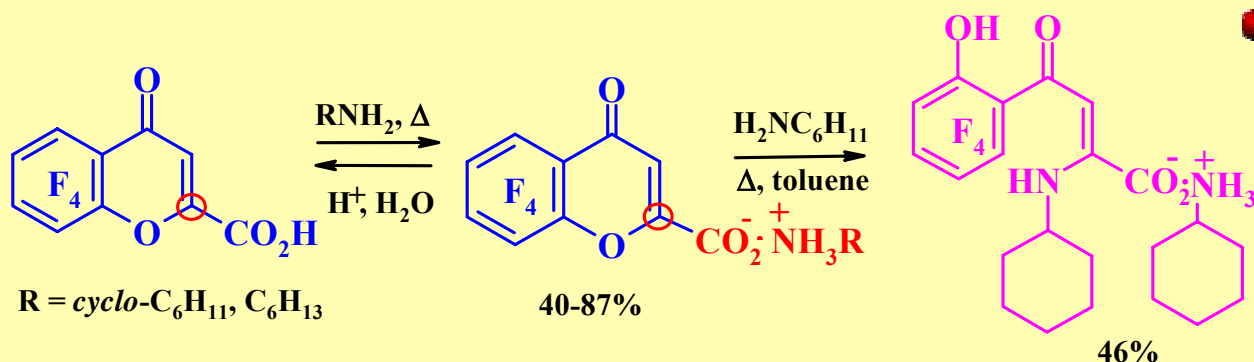


Reactions of tetrafluorochromone-2-carboxylic acids with monoamines

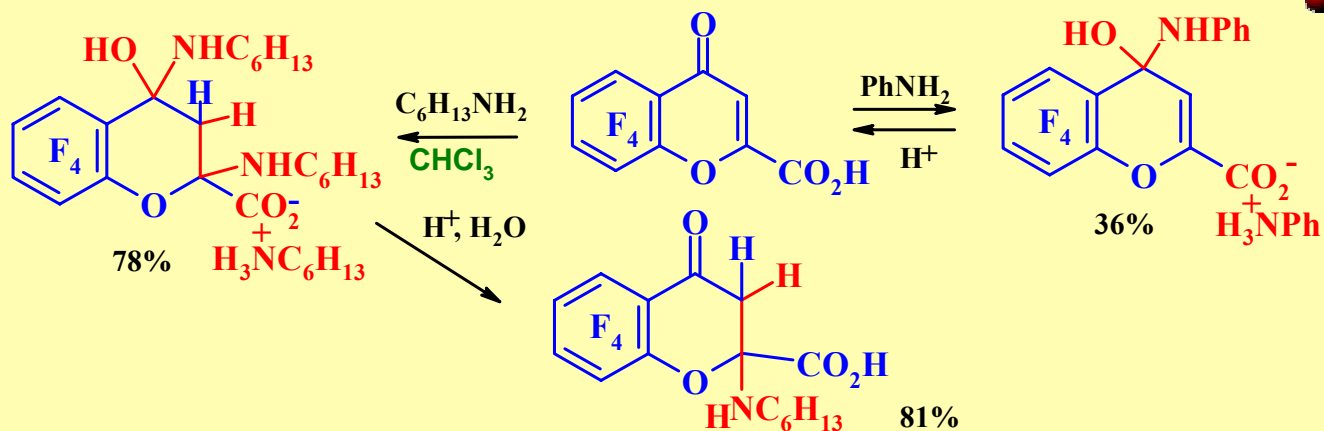
10



● Reactions with an excess of ammonia give α -aminoacids



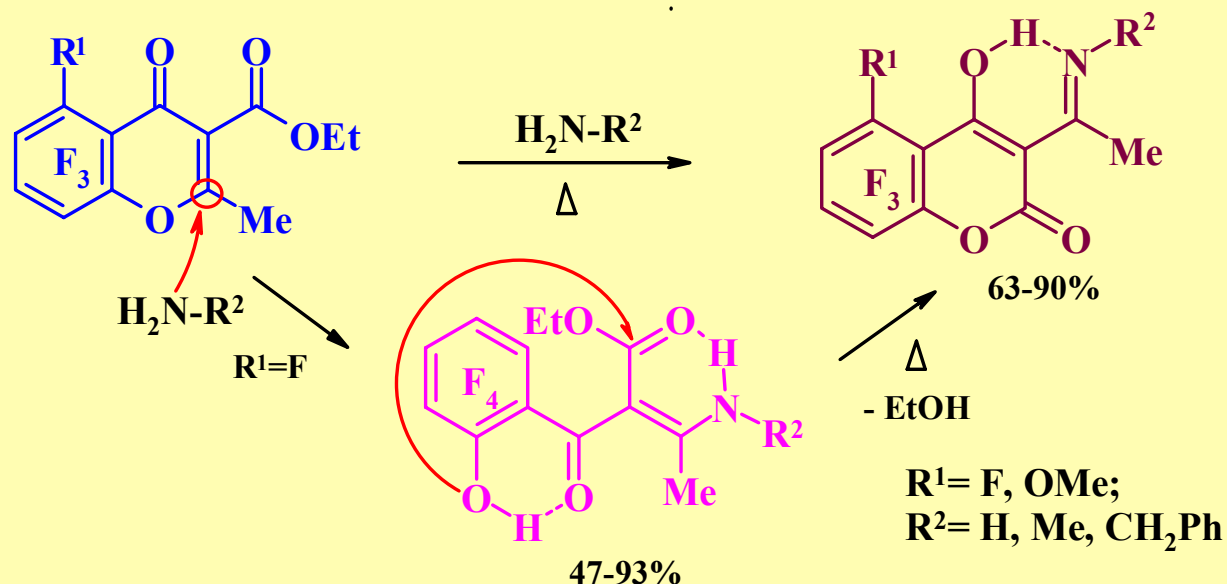
● Refluxing with cyclohexyl- and hexylamines affords the salts. Cyclohexylammonium salt with an excess of the amine forms product of opening chromone cycle.



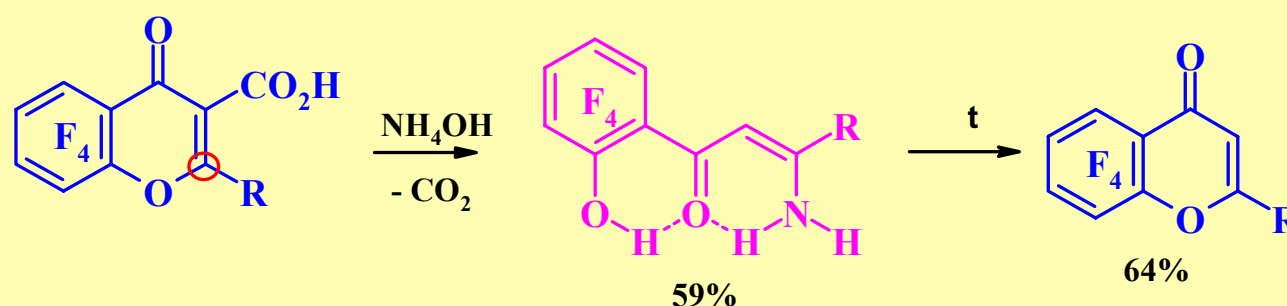
● Addition at the activated $\text{C}=\text{C}$ bond and the carbonyl group proceeds in the reaction with aniline, hexylamine

Reactions of 2-methyl-5,6,7,8-tetrafluorochromone-3-carboxylates with monoamines

11



3-Ethoxycarbonylchromones react with aqueous ammonia and benzylamine at the C-2 position to form α -substituted β -oxo esters, which can be transformed into 3-acetimidoyl-4-hydroxy-coumarins



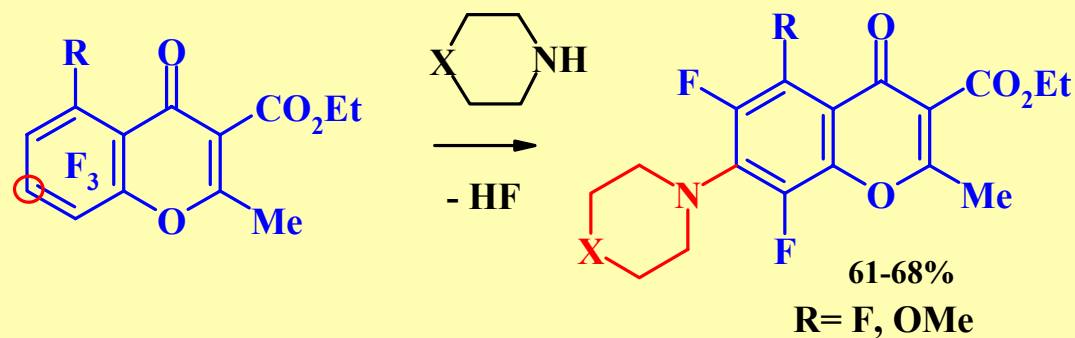
Chromone-3-carboxylic acid forms with aqueous ammonia β -aminovinyl-ketone, which may be cyclized into 2-methyl-tetrafluorochromone.

Prudchenko A.T., Barkcash V.A., Vorozhctov N.N. Russ. Chem. Bull., 1965. (6). 1798-1801.
 Filler R., Rao Y. S., Biezais A., Miller F. N., Beaucaire V. D. J. Org. Chem., 1970. 35(4). 930-935.
 Saloutin V.I., Skryabina Z.E., Bazyl' I.T., Chupakhin O.N. J. Fluorine Chem. 1999, 94 (1), 83-90.

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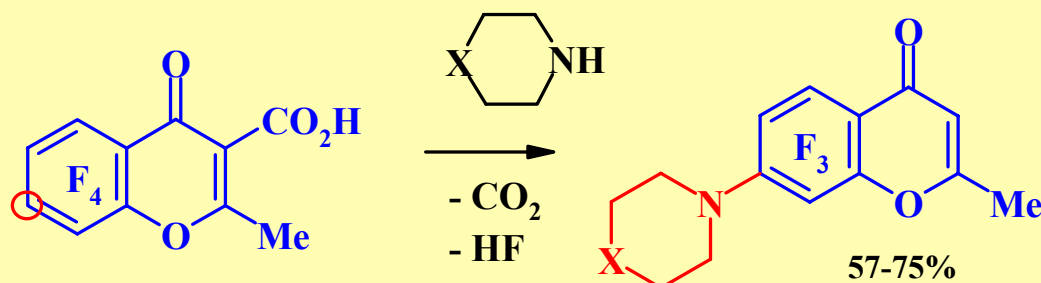
Reactions of 2-methyl-5,6,7,8-tetrafluorochromone-3-carboxylates with the secondary amines

12



X = O, NMe, CH₂

● Reactions of 3-ethoxy-carbonylchromones with secondary amines give 7-substituted chromones



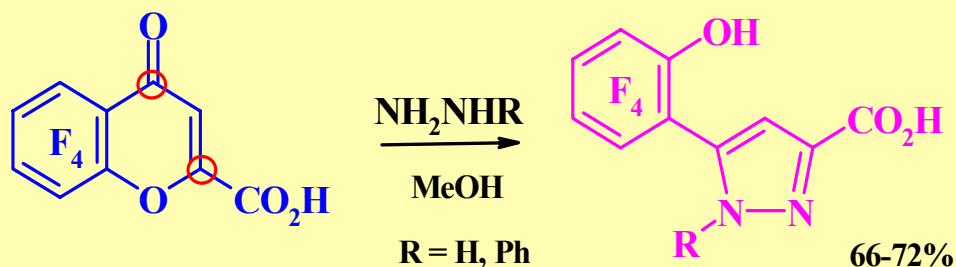
● Decarboxylation and displacement of fluorine atom at the C-7 position take place in the reaction of chromone-3-carboxylic acid with secondary amines

Saloutin V.I., Skryabina Z.E., Bazyl' I.T., Chupakhin O.N. J. Fluorine Chem. 1999, 94 (1), 83-90.

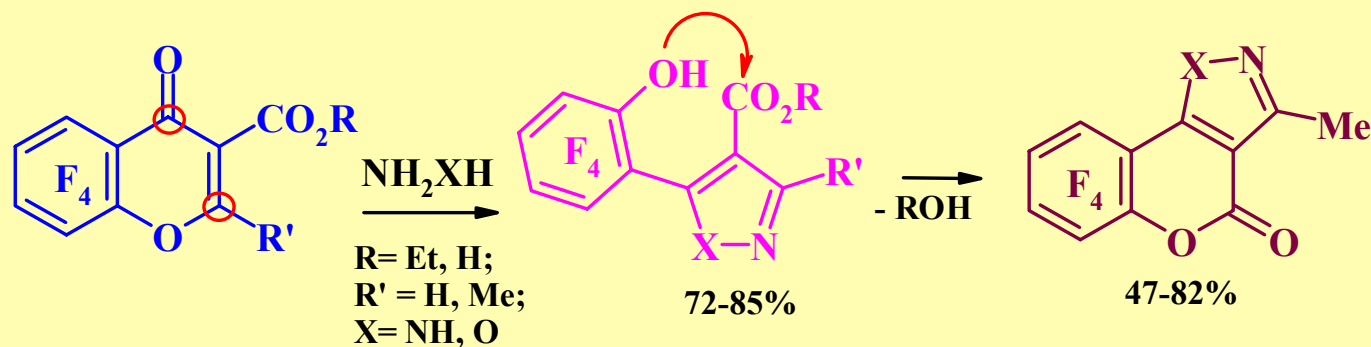
Kisil' S.P., Burgart Ya.V., Saloutin V.I., Chupakhin O.N. J. Fluorine Chem. 2001, 108 (2), 125-131.

Interaction of 5,6,7,8-tetrafluorochromone-2(3)-carboxylates with α -dinucleophiles

13



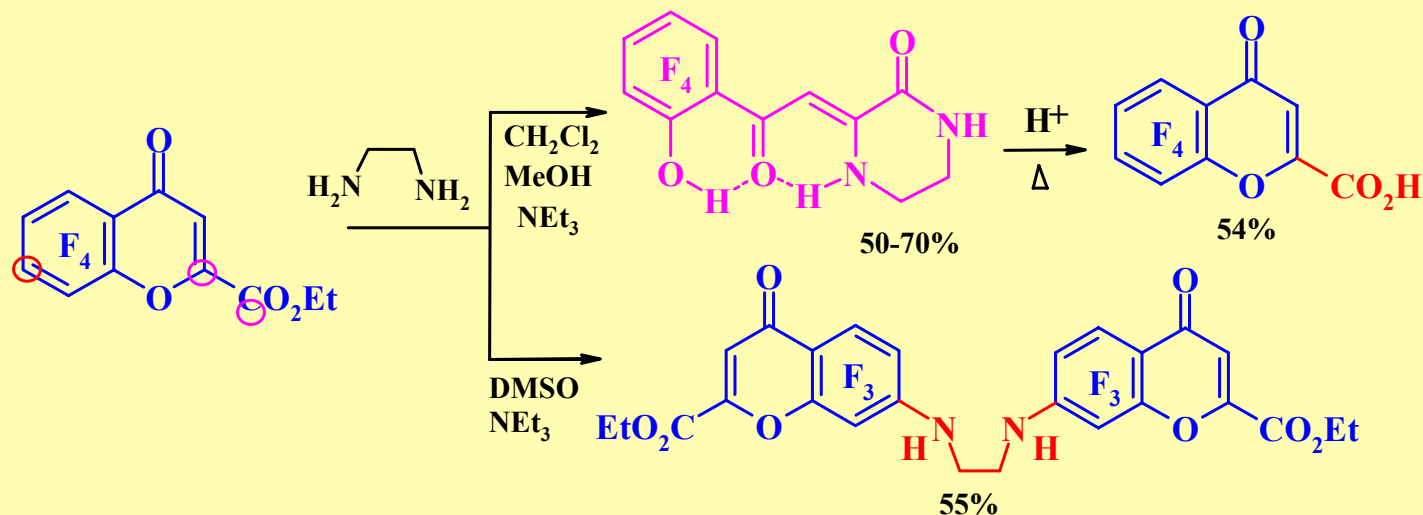
Pyrazole-3-carboxylic acids were derived from the reaction of chromone-2-carboxylic acid with hydrazines.



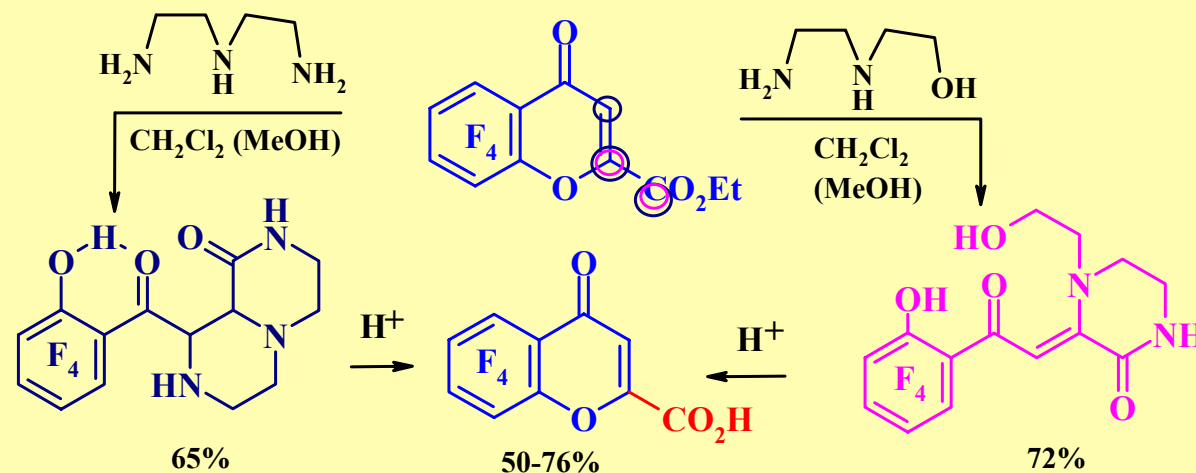
Chromone-3-carboxylates react with α -dinucleophiles at the C-2 to form the substituted pyrazoles and isoxazoles, which may be cyclized into coumarino-isoxazole(pyrazole).

Interaction of 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone with ethylenediamine and its derivatives

14



● Reaction with ethylenediamine can lead to piperazinone or the 7-substituted product

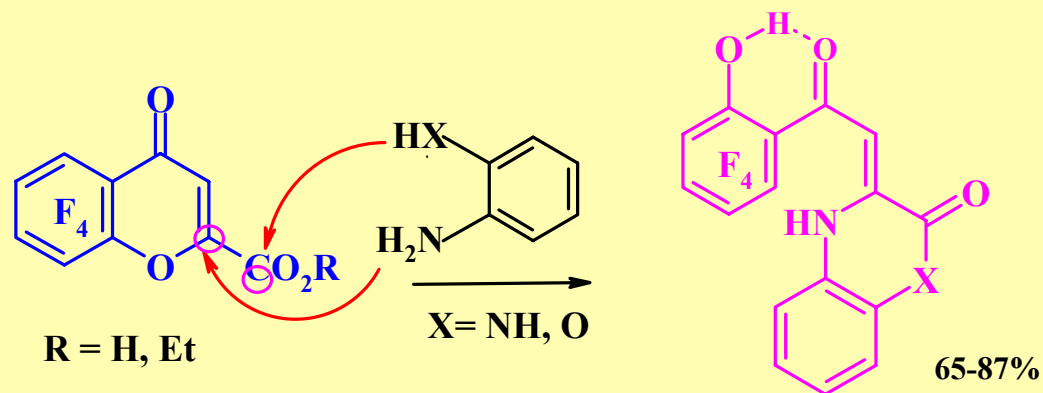


● Interaction:

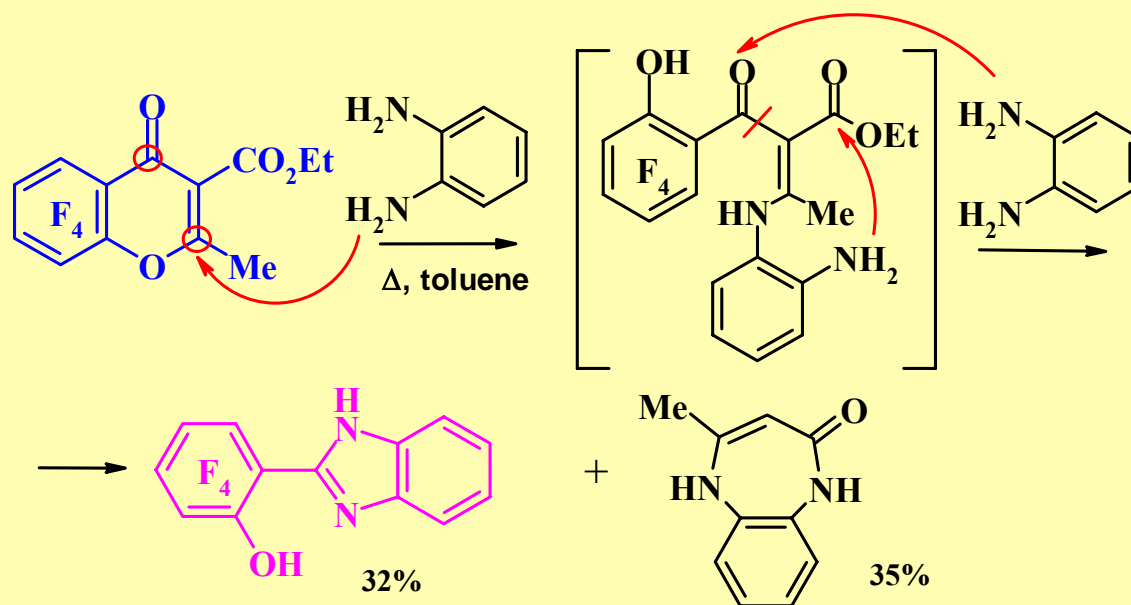
- with diethylenetriamine affords pyrazino[1,2-*a*]-pyrazinone
- with *N*-hydroxyethylethylenediamine - piperazinone

Interaction of 5,6,7,8-tetrafluorochromone-2(3)-carboxylates with aromatic dinucleophiles

15



● Tetrafluorochromone-2-carboxylates react with *o*-phenylenediamine to give quinoxaline. Benzoxazinone can be obtained from the reaction with *o*-aminophenol.



● 3-Ethoxycarbonyl-2-methyl-tetrafluorochromone is cleaved in the reaction with *o*-phenylenediamine

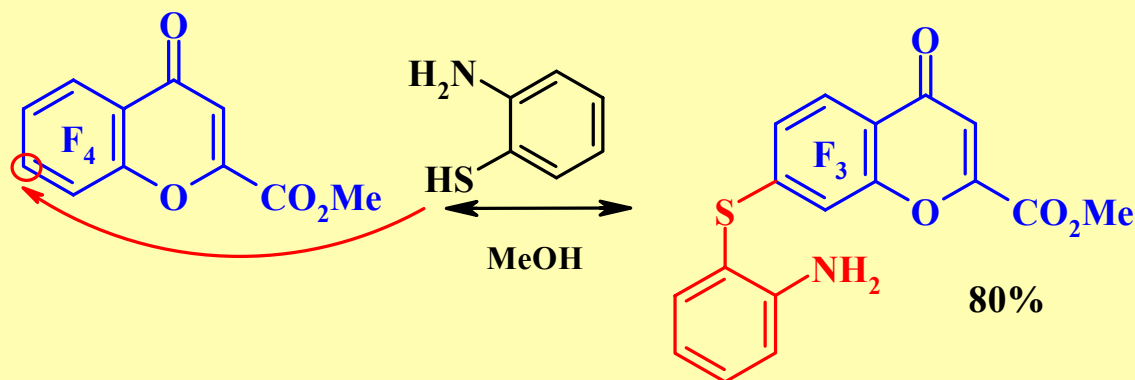
Saloutin V.I., Perevalov S.G., Chupakhin O.N. J. Fluorine Chem. 1999, 96 (1), 87-93.

Saloutin V.I., Skryabina Z.E., Bazyl' I.T., Chupakhin O.N. J. Fluorine Chem. 1999, 94 (1), 83-90.

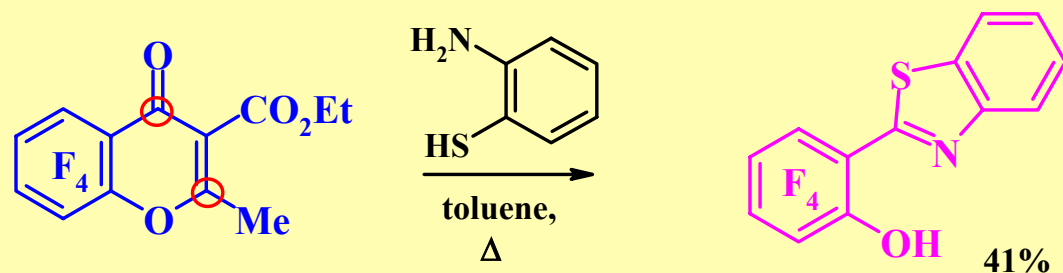
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Interaction of 2(3)-alkoxycarbonyl-5,6,7,8-tetrafluorochromones with *o*-aminothiophenol

16



2-Methoxycarbonylchromone with *o*-aminothiophenol forms the 7-substituted product.

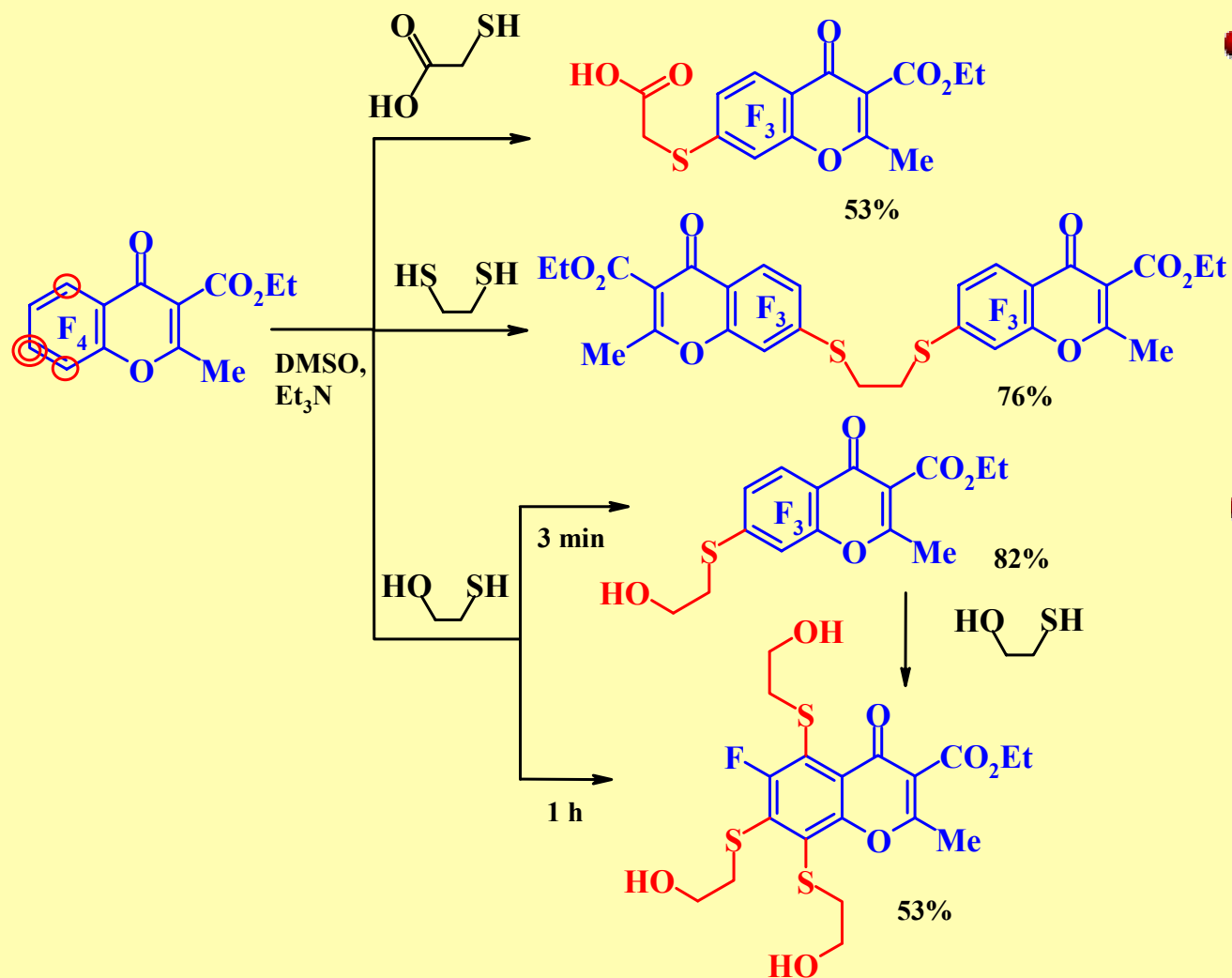


Interaction of 3-ethoxycarbonyl-2-methyltetrafluorochromone with *o*-aminothiophenol results in the formation of benzothiazole

Saloutin V.I., Perevalov S.G. et al. J. Fluorine Chem. 1999, 96 (1), 87-93.
Bazyl' I.T., Kisil' I.T. et al. J. Fluorine Chem. 2000, 103 (1), 3-12.

Reactions of 3-ethoxycarbonyl-2-methyl-5,6,7,8-tetrafluorochromone with S-nucleophiles

17

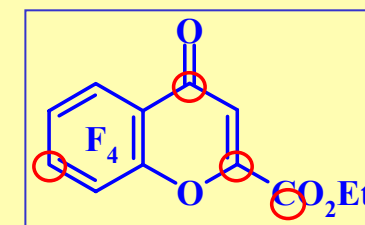
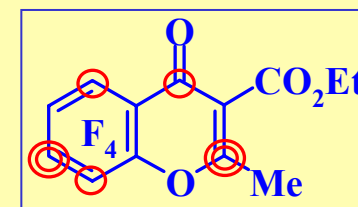
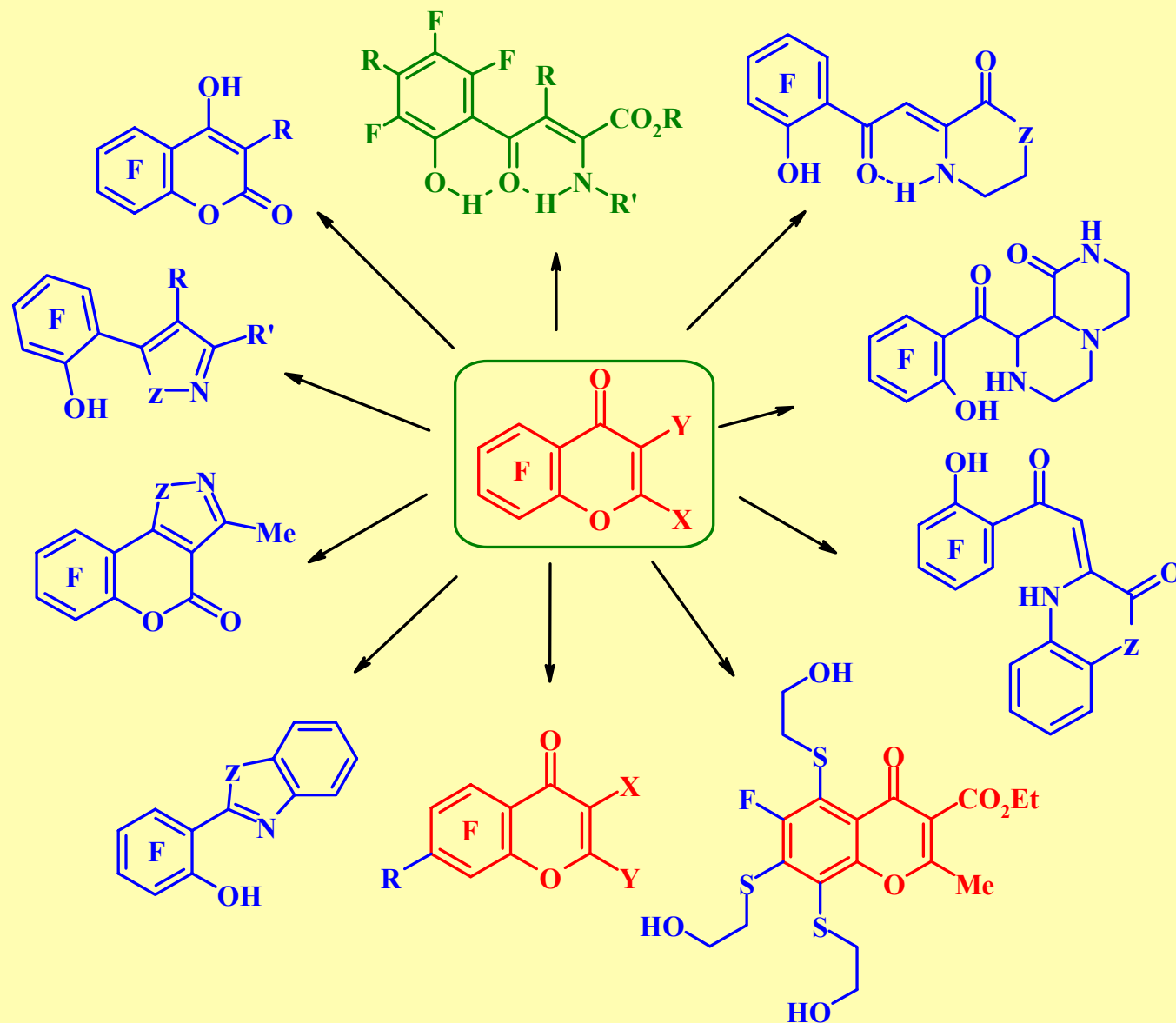


Reactions with mercaptoacetic acid and 1,2-ethanedithiol give the 7-substituted products

Interaction with 2-mercaptoethanol can lead to the formation of 7-mono- or 5,7,8-trisubstituted chromones

Conclusion

18



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Our research group

19



Prof. Viktor Saloutin



Igor' Bazyl'



Dr. Zinaida Skryabina



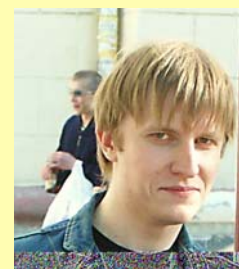
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