Efficient and Inexpensive Synthesis of A Functionalized Pyrimidine

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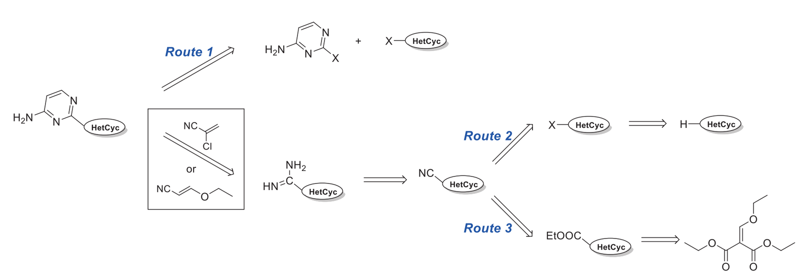
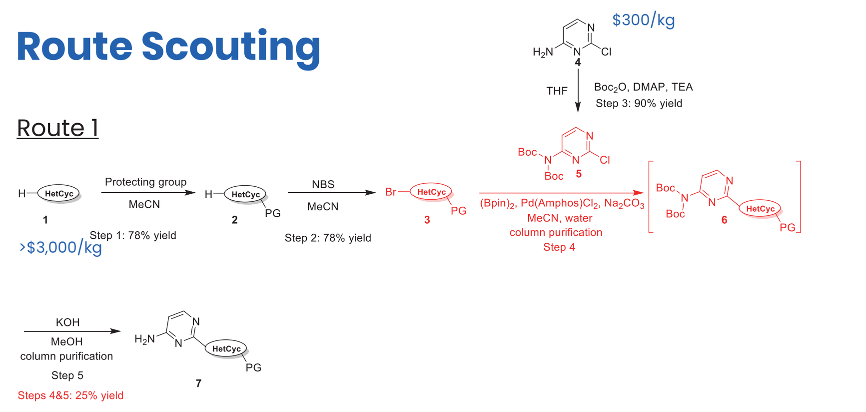
Retro-synthetic Analysis

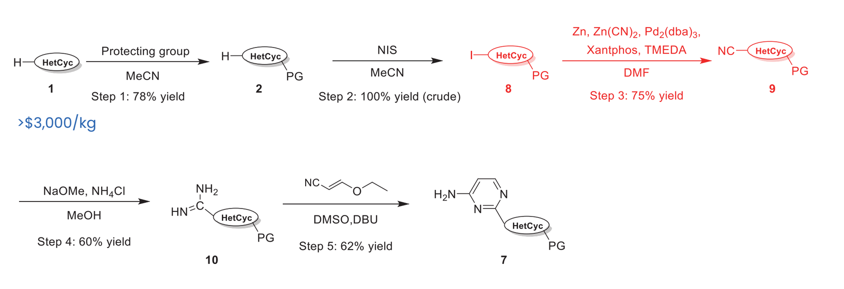


Route Scouting



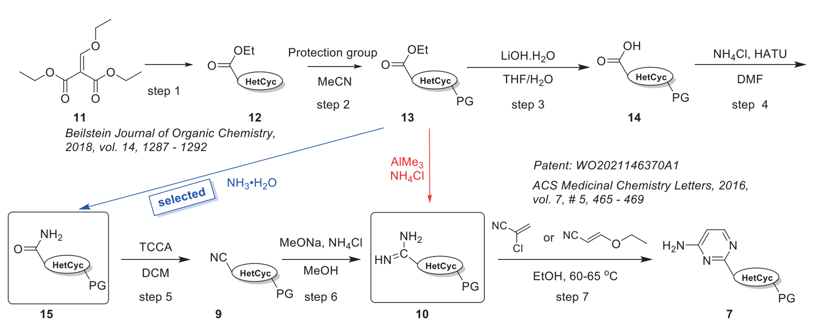
Major issues:
- High cost of starting material **1**
- Reaction profile of Step 4 was very messy (~30% IPC purity of 6) due to de-halogenation of two SMs and de-Boc of Cmpds. **5** & **6**; HTS failed to identify acceptable reaction conditions.
- Chromatographic column purifications were required for both steps 4 & 5
- Low isolated yield for steps 4 & 5

Route 2



Major issues:
- High cost of starting material **1**
- Step 3 reproducibility: highly rely on the quality of catalyst/ligand, mixing efficiency and inert condition. If conversion is low, all starting material Cmpd. **8** decomposes back to Cmpd. **2**
- High cost for step 3 due to required high loading of Pd catalyst and ligand.

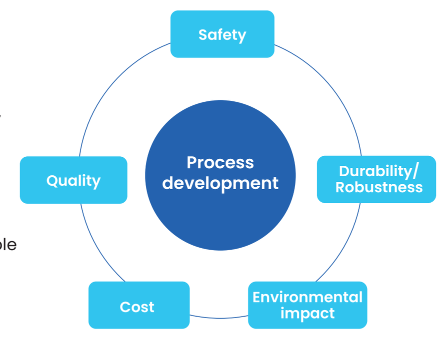
Route 3: constructing amidine **10** while avoiding expensive & problematic catalytic cyanation



- Feasibility of route was preliminarily demonstrated
- Route from ester **13** to amide **15** was also explored. Ester-amide exchange performed well, and was selected for further development
- Route from ester **13** directly to amidine **10** will be tried in future

Aspects for Process Development

- Better control of heat and mass transfer
- Avoid use and isolation of unstable, hazardous and energetic reagents, starting materials and intermediates



- Impurity control strategy to meet strict quality specification of product
- Meet preset criteria for mfg. process and analytical activities
- Quality by Design principle

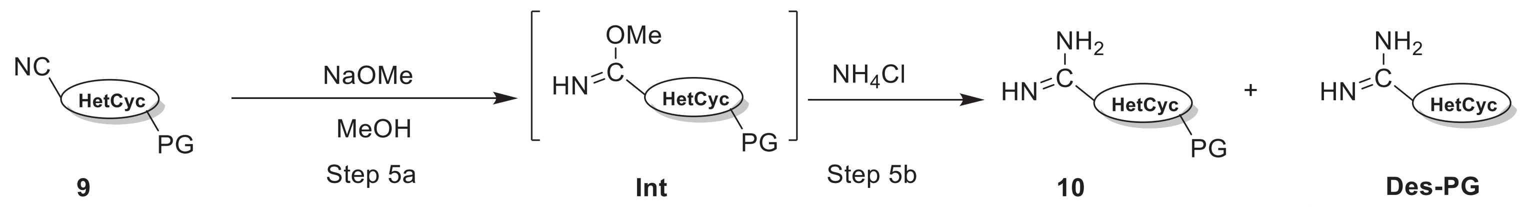
- Consistent and reliable process performance despite different equipment and site, scale change and variations in process parameters
- Supply of materials is stable, and quality is consistent
- Stable intermediates for isolation, shipment and storage

- Material cost: solvents, reagents, catalyst, etc.
- Labor cost: operators, analysts, etc.
- Production cost: production cycle time, equipment, instruments, waste treatment, cleaning cost, etc.

- Incorporation of green chemistry principles into synthetic route design
- Selection of reagents and solvents based on atom economy and green principles

Zhang, Tony Y. Chemical Reviews, **2006**, 106(7), 2583–2595.

Step 5



Equivalents of reagents and reaction temperature

Entry	NaOMe (equiv.)	MeOH (Vol)	Step 5a T (°C)	Step 5a t (h)	Step 5a IPC (9 / Int)	NH$_4$Cl (equiv.)	Step 5b T (°C)	Step 5b t (h)	Step 5b IPC 9 / Int / 10 / Des-PG
1	1.25	20	40-50	18	11.3 / 87.8	3.5	40-50	19	14.9 / 0.14 / 53.7 / 26.8
2	4.5	20	40-50	20	8.22 / 89.0	3.5	40-50	19	13.1 / 83.6 / 0 / 0
3	1.25	20	40-50	2	15.0 / 84.7	2.5	20-30	20	12.7 / 6.6 / 79.7 / 0.8

- Step 5a is reversible; conversion could not be completed;
- Ratio of NaOMe/NH$_4$Cl is important; highly excess NH$_4$Cl led to des-PG impurity growth in Step 5b.

- Add NaOMe and NH$_4$Cl alternately to drive conversion of step 5a while mitigating PG- deprotection.

Reagent	Sol.	T (°C)	T (h)	9 / Int / 10	Des-PG impurity
NaOMe: 1.25 eq	MeOH: 10V	40-50	2	12.6 / 83.5 / 0	0%
+NH$_4$Cl:2.5 eq		20-30	18	12.0 / 2.6 / 80.7	0.5%
+NaOMe: 2.0 eq	MeOH: 10V	40-50	2	4.5 / 21.7 / 69.6	0.4%
+NH$_4$Cl:2.5 eq		20-30	18	4.0 / 0.3 / 90.0	1.3%

- Conversion of step 5a is improved, and des-PG impurity is suppressed

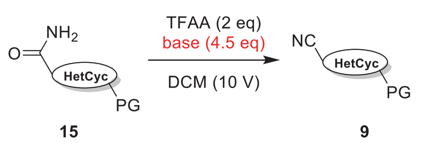
From:

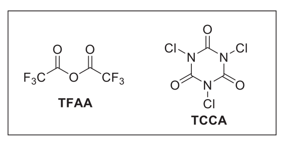
From		To
1.0 eq SM 2.5 eq NaOMe, 3.5 eq NH$_4$Cl 20V MeOH 45°C	• Charge NaOMe and NH$_4$Cl alternately to improve conversion • Reduce reaction volume	1.0eq SM 1.2+2.0 eq NaOMe, 2.5+2.5 eq NH$_4$Cl 10V MeOH 40-50 °C for step 5a 20-30 °C for step 5b
Filter, concentrate filtrate, and slurry with EtOAc	• Isolate free base instead of salt through base wash and crystallization • Yield is improved from 60% to 75%	Filter, concentrate filtrate, dilute with DCM, wash with aqueous Na$_2$CO$_3$ solution, extract with DCM, concentrate and switch with EtOAc. Filter and dry.

To:

Demo result: 100 g scale, 75.0% isolated yield, 99.9% purity, 98.2% assay

Step 4

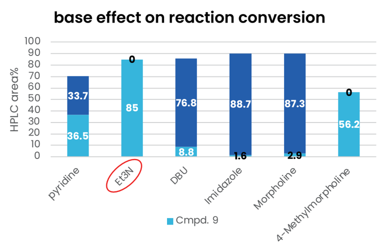




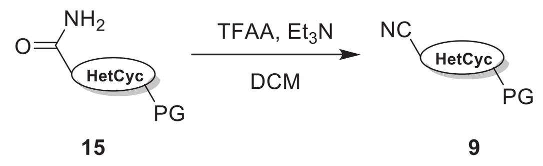
- Screen reagent (TFAA>TCCA) and temp. (no significant effect)
- Reduce reagent equiv. and solvent vol.

Entry	Reagents	Solvent	Temp (°C)	Time (h)	IPC (HPLC area%) Cmpd. 15 / Cmpd. 9
1	DIPEA: 3.0eq TCCA: 1.2eq	DCM (10 V)	0-10	20	34.3 / 9.8
2	DIPEA:4.5eq TFAA: 2.0eq	DCM (10 V)	20-30	18	3.9 / 75.1
3	Et$_3$N:4.5eq TFAA:2.0eq	DCM (10 V)	20-30	2 +18	0/90.3 0/97.4
4	Et$_3$N:4.5eq TFAA:2.0eq	DCM (10 V)	0-10	2 +18	2.8/89.6 0/89.6
5	TEA:3.5eq TFAA:1.5eq	DCM (5 V)	0-10	2	1.5/94.5

- Et$_3$N works best among screened organic bases



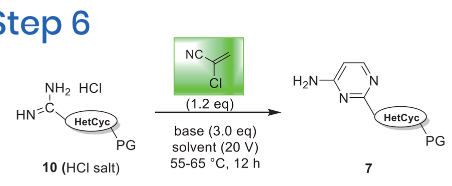
- TFAA/Et$_3$N was selected due to better conversion and reaction impurity profile



From:		To:
1.0eq SM 3.0eq DIPEA, 1.1eq TCCA 10V DMF 0-25 °C, 14hrs	• Replace TCCA with TFAA to avoid allergic reagent and improve reaction profile • Replace solvent and reduce volume	1.0eq SM TEA: 3.5eq, TFAA: 1.5eq 5V DCM 0-10 °C, 17hrs
Wash with brine, dry with Na$_2$SO$_4$, filter and concentrate to dryness	• Develop extraction and crystallization process to purify product • Yield is improved from 48% to 86%	Quench with water, extract with DCM, concentrate and crystallize with DCM/MTBE. Filter and dry

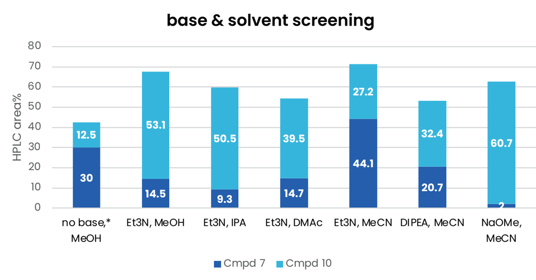
Demo result: 120 g scale, 86.1% isolated yield, 99.9% purity, 99.7% assay

Step 6

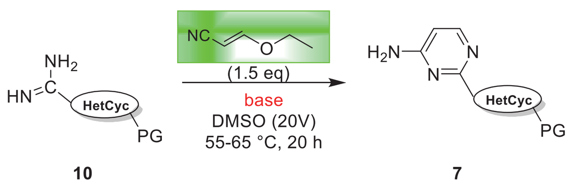


pyrimidine ring formation w/ 2-chloroprop-2-enenitrile:
Patent: *WO2021146370A1*

- Tried 2-chloroprop-2-enenitrile as in the patent literature: low to moderate conversion

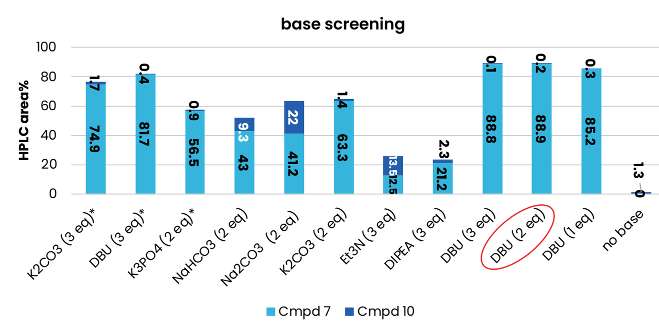


* Freebase of **10** was used



pyrimidine ring formation w/ 3-ethoxyacrylonitrile:
ACS Medicinal Chemistry Letters, **2016**, vol. 7, # 5, 465 – 469

- Use of 3-ethoxyacrylonitrile provided higher conversion in general
- Use of **10** as freebase gave better results and easier handling in Step 5
- DBU performed best among screened inorganic & organic bases

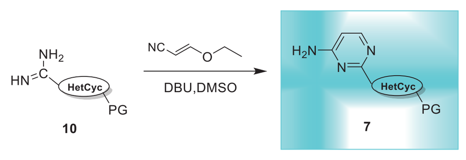


* HCl salt of **10** was used

- Further reduction of reagent equiv. with DBU (2 eq) in DMSO (5V) at 55-65 °C for 18h:

3-ethoxyacrylonitrile (equiv.)	IPC (HPLC area%) Cmpd. 10 / Cmpd. 7
1.1	1.0 / 90.5
1.2	0.6 / 91.9
1.3	0.5 / 92.4

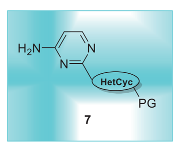
Solubility study of Cmpd. **7** to determine extraction solvent in the work-up



Solvents (20-30°C)	Volume	Solvents (20-30°C)	Volume
MeOH	4V	DCM	10V
EtOH	10V	DMSO	10V
IPA	30V	DMF	10V
Acetone	34V	MeCN	100V
THF	150V	1,4-dioxane	180V
2-Me-THF	>1000V	MTBE	>1000V
EtOAc	>1000V	toluene	>1000V
N-heptane	>1000V	H$_2$O	>1000V

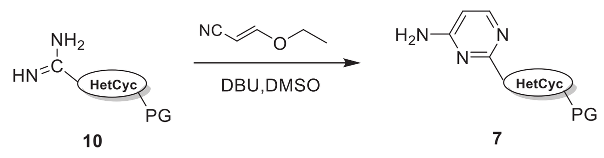
- DCM was selected. Reaction solvent DMSO can be removed by water wash.

Crystallization study of Cmpd. **7** to determine crystallization solvent system for purity upgrade and material recovery



Solvent system	Input purity	Purity of wet cake	Loss in mother liquor
THF	87%	99.8%	11%
MeCN	87%	99.5%	20%
DCM/n-heptane (4/16, v/v)	87%	91.0%	Less than 1%
DCM/EtOAc (4/16, v/v)	87%	99.6%	11%
IPA/n-heptane (5/15, v/v)	87%	99.7%	19%
IPA/water (5/15, v/v)	87%	97.2%	More than 40%

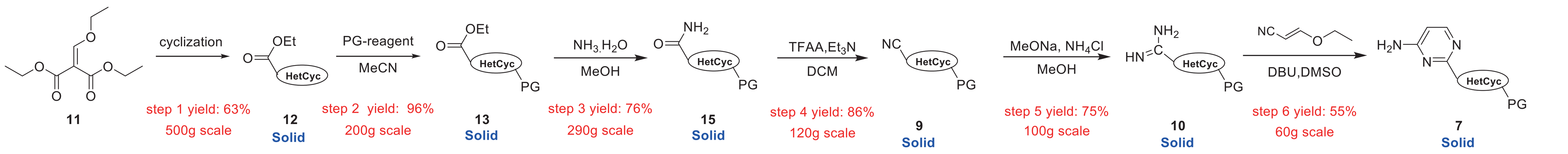
- DCM/EtOAc was selected to avoid solvent switch with acceptable impurity purging efficiency.



From:		To:
1.0eq SM 1.0eq 2-chloroprop-2-enenitrile 10V EtOH 60 °C, 3hrs	• Screen reagent, replace 2-chloroprop-2-enenitrile with 3-ethoxyacrylonitrile; • Reduce reaction volume	1.0eq SM 1.2eq 3-ethoxyacrylonitrile; 2eq DBU 5V DMSO 55-65 °C, 22hrs
Silica gel column	• Isolate free base instead of salt through base wash and crystallization • Yield is significantly improved from 14% to 55%	Dilute with DCM, wash with water, extract with DCM, concentrate, and crystallize with DCM and EtOAc. Filter and dry.

Demo result: 60 g scale, 55% isolated yield, 100% purity, 99.1% assay

Route 3 after process optimization



- Inexpensive and readily available starting materials
- No transition-metal catalyzed chemistry; good robustness in lab scale-up
- Process is ready for kg scale-up