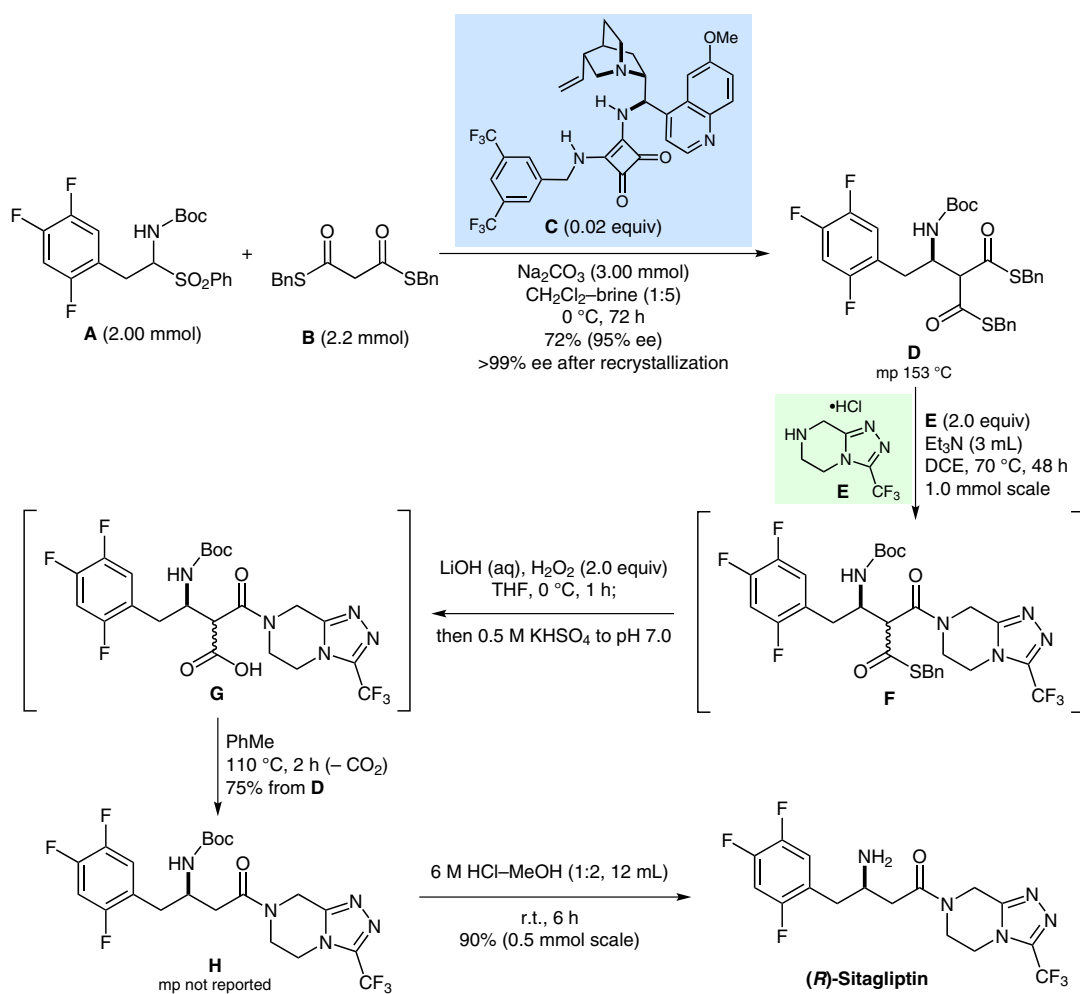


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Direct Catalytic Asymmetric Mannich Reaction with Dithiomalonates as Excellent Mannich Donors: Organocatalytic Synthesis of (*R*)-Sitagliptin

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Synthesis of (*R*)-Sitagliptin



Significance: The key step in the synthesis of (*R*)-sitagliptin depicted is an asymmetric Mannich reaction of dithiomalonate **B** with bench-stable α -amidosulfone **A** catalyzed by quinidine-derived squaramide catalyst **C** (2 mol%). The reaction proceeds at 0 °C under aqueous biphasic conditions to give Mannich adduct **D** in 72% yield and 95% ee. A single recrystallization affords **D** in >99% ee. Sixteen examples of the reaction demonstrate its broad scope and utility.

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Comment: The superior reactivity of dithiomalonate **B** compared with monothiomalonates and malonates as Mannich donors is attributed to the higher acidity of its α -hydrogen. Under the reaction conditions, the α -amidosulfone undergoes elimination of sodium benzenesulfinate to an *N*-Boc-protected imine which reacts before tautomerization to the enamine can occur. Sitagliptin (Januvia) is a DPP-4 inhibitor that is prescribed for the treatment of type 2 diabetes.

Category

Synthesis of Natural Products and Potential Drugs

Key words

sitagliptin

DPP-4 inhibitor

asymmetric Mannich reaction

β -amino acids

dithiomalonates

organocatalysis

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