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A Continuous Kilogram-Scale Process for the Manufacture of 7-Ethyltryptophol

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ABSTRACT: An expeditious and multikilogram-scale process for the synthesis of 7-ethyltryptophol via a continuous flow reactor from 2-ethylphenylhydrazine and 4-hydroxybutyraldehyde in higher and high yield was described. The main steps in this synthesis involved not only the generation of the hydrazone intermediate in situ but also the catalysis of the subsequent [3 + 3] sigmatropic rearrangement in the tandem loop reactor. Decomposition of the intermediate hydrazone was found to be a key factor resulting in low yield.

INTRODUCTION

Application of continuous flow synthesis is growing rapidly in both academia and the pharmaceutical industry. Continuous flow reactors in synthesis offer the following unique advantages over traditional batch vessels: (a) the decrease of reactor size and increase in surface-to-volume ratio significantly reinforce mass and heat transfer, (b) the feasibility and device flexibility of continuous flow synthesis offer fewer transport limitations which minimizes chemical hazards and moderately harsh conditions, (c) precise control of reaction variables such as temperature, pressure, residence time, and stoichiometry enhances the control of the overall reaction rates and improves yield and selectivity, (d) multistep synthesis in a single continuous flow process can be set up by connecting several reactors or processes in series, and (e) continuous flow synthesis can readily be scaled-up in numbering up and is ideal for automation.[1]

Widespread occurrence of indoles in natural products and biologically active compounds has led to a continued interest in the practical synthesis of the indole nucleus.[2] Of prevailing pharmaceutical importance is 7-ethyltryptophol which is a key intermediate for the clinically effective analgesic and antiinflammatory drug etodolac. Etodolac has been shown to possess an exceptional safety profile with respect to the gastrointestinal and renal tract, and it has also been proved to have the potential to retard the progression of skeletal changes in rheumatoid arthritis.[3]

Despite the diverse and creative approaches that have been developed so far, the classical Fischer indole synthetic methodology which involves hydrazone formation and subsequent [3 + 3] sigmatropic rearrangement remains the benchmark method (Scheme 1).[4] The development of one-pot approaches to the assembly of the indole skeleton which obviates the isolation of the unstable arylhydrazones is attracting considerable attention due to both its economical and its ecological importance. Some reported examples within this context are (1) one-pot synthesis of 5-substituted *N*,*N*-dimethyltryptamine with 4% H_2SO_4 as catalyst;[5] (2) one-pot synthesis of 1,2,3,4-tetrahydrocarbazole with trifluoroacetic anhydride as catalyst, necessitating the recycling of trifluoroacetic acid;[6] (3) one-pot synthesis of the indole nucleus using K-10 montmorillonite as catalyst;[7] (4) one-pot synthesis with Lewis acidic ionic liquids such as 1-butylpyridinium chloride·$3AlCl_3$ or choline chloride·$2ZnCl_2$ as catalysts and solvents.[8] However, several kinds of reported byproducts[9] might form through further reactions of the intermediate hydrazone **3** or **1** with excess 2,3-dihydrofuran (DHF) (Figure 1) during the one-pot synthesis methods.

Our previous work[10] on the synthesis of **1** has achieved a certain progress in a batch reactor by taking the following methods including the control of the pH during the formation of the hydrazone, the removal of excess 4-hydroxybutyraldehyde with $NaHSO_3$, the adjustment of the addition rate of H_2SO_4, the dilution of the reaction system, and extraction of the product formed in situ in the Fischer cyclization step. However, the product yield was still not satisfying, and the process was a little time consuming. Accordingly, we focused on a scalable and efficient continuous process for the Fischer indole synthesis of **1**.

RESULTS AND DISCUSSIONS

Process A. Our original process discussed in this document was the direct conversion of the commonly used one-pot batch methodology to a homogeneous continuous flow system. Scheme 2 shows the continuous flow reactor experimental setup. Solution A of commercially available **2** hydrochloride in ethylene glycol/water (2:5) with a concentration of 0.8 M together with solution B of DHF (1 equiv) in ethylene glycol/water (2:5) with a concentration of 0.8 M were pumped into the residence loop reactor (Hastelloy tube, 7 mm o.d., 6 mm i.d.) via a T-joint (7 mm i.d.) by two peristaltic pumps (**P1**, **P2**, Boading Longer, China), respectively. The mixture flowed through residence loop I which was preheated and kept at 100 °C by hot oil at a total flow rate of 200 mL/min. The reactor allowed for a mixing period in which the hydrazone could be generated immediately in situ and

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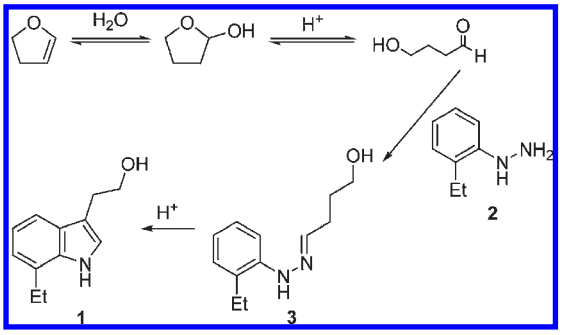
then catalyzed the subsequent [3 + 3] sigmatropic rearrangement in residence loop I; reaction was terminated in residence loop II by cooling the mixture by cold water. After a residence time of 30 min in loop I, streams were typically analyzed by HPLC[11] at about 65% of **1**, less than 5% of **3**, and byproducts (totally about 30%). Further analysis of byproducts indicated only a trace of triol **4**; however, a quantity of **7a** and a novel byproduct **8** (Scheme 3). The results demonstrated the consecutive reaction between **1** and DHF has dropped substantially in the continuous flow process; however, hydrazone **3** still could react with excess DHF while cyclizing to indole, and could also cyclize to cinnoline.

Scheme 1. Synthesis of 7-ethyltryptophol 1



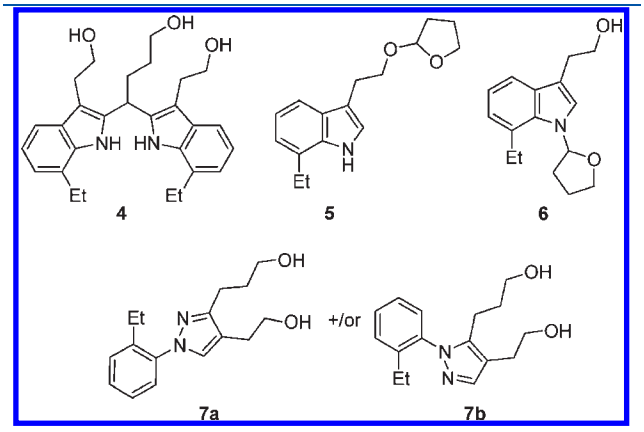
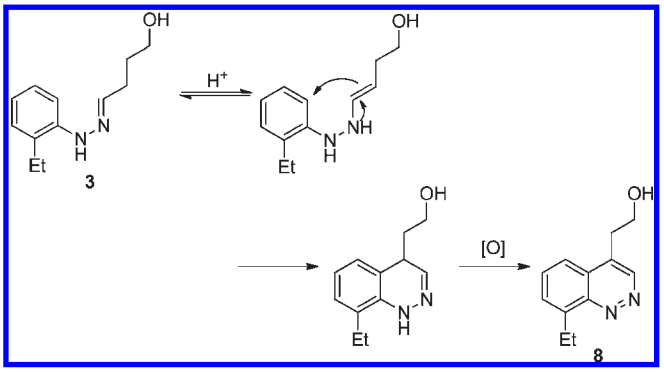


Figure 1. Byproducts in the preparation of **1**.

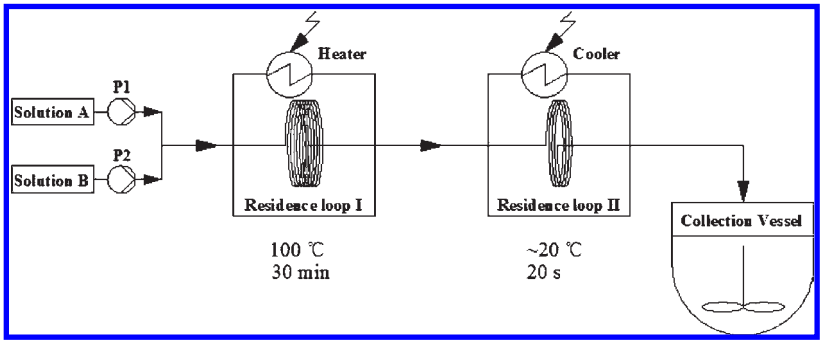
Process B. According to the problems of the first method, an improved process was developed by generating the hydrazone **3** under neutral condition in residence loop I, and then catalyzing the cyclization with 8% aqueous sulfuric acid in the tandem loop reactor II (Scheme 4). Experimental parameters (flow rate, residence time, and temperature) of synthesizing hydrazone were initially optimized separately. The temperature of 60 °C with a residence time of about 5 min led to a conversion of 100% by HPLC. Isolation of this intermediate was unnecessary; the hydrazone was used directly in the cyclization step in a continuous flow manner. The [3 + 3] sigmatropic rearrangement catalyzed by sulfuric acid was undertaken at 100 °C in the tandem residence loop II. With the aim at quenching the reaction at reaction completion, the mixture was cooled to nearly 20 °C in loop III, and the residual acid was neutralized by 30% aqueous NaOH. Full conversion of **3** was completed in 16 min; however, side reactions were still detected by HPLC including **4** (0.8%), **7a** (13%), and **8** (8%). Yield of **1** was only about 55% corrected for purity. After extensive efforts, we found that reducing the concentration from 0.4 to 0.1 M reduced the rate formation of **8**; however, the impurty **7a** remained. We were confused as to where the DHF or 4-hydroxybutyraldehyde came from? The only possible source was the decomposition of hydrazone **3**.

Decomposition study. An extra decomposition test of **3** was systematically investigated by varying temperature and acidity in the same solvents and concentration with the above process (Figure 2). It was found that the decomposition rate was not so fast within the first few minutes, which makes possible a higher yield process by shortening the reaction time.

Scheme 3. Novel Side Reaction



Scheme 2. Schematic of Process A[a]



[a] Solution A is 0.8 M **2** hydrochloride in ethylene glycol/water (2:5) with a flow rate of 100 mL/min, solution B is 0.8 M DHF in ethylene glycol/water (2:5) with a flow rate of 100 mL/min.

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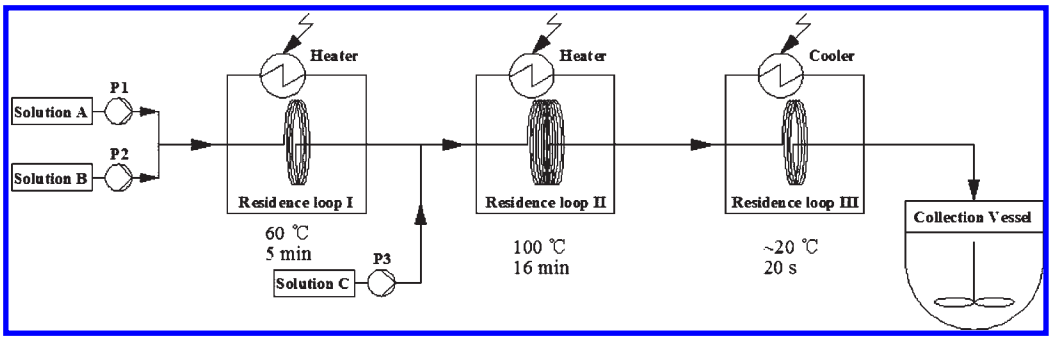
Scheme 4. Schematic of Process B[a]



[a] Solution A is 0.2−0.8 M **2** hydrochloride and NaOH (1 equiv) in ethylene glycol/water (2:5) with a flow rate of 100 mL/min, solution B is 0.2−0.8 M DHF in ethylene glycol/water (2:5) together with 0.5−1 mL hydrochloric acid stirred for 10 minutes in advance with a flow rate of 100 mL/min; solution C is 8% sulfuric acid with a flow rate of 50 mL/min.

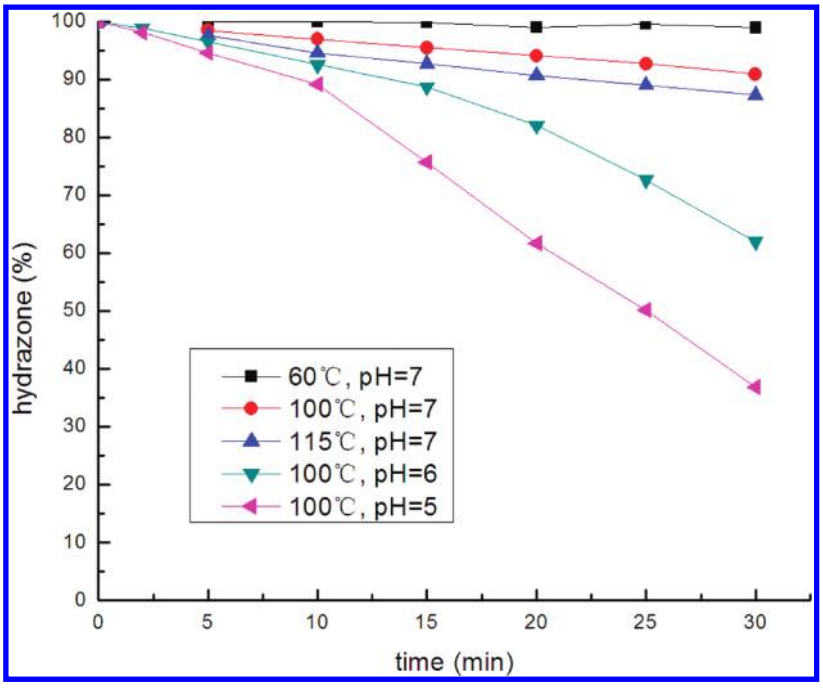


Figure 2. With the increase of temperature and the decrease of pH values, the hydrazone decomposed much more rapidly. These procedures generated only a small amount of product **1**: pH = 7 (none), pH = 6 (3%), pH = 5 (10%).

Process C. On the basis of the results of decomposition study, a new optimized process was then undertaken, and optimal conditions were achieved by flowing a solution of **2** in ethylene glycol/water (5:2) together with a stream of 4-hydroxybutyraldehyde (1 equiv, generated from DHF beforehand) in ethylene glycol/water (5:2) at 115 °C for 20 s, followed by the introduction of 115 °C 50% aqueous sulfuric acid into the loop reactor (7 mm o.d., 6 mm i.d.) for about 4 min. The mixture was cooled when it flowed through the cooling loop, and the reaction was terminated by neutralizing the residual acid with 30% aqueous NaOH (Scheme 5). Ethylene glycol was removed by extraction into water, while **1** was extracted by MTBE and subsequently analyzed by HPLC, indicating at least 98% of **1**, and only trace of **7a** and **8**. The yield of **1** was 73−75% corrected for purity.

For comparative purposes, the reaction was run both as a one-pot batch process on a 1-kg scale, using the same temperature and concentration of reagents as optimized in Process C. It was found that such conditions gave only moderate conversion (Table 1) and selectivity (Figure 3). The precise control of temperature distribution and the efficient heating and mixing associated with flow technique minimized the formation of byproducts and ensured that this chemical transformation proceeded at faster rates by increasing the amount of acid compared to that from the batch system.

CONCLUSION

In summary, an expeditious and high-yielding process for the synthesis of **1** from **2** and 4-hydroxybutyraldehyde via a continuous flow reactor has been set up. The process is amenable both for the preparation of analogous compounds and for scaling-up by operating several reactors with high throughput in parallel. Due to the rapid decomposition of **3**, it remains a challenging task to obtain a more satisfying yield.

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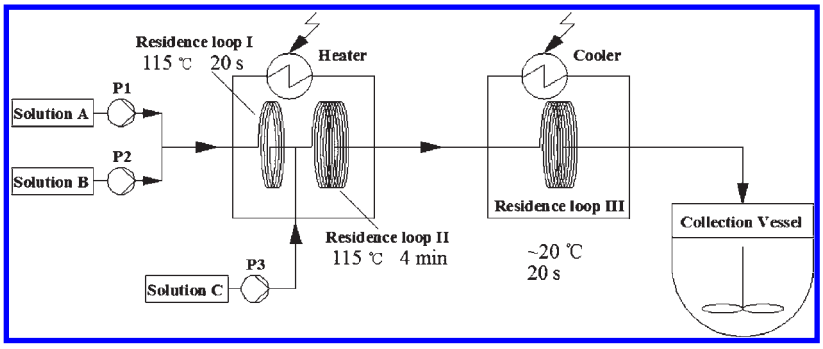
Scheme 5. Schematic of Process C[a]



[a] Solution A is 0.8 M **2** hydrochloride and NaOH (1 equiv) in ethylene glycol/water (5:2) with a flow rate of 230 mL/min; solution B is 0.8 M DHF in ethylene glycol/water (5:2) together with 0.5−1 mL hydrochloric acid stirred for 10 minutes in advance with a flow rate of 230 mL/min; solution C is 50% sulfuric acid with a flow rate of 40 mL/min.

Table 1. Comparison of results

operate manner	conversion (%)[a]	purity (%)	yield (%)[b]
batch process	93	60.2	45
continuous process	100	82.6	75

[a] Conversion of hydrazone was determined by HPLC at 275 nm. [b] Yield of **1** was corrected for purity.

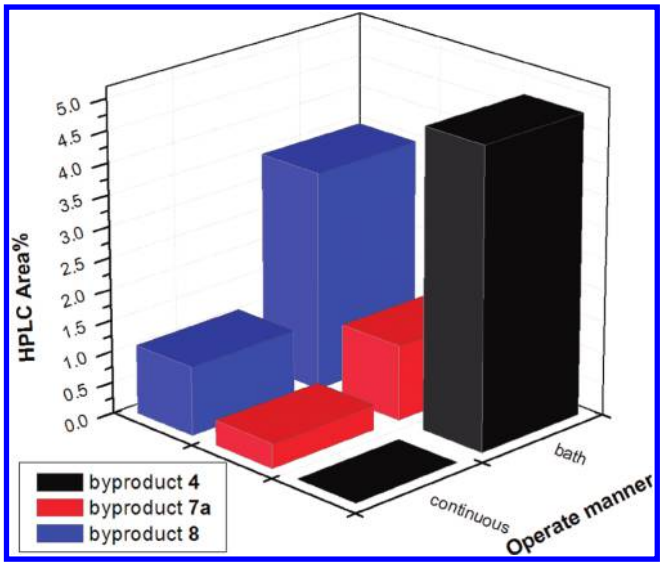


Figure 3. Comparison of byproducts.

EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and were used without further purification. Solution A [**2** hydrochloride (1 kg, 5.79 mol) and sodium hydroxide (0.23 kg, 5.79 mol) in ethylene glycol (20 L) and water (8 L) under nitrogen] and solution B [DHF (0.41 kg, 5.79 mol) with 0.5−1 mL hydrochloric acid in ethylene glycol (20 L) and water (8 L) which was stirred for 10 min in advance] were respectively pumped into the residence loop I via a T-joint by **P1** and **P2** at a flow rate of 230 mL/min, after a residence time of 20 s at 115 °C. Solution C of 50% aqueous sulfuric acid (preheated to 115 °C) was introduced into the tandem loop II by **P3** at a flow rate of 40 mL/min. Reagents were maintained in loop II for about 4 min, and then the mixture was cooled to nearly 20 °C by cold water flowing through loop III while the indole cyclization was terminated by neutralizing the residual acid with 30% aqueous NaOH. The solution was mixed with NaCl (1.6 kg) and extracted with MTBE (3 × 21 L), and the combined organic extracts were washed with water (3.5 L), aqueous $NaHSO_3$ (5%, 3.5 L), aqueous $NaHCO_3$ (saturated, 3.5 L), and water (3.5 L). After solvent evaporation in vacuo, the initially obtained oil solidified to afford 0.99 kg of reddish solid in 82.6% purity and 75% yield corrected for purity of **1**. On a 10-kg scale, this convenient procedure afforded a 73.6% yield of **1** at 83.1% purity. Isolation of **1** was unnecessary, for it was used directly in the further synthesis of etodolac in the commerical process.

Characterization data of compound 1: ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 8.05 (br s, 1H), 7.47 (d, 1H, J = 8.0 Hz), 7.11−7.04 (m, 3H), 3.90 (t, 2H, J = 6.5 Hz), 3.03 (t, 2H, J = 6.0 Hz), 2.85 (q, 2H, J = 8.0, 15.5, 23.0 Hz), 1.36 (t, 3H, J = 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 13.9, 24.1, 28.9, 62.6, 112.5, 116.4, 119.6, 120.6, 122.0, 126.5, 127.0, 135.1.

Characterization data of compound 7a: MS: $(M + H^+)$ 275. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.40 (s, 1H), 7.34−7.32 (m, 2H), 7.27−7.25 (m, 2H), 5.30 (s, 1H), 3.80 (t, 2H, J = 5.6 Hz), 3.70 (t, 2H, J = 5.8 Hz), 2.80 (t, 2H, J = 6.9 Hz), 2.75 (t, 2H, J = 6.5 Hz), 2.57 (q, 2H, J = 7.6, 15.1, 22.6 Hz,), 2.00−1.93 (m, 2H), 1.10 (t, 3H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 14.8, 23.0, 24.4, 27.0, 31.2, 62.1, 62.9, 115.9, 126.4, 126.5, 128.5, 129.6, 130.3, 139.3, 139.8, 151.7. IR (KBr) ν/cm^{-1}: 3416, 2935, 2868, 1684, 1500, 1456, 1377, 1045, 764. HRMS (ESI) m/z: Calcd for $C_{16}H_{22}N_2O_2$, $(M + H^+)$: 274.3572. Found: 274.3581.

Characterization data of compound 8: MS: $(M + H^+)$ 203. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.68 (s, 1H), 7.65−7.58 (m, 3H), 4.22 (t, 2H, J = 5.6 Hz), 3.51 (q, 2H, J = 7.5, 15.0, 22.5 Hz), 3.41 (t, 2H, J = 5.6 Hz), 1.46 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 15.3, 24.4, 38.1, 61.9, 122.4, 124.1, 126.6, 128.3, 131.4, 143.8, 148.0, 155.3. IR (KBr) ν/cm^{-1}: 3420, 2964, 2929, 2876, 1654, 1556, 1503, 1453, 1057, 779. HRMS (ESI) m/z: Calcd for $C_{12}H_{14}N_2O$, $(M + H^+)$: 202.2518. Found: 202.2521.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) HPLC conditions: RP-18 column, 250 mm × 4.0 mm, eluted at 1.0 mL/min with 50:25:25 0.03 M NaH_2PO_4 aqueous/CH_3CN/CH_3OH, 275 nm.