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Continuous-Flow Diazotization for Efficient Synthesis of Methyl 2-(Chlorosulfonyl)benzoate: an Example of Inhibiting Parallel Side-reactions

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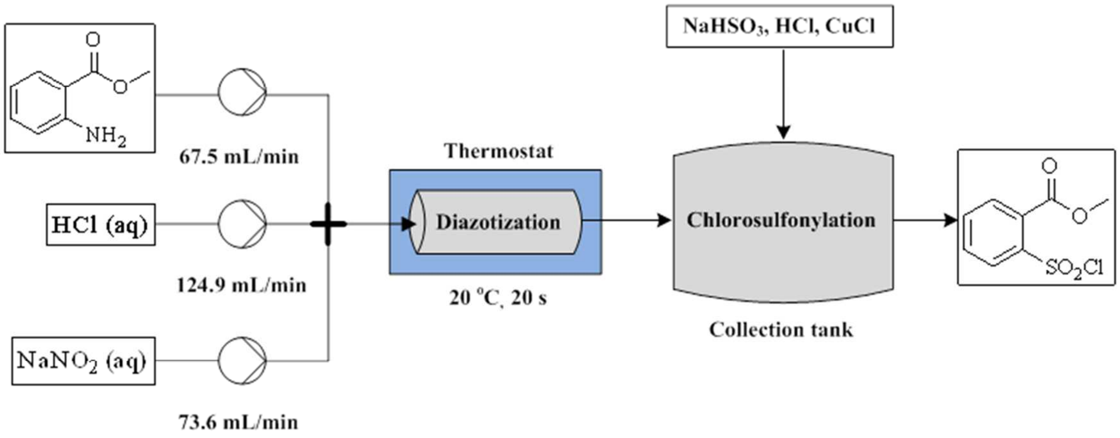
TOC Graphic:


NaHSO3, HCl, CuCl
67.5 mL/min
Thermostat
HCl (aq)
Diazotization
Chlorosulfonylation
124.9 mL/min
20 °C, 20 s
Collection tank
NaNO2 (aq)
73.6 mL/min

Abstract:

An expeditious process for the highly efficient synthesis of methyl 2-(chlorosulfonyl)benzoate was described, which involved the continuous-flow diazotization of methyl 2-aminobenzoate in a 3-inlet flow reactor via a cross joint followed by chlorosulfonylation in the tandem tank reactor. The side reaction such as hydrolysis was decreased eminently from this continuous-flow process even at high concentration of hydrochloric acid. The mass flow rate of methyl 2-aminobenzoate was 4.58 kg/h, corresponding to an 18.45 kg/h throughput of diazonium salt solution. The potential of inhibiting parallel side reactions by conducting in a flow reactor was successfully demonstrated in this method.

Key Words: Diazotization, Continuous-flow, Parallel side-reaction, Chlorosulfonylation.

Introduction

Sulfonyl chlorides are versatile precursors for the synthesis of many pharmaceutically active compounds, including sulfonamides[1], sulfonylfluorides[2], sulfonate esters[3], sulfones[4], and sulfinic acids[5]. Among which, methyl 2-(chlorosulfonyl)benzoate is a key intermediate for the synthesis of important intermediates and biological active compounds (Figure 1), such as Saccharin[6], HNO donor[7], farnesyltransferase inhibitor[8] and acetohydroxyacid synthase inhibitor[9].

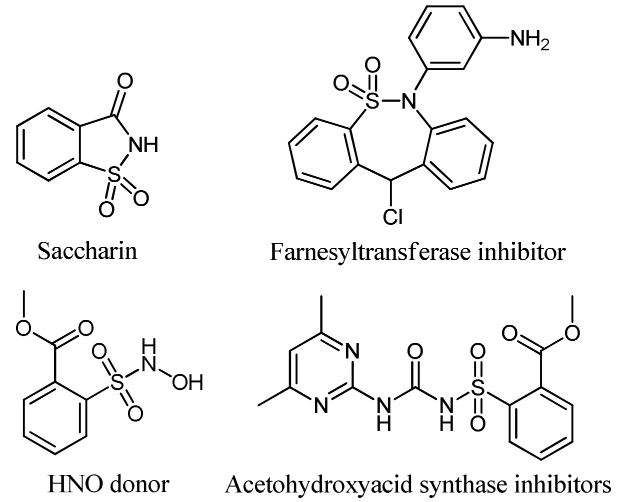
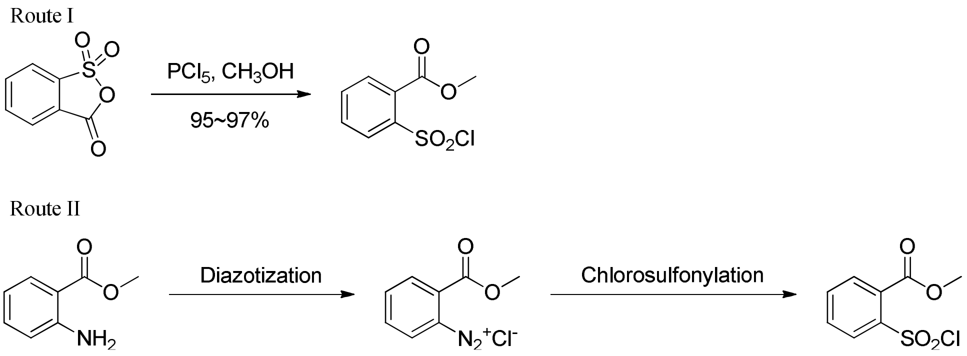


Figure 1. Compounds derived from the methyl 2-(chlorosulfonyl)benzoate moiety.

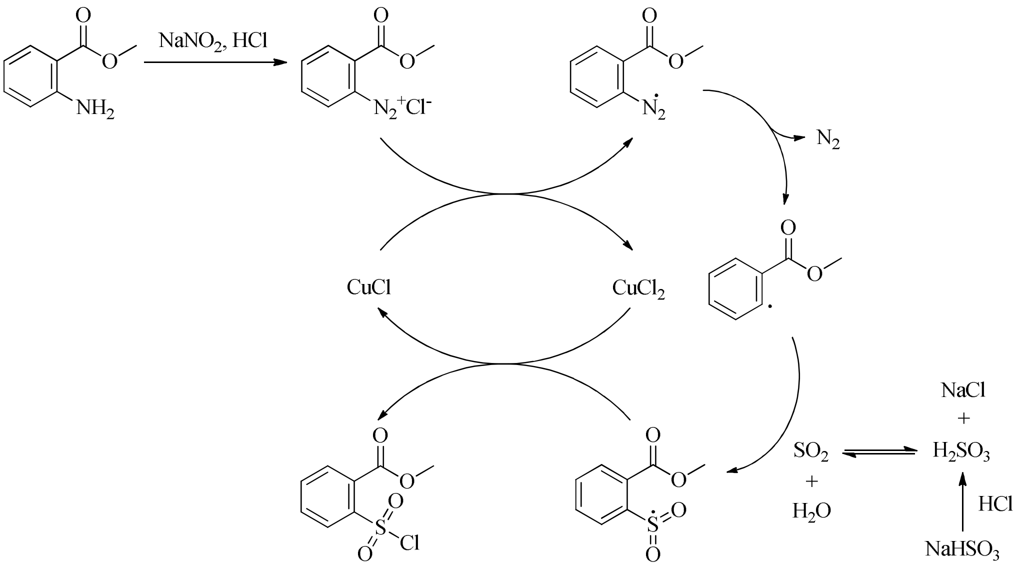
Preparation of methyl 2-(chlorosulfonyl)benzoate was summarized in two different synthetic routes (Scheme 1). In the Route I, 2-sulfobenzoic anhydride was treated with phosphorus pentachloride and methanol to give the desired products in excellent yield[10]. Nonetheless, the application of this method was relatively limited due to the lack of availability of raw materials. As a consequence, the diazotization of methyl 2-aminobenzoate followed by chlorosulfonylation in Route II was established as the compatible method for the synthesis of target compound[6].

Scheme 1. Synthetic routes of methyl 2-(chlorosulfonyl)benzoate



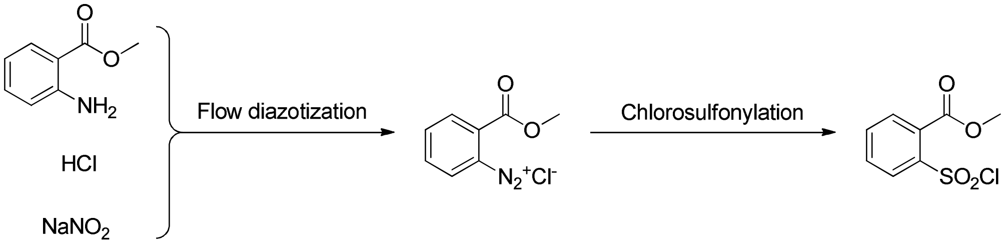
Diazotization of methyl 2-aminobenzoate could be easily conducted under aqueous solution of sodium nitrite and hydrochloric acid at low temperature (such as 0 °C). The resulting diazonium salt was then subjected to the stepwise sulphination and oxidation-chlorination with $SO_2/Cl_2/CuCl$[6,11], or one-step copper-catalyzed chlorosulfonylation with user-friendly reagent $NaHSO_3$[12]. We adopted the latter method for the synthesis of methyl 2-(chlorosulfonyl)benzoate. The proposed mechanism[11,15d] for the reaction sequence is shown in Scheme 2. The aryl diazonium chloride **2** is first reduced to the diazenyl radical **3a** by the Cu(I) catalyst; liberation of nitrogen generates the aryl radical **3b**. This radical species could then attack the SO_2 molecule generated *in situ* to yield **3c**, which Cu(II) was reduced to Cu(I) and the catalytic cycle was completed with chloride anion combining to yield the sulfonyl chloride adduct **3**. However, this approach did engender important safety concerns due to the highly explosive diazonium salt which may decomposed intensively under a relatively high temperature while releasing heat and out-gassing. To reduce the safety hazards, we envisioned the development of a continuous-flow process for the multistep synthesis of methyl 2-(chlorosulfonyl)benzoate. Continuous-flow technology offers significant benefits over batch methods, including precise control of temperature, stoichiometry, and residence time; high reproducibility; easy scale up, and commendable inhibition of consecutive side reactions[13]. The increase in surface area to volume ratio under flow conditions renders massive heat transfer. Finally, safety hazards in handling exothermic reactions associated with explosive intermediates are minimized owing to the reduced volume in the vessel of continuous flow reaction[14].

Scheme 2. Proposed mechanism for chlorosulfonylation reaction.



There have been several reports on generating diazonium salts as reactive intermediates (followed by iododeamination, chlorodeamination, azo dyes, and chlorosulfonylation) using micro flow technology[15]. Compared to a micrometer-scale reactor, a millimeter-scale reactor, due to its relatively high productivity, is easier to proceed in industrial production[16]. Our group has been committed to develop the continuous diazotization process in millimeter-scale[17], and herein, we describe a continuous-flow diazotization process for synthesis of methyl 2-(chlorosulfonyl)benzoate under mild condition (Scheme 3).

Scheme 3. Adapted synthetic route of methyl 2-(chlorosulfonyl)benzoate



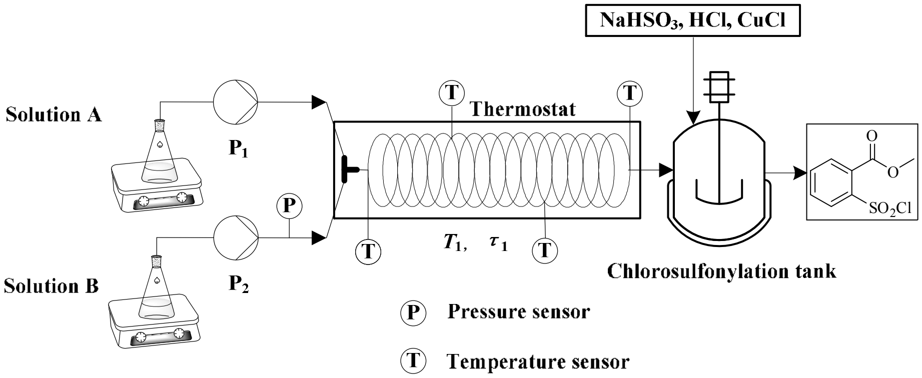
Results and discussions

Initial design of continuous-flow process.

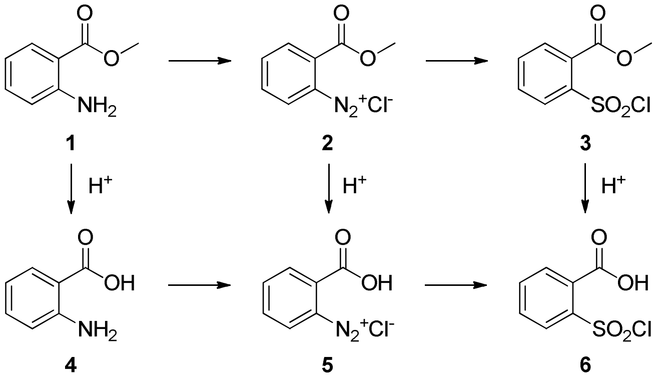
Under the safety consideration, DSC measurement has been carried out and the results (details can be found in supporting information) revealed that diazonium salt solution is relative stable at around 20 °C. Then the diazonium salt gradually decomposed as the increasement of temperature. When it arrived at 80 °C, the heat release rate became much higher where the rate of decomposition speed up as well. Heat release reached a maximum number at 113 °C. The total heat released from diazonium salt solution is about 437 kJ/kg, indicating diazotization as a potential hazardous procedure. Therefore, continuous-flow diazotization process is highly demanded. For a continuous-flow process, the fluidity of reagents is another important factor that has to be considered. In this procedure, water solubility of the diazonium salt is very good while the target product is agglomeration of the particles, and tends to clumped together.

So the initial process was designed with a combination of continuous-flow diazotization and batch quench process (Scheme 4). In this design, two peristaltic pumps (P_1, P_2, Baoding Longer, China) loaded with pump tubing connected by a T-joint that was connected to reaction tube (Hastelloy C276[18], 3 mm i.d., 5 mm o.d.). The reaction tube was immersed in a thermostat controlled water bath. Reaction temperature inside the reactor was monitored by temperature sensors (four sensors distributed uniformly in reaction tube). The temperature profile was completed smoothly, due to the much higher circulation flow rate of water bath in contrast to the flow rate of the reactants, which would lead reactor to reach the near isothermal conditions. A pressure sensor was installed to monitor the backpressure in the reactor. In case the pressure was abnormal, the pumps would be stopped immediately so that the pump tubing won't get ruptured. Solution A of methyl 2-aminobenzoate in concentrated hydrochloric acid together with solution B of 40 wt % aqueous sodium nitrite were prepared and pumped into the reaction tube. The flow rates[19] were 122.8 mL/min and 46.7 mL/min respectively and the molar ratio of methyl 2-aminobenzoate: HCl : $NaNO_2$ was 1.0 : 3.0 : 1.1. After a residence time (τ_1) in reaction tube, diazo solution flowed into the tank at atmospheric pressure which was placed with aqueous $NaHSO_3$ (1.5 equiv, 15 wt %), hydrochloric acid (2.0 equiv, 37 wt %) and CuCl (0.01 equiv) beforehand. Tail gas was absorbed by aqueous sodium hydroxide. The chlorosulfonylation reaction was stirred by a mechanical agitator at 0 ^{o}C for about 5 h till the reaction ended[20], and about 1.4 equiv of excess HCl was left (balanced equations can be found in supporting information) to maintain acidic condition. The suspended solid was then collected by vacuum filtration, washed with water and dried under vacuum at below 35 ^{o}C to give crude product. Unfortunately, an undesired hydrolysis by-product **6** (Scheme 5) was mainly obtained when $\tau_1 = 10$ s, $T_1 = 25$ ^{o}C. The similar results were observed even reaction temperature (T_1) and residence time (τ_1) were varied.

Scheme 4. Initial design of continuous-flow process[a]



[a] Solution A is including methyl 2-aminobenzoate (2.59 M) with 3.0 equiv of concentrated hydrochloric acid (37 wt %) under a flow rate of 122.8 mL/min; solution B is aqueous sodium nitrite (7.48 M) under a flow rate of 46.7 mL/min. Reaction tube is a Hastelloy C276 tube with 3 mm i.d. and 5 mm o.d.. Aqueous solution of $NaHSO_3$ (1.5 equiv, 15 wt %), hydrochloric acid (2.0 equiv, 37 wt %) and CuCl (0.01 equiv) are pre-placed in the collection tank.



Scheme 5. Plausible formation of by-products through hydrolysis.

It’s plausible that inhibiting the hydrolysis of ester had priority in this work. The possible origins of by-product **6** were shown in Scheme 4. In theory, the raw material **1**, intermediate **2**, and product **3** could be hydrolyzed with the treatment of hydrochloric acid. In order to figure out the main hydrolysis rate law, test experiments of **1** were conducted. Material **1** was added into hydrochloric acid at given concentrations and temperatures, samples were collected and then poured into ice water at definite time intervals in which the resulting products were analyzed by HPLC. The results were shown in Figure 2. It was found that the hydrolysis rate of methyl 2-aminobenzoate increased significantly with increasing temperature. Hydrolysis rate was enhanced remarkably with prolonged reaction time at high concentration of hydrochloric acid while no obvious hydrolysis (less than 1%) occurred at low concentration of hydrochloric acid. In a word, hydrolysis hardly occurred at low concentration of hydrochloric acid, or at high concentration together with very short residence time. Considering that **2** and **3** were presented in low concentration of hydrochloric acid at low temperature, by-product **6** was mainly derived from **4**. In other words, the aniline has been hydrolyzed before diazotization, which was a fatal flaw of initial design process.

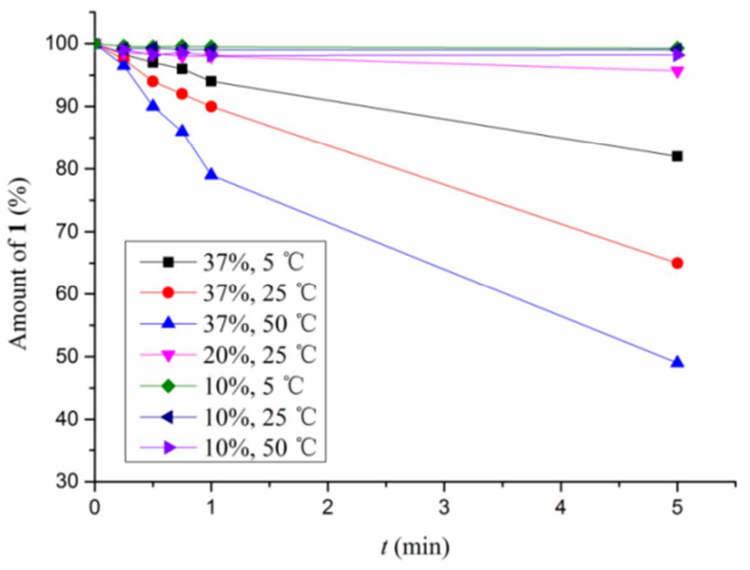


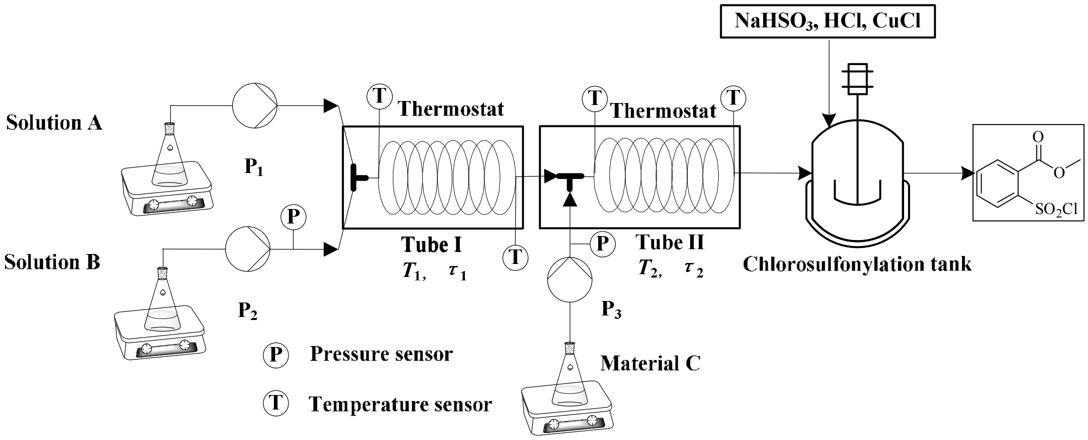
Figure 2. Hydrolysis of **1** in different concentrations of hydrochloric acid at various temperatures.

Further design of continuous-flow process.

Based on previously experimental dada, we decided to restrain the hydrolysis side reaction by reducing the concentration of hydrochloric acid. However, reducing the initial concentration of reagents by adding water will cause more waste water. Thus a converged route of three feed streams flowed into the reactor was designed. showed The continuous-flow reactor experimental setup was displayed in Scheme 6, in which two peristaltic pumps (P_1, P_2) loaded with tubing connected by a T-joint that was connected to reaction tube I (Hastelloy C276, 3 mm i.d., 5 mm o.d.). The third pump (P_3) loaded with tubing connected by another T-joint that was connected to reaction tube II (Hastelloy C276, 3 mm i.d., 5 mm o.d.). The reaction tubes were immersed in two thermostat controlled water baths, respectively. Reaction temperature inside the reactor was monitored by temperature sensors (four sensors distributed uniformly in reaction tube). Two pressure sensors were used to monitor the backpressure in the reactor, and if the pressure was abnormal, the pumps would be stopped immediately so that the pump tubing won't rupture. Solution A of concentrated hydrochloric and solution B of 40 wt %aqueous sodium nitrite were pumped into the reaction tube with the flow rates of 124.9 mL/min and 73.6 mL/min, respectively.

The concentration of hydrochloric acid was diluted when contacted with each other. After a residence time (τ_1) in reaction tube I, material C of methyl 2-aminobenzoate was introduced into tube II with a flow rate of 67.5 mL/min where diazotization took place. After another residence time (τ_2), diazo solution was outflowed from the reaction tube and accumulated in collection tank, which was placed with aqueous $NaHSO_3$ (1.5 equiv, 15 wt %), hydrochloric acid (2.0 equiv, 37 wt %) and CuCl (0.01 equiv) beforehand. For a same molar flow ratio of diazotization, the stoichiometry in the quench tank was not changed compared with initial design process. After the reaction was completed, product was obtained by the same method as initial design process.

Scheme 6. Further design of continuous-flow process[a].



[a] Solution A is hydrochloric acid (37 wt %) with a flow rate of 124.9 mL/min; solution B is 7.48 M aqueous sodium nitrite with a flow rate of 73.6 mL/min; material C is liquid methyl 2-aminobenzoate with a flow rate of 67.5 mL/min. Reaction tube I and II are Hastelloy C276 tube with 3 mm i.d and 5 mm o.d.. Aqueous solution of $NaHSO_3$ (1.5 equiv, 15 wt %), hydrochloric acid (2.0 equiv, 37 wt %) and CuCl (0.01 equiv) are pre placed in the collection tank.

The optimization of experimental parameters was systematically investigated by varying the reaction temperature and residence time under convenient continuous-flow conditions. According to the sequence of Scheme 6, T_1 and τ_1 were investigated firstly while T_2 = 25 ^{o}C, τ_2 = 10 s and molar flow ratio of **1** : $NaNO_2$ = 1.0 : 1.1. As shown in Figure 3, the yield[21] of **3** was decreased with increasing temperature (T_1), and also prolonged residence time (τ_1). In order to find out the reason, another set of experiments were carried out (using the reactor system as shown in Scheme 6). Molar flow ratio of $NaNO_2$ was increased by increasing flow rate of P_2 when $\tau_1 = 1$ s, $T_2 = 25$ °C, $\tau_2 = 10$ s, tube length was adjusted to maintain the definite residence time, and results were shown in Figure 4. The yield increased by increasing molar flow ratio of $NaNO_2$ at relatively high T_1 (25 °C), but no significant change occurred at low T_1 (-5 °C). In addition, as increasing amount of $NaNO_2$ at 25 °C, azo-coupling by-product (Figure 5) was minimized significantly (HPLC area percent decreased from 8% to 1%). Considering that the unstable nitrous acid generated in tube I is prone to be decomposed at relatively high temperature, we thus attributed the reason of diminished yield to the decomposition of nitrous acid. Overall, preventing decomposition of nitrous acid was another steppingstone of the work.

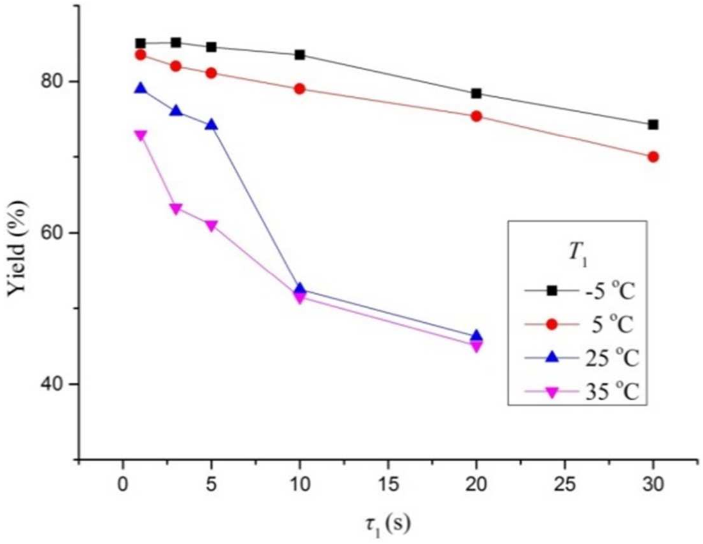


Figure 3. The effect of T_1 and τ_1 on the yield.

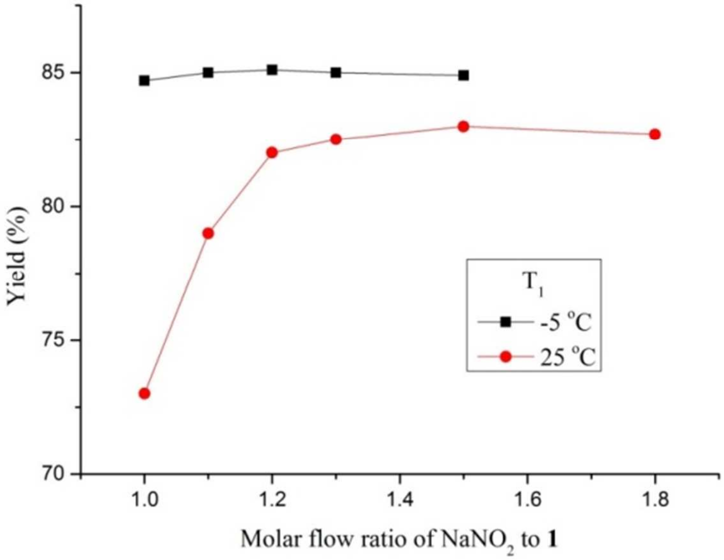


Figure 4. The effect of molar flow ratio of NaNO$_2$ to **1** on the yield.

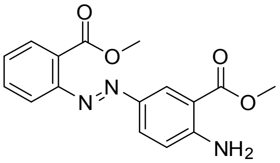


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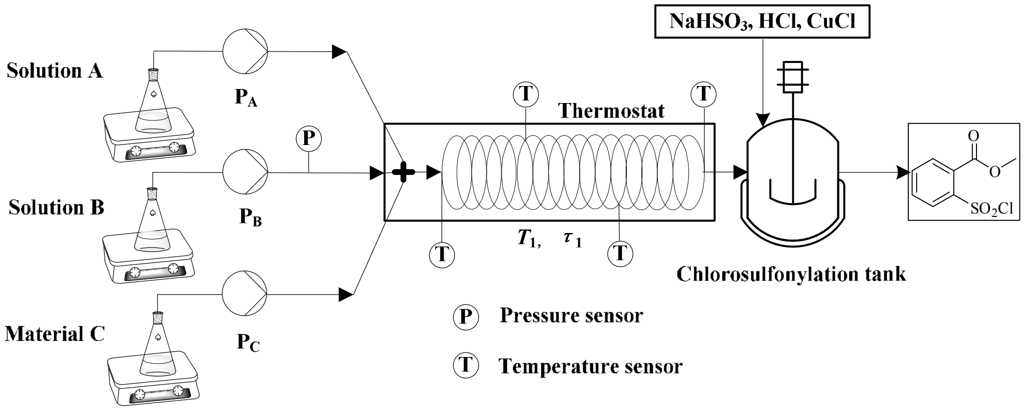
Figure 5. Structure of azo-coupling by-product.

Advanced design of continuous-flow process.

In account of restraining hydrolysis of ester, inhabiting decomposition of nitrous acid and conducting the reaction at moderate temperature, an advanced design process was carried out. The advanced experimental setup was displayed in Scheme 7, three pumps (P$_1$, P$_2$, P$_3$) loaded with tubing connected by a cross-joint that was connected to reaction tube (Hastelly C276, 3 mm i.d., 5 mm o.d.). The reaction tube was immersed in thermostat controlled water bath. Reaction temperature inside the reactor was detected by temperature sensors (four sensors distributed uniformly in reaction tube). A pressure sensor was used to evaluate the backpressure in the reactor. While the pressure was abnormal, the pumps would be turned off immediately so that the pump tubing won't get ruptured. Concentrated hydrochloric acid (solution A), 40 wt % aqueous solution of sodium nitrite (solution B) and methyl 2-aminobenzoate (material C) were pumped into the reaction tube. The following steps were introduced as previous. Hydrochloric acid was diluted when all reagents mixed with each other, and the generation of nitrous acid and diazotization were carried out simultaneously. With reaction conditions: molar flow ratio of **1** : HCl : $NaNO_2$ was 1.0 : 3.0 : 1.1, the results from optimized condition was concluded in Figure 6. The yield of **3** was increased to 90% when $T_1 = 20\ ^{o}C$ and $\tau_1 = 20$ s. The azo byproduct was minimized to < 0.1%[22]. Both long τ_1 with high T_1 and short τ_1 with low T_1 led to the decreasement of yield. The acceleration of reaction rate was observed with increasement of temperature, while higher temperature along with longer residence time resulted in the decomposition of diazonium salt. At low temperature and shorter residence time, the conversion of amine was not completely achieved.

Scheme 7. Advanced design of continuous-flow process[a]



[a] Solution A is hydrochloric acid (37 wt %) with a flow rate of 124.9 mL/min; solution B is 7.48 M aqueous sodium nitrite with a flow rate of 73.6 mL/min; material C is liquid methyl 2-aminobenzoate with a flow rate of 67.5 mL/min. Reaction tube is Hastelloy C276 tube with 3 mm i.d and 5 mm o.d.. Aqueous $NaHSO_3$ (1.5 equiv, 15 wt %), hydrochloric acid (2.0 equiv, 37 wt %) and CuCl (0.01 equiv) are pre placed in the collection tank.

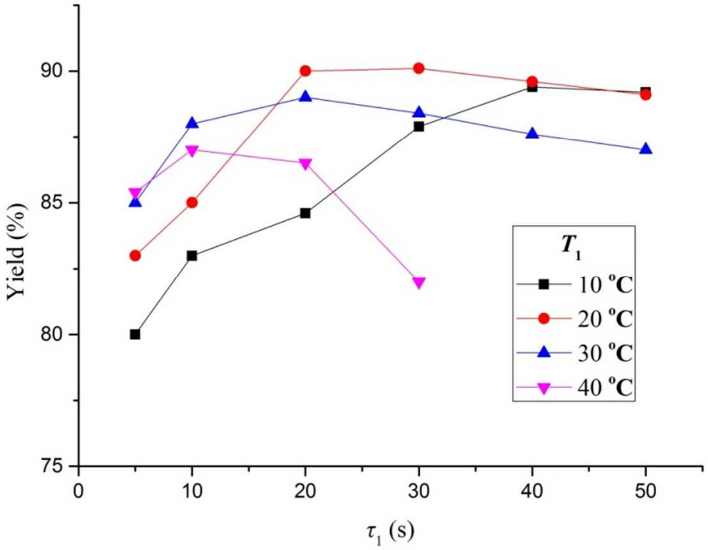


Figure 6. Effect of diazotization reaction temperature and residence time on the yield.

With optimum continuous-flow diazotization in hand, chlorosulfonylation conditions were investigated. The reaction temperature was studied firstly. As displayed in Figure 7a, a slight improvement on the yield was achieved while the reaction temperature was kept at 20 °C. However, higher temperature provided lower product yield with the assumption that the diazonium salt might be decomposed and the product could be hydrolyzed under such condition.

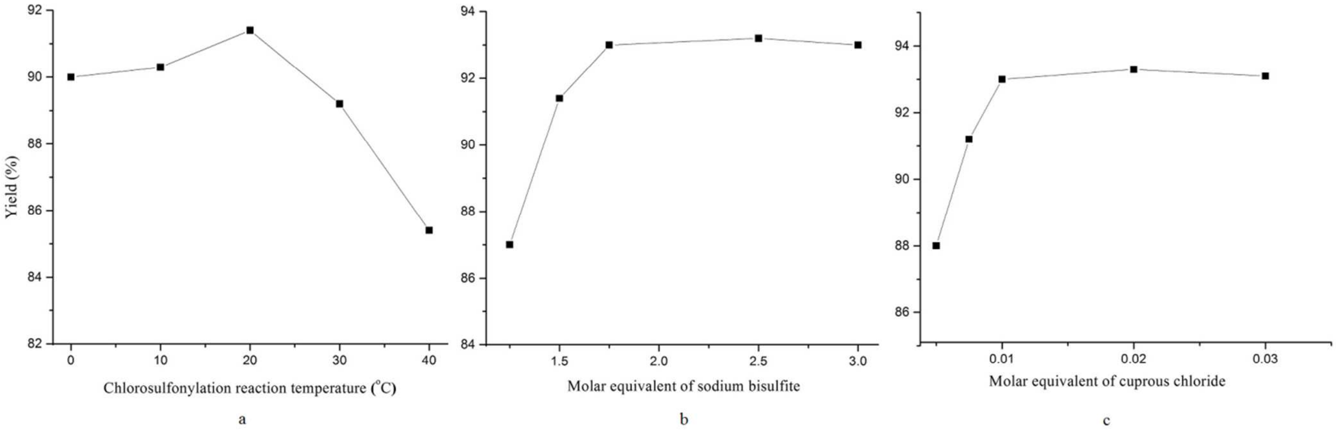


Figure 7. Effect of parameters towards the yield of chlorosulfonylation.

Next, the amount of sodium bisulfite and cuprous chloride were examined respectively with optimized conditions. Chlorosulfonylation reactions were conducted at 20 °C. Figure 7b revealed the effect of the amount of sodium bisulfite, in which the yield increased with increasing amount of sodium bisulfite before a max value was reached and continued increasing affected scarcely on the yield. Figure 7c showed the effect of the amount of cuprous chloride, and similar effect was observed. Chlorosulfonylation reaction was insufficient with the lack of sodium bisulfite or cuprous chloride. Finally, the yield of **3** was improved to 93% when molar equivalents of sodium bisulfite and cuprous chloride were employed in 1.75 and 0.01 equiv respectively.

Though it was proved to be stable at 20 ^{o}C by DSC measurement and diazonium salt was still accumulated in the collection tank, temperature profile of chlorosulfonylation was investigated. As shown in Figure 8, reaction temperature was nearly invariant at constant-temperature water bath condition, while reaction temperature was increased at intervals of 10 ^{o}C during the first 90 min and intervals of 3 ^{o}C during the next 3 h under adiabatic condition. In brief, the exothermic process of chlorosulfonylation was conducted smoothly, and the chlorosulfonylation reaction was relatively safe at the condition of external heat transfer.

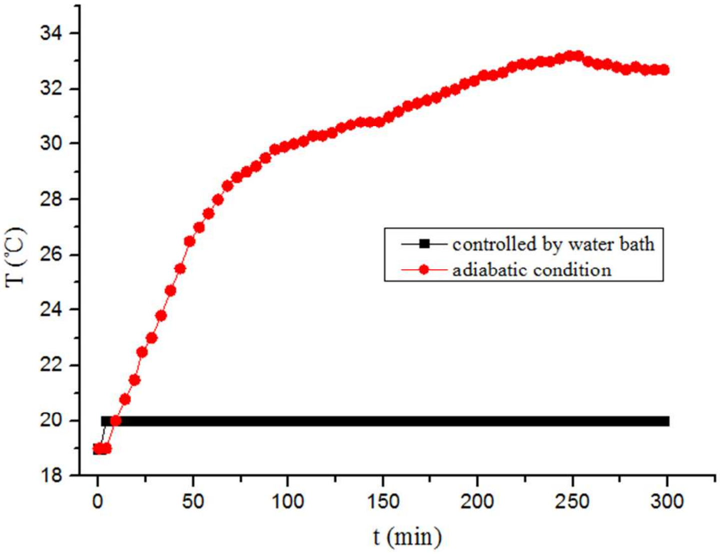


Figure 8. Temperature curve of chlorosulfonylation reaction.

To emphasize the advantage of continuous-flow synthesis, the comparison between continuous-flow technology and batch manner was summarized in Table 1. Based on the analysis of hydrolysis, diluted concentration of hydrochloric acid and low diazotization reaction temperature were chosen in batch experiment, *i.e.* sodium nitrite and methyl 2-aminobenzoate were added to hydrochloric acid (20 wt%) simultaneously affording diazonium salt at 0−5 ^{o}C. The same sulfonylation conditions with advanced design process were adopted to obtain product **3** with high yields. It should be pointed out this advanced continuous-flow process is able to perform well in the condition of concentrated hydrochloric acid.

Table 1. Comparison of diazotization in different operate manners

operate manner	concentration of hydrochloric acid (%)	reaction temperature (^{o}C)	reaction time	yield of **3** (%)
batch	20	0−5	Stirred for 0.5 h after addition of $NaNO_2$	84
further design flow process	37	25	13 s	85
advanced design flow process	37	20	20 s	93

Conclusion

In summary, a practical continuous-flow diazotization process for the synthesis of methyl 2-(chlorosulfonyl)benzoate from methyl 2-aminobenzoate was developed. The in situ generated nitrous acid for diazotization in a 3-inlet flow reactor via a cross joint was found to be crucial for inhibiting potential side reaction such as hydrolysis. The optimized continuous-flow diazotization could proceed smoothly at high concentration of hydrochloric acid and moderate temperature, avoiding the inconvenience arised from batch technology. The continuous-flow technology was demonstrated to restrain parallel side-reactions in a practical and efficient manner. The process could be potentially applied for the preparation of analogous compounds from low-melting point anilines.

Experimental section:

All the chemical reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Buchi 540 melting point apparatus and uncorrected. The MS and HRMS data were recorded by Thermo LCQ advantage and Bruker II OTOFMS respectively. The IR data was determined by Therno Nicolet AVATA 370. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz spectrometer using tetramethylsilane (TMS) as the internal standard. High-performance liquid chromatography (HPLC) analysis was carried out on an Agilent 1200 system. The moisture was detective by Metrohm 870 KF Titrino Plus water meter.

General Procedure of Hydrolysis Experiment. Hydrochloric acid (0.3 mol) with definite concentration was placed in a 250 mL three neck round bottom flask which was immersed in a water bath at definite temperature. Methyl 2-aminobenzoate (2.0 g, 13.2 mmol) was poured into the flask. The mixture was stirred vigorously by a mechanical agitator. Samples (1 mL each time) were collected at definite time intervals and poured into ice water (10 g) as soon as possible to quench reaction. Then samples were analyzed by HPLC (Agilent 1200 system equipped with a C-18 250 mm × 4.0 mm column and detected at 254 nm, eluted with 70 : 30 CH_3OH/H_2O at 0.8 mL/min).

Continuous-flow Experimental Procedure of Advanced Design[23]. As shown in scheme 7, solution A of hydrochloric acid (592 g, 37 wt %, 6.0 mol), solution B of aqueous sodium nitrite (380 g, 40 wt %, 2.2 mol) and solution C of methyl 2-aminobenzoate (302 g, 2.0 mol) were pumped into the flow reactor via a cross joint by P_1, P_2 and P_3 at the flow rates of 124.9 mL/min, 73.6 mL/min and 67.5 mL/min, respectively. After a residence time of 20 s at 20 ^{o}C in reaction tube (Hastelloy C276 tube with 3 mm i.d. and 5 mm o.d.), reaction mixture outflowed the tube (backpressure of the reactor was about 0.08 MPa) and accumulated in the collection tank at atmospheric pressure (filled with 2428 g of 15 wt % aqueous $NaHSO_3$, 395 g concentrated hydrochloric acid and 1.98 g of CuCl, pre-cooled to 0 ^{o}C), which was stirred by a mechanical agitator. Then increase the reaction temperature to 20 ^{o}C, and the reaction was maintained for 5 h. Tail gas was absorbed by sodium hydroxide solution. Then the suspended solid was collected by vacuum filtration, washed with water (2 × 300 mL), and dried under vacuum at below 35 °C to give 447 g crude solid product in 95% isolated yield with 98% purity and about 0.5% moisture[24]. HPLC conditions: Agilent 1200 system equipped with a XB-C18 250 mm × 5.0 mm column and detected at 210 nm, eluted with 58 : 42 CH_3CN/H_2O at 1.0 mL/min.

Characterization data of compound **3**: Mp: 58−60 °C. MS ($M+Na^+$): 257. ^1H NMR ($CDCl_3$, 400 MHz) δ/ppm: 8.15 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.81−7.71 (m, 3H, Ar-H), 3.99 (s, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ/ppm: 53.4, 129.1, 130.1, 131.5, 132.4, 135.2, 141.7, 166.2.

Characterization data of compound **7**: Mp: 118−120 °C. MS ($M+H^+$): 314. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{15}N_3NaO_4$, ($M + Na^+$): 336.0960. Found: 336.0899. IR (KBr) *v*/cm^{-1}: 3447, 3339, 1717, 1714, 1699, 1594. ^1H NMR ($CDCl_3$, 400 MHz) δ/ppm: 8.50 (s, 1H, Ar-H), 7.88 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.76 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.60 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.41 (t, *J* = 7.2 Hz, 1H, Ar-H), 6.71 (d, *J* = 9.2 Hz, 1H, Ar-H), 6.28 (br s, 2H, $-NH_2$), 3.91 (s, 3H, $-CH_3$), 3.89 (s, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ/ppm: 168.2, 168.0, 152.9, 151.6, 143.4, 131.7, 131.2, 129.4, 128.8, 128.0, 126.3, 118.9, 117.1, 109.8, 52.3, 51.9.

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Supporting Information

DSC on diazonium salt solution; photos of equipment sets; copies of $^1H/^{13}C$ NMR, HPLC, MS, HRMS, IR spectrums for compounds; balanced equations for calculation of excess acid

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(18) Hastelloy C276 has a good performance of corrosion-resistant in concentrated hydrochloric acid and it would not accelerate the decomposition of diazonium salt, similar result has been reported in reference 11. Because of the poor performance of heat transfer, plastic pipe was not recommended at such conditions.

(19) Before starting reaction, the pumps were calibrated with corresponding materials. During the reaction, mass flow rates were monitored by the decrease of three materials' weights. Overall, the feed solutions are on balances. One exception was after long-term use, the accuracy of flow rate decreased because of fatigue damage on pump tubing. The peristaltic pump is pulsatile, and the stoichiometry was affected apparently at low rotation speed, but not affected obviously at high rotation speed, so thinner pump tubing and high revolution were suggested.

(20) Reaction was monitored by wine-red color resulted from reaction between diazonium salt and 1-amino-8-naphthol-3,6-disulfonic acid. In this process, another 0.5 h agitation was maintained after no color change.

(21) All yields in Figure 3, 4, 6, 7 and Table 1 were assay yields.

(22) Diazotization reaction end point can be determined by the existence of azo byproduct, because if diazotization isn't complete, the aniline will react with the dizaonium salt to form azo byproduct.

(23) The experimental duration of this process was only 4 min, and the longest duration run among our optimization was only tens of minutes. We focused on establishing a process for synthesis of target product and optimizing reaction parameters to modify yield, so we haven't considered running the

lab-scale system for a long duration. A more than 10 min duration experiment can be achieved by using larger volume of flasks, however the service life of pump tubing was only tens to hundreds of hours, and the flow accuracy decreased with longer running time. Much longer duration (such as 1000s of hours) experiment can be achieved by using more industrial equipment including pumps, automated control system, etc. just like the Balz-Schiemann reaction equipment displayed in supporting information.

(24) The sulfonyl chloride product is easily hydrolyzed to sulfonic acid byproduct by moisture, so keeping a relative low temperature during drying is necessary. However, about 1.5% sulfonic acid byproduct was still detected.