

Continuous-Flow Synthesis of 2-amino-4-(ethylsulfonyl) phenol via Integrated Oxidation and Nitration

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Abstract

A safe and scalable synthesis of 2-amino-4-(ethylsulfonyl) phenol has been established. The route commences with the alkylation of commercially available 4-chlorobenzenethiol using ethyl iodide to afford (4-chlorophenyl) (ethyl)sulfane. A key feature of this work is the implementation of a telescoped continuous-flow platform that seamlessly integrates two inherently hazardous transformations: the oxidation of the sulfide to the sulfone by $\text{NaClO}_2/\text{AcOH}$, followed immediately by regioselective nitration with an $\text{HNO}_3/\text{H}_2\text{SO}_4$ mixture to yield 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene. Subsequent hydrolysis and an iron (III)-catalyzed reduction furnished the target aminophenol intermediate. Finally, condensation with 2-naphthoic acid, promoted by Eaton's reagent, delivered the active pharmaceutical ingredient (API) ezutromid. This continuous-flow strategy effectively mitigates the safety risks associated with the oxidation and nitration steps while demonstrating robust scalability. The process reliably produces batches exceeding 100 g (with single-pass oxidation throughput reaching 140 g), maintains high selectivity throughout, and requires only straightforward aqueous workups.

Introduction

2-Amino-4-(ethylsulfonyl)phenol (**1**) is a versatile intermediate with two critical applications. First, it serves as a precursor for the monomer 2-methacrylic acid 6-{4'-[5-(ethylsulfonyl)benzoxazol-2-yl]biphenyl-4-yloxy}hexyl ester (MBBS) [1], which is polymerized into a thermotropic polymethacrylate (PBBS). This polymer contains monolithic photoactive mesogens and is designed for high-chromophore-content liquid crystalline media. Second, it acts as a key building block for ezutromid (5-(ethylsulfonyl)-2-(naphthalen-2-yl)benzo[d]oxazole), a first-in-class utrophin modulator. Ezutromid has demonstrated clinical promise for treating Duchenne muscular dystrophy (DMD), a fatal muscle-wasting disorder[2-4]. (**Scheme 1**)

To date, two synthetic routes toward compound **1** have been reported. In the first route [5], 4-methoxybenzenesulfonyl chloride serves as the starting material and is reduced to the corresponding sodium 4-methoxybenzenesulfinate using Na_2SO_3 as the reductant. Subsequent condensation with ethyl iodide yields 1-(ethylsulfonyl)-4-methoxybenzene, which then undergoes nitration with 65% nitric acid to afford the key intermediate 4-(ethylsulfonyl)-1-methoxy-2-nitrobenzene (**2**). In the second route [6], 4-chlorobenzenethiol is condensed with ethyl iodide to give (4-chlorophenyl)(ethyl)-sulfane, which is subsequently oxidized with hydrogen peroxide to produce 1-chloro-4-(ethylsulfonyl)benzene. Nitration of this intermediate with nitric acid furnishes 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (**3**). Both intermediates **2** and **3** can be hydrolyzed to obtain 4-(ethylsulfonyl)-2-nitrophenol (**4**). Finally, palladium- or nickel-catalyzed hydrogenation of **4** provides the target compound 2-amino-4-(ethylsulfonyl)phenol (**1**).

The first route is hampered by the stoichiometric use of Na_2SO_3 (3.0 equiv relative to substrate), raising environmental concerns regarding waste streams. Furthermore, the condensation of sodium 4-methoxybenzenesulfinate with ethyl iodide delivers the product in a modest 77% yield. Furthermore, both

routes suffer from significant safety liabilities, particularly the hazardous nature of the sulfide-to-sulfone oxidation and the nitration step. Collectively, these limitations underscore the need for a safer and more sustainable synthetic strategy toward 2-amino-4-(ethylsulfonyl) phenol (**1**).

In recent years, continuous-flow synthesis has emerged as a superior paradigm for mitigating the inherent hazards of energetic processes, such as organometallic reactions, explosive diazo, diazonium and azide compounds involved reactions, oxidations, nitrations, and diazotizations, with numerous examples now established at industrial scale [7-10]. Capitalizing on the cost-effectiveness of the starting materials and the robust yields of the **second route**, we adapted this sequence for flow chemistry. While the condensation of 4-chlorobenzenethiol with ethyl iodide proceeded efficiently, the critical oxidation of the sulfide to the sulfone was redesigned using sodium chlorite (NaClO_2) as a safer alternative to traditional peroxide reagents, affording excellent conversion and selectivity. Herein, we report a continuous-flow strategy for the synthesis of 2-amino-4-(ethylsulfonyl)phenol (**1**).

Results and Discussion

Reaction of 4-chlorothiophenol with iodoethane in the presence of Na_2CO_3 in acetonitrile afforded 1-chloro-4-(ethylthio)benzene in 99% isolated yield (99% HPLC purity). The high purity of the crude product allowed its direct use in the next step without further purification.

Oxidation of 1-chloro-4-(ethylthio)benzene

The oxidation of sulfides to sulfones represents a crucial yet inherently hazardous step in this synthesis. While numerous protocols exist—including transition-metal or metallosilicate-catalyzed oxidations using H_2O_2 [11-15], DES-mediated systems [16], solvent-dependent chemoselective oxidations with Oxone® [17], and electrochemical methods employing water as the oxygen source [18]—these methods frequently suffer from drawbacks such as heavy-metal residues, high inorganic waste streams, or the requirement for specialized equipment. Critically, the handling of peroxides presents substantial safety liabilities upon scale-up.

In contrast, we have previously established NaClO_2 as a versatile and environmentally benign oxidant for the conversion of tertiary amines to amides [19-20], benzylic C–H bonds to carbonyls [21], and sulfides to sulfoxides/sulfones [22]. These transformations exhibit a marked dependence on pH: buffered aqueous conditions favor sulfoxide formation, whereas the introduction of organic acids selectively drives the production of sulfones. Initial batch optimization revealed that oxidizing 1-chloro-4-(ethylthio)benzene with 3.0 equiv of NaClO_2 in acetic acid afforded high selectivity but required a prolonged reaction time of 7 h (**Table 1**, Entry 1). Reducing the oxidant loading to 2.0 equiv compromised the selectivity (**Table 1**, Entry 2). Attempts to scale this batch protocol to over 10 g input triggered a pronounced exotherm accompanied by the release of yellow fumes (presumed to be ClO_2), underscoring the intrinsic safety risks of the batch mode. Consequently, the process was transitioned to a continuous-flow regime (**Figure 1**). Gratifyingly, this shift facilitated complete conversion within a mere 5 min residence time while maintaining excellent selectivity (**Table 1**, Entry 3). Unlike the batch mode, the flow

system exhibited remarkable robustness; decreasing the oxidant loading did not erode selectivity (**Table 1**, Entries 4 and 5). Further optimization revealed that extending the residence time to 10 min allowed for a reduction in NaClO₂ loading to 2.0 equiv without sacrificing yield (**Table 1**, Entry 6), though further decreases in oxidant resulted in a marked drop in selectivity (**Table 1**, Entry 7). Using these optimized parameters, the flow oxidation was successfully scaled up, delivering 140 g of the target sulfone over a 700-min continuous run.

Table 1. Optimization of the oxidation of 1-chloro-4-(ethylthio) benzene to 1-chloro-4-(ethylsulfonyl)benzene.

Entry	Reaction mode	Oxidant (equiv.)	Residence time	Conv. (%) ^b	Ratio of products (sulfone: sulfoxide) ^b
1 ^a	Batch	3.0	7 h	100	97: 3
2 ^a	Batch	2.0	7 h	100	87: 13
3 ^c	Continuous	3.0	5 min	100	99: 1
4 ^c	Continuous	2.5	5 min	100	99: 1
5 ^c	Continuous	2.0	5 min	100	95: 5
6 ^c	Continuous	2.0	10 min	100	99: 1
7 ^c	Continuous	1.5	10 min	100	84: 16

^a Reaction conditions: 1-chloro-4-(ethylthio)benzene (5 mmol) in acetic acid (10 mL), 70 °C, NaClO₂ in 10 mL water; ^b ratio was detected by HPLC(area normalization).); ^c 1-chloro-4-(ethylthio)benzene (20 mmol) in 20 mL acetic acid, and aqueous NaClO₂ (20 mL) were delivered at set flow rates into a microchannel reactor (tube length: 2 m, inner diameter: 1 mm) immersed in a thermostatic oil bath (70 °C).

Nitration of 1-chloro-4-(ethylsulfonyl)benzene

Nitration represents a significant hazard in organic synthesis owing to its highly exothermic nature and the potential for thermal runaway [23]. To date, various nitration systems—including classical mixed acid (H₂SO₄/HNO₃), H₂SO₄/KNO₃ and Fe(NO₃)₃/HFIP, have been developed for the synthesis of nitrobenzene derivatives [24]. In this study, these systems were evaluated using 1-chloro-4-(ethylsulfonyl)benzene as a model substrate. While the H₂SO₄/HNO₃ and H₂SO₄/KNO₃ systems afforded high yields (**Table 2**, entries 1 and 2), the Fe(NO₃)₃/HFIP system proved ineffective (**Table 2**, entry 3). Consequently, the H₂SO₄/HNO₃ system was selected for implementation in a continuous-flow reactor. This approach demonstrated

excellent compatibility with the flow regime, yielding the desired product in high efficiency with a residence time of just 10 minutes at 70 °C.

Table 2. Nitration of 1-chloro-4-(ethylsulfonyl)benzene.

Entry	Reaction mode	Nitration system	Temp. (°C)	Reaction Time	Conv. (%) ^e	Select. (%) ^e
1 ^a	Batch	H ₂ SO ₄ /HNO ₃	70	2h	97	94
2 ^b	Batch	H ₂ SO ₄ /KNO ₃	80	4h	98	95
3 ^c	Batch	Fe(NO ₃) ₃ /HFIP	100	12h	0	—
4 ^d	Continuous	H ₂ SO ₄ /HNO ₃	70	10min	98	97

Reaction conditions: ^a1-chloro-4-(ethylsulfonyl)benzene (5 mmol), 98% H₂SO₄ (5g), 65%HNO₃ (0.86g); ^b as Entry 1, and KNO₃ (1g) was used instead of 65%HNO₃; ^c as entry 1, and Fe(NO₃)₃·9H₂O (1.0 equiv) in combined with HFIP (0.5 M) was used instead of H₂SO₄/HNO₃; ^d1-chloro-4-(ethylsulfonyl)benzene(20mmol) in 98% H₂SO₄ (12.6ml), and conc. HNO₃ 4.2ml were delivered at set flow rates into a microchannel reactor (tube length: 2 m, inner diameter: 1 mm) immersed in a thermostatic oil bath (70 °C); e conversion and selectivity was determined by HPLC.

Synthesis of 4-(ethylsulfonyl)-2-nitrophenol

The hydrolysis of 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene proceeds efficiently in the presence of aqueous sodium hydroxide, affording the desired product in excellent yield. The workup is straightforward, and the resulting crude product exhibits sufficient purity to be directly carried forward to the subsequent reduction step.

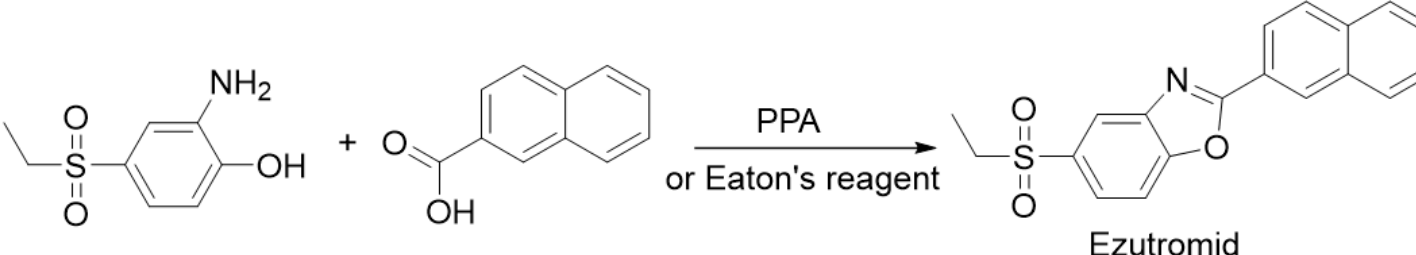
FeCl₃/charcoal catalyzed reduction of 4-(ethylsulfonyl)-2-nitrophenol with aqueous hydrazine as reductant: The reduction of nitro groups can be achieved through various methods [25-27], including palladium-, platinum-, or nickel-catalyzed hydrogenation over charcoal, as well as Fe (III)- or Co (II)-catalyzed transfer hydrogenation using hydrazine hydrate as the hydrogen source. Owing to considerations of operational convenience and safety, the Fe(III)-catalyzed transfer hydrogenation was selected to reduce 4-(ethylsulfonyl)-2-nitrophenol to the corresponding 2-amino-4-(ethylsulfonyl)phenol.

Synthesis of ezutromid

With the key intermediate secured, initial efforts toward the synthesis of ezutromid employed polyphosphoric acid (PPA) as the condensing agent. While 2-amino-4-(ethylsulfonyl)phenol and 2-naphthoic acid successfully coupled under these conditions, PPA proved suboptimal for large-scale manufacturing. Its extreme viscosity complicated workup procedures, and the high temperatures

required for handling the neat reagent posed inherent safety risks. Moreover, the modest yields were unsatisfactory for process scale-up, necessitating the identification of a superior dehydrating agent. Eaton's reagent emerged as a viable alternative [28], unlike PPA, it exhibits low viscosity and has been widely utilized in acid-mediated transformations [29-35]. Adopting this strategy, we successfully implemented Eaton's reagent for the synthesis of ezutromid, achieving high yields and excellent selectivity. (**Table 3**)

Table 3 Synthesis of Ezutromid promoted by PPA or Eaton's reagent respectively

			
Entry	Reaction System	Temperature (°C)	Yield (%) ^a
1 ^b	PPA	150	62
2 ^c	Eaton's reagent	80	83

^a isolated yield; ^b Reaction conditions: 2-amino-4-(ethylsulfonyl)phenol (1.06g, 5

mmol) and 2-naphthoic acid (0.85g, 5 mmol), PPA (12 g) was stirred at 150 °C for 2 h. ^c

2-amino-4-(ethylsulfonyl)phenol (1.03g, 5 mmol) and 2-naphthoic acid (0.86g, 5 mmol),

Eaton's reagent (5 mL) was stirred at 80 °C for 2 h.

Conclusion

A practical, scalable five-step synthesis of 2-amino-4-(ethylsulfonyl)phenol is reported. Implementing a continuous-flow strategy for the hazardous oxidation and nitration stages markedly enhanced process safety and reaction selectivity. Relative to traditional batch methods, the flow system improved reagent utilization, significantly reducing stoichiometric excess. Crucially, the route bypasses chromatographic purification; all intermediates were isolated via high-yielding crystallizations with excellent purity. Leveraging this key intermediate, Ezutromid was successfully synthesized using Eaton's reagent as a promoter under mild conditions, affording the target compound in high yield with good selectivity.

Experimental

All reagents and solvents were used as received without further purification unless otherwise specified. ¹H NMR spectra were recorded on a 400 MHz spectrometer using CDCl₃ or DMSO-d₆ as the solvent.

Chemical shifts (δ) are reported in ppm relative to the residual solvent peak. HPLC analysis was performed to determine purity and conversion.

General Procedures: Reverse-phase HPLC was performed on an Agilent 1260 Series HPLC instrument using the following methods: Column: Zorbax SB-C18 RP (150 mm $\times$ 4.6 mm, 3.5 μ m). Conditions: Flow rate 1 mL/min; 30 $^{\circ}$ C; Mobile phase: (A) water, (B) acetonitrile, (C) methanol. Gradient: 0–4 min, 65–10% A, 25–80% B, 10% C; 4–7 min, 10% A, 80% B, 10% C; 7–14 min, 10–65% A, 80–25% B, 10% C; 14–16 min, 65% A, 25% B, 10% C. UV detection at 230 nm. Retention times are uncorrected; molar ratios are determined by area normalization.

Preparation of 1-chloro-4-(ethylthio)benzene: To a solution of *p*-chlorothiophenol (14.40 g, 0.10 mol) in acetonitrile (100 mL) were added iodomethane (17.16 g, 0.11 mol) and sodium carbonate (10.60 g, 0.10 mol). The mixture was heated under reflux for 5 h, at which point TLC indicated complete consumption of the starting material. After cooling to room temperature, the suspension was filtered to remove inorganic salts. The filtrate was concentrated under reduced pressure to afford 17.00 g (99% yield) of the desired thioether as a colorless oil. HPLC purity: 99% (sufficient for the next step). ^1H NMR (400 MHz, Chloroform- d) δ 7.26 (s, 4H), 2.93 (q, J = 7.3 Hz, 2H), 1.31 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 135.2, 131.8, 130.4, 129.0, 27.9, 14.3.

Preparation of 1-Chloro-4-(ethylsulfonyl)benzene:

Batch oxidation: To a 100 mL three-necked round-bottom flask equipped with a stir bar and charged with 1-chloro-4-(ethylthio)benzene (3.40 g, 20 mmol) and acetic acid (10 mL) was added an aqueous solution of NaClO_2 (6.81 g in 12 mL H_2O) via syringe pump over 4 h at 70 $^{\circ}$ C. After stirring at this temperature for an additional 1 h (monitored by TLC), the reaction was quenched by the addition of aqueous sodium sulfite. The volatiles were removed under reduced pressure, and the resulting residue was partitioned between H_2O and CH_2Cl_2 . The organic phase was separated, dried anhydrous Na_2SO_4 , filtered, and concentrated in vacuo to afford the title compound as a colorless oil (4.01 g, 97% yield, 91% HPLC purity).

Continuous-Flow Oxidation: A solution of 1-chloro-4-(ethylthio)benzene (3.4 g, 20 mmol) in AcOH (10 mL, Solution A) was loaded into Feed Reservoir 1. A solution of NaClO_2 (80% assay, 4.53 g, 40 mmol, 2.0 equiv) in H_2O (20 mL, Solution B) was loaded into Feed Reservoir 2. As depicted in **Figure 1**, the reservoirs were connected to Pump 1 and Pump 2, respectively. Based on the stoichiometric ratio, flow rates were set to 0.05 mL/min (Solution A) and 0.10 mL/min (Solution B). The streams were combined in a Y-micromixer and passed through a heated microchannel reactor (2 m $\times$ 1 mm i.d., 70 $^{\circ}$ C). With a residence time of $\sim$ 10 min, the effluent was collected in a receiver flask. HPLC analysis confirmed complete conversion ($>99\%$) and high selectivity ($>99\%$). The collected product stream was quenched with aqueous sodium sulfite, concentrated under reduced pressure, and the residue was redissolved in dichloromethane, filtered, and concentrated under vacuum to afford the title sulfone as a colorless oil (4.03 g, 98.7% yield, 97% HPLC purity). ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, J = 8.6 Hz, 2H), 7.54 (d, J =

8.7 Hz, 2H), 3.11 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 140.5, 137.0, 129.8, 129.6, 50.7, 7.4. MS (ES-API): m/z $[\text{M} + \text{Na}]^+ = 227$.

Scale-up of the continuous oxidation process:

To evaluate the scalability of the continuous-flow oxidation protocol, the process was transferred to a larger reactor configuration (**Figure 1**). The internal diameters of all tubular reactors and Y-mixers were increased from 1 mm to 3 mm. Two precision metering pumps (PEEK, 100 mL capacity) were employed to deliver the reagent solutions.

Solution A was prepared by dissolving 1-chloro-4-(ethylthio)benzene (137.62 g, 0.80 mol) in acetic acid (400 mL). Solution B was prepared separately by dissolving sodium chlorite (80% assay, 180.95 g, 1.60 mol) in water (800 mL). Solution A was pumped at 0.50 mL/min and Solution B at 1.00 mL/min through Teflon® Y-mixers (3 mm i.d.) into Teflon® tubular reactors (2 m $\times$ 3 mm i.d.) maintained at 70 °C. Back-pressure was regulated at 150 psi using a back-pressure regulator.

After steady-state operation was established, the reactor effluent was collected continuously over a period of 700 min. The collected product stream was quenched with aqueous sodium sulfite, concentrated under reduced pressure, and the residue was redissolved in dichloromethane, filtered, and concentrated under vacuum to afford 1-chloro-4-(ethylsulfonyl)benzene as a colorless oil (140 g, 98% isolated yield, 98% HPLC purity). This continuous operation demonstrated the robustness of the flow-chemistry protocol and confirmed its suitability for scale-up production.

Preparation of 1-Chloro-4-(ethylsulfonyl)-2-nitrobenzene:

Nitration of 1-Chloro-4-(ethylsulfonyl)benzene with $\text{H}_2\text{SO}_4/\text{HNO}_3$ system (Batch reaction): To a 100 mL three-necked flask equipped with a stir bar was added crude 1-chloro-4-(ethylsulfonyl) benzene (1.02 g, 5mmol) followed by 98% H_2SO_4 (5g). The mixture was heated to 70 °C, and 65% HNO_3 (0.86g, 8.8mmol) was added dropwise over 5 min. After the addition was complete, the reaction was stirred at 80 °C for 2 h (monitored by TLC). The mixture was then carefully poured onto crushed ice (50 g). The resulting yellow precipitate was collected by vacuum filtration, washed with cold water, and dried in vacuo to afford 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene as a yellow solid (1.17 g, 94% yield, 93% HPLC purity).

Nitration of 1-Chloro-4-(ethylsulfonyl) benzene with $\text{H}_2\text{SO}_4/\text{KNO}_3$ system (batch reaction): To a 100 mL three-necked flask was added crude 1-chloro-4-(ethylsulfonyl)benzene (1.01 g, 5mmol) and 98% H_2SO_4 (5.04 g). The mixture was heated to 80 °C, and KNO_3 (1.03 g, 10mmol) was added portion-wise. After addition, the mixture was stirred for 4 h (monitored by TLC). The reaction mixture was poured into ice water (50 g), and the resulting yellow solid was collected by filtration and dried to afford 1.18 g of crude product. Yield: 95%. HPLC purity: 95%.

General Procedure for Continuous-Flow Nitration: A solution of crude 1-chloro-4-(ethylsulfonyl) benzene (5.02 g, 20 mmol) in concentrated H_2SO_4 (98%, ~12.6 mL; Solution A) was charged to Feed Reservoir 1. Concurrently, concentrated HNO_3 (65%, 5.8 g, ~4.2 mL; Solution B) was loaded into Feed Reservoir 2. The

continuous-flow system was pre-equilibrated in an oil bath set to 70 °C. Solutions A and B were pumped at flow rates of 0.09 mL/min and 0.03 mL/min, respectively, affording a combined residence time of approximately 10 min within the microchannel reactor (maintained at 70 °C). The effluent was quenched into ice water (50 g), and the precipitated yellow solid was isolated via filtration. After drying, 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene was obtained as a yellow solid (4.73g, 95% yield). HPLC analysis confirmed >99% conversion and a purity of 97%. ¹H NMR (400 MHz, Chloroform-d) δ 8.41 (s, 1H), 8.05 (d, J = 6.3 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 3.19 (q, J = 7.4 Hz, 2H), 1.35 (t, J = 7.5 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 138.8, 133.3, 133.0, 132.3, 129.6, 125.7, 50.7, 7.4.

General Procedure for Hydrolysis: To a 2 L round-bottom flask equipped with a mechanical stirrer was added a suspension of 1-chloro-4-(ethylsulfonyl)-2-nitrobenzene (2.51 g, 9.8 mmol) in a 10 wt% aqueous NaOH solution (about 20 g, 50mmol). The reaction mixture was heated to 100 °C and stirred for 1 h, at which point TLC analysis indicated complete consumption of the starting material. Upon cooling to ambient temperature (20 °C), the mixture was acidified to pH 1.0 with concentrated HCl. The resulting precipitate was stirred for an additional 30 min, collected by filtration, washed thoroughly with deionized water, and dried in vacuo. This afforded 4-(ethylsulfonyl)-2-nitrophenol as a crude solid (2.21 g, 96% yield). HPLC analysis confirmed a purity of 97%. ¹H NMR (400 MHz, Chloroform-d) δ 10.97 (s, 1H), 8.71 (s, 1H), 8.08 (d, J = 11.1 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 3.16 (q, J = 7.4 Hz, 2H), 1.33 (t, J = 7.4 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 158.5, 136.2, 133.3, 131.0, 126.7, 121.6, 50.8, 7.5.

Reduction of 4-(ethylsulfonyl)-2-nitrophenol for 2-Amino-4-(ethylsulfonyl)phenol: To a 100 mL three-necked round-bottom flask charged with 4-(ethylsulfonyl)-2-nitrophenol (1.15 g, 5mmol) in ethanol (10 mL) was added FeCl₃ (0.13 g) supported on activated carbon (0.52 g). The suspension was brought to reflux, and 80 wt% hydrazine hydrate (1.56 g, 25mmol) was introduced dropwise. After stirring at reflux for 2 h (TLC monitoring), the mixture was filtered hot. The filtrate was concentrated under reduced pressure to remove the solvent, and the residue was partitioned between H₂O (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. Recrystallization from water (10 mL) yielded the pure product as an off-white solid. The solid was collected by filtration, washed with 50% EtOH (3 × 5 mL), and dried in vacuo to afford 2-amino-4-(ethylsulfonyl) phenol (0.87 g, 87% yield). HPLC purity: 99%. ¹H NMR (400 MHz, DMSO-d₆): δ 10.17 (s, 1H), 7.05 (d, J = 2.3 Hz, 1H), 6.90 (dd, J = 8.2, 2.3 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 5.10 (s, 2H), 3.07 (q, J = 7.4 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 148.3, 135.6, 130.2, 119.8, 115.2, 114.9, 50.8, 7.6. MS (ES-API): m/z [M - H]⁺ = 200.

Preparation of ezutromid using PPA and Eaton's reagent:

Using PPA as promoter [36]: (Ethylsulfonyl)-2-aminophenol (0.20g, 1.00 mmol) was heated with β-naphthoic acid (0.18g, 1.05 mmol) in polyphosphoric acid (PPA, 3.01 g) at 150 °C for 2–3 h. The reaction mixture was poured into ice–water and neutralized with 10% aqueous NaOH. The product was extracted with ethyl acetate, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue

was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford ezutromid (0.21 g, 62% yield).

Using Eaton's reagent as promoter: To a stirred solution of Eaton's reagent (3 mL, 8 wt% P₂O₅ in MsOH) were added (ethylsulfonyl)-2-aminophenol (0.20 g, 1.00 mmol) and β-naphthoic acid (0.19 g, 1.10 mmol). The resulting mixture was heated at 80 °C for 2 h and monitored by TLC until completion. The reaction mixture was poured into ice–water and neutralized with 10% aqueous NaOH. The product was extracted with ethyl acetate, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford ezutromid (0.28 g, 83% yield). HPLC purity: 99%.

¹H NMR (400 MHz, Chloroform-d) δ 8.82 (s, 1H), 8.38 (s, 1H), 8.32 (d, J = 6.9 Hz, 1H), 8.06 – 7.90 (m, 4H), 7.79 (d, J = 8.5 Hz, 1H), 7.68 – 7.56 (m, 2H), 3.21 (q, J = 7.4 Hz, 2H), 1.33 (t, J = 7.4 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 165.6, 153.9, 142.9, 135.3, 135.2, 132.9, 129.1, 129.0, 128.4, 128.0, 127.2, 125.4, 123.9, 123.4, 121.0, 111.39, 51.1, 7.6. MS (ES-API): m/z [M +H]⁺ = 338.

Declarations

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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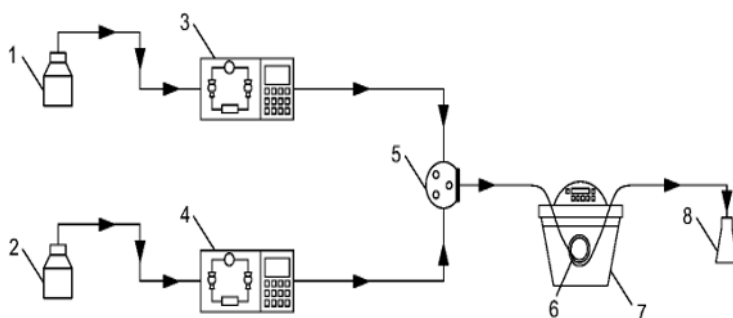
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Scheme

Scheme 1 and 2 are available in the Supplementary Files section.

Figures



1. Feed reservoir A (substrate solution); 2. Feed reservoir B (oxidant solution); 3. Pump 1; 4. Pump 2; 5. Y-type micromixer; 6. Microchannel reactor; 7. Thermostatic oil bath; 8. Collection vessel.

Figure 1

Schematic diagram of the continuous-flow experimental setup.

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