

Pilot-Scale Flow Synthesis of Hydantoins via the Bucherer-Bergs Reaction

Matthew T. Graves

Temple University

Kyle N. Brunner

Temple University

Christian E. Schafmeister

meister@temple.edu

Temple University

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Abstract

Hydantoins are valuable structural motifs with broad applications in medicinal chemistry and synthetic organic chemistry, particularly as core structures in anticonvulsants and as intermediates in the synthesis of unnatural amino acids. The Bucherer–Bergs reaction remains a foundational method for hydantoin synthesis; however, conventional batch protocols suffer from extended reaction times, modest yields, and significant safety concerns associated with handling cyanide. Here, we present the optimization and pilot-scale implementation of a continuous flow Bucherer–Bergs reaction that directly addresses these challenges. Systematic tuning of residence time, temperature, and solvent composition enabled a robust and scalable process that delivers hydantoin at up to 96.2% isolated yield under milder and more cost-efficient conditions than previously reported.[1] Improving reagent stability and preventing in-line precipitation enabled this conversion at a pilot scale, being demonstrated in a 600 g, 24-hour reaction. This work underscores the power of flow chemistry to modernize classical reactions for safer, more efficient, and industrially relevant applications.

ARTICLE HIGHLIGHTS

- Streamlines hydantoin synthesis in continuous flow with shorter reaction times and steady high yield.
- Identifies and fixes points of failure in aqueous reagents when scaling up.
- Demonstrates safe, sustained operation for 24 hours at a 600 g scale.

IMPACT OF FLOW

Implementing the Bucherer–Bergs reaction under continuous flow conditions results in substantial improvements over traditional batch processes. In batch, this reaction is often characterized by long reaction times, moderate to low yields, and significant safety concerns, particularly when scaling up due to the use of potassium cyanide and elevated temperatures. Flow chemistry addresses these challenges by enabling fine control over reaction parameters such as temperature, pressure, and residence time. The continuous system facilitates reproducible synthesis of high purity hydantoins, with shorter reaction durations and improved yields. Furthermore, flow reactors inherently offer a safer platform for handling hazardous reagents as only small volumes are present in the high temperature and pressure reaction conditions at any given time and are confined within secondary containment. These factors combine to minimize the risk associated with over pressurization or reagent exposure, especially during prolonged operation. The application of flow chemistry to this classical transformation not only enhances efficiency and safety but also facilitates practical scalability to pilot-scale production.

INTRODUCTION

The Bucherer-Bergs reaction is a versatile method for synthesizing 5-substituted and 5,5-disubstituted hydantoins from ketones and aldehydes (Fig. 1a).[2] Hydantoin derivatives exhibit significant bioactivity

and have broad pharmaceutical applications.[3] Notably, phenytoin remains the benchmark treatment for tonic-clonic and focal motor seizures, with additional neuroprotective effects under investigation (Fig. 1b).[3] Additionally, hydantoins serve as key precursors in the synthesis of unnatural amino acids, such as the bis-amino acid derivatives used by the Schafmeister lab for the synthesis of Spiroligomer™ macromolecules (Fig. 1c).[4]

Despite their utility, batch Bucherer–Bergs reactions typically suffer from several drawbacks, primarily low yields and long reaction times. For example, the installation of a hydantoin motif onto a proline derivative over 72 hours results in only a 58.7% yield of the desired product (Fig. 2a).[1] Given that this transformation is a single step within the multistep synthesis of bis-amino acids, such inefficiencies significantly diminish the overall yield, and necessitate purification steps like flash chromatography.[1] Beyond this, the use of potassium cyanide raises critical safety and environmental concerns, especially when scaling the reaction to pilot and industrial levels.

Flow chemistry offers advantages in overcoming these limitations.[5] Batch chemistry refers to performing reactions in nonflowing environments, such as a reaction stirring in a round bottom flask.[6] Flow chemistry is the process of performing chemical processes in a continuously flowing stream.[6] By continuously flowing reagents through a reaction system, flow chemistry enables precise control over reaction conditions, facilitates pressurization, allows heating beyond traditional reflux temperatures, and enhances interfacial mixing in biphasic systems.[6]

Previous work by the Kappe and Correa Labs have demonstrated a flow-based Bucherer-Bergs methodology that offers improved yields and safer handling of cyanide containing materials.[5] In their work they report performing the reaction under 20 bar at 120°C with a residence time (RT) of 32 minutes and a production rate of 2.5 grams of product per hour (Fig. 2b).[5] Building on this work, we report a flow process that expands the utility of this transformation by reducing the reaction temperature, shortening the residence time, and preventing precipitation while maintaining the advantages of the continuous flow process to achieve a production rate of 28 grams of product per hour (Fig. 2c). These modifications also broaden the synthetic application of this reaction by enabling transformations on compounds containing thermally sensitive function groups such as tert-butyl esters, Fmoc carbamates, and diazos. [7, 8] These advancements collectively enhance the practicality and scalability of the reaction, making it more accessible for both laboratory-scale synthesis and industrial applications.

EXPERIMENTAL

General Information

All commercially available reagents were used as received without additional purification. Reaction analysis and high resolution mass spectroscopy was performed via LCMS on an Agilent 1260-90 (Ascentis Express C18 Column, Dimensions: 5.0 cm x 2.1 mm, 2.7 µm packing) coupled to an Agilent 6520 Accurate Mass Measurement Q-ToF (ESI Source) with a 5-100% water/acetonitrile (0.1% formic

acid) gradient at a flow rate of 1.0 mL/min. 1-benzyl 2-(tert-butyl) (R)-4-oxopyrrolidine-1,2-dicarboxylate (compound **1**) was used as the starting material and was purchased from WuXi Apptec.

Flow System Equipment

For all flow reactions, a Vapourtec RS-200 flow system was used. Two BPR assemblies were used to achieve 17 bar of pressure. For small scale experiments, a single Vapourtec PFA tubing reactor (10 mL) was used. For large scale experiments, four reactors were used (40 mL total). The reactor module was used to control the temperature of the reactors. Additional information regarding the small and large-scale flow setup can be found in the supplemental information (S1 and S2).

Flow Reactions

The Bucherer–Bergs transformation of compound **1** was carried out in a two-stream continuous-flow setup. Fresh stock solutions were prepared on the day of use: an organic stream containing compound **1** in the selected solvent and an aqueous stream containing KCN and $(\text{NH}_4)_2\text{CO}_3$ in deionized water. Prior to each reaction the lines were primed with the corresponding solvents as the reactor was brought to operating temperature and pressure, and then the feed was switched to reagents at equal volumetric flow unless otherwise noted. Flow rates were set to achieve the desired RT. Precise RTs, temperature, and organic solvents used during optimization and scale-up are summarized in table 1. At the end of each run, feeds were returned to solvent to displace the reactor contents, and the system was flushed according to the cleaning procedure described in the supplemental information. Samples were analyzed by LCMS to assess conversion, and yield were determined by UV quantitation performed at 220 nm, which corresponds to the strong absorbance band of the benzyloxycarbonyl (Cbz) present on all compounds. Peak identities were verified by retention time and mass spectra from the LCMS trace.

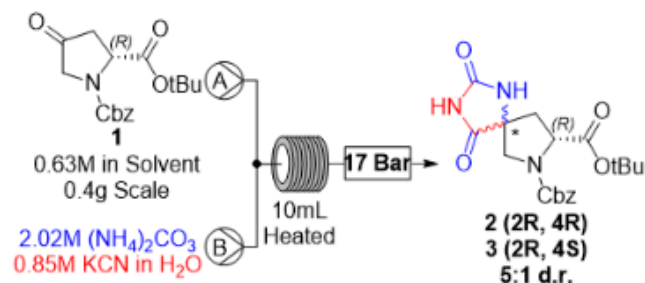
Cyanide Safety

All cyanide solutions were prepared and handled in a single fume hood with appropriate PPE and dedicated cyanide-waste containers; quenching and disposal followed institutional protocols. Airborne HCN was monitored with a BW Solo single-gas HCN detector throughout setup, operation, and workup.

RESULTS & DISCUSSION

Small Scale Optimization

To evaluate the Bucherer–Bergs reaction under small-scale flow conditions, an RS-200 Vapourtec system was used and equipped with a 10 mL PFA tube reactor that was heated, and back pressure regulators to achieve 17 bar of system pressure (Table 1). Solution pump speeds were adjusted to achieve the appropriate RT for the 10 mL reactor. Beginning with the reaction conditions reported by Kappe and Correa, we systematically optimized the reaction by injecting 2 mL of each reagent and conducting experiments under the conditions outlined in Table 1.

Table 1 Small Scale Bucherer-Bergs Reaction Optimization

Entry ^a	RT (min)	T (°C)	Solvent ^b	Yield ^c
1	30	120	EtOH	41.5%
2	20	120	EtOH	61.9%
3	15	120	EtOH	72.9%
4	10	120	EtOH	76.8%
5	10	100	EtOH	94.0%
6	10	90	EtOH	94.0%
7	10	90	MeOH	89.8%
8	10	90	IPA	92.6%
9	10	90	EtOAc	15.1%
10	10	95	EtOH	95.6%

^a 2 mL of each reagent solution simultaneously injected for each reaction. ^b Organic solvent in 1:1 Organic:Aqueous solution. ^c Combined yield of compounds 2 & 3 determined by LCMS analysis

The initial conditions were obtained through a combination of our labs previously optimized batch Bucherer-Bergs reaction, and the Kappe and Correa labs previously published Bucherer-Bergs flow conditions.[1, 5] From a desire to obtain a greater scale, the solvent system was selected as a one-to-one aqueous and organic solution. The initial organic solvent and reaction equivalents were from our labs previously published synthesis, and the concentration of each solution was based on this.[1] For these solutions, the ammonium carbonate and potassium cyanide reagents are from the aqueous solution, and compound **1** is dissolved in the organic solution. The initial temperature and RT were from the Kappe and Correa labs (Table 1 entry 1).[5] Finally to evaluate the necessary back pressure for the system, 1 mL of each solution was simultaneously moved through the system under the initial 120°C temperature conditions. Using a Vapourtec variable back pressure regulator, the system pressure was increased until no bubbles were observed in the system. For our reaction this was at 16.3 bar and is a result of reagents that degrade into gaseous components. To ensure that adequate pressure is maintained, a system pressure of 17 bar was selected for the reaction.

These initial conditions resulted in complete conversion of the ketone to hydantoin. However, due to compound **1** containing a tert-butyl ester, nearly half of the product degraded into the deprotected carboxylic acid, resulting in a 41.5% yield of compounds **2** & **3** (Table 1 entry 1). We began optimizing the reaction by reducing the RT, which led to an increase in the yield of product until it reached a yield of 76.8% with a 10-minute RT (Table 1 entries 1-4). This was expected, as previously published methodology likely required a longer reaction time from the use of a biphasic solvent system, which needs consistent, intensive mixing to reduce reaction time.[6] From here the effect of reaction temperature was evaluated, and we found that higher yields were achieved with lower temperatures, with 95°C showing the highest yield of 95.6% (Table 1 entries 4-6, 10).

Another observation was that at 90°C, periodic pressure fluctuations were detected, where the system's pressure would rise by 1.0-2.0 bar for a few seconds prior to stabilizing. We attributed this to precipitation of the aqueous reagents upon initial mixing with the ethanol solution. This was confirmed by repeating the reaction conditions, without reagents dissolved in the organic solution. As similar pressure fluctuations were still observed, the source was determined to be from the aqueous reagents.

The effects of various solvents were similarly explored, focusing on polar, protic solvents (Table 1 entries 6-9). Use of methanol and isopropyl alcohol resulted in the solution becoming a slurry containing white precipitate when exiting the heated reactor, which could result in system clogging when run at a higher scale. In contrast, ethanol, consistent with batch conditions, was determined to be the ideal organic cosolvent with a yield of 94.0%. The reaction carried out with ethyl acetate demonstrated the effect of a biphasic solvent system at reduced RT and temperature, which resulted in a poor yield of 15.1%.

These conditions were then applied to a continuous flow run, where 45mL of each reaction solution was continuously pumped through the system, corresponding to nine reactor volumes. Each reactor volume was collected separately and analyzed via LCMS to ensure consistent reactivity and found that the average yield was 96.6%, with a standard deviation of 0.3% (Figure 3, Table S2). The increased yield compared to individual optimization experiments is attributed to the reaction reaching its steady-state condition during continuous operation.[6]

Pilot Scale-Up

To achieve a greater scale of production, the flow system was increased to contain four, 10 mL PFA tube reactors (Figure 4). Additionally, it was found that when running the reaction at this scale, precipitation would form in the first reactor that would clog the system. This was fixed through the use of a Vapourtec heated mixing tube reactor, which preheats 0.4 mL of each reagent line, prior to combining in a 10 mL reactor (Figure 4). With the use of this reactor, no spikes in pressure were detected and no visual precipitation in the lines was observed.

To ensure that the increase in scale did not affect reactivity, a flow reaction was repeated with 8 mL of each reagent solution using optimized conditions and was found to have a yield of 96.3%. As this was consistent with small scale results, a large-scale continuous flow reaction was then performed. In this,

950 mL of each solution was consumed in the reaction over the course of 7.9 hours. During this longer reaction, product collection was segmented into 50 mL aliquots to ensure consistent results and resulted in a yield of 97.1% with a standard deviation of 0.2% from LCMS analysis (Table S3). Following ethyl acetate extraction and concentration, 217.1 g of product were isolated over 7.9 hours, resulting in a yield of 93.6%.^[1]

One observation during this run was that the aqueous reagent solution slowly turned yellow over time. To prevent this, we found that placing the aqueous solution in an amber colored bottle and purging the bottle with nitrogen prevented this discoloring for 5 days (Figure S3).

A 24-hour reaction was performed, where 2.9 L of each solution was consumed over 24 hours. Product collection was divided into 8 hour, or 1.9 L, aliquots to ensure consistent reactivity. In this we found consistent reactivity across the 24 hours via LCMS analysis, with a yield of 96.9% with a standard deviation of 0.3% (Table S4). Following extraction and concentration 679 g of hydantoin product was isolated, resulting in a 96.2% yield and demonstrating a production rate of 28.0 g/hr (Figure 4).

CONCLUSIONS & OUTLOOK

We have demonstrated an improved methodology for performing the Bucherer-Bergs reaction, by taking advantage of flow chemistry. The reaction has been optimized to provide high yields of hydantoin using milder conditions that are more compatible with temperature labile groups and safer operation for the chemist. These conditions have further been demonstrated on a pilot scale, enabling higher throughput compared to previous flow and batch chemistry methodologies. These advancements enhance both the practicality and scalability of the reaction, making it more accessible for laboratory-scale synthesis and industrial applications.

STATEMENT AND DECLARATIONS

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SUPPORTING INFORMATION

Supplemental material contains characterization of compounds **1-4** including NMRs and LCMS UV chromatograms.

The authors declare the following competing financial interest: Dr. Christian Schafmeister is Chief Technology Officer and Co-founder of LadderBio Inc, a company that is commercializing Spiroligomer™ technology.

AUTHOR INFORMATION

Corresponding author

meister@temple.edu

Additional information regarding the authors

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ORCID

Matthew T. Graves, 0000-0001-8176-427X

Kyle N. Brunner, 0009-0007-2417-539X

Christian E. Schafmeister, 0000-0002-8686-7363

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References

1. Cheong JE, Pfeiffer CT, Northrup JD, Parker MFL, Schafmeister CE (2016) An improved, scalable synthesis of bis-amino acids. *Tetrahedron Letters* 57:4882–4884. <https://doi.org/10.1016/j.tetlet.2016.09.032>
2. Edward JT, Jitrangsri C (1975) Stereochemistry of the Bucherer–Bergs and Strecker Reactions of 4-*tert*-Butylcyclohexanone. *Can J Chem* 53:3339–3350. <https://doi.org/10.1139/v75-477>
3. Kalník M, Gabko P, Bella M, Koóš M (2021) The Bucherer–Bergs Multicomponent Synthesis of Hydantoins—Excellence in Simplicity. *Molecules* 26:4024. <https://doi.org/10.3390/molecules26134024>
4. Xie Y, Luo D, Wiener J, Tang S, Chepyshev S, Schafmeister C (2022) Development of Fmoc-Protected Bis-Amino Acids toward Automated Synthesis of Highly Functionalized Spiroligomers. *Org Lett* 24:3421–3425. <https://doi.org/10.1021/acs.orglett.2c01295>
5. Monteiro J, Pieber B, Corrêa A, Kappe C (2015) Continuous Synthesis of Hydantoins: Intensifying the Bucherer–Bergs Reaction. *Synlett* 27:83–87. <https://doi.org/10.1055/s-0035-1560317>

6. Plutschack MB, Pieber B, Gilmore K, Seeberger PH (2017) The Hitchhiker's Guide to Flow Chemistry. *Chem Rev* 117:11796–11893. <https://doi.org/10.1021/acs.chemrev.7b00183>
7. Cole KP, Ryan SJ, Groh JM, Miller RD (2017) Reagent-free continuous thermal tert-butyl ester deprotection. *Bioorganic & Medicinal Chemistry* 25:6209–6217. <https://doi.org/10.1016/j.bmc.2017.03.020>
8. Höck S, Marti R, Riedl R, Simeunovic M (2010) Thermal Cleavage of the Fmoc Protection Group: FH – HES. *Chimia* 64:200. <https://doi.org/10.2533/chimia.2010.200>

Figures

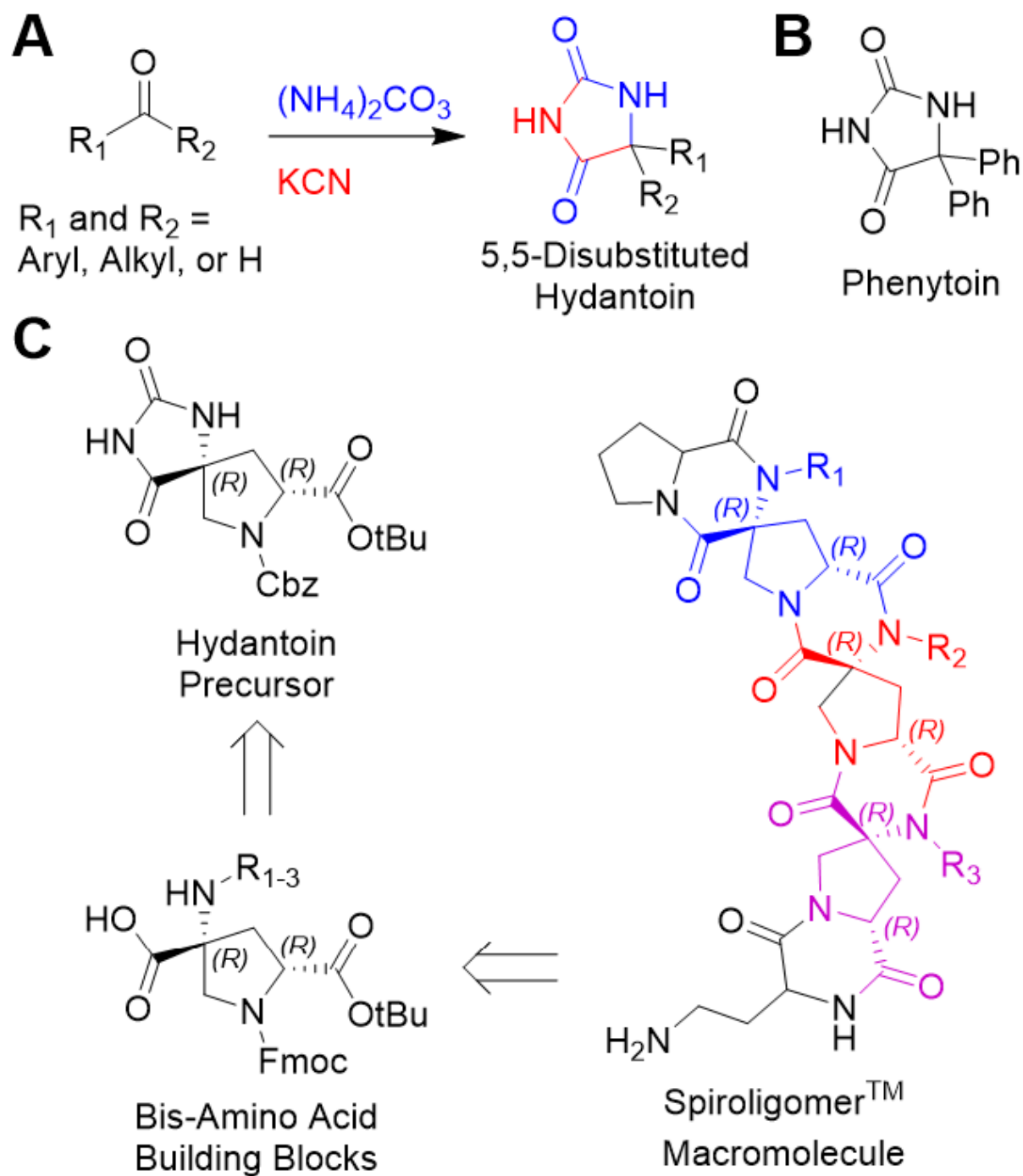


Figure 1

(a) General Bucherer-Bergs reaction for the synthesis of hydantoins.[2] (b) Medicinal hydantoin example. [3] (c) Example of unnatural amino acids that are synthesized from hydantoin precursors, and their synthetic application[4]

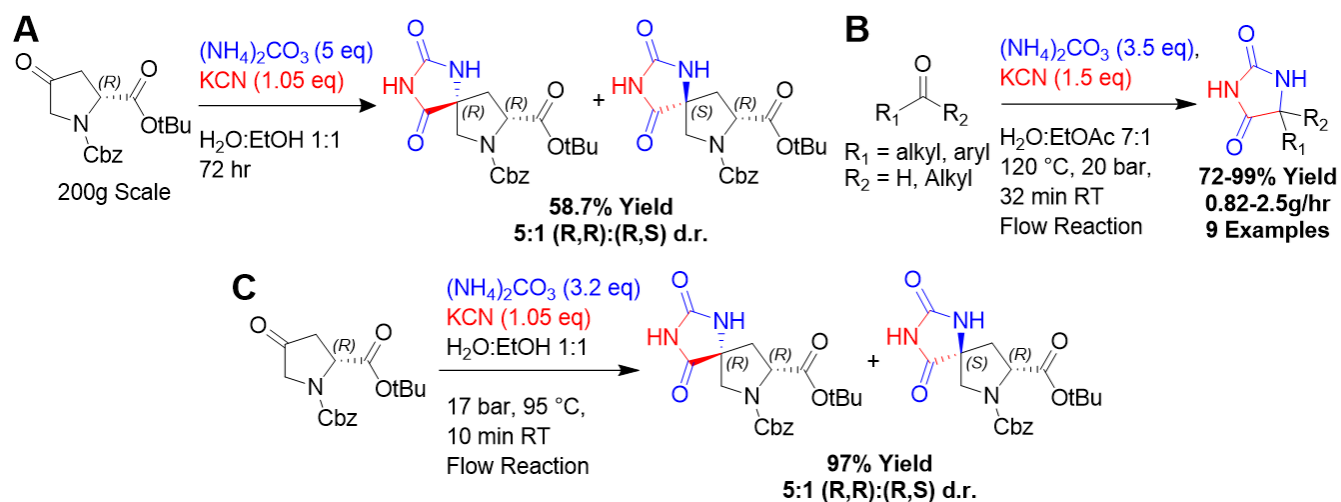


Figure 2

(a) Previously published example of a batch Bucherer-Bergs reaction.[1] (b) Previously published Bucherer-Bergs flow methodology.[5] (c) This work

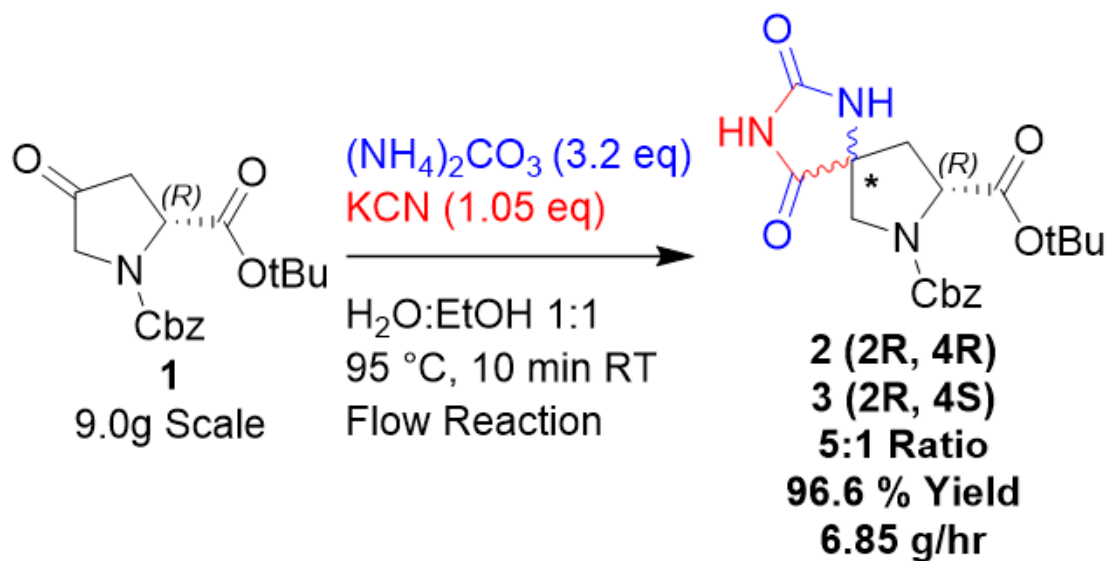


Figure 3

The optimized small scale continuous flow Bucherer-Bergs reaction

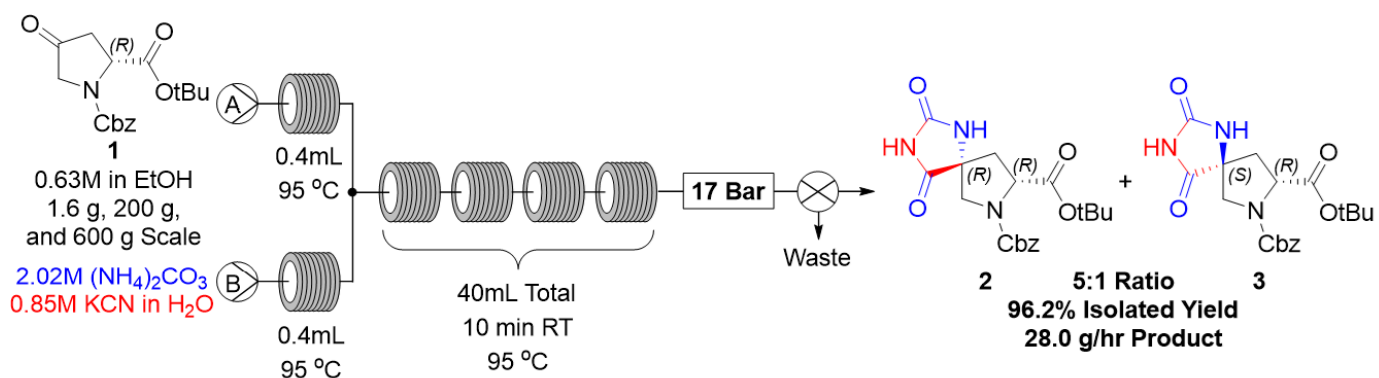


Figure 4

The Large-scale flow system schematic

Supplementary Files

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