

Synthesis of AZD7624

Category

Synthesis of Natural Products and Potential Drugs

Key words

AZD7624

cyclopropanation

Buchwald–Hartwig reaction

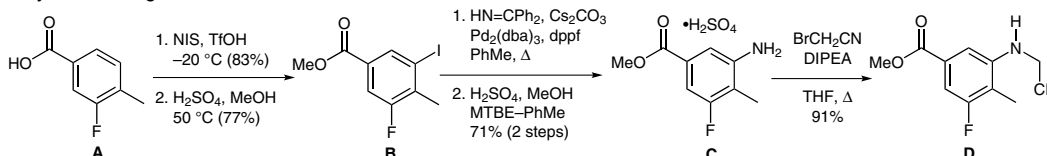
de Meijere reaction

Kulinkovich reaction

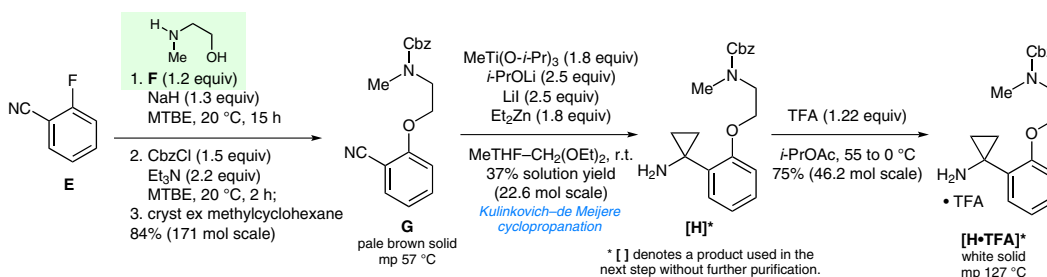
Synfact
of the
Month

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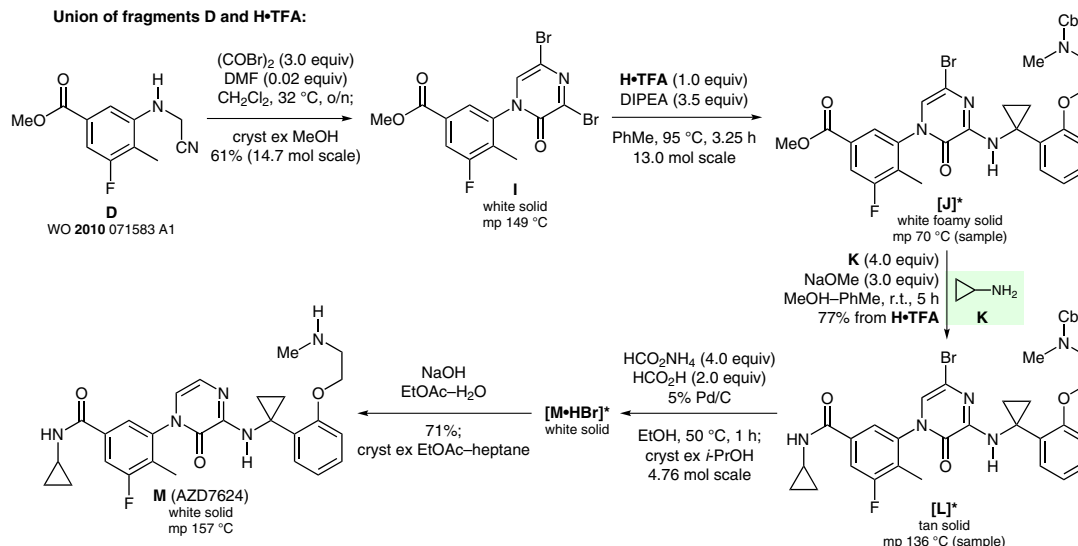
Synthesis of fragment D:



Synthesis of fragment H•TFA:



Union of fragments D and H•TFA:



Significance: The p38 α mitogen-activated protein kinase is expressed and activated in several cell types associated with chronic obstructive pulmonary disease (COPD). AZD7624 inhibits p38 α but its development was halted after phase 2a trials failed to show any benefit over placebo. The synthesis depicted delivered 5.3 kg of API.

Comment: A noteworthy feature of the synthesis is the implementation of the de Meijere modification of the Kulinkovich cyclopropanation that converts the benzonitrile **G** to the cyclopropylamine **H** in 37% yield on a 22.6 mol scale. On a laboratory scale the yield was 57%. For an alternative synthesis of AZD7624, see: WO 2017 162304 A1.