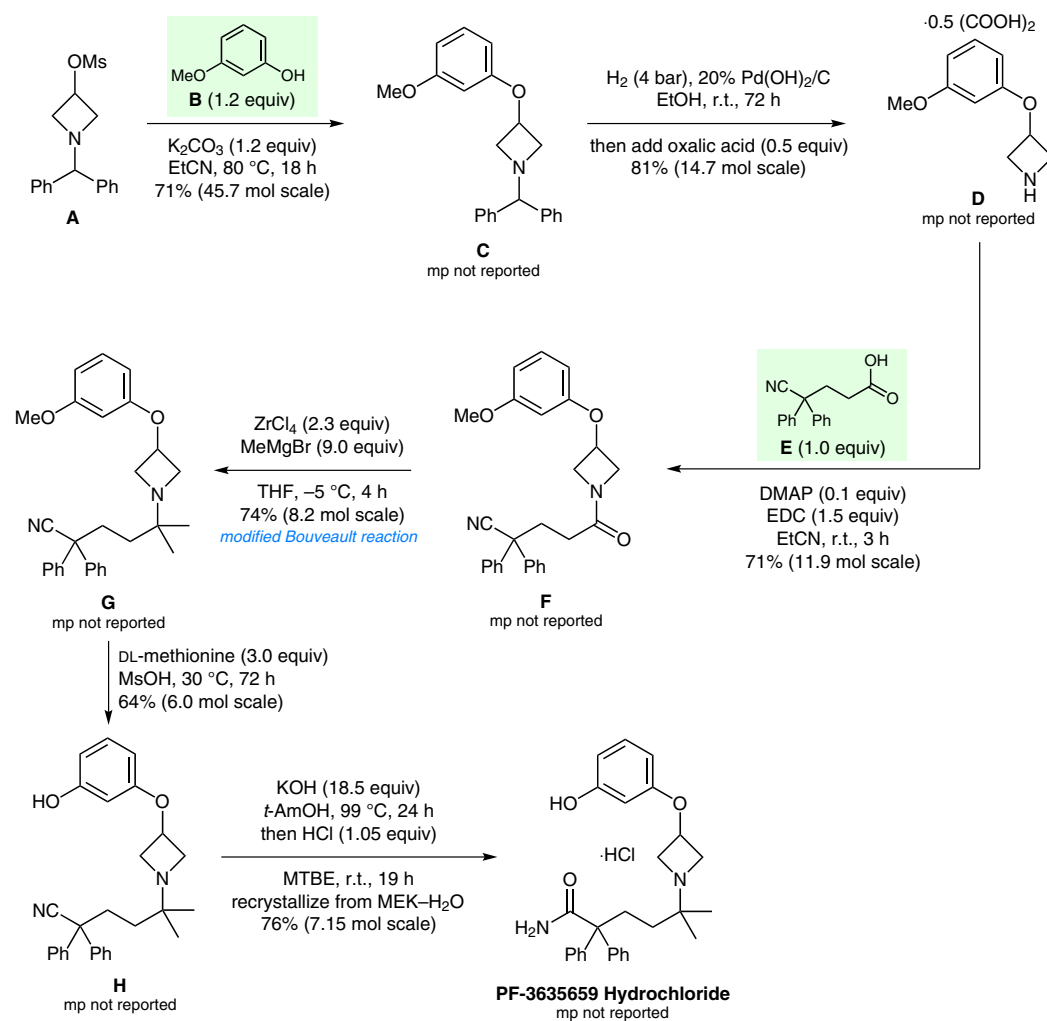


B. R. DILLON,\* D. F. ROBERTS,\* D. A. ENTWISTLE, P. A. GLOSSOP, C. J. KNIGHT,  
 D. A. LAITY, K. JAMES, C. F. PRAQUIN, R. S. STRANG, C. A. L. WATSON (PFIZER GLOBAL  
 RESEARCH AND DEVELOPMENT, SANDWICH, UK)  
 Development of a Scalable Synthesis of a Geminal Dimethyl Tertiary Amine as an Inhaled Muscarinic Antagonist for  
 the Treatment of COPD  
*Org. Process Res. Dev.* **2012**, *16*, 195–203.

## 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<sub>3</sub> 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.

**SYNFACTS Contributors:** Philip Kocienski  
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**Comment:** A noteworthy feature of the synthesis is the reaction of amide **F** with MeMgBr in the presence of ZrCl<sub>4</sub> (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.

Category

Synthesis of Natural  
 Products and  
 Potential Drugs

Key words

PF-3635659

muscarinic M<sub>3</sub>  
 antagonists

Bouveault reaction

*gem*-dimethylation

zirconium  
 tetrachloride

**SYNFACTS**  
*of the month*