Z. SHI* ET AL. (BRISTOL-MYERS SQUIBB CO., NEW BRUNSWICK AND PRINCETON, USA)
Development of a Practical Synthesis of a p38 Kinase Inhibitor via a Safe and Robust Amination
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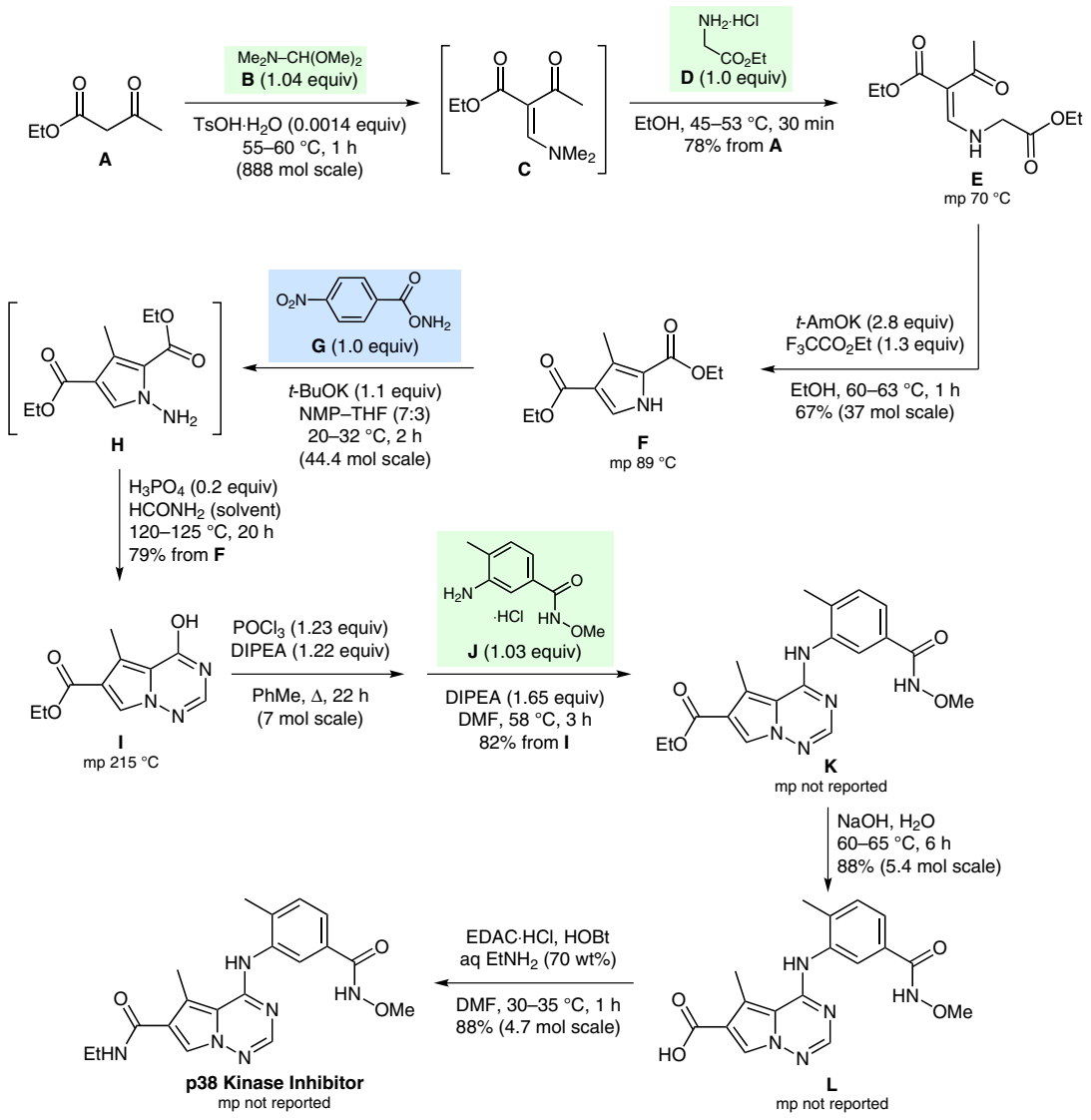
Synthesis of a p38 Kinase Inhibitor



Significance: The target pyrrolotriazine is a p38 kinase inhibitor that was a lead compound for the treatment of rheumatoid arthritis. The synthesis depicted features a safe and scalable N-amination of the pyrrole **F** using *O*-(4-nitrobenzoyl)hydroxylamine (**G**). The synthesis delivered 1.6 kg of active pharmaceutical ingredient (API) in 26% overall yield.

Comment: Competing ester hydrolysis products generated in the condensation of **E** to the pyrrole **F** were minimized by adding ethyl trifluoroacetate as a water scavenger. A large-scale process for the synthesis of the crystalline *O*-4-(nitrobenzoyl)-hydroxylamine (**G**) is described.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

p38 kinase inhibitors

amination

***O*-(4-nitrobenzoyl)-hydroxylamine**

pyrrolotriazines