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1,2,3-Triazole Synthesis: Development of Safe and Effective Batch and Continuous Manufacturing Processes

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ABSTRACT: In this paper, we present the development of a safe water-based synthesis of 1,2,3-triazole using cheap raw materials. Starting from glyoxal and hydrazine, a safe and efficient three-step end-to-end continuous process was developed. This protocol transforms heterogeneous batch reactions into a homogeneous streamlined continuous flow system. This advancement not only obviated the separation of hazardous intermediates, thereby mitigating potential risks, but also significantly diminished the reaction time of each step. This has ensured a rapid and stable supply of 1,2,3-triazole for downstream product development such as tazobactam. Additionally, the study delves into the insights gained from transitioning from batch reactions to continuous flow processes, highlighting the practical and safety benefits of continuous flow synthesis.

KEYWORDS: *1,2,3-triazole synthesis, water solvent, batch process, end-to-end continuous flow synthesis*

1. INTRODUCTION

1,2,3-Triazoles serve as versatile synthons in organic synthesis and hold significant importance as raw materials in the synthesis of many drugs and activated biological molecules.[1] One notable example is tazobactam (Scheme 1), a component of Tazocin (tazobactam piperacillin), functioning as a β-lactamase inhibitor, which prolongs the serum half-life of the broad spectrum β-lactam antibiotic piperacillin by slowing its enzymatic hydrolysis.[2] As a key subunit of tazobactam, 1,2,3-triazole is essential in the manufacturing of this active pharmaceutical ingredient (API).

In 2017, a worldwide shortage of Tazocin arose due to a disruption (colloquially described as an explosion, with limited details and supporting references) in a Chinese factory responsible for manufacturing one of the key intermediates. The shortage had widespread consequences and garnered enough concern to draw the attention of the World Health Organization (WHO), as Tazocin plays a vital role in treating infections, especially those caused by bacteria resistant to standard antibiotics. Moreover, this event underscores the vulnerability of the pharmaceutical supply chain, emphasizing the imperative for additional research to establish safe and reliable manufacturing protocols, thereby preventing such disruptions in the future.

In response to the shortage and the imperative for a stable supply chain, efforts have been directed toward developing a second-generation synthetic route to tazobactam.[3] A key aspect of this initiative is to establish a secure and commercially viable method for synthesizing 1,2,3-triazole at scale, ensuring a consistent and uninterrupted supply of this raw material for the synthesis of life-saving drugs.

While 1,2,3-triazole itself exhibits remarkable stability, its synthetic routes tend to involve energetic intermediates. The main routes used to prepare 1,2,3-triazole can be divided into three main types (Scheme 1): (1) click cycloadditions of azides and alkynes (path a);[4−6] (2) oxidative cleavage of benzotriazole (path b);[7] and (3) oxidative cyclization of glyoxal dioxime, dihydrazone, or oxime hydrazone derivatives, such as dichloroacetaldehyde hydrazones (paths c and d).[8,9]

Among the various routes to 1,2,3-triazole, the one deemed most suitable for further development into an industrially viable route was the one that started from glyoxal via the dihydrazone.[9] Taiho, the inventor's company, successfully demonstrated a fully telescoped process in water (Scheme 2), enhancing its appeal as an industrial prospect. The high specific heat of water, allowing the solvent to absorb any generated heat energy, serves as a critical safety feature in this process. If this process could be demonstrated to be operated safely, it would represent a very attractive industrial route to 1,2,3-triazole.

To bolster the safety of the manufacturing process, the strategic implementation of continuous flow processes has emerged as a noteworthy consideration. Flow chemistry,[10−16] with its inherent benefits of enhanced safety, safe handling of reactive intermediates, precise control over reaction parameters, and increased efficiency, holds immense promise for the industrial-scale synthesis of 1,2,3-triazole. By adoption of a continuous flow approach, potential hazards associated with

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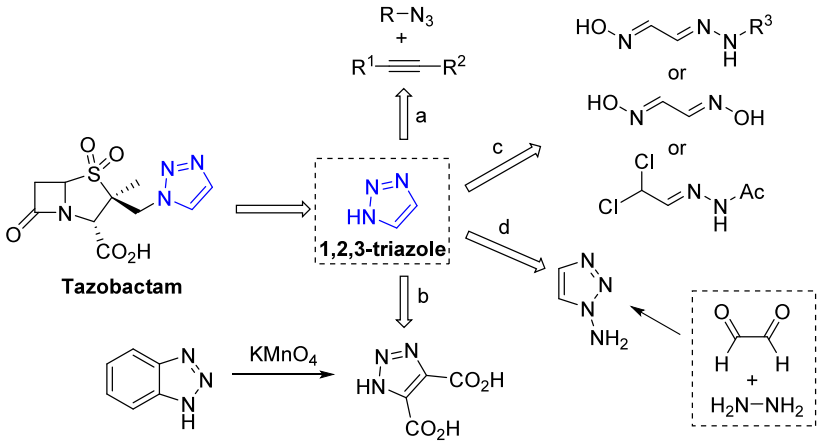
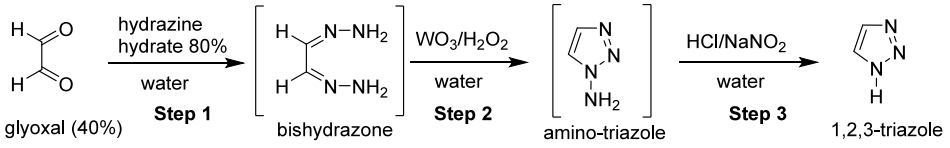
Scheme 1. Tazobactam Structure and Retrosynthetic Analysis of 1,2,3-Triazole



Scheme 2. Taiho Process for 1,2,3-Triazole Synthesis



batch processing can be mitigated, ensuring a more controlled and secure manufacturing environment. This innovative application aligns seamlessly with the ongoing efforts to develop a safe and efficient synthesis route of 1,2,3-triazole that not only enhances safety protocols but also contributes to the overall efficiency and sustainability of the industrial production process.

2. RESULTS AND DISCUSSION

2.1. Modifications to the Batch Process. The original Taiho process underwent significant modifications to achieve satisfactory efficiency and safety in industrial operations. These modifications included (1) adjustment of the molar ratio of hydrazine to glyoxal from 0.8:1 to 2.2:1 to maximize the yield of the bishydrazone; (2) conducting the reaction in a more concentrated manner; (3) performing step 1 at a lower temperature; and (4) utilization of continuous extraction of the final isolation of 1,2,3-triazole from water. These refinements resulted in a comparable overall yield to the original patent process, yielding 1,2,3-triazole in 59% yield on a scale of 250 g of 40% glyoxal solution.

Process Safety Testing. The main basis of safety for this process was underpinned by the exclusive use of water as a solvent throughout all steps, leveraging its high specific heat. Nevertheless, comprehensive safety testing was conducted on the batch process due to the presence of high-energy functional groups in certain intermediates, such as the Step 2 intermediate, 1-amino-1,2,3-triazole, which features four contiguous nitrogen atoms. Additionally, the purification of the final product, 1,2,3-triazole, through vacuum distillation required the application of high temperatures.

This three-step telescoped 1,2,3-triazole synthesis (Scheme 2) involves two nonisolated intermediates (glyoxal bishydrazone and 1-amino-1,2,3-triazole). The formation of 1-amino-1,2,3-triazole (step 2) was found to be highly exothermic (−525 kJ) with an adiabatic temperature rise (ΔT_{ad}) of 211 °C during the addition of 50% hydrogen peroxide (data obtained from reaction calorimeter (RC) study; see Table 1). The maximum temperature for synthetic reaction (MTSR) of 246 °C in this 1-amino-1,2,3-triazole reaction mass shows a low onset of decomposition, which is confirmed by the thermal screening unit (TSU) (see details in the Supporting Information (SI)). Based on these results, the formation of 1-amino-1,2,3-triazole falls into the E category by the Stossel classification, posing a potential risk of runaway reaction if cooling fails (see details in the SI). Additionally, the addition of 37% HCl to the 1-amino-1,2,3-triazole reaction mixture in step 3 was found to be exothermic (−9.79 kJ) with ΔT_{ad} = 6 °C, and the subsequent addition of an aqueous solution of sodium nitrite ($NaNO_2$) and the formation of 1,2,3-triazole were also exothermic (−73.14 kJ) with ΔT_{ad} = 40 °C (Table 1).

Table 1. Thermal Data on Oxidative Cyclization (Step 2) and Deamination (Step 3)

operation	heat of reaction (kJ)	heat of reaction (kJ/mol)	adiabatic temperature rise (°C)
50% H_2O_2 addition	−525	−610	+211
HCl addition	−9.79	−23	+6
$NaNO_2$ addition	−73.14	−170	+40

The thermal stability of the crude 1,2,3-triazole was also screened in a differential scanning calorimeter (DSC), revealing an onset of decomposition exotherm at 242 to 388 °C with energy of −1776 J/g ($\Delta T_{ad} \approx$ 888 °C) (see details in the SI).[17] Thus, based on a modified Yoshida correlation,[18] 1,2,3-triazole was suspected to be potentially shock-sensitive, raising concerns about a potential explosion risk that merited further investigation. In addition to the DSC testing, we studied the thermal stability of 1,2,3-triazole under adiabatic conditions using an accelerating rate calorimeter (ARC) instrument, which showed an exotherm at 225 °C with a self-heating rate of >56.39 °C/min accompanied by a significant pressure rise event (see details in the SI).

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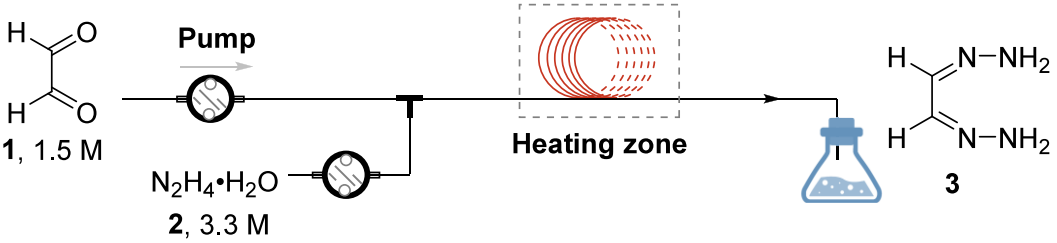
Table 2. General Flow Setup and Optimization Studies for Glyoxal Bishydrazone 3[a]



entry	reactor type	T (°C)	t_R (min)	total flow rate (μL/min)	NMR yield (%)[b]
1[c]	1/16″, (1.8 mL)	100	36	50	60
2[c]	1/16″, (1.8 mL)	90	36	50	74
3[c]	1/8″, (2.0 mL)	80	20	100	83
4[c]	1/8″, (2.0 mL)	70	20	100	93
5[c]	1/8″, (2.0 mL)	60	20	100	92
6	1/8″, (2.0 mL)	50	20	100	93
7	1/8″, (2.0 mL)	40	20	100	84
8	1/8″, (2.0 mL)	50	40	50	94
9	1/8″, (2.0 mL)	50	14.2	140	82
10	1/8″, (2.0 mL)	50	10	200	87
11	1/4″, (30 mL)	50	20	1500	clogged
12[d]	**1/4″, (30 mL)**	**50**	**20**	**1500**	**94**

[a]The total flow rate is the combined sum of the flow rates of the two raw material flow rates, which were identical. [b]^{1}H NMR yields based on analysis of the crude ^{1}H NMR spectra using CH_2Br_2 as an internal standard. [c]Partial clogging was observed. [d]The two raw materials were premixed in a bottle, resulting in a glyoxal concentration of 1.1 M. As the concentration increased, the residence time needed to be extended to 20 min.

These interim results strongly highlight the potential risks associated with this process on an industrial scale. Consequently, they serve as a compelling catalyst for the transition from the current batch process to a continuous one, aiming to minimize the inventory of potentially hazardous intermediates and enhance overall safety.

2.2. Development of a Continuous Flow Process. Upon a detailed analysis of the batch protocol, we identified several advantages associated with the transition to a flow synthesis, which include (a) accelerating the Step 1 reaction through safe heating in the flow reactor, leveraging enhanced heating and mixing efficiency; (b) utilizing a tungsten oxide (WO_3) packed bed reactor to avoid an additional catalyst separation step;[19] (c) minimizing the explosion risk in Step 2 between unreacted hydrazine and H_2O_2; and (d) integrating in-line purification techniques to obtain the crude product in a continuous fashion. Consequently, we aimed to design a telescopic three-step continuous flow system to enable the large-scale safe production of 1,2,3-triazole.

Glyoxal Bishydrazone Generation (Step 1) in Flow. To identify the appropriate conditions for this step in the continuous flow system, we initiated an optimization of parameters using the flow system comprising Asia syringe pumps and perfluoroalkoxy (PFA) tubular reactors, and the reaction yield was monitored by ^{1}H NMR spectroscopy. As depicted in the flow scheme (Table 2), an aqueous solution of glyoxal (1.5 M) was mixed with an aqueous solution of hydrazone (3.3 M, 2.2 equiv), and the mixure was flowed through the heating zone for the condensation reaction. An excess of hydrazone was used to ensure full conversion, as confirmed previously in the batch reaction. In this step, temperature is of great significance; thus, temperature screening was conducted in the range of 40−100 °C.

For the 1/16 in. tubular reactor (o.d. = 1.6 mm, i.d. = 0.8 mm), relatively low yields and partial clogging (potentially due to the oligomerization of raw materials) were observed at higher temperature (Table 2, entries 1 and 2). A higher yield was achieved by enlarging the tubular reactor to 1/8 in. PFA tubing (o.d. = 3.2 mm, i.d. = 1.6 mm) and lowering the reaction temperature, effectively mitigating clogging issues (entries 3−7). Furthermore, the residence time (t_R) could be shortened to 14.2 min with good yield (entries 8−10). It should be noted that the glyoxal bishydrazone **3** was also obtained in 94% yield when the two raw materials were premixed in a bottle (entry 9). Additionally, this premixing procedure effectively prevented the clogging problem caused by the large number of solids produced when the two raw materials were mixed within an expanded reactor using 1/4 in. PFA tubing (o.d. = 6.4 mm, i.d. = 4.8 mm) (entry 11). Finally, the optimal conditions for this step were identified as performing the condensation at 50 °C for t_R = 20 min with the two materials premixed in a bottle (entry 12).

1-Amino-1,2,3-triazole Generation via Oxidative Cyclization (Step 2) in Flow. In the batch reaction, the formation of 1-amino-1,2,3-triazole was conducted by combining compound **3** with H_2O_2, catalyzed by WO_3 at room temperature. In an effort to seamlessly transition to the flow system, we initially attempted the oxidation reaction using a WO_3 packed bed reactor. However, this approach resulted in only approximately 50% yield, even after screening various parameters, including temperature, flow rate, reaction time, and equivalents of H_2O_2. Moreover, this approach exhibited poor reproducibility, likely due to issues such as uneven mixing and use of excess catalysts in the WO_3 packed bed reactor, significantly limiting its suitability for large-scale production (see the SI for details).

To address these challenges, subsequent analysis and experimentation led to the discovery of an inexpensive catalyst, sodium tungstate dihydrate ($Na_2WO_4{\cdot}2H_2O$), which exhibits similar catalytic character and serves as an effective substitute for WO_3, yielding comparable results in the batch reaction.[20] Additionally, $Na_2WO_4{\cdot}2H_2O$ exhibits good water solubility, enabling the oxidation cyclization reaction in a homogeneous

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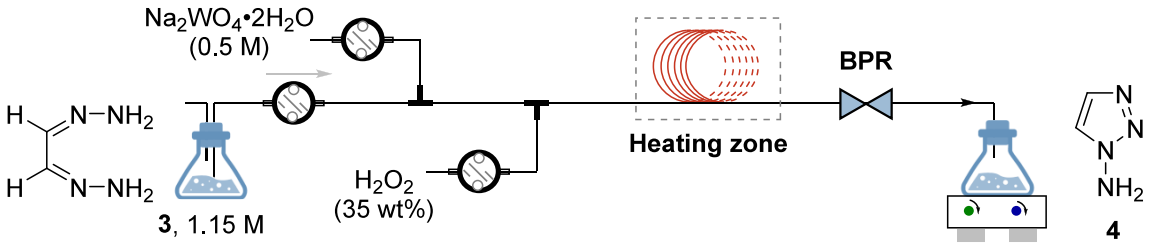
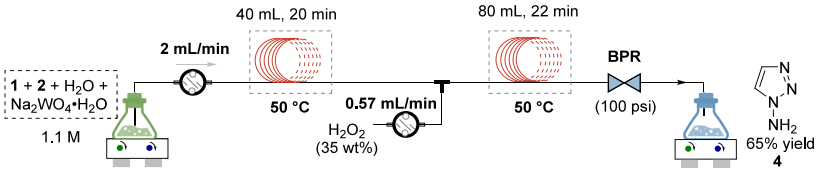
Table 3. General Flow Setup and Optimization Studies for 1-Amino-1,2,3-triazole 3[a]



					flow rates (μL/min)			
entry	equiv of H_2O_2	T (°C)	loading of $Na_2WO_4{\cdot}2H_2O$ (mol %)	t_R (min)	**3**	$Na_2WO_4{\cdot}2H_2O$	H_2O_2	NMR yield (%)[b]
1	2	rt	5	11	250	28.6	49.4	55 (10)
2	2.5	rt	5	10.5	250	28.6	61.7	69 (ND)
3	3	rt	5	10.5	250	28.6	74	74 (ND)
4	3	rt	5	13	200	23	59.2	75 (ND)
5	3	rt	5	18	150	17.3	44.4	74 (ND)
6	3	rt	3	11	250	17.2	74	65 (10)
7	3	rt	1	11	250	5.7	74	46 (52)
8	3	50	1	11	250	5.7	74	53 (34)
9	3	60	1	11	250	5.7	74	60 (17)
10[c]	**3**	**50**	**1**	**22**	**250**	**5.7**	**74**	**70 (ND)**
11[c]	3	50	1	22	250	0	74	8 (82)

[a]Conditions: **3** (1.15 M), H_2O_2 (35 wt %), $Na_2WO_4{\cdot}2H_2O$ (0.5 M), 1/8 in. PFA tubing (6 mL), 40 psi BPR, and an Asia syringe pump were used to screen reaction conditions. [b]^{1}H NMR yields based on analysis of the crude ^{1}H NMR spectra using CH_2Br_2 as an internal standard. Recovered yields of raw materials are shown in parentheses. ND = not detected. [c]1/8 in. PFA tubing (12 mL) was used.

Scheme 3. End-to-End Two-Step Flow Synthesis of 1-Amino-1,2,3-triazole (4)[a]



[a]Step 1: **1** (500 mmol, 1 equiv), **2** (1100 mmol, 2.2 equiv), $Na_2WO_4{\cdot}2H_2O$ (5 mmol, 1 mol %), and addition of water to the bottle until the volume reached 450 mL. 1/4 in. PFA tubing (40 mL) and an Asia syringe pump were used, and the flow rate was 2 mL/min. Step 2: The flow rate of H_2O_2 (35 wt %, 3 equiv) was 0.57 mL/min. 1/4 in. PFA tubing (80 mL), 100 psi BPR, and an Asia syringe pump were used. The reaction yield was monitored by ^{1}H NMR using CH_2Br_2 as an internal standard. To prevent backflow, a check valve was installed at the termination of Step 1 along with an additional check valve at Step 2 specifically for H_2O_2 prior to the mixing process.

phase. We then conducted the transformation in flow using syringe pumps and 1/8 in. PFA tubing.

As depicted in Table 3, the aqueous solution of **3**, directly generated from Step 1 and used without purification, was sequentially combined with aqueous $Na_2WO_4{\cdot}2H_2O$, followed by H_2O_2. A 40 psi back-pressure regulator (BPR) was employed to stabilize the pressure. Initial experiments showed that the reaction was incomplete when using 2 equiv of H_2O_2, with some compound **3** remaining and product **4** obtained in 55% yield (entry 1). To achieve full conversion of raw material **3**, the stoichiometry of H_2O_2 was investigated by increasing the number of equivalents from 2 to 2.5 and further to 3. An increase in the amount of H_2O_2 resulted in increased yields of 1-amino-1,2,3-triazole **4** (entries 1−3). Lengthening the t_R value did not significantly affect the reaction yield (entries 4 and 5). Considering that $Na_2WO_4{\cdot}2H_2O$ transformed into an insoluble white solid under acidic conditions in Step 3 when conducted in batch (although it has no impact on the reactivity of Step 3), reducing the catalyst amount became a crucial consideration for sustained operation in the continuous flow system. Lowering the amount of catalyst to 1 mol % demonstrated good catalytic capability while maintaining an excellent mass balance (entry 7 vs 3). While higher temperatures enhanced the conversion, it simultaneously led to a reduction in the mass balance (entries 7−9). Ultimately, a relatively high yield was achieved by extending the t_R to 22 min in the presence of 1 mol % catalyst at 50 °C (entry 10). Under these optimal conditions, a control experiment was performed in the absence of $Na_2WO_4{\cdot}2H_2O$ in the flow, revealing the crucial role of the catalyst in the reaction (entry 11).

We further endeavored to convert the stepwise flow synthesis (Steps 1 and 2) into an integrated end-to-end continuous flow. We discovered that the incorporation of the $Na_2WO_4{\cdot}2H_2O$ catalyst directly in Step 1 not only eliminated the need for an additional pump but also improved the efficiency of Step 1 by inhibiting the oligomerization of raw materials—a solid byproduct formed when the two substrates interacted within the 1/4 in. PFA tubing, causing clogging issues in the system. Furthermore, the outcomes obtained from this streamlined two-step flow synthesis in 1/4 in. PFA tubing demonstrate a high degree of consistency with those achieved in the stepwise continuous flow synthesis conducted in 1/8 in. PFA tubing, with an overall yield of 65% (Scheme 3). These

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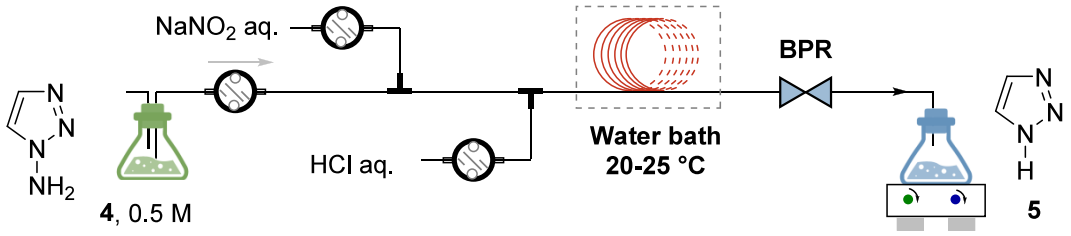
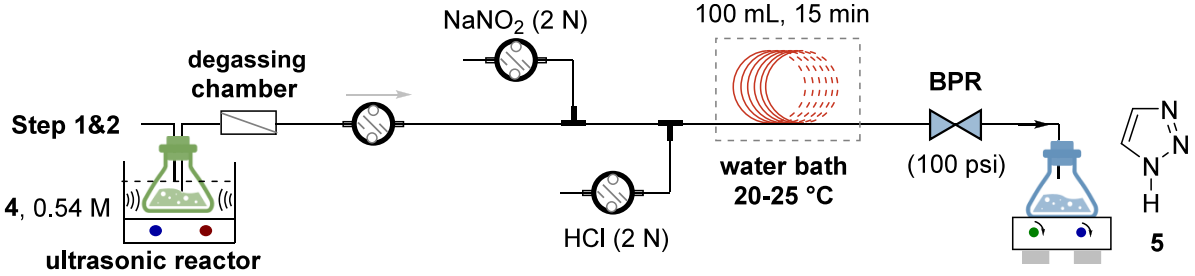
Table 4. General Flow Setup and Optimization Studies for 1,2,3-Triazole (5)[a]



				flow rates (μL/min)			
entry	equiv of $NaNO_2$	equiv of HCl	t_R (min)	4	$NaNO_2$	HCl	NMR yield (%)[b]
1	2	1	9	100	100 (1 N)	25 (2 N)	50 (41)
2	2	1	12	75	75 (1 N)	18.8 (2 N)	50 (34)
3	2	1	18	50	50 (1 N)	12.5 (2 N)	54 (40)
4	2	1.5	18	50	50 (1 N)	18.8 (2 N)	69 (19)
5	2	2	18	50	50 (1 N)	25 (2 N)	90 (ND)
6	2	3	15	50	50 (1 N)	37.5 (2 N)	91 (ND)
7	**2**	**2**	**20**	**50**	**25 (2 N)**	**25 (2 N)**	**90 (ND)**

[a]Conditions: 4 (0.5 M), $NaNO_2$ (2 equiv, 1 or 2 N), HCl (2 N), 1/8 in. PFA tubing (2.4 mL), 40 psi BPR, and an Asia syringe pump were used to screen reaction conditions. [b]^{1}H NMR yields based on analysis of the crude ^{1}H NMR spectra using CH_2Br_2 as an internal standard. The recovered yields of raw materials are shown in parentheses.

Table 5. Optimization Studies for the Deamination Step in the Telescopic Three-Step Flow Synthesis[a]



				flow rates (mL/min)			
entry	equiv of $NaNO_2$	equiv of HCl	t_R (min)	4	$NaNO_2$ (2 N)	HCl (2 N)	NMR yield (%)[b]
1	2.9	2.9	15	2.57	2.0	2.0	56
2[c]	2.9	2.9	15	2.57	2.0	2.0	45
3	3.2	2.9	15	2.57	2.25	2.0	70
4	**3.6**	**2.9**	**14**	**2.57**	**2.5**	**2.0**	**83**
5	4.0	2.9	14	2.57	2.75	2.0	83
6	3.6	2.9	14	2.57	2.5	2.25	76
7	3.6	2.9	14	2.57	2.5	2.5	76

[a]4 (0.54 M), $NaNO_2$ (2 N), HCl (2 N), 1/4 in. PFA tubing (100 mL), 100 psi BPR, and an Asia syringe pump were used to screen reaction conditions. In the telescopic three-step flow synthesis, the solution from the second step was sonicated for 1 h before proceeding to the third step. [b]^{1}H NMR yields based on analysis of the crude ^{1}H NMR spectra using CH_2Br_2 as an internal standard. [c]Without a degassing chamber.

results illustrate the feasibility of scaling up this end-to-end telescope synthesis method.

Deamination to Synthesize 1,2,3-Triazole (Step 3) in Flow. In the established batch conditions, the addition of concentrated HCl into the reaction mixture would generate a significant number of solids. The incompatibility of solids poses a huge challenge in continuous flow systems. After various evaluations, we discovered that altering the addition sequence by adding the aqueous $NaNO_2$ first and reducing the concentration of aqueous HCl effectively mitigated the challenge of solid formation.

We then studied the reaction using 1/8 in. PFA tubing in a continuous flow system with an Asia syringe pump. As captured in the flow scheme (Table 4), the reaction mixture of 4, produced directly from Step 2 and used without purification, was sequentially combined with aqueous $NaNO_2$, followed by aqueous HCl (2 N). which successfully avoided a solid clogging issue in the flow system. The screening of t_R using 2 equiv of aqueous $NaNO_2$ and 1 equiv of aqueous HCl revealed that extended t_R did not significantly enhance the yield and conversion (Table 4, entries 1−3). Subsequent investigation into varying the number of equivalents of HCl demonstrated a substantial improvement in both conversion and yield when 2 equiv of HCl was used (entries 3−6). Noteworthily, the yield of the reaction was not affected by the concentration of aqueous $NaNO_2$ (entry 7).

Subsequently, we sought to consolidate the three steps into a single, continuous process utilizing 1/4 in. PFA tubing for large-scale synthesis. However, a challenge emerged during the implementation of the telescopic three-step flow system: the

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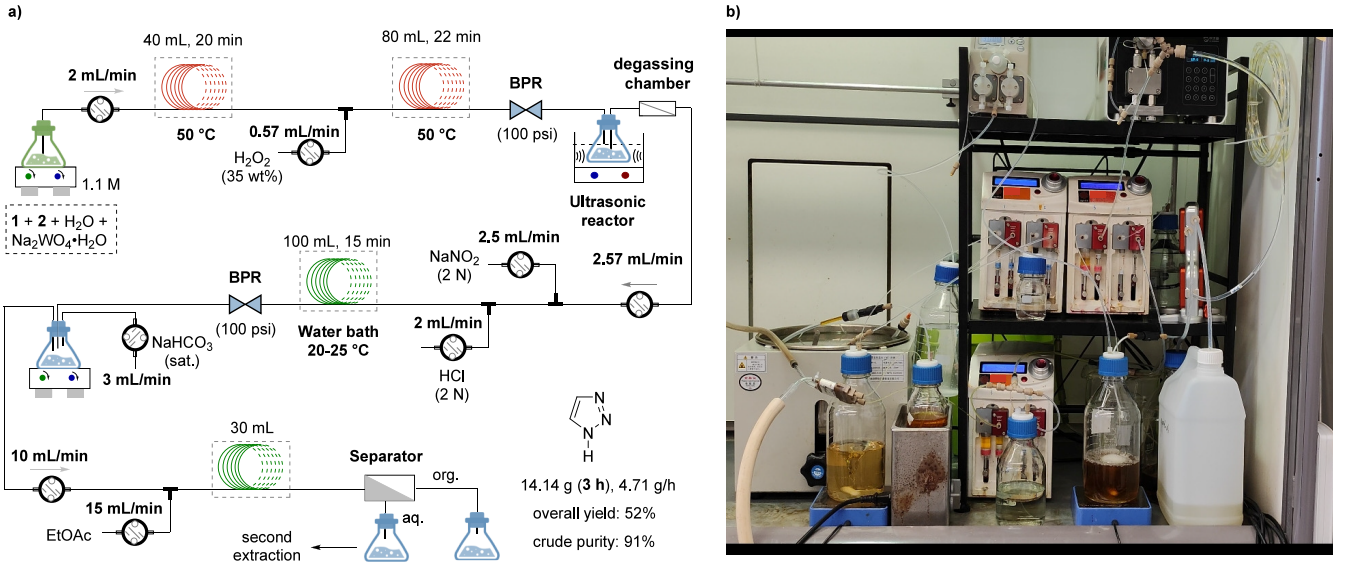
Scheme 4. (a) Flowchart for the Continuous Telescopic Three-Step Flow Synthesis of 1,2,3-Triazole (5); (b) Setup of the Flow Platform for the Synthesis of 1,2,3-Triazole[a]



[a]The function of each piece of equipment is detailed in Figure S14. A degassing chamber (from IDEX) was used to assist in degassing, and a SEP-200 separator (from Zaiput) was used for separation. To prevent backflow, check valves were installed at each stage of liquid mixing, ensuring a one-way flow and enhancing the overall system reliability.

generation of a significant volume of gas in Step 2. This gaseous byproduct, upon entering the Asia syringe pump, adversely affected the flow rate in Step 3, thereby altering the reaction conditions. To mitigate this, degassing the reaction mixture after Step 2 was deemed essential. Additionally, the presence of excess H_2O_2 in Step 2, along with the likelihood that dissolved oxygen gas could be produced, which could directly oxidize $NaNO_2$, necessitated the use of increased numbers of equivalents of both $NaNO_2$ and HCl in Step 3. Initially, we employed an ultrasonic reactor in conjunction with a degassing chamber for the degassing process, resulting in a 56% yield (Table 5, entry 1). Noteworthily, this yield was significantly decreased when using the ultrasonic reactor alone (entry 2). Further screening the number of equivalents of $NaNO_2$ culminated in a substantial enhancement of the reaction yield, reaching 83% (entries 3−5). The yield remained consistent under these conditions, even with variations in the number of equivalents of aqueous HCl (entries 4, 6, and 7).

End-to-End Continuous Flow Synthesis of 1,2,3-Triazole. Based on the preliminary optimizations, we successfully established a continuous end-to-end three-step flow system for the synthesis of 1,2,3-triazole. As illustrated in Scheme 4, the optimized conditions of each step were successfully adapted in this end-to-end flow system. To facilitate the continuous extraction and isolation of 1,2,3-triazole from the reaction mixture, we incorporated an in-line purification module using a commercially available liquid−liquid separator (Zaiput). In the purification process, the pH value was regulated within the range 8−9 by employing a saturated aqueous $NaHCO_3$ solution, thereby optimizing the extraction efficiency in the continuous extraction step. Ultimately, after smoothly operating within this telescopic three-step continuous flow system, we collected 14.14 g of 1,2,3-triazole over a 3 h period, achieving an average output of 4.71 g/h. The crude yield was 52%, and the crude purity was determined to be 91% by ^{1}H NMR analysis. Noteworthily, a secondary extraction of the aqueous solution was required to further enhance the extraction efficiency of the product from the aqueous phase. Furthermore, the hourly output could be tailored by changing the volume of the PFA tubing in each step accordingly.

3. CONCLUSION

In this study, we successfully converted 250 g of 40% glyoxal solution into 1,2,3-triazole in water utilizing a three-step batch process with cost-effective and widely accessible raw materials. Substantial advancement was achieved by developing a telescopic continuous three-step flow system, significantly enhancing the efficiency and safety of the synthetic process. Notably, in the crucial oxidation−cyclization reaction, we replaced the heterogeneous WO_3 catalyst used in the batch process with $Na_2WO_4{\cdot}2H_2O$, which is cheap and water-soluble, smoothly transitioning to a homogeneous reaction in the flow system. Furthermore, a liquid−liquid separator was employed for the continuous extraction of the final product from the crude aqueous reaction mixture. The overall yield of the three-step continuous flow process for 1,2,3-triazole **5** was 52%, providing a safer and more viable manufacturing pathway for the production and further development of downstream products.

4. EXPERIMENTAL SECTION

4.1. General Remarks. All reagents and solvents were purchased from commercial vendors and used without further purification. Reaction progress was monitored by HPLC in area percent. HPLC samples were analyzed using an Agilent 1200 system equipped with a UV-DAD detector. The HPLC column was YMC ODS AQ with dimensions of 25 cm × 4.6 mm and a 5 μm particle size. A Mettler Toledo Reaction Calorimeter with a standard AP01 reactor with pitched-blade stirrer, a 25 W C-22 calibration heater, and Tr probe C-22 along with a Ritter gas meter were used in combination with i-control software. The quick calibration option was used for the calibrations in the AP01. Thermal stability of the reaction

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mixture was performed in a thermal screening unit by HEL with a 10 mL glass test cell fitted with a 1/4 Kovar neck stainless nut and ferrule. Differential scanning calorimetry was performed on a Mettler Toledo DSC using a 40 μL high-pressure gold crucible, rupture disk, and lid over the temperature range of 30−400 °C at a ramp rate of 5 K/min. Adiabatic calorimeter experiment was performed in an accelerating rate calorimeter by Thermal Hazard Technology (THT) with a 10 mL Hastelloy bottom clip test cell.

4.2. Batch Process. *Step 1: Glyoxal to Bishydrazone.* Water (500 mL) was charged into a 3 L four-neck round-bottom flask at 25−30 °C. Hydrazine hydrate 80% solution (238 g, 3.79 mol) was added at 25−30 °C, and the mixture was stirred at 25−30 °C for 15 min. Glyoxal 40% solution in water (250 g, 1.72 mol) was added slowly at 25−45 °C over 10−30 min, which was exothermic from 25 to 45 °C. The reaction mixture was heated to 60−70 °C and stirred for 300−360 min. The reaction was monitored by HPLC for completion. The reaction mixture was used as such for the next step.

Step 2: Bishydrazone to 1-Amino-1,2,3-triazole. The reaction mixture was cooled to 20−30 °C. Tungsten(VI) oxide (4 g, 0.017 mol) was added at 20−30 °C, and the mixture was stirred for 10 min. Hydrogen peroxide 50% solution (235 g, 3.45 mol) was added dropwise at 20−30 °C over 60−120 min. The reaction mixture was stirred at 20−30 °C for 720−900 min (a change in reaction mass color from yellow to orange was observed). The reaction was monitored by HPLC for completion (unreacted bishydrazone limit was not more than 2%). The reaction mass was filtered, and a clear filtrate was collected. Purified water (100 mL) was used to wash the residue, and the combined clear filtrate was used for the next step.

Step 3: 1-Amino-1,2,3-triazole to 1,2,3-Triazole. The clear filtrate was charged into a 5 L four-neck round-bottom flask and cooled to 0−5 °C. HCl (225 g, 2.16 mol) was added into the reaction mixture at 0−10 °C, and exothermicity was observed. The reaction mass was cooled to 0−5 °C. $NaNO_2$ solution (107 g, 1.5518 mol in 200 mL of water) was added slowly at 0−5 °C for 180−240 min; frothing was observed during addition. The reaction mixture was stirred at 0−5 °C for 30 min. The reaction was monitored by HPLC for unreacted 1-amino-1,2,3-triazole (limit not more than 1%). The reaction mixture was slowly warmed to 25 °C in 120 min and stirred for 120−150 min. Solid sodium hydroxide (37−40 g) was added to the reaction mixture to adjust the pH to 7.0 to 8.0. Activated carbon (10 g) was added to the aqueous solution, and the mixture was stirred at 25−30 °C for 30−45 min. The reaction mixture was filtered and washed with purified water (100 mL) at 25−30 °C. The filtrate (∼1800 mL) was charged into the 2 L continuous extractor, and ethyl acetate (1500 mL, 15 vol) was added at 25−30 °C. The receiving flask (containing ethyl acetate) was heated to 100−120 °C. Reflux was continued for continuous extraction at 100−120 °C for 900 to 1080 min. The reaction mixture was cooled to 25−30 °C, and the layers were separated. The aqueous layer was sent to the effluent treatment plant. The organic layer was distilled at 40−45 °C to obtain the crude mass, which was taken into a distillation setup and distilled at 130 °C under vacuum to collect 1,2,3-triazole (70 g, 1.01 mol) as the main fraction.

4.3. Flow Synthesis: Preparation of 1,2,3-Triazole through End-to-End Continuous Flow Synthesis. The flow synthesis is presented in Scheme 4, and detailed equipment setup information is given in Table S6. A 1.1 M reaction solution was prepared by dissolving glyoxal (1 equiv), hydrazine hydrate (2.2 equiv), and $Na_2WO_4{\cdot}2H_2O$ (1 mol %) in water. The solution was then pumped at a flow rate of 2 mL/min into reaction loop 1 at 50 °C for 20 min. Subsequently, the first-step reaction mixture was mixed with H_2O_2 (35%, pump at 0.57 mL/min) in reaction loop 2 at 50 °C for 22 min and passed through a 100 psi BPR. The resulting second-step reaction mixture was transferred into a reservoir bottle, while the ultrasonic reactor was activated. Throughout the ongoing reaction, the mixture in the collection bottle underwent continuous sonication for 1 h. The mixture in the reservoir bottle passed through a degassing chamber at a flow rate of 2.57 mL/min. It was then mixed successively with aqueous $NaNO_2$ (pump at 2.5 mL/min) and aqueous HCl (pump at 2 mL/min). This mixture then traversed a water bath to maintain reaction loop 3 at room temperature for an additional 20 min, again regulated by a 100 psi BPR. Subsequently, it flowed into another reservoir bottle while saturated sodium bicarbonate solution was added (pump at 3 mL/min). Finally, the quenched mixture (pump at 10 mL/min) was mixed with ethyl acetate (pump at 15 mL/min) in reaction loop 4 and then separated by a liquid−liquid separator, and the organic and aqueous phases were collected independently. The aqueous phase underwent a second extraction, and the organic phase was concentrated in vacuo to obtain the crude product. After smoothly operating within this telescopic three-step continuous flow system, we collected 1,2,3-triazole over a 3 h period (start timing based on the third step). The crude yield was 52%, and the crude purity was determined to be 91% by ^1H NMR analysis. (To prevent backflow, check valves were installed at each stage of liquid mixing, ensuring a one-way flow and enhancing the overall system reliability.)

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.4c00020.

General procedures, tables of reaction optimizations, analytical data, and characterization data for all the products (PDF)

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Notes

The authors declare no competing financial interest.

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