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β-Cyclodextrin–polyurethane polymer: a neutral and eco-friendly heterogeneous catalyst for the one-pot synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives *via* the Hantzsch reaction under solvent-free conditions

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Abstract: An efficient synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives using a *β*-cyclodextrin–polyurethane polymer (*β*-CDPU) as a stationary micro-vessel and neutral heterogeneous catalyst *via* a four component coupling of aldehydes, *β*-ketoester (2 mol) and ammonium acetate under solvent-free conditions is described. Compared with the classical Hantzsch reaction, this new method has the advantages of good yield, short reaction time and methodological simplicity. *β*-CDPU was proved to be an efficient heterogeneous catalyst that could be easily handled and removed from the reaction mixture by simple filtration, and also recovered and reused without loss of reactivity.

Keywords: *β*-cyclodextrin–polyurethane polymer; 1,4-dihydropyridine and polyhydroquinoline derivatives; heterogeneous catalyst; four-component coupling; solvent-free.

INTRODUCTION

The development of simple synthetic routes for complex organic molecules from readily available reagents is an important task in organic synthesis. In recent years, the development of new multicomponent reactions (MCRs) and the improvement of known MCRs are important areas of research in organic, combinatorial and medicinal chemistry.[1–3] As opposed to the classical route to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one-pot and offer a facile execution, high atom-economy and high selectivity and yields.[4–7]

Dihydropyridines and their derivatives (DHPs) have received considerable attention of synthetic and medicinal chemists because of their broad spectrum of

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biological and pharmaceutical activities.[8–15] These derivatives show antihypertensive, vasodilator, antimutagenic, antitumor, anticonvulsant, antidiabetic, antianxiety, antidepressive, analgesic, seditative, bronchodilator, hypnotic and anti-inflammatory activities.[16–20] Furthermore, these compounds are used as calcium channel blockers for the treatment of cardiovascular diseases including hypertension.[21] Recent studies have shown that 1,4-DHPs exhibit several other medicinal properties, which indicates the remarkable potential of novel DHP derivatives as a source of valuable drug candidates.[22]

Due to the biological importance associated with these compounds, numerous methods have been reported for their synthesis. However, many of these methodologies suffer from several drawbacks, such as a long reaction time, an excess of organic solvent, low product yields, expensive reagents, harsh conditions and the occurrence of several side products and difficulties in the recovery and reusability of the catalysts. Due to these problems, the development of an efficient, novel and versatile method for the preparation of 1,4-DHPs is an important aspect and is an active on-going research area. There is also scope for further improvement towards mild reaction conditions and higher yields.

With the increasing public concern over environmental degradation, the elimination of volatile and toxic organic solvents in chemical processes represents very powerful procedures for green chemical technology from both the economic and synthetic points of view.[23–25] They have many advantages, such as reduced pollution, lower cost, and simplicity in processing, which are beneficial to the industry as well as to the environment. There is also another route to combine economic aspects with environmental protection, *i.e.*, the use of heterogeneous catalysts.

Recently, the use of solid supported catalysts[26] has received considerable importance in organic synthesis because of their ease of handling, reduced reaction times, greater selectivity, simple workup, and recoverability of the catalysts. With this goal in mind and in continuation of on-going research into the employment of β-cyclodextrin–polyurethane as a stationary micro-vessel and heterogeneous catalyst in organic transformations,[27–32] herein, a green approach is reported for the synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives *via* the Hantzsch reaction catalyzed by β-CDPU resin as a neutral and eco-friendly polymeric catalyst under solvent-free neat conditions.

EXPERIMENTAL

The chemicals were purchased from Fluka, Merck or Aldrich. β-Cyclodextrin was heated at 80 °C under vacuum for 30 min before use to remove traces of moisture. The yields refer to the isolated crude products. The NMR spectra were recorded in acetone-d_6 or $CDCl_3$ on a Bruker Avance DPX 400 MHz spectrometer using TMS as the internal standard. The purity determination of the products and the reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates. The FT-IR spectra of the β-cyclodextrin–polyurethane were recorded as potassium bromide discs on a BOMEM MB-Series1998 FT-IR spectrophotometer.

Preparation of β-*cyclodextrin–polyurethane polymer*

The *β*-cyclodextrin–polyurethane polymer (*β*-CDPU) was synthesized by reacting *β*-CD with hexamethylene diisocyanate, HMDI, in dry DMF according to Yilmaz *et al*.[33] Briefly, two grams of *β*-CD (1.76 mmol) were dissolved in 15 mL of dry DMF in a 100 mL round bottom flask at room temperature. To the solution, 17.6 mmol of HMDI in 5 mL of dry DMF was added dropwise. Then the mixture was stirred at 70 °C for 3 h. The resin was filtered off and washed with acetone several times. The polymer was dried under vacuum at 80 °C overnight.

General procedure for the synthesis of 1,4-DHPs

The *β*-CDPU resin (0.15 g) was added to a magnetically stirred mixture of aromatic aldehyde **1** (1 mmol), ethyl acetoacetate **2** (2 mmol) and ammonium acetate **3** (1.2 mmol). The resulting reaction mixture was stirred at 80 °C for the appropriate time. After completion of the reaction, as indicated by TLC (using *n*-hexane/ethyl acetate (5:1)), the reaction mixture was cooled to room temperature and the crude product extracted with CH_2Cl_2. The organic solvent was removed by simple evaporation. Finally, the crude product was recrystallized from $EtOH/H_2O$ to afford the corresponding pure 1,4-dihydropyridine derivatives in high yields. All the compounds were characterized based on spectroscopic data (IR, ^1H- and ^{13}C--NMR) and by comparison with those reported in the literature. The spectral data is given in the Supplementary material to this paper.

General procedure for the synthesis of polyhydroquinolines

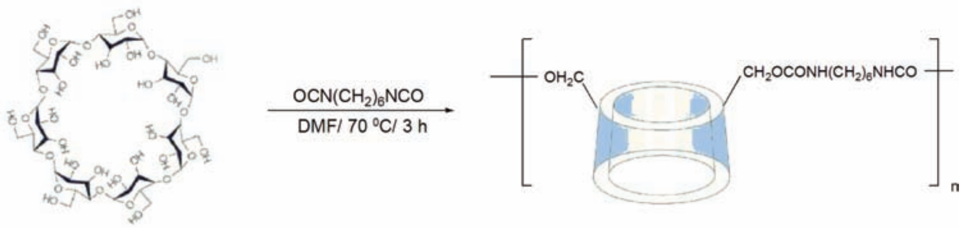
A mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol), ammonium acetate (1.5 mmol), ethyl acetoacetate (1 mmol), and *β*-CDPU resin (0.15 g) was heated at 80 °C with stirring for 10–30 min. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with CH_2Cl_2 and the catalyst was filtered off. The organic solvent was removed by simple evaporation and the pure product was obtained by recrystallization from ethanol. The catalyst was recovered by filtration, washed with water and methanol, dried at room temperature and reused several times for the same reaction.

The spectral data are given in the Supplementary material to this paper.

RESULTS AND DISCUSSION

β-Cyclodextrin (*β*-CD) is a torus-shaped cyclic oligosaccharide composed of seven D-glucopyranose units connected by *α*-(1,4)-linkages. These macromolecules possess a characteristic toroidal shape with a well-defined lipophilic cavity and a hydrophilic exterior that is suitable for the inclusion binding of appropriately sized guest compounds. This outstanding property has long been utilized in the pharmaceutical, food, cosmetic and textile industries and has found applications in the field of catalysis, environmental remediation, chemical sensing, and enantiomeric separations. Various methods for insoluble CD production and/or immobilization on solid supports have been successfully developed and used. Hexamethylene diisocyanate (HMDI) is a widely used linker for the fabrication of drug delivery vehicles with reportedly a very low degree of toxicity.

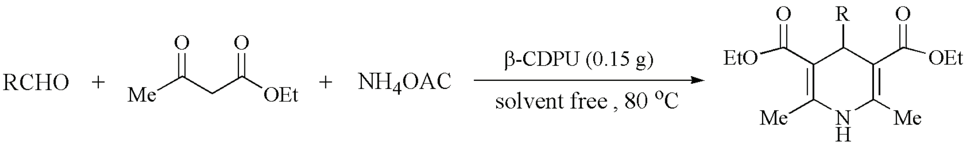
Bearing all this in mind, in the present work, *β*-CD was incorporated into a cross-linked polymeric form using hexamethylene diisocyanate. Using this strategy, the recycling of *β*-CD would become feasible and its discharge into the environment significantly minimized to non-harmful levels. The polymeric network was synthesized in the reaction depicted in Scheme 1.



Scheme 1. Synthesis of the *β*-CD based polymer.

The polymerization of *β*-CD molecules with the assistance of hexamethylene diisocyanate (HMDI) was confirmed by FT-IR analysis. Evidence of polymerization was the disappearance of the isocyanate peak in the IR spectrum at about 2280 cm^{-1}. The IR spectrum of the polymer showed characteristic absorption bands at 3360 and 1718 cm^{-1}, corresponding to NH and C=O groups. NHCO stretching was also observed at 1570 cm^{-1}.

In order to investigate the possible catalytic properties of the *β*-CDPU resin in the Hantzsch reaction, the four-component coupling of aldehydes, *β*-ketoester and ammonium acetate under solvent-free conditions was chosen (Scheme 2).



Scheme 2. Synthesis of the 1,4-dihydropyridine derivatives.

Initially, a mixture of benzaldehyde, ethyl acetoacetate and ammonium acetate was studied as the model reaction to determine whether the use of the polymeric catalyst was efficient and to determine the optimized conditions. The results are given in Table I.

The temperature had a critical effect on the reaction yield and no reaction occurred at room temperature, even after two hours. However, heating the reaction mixture at 80 °C afforded the product in 89 % yield (reaction conditions 3). For yield improvement, the effect of the catalyst loading was also studied. Increasing the catalyst loading from 0.15 to 0.20 g did not significantly affect the yield, while the reaction in the absence of the polymeric catalyst at 80 °C gave the product in only 10 % yield after 3 h.

TABLE I. Optimization of reaction conditions for the four-component coupling of benzaldehyde, ethyl acetoacetate and ammonium acetate

Entry	*β*-CDPU amount, g	Temperature, °C	Ammonium acetate amount, mmol	Time, min	Yield, %
1	0.00	80	1.5	180	10
2	0.1	80	1.5	30	89
3	0.15	80	1.5	15	89
4	0.2	80	1.5	15	90
5	0.15	25	1.5	120	Trace
6	0.1 5	60	1.5	45	72
8	0.15	90	1.5	15	87
9	0.15	80	1	55	68
10	0.15	80	2	15	90

With the optimized conditions in hand, an array of aromatic aldehydes were treated with ethyl acetoacetate and ammonium acetate using 0.15 g of *β*-CDPU at 80 °C whereby the desired products were afforded in high to excellent isolated yields (86–94 %) (Table II). Aromatic aldehydes, however, provided better yields in comparison with their aliphatic counterparts. With regard to substituents, both aldehydes with electron-withdrawing and electron-donating groups participated in the reaction, but the former reacted better.

TABLE II. Synthesis of the 1,4-dihydropyridine derivatives catalyzed by *β*-CDPU under solvent-free conditions at 80 °C

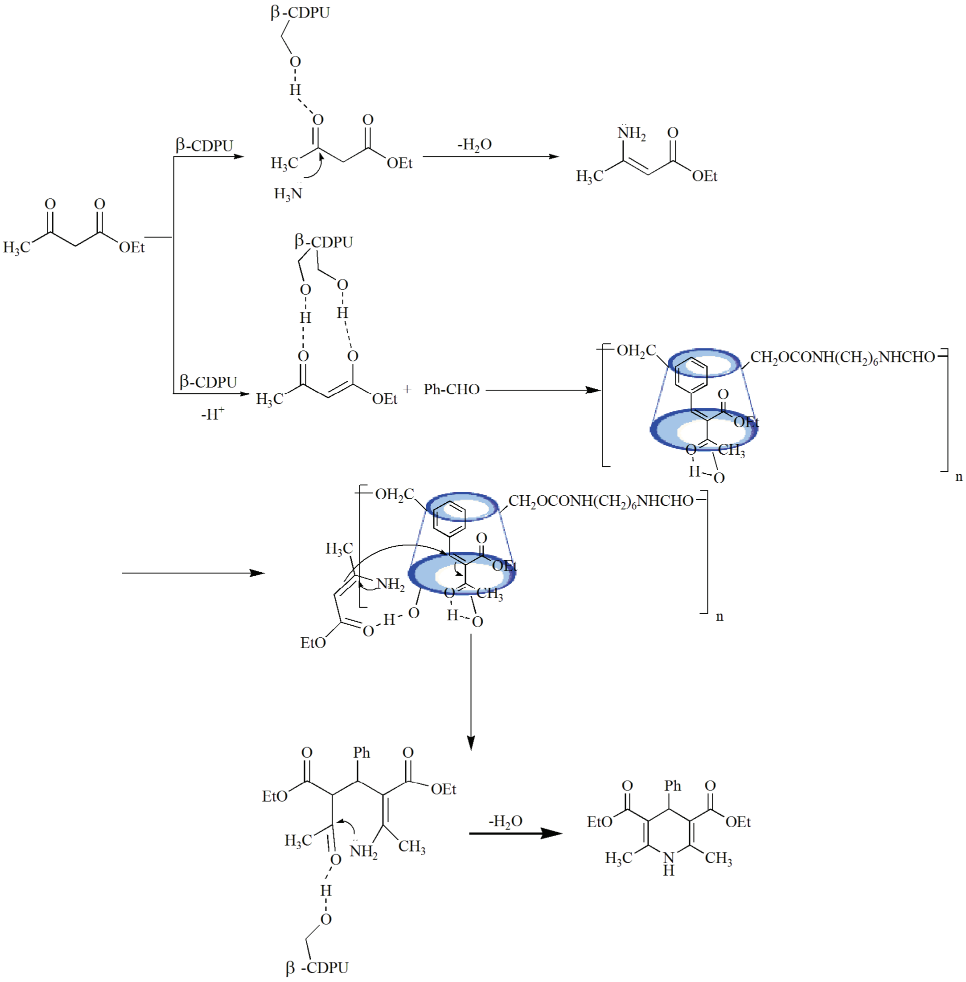
Compound	R	Time, min	Yield, %
1	C_6H_5	15	89
2	4-$CH_3OC_6H_4$	20	92
3	4-OHC_6H_4	30	86
4	4-ClC_6H_4	20	87
5	4-CNC_6H_4	15	92
6	4-$EtOC_6H_4$	35	88
7	4-$(CH_3)_2NC_6H_4$	45	92
8	4-$NO_2C_6H_4$	15	94
9	2-ClC_6H_4	20	90
10	2-$NO_2C_6H_4$	25	88

In view of environmentally friendly methodologies, recovery and reuse of a catalyst is highly desired. The *β*-CDPU polymer did not suffer from extensive mechanical degradation and was quantitatively recovered by simple filtration and washing with water and methanol. It could be reused for subsequent reactions. Recycled *β*-CDPU showed no loss of efficiency with regard to yield after four successive runs (Table III).

The high reaction rate observed in the present method could be attributed to the fact that the hydrophobic central cavities of *β*-CD units in the *β*-CDPU polymer acted as a micro-vessel and accommodated the nonpolar compounds. In addition, the hydrophilic exterior due to the outer OH of the *β*-CD cavity promoted the reaction *via* hydrogen bonding (Scheme 3).

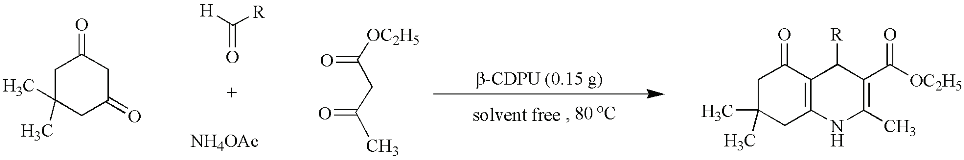
TABLE III. Recyclability of the *β*-CDPU polymer

Entry	Yield, %
1	89
2	87
3	87
4	84



Scheme 3. A plausible mechanism of the reaction.

After the success of this first set of Hantzsch reactions catalyzed by *β*-CDPU resin, the reaction was extended to the synthesis of polyhydroquinoline derivatives. Thus, various aromatic aldehydes were treated with dimedone, ammonium acetate and ethyl acetoacetate under the optimized reaction conditions for preparation of 1,4-dihydropyridines derivatives (Scheme 4). The results are summarized in Table IV, which indicate that the desired products were formed in high isolated yields and in appropriative times.



Scheme 4. Synthesis of the polyhydroquinoline derivatives.

TABLE IV. Synthesis of the polyhydroquinoline derivatives *via* unsymmetrical Hantzsch reactions catalyzed by *β*-CDPU

Compound	R	Time, min	Yield, %	M.p. / °C (found)	M.p. / °C (reported)
11	C_6H_5	10	90	224–226	227–229[34]
12	4-ClC_6H_4	10	84	242–243	245–246[35]
13	4-OHC_6H_4	25	90	237–238	238–240[36]
14	4-$CH_3C_6H_4$	15	89	260–262	260–262[34]
15	4-$N(CH_3)_2C_6H_4$	30	92	227–230	229–231[37]
16	4-$NO_2C_6H_4$	10	86	242–246	242–244[38]
17	2-ClC_6H_4	15	93	208–211	–
18	2-$NO_2C_6H_4$	15	87	202–206	–

CONCLUSIONS

In conclusion, an easy, efficient and green protocol for the synthesis of 1,4-dihydropyridines and polyhydroquinoline derivatives under solvent-free neat conditions *via* an improved Hantzsch reaction catalyzed by *β*-CDPU polymer has been reported. The method offers marked improvement with its operational simplicity, short reaction time and high yields of pure products without use of any organic solvent.

SUPPLEMENTARY MATERIAL

Spectral data for the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

β-ЦИКЛОДЕКСТРИН–ПОЛИУРЕТАНСКИ ПОЛИМЕР: НЕУТРАЛАН И ЕКОЛОШКИ ПРИХВАТЉИВ ХЕТЕРОГЕНИ КАТАЛИЗАТОР У СИНТЕЗИ ДЕРИВАТА 1,4-ДИХИДРОПИРИДИНА И ПОЛИХИДРОХИНОЛИНА ХАНЧОВОМ (*HANTZSCH*) РЕАКЦИЈОМ У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ У ОДСУСТВУ РАСТВАРАЧА

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Описана је примена циклодекстрин–полиуретанског полимера (β-CDPU) у синтези деривата 1,4-дихидропиридина и полихидрохинолина. β-CDPU је присутан као стационарна микропосуда и хетерогени катализатор у реакцији куплована четири реакционе компоненте, алдехида, β-кетоестра (2 mol) и амонијум-ацетата, без присутног растварача. У поређењу са класичним реакционим условима Ханчове (*Hantzsch*) реакције, описани поступак као предност има бољи принос, кратко реакционо време и једноставнију методологију. β-CDPU је ефикасан хетерогени катализатор, лак за коришћење и лако се уклања из реакционе смесе филтрирањем, а може се поново користити без губитка активности.

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