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EDGE ARTICLE

End-to-End Continuous Flow Synthesis and Purification of Diphenhydramine Hydrochloride Featuring Atom Economy, In-Line Separation, and Flow of Molten Ammonium Salts

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A continuous end-to-end synthesis and purification of diphenhydramine hydrochloride featuring atom economy and waste minimization is described. Combining a 1:1 molar ratio of the two starting material streams (chlorodiphenylmethane and N,N-dimethylaminoethanol) in the absence of additional solvent at high temperature gives the target compound directly as a molten salt (ionic liquid above 168 °C) in high yield. This represents the first example of continuous active pharmaceutical ingredient (API) production in this manner. Six of the twelve principles of green chemistry as defined by the American Chemical Society are achieved, most prominently waste minimization and atom economy.

Introduction

Discovered nearly seventy years ago by George Rieveschl,[1] diphenhydramine (**1**, Figure 1) is an important H_1-antagonist still in modern use. It is the most prominent of the ethanolamine-based antihistamines and among other applications is used to treat the common cold, lessen symptoms of allergies, and act as a mild sleep aid. The HCl salt form of diphenhydramine (**2**) is the active pharmaceutical ingredient in well-known over-the-counter medications such as Benadryl, Zzzquil, Tylenol PM, and Unisom. As a well-established treatment, little recent research has been invested in the production of this compound. Nevertheless, because the global demand of diphenhydramine is large by pharmaceutical standards (>100 tonnes per annum), improved manufacturing *via* continuous flow synthesis may offer several advantages. Described herein is such a synthesis of diphenhydramine hydrochloride (**2**, Figure 1) that features flowing of this substance as a neat, molten ammonium salt through the reactor as it forms, atom economy, avoidance of solvent, and minimal post-synthesis processing.

Use of continuous manufacturing in this application illustrates six of the twelve principles of green chemistry as described by the ACS.[2] Highlighted are waste minimization, atom economy (incorporation of all atoms of starting material into final product), the design of less hazardous chemical synthesis (elimination of chlorobenzene as a solvent, commonly used in manufacturing of **2**), the elimination of auxiliaries and solvents (solvent use in synthesis eliminated and reduced in processing)), reduced derivatization (no Br^-/Cl^- counter-ion exchange, commonly performed in manufacturing of **2**), and inherently safe chemistry for accident prevention (small reactor, decreased amount of chemicals reacting at any point).

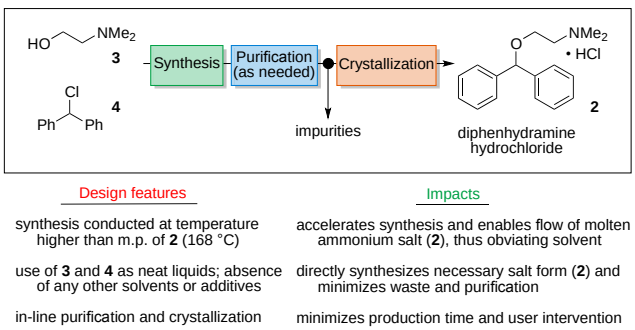

Fig. 1. Continuous end-to-end synthesis, purification, and crystallization of diphenhydramine hydrochloride (**2**).

Continuous production (CP) has gained considerable traction in the pharmaceutical and fine chemicals manufacturing industries.[3] Interest stems from potential cost and savings,[4] process intensification,[5] and improved performance in relation to batch operations.[6] Comprehensive summaries of chemical synthesis conducted in flow and discussions of the associated benefits have appeared in the past several years.[7]

Continuous flow chemistry also appears to be particularly well poised to contribute to the movement toward green, sustainable processes. For example, the ACS Presidential Roundtable on Sustainable Manufacturing (SMRT), lists process intensification as the top priority for Next Generation Chemical Manufacturing, where continuous flow is largely detailed as the solution.[8] Furthermore, the ACS Green Chemistry Institute (GCI), in partnership with several global pharmaceutical companies, described several key research areas for sustainable manufacturing.[9] The most critical field was voted to be continuous processing (CP), and the positive impact of CP on

several other of the prioritized research areas was also averred.

Also unequivocally clear was the importance of improved post-synthetic handling and processing of material (e.g., crystallizations, separations, chromatography, drying, and other forms of purification). With all of these considerations in mind, we set out to develop an end-to-end continuous process for the synthesis, purification, and crystallization of diphenhydramine (Figure 1).

Results and Discussion

Diphenhydramine is generally synthesized via one of two sequences. Rieveschl's original approach, which employs *N*,*N*-dimethylaminoethanol (DMAE, **3**), bromodiphenylmethane (**5**), base, and solvent, continues to be used today on production scale (batch).[10]

The second involves *p*-toluenesulfonic acid-promoted etherification of benzhydrol (**6**) by DMAE,[11] which is amenable to flow synthesis, provided that water is removed from solution in order to shift the equilibrium in the desired direction á la Le Chatelier. We effected this tactic by allowing water to vaporize as it formed in a flow reactor, and use of a 75 psi back-pressure regulator (bpr) was optimal. (See Supporting Information for details.) Lower pressure bprs were not as effective because the greater volume of the vaporized water significantly shortened the residence time and led to incomplete conversion. Alternatively, higher pressure bprs kept water in the condensed phase. Without removal of water in this fashion, the yield of the desired peaked near 30%, and in all cases, self-condensation of benzhydrol to give dibenzhydryl ether (**7**) was a significant competing process. Variation of the 2-aminoethanol stoichiometry was not effective in producing the desired ether in greater than 67% yield, and thus this route was abandoned.

Our focus next turned toward using bromodiphenylmethane (**5**) as a starting material (Table 1, entries 1-5). *N*-methylpyrrolidinone was chosen as a high-boiling-point solvent capable of solvating the high concentrations of ammonium salts (2.0 M) formed *in situ*. Thus, aminoalcohol **3** was pumped as a neat liquid in the absence of an external base, and the solution was heated at 140 °C with a residence time (t_R) of 5 min. After work up with aqueous sodium hydroxide, 47% yield of desired **1** was obtained, along with concomitant production of benzhydrol and ether **7**. As elevated temperature might be the cause of side-product generation from reaction with solvent or adventitious water, lower temperature was explored. Below 140 °C, significantly less diphenhydramine was produced, despite the observation that all starting material had been consumed. The mass balance based on consumption of **5** was likely due to conversion to benzhydrol in the quench with aqueous base. Elevating the temperature to 160 or 180 °C led to considerable gains in yield, but not beyond 77%. Use of excess aminoalcohol (up to 1.6 equiv) provided only modest gains in yield, reaching a maximum of 82%. Higher dibenzyl halide concentrations resulted in clogging of the reactor.

Chlorodiphenylmethane (**4**) was thus examined with the hope that a less reactive dibenzyl halide might lead to more selective product formation (entries 6-8) and that it would also provide a means to synthesize the necessary HCl salt form *directly*, thus avoiding subsequent counterion exchange. Conditions identical

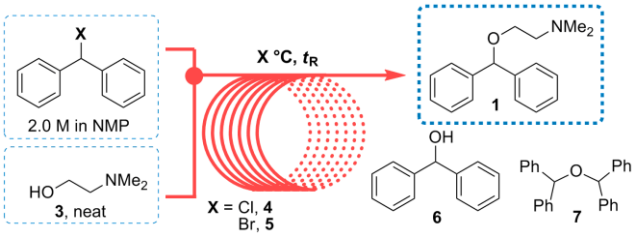

Table 1. Diphenhydramine and by-products afforded in NMP.[a]

Entry	X	Temp (°C)	t_R (min)	**1**:**6**:**7**:SM	Yield[b]
1	Br, **5**	100	5	21:69:10:0	7%
2	Br, **5**	120	5	43:48:8:0	13%
3	Br, **5**	140	5	71:22:7:0	47%
4	Br, **5**	160	5	87:5:8:0	77%
5	Br, **5**	180	5	82:5:13:0	70%
6	Cl, **4**	180	5	63:5:6:25	59%
7	Cl, **4**	180	10	77:5:8:10	73%
8	Cl, **4**	180	20	86:4:8:2	80%

[a] See Experimental for details. [b] Yield determined from ^{1}H NMR with external standard.

to those found above led to 59% yield, with marked quantities of starting material observed after quench. An increase in residence time effected conversion of the majority of remaining starting material giving 80% yield.

Unlike **5**, chlorodiphenylmethane possesses a low melting point, slightly below room temperature. Side-product formation might stem from participation by the solvent, either by reacting directly with halodiphenylmethane or from the presence of adventitious water. Rather than examining other solvents with large dielectric constant such as *N*,*N*-dimethylformamide (DMF), where oxygen atom abstraction should more readily occur, or dimethyl sulfoxide (DMSO) which would oxidize the dibenzyl halide, our attention was turned to running the reaction even more simply: neat, with excess aminoalcohol (if necessary) functioning as solvent (Table 2).

Eliminating the use of solvent and incorporating a threefold excess of **3** improved the transformation significantly (entry 1). Neat **4** and aminoalcohol were flowed together in a 1:4 ratio (corresponds to [chlorodiphenylmethane]$_0$ = 1.75 M, i.e., similar

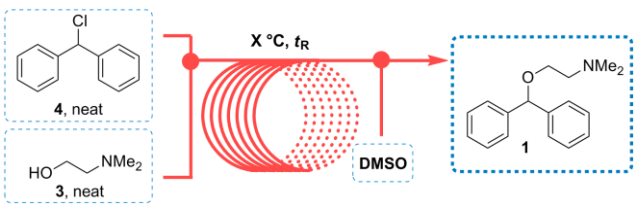

Table 2. Elimination of solvent under continuous flow parameters for the synthesis of diphenhydramine.[a]

Entry	Equiv **3**	t_R (min)	Temp (ºC)	**1**:**6**:**7**:**4**	Yield[b]
1	4	16	175	97:3:0:0	91%
2	3	16	175	98:2:0:0	92%
3	2	16	175	96:2:2:0	91%
4	1	16	175	92:4:4:0	86%
5	1	32	175	89:4:7:0	85%[b]
6	1	16	200	93:1:6:0	78%[b]

[a] See Experimental for details. [b] Average yield obtained in three runs (^{1}H NMR, external standard). [c] Single experiment.

concentration to studies with added solvent (above). With a reactor temperature of 175 °C (t_R = 16 min), 91% yield was obtained. Significantly, very little benzhydrol and ether **7** were observed. To prevent crystallization of the desired hydrochloride salt **2** in the flow reactor (and hence, clogging), DMSO was plumbed into the reaction mixture as a carrier solvent. Decreasing the amount of DMAE to a twofold or molar excess (1:3 and 1:2 ratio of **4**:**3**, respectively) maintained the benefits of solvent avoidance and flow of neat reagents (entries 2 and 3).

Excess DMAE could be eliminated entirely; however, this approach requires flowing of the highly crystalline product. Nevertheless, with a melting point of 168 °C, the product API could be handled (flowed) as an ionic liquid. Several recent reports detail the solventless continuous synthesis of ionic liquids.[12] Nevertheless, the melting point of diphenhydramine hydrochloride is significantly higher than these compounds, and this tactic has not been used for the production of pharmaceuticals.

This approach (neat, 1:1 stoichiometry, product as ionic liquid) met with experimental success. PFA tube reactors with 0.03" inner diameter (i.d.) were prone to rupture, but narrower tubing (0.02" i.d.), i.e., thicker walled, provided the requisite strength. A yield of 86% was obtained at 175 °C (t_R = 16 min). This serves as the first example of continuous synthesis of API as an ionic liquid. Additionally, the method presents a solution to solid formation in continuous processes, still a major obstacle in the production of pharmaceuticals,[13] and with recent interest centered on the formulation of APIs as ionic liquids,[14] this strategy might find additional applicability. Higher temperatures and longer reaction times led to greater byproduct formation. Duplication of this result in batch on significant scale would be greatly complicated by crystallization of the cooling ammonium salt during transport and handling.

Small amounts of diphenylmethane, 1,1',2,2'-tetraphenylethane (**8**), and benzophenone (**9**) accounted for the remainder of mass balance in the reaction. Tetraphenylethylene (**10**) and dichlorodiphenylmethane (**11**) were not observed. Homolytic cleavage of the carbon-chlorine bond, caused thermally, by light, or adventitious oxygen would account for the observed byproducts, and thus we investigated this possibility. Consistent with this notion was the observation that, trace amounts of benzophenone (which could provide photosensitization) would appear over time in samples of the chlorodiphenylmethane starting material. Chlorodiphenylmethane was thus recrystallized from hexanes at –30 °C, removing all impurities. The reaction was then conducted with the purified material, but byproduct formation was not suppressed. To prevent interference from light, the heating bath was shielded with Al foil, but this modification did not alter the reaction outcome. In the event that dissolved oxygen was the culprit, argon was bubbled through reagents prior to loading in syringes, but again byproduct formation persisted. Finally, butylated hydroxytoluene (**12**, BHT, 10 wt. %) was added to the DMAE feedstock in order to scavenge possible radicals in solution. Nevertheless no change in product distribution was noted. These changes suggest that deleterious radical formation do not contribute to the generation of the observed by-products.

With a continuous synthetic pathway developed, we shifted

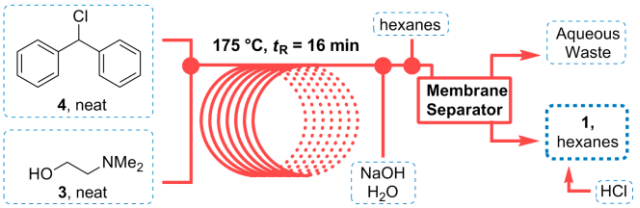

Table 3. Optimization of in-line quench, separation, and crystallization.[a]

Entry	Equiv 3	**1**:**6**:**7**:**4**	Yield (ext)[b]	Yield (cryst)[c]
1	4	99:1:0:0	89	93
2	3	98:2:0:0	89	89
3	2	97:2:1:0	93	92
4	1	97:1:1:1	88	83

[a)] See Experimental for details. [b)] Average yield obtained in three runs (^{1}H NMR, external standard). [c)] Isolated yield, average of three runs.

our attention to post-synthetic processing of the API (Table 3). Any excess DMAE would lead to a mixture of dimethylaminoethanol hydrochloride (**13**) and diphenhydramine hydrochloride. As a result, a continuous in-line extraction was developed to yield the desired ammonium salt **2**. Since the appearance of continuous liquid-liquid separations in microreactors *via* selectively wettable membranes,[15] several applications of the technology have been reported in the synthesis community.[16]

In place of DMSO, preheated aqueous NaOH (3 M) was combined with the reaction stream to neutralize ammonium salts **2** and **13**. When not preheated, the reaction and neutralization mixtures did not combine in a homogeneous fashion and upon cooling of the API, the reactor clogged. Upon exiting the pressurized system, hexanes were added to extract the neutralized tertiary amine **1** in conjunction with an in-line separator to remove the aqueous waste. To the hexanes solution, 5 M HCl in isopropanol was added in order to precipitate diphenhydramine hydrochloride. The separation proceeded smoothly and with minimal product loss, giving approximately 90% overall yield.

Choice of extraction solvent, acid source, and method of neutralization were all very important in successful production of solid API under continuous conditions. Extraction with ethyl acetate and ether were effective; however, they dissolved enough water so that the ammonium salt precipitated as an oil, rather than a powder (Karl Fischer titration, >20,000 ppm H_2O). Chloroform absorbed less water (<700 ppm H_2O) but prevented precipitation of the salt. In contrast, hexanes absorbed minimal water after extraction (<150 ppm H_2O) and induced very rapid precipitation of diphenhydramine hydrochloride salt. Product purity was above 95% when only 1 or 2 equivalents of **3** were added. No specified impurities are established by the US Pharmacopeia, but the recently developed system of Myerson and coworkers could possibly be employed to reach the requisite 98% purity level of **2**.[17]

We reasoned that solutions to these problems would be realized by direct crystallization of **2** from the reaction stream, which would also provide a further improvement to the purification process of diphenhydramine. Waste associated with extraction would be minimized, and in principle, the HCl formed *in situ* from condensation could be used to formulate the hydrochloride salt of **1**. The use of equivalent stoichiometries of

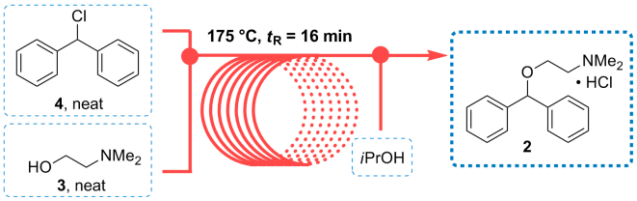

Table 4. Atom economy and waste minimization *via* direct crystallization of **2** from isopropanol.[a]

Entry	Isopropanol : Rxn Mixture[b]	Yield[c]	**2** : **13**
1	3 : 1	73 %	13.0 : 1
2	2 : 1	71 %	15.7 : 1
3	1 : 1	84 %	13.6 : 1

[a)] See Experimental for details. [b)] Volume of isopropanol mixed with reaction stream. [c)] Yield from ^{1}H NMR with external standard.

4 and **3** affords this possibility through elimination of excess DMAE (Table 4). Heated isopropanol joined the reaction stream post-synthesis but before the back-pressure regulator in order to prevent crystallization in the reactor prior to collection. Using either two or three parts of isopropanol compared to volume of reaction mixture resulted in approximately 70% yield of diphenhydramine after cooling to room temperature. The maximum yield, 84%, was obtained using 1 part isopropanol, but some *N*,*N*-dimethylaminoethanol hydrochloride salt persisted (approx. 6%). Excess DMAE hydrochloride can easily be removed by a subsequent recrystallization from isopropanol.

Conclusions

Placing a new twist on a venerable compound, a very effective end-to-end continuous flow process was developed for the synthesis of benadryl with a number of advantages, real-time in-line purification being among them. With solvent minimization, waste of the continuous flow process is greatly reduced, leading to lower operation costs and hazards associated with excess and disposal. The ability to heat well above the boiling point of all reaction components (particularly DMAE) affords high rates of reaction, and the resultant molten salt can be easily handled and transported *via* pumping, an operation likely to be troublesome under batch conditions on any significant scale. Additionally, the synthesis achieves complete atom economy, taking the product of condensation, HCl, and directing it toward formulation of the API itself.

Finally, the 1:1 ratio of starting materials provides the added benefit of high throughput and production rate. With our 720 µL reactor serving as a model system and equal stoichiometry of reactants, 2.42 g/h of API **2** can be produced. When 4 equiv of DMAE are used the output decreases to 1.23 g/h. Real-time crystallization affords similar reductions in waste when compared to a process utilizing extractions. With direct crystallization from isopropanol and a 1:1 ratio of chlorodiphenylmethane to DMAE, 3.13 mL/h of waste is generated, whereas, the extraction process would produce 23.2 mL/h of waste. This study also demonstrates the feasibility of directly synthesizing an API *salt form neat (no added solvent)* by taking advantage of the ability to flow molten ammonium salts (i.e., above the melting point of the salt), a strategy that would be of limited utility in large scale batch manufacturing. As this feature highlights many principles of green chemistry by providing significant process intensification, throughput increases, equipment footprint reduction, and minimization of waste, we are currently investigating the generality of this approach to the continuous manufacturing and purification of pharmaceuticals.

Acknowledgement

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Experimental

Solvents and reagents were purchased from Sigma-Aldrich and used as received. Reactors were constructed from high-purity PFA tubing bought from Upchurch Scientific with 0.03" i.d. when employing NMP or 0.02" i.d. when solventless conditions were used. Harvard Apparatus PhD Ultra syringe pumps were used to pump reagents and solutions from 8 mL stainless steel syringes. Pressure was controlled using 250 psi back-pressure regulator cartridges from IDEX. Reagent streams were combined using Tefzel T-mixers with 0.02" i.d. (IDEX), and reaction mixture and post-synthethic carrier streams were combined in a stainless-steel T-mixer with 0.04" i.d. (IDEX) heated at 175 °C.

The separator employed was constructed from two stainless steel plates sandwiching a Zefluor membrane (pore size, 1.0 µM, see Supporting Information for diagram). Identical channels were etched into each stainless steel plate causing fluid to proceed through the path in a repeating U-shaped zig-zag pattern. The groove cut into each plate was 1 mm in depth, 2 mm wide, and had a total path length of 157 mm. One plate, designated as A, had two ports one at the beginning of the groove, the other at the end of the groove. The other plate, designated as B, had only one port which was at the end of the groove. The 316 Stainless Steel plates were manufactured in the MIT central machine shop. A pressure differential was established across the membrane by placing different lengths of tubing at the exit ports. A 100 cm segment of tubing (0.03" i.d.) was placed at exit Port A, and a 30 cm segment of tubing (0.03" i.d.) was placed at Exit Port B. The biphasic mixture entered the separation channel from the entry port on Plate A. The aqueous layer, after passing through the channel, exited the separator without wetting the Zefluor membrane through a port at the end of the groove also on Plate A. The organic layer wet the Zefluor membrane upon passing through the separation channel, and exited the extraction chamber through a port at the end of the groove on Plate B.

For each data point, sample was collected in a scintillation vial over 5 minutes. Analysis was conducted in triplicate, with average values taken. Yield and ratios were determined either by NMR or by mass and isolated yield. Mesitylene was used as an external standard to diphenhydramine. T_1 spin-lattice relaxation times were measured for all signals in the system and a delay time of 30 seconds was applied between pulses. Multipoint baseline correction was applied to all spectra along with line-

broadening equal to peak width at half-height.

Diphenhydramine 1. *Method A, NMP as solvent:* Either bromodiphenylmethane (3.95 g, 16.0 mmol) or chlorodiphenylmethane (3.24 g, 16.0 mmol) was dissolved in NMP to give 8 mL of a 2.0 M solution. The solution was loaded into a Harvard Apparatus stainless steel syringe. DMAE was drawn into a second stainless steel syringe (8.0 mL, 9.93 M). A 720 μL reactor was constructed from 0.03" i.d. high purity PFA tubing, and the system was pressurized to 250 psi. To give a 5 min T_R, the halodiphenylmethane solution was pumped at a rate of 120 μL/min and the aminoalcohol was pumped at 24 μL/min. Flow rates were adjusted accordingly to give different times of reaction. After four residents, reaction solution was collected for analysis. Sample was collected for five minutes, diluted with 4 mL of 3M NaOH solution (aq.) and 2 mL of diethyl ether. Diphenhydramine was extracted from the aqueous layer and the procedure was repeated twice more. The organic fractions were collected, dried with $MgSO_4$, and concentrated. Mesitylene (167 μL, 1.20 mmol) was added to the diphenhydramine oil and mixed along with $CDCl_3$. The thoroughly mixed solution was analyzed by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.19 (m, 10H), 5.44 (s, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 6H).

Method B, no reaction solvent and DMSO used as a carrier post reaction: Chlorodiphenylmethane was loaded into a stainless steel syringe (8.0 mL, 5.62 M) as was DMAE (8.0 mL, 9.93 M). A 720 μL reaction loop was constructed from 0.02" i.d. high purity PFA tubing. To afford a 16 minute T_R, a total flow rate of 45 μL was employed. When 4 equivalents of DMAE were present, chlorodiphenylmethane flowed at 13.8 μL/min and DMAE at 31.2 μL/min. DMSO was pumped at 180 μL/min and a 120 μL loop of the solvent was preheated to the temperature of the reaction prior to joining the diphenhydramine hydrochloride at a stainless steel T-mixer (0.04" i.d.) also heated to the temperature of the reaction. The DMSO/diphenhydramine hydrochloride mixture flowed through a 120 μL segment of tubing for mixing before exiting the 250 psi back-pressure regulator. Four residents were allowed to pass prior to collecting a 5 minute sample for analysis which was diluted with 4 mL of 3M NaOH solution (aq.) and 2 mL of diethyl ether. Diphenhydramine was extracted from the aqueous layer and the procedure was repeated twice more. The organic fractions were collected, dried with $MgSO_4$, and concentrated. Mesitylene (54.0 μL, 388 μmol) was added to the diphenhydramine oil and mixed along with $CDCl_3$. The thoroughly mixed solution was analyzed by ^{1}H NMR.

Method C, in-line quench, extraction, and crystallization: Chlorodiphenylmethane was loaded into a stainless steel syringe (8.0 mL, 5.62 M) as was DMAE (8.0 mL, 9.93 M). A 720 μL reaction loop was constructed from 0.02" i.d. high purity PFA tubing. To afford a 16 minute T_R, a total flow rate of 45 μL was employed. When 3 equivalents of DMAE were present, chlorodiphenylmethane flowed at 16.7 μL/min and DMAE at 28.3 μL/min. 3 M NaOH (aq.) was pumped at 180 μL/min and a 120 μL loop of the neutralizating agent was preheated to the temperature of the reaction prior to joining the reaction mixture at a stainless steel T-mixer (0.04" i.d.) also heated to the temperature of the reaction. The NaOH/diphenhydramine hydrochloride mixture flowed through a 120 μL segment of tubing for mixing before exiting the 250 psi back-pressure regulator. Hexane was flowed into the API stream at 180 μL/min and mixing was effected by passing the stream through a 405 μL coil of tubing prior to entering the separator. The hexanes were collected after exiting Plate B. To obtain the yield post-extraction, sample was collected for five minutes and concentrated. Mesitylene (65.3 μL, 470 μmol) was added as an external reference, and the sample was analyzed by ^{1}H NMR. To obtain yield from crystallization, 5 M HCl in isopropanol was added at 18.9 μL/min directly to a scintillation vial collecting sample from the separator. The solution was rapidly stirred and an off-white solid precipitated. The solid was washed twice with hexanes. The solids were analyzed by elemental analysis and ^{1}H NMR (D_2O). ^{1}H NMR (400 MHz, D_2O) δ 7.25 (m, 10H), 5.38 (s, 1H), 3.56 (t, *J* = 5.0 Hz, 2H), 3.17 (t, *J* = 5.0 Hz, 2H), 2.70 (s, 6H). Anal Calcd for $C_{17}H_{22}NOCl$: C, 69.95; H, 7.60; N, 4.80. DMAE:**7** = 1:1 Found: C, 69.59; H, 7.71; N, 4.81. DMAE:**7** = 2:1 Found: C, 69.60; H, 7.68; N, 4.81. DMAE:**7** = 3:1 Found: C, 69.43; H, 7.39; N, 4.82. DMAE:**7** = 4:1 Found: C, 69.36; H, 7.45; N, 4.78.

Method D, direct crystallization with isopropanol. Chlorodiphenylmethane was loaded into a stainless steel syringe (8.0 mL, 5.62 M) as was DMAE (8.0 mL, 9.93 M). A 720 μL reaction loop was constructed from 0.02" i.d. high purity PFA tubing. To afford a 16 minute T_R, a total flow rate of 45 μL was employed. When 1 equivalents of DMAE was present, chlorodiphenylmethane flowed at 28.7 μL/min and DMAE at 16.3 μL/min. Isopropanol was pumped at 45 μL/min and a 120 μL loop of the crystallizing agent was preheated to the temperature of the reaction prior to joining the reaction mixture at a stainless steel T-mixer (0.04" i.d.) also heated to the temperature of the reaction. The NaOH/diphenhydramine hydrochloride mixture flowed through a 120 μL segment of tubing for mixing before exiting the 250 psi back-pressure regulator. After passing four residents of solution, sample for analysis was collected for five minutes. After collecting, the sample was cooled to 5 ºC. The mother liquor was decanted and the solid was rinsed twice with cold acetone. The solid was dissolved in D_2O and DMF was added as an external standard (62.7 μL, 807 μmol). Yield and ratios were analyzed by ^{1}H NMR.

Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed design and photographs of liquid/liquid separator as well as ^{1}H NMR obtained to determine yield. See DOI: 10.1039/b000000x/

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