Fermion

The story of ODM-204

NIPCF 2023

Fermion is a subsidiary of Orion Corporation

Fermion Today

Fully owned subsidiary of Orion Corporation

- New chemical entities for Orion's existing and new proprietary products
- Develops, manufactures and sells active pharmaceutical ingredients (APIs)
- Markets drug product contract manufacturing services of Orion

Fermion in 2022
Net sales: EUR 122,2 million (+10 %) • 56 % Internal, 44 % External
Main market areas are the United States, Europe, India, South Africa and Japan, > 200 customers
Ca. 30 products, both innovative and generic APIs
Head office, R&D, bench scale production, regulatory department in Espoo
Two commercial manufacturing sites: Hanko and Oulu
Personnel: ca. 380

Locations And Facility Profiles

Turku Plant | ~500 SC and QM employees

Dosage forms
- Hormone gels & solutions
- Tablets & capsules
- Potent & cytotoxic tablets & capsules
- Creams & ointments

Salo Plant | ~110 SC and QM employees
- Centralized warehouse
- Tablet packaging
- Serialization

Hanko Fermion plant | ~180 employees
- Large volume APIs
- Potent OEB4 APIs

Oulu Fermion plant | ~100 employees
- Highly potent, OEB4-5 APIs
- Cytotoxic APIs
- OEB5 micronization

Kuopio Plant | ~50 SC and QM employees

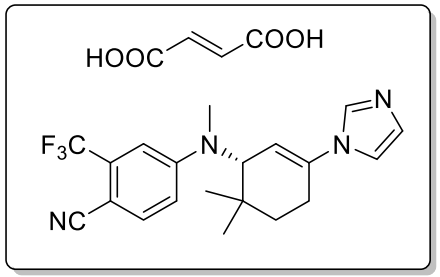
Dosage forms
- Non-sterile liquids, suspensions
- Nasal & topical sprays, drops
- Rectal enemas

Espoo Plant | ~730 SC and QM employees

Dosage forms
- Small-volume parenterals
- Tablets & capsules
- Inhalations

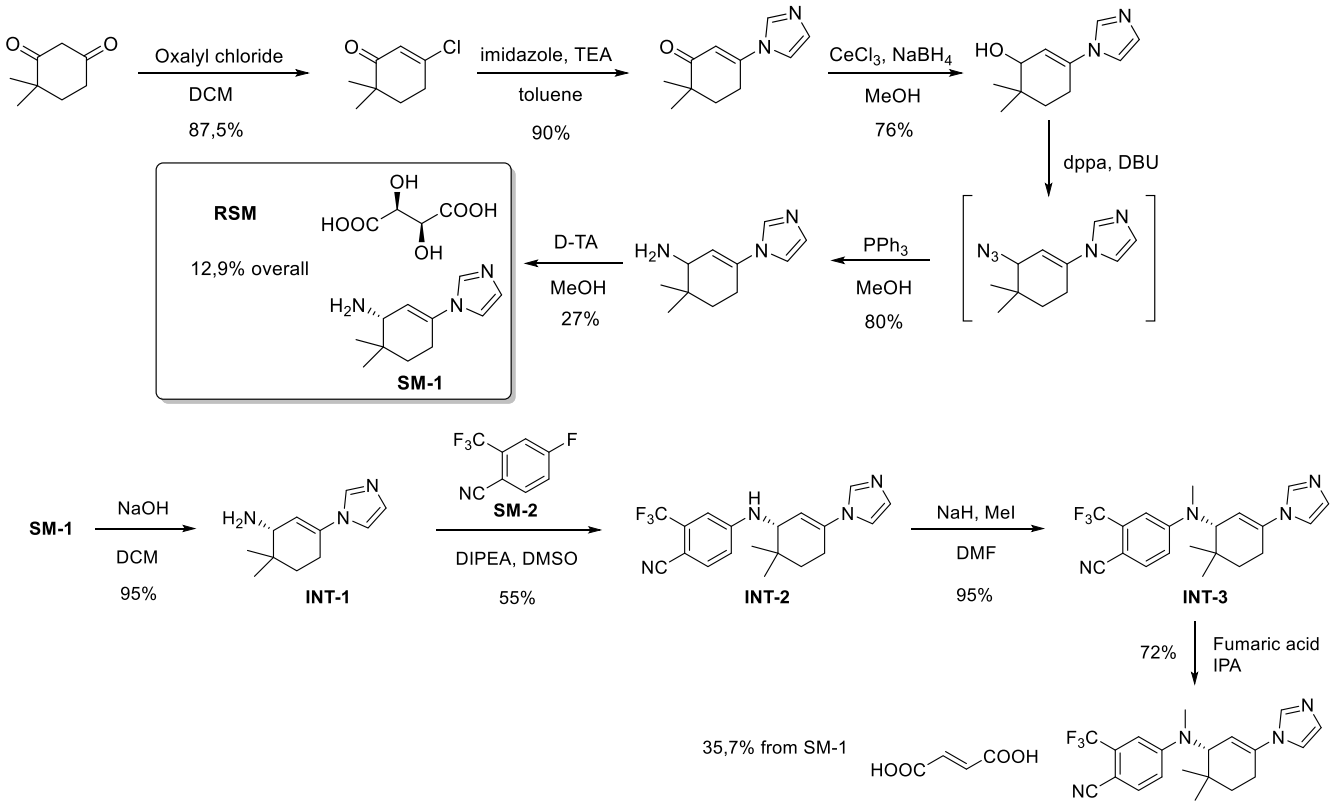
- Kilo-scale R&D API unit

ODM-204

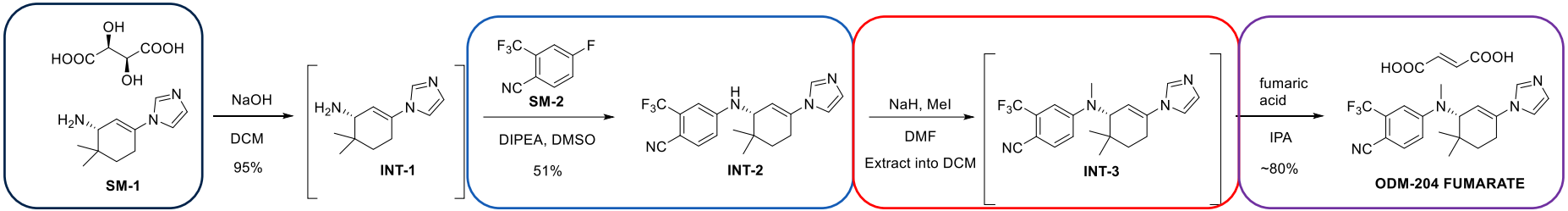


- Developed as a dual CYP17 / androgen receptor inhibitor for the treatment of prostate cancer by Orion
- Process development started at Fermion 2013
- Total of 5 GMP campaigns were conducted in addition of an initial technical campaign
- Terminated 2015

The route


Oxalyl chloride
DCM
87,5%
imidazole, TEA
toluene
90%
CeCl3, NaBH4
MeOH
76%
dppa, DBU
PPh3
MeOH
80%
D-TA
MeOH
27%
RSM
12,9% overall
SM-1
NaOH
DCM
95%
INT-1
SM-2
DIPEA, DMSO
55%
INT-2
NaH, MeI
DMF
95%
INT-3
72%
Fumaric acid
IPA
35,7% from SM-1

Technical campaign

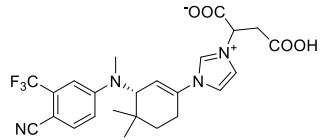


- Azide chemistry
- Availability

- Low yield
- Large volume (>30x)
- Horrible extractions

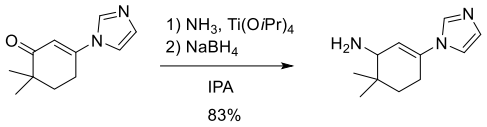
- NaH/DMF
- NaH bags dissolve in DCM

- A new impurity (> 10%)

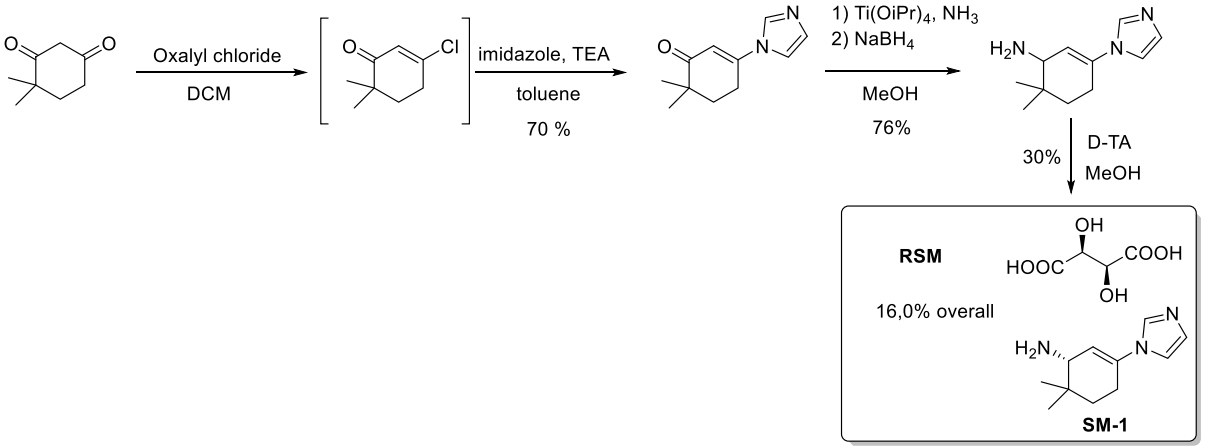


SM-1

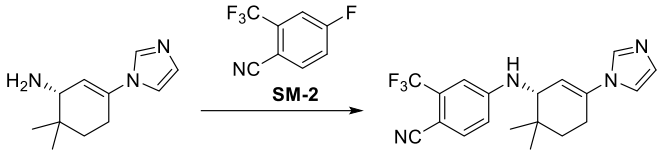
- Azide-chemistry, while fine for delivering the initial batches, was not deemed to be good enough for any further scale-up.
- Extensive testing showed that Lewis acid mediated condensation of ammonia with the ketone followed by reduction of the resulting imine is possible.



- Besides this major change, the process was streamlined



SnAr



Initial:

1. Dissolve INT-1 in DMSO (5x).
2. Add SM-2 (1.02eq.) and DIPEA (2.0 eq).
3. Heat to 80 ± 5˚C and hold for 8h.
4. Add DCM (17.5x) and water (18x) at 20˚C.
5. Water (5.37x) is added slowly with vigorous agitation.
6. Separate and extract aq. layer twice with DCM (7.5x).
7. Wash combined organics with three times with water (7.5x).
8. Solvent swap to CPME (7.5x).
9. Cool to 0˚C and isolate.

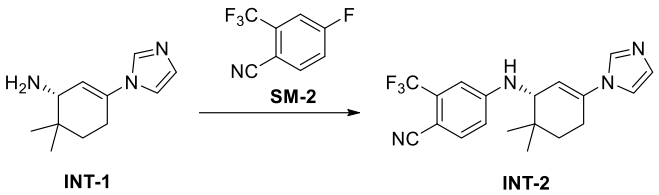
Optimized:

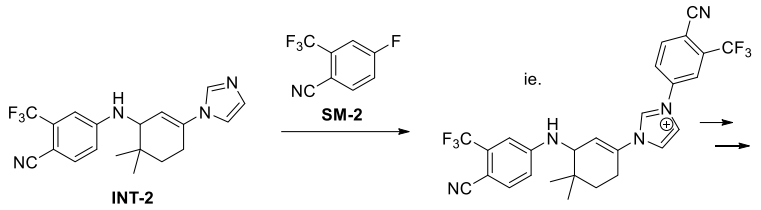
1. Dissolve INT-1 in DMSO (3.7x).
2. Add SM-2 (1.03eq.), DIPEA (0.3eq.) and TMSOEt (1.18eq.).
3. Heat to 85 ± 5˚C and held for 10h.
4. Cool to 15 ± 5˚C.
5. Add EtOAc (3x), toluene (1.6x).
6. Add water (5.4x) slowly with vigorous agitation. Seed when about 50% of the water has been added.
7. Cool to 7 ± 3˚C and stir for 1h.
8. Isolate.

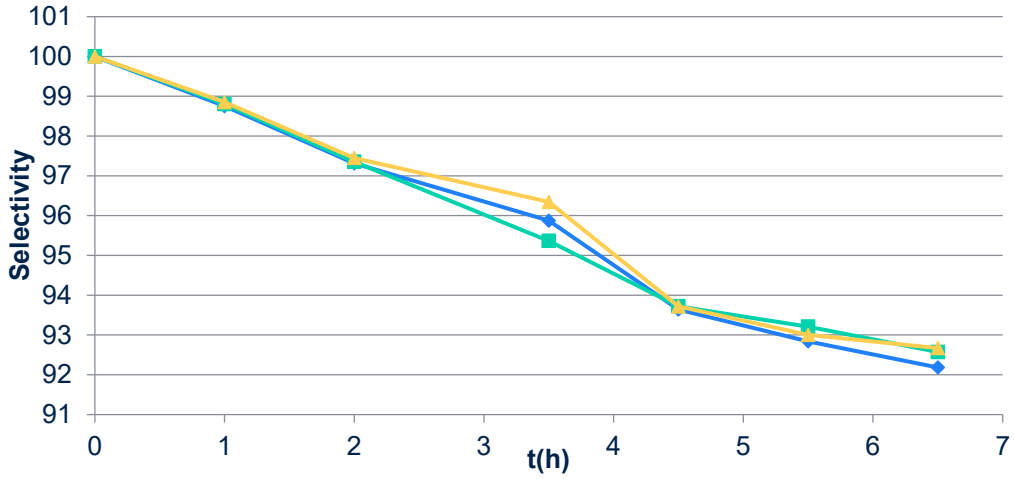
47-49%, >99.8 a-%

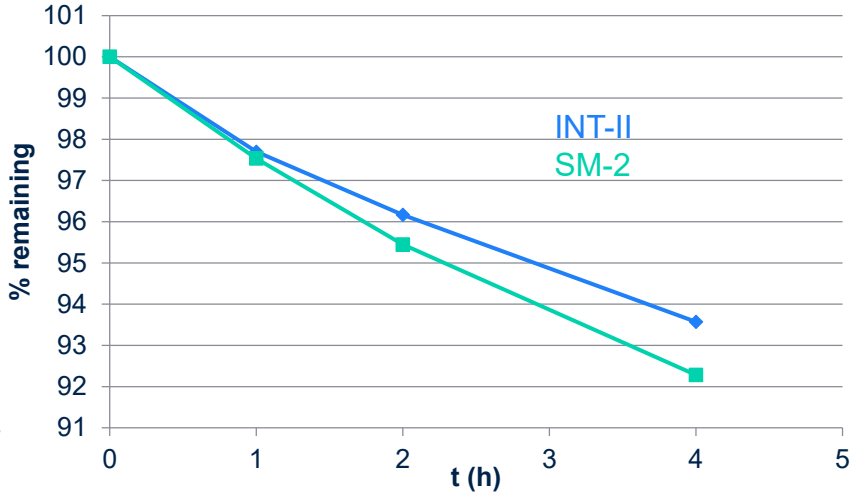
- High volumes and poor separations solved
- What about the yield?

SnAr – reaction profile



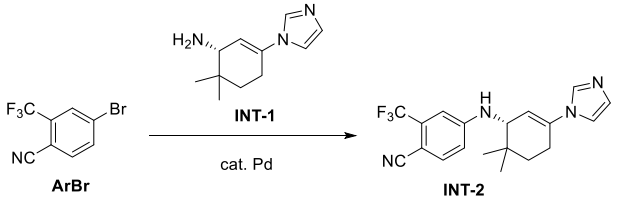






Much over 50% yield is not possible

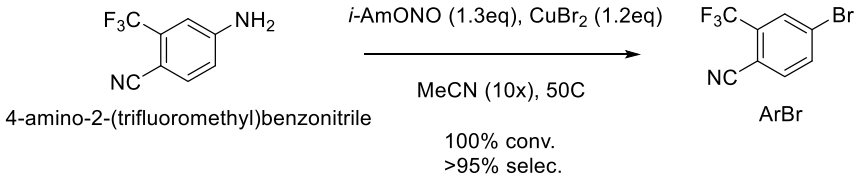
Different coupling chemistry



- Preliminary Buchwald-Hartwig experiments seemed promising.
- ArBr was not available at the time (10g for ~800USD).
- Corresponding aniline is readily available and cheap.
  - Probably just a matter of demand.
- Whilst sourcing - need to find a method to produce ArBr for process development.

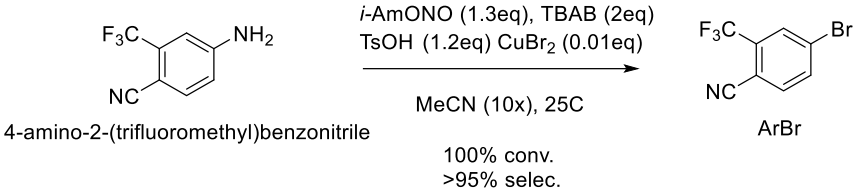
Sandmeyer

- After some experimentation the following conditions seemed suitable



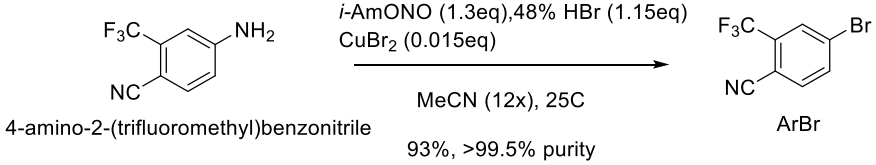
Cu residues very difficult to remove

- Following a paper with catalytic copper (Tetrahedron, 66, 2010, 7418-7422)



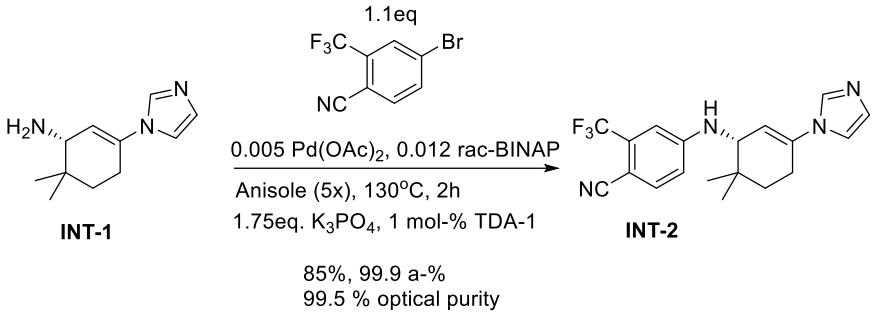
No copper residues, but massive amounts of reagents needed

- Actually TBAB + TsOH is just a way to produce anhydrous HBr



~1kg produced in lab to support PRD

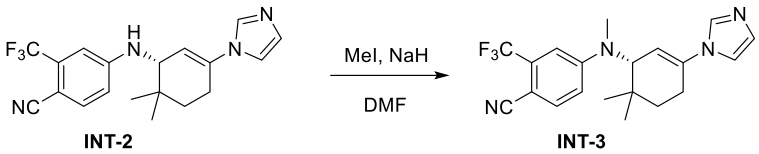
Buchwald-Hartwig coupling

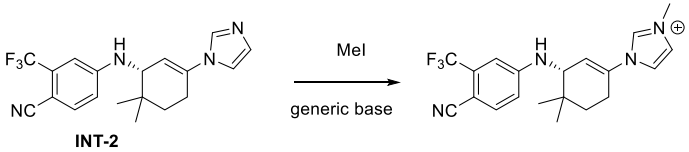


1. INT-1 is dissolved in anisole (5x) under nitrogen.
2. 4-Bromo-2-(trifluoromethyl)benzonitrile (1.1eq.), K_3PO_4 (1.75eq.) and TDA-1 (0.01eq.) are charged.
3. The mixture is degassed by repeated vacuum/nitrogen cycles.
4. $Pd(OAc)_2$ (0.005eq.) and rac-BINAP (0.012 eq.) are added.
5. The mixture is heated to 130˚C over 1h and held for 2hrs.
6. The reaction is cooled to 75˚C after which MeCN (1x) is added followed by water (4x).
7. The biphasic mixture is seeded if necessary and then cooled to 20˚C over 2-3hrs.
8. The mass is further cooled to 0˚C and stirred for 1-2hrs.
9. The mass is filtered and washed with water (3x) and cold IPA (3x).

Never scaled up ☹

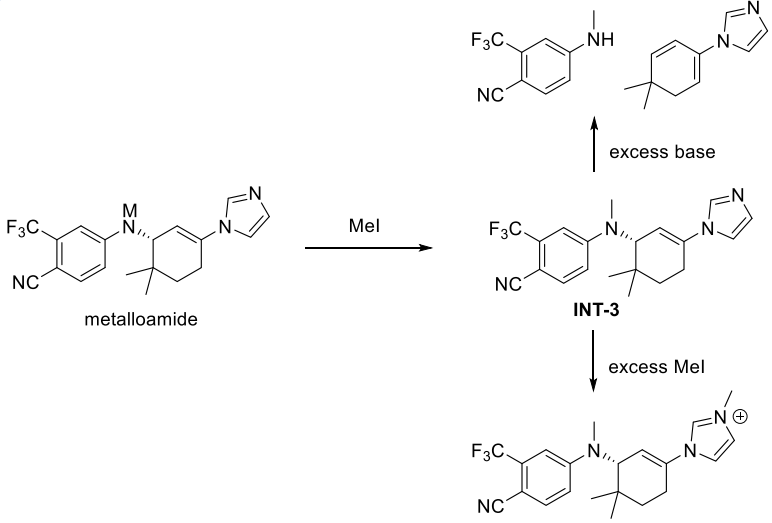
N-methylation



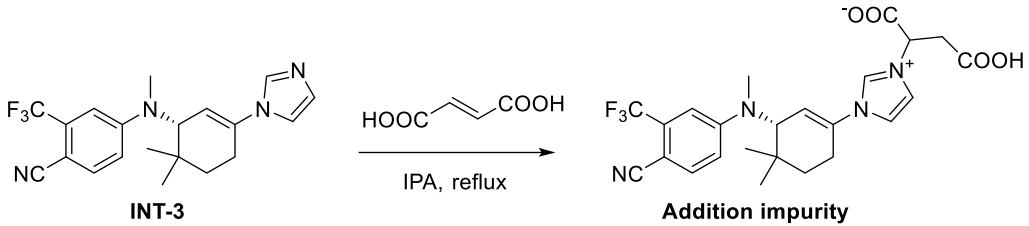


- Need to find alternative for NaH/DMF
- NaH is “special”
- Considerations:
  - INT-2 has low solubility outside of “strong” solvents
  - INT-2 is difficult to purge – conversion needs to be high
  - Imidazole is much more nucleophilic than aniline
  - Stoichiometry is very important!

  - Two potential bases were identified: NaOtBu, NaHMDS
  - Small scale lab testing NaOtBu and NaHMDS ~equivalent
    - With NaOtBu all-around decomposition
    - With NaHMDS products related to elimination pathway



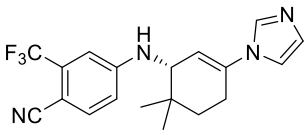
Addition impurity



- During the salt formation mixture of INT-3 and fumaric acid was heated to solution then concentrated by distillation (3h-5h duration)
- ~10% of addition impurity was formed during this distillation

- Corrective action used in the GMP batches was to
  - dissolve INT-3 and fumaric acid separately
  - polish filter them separately
  - combine the solutions with seeding
  - immediately start cooling
  -> addition impurity < 0.2 a-%

Endgame: 1st iteration



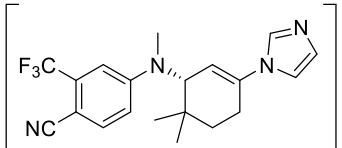
INT-2

7kg input

1) NaHMDS (40% in THF, **0.9eq**)
2) MeI (**1.0eq**)
3) NaHMDS (**0.2eq**)
4) MeI (**0.3eq**)

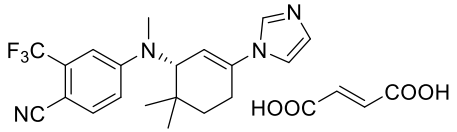
DMF (7x), < 10 °C

1) Water (6x)
2) Extract with MTBE (8x)
3) Back extract (6x)
4) Wash combined organics (6x)
5) Solvent swap into IPA (2.5x)

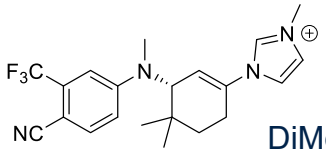


INT-3

1) heat to 55°C
2) fumaric acid (1eq) in IPA (6x)
3) Seed
4) cool to 0°C over 6h
5) filter



ODM-204 FUMARATE



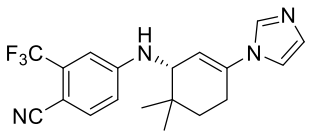
DiMeIm

Batch	Assay yield (%)	Purity (a-%)	DiMeIm
1	88.8	86.4	10.4
2	96.8	96.1	2.1

- Large amounts of DiMeIm indicates too large MeI charge in the 1st batch
- The second charges very small at this scale
- End product quality good

Batch	Yield (%)	Purity (a-%)
1	71.0	99.6
2	72.5	99.9

Endgame: 2nd iteration



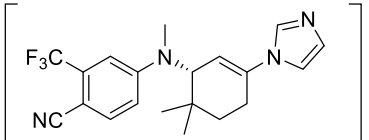
INT-2

5kg input

1) NaO*t*Bu (1.1eq)
2) MeI (**1.0eq**)
3) NaO*t*Bu (**0.2eq**)
4) MeI (**0.3eq**)

DMF (4.5x) THF (1.8x), < 10 °C

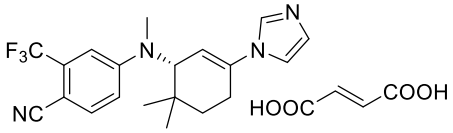
1) Water (7x)
2) Extract with MTBE (8x)
3) Back extract (6x)
4) Wash combined organics (5x)
5) Solvent swap into IPA (2.5x)



INT-3

Batch	Assay yield (%)	Purity (a-%)
1	79.9	92.2
2	79.1	96.3

1) heat to 55°C
2) fumaric acid (1eq) in IPA (6x)
3) Seed
4) cool to 0°C over 6h
5) filter

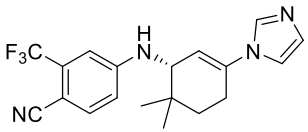


ODM-204 FUMARATE

- As expected NaOtBu produced whole spectrum of degradation products
- Dosing was even more difficult

Batch	Yield (%)	Purity (a-%)
1	72.7	98.3
2	77.1	99.2

Endgame: 3rd iteration



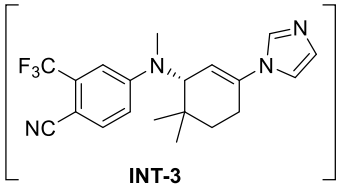
INT-2

15kg input

1) NaHMDS (40% in THF, **1.05eq**)
2) MeI (**1.05eq**)
4) MeI (**0.12eq**)
3) NaHMDS (**0.2eq**)

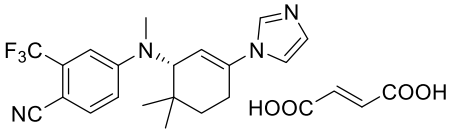
DMF (4.5x), < 10 °C

1) Water (7x)
2) Extract with MTBE (6x)
4) Wash combined organics (2.5x)
5) Solvent swap into IPA (2.5x)



INT-3

1) heat to 55°C
2) fumaric acid (1eq) in IPA (6x)
3) Seed
4) cool to 0°C over 6h
5) filter

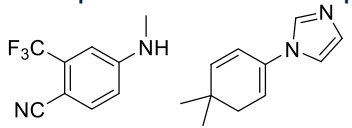


ODM-204 FUMARATE

Batch	Yield (%)	Purity (%)
1	81.6	99.7
2	79.9	99.7
3	80.8	99.9
4	81.4	99.9

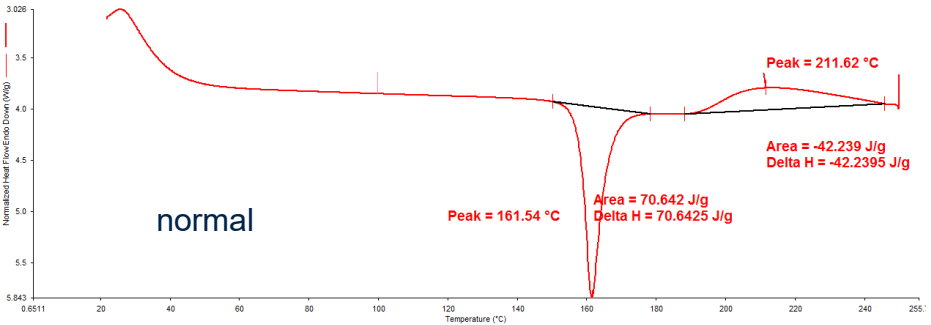
Batch	Assay yield (%)	Purity (a-%)
1	89.8	95.5
2	91.4	98.2
3	87.9	97.6
4	90.5	96.6

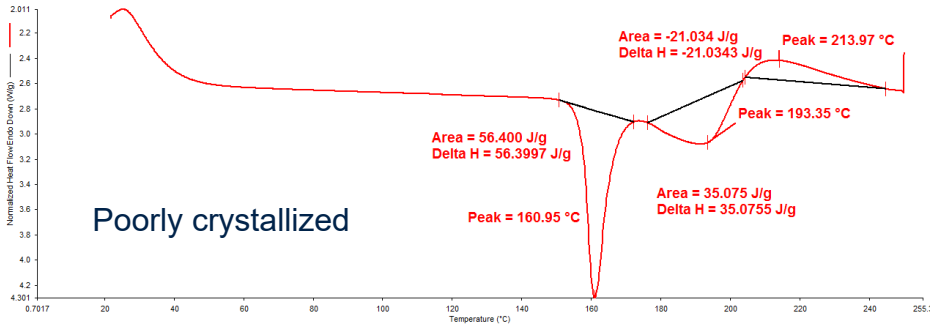
Only the expected elimination products seen

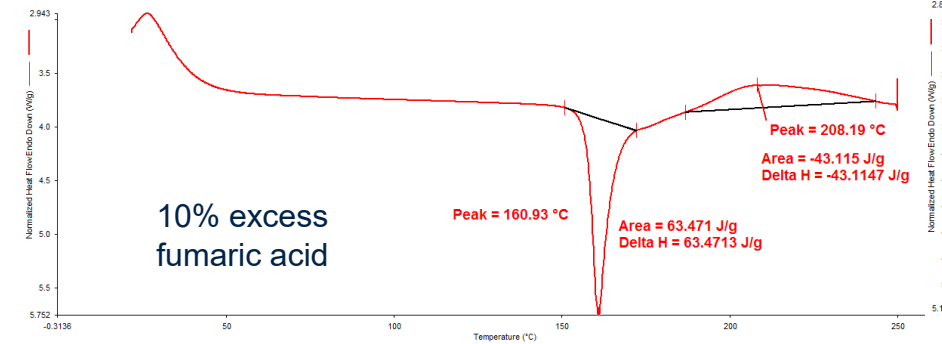


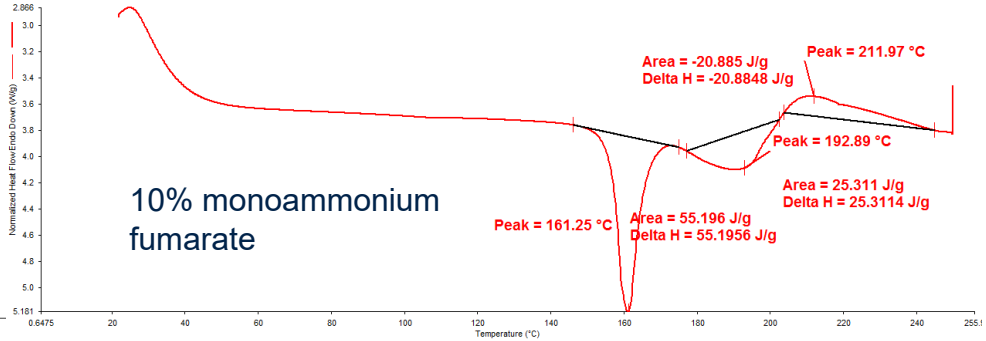
- 2 batches crystallized “suspiciously”
- Assay was on the lower end of spec -> reprocessed

Strangely crystallized ODM-204



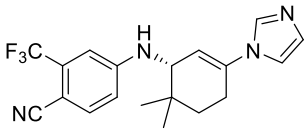






Problem is ammonia released from HMDS – or is it?

Endgame: 4th iteration



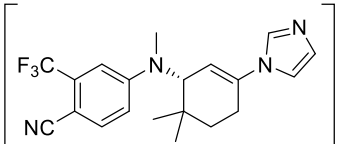
INT-2

15kg input

1) NaHMDS (40% in THF, **1.05eq**)
2) MeI (**1.05eq**)
4) MeI (**0.1eq**)
3) NaHMDS (**0.1eq**)

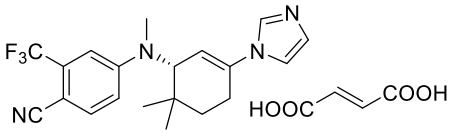
DMF (4.5x), < 10 °C

1) Water (7x), **AcOH (0.23eq)**
2) Extract with MTBE (6x)
4) Wash combined organics (2.5x)
5) Solvent swap into IPA (2.5x)



INT-3

1) heat to 55°C
2) fumaric acid (1eq) in IPA (6x)
3) Seed
4) cool to 0°C over 6h
5) filter



ODM-204 FUMARATE

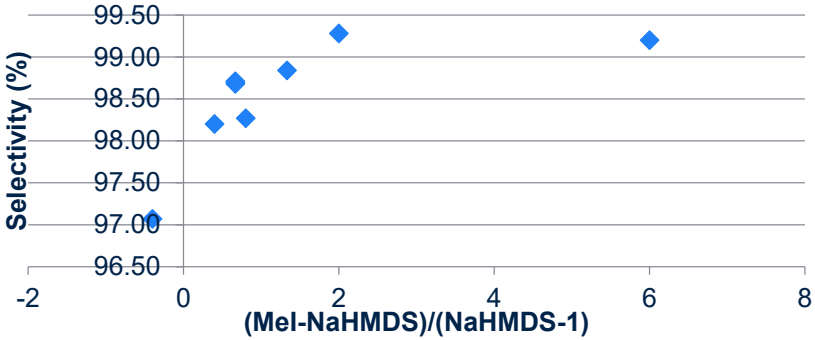
Batch	Assay yield (%)	Purity (a-%)
1	95.6	98.1

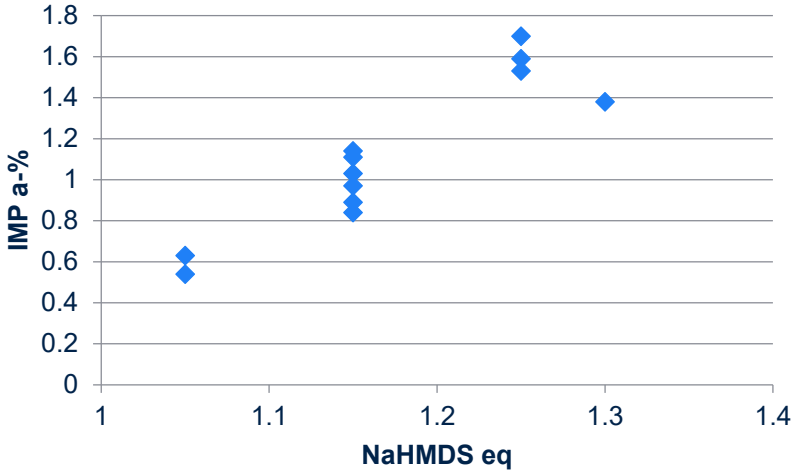
Batch	Yield (%)	Purity (%)
1	78.5	99.8

Addition of catalytic acetic acid was enough to help decompose HMDS

Further development

- Solvent change from DMF/THF to pure THF is possible – deprotonated INT-2 is highly soluble in THF
  - Much more robust reaction
  - Portionvise addition of reagents no longer needed

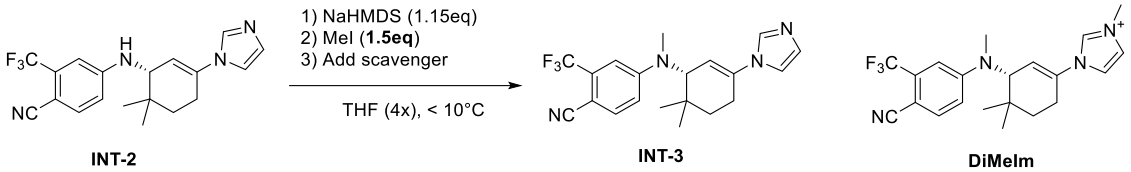




- Interestingly, excision of DMF from the process completely removed the ammonium fumarate problem

Further development

- Overmethylation can occur with prolonged extractions due to presence of excess MeI -> introduce a quench



MeI (eq.)	Scavenger	Scavenger amount (eq.)	Dimeim 1h (a-%)	Dimeim 18h (a-%
1.5	None	-	0.76	4.30
1.5	Diethanolamine	0.5	0.21	0.27
1.5	Glycine	0.5	0.51	1.02
1.5	Diethanolamine	0.75	0.25	0.61
1.5	Imidazole	0.5	0.50	5.23
1.5	Ethylenediamine	0.5	0.51	1.14
1.2	Diethanolamine	0.3	0.0	0.57
1.5	Morpholine	1.0	0.12	0.10
1.5	Piperazine	1.0	0.25	0.28
1.2	Morpholine	0.3	0	0
1.45	Morpholine	0.4	0	0

Thank you


Fermion