Synthesis of fluorinated pyrimidinones using fluoro-malonate and fluoro-ketoester « building blocks »

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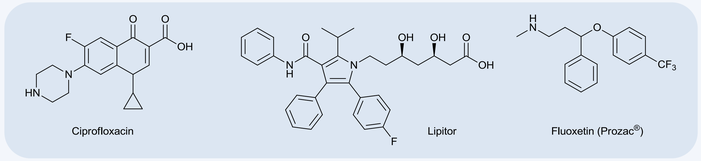
Introduction

❑ Significant role of organofluorine chemistry in the majority of the spectacular and technological developments of the past century, due to the specific properties of fluorine atom

❑ Approximately 30% of new pharmaceutical and agrochemical systems that enter the market bear fluorine atoms



❑ Development of continuous flow methodology for the selective synthesis of fluoroheterocyclic systems by fluorination of diketones to corresponding fluorodiketones followed by sequential cyclization to appropriate fluoroheterocycles

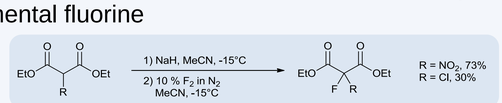
❑ Only a few patents dealing with using fluoro-malonates as « building block » for the synthesis of fluorinated biologically active systems

Synthesis of fluoro-malonates

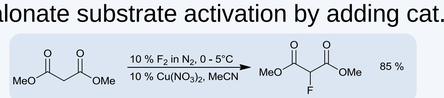
❑ Previous studies: replacement of enolic hydrogen atom by fluorine using electrophilic fluorinating agent (NFSI or Selectfluor®) to fluorinate malonate esters

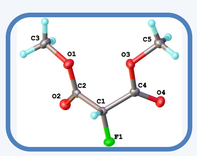
❑ Direct fluorination of malonates using fluorine diluted in nitrogen

▪ Previous studies: reaction of substituted dialkyl malonate salts with elemental fluorine



▪ Malonate substrate activation by adding cat. $Cu(NO_3)_2$

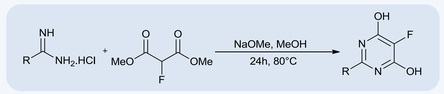




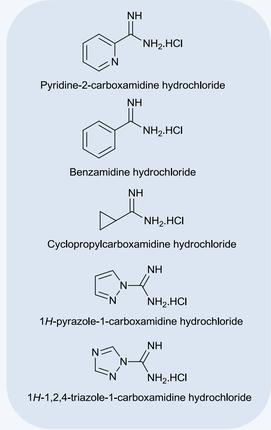
Synthesis of fluoro-heterocycles

❑ Synthesis of fluorinated pyrimidinones from previously synthesized monofluoro-malonates

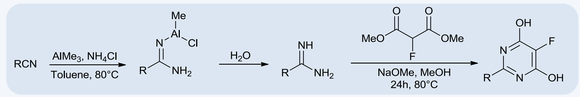
▪ with different commercially available amidine hydrochlorides



Entry	Substrate (1 eq.)	Yield
(1)	Pyridine-2-carboxamidine hydrochloride	72%
(2)	Benzamidine hydrochloride	76%
(3)	Cyclopropylcarboxamidine hydrochloride	89%
(4)	*1H*-Pyrazole-1-carboxamidine hydrochloride	51%
(5)	*1H*-1,2,4-triazole-1-carboxamidine hydrochloride	65%



▪ with synthesized amidines via Garigipatis procedure



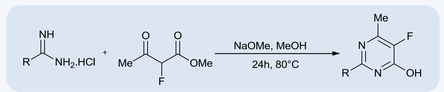
Entry	Substrate (1 eq.)	R	Yield
(1)	Heptyl cyanide	H_3C-$(CH_2)_6$	quant.
(2)	Octyl cyanide	H_3C-$(CH_2)_7$	quant.
(3)	Undecyl cyanide	H_3C-$(CH_2)_{10}$	80%

❑ Structural comparison between products from monofluoro-ketoester and monofluoro-malonate

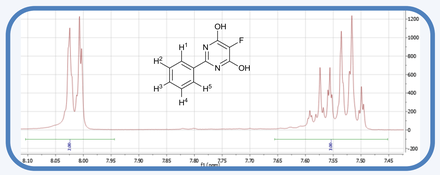
▪ Application of the same synthetic method to monofluoro-ketoester substrates

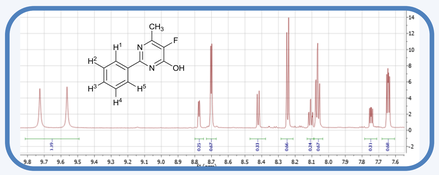
▪ Synthesis with two different commercially available amidine hydrochlorides

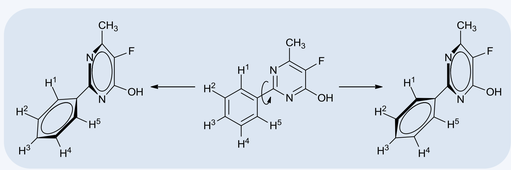
▪ Synthesis of rotamers confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy and GC-MS spectrometry



Entry	Substrate (1 eq.)	Yield
(1)	Pyridine-2-carboxamidine hydrochloride	97%
(2)	Benzamidine hydrochloride	quant.







Conclusions

❑ Large scale synthesis of fluoro-malonate esters using direct fluorination reactions (10 % F_2 in N_2)

❑ Synthesis of a range of fluoro-pyrimidinones using either fluoro-malonates or fluoro-ketoesters as « building blocks »

❑ In case of using fluoro-ketoesters: proof of the synthesis of rotamers by structural analysis

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