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Flow synthesis of n-substituted 5-benzylidinethiazolidine-2,4-dione

Síntese de fluxo de n-substituído 5-benzilidina-2,4-diona

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ABSTRACT

Process intensification based on micro reactor technology allows safe manner and a new pathway to run organic synthesis due to its intrinsic characteristics, and can reduce time-to-market of new drugs. The main objective of this work was to study the batch and flow reaction of five n-substituted 5-benzylidenethiazolidine-2,4-dione heterocyclic intermediates present in the synthesis of glitazone class drugs, in capillary micro reactor. Batch process was conducted with ethanol as solvent at the boiling point and pyrrolidine as promoting base of the reaction. Higher yields were obtained in shorter reaction times in temperatures above solvent boiling point. Also, we evaluated that 3.8 micro reactors in parallel would be necessary to reach the same mean molar flow rate of a 60 mL batch reactor. Kinetic and thermodynamic study indicated that the reaction followed the second-order model and allowed estimating its main thermodynamic parameters. The continuous flow micro reactor proved to be an efficient alternative to the batch process in scaling up the production of Active Pharmaceutical Ingredient intermediates (APIs).

Keywords: flow synthesis, capillary micro reactor, process intensification, thiazolidine-2,4-dione, batch process.

RESUMO

A intensificação do processo com base na tecnologia de micro reactores permite uma forma segura e uma nova via para realizar a síntese orgânica devido às suas

características intrínsecas, e pode reduzir o time-to-market de novos fármacos. O principal objectivo deste trabalho foi o estudo da reacção de lote e fluxo de cinco intermediários heterocíclicos n-substituídos 5-benzilidenothiazolidina-2,4-diona presentes na síntese de fármacos da classe glitazona, em micro reactor capilar. O processo batch foi conduzido com etanol como solvente no ponto de ebulição e pirrolidina como base promotora da reacção. Foram obtidos maiores rendimentos em tempos de reacção mais curtos em temperaturas acima do ponto de ebulição do solvente. Também avaliamos que seriam necessários 3,8 micro reactores em paralelo para atingir a mesma taxa média de fluxo molar de um reactor descontínuo de 60 mL. O estudo cinético e termodinâmico indicou que a reacção seguiu o modelo de segunda ordem e permitiu estimar os seus principais parâmetros termodinâmicos. O micro reactor de fluxo contínuo provou ser uma alternativa eficiente ao processo descontínuo ao aumentar a produção de intermediários de ingredientes farmacêuticos activos (APIs).

Palavras-chave: síntese de fluxo, micro reactor capilar, intensificação do processo, tiazolidina-2,4-diona, processo descontínuo.

1 INTRODUCTION

Over the last decade emerged a number of researches about miniaturization of equipment with purpose of intensifying process. Process technology and micro-system technology are interdisciplinary subjects, covering chemistry, physics, biology, and engineering fields (ETCHELLS, 2005; ROBERGE et al., 2008). The purpose of Process Intensification is to develop apparatuses and techniques that lead to improvements in manufacturing and processing, reduction of equipment size, improve relation between production and capacity, flexibility, lower energy consumption, less waste generation, thus becoming a cheap and sustainable technology. These approaches are also seen in industry 4.0 concept (ETCHELLS, 2005; SIMÕES; PEREIRA; MOTA, 2022). In 2007 the American Chemical Society and the Green Chemistry Institute promoted a roundtable with big pharmaceutical industries to discuss application of green chemistry and engineering to discover, develop and produce new drugs. The main areas of green research were defined, which process intensification, and mainly continuous-flow process were one of the priority subjects (JIMÉNEZ-GONZÁLEZ et al., 2011).

As an option to process intensification, continuous-flow micro reactors are taking now research laboratories around the world due to their improvements in chemical transformation (KOCKMANN; GOTTSPONER; ROBERGE, 2011). Micro reactor is any device used in continuous-flow chemistry (TONHAUSER et al.,

2012), with internal space smaller than 1 millimeter, which is possible to great controlling of reactional conditions. Due to its reduced internal space, continuous-flow micro reactors present an excellent heat and mass transfer control due to high surface/volume ratio, efficient mixing, caused by reduced diffusion paths, increased contact between molecules, fast kinetics, high conversion, yield and selectivity, safer work with explosive and toxic chemicals, reducing waste generation and increasing product purity (PORTA; BENAGLIA; PUGLISI, 2016; TONHAUSER et al., 2012; WILES; WATTS, 2012; XU et al., 2015). In general, the pressure and temperature control are easier if compared with batch reactors, therefore the process is reliable and reproductive (PORTA; BENAGLIA; PUGLISI, 2016). The carrying out of experiments is ease and stimulates the creation of chemical libraries (WILES; WATTS, 2010; XU et al., 2015).

Recent innovations in the pharma industry concern about the paradigm shift related to traditional batch processes for synthesis in flow, an important field of process intensification. Flow manufacturing draws attention to the ease of scale-up process, reduction of investment and operating costs, reduction of API costs, the main cost of a drug (BALOGH et al., 2018).

With these factors in mind, the Food and Drug Administration (FDA) has flagged for flexibility in the implementation of flow manufacturing by pharma industries to improve product quality and eliminate the shortage of drugs and recalls. For example, in a batch process, the amount of drug produced depends on the size of the reactor and its demand, while in a continuous flow process the quantity produced, or batch, can be defined by a date/time stamp, amount of drug produced or the amount of reagent fed. These control methods allow the producer to isolate the minimum amount of product that is defective, reducing waste and shortage of the drug. In addition, groups such as “Medicine 4 All”, supported by Bill and Melinda Gates Foundation are transforming the way APIs are manufactured, fostering the development of integrated plants at universities and bringing this technology to industry and population who needs pharmaceuticals with high added value at low cost (FOOD AND DRUG ADMNISTRATION, 2017; MEDICINE FOR ALL, 2022). Based on this background, the synthesis of five important *n*-substituted 5-benzylidenethiazolidine-2,4-dione derivatives (Fig. 1, Table 1) are compared in batch and flow processes.

Figure 1 - Scheme of synthesis of *n*-substituted 5-benzylidenethiazolidine-2,4-dione derivatives.

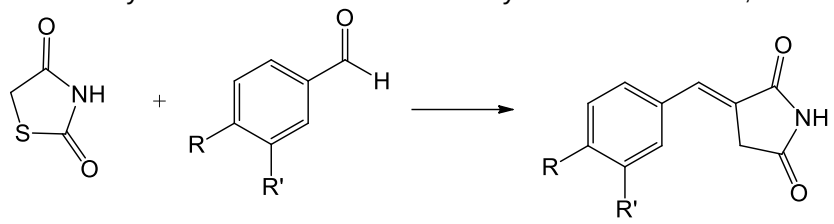


Table 1 - Aldehyde R and R' substituent

Compound	R	R’
1	H	H
2	OCH_3	H
3	NO_2	H
4	OH	OCH_3
5	OCH_3	OH

2 MATERIALS AND METHODS

2.1 CHEMICALS

Thiazolidine-2,4-dione (TZD) (90 %) was synthesized according to the method described by Pinheiro et al. 2018, whereas anisaldehyde (98 %), benzaldehyde (95%), p-nitrobenzaldehyde (98%), vaniline (97%), isovaniline (97%), pyrrolidine (99%) and acetonitrile (99.93%) were purchased from Sigma-Aldrich/Merck (Darmstadt, Germany); ethanol (99.8 %) and acetic acid (99.7%) were purchased from Labsynth (Diadema, SP, Brazil). All reagents and solvents were used without prior purification, whereas solutions for HPLC-UV analyses were prepared with deionized water (Direct-Q8 UV water-purification system, Millipore/ Merck, Darmstadt, Germany). The other solutions were prepared with water purified by using reverse osmosis (OS 10 LXE purifier, Gehaka, São Paulo, SP, Brazil).

2.2 EXPERIMENTAL SETUP

The micro reactor system was provided with a two-channel syringe pump, model Asia (Syrris, Royston, UK). Each channel had one 1.0 mL and one 0.5 mL syringe that continuously pumped the reaction medium through two 1.0 mL borosilicate glass micro reactors arranged in series, able to withstand a maximum pressure and temperature of 20 bar and 250°C, respectively. For heating was used

a Heater (Syrris, Royston, UK). The pressure was controlled through a Back-Pressure Regulator (Syrris, Royston, UK).

2.3 BATCH SYNTHESIS

The batch reaction was carried out according to Silva et al., 2019. TZD (4 mmol) and aldehyde (4 mmol) were dissolved in ethanol (60 mL), which corresponded to an equimolar concentration of 0.067 M. The system was heated to reflux and then pyrrolidine was added at the selected concentration. Samples were collected at 2, 4, 8, 12, 16, 20, 50, 80, 180, 330 and 480 min. The reaction was maintained at reflux for 8 h, and the reactant conversion and product yield were determined by using a HPLC-UV system (model Prominence 20AD, Shimadzu, Kyoto, Japan), equipped with a column (5 mm·25 cm; model Ascentis C18, Sigma-Aldrich/Merck). After 8 h, the crude product was crystallized with acetic acid (5 mL) and distilled water (60 mL) and then filtered under vacuum and finally recrystallized in ethanol.

2.4 FLOW SYNTHESIS

To perform the flow synthesis in flow, the same reaction medium composition and reactant concentration (0.067 M) as for the batch process were used. Two solutions were prepared in two flasks (A and B). In flask A, TZD (4 mmol) was completely solubilized in ethanol (30 mL), pyrrolidine was added at the selected concentration, and the solution was stirred again. In flask B, aldehyde (4 mmol) was added in ethanol (30 mL), and the resulting solution was stirred for 20 min. Both solutions were then pumped separately through the micro reactor. The reaction conversion was studied as a function of time, by varying the mean residence time (τ = reactor volume/total volumetric flow rate) from 2 to 20 min and the temperature from 78 to 160°C. The product was purified as for the batch process.

2.5 ANALYTICAL METHODS

The products were characterized by ^{1}H NMR spectroscopy (model Avance 300 MHz, Bruker, Billerica, MA, USA) and quantified by a high performance liquid chromatograph with ultraviolet detection (HPLC-UV), model Prominence 20AD

(Shimadzu), equipped with a TSKgel® ODS-100V C18 (25 cm x 4.6 mm, 3 µm, Sigma-Aldrich/Merck) column. All NMR spectrum is shown in Supporting Information.

2.6 COMPARISON BETWEEN BATCH AND CONTINUOUS PROCESSES

To compare the performance of the continuous process with that of the batch process, the number of parallel micro reactors, n_{MR}, required to reach a mean molar flow rate equal to that of the batch process was determined according to Eq. 1 (Pinheiro et al., 2018).

$$n_{MR} = \frac{\dot{m}_B}{\dot{m}_{MR}} \quad (1)$$

where $\dot{m}_B$ (mol.min^{-1}) is the mean molar flow rate in batch process and $\dot{m}_{MR}$ (mol.min^{-1}) is the molar flow rate in flow process and were calculated from Eqs. (2) and (3):

$$\dot{m}_B = C_F \frac{V_B}{t_B} \quad (2)$$

$$\dot{m}_{MR} = F \; x \; C_{out} \quad (3)$$

where C_F (mol L^{-1}) is the product molar concentration at the end of the batch process, V_B (mL) is the batch reactor volume, t_B (min) is the time duration of the batch process, F (mL min^{-1}) is the total volumetric flow rate of the continuous process in the micro reactor, and C_{out} (mol L^{-1}) is the outlet product molar concentration.

3 RESULTS AND DISCUSSION

3.1 BATCH SYNTHESIS OF N-SUBSTITUTED 5-BENZYLIDENETHIAZOLIDINE-2,4-DIONE

The synthesis of *n*-substituted 5-benzylidenethiazolidine-2,4-dione in batch has previously been reported by other authors (BRUNO et al., 2002; MISHRA; SACHAN; CHAWLA, 2015), whom reported reaction times from 16 to 24 h. Our research group recently reported this reaction with two different substituents of the

aromatic ring in the aldehyde, which was observed the mean reaction time of 8 h using piperidine as promoting base. For this study, another base, pyrrolidine, a cyclic secondary amine exhibited better results than piperidine that compared to piperidine, reduced the reaction time drastically (8 h in piperidine for 2 h in pyrrolidine, on average). In addition, batch reactions were performed to verify solid formation in the reaction medium, since clogging may occur and obstruct and damage the micro channels chip in continuous flow synthesis.

Batch reactions were performed with 0.026, 0.033 and 0.040 M of pyrrolidine in ethanol at reflux for 480 min. Table 2 shows the product yield and their corresponding reaction time to reach maximum product yield ($Y_{p,max}$) for compounds **1** to **5**.

Table 2 – Maximum product yield (Y_{max}) of five *n*-substituted 5-benzylidenethiazolidine-2,4-dione in batch process by varying pyrrolidine concentration, $C_{pyrrolidine}$ = 0.026, 0.033 and 0.040 M.

$C_{pyrrolidine}$ (M)	Compound	R	R'	*t* (min)	$Y_{p,max}$ (%)
0.026	**1**	H	H	70	70.6 ± 7.7
	2	OCH_3	H	50	96.4 ± 0.0
	3	NO_2	H	180	46.2 ± 2.3
	4	OH	OCH_3	180	97.0 ± 2.7
	5	OCH_3	OH	70	69.4 ± 14.5
0.033	**1**	H	H	100	99.0 ± 0.0
	2	OCH_3	H	50	100.0 ± 4.3
	3	NO_2	H	180	43.7 ± 2.9
	4	OH	OCH_3	180	94.0 ± 0.7
	5	OCH_3	OH	70	72.5 ± 5.7
0.040	**1**	H	H	16	98.3 ± 0.9
	2	OCH_3	H	100	100,0 ± 6.3
	3	NO_2	H	330	48.6 ± 5.5
	4	OH	OCH_3	180	94.4 ± 2.9
	5	OCH_3	OH	100	95.2 ± 3.0

Increasing of pyrrolidine concentration was essential to obtain higher yields in less time for compound **1**, whereas for compound **2** and **3** the increase of the concentration of pyrrolidine to 0,040 M reduced the yield. Compound **4** was not significantly influenced by pyrrolidine concentration, considering that the average yield was ± 95.0% in 180 min of reaction. The reaction yield increased with pyrrolidine concentration, however, for compound **5** in 0,040 M the reaction time was bigger than for 0.026 and 0.033 M pyrrolidine concentration.

The results in Table 1 show that when the substituent on the aromatic ring is an activating group the reaction achieves higher yields, in some cases 100%. However, the lowest value of product yield was with the aromatic ring substituent

being the most deactivating group (NO_2, compound **3**), and even maintaining the reaction up to 13 h the yield did not increase significantly (results not shown). In this case, it is also noted that catalyst concentration did not influence the product yield.

Continuing the study of transposition to flow synthesis in the micro reactor, we followed with the concentration of 0.033 M, for which, in average, were obtained the higher product yields in shorter reaction time.

3.2 SYNTHESIS OF *N*-SUBSTITUTED 5-BENZYLIDENETHIAZOLIDINE-2,4-DIONE IN CONTINUOUS FLOW MICRO REACTOR

After establishing the optimum pyrrolidine concentration in batch synthesis, the next step was to investigate the *Knoevenagel* condensation in capillary micro reactors, which allowed working at temperatures above the boiling point of ethanol, maintaining the liquid state, due to pressures above the atmospheric pressure. It was possible to explore the behavior of the flow reaction and verify the influence of the mean residence time (τ) and temperature (T) on the product yield.

For continuous flow synthesis in micro reactor, τ was varied between 2 and 20 min and the temperature (T) between 78 and 160°C. Figure 2 shows the product yield as a function of T and τ for all compounds, and Table 3 summarizes the best conditions of continuous flow synthesis for each derivative in terms of T, τ and maximum yield $Y_{p,max}$. Increasing of T and τ favored product formation of the five aldehydes studied. In addition, the increase of T favored product formation at shorter residence time (2, 4 and 8 min), but negligible influence was observed for residence time higher than 12 min. The same tendency was observed for $T >$ 120°C to the 5 compounds studied, showing that the reaction reaches its limit around 120°C. We also observed that in some cases the product yield decreased for T = 160°C. It is possible that, for higher temperatures, consecutive reactions or degradation were favored, which will be confirmed later (Sect. 3.4).

Figure 2 – Yield (Y_p) of five *n*-substituted 5-benzylidenethiazolidine-2,4-dione in continuous flow micro reactor by varying temperature (78, 100, 120, 140 and 160°C) and residence time (2, 4, 8, 12, 16 and 20 min). 2A) Benzaldehyde **1**; 2B) Anisaldehyde **2**; 2C) *p*-Nitrobenzaldehyde **3**; 2D) Vaniline **4**; 2E) Isovaniline **5**.

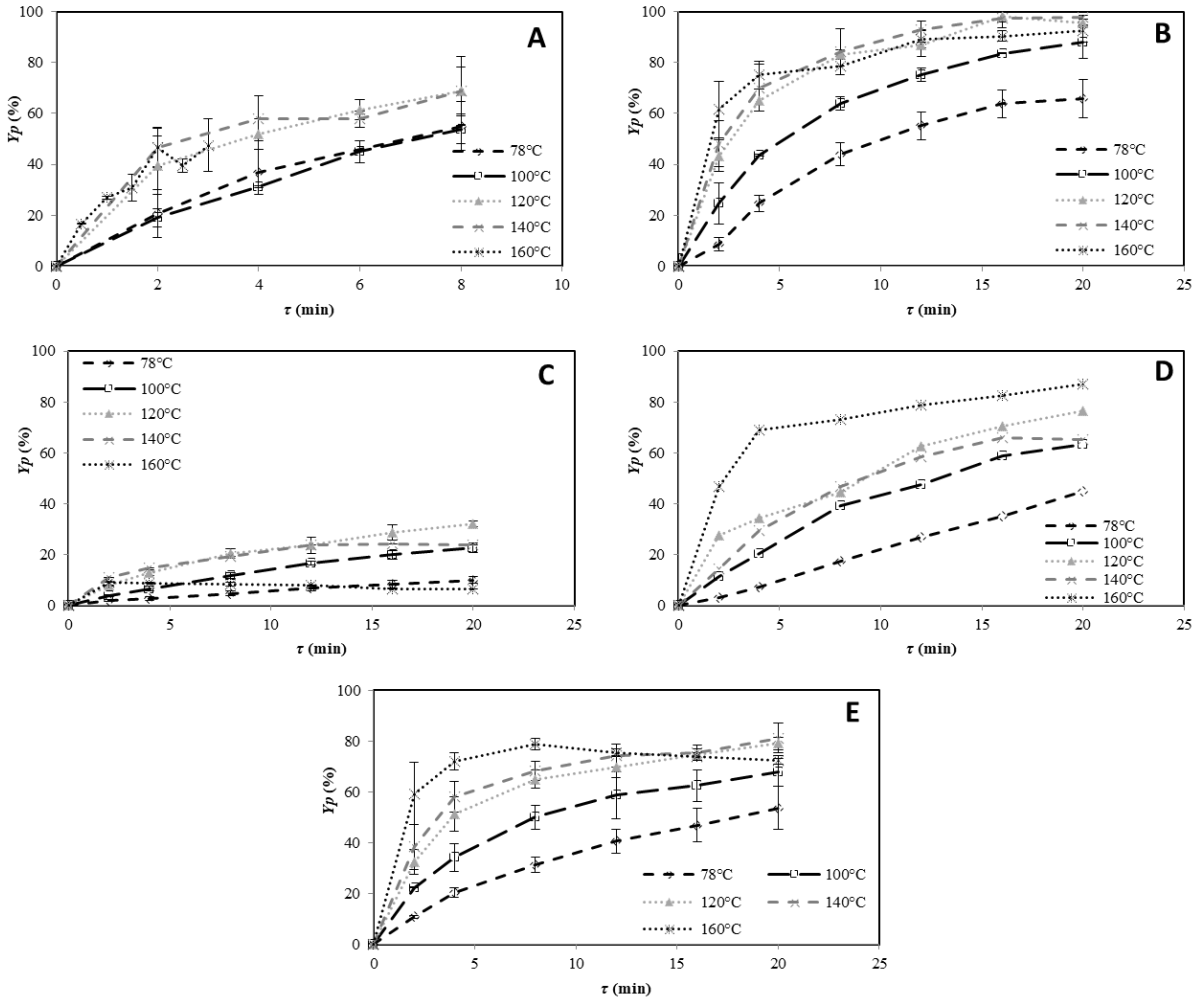


Table 3 – Maximum yield ($Y_{p,max}$) obtained in flow synthesis of *n*-substituted 5-benzylidenethiazolidine-2,4-dione derivatives

Compound	T (°C)	τ (min)	$Y_{p,max}$ (%)
1	120	8	70 ± 3,9
2	140	16	97 ± 0,1
3	120	20	32 ± 1,0
4	160	20	87 ± 3,2
5	140	20	81 ± 2,0

In flow synthesis of compound **1,** we observed that for $T \geq 100$°C and $\tau > 10$ min the product crystallized inside the reactor, what could be caused by high product concentration, and low solubility, or insoluble degradation products. In this case, we had to be careful when increasing temperature and residence time to not clogging the micro reactor. By this reason, we had to maintain $\tau < 10$ min. We observed that the yield increased slightly for temperatures higher than 120°C.

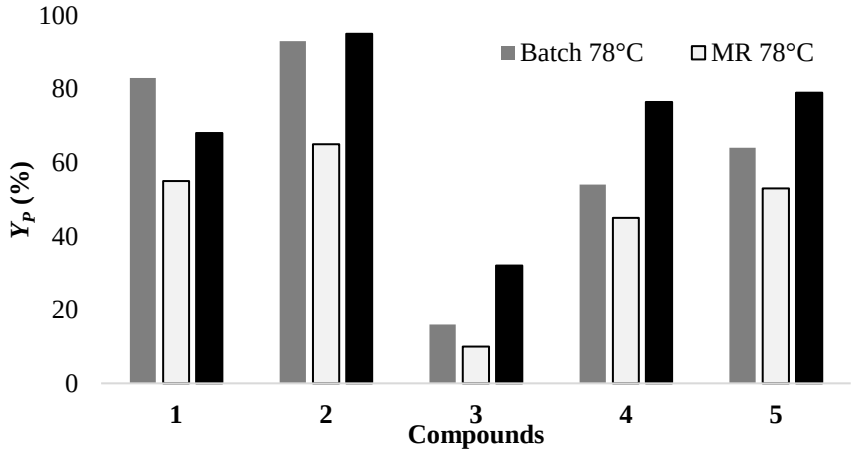
The highest yield was 68.9% at 120°C and τ = 8 min. We observed that the highest yield for compound **3** (32.0%) was obtained at 120°C and 20 min. Also we observed low yields for aldehyde having deactivating group (NO_2^-, compound **3**) also for flow synthesis, even with higher temperatures. We also observed yield decrease for 140°C and 160°C, probably due to consecutive reactions or product degradation.

3.3 COMPARISON OF BATCH AND FLOW PROCESSES

Figure 3 shows the results of product yield for batch and continuous flow of the tested derivatives. For comparison the batch tests were performed at the boiling point of solvent and the yield determined for 20 min reaction time, while for flow synthesis, T = 120°C and mean residence time τ = 20 min.

When compared for the same conditions, batch presented higher yields than for flow synthesis for all derivatives, since the half-life time ($t_{1/2}$ > 10 min), what means the reaction is controlled by kinetic rather than diffusion (ROBERGE et al., 2005). However, this type of reaction is advantageous in continuous flow microreator, considering that at 120°C the yield of product is higher in 20 min for compounds **2**, **3**, **4** and **5**.

Figure 3 - Comparison of yields of five *n*-substituted 5-benzylidenethiazolidine-2,4-dione in batch and flow processes (compound **1** (τ = 8 min); compound **2** (τ = 20 min); compound **3** (τ = 20 min); compound **4** (τ = 20 min); compound **5** (τ = 20 min); MR = micro reactor



Using the experimental results obtained for the batch and flow processes, it was determined the number of micro reactors in parallel (n_{MR}) necessary to have the same mean molar flow rate of a batch reactor operating under standard

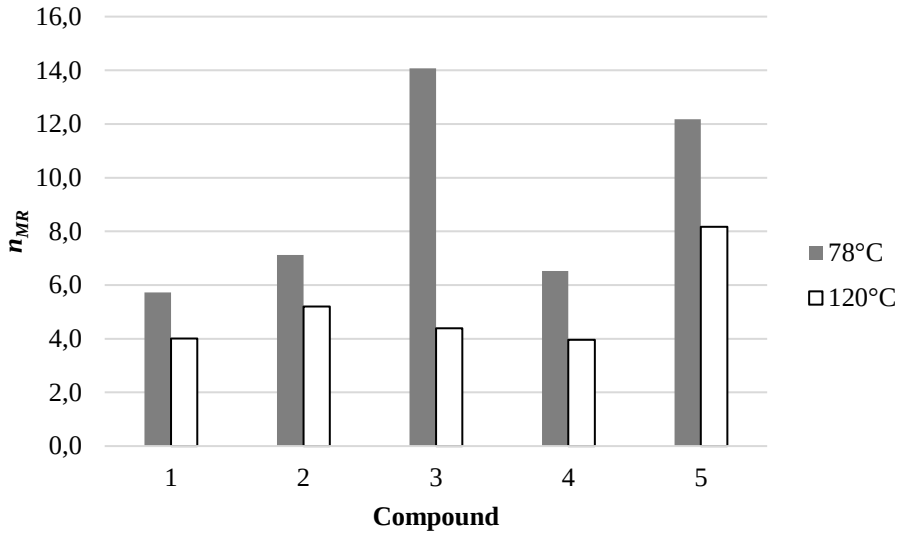
conditions (V = 60 mL, reaction time = 480 min, for the same product and synthesis protocol) (PINHEIRO et al., 2018)

For this purpose, the reaction time was fixed in the batch process, for which the stabilization of the product yield was observed, 100, 180, 180, 180, 70 min for compounds **1**, **2**, **3**, **4** and **5**, respectively. The mean residence time was also fixed (τ = 20 min) for all compounds **1**, **2**, **3**, **4** and **5** and temperatures 120, 140, 120, 160, and 140°C, respectively, for which the highest yields were obtained (Table 3).

For compound **1** the mean residence time was set at 8 min due to microchannel clogging in the microchannel at $T \geq 100$°C, as mentioned above.

Figure 4 shows that the number of micro reactors in parallel, n_{MR}, decreased with increasing temperature, due to the increase in product yield. At 78°C, the number of equivalent micro reactors was 5.7, 7.1, 14.1, 6.5 and 12.2 for products **1**, **2**, **3**, **4** and **5**, respectively. While at 120°C, n_{MR} = 4.0, 5.2, 4.4, 4.0 and 8.2, respectively. The equivalent number of microreactors also gives an idea of the increase in molar production in the flow process.

Figure 4 - Effect of temperature (T) on the number of parallel micro reactors (n_{MR}).
Operational condition: V_{MR} = 2.0 mL, V_{Batch} = 60 mL, time of reaction in the batch = 120min.
Mean residence time: Compound **1** (8 min), **2** (20 min), **3** (20 min), **4** (20 min),**5** (20 min)



3.4 KINETIC AND THERMODYNAMIC PARAMETERS

Micro reactors are especially useful to determine the kinetics of chemical reactions, since they allow operating at very short residence times in a safe and reproductive way under steady-state conditions (JENSEN, 2017). With this aim in

mind, the first-and second-order kinetic models were tested, the latter being the one that showed the best fit to the experimental data (Table 4). For the first time for these reactions, the activation energy (*Ea*) was estimated by the Arrhenius model and the activation enthalpy (ΔH^+), entropy (ΔS^+), and Gibbs free energy (ΔG^+) (Table 4) by the Eyring model (Eq. 4), for the Transition State (HILL; ROOT, 2014):

$$k = \frac{k_B T_k}{h} e^{\Delta S^+/RT_k} e^{-\Delta H^+/RT_k} \quad (4)$$

Where, *k* is the reaction rate constant, k_B is the Boltzmann constant, *h* is the Planck constant, *R* the ideal gas constant, and T_k the absolute temperature.

Table 4 summarizes the results of Kinetic and thermodynamic parameters obtained in batch and flow processes.

Table 4 - Second-order rate constant (*k*), activation energy (*Ea*), enthalpy (ΔH^+), entropy (ΔS^+), and Gibbs free energy (ΔG^+) estimated for the synthesis of compounds **1, 2, 3, 4** and **5.** Equimolar concentrations of TZD and aldehydes = 0.067M.

Compound	Parameter	Batch	Continuous flow micro reactor				
		78°C	78°C	100°C	120°C	140°C	160°C
1	*k* x 10^2 (M^{-1} s^{-1})	6.16	2.53	4.42	7.20	7.20	10.3
	Ea x 10^3 (kcal mol^{-1}) [a]		4.91				
	ΔH^+ x 10^3 (kcal mol^{-1}) [b]		4.13				
	ΔS^+ x 10^3 (kcal mol^{-1} K^{-1}) [b]		-46.4				
	ΔG^+ x 10^3 (kcal mol^{-1}) [c]		20.4	21.3	22.4	23.3	24.2
2	*k* x 10^2 (M^{-1} s^{-1})	3.73	1.77	3.64	6.30	19.0	13.4
	Ea[a] x 10^3 (kcal mol^{-1}) [a]		8.46				
	ΔH^+ x 10^3 (kcal mol^{-1}) [b]		7.69				
	ΔS^+ x 10^3 (kcal mol^{-1} K^{-1}) [b]		-46.9				
	ΔG^+ x 10^3 (kcal mol^{-1}) [c]		24.2	25.1	26.1	27.1	28.0
3	*k* x 10^2 (M^{-1} s^{-1})	0.48	0.39	0.56	0.61	1.00	0.92
	Ea[a] x 10^3 (kcal mol^{-1}) [a]		3.99				
	ΔH^+ x 10^3 (kcal mol^{-1}) [b]		3.23				
	ΔS^+ x 10^3 (kcal mol^{-1} K^{-1}) [b]		-48.8				
	ΔG^+ x 10^3 (kcal mol^{-1}) [c]		20.4	21.3	22.4	23.4	24.4
4	*k* x 10^2 (M^{-1} s^{-1})	2.17	1.54	5.85	8.03	8.62	20.5
	Ea[a] x 10^3 (kcal mol^{-1}) [a]		8.24				
	ΔH^+ x 10^3 (kcal mol^{-1}) [b]		7.47				
	ΔS^+ x 10^3 (kcal mol^{-1} K^{-1}) [b]		-47.0				
	ΔG^+ x 10^3 (kcal mol^{-1}) [c]		24.0	24.9	25.9	26.9	27.8
5	*k* x 10^2 (M^{-1} s^{-1})	2.90	1.77	3.49	5.44	8.00	14.7
	Ea[a] x 10^3 (kcal mol^{-1}) [a]		7.42				
	ΔH^+ x 10^3 (kcal mol^{-1}) [b]		6.64				
	ΔS^+ x 10^3 (kcal mol^{-1} K^{-1}) [b]		-47.1				
	ΔG^+ x 10^3 (kcal mol^{-1}) [c]		23.2	24.1	25.1	26.1	27.0

a) Value estimated by the Arrhenius model; b) values estimated by the Eyring model; c) values estimated by the equation $\Delta G^+ = \Delta H^+ - T\Delta S^+$

Table 4 shows that in batch, the rate constant, *k*, for compound **3** is on average 7.7 times smaller than that for **1**, **2**, **4** and **5**, probably due to the ring substituent NO_2. All rate constant in batch at 78°C are larger than in continuous flow micro reactor at 78°C and this is due to the reaction, that is slow ($t_{1/2}$ > 10 min), as explained in Sect. 3.3. In the flow process, the higher temperatures enhance *k*, which explains the higher values of product yield.

At temperatures where a drop in yield is observed, a reduction in the values of the rate constant is also observed (compound **2** and **3** at 160°C).

The values of ΔH^+ represent enthalpy related to the transition state. All values of ΔH^+ are positive which indicates that the enthalpy in the transition state is greater than that of the starting reagents and that the increase of the temperature, implying a higher energy supply, enhance the formation of the activated complex and consequent consumption of TZD and aldehyde.

With regard to the values of ΔS^+, the same values were obtained for all solvents, as expected for bimolecular reactions that form only a single molecule. The entropy variation in the transition state was negative, since before dehydration there occurs the formation of an adduct, with TZD and aldehyde combining to a single molecule (SILVA et al., 2019).

The ΔG^+ values show the same order of magnitude for all aldehydes, which was expected due to reaction mechanism. The fact that the values are positive indicates that the equilibrium constant of the transition state is very small, which is expected, indicating the spontaneity of the reaction, justifying the need for a promoter base.

4 CONCLUSION

Micro reactor technology was applied to synthesize five *n*-substituted 5-benzylidenethiazolidine-2,4-dione. First, we investigated the reaction in batch in terms of reaction time and base concentration. With the results in batch we transposed the synthesis of all five n-substituted 5-benzylidenethiazolidine-2,4-dione to continuous flow, varying residence time and temperatures. At 78°C batch process presented higher yields in shorter reaction time than in continuous flow. However, increasing the temperature up to 120°C in flow conditions higher yields

were obtained for all tested compounds.

The comparison of the batch process with the flow process in the synthesis of compound **4**, showed that 4 micro reactors, with a volume of 2 mL, operating in parallel, at a temperature of 120°C, could have the same molar production of a batch reactor, with a volume of 60 mL at 78°C.

This study was concluded with the determination of kinetic and thermodynamic parameters. This investigation can go on further to a complete multi step synthesis of APIs with the TZD pharmacophore group. In conclusion capillary continuous flow micro reactors showed suitable to run *Knoevenagel* condensation reactions.

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Highlights

-Use of pyrrolidine as base in the synthesis of *n*-substituted 5-benzylidenethiazolidine-2,4-dione;
-Transposition of *Knoevenagel* condensation from batch to flow process;
-Comparison of the synthesis of five *n*-substituted 5-benzylidenethiazolidine-2,4-dione derivatives in batch and flow
-Equivalence of batch/flow processes
-First-time evaluation of kinetics and thermodynamics parameters of these synthesis

Nomenclature:

Y: Yield

Y_{max} = Maximum Yield

n_{MR} [–]: Number of parallel micro reactors

C_F [M]: Final product concentration of the batch process

V_B [L]: Volume of batch reactor

t_B [min]: Time duration of the batch process

F [mL min^{-1}]: Total volumetric flow rate

C_{out} [M]: outlet product concentration in the micro reactor

τ: Mean residence time

k: Reaction rate constant

k_B*:* Boltzmann constant

h: Planck constant

R: ideal gas constant

Tk: the absolute temperature

Abbreviation:

API: Active Pharmaceutical Ingredient

MR: Micro reactor

TZD: thiazolidine-2,4-dione

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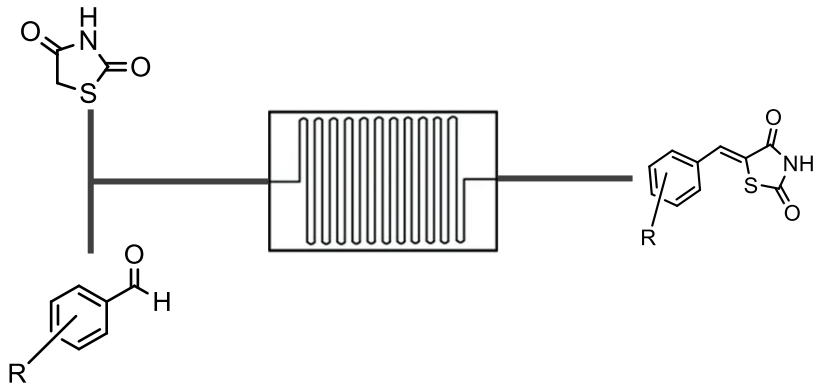
GRAPHICAL ABSTRACT



APPENDIX A: RESIDENCE TIME

Residence time (τ) is given by Eq (A.1):

$$\tau = \frac{Q}{D} \quad \text{(A.1)}$$

Where *Q* is flow rate and *D* is the diameter of microchannels.