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Trifluoroacetic Anhydride as Acylating Agent and Dehydrant in One-pot Synthesis of Nirmatrelvir

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ABSTRACT Nirmatrelvir is an effective ingredient in the anti COVID-19 drug Paxlovid. There were two key steps in the original synthetic route, which involved trifluoroacetylation and dehydration. A facile and efficient synthesis of nirmatrelvir is described in this work. Intermediate **7** was converted to nirmatrelvir in one-pot synthesis with trifluoroacetic anhydride. In addition, the condensation and deprotection conditions were optimized. The yield of nirmatrelvir produced from 1raised from 51.6% to 72.5%.

KEYWORDS Nirmatrelvir, Acetylation, Dehydration, Trifluoroacetic anhydride.

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INTRODUCTION

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been going on.[1] Nirmatrelvir (PF-07321332) is an orally bioavailable SARS-CoV-2 M^{pro} inhibitor in Paxlovid, which is authorized by FDA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients to reduce the risk of hospitalization or death that who are at high risk for progression to severe COVID-19.[2-4] Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) got its Emergency Use Authorization by FDA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients on December 22, 2021.[5] Paxlovid has been reported to reduce the risk of hospitalization or death by 89% that who are at high risk for progression to severe COVID-19.[6] Besides, SARS-CoV-2 Omicronvariant is highly sensitive to nirmatrelvir.[7]

The original synthesis of nirmatrelvir was described by Owen *et al*. [**Scheme 1**].[8] The intermediate **3** was obtained from **1** after deprotection and trifluoroacetylation. Another intermediate **5** was generated by condensation of **3** and **4**. The amide of **5** was converted to cyano to furnish desired nirmatrelvir by dehydration with Burgess reagent. Condensation, N-trifluoroacetylation of amine with ethyl trifluoroacetateand dehydration with Burgess reagent are key steps in this synthetic route. Herein, we report a facile and efficient synthesis of nirmatrelvir.

RESULTS AND DISCUSSION

Anhydride is one kind of common reagents for aminoacylation which is also could be used in amide dehydration.[9,10] Trifluoroacetic anhydride is a frequently used dehydration reagent, which can convert amidetocyano. Considering the existence of trifluoroacetyl and cyano in the structure of nirmatrelvir, we planned to develop a new synthetic method, using trifluoroacetic anhydride to complete trifluoroacetylation and dehydration in one step. Whether intermediate **7** can be completed simultaneously

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reduce corrosivity and toxicity. Finally, the total yield of nirmatrelvir produced from compound **1** over three steps raised from the original 51.6–72.5%.

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