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Graphical Abstract

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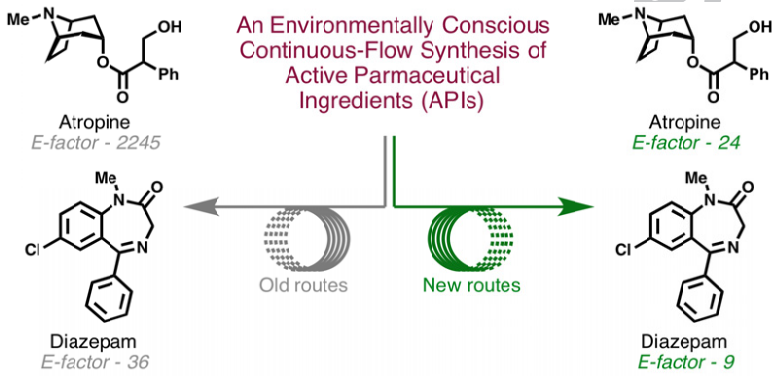

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ABSTRACT

Minimizing the waste stream associated with the synthesis of active pharmaceutical ingredients (APIs) and commodity chemicals is of high interest within the chemical industry from an economic and environmental perspective. In exploring solutions to this area, we herein report a highly optimized and environmentally conscious continuous-flow synthesis of two APIs identified as essential medicines by the World Health Organization, namely diazepam and atropine. Notably, these approaches significantly reduced the E-factor of previously published routes through the combination of continuous-flow chemistry techniques, computational calculations and solvent minimization. The E-factor associated with the synthesis of atropine was reduced by 94-fold (about two orders of magnitude), from 2245 to 24, while the E-factor for the synthesis of diazepam was reduced by 4-fold, from 36 to 9.

1. Introduction

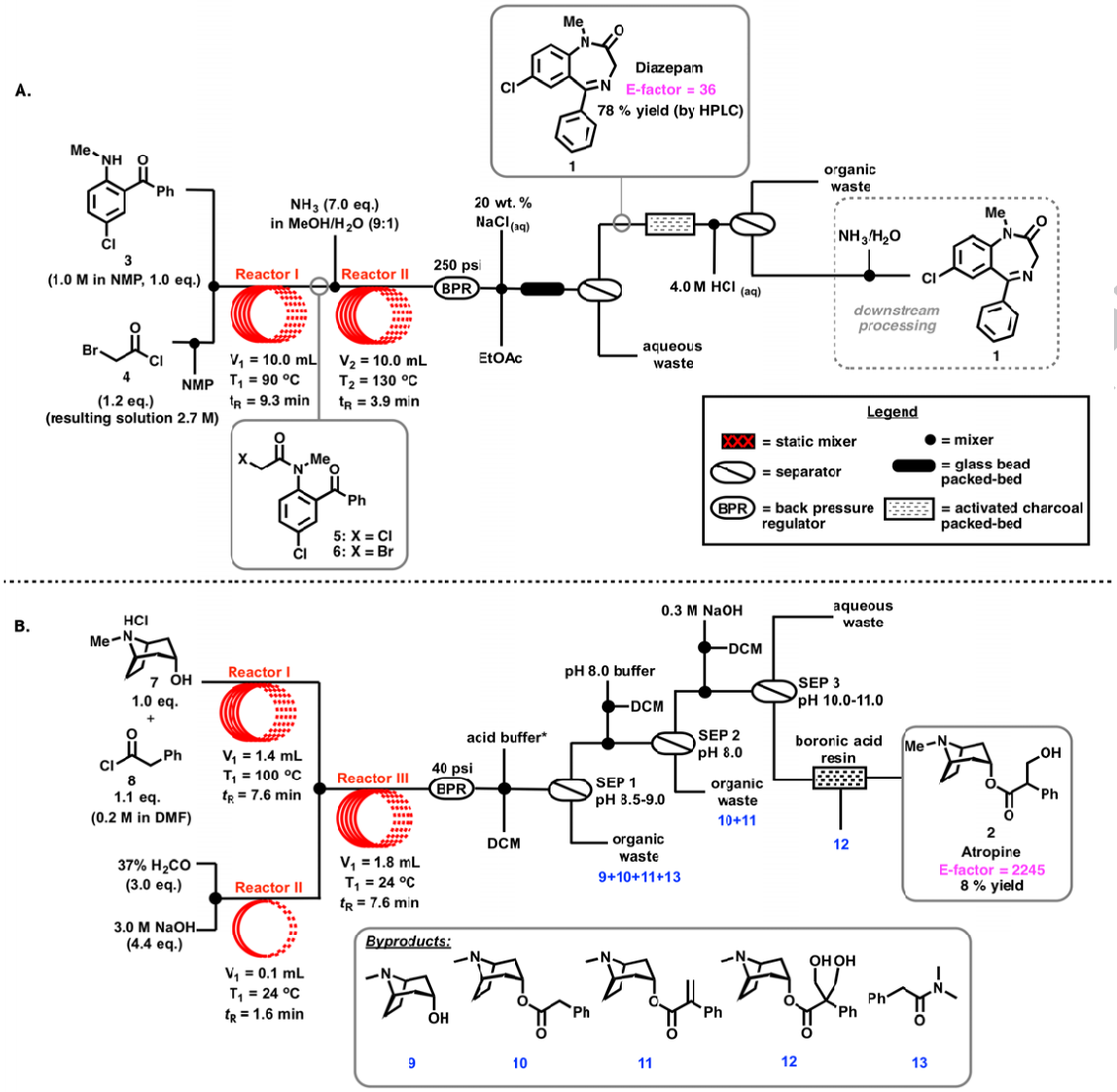
A growing interest in minimizing waste generation associated with chemical synthesis drives chemists towards more sustainable alternatives to traditional synthesis.[1,2] Various mass-based metrics such as E-factor,[3] process mass intensity (PMI),[4] and atom economy[5,6] have been used to define efficiencies of chemical manufacturing processes.[7,8] The E-factor was proposed by Sheldon and is calculated for a given reaction or for a synthetic route. It is defined as the ratio of the mass of waste produced (excluding water) to that of product obtained (Equation 1). The number estimates the efficiency of a chemical process, i.e. higher E-factors indicate larger amounts of waste and a less ideal process. Many factors contribute to the increase in E-factor in synthetic processes: (*i*) low yield of the desired product, *(ii)* excess reagents, *(iii)* long, multi-step reaction sequences and *(iv)* extraction and purification solvents. Usually, the value tends to increase with the molecular complexity of the product. This trend becomes evident when considering the increasing average E-factor from the bulk chemical (<1 - 5), to fine chemical (5 - 50), to pharmaceutical industries (25 - >100).[3]

Equation (1): E(nvironmental)-factor = kg waste/kg product

Numerous industries are concerned with the environmental impacts of their operations, and yet, the poorest E-factors in the chemical sector are found in pharmaceuticals.[3] Fortuitously, the pharmaceutical industry is continuously adapting and evolving to improve the time between hit-to-lead discovery and production of the target molecule while driving towards sustainable approaches.[9,10] In facilitating both of these requirements, continuous-flow chemistry has gained momentum given its numerous advantages over traditional batch processes.[11] We propose that mindfully using flow technologies could facilitate syntheses while significantly reducing waste production. The benefits of flow chemistry include *(i)* precise control of reaction conditions due to efficient heat and mass transfers, *(ii)* high reaction reproducibility, *(iii)* the possibility of system automation, *(iv)* safer handling of hazardous reagents along with *(v)* a decreased reactor footprint.[12–18]

These attractive properties can minimize waste generation and correlate with reaction efficiency.[12–18] In this respect, utilizing continuous-flow to mediate reaction telescoping can avoid wasteful isolation and purification sequences. Taking advantage of the rapid heat transfer present in flow systems allows for higher reaction concentrations; less solvent is required as a heat-transfer medium. Neat solids can also be used in continuous-flow systems at temperatures above their melting points, removing need for solvent.[19] As reaction scale increases during the drug design process, continuous-flow enables a straightforward and linear scale-up with minimal re-optimization compared to traditional batch processes. A combination of the above factors results in a reduction in environmental impact.[12]

The structural complexity of many active pharmaceutical ingredients (APIs) typically implies an elaborate synthesis.[2] Although in recent years continuous-flow chemistry has emerged as a powerful tool for streamlining multi-step syntheses,[13,20–28] little focus has been put on targeting waste reduction. With this in mind, we aimed to synthesize APIs diazepam **1** and atropine **2**



Scheme 1. Previously reported continuous-flow syntheses of diazepam **1** (A) and atropine **2** (B).

with dramatically lower E-factor by taking advantage of the beneficial properties of continuous-flow chemistry. In considering that the pharmaceutical industry produces chemicals with E-factors ranging from 25 to more than 100, we aimed to attain an E-factor less than 25 for both APIs.

Diazepam **1** and atropine **2** are two APIs identified by the World Health Organization (WHO) as essential medicines.[19] Since the discovery of 1,4-benzodiazepine derivatives as central nervous system depressants, considerable research has been carried out on compounds featuring this interesting seven-membered ring system.[29] Diazepam **1**, commercially known as Valium, is used to treat anxiety and epilepsy.[30] First synthesized by Leo Sternbach at Hoffman-La Roche in 1959, it entered the market in 1963 and became the top selling pharmaceutical in the United States between 1968 and 1982.[31] Atropine **2** (*D/L*-hyoscyamine) is a naturally occurring alkaloid of the tropane family found in several solanaceous plants.[32,33] It is a competitive, non-selective antagonist of muscarinic acetylcholine (M2) receptors. It serves as a preoperative and sedation drug for short-term medical procedures.[34] This molecule was first synthesized in 1879 by Landenburg *via* a Fischer Speier esterification of tropine with tropic acid in the presence of hydrochloric acid.[35] Although several syntheses have been examined to pursue this challenging target[35–37], the majority of commercial atropine is still primarily extracted from plants.[32,33]

Our group recently demonstrated the continuous-flow syntheses of diazepam **1** and atropine **2**.[19,28] These prior syntheses gave E-factor values of 36 and 2245 for diazepam **1** and atropine **2** respectively (Scheme 1). Herein, we report our efforts to decrease the E-factor below 25 for each synthesis by minimizing solvent usage, improving synthetic route to minimize byproduct formation, and employing computational analysis to improve the purification of the target molecule.

2. Results and Discussion

*2.1. The synthesis of diazepam **1***

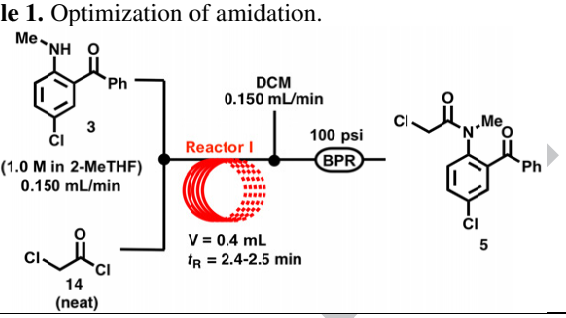
The previously reported continuous-flow synthesis of diazepam began with an amidation reaction between bromoacetyl chloride **4** and 5-chloro-2-(methylamino)benzophenone **3** in N-methyl-2-pyrrolidone (NMP) to produce a mixture of amides **5** and **6** (Scheme 1A).[19] Next, a solution of ammonia in MeOH / H_2O was mixed with the reaction stream to cyclize amides **5** and **6** into diazepam **1**. The crude mixture then underwent two subsequent in-line extractions. The first extraction removed water-soluble impurities through the addition of an aqueous sodium chloride

(NaCl, 20 wt. %) and ethyl acetate (EtOAc). With diazepam **1** residing in the organic phase, separation from the aqueous phase was achieved by a gravitational phase-separator. A 78% yield was obtained after the first extraction. The organic stream was then passed through a charcoal column and mixed with a stream of aqueous HCl (4 M) to protonate diazepam **1** and enable its extraction into the aqueous phase. This second in-line extraction removed organic soluble impurities from the product stream. Next, protonated diazepam **1** was separated from the organic stream through an additional gravitational phase-separator. The product was isolated in a pure form after a continuous recrystallization process using downstream neutralization with aqueous ammonium hydroxide.

The calculated E-factor up to the first work-up is 36 for this process (Scheme 1A); our target was to decrease it below 25. Solvent is often the primary contributor to E-factor[3], and in this instance, extraction with EtOAc contributes to two thirds of the waste produced. In order to eliminate the need for a separate extraction solvent, we investigated a solvent that could be used for both reaction and extraction purposes. We chose 2-methyltetrahydrofuran (2-MeTHF) for several factors: *(i)* the solubility of the starting materials and most products were within a reasonable range to enable reaction concentrations >0.9 M, *(ii)* the low density at 0.85 g/mL minimizes the mass of waste produced, (*iii*) 2-MeTHF is not reactive with the reagents at high temperatures, and (*iv*) 2-MeTHF is immiscible with water, i.e. enables an in-line aqueous extraction without additional solvent.

After identifying 2-MeTHF as an ideal solvent, we began screening conditions for the amidation step between a solution of benzophenone **3** (1 M in 2-MeTHF) and neat chloroacetyl chloride ($ClCH_2COCl$) **14** (Table 1). To prevent clogging at the end of the reactor upon cooling or at the BPR, dichloromethane (DCM) was used to dilute the reaction stream. As demonstrated in the previous flow process, the amidation proceeds even in the absence of a base. Upon heating to 80 °C with 1.25 equiv. of $ClCH_2COCl$ **14**, amide **5** was obtained in near quantitative yields (Table 1, Entries 2 and 3). Decreasing the temperature to 70 °C resulted in a 20% decrease in yield (Entry 1), and decreasing the $ClCH_2COCl$ **14** addition also resulted in lower yields (Entries 4-7). The E-factor for this step was improved slightly by using neat $ClCH_2COCl$ **14** instead of a 2.7 M solution of $BrCH_2COCl$ **4** in NMP. Furthermore, this approach led to a four-fold decrease of the reaction time (from 9.3 min down to 2.4 min).

Table 1. Optimization of amidation.

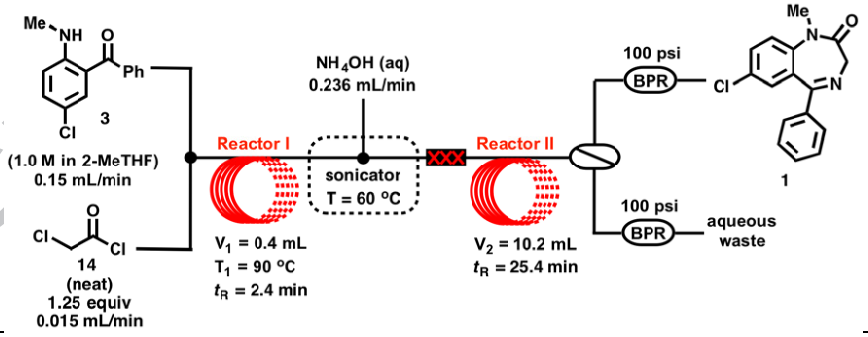


Entry	**Reactor I** temperature (°C)	$ClCH_2COCl$ **14** Flow rate (µL/min)	$ClCH_2COCl$ **14** Equiv	Yield (%)[a]
1	70	15.0	1.25	79
2	80	15.0	1.25	98
3	90	15.0	1.25	99
4	80	13.5	1.13	89
5	90	13.5	1.13	92
6	120	13.5	1.13	88
7	120	12.0	1.00	83

[a]Isolated yields. Reaction was quenched with aqueous saturated $NaHCO_3$ solution within the collection vial.

With the amidation reaction optimized, we then investigated the telescoped synthesis of diazepam **1** (Table 2). When determining a suitable ammonia source, aqueous ammonium hydroxide was chosen to avoid addition of excess organic solvent. In addition, an aqueous stream was necessary to prevent clogging due the formation of ammonium chloride. Upon the addition of ammonium hydroxide, amide **5** precipitated out of solution. To prevent clogging at the T-mixer, ammonium hydroxide addition was performed in a heated sonicating bath. At 60 °C, no reaction occured in the sonicating bath. To ensure efficient mixing had happened between the aqueous and organic phases, a static mixer was installed between the ammonium

Table 2. Cyclization optimization to produce diazepam **1**.



Entry	NH_4OH (NH_3 28 – 30 wt. %) to H_2O vol. ratio	NH_4OH Equiv.	**Reactor II** temperature (°C)	Yield (%)[a]
1	No dilution	23	90	49
2	No dilution	23	100	NA[b]
3	1:1	11	120	41
4	3:1	14	100	46
5	3:1	14	110	51
6	3:1	14	120	NA[b]
7	4:1	18	100	46
8	4:1	18	110	41
9	4:1	18	120	NA[b]
10	9:1	21	100	55
11	9:1	21	110	NA[b]

hydroxide addition and Reactor II.

The initial screening was performed with concentrated ammonium hydroxide solution (ca. 28-30 wt. % based in NH_3) with a reactor temperature of 90 °C, which resulted in a 49% yield (Table 2, Entry 1). When the reactor temperature was increased to 100 °C, violent gas evolution was observed in the reactor and no product was formed (Entry 2). Because neither 2-MeTHF or water alone would result in gas evolution when passed through the heated reactor, we hypothesized the gas present was gaseous ammonia. To prevent ammonia gas evolution, the backpressure was first increased. However, installing backpressures >100 psi resulted in pump failure. We therefore screened different dilutions of the ammonium hydroxide solution. By diluting the concentrated NH_4OH solution in a 1:1 vol. ratio with water, Reactor II could operate at 120 °C without gas evolution (Entry 3). However, a concomitant drop in yield to 41% prompted screening both ammonium hydroxide dilutions and reactor temperatures. When the solution was diluted to a 3:1 or 4:1 volume ratio in water, the reactor could be heated to 110 °C without gas evolution (Entries 4-9) with only minimal changes in yield observed. Diluting the solution to a 9:1 vol. ratio in water and passing the resulting solution through a reactor heated to 100 °C provided a 55% yield (Entry 10). Further heating the reactor to 110 °C resulted in detrimental gas evolution (Entry 11). With a 55% yield of diazepam **1** in hand, our target E-factor was reached at 9. Furthermore, experiments demonstrated that the static mixer before Reactor II could be removed since a negligible change in yield from 55% to 51% was obtained (Table 2, Entry 12).

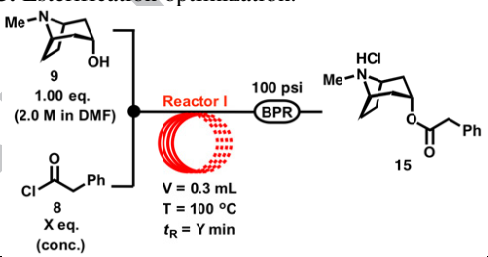
Improving an already efficient synthesis was not trivial, but overall, the E-factor for the synthesis of diazepam **1** was decreased by 4-fold (from 36 down to 9) and now resides in the range of fine chemicals processes. A key point contributing to this success was the simplified setup achievable upon using 2-MeTHF as both the reaction and extraction solvent.

*2.1. The synthesis of atropine **2***

Our previous synthesis of atropine **2** (Scheme 1B)[28] reported in 2015 was unfortunately met with the formation of several byproducts. Although initial esterification of the tropine•HCl salt **7** with phenylacetyl chloride **8** ($Cl(CO)CH_2Ph$) gave the corresponding ester **10** in complete conversion, the subsequent aldol condensation using aqueous formaldehyde and aqueous sodium hydroxide (3 M NaOH) was challenging. Atropine **2** is very sensitive to elimination affording the thermodynamically more stable apoatropine **11**. Furthermore, the tropine ester bond is prone to saponification in basic conditions yielding tropine **9**. Additionally, the double aldol adduct **12** is observed concomitantly with DMF degradation adduct **13**. Since these byproducts are structurally similar, an extensive set of in-line extractions were needed to obtain the desired product in high purity. The mass of DCM used for the three extractions contributed up to 63% of the waste generated and gave rise to an E-factor of 2245. The other main contributor to the high E-factor for this synthesis is the low overall yield of atropine **2** obtained (8%). In order to decrease the E-factor for the synthesis of atropine **2**, several aspects were investigated herein: *(i)* improvement of the esterification transformation, *(ii)* minimization of byproduct formation in the aldol transformation, and (*iii*) design of a new extraction procedure avoiding the use of DCM.

First, the esterification was optimized to increase concentration, minimize equivalents, and reaction time, and maximize conversion (Table 3). In the previous synthesis, tropine•HCl **7** and phenylacetyl chloride **8** were added from a single stock solution.[28] This forced the use of the tropine•HCl salt **7** to prevent unwanted reactivity prior entry into the reactor. Using two distinct incoming streams, *i.e*. tropine **9** in DMF and neat phenylacetyl chloride **8**, allowed use of the tropine free base in a 10-fold concentration increase. Using 1.05 equiv. of phenylacetyl chloride **8** as a 2 M solution in DMF gave 80% conversion in a 10 minutes residence time (Entry 1). The addition of larger ratios of phenylacetyl chloride **8** increased conversion to 87% (Entry 2). Complete conversion was obtained in 10 minutes when using neat phenylacetyl chloride **8** (Entry 3). Notably, the residence time could be further decreased to 3.5 minutes while maintaining complete conversion (Entry 5). This improvement of reaction time also prevented the formation of byproduct **13**. Satisfyingly, tropine **9** was able to be used in concentrations close to saturation and phenylacetyl chloride **8** was used neat. This ensured high throughput while reducing waste and solvent quantities. Additionally, the use of two streams of reagents allowed for the tertiary amine of ester **15** to act as an internal base for the reaction, removing the need for additional base in the second step.

Table 3. Esterification optimization.

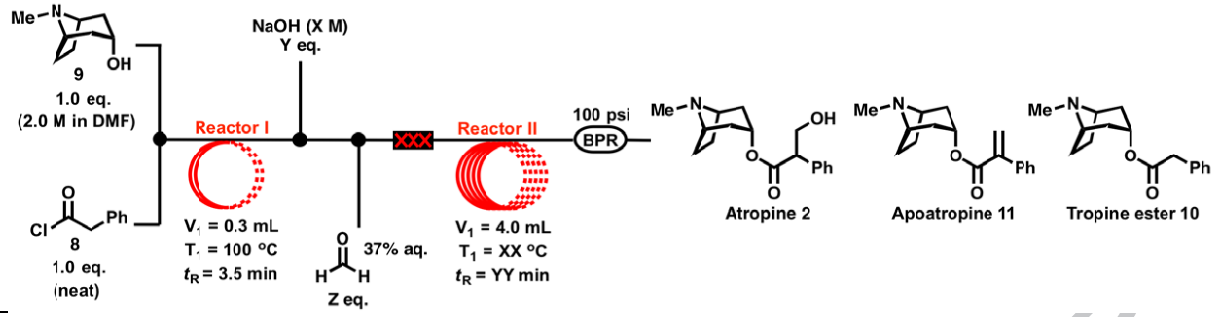


Entry	$Cl(CO)CH_2Ph$ **8** equiv.	$Cl(CO)CH_2Ph$ **8** conc. (M)	t_R (min)	Conversion (%)[a]
1[b]	1.05	2.0[c]	10	80
2[b]	1.10	2.0[c]	10	87
3	1.00	7.6[d]	10	99
4	1.00	7.6[d]	7.0	99
5	1.00	7.6[d]	3.5	99

[a]GCMS conversion. [b]40 psi BPR. [c]Solution in DMF. [d]Neat.

Next, the challenging optimization of the aldol addition to produce atropine **2** was examined (Table 4). Previously, the use of super-stoichiometric amounts of sodium hydroxide (4.4 equiv.) favored E_1CB elimination to form apoatropine **11** and lead to the cleavage of the tropine ester bond to yield tropine **9**.[28] Byproduct **12** was a result of a double addition of formaldehyde, again favored by the use of super-stoichiometric amount of formaldehyde (3 equiv.). It was found that alterations made to the esterification reaction (increasing concentration, modifying stoichiometry, and switching from tropine•HCl **7** to tropine free base **10**) significantly affected the tandem sequence. The DMF solution exiting the first reactor was oversaturated and the tubing required heating (≥50 °C) to prevent crystallization of the mixture. This highlights another advantage of continuous-flow which is the possibility of pumping a solid above its melting point. Upon addition of NaOH and formaldehyde, formation of a slug-flow type regime was observed as the incoming stream is only sparingly miscible with the reagents needed for the second step. A static mixer was added to improve the mixing before entering the second reactor.

Table 4. Aldol optimization to produce atropine **2**.



Entry	NaOH Conc (M); Equiv	H_2CO Equiv	**Reactor II** temperature (°C)	**Reactor II** tR (min)[a]	Conversion (%)[b,c]	Ratio **11**:**2**:**10**[b]
1	3; 3	6	23	8	0	0:0:1
2	3; 3	6	50	8	30	0.14:1:2.7
3	3:3	6	50	24	53	0.8:1:1.6
4	3; 3	6	100	8	49	0.88:1:2
5	3; 3	6	150	8	67	2.7:1:1.8
6	3;1.2	6	100	24	78(44[e])	0.64:1:0.45
7	3;1.2	6	100	8	67	0.65:1:0.8
8	1;1.2	6	100	8	75	0.8:1:0.6
9	1;1.2	6	100	8	64[d]	0.54:1:0.85
10	1;1.2	3	100	8	40	0.5:1:2.3

[a]Reactor size was adjusted to match the desired residence time. [b]Determined by ^{1}H NMR of the crude mixture. [c]Conversion of tropine ester **10** to atropine **2** and apoatropine **11**. [d]Static mixer was removed. [e]NMR yield using trimethoxybenzene as an internal standard.

Under these modified conditions, no conversion of the tropine ester **10** to the desired product **2** was observed at room temperature (Entry 1) when three equiv. of 3 M NaOH were used. Furthermore, the byproduct arising from double hydroxymethylation **12** was not observed. Increasing the temperature to 50 °C gave a 30% conversion for a residence time of eight minutes (Entry 2). Further increasing the temperature to 100 °C or lengthening the reaction time to 24 minutes increased both the conversion to 49% and 53%, respectively (Entries 3 and 4). A further increase in conversion was observed at 150 °C, but higher temperatures led to augmented elimination to **11** (Entry 5.) Decreasing the amount of base to 1.2 equiv. (i.e. 0.2 equiv. for the aldol reaction and 1 equiv. for the deprotonation of **15**) at 100 °C afforded 78% conversion with a 0.64 to 1 ratio of **11** to **2** (Entry 6). Notably, the reaction time could be decreased to 8 minutes when using a 1 M solution of NaOH while maintaining a conversion of 75% (Entry 8). Achievement of this lower reaction time is likely due to improved mixing between the slugs enabled by the additional water in the reactor. The static mixer was still needed under these conditions as about 10% conversion was lost upon its removal (Entry 9). Attempts to decrease the amount of formaldehyde resulted in reduced conversion (Entry 10).

The two-step sequence to obtain atropine **2** was improved and a yield of 44% was obtained under optimal condition (Table 4, Entry 6). A better control of the reaction was achieved and half of the undesired byproducts were eliminated from the product distribution. The E-factor obtained before the in-line extraction is seven, a significant improvement compared to 123 obtained at the same point in the previous synthesis.

Next, the in-line purification of atropine **2** was explored to identify an optimal extraction solvent while minimizing the quantity of solvent required. We envisaged that controlling the pH of the product stream would allow atropine to be separated from its byproducts based upon differences in pKa. To expedite this process, the distribution coefficients of atropine **2** and its byproducts in various organic solvents were calculated from pH 1-14 using SPARC computational modeling (Figure 1A-D).[38,39] In SPARC, coefficients are calculated from algorithms analyzing quantitative structure-activity relationships through linear free-energy relationships and quantum effects based around perturbation molecular orbital methods. A variety of molecular descriptors are harnessed to calculate solute-solvent interaction based upon dispersion, induction, dipole-dipole and hydrogen bonding interactions. The logD values generated are calculated with respect to water at standard temperature and pressure.

The calculated values suggested that DCM was not an ideal extraction solvent in the process since atropine **2** is soluble in it at all pH values. However, greener solvents could be used to achieve good separation (Figure 1A-D). The computational models indicate that diethyl ether, toluene, butyl acetate, 2-MeTHF, *N*-butyl ether and ^{t}butyl methyl ester have appropriate extraction properties to isolate atropine **2** from the mixture. At pH values below 7, atropine **2** and byproduct **9** would remain in the aqueous phase while the byproducts **10** and **11** would predominantly transfer to the organic phase. Next, simply adjusting the pH of the solution to >9 would drive atropine **2** into the organic phase while byproduct **9** stays in the aqueous layer. This pH-controlled extraction was tested with diethyl ether, butyl acetate and ^{t}butyl methyl ester under typical batch techniques (Supplementary Information). Diethyl ether was optimal with atropine **2** remaining in the aqueous phase at pH 6.5 and then transferring quantitatively into the organic phase at pH 10.

Next, this extraction process was translated into continuous-flow (Figure 2E). In analyzing the performance of this process, a 1:1 mixture of atropine **2** and apoatropine **11** were mixed in buffer (pH 6.5, NH_4Cl, 0.42 M) and flowed through a Zaiput liquid-liquid separator module with diethyl ether as the organic phase. In agreement with both the computational calculations and our batch model, quantitative levels of the byproduct (apoatropine **11**) were extracted into diethyl ether, leaving only atropine **2** in the aqueous phase. Although atropine **2** could be further abstracted into organic solvents at >pH 9 (Supporting Information), it can also be crystalized from the aqueous phase in the future downstream processes.[40] The decision to isolate

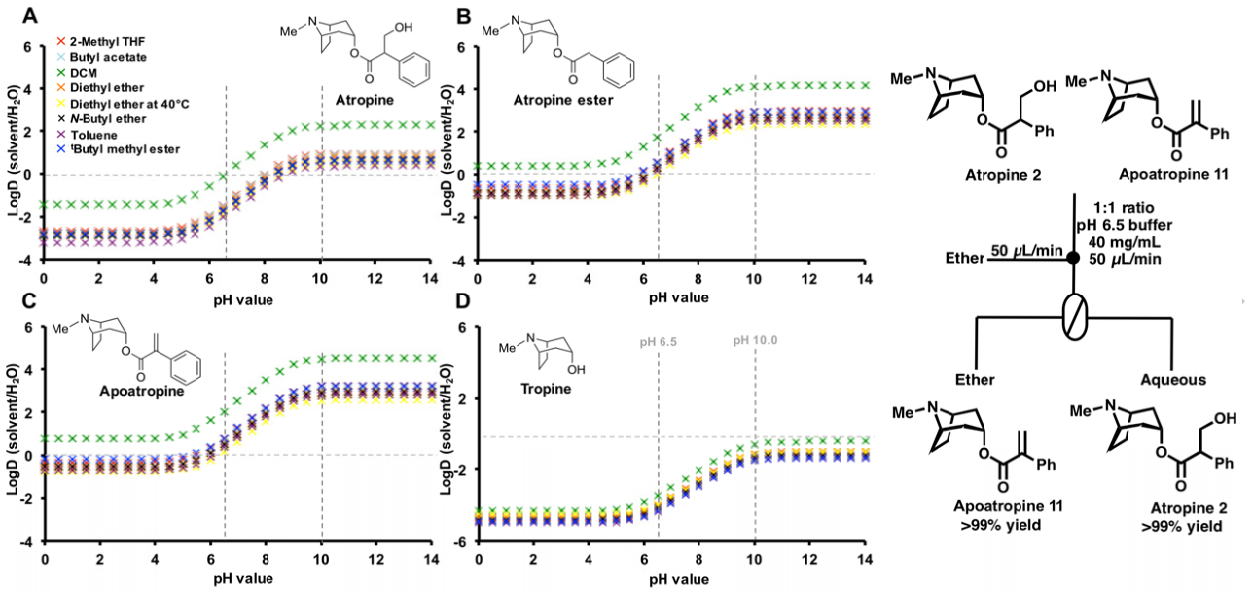
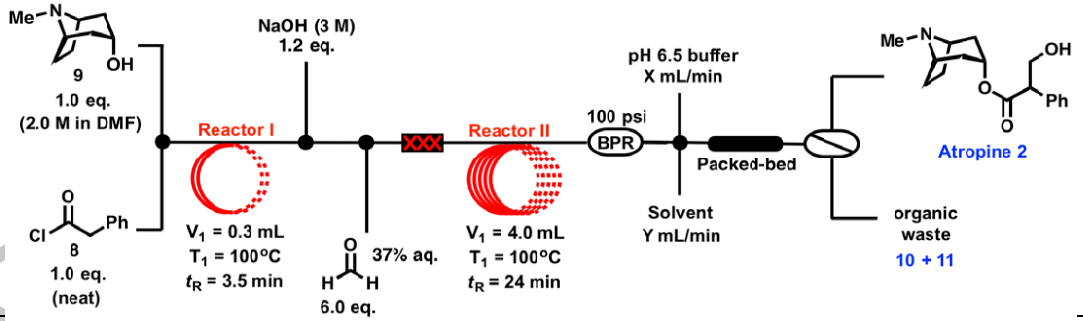


Figure 1. Computational data for the effective separation of atropine **2** from byproducts **9**, **10**, and **11** and the model continuous-flow purification platform. A) The LogD values for atropine **2** in a range of solvents. As shown here, DCM is less effective in retaining atropine **2** under acidic conditions. B) The LogD values for the atropine ester byproduct **10** in a range of solvents. This byproduct is soluble at all pH values in DCM. C) The LogD values for apotropine **11** in a range of solvents. This species is soluble in DCM at all pH values. D) The LogD values for tropine **9** in a range of solvents. E) The data generated in these computational plots was used as a guideline to design an effective continuous-flow separation. Batch related separation experiments to derive ether as the most effective solvent are available in the Supplementary Information.

atropine in the aqueous phase further lowered the E-factor by removing the need for additional organic solvent while decreasing reactor footprint.

This purification model was then tested on the optimized flow system (Table 5). Clogging was observed when pH 6.5 buffer was added to the reaction stream. A cross mixer was used in order to add the diethyl ether and the buffer at once and prevent precipitation. When a 1:1 ratio of pH 6.5 buffer to incoming reaction stream was used, the desired extraction pH was not reached and only traces of atropine **2** were extracted in the aqueous layer (Entry 1). Increasing the flow rate of buffer allowed the system to reach the desired extraction pH, *i.e.* 6.5 (Entry 2). Disappointingly, the selectivity for the exclusive extraction of atropine **2** was lost. It is presumed that the residual DMF coming from the esterification reaction affected the product distribution during the extraction. We then investigated the addition of a packed-bed to aid with mixing. A 6 cm packed-bed containing stainless steel (SS) beads was used with no

Table 5. Optimization of in-line atropine **2** extraction.



Entry	Aqueous quench; mL/min	Solvent; mL/min	Packed-bed content; length (cm)	pH of aqueous stream	Aqueous stream content[a]	Organic stream content[b]
1	pH 6.5 buffer[c], 0.3[c]	Et_2O, 0.6	NA	9	traces 2	2+10+11
2	pH 6.5 buffer[c], 0.4	Et_2O, 0.6	NA	6.5	2+10+11	2+10+11
3	pH 6.5 buffer[c], 0.4	Et_2O, 0.6	SS beads; 6	6.5	2+10+11	2+10+11
4	pH 6.5 buffer[c], 0.4	Et_2O, 0.6	Sand; 23	6.5	2+10+11	2+10+11
5[d]	pH 6.5 buffer[c], 0.4	Et_2O, 0.3 (x2)	Sand; 6 (x2)	6.5	2+10+11	2+10+11
6	water, 0.3	Et_2O, 0.15	Sand; 6	11	2+10+11	2+10+11
7	water, 0.3	DCM, 0.15	Sand; 6	11	2+10+11	2+10+11
8	water, 0.3	PhMe, 0.15	Sand; 6	11	2[e] (22%[f])	2+10+11 (1:0.95:0.72[g])

[a] Determined by ^{1}H NMR after basification to pH 10 adjustment and DCM extraction. [b] Determined by ^{1}H NMR. [c] NH_4Cl buffer (0.42 M) [d] 1:1 ratio of 6.5 buffer to incoming reaction stream (295 uL/min). Reaction stream was met with 6.5 buffer stream and 1st Et_2O stream (0.3mL/min), mixed through a 6 cm packed-bed, extracted once. The resulting aqueous stream was met with 2nd Et_2O stream (0.3 mL/min), mixed in a second 6 cm packed-bed and extracted again. [e] Contains 4% of **11** and 6% of **10** by ^{1}H NMR. [f] Yield based on ^{1}H NMR using trimethoxybenzene as an internal standard.[g] Ratio of

improvement in extraction efficiency (Entry 3). A longer (23 cm) packed-bed containing sand was used without any improvement in extraction efficiency but did lead to a smaller pressure drop in the system compared to the SS bead column (Entry 4). Performing two extractions with Et_2O likewise resulted in an undesired mixture of products. Re-examining the data in Figure 1 indicated that atropine **2** has a greater affinity for water at elevated pH compared to the other byproducts such as apoatropine **11** and the tropine ester **10**, with the exception of tropine **9**. This observation is also consistent with experimental data (Table 5, Entry 1). Initially, an extraction at basic pH was not considered due to the possible elimination of atropine **2** to apoatropine **11** or ester cleavage to yield tropine **9**. The similar solubility of atropine **2** and tropine **9** at elevated pH was also a concern for using this approach. Fortunately, our optimized conditions for the synthesis of atropine **2** did not yield any residual tropine **9** and we were hence encouraged to explore extraction under basic condition (pH >8). Although diethyl ether and DCM did not yield a clean extraction (Entries 6 and 7), no additional apoatropine **11** was formed in the process. Gratifyingly, toluene (PhMe) was able to selectively extract atropine **2** from the mixture (Entry 8). This finding corroborates the computational data (Figure 1A) that indicated a smaller logD for atropine **2** in PhMe at pH 11.

Overall, the full synthesis of atropine **2**, including the extraction, gave a 22% yield of the desired product. This transposes to nearly a 3-fold increase in yield and a significantly improved E-factor of 24, a 94-fold difference from the previous route.

3. Conclusion

The expedited synthesis of APIs has been aided by the development of continuous-flow approaches. However, the environmental consequences of syntheses are rarely considered. We presented efficient E-factor optimization strategies for the synthesis of two essential APIs: atropine and diazepam. Notably, our approaches significantly reduced the waste generated in both routes through the combination of continuous-flow chemistry techniques, computational calculations and solvent minimization. Diazepam waste was decrease by four-fold and now resides in the range of fine chemicals processes. Atropine displays an impressive two orders of magnitude improvement in term of sustainability. We believe the continuous-flow technology and rational strategies discussed herein to reduce the E-factor pave the way for further APIs syntheses that are more environmentally conscious.

4. Experimental

4.1 Material and methods

Unless otherwise indicated, all commercially available reagents and solvents were used directly from the supplier without further purification. Membrane liquid-liquid separators and backpressure regulators (BPRs) were purchased from Zaiput Flow Technologies, and the PTFE microfiltration membranes were bought from Pall Zefluor with 0.5 or 1.0 µm pore size. The reactors were constructed from high-purity perfluoroalkoxy (PFA) tubing with 1/16" OD and 0.03″ ID and PEEK fittings purchased from IDEX Health & Science Technologies, unless otherwise noted. Harvard Apparatus PhD Ultra syringe pumps were used to pump reagents and solutions from 8-mL high-pressure stainless steel syringe with 1/16" SWAGELOCK® from Harvard Apparatus unless otherwise noted. A 5 mL glass syringe was used with phenylacetyl chloride due to incompatibility with stainless steel. The packed-bed scavenger was assembled from a stainless steel tube (1/4" OD, 3/16" ID), Stainless Steel (SS) frits 0.20 µm, and stainless steel 1/16″ female nut from SWAGELOCK®. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using $CDCl_3$ (7.27 ppm) or d_6-DMSO (2.50 ppm), unless otherwise indicated on a Varian 500 MHz spectrometer or Bruker 400 MHz spectrometer.

4.2 Synthetic procedures

Diazepam **1**: A 25 mL solution of 5-chloro-2-(methylamino)benzophenone (6.14 g, 1 M) and dodecane (0.57 mL, 0.1 M) in 2-MeTHF was loaded into a SS syringe and pumped via syringe pump into the system at 0.15 mL/min and neat chloroacetyl chloride was loaded into a SS syringe and pumped via syringe pump at 0.015 mL/min. The streams met in a T-mixer (0.02" ID) before entering a reactor made from 0.04" ID PFA tubing (0.4 mL volume) preheated to 90 °C in an oil bath. Upon exiting the reactor, the stream was met with aqueous NH_4OH solution (28-30 wt % diluted in water in a 9:1 volumetric ratio) pumped at 0.234 mL/min via syring pump in a sideways T-mixer (0.04" ID) that was sitting in a sonication bath preheated to 60 °C. Upon exiting the sonicating bath, the stream entered the second reactor made of 0.04" ID PFA tubing (10.2 mL volume) that was preheated to 100 °C in an oil bath. An in-line separation was then performed using a membrane separator containing a 1.0 µm pore PTFE microfiltration membrane. Two BPRs set to 100 psi were installed at the end of the reactor on each side of the membrane separator. The entire system was equilibrated for 1 h, and product collection lasted for 1 h. The solution collected contained diazepam with a 49% calibrated yield determined by GC analysis with dodecane as the internal standard. This solution was then passed through a packed-bed of activated charcoal at 0.15 mL/min, then a sample (0.90 mL) was collected and diazepam **1** was isolated by automated flash chromatography (R_f = 0.19 in 30% EtOAc/hexane) as a colorless solid (0.103 g, 40% yield). ^{1}H NMR and ^{13}C NMR in $CDCl_3$ are in accordance with reported literature values.[14]

Atropine **2**: The solution of tropine (2 M in DMF) was loaded in two stainless steel (SS) syringe. Neat phenylacetyl chloride was loaded into a dry 5 mL luer-lock glass syringe. The solutions where pumped (using a Harvard Apparatus Syringe Pump) at 69.2 µL/min and 18.3 µL/min respectively. The solutions met in a T-mixer (0.02" id) at room temperature and were then warmed to 100 °C in a 300 µL reactor (87.5 µL/min total flow rate = 3.5 min residence time). Importantly, the stream exiting the T-mixer had to be rapidly warmed to 100 °C, otherwise clogging occurred. The stream exiting the first reactor was then connected to a T-mixer (0.02" id) and met a stream of 3 M NaOH pumped by an SS HPLC pump (56 µL/min, 1.2 equiv.). A 15 cm (0.02" id) segment of tubing was placed before the 2nd T-mixer where formaldehyde (37% aq, 65.4 µL/min, 6 equiv.) was added using a Harvard Apparatus Syringe Pump and two 8 mL SS syringe. The reaction mixture (209 µL/min total flow rate) was then reacted at 100 °C for 24 min in a 5 mL reactor (0.03" id) that was capped with a 100 psi BPR. After exiting the BPR, the reaction stream was mixed using a cross-mixer (0.02" id) both water (0.3 mL/min, HPLC pump) and PhMe (0.15 mL/min, pumped using a MilliGat M6 pump purchased from Valco Intruments Co. Inc.). The resulting slug-flow mixture (0.659 mL/min) was passed through a 6 cm SS sand-filled packed-bed for mixing purposes. An in-line extraction using a Zaiput liquid-liquid extractor (membrane = 0.5 µm) was achieved and both the aqueous and organic streams were collected in separate scintillation vials. The system was equilibrated for 1h, then the products were collected for 20 min. The organic stream was collected in an empty vial but the aqueous stream (measured at pH 11) was collected in a vial containing DCM to extract the product from water and

prevent elimination/degradation. The organic stream was concentrated *in vacuo*. A mixture of **2**:**10**:**11** was obtained (^{1}H NMR ratio 1:0.95:0.72) 332 mg total mass, 22% yield of **2**. The aqueous stream was extracted with DCM, concentrated *in vacuo*. Atropine **2** was obtained in 176 mg, 22% yield. ^{1}H NMR and ^{13}C NMR in $CDCl_3$ are in accordance with reported literature values.[41]

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Supplementary Material

Supplementary data associated with this article can be found, in the online version.