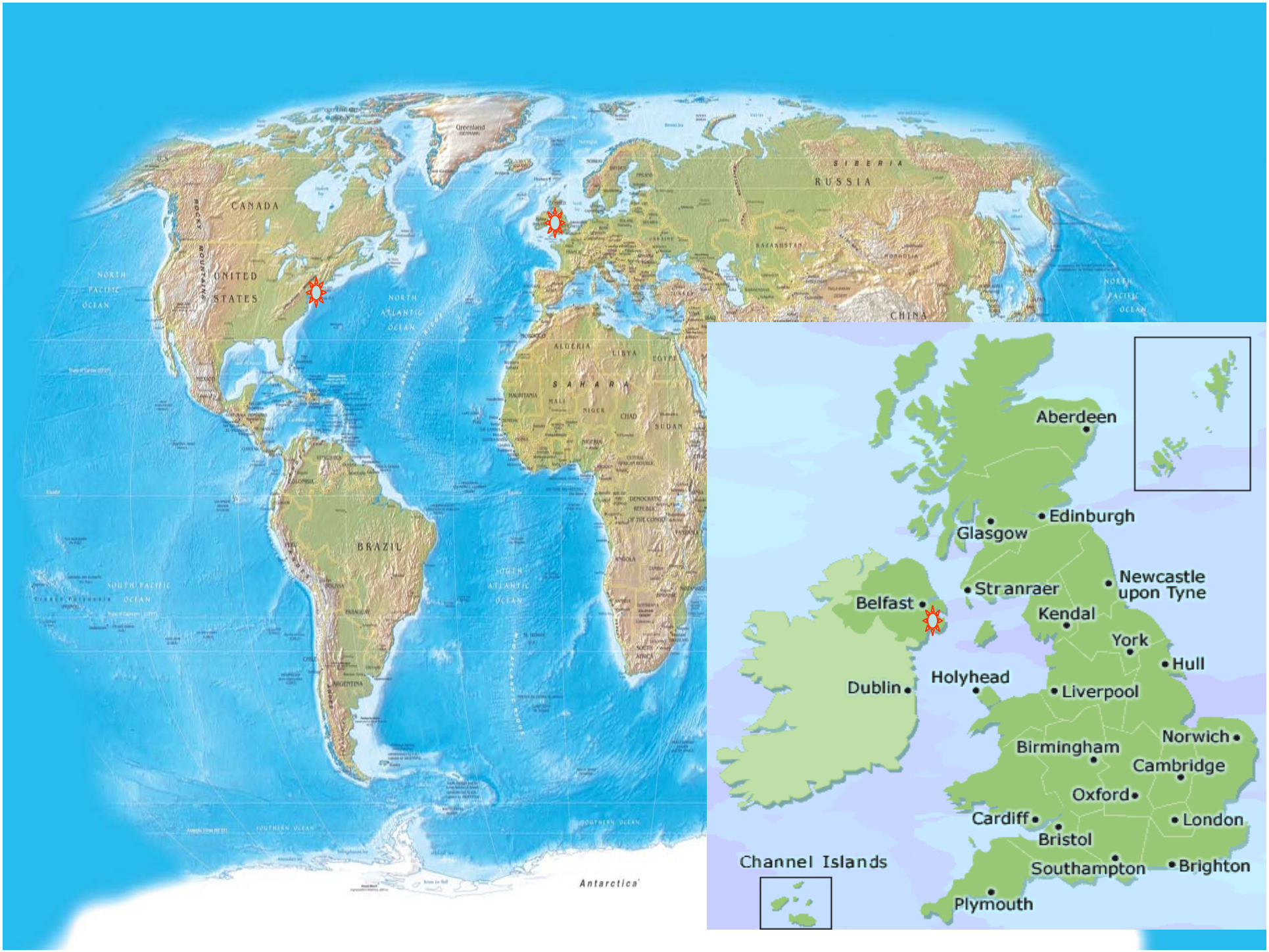
Development of an Efficient and Practical Route for the Multi-kilogram Manufacture of Cyanopyridone AZ10527409 and Chloropyridine AZ10146848

Conchita Fdez Garcia, 19-21 March 2012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CHINA
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MOROCCO
ALGERIA
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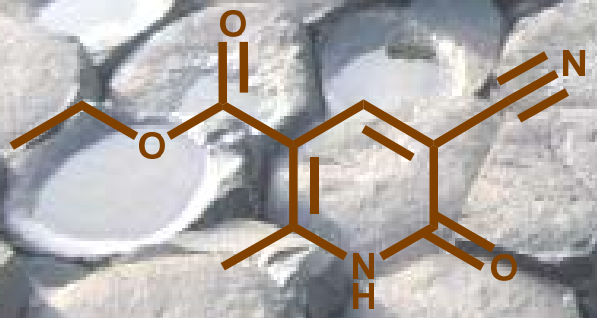
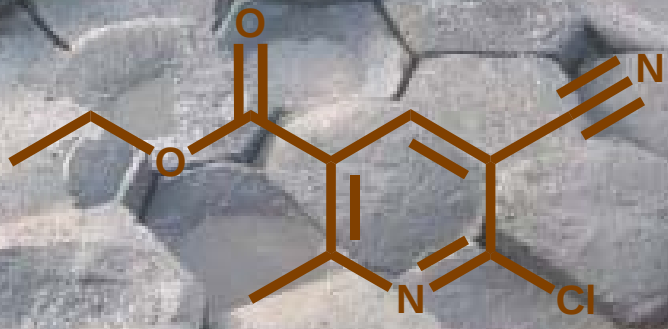
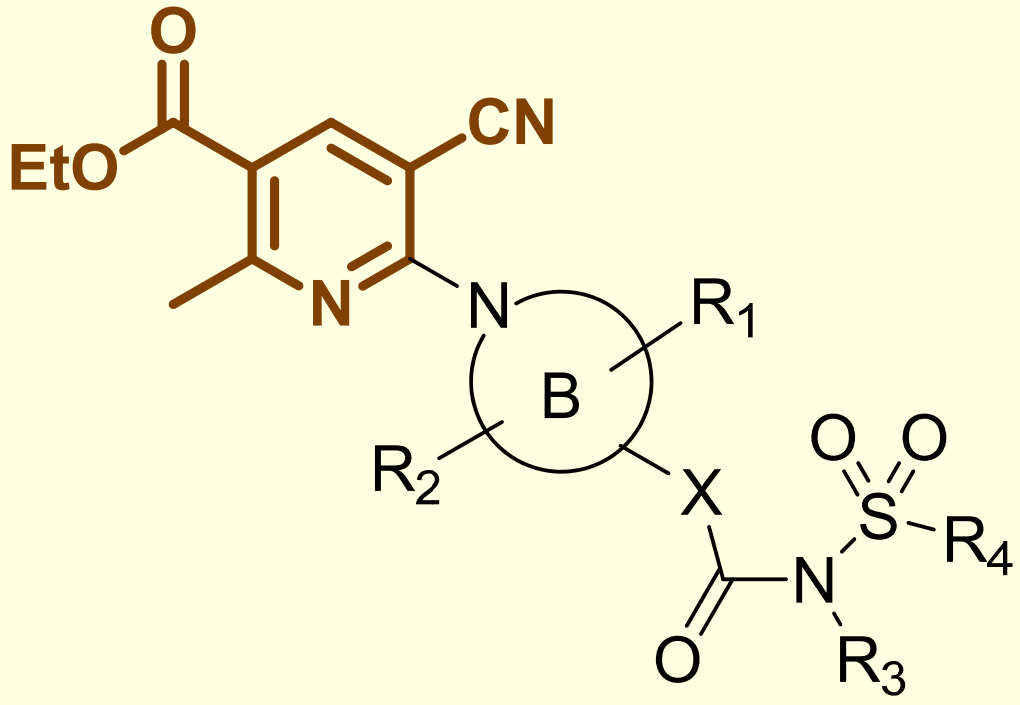


Cyanopyridone
AZ10527409



Chloropyridine
AZ10146848

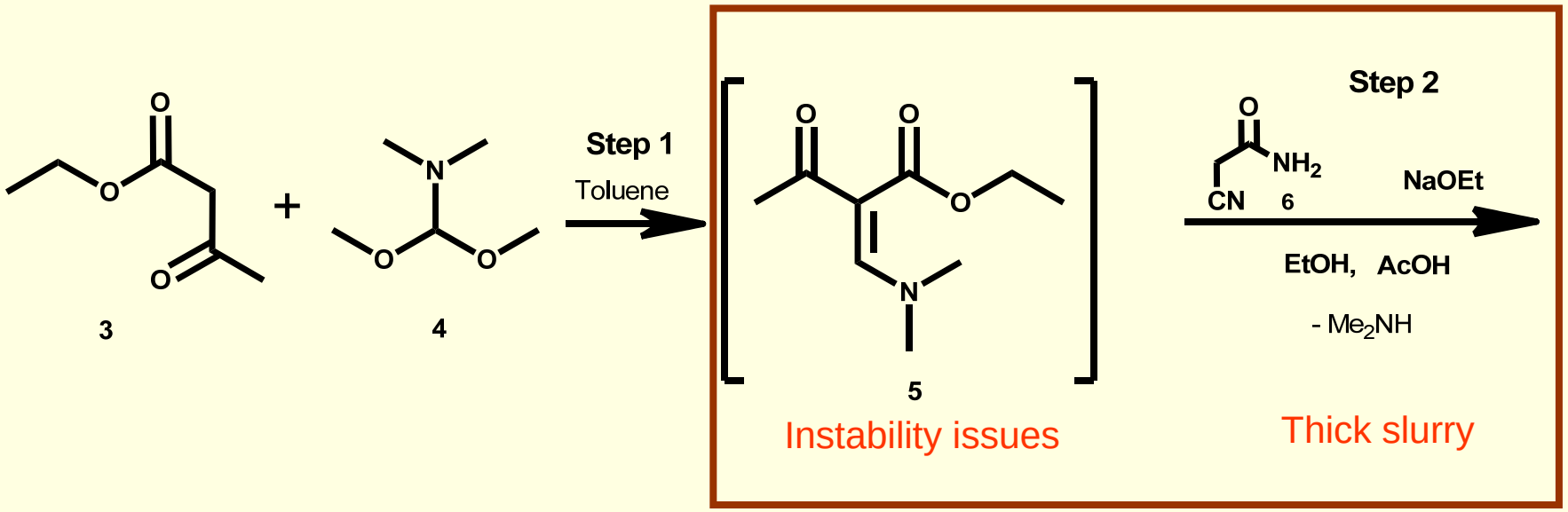
- Key intermediates to an AstraZeneca development candidate use in the treatment of platelet aggregation disorders as P2Y12 inhibitors.

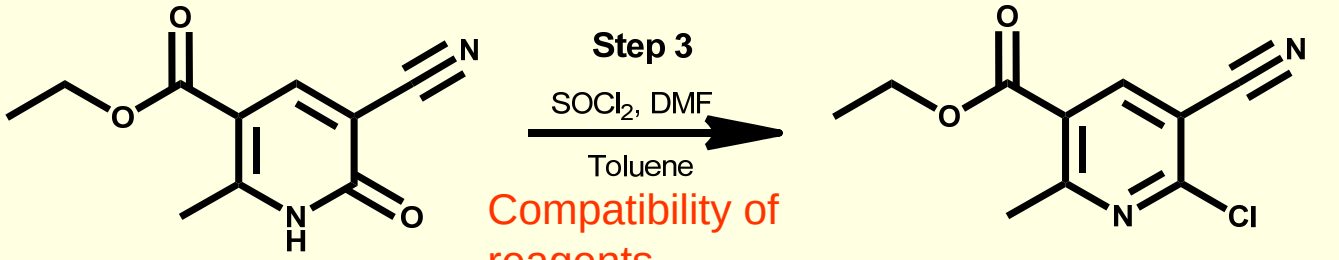


Background:

- Initial kilogram-scale route highlighted areas of concern.
- New route was required to produce multi-kilogram quantities of these intermediates in a very short timeframe.

Original route - Problems





Pyridone, 1

51%

Purity issues

Chloro-pyridine, 2

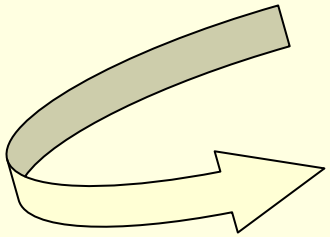
20%

Colour of isolated material

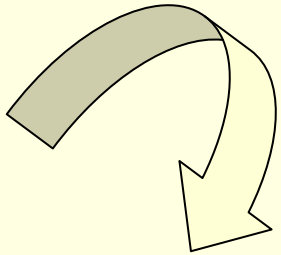
Entry	Base/Solvent (5 vols to 11g of enaminone 3)	Temp.	IPC, HPLC:Product/imp.1/ imp. 2	Isolated Yield of AZ10527409/purity by HPLC	Comments
1	NaOEt/EtOH	78ºC	78.2/10.6/0.1	59%/>98%	Stirring v. difficult
2	NaOEt/EtOH	25ºC	86.6/9.7/0.1	72%/>98%	Stirring difficult
3	NaOEt/EtOH	0ºC	88.0/7.4/0.2	74%/>98%	Stirring difficult
4	NaOEt/EtOH	-15ºC	86.0/6.4/4.2	72%/>98%	Stirring difficult
5	NaOEt/MeCN	25ºC	_	60%/>97%	Stirring difficult
6	NaOEt/DMSO	25ºC	74.8/19.5/0.1	64%/>98%	Homogeneous solution
7	NaOEt/DMF	25ºC	_	60%/>98%	Stirring difficult
8	NaOEt/NMP	10ºC	_	60%/>98%	Stirring v. difficult
9	NaOEt/tetragl.	25ºC	_	62%/>98%	Stirring v. difficult
10	NaO^{t}Bu/DMF	25ºC	_	60%/>98%	Stirring difficult
11	KO^{t}Bu/DMSO	25ºC		62%>98%	Homogeneous solution
12	NaH/DMSO	25ºC	_	62%/>95%	Homogeneous solution
13	K_2CO_3/DMSO	25ºC	_	40%/75%[a]	Stirring ok
14	K_2CO_3/acetone	25ºC	_	45%/33%[b]	Stirring difficult
15	K_2CO_3/water	25ºC	_	0%[c]	Homogeneous solution

[a] 3:1 mixture of AZ10527409 and imp.2 was isolated. [b] 1:2 mixture of AZ10527409 and imp. 2 was isolated. [c] 27% yield of imp.2 was isolated.

Stability concerns
Poor yields
Difficult isolations



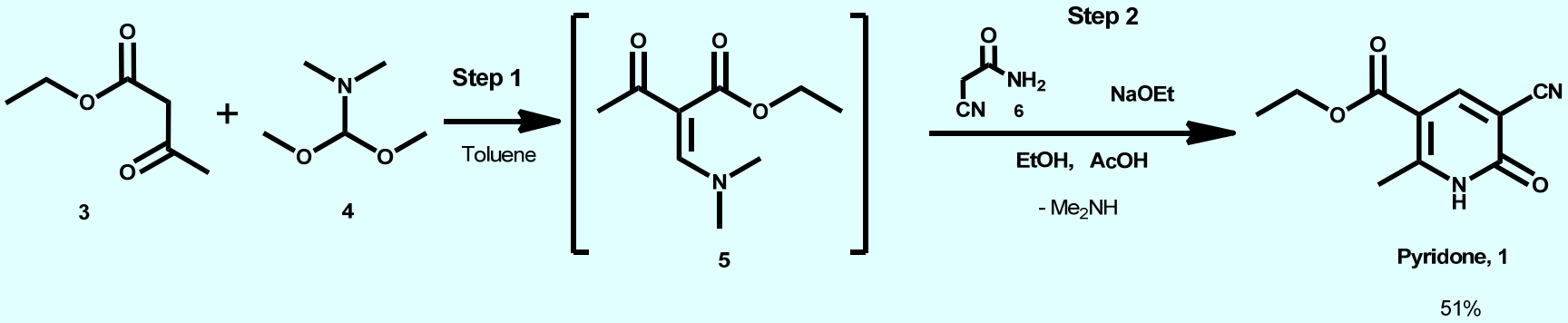
Literature search



Similar chemistry to the current route used for the synthesis of pyridinones

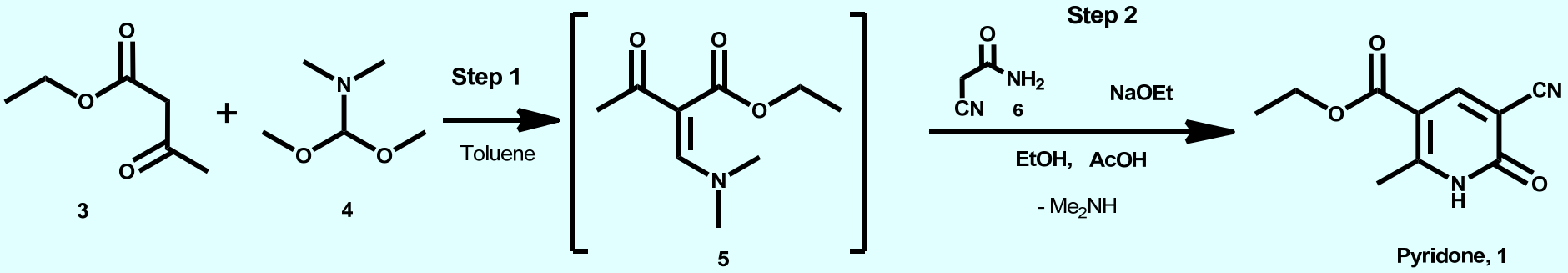
Better understanding of the reaction and the generation of the process impurities was fundamental.

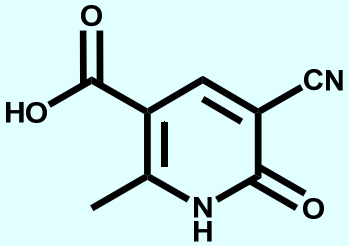
Steps 1-2: Impurity investigation:



Temp.	IPC, HPLC: Product/imp.1/ imp. 2
78°C	78.2/10.6/0.1
25°C	86.6/9.7/0.1
0°C	88.0/7.4/0.2
-15°C	86.0/6.4/4.2

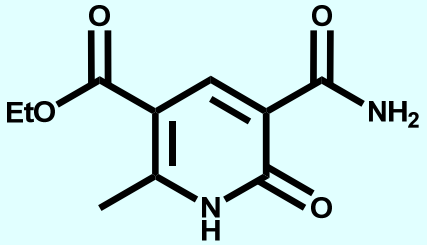
Steps 1-2: Impurity investigation:





Impurity 1

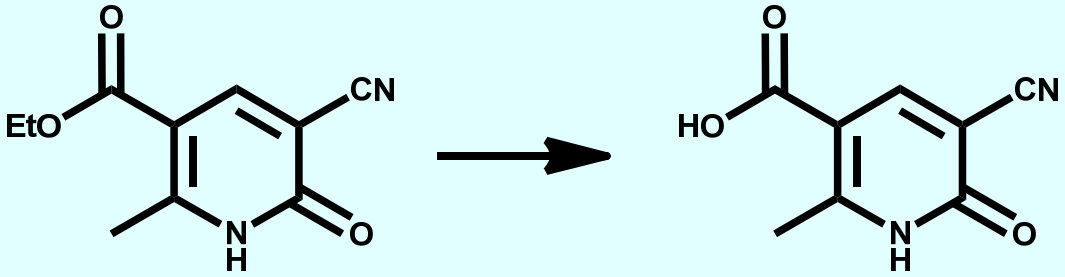
MW= 178



Impurity 2

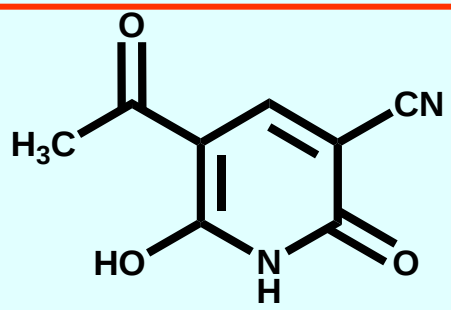
MW =224

Impurity investigation:



Pyridone MW= 178

^{1}H and ^{13}C NMR spectroscopy data supported a methyl ketone moiety by the carbonyl peak at 192 ppm in the ^{13}C NMR spectrum matching the acetyl group.

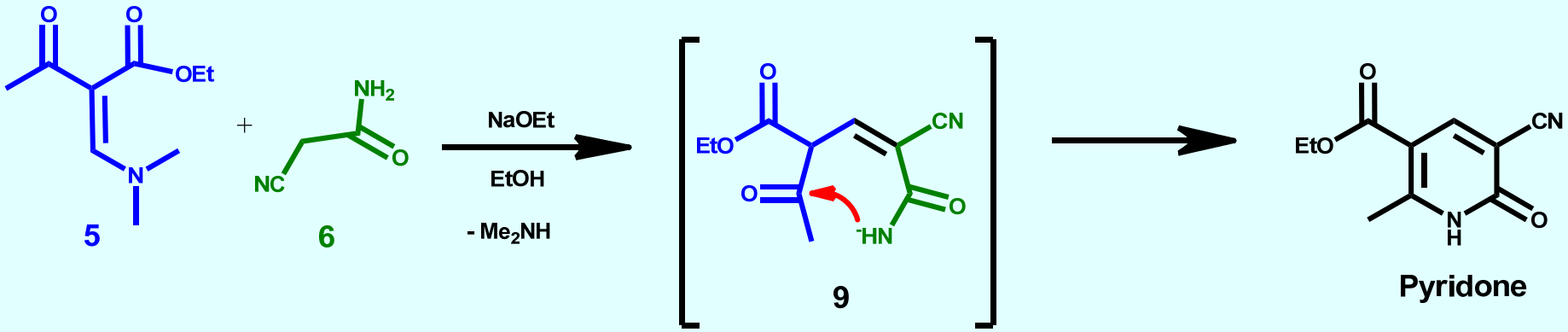


Impurity 1

MW= 178

Revised assigment: methyl ketone

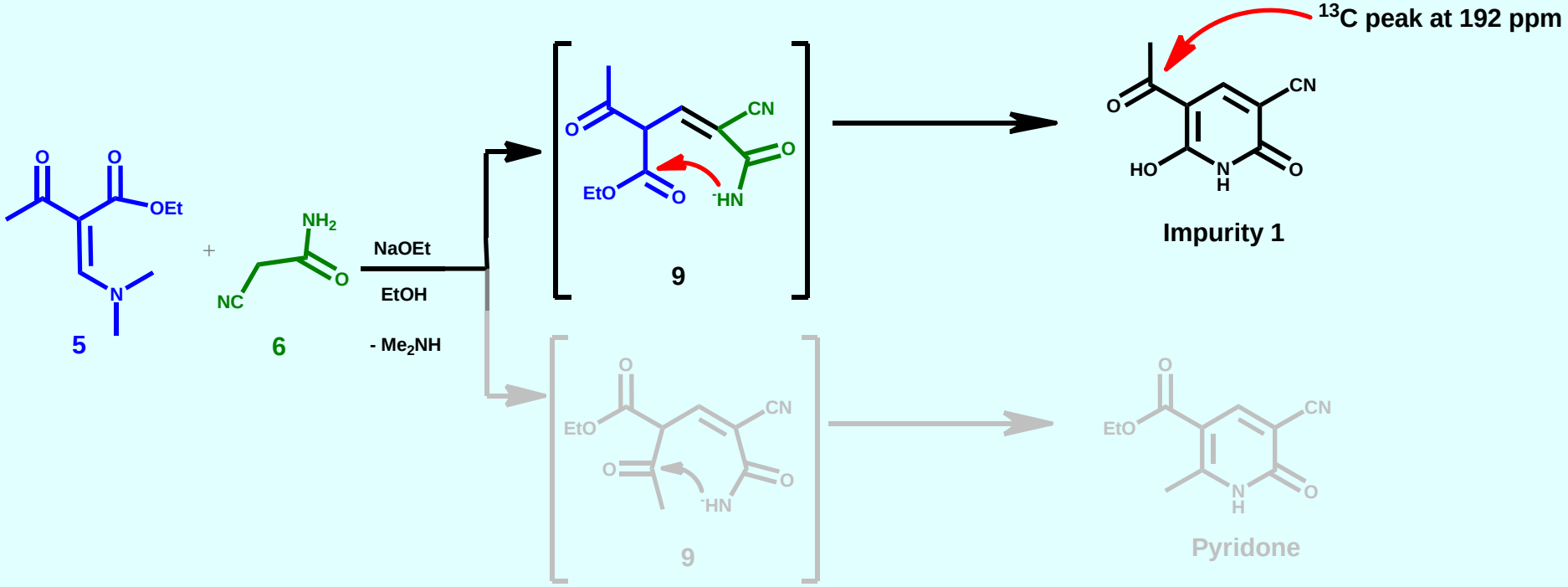
Impurity investigation:



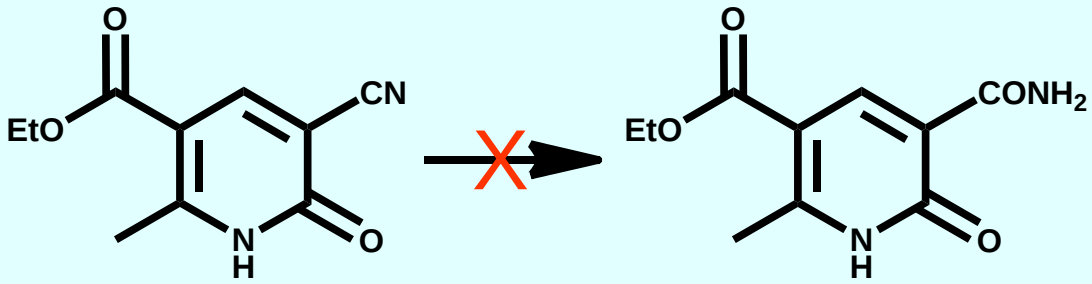
Mode of condensation to afford **1** is that between the amide nitrogen and the carbonyl of the ketone in **9**.

Impurity investigation:

The condensation of the amide nitrogen with the carbonyl of the ester in intermediate **9** accounts for the formation of ketone impurity 1.

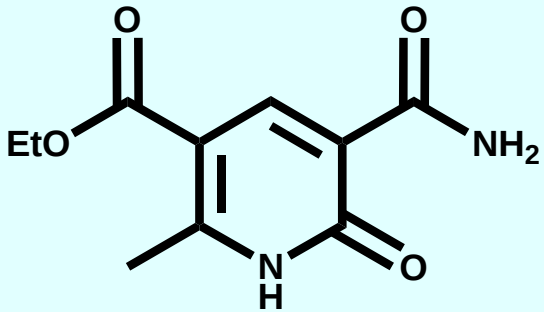


Impurity investigation:



Pyridone MW= 224

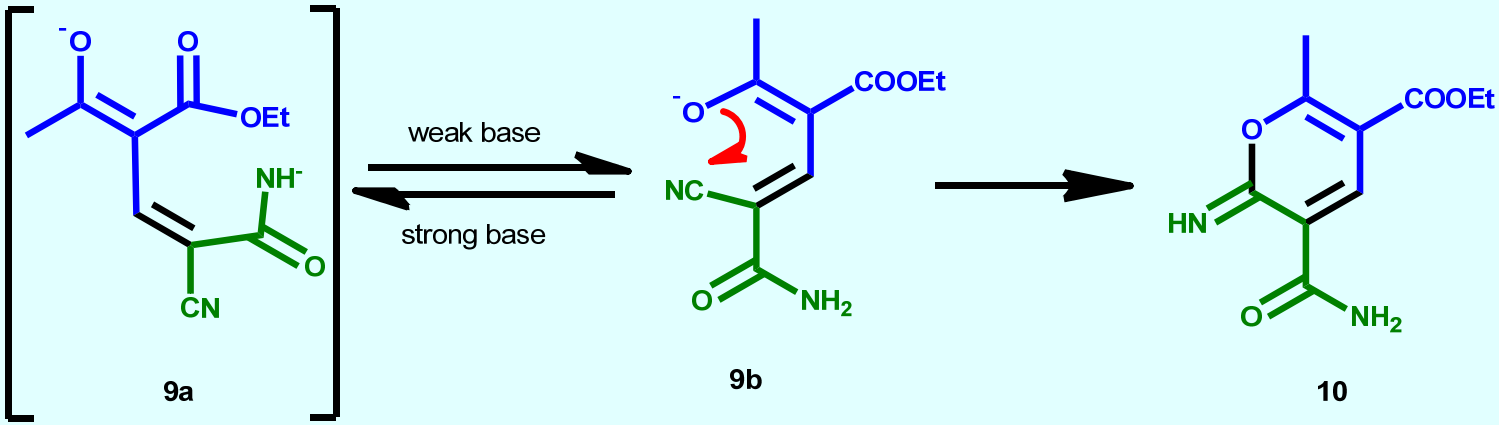
Experimental observation showed higher concentration of impurity 2 formed at lower temperatures or when a weaker base (e.g. K_2CO_3) was used.



Impurity 2

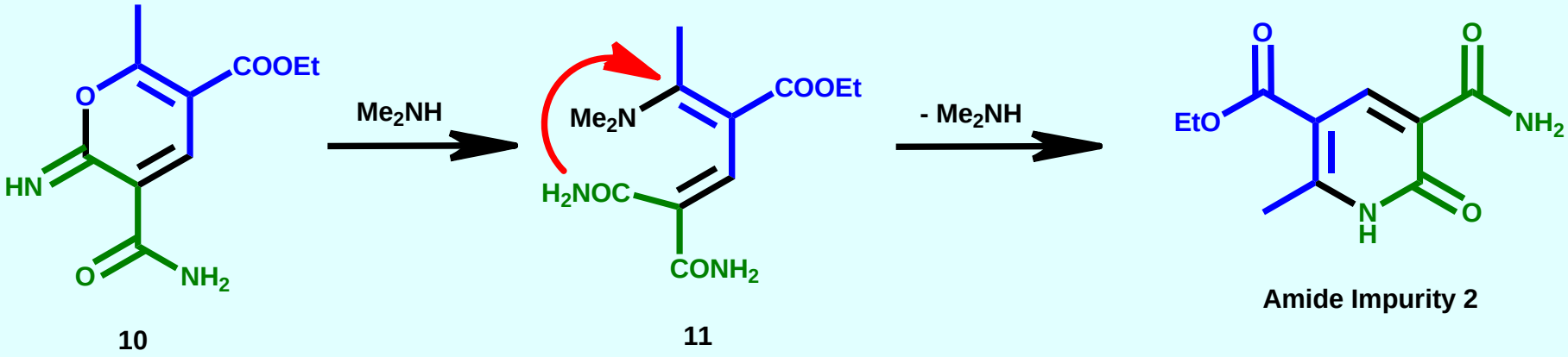
MW =224
Amide

Impurity investigation:



- Equilibrium of **9a/9b** towards the enolization of the β-ketoester (**9b**) instead of deprotonation of the amide nitrogen (**9a**).
- The intramolecular condensation whereby ketonic oxygen attacks the cyano group of **9b** to give the pyran intermediate **10**…..

Impurity investigation:



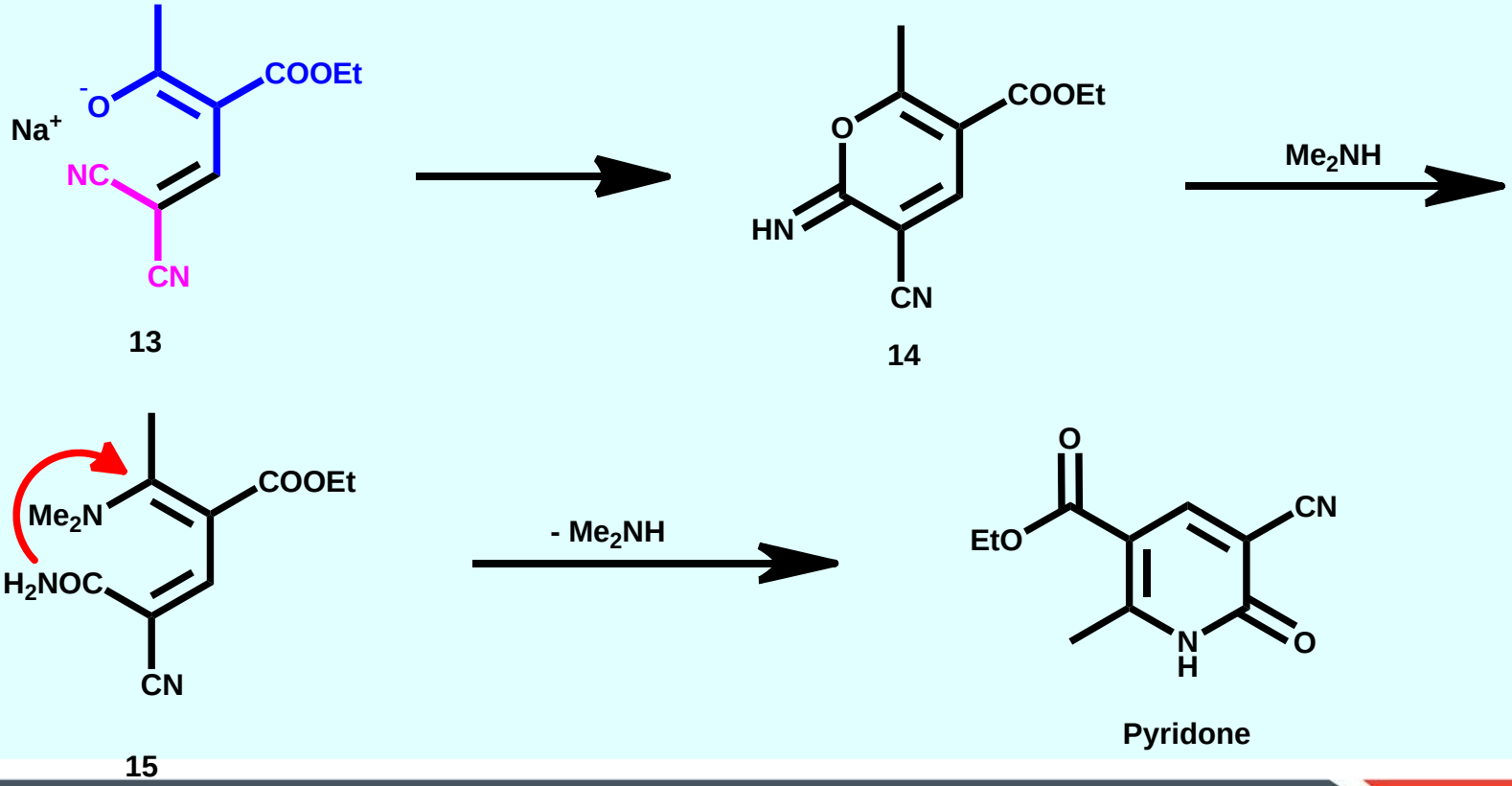
10 **11** **Amide Impurity 2**

- Ring opening of the pyran intermediate **10** by the reaction of dimethylamine released in step 2 to form the diamide intermediate **11.**
- Ring closure via elimination of dimethyl amine affords impurity 2.

Impurity investigation:

- Experimental confirmation of pathway.
- Apply this pathway to make target molecule.

- Demonstration by replacement of cyanoacetamide with malononitrile.

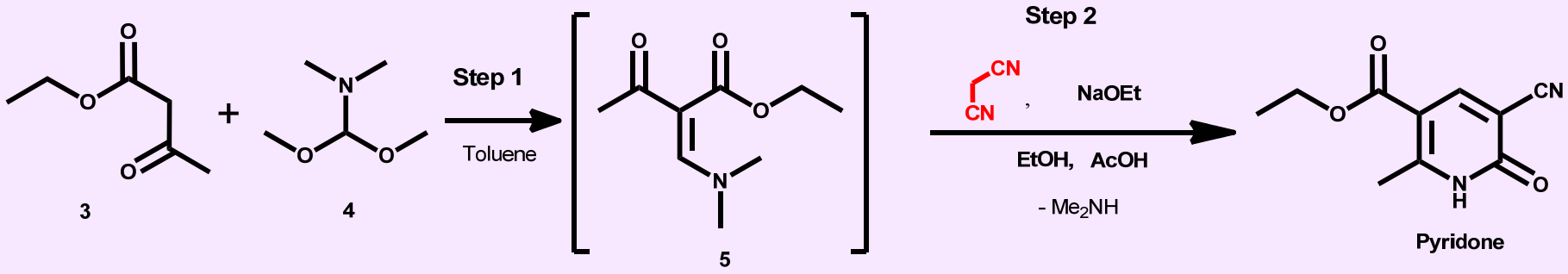


Results from impurity investigation

- Mechanism of formation of impurity 1 understood.
- Mechanism of formation of impurity 2 confirmed.
- Chemistry demonstrated using malononitrile.

Understanding of the mechanism gained for impurities 1 and 2 allowed us to select the new conditions to target pyridone compound.

Steps 1-2:
During the Process Development…



Order of addition - to avoid self condensation of malononitrile.

+ Slow addition of malononitrile solution in ethanol to enamino reaction mixture.

During the Process Development…

Use of weaker base: Triethylamine.

+ Easily-stirred and almost homogeneous mixture up to the quench with acetic acid.
+ Catalytic amounts - Dimethylamine generated during the reaction.

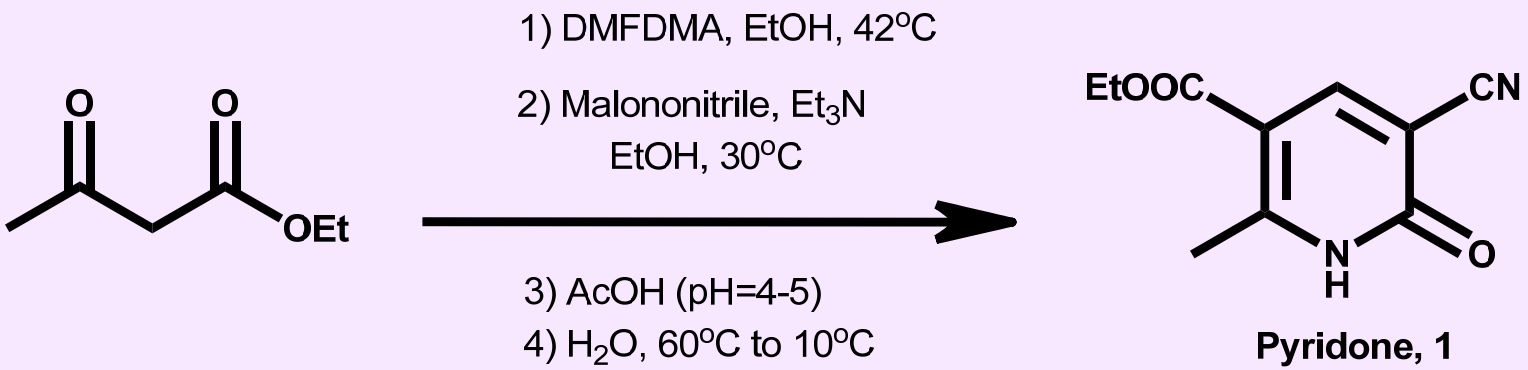
Ethanol as a solvent for step 1 and 2.

+ Telescope step 1 and 2.
+ Isolation by crystallisation on addition of water.

Stability concerns **Poor yields**

Thick slurries **Difficult isolations**

New Steps1-2

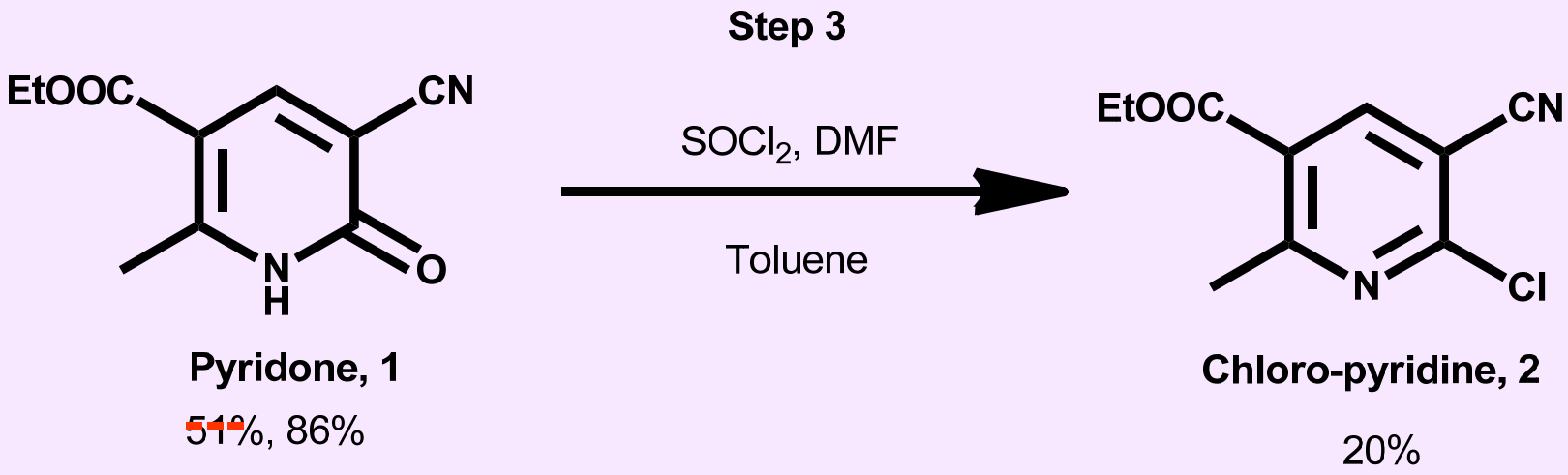


Pyridone, 1

500g scale:

Yield: 86%
Weight: 536 g
Purity: 99.5 % area
Assay: 100.8 % w/w

Step 3: Original conditions



Pyridone, 1

51%, 86%

Chloro-pyridine, 2

20%

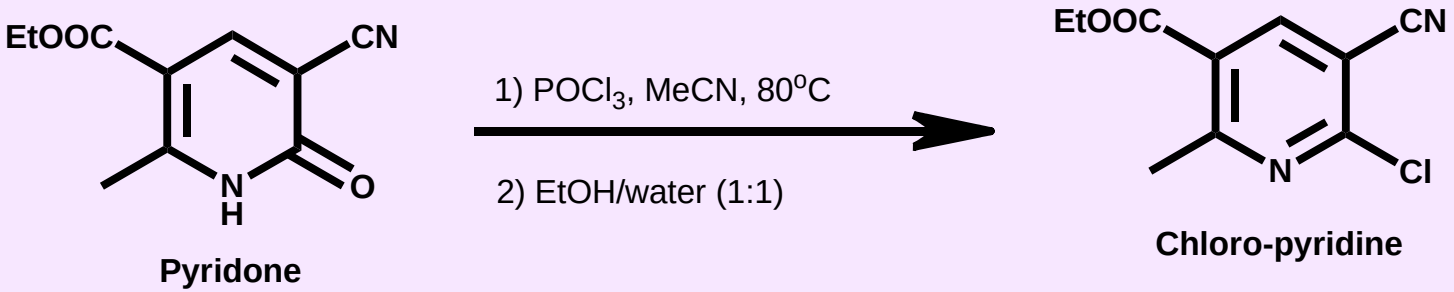
- Potential generation of genotoxic dimethylcarbamoyl chloride (DMCC).
- Lengthy work up and low yield.

Step 3: New conditions

- Alternative chlorinating agent: $POCl_3$
- Solvent: Acetonitrile.
- Aqueous work up.
- Avoid neutralisation. Chloropyridine, even under strongly acidic conditions (pH <1), is easily extracted into an organic phase like MTBE or ethyl acetate.
- Crystallisation was found to be excellent from either methanol, ethanol or isopropanol in 1:1 ratio with water.
- Solvent exchange to ethanol proceeded very efficiently.

DMCC **Work up** **Yield**

New step 3



Pyridone **Chloro-pyridine**

500g scale: **Yield: 89 %**
Weight: 484 g
Purity: 99.7 %area
Assay: 100.5 % w/w

But the colour…

Colour of Chloropyridine **2**

- This was found to be due to **charring** of the material on the walls of the reactor.
- The reaction temperature was lowered from acetonitrile at reflux to 70-75^{o}C.
- Colour check of the MTBE product solution at the end of the aqueous work-up was also introduced.
- Charcoal treatment on the solution could be performed in the event of problems with colour before the solvent exchanged into ethanol.
- Typical colour: Pale yellow vs. brown solid observed in the original process.

In summary:

1. **Process development** including 0.5kg run: Oct-Dec 2006.
2. **“Demo” batch**: 903g by 02 May 2007 (99.7% area pure).
3. **Manufacture**: 27.5Kg by 27 Jun 2007 (99.6% area pure).
4. **Manufacture**: 52kg by 31 Jul 2007 (99.6% area pure).

The overall yield of chloropyridine **2** from ethyl acetoacetate increased from 15% to 73% without the need for extra purifications post-isolation.

The characterisation of key impurities and the understanding of the mechanism of their formation led directly into to the development of the process.

Acknowledgements

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Thank you for your attention!

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