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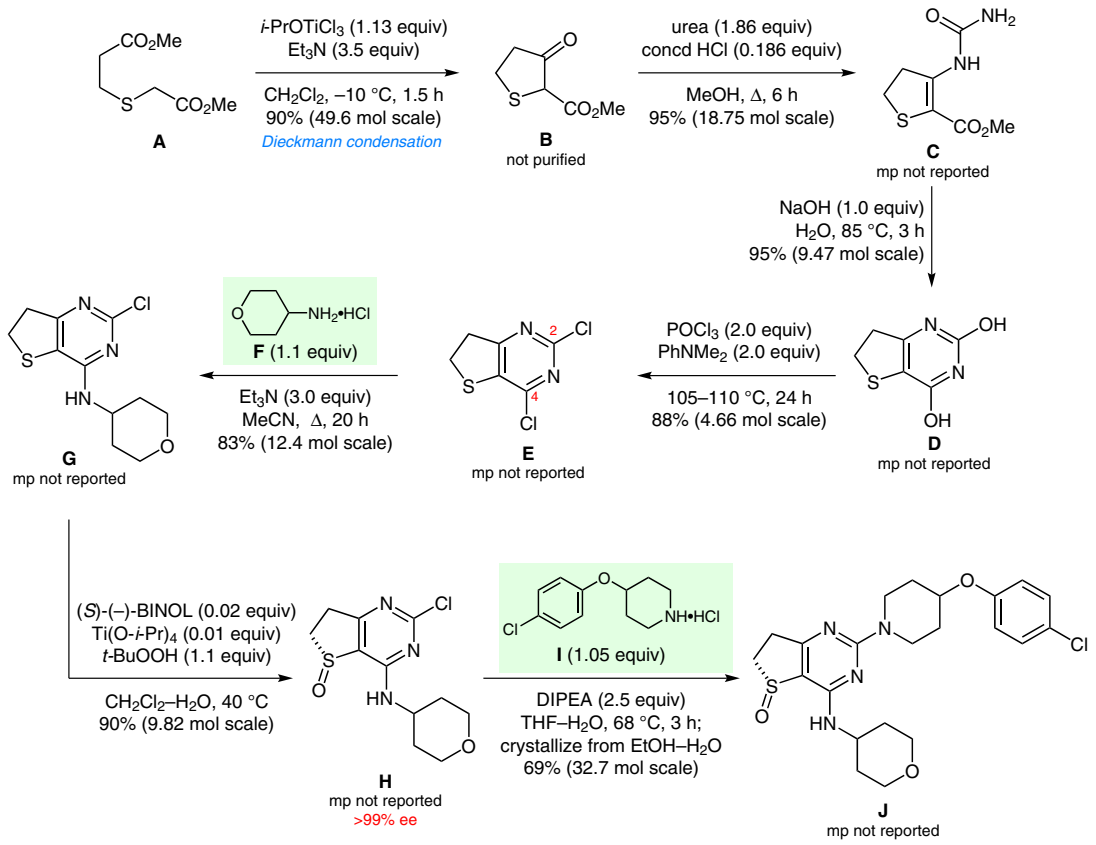
Development of a Practical Process for the Synthesis of PDE4 Inhibitors
Org. Process Res. Dev. **2016**, *20*, 982–988.

Synthesis of PDE4 Inhibitors



Significance: The target phosphodiesterase type 4 (PDE4) inhibitor **J** is of interest for the treatment of chronic obstructive pulmonary disease. The multikilogram-scale synthesis depicted features a highly regioselective Dieckmann condensation (**A** → **B**) required for the construction of the dihydrothieno[3,2-*d*]pyrimidine **D** and the asymmetric sulfoxidation of intermediate **G** using the conditions of Uemura and co-workers (*J. Org. Chem.* **1993**, *58*, 4529).

Comment: The transformation **E** → **G** was accompanied by 15% of the product resulting from displacement of the chlorine at C2. Investigation of alternative bases and solvents failed to improve the regioselectivity; however, the undesired regioisomer was significantly more soluble than **H** and was completely removed from the product during the isolation by filtration.

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Category
Synthesis of Natural Products and Potential Drugs

Key words
phosphodiesterase type 4 inhibitors
Dieckmann condensation
asymmetric sulfoxidation

Synfact of the month

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