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Continuous Flow Doebner–Miller Reaction and Isolation Using Continuous Stirred Tank Reactors

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Supporting Information

ABSTRACT: Continuous flow Doebner–Miller synthesis of different quinaldines from respective anilines is demonstrated using sulfuric acid as a homogeneous catalyst. The extent of reaction was monitored for various parameters, namely, temperature, residence time, mole ratio of sulfuric acid to substrate, mole ratio of crotonaldehyde to substrate, and so forth. Continuous stirred reactors in series were used as a preferred configuration for this rection that generates byproduct in the form of sticky solid material. The approach has been extended for six different anilines, and the results are compared with batch reactions. Continuous stirred reactors in series with distributed dosing of crotonaldehyde facilitated a continuous flow reaction with lower byproduct formation, increased yields, and continuous workup and is a scalable approach.

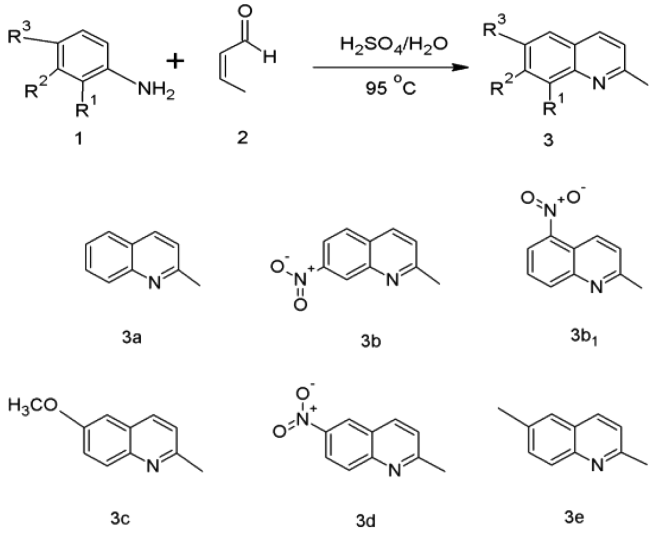
1. INTRODUCTION

Quinaldine is usually isolated from coal tar using sulfuric acid followed by precipitation with ammonia. Several methods of synthesizing quinaldine using homogeneous acid catalysts are known.[1] Literature shows the importance of quinaldine and its derivatives as potential biologically active compounds with pharmacological applications.[2] These groups are also found in natural products and have an application in the synthesis of drugs for antiallergic,[3] anti-inflammatory, antiasthmatic,[4] antimicrobial,[5] antimalarial,[6] antibacterial,[7] and antihypertensive[8] symptoms. In addition to this quinaldine synthesis is also used for the preparation of nano- and mesostructures with enhanced electronic and photonic properties.[9] Despite their applications in the area of medicine, pharmaceutical, and industry, few methods of synthesis of quinaldine and its derivatives have been reported.[8] These methods involve Skraup's synthesis,[10] Doebner–Miller synthesis,[11] and Friedlander synthesis.[12]

In the recent years the continuous flow synthesis has helped to design process that can optimize the use of resources. Due to the wide range of applications of quinaldine and its derivatives, it is advantageous to focus on the flow synthesis of these chemicals. Different methods of synthesis such as the use of microwave[2,5,11] and use of different catalysts[13−16] that enhance the reaction rates are reported in the literature. However, the commercial scale applicability of such methods has not been demonstrated either due to insufficient evidence of usefulness of microwave for large-scale synthesis[17] or discontinuous availability of the specific catalysts. In view of these issues, here we present an approach that shows continuous-flow Doebner–Miller synthesis of quinaldines. Initially reactions are conducted batch wise which helped to design and carry out continuous reactions for these ring compounds.

The mechanism of quinaldine synthesis from anilines is well-known and is given in the Supporting Information. The typical reaction of an aniline with an active aldehyde, namely, crotonaldehyde in strongly acidic medium, undergoes Michael addition of the aniline to the α,β-unsaturated carbonyl compound[18] followed by subsequent cyclization and aromatization (Scheme 1).[13] Depending upon the activity of aniline, these reactions are carried out at high temperature and also in the presence of highly acidic medium (viz., sulfuric acid or phosphoric acid).[11,15] In general, while the use of *o*-phosphoric acid results in high yield of the desired product, the process may not be economical due to high costs of phosphoric acid which cannot be recovered and reused. In view of this here we present the outline of this paper. After the Introduction, we

Scheme 1. Reaction of an Aniline 1 with Crotonaldehyde 2 To Synthesize Quinaldine 3 (R^1: H, R^2: H, NO_2, R^3: H, NO_2, CH_3, OCH_3)



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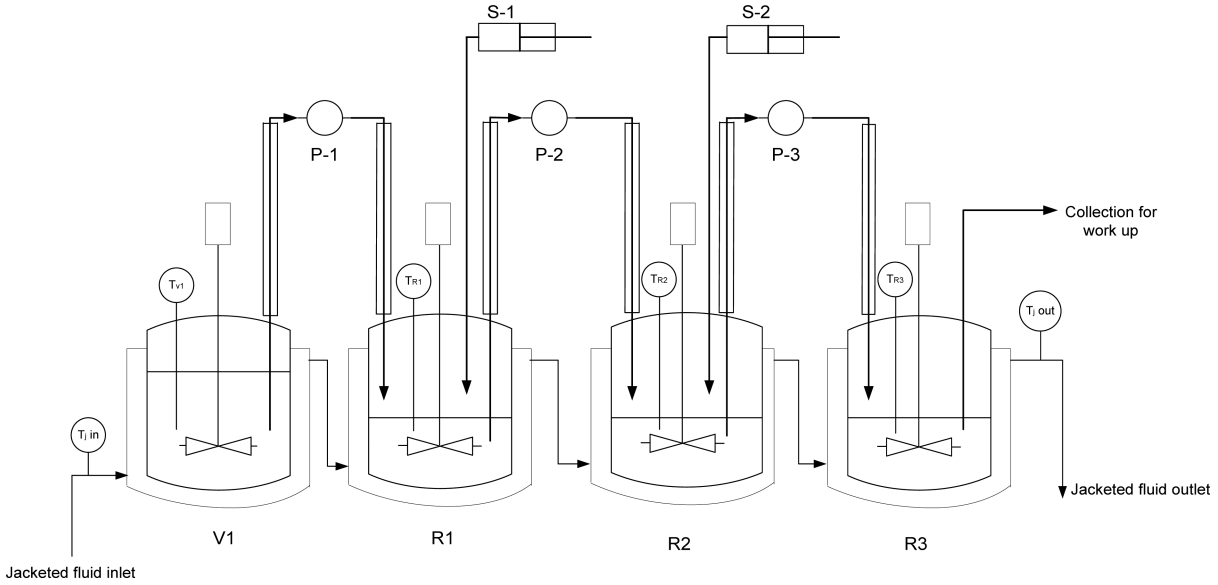

Figure 1. Schematic of continuous synthesis of quinaldine (P − pump, R − reactor, V − vessel, S − syringe pump, T − temperature indicators).

discuss the experimental setup and experimental procedure, including the workup procedure for isolation of the product. Followed by this, we discuss the results in detail and then conclude with important observations and recommendations.

2. EXPERIMENTAL SECTION

2.1. Batch Experiments. Initially the reactions are conducted in a batch reactor, and the effect of sulfuric acid concentration on the yield of the product was monitored. A batch setup consists of a jacketed glass reactor with four baffles and an overhead stirrer. Reaction temperature is maintained by circulating water through circulator (Julabo, Germany). A typical batch reaction was carried out at different temperatures for about 200 min. The addition of crotonaldehyde was done over a longer period. Samples were taken periodically to monitor the progress of the reaction. Reactant (aniline), sulfuric acid (55% w/w), and water are added from one end of the vessel by funnel and stirred. At lower temperatures the reaction mixture was seen to remain turbid, while it starts becoming homogeneous once at temperature above 85 °C and becomes a clear solution at 92 °C. Since the purpose of the work was to transform a batch process into continuous, it was desired to have a clear solution, and hence all further experiments were conducted above 92 °C. Upon continuous heating once the reaction mixture becomes clear, crotonaldehyde was added continuously using a syringe pump. A fixed quantity of crotonaldehyde was added for different time spans, and the reaction progress was monitored on HPLC.

2.2. Product Recovery Protocol. After completion of reaction, the reaction mass is cooled to 50 °C at which the soluble polymer and product can be removed easily. The reaction mass is mixed with water and 20% NaOH to increase the pH close to 1, which makes the polymer get precipitated,[19] which is then filtered and given a water wash. To the filtrate, 40% NaOH solution is added to make the reaction mixture initially neutral and then slightly basic, i.e., pH ∼ 8, under which the product precipitates out of the mixture.[20] The reaction mass is then filtered under vacuum to recover product.

It is observed from the batch reactions that the reaction comes under the category of slow reaction which forms the sticky mass of polymer along with desired quinaldine. The polymer suspension can be kept in nonagglomerated form by diluting the solution by as much as four times, which might be useful for transforming this reaction in small flow reactors. However, at the reaction conditions explained in subsection 2.1, handling this sticky mass of polymer would be a major challenge in small flow reactor.[21] Hence, a continuous stirred tank reactor (CSTR) or mixed flow reactor is a suitable reactor configuration where the handling of polymer and controlling its formation is possible by maintaining the dilute conditions in the reaction vessel.

2.3. Continuous Flow Synthesis and Recovery. The flow synthesis experimental setup consisted of stock solution vessels, three baffled and jacketed glass reactors with overhead stirrers, three peristaltic pumps (Longer pump BT300-2J), two syringe pumps (Longer LSP02-1B), and a heating fluid circulator (Julabo, Germany). The schematic of the setup is shown in Figure 1. Each CSTR was equipped with a disk turbine of standard size (D/T = 0.33) to keep polymeric material in suspension. A stock solution of reactant, sulfuric acid, and water is prepared in jacketed vessel V1 and heated to 92 °C to make it a clear solution. The reactant dissolved in sulfuric acid and crotonaldehyde enter in the first CSTR (R1). Crotonaldehyde is dosed independently in two reactors using syringe pumps (S1 and S2). Flow rates of the pumps are adjusted such that the desired residence time in each reactor is identical (i.e., volumetric flow rate in second reactor is higher than the first). The residence time was changed by changing the flow rates. Peristaltic pumps were used for transfer of reaction mixture between the subsequent reactors. The transfer lines between two vessels were insulated to avoid any significant drop in the temperature during reaction.

The start-up procedure is given in the Supporting Information. Periodically samples were collected from each CSTR to confirm that the real steady state is achieved. Upon reaching the steady state samples were collected from each CSTR to monitor the conversion on HPLC. This was repeated several times over a period of five times the residence time for the system. The temperature was monitored at the inlet and outlet of each CSTR on process side as well as the utility side.

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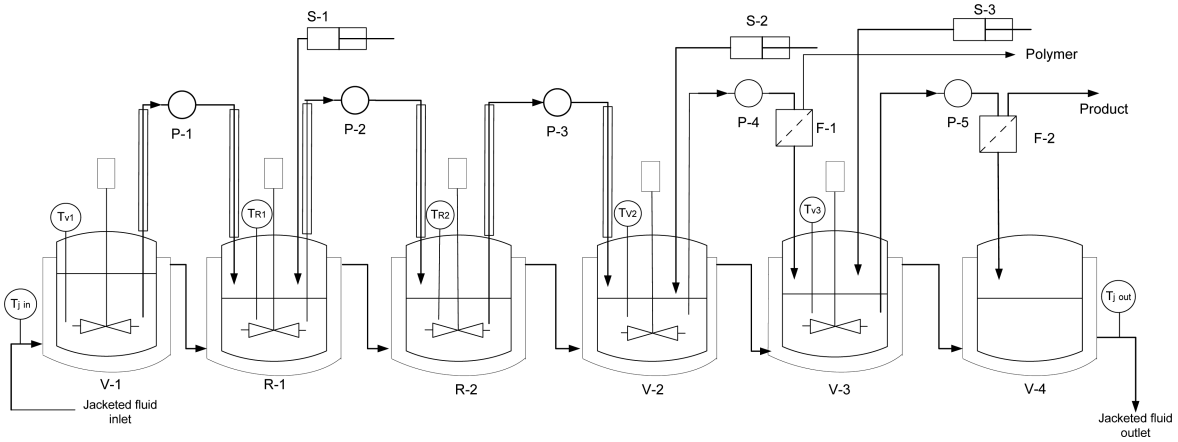

Figure 2. Schematic of continuous synthesis of quinaldine followed by continuous workup (P − pump, R − reactor, V − vessel, F − Filter, S − syringe pump [S1 − crotonaldehyde, S2/S3 − NaOH]).

In addition to the residence time in the reactors R1 and R2, an additional residence time of 1 h was given using a third CSTR R3 that helped to achieve complete conversion of the aniline.

Batch separation of the product from the reaction mixture is a time-consuming process, and there are handling losses. In view of this the two-step workup was also made continuous using two additional CSTRs in series (Figure 2). The stoichiometry for workup was maintained the same as in a batch experiment. Thus, to the continuous stream of reaction mixture from R2 that enters V2, sodium hydroxide solution was fed to facilitate increase in pH to 1. This helped precipitation of polymer from the reaction mass. pH in V2 was constantly monitored using a pH meter, and the suspension was fed to the next CSTR (V3) using a peristaltic pump through a continuous vacuum filtration unit, where polymeric material gets separated from the reaction mass. The filtrate, along with 30% sodium hydroxide solution in water, are fed to V3 simultaneously to achieve higher pH (>8) that helps the product to precipitate. The outlet of V3 was again continuously passed through a filtration unit where the product gets isolated and the filtrate is collected in V4. The product is removed, dried, and weighted to obtain the yield for a wide range of temperature and flow rate/residence time conditions.

3. RESULTS AND DISCUSSION

It is necessary to understand the nature of reaction at different parameters, namely, the flow rate/residence time, temperature, and sulfuric acid concentration, on conversion and selectivity in a batch reactor. It is observed from initial set of experiments that the percentage of sulfuric acid plays a key role in deciding the yield of the product. Hence this parameter was first optimized in batch reactions.

Experiments were carried out at different sulfuric acid concentrations for reaction of 4-nitroaniline with crotonaldeyde (addition time 90 min) at 92 °C followed by a maintaining period for 2 h. For H_2SO_4 equivalent concentrations of 30%, 50%, 60%, and 75%, the % conversions (% yield of 4-nitroquinaldine given in bracket) are 75.4 (57.6), 100 (76.7), 95 (66.8), and 99 (63.8), respectively. The conversion and % yield are maximum at 50% (w/w) sulfuric acid concentration, i.e., 1 equiv of aniline and 7.26 equiv of sulfuric acid. A higher concentration of sulfuric acid makes a favorable condition for the polymerization of crotonaldehyde in the reaction mixture, which reduces the availability of crotonaldehyde for the desired reaction. Further the porous sticky polymer mass adsorbs the organic substrate on its surface, thereby reducing the availability of free substrate for reaction. On the other hand a very low concentration of sulfuric acid causes less protonation of the intermediates in the reaction which does not help completing the reaction and results in poor yields of the product. Since the polymerization of aldehyde is an unavoidable parallel reaction, a balance between rates of different reactions, an optimal concentration of sulfuric acid provides a better yield of the product by reducing the rate of polymerization. Experiments were carried out for other anilines as well. In order to confirm the above observations, experiments were repeated at 70% sulfuric acid for others anilines. The yields for different anilines are aniline (45%), 3-nitroaniline (42.8%), *p*-toluidine (52%), *p*-anisidine (32%), and 4-nitroaniline (61%), respectively, which are lower than those with 50% sulfuric acid. Since crotonaldehyde polymerization is unavoidable, either the rate of addition of crotonaldehyde or its quantity needs to be further optimized to ensure that quinaldine formation is maximized.

Experiments were carried out for studying the effect of crotonaldehyde concentration on the yield of 6-nitroquinaldine. Results are shown in Table 1, and 1.67 mol equiv of crotonaldehyde was seen to be reasonable for these experiments, where the yield of the product does not increase significantly by further increasing the quantity of crotonaldehyde. With these conditions that give the maximum yield from batch experiments, continuous flow synthesis of quinaldine was performed for different substrates. The substrates include aniline, 4-nitroaniline, 3-nitroaniline, *p*-toluidine, and *p*-anisidine. Experiments were carried out at 95 °C and two

Table 1. Effect of Crotonaldehyde Concentration (Mole Ratio of Crotonaldehyde to 4-Nitroaniline) at 50% Sulfuric Acid for Reaction with 4-Nitroaniline as a Starting Material To Obtain 6-Nitroquinaldine

mole ratio	% conversion	% yield	
1.0	45.9	29.5[a]	23.1[b]
1.25	94.5	61.81[a]	57.1[b]
1.67	100	76.74[a]	74.0[b]
2.28	100	79.17[a]	75.0[b]

[a]HPLC yield. [b]isolated yield.

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CSTRs in series. To each of these CSTRs crotonaldehyde was fed using separate pumps and the residence time in each CSTR was maintained at 45 min. The reaction mass was collected in a third CSTR where it was maintained for 60 min at the reaction temperature. This yields a total residence time of 150 min, which is lesser than 200 min as in batch reactor. The outlet of this CSTR was used for collecting the product mass for workup as explained in Section 2. The total residence provided in this configuration is same as the batch time. The comparison of batch and continuous experiments for different substrates is given in Figure 3.

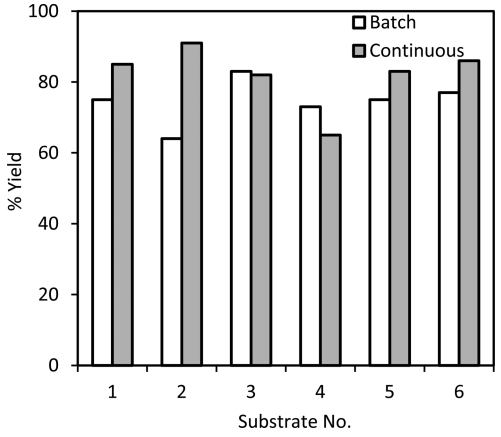

Figure 3. Comparison of yield from batch and continuous flow synthesis of various quinaldines for different anilines (1: aniline, 2: 3-nitroaniline, 3: *p*-toluidine, 4: *p*-anisidine, 5: *p*-chloroaniline, 6: 4-nitroaniline).

With *p*-chloroaniline as a starting material, continuous reactions have issues like the solubility of reactant and transfer of material in flow configuration. In this case the reactor set up has to be modified with proper insulation to the tubing, which can avoid precipitation of solids along the walls of the tubes. With 3-nitroaniline as a starting material, two isomers, namely, 5-nitroquinaldine as a major product and 7-nitroquinaldine, are formed which are confirmed by NMR. The comparison of conversion between batch and CSTRs in series showed that, while a batch reactor when operated for sufficiently longer time would always achieve complete conversion, CSTRs in series helped to achieve as much as 92−96% conversion depending upon the substrate. A relatively diluted condition of the reaction mixture in both the CTSRs results in slightly less conversion. However, this characteristic also helped to improve the selectivity of the desired product which can be seen in Figure 4. Comparison of selectivity between a batch reactor and CSTR shows higher selectivity for the case of aniline, 4-nitroaniline, and 3-nitroaniline. The amount of polymer formed in batch reactor was higher than in CSTR due to dilution of inlet crotonaldehyde concentration. Hence the configuration of CSTRs in series is favorable for slow reactions. It is possible to enhance the reaction rates by increasing temperature; however in that case the rate of polymerization increases significantly and gives very low conversions of aniline.

As mentioned before, the isolation of the product happens in two stages and is time-consuming with handling losses which can be avoided in continuous isolation with better yield of the product. In all the cases mentioned above the isolation was carried out in continuous mode. The molarity of sodium hydroxide solutions need be 4 and 8.75 M for the first and

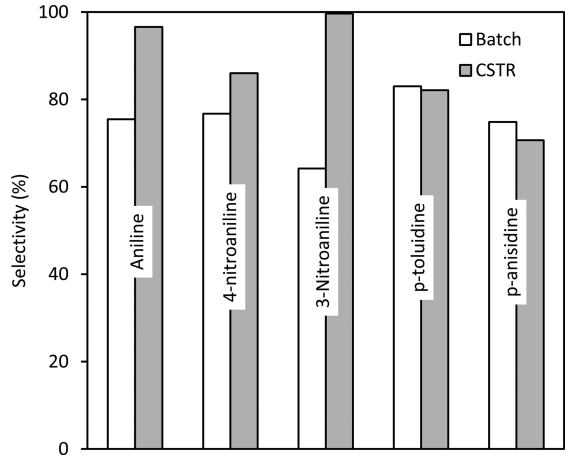

Figure 4. Selectivity of the desired product with different substrates.

second stages of workup. The residence time for either reactors is lesser than 10% of the reaction time, and hence workup needs relatively small volume CSTRs. In general continuous workup has resulted in higher yields when compared to batch operation. For the case of 6-nitroquinaldine yield from continuous isolation is 88.9% when compared to 86% obtained from batch approach. The continuous isolation of other aniline derivatives can be performed in the same manner by adjusting the molar requirement of alkaline solution. While all the products are solids, some may require further purification through recrystallization or column chromatography after the workup. Also, if the workup temperature is higher than the melting point of the product, workup yields an oily layer which can be separated continuously by layer separation or a membrane filter. Thus, among the recent reports on multistep synthesis (which largely ensure to keep the reaction mass in fluid phase) followed by its workup using variety of separation techniques,[22,23] simple techniques like pH adjustment, use of antisolvent, or catch-and-release approach[24] will actually help to make the translation from lab scale to kilo scale much faster. Hence the optimized percentage of sulfuric acid, lower crotonaldehyde concentration, and flow reactor configuration along with continuous isolation together make this process green, economical, and commercially viable. The approach is extendable for other systems where different aldehydes can be used in the reaction.

4. CONCLUSIONS

The Doebner−Miller synthesis of quinaldine and its derivatives is demonstrated in continuous flow conditions. In the absence of using any solvents the reaction was not suitable to be conducted in tubular reactors as sticky polymer clogs the channels and tubes almost instantaneously. Hence a reactor configuration that consists of CSTRs in series is used.

The effect of mole ratio of crotonaldehyde to aniline, concentration of sulfuric acid, reaction temperature, and residence time were studied, and a set of parameters that gives maximum yields for different anilines is identified. The flow synthesis approach is found to give better yields than batch process.

At a residence time identical to the batch reaction time, distributed dosing of crotonaldehyde to a configuration of CSTRs in series helped to achieve better yields than a batch. Continuous workup by a change of pH helped to recover the product in an elegant manner. Reactions of six different anilines

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are demonstrated. This helps to have a better control on the overall reaction and isolation. The procedure is extendable for variety of substrate combinations and results in an intensified process with a smaller footprint, a lesser generation of undesired yet unavoidable polymer, and a continuous operation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00179.

S1: Reaction mechanism, S2: Experimental protocol for CSTRs in series, S3: Physical properties of substrates and products, S4: H^1 NMR data, S5: HPLC Chromatograms, and S6: GCMS data for select products (PDF)

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Notes

The authors declare no competing financial interest.

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