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An innovation for development of Erlenmeyer–Plöchl reaction and synthesis of AT-130 analogous: a new application of continuous-flow method†

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The development of eco-friendly and efficient processes *via* one-pot multicomponent synthesis is a very attractive topic. In this work, the Erlenmeyer–Plöchl azlactone synthesis was carried out through unique, safe, fast and practical conditions without any catalyst, applying a simple microreactor and gave the corresponding products exclusively. A continuous, first microflow synthesis of *N*-benzoylglycine carbamide derivatives as AT-130 analogues catalyzed by Nafion-H@SPIONs was also established successfully.

Introduction

Enhancing the efficiency of a reaction and at the same time reducing the number of unnecessary synthetic steps is a substantial challenge in the development and progress of any chemical process.[1] Moreover, establishing a sustainable one-pot synthetic strategy is a fundamental concern in organic synthesis.[2] In green chemistry, an eco-friendly reaction is defined as "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products" and focuses on minimum hazard as the criteria while designing new chemical processes.[3] This may involve alternative reaction activation approaches, such as microwave and ultrasonic irradiation in mechanochemical mixing[4] or microreactor technology.[5] Currently, many recent papers point out a growing interest in developing microflow technology in various organic transformations.[6] This technology, by increasing the performance of heat- and mass-transfer characteristics and the ability to efficiently optimize reaction conditions by controlling residence time, has developed as a precise attractive process intensification tool.[7] Moreover, the results illustrate that at a very short residence time in the microreactor, even after scaling up, the obtained yields were much higher than when using conventional stirring.[8]

Recently, catalyst and/or solvent-free reactions, in order to meet the environmental demands, have become an important aspect in organic transformations and great efforts have been and still are being made to find and develop new ones.[9]

The strategy of one-pot condensation reactions leading to interesting heterocyclic scaffolds is particularly useful for the creation of diverse drug-like molecules for biological screening.[10] One of the most attractive condensation reactions is the Erlenmeyer–Plöchl reaction that has been used for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolone derivatives[11] and has a significant place in the realm of pharmaceutical and biological sciences.[12] For instance, almazolone as an alkaloid bearing azlactone core, was isolated from the Senegalese alga *Haraldiophyllum* sp. and synthesized experimentally.[13] These systems also play a crucial role for the synthesis of hydrogel supports for *in vivo* cell growth.[14] Moreover, L-*m*-tyrosine can be synthesized on larger-scale *via* a modification of the Erlenmeyer's azalactone synthesis.[15] On the other hand, recent efforts have been directed toward the development of Michael additions of azlactones for the synthesis of α-amino acid derivatives.[16] Hence, due to their significance specially from medicinal and biological points of view, extensive effort has been focused on the development of easy and efficient synthetic methods of this heterocyclic nucleus.[17] The Erlenmeyer–Plöchl reaction is basically the condensation of an aldehyde with hippuric acid with acetic anhydride as dehydrating agent and the presence of a catalyst is essential.[18] A variety of modified methods utilizing different catalysts have been used successfully so far for performing this condensation.[19] However, most of them require refluxing for hours in toxic organic solvents, use of expensive or corrosive catalysts and tedious work-up. As a consequence, implementation of eco-friendly and straightforward chemical methods remains a particularly interesting task. In order to improvement the synthetic strategy to develop the ultimate green Erlenmeyer–Plöchl reaction, herein, we present the first catalyst-free and solvent-free efficient synthesis

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of azlactones *via* a lab-scale continuous flow synthesis, as a truly benign manner of the classic azlactone synthesis (Scheme 1).

In this specific case, it was realized that this technology opens the opportunity to have a green and rapid azlactone synthesis.

Result and discussion

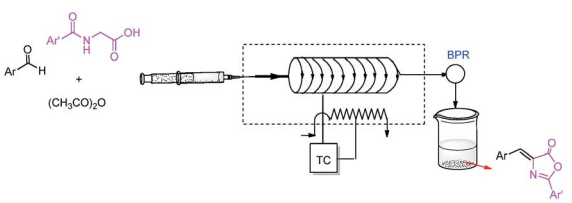
The major component of the apparatus included a simple setup using a syringe pump connected to the microreactor. The microreactor system used in this study includes an in-house-made tubing glass reactor which can be implemented in any chemistry laboratory. The microtube reactor was fabricated in a glass column (internal diameter, 0.5 mm; internal volume, 0.6 mL; length, 200 cm), which was placed in a water bath. A temperature controller (TC) was used for balancing and setting up heating and a back-pressure regulator (BPR) for pressure control (Scheme 1).

The reaction was initially screened to understand the influence of key factors in this process. Therefore, as a template reaction 4-chlorobenzaldehyde (0.2 M), hippuric acid (0.2 M) in acetic anhydride, were fed to the reactor *via* a syringe at ambient pressure and the influence of the temperature (60, 70, 80, 90 and 100 °C) and residence time effects (t_R: 30, 40, 50, and 60 min) on the yield of the desired product were investigated. Initially, the temperature was stepwise increased to 100 °C, at constant residence time (30 min).

Periodic analyses of the mixture illustrated that the corresponding product could be reached in 31% yield at 60 °C (t_R: 30 min) while achieving a good yield (72%) at 100 °C (t_R: 30 min). Increasing the temperature further did not improve the yield. Further examination showed a great improvement on yields by increasing of residence time. As shown in Fig. 1, surprisingly the yield increased to 85% at 90 °C with t_R = 50 min. Lower yields were obtained at lower temperature or residence time. As illustrated, further increase of these two crucial factors (temp. > 90 °C and/or t_R > 50 min) has no remarkable influence on the yield of the product. Therefore 0.72 ml h^{-1} was furnished as the optimum flow rate for this process.

Furthermore, comparison of the batch and continuous flow systems clearly showed the merit of the new technique in this transformation (Table 1).

We next investigated the scope and generality of this procedure with regard to both aryl aldehydes and hippuric acids as substrates under catalyst-free conditions. The representative results of the investigation are summarized in Table 2. In



Scheme 1 Microflow set-up for the preparation of Erlenmeyer–Plöchl reaction.

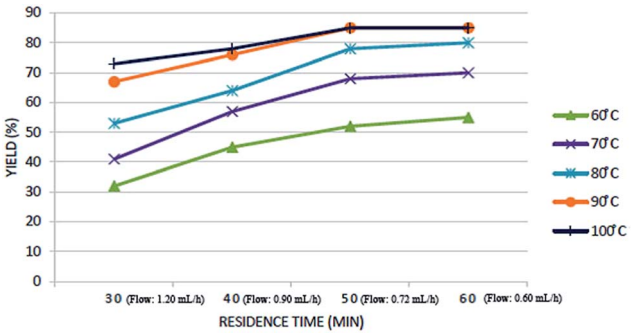


Fig. 1 Effects of temperature and residence time in the microflow azlactone synthesis.

general, various substitutions on the aromatic ring of aryl aldehydes, which bear electron-neutral (Table 2, entries 1, 13 and 14), electron-deficient (Table 2, entries 2–10 and 15), or electron-rich substituents (Table 2, entries 11 and 12) afforded the desired products in high to excellent yields.

Moreover, by using terephthalaldehyde under the same conditions, the corresponding bis-azlactone **A** was obtained exclusively (Scheme 2).

Next, these results encouraged us to expand our investigation to design a microflow system for the synthesis of AT-130 analogues.

Investigation for designing of new and effective anti hepatitis B virus (HBV) compounds is a challenge for biologists, pharmaceuticals and organic chemists.[20] Since the discovery of the naturally occurring **1**, clinically used as an anti-HBV agent AT-130, the *N*-benzoylglycine carbamide pharmacophore has attracted considerable attention owing to the biological activity associated with such compounds (Fig. 2).[21]

Up to now, only rare examples have been reported for the preparation of AT-130 analogues.[21,22] However, they have some drawbacks such as low functional group tolerance, the requirement of harsh conditions such as needing long reaction times or using an expensive metallic catalyst. Moreover, in pharmaceutical products, metal residues are highly challenging, and thus should be kept to a minimum.

Therefore, creating of a new route for the synthesis of these fine compounds could be an appealing approach.

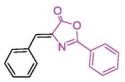
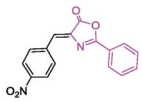
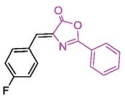
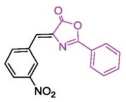
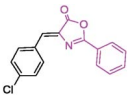
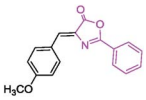
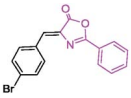
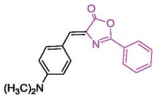
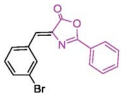
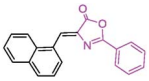
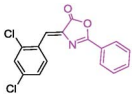
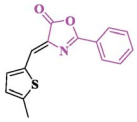
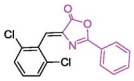
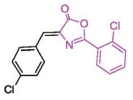
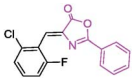
Inspired by our recent report on the Dakin–West reaction *via* a continuous flow system using Nafion-H@SPIONs as a new nano-catalyst,[23] and the successful results from the synthesis of azlactones *via* a continuous microflow system, we envisioned that the integration of this set into a microreactor device to afford AT-130 analogues directly, could be valuable.

Table 1 Comparison of batch and continuous flow systems for the synthesis of the model reaction[a]

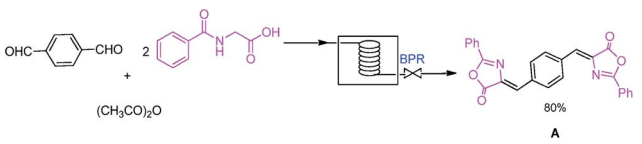
Method	Temp. (°C)	Time (min)	Yield (%)
Flow reactor	90	50	87
Batch reactor	90	50	23

[a] Isolated yield.

Table 2 Catalyst-free Erlenmeyer–Plöchl reaction in a microreactor

Entry	Product	Yield[a] (%)	Entry	Product	Yield[a] (%)
1		85	9		81
2		88	10		81
3		87	11		92
4		90	12		93
5		84	13		89
6		82	14		85
7		83	15		82
8		86			

[a] Isolated yield.



Scheme 2 Synthesis of the bis-azlactone A in the microreactor.

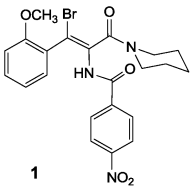
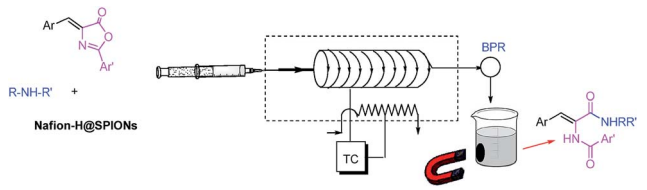


Fig. 2 A *N*-benzoylglycine carbamide derivative with the anti-HBV activity.

Therefore, according the aforementioned explanations, we decided to establish a microflow method for the synthesis of AT-130 analogues through condensation reaction of amines with azlactone derivatives catalyzed by Nafion-H@SPIONs (Scheme 3).



Scheme 3 Microflow set-up for the synthesis of *N*-benzoylglycine carbamide.

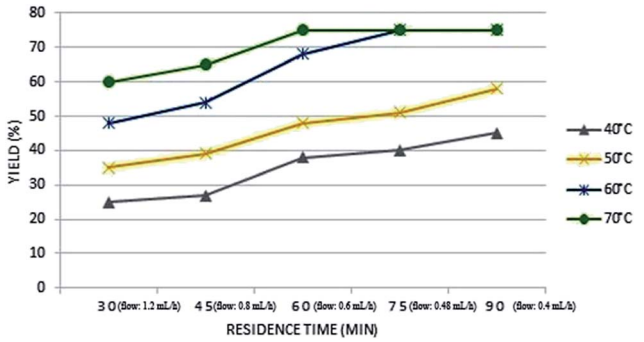


Fig. 3 Optimization of the reaction conditions for the continuous flow synthesis of *N*-benzoylglycine carbamide.

Table 3 Optimization reaction of 4-(4-chlorobenzylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one and *p*-toluidine in the presence of Nafion-H@SPIONs under the flow reaction[a]

Entry	Nafion-H loading (mol%)	Yield[b] (%)
1	—	5
2	0.186	50
3	0.215	62
4	0.28	70
5	0.35	75
6	0.35[c]	75

[a] Reaction condition: 4-(4-chlorobenzylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one (1.0 eq.), and *p*-toluidine (1.0 eq.) in the presence of 60 mg Nafion-H@SPIONs. [b] Isolated yield. [c] In 70 mg Nafion-H@SPIONs.

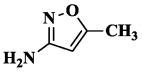
Table 4 Comparison of the batch and continuous flow systems for synthesis of *N*-benzoylglycine carbamide

Method	Temp. (°C)	Time (min)	Yield[a] (%)
Flow reactor	60	75	75
Batch reactor	60	75	24

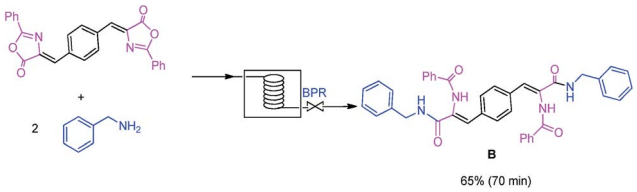
[a] Isolated yield.

This method is novel, very practical and simple. We started by employing a similar microreactor system used for the azlactone synthesis. Hence, a sonicated mixture of an azlactone (1 eq.), a primary or secondary amine (1.0 eq.) and Nafion-H@SPIONs (60 mg containing of 0.35 mol% Nafion-H) in acetonitrile (10 ml) was injected to the microreactor by

Table 5 *N*-Benzoylglycine carbamide synthesis catalyzed by Nafion-H@SPIONs in the microreactor

Entry	Ar	Ar′	Amine	Yield[a] (%)	Residence time/min
1	*p*-FC_6H_4	C_6H_5	$CH_3CH_2NH_2$	89	40
2	*p*-ClC_6H_4	C_6H_5	$CH_3CH_2NH_2$	88	50
3	*p*-$MeOC_6H_4$	C_6H_5	$CH_3CH_2NH_2$	75	70
4	*p*-ClC_6H_4	C_6H_5	$C_6H_5CH_2NH_2$	79	72
5	*p*-$NO_2C_6H_4$	C_6H_5	$C_6H_5CH_2NH_2$	78	60
6	*p*-$MeOC_6H_4$	C_6H_5	$C_6H_5CH_2NH_2$	67	77
7	*p*-ClC_6H_4	*o*-ClC_6H_4	$C_6H_5CH_2NH_2$	89	34
8	*p*-$MeOC_6H_4$	C_6H_5		86	65
9	*p*-ClC_6H_4	C_6H_5	*p*-$MeC_6H_5NH_2$	75	75
10	*p*-$NO_2C_6H_4$	C_6H_5	*p*-$MeC_6H_5NH_2$	74	67
11	*p*-$NO_2C_6H_4$	C_6H_5		70	78

[a] Isolated yield.



Scheme 4 Synthesis of the bis-*N*-benzoylglycine carbamide **B** in the microreactor.

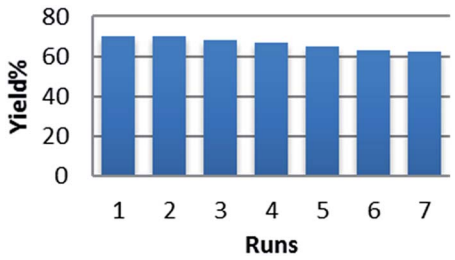


Fig. 4 Reusability of Nafion-H@SPIONs.

a syringing pump. It should be noted that after the reaction was finished, the catalyst could be separated from the mixture by using a permanent magnet.

Also, as a model reaction, we started our investigation by using of 4-(4-chlorobenzylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one and 4-methylaniline. Initially, a flow rate of 0.48 ml h^{-1} was selected with a temperature range between 40 to 70 °C. The temperature screening illustrated that at 60 °C gave the best result (75% isolated yield, Fig. 3).

Next, we screened for the effect of the immobilized amount of Nafion-H on the SPIONs when we run steady-state experiments at 60 °C and 75 min of residence time (0.48 ml h^{-1}). It turned out that the rate and the efficiency of the product, heavily depends on Nafion-H. As shown in Table 3, in the absence of Nafion-H the product was obtained in very low yields, however, remarkable yields were obtained when the same reaction carried out with utilizing of Nafion-H loading.

Compared with the results in Table 3 it can be concluded that the optimum amount of the catalyst is 60 mg containing of 0.35 mol% Nafion-H.

In Table 4, comparison between the batch and microflow processes is illustrated. These data show that in the microreaction process the yield is increased remarkably.

Subsequently, we confirmed the scope of this process by surveying a broad range synthesis of *N*-benzoylglycine carbamide (Table 5).

As evidenced by the results in Table 5, azlactones with different substituents smoothly reacted with primary/secondary amines or anilines, and produced the corresponding products in generally good to high yields. It was observed that the efficiency of this transformation is significantly influenced by the electronic properties of the substituents on the azlactone ring and the kind of the amine. This protocol was found to be tolerant to a variety of functional groups such as F, Cl, MeO or NO_2 on the aromatic ring. To our delight, we also surveyed the scope of the reaction with respect to the amine components. In general, it was found that the electronic effect on the N-atom of the amine is also effective in this transformation.

It is worthwhile to note that when bis-azlactone **A** was used as the substrate, the reaction also proceeded smoothly and the desired bis-*N*-benzoylglycine carbamide **B** was obtained successfully (Scheme 4).

The reusability of the catalyst was also evaluated with the template reaction. After the reaction was completed, it was cooled and acetone (10 ml) was added. The catalyst was separated with a permanent magnet, washed with ethanol and water and dried at 120 °C. The results demonstrated recyclability and its excellent stability under the reaction conditions (Fig. 4). Indeed, these results in combination with the straightforward method for separation of the catalyst from the reaction mixture make it an excellent and practical candidate for further applications in microflow systems.

In conclusion, we have established a simple, fast, practical and efficient system for the continuous flow and catalyst-free Erlenmeyer–Plöchl azlactone synthesis. Moreover, this procedure enables us to prepare *N*-benzoylglycine carbamides *via* combination of a nanocatalyst and the microflow system. Conversion rates in the microreactor are faster than those of the batch system and the products are obtained in good yields with high purity. Furthermore, the high recyclability of the catalyst is another main advantage of the process. Further scope of this method is in progress in our laboratory.

Experimental

All chemicals were purchased from Merck and Sigma-Aldrich. Nafion-H@SPIONs was synthesised according to our paper.[23] All known organic products were identified by comparison of their physical and spectral data with those of authentic samples. Thin layer chromatography (TLC) was performed on UV-active aluminum-backed plates of silica gel (TLC Silica gel 60 F254). ^{1}H, and ^{13}C NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ with chemical shift (δ) given in ppm. Coupling constants are given in Hz. The FT-IR spectra were taken on a Nicolet-Impact 400D spectrophotometer in KBr pellets and reported in cm^{-1}. Melting points were determined using Stuart Scientific SMP2 apparatus and are uncorrected.

General procedure for the Erlenmeyer–Plöchl reaction in a microreactor system

A microreactor system containing microtube reactor immersed in a water bath, and a syringing pump were used. The syringing pump was equipped with one syringe (1 ml). In the syringe, a solution of 4-chlorobenzaldehyde (0.2 M) and hippuric acid (0.2 M) in acetic anhydride were charged. Next, the mixtures were fed into the system by syringe pump (flow rate: 0.72 ml h^{-1}) at 90 °C. After the residence time was reached (50 min), the discharge was collected in a glass vessel. Ethanol (5 ml) was added to it and stirred for 10 min until a yellow solid precipitated. The mixture was cooled in an ice bath and then an aqueous solution (20%) of $NaHCO_3$ (10 ml) was added. After filtration, the pure products were recrystallized from ethanol in 80–93% yields. Most of the products are known in the literature and were identified by comparison of their FT-IR and NMR with literature data. As a sample, the characterization data for (*Z*,*Z*)-4,4′-(1,4-phenylenedimethylidyne)bis(2-phenyl-5(4*H*)-oxazolone) (**A**) is:

IR (KBr) ν_{max} = 3039, 1789, 1762, 1653, 1548, 1327, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.57–7.60 (5H, m), 7.65–7.69 (2H, m), 8.21–8.27 (4H, m), 8.32 (5H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 125.41, 128.60, 129.06, 130.08, 132.68, 133.72, 134.64, 135.86, 164.28, 167.38 ppm; MS (EI): *m*/*z* = 420.18, 287.78, 104.89, 76.88.

General procedure for the synthesis of *N*-benzoylglycine carbamides catalyzed by Nafion-H@SPIONs in a microreactor system

A microreactor system containing a microtube reactor immersed in a water bath, and a syringing pump were used. The syringing pump was equipped with one syringe (1 ml). In the syringe, a sonicated mixture of an azlactone (1.0 eq.), a primary or secondary amine (1.0 eq.) and Nafion-H@SPIONs (60 mg containing of 0.35 mol% Nafion-H) in acetonitrile (10 ml) were charged. The mixtures were fed into the system by syringe pump (flow rate: 0.48 ml h^{-1}) at 60 °C. After the residence time was reached (75 min), the discharge was collected in a glass vessel equipped with an external permanent magnet. The collected catalyst by the magnet, washed two times with absolute ethanol (2 × 1 ml), air-dried, and used directly for the next run. After separation of the catalyst from the resulting crude product, the mixture was cooled to the room temperature. Subsequently, water was added and the related product was filtered off and recrystallizated in hot ethanol. Most of the products are known in the literature and were identified by comparison of their FT-IR and NMR with literature data. As a sample, the characterization data for *N*,*N*′-(1*Z*,1′*Z*)-1,1′-(1,4-phenylene)bis(3-(benzylamino)-3-oxoprop-1-ene-2,1-diyl)dibenzamide (**B**) is:

IR (KBr) ν_{max}: 3315, 3062, 2924, 1651.7, 1521.6, 1474, 1276, 697; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 4.36 (d, 4H, J = 5.75 Hz, CH_2 benzylic); 7.17–7.20 (m, 3H, Ar), 7.20–7.31 (m, 9H, Ar), 7.44–7.58 (m, 10H, Ar), 7.96 (d, 4H, J = 7.45 Hz, Ar), 8.70–8.72 (t, 2H, J = 5.65 Hz, carbamoyl), 9.98 (s, 2H, benzamide). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 42.57, 126.49, 127.06, 127.73, 127.86, 128.06, 128.19, 129.35, 130.58, 131.58, 133.79, 134.47, 139.71, 164.89, 165.99.

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