DEVELOPMENT OF ROBUST, ENVIRONMENTALLY RESPONSIBLE PROCESSES FOR NEW CHEMICAL ENTITIES

Tofacitinib citrate

Rajappa Vaidyanathan
Welcome to R&D

In the Pipeline
Investigational Compound News
R&D Areas of Focus
Cycle of Discovery Lab Tours
R&D Organization
Major R&D Facilities
Clinical Trials
Expanded Access to Investigational Medicines
Investigator-Sponsored Research

BMS.com Home » Research » Major R&D Facilities

Major R&D Facilities

Bristol-Myers Squibb’s drug discovery and development work takes place across a network of state-of-the-art facilities worldwide.

Bangalore, India

The Biocon Bristol-Myers Squibb Research & Development Center (BBRC) is a collaboration between Bristol-Myers Squibb and Syngene International, a Biocon group company, and is based in Bangalore, India. This state-of-the-art 200,000 sq ft facility houses integrated R&D capabilities for over 450 scientists. Fully operational since 2009, the site is involved in Target Identification, Lead Discovery and Lead Optimization all the way through to early stage Pharmaceutical Development and Clinical Biomarkers R&D.
TOFACITINIB CITRATE

- Orally active, potent, selective, reversible inhibitor of Janus kinase discovered and developed by Pfizer Inc
- Potent immunosuppressant/immunomodulator recently approved in the US for the treatment of rheumatoid arthritis
- Also under development for the treatment of:
  - Psoriasis
  - Dry eye
  - Crohn’s disease
  - Ulcerative colitis
  - Transplant rejection
REPRESENTATIVE RESPONSE: PSORIASIS

Baseline

Day 14
RETROSYNTHETIC STRATEGY
RETROSYNTHETIC STRATEGY

RETROSYNTHETIC STRATEGY

= Head-piece

= Coupling Partner
OUTLINE

- Approaches to “Head-Piece”
- Choice and Synthesis of “Coupling Partner”
- Development of “End-Game”
  - Lessons Learned
HEAD-PIECE

= Head-piece

= Coupling Partner
ORIGINAL ROUTE TO HEAD-PIECE

1. BnCl, Acetone
2. NaBH₄, EtOH
56%

1. BF₃•OEt₂, THF
2. BH₃•THF
3. MeOH, CaCl₂, H₂O
4. H₂O₂
5. NaOH
6. p-TsOH•H₂O
74%
ORIGINAL ROUTE TO HEAD-PIECE

1. SO$_3$pyr, Et$_3$N, DMSO
2. Aq NH$_3$/PhCH$_3$ extractions

1. MeNH$_2$, EtOH, HOAc
2. NaBH$_4$, THF, HOAc
3. HCl, EtOH

74%
ORIGINAL ROUTE TO HEAD-PIECE

1. BnCl, Acetone
2. NaBH₄, EtOH
   56%

1. BF₃•OEt₂, THF
2. BH₃•THF
3. MeOH, CaCl₂, H₂O
4. H₂O₂
5. NaOH
6. p-TsOH•H₂O
   74%

1. SO₃•pyr, Et₃N, DMSO
2. Aq NH₃/PhCH₃ extractions
   62%

1. 2 N NaOH, 2-PrOH/MeOH
2. Di-δ-toluoyltartaric acid
   26%
6.6% overall yield

PYRIDINE REDUCTION ROUTE

PYRIDINE REDUCTION ROUTE

1. (MeO₂C)₂O, t-BuOK, 2-MeTHF
2. H₂O, H₃PO₄
3. Toluene

90%

1. 5% Rh/C (3 wt%), H₂, HCl, MeOH
2. Toluene

30:1 cis:trans

1. PhCHO, NaHB(OAc)₃, PhCH₃
2. Aq NaOH
3. Conc. HCl

87%
FLOW HYDROGENATION

H₂ gas

Substrate

Solution of substrate trickles over catalyst exposed to H₂

Product

HEL FlowCat prototype

HEL FlowCat commercial unit

FLOW HYDROGENATION

- 100 g hydrogenated with 1 g of catalyst which was still active
- Longer flow time = lower catalyst loading
- 1% loading in flow performs as well as 3% batch loading
- Loading important because Rh is a major cost contributor

\[
\begin{align*}
\text{Me} & \quad \text{HN} & \quad \text{O} & \quad \text{Me} \\
\text{HN} & \quad \text{O} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{HN} & \quad \text{O} & \quad \text{Me} \\
\text{HN} & \quad \text{O} & \quad \text{Me}
\end{align*}
\]

1 mL/min substrate solution
20 mL/g substrate
80 mL/min H₂ (STP)
90 bar
72 g/day throughput from 1/4” ID column
FLOW HYDROGENATION

Cis / trans ratio, Conversion

<table>
<thead>
<tr>
<th>Volumes MeOH (mL/g)</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>86:1, 100%</td>
<td>49:1, 86%</td>
<td>24:1, 50%</td>
</tr>
<tr>
<td>0.75</td>
<td>86:1, 100%</td>
<td>56:1, 100%</td>
<td>26:1, 86%</td>
</tr>
<tr>
<td>1.0</td>
<td>132:1, 100%</td>
<td>58:1, 100%</td>
<td>26:1, 100%</td>
</tr>
</tbody>
</table>

Greater effective catalyst loading

More concentrated

Greater effective

Higher throughput

Substrate flow rate (mL/min)
**PYRIDINE REDUCTION ROUTE**

1. (MeO₂C)₂O, t-BuOK, 2-MeTHF
2. H₂O, H₃PO₄
3. Toluene

90% →

1. 5% Rh/C (3 wt%), H₂, HCl, MeOH
2. Toluene

30:1 cis:trans

1. PhCHO, NaHB(OAc)₃, PhCH₃
2. Aq NaOH
3. Conc. HCl

87% →

1. 2 N NaOH, MTBE
2. Dibenzoyl-L-tartaric acid, 2-PrOH

46% →

1. LiAlH₄, THF
2. HCl, 2-PrOH

90% →

[Structures and reactions depicted in the image.]

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21
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PYRIDINE REDUCTION ROUTE

Overall yield: 32.5% (65% of theory)
CHOICE OF COUPLING PARTNER

= Head-piece

= Coupling Partner
4-CHLOROPYRROLOPYRIMIDINE

\[ \text{EtO} \quad \text{CN} \quad + \quad \text{Br} \quad \text{EtO} \quad \text{OEt} \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{Nal}} \quad \text{EtO} \quad \text{CN} \quad \text{OEt} \quad \text{EtO} \quad \text{OEt} \quad \xrightarrow{1. \text{H}_2\text{N} \quad \text{NH}_2 \quad \text{NaOEt, EtOH}} \quad \text{EtO} \quad \text{CN} \quad \text{OEt} \quad \xrightarrow{2. \text{HOAc}} \quad 33\% \ (2 \text{ steps}) \]

\[ \text{HS} \quad \text{N} \quad \text{NH}_2 \quad \text{EtO} \quad \text{OEt} \quad \xrightarrow{\text{Raney Ni, Aq NH}_3} \quad \text{N} \quad \text{NH}_2 \quad \text{EtO} \quad \text{OEt} \quad \xrightarrow{\text{Conc. HCl}} \quad 75\% \ (2 \text{ steps}) \]

\[ \text{Cl} \quad \xrightarrow{\text{POCl}_3, \text{i-Pr}_2\text{NEt, PhCH}_3} \quad 84\% \]
COUPLING: FIRST GENERATION APPROACH

- Slow coupling reaction: four days to achieve reasonable conversion
- Excess 4-chloropyrrolopyrimidine required
INVESTIGATION OF COUPLING STEP

= Head-piece

= Coupling Partner
## INVESTIGATION OF COUPLING STEP

The reaction involves the coupling of an amine substrate with a chlorinated pyrimidine derivative. The product is a pyrazine ring with substituents $R^1$ and $R^2$.

<table>
<thead>
<tr>
<th>Amine Substrate</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic amine</td>
<td>4 + days</td>
</tr>
</tbody>
</table>
**INVESTIGATION OF COUPLING STEP**

\[
R^1_N\text{H} + R^2_N\text{H} + Cl_N\text{H} \rightarrow R^1_NR^2_N\text{H}
\]

<table>
<thead>
<tr>
<th>Amine Substrate</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me\text{N}H \quad \text{MeN}Ph</td>
<td>4 + days</td>
</tr>
<tr>
<td>Me\text{N}H \quad \text{C}<em>6 \text{H}</em>{12}</td>
<td>6 h</td>
</tr>
</tbody>
</table>

INVESTIGATION OF COUPLING STEP

\[
\text{R}^1\text{N} - \text{R}^2 + \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{N}
\end{array} \rightarrow \begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

<table>
<thead>
<tr>
<th>Amine Substrate</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂N₄Me₂N₄Me₂N₄Me₂N₄</td>
<td>4 + days</td>
</tr>
<tr>
<td>Me₂NPh₄Me₂N₄Me₂N₄</td>
<td>6 h</td>
</tr>
<tr>
<td>Me₄N₄Me₂N₄</td>
<td>6-8 h</td>
</tr>
</tbody>
</table>

29
### INVESTIGATION OF COUPLING STEP

![Chemical Reaction Diagram](attachment:chemical_diagram.png)

<table>
<thead>
<tr>
<th>Amine Substrate</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="Molecule 1" /></td>
<td>4 + days</td>
</tr>
<tr>
<td><img src="" alt="Molecule 2" /></td>
<td>6 h</td>
</tr>
<tr>
<td><img src="" alt="Molecule 3" /></td>
<td>6-8 h</td>
</tr>
<tr>
<td><img src="" alt="Molecule 4" /></td>
<td>Very Slow</td>
</tr>
</tbody>
</table>

R = t-Bu, Bn
INVESTIGATION OF COUPLING STEP

<table>
<thead>
<tr>
<th>Amine Substrate</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me_N_H_Ph</td>
<td>4 + days</td>
</tr>
<tr>
<td>Me_N_Ph</td>
<td>6 h</td>
</tr>
<tr>
<td>Me_N_Ph</td>
<td>6-8 h</td>
</tr>
<tr>
<td>Me_N_Ph_OR</td>
<td>Very Slow</td>
</tr>
</tbody>
</table>

- **Amine deactivated due to inductive effect of β-amino substituent**

- **Increasing nucleophilicity of amine might be challenging**

- **Increase electrophilicity of coupling partner**
COUPLING: SECOND GENERATION

\[ \text{Cl} \quad \text{N} \quad \text{Cl} \]

\[ \text{p-TsCl, NaOH, Acetone} \quad 85\% \]

\[ \text{Cl} \quad \text{N} \quad \text{Ts} \]
COUPLING: SECOND GENERATION

\[
\text{Cl} \xleftarrow{\text{p-TsCl, NaOH, Acetone}} \text{Ts}
\]

\[
\begin{align*}
\text{Me} & \text{Me} \\
\text{N} & \text{N} \\
\text{N} & \text{Cl} \\
\text{N} & \text{H}
\end{align*}
\]

\[
\text{Cl} \xrightarrow{\text{K}_2\text{CO}_3, \text{H}_2\text{O}} \text{Ts}
\]

\[
\begin{align*}
\text{Me} & \text{Me} \\
\text{N} & \text{N} \\
\text{N} & \text{Ts} \\
\text{N} & \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{HO}_2\text{C} & \text{HO}_2\text{C} \\
\text{O} & \text{OR} \\
\text{O} & \text{R= p-toluoyl}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \text{Me} \\
\text{N} & \text{N} \\
\text{N} & \text{Ts} \\
\text{N} & \text{Ph}
\end{align*}
\]

85%  77%
COUPLING: SECOND GENERATION

\[
\begin{align*}
\text{Cl} & \quad \overset{p\text{-TsCl, NaOH}}{\longrightarrow} & \text{Cl} & \quad \overset{\text{Acetone}}{\longrightarrow} & \text{Ts} & \\
\text{H} & \quad \overset{85\%}{\text{N}} & \quad \overset{\text{K}_2\text{CO}_3, \text{H}_2\text{O}}{\longrightarrow} & \overset{77\%}{\text{R}= p\text{-toluoyl}} & \overset{\text{NaOH}}{\longrightarrow} & \text{Ts} \quad \overset{95\%}{\text{Ph}}
\end{align*}
\]
COUPLING: SECOND GENERATION

Issue:
- Protection-deprotection sequence wasteful
ALTERNATIVE ACTIVATION STRATEGY

Slow coupling (4+ days)
ALTERNATIVE ACTIVATION STRATEGY

Slow coupling (4+ days)

Wasteful protection-deprotection sequence
ALTERNATIVE ACTIVATION STRATEGY

Slow coupling
(4+ days)

Wasteful protection-deprotection sequence

EWG = Reducible group
Cl??
Brit. Pat. 812,366 (April 22, 1959)
COUPLING STRATEGY BREAKTHROUGH
THE REDUCTION

The reduction of the molecule shown on the left results in the formation of the molecule on the right. The head-piece and coupling partner are indicated in the diagram.
1. H₂, Pd(OH)₂/C (20 wt%) 
2-PrOH, HOAc

2. NaOH; Extract with toluene
3. Crystallize

84%
**DEBENZYLATION/DECHLORINATION**

1. $\text{H}_2$, Pd(OH)$_2$/C (20 wt%) 
   2-PrOH, HOAc
2. NaOH; Extract with toluene 
3. Crystallize

84%

$\text{Me}$

$\text{N}$

$\text{Ph}$

$\text{Cl}$

$\text{N}$

$\text{H}$

$\text{Me}$

$\text{N}$

$\text{Ph}$

$\text{Me}$

$\text{N}$

$\text{H}$

$\text{H}_2$, Pd(OH)$_2$/C (10 wt%), H$_2$O

$\text{Me}$

$\text{N}$

$\text{H}$

$\text{Me}$

$\text{N}$

$\text{H}$

$\text{N}$

$\text{H}$

$\text{HCl}$

$\text{H}_2$ in situ yield >99%
DEBENZYLATION/DECHLORINATION

1. $\text{H}_2$, Pd(OH)$_2$/C (20 wt%) in 2-PrOH, HOAc
2. $\text{NaOH}$; Extract with toluene
3. Crystallize

84%

$\text{H}_2$, Pd(OH)$_2$/C (10 wt%), $\text{H}_2\text{O}$

>99% in situ yield

$\text{H}_2$, Pd(OH)$_2$/C (1 wt%) in $\text{H}_2\text{O}$, HCl (1 equiv)

>99% in situ yield
THE AMIDATION STEP

[Chemical structures and reactions depicted in the image]

= Head-piece

= Coupling Partner
FIRST GENERATION AMIDATION

- Step-wise amidation from isolated amine
- Residues from amide coupling agents contaminated final product
- Modest yields
AMIDATION ATTEMPTS

- Screened a variety of common activation/amidation conditions
  - CDI, SOCl₂, (COCl)₂, EDCI/HOBt etc.
- Most resulted in slow reactions, incomplete conversions, multiple by-products
AMIDATION ATTEMPTS

Issues:
- Use of CH₂Cl₂ undesirable
- Presence of impurities necessitated multiple reworks
- Activation/amidation perhaps wasteful
- Still modest yields
BEST CONDITIONS THUS FAR
AMIDATION CONSIDERATIONS

- Need amidation conditions that generate innocuous by-products
- Prefer a single solvent for HCl salt-break and amidation reaction
  - Water immiscible polar organic solvent
1-Butanol emerged as extraction solvent of choice from screening.

Excellent azeotrope with water (43% water; bp of azeotrope = 93 °C)
AMIDATIONS USING THE ESTER

- Reaction stalled at ~80% conversion
  - Required prolonged heating for complete conversion
  - Significant by-product formation
  - ~70% yield

AMIDATIONS USING THE ESTER

Reaction stalled at ~80% conversion
- Required prolonged heating for complete conversion
- Significant by-product formation
- ~70% yield

➢ Amine: base or nucleophile?

BASE SCREEN IN PROPYLENE GLYCOL

![Chemical Structures and Reaction Scheme]

- **Chemical Structures:**
  - DBU
  - TMEDA
  - Me, Et, i-Pr
  - Conversion vs. Time Graph

- **Reaction Scheme:**
  - DBU
  - TMEDA
  - Me, Et, i-Pr
  - Conversion vs. Time Graph

- **Temperature:**
  - 55 °C

- **Reaction Products:**
  - Chemical structures are shown, indicating the products of the reaction.
BASE SCREEN IN PROPYLENE GLYCOL

Base, Propylene Glycol
55 °C
BASE SCREEN IN 1-BUTANOL

Chemical reaction:

\[
\begin{align*}
\text{MeN} & \text{NNNH} \\
\text{N} & \text{NNNH}
\end{align*}
\]

\[\text{EtO}^+\text{CN} \xrightarrow{\text{Base, 1-Butanol, 25 °C}} \text{Me} \text{NN} \text{NNNH} \text{N} \text{NNNH} \text{N}
\]

Conversion graph:

- **Conversion** vs **Time (h)**

- **0%** to **100%** conversion over **0** to **20** hours.

Chemical structures:

- DBU
- DMAP
- i-Pr₂NEt
- TMEDA
FINAL AMIDATION CONDITIONS

\[
\begin{align*}
\text{Me} & \text{N} \quad \text{Me} \\
\text{N} & \quad \text{Me} \\
\text{EtO} & \quad \text{CN} \\
\text{DBU (1.0 equiv),} & \quad \text{1-BuOH, 25 °C} \\
\text{93% of citrate} & \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{CN} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{N} \\
\text{EtO} & \quad \text{CN} \\
\text{DBU (0.5 equiv),} & \quad \text{1-BuOH, 40 °C} \\
\text{93% of citrate} &
\end{align*}
\]
PROPOSED PATHWAY

PROPOSED PATHWAY

AMIDINES AS NUCLEOPHILIC CATALYSTS

DBU: 50-fold rate acceleration vs. DABCO
20-fold rate acceleration vs. DMAP

Aggarwal, V. K.; Mereu, A.
AMIDINES AS NUCLEOPHILIC CATALYSTS

Aggarwal, V. K.; Mereu, A.
*Chem. Commun.* **1999**, *2311–2312*

DBU: 50-fold rate acceleration vs. DABCO
20-fold rate acceleration vs. DMAP

Shieh, W. C.; Dell, S.; Repic, O.

DBU: 6-fold rate acceleration vs. DABCO
38-fold rate acceleration vs. DMAP
AMIDINES AS NUCLEOPHILIC CATALYSTS

Aggarwal, V. K.; Mereu, A.  
*Chem. Commun.* **1999**, *2311–2312*

Shieh, W. C.; Dell, S.; Repic, O.  

*J. Org. Chem.* **2009**, *74*, *9490–9496*
EXEMPLARY EXAMPLES

\[
\begin{align*}
R^1\text{NH} & \quad \text{EtO} & \quad \text{R}^1\text{CN} \\
R^2 & & \quad \text{DBU (0.5 equiv), 2-MeTHF} & \quad \text{R}^2 \text{CN}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Amine</th>
<th>Amide</th>
<th>t_{1/2} (min)</th>
<th>With DBU</th>
<th>Without DBU</th>
<th>T (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(-)\text{CCHC(-)NH} &amp; Ph(-)\text{CCHC(-)CN} &amp; &lt;15 &amp; 64% in 15 &amp; 520 &amp; 40 &amp; 95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**EXAMPLES**

**Reaction Scheme:**

\[ R^1\text{NH} \quad \overset{\text{EtO} \quad \text{CN}}{\xrightarrow{\text{DBU (0.5 equiv), 2-MeTHF}}} \quad R^1\text{N} \quad \text{CN} \]

<table>
<thead>
<tr>
<th>Amine</th>
<th>Amide</th>
<th>$t_{1/2}$ (min)</th>
<th>With DBU</th>
<th>Without DBU</th>
<th>T (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph\text{-}CH\text{-}CH\text{-}CH\text{-}CH}_2\text{NH}</td>
<td>Ph\text{-}CH\text{-}CH\text{-}CH\text{-}CH}_2\text{NH}_2</td>
<td>&lt;15</td>
<td>64% in 15</td>
<td>520</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>Ph\text{-}CH\text{-}CH\text{-}CN</td>
<td>Ph\text{-}CH\text{-}CH\text{-}CH\text{-}CH}_2\text{NH}_2</td>
<td>&lt;10</td>
<td>62% in 10</td>
<td>&gt;360</td>
<td>20</td>
<td>95</td>
</tr>
</tbody>
</table>
### EXAMPLES

R<sup>1</sup>\(\text{NH}\)\(\text{R}^2\) \(\xrightarrow{\text{EtO}}\) \(\text{CN}\) \(\xrightarrow{\text{DBU (0.5 equiv), 2-MeTHF}}\) \(\text{R}^1\text{N}\)\(\text{CN}\)

<table>
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<tr>
<th>Amine</th>
<th>Amide</th>
<th>(t_{1/2}) (min)</th>
<th>With DBU</th>
<th>Without DBU</th>
<th>T (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(-\text{CH}2)-NH</td>
<td>Ph(-\text{CH}2)-N(\text{CN})</td>
<td>(&lt;15)</td>
<td>520</td>
<td>40</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Ph(-\text{CH}2)-NH(\text{2})</td>
<td>Ph(-\text{CH}2)-N(\text{CN})</td>
<td>(&lt;10)</td>
<td>360</td>
<td>20</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Ph(-\text{CH}2)-NH(\text{Me})</td>
<td>Ph(-\text{CH}2)-N(\text{CN})</td>
<td>180</td>
<td>&gt;960</td>
<td>20</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>

*No product seen*
### EXAMPLES

The reaction involves the conversion of an amine to an amide under the catalytic action of DBU (0.5 equiv) in 2-MeTHF.

<table>
<thead>
<tr>
<th>Amine</th>
<th>Amide</th>
<th>$t_{1/2}$ (min)</th>
<th>With DBU</th>
<th>Without DBU</th>
<th>T (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylethylamine</td>
<td>Phenyldihydropyridine</td>
<td>&lt;15</td>
<td>64% in 15</td>
<td>520</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>Phenylglycine</td>
<td>Phenylpropionitrile</td>
<td>&lt;10</td>
<td>62% in 10</td>
<td>&gt;360</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>Phenylethyamine</td>
<td>Phenylacetone</td>
<td>180</td>
<td></td>
<td>&gt;&gt;960</td>
<td>20</td>
<td>89</td>
</tr>
<tr>
<td>Phenylethyamine Me</td>
<td>Phenylacetone Me</td>
<td></td>
<td></td>
<td>No product seen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrrolidine</td>
<td>Pyrrolidone</td>
<td>10</td>
<td></td>
<td>&gt;&gt;360</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No product seen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**EXAMPLES**

![Chemical Reaction Diagram](image)

<table>
<thead>
<tr>
<th>Amine</th>
<th>Amide</th>
<th>$t_{1/2}$ (min)</th>
<th>With DBU</th>
<th>Without DBU</th>
<th>T (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph(\text{C}6\text{H}4\text{NH})</td>
<td>Ph(\text{C}6\text{H}4\text{N}\text{O}\text{C}\text{CN})</td>
<td>&lt;15</td>
<td>15</td>
<td>520</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>Ph(\text{C}6\text{H}4\text{NH}_2)</td>
<td>Ph(\text{C}6\text{H}4\text{N}\text{H}\text{C}\text{O}\text{CN})</td>
<td>&lt;10</td>
<td>10</td>
<td>&gt;360</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>Ph(\text{C}6\text{H}4\text{NH}) Me</td>
<td>Ph(\text{C}6\text{H}4\text{N}\text{Me}\text{O}\text{C}\text{CN})</td>
<td>180</td>
<td></td>
<td>&gt;&gt;960</td>
<td>20</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No product seen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph(\text{C}6\text{H}4\text{NH})</td>
<td>Ph(\text{C}6\text{H}4\text{O}\text{N}\text{C}\text{CN})</td>
<td>10</td>
<td></td>
<td>&gt;&gt;360</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No product seen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
END-GAME
**END-GAME**

\[
\text{Me}_3\text{N-CH-Ph} \cdot 2\text{HCl} + \text{Cl}_2\text{N-CH-CH}_{\text{C}}\text{H-CH}_2\text{N-CH}_{\text{C}}\text{H} \xrightarrow{\text{K}_2\text{CO}_3, \text{H}_2\text{O}} \text{Me}_3\text{N-CH-CH}_{\text{C}}\text{H-CH}_2\text{N-CH}_{\text{C}}\text{H} \quad 97\%
\]

\[
\text{H}_2, \text{Pd(OH)}_2/\text{C} (1 \text{ wt\%}) \xrightarrow{\text{H}_2\text{O}, \text{HCl} (1 \text{ equiv})} \text{Me}_3\text{N-CH-CH}_{\text{C}}\text{H-CH}_2\text{N-CH}_{\text{C}}\text{H} \cdot x\text{HCl}
\]

1. Add NaOH
2. Extract with 1-BuOH
3. Wash with H\text{H}_2\text{O}
4. Distill (→ H\text{H}_2\text{O})
END-GAME

\[
\begin{align*}
\text{Me} &\text{N} &\text{Ph} &\quad 2\text{HCl} \\
\text{Me} &\text{N} &\text{Ph} &\quad + \\
\text{Cl} &\text{N} &\text{Cl} &\quad \text{K}_2\text{CO}_3, \text{H}_2\text{O} \\
\text{Cl} &\text{N} &\text{Cl} &\quad 97\% \\
\text{H}_2, \text{Pd(OH)}_2/\text{C} (1 \text{ wt\%}) &\quad 1. \text{ Add } \text{NaOH} \\
\text{H}_2\text{O}, \text{HCl} (1 \text{ equiv}) &\quad 2. \text{ Extract with } 1\text{-BuOH} \\
\text{1. Wash with } \text{H}_2\text{O} &\quad 3. \text{ Distill (– } \text{H}_2\text{O)} \\
\end{align*}
\]

1. \(\text{EtO}\)\(\text{CN}\) \(\text{DBU}, 1\text{-BuOH, } 25^\circ\text{C}\)

2. \(\text{Citric acid, CH}_3\text{CN, H}_2\text{O}\)

85-90\%
END-GAME

\[
\text{Me}_{\text{Me}}\text{NH}_{\text{Ph}}^\text{2HCl} + \text{Cl}_{\text{Cl}}\text{Cl}_{\text{Cl}}\text{Ph}_{\text{Ph}} \xrightarrow{\text{K}_2\text{CO}_3, \text{H}_2\text{O}} \text{97\%}
\]

\[
\text{H}_2, \text{Pd(OH)}_2/\text{C (1 wt\%)} \xrightarrow{\text{H}_2\text{O}, \text{HCl (1 equiv)}} \text{Me}_{\text{Me}}\text{NH}_{\text{Ph}}^\text{xHCl} \xrightarrow{1. \text{Add NaOH} \atop 2. \text{Extract with 1-BuOH} \atop 3. \text{Wash with H}_2\text{O} \atop 4. \text{Distill (\text{H}_2\text{O})}} \text{Me}_{\text{Me}}\text{NH}_{\text{Ph}}^\text{2HCl}
\]

\[
\text{EtO}_{\text{EtO}}\text{CN} \xrightarrow{\text{DBU, 1-BuOH, 25 \degree C}} \text{Me}_{\text{Me}}\text{NH}_{\text{Ph}}^\text{2HCl} \xrightarrow{\text{Citric acid,} \atop \text{CH}_3\text{CN, H}_2\text{O} \atop 85-90\%} \text{CP-690550-10}
\]
CONCLUSIONS

- Developed a robust, sustainable process for the manufacture of tofacitinib citrate
  - First two steps in water
  - Second and third steps telescoped
  - Minimized waste
  - Atom economical process (Major by-products: KHCO$_3$, KCl, HCl, toluene, ethanol, DBU-citrate)
  - Direct drop isolation of API (>99.5% pure)

- Discovered that DBU catalyzes amidations of cyanoacetates
  - Mild and efficient conditions
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- Frank Urban
- Stanley Walinsky

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- Jian Jin
- Dennis E. Bourassa

“Coupling partner”
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- Stephen E. Hubbs

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