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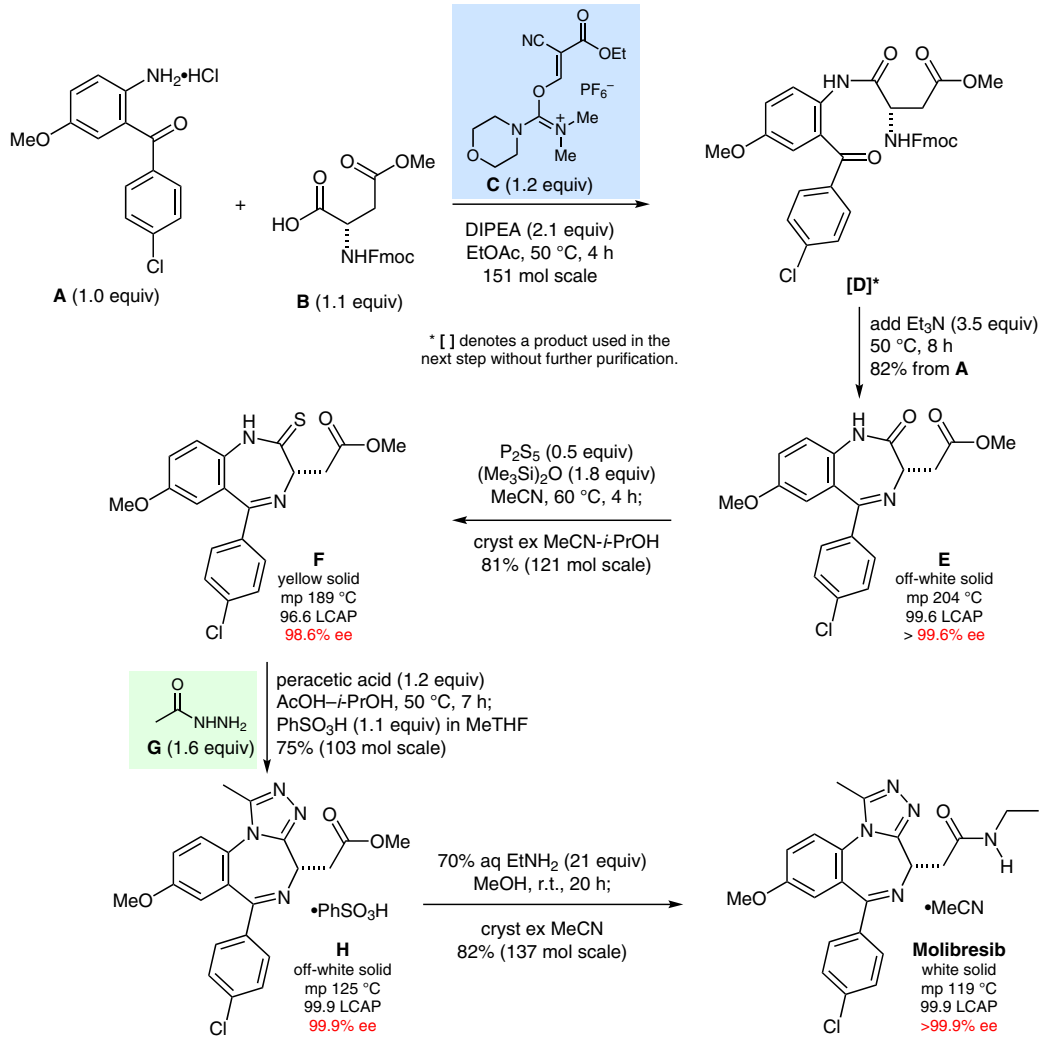
Preparation of Methyltriazolo[1,4]benzodiazepine via Oxidative Activation of a Thiolactam for the Synthesis of BET Inhibitor Molibresib

*J. Org. Chem.* **2022**, *87*, 1961–1970, DOI: 10.1021/acs.joc.1c00563.

# Synthesis of Molibresib




**Significance:** Molibresib (GSK525762) is an inhibitor of the interaction between bromo and extra-terminal (BET) bromodomain proteins that is of interest for the treatment of solid tumors. The concise synthesis of molibresib depicted started with the commercially available ketone **A** and delivered 52 kg of product in 41% yield and 99.9% ee. For the discovery synthesis of molibresib, see: E. Nicodeme et al. *Nature* **2010**, *468*, 1119.

**Comment:** Construction of the core methyltriazolo-[1,4]benzodiazepine **H** was achieved by oxidative activation of the thiolactam **F** via a sulfenic acid (RS–OH) that underwent substitution by acetylhydrazide (**G**), followed by an acid-catalyzed cyclocondensation. The mild conditions for the methyltriazole formation avoided racemization of the sensitive stereocenter.

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Synfacts 2022, 18(05), 0461 Published online: 20.04.2022
**DOI:** 10.1055/s-0041-1738026; **Reg-No.:** K01122SF



**Category**

**Synthesis of Natural Products and Potential Drugs**

**Key words**

**molibresib**

**BET inhibitor**

**thiolactams**

**oxidative activation**

**1,4-benzodiazepine ring formation**

**triazole ring formation**

Synfact of the Month