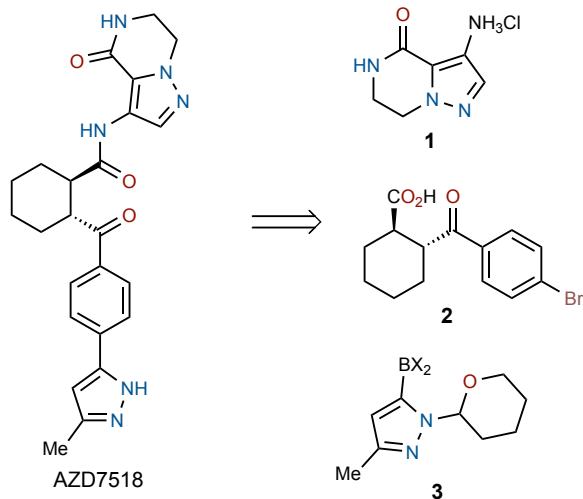
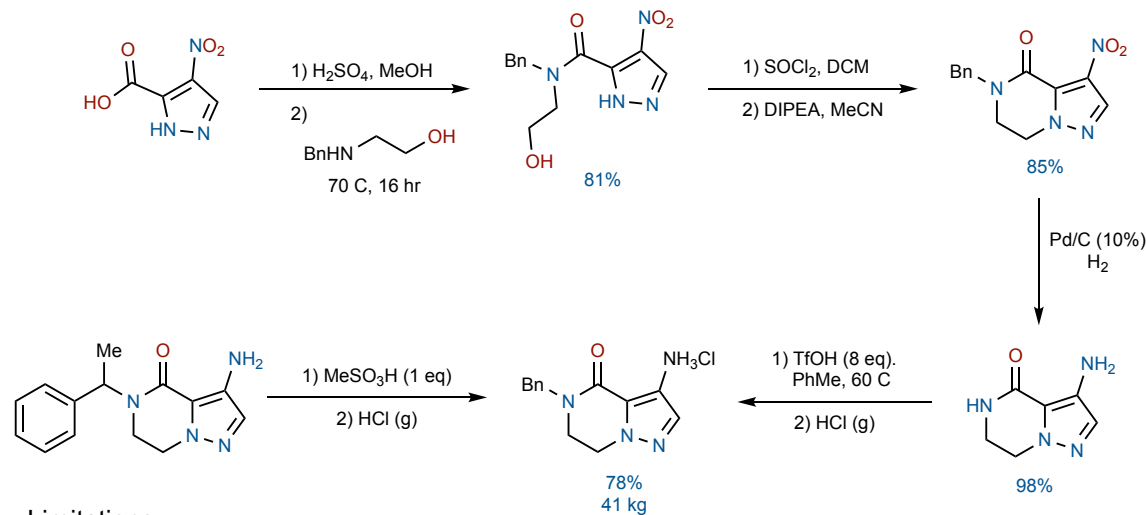


Target Compound and Retrosynthesis

Established Route to 1



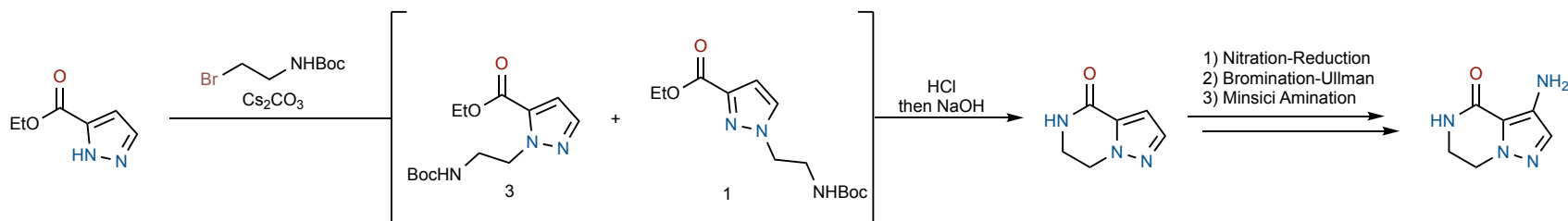
Project team had goal of 730 kg of HCl salt **1** in 18 months for clinical trial scale-up.



Limitations –

1. Nitropyrazole is challenging to make.
2. Eight eq. of TfOH required for benzyl deprotection – 5 kg required for 1 kg of API.
3. DCM required as solvent and is an environmental and safety concern on scale.

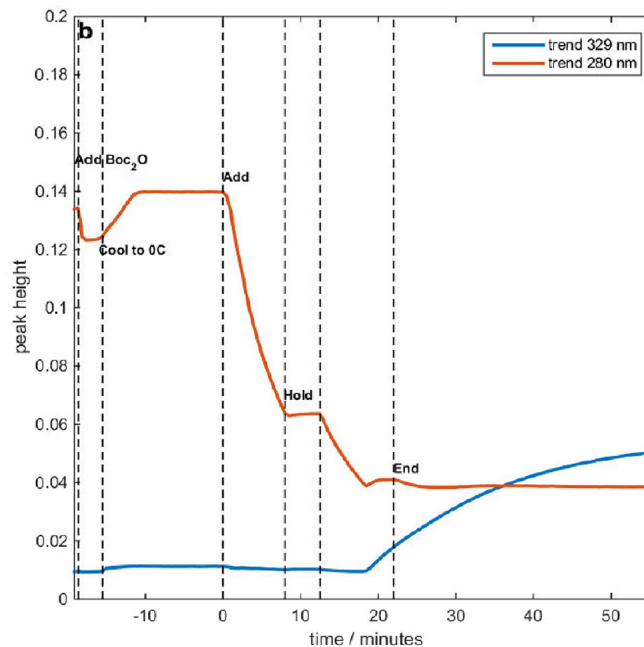
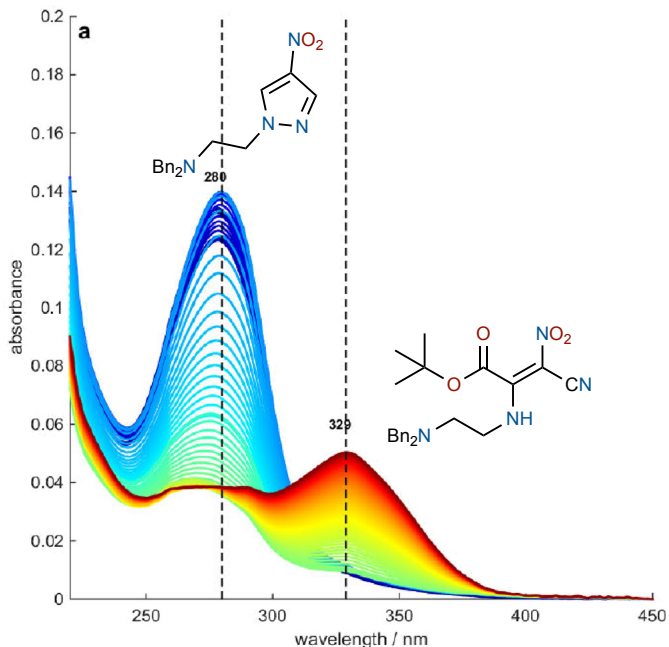
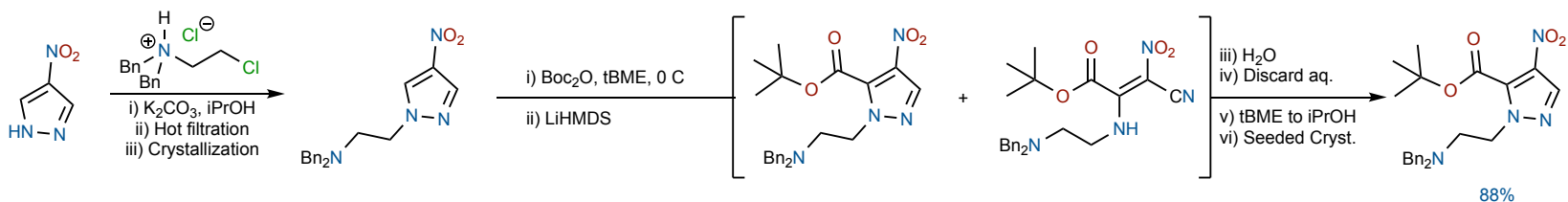
Alternative Routes



Limitations –

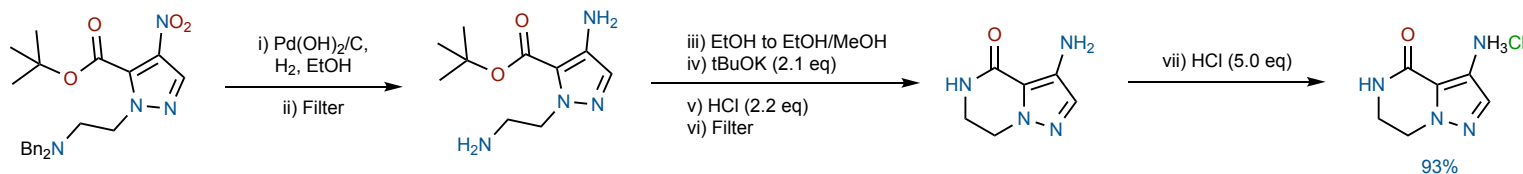
1. Nitration/Reduction: Nitration is not amenable to multi-kilogram scale due to evolution of NO_2 and a large exotherm was observed even on 500 mg scale.
2. Bromination/Ullman: Numerous impurities were present and proto-debrominated material formed in the reaction.
3. Mitsunobu Amination: A large number of unidentified organic impurities were formed in the reaction.

Non-Cryogenic Lithiation and Alkoxyacylation



Key Take-Aways:

- 280 nm peak corresponds to starting material
- As LiHMDS is added consumption of SM matches with IR monitored consumption of Boc_2O . Shows decrease in 280 nm peak as base is added is due to reaction of Boc_2O , not just deprotonation.
- Ring opened impurity (329 nm) begins to form at the end of the reaction when the concentration of SM is low and LiHMDS is present,



This route allowed for the production of 1036 kg of the required HCl salt in 18 months! Still a long way to go in terms of environmental impact and minimizing costs, but very impressive given strict timeline.