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Discovery of the Soluble Guanylate Cyclase Stimulator Vericiguat (BAY 1021189) for the Treatment of Chronic Heart Failure

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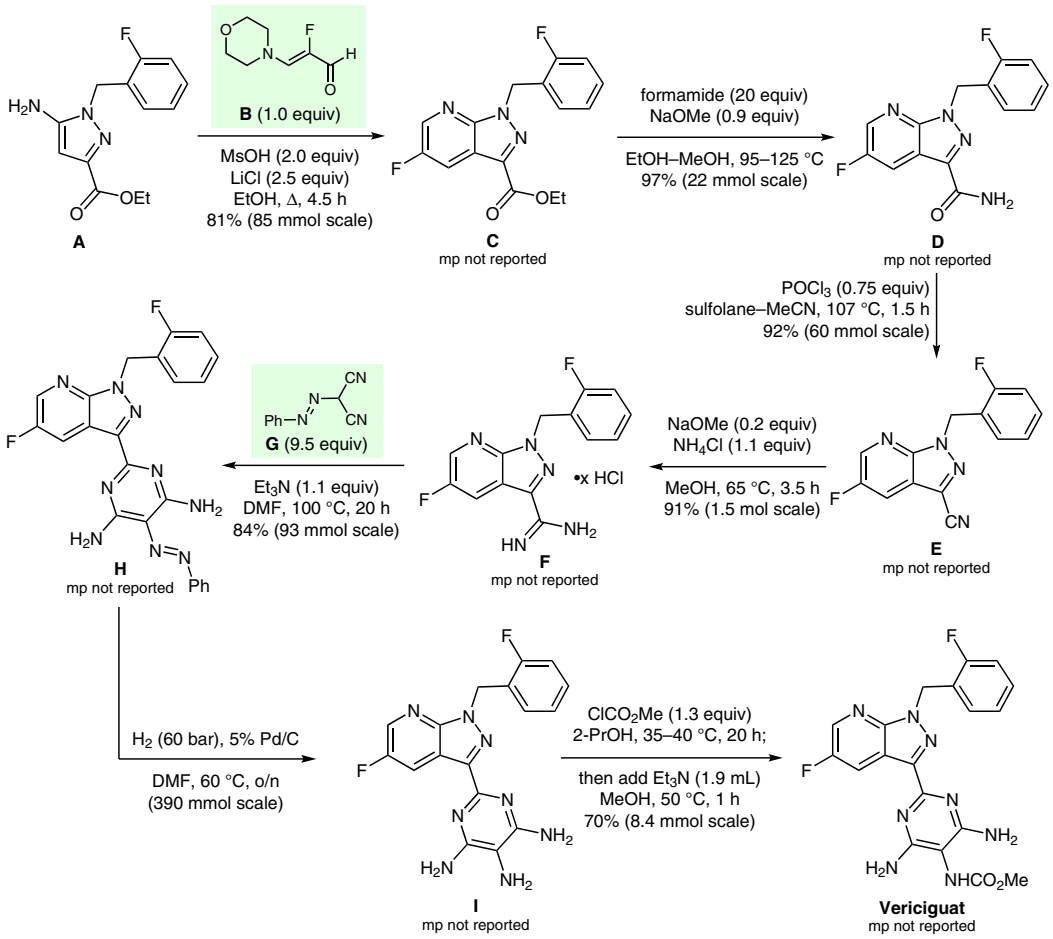
Synthesis of Vericiguat



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)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate **C** by condensation of the 5-amino-1*H*-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.

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