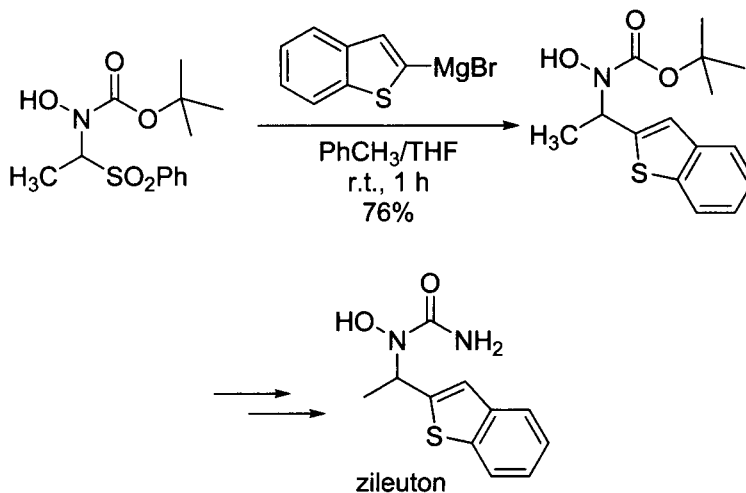


Metal–Halogen Exchange

The Grignard reaction is an important carbon–carbon bond-forming reaction that is widely used in organic synthesis. The utility of the Grignard reaction in synthesis of functionalized thiophenes can be seen in the reported synthesis of zileuton (Zyflo), an inhibitor of 5-lipoxygenase. The benzothiophene-based Grignard reagent displaces the sulfone of tert-butyl hydroxy(1-(phenylsulfonyl)ethyl)carbamate to form the zileuton precursor in 76% yield.⁷⁸



Friedel–Crafts Reaction

The importance and versatility of the Friedel–Crafts reaction in thiophene chemistry can be seen in the following examples of duloxetine synthesis involving Friedel–Crafts acylations. Duloxetine (Cymbalta) is a serotonin–norepinephrine reuptake inhibitor (SNRI) known for its use as an antidepressant.