Synthesis of a Glucokinase Activator

Significance: Glucokinase mediates glucose metabolism in the liver and insulin release in the pancreas. The target molecule selectively activates liver glucokinase with diminished risk of hypoglycemia. It is a lead for the treatment of type 2 diabetes. A major challenge in the synthesis depicted was the formation of amide I by the condensation of the racemization-prone carboxylic acid G with the weakly nucleophilic 6-aminonicotinic ester H. Best results were obtained using n-propanesulfonic anhydride (T3P) as the condensing agent.

Comment: The N-alkylation of imidazole E was studied extensively to achieve high regioselectivity with minimal racemization. Best results were obtained using potassium phosphate as base and ethyl acetate as solvent, in which case the regioselectivity was 96:4. The unwanted regioisomer and epimer was removed by crystallization of the salt prepared from (R)-α-methylbenzylamine. A further complication was the hydrolytic lability of the hard-won amide bond in I.

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