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A novel micro-flow system under microwave irradiation for continuous synthesis of 1,4-dihydropyridines in the absence of solvents via Hantzsch reaction

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ABSTRACT

γ-Fe_2O_3 nanoparticles were synthesized in the valve-assisted micromixer. The resulting nanoparticles were characterized by X-ray diffraction (XRD), transmission electron microscopy (TEM). In the packed bed flow reactor, the investigation concerning the comparison of different heating methods demonstrated that microwave irradiation displayed the best reaction efficiency compared with air heating and oil-bath heating. A novel micro-flow system under microwave irradiation was designed and employed in the condensation of aldehyde, ethyl acetoacetate and ammonia. Under optimized conditions, Hantzsch reaction conducted well, resulting in a yield of 98.7% and excellent selectivity. In addition, this novel process worked well for other substrates.

1. Introduction

Multicomponent reactions afford the products in good yields and allow the assembly of complex compounds due to their intrinsic atom economy, selectivity, simplicity, and energy efficiency [1–3]. Thus, the development and improvement of new multicomponent reactions are an area of considerable interest. Recently, much attention has been directed towards 1,4-dihydropyridines because these compounds have shown extensive applications in the field of drugs and pharmaceuticals [4]. Since the first synthesis of 1,4-dihydropyridines was reported in 1882, several 1,4-dihydropyridines have been commercially used as calcium channel blockers [5] and regeneration agents of reduced nicotinamide adenine dinucleotide [6]. Additionally, 1,4-dihydropyridines have also been used as reducing agents [7] and synthetic intermediates [8] in organic transformations. In general, 1,4-dihydropyridines are synthesized by Hantzsch reaction [9], which involved Knoevenagel condensation and the formation of enaminoester. Subsequently, Michael addition and intramolecular condensation provide the 1,4-dihydropyridines in moderate yields. However, this classic method suffers from several disadvantages, such as longer reaction time and lower yield [10]. Thus, the development of a simple, efficient and versatile method for 1,4-dihydropyridine derivatives has been an active area of research. The progress in developing more efficient and versatile methods was remarkable, including microwave irradiation [11], ionic liquid [12], and solid-phase organic synthesis techniques [13]. With the aim of highly efficient synthesis of 1,4-dihydropyridines, several catalysts have been employed in the preparation process, such as solid acid [14], chitosan [15], sulfated polyborate [16], and organo-catalysts [17].

Although homogeneous catalysts are desirable due to their high catalytic activities and selectivity, the separation of homogeneous catalysts from the reaction mixture are tedious. In recent years, there has been increasing emphasis on the development of heterogeneous catalysis in synthetic chemistry in view of easy separation. Moreover, improved reaction efficiency was obtained by nano-sized heterogeneous catalysts due to their extremely small size and large specific surface area [18,19]. Koukabi et al. described a novel process for 1,4-dihydropyridines catalyzed by an active and magnetically recoverable nano-iron oxide [20]. However, catalyst deactivation caused by active sites block was the main hindrance of metal oxides in Hantzsch reaction. It could be expected that the continuous removal of products and poisons from the surface of metal oxides would be favorable for the formation of target compounds in a continuous mode [21].

Micro-flow system could offer short diffusion pathways and enhanced mass transfer rates, resulting in higher yield and better selectivity [22]. Additionally, higher safety could be obtained due to real-time online reaction with a small amount [23]. Thus, this methodology has been widely used in organic chemistry [24], analytic chemistry

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[25], and biotechnology [26]. Increased reaction rate, reduction of side products and improved product purity could be obtained in the microwave chemistry compared with conventional heating. However, the use of high-volume reactors was limited to the penetration depth of microwave. Process intensification could be realized in a continuous flow system whose feature size was several micrometer to a few millimeters. Thus, integration of process intensification in flow system and higher heating efficiency in microwave heating would eliminate the main drawback of microwave, resulting in an efficient and sustainable production. [27]. Waste cooking oil conversion as high as 99.2% was achieved in the fixed bed flow process under microwave irradiation [28]. A thin Cu film was deposited on the inner wall of flow reactor tubes, resulting in improved efficiency of microwave absorption under continuous conditions [29]. In view of these observations, several documents concerning theoretical research and design of microwave-assisted flow reactor were reported [30].

In our previous study, three co-doped TiO_2 nanoparticles synthesized by using a continuous precipitation method were first employed in a packed bed microreactor to conduct the degradation of organic waste [31]. Motivated by the remarkable progress of heterogeneous catalysis in micro-flow systems [32], γ-Fe_2O_3 nanoparticles were filled into a fixed bed flow reactor for the Hantzsch reaction (Fig. 1). Meanwhile, comparison among three heating methods (oil-bath heating, air heating and microwave heating) was also conducted to confirm the appropriate heating method. On the basis of these research, a novel flow reactor under microwave irradiation was designed and applied in the synthesis of 1,4-dihydropyridines.

2. Experimental

All the reagents used in this study were commercially available. Standard analytical reagents were purchased from Sigma-Aldrich Co. LLC. The quantitative analysis was performed on a liquid chromatograph system (Agilent 1260). ^{1}H NMR spectra (300 MHz) was recorded on a Bruker Avance AV-300 spectrometer. TEM measurements were performed on a JEM-200 CX electron microscopy operated at an acceleration voltage of 200 kV. Samples for TEM measurements were suspended in ethanol and dispersed ultrasonically. The XRD patterns were obtained on a Bruker D8 ADVANCE X-ray diffractometer with Cu Kα radiation at 40 kV and 40 mA. DigitalMicrograph software was employed in the analysis of TEM images. The capillary columns (id = 4 mm, length = 15 cm) made of polytetrafluoroethylene were employed in the subsequent study. The resulting nanoparticles were filled in the capillary column.

2.1. Catalyst preparation

γ-Fe_2O_3 was prepared in a valve-assisted micromixer by co-precipitation of iron (II) precursor and an alkaline solution. 10 g $FeSO_4{\cdot}7H_2O$ was dissolved in distilled water (50 mL). 5 mL ammonia water (28 wt%) was dissolved in distilled water (50 mL). $FeSO_4{\cdot}7H_2O$ solution (1.04 mL/min) and $NH_3{\cdot}H_2O$ solution (1.00 mL/min) were flowed into the valve-assisted micromixer. After centrifugation, the precipitates were washed with ammonium carbonate solution (1 wt%) until no sulfonate ion was detected. Subsequently, the obtained particles were dried under microwave irradiation at 175 W for 20 min. Finally, the precipitates were washed with sodium carbonate solution and dried under microwave irradiation at 175 W for 20 min, resulting in γ-Fe_2O_3 nanoparticles [33].

2.2. Reactor design

Micro-flow system under air heating. This system was assembled with fixed bed flow reactor (Vapourtec Ltd) and R4 reactor heater (Vapourtec Ltd). The temperature inside the fixed bed flow reactor was adjusted by the R4 reactor heater.

Micro-flow system under oil-bath heating. This system was assembled with fixed bed flow reactor (Vapourtec Ltd) and magnetic stirrers (IKA Ltd). The temperature inside the fixed bed flow reactor was adjusted by magnetic stirrers.

Micro-flow system under microwave irradiation. This system was assembled with fixed bed flow reactor (Vapourtec Ltd) and homemade single-mode cavity microwave system. The single-mode cavity microwave system was consisted of microwave generation system, microreaction system, sample injection system and temperature control system.

2.3. Typical Friedel-Crafts reaction in batch mode

Aromatic aldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1.5 mmol) were stirred together. Then a catalytic amount of γ-Fe_2O_3 (0.15 mmol) nanoparticles were added into the reaction mixture. After the completion of the reaction monitored by TLC, the reaction mixture was cooled and diluted with ethyl acetate. The recovery of γ-Fe_2O_3 nanoparticles was successfully realized through the use of a magnetic stirrer bar, providing clear organic layer. Subsequently, the organic solution was treated with sodium carbonate solution and distilled water, respectively. The organic layer was concentrated under vacuum and the expected product was isolated by column chromatography.

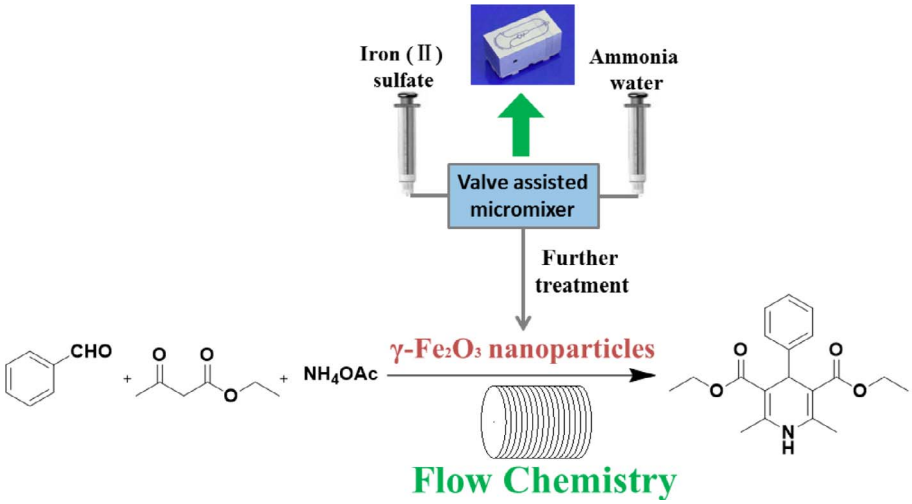

Fig. 1. A micro-flow system for the Hantzsch reaction.