Synthesis of Thiomorpholine via a Telescoped Photochemical Thiol-ene/Cyclization Sequence in Continuous Flow

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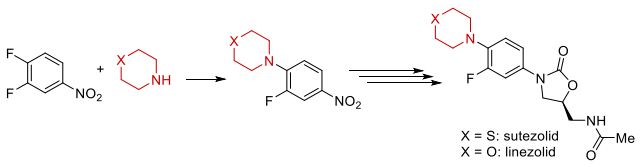
Supporting Information Placeholder

ABSTRACT: A procedure for the continuous flow generation of thiomorpholine in a two-step telescoped format was developed. The key step was the photochemical thiol-ene reaction of cysteamine hydrochloride and vinyl chloride as low-cost starting materials under highly concentrated (4 M) conditions, leading to the corresponding half-mustard intermediate in quantitative yield. Thiomorpholine was subsequently obtained by a base-mediated cyclization. The robustness of the process was demonstrated by performing the reaction for 7 h (40 min overall residence time) isolating the desired thiomorpholine via distillation.

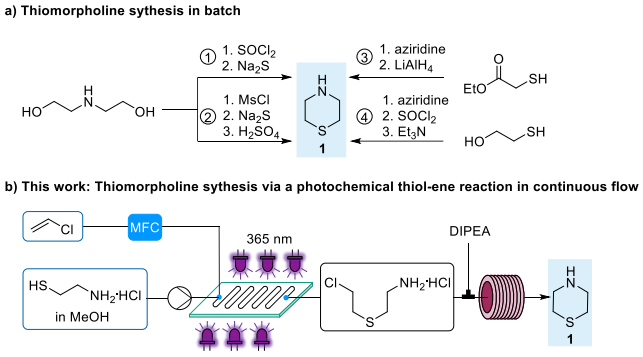
The thiomorpholine moiety is an important structural motif that is incorporated into a variety of active pharmaceutical ingredients (APIs) because of its interesting pharmacological profile, including antimalarial, antibiotic, antioxidant or hypolipidemic activity.[1] A prominent example is the oxazolidinone antibiotic sutezolid that is currently in phase 2 clinical trials for the treatment for multidrug-resistant tuberculosis (MDR-TB). Due to its improved therapeutic potential, it is considered to be a promising replacement for the FDA-approved, first-generation drug linezolid, the morpholine analog of sutezolid (Scheme 1).[2] However, the Medicines for All Institute (M4ALL) conducted techno-economic analyses of the routes toward sutezolid (see Scheme S1)[3,4] that identified thiomorpholine as the most significant cost driver. In order to be cost competitive with linezolid, and therefore accessible to low- and middle-income countries, a scalable route to generate thiomorpholine from low-cost starting materials is highly desirable.

Scheme 1. First Reaction Step Toward Sutezolid/Linezolid



Approaches toward the synthesis of thiomorpholine (**1**) are displayed in Scheme 2a and include the transformation of diethanolamine to **1** via generation of an amino-mustard species and its cyclization by treatment with sodium sulfide (routes 1 and 2).[5,6] Starting from ethyl mercaptoacetate and aziridine, **1** can be obtained by $LiAlH_4$ reduction of the generated thiomorpholin-3-one (route 3).[7] Another strategy involves the reaction of 2-mercaptoethanol with aziridine and further conversion to 2-(2-chloroethylthio)ethylamine hydrochloride, which is then cyclized with Et_3N to **1** (route 4).[8] These procedures are rather time consuming (2−54 h) and isolation of thiomorpholine is achieved in 44−81% overall yield after either a distillative work-up[6–8] or crystallization as HCl salt.[5] Although most of the reported routes use low-cost starting materials, they also generate nitrogen- or half-mustards, respectively, and thus producing these molecules on scale in a standard laboratory environment would be a safety challenge.

Scheme 2. Syntheses Toward Thiomorpholine.



We were inspired to develop an alternative, time- and atom-efficient continuous flow route toward thiomorpholine based on the thiol-ene reaction of cysteamine and vinyl chloride (VC). Thiol-ene reactions fall into the category of click chemistry due to their high yield, solvent and oxygen tolerance, and absence of byproducts.[9–11] They proceed via a free-radical mechanism, and initiation is typically achieved either with UV irradiation or by thermolysis of a chemical additive. This strategy would lead to the same half-mustard 2-(2-chloroethylthio)ethylamine hydrochloride intermediate reported by Asinger et al. (route 4, Scheme 2a)[8] in one step, which

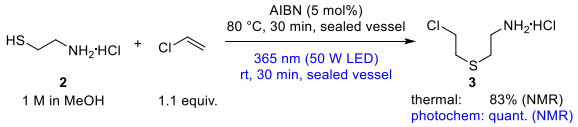
is then further cyclized without isolation under basic conditions to **1** (Scheme 2b). Both reagents are considered as low-cost bulk materials, with cysteamine itself being a high-volume FDA approved drug, ensuring a stable supply. VC on the other hand, is one of the world's most important commodity chemicals with an annual production of ca. 13 million metric tons.

However, since VC is supplied as a compressed, liquefied gas, is highly toxic, flammable, and a Group 1 human carcinogen,[12] and the generated intermediate is a half-mustard, the process is best conducted in a telescoped continuous flow format.[13,14] Low reactor volumes ensure that only a small amount of material is present at any given time, thus hazardous materials can be safely handled in continuous flow. [15–18] In addition, head space issues are eliminated, gaseous reagents can be dosed precisely and processes can be seamlessly translated from lab to industrial scale.[19,20] Photochemical reactions typically can be improved when performed within the narrow channels of a microreactor combined with state-of-the-art LED irradiation technology.[21–23]

Preliminary studies on the thermal and photochemical thiol-ene reaction were performed employing vinyl acetate as a more convenient and readily available alkene precursor on lab scale, compared with VC (see Supporting Information). These studies revealed that cysteamine as free base furnished 2-methyl-1,3-thiazolidine as major product (Figures S1, S2), but as HCl salt the desired intermediate 2-aminoethylthioethyl acetate was obtained (Figures S3−S5). Methanol proved to be the solvent of choice, as cysteamine showed poor solubility in other solvents (e.g., MeCN, THF, toluene, DCM). With this information in hand, we next turned our attention to VC, which is expected to be the superior alkene building block with respect to atom-economy, material availability and reactivity.

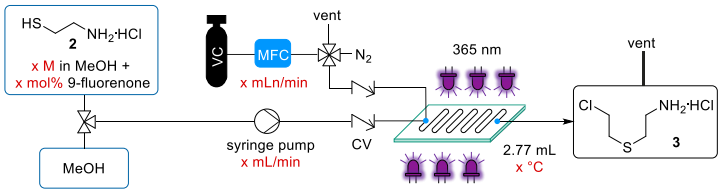
For batch optimizations, 1.1 equiv. VC (bp −13.4 °C) were condensed into a 1 M solution of cysteamine hydrochloride (**2**) in MeOH (Figure S11). This procedure allowed more accurate dosing of VC compared to simply sparging the solution with VC, which results in a higher amount of VC in the headspace and thus less conversion to product. A quick comparison of the thermal (80 °C, 30 min, 5 mol% AIBN) and photochemical (rt, 30-60 min, 365 nm) reaction provided similar results as with vinyl acetate: The photochemical route proved to be highly selective, and a quantitative yield of 2-(2-chloroethylthio)ethylamine hydrochloride (**3**) by NMR was obtained, versus 83% thermally (Scheme 3).

Scheme 3. Thiol-ene Reaction of Cysteamine Hydrochloride with Vinyl Chloride in Batch



We moved forward to optimization studies in continuous flow using a commercial plate-based flow photoreactor (Corning AFR, Lab Photo Reactor)[24] and the set-up shown in Table 1. VC was fed via a calibrated mass flow controller (MFC), which allowed accurate dosing of the gas. Since VC is provided as a compressed, liquefied gas at 3 bar, the maximum outlet pressure was limited to 1 bar, which prevented performing the reaction at gas flow rates higher than ca 12 mln/min and thus higher throughput. In addition, the integration of a back pressure regulator (BPR) was not suitable, most likely resulting in less VC dissolved in solution and a lower residence time than calculated. Employing a 1 M solution of **2** in MeOH, a calculated maximum residence time[25] of 10 min and irradiation at 365 nm, provided NMR yields of only 53–58% (Table 1, entries 1 and 2). By lowering the temperature from 20 °C to 6 °C, the yield dropped to 18% (entry 3).

Table 1. Optimization Studies of the Photochemical Thiol-ene Reaction of 2 with Vinyl Chloride in Continuous Flow[a]



entry	conc of 2 [M]	9-FL [mol%]	T [°C]	equiv. VC	flow rates [mL/min]		NMR yield [%]
					2	VC	
1	1	–	20	1.1	0.277	6.6	53
2	1	–	20	1.0	0.277	6.1	58
3	1	–	6	1.0	0.277	6.1	18
4[b]	1	5	20	1.0	0.277	6.1	87
5[b]	2	5	20	1.0	0.277	12.1	93
6[c]	4	5	20	1.0	0.139	12.1	>99
7	4	1	20	1.0	0.139	12.1	>99
8	**4**	**0.1**	**20**	**1.0**	**0.139**	**12.1**	**>99**
9	4	–	20	1.0	0.139	12.1	98

a…Conditions: Liquid feed: **2**, 9-fluorenone (9-FL), and methyl benzoate as internal standard were dissolved in MeOH (25 mL volumetric flask). CV: check valve. See Experimental Section for more details and Table S1 for a full optimization table.
b…Degassing of the liquid substrate feed with Ar.
c…With or without degassing.

The poorer performance in flow was not unexpected, since an extremely low absorption coefficient of **2** was determined (ε = 0.025 $Lmol^{-1}cm^{-1}$ at 363 nm), resulting in an absorption of only about 1% of the incident light at a concentration of 1 M due to the short path length of 0.04 cm (plate´s channel size). More details can be found in the Supporting Information. Therefore, it appeared advantageous to employ a photocatalyst, a common practice for this photochemical reaction. For thiol-ene reactions in continuous flow, 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photoinitiator or $Ru(bpy)_3(PF_6)_2$ as photocatalyst have been reported.[26–28] While $Ru(bpz)_3(PF_6)_2$ has been reported to catalyze the thiol-ene reaction of similar thiol substrates such as cysteine methyl ester via a single electron transfer (SET) mechanism,[29] it was important to avoid expensive metal catalysts in our approach. Therefore, to accelerate this reaction, we envisioned employing 9-fluorenone (9-FL) as inexpensive photocatalyst.[30] Although the oxidation potential of the T^1 exited state of 9-FL (+0.96 V *vs* SCE)[31] would suffice to oxidize cysteamine (+0.92 V *vs* SCE)[32] it might also act via energy transfer catalysis.[33–35] However, it is difficult to distinguish the two pathways experimentally.

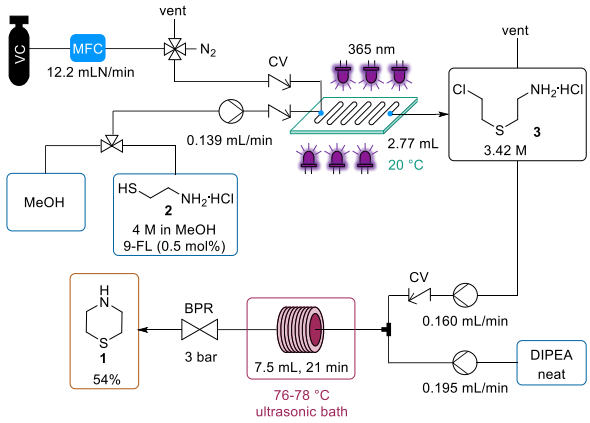
As expected, the addition of 5 mol% of 9-FL increased the yield to 87% (entry 4). A further improvement in yield could only be accomplished by increasing the concentration of the liquid substrate feed (entries 5 and 6, see also Figure S10). The maximum achievable concentration was 4 M, providing **3** in quantitative yield. It has to be noted that for such highly concentrated solutions of **2**, dissolution is aided by sonication and that crystallization occurs upon cooling below room temperature. Although the thiol-ene reaction is rather insensitive toward O_2, the photocatalyst might be quenched by O_2. Hence, the liquid substrate feed – containing **2**, methyl benzoate as internal standard and 9-FL – was additionally degassed by sparging with argon for ca. 1 min. Interestingly, no change in reactivity was observed whether the liquid feed was degassed or not (entry 6). Further optimizations revealed that the sensitizer concentration can be reduced to 0.1 mol% (720 mg/L) without compromising the yield (entries 7 and 8). Remarkably, at such a high concentration the reaction proceeded to 98% yield (*vs* 58% at 1 M) even without sensitizer (entry 9). Under optimized conditions − 4 M solution of **2**, 1 equiv. VC, 0.1−5 mol% 9-FL, 20 min residence time − intermediate **3** was generated with a throughput of 5.9 g/h.

Interestingly, gas formation was observed at the reactor outlet, although only an equimolar amount of VC was employed. Therefore, an isolation experiment was performed. As the isolated yield was in agreement with the ^{1}H NMR yield (see Supporting Information and Figures S12 and S13), no further investigations were conducted. It also has to be noted that over the course of the reaction the volume of the liquid stream increased by 17%, resulting in a reduced concentration of intermediate **3** of 3.42 M.

For the cyclization of intermediate **3** to thiomorpholine, a base screen was first performed in batch (Table S2). Full conversion of **3** was achieved and thiomorpholine was obtained with an NMR yield of 86−89% after 5 min at 100 °C by employing 2 equiv. of either Et_3N, DIPEA or DBU. Et_3N was successfully used for this reaction by Asinger et al.,[8] however, since precipitation was observed, this base was unsuitable for a flow protocol. With respect to cost efficiency, we decided to explore the telescoped thiol-ene/cyclization reaction with DIPEA.

Since the cyclization proceeds faster at temperatures above the boiling point of MeOH, a back pressure regulator (BPR) set to 3 bar was installed. Due to the outlet pressure limitation of 1 bar of the VC cylinder, a hold vessel needed to be introduced to collect the exit stream of the thiol-ene reaction, which was then further pumped to be mixed with 2 equiv. of neat DIPEA (Scheme 4 and Figure S17B). This hold vessel also functioned as a gas separator. The thiol-ene reaction was performed under the conditions depicted in entry 8 in Table 1 using 0.1 mol% of 9-FL. We realized that a simple T-mixer did not provide efficient mixing resulting in lower thiomorpholine yields. When introducing a coil filled with glass beads (PFA, 1.6 mm ID, 3.2 mm OD, 0.5 mL void volume when filled) after the T-mixer, which functions as both a mixing and reaction unit, the same outcome as in batch was observed: an 87% NMR yield could be achieved at 100 °C and 5 min residence time (Figure S14).

Scheme 4. Telescoped Continuous Flow Procedure toward Thiomorpholine.



Finally, we performed a long run to demonstrate the robustness of this process. For this purpose, the concentration of 9-FL was increased to 0.5 mol% to ensure a stable performance over a multihour run. After experiencing clogging issues with the above-mentioned set-up at process times >1 h, a 7.5 mL coil (0.8 mm ID, 1.6 mm OD) that was immersed in an ultrasonic bath[36] was used as residence time unit at a temperature of 76−78 °C. With this set-up, the process was constant for 7 h after reaching steady state (Scheme 4 and Figure 1). Yields of intermediate **3** and thiomorpholine of ≥98% and 84%, respectively, by NMR were achieved (Figure 1), which matches well with previous optimizations. After distillation, 12.74 g (54% overall) of thiomorpholine was isolated, which corresponds to a throughput of 1.8 g/h. The difference between isolated and NMR yield is related to losses during distillation (see the Supporting Information), which has not been fully optimized at this small scale. However, we expect these losses to be minimal when an improved work-up procedure is employed on larger scale.

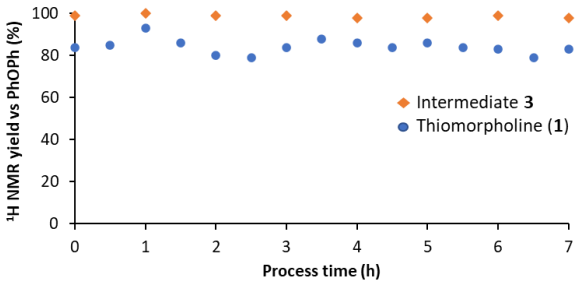


Figure 1. 7 h run of the telescoped thiol-ene/cyclization sequence toward thiomorpholine. For conditions, see Scheme 4 and the Experimental Section.

In conclusion, we have developed a continuous flow process for the atom- and time-efficient generation of thiomorpholine by using

readily available cysteamine (as its hydrochloride salt) and vinyl chloride as bulk materials. The telescoped photochemical thiol-ene/cyclization sequence furnished thiomorpholine at laboratory scale in 54% overall isolated yield (84% NMR yield) after distillation, which was comparable to most of the reported procedures (44–81%).[5–8]

Key to this telescoped sequence was the continuous photochemical thiol-ene reaction, which proceeded under highly concentrated conditions (4 M solution of **2**), low amounts of 9-fluorenone as photocatalyst (≤0.5 mol%) and quantitative yield of **3**. Due to the low pressure of the VC gas cylinder, the throughput on lab scale was limited to a maximum of 5.9 g/h of intermediate **3**, and in turn of 1.8 g/h of thiomorpholine. To achieve higher production capacity, VC is best processed in liquid form, as is common in polyvinyl chloride (PVC) production. On lab scale, this technique is too high risk and impractical, however, with the appropriate equipment, this reaction has the potential to be safely scaled in a continuous flow format at production scale. Several photochemical reactions have been demonstrated in continuous flow on production scales,[23,37–39] which supports this assessment.

EXPERIMENTAL SECTION

General Methods. All materials were purchased from commercial sources (TCI, Sigma-Aldrich, AirLiquide) and used without further purification. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, m and brs are used to indicate singlet, doublet, triplet, quadruplet, multiplet and broad singlet. GC-FID chromatography was performed using a Shimadzu GC FID 230 gas chromatograph with a flame ionization detector (FID). Helium, used as the carrier gas (40 cm sec^{-1} linear velocity), goes through a RTX-5MS column (30 m × 0.25 mm ID × 0.25 μm). The injector temperature is set to 280 °C. After 1 min at 50 °C, the column temperature is increased by 25 °C min^{-1} to 300 °C, then held for 4 min at 300 °C. The gases used in the detector for flame ionization are hydrogen and synthetic air (5.0 quality). GC-MS analysis was performed on a Shimadzu GCMS-QP2010 SE coupled with a DSQ II (EI, 70 eV). A fused silica capillary column Rtx-5MS column (5% diphenyl, 95% dimethylpolysiloxane, 30 m × 0.25 mm × 0.25 μm) was used. The injector temperature was set at 280 °C. After 1 min at 50 °C, the oven temperature was increased by 25 °C/min to 300 °C and kept at 300 °C for 3 min. As a carrier gas, helium at 40 cm s^{-1} linear velocity was used. MS conditions were: ionization voltage of 70 eV, acquisition mass range 50–450 *m/z*. Mass spectral libraries (Wiley Registry of Mass Spectral Data 11th Edition, NIST/EPA/NIH Mass Spectral Library 14) were searched with NIST MS Search software. LC-MS analysis was carried out on a Shimadzu instrument using a C18 reversed-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 μm) using mobile phases A (H_2O/MeCN 90:10 (v/v) + 0.1% HCOOH) and B (MeCN + 0.1 % HCOOH) at a flow rate of 0.6 mL/min. The following gradient was applied: hold at 5% solvent B until 2 min, increase to 20% solvent B until 8 min, increase to 100% solvent B until 16 min and hold until 22 min at 100% solvent B. Low resolution mass spectra were obtained on a Shimadzu LCMS-QP2020 instrument using electrospray ionization (ESI) in positive or negative mode. Melting points were obtained on a Stuart melting point apparatus in open capillary tubes. Batch reactions above the boiling point of MeOH were performed in an Initiator+ single-mode microwave reactor from Biotage, using 2.5 mL Pyrex vials. The reaction temperature was controlled by an external infrared sensor. Reaction times refer to hold times at the temperature indicated. UV/vis spectra were recorded using a fiber-coupled Avantes Starline AvaSpec-2048 spectrometer and were processed using Avasoft 8.7 software. A commercial continuous flow photoreactor (Corning Advanced-Flow Lab Photo Reactor) was used.

CAUTION: Vinyl chloride is a highly toxic, flammable, and carcinogenic gas. Laboratory personnel working with vinyl chloride must familiarize themselves with the potential hazards and prevention measures. It is recommended to use a dedicated gas detector.

Continuous Flow Procedure for the Photochemical Thiol-ene Reaction of Cysteamine Hydrochloride with Vinyl Chloride (Table 1): The liquid feed solution was prepared by dissolving cysteamine hydrochloride, 9-fluorenone, and methyl benzoate as internal standard in a volumetric flask (25 mL) in MeOH. The solution was degassed by sparging with Ar using a balloon and needle. The thermostats were set to the desired temperature beforehand (respective temperature for the reaction, 15 °C LED-cooling). The liquid feed was directly pumped from the volumetric flask using a syringe pump (Syrris-Asia) at maximum flow rate (2.5 mL/min) until the reactor was filled with the substrate solution. Then, the flow rate was reduced to the desired value, the LEDs were turned on (365 nm, 100% intensity) and the MFC was set to deliver the desired amount of VC. After reaching steady state (about 20 minutes), a sample was collected. 100 μL of this sample were diluted with 500 μL of MeOH-d4 and analyzed by ^{1}H NMR (300 MHz).

Telescoped Continuous Flow Procedure for the Synthesis of Thiomorpholine: The liquid feed solution was prepared by dissolving cysteamine hydrochloride (45.44 g, 0.4 mol), 9-fluorenone (0.36 g, 2 mmol, 0.5 mol%) and diphenyl ether (7.264 g, 0.04 mol) as internal standard in a volumetric flask (100 mL) in MeOH. Dissolution was aided by sonication. The thermostats were set to the desired temperature beforehand (20 °C reaction, 15 °C LED-cooling). The liquid feed was directly pumped from the volumetric flask using a syringe pump (Syrris-Asia) at maximum flow rate (2.5 mL/min) until the reactor was filled with the substrate solution. Then, the flow rate was reduced to the desired value (0.139 mL/min), the LEDs were turned on (365 nm, 100% intensity) and the MFC was set to deliver the desired amount of VC (12.1 mLn/min, p = 0.8−0.9 bar). After reaching steady state (about 20 minutes) the output of the reactor was connected to the gas separator/hold vial. About 15 min later, the two pumps delivering the thiol-ene mixture and DIPEA (neat) were turned on and set to the corresponding flow rates (see Scheme 4). The sonication was turned on, the ultrasonic bath was set to the desired temperature (80 °C) beforehand. The temperature of this water bath equilibrated between 76-78 °C and was monitored by a K-type thermometer. 50 min later the cyclization reaction had reached steady state and the reactor output was collected for 7 h (7 fractions of 1 h each). During this time, the thiol-ene mixture in the hold vial was sampled every 1 h (100 μL diluted with 500 μL of MeOH-d4 and analyzed by ^{1}H NMR (300 MHz)). The output of the cyclization reaction was collected every 30 min (100 μL diluted with 500 μL of MeOH-d4 and analyzed by ^{1}H NMR (300MHz)). To the combined fractions 1 M HCl (140 mL) and EtOAc (300 mL) were added. After separation of the phases, the organic phase was washed with 1 M HCl (3×25 mL) until no more thiomorpholine could be detected in the organic phase by LC-MS. Next, ~4 M NaOH was added to the combined aq. phases until pH >13 and extracted 3 x with DCM. Additional NaOH was added, because the pH dropped to ~12. The aqueous phase was further extracted with DCM until no more thiomorpholine could be detected in the aqueous phase by LC-MS. The combined organic fractions were dried over Na_2SO_4, filtered and the solvent was removed by evaporation (100 mbar at 40 °C water bath). After vacuum distillation, 12.74 g (54% overall) thiomorpholine (**1**) was obtained as a colorless oil. Bp: 58-64 °C at 20 mbar.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09–3.05 (m, 4H), 2.57–2.53 (m, 4H), 1.52 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.9, 28.3. The data are in agreement with previously published values.[6,8]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional experimental details, photographs of reactor set-up, further optimizations studies, ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Asirvatham, S.; Thakor, E.; Jain, H. Morpholine and Thiomorpholine: A Privileged Scaffold Possessing Diverse Bioactivity Profile. *J. Chem. Rev.* **2021**, *3*, 247–272. https://doi.org/10.22034/JCR.2021.295839.1123.

(2) Foti, C.; Piperno, A.; Scala, A.; Giuffrè, O. Oxazolidinone Antibiotics: Chemical, Biological and Analytical Aspects. *Molecules* **2021**, *26*, 4280. https://doi.org/10.3390/molecules26144280.

(3) Pearlman, B. A.; Perrault, W. R.; Barbachyn, M. R.; Manninen, P. R.; Toops, D. S.; Houser, D. J.; Fleck, T. J. Process to Prepare Oxazolidinones. US5837870A, November 17, 1998.

(4) Arora, S. K.; Patil, V. J.; Nair, P. S.; Dixit, P. P.; Ajay, S.; Sinha, R. K. Antimycobacterial Compounds. US7691889B2, April 6, 2010.

(5) Hückstadt, H.; Mayer, K.-H. Tetrahydro-1,4-Thiazin (Thiamorpholin). *Synthesis* **1970**, 183.

(6) Kosukegawa, O. Preparation of Thiomorpholine. JP2000256337A, September 19, 2000.

(7) Sommers, A. H.; Horrom, B. W. New Syntheses of Thiamorpholine. The Reduction of Mono- and Diketothiazanes by Lithium Aluminum Hydride. *J. Am. Chem. Soc.* **1954**, *76*, 1187–1188. https://doi.org/10.1021/ja01633a088.

(8) Asinger, F.; Saus, A.; Hartig, J.; Rasche, P.; Wilms, E. Zur Kenntnis der Reaktionsfähigkeit des unsubstituierten Thiomorpholins und alkylsubstituierter Thiomorpholine. *Monatsh. Chem.* **1979**, *110*, 767–789.

(9) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chemie Int. Ed.* **2001**, *40*, 2004–2021. https://doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.

(10) Hoyle, C. E.; Bowman, C. N. Thiol-Ene Click Chemistry. *Angew. Chemie Int. Ed.* **2010**, *49*, 1540–1573. https://doi.org/10.1002/anie.200903924.

(11) Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. Thiyl Radicals in Organic Synthesis. *Chem. Rev.* **2014**, *114*, 2587−2693. https://doi.org/10.1021/cr400441m.

(12) https://haz-map.com/Agents/15 (accessed May 19, 2022)

(13) Webb, D.; Jamison, T. F. Continuous Flow Multi-Step Organic Synthesis. *Chem. Sci.* **2010**, *1*, 675–680. https://doi.org/10.1039/c0sc00381f.

(14) Domokos, A.; Nagy, B.; Szilágyi, B.; Marosi, G.; Nagy, Z. K. Integrated Continuous Pharmaceutical Technologies—A Review. *Org. Process Res. Dev.* **2021**, *25*, 721–739. https://doi.org/10.1021/acs.oprd.0c00504.

(15) Dallinger, D.; Gutmann, B.; Kappe, C. O. The Concept of Chemical Generators: On-Site On-Demand Production of Hazardous Reagents in Continuous Flow. *Acc. Chem. Res.* **2020**, *53*, 1330–1341. https://doi.org/10.1021/acs.accounts.0c00199.

(16) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology - A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chemie Int. Ed.* **2015**, *54*, 6688–6728. https://doi.org/10.1002/anie.201409318.

(17) Kockmann, N.; Thenée, P.; Fleischer-Trebes, C.; Laudadio, G.; Noël, T. Safety Assessment in Development and Operation of Modular Continuous-Flow Processes. *React. Chem. Eng.* **2017**, *2*, 258–280. https://doi.org/10.1039/c7re00021a.

(18) Chen, Y.; Cattoen, M.; Monbaliu, J.-C. M. Mitigation of Chemical Hazards under Continuous Flow Conditions. In *Flow Chemistry − Fundamentals*, Darvas, F.; Dormán, G.; Hessel, V.; Ley, S. V., Eds.; De Gruyter: Berlin, 2021; pp 269−312.

(19) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017**, *117*, 11796–11893. https://doi.org/10.1021/acs.chemrev.7b00183.

(20) Mallia, C. J.; Baxendale, I. R. The Use of Gases in Flow Synthesis. *Org. Process Res. Dev.* **2015**, *20*, 327–360. https://doi.org/10.1021/acs.oprd.5b00222.

(21) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016**, *116*, 10276−10341. https://doi.org/10.1021/acs.chemrev.5b00707.

(22) Williams, J. D.; Kappe, C. O. Recent Advances toward Sustainable Flow Photochemistry. *Curr. Opin. Green Sustain. Chem.*. **2020**, *25*, 100351. https://doi.org/10.1016/j.cogsc.2020.05.001.

(23) Buglioni, L.; Raymenants, F.; Slattery, A.; Zondag, S. D. A.; Noël, T. Technological Innovations in Photochemistry for Organic Synthesis: Flow Chemistry, High-Throughput Experimentation, Scale-up, and Photoelectrochemistry. *Chem. Rev.* **2022**, *122*, 2752–2906. https://doi.org/10.1021/acs.chemrev.1c00332.

(24) https://www.corning.com/worldwide/en/innovation/corning-emerging-innovations/advanced-flow-reactors.html (accessed May 19, 2022)

(25) The calculated maximum residence time is based on the liquid flow rate without taking the gas flow into account.

(26) Janssens, P.; Debrouwer, W.; Van Aken, K.; Huvaere, K. Thiol−Ene Coupling in a Continuous Photo-Flow Regime. *ChemPhotoChem* **2018**, *2*, 884–889. https://doi.org/10.1002/cptc.201800155.

(27) Konan, K. E.; Abollé, A.; Barré, E.; Aka, E. C.; Coeffard, V.; Felpin, F.-X. Developing Flow Photo-Thiol–Ene Functionalizations of Cinchona Alkaloids with an Autonomous Self-Optimizing Flow Reactor. *React. Chem. Eng.* **2022**. https://doi.org/10.1039/D1RE00509J.

(28) Santandrea, J.; Kairouz, V.; K. Collins, S. Continuous Flow Science in an Undergraduate Teaching Laboratory: Photocatalytic Thiol–Ene Reaction Using Visible Light. *J. Chem. Educ.* **2018**, *95*, 1073–1077. https://doi.org/10.1021/acs.jchemed.7b00639.

(29) Tyson, E. L.; Ament, M. S.; Yoon, T. P. Transition Metal Photoredox Catalysis of Radical Thiol-Ene Reactions. *J. Org. Chem.* **2013**, *78*, 2046–2050. https://doi.org/10.1021/jo3020825.

(30) Standard prices from Sigma-Aldrich are 76.80 € for 500 g 9-fluorenone (98%) and 172 € for 1 g $Ru(bpy)_3(PF_6)_2$.

(31) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075–10166. https://doi.org/10.1021/acs.chemrev.6b00057.

(32) El-Hallag, I. S.; Al-Youbi, A. O.; Obaid, A. Y.; El-Mossalamy, E. H.; El-Daly, S. A.; Asiri, A. M. Electrochemical Investigation of Cysteamine at Carbon Fiber Microdisk Electrode. *J. Chil. Chem. Soc.* **2011**, *56*, 837–841. https://doi.org/10.4067/S0717-97072011000400003.

(33) Steiner, A.; De Frutos, O.; Rincón, J. A.; Mateos, C.; Williams, J. D.; Kappe, C. O. N -Chloroamines as Substrates for Metal-Free Photochemical Atom-Transfer Radical Addition Reactions in Continuous Flow. *React. Chem. Eng.* **2021**, *6*, 2434–2441. https://doi.org/10.1039/d1re00429h.

(34) Williams, J. D.; Nakano, M.; Gérardy, R.; Rincón, J. A.; De Frutos, Ó.; Mateos, C.; Monbaliu, J. C. M.; Kappe, C. O. Finding the Perfect Match: A Combined Computational and Experimental Study toward Efficient and Scalable Photosensitized [2 + 2] Cycloadditions in Flow. *Org. Process Res. Dev.* **2019**, *23*, 78–87. https://doi.org/10.1021/acs.oprd.8b00375.

(35) Xia, J. B.; Zhu, C.; Chen, C. Visible Light-Promoted Metal-Free C-H Activation: Diarylketone-Catalyzed Selective Benzylic Mono- and Difluorination. *J. Am. Chem. Soc.* **2013**, *135*, 17494–17500. https://doi.org/10.1021/ja410815u.

(36) Monnier, H.; Wilhelm, A. M.; Delmas, H. Effects of Ultrasound on Micromixing in Flow Cell. *Chem. Eng. Sci.* **2000**, *55*, 4009–4020. https://doi.org/10.1016/S0009-2509(00)00067-1.

(37) Donnelly, K.; Baumann, M. Scalability of Photochemical Reactions in Continuous Flow Mode. *J. Flow Chem.* **2021**, *11*, 223–241. https://doi.org/10.1007/s41981-021-00168-z.

(38) Steiner, A.; Roth, P. M. C.; Strauss, F. J.; Gauron, G.; Tekautz, G.; Winter, M.; Williams, J. D.; Kappe, C. O. Multikilogram per Hour Continuous Photochemical Benzylic Brominations Applying a Smart Dimensioning Scale-up Strategy. *Org. Process Res. Dev.* **2020**, *24*, 2208–2216. https://doi.org/10.1021/acs.oprd.0c00239.

(39) Lévesque, F.; Di Maso, M. J.; Narsimhan, K.; Wismer, M. K.; Naber, J. R. Design of a Kilogram Scale, Plug Flow Photoreactor Enabled by High Power LEDs. *Org. Process Res. Dev.* **2020**, *24*, 2935–2940. https://doi.org/10.1021/acs.oprd.0c00373.