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.