

Letter to Editor

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Challenges in the Synthesis of Remdesivir

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Dear Editor

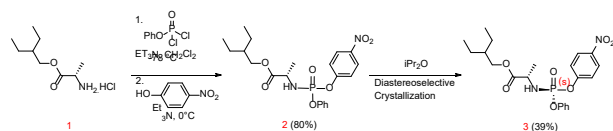
Remdesivir is one of the most widely used drugs against coronavirus disease 2019 (COVID-19). This compound is synthesized by Gilead Sciences Company and sold under the brand called Veklury (1). In addition, remdesivir is a prodrug that acts as a ribonucleotide inhibitor of viral RNA polymerase. It releases GS-441524 monophosphate nucleoside into the cell and then converts it to a triphosphate derivative. GS-441524 triphosphate is a viral RNA-dependent RNA-polymerase (RdRp) inhibitor (2).

Considering the helpful performance of this drug against Ebola, more than 50 countries have used this drug against COVID-19 (3).

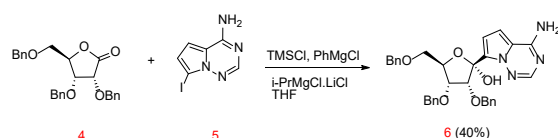
Siegel et al reported a well-known method for the synthesis of remdesivir (4). This editorial will survey the challenges and problems of this method in the chemistry laboratory.

The main challenge of this method is its many synthetic steps. Given that each step requires separation and purification of the product, the high number of synthetic steps reduces the product yields, and it is also a time-consuming process.

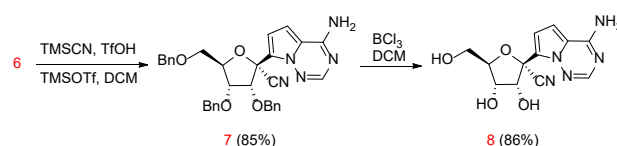
The first challenge starts from the first step, where compound 1 must react with phenyl dichlorophosphate at -78 °C. The reaction at this temperature is uneasy. The obtained product from this step is a racemic mixture that may be separated by diastereoselective crystallization. This separation reduces 50% of the product.



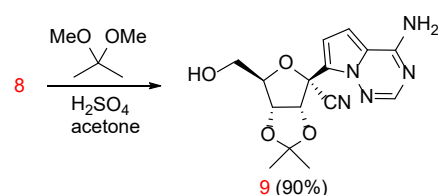
In the presence of the Grignard reagent, compound 4 binds to compound 5 that requires an absolute dry medium.



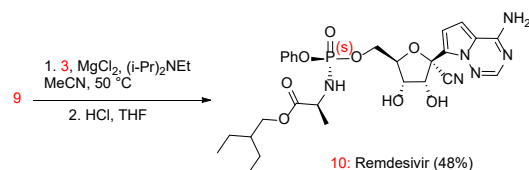
Fortunately, the stereochemistry chemistry of the chiral reaction centers does not change in the conversion of 6-to-7 and 7-to-8.



Although the protection of the vicinal hydroxyl groups on the ribose ring seems simple, the nitrogen atoms of compound 8 react with sulfuric acid and make it challenging to release compound 9 from the salt.



Finally, the binding of compound 3 to compound 9 produces a diastereomeric mixture that requires separation.



According to the mentioned problems, the synthesis of remdesivir seems complicated although this synthetic method is executable in the chemical laboratory by an expert research team and sufficient equipment.

Conflict of Interests

The author declares no conflict of interests.

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