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Synthesis, characterization, and application of monodisperse poly L-Dopa microspheres

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Abstract: In this study, 3,4-dihydroxy-L-phenylalanine (L-Dopa) was solvothermally polymerized to monodisperse microspheres 1 μm in diameter. Polymerization was carried out in dimethylformamide containing appropriate amounts of urea and L-Dopa at 120 °C for 24 h. Synthesis of the polymer in basic aqueous solution under hydrothermal conditions or via conventional heating resulted in the formation of bulky powders including irregularly shaped particles of the polymer. The morphologies of the synthesized polymers were characterized by scanning electron microscopy (SEM). The microspheres synthesized by solvothermal method (with $\sim$1 μm average diameter) were clearly observable in SEM micrographs. The thermal stability of the synthesized polymer was studied by thermogravimetry and differential scanning calorimetry techniques. It was recognized that the polymer is thermally stable at more than 200 °C. Applicability of the polymer microspheres was investigated for catalyzing the reaction of one-pot multicomponent synthesis of dihydrofurans. Several dihydrofuran derivatives were successfully synthesized using poly L-Dopa as a novel, environmentally friendly, and efficient catalyst with efficiency of more than 90%. Poly L-Dopa is easily separated by filtration from the reaction mixture. It can be used several times without decreasing the catalyzing activity after washing by suitable solvents.

Key words: Dopamine, L-Dopa, hydrothermal, microspheres, Knoevenagel, trans-2,3-dihydrofurans

1. Introduction

Polydopamine (PDA) has stimulated tremendous attention due to its widespread potential applications, including energy, biomedical science, water treatment, sensing, and catalyzing oxygen reduction reactions.[1–12] Liu et al. published a review paper in 2014 regarding the synthesis and application of PDA and its derivatives by reviewing more than 400 articles.[13] PDA is mostly prepared by solution oxidation under alkaline conditions (pH $>$7.5) using oxygen as an oxidant. Although the polymerization of dopamine occurs at ambient temperature in a few days, it can be accelerated to several hours at elevated temperature. Microsphere particles of PDA have been prepared by chemical oxidation of dopamine at ambient pressure or hydrothermal conditions and were reported by other research groups.[14–18] Fu et al. reported the preparation of PDA microspheres by oxidation of dopamine dissolved in ethanol (with the help of Tris (hydroxyl methyl) amino methane base) at room temperature; after that, the mixture was stirred for 3 days.[15] PDA was then coated by Fe_3O_4 nanoparticles and used as a catalyst in the reactions of oxidation of benzidine derivatives.[15] PDA microspheres were also synthesized by Guo et al. in an ethanol/water mixed solvent containing NH_4OH; after that, the solution was stirred at room temperature for 30 h.[16] It was filled into the Pebax matrix to prepare the mixed polymeric

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membrane for the separation of CO_2 from a CO_2-CH_4 gas mixture.[16] Wang et al. reported the preparation of PDA as microspheres and poly L-Dopa (PDopa) as an amorphous mass in alkaline aqueous solutions containing respective monomers and Tris(hydroxyl methyl)-amino methane, buffered at pH 8.5, heated to 80 °C, and stirred for 12 h. After that the mixture was cooled to room temperature and the reaction solution was stored under ambient conditions for 5 days to complete the polymerization reaction.[14] The TEM pictures of resultant polymers indicated that the PDA is prepared as microsphere particles, whereas the morphology of the resultant PDopa is amorphous.[14]

Similar to dopamine, L-Dopa can be polymerized to PDopa, either under ambient conditions or with an intensively promoted rate in alkaline water at high temperature.[14] In contrast to PDA, PDopa has attracted much less attention in both science and technological applications so far. L-Dopa, in addition to having catechol and amine groups, has one carboxylic group that makes it distinct from dopamine (Figure 1). Its state changes depending on the pH of the solution. It varies from cationic to zwitterionic and then anionic as the solution acidity decreases.[19] However, at the pH levels around its isoelectric point, there are always fractions available in the zwitterionic form.[19]

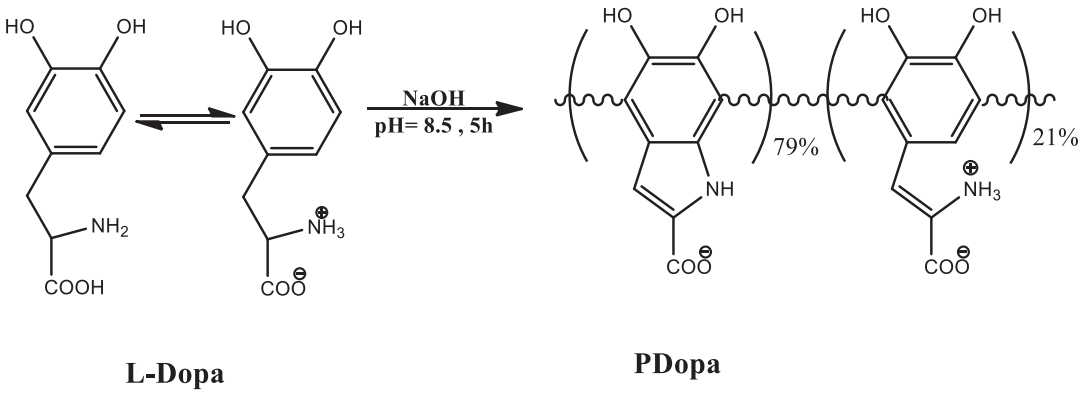


Figure 1. Formation of PDopa via self-polymerization of L-Dopa at 80 °C and pH 8.5.[20]

As a result of the presence of the carboxyl groups on the polymer backbone (with a fairly low pKa ca. 2.3), PDopa can be considered as a negatively charged multifunctional polyanion and is soluble in water, whereas PDA is insoluble and precipitates in water.[20] The molecular structure of PDopa has been well established by X-ray photoelectron spectroscopy (XPS) experiments (Figure 1). The polyanionic nature of PDopa, due to the presence of carboxylate anions, has been recognized in experiments.[20]

As noted above, the polymerization of dopamine and L-Dopa at ambient temperature requires a long time to complete the reaction. However, it seems that if the polymerization is carried out under solvothermal conditions, the reaction time considerably decreases. Under these conditions, the rate of reaction is sufficiently high to complete the reaction in a few hours. Moreover, based on our literature survey, the synthesis of polydopamine microspheres has been previously reported but there is no report on the synthesis of poly L-Dopa microspheres.

Herein we report the solvothermal synthesis of PDopa in aqueous and organic solvents in a few hours. The successful preparation of PDopa microspheres under dimethylformamide (DMF) and thermal conditions is introduced. The polymers are characterized by scanning electron microscopy (SEM) and thermal analysis methods. The PDopa application is reported for facile chemo- and stereoselective synthesis of highly substituted

trans-2,3-dihydrofuran derivatives from 1,3-dicarbonyl compounds, benzaldehyde, and pyridinium ylide for the first time. The reactions are completed within 1–2 h and the pure products are isolated in high yields. PDopa catalyst can be used in moderate conditions and is easily separated by filtration from the reaction medium. It is reusable for several times without losing activity after being washed by a suitable solvent. The employment of PDopa as a catalyst in accelerating multicomponent syntheses has not been previously reported. Structures with dihydrofuran moiety are an attractive class of natural compounds with a wide range of biological activities. Therefore, the interest of organic chemists in the synthesis of dihydrofurans has been increasingly stimulated during the past few years.[21−28] The syntheses of complex pharmaceutical and therapeutic molecules including dihydrofurans via one-pot multicomponent reactions (MCRs) have also attracted a great deal of attention with the growth of environmental concerns.[29−31] Various protocols have been developed for the synthesis of fused dihydrofuran structures in recent years. Wang et al. reported a diastereoselective synthesis of fused-ring trans-2,3-dihydrofurans by the MCR of dimedone/4-hydroxycoumarin, aryl aldehydes, and activated bromoalkanes in the presence of an excess of pyridine and triethylamine as a catalyst.[32] Another diastereoselective MCR synthesis of trans-2,3-dihydrofuran[3,2-c]coumarins catalyzed by the combination of pyridine and [bmim]OH ionic liquid was reported by Altieri et al.[33] This synthesis was also conducted by Khan et al. in the presence of pyridine and NaOH catalysts in aqueous medium under reflux conditions.[34] A trans-stereochemistry was established from the ^{1}H NMR coupling constants of the methine protons in positions C2 and C3.[34] The J coupling constant for the trans-isomers was in the range of 2.8–6.0 Hz, whereas the coupling constant for a cis-2,3-dihydrofuran derivative was 10 Hz.[34] A modified protocol for diastereoselective synthesis of differently substituted trans-2,3-dihydrofuro[3,2-c]coumarins was developed by a one-pot MCR via in situ-generated α-tosyloxyketones in the presence of pyridine and trimethylamine catalyzers.[35] Samant et al. reported the results of the MCR reaction of 4-hydroxycoumarin, aldehydes, and 2-bromo-1-phenylethanone to prepare trans-2,3-dihydrofuro[3,2-c]coumarins using 4-dimethylaminopyridine (DMAP) as an efficient and environmentally benign catalyst. The reaction was further accelerated by microwaves.[36] Recently, a regioisomeric synthesis of some highly functionalized dihydrofuro[2,3-d]pyrimidines from one-pot three-component reaction of barbituric acids, aryl aldehydes, and pyridinium bromides in the presence of triethylamine as a base was introduced by Bhuyan et al.[37] During the reaction, nitrogen ylides were formed and involved in [4+1] annulation as well as [2+1] annulation processes in which the two regioisomeric compounds were produced after intramolecular ring transformation. Diastereoselective synthesis of dihydrofurocoumarin via a three-component reaction of aldehyde, pyridinium salt, and 4-hydroxycoumarin in an aqueous medium was reported by An et al.[38] They noted that this method avoids excessive use of pyridine and trimethylamine catalysts. Tangeti et al. introduced a diastereoselective synthesis of fused dihydro-1H-furo[2,3-c]pyrazole by a one-pot four-component reaction of β-keto ester, hydrazine, aromatic aldehyde, and pyridinium ylide in the presence of triethylamine under microwave irradiation in solvent-free conditions.[39] Several further publications involving attempts to develop a novel method for the efficient and green synthesis of various dihydrofurans are available in the literature. This tremendous volume of research devoted to the synthesis of dihydrofurans using various catalysts and bases is an indication of the importance of these compounds.

In the above mentioned reported procedures, either the efficiency of the reaction is low or the time required is very long to achieve acceptable efficiency for the reaction, and there is a need to develop a catalyst and a methodology that can run the reaction with an enhanced rate and efficiency. Thus, we decided to study the reaction of 1,3-dicarbonyl compounds, aldehydes, and activated bromoalkanes in order to develop

an efficient and environmentally friendly catalyst for rapid and efficient synthesis of trans-2,3-dihydrofurans. In this study, we report a highly efficient procedure for the synthesis of trans-2,3-dihydrofurans **4** by one-pot, three-component reaction of 1,3-diketone compounds **1**, aldehydes **2**, and phenacyl bromide derivatives **3** using PDopa as an environmentally friendly, reusable, nontoxic, and highly active catalyst (Figure 2).

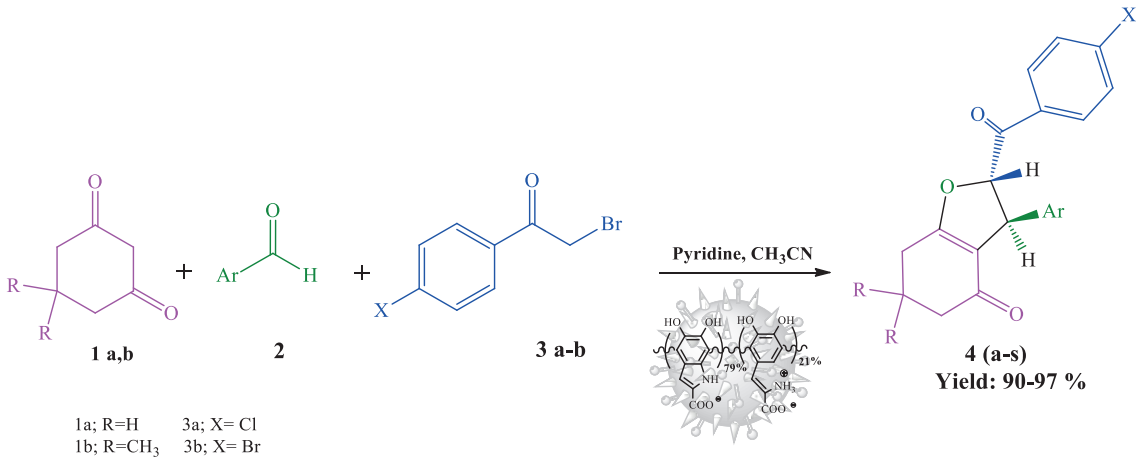


Figure 2. Synthesis of trans-2,3-dihydrofurans using PDopa as a novel and efficient catalyst.

2. Results and discussion

Figure 3a (panels A and B) shows the SEM micrographs of PDopa prepared via the conventional chemical oxidation reaction of L-Dopa in alkaline aqueous and DMF solutions at 70 °C for 24 h, respectively. As is observable, PDopa is synthesized as amorphous particles in aqueous solution, whereas in DMF it is partly converted to polymer microspheres. For further investigation, the oxidative polymerization of L-Dopa was carried out under hydrothermal and solvothermal conditions in the presence of urea as a base and heating to 120 °C for 24 and 12 h in aqueous and DMF solutions, respectively (Figures 3a (panel C) and 3b (panel A)). As is clearly seen, PDopa is synthesized in the form of accumulated particles stacked together in aqueous solution, whereas the polymer prepared in DMF solution mainly has microsphere morphology. Figure 3b (panels B and C) shows the morphologies of the solvothermally prepared polymers in DMF heated to 120 °C for 16 and 24 h, respectively. It is observed that the conversion process of the small grains into larger uniform spheres with average diameter of 1 μm is completed whenever the reaction time is increased to 24 h.

As mentioned in Section 1, PDopa take the form of a polyanion as the pH of the solution increases. The hydrophobic backbone of PDopa comprising benzene and indole rings is solvated by DMF, whereas the hydrophilic carboxylate anions tend to enter a spherical space away from DMF molecules. Therefore, the polymer chains are shaped in the form of microspheres. This situation, however, is quite the opposite in aqueous solution. The polymer chains are arranged so that their hydrophilic moieties (carboxylate groups) can be easily hydrated by water molecules. Azari et al. reported a similar arrangement of PDopa molecules whenever they polymerized L-Dopa on the surface of the polyamide membrane in Tris-HCl solution buffered at pH 8.2.[19] They indicated that the hydrophobic backbone of PDopa is attached to the hydrophobic polyamide surface, whereas the hydrophilic carboxylate anion moieties are arranged towards the aqueous solution.[19]

In order to study the effect of temperature on the morphological evolution of PDopa, the polymer was prepared by the solvothermal method at various temperatures ranging from 90 to 130 °C for 24 h (Figure 3c

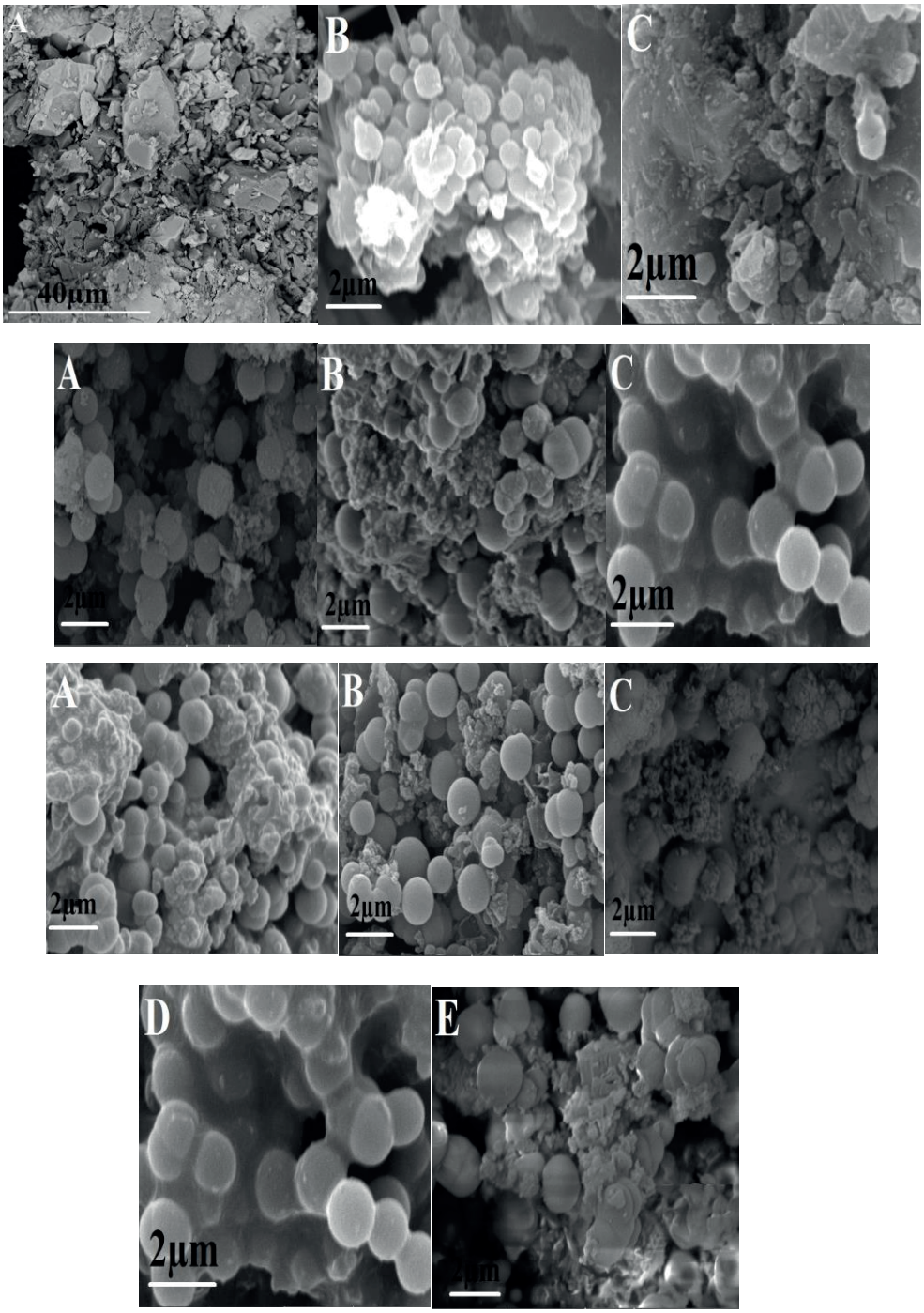


Figure 3. a. Micrograph images of A- PDopa synthesized by oxidative polymerization in alkaline solution stirred at room temperature for 48 h; B- PDopa synthesized in DMF solution at elevated temperature (70 °C) for 48 h; C- hydrothermally synthesized PDopa in the presence of urea heated to 120 °C for 24 h. b. Micrograph images of A- PDopa synthesized in DMF solution containing urea in solvothermal conditions heated to 120 °C for 12 h, B- 16 h, C- 24 h. c.Micrograph images of PDopa synthesized in DMF solution containing urea in solvothermal heating for 24 h at A- 90 °C, B- 100 °C, C- 110 °C, D- 120 °C, and E- 130 °C.

(panels A–E)). By increasing the temperature up to 120 °C, the small grains join together and form larger spheres. However, further increase of the temperature has a negative effect on the formation of the microspheres of PDopa, and therefore some of them infuse to form bulky masses (Figure 3c (panel E)).

Figure 4 shows the IR spectrum of PDopa prepared by DMF thermal synthesis in the presence of urea in 120 °C for 24 h. Appearance of peaks at 3205 cm^{-1} (NH_3^+ stretching) and 1644 and 1497 cm^{-1} for N-H bending and at 1569 and 1395 cm^{-1} for COO^- is good evidence of the formation of the zwitterionic structure illustrated in Figure 1.

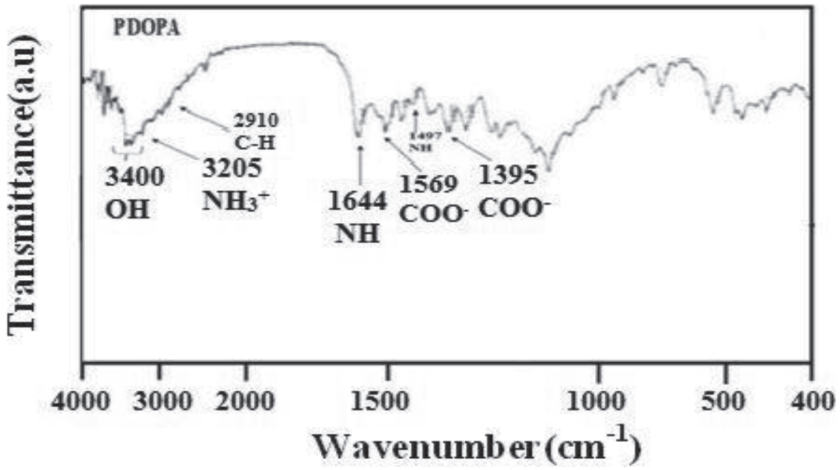


Figure 4. IR spectrum of PDopa in the form of KBr pellet.

To investigate the thermal stability of the prepared PDopa microspheres, thermogravimetry and differential scanning calorimetry analyses were carried out, and the thermograms are shown in Figure 5. There is a small mass change around 49–85 °C in the thermogravimetry plot, which corresponds to the endothermic peak that appeared in the DSC thermogram and is correlated to the evaporation of the adsorbed solvent on the surface of PDopa microspheres. After that, the polymer is thermally stable up to 229 °C. At higher temperatures, it undergoes an exothermic degradation process with a mass loss of ∼27% of the initial sample, which probably corresponds to the elimination of CO_2 from the polymer backbone. The polymer can then be used as a thermal stable catalyst without degradation for those reactions that are conducted at temperatures lower than 200 °C.

The polymer chains contain carboxylate anions on the indole and also nonclosed-ring moieties (Figure 1), providing a large number of basic active sites on each polymer fiber to act as an efficient catalyst in Knoevenagel reactions. Table 1 compares the applicability of various bases and acids for catalyzing the reaction of the synthesis of dihydrofurans **4a**. As is seen, in the absence of the catalyst, the reaction does not proceed to yield the desired product even after 6 h of refluxing the mixture. Therefore, the catalyst plays an important role in this reaction. Various catalysts including piperidine, DMAP, K_2CO_3, $SnCl_2$, p-TSA, and PDopa were used and their applicability was evaluated in catalyzing the reaction. As is obvious, among the catalysts used, PDopa resulted in the highest yield (more than 80%) even for a short refluxing time (1.5 h).

Solvents also play an important role in this reaction, and therefore the effects of various solvents including EtOH, toluene, THF, DMF, and CH_3CN were examined in the reaction (Table 1, entries 7–11). Among all these solvents, CH_3CN was found to be the best solvent to achieve high efficiency. (Table 1, entry 11). The mechanism of the reaction can be considered as the steps depicted in Figure 6.

Table 1. Optimization of the reaction conditions for synthesis of **4a** (Figure 6).

Entry	N-heterocycle	Catalyst	Reaction conditions	Time (h)	Yield (%)[a]
1	Pyridine	No catalyst[b]	EtOH, re?ux	6	No reaction
2	Pyridine	Piperidine[c]	EtOH, reflux	3	44
3	Pyridine	DMAP[c]	EtOH, re?ux	3	Trace
4	Pyridine	K_2CO_3[c]	EtOH, re?ux	3	26
5	Pyridine	$SnCl_2$[c]	EtOH, re?ux	3	11
6	Pyridine	p-TSA[c]	EtOH, re?ux	3	9
7	Pyridine	PDopa[d]	EtOH, re?ux	3	84
8	Pyridine	PDopa[d]	Toluene, re?ux	3	81
9	Pyridine	PDopa[d]	THF, re?ux	3	86
10	Pyridine	PDopa[d]	DMF, re?ux	1.5	88
11	Pyridine	PDopa[d]	CH_3CN, re?ux	1.5	90

[a] Isolated yield.
[b] Aldehyde (1 mmol), phenacyl bromide (1 mmol), dimedone (1 mmol), under reflux conditions.
[c] Aldehyde (1 mmol), phenacyl bromide (1 mmol), dimedone (1 mmol), catalyst (20 mol%), under reflux conditions.
[d] Aldehyde (1 mmol), phenacyl bromide (1 mmol), dimedone (1 mmol), catalyst (0.03 g), under reflux conditions.

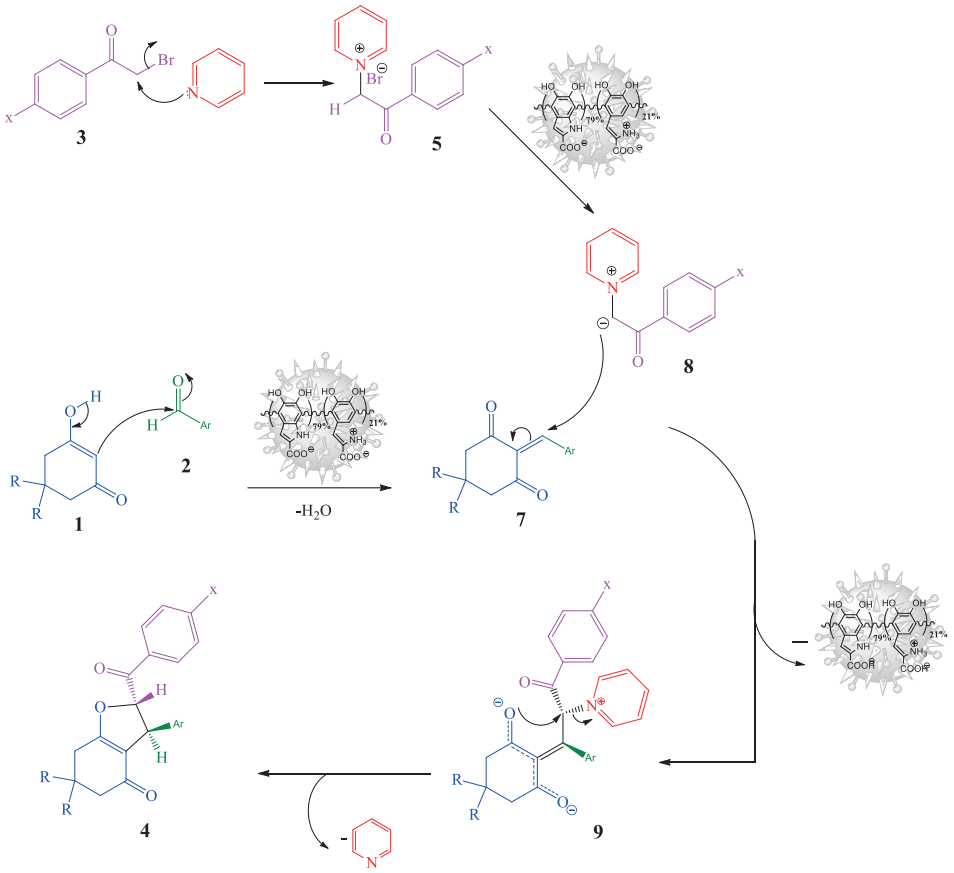


Figure 6. Plausible mechanism for the formation of dihydrofurans in the presence of PDopa.[34]

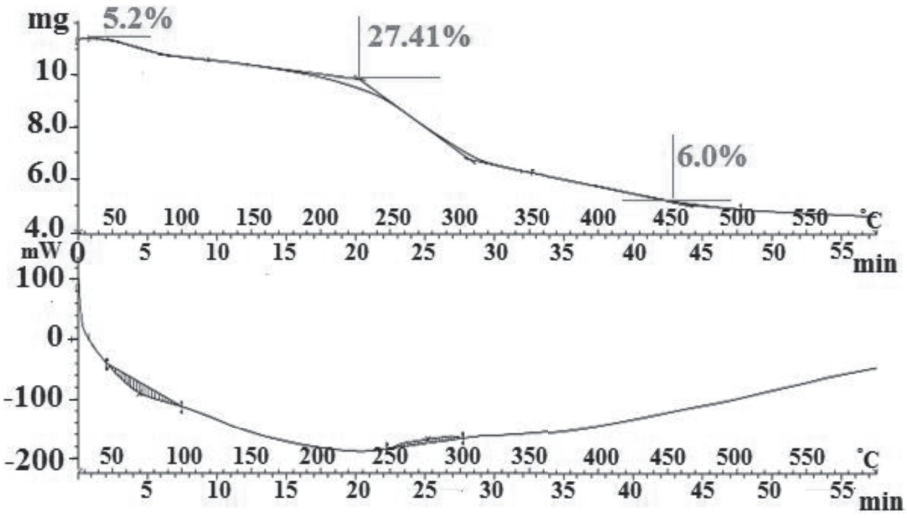


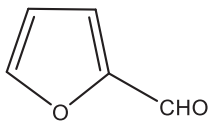
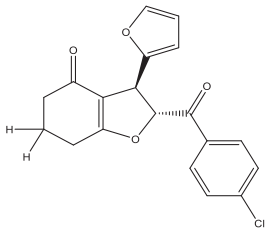
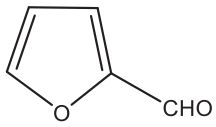
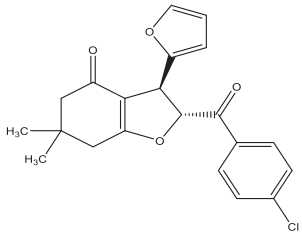
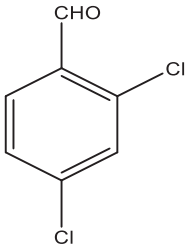
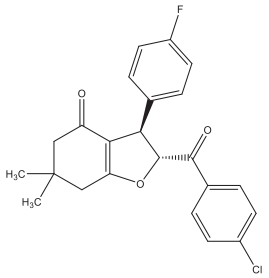
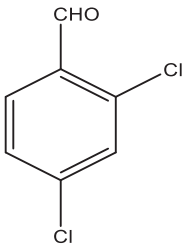
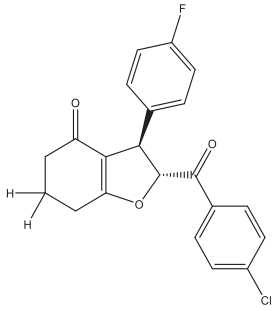
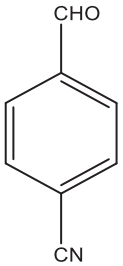
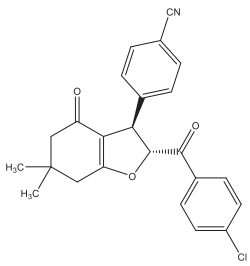
Figure 5. TG (top) and DSC (bottom) thermograms of PDopa microspheres solvothermally prepared in DMF at 120 °C for 24 h.

With the addition of pyridine to phenacyl bromide **3**, the reaction is immediately started and a white crystalline salt (**5**) is formed. In the next step, **1**, **2**, and PDopa (catalyst) were added to the mixture and stirred vigorously so that the color of the mixture gradually turned from orange to a dark color. As shown in Figure 6, PDopa, comprising very active sites of $-COO^-$, plays a vital role to remove C-H acids from compounds **1** and **5** to produce strong nucleophiles that react with **2** and **7** through Knoevenagel condensation and Michel addition, respectively. In the absence of a strong basic catalyst such as PDopa, efficiencies of both reactions are significantly low. Finally, an intramolecular SN2 substitution reaction is performed and product **4** is formed. The ^{1}H NMR, ^{13}C NMR, and IR spectra and respective derived spectral data for synthesized compounds are introduced in the Supplemental information. Spectral data are in very close agreement with those reported in the literature.[27]

In optimized conditions, the applicability of PDopa as an efficient and novel catalyst was studied for the reaction of various phenacyl bromide derivatives, aromatic aldehydes, and 1,3-dicarbonyl compounds, and the results are listed in Table 2. A trans-stereochemistry was established from the ^{1}H NMR coupling constants of the methine protons in positions C2 and C3.[34] The J coupling constant for the trans-isomers was in the range of 2.8–6.0 Hz, whereas the coupling constant for a cis-2,3-dihydrofuran derivative was 10 Hz.[34]

In conclusion, the current work describes the synthesis of monodisperse microspheres of PDopa under DMF and thermal conditions at 120 °C for 24 h. The prepared polymers were characterized by IR, TG, DSC, and SEM techniques. The effects of reaction time and temperature on the morphology of the polymers were investigated. It was shown that the formation of the monodisperse microspheres of PDopa with 1 μm diameter and smooth surface is completed as the temperature of the reaction increases from 90 to 120 °C and as the time rises from 12 to 24 h. The synthesis of the polymer in aqueous solutions resulted in irregular particles of the polymer stacked together, forming an amorphous bulky powder. The prepared PDopa microspheres were used as a reusable, efficient, and green catalyst for the synthesis of trans-2,3-dihydrofurans by one-pot three-component reaction of phenacyl bromide derivatives, 1,3-diketone compounds, and aldehydes for the first time. The catalyst can be readily recovered by filtration and can also be recycled several times without appreciable loss of activity. It has benefits such as high efficiency and reusability, low reaction time, and easy workup. It

Table 2. Synthesis of dihydrofuran derivatives using poly L-dopa under reflux conditions.

Entry	Aldehyde	Product		Time(h)	Yield (%)	Melting point, mp (°C)*
1			**4a**	2	90	170–173
2			**4b**	2	87	166–169
3			**4c**	1.5	93	115–118
4			**4d**	1.5	95	160–163
5			**4e**	1	88	184–185

*All melting points are in good agreement with those reported by Golchin et al.[27]

Table 2. Contunied.

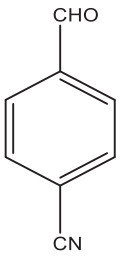
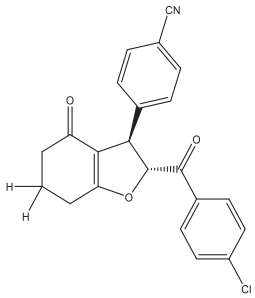
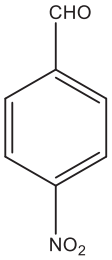
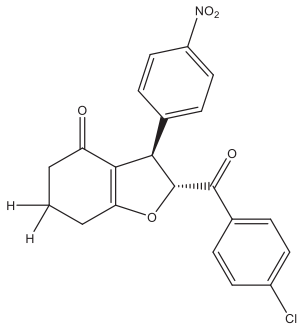
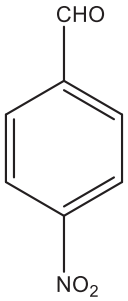
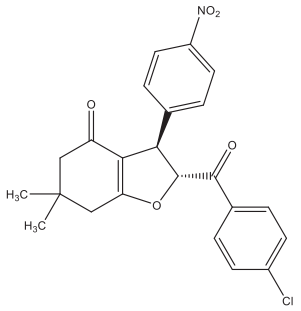
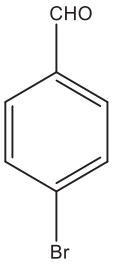
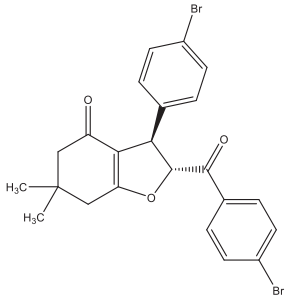
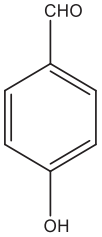
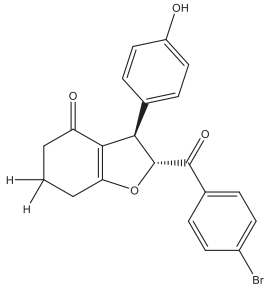
Entry	Aldehyde	Product		Time(h)	Yield (%)	Melting point, mp (°C)*
6			**4f**	1	91	157–159
7			**4g**	1	96	198–200
8			**4h**	1	95	209–210
9			**4i**	1.5	85	134–137
10			**4j**	3	82	147–148

Table 2. Contunied.

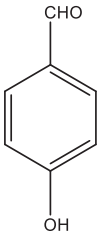
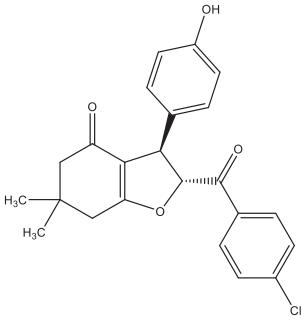
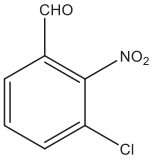
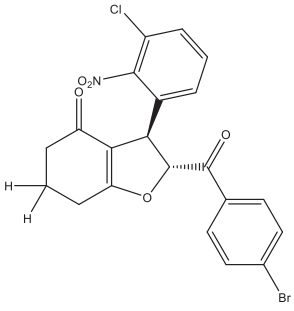
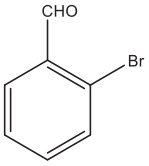
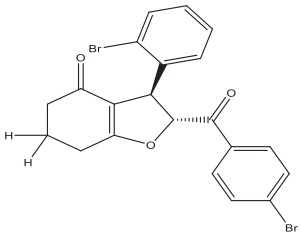
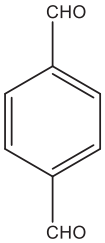
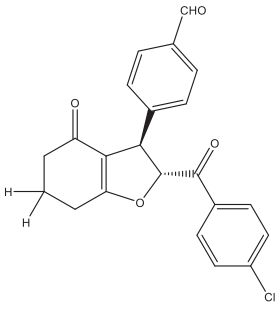
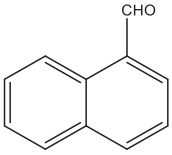
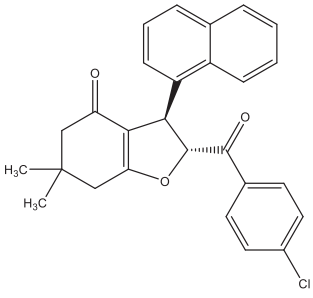
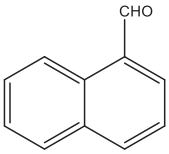
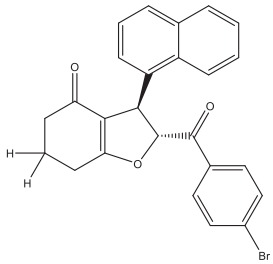
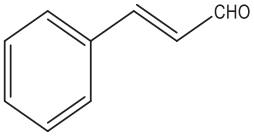
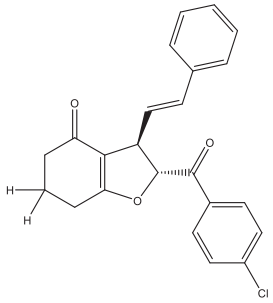
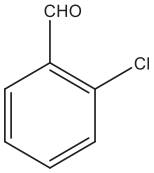
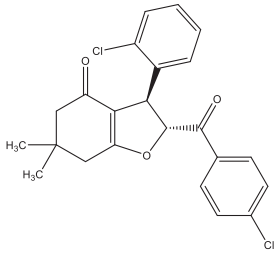
Entry	Aldehyde	Product		Time(h)	Yield (%)	Melting point, mp (°C)*
11			**4k**	3	86	156–158
12			**4l**	1.5	92	195–197
13			**4m**	1.5	87	180–181
14			**4n**	2.5	89	205–206
15			**4o**	2.5	91	160–162

Table 2. Contunied.

Entry	Aldehyde	Product		Time(h)	Yield (%)	Melting point, mp (°C)*
16			**4p**	2.5	91	168–170
17			**4q**	2.5	81	152–154
18			**4r**	2	95	139–141

is environmentally benign and reduces the amount of waste products. Evaluation of the applicability of PDopa for catalyzing other reactions based on its basic properties is in progress in our lab. Monodisperse microspheres of PDopa are also good candidates for in vivo clinical use such as drug delivery, treating lipoatrophy in AIDS patients, and embolization therapies since they have a controlled shape and size; are biocompatible, safe, and stable; and display desired functionality in patients.[40]

3. Experimental

L-Dopa ($\geq$98%) was purchased from Fluka. Urea ($\geq$98%), aldehydes (95%–97%), phenacyl bromide (98%), pyridine (99%), 1,3-cyclohexadione (97%), and 5,5-dimethyl-1,3-cyclohexadione (97%) were from Merck. All chemicals were used without further purification. The structures of all the products were characterized by melting point measurements and IR and NMR techniques. All melting points were recorded using an Electrothermal 9100 apparatus. IR spectra were obtained using a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance instrument (^{1}H at 400.1 MHz, ^{13}C at 100.1 MHz) with TMS as an internal standard. Chemical shifts were reported in parts per million (ppm) and coupling constants (J) were given in Hz. Thermogravimetric and differential scanning calorimetric experiments were carried out

on a Mettler Toledo TGA/DSC1 simultaneous device over a temperature range of 30–600 °C with a heating rate of 10 °C min^{-1}. The surface morphology of the synthesized materials was studied by scanning electron microscopy (VEGA3, Tescan, Czech Republic).

3.1. Preparation of PDopa via the solvothermal method

In a typical synthesis, L-Dopa (0.134 g) and urea (0.134 g) were dissolved in 50 mL of DMF (or distilled water), poured in a 100-mL Teflon-lined autoclave, and heated to 120 °C for 24 h. After the reactor was cooled to room temperature, the obtained black suspension solution showed the formation of PDopa. The black PDopa precipitates were filtered and thoroughly washed with water, ethanol, acetone, and acetonitrile solvents and vacuum-dried at an elevated temperature (60 °C) for subsequent uses. For comparison, PDopa was synthesized by a conventional heating method. For this purpose, the above mentioned solutions were prepared and heated to 70 °C for 48 h at ambient pressure.

3.2. One-pot three-component diastereoselective synthesis of trans-2,3-dihydrofurans catalyzed by poly L-Dopa microspheres

In a typical experiment 1.0 mmol pyridine and 1.0 mmol phenacyl bromide were dissolved in 5.0 mL of acetonitrile and stirred at room temperature for 2 min to form a white sediment powder. Then 1.0 mmol 1,3-dicarbonyl compounds, 1.0 mmol aromatic aldehydes, and 0.032 g of PDopa as the catalyst were added and refluxed for 4–6 h. After the reaction was completed the mixture was cooled down to room temperature and the catalyst was removed by simple filtration, cleaned by several washings with acetonitrile solvent, and dried for subsequent uses. The solvent of the filtered solution was then evaporated completely and the residual was dispersed in distilled water, filtered, and dried at ambient temperature and pressure and finally recrystallized from ethanol solution.

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