

## Synthesis of a BACE1 Inhibitor

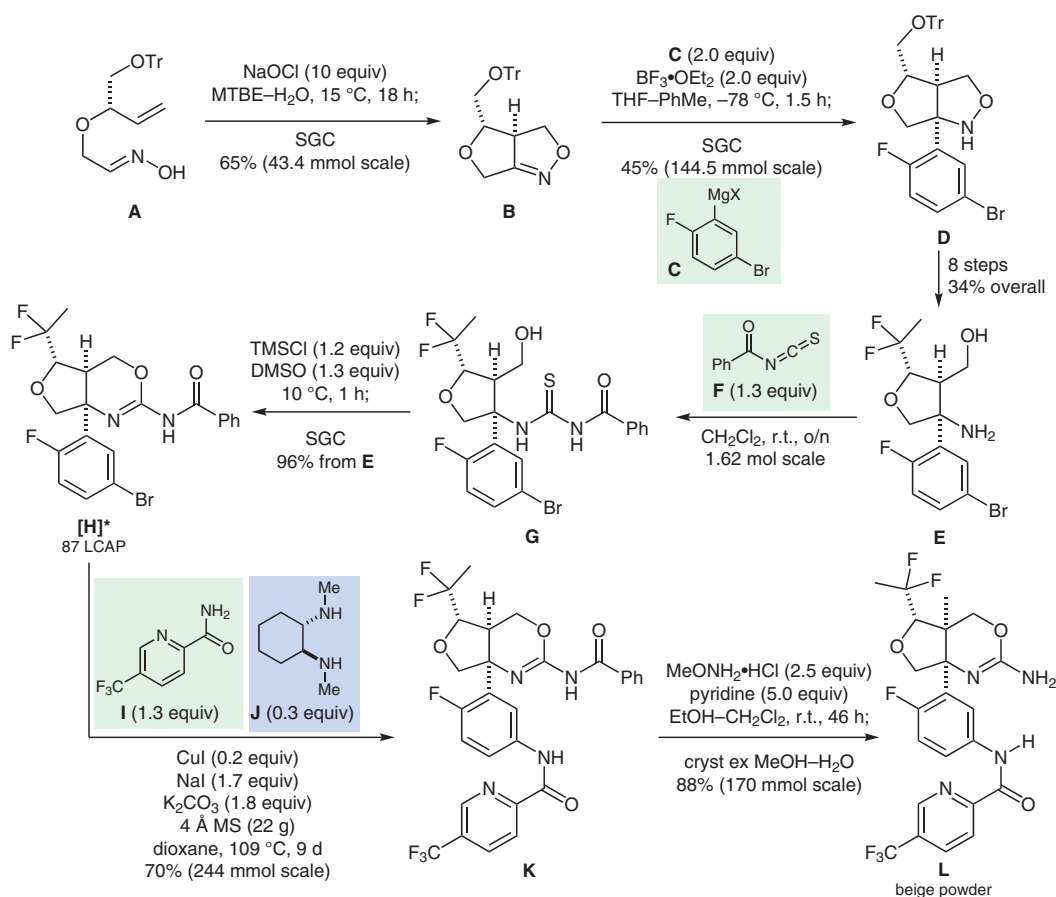
Category

Synthesis of Natural Products and Potential Drugs

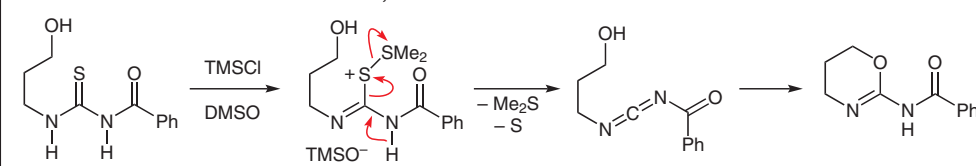
Key words

BACE1 inhibitor  
Alzheimer's disease  
thioureas  
2-amino-1,3-oxazines  
N-arylation  
copper(I) iodide

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### Mechanism for the formation of 2-amino-1,3-oxazines from thioureas:



**Significance:** The target molecule **L**, an inhibitor of the  $\beta$ -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**  $\rightarrow$  **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%