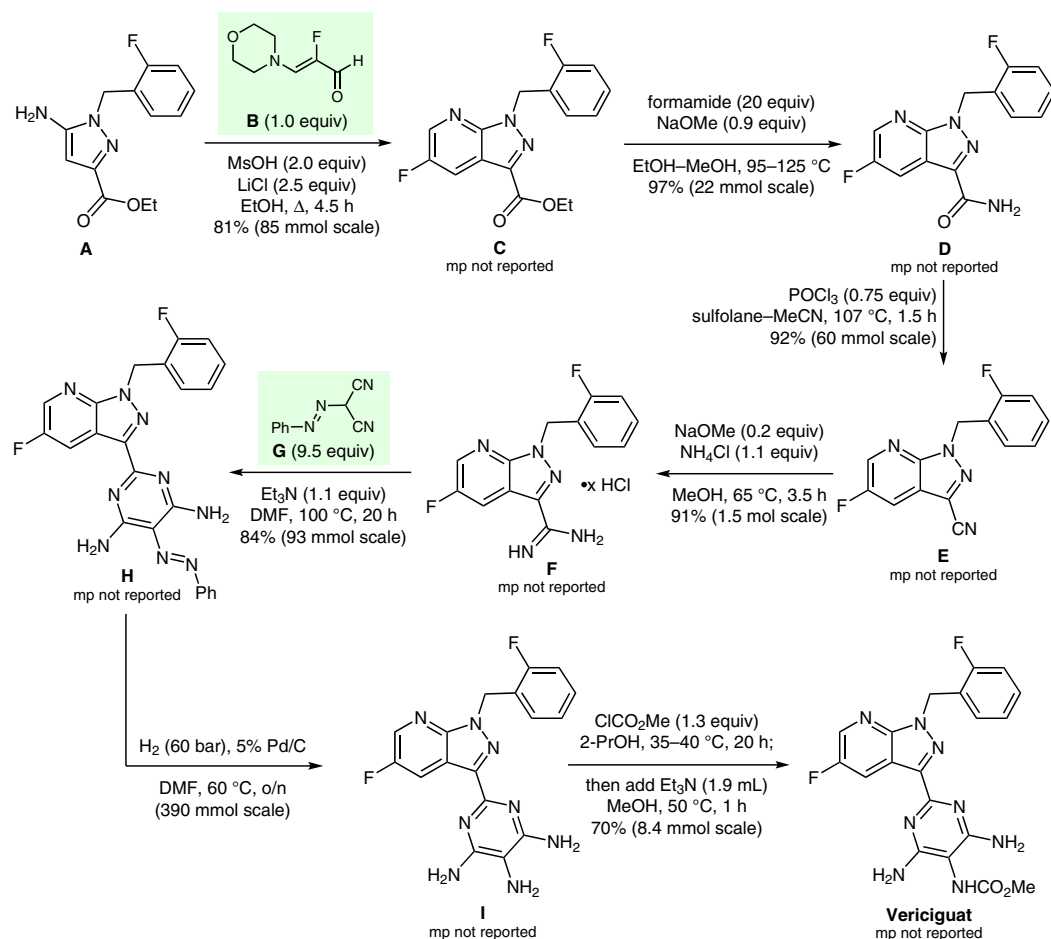


Synthesis of Vericiguat



Significance: Vericiguat (BAY 1021189) is an orally available soluble guanylate cyclase (sGC) stimulator that has entered phase-three trials for the once-daily treatment of chronic heart failure. Key steps in the synthesis depicted are (1) construction of the 5-fluoro-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate **C** by condensation of the 5-amino-1H-pyrazole-3-carboxylate **A** with the aldehyde **B** and (2) construction of the pyrimidine-4,5,6-triamine derivative **H** through reaction of [(E)-phenyldiazenyl]malononitrile (**G**) with amidine **F**.

Comment: Experimental details are provided for the noteworthy four-step synthesis (not shown) of the crystalline 2-fluoro-(3-morpholin-4-yl)acrylaldehyde **B** from commercially available 2,2,3,3-tetrafluoro-1-propanol. The synthesis of pyrazole **A** is described in a patent (A. Straub et al. WO 2000/006569 A1). The [(E)-phenyldiazenyl]malononitrile (**G**) was generated in situ by reaction of phenyldiazonium chloride with malononitrile.

vericiguat

soluble guanylate cyclase stimulator

(E)-phenyldiazenylmalononitrile

pyrimidine-4,5,6-triamine ring formation

1H-pyrazolo[3,4-b]pyridine ring formation