

A Sustainable Synthesis of the SARS-CoV-2 M^{pro} Inhibitor Nirmatrelvir, the Active Ingredient in Paxlovid

Joseph R. A. Kincaid,‡ Juan C. Caravez,‡ Karthik S. Iyer,‡ Rahul D. Kavthe, Nico Fleck, Donald H. Aue, and Bruce H. Lipshutz*

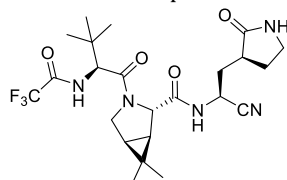
Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States

KEYWORDS: COVID-19, nirmatrelvir, Paxlovid, thioester, amide dehydration, sustainability

ABSTRACT: A 7-step, 3-pot synthesis of the antiviral drug nirmatrelvir is described, arriving at the targeted drug in 70% overall yield. Critical amide bond-forming steps utilize new green technology that completely avoids traditional peptide coupling reagents, as well as epimerization of stereocenters. Likewise, dehydration of a primary amide to the corresponding nitrile is performed and avoids use of the Burgess reagent and chlorinated solvents. Direct comparisons with the original literature procedures highlight both the anticipated decrease in cost and environmental footprint associated with this route, potentially expanding the availability of this important drug worldwide.

INTRODUCTION

The ongoing COVID-19 pandemic caused by the SARS-CoV-2 virus and its variants represents a once in a century public health disaster that continues to impact mankind, as well as the global economy.¹ The disease has created an urgent need for rapid development of both preventative measures (e.g., vaccines) and post-infection treatment options.² Both aims have been achieved in record time, the latter initially being driven by investigations into repurposing existing drugs, which has produced relatively few effective treatment options.³ The search for novel SARS-CoV-2 antivirals, on the other hand, has led to the development of molnupiravir by Merck,⁴ EDP-235 by Enanta,⁵ S-217622 by Shionogi,⁶ and several others.⁷ The first such antiviral to receive approval by the FDA, Paxlovid, is an orally-active combination of the SARS-CoV-2 main protease inhibitor nirmatrelvir (**1**; PF-07321332) and the HIV antiviral ritonavir, disclosed by Pfizer in late 2021.⁸ This drug combination was shown to reduce risk of progression to severe COVID-19 in high-risk, symptomatic patients by 89% compared to placebo,⁹ exemplifying the crucial role the drug is expected to play worldwide in the continuing efforts to combat the COVID-19 pandemic.



1; nirmatrelvir

In addition to cost, the environmental impact associated with the synthesis of nirmatrelvir in such an immediate and high demand situation cannot be overlooked, especially since the prescribed dosage is 3 g of total API per patient over the course of the 5-day treatment. While Pfizer's more

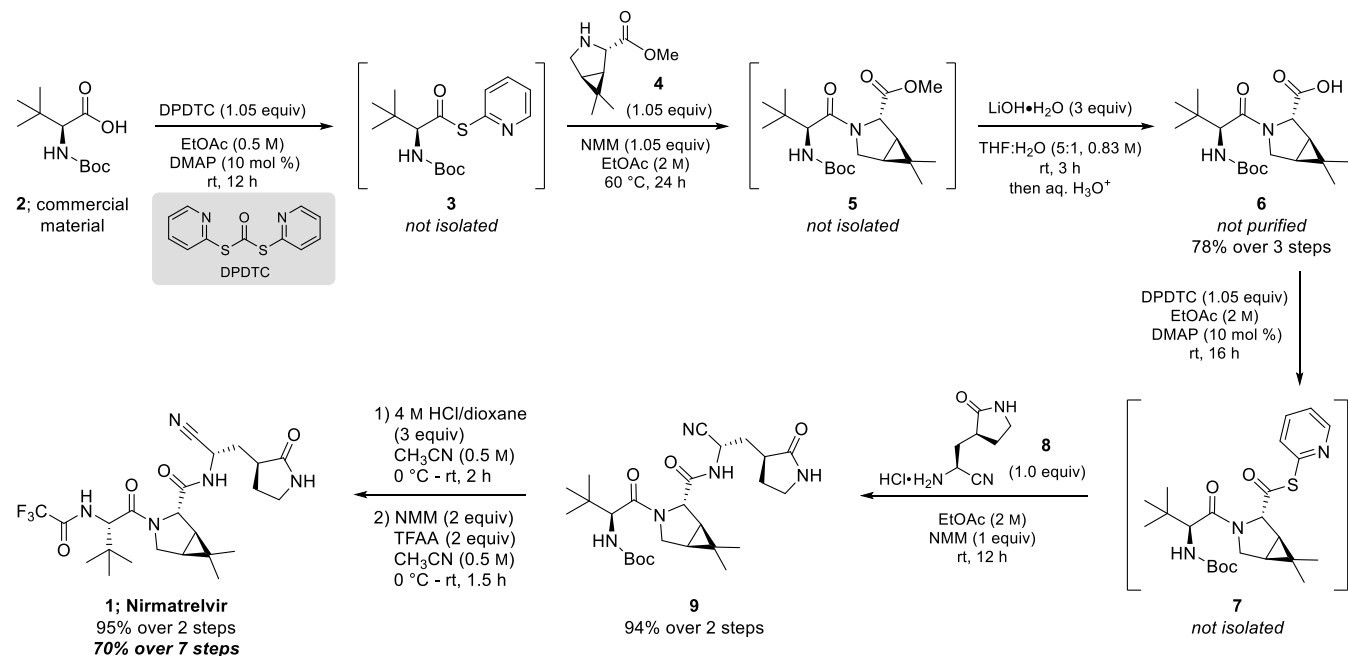
recently reported route to nirmatrelvir¹⁰ improves upon their originally reported methodology,^{8a} there are still numerous opportunities to reduce the amount of waste generated by the existing routes, especially focusing on use of a variety of organic solvents, and peptide coupling reagents. Therefore, there clearly exists an urgent need for the development of both a green and economically attractive synthesis of nirmatrelvir.

RESULTS AND DISCUSSION

In continuing our group efforts to develop scalable routes to APIs under cost effective and environmentally friendly conditions,¹¹ and in an ongoing partnership with the Bill and Melinda Gates Foundation initially formed for purposes of preparing APIs for the treatment of malaria (e.g., pyronaridine),^{11a} we have developed a route to nirmatrelvir that simultaneously addresses these issues while maximizing both time and pot economies (Scheme 1).¹² Furthermore, special attention has been directed towards avoiding epimerization of chiral centers during crucial peptide bond-forming steps. Workups, which often give rise to enormous volumes of both organic and aqueous waste, have also been streamlined; only simple, in-pot aqueous washes are involved, as are minimal amounts of far greener (and recoverable) organic solvents (e.g., EtOAc).¹³ The strategy selected for the synthesis of nirmatrelvir, therefore, focused on the inherent benefits on scale of a convergent route.¹⁴ Moreover, it seemed advantageous to perform our Pd-catalyzed amide dehydration¹⁵ in this convergent fashion, as subsequent steps provide opportunities to limit the amount of residual Pd in the final API.

The 1-pot thioesterification/amide bond formation featured in this sequence,¹⁶ which uses di-2-pyridyldithiocarbonate (DPDTC)¹⁷ to activate the carboxylic acid, avoids traditional peptide coupling reagents (e.g., HATU, DCC, COMU, T3P, etc.) and epimerization, and

Scheme 1. The Overall Route to Nirmatrelvir



allows for facile removal of the (odorless) 2-mercaptopyridine by-product via an in-flask extraction with limited amounts of aqueous hydroxide. In contrast to the by-products of conventional amide bond coupling reagents,¹⁸ benign 2-mercaptopyridine can also be easily recovered for recycling to DPDTC (see SI-1, section 4). Both intermediate thioesters **3** and **7** are stable, isolable species constituting activated carboxylic acids, potentially simplifying their large-scale manufacture and distribution compared to other activated species. In this sequence, however, their individual isolation/purification was not required.

3-Step, 1-pot sequence en route to intermediate 6

Commercially available *N*-Boc protected *t*-leucine (**2**) was converted to its thioester derivative **3** using DPDTC in environmentally preferable EtOAc¹³ containing catalytic DMAP at rt. Product **3** was then processed via simple in-flask treatment with aqueous base, followed (after removal of the aqueous phase and EtOAc) by addition of bicyclic proline **4**, *N*-methylmorpholine (NMM), and EtOAc.¹⁹ Gentle heating led to the desired amide bond in product **5**. This newly formed peptide containing a methyl ester originally present in **4**, was then hydrolyzed with LiOH in aqueous THF, after which the reaction mixture was neutralized with aqueous HCl and then extracted with minimal EtOAc to afford **6** (78% over 3 steps). It is noteworthy that the product did not require purification since the small amounts of impurities present, primarily 2,2'-dipyridyldisulfide, were of no synthetic consequence. It was, however, necessary to adjust the stoichiometry of reagents used in the second thioesterification step based on the amounts of impurities present in crude **6** (as determined by quantitative NMR).

2-Step, 1-pot sequence en route to intermediate 9

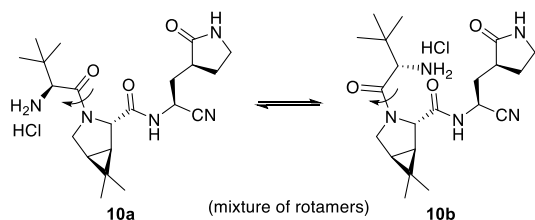
Carboxylic acid **6** was subjected to thioester formation in the same manner as used earlier to form **3**. The resulting **7**,

without isolation, was then treated with nitrile amine salt **8** in concentrated EtOAc (2 M) at rt to afford **9** (94% over 2 steps). This convergent approach avoids the linear route used by Pfizer involving a primary amide intermediate that then requires the Burgess reagent to effect dehydration. While column chromatography was required in our hands for isolation of pure **9** owing to practical limitations associated with small academic work, large-scale purification of this intermediate should be possible by precipitation.

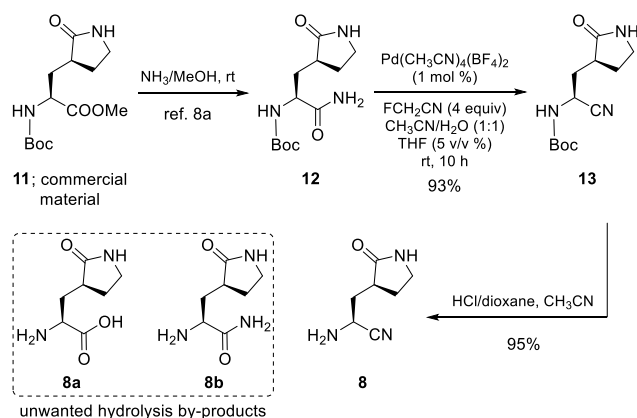
2-Step, 1-pot sequence en route to nirmatrelvir (1)

Intermediate **9** was initially dried azeotropically using recoverable toluene. *N*-Boc Deprotection was then carried out using a concentrated solution of HCl/dioxane in CH₃CN. All attempts using standard conditions involving TFA were quite low-yielding and involved creation of multiple side-products, presumably including various materials resulting from epimerization due to the presence of TFA.²⁰ Use of HCl, however, was very clean and led to an initial mixture of conformers, likely to be a rotameric mix associated with the tertiary amide present (**10a** and **10b**, Scheme 2) as seen by Pfizer with related compounds bearing the same bicyclic proline moiety,^{8a} and supported by variable temperature ¹H NMR (see SI-1, section 3.7). Remarkably, and unexpectedly, it was also observed that greater degrees of epimerization occurred during subsequent trifluoroacetylation when the kinetically formed proportion of the minor conformer was used. Interestingly, equilibration of the *N*-Boc deprotected material, which was a 70:30 mixture of the initially formed HCl salt, at rt overnight reproducibly led to a ratio of conformers between 94:6 and 96:4. After equilibration, the solvent and excess HCl were removed in vacuo and the resulting amine hydrochloride salt was subjected to trifluoroacetic anhydride (TFAA) and NMM to install the trifluoroacetamide moiety. Removal of TFAA and NMM via aqueous washes afforded nirmatrelvir (**1**) in 95% yield over this 1-pot, 2 step approach, and with 95% purity by HPLC. Small amounts of the undesired

Scheme 2: The rotameric mixture of intermediate amine salts 10a and 10b following *N*-Boc deprotection.



Scheme 3: Preparation of aminonitrile 8



diastereomer could be effectively removed by formation and recrystallization of the MTBE solvate, as described previously by Pfizer.^{8a} The resulting nirmatrelvir was isolated seemingly as a pure rotamer based on NMR data (see Figure S8 in SI-1).

The proton NMR spectrum of nirmatrelvir (**1**) (obtained prior to treatment with MTBE) in dimethylsulfoxide solvent showed mainly one rotamer, with only ca. 5% of the minor rotamer present. DFT calculations on conformers of nirmatrelvir were carried out looking to support observations that nirmatrelvir and related compounds featuring the bicyclic proline residue in **1** exist as two rotamers about the tertiary amide bond that are unusually slow to equilibrate at room temperature as seen in the NMR spectrum (see SI-2). Calculations at the B3LYPD3BJ/6-31+G(d,p) level in the gas phase and in acetonitrile using the SMD solvation model showed a predominance of the rotamer with the tertiary amide carbonyl group participating in a cyclic, 7-membered ring-containing a hydrogen bond to the NH of the pyrrolidinone side-chain amide (Figure 1). The structure of the minor rotamer (calculated in acetonitrile) is shown in Figure 2 with two marginal long-distance, non-linear hydrogen bonds. The rotational free energy barrier for nirmatrelvir in acetonitrile was calculated to be 25.25 kcal mol⁻¹ at 298 K, significantly higher than the experimental barrier of 17.77 kcal mol⁻¹ for acetamide in acetonitrile solvent.²¹

Synthesis of intermediate 8

The commercially available *N*-Boc protected methyl ester **11** was converted to the corresponding primary amide **12** using the published procedure (methanolic ammonia; Scheme 3).^{8a} Although Pfizer's approach to the dehydration of their primary amide relied on the Burgess reagent

in chlorinated solvent,^{8a} **12** could alternatively be smoothly dehydrated applying recently disclosed technology based on an "amide exchange",^{15,22} that is, using commercially available fluoroacetonitrile²³ as the sacrificial acceptor of water under Pd-catalyzed conditions, resulting in nitrile **13** (93%).

N-Boc Deprotection of **13** using HCl in various organic solvents was initially problematic in that adventitious water present in both the solvent and starting material **13** led to varying degrees of hydrolysis (13-30+%) to form carboxylic acid **8a** and/or primary amide **8b**. It was anticipated that hydrolysis could also occur during Boc-deprotection of **9**. Formation of by-products **8a** and **8b** were minimized via azeotropic removal of residual water in **13** using recoverable toluene under high vacuum. Prior observations by BMS on related nitriles indicated that inclusion of a sacrificial nitrile, such as CH₃CN, reduced undesired competitive hydrolysis during *N*-Boc deprotection, likewise under acidic conditions.²⁴ Indeed, applying both procedures (azeotropic drying of the educt and then

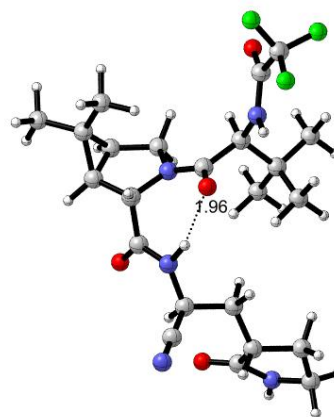


Figure 1. B3LYPD3BJ/6-31+G(d,p)/SMD(MeCN) optimized structure in acetonitrile for the *major* rotamer of **1**. Hydrogen bond O-H distance = 1.96 Å. Atom colors: nitrogen, blue; oxygen, red; fluorine, green.

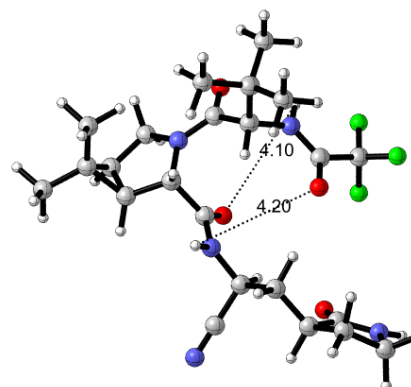


Figure 2. B3LYPD3BJ/6-31+G(d,p)/SMD(MeCN) optimized structure in acetonitrile for the *minor* rotamer of **1**. Weak hydrogen bond O-H distances = 4.10, 4.20 Å. Atom colors: nitrogen, blue; oxygen, red; fluorine, green.

adding dry CH₃CN) afforded the desired nitrile amine **8** as its HCl salt (95%) with only 3% hydrolysis. Separation and removal of residual **8a** and/or **8b** could be easily accomplished by dissolving the mixture in MeOH and precipitating pure **8** using ice-cold Et₂O.

This convergent route to nirmatrelvir has been accomplished in 70% overall yield, a considerable improvement over the 48% reported by Pfizer.^{8a} Table 1 summarizes a direct comparison of several additional key features associated with each route with respect to environmental aspects, as well as potential costs. Importantly, given the global volumes of drug needed (leading to a projected \$22 billion in revenue),²⁵ and using Sheldon's E Factors²⁶ as a reasonable guide to waste creation, the sequence described herein is suggestive of a far more attractive process. What the E Factors do not highlight, however, is the significant decrease in *hazardous* waste generated, including chlorinated solvents, DMF, and excess reagents such as HATU and the Burgess reagent.

Table 1: comparisons between this work and Pfizer's route^{8a} to nirmatrelvir (1)

reaction parameter	Pfizer	this work
amide bond formations	uses HATU, EDCI non-recyclable waste solvents: DMF, MEK	uses DPDTC recyclable 2-mercaptopyridine solvent: EtOAc
amide dehydration	Burgess reagent solvent: CH ₂ Cl ₂	cat. Pd, FCH ₂ CN solvent: H ₂ O/CH ₃ CN
N-Boc-deprotection	solvent: CH ₂ Cl ₂	solvents: CH ₃ CN, dioxane
E Factor (all waste)	214	120*
E Factor (excluding aq. waste)	108	54*
overall yield	48%	70%

*Artificially elevated due to scale; see ref. 27.

CONCLUSIONS

The sequence to nirmatrelvir outlined herein provides streamlined, efficient, convergent, cost-effective, and environmentally responsible access to a highly valued drug for treatment of COVID-19. Particularly notable and distinguishable features associated with this route include:

- peptide bond constructions that take place in 1-pot processes in highly concentrated EtOAc that avoid traditional peptide coupling reagents, which can otherwise be costly, dangerous, and produce considerable waste, especially at scale.

- use of our newly developed, green technology for primary amide dehydrations, applied to a "real" molecule, that by-passes prior employment of unattractive reagents at scale (e.g., the Burgess reagent).

- conditions that avoid potentially costly separation of unwanted isomers due to epimerization.

- a reduced environmental footprint, thereby avoiding much of the waste being generated by the currently utilized routes.

- new insights gained regarding nirmatrelvir based on previously unknown high-level calculations and modeling studies.

ASSOCIATED CONTENT

Supporting Information-1.

Experimental procedures, optimization details, and analytical data (NMR, HPLC, and MS).

Supporting Information-2.

DFT calculations.

This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

***Bruce H. Lipshutz** – Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States; orcid.org/0000-0001-9116-7049
Email: lipshutz@chem.ucsb.edu

Authors

Joseph R. A. Kincaid – Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States; orcid.org/0000-0003-4976-7432

Juan C. Caravez – Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States; orcid.org/0000-0002-5679-7536

Karthik S. Iyer – Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States; <https://orcid.org/0000-0003-4566-2721>

Rahul D. Kavthe – Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States

Nico Fleck – Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States

Donald H. Aue – Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States; <https://orcid.org/0000-0002-2036-523X>

Author Contributions

All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

The authors declare no competing financial interest.

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We warmly dedicate this manuscript to the memory of our friend, and former student, Dr. Alex B. Wood, whose graduate work here at UCSB figured prominently in this synthesis.

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(19) The academic scale at which this route was developed necessitated dilution of the reaction medium with EtOAc prior to aqueous extraction. This accounts for the EtOAc being concentrated following aqueous washes, and then being freshly added to bring the concentration to the desired level for use in the following step. Such handling would not be involved on scale up.

(20) We found that exposing pure nirmatrelvir to TFA led to 8% epimerization by chiral HPLC analysis, whereas exposure to either excess base (NMM) or HCl did not lead to epimerization (see SI-1 section 3.7, especially Fig. S9).

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(23) It is appreciated that fluoroacetonitrile may be undesirable owing to both its cost and the toxicity of the fluoroacetamide by-product. Crystallization of educt **13** is sufficient to remove this impurity, however, if it is not deemed safe on scale, methoxyacetonitrile is a viable alternative (see SI-1 Table S5, entry 23).

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(25) (a) The Next Generation of COVID-19 Antivirals – C&EN (2022) <https://cen.acs.org/business/next-generation-COVID-19-antivirals/100/i11> (accessed July 13, 2022). (b) Pfizer sticks to guns on \$22B Paxlovid sales despite reports of lagging demand – Fierce Pharma (2022) <https://www.fiercepharma.com/pharma/pfizer-echoes-hopes-22b-paxlovid-sales-despite-reports-lagging-demand> (accessed July 13, 2022).

(26) (a) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273–1283. (b) Sheldon, R. A. *Green Chem.* **2017**, *19*, 18–43.

(27) The actual E Factor of this sequence would likely be much lower on scale, as dilution of the reaction medium would not be necessary (also, see ref. 19).

ToC graphic

