Organic Process Research & Development

Technical Note

A Continuous Flow Process for The Synthesis of 2-Ethylphenylhydrazine Hydrochloride

Zhiqun Yu, Gang Tong, Xiaoxuan Xie, Pengcheng Zhou, Yanwen Lv, and Weike Su

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.5b00115 • Publication Date (Web): 12 Jun 2015

Just Accepted

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A Continuous Flow Process for The Synthesis of 2-Ethylphenylhydrazine Hydrochloride

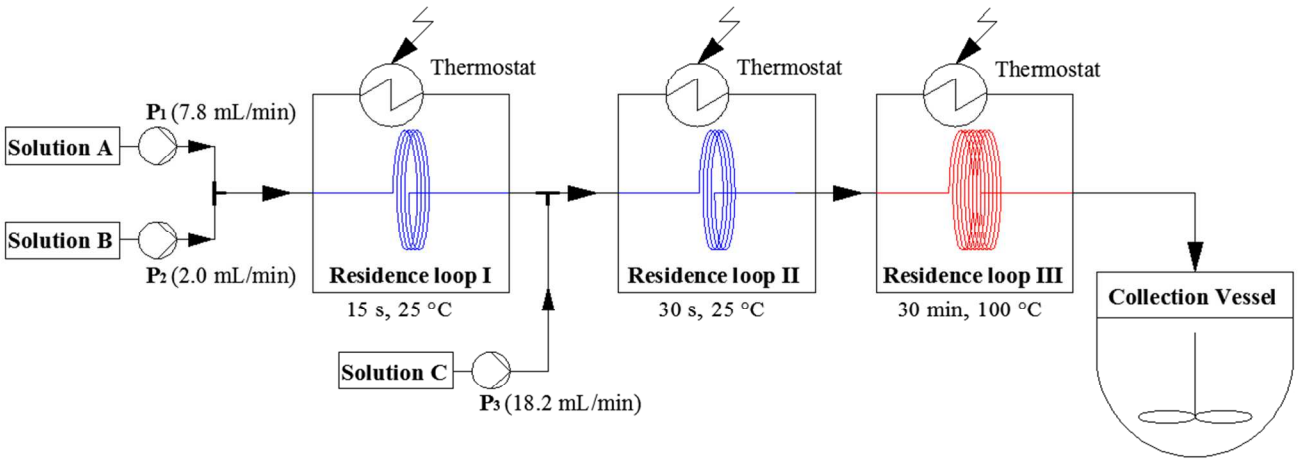
Zhiqun Yu,[†] Gang Tong,[†] Xiaoxuan Xie,[†] Pengcheng Zhou,[†] Yanwen Lv,[‡] and Weike Su*[,†]

[†] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P.R. China.*

[‡] *Quzhou University, Quzhou 324000, P.R. China.*

* Corresponding author: Tel: (+86)57188320899. E-mail: pharmlab@zjut.edu.cn.

Table of Contents Graphic:



Abstract: An expeditious process for synthesis of 2-ethylphenylhydrazine hydrochloride *via* a continuous flow reactor from 2-ethylaniline in 94% yield was described. The main steps in this synthesis involved not only the generation of diazonium salt intermediate *in situ*, but also the temperature-programmed reduction by sodium sulfite in the tandem loop reactor. Total residence time was reduced to less than 31 min by increasing reaction temperature and thereby taking advantage of improved mass and heat transfer of a continuous flow system. Purification process was simplified by extraction of impurities *in situ*.

Keywords: continuous flow; diazotization; temperature-programmed reduction; 2-ethylphenylhydrazine hydrochloride

Introduction

Aryl hydrazine moiety has been shown as a key pharmacophore in many pharmaceutically active agents[1]. Target product 2-ethylphenylhydrazine hydrochloride is an important starting material for synthesis of Etodolac, which is a nonsteroidal anti-inflammatory drug (NSAID) licensed for the treatment of inflammation and pain caused by osteoarthritis and rheumatoid arthritis[2].

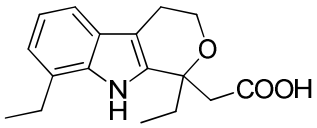
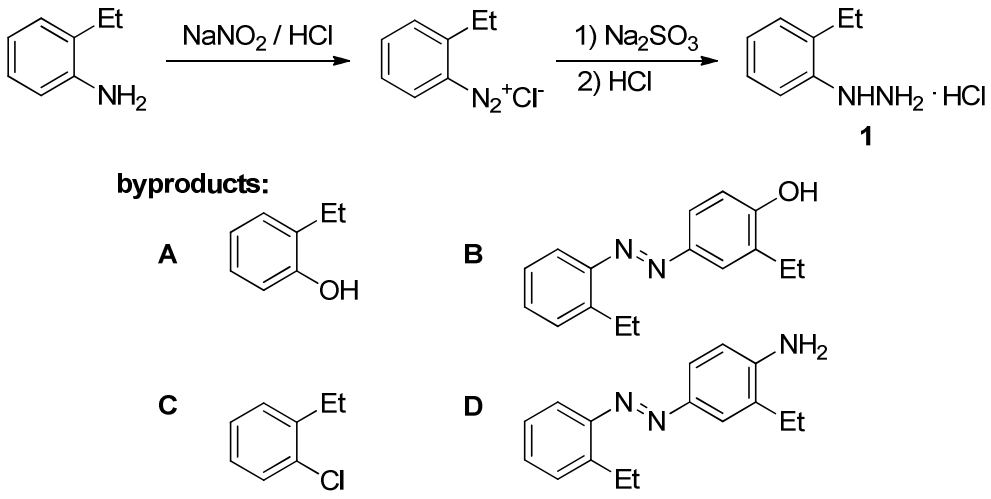


Figure 1. Etodolac.

Preparation of 2-ethylphenylhydrazine hydrochloride can be fulfilled by diazotization of 2-ethylaniline to form the diazonium salt, which is subsequently reduced in different approaches to form the final product. One approach is Japp–Klingemann reaction with *β*-keto-acid and hydrazinolysis of hydrazone[3]. Versatility of this method is limited by long reaction route and low yield. Another approach is reduction of diazonium salt by reductants (e.g. $SnCl_2$, Na_2SO_3, $NaHSO_3$, etc),[4] which is the benchmark method for preparation of aryl hydrazines. However, some disadvantages that amount of wastes, byproducts, low efficiency, yield stability and yield reliability are still need to be improved especially in scale-up of batch process.

Scheme 1. Synthetic route and byproducts



We adopted the second approach in synthesis of 2-ethylphenylhydrazine hydrochloride (Scheme 1). The synthesis started by reducing 2-ethylaniline with sodium nitrite in the presence of hydrogen chloride followed by reduction of the diazonium salt, the use of sodium sulfite as reductant can avoid post processing problems caused by tin (II) chloride. Hydrazine hydrochloride **1** was precipitated from aqueous phase, followed by recrystallization to obtain qualified product (purity ≥ 98%). Diazotization of aromatic amines is usually exothermic and fast, and usually performed on the bulk scale in anhydrous conditions at low temperature. Researches[5] have confirmed that diazotization presented potential safety hazards for scale-up. Thus, we turned our attention to developing a continuous flow process to address the safety concerns. Continuous flow technology offers many advantages over batch methods, including precise control of stoichiometry, residence time, and temperature; high reproducibility; easy to scale-up; and often better reaction yields[6]. The much higher surface area to volume ratio under flow conditions renders highly efficient heat transfer. Furthermore, safety hazards in handling exothermic reactions associated with explosive intermediates are minimized while involving in a much smaller volume in the reaction train[7].

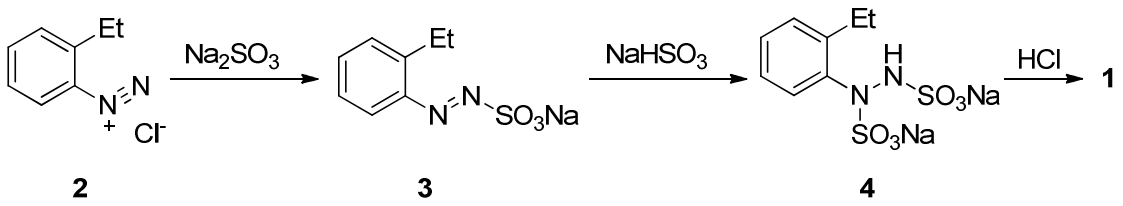
Results and discussion

Adapting the Batch Process to Continuous Flow.

For a great many industrial processes covered, diazotization of aromatic amines in batch manner has been well studied[8]. A continuous diazotization of anilines under substantially adiabatic conditions was reported by Kidler et al. from the dye industry[9]. More recently, there have been several reports on generating diazonium salts as reactive intermediates (followed by iododeamination, chlorodeamination, azo dyes, and chlorosulfonylation) using flow technology[10]. Compared to micrometer scale reactor, millimeter scale reactor, due to its relatively high productivity, is easier to promote in industrial production. Browne *et al.*[11] reported the generation and reduction of diazonium salts using vitamin C for synthesis of hydrazines in a microreactor. Li *et al.*[12] developed a continuous non-aqueous diazotization process in tandem with batch type reduction for syntheses of aryl hydrazines, however, the use of $SnCl_2$ went against the promotion of technology application. Our group has been committed to continuous diazotization process[13], and herein wish to establish a continuous flow process for synthesis of 2-ethylphenylhydrazine hydrochloride[14].

Mechanism for reduction of diazotization by sodium sulfite has been revealed[15] as shown in Scheme 2. Diazenesulfonate **3** which has poor water solubility and poor thermal stability can be formed *via* fast nucleophilic substitution from diazonium chloride **2** and sodium sulfite. Then nucleophilic addition takes place between **3** and sodium bisulfite, followed by hydrolysis in hydrochloric acid to form final product **1**. The transformation from **3** to **4** is relatively slow compared to nucleophilic substitution step. In the design of a continuous flow process for synthesis of **1**, our objectives were to avoid the accumulation and isolation of energetic intermediates **2** and **3**, and to combine continuous diazotization and reduction within one flow reactor.

Scheme 2. Mechanism for reduction of diazotization

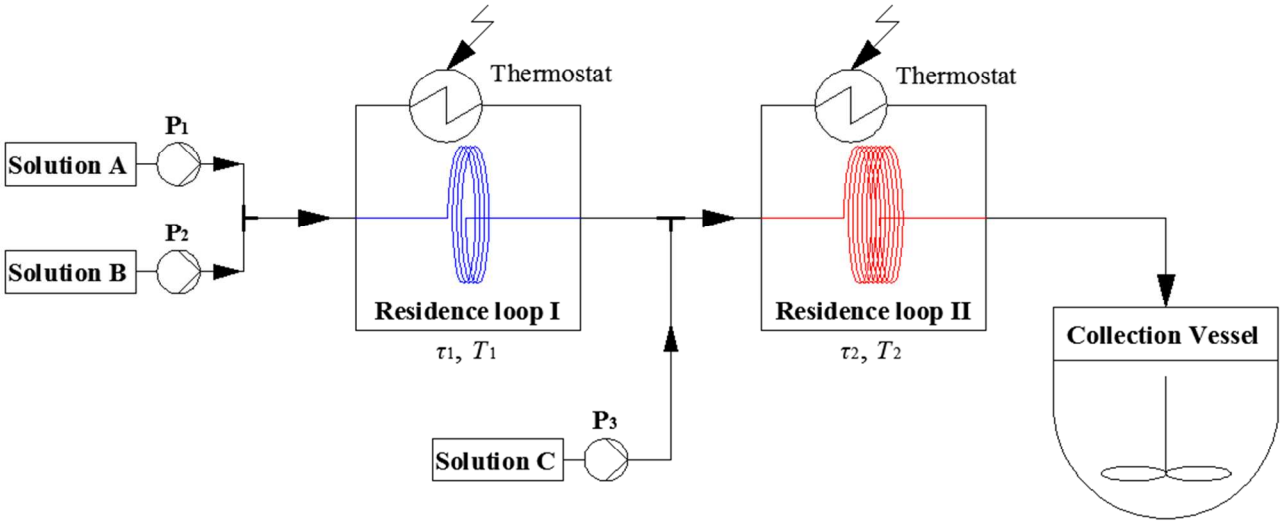


2 **3** **4**

Initial Process Design.

The original process discussed in this document was the direct conversion of the commonly used batch methodology to a continuous flow system. Scheme 3 shows the continuous flow reactor experimental setup. The equipment consists of two peristaltic pumps (**P**$_1$, **P**$_2$, Baoding Longer, China) loaded with tubing connected by a T-mixer which was connected to residence loop I (Hastelloy, 3 mm i.d., 5 mm o.d.). The reacting tube was immersed in a thermostat controlled water bath. Solution **A** of 2-ethylaniline in hydrochloric acid together with solution **B** of aqueous sodium nitrite were pumped into reacting tube respectively. After a residence time (τ_1) in loop I, solution **C** of aqueous sodium sulfite was introduced into the reactor. Reduction of diazonium salt was taken place in residence loop II (SS316, 3 mm i.d., 5 mm o.d.) with another residence time (τ_2), followed by hydrolysis with hydrochloric acid in collection vessel to form final product **1**. To avoid air pollution, tail gas (SO_2) was absorbed by sodium hydroxide solution to reproduce sodium sulfite. Crude product was purified by recrystallization from water.

Scheme 3. Schematic of initial process experimental setup[a]

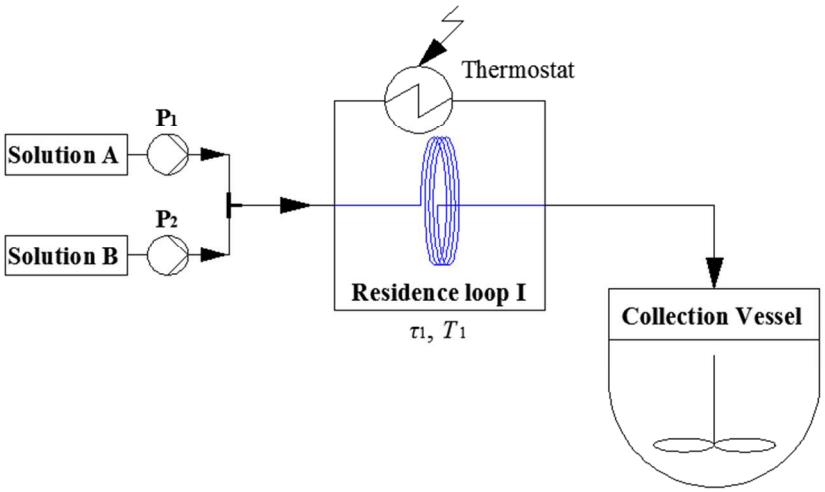


[a] Solution **A** is 2-ethylaniline in hydrochloric acid, solution **B** is aqueous sodium nitrite, solution **C** is aqueous sodium sulfite. Residence loop I is Hastelloy tube with 3 mm i.d., 5 mm o.d., residence loop II is SS316 tube with 3 mm i.d., 5 mm o.d..

Optimization of this process started with continuous diazotization in tandem with reduction of diazonium salt in batch manner (Scheme 4). This procedure was greatly facilitated by continuous flow conditions and a significant number of runs were rapidly conducted in a sequential manner. The experimental parameters were systematically investigated by varying residence time (τ_1) and temperature (T_1). Solution **A** was 1.5 M 2-ethylaniline in 3.0 equiv hydrogen chloride aqueous with a flow rate of 7.8 mL/min, solution **B** was 6.0 M sodium nitrite aqueous with a flow rate of 2.0 mL/min, reductive conditions was same with literature parameters (2.5 equiv Na_2SO_3, 70-75 ^oC, 2-3 h)[16]. The results were shown in Figure 2. Maximum yield of 75% was obtained when τ_1 = 15 s, T_1 = 25 ^oC. Both long τ_1 with high T_1 and short τ_1 with low T_1 lead to yield decreases. Raising the temperature can accelerate the reaction rate, however, higher temperature along with longer residence time lead to decomposition of diazonium salt. On the contrary, aniline was conversed incompletely while lower

temperature along with shorter residence time.

Scheme 4. Schematic of continuous diazotization experimental setup[a]



[a] Solution **A** is 2-ethylaniline in 3.0 equiv hydrochloric acid with a flow rate of 7.8 mL/min, solution **B** is aqueous sodium nitrite with a flow rate of 2.0 mL/min. Residence loop I is Hastelloy tube with 3 mm i.d., 5 mm o.d..

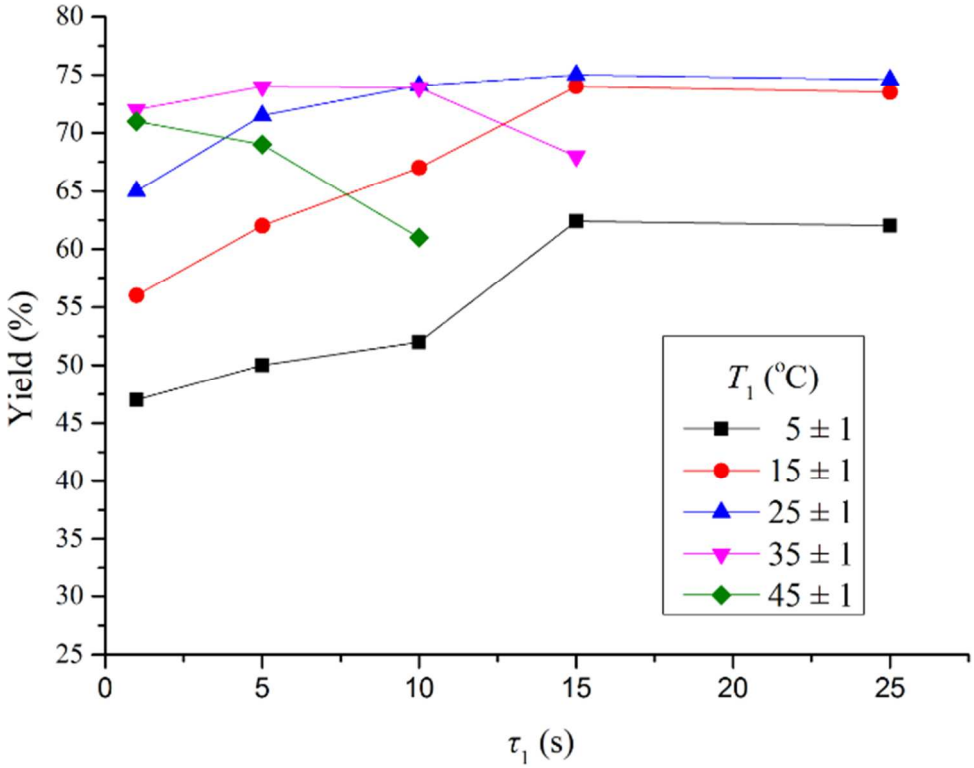


Figure 2. Effect of temperature and residence time on diazotization. Yields of **1** were calculated from 2-ethylaniline.

Amount of sodium nitrite was then optimized. Molar flow ratios of sodium nitrite to 2-ethylaniline were varied by adjusting flow rate of solution **B**. Results were shown in table 1. Sodium nitrite can be slightly excessive to 1.03 equiv, while too much overdose leads to decreased yields since excessive nitrous acid may accelerate decomposition of diazonium salt.

Table 1. Effect of amount of sodium nitrite

Sodium nitrite / 2-ethylaniline[a]	Yield (%)[b]
1.00	72
1.03	75
1.05	75
1.08	73
1.10	69

[a] Molar flow ratios of sodium nitrite to 2-ethylaniline.
[b] Yields of **1** were calculated from 2-ethylaniline.

With diazotization parameters in hand, optimization of continuous reduction was then undertaken. Experiments were carried out in accordance with procedure of Scheme 3. Solution **A** was 1.5 M 2-ethylaniline in 3.0 equiv hydrogen chloride aqueous with a flow rate of 7.8 mL/min, solution **B** was 6.0 M sodium nitrite aqueous with a flow rate of 2.0 mL/min, Solution **C** was 1.8 M aqueous sodium sulfite with a flow rate of 16.2 mL/min (molar flow ratio was 2.5 equiv to 2-ethylaniline). Residence time (τ_2) was prolonged by increasing the tube length while maintaining the same flow rates. Reductive temperature (T_2) was investigated varying from traditional batch process parameter (70 ^{o}C) to maximum temperature at atmospheric pressure. However, the result was not satisfied (maximum yield was 80% when τ_2 = 30 min, T_2 = 100 ^{o}C) due to the formation of a black tar. The main reason could be thermal decomposition of diazonium chloride **2**, during formation of **3**. Amount of reductant was also optimized (Table 2). Molar flow ratios of sodium sulfite to 2-ethylaniline were varied by adjusting flow rate of

solution **C**, but only slight increase in yield was gained. The yield of **1** was 81% when 2.8 equiv of sodium sulfite was used, more amount can't get further raise due to decomposition of diazonium salt.

Table 2. Effect of amount of sodium sulfite

Sodium sulfite / 2-ethylaniline[a]	Yield (%)[b]
2.0	69
2.3	76
2.5	80
2.8	81
3.0	81

[a] Molar flow ratios of sodium sulfite to 2-ethylaniline.
[b] Yields of **1** were calculated from 2-ethylaniline.

Advanced Process Design.

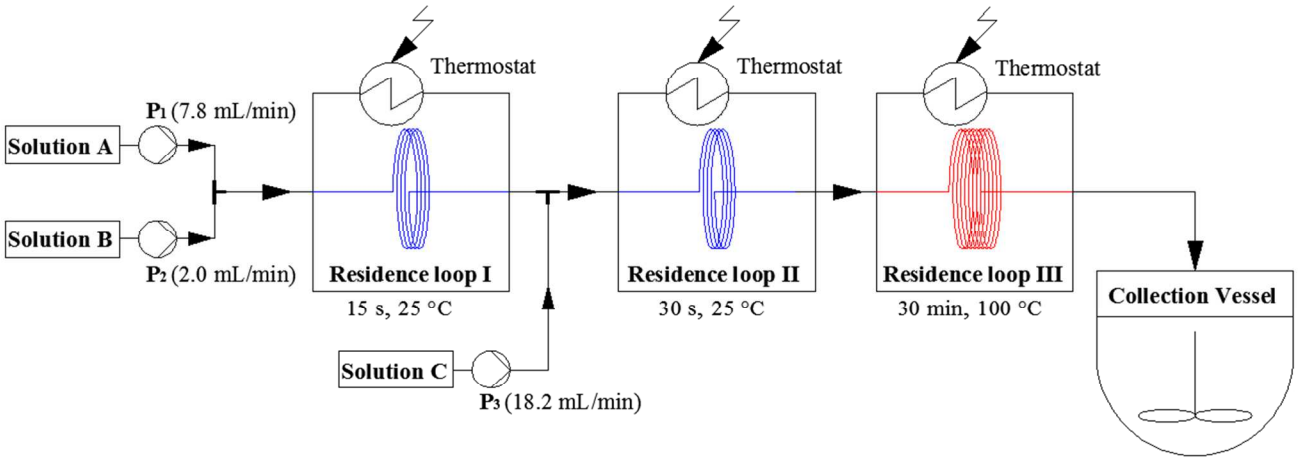
According to the thermal decomposition problems of initial method, an improved process was developed by temperature-programmed reduction. Diazenesulfonate **3** was generated at a slightly lower temperature and then intermediate **4** was formed at a higher temperature. The primary challenge of this continuous process was poor solubility of diazenesulfonate **3** and the problem of clogging tube. A dilute concentration of regents will increase the burden of subsequent processes, and seems not an economic method. Therefore, increasing diameter of reacting tube was chosen for the improved process.

An advanced optimized process was then designed (Scheme 5), and optimal conditions were achieved by flowing solution **A** (1.5 M 2-ethylaniline in hydrochloric acid aqueous) together with solution **B** (6.0 M sodium nitrite aqueous) for a residence time of 15 s at 25 ^{o}C, followed by introduction of solution **C** (1.8 M aqueous sodium sulfite) into the reactor for a residence time of about 30 s at 25 ^{o}C and then 30 min at 100 ^{o}C[17]. Residence loop III was heated by oil bath and the temperature was regulated by a thermostat. The flow rates of three solutions were 7.8, 2.0, 18.2 mL/min respectively, and molar flow

ratio of 2-ethylaniline to $NaNO_2$ to Na_2SO_3 was 1.0 : 1.03 : 2.8. Inner diameters of residence loop II and III were both 6 mm. With these adjustments, yield of **1** was significantly improved to 92~93% with a pressure drop of less than 1 bar.

Though a significantly improvement of yield was gained, qualified product of more than 98% purity was only obtained after recrystallization. Some modifications of this process were required to facilitate purification process. Toluene was added in the hydrolysis reactor, impurities were extracted into organic layer while hydrolysis by hydrochloric acid. Bright white crystals of target product were precipitated while cooling the mixture, after filtration and drying, a purity of more than 99% was got directly. A slight increase of yield of approximately 1% was also achieved.

Scheme 5. Schematic of advanced process experimental setup[a]



[a] Solution **A** is 1.5 M 2-ethylaniline in 3.0 equiv hydrochloric acid, solution **B** is 6.0 M aqueous sodium nitrite, solution **C** is 1.8 M aqueous sodium sulfite. Residence loop I is Hastelloy tube with 3 mm i.d., 5 mm o.d., residence loop II and III are SS316 tube with 6 mm i.d., 8 mm o.d., the volume of three residence loops are 2.45 mL, 14 mL, 840 mL respectively.

To underline the advantages of the proposed flow synthesis, a comparison with the reaction performed in batch manner was summarized in table 3. Molar ratio of reagents in batch reaction was same with continuous flow, the sequence of operations was diazotization of 2-ethylaniline at 0 ^{o}C followed by the temperature-programmed reduction of diazonium salt[4b].

Table 3. Comparison of batch process with continuous process

Operate manner	Batch	Continuous flow
Yield (%)	87	94
Purity (%)	99 (after recrystallization)	99
Reaction time	stirred for hours after completing the addition of reagents	Diazotization: 15 s Reduction: 30.5 min

Conclusion

In summary, an expeditious and high-yielding process for synthesis of 2-ethylphenylhydrazine hydrochloride from 2-ethylaniline *via* a continuous flow reactor has been set up. Thermal decomposition of diazonium salt was avoided by temperature-programmed reduction, and product isolation and purification method was polished by extraction *in situ*. The process is readily adapted for preparation of analogous compounds and can easily be scaled-up by increasing reactor size or operating several reactors with high throughput in parallel. The apparatus used to deliver the results for the large scale experiment is still being used for further batches.

Experimental Section

All chemicals were purchased from commercial sources and were used without further purification. Melting points were determined on Buchi 540 melting point apparatus and were uncorrected. ^{1}H NMR

spectra was recorded on Varian 400 MHz spectrometer using tetramethylsilane (TMS) as internal standard. HPLC analysis for **1** was carried out on an Agilent 1200 system equipped with a RP-18 250 mm × 4.0 mm column and detected at 275 nm, eluted with 50:25:25 0.03 M NaH_2PO_4 aqueous/CH_3CN/CH_3OH at 1.0 mL/min.

Continuous flow experimental procedure of advanced process. As shown in Scheme 5, solution **A** of 2-ethylaniline (303 g, 2.5 mol), 30% aqueous hydrochloric acid (911 g, 7.5 mol) in 432 g of water, and solution **B** of sodium nitrite (178 g, 2.6 mol) in 357 g of water were pumped into the flow reactor *via* a T-joint by $\mathbf{P_1}$ and $\mathbf{P_2}$ at flow rates of 7.8 mL/min and 2.0 mL/min respectively, after a residence time of 15 s at 25 ^oC in residence loop I (Hastelloy, 3 mm i.d., 5 mm o.d.), solution **C** of sodium sulfite (882 g, 7 mol) in 3528 g of water was introduced into the reactor by $\mathbf{P_3}$ at a flow rate of 18.2 mL/min, after another residence time of 30 s at 25 ^oC in residence loop II (SS316, 6 mm i.d., 8 mm o.d.) and 30 min at 100 ^oC in residence loop III (SS316, 6 mm i.d., 8 mm o.d.), mixture flowed through the outlet and accumulated in the collection vessel (filled with 100 g of toluene and 1458 g of hydrochloric acid in advance, and preheated to 100 ^oC). Continuous stirring was done vigorously. Large amount of gas was released, and SO_2 was absorbed by sodium hydroxide solution. After flow reaction was complete, reaction mixture was stirred for another 30 min. Then hot solution was separated in a separator funnel and toluene was recovered by distillation. The aqueous phase was cooled to 0 ^oC, and solid was precipitated. The precipitate was filtered and dried in vacumm to give bright white crystals (406 g) in 94% yield with 99% HPLC purity. M.p. 180-181 ^oC, ^1H NMR (400 MHz, d_6-DMSO) δ/ppm: 10.20 (s, 3H), 7.17-7.11 (m, 2H), 6.97 (d, 1H, J = 8.0 Hz), 6.91 (t, 1H, J = 7.6 Hz), 2.58 (q, 2H, J = 7.6 Hz), 1.15 (t, 3H, J = 7.6 Hz).

Acknowledgment

We are grateful for the National Natural Science Foundation of China (No. 21406203) and Zhejiang Technology and Service Platform of New Drug Innovation (PNDI) (No. 2011E61003) for financial support.

References

(1) (a) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Hiroyoshi, H. *J. Med. Chem.* **1989**, *32*, 421–428. (b) Pete, B. L.; Bitter, I. N.; Harsányi, K. L. N.; Tõke, L. S. *Heterocycles* **2000**, *53*, 665–673.

(2) (a) Hughes, P.; DeVirgilio, J.; Humber, L. G.; Chau, T.; Weichman, B.; Neuman, G. *J. Med. Chem.* **1989**, *32*, 2134–2137. (b) Soll, R. M.; Guinosso, C.; Asselin, A. *J. Org. Chem.* **1988**, *53*, 2844–2847. (c) Humber, L. G.; Christopher, A.; Demerson, C. A.; Swaminathan, P.; Birdt, P. H. *J. Med. Chem.* **1986**, *29*, 871–874.

(3) González, A. *Synthetic Commun.* **1991**, *21*, 669–674.

(4) (a) Demerson, C. A.; Humber, L. G. US 4585877, 1986. (b) Dai, L. Y.; Wang, X. Z.; Chen, Y. Q. *J. Chem. Ind. Eng. (China)* **2005**, *56*, 1536–1540.

(5) Petrillo, G.; Novi, M.; Garbarino, G.; Dell'Erba, C. *Tetrahedron* **1986**, 42, 4007–4016.

(6) (a) Hessel, V. *Chem. Eng. Technol.* **2009**, *32*, 1655–1681. (b) Wahab, B.; Ellames, G.; Passey, S.; Watts, P. *Tetrahedron* **2010**, *66*, 3861–3865. (c) Riva, E.; Gagliardi, S.; Mazzoni, C.; Passarella, D.; Rencurosi, A.; Vigo, D.; Rencurosi, A. *Tetrahedron* **2010**, *66*, 3242–3247. (d) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17–57. (e) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38–54. (f) Wiles, C.; Watts, P. *Green Chem.* **2014**, *16*, 55–62.

(7) (a) Kulkarni, A. A.; Kalyani, V. S.; Joshi, R. A.; Josh, R. R. *Org. Process Res. Dev.* **2009**, *13*, 999–1002. (b) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4017–4021. (c) Yu, Z. Q.; Lv, Y. W.; Yu, C. M.; Su, W. K. *Org. Process Res. Dev.* **2013**, *17*, 438–

442.

(8) Zollinger, H. *Diazo Chemistry I: Aromatic and Heteroaromatic Compounds*; VCH Verlagsgesellschaft mbH: D-69451 Weinheim, 1994.

(9) Kindler, H.; Schuler, D. US 3423391, 1964.

(10) (a) Malet-Sanz, L.; Madrzak, J.; Holvey, R. S.; Underwood, T. *Tetrahedron Lett.* 2009, 50, 7263−7267. (b) Fortt, R.; Wootton, R. C. R.; de Mello, A. J. *Org. Process Res. Dev.* **2003**, *7*, 762−768. (c) Wootton, R. C. R.; Fortt, R.; de Mello, A. J. *Lab Chip* **2002**, *2*, 5−7. (d) Malet-Sanz, B.; Madrzak, J.; Ley, S. V.; Baxendale, I. R. *Org. Biomol. Chem.* **2010**, *8*, 5324−5332. For more reviews on diazonium and diazo compounds in flow, see: (e) Mueller, S. T. R.; Wirth, T. *ChemSusChem* **2015**, *8*, 245−250. (f) Deadman, B. J.; Collins. S. G.; Maguire, A. R. *Chem. Eur. J.* **2015**, *21*, 2298–2308.

(11) Browne, D. L.; Baxendale, I. R.; Ley, S. V. *Tetrahedron* **2011**, *67*, 10296−10303.

(12) Li, B.; Widlicka, D.; Boucher, S.; Hayward, C.; Lucas, J.; Murray, J. C.; O'Neil, B. T.; Pfisterer, D.; Samp, L.; VanAlsten, J.; Xiang, Y.; Young, J. *Org. Process Res. Dev.* **2012**, *16*, 2031−2035.

(13) (a) Yu, Z. Q.; Lv, Y. W.; Yu, C. M. *Org. Process Res. Dev.* **2012**, *16*, 1669−1672. (b) Yu, Z. Q.; Lv, Y. W.; Yu, C. M.; Su, W. K. *Tendrahedron Lett*. **2013**, *54*, 1261−1263.

(14) As an extension of previous work: Lv, Y. W.; Yu, Z. Q.; Su, W. K. *Org. Process Res. Dev.* **2011**, 15, 471−475.

(15) (a) Pan, F. Y.; Yang, J. G. *Chin. J. Pharm.* **1998**, *29*, 89. (b) Chen, Y. J.; Xu, D. J.; Hao, J.; Wang, Y. *J. Shenyang Inst. of Chem. Technol.* **1999**, *13*, 243−247.

(16) Patel, V. R.; Desai, H. T. *J. At. Mol.* **2013**, *3*, 520–523.

(17) With large amount of solute in this aqueous reaction system and pressure drop, the boiling point was elevated, thus, no evident out gassing under the reaction temperature of 100 ^{o}C.