B. R. DILLON,* D. F. ROBERTS,* D. A. ENTWISTLE, P. A. GLOSSOP, C. J. KNIGHT, D. A. LAITY, K. JAMES, C. F. PRAQUIN, R. S. STRANG, C. A. L. WATSON (PFIZER GLOBAL RESEARCH AND DEVELOPMENT, SANDWICH, UK)

Development of a Scalable Synthesis of a Geminal Dimethyl Tertiary Amine as an Inhaled Muscarinic Antagonist for the Treatment of COPD

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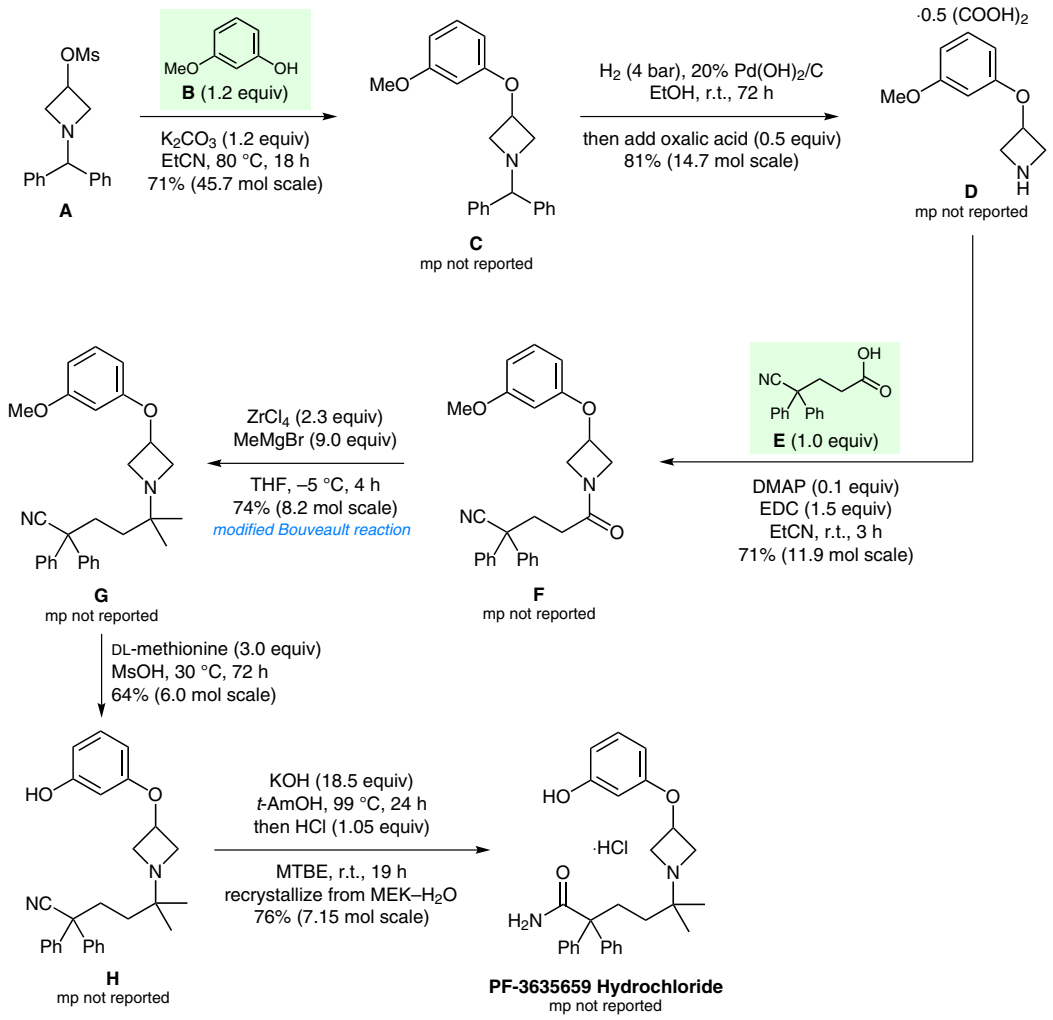
Synthesis of PF-3635659



Significance: Chronic obstructive pulmonary disease (COPD) is projected to become the third leading cause of death worldwide by 2020. PF-3635659 is a once-daily, inhaled muscarinic M_3 antagonist that has entered phase II clinical trials for the treatment of COPD. The synthesis depicted delivered 2.6 kg of the hydrochloride salt and benefited from crystalline intermediates at every stage.

Comment: A noteworthy feature of the synthesis is the reaction of amide **F** with MeMgBr in the presence of $ZrCl_4$ (a variant of the classical Bouveault reaction) to give the sterically encumbered *gem*-dimethyl amine **G** in 74% yield on an 8.2 mol scale. Late-stage demethylation of the phenol methyl ether **G** using methionine in methanesulfonic acid avoided the genetic toxicity problems of the more commonly used boron tribromide.

SYNFACTS Contributors: Philip Kocienski
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Category

Synthesis of Natural Products and Potential Drugs

Key words

PF-3635659

muscarinic M_3 antagonists

Bouveault reaction

***gem*-dimethylation**

zirconium tetrachloride