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SYNFACTS Highlights in Chemical Synthesis

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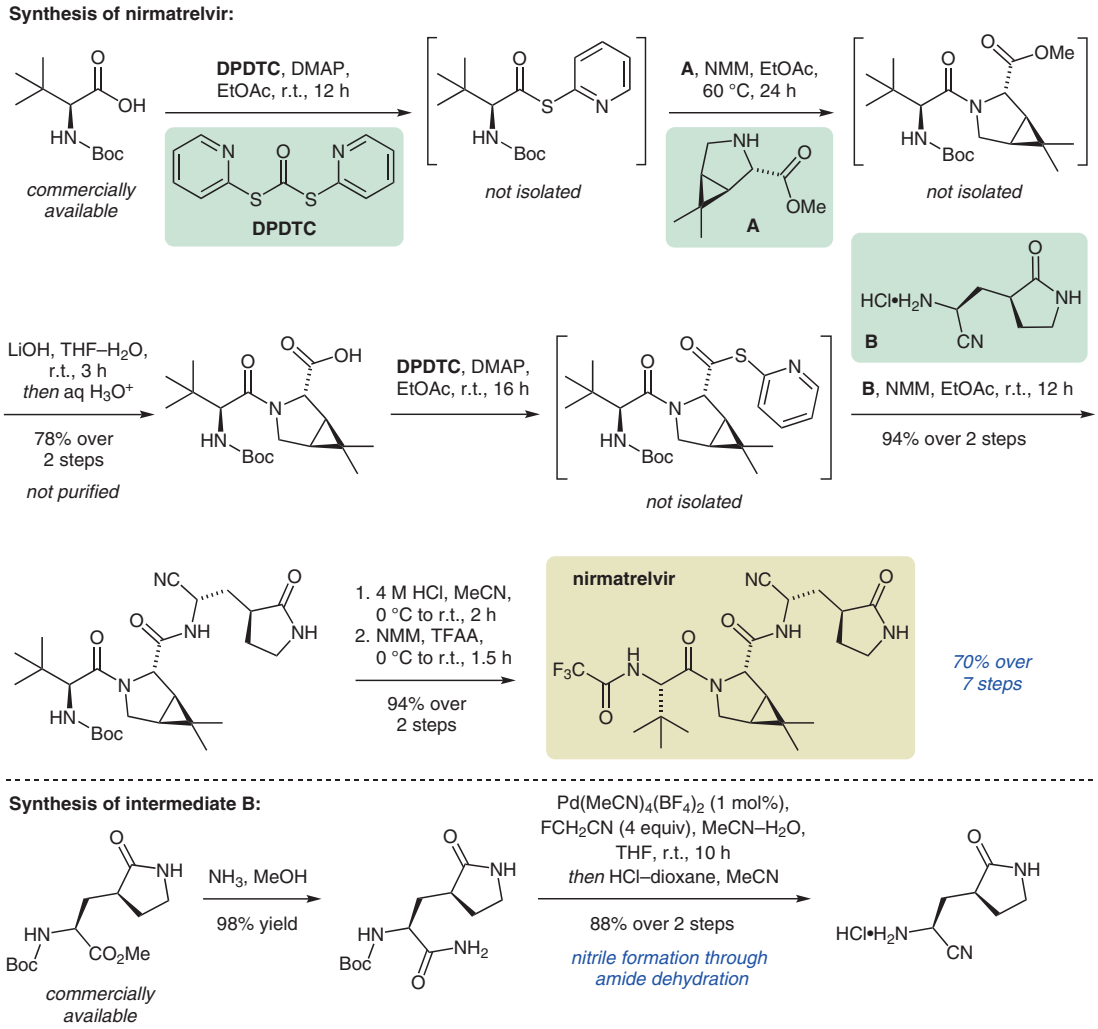
A Sustainable Synthesis of the SARS-CoV-2 M^{pro} Inhibitor Nirmatrelvir, the Active Ingredient in Paxlovid
Commun. Chem. **2022**, *5*, 156 DOI: 10.1038/s42004-022-00758-5.

A Green High-Yielding 7-Step Synthesis of Nirmatrelvir



Significance: Nirmatrelvir is one of the active ingredients in Pfizer's COVID-19 drug Paxlovid®. Although a sustainable synthesis of nirmatrelvir was published in 2021 with 48% overall yield (*Science* **2021**, *374*, 1586), here the authors report a greener and higher-yielding approach that avoids the use of peptide coupling reagents and Burgess reagent. These modifications significantly decrease the cost and waste generated, making it more scalable, environmentally friendly, and economically attractive.

Comment: The synthesis of nirmatrelvir is completed in seven steps with 70% overall yield, starting from commercially available *N*-Boc-protected *tert*-leucine. Key feature of the synthesis is the use of di-2-pyridyldithiocarbonate (**DPDTC**) in order to activate the carboxylic acid as a thioester and subsequently form a peptide bond. Formation of the nitrile key moiety was achieved via a smooth and high-yielding palladium-catalyzed dehydration with no racemization.

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