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Efficient Method for the Synthesis of Amino-1,3-Oxazines from Thioureas
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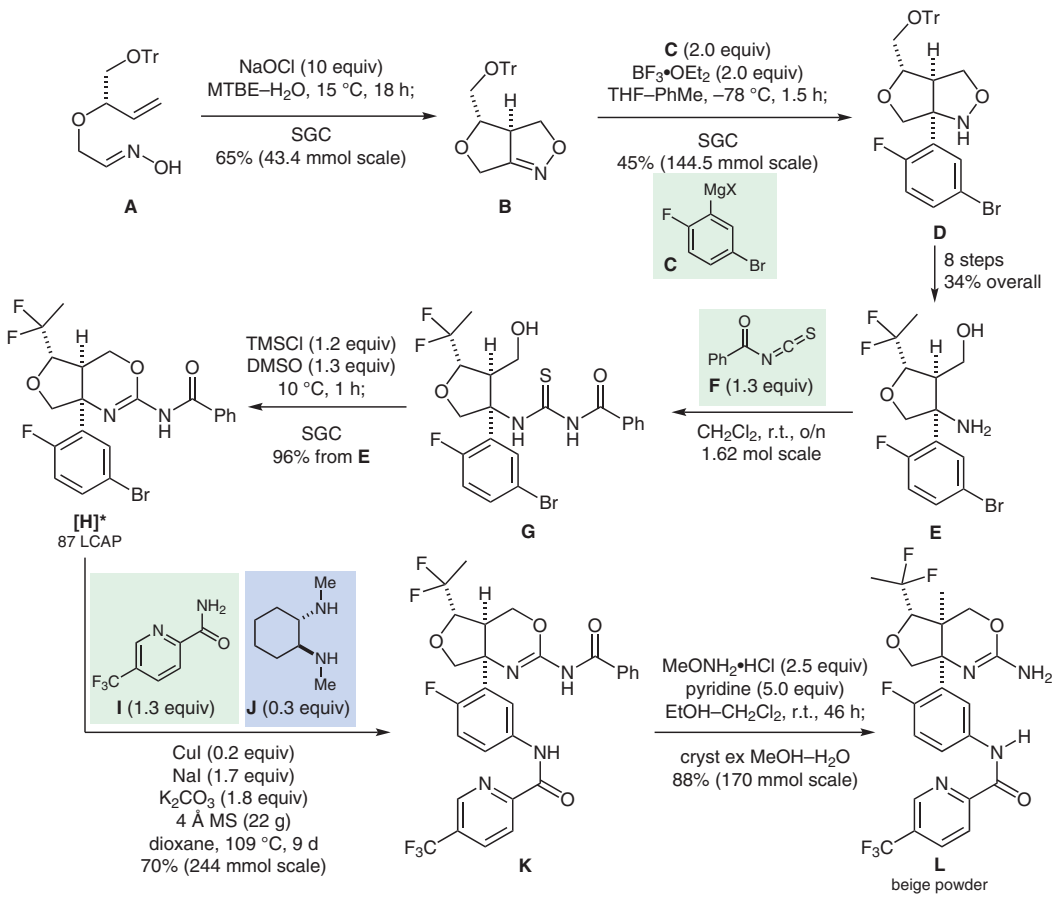
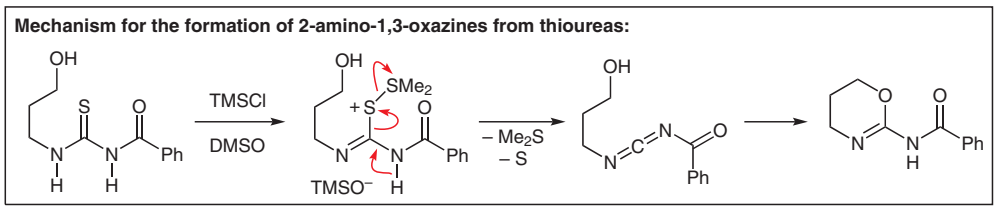
Synthesis of a BACE1 Inhibitor





Significance: The target molecule **L**, an inhibitor of the β-amyloid cleaving enzyme 1 (BACE1), is of interest for the treatment of Alzheimer's disease. A synthesis of **L** was recently disclosed (US **2019** 0106434 A1) that features the reaction of *N*-benzoyl thiourea **G** with TMSCl in DMSO at 10 °C to give 2-amino-1,3-oxazine **I** in 96% yield. Eight simpler examples of the cyclization reaction are described.

Comment: The key cyclization reaction **G** → **H** can be performed by reacting either TMSCl or HCl with DMSO to form sulfonium salts, which can activate the thiourea, enabling the elimination of dimethyl sulfide and sulfur to form a carbodiimide intermediate, which cyclizes to form the 2-amino-1,3-oxazine. The overall yield for the 18-step synthesis is 7.5%

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