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Oxydation of heterocycle, an advance for efficient synthesis of active molecules

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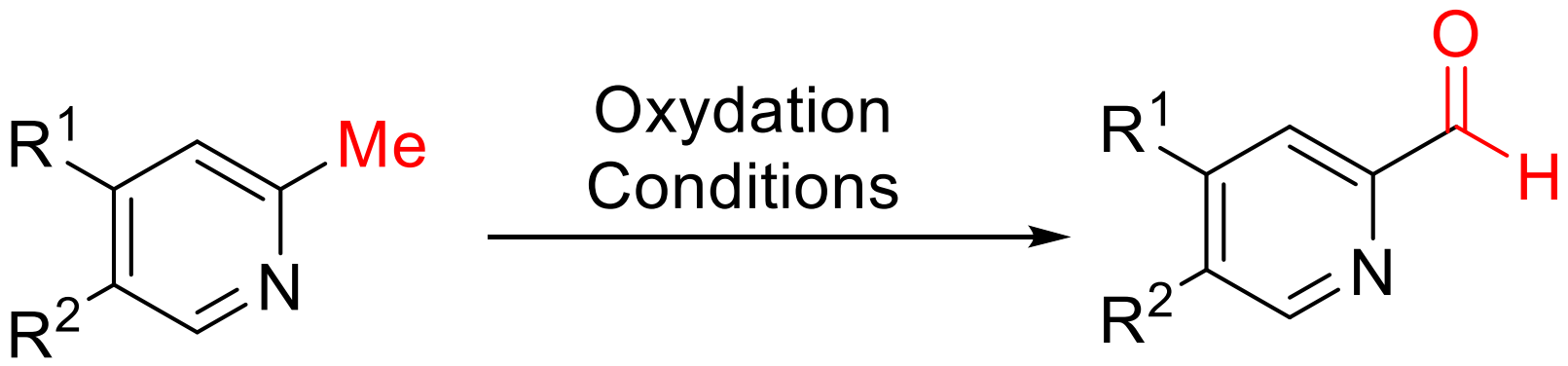
Oxydation of heterocycle, an advance for efficient synthesis of active molecules

Graphical Abstract



Abstract

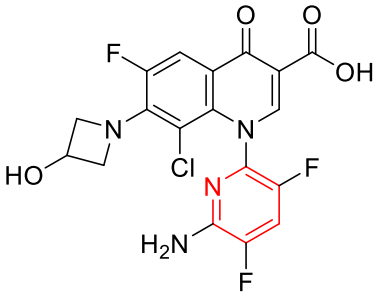
Heterocycles play an important role in therapeutic chemistry. Currently, more than 85% of all biologically active molecules contain at least one heterocycle. The FDA (Food and Drug Administration) database reveals that 14% of active ingredients containing a nitrogen heterocycle are pyridines, mainly mono- or di-substituted. Therefore, the study of mono-, di-, and tri-substituted pyridine's reactivity is important in the development of new biologically active molecules. In this study, we focused on a particular family of pyridines: 2-pyridinecarboxaldehydes. The latter are often obtained by oxidation of the corresponding 2-methylpyridines. However, these reactions usually require the use of dangerous reagents such as oxygen, or expensive catalysts.

Oxidation reactions are very common in organic chemistry, but aldehydes can be susceptible to overoxidation to carboxylic acids. It is therefore essential to develop and optimise oxidation conditions to limit this undesirable subproduct. In our laboratory, we have developed a method for oxidation of various 2-methylpyridines to their 2-pyridinecarboxaldehyde analogues, whereas limiting overoxidation. This method led to better yields than those described in the literature, while simplify the operating mode.

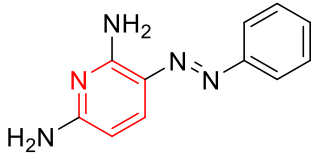
Keywords: Oxydation ; Pyridine ; Heterocycles ; Organic chemistry

Introduction

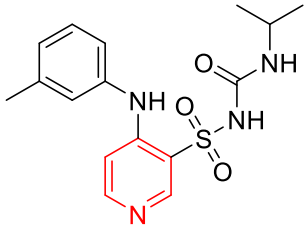
FDA data base : 30% of active ingredients containing a nitrogen heterocycle, are pyridines.



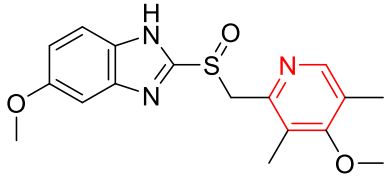
Delafloxacin
Antibiotic



Phenazopyridine
Urinary tract analgesic

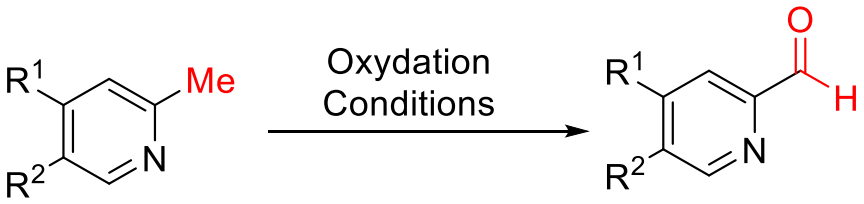


Torasemide
Loop diuretic



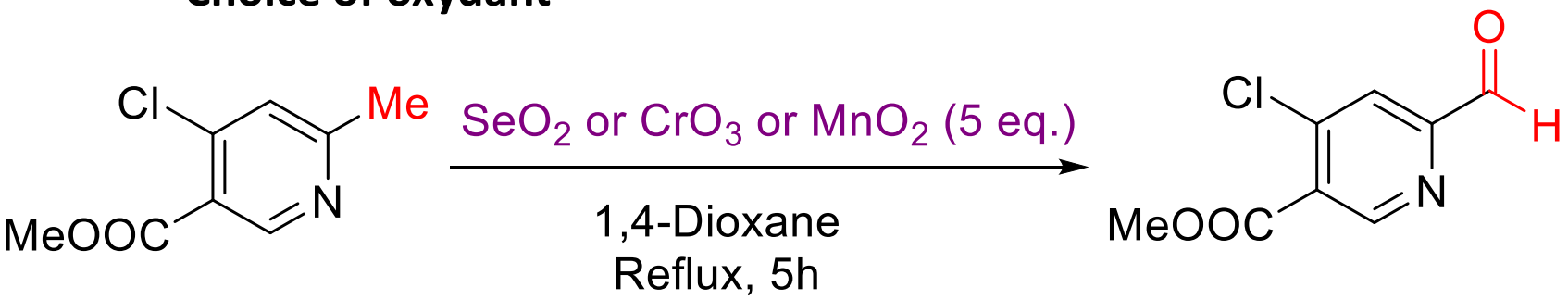
Omeprazol
Proton-pump inhibitor

➔ **It's very important to have an easy acces to this skeleton**



Results and discussion

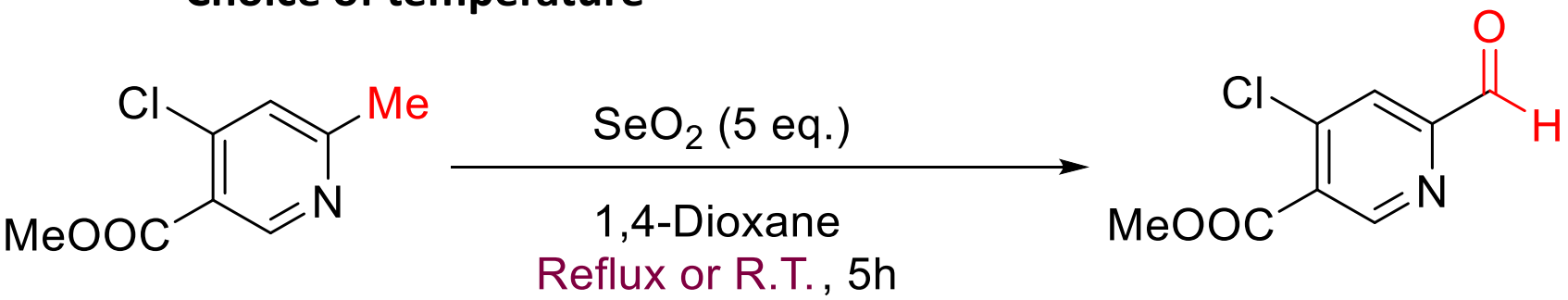
Choice of oxydant



Oxydant	% Substrate	% Aldehyde	% Acid
SeO_2	5	36	59
CrO_3	100	0	0
MnO_2	100	0	0

Results and discussion

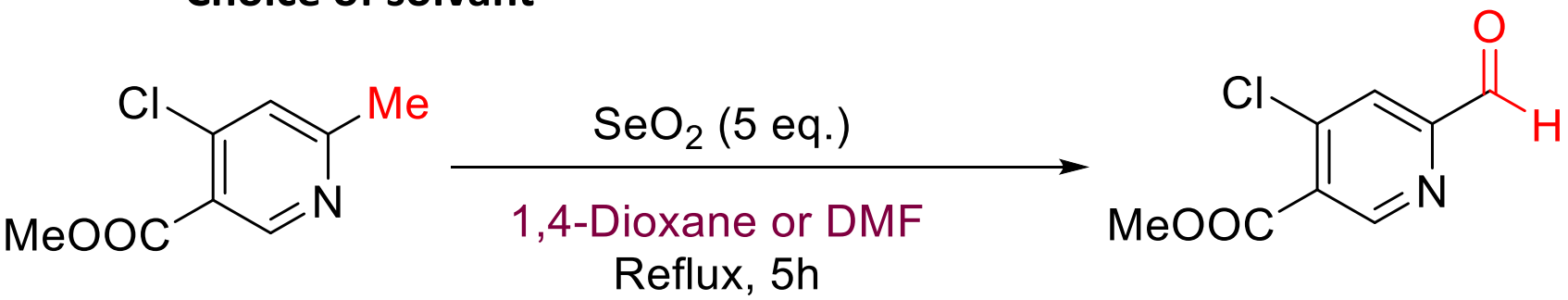
Choice of temperature



Temperature	% Substrate	% Aldehyde	% Acid
Reflux	5	36	59
R.T	71	14	15

Results and discussion

Choice of solvant

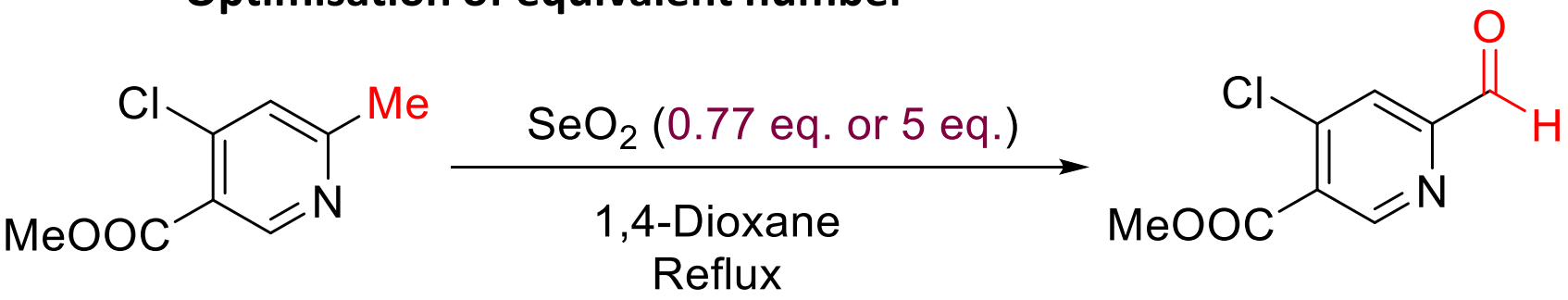


Solvant	% Substrate	% Aldehyde	% Acid
1,4-Dioxane	5	36	59
DMF	0	0	0

Degradation

Results and discussion

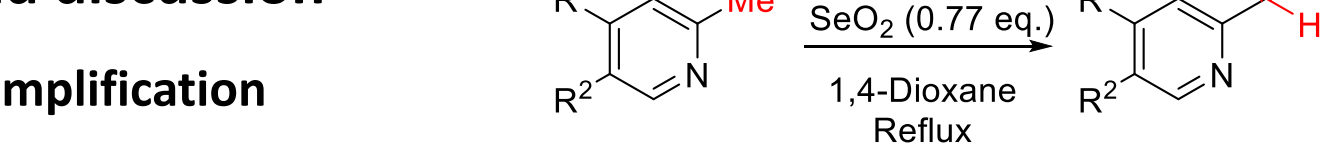
Optimisation of equivalent number

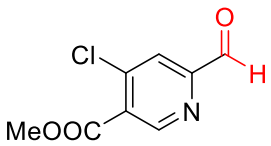


Equivalent	Isolated yield %
5	30
0.77	46

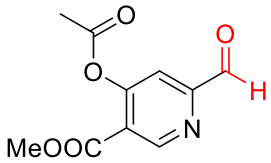
Results and discussion

Exemplification

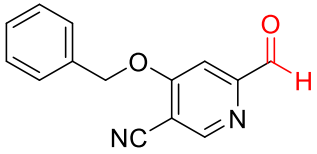




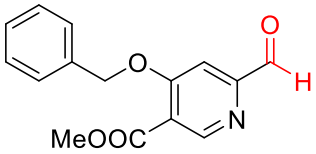
Yield % (SeO_2 eq)
46% (0.77 eq)
30% (5 eq)



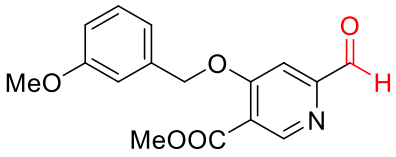
Yield % (SeO_2 eq)
48% (0.77 eq)
5% (5 eq)



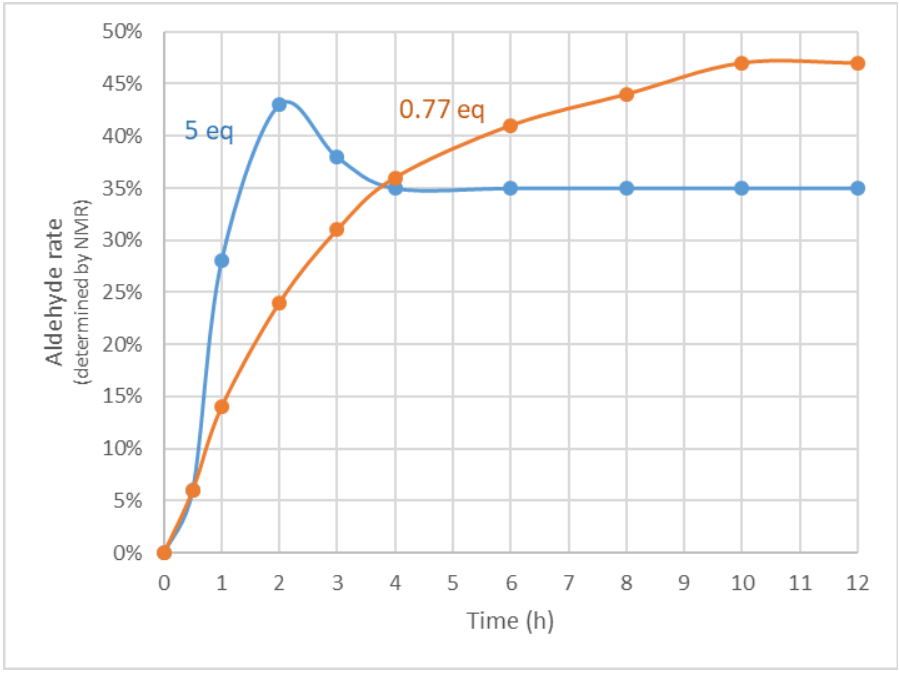
Yield % (SeO_2 eq)
51% (0.77 eq)
39% (5 eq)



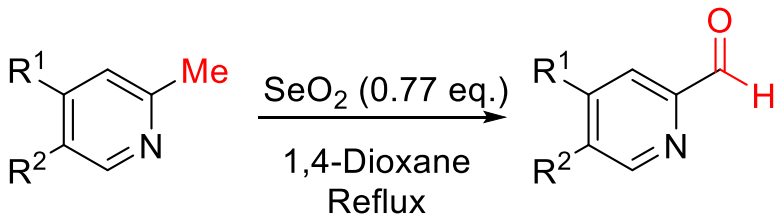
Yield % (SeO_2 eq)
62% (0.77 eq)
46% (5 eq)



Yield % (SeO_2 eq)
51% (0.77 eq)
27% (5 eq)



Conclusions



- Best yield improvement : ↗ 43%
- Less good yield improvement : ↗ 12%
- Increased stability of the aldehyde during the reaction
- Excess of substrate recyclable

Acknowledgments

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