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Continuous-Flow Process for the Synthesis of *m*-Nitrothioanisole

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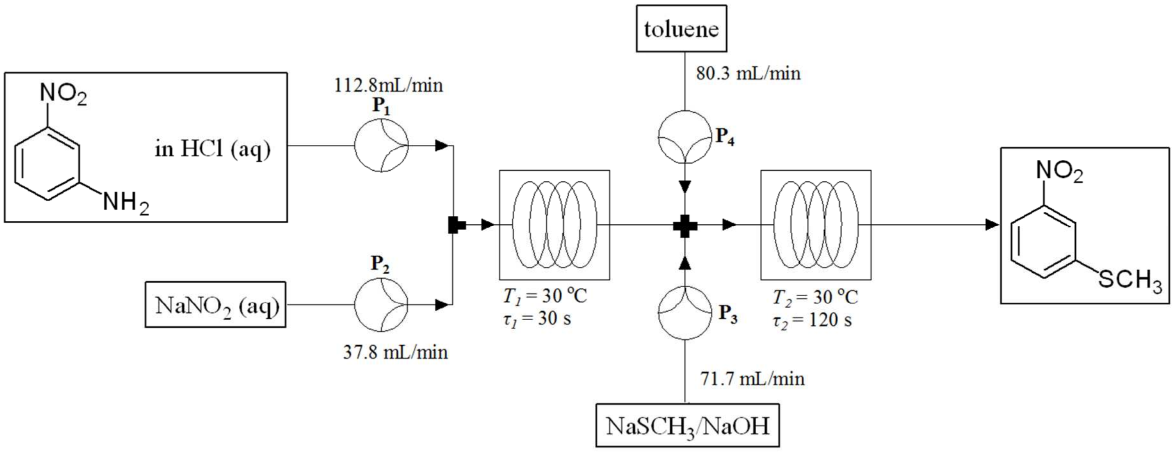
TOC Graphic:


NO2
NH2
in HCl (aq)
112.8mL/min
P1
NaNO2 (aq)
P2
37.8 mL/min
T1 = 30 °C
τ1 = 30 s
toluene
80.3 mL/min
P4
P3
71.7 mL/min
NaSCH3/NaOH
T2 = 30 °C
τ2 = 120 s
NO2
SCH3

Abstract: A continuous-flow process for the preparation of *m*-nitrothioanisole has been set up. The starting material *m*-nitroaniline was diazotized to give diazonium chloride, followed by azo-coupling with sodium thiomethoxide to give 1-(methylthio)-2-(3-nitrophenyl)diazene, then dediazoniated to gain *m*-nitrothioanisole in high yield. The continuous-flow process minimized accumulation of the energetic intermediate diazonium salt and has a better capacity for adapting large-scale production. A solvent was introduced in azo-coupling section to create a biphasic flow system. Side products were inhibited eminently in this flow process.

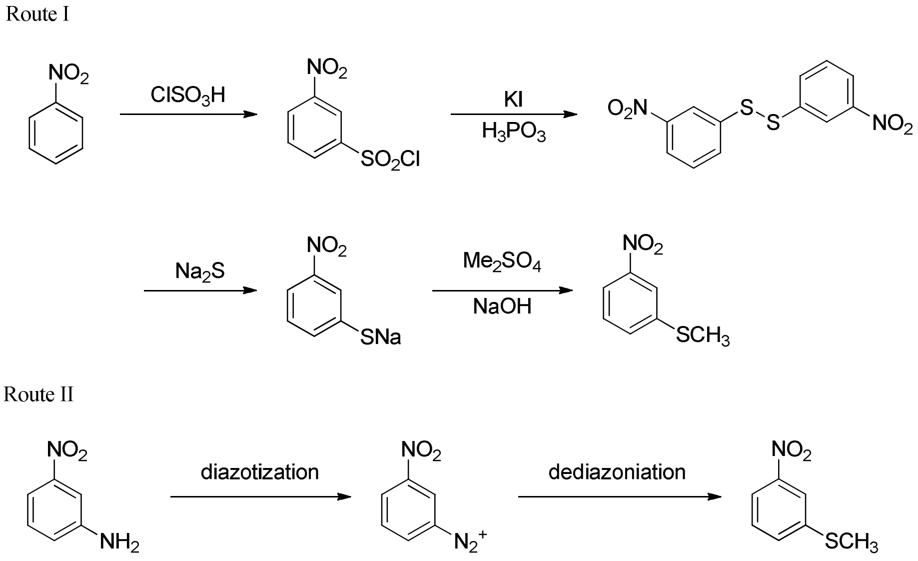
Key Words: Diazotization, continuous-flow, azo-coupling, dediazoniation, m-nitrothioanisole.

Introduction

An aromatic sulfide has been shown to be a universal pharmacophore in many pharmaceutically active agents[1]. The target molecule *m*-nitrothioanisole is an important start material for the synthesis of tricyclic antidepressant (Thioridazine) and also has been used for the synthesis of SIRT2 inhibitor[2] and antimalarial agents[3].

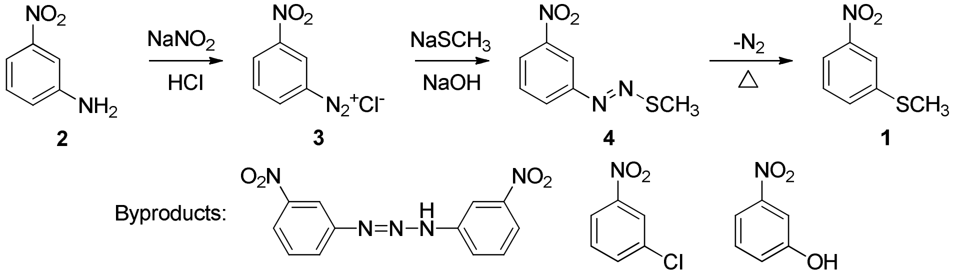
Among several synthetic methods that have been reported, two of them showed potential for applying to mass production (Scheme 1). Route I[1] started with nitrobenzene, treated with chlorosulfonic acid to give 3-nitrobenzene-1-sulfonyl chloride, after recrystallization, 3-nitrobenzene-1-sulfonyl chloride was added in portions to a mixture of potassium iodide and phosphorous acid in water to gain 1,2-*bis*(3-nitrophenyl)disulfane. Then the reaction mixture was filtered and the filtrate was reacted with sodium sulfide and dimethyl sulfate in sequence to give *m*-nitrothioanisole (total yield of 61%). Another significant method involved diazotization of *m*-nitroaniline followed by azo-coupling and dediazoniation of diazonium salt (route II). Prakash *et al.*[4] and Majek *et al.*[5] reported their applications of this route in lab scale with total yield of 69% and 60%, respectively. These methods still have some disadvantages need to be solved, such as the first route suffers from long reaction steps and environmental unfriendly reagents like dimethyl sulfate, phosphorous acid, chlorosulfonic acid and etc. While the second route, the cost of chemical materials is relative higher and its yield is moderate.

Scheme 1. Synthetic routes of *m*-nitrothioanisole



We chose the second approach to modify for its convenience in terms of operation and showed promising potential for improving yield. Aqueous sodium nitrite was selected as diazotization agent, along with sodium thiomethoxide as methanethiolate donator (Scheme 2). In this route, the energetic intermediates **3** and **4** are very unstable, in a condition of relatively high temperature or high pH value, they may decompose while releasing nitrogen, and that may cause some safety issues, especially in large scale manufacture[6]. Due to the high reactivity of diazonium salt, insufficient mixing in large vessel may lead to undesired coupling product or other byproducts (Scheme 2). Obviously, side reactions are mainly consecutive reactions to diazotization, and applying flow reaction technology is an effective way to avoid consecutive side reactions. Thus, we decided to adapt this process to continuous-flow to address the safety concerns and improve the yield by reducing byproducts.

Scheme 2. Reaction mechanism of *m*-nitrothioanisole from *m*-nitroaniline



Compared to batch technology, continuous-flow technology has some remarkable advantages[7]. The precise control of reaction parameters (including reaction temperature, residence time and stoichiometry, *etc.*) is easier; the selectivity is improved; high reproducibility; easier to scale-up; and often better reaction yields. Plus, the volume of reactor is smaller, so that the hazard is minimized and the heat transfer efficiency is improved, so that the thermal unstable energetic intermediates are prevented to decomposition[8]. in batch manner，the generated diazonium salt is usually added to another material slowly，yet by using flow reaction technology, there is no need to wait to the whole batch is completed which the energetic intermediate can be directly treated by following process continuously. Thus we turned our interest to develop a continuous-flow process which is not only for diazotization, but also include subsequent steps.

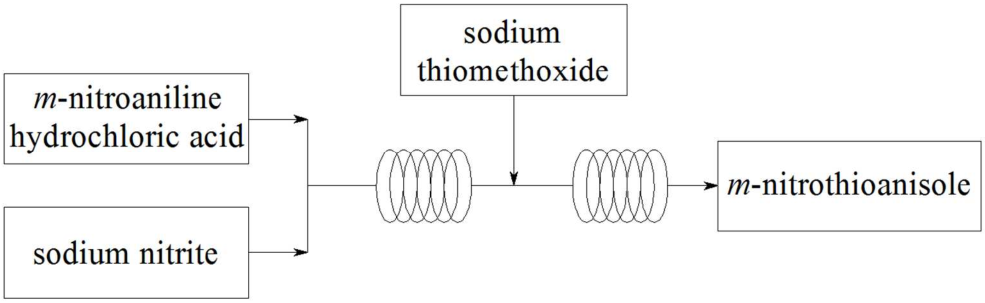
Results and Discussion

Adapting the Batch Process to Continuous-Flow.

For a great many industrial processes covered, the diazotization of aromatic amine has been well studied[9]. In this century, continuous diazotization microreactors followed by iododeamination, chlorodeamination, azo dyes, and chlorosulfonylation have been reported[10]. All these reaction processes are well performed, but microreactor has its limitation of scale-up. Compared to micrometer scale reactor, millimeter scale reactor, due to its relatively higher productivity, is easier to promote in industrial production. Continuous-flow processes of diazotization using millimeter scale reactors has been studied in our previously works[11]. We herein aimed to apply this technology to the synthesis of **1**.

As shown in Scheme 3, the original thought was two streams (*m*-nitroaniline in aqueous hydrochloride and aqueous sodium nitrite) pumped into a reaction tube for diazotization in Loop I, and then introduced another stream of aqueous sodium thiomethoxide, after dediazotization in Loop II to gain *m*-nitrothioanisole.

Scheme 3. Original design of continuous flow process



Before we started adapting, trails in batch chemistry were done to conduct the method and their yields approximately 60%. In these trials, the diazotization of **2** showed a promising potential to adapt to continuous-flow, but the intermediate 1-(methylthio)-2-(3-nitrophenyl)diazene (**4**) is insoluble in reaction system, and very sticky. In the consideration of the reaction tube may be fouled and clogged, we decided to adapt the diazotization process and following processes separately.

Primitive Continuous-flow Process

The primitive continuous-flow set-up was shown in Figure 1. Commercially available arylamine **2** was combined with hydrochloric acid as one feed stream (material A) and sodium nitrite in water as a separate stream (material B). These two streams were pumped into a loop reactor (Hastelloy, 3 mm i.d., 5 mm o.d.) *via* a T-joint (Hastelloy, 3 mm i.d.) by two peristaltic pumps (**P_1**, **P_2**, Baoding Longer, China), respectively, and the molar flow ratio between aniline hydrochloride and sodium nitrite was set according to their equivalents in batch process. The reaction tube was submerged by water bath in a thermostat. The reactants were directly flowed into a stirring collection vessel containing aqueous sodium thiomethoxide and sodium hydroxide. In the collection vessel, reaction mixture was stirred for 0.5 h at 40 °C, and then heated the collection vessel to 70 °C for 2 h. Then the reddish brown oil layer was separated by gravity and the samples were analyzed by GC.

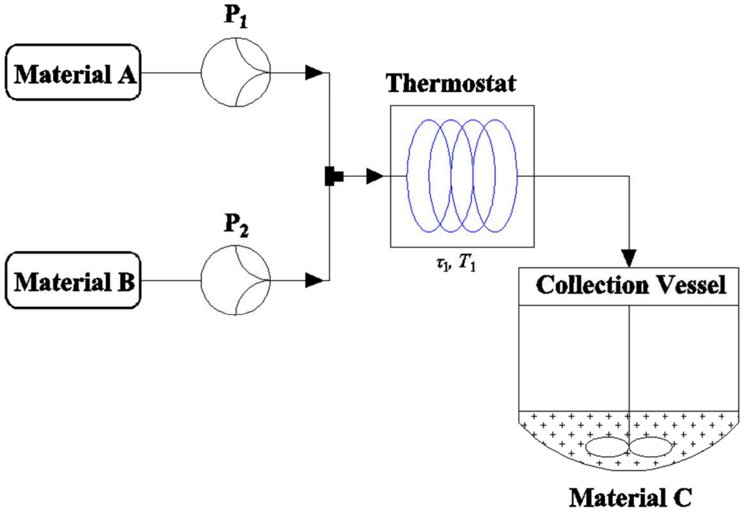


Figure 1. Primitive Continuous-flow Process. Material A is 1.29 M *m*-nitroaniline in 2.6 equiv. of hydrochloric acid with a flow rate of 112.8 mL/min, material B is 4.24 M aqueous sodium nitrite. Material C is a mixture of 1.2 equiv. of sodium thiomethoxide (2.05M) and 0.58equiv. of aqueous sodium hydroxide which was added in collection vessel before the operation.

The operation of this diazotization process is relatively convenient, once the parameters was set and corrected. Started the peristaltic pumps, let materials pumped into the loop reactor respectively, and synthesized **3** was flowed into collection vessel for following process. The related parameters of diazotization in continuous-flow process are residence time τ_1 and reaction temperature T_1, therefore sets of reaction conditions involved τ_1 and T_1 were tested to find an appropriate reaction condition. The results were shown in Figure 2, the yield was increased to a constant value with prolonged residence time at low reaction temperature (less than 10 °C), while it was increased to a peak value followed by a decrease with prolonged residence time at relative high reaction temperature (excess than 20 °C). The yield was not monotonic rise over time at the same temperature, and that's because the reaction rate of diazotization was overwhelmed by the reaction rate of decomposition after peak. The maximum yield (68%) of **1** was achieved at about T_1 = 30 °C, τ_1 = 30 s.

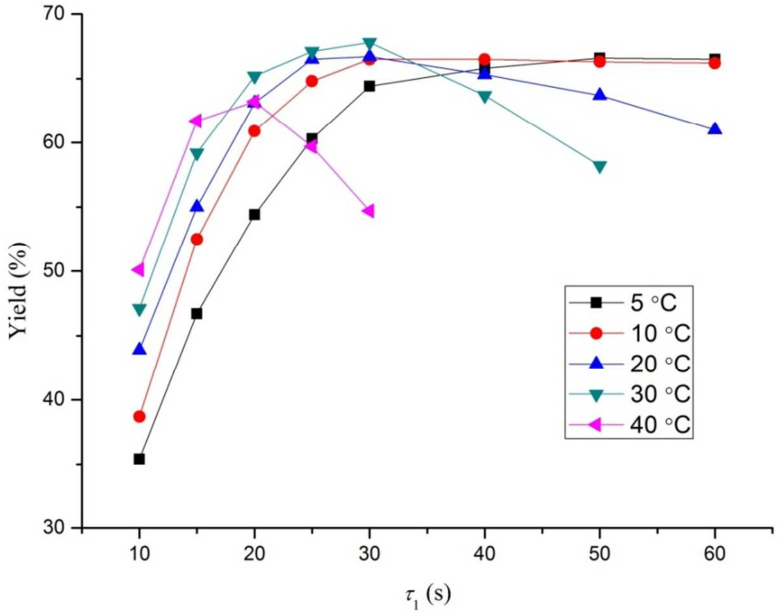


Figure 2. Effect of temperature (T_1) and residence time (τ_1) on the yield of *m*-nitrothioanisole.

After reaction temperature (T_1) and residence time (τ_1) were settled, the reaction system was run with different molar flow ratio to optimize the usage of sodium nitrite. The results were shown in Figure 3. It turned out the molar flow ratio between aniline hydrochloride and sodium nitrite were 1 : 1.1 as we adopted in previously trials.

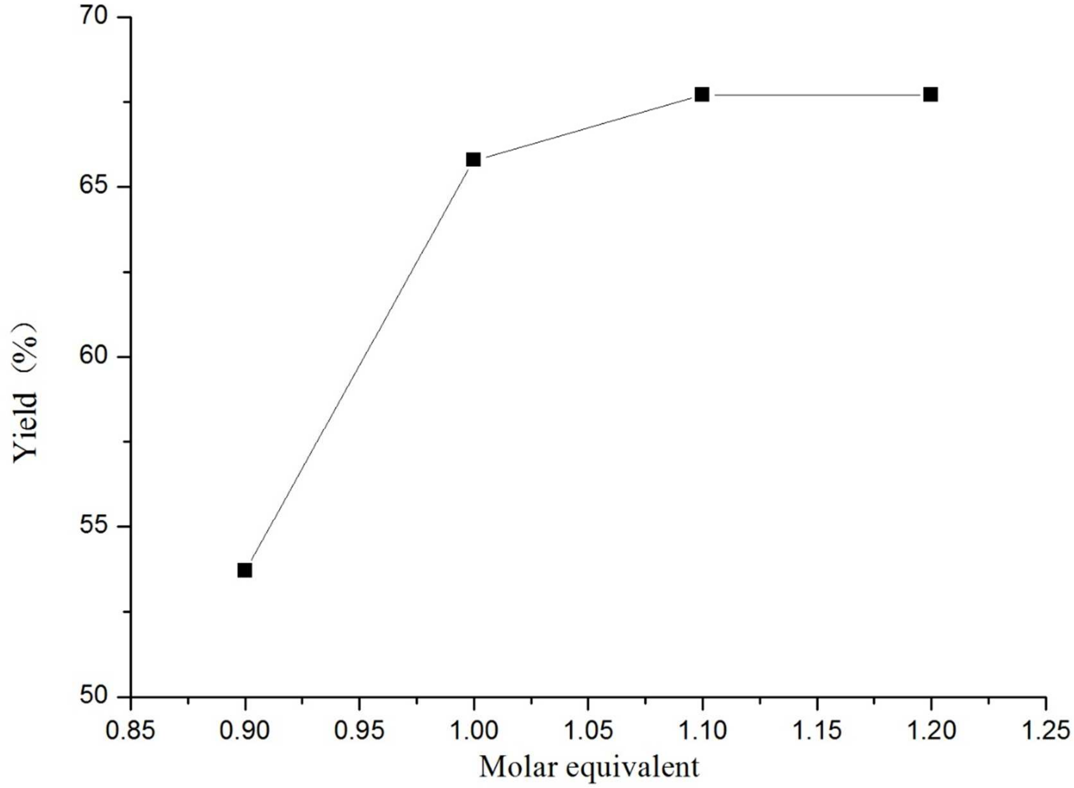


Figure 3. Effect of molar flow ratio of sodium nitrite : *m*-nitroaniline on the yield of *m*-nitrothioanisole.

Advanced Continuous-Flow Process

The primitive continuous-flow process of diazotization was successfully functioning, however, the adapting of batch chemistry to continuous-flow only half-way through. The yield was still lower than our expectation and byproducts were analyzed and identified by GC-MS. As shown in Scheme 4, reduction byproducts **6** (12%), **7** (~1%), and **8** (~1%), were found in crude product. According to the result, byproducts are caused by reduction. Of all the chemicals in this process, sodium thiomethoxide is the most likely reducing agent. Therefore, we tried to separate 4 from reaction mixture and heated it to dediazoniation, we found this method is very dangerous since **4** is extremely explosive in dry condition. So introducing a co-solvent to extract **4** and created a biphasic system came out. This method could prevent the intermediate **4** from being reduced, and also solve the transportation problem.

Scheme 4. The reduction side-reactions

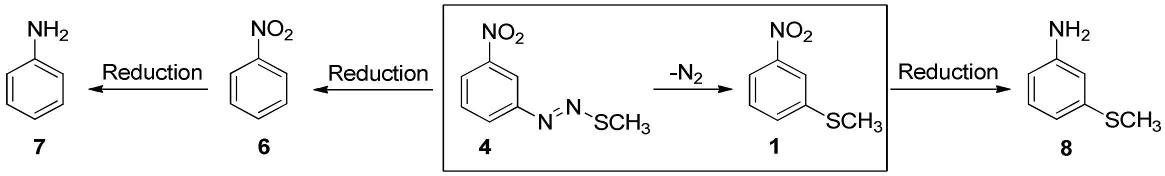


Table 1. Introduction of different solvents

Entry	Solvent	Purity (%)[a]	Yield (%)[b]
1	1,2-dichloroethane	89	74
2	toluene	88	74
3	petroleum ether[c]	88	73

[a]Purity was determined by GC. [b]Yield was corrected on purity. [c]Boiling point was 90-120 °C.

Reactions were run in the same continuous-flow set-up as shown in Figure 1, different inert solvents, toluene (aromatic), 1,2-dichloroethane (halogenated hydrocarbon) and petroleum ether (ether) were tested to perform in this design. Adding 6 mL solvent to every 1 g of **2** within aqueous sodium thiomethoxide and sodium hydroxide in collection vessel, and the results were showed in Table 1. As we expected, the introduction of solvent showed an eminent improvement on yield, and the amount of main reduction byproduct **6** was reduced to about 8%, byproducts **7** and **8** were less than 1%. Since the influence of different species to result was negligible, we didn't expend the candidates, and in the consideration of recycling rate of the solvent, toluene was selected.

After the solvent toluene was selected, this process was run several times to determine the appropriate ratio of the volume of solvent to the mass of *m*-nitroaniline. The different usages of solvent would lead to different concentrations, therefore we conducted these trials with different reaction times which depend on the outgassing of the each trial. As shown in Figure 4, the volume-mass ratio had little effect on the yield.

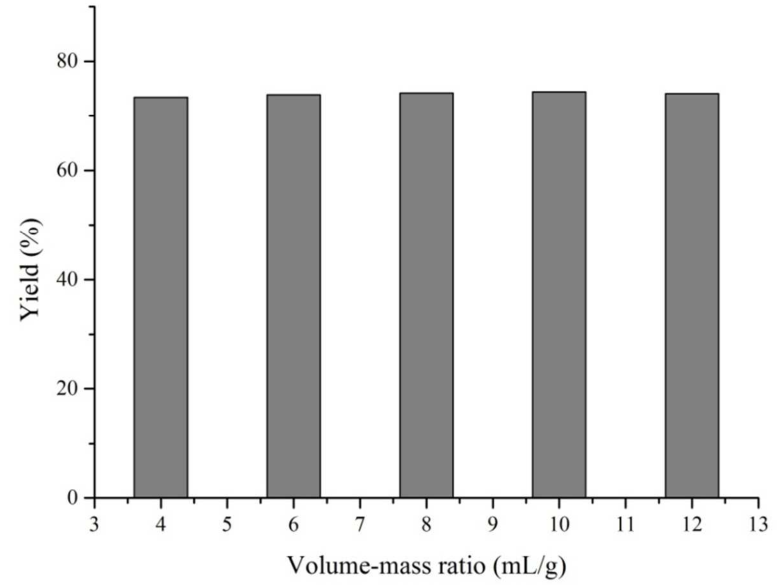


Figure 4. Effect of volume-mass ratio of toluene to *m*-nitroaniline.

Although the ideal result didn't came out, yet the original problem of set up a continuous-flow process to conduct diazotization and following process was solved. By introducing a solvent to extract **4** while it was being formed in reactor could prevent reaction tube clogged. However, due to the dediazoniation is a time-consuming and outgassing process, the reaction tube needs to be extremely long to give adequate residence time, and in that case, the pressure drop was beyond our acceptance range. Therefore, dediazoniation was rearranged in collection vessel. As shown in Figure 5, the device used two peristaltic pumps (**P**$_1$, **P**$_2$) to introduce the feed streams of combination of **2** and hydrochloric acid (material A) and aqueous sodium nitrite (material B). A T-joint (Hastelloy, 3 mm i.d.) was used as a mixer, which was connected with reaction tube (Hastelloy, 3 mm i.d., 5 mm o.d.). The reaction mixture from diazotization tube then entered into a cross joint and mixed with two other streams of combination of aqueous sodium thiomethoxide and sodium hydroxide (material C) and toluene (material D) which were pumped by pumps (**P**$_3$, **P**$_4$), respectively. Then the mixture was entered into another tube reactor (SS316L, 6 mm i.d., 8 mm o.d.) for azo-coupling. The mixture was collected in a vessel, heated to dediazoniation at 70 °C for 2 h, and then separated. The solvent was removed from organic phase to afford the crude product.

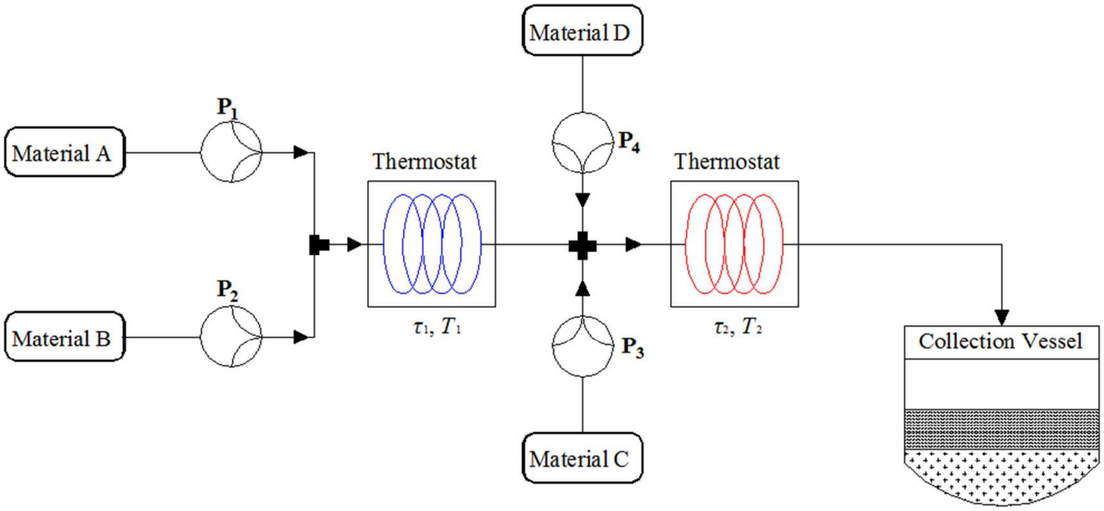


Figure 5. Continuous-flow process of diazotization & azo-coupling. Material A is 1.29 M *m*-nitroaniline in 2.6 equiv. of aqueous hydrochloric acid with a flow rate of 112.8 mL/min. Material B is 4.24 M aqueous sodium nitrite with a flow rate of 37.8 mL/min. Material C is 2.09 M sodium thiomethoxide in aqueous sodium hydroxide with a flow rate of 71.7 mL/min. Material D is toluene with a flow rate of 80.3 mL/min. Diazotization coil is Hastelloy coil with 3 mm i.d. and 5 mm o.d.. Azo-coupling coil is SS316L coil with 6 mm i.d. and 8 mm o.d..

Then, tests were run to determine the temperature (T_2) and residence time (τ_2) of azo-coupling reaction. The flow rate of material C was 83.6 mL/min. The residence time was varied by adjusting tube length, and the results were shown in Figure 6. Lower temperature resulted in slow conversion rate, while higher temperature led to a decrease of yield and the decline rate increased with the rising temperature. That's because during the generation of **4** from diazonium chloride **3**, there was a side reaction of **3** decomposed while release nitrogen and became phenolic product. This side reaction rate raised along with reaction T_2 rose, thus, yield decreased at higher T_2. Therefore, a maximum yield of

84.5% was obtained when T_2 of 30 °C and τ_2 of 150 s was selected.

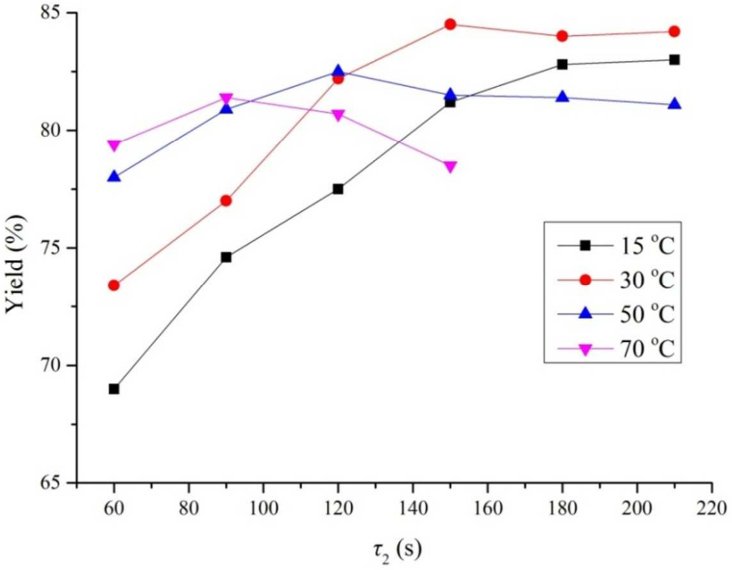


Figure 6. Effect of T_2 and τ_2 on the yield of *m*-nitrothioanisole.

On top of that, with better control of reaction parameters in continuous-flow reactor, the usage of sodium thiomethoxide may reduce (which is 1.2 equiv. in batch chemistry). Since the sodium thiomethoxide could lead to reduction side products, and as the advantages of continuous-flow technology that was mentioned previously. The molar flow ratio of sodium thiomethoxide : **2** was optimized by adjusting the flow rate of material C. As shown in Figure 7, the molar equivalent of sodium thiomethoxide was reduced to 1.03 with a slight increase of yield[12]. A maximum yield of 89% was achieved, and the purity of crude product was 91%. Further purification can be fulfilled by distillation.

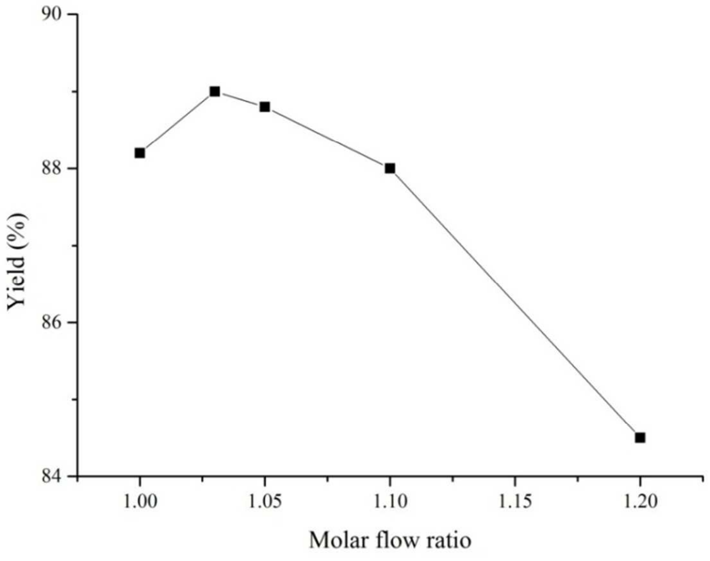


Figure 7. Effect of molar flow ratio of sodium thiomethoxide : **2** on the yield of *m*-nitrothioanisole.

To underline the advantages of the proposed flow synthesis, a comparison with the reaction performed in a batch manner is summarized. Figure 8 shows the comparison of byproducts in different operate manner. The yields of different processes are listed on Table 2 to make a comparison. It is very obviously that advanced continuous-flow process performed better than others.

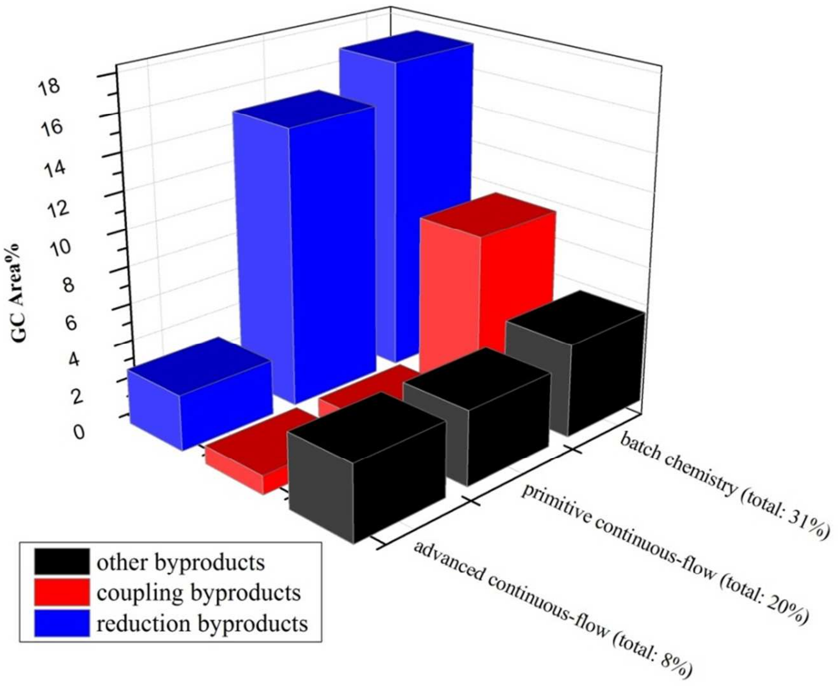


Figure 8. Content of byproducts of different operate manner.

Table 2. Comparison of different operate manner.

operate manner	purity (%)[a]	yield (%)[b]
Batch	66	61
Advanced Continuous Flow Process	91	89

[a]Purity was determined by GC. [b]Yield was corrected on purity.

Conclusion

We have described a continuous-flow process allowing the save handling of the energy intermediates, in this case, diazonium salt. Using flow technology to solve problems caused by active intermediates has become an effective measure. But in this process particularly, we faced another difficulty. In standard diazotization model, side reaction is a consecutive reaction, which means we can apply flow chemistry technology by setting appropriate residence time to keep reaction stays in main reaction. Yet, azo-coupling, on the other hand, due to the nucleophilicity and reductivity, side reaction is a parallel reaction, and that is hard to solve by normal flow chemistry technic. Therefore, we introduced a solvent to create a liquid-liquid biphasic system to reduce the exposure of sodium nitrite in aqueous phase and products (including azo-coupling product and final product). This method was proved successful for its yield was raised to 89% and the byproducts were reduced eminently. We thought this could be a new way to deal with similar situations in continuous-flow process.

EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and were used without further purification. Gas chromatography (GC) analysis was carried out on *an* Agilent 6890 gas chromatograph. GC conditions: HP-5 column 30 m × 0.32 mm × 0.25 μm, carrier gas: gas: helium (1.2 mL/min), injection temp.:

270 °C, detector temp.: 290 °C, oven: 150 °C (5 min hold) → 260 °C (250 °C/min, 10 min hold). ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS, $\delta = 0$) as an internal standard at ambient temperature on a Varian 400 MHz spectrometer.

Batch Experiment. *m*-Nitroaniline (13.8 g, 0.1 mol) was placed in an 100 mL glass jar then added hydrochloric acid (31%, 38.4g, 0.26 mol) and 40.9 mL water with stirring. The mixture was heated to 80 ^{o}C for 30 min, and then cooled gradually while stirring. Aqueous sodium nitrite was prepared from sodium nitrite (7.6 g, 0.11 mol) and 22.8 mL water at room temperature. After aniline hydrochloride was cooled to 0 ^{o}C, the aqueous sodium nitrite was added. Diazotization was initiated by the slow addition of the aqueous sodium nitrite, and the temperature was kept below 0 ^{o}C. After addition completed, the mixture continued to stir for 0.5 h while the temperature of reaction mixture was maintained at 0 ^{o}C. The mixture was then added to a 500 mL flask with well-mixed sodium thiomethoxide (20%, 42.1 g, 0.12 mol), sodium hydroxide (2.32 g, 0.058 mol) and 20 mL water in it at 40 ^{o}C. After addition, the mixture maintained this temperature for 0.5 h before heated it to 70 ^{o}C. After 2 h, separated the mixture, the brownish solid was obtained. 15.6 g of crude product in 92.3% yield and 65.7% purity was obtained. Sample for characterization was gained by column chromatography with petroleum ether and ethyl acetate as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.01 (t, 1H, $J = 2.0$ Hz), 7.92 (m, 1H), 7.50 (m, 1H), 7.41 (t, 1H. $J = 8.0$ Hz), 2.55 (s, 3H). Literature data[5]: 8.00 (t, $J = 2.0$ Hz, 1H), 7.91 (ddd, $J = 8.1$ Hz, $J = 2.0$ Hz, $J = 1.0$ Hz, 1H), 7.48 (ddd, $J = 7.9$ Hz, $J = 1.8$ Hz, $J = 1.0$ Hz, 1H), 7.39 (t, $J = 8.0$ Hz, 1H), 2.51 (s, 3H).

Advanced Continuous-flow Process. As shown in Figure 5, a mixture of *m*-nitroaniline (138 g, 1 mol), hydrochloric acid (31%, 390g, 2.6 mol) and 409 mL water was prepared. Aqueous sodium nitrite was prepared from sodium nitrite (75.9 g, 1.1 mol) and 163 mL water. The aniline hydrochloride and aqueous sodium nitrite were pump into the tube reactor (Hastelloy, 3 mm i.d., 5 mm o.d.), which was immersed in a thermostat (30 ^{o}C), via a T-joint by P_1 and P_2 at flow rates of 112.8 mL/min and 37.8 mL/min, respectively. After a residence time of 30 s, a mixture of sodium thiomethoxide (20%, 360.5 g, 1.03 mol) and sodium hydroxide (26.4 g, 0.66 mol) in 170 mL water and toluene were pumped into the tubular react system via a cross mixer by P_3 and P_4 at flow rates of 71.7 mL/min and 80.3 mL/min and converged with diazonium salt. Then, the mixture flowed into the second tube reactor which was immersed in a thermostat (30 ^{o}C), after a residence time of 150 s, the mixture flowed through the outlet and accumulated in the stirring collection vessel which had been maintain at 80 ^{o}C. The mixture was stirred in the vessel for 100 min, and then the mixture was separated. Collected the organic phase and distilled to removed solvent, the yellowish solid was obtained. About 165 g of crude product in 97.6% yield and 91.4% purity was obtained. Further purification can be fulfilled by distillation on commercial demand.

ACKNOWLEDGMENT

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