Process Research and Development of the Tyrosine Kinase Inhibitor Varlitinib Tosylate (ARRY-543 Ditosylate)

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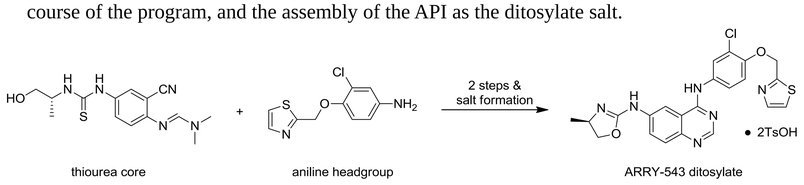
Abstract

ARRY-543 is an orally active, potent small molecule tyrosine kinase inhibitor targeting both EGFR and ErbB2. The compound is a reversible, ATP-competitive inhibitor with nanomolar potency in both in vitro and in cell-based assays showing strong activity against EGFR, ErbB2 and ErbB4. In order to support clinical requirements the Process Research group was challenged to develop a robust and scalable route that would deliver the API with an acceptable purity profile. During the course of the research and development related to this program the chemical processes were optimized and streamlined, a method using ReactIR to control impurity formation was developed, and novel methodology for the preparation of 2-aminothiazolines was identified. Ultimately a multi-kilogram campaign was executed that produced over 170 kg of Varlitinib tosylate (ARRY-543 ditosylate).

Background

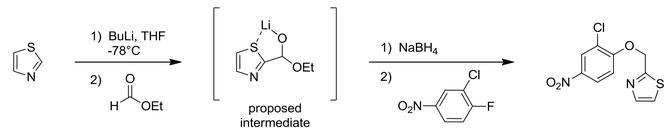
ARRY-543 is assembled convergently from a thiourea core and an aniline head group as depicted in the scheme below. The main goal of this project was to develop processes that would reproducibly deliver the API without excessive levels of impurities related to the potential hydrolysis of the amino-oxazoline moiety. This poster will describe the preparation of the two building blocks, some of the methodology developed over the course of the program, and the assembly of the API as the ditosylate salt.



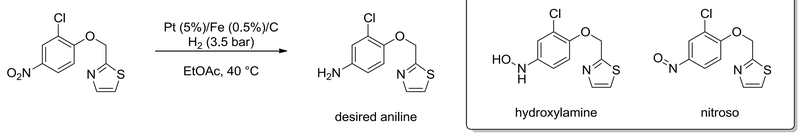
thiourea core | aniline headgroup | ARRY-543 ditosylate

Telescoped Formylation/S_NAr Protocol

Originally the thiazole component was prepared by lithiation of bromothiazole followed by formylation with DMF. Although the chemistry worked well, isolation of the very polar aldehyde was difficult. It was discovered that lithiation of thiazole followed by addition of ethyl formate gave a mixture that could be telescoped into a reduction and subsequent S_NAr reaction. Presumably coordination of the heterocycle to the intermediate lithio-species plays a role. Use of ethyl formate eliminated any potential amine related impurities that would be formed if a typical formamide reagent were used for this protocol.



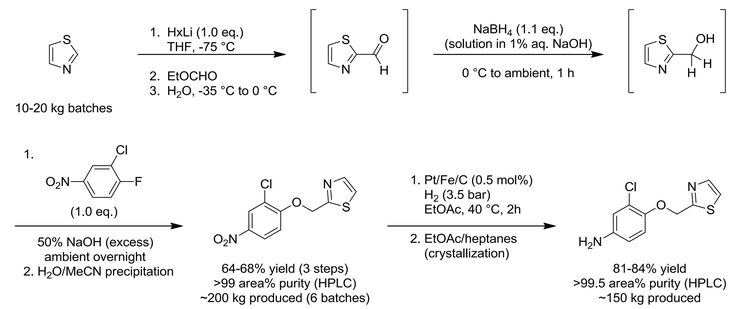
Nitro Reduction in the Presence of a Chloroarene



The presence of the aryl chloride eliminated the option of hydrogenation using a Pd catalyst.

- Chemical reductions worked but isolations and purity profiles were not suitable.
- Hydrogenation using PtO_2 worked for small scale deliveries.
  - PtO_2 is not ideal for use in the plant due to poor mixing.
- Pt supported on carbon was identified as a viable catalyst.
  - Bimetallic catalysts proved to be superior (faster conversion with complete reduction).
  - Pt/Fe/C was selected, no hydroxylamine or nitroso intermediates were detected.

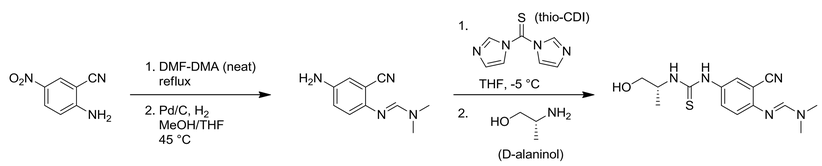
Scale-up of the Aniline Headgroup



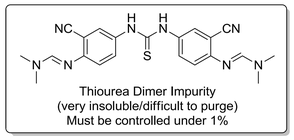
Comments on Scale-up of these processes:

- Hexyl lithium (HxLi) identified as a more process friendly lithiation reagent.
- $NaBH_4$ added as a solution to address safety concerns with addition of solid reagents.
- Fe doped Pt catalyst allowed for lower catalyst loading and subsequent cost savings.

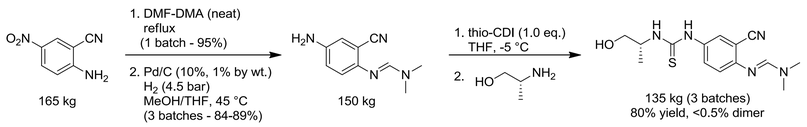
Scale-up Issues with Preparation of the Thiourea Core



- Formamidine formation and nitro reduction are reliable.
- Unsymmetrical thiourea formation was unpredictable.
  - Initial scale-up: 15% of the thiourea dimer was formed.
  - Impurity levels increased due to low potency thio-CDI.
  - Assessing the potency of bulk thio-CDI is difficult.

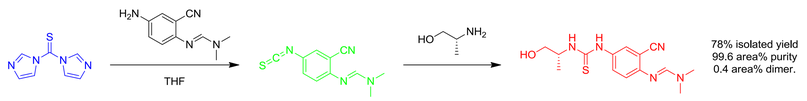


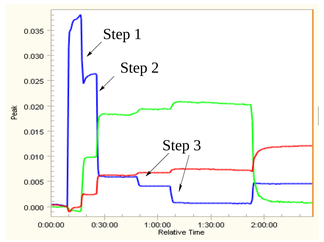
Scale-up of the Thiourea Core



- The dimer level was controlled by multiple sub-stoichiometric charges of aniline substrate.
  - In-process HPLC analysis performed after every charge.

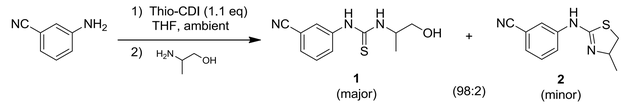
Proof-of-Concept: Use of ReactIR to Minimize Symmetrical Dimer Formation



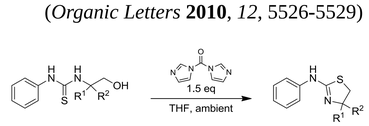


- Step 1: Initial charge of aniline (45% of theoretical).
  - A solution forms.
- Step 2: Second charge (40% of theoretical).
  - Allows for calculation of final charge requirement.
- Step 3: Final charge to consume 98% of thio-CDI.
  - Performed in two portions, each resulting in the predicted decrease in adsorption.
- Following the consumption of thio-CDI, D-alaninol was charged to the reaction mixture.
  - Consumption of the isothiocyanate is observed with the production of the thiourea.

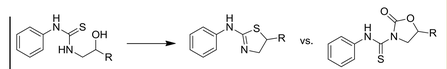
Methodology to Selectively Prepare 2-aminothiazolines



- Thiazoline formation was identified as a by-product in thio-CDI mediated thiourea formation.
- A mild and selective protocol for the preparation of 2-aminothiazolines was discovered.
  - Thio-CDI and CDI both effectively promote this selective cyclization (*Organic Letters* **2010**, *12*, 5526-5529)



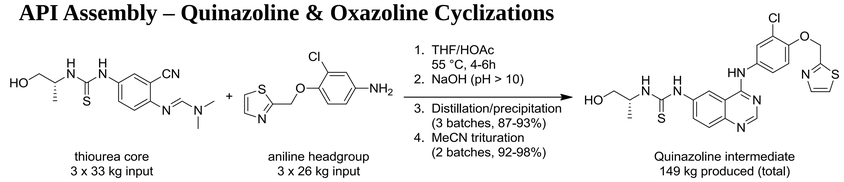
- Alkyl & aryl substitution tolerated adjacent to the amine of the amino alcohol component.
  - Isolated yields range from 71-88%.
  - Higher yields observed with bulkier substituents.



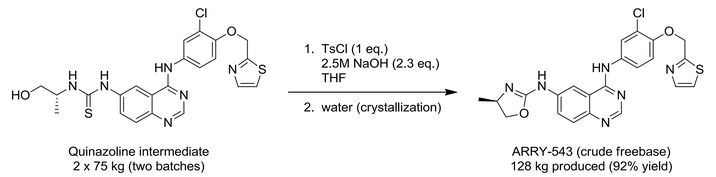
R	Yield of 14	Yield of 15
Et	Not detected	99%
CF_3	Not detected	88%
4-OMe-Ph	81%	4%
Ph	67%	29%
4-CF_3-Ph	62%	27%

- Substitution adjacent to the oxygen of the amino alcohol component influences mode of cyclization.

API Assembly – Quinazoline & Oxazoline Cyclizations

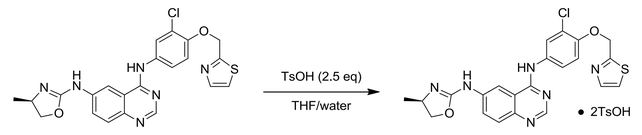


- Dimroth rearrangement promoted using acetic acid as a co-solvent.
- The product is crystallized after neutralization and removal of THF by distillation.
  - Significant amount of NaOAc present after neutralization (requires thorough washing).
  - Trituration with MeCN improves the purity of the product.



- Conversion is fast and the protocol is operationally simple.
- The impurity profile is dependent upon the quality of the input and the reaction conditions.
- A heat cycle of the final slurry was implemented to improve filtration rate.

Ditosylate Salt Formation



- Salt formation gives a highly crystalline product with improved quality.

Conclusions

- A novel methodology for the preparation of 2-aminothiazolines was developed.
- A PAT technique using ReactIR was developed to minimize formation of an undesired by-product.
- The processes developed are robust, reliable, and fit for purpose for manufacture of ARRY-543 on multi-kilogram scale.
- Over 170 kg of ARRY-543 ditosylate has been prepared using the described route.