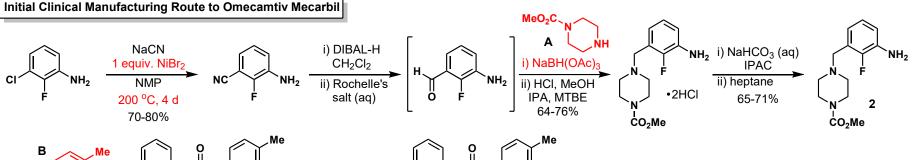
- **Omecamtiv Mecarbil (1)**
- A first-in-class direct activator of cardiac myosin
- Being evaluated as a potential treatment for chronic heart failure
- To support the drug development program including Phase 3 studies, practical access to multihundred-kilogram quantities of 1 were required.

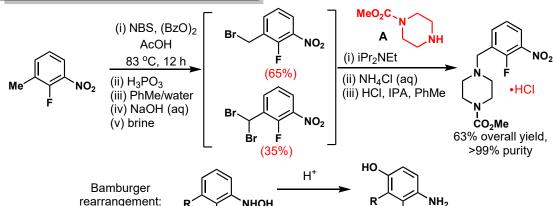




Issues include:

- 1. Stoichiometric amount of Ni, long reaction times and high T
- 2. Overreduction and polyalkylation necessiates salt-formation and salt-break crystallization steps
- 3. Instability and potential mutagenicity of isocyanate compound B

Kilo-lab Process for Aniline Intermediate (2)



НОН

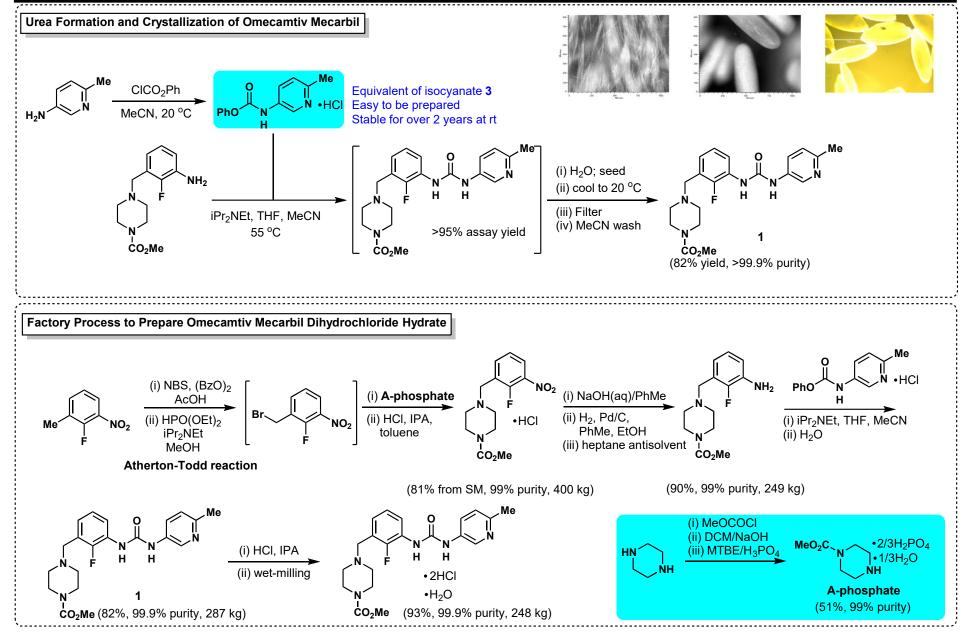
(i) H₂, Pd(Fe)/C MeOH, H₂O (ii) filter catalyst (iii) NaOH, NaHCO₃ (iv) NaCl, H2O antisolvent CO₂Me

Issues include:

- 1. 2:1 mixture of mono vs dibrominated product
- 2. Commercial batches of **A** contains residual piperazine
- 3. Nitro-HCl salt promoted the formation of Bamburger product
- 4. Leaching of iron from Pd(Fe)/C catalyst
- 5. Fe-modified catalyst not effective in reducing hydroxylamine

Org. Process Res. Dev. 2019, 23, 1558-1567

POTW: Omecamtiv Mecarbil



Org. Process Res. Dev. 2019, 23, 1558-1567