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Article

Continuous-Flow Hofmann Rearrangement Using Trichloroisocyanuric Acid for the Preparation of 2-Benzoxazolinone

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ABSTRACT: A continuous-flow preparation of 2-benzoxazolinone via the Hofmann rearrangement of salicylamide has been implemented employing trichloroisocyanuric acid as the stable and atom-economic chlorinating agent. The system was optimized to avoid solid accumulation and allow the preparation of hundreds of grams of the pure desired material over a working day. Furthermore, a trichloroisocyanuric acid (TCCA)-based chlorination of 2-benzoxazolone to the corresponding 5-chloro derivative was also carried out under batch conditions.

KEYWORDS: *Hofmann rearrangement, continuous, flow chemistry, 2-benzoxazolinone, trichloroisocyanuric acid, Orton rearrangement*

INTRODUCTION

2-Benzoxazolinone and more generally benzoxazolone derivatives are valuable moieties for the preparation of a range of important biologically active materials. Benzoxazolone derivatives have found promise as anticancer,[1,2] antimycobacterial,[3,4] anti-HIV-1,[5] anticonvulsant,[6−8] anxiolytic,[9] and insecticide agents.[10] Classical methodologies for their preparation start from 2-aminophenol employing carbonic acid derivatives such as phosgene,[11,12] carbonates,[13,14] carbamates,[4,15] urea,[16−18] or carbon dioxide.[19] Alternative preparation methods exploiting Pd-catalyzed oxidative carbonylation,[20,21] metal-catalyzed CH amidation,[22−24] visible-light-induced CH amination,[25] and Curtius rearrangement[26] have also been developed over the past years.

First reported by Graebe and Rostovzeff, the Hofmann rearrangement of salicylamide was also investigated in 1902 adopting sodium hypochlorite as the chlorinating agent to isolate the 2-benzoxazolinone in 33% overall yield.[27,28] The Hofmann reaction has been adopted widely as a methodology to access the more reactive electrophilic isocyanate species that are capable of reacting with numerous nucleophiles to form amines, carbamates, and ureas.[29−35] Different halogenating agents have also been trialed such as sodium hypochlorite, *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), NaBr, *N*-bromoacetamide (NBA), and trichloroisocyanuric acid (TCCA). In addition, other activating agent have also been used to induce the rearrangement such as bis-(trifluoroacetoxy)iodobenzene (BTI) and phenyliodine diacetate (PIDA).

Trichloroisocyanuric acid has been gaining attention in the last decade as a valuable alternative to other toxic and less easily handled chlorinating agents. Its high thermal stability and active chlorine content (91.5 wt % of active chlorine) make TCCA of potential use in industry as an easy-to-handle and atom-economic reagent.[36,37] TCCA is soluble in most common organic solvents such as acetone, acetonitrile, ethyl acetate, methanol, and toluene, and its byproduct (cyanuric acid, which is much less soluble in the same solvents)[38] can be easily filtered from the reaction solution. The white solid cyanuric acid could either be safely disposed as it slowly degrades (biodegradable) or recovered for reuse. TCCA has widely been described as an efficient chlorinating agent for ketones, alkenes, acids, esters, arenes, heterocycles, imides, and amides for the synthesis of α-chloro ketones, esters, chlorohydrins, *N*-chloroamides, *N*-chloroimides, and chloro-substituted arenes or heterocycles.[36,37,39−59] It has also found value in converting carboxylic acids into acid chlorides when coupled with strong Lewis bases such as triphenylphosphine to avoid the use of noxious reagents such $POCl_3$, PCl_5, and $SOCl_2$.[60−65] Recently, it has been employed as an alternative and more selective agent for the halogenation of methane to chloromethane.[66−68]

Flow chemistry and its potential for developing continuous manufacturing processes have reached a general acceptance level across a range of chemical processing industries as it allows for increased safe handling of toxic and hazardous reagents as well as improved heat and mass transfer phenomena.[69−75] To the best of our knowledge, few continuous-flow systems have been reported for the Hofmann rearrangement.[35,76,77] However, the ones reported required homogeneous reaction conditions involving low concentrations and/or unstable halogenating agents such as sodium hypochlorite. We reported here the first continuous-flow system for the preparation of 2-benzoxazolinone starting from salicylamide as a liquid−liquid biphasic system employing TCCA as the active chlorinating agent.

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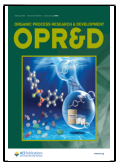
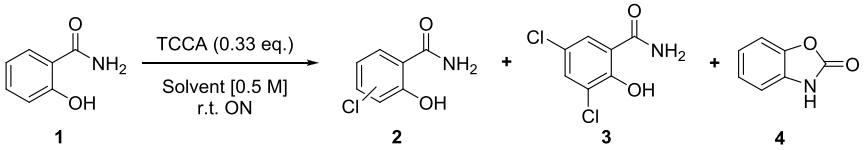


Table 1. Reaction Conditions Investigated for the Hofmann Reaction of 1 to 4



		^{1}H NMR peak ratio			
entry[a]	solvent	1	2 (*o*:*p*)	3	4
1	MeOH	0.18	0.67 (2:3)	0.15	0
2	EtOAc	0.39	0.44 (1:5)	0.17	0
3	0.5 M NaOH	0.57	0.16 (1:1)	0.06	0.21
4	H_2O:EtOAc[b]	0.28	0.27 (1:1)	0.05	0.4

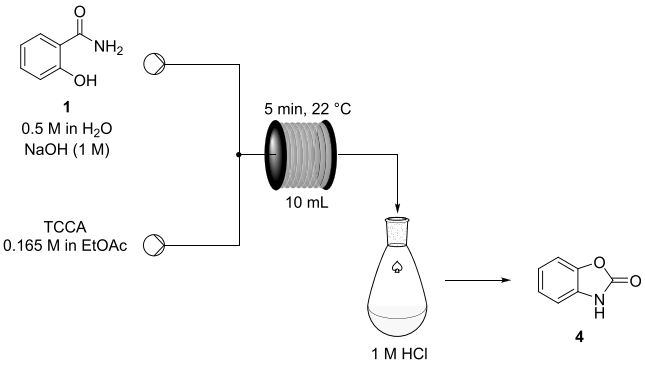
[a]The reaction were carried out on 15 mmol scale. [b]2 equiv of NaOH was added.

RESULTS AND DISCUSSION

To commence the investigation, we performed a general solvent screen (solubility and reactivity profiling). Each reaction was carried out employing 0.33 equiv of TCCA (1 equiv of active Cl^+) with the addition of the solid chlorinating agent in one portion at room temperature (0.5 M solution of the salicylamide). After the addition, a rise of temperature (roughly up to 40 °C for the 30 mL volume) was observed and the reaction lasted around 3 to 5 min from the moment when the exothermicity and the precipitate (cyanuric acid) started to form. The reaction was sampled and then left stirring overnight to assess time on the extent of chlorination. For the reaction performed in EtOAc, the product was purified by chromatography with the main compounds isolated being the chlorophenol derivatives of **1** (compounds **2** and **3**). The other reaction mixtures were analyzed via ^{1}H NMR (Table 1). The experiments run in either MeOH or EtOAc did not form the desired product, with principle chlorination occurring on the aromatic ring (Table 1, entries 1 and 2). To our delight, the reaction conducted in a 0.5 M sodium hydroxide solution (1 equiv) yielded a good level of the desired material **4** (Table 1, entry 3). The use of a biphasic system and addition of 2 equiv of NaOH (1 M concentration) drastically increased the conversion, suggesting that the amount of chlorinating agent was sufficient to perform a full chlorination of **1** subject to determining the correct amount of the base (entry 4).

Having identified a basic set of batch conditions, we decided to set up a flow apparatus that would allow the opportunity to create an efficient continuous production of the 2-benzoxazolinone **4** while also offering good control over the exothermic nature of the reaction. The setup consisted of two peristaltic pumps connected via a Y-piece union to a FEP coil reactor (10 mL, i.d. 0.078 in., o.d. 1/16 in.). The flow coil and Y-piece were placed in an incubator bath set to maintain room temperature (22−25 °C). A 0.5 M solution of **1** in an aqueous 1 M solution of NaOH was pumped (1 mL/min) and merged with a 0.165 M solution of TCCA dissolved in EtOAc (1 mL/min) (Scheme 1). The biphasic solution experienced 5 min of contact time in the coil and was then collected into a flask where a 1 M solution of HCl was placed to quench the reaction. During the 40 min of collection, no significant precipitation was observed. The organic phase was separated and concentrated under vacuum to yield **4** in a low conversion of 18.5% to the desired product. The mixture consisted mainly of the chloro-phenol derivative **2** (41.9% yield). Increasing the temperature and reducing the residence time did not significantly change the final outcomes (Table 2, entries 2 and 3).

Scheme 1. Flow Setup Installed for the Continuous Preparation of 4



Interestingly, using qualitative analysis, we noticed that a significant amount of starting material **1** (∼15%) was missing from the reaction mixture, which was lost to the aqueous phase after the acid quenching. Based on this observation, we deduced that the missing product may be the 2-hydroxyaniline (from the isocyanate hydrolysis) that becomes protonated under the acidic conditions. This would also help rationalize the increase in the desired product **4** when reducing the residence time from 5 to 2.5 min (Table 2, entries 2 and 3). To reduce the hydrolysis, we explored decreasing the base (from 2 to 1 equiv); however, the conditions seem to encourage the chlorination on the aromatic ring (entry 4). This new outcome could be attributed to a pH dependence of the reaction. The pK_a's of the starting material, product, and intermediates were thus calculated using the MarvinSketch v. 17.1.16.0 software (Scheme 2).

The most acidic proton belongs to the cyanuric acid waste product **6**. Based on the determined parameters, the starting material **1** would be solubilized in water as its sodium phenolate salt but would exist again as its protonated form once N-chlorination occurred (based upon the limiting base in the mixture). As noted from our experiments, if the salicylamide (**1**) is in its neutral form, the aromatic ring is primed for preferential chlorination (Table 1, entries 1 and 2). This explains the formation of a large amount of the chlorophenol **2** when only 1 equiv of the base was employed (Table 2, entry 4). In addition, as the second deprotonation of **6** has a comparable pK_a (8.77 for **6** vs 8.21 for **1**) to the phenol **1**, a second equivalent would still result in the same outcome, as

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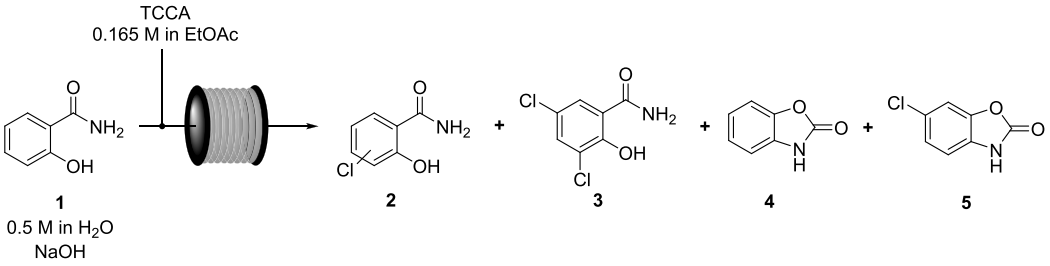
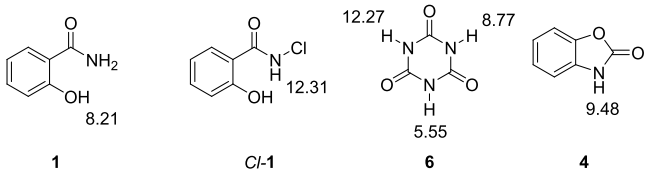
Table 2. Reaction Conditions Investigated for the Continuous Preparation of 4



entry[a]	equiv NaOH	t (min)	T (°C)	conv. (%)[b]	4 (%)[b]	2 (%)[b]	3 (%)[b]	5 (%)[b]
1	2	5	22−25	81.3	18.5	41.9	6.0	0
2	2	5	45−50	79.1	19.4	39.0	6.4	0
3	2	2.5	22−25	83.4	25.6	38.0	4.5	0
4	1	5	22−25	75.7	5.4	63.2	10.4	0
5	4	5	22−25	98.7	73.5	2.4	0.3	6.6
6	4	2.5	22−25	100	78.2	0	0	11.6
7	3.5	2.5	22−25	98.4	78.6	6.2	1.1	4.0
8	4.5	2.5	22−25	100	77.6	0	0	11.7
9[c]	4	2.5	22-25	100	73.5	0	0	19

[a]The experiments were carried out on a 30 min collection having previously reached the steady state after 10 min. [b]Based on ^{1}H NMR spectra using 1,2-dimethoxybenzene as the internal standard. [c]Total flowrate = 10 mL min^{-1} and volume coil = 25 mL.

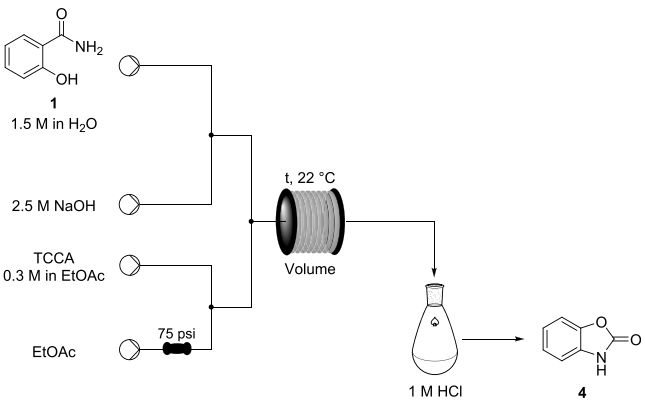
Scheme 2. Predicted pK_a of 1, *Cl*-1, 6, and 4 Simulated by the MarvinSketch v.17.1.16.0 Software



confirmed by experimental data (Table 2, entries 1−3). Consequently, 4 equiv of sodium hydroxide was thought to be required to avoid chloro-phenol **2** formation. To our delight, a significant increase in the conversion to the desired product **4** was observed when 4 equiv of NaOH was employed (73.5% yield), with a steep reduction in the accompanying chloro-product **2** (Table 2, entry 5). However, under these new conditions, a new chlorinated byproduct **5** started to form, which increased when lowering the residence times to 2.5 min (Table 2, entries 5 and 6). Slightly changing the equivalents of the base did not change the yield of **4**; however, it strongly influenced the composition of the final mixture (Table 2, entries 7 and 8). In an attempt to improve the contact surface area between the two phases, a higher flow rate of 10 mL min^{-1} (increased turbulence and mixing) was investigated while keeping the residence time constant (i.e., using a larger 25 mL reactor volume); however, no improvement was obtained (Table 2, entry 9). Therefore, we decided to test the scale-up and concentration of the reaction.

To increase the throughput of the flow system, a more concentrated solution of **1** was prepared; 1.5 M was found to be the highest concentration to avoid the precipitation of **1**. This would necessitate a rise in concentration of the NaOH; hence, a 6 M solution was prepared. Working on such high concentrations was noted to be detrimental to the starting material **1**, which showed evidence of hydrolysis especially when running at scales with a large stock solution over prolonged processing times. Consequently, we modified the flow setup to become a four-pump input system (Table 3).

Table 3. Flow Apparatus and Reaction Conditions Employed for the Continuous-Flow Synthesis of 2-Benzoxazolinone (4)



entry[a]	t (min)	conversion (%)[b]	yield 4 (%)[b]	yield 2 (%)[b]	yield 3 (%)[b]	yield 5 (%)[b]
1	0.5	99.5	96.3	2.6	0.5	0.1
2	1	99.6	96.7	1.3	0	0.003
3	3	100.0	89.1	0	0	0.01

[a]The experiments were carried out using 30 min collection having previously reached steady-state operation after 10 min. [b]Based on ^{1}H NMR spectra using 1,2-dimethoxybenzene as the internal standard. For entry 3, the temperature at the final T-mixer was externally monitored using a Fluke 561 infrared handheld thermometer as 27−29 °C and at 18 cm along the subsequent coil reactor length (hottest spot) as 48−51 °C. This temperature was easily regulated using a circulating water bath set at 22 °C. Solution inputs were at RT = 20 °C.

This four-pump system also facilitated easy cleaning by switching off and on the different reagents' pumps (flushing with NaOH or EtOAc). We also anticipated that, by increasing the concentrations, we could increase reaction kinetics and thus potentially further reduce the residence time (increase the throughput). Therefore, three different residence times were investigated, and to our delight, after 30 s, the desired material

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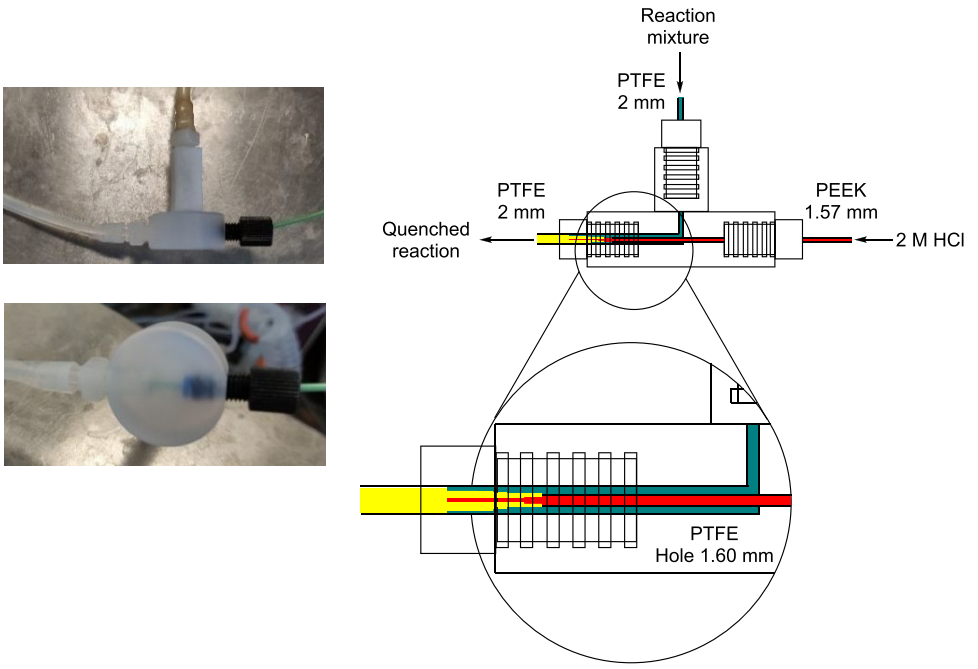

Figure 1. Representation of the mixer engineered to avoid clogging: pictures (left-hand side), and scheme (right-hand side).

was obtained in over 96.3% yield (>95% purity). Only 3.1% of the ring chlorinated materials **2** and **3** were formed, and 0.1% of **5** was found in the final material. In contrast, an increase in the residence time to 3 min had a detrimental impact on the final isolated yield, albeit accompanied by a large reduction in the byproducts (this result we currently do not fully understand).

Having determined a new set of processing conditions, we next assessed adding a continuous quenching step through the addition of a hydrochloric acid stream. Following the Hofmann rearrangement, the reaction mixture is highly alkaline, keeping the formed cyanuric acid and desired product **4** completely solubilized in the aqueous phases. However, the cyanuric acid is poorly soluble in water/ethyl acetate and precipitates out after pH adjustment (pH 3). The generation of a precipitation in the small dimension coil of the flow reactor could easily lead to solid accumulation and clogging of the flow system, a notoriously problematic issue associated with small dimension flow reactors and a scenario often best avoided, although solutions do exist.[78−81]

Solid formation when merging two streams can result in particulate accumulation in small areas within the mixer where sheer is low, which does not facilitate the solid propagation through the unit. To solve this problem, a simple modification of the mixer can be engineered to allow a contact interface axial to the tubing, preventing solid accumulation within the mixer's walls (Figure 1). As such, a tee-piece connector was drilled to create a 1.6 mm diameter thru hole that allows the passage of a length of 1/16″ (1.57 mm) o.d. PEEK tubing through which the hydrochloric acid quenching solution was pumped. This was inserted into a 2 mm tubular coil reactor (10 mL) where the quenching takes place. Using this setup (Figure 1), the flow system was run repeatedly for over 8 h working days without any issue and allowed generation of 188 g of the desired material **4** (95% purity) to be isolated (per run) after solvent removal (throughput = 23.5 g h^{-1} and STY = 1.56 g h^{-1} mL^{-1}) (Figure 2).

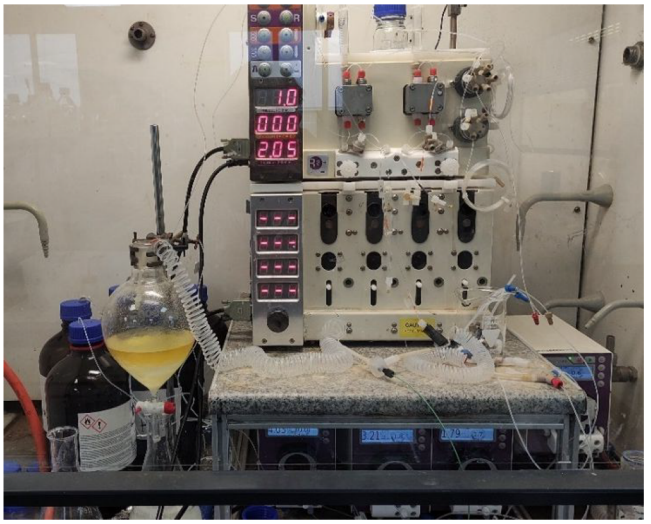

Figure 2. Flow apparatus designed for the continuous preparation of 2-benzoxazolinone (**4**).

Finally, during the optimization phase, we noted that increasing the ratio of **1**/TCCA (0.59 equiv of TCCA) formed a 1:1 mixture of **4** and the further chlorinated material **5**. Based upon this observation, we wondered whether we could achieve a selective chlorination of the 2-benzoxazolinone (**4**) to the derivative **5** employing TCCA as the chlorinating agent (Table 4). Addition of the TCCA chlorinating agent to a solution of previously prepared and isolated **4** formed a new species, as indicated by thin layer chromatography (TLC). When the mixture was sampled for ^{1}H NMR analysis, it reacted strongly with *d*-DMSO, suggesting the presence of active chlorine in the molecule. Analysis of this NMR sample indicated that compound **4** was present (Table 4, entry 1) but was not the material originally isolated. As such, chlorination must have occurred at nitrogen forming *Cl*-**4** as the initially isolated intermediate that was itself an active chlorinating

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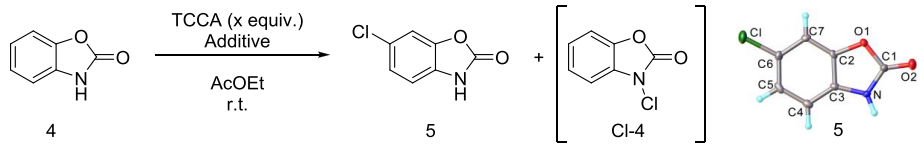
Table 4. Reaction Conditions for the Chlorination of 4 into 5 in Batch



entry[a]	TCCA equiv	additive	conversion (%)[b]	yield 5 (%)[b]
1	0.33			
2	0.33	HCl aq. (2.6 equiv)	100	51
3	0.66	HCl aq. (2.6 equiv)	100	81

[a]The experiments were carried out on a 200 mmol scale. [b]Based on ^{1}H NMR spectra using 1,2-dimethoxybenzene as the internal standard.

species. Para-chlorination through Orton rearrangements of *N*-chloro acetanilides has been described in the literature conducted under acidic conditions or via photo-excitement.[82−84] To our delight, the addition of 2.6 equiv of a concentrated HCl solution (pH = 1) to the N-chlorinated intermediate reaction mixture resulted in the formation of a white suspension that was filtered and washed with water to remove cyanuric acid (note: as an excess of TCCA is used, this mixture also likely includes hypochlorous acid or hypochlorite as part of the reaction waste). The material isolated in 51% yield and 92% purity was identified as compound **5**. An improved isolated yield of 81% (following recrystallization from EtOAc) was achieved when the equivalents of TCCA (0.66 equiv) were doubled (entry 2). The resolution of the SCXRD further confirmed the chlorination in position 5. Any further increase in the TCCA chlorinating agent results in reduced purity and ultimately lower recovery. However, the reaction was easily performed and was regularly run at 200 mmol scale without any issue, allowing easy access to the 5-chlorinated derivative **5** in good yields. No further optimization of this process has been performed.

CONCLUSIONS

A continuous-flow system was implemented to efficiently convert salicylamide (**1**) to the benzoxazolone material **4** through Hofmann rearrangement. The system employs TCCA as a cheap, stable, and atom-efficient chlorinating agent. Despite the precipitation of the cyanuric acid, we were able to stabilize and avoid solid accumulation through minor modifications of the equipment and enable the preparation of 188 g of the final material in a standard 8 h working day, equating to a throughput of 23 g h^{-1} (95% isolated yield and STY = 1.56 g h^{-1} mL^{-1}). This represents the first example of efficient TCCA-based chlorination under flow conditions described in the literature. In addition, an efficient methodology for the further chlorination of the material benzoxazolone **4** was identified again employing a TCCA-based N-chlorination followed by acid-catalyzed Orton rearrangement that allows access to the corresponding compound **5** in 81% isolated yield.

EXPERIMENTAL SECTION

General Consideration. Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Substrates, their precursors, and reagents were purchased from Alfa Aesar, Sigma Aldrich, Fluorochem, TCI, or Acros Organics and used as received. ^{1}H NMR spectra were recorded on a Bruker Avance-400 instrument and are reported relative to the residual solvent: $CDCl_3$ (δ 7.26 ppm) and d_6-DMSO (δ 2.50 ppm). ^{13}C-NMR spectra were recorded on the same instruments and are reported relative to $CDCl_3$ (δ 77.16 ppm) and d_6-DMSO (δ 39.52 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ/ppm) (multiplicity, coupling constant (Hz), and integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s, br = broad singlet, and app. = apparent. Data for ^{13}C-NMR are reported in terms of chemical shift (δ_C/ppm). Single crystal X-ray diffraction experiments were carried out on a Bruker D8 Venture diffractometer with a PHOTON 100 CMOS area detector using Mo Kα radiation from Incoatec IμS microsources with focusing mirrors. The crystals were cooled using a Cryostream 700 (Oxford Cryosystems, Oxford, Oxfordshire, UK) open-flow N2 gas cryostat. The structures were solved by dual-space intrinsic phasing (SHELXT program)[85] and refined by full-matrix least squares using the SHELXL[86] software on the Olex2 platform.[87] IR spectra were obtained using a Perkin Elmer Spectrum Two UATR Two FT-IR Spectrometer (neat, ATR sampling), with the intensities of the characteristic signals being reported as weak (w, <20% of the tallest signal), medium (m, 21−70% of the tallest signal), or strong (s, >71% of the tallest signal). Low- and high-resolution mass spectrometry was performed using the indicated techniques. Low-resolution gas chromatography−mass spectrometry (GC−MS) was performed on a Shimadzu QP2010-Ultra equipped with an Rxi-5Sil MS column (0.15 μm × 10 m × 0.15 mm) in EI mode. Low-resolution liquid chromatography−mass spectrometry (LC−MS) was performed using a Waters TQD mass spectrometer and an Acquity UPLC BEH C18 1.7 μm column (2.1 × 50 mm) in ESI mode. ESI-HRMS was performed using a Waters QtoF Premier mass spectrometer. For accurate mass measurements, the deviation from the calculated formula is reported in ppm. Reactions were conducted in flow using Vapourtec SF-10 as peristaltic pumps and Vapourtec R-series as piston pumps. PTFE (2 mm i.d.) and PEEK tubing (1/16″ o.d.) were also adopted along with a Uniqsis glass static mixer reactor block 2 input (volume = 0.27 mL). All the connector tubings were 1/4″-28 thread. SiO_2 column chromatography was performed using a Sigma Aldrich silica gel (grade 9385, pore size 60 Å) and standard manual column apparatus. For TLC, Sigma Aldrich glass-backed plates were used, and visualization was performed using UV irradiation or a $KMnO_4$ stain. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator, and high vacuum was achieved using an Edwards RV5 pump and Schlenk line. Kugelrohr distillation was performed using a Buchi Glass Oven B-3585, and vacuum distillation was performed using a Buchi V-700 vacuum pump equipped with

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a V-850 vacuum controller attached to a standard distillation pig setup.

General Procedure for the Screening of the Reaction Conditions. To a solution of salicylamide (2.06 g, 15 mmol, 1 equiv) in the desired solvent, TCCA (1.3 g, 5 mmol, 0.33 equiv) was added in one portion. The mixture was left stirring overnight at room temperature. The solution was then filtered and concentrated in a vacuum. The residue was then analyzed via ^{1}H NMR spectra and purified via flash chromatography (eluent: EtOAc/Hex 2:8).

General Procedure for the Hofmann Reaction in Biphasic Conditions. To an aqueous 1 M solution of sodium hydroxide (15 mL) and 0.5 M of salicylamide (2.06 g, 15 mmol, 1 equiv), TCCA solid (1.3 g, 5 mmol, 0.33 equiv) or a solution of it in EtOAc was added in one portion. The reaction was stirred until the change of color from yellow to red and then quenched with a 1 M solution of HCl. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was analyzed via GC−MS and ^{1}H NMR.

General Procedure for the Preparation of 5. In an ice-cooled solution of **4** (1:1 **4**:**5** mixture, 136.1 g, 534 mmol, 1 equiv), a concentrated hydrochloric solution (50 mL, 600 mmol, 2.6 equiv) was slowly added. TCCA (90 g, 352 mmol, 0.66 equiv) was added portion-wise to control the exothermicity. The white suspension was then filtered and washed with water until neutralization of the mother liquor. The solid was then crystallized from EtOAc to yield **5** (52 g, 81% yield).

General Procedure for the Preparation of 4 under Flow Conditions: Two-Pump System. A 0.5 M aqueous solution of **1** and NaOH (from 0.5 to 2 M) was pumped through a peristaltic pump (blue pump tube) and merged with a 0.165 M solution of TCCA in EtOAc at various flow rates. The TCCA solution was pumped via a peristaltic pump (PEEK-Blue pump tube). The mixer employed was a PEEK Y-mixer $^1/_4$-28 .040 inch (IDEX HS). The reaction stream was directed into a 2 mm i.d. PTFE coil reactor with various volumes (10−25 mL). The output stream was then collected into a 250 mL round-bottom flask filled with a 1 M solution of hydrochloric acid. The layers were partitioned, and the organic layers were then treated with brine and dried over Na_2SO_4. The solution was then concentrated and analyzed through ^{1}H NMR.

General Procedure for the Preparation of 4 under Flow Conditions: Four-Pump System. A 1.5 M solution of **1** and NaOH in water was pumped through a peristaltic pump (blue pump tube) and merged with a 2.5 M solution of NaOH that was pumped via a peristaltic pump (blue pump tube). The two streams were efficiently mixed employing a Uniqsis glass static mixer reactor block 2 input (volume = 0.27 mL). The solution of TCCA in EtOAc merged with a stream of AcOEt though a PEEK tee-mixer $^1/_4$-28 0.020 inch (IDEX HS). The pure solvent was pumped via a piston pump of the Vapourtec R-series. The merged stream was then mixed with the solution of 1 and NaOH into a 5 mL coil reactor (2 mm i.d.). The output of the reactor was quenched with a 2 M solution of hydrochloric acid through the above-cited modified mixer (Figure 1). The reaction stream was directed into a 10 mL coil reactor (2 mm i.d.). The biphasic solution was collected into a separatory funnel where the aqueous and organic layers were continuously separated. The combined organic layers were dried over Na_2SO_4 and concentrated to yield **4** as a white crystalline powder (188 g, 95% isolated yield).

*Benzo[d]oxazol-2(3H)-one (**4**).* ^{1}H NMR (400 MHz, DMSO) δ 11.62 (s, 1H), 7.31−7.23 (m, 1H), 7.18−7.03 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 154.42, 143.36, 130.35, 123.80, 121.86, 109.79, 109.53. FT-IR (neat) ν (cm^{-1}) 3202 (NH, m), 1726 (C═O, s), 1476 (s), 1396 (s), 1306 (m), 1253 (s), 1147 (s), 938 (s), 683 (s). LC−MS (ESI+) Rt = 1.30 min m/z [M + H]$^+$ = 136.3. HR-MS calculated for $C_7H_6NO_2$ 136.0399, found 136.0391 (Δ = −0.8 mDa). m.p. 139.3−142.1 °C.

*5-Chloro-benzo[d]oxazol-2(3H)-one (**5**).* ^{1}H NMR (599 MHz, DMSO) δ 11.80 (s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.18 (dd, J = 8.3, 2.0 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 154.16, 143.79, 129.47, 125.78, 123.63, 110.71, 110.19. FT-IR (neat) ν (cm^{-1}) 3199 (OH, br), 1725 (C═O, s), 1623 (m), 1476 (s), 1390 (m), 1293 (m), 1241 (m), 1150 (w), 1058 (w), 917 (s), 852 (w), 811 (w). LC−MS (ESI+) Rt = 1.84 min m/z [M + H]$^+$ = 170.2. HR-MS calculated for $C_7H_5NO_2Cl$ 170.0009, found 170.0001 (Δ = −0.8 mDa). m.p. 190.3−192.3 °C. Crystal data for $C_7H_4ClNO_2$ (M = 169.56 g/mol): monoclinic, space group $C2/c$ (no. 15), a = 12.918(2) Å, b = 7.0203(13) Å, c = 30.578(5) Å, β = 93.923(6)°, V = 2766.5(9) Å^3, Z = 16, T = 120 K, μ(Mo Kα) = 0.489 mm^{-1}, D_{calc} = 1.628 g/cm^3, 15,128 reflections measured (5.342° ≤ 2Θ ≤ 49.99°), 2441 unique (R_{int} = 0.0618, R_{sigma} = 0.0411), which were used in all calculations. The final R_1 was 0.0854 ($I > 2\sigma(I)$) and wR_2 was 0.2200 (all data). CDCC reference number: CCDC-2112958.

*Salicylamide (**1**).* ^{1}H NMR (400 MHz, DMSO) δ 13.04 (s, 1H), 8.40 (s, 1H), 7.91 (s, 1H), 7.84 (dd, J = 7.9, 1.7 Hz, 1H), 7.40 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 6.90−6.81 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 172.19, 161.18, 134.17, 128.14, 118.42, 117.47, 114.37. FT-IR (neat) ν (cm^{-1}) 3391 (NH, m), 3177 (NH, m), 1673 (C═O, m), 1625 (C═O, s), 1589 (m), 1493 (m), 1445 (s), 1421 (s), 1358 (m); 1301 (m), 1246 (m), 1120 (m), 847 (s), 746 (s). LC−MS (ESI+) Rt = 1.14 min m/z [M + H]$^+$ = 138.3. HR-MS calculated for $C_7H_8NO_2$ 138.0555, found 138.0542 (Δ = −1.3 mDa). m.p. 138.9−143.3 °C.

*3-Chloro-2-hydroxybenzamide (o-**2**).* ^{1}H NMR (400 MHz, DMSO) δ 14.09 (s, 1H), 8.62 (s, 1H), 8.17 (s, 1H), 7.84 (dd, J = 8.0, 1.5 Hz, 1H), 7.59 (dd, J = 7.9, 1.5 Hz, 1H), 6.98−6.80 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.13, 157.41, 134.11, 126.58, 121.04, 118.58, 115.20. FT-IR (neat) ν (cm^{-1}) 3497 (NH, w), 3438 (NH, w), 3393 (NH, w), 3187 (OH, w), 2745 (CH, w), 1665 (C═O, m), 1616 (m), 1580 (m), 1474 (m), 1444 (m), 1367 (m), 1261 (m), 1217 (m), 1103 (m), 846 (m), 741 (s). LC−MS (ESI+) Rt = 1.63 min m/z [M + H]$^+$ = 172.9. HR-MS calculated for $C_7H_8NO_2$ 172.0165, found 172.0157 (Δ = −0.8 mDa). m.p. 138.9−143.3 °C., m.p. 164.2−170.3 °C.

*5-Chloro-2-hydroxybenzamide (p-**2**).* ^{1}H NMR (400 MHz, DMSO) δ 13.01 (s, 1H), 8.45 (s, 1H), 8.04 (s, 1H), 7.95 (d, J = 2.6 Hz, 1H), 7.44 (dd, J = 8.9, 2.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 170.66, 159.69, 133.72, 127.54, 122.03, 119.37, 115.77. LC−MS (ESI+) Rt = 1.60 min m/z [M + H]$^+$ = 172.7. HR-MS calculated for $C_7H_8NO_2$ 172.0165, found 172.0153 (Δ = −1.2 mDa).

*3,5-Dichloro-2-hydroxybenzamide (**3**).* ^{1}H NMR (400 MHz, DMSO) δ 14.14 (s, 1H), 8.70 (s, 1H), 8.33 (s, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H).

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■ ASSOCIATED CONTENT

Supporting Information

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Associated spectra characterization data for compounds **1**, **2**, **4**, and **6** (PDF)

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Notes

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■ ABBREVIATIONS

TCCA, trichloroisocyanuric acid; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NBA, *N*-bromoacetamide; BTI, bis(trifluoroacetoxy)iodobenzene; PIDA, phenyliodine diacetate; ^{1}H NMR, ^{1}H nuclear magnetic resonance; PEEK, polyether ether ketone; PTFE, polytetrafluoroethylene; SCXRD, single crystal X-ray diffraction; EtOAc, ethyl acetate; TLC, thin layer chromatography

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