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Continuous flow synthesis of some 6- and 1,6-substituted 3-cyano-4-methyl-2-pyridones

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Abstract: In this study, six 6- and 1,6-substituted-3-cyano-4-methyl-2-pyridones were synthesized in a continuous flow microreactor system. The syntheses were realized at room temperature and the obtained results were compared to those achieved within classical syntheses. In order to optimize the continuous flow syntheses and increase the yield of the products, the retention time in the microreactor was varied by changing the flow rates of the reactant solutions. Furthermore, the reaction was optimized for 3-cyano-4,6-dimethyl-2--pyridone and 3-cyano-6-hydroxy-4-methyl-2-pyridone, which are comercially important in the pharmaceutical and dye industries. Both 2-pyridones were obtained in satisfactory yield of *circa* 60 % in less than 10 min. The resulting compounds were characterized by their melting points, FT-IR, ^{1}H-NMR and UV–Vis spectra. The efficiency of the presented method for the synthesis of 2-pyridone-based molecules has promising potential for industrial production.

Keywords: microreactor; 2-pyridone; batch; flow synthesis; process intensification.

INTRODUCTION

The continuous flow method has gained much attention in the field of organic synthesis.[1,2] On the laboratory scale, a reaction in continuous flow is typically run in a capillary microreactor, which represents the mixing and reacting components of the continuous flow assembly.[3] The specific characteristics of a microreactor are more efficient mass and heat transfers because of the large surface to volume ratio, which allows improved productivity with respect to a batch system.[4,5] Furthermore, automated process control and facilitated

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scale-up reduce the costs and time needed to transfer the process from the laboratory to the industrial level.[6]

In the pharmaceutical industry, 3-cyano-2-pyridone and its derivatives are significant final products and intermediates in the synthesis of complex biologically active compounds.

More specifically, the 2-pyridone structure can be found in various pharmaceutical products mentioned hereafter.[7] Commercially important cardiotonics used for the therapy of heart failure, milrinone and amrinone, possess a 2-pyridone core.[8] Antibiotics based on the 2-pyridone moiety (*e.g.*, pilicides) could be applied in the treatment of bacterial infections caused by Gram-negative bacteria.[9] The 2-pyridone core has a significant role in the industrial production of disperse azo dyes.[10,11] Moreover, recent studies have shown that azo dyes could be synthesized in a continuous flow microreactor system, in high yields, indicating that this technology has great potential in organic synthesis.[12]

Due to strong biological activity and wide commercial application in industry, the synthesis of 2-pyridone and its derivatives have been widely investigated.[7] The general procedure for obtaining substituted 3-cyano-2-pyridones is in a condensation reaction of 1,3-dicarbonyl compounds with cyanoacetamide in the presence of various catalysts, typically in polar solvents, and external heating.[7] The syntheses of these molecules were mostly studied in a classical batch system and under a microwave assisted method under different reaction conditions.[13,14] Microwave-assisted synthesis provides outstanding results in terms of yield and purity of the desired product,[13] but the deficiencies of this method are difficulty in scale-up and transition into an industrial level of production. Furthermore, traditional and microwave-assisted syntheses of 2-pyridone-based molecules include heating of the reaction mixture, either by conventional heating (*e.g.*, oil or water bath) or microwave heating. Altogether, the disadvantages of the classical synthetic method, such as the application of high temperature, prolonged reaction time, complicated process control and additional solvent consumption for purification of the final product, could be overcome by using a microreactor assembly where the synthesis is performed at the room temperature and the products are obtained in a relatively short period in satisfactory yield.

In this paper, a novel approach to the synthesis of six 6- and 1,6-substituted 3-cyano-4-methyl-2-pyridones was realized in a continuous flow system at room temperature. The obtained results were compared in terms of yields and reaction times to those achieved in a batch system. More specifically, the synthesis was optimized for derivatives **1** and **2**, which were obtained in good yields of *circa* 60 % in less than 10 min. The chemical structure and purity of the resulting products were confirmed by their melting points, and FT-IR, ^{1}H-NMR and UV–Vis data.

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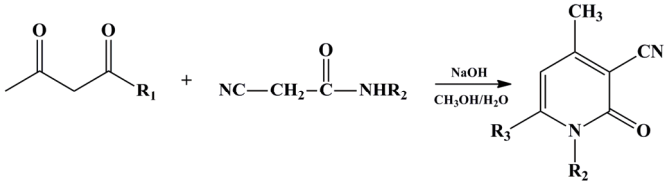
EXPERIMENTAL

General

All starting materials were obtained from Merck or Fluka, and were used without further purification. The synthesis of six 6- and 1,6-substituted 3-cyano-4-methyl-2-pyridones was performed in a continuous flow system, at the room temperature, and in a batch system (using heating and stirring). In the continuous flow, 6- and 1,6-substituted 3-cyano-4-methyl-2-pyridones were obtained from the corresponding 1,3-dicarbonyl reagents and *N*-substituted cyanoacetamides, using NaOH as a catalyst, in a methanol/water mixture (Scheme 1). In the batch system, the same six 2-pyridones were synthesized according to modified literature procedures;[13] details are given in the Supplementary material to this paper. The efficiency of the continuous flow assembly was investigated by comparing reaction times and yields of the resultant products to those of the classical method of synthesis.



Compound	R_1	R_2	R_3
1	CH_3	H	CH_3
2	OCH_2CH_3	H	OH
3	CH_3	CH_2CH_2OH	CH_3
4	OCH_2CH_3	CH_2CH_2OH	OH
5	CH_3	$CH_2CH_2CH_3$	CH_3
6	OCH_2CH_3	$CH_2CH_2CH_3$	OH

Scheme 1. The synthetic path for the preparation of 6- and 1,6-substituted 3-cyano-4-methyl-2-pyridones in the continuous flow system.

The chemical structure and the purity of the obtained compounds were confirmed by melting points, and FT-IR, ^{1}H-NMR and UV–Vis spectral data. The melting points were determined in capillary tubes on an automated melting point system Stuart SMP30. The FT-IR spectra were recorded on a Bomem MB-Series FT-IR spectrophotometer, in the form of KBr pellets. The ^{1}H-NMR spectral measurements were performed on a Bruker Ascend 400 instrument at 400 MHz. The spectra were recorded at room temperature in DMSO-d_6. The chemical shifts are expressed in ppm values referenced to TMS. The UV–Vis absorption spectra were recorded on a Shimadzu UV–Vis 1700 spectrophotometer in the region 200–600 nm at a concentration 5×10^{-5} mol·L^{-1}. The resulting data are given in the Supplementary material and are in accordance with those known from the literature.

The set-up of the continuous flow microreactor assembly

The continuous flow microreactor assembly consisted of three pumps (LC-20AD XR, Shimadzu Manufacturing Inc., USA), two T-shaped mixers and a PEEK (polyether ether ketone) capillary microreactor (inner diameter 0.5 mm, volume 5 mL, length 25 m), shown in Fig. 1.

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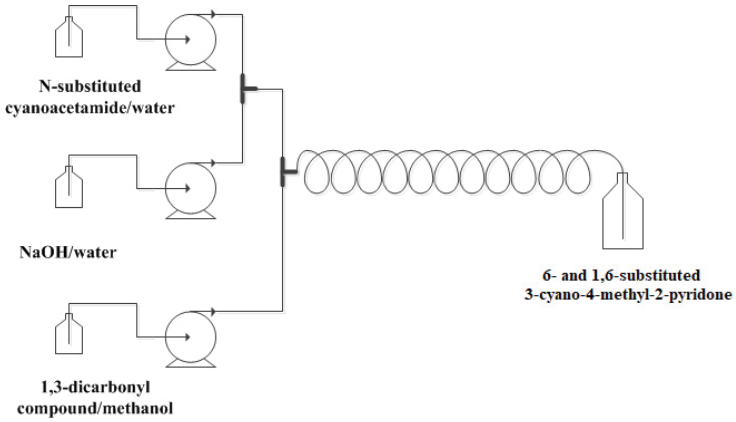

Fig. 1. The microreactor assembly.

Water solutions of the corresponding *N*-substituted cyanoacetamide and NaOH were introduced into the first mixer. The resulting mixture was passed to the second mixer where a solution of a 1,3-dicarbonyl compound in methanol was added. The final mixture was delivered to the PEEK capillary microreactor to conduct the 2-pyridone condensation reaction (Scheme 1). The following reaction was inhibited by concentrated HCl in the receiving test tube at the output of the capillary microreactor. In order to obtain higher yields, the residence time in microreactor was adjusted by changing the flow ratios. The reaction was performed at room temperature. The preparation of the reactant solutions for synthesis in the continuous flow microreactor system and the work-up of reaction mixture are given in the Supplementary material.

Two sets of experiments were performed. The first set of experiments was conducted using equimolar concentrations of *N*-substituted cyanoacetamide and 1,3-dicarbonyl compound solutions. In the second part of the experiment, the reaction of condensation was further optimized for compounds **1** and **2** by changing mole ratios and concentrations of the starting reactants.

RESULTS AND DISCUSSION

In the first set of experiments, six 6- and 1,6-substituted 3-cyano-4-methyl-2--pyridones were synthesized from 1,3-dicarbonyl reagent (DCR) and the corresponding *N*-substituted cyanoacetamide (CAA, equimolar concentration, 0.6 $mol \cdot L^{-1}$) in the continuous flow microreactor system. Sodium hydroxide solution was used as a catalyst (0.7 $mol \cdot L^{-1}$), and the synthesis was performed at the room temperature, as previously described. In order to improve the yield of the products, the flow rates of the starting reactants were varied. Comparatively, the same 2-pyridones were synthesized in the batch system (using reflux and stirring) and the obtained results are given in Table I.

As indicated in Table I, all the products were prepared starting from the total flow rate of the reaction mixture of 0.06 $mL \cdot min^{-1}$ except in the synthesis of compound **1**. The use of this flow rate to produce compound **1**, caused clogging of the capillary microreactor, induced by long residence time of the reaction

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mixture in the continuous flow system. Thus, the starting flow rate in the synthesis of compound **1** was 0.3 mL·min^{-1}. Furthermore, the increase of the flow rate generally led to a decrease of the yield, except in the case of compound **1** where increasing of the flow rate from 0.3 mL to 0.6 mL·min^{-1} led to increased yield. Increasing the flow rate decreased the residence time in the microreactor and gives lower yields.

TABLE I. The optimization of the flow rate in first set of experiments and yields obtained in the batch system

Compound	Continuous flow system						Batch system	
	F (DCR)[a] mL·min^{-1} c = 0.6 mol·L^{-1}	F (CAA)[b] mL·min^{-1} c = 0.6 mol·L^{-1}	F (NaOH)[c] mL·min^{-1} c = 0.7 mol·L^{-1}	F_t[d] mL·min^{-1}	t[e] min	Y[f] %	t[g] min	Y[h] %
1	0.1	0.1	0.1	0.3	16.3	50	60	60
1	0.2	0.2	0.2	0.6	8.2	59		
1	0.3	0.3	0.3	0.9	5.4	42		
1	0.4	0.4	0.4	1.2	4.1	42		
2	0.02	0.02	0.02	0.06	81.7	22	480	61
2	0.03	0.03	0.03	0.09	54.4	10		
3	0.02	0.02	0.02	0.06	81.7	30	240	60
3	0.03	0.03	0.03	0.09	54.4	30		
4	0.02	0.02	0.02	0.06	81.7	6	480	59
5	0.02	0.02	0.02	0.06	81.7	25.5	240	40
5	0.03	0.03	0.03	0.09	54.4	20		
6	0.02	0.02	0.02	0.06	81.7	2	480	31

[a]Flow rate of 1,3-dicarbonyl compound solution; [b] flow rate of *N*-substituted cyanoacetamide solution; [c] flow rate of sodium hydroxide solution; [d] total flow rate of the reacting mixture; [e]residence time in the microreactor; [f]obtained yield in the continuous flow system; [g]reaction time in the batch system; [h]obtained yield in the batch system

However, the results obtained from the synthesis of *N*-substituted 3-cyano-4--methyl-2-pyridones under continuous flow synthesis (Table I) indicated that this method is not convenient for the synthesis of these molecules. Mijin *et al.*[13] reported the synthesis of different *N*-substituted 3-cyano-4,6-dimethyl-2-pyridones using a microwave-assisted method. The results obtained under microwave method have shown that is possible to obtain these products in very short reaction time (7 min) and high yield. Therefore, it could be concluded that the microwave-assisted synthesis of *N*-substituted 2-pyridones is more efficient than the flow method. The synthesis in the continuous flow system was slower because it was performed at the room temperature, in comparison to the microwave method where the higher applied temperatures (and higher consumption of energy) increase the reaction rate, thus leading to good yields in a shorter reaction time.

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On the other hand, the flow synthesis acquired compound **1** in the good yield in a very short reaction time (60 %, 8.2 min, room temperature) in comparison to the classical method (60 %, 60 min, reflux) and thus, the synthesis of compound **1** was further optimized. Furthermore, the synthesis of compound **2** did not result in the satisfactory level of conversion in the first set of experiments, but taking into account the commercial significance of this molecule in the production of various dyes,[7] further investigation of its synthesis in the continuous flow system was also undertaken.

The concentration of the starting materials for the synthesis of compounds **1** and **2** was increased, and the mole ratios were changed at the same flow rates of each starting compound. The mole ratios of acetylacetone or ethyl acetoacetate (1.0 mol·L^{-1}), cyanoacetamide (1.5 mol·L^{-1}) and NaOH (2.0 mol·L^{-1}) were set at 1:1.5:2, respectively.

TABLE II. The optimization of the flow rate in the synthesis of 3-cyano-4,6-dimethyl-2-pyridone (**1**) and 3-cyano-6-hydroxy-4-methyl-2-pyridone (**2**)

F (acetylacetone/ethyl acetoacetate)[a] / mL·min^{-1} c = 1.0 mol·L^{-1}	F (cyanoacetamide)[b] mL·min^{-1} c = 1.5 mol·L^{-1}	F (NaOH)[c] mL·min^{-1} c = 2.0 mol·L^{-1}	F_t[d] mL·min^{-1}	t[e] min	Y (**1**/**2**)[f] %
0.1	0.1	0.1	0.3	16.3	60/59
0.2	0.2	0.2	0.6	8.2	61/59
0.3	0.3	0.3	0.9	5.4	61/52
0.4	0.4	0.4	1.2	4.1	59/45

[a]Flow rate of acetylacetone or ethyl acetoacetate solution; [b]flow rate of cyanoacetamide solution; [c]flow rate of sodium hydroxide solution; [d]total flow rate of reaction mixture; [e]residence time in the microreactor; [f]obtained yield of compound **1** or **2**

By comparing the results shown in Tables I and II, it could be concluded that the increase in concentration in the synthesis of compound **1** did not significantly affect an increase in the yield. On the contrary, when the optimization of compound **2** was performed, the change in the molar concentration and the ratios of ethyl acetoacetate, cyanoacetamide and NaOH led to an increase of the yield, as shown in Table II. Moreover, by comparing the yields of compound **2** obtained in the continuous flow system with those derived under conventional conditions (reflux, 480 minutes), it is evident that the former method acquired higher yields in a shorter reaction time, 59 % in 8.2 min in comparison to 61 % in 480 minutes, respectively.

CONCLUSIONS

Six different 2-pyridones were obtained under continuous flow synthesis. Compared to the conventional method, the use of the particularly controlled continuous flow assembly allowed fast and effective preparation of compounds **1** and **2**. The main advantage of this system is that the reaction was realized at

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room temperature within a relatively short reaction time. Optimization of the novel method for compounds **1** and **2** resulted in good yields (61 % yield in 5.4 min for compound **1** and 59 % yield in 8.2 min for compound **2**). Improved process control was enabled by managing the automated flow, which allows for changes in the flow ratio of the starting solutions in the system, during the synthesis. Another advantage of the microreactor system compared to the batch method is the energy efficiency of the former, since the reaction was performed at room temperature. The continuous flow synthesis is a safe method, because the reaction occurs in a closed system and contact with potentially dangerous substances is minimized. Additionally, scale up and the transition from a laboratory to an industrial level are facilitated, unlike in batch systems. Thus, the presented method for the synthesis of 2-pyridone-based compounds has promising potential in the process industry. However, the level of conversion of *N*-substituted 4-methyl-3-cyano-2-pyridones was low, which led to the conclusion that this method is not suitable for the synthesis of these compounds.

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ИЗВОД

СИНТЕЗА 6- И 1,6-СУПСТИТУИСАНИХ 3-ЦИЈАНО-4-МЕТИЛ-2-ПИРИДОНА МЕТОДОМ КОНТИНУАЛНОГ ПРОТОКА

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У овом раду приказана је синтеза шест 6- и 1,6-супституисаних 3-цијано-4-метил-2-пиридона употребом микрореактора за континуалну синтезу. Синтеза је извршена на собној температури и добијени резултати су упоређени са резултатима добијеним класичним поступком. У циљу оптимизације поступка синтезе континуалним протоком и повећања приноса производа, мењано је ретенционо време у микрореактору променом протока раствора реактаната. Такође, оптимизована је реакција добијања 3-цијано-4,6-диметил-2-пиридона и 3-цијано-6-хидрокси-4-метил-2-пиридона који су комерцијално важни за фармацеутску индустрију и производњу боја. Оба 2-пиридона су добијена у задовољавајућем приносу од око 60 % за мање од 10 min. Синтетисана једињења су окарактерисана тачком топљења, FT-IR, ^{1}H-NMR и UV–Vis спектрима. Ефикасност развијеног поступка има добар потенцијал за индустријску примену.

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