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Synthesis of 3,4-dihydropyridin-2-one derivatives in convergent mode applying bio catalyst vitamin B_1 and polymer supported catalyst PEG–SO_3H from two different sets of building blocks

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ABSTRACT

Two highly efficient, green protocols have been developed for the synthesis of 3,4-dihydropyridin-2-one derivatives from different starting materials exploring two reaction specific catalysts, vitamin B_1 (VB_1), and PEG–SO_3H. VB_1 catalyzed simple and convenient protocol has been developed for the synthesis of 3,4-dihydropyridin-2-one derivatives by the installation of aldehyde, cyanoacetamide, and 1,3-dicarbonyl compounds. In addition, 3,4-dihydropyridin-2-one derivatives have also been synthesized by simply combining aldehyde, malononitrile, and 1,3-dicarbonyl compounds via the formation of 4*H*-pyran nucleus and PEG–SO_3H catalyzed one-pot rearrangement.

In recent years, much attention has been devoted toward dihydropyridone derivatives due to their significant therapeutic and biological activities, such as antibacterial,[1] antifungal,[2] and antitumor,[3] also served as HIV-1 specific reverse transcriptase inhibitors.[4] Homoclausenamide[5] and neoclausenamide[6] are 3,4-dihydropyridin- 2-one and pyrrolidin-2-one core containing alkaloids, respectively, isolated from the leaf extract of Rutaceae clausena lansium (Lour.) skeels, a fruit tree widely distributed in the southern China. Pyridone **I**, (Fig. 1) has been found to be specific non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus-1 (HIV-1) and pyridone **II** (Fig. 1) shows very strong antiprotozoal and antimicrobial activity.[7,8] Milrinone (**III**), (Fig. 1) Amrinone (**IV**),[9] (Fig. 1) and their analogues[10–12] are potent cardiotonic agents for the treatment of heart failure. 2-Pyridones are also used as an important intermediate for the synthesis of biologically and pharmacologically potent polycyclic compounds as illustrated by the recent synthetic approaches toward the camptothecin family of antitumor agents.[13]

The astonishing drug activity of the 2-pyridone derivatives not only attracted many synthetic and medicinal chemists to synthesize this heterocyclic nucleus but also became an active research area of enduring interest. So far, only a few convenient methods have been reported in the literature.[14–18] Although these methods are very helpful for the construction of 3,4-dihydropyridin-2-one core containing heterocyclic molecules, still these classical reactions have significant drawbacks such as availability of precursors, functional group compatibility, long reaction time, and harsh reaction conditions, which limit their scope. Multicomponent coupling reaction (MCR) is a powerful synthetic tool for the synthesis of biologically active compounds.[19] In recent years, with the increasing environmental concerns, development of environmentally benevolent organic reactions has become a crucial and challenging research area in modern organic chemistry. Herein, we have uncovered two highly efficient and environmentally benign multicomponent coupling reactions catalyzed by VB_1 and PEG–SO_3H for the synthesis of 3,4-dihydropyridin-2-one derivatives. VB_1 is a nonflammable, inexpensive, and non-toxic reagent which has been used as the catalyst for the synthesis of heterocyclic compounds, such as pyrimidinones,[20a] dihydropyridines,[20b] and 1,2-dihydronaphth[1,2-*e*][1,3]oxazine-3-one.[20c] PEG–SO_3H is a polymer supported catalyst that is functionalized by acidic groups and is a mild, non-volatile, and non-corrosive organic acid which has been used for the synthesis of several heterocyclic molecules.[21] These reports inspired us to explore the utility of these green catalysts in the synthesis of an array of 3,4-dihydropyridin-2-one derivatives.

At the commencement of our work we focused on systematic assessment of different catalysts for the two model reactions (Schemes 1 and 2). A wide array of catalysts including $ZnCl_2$, $MgCl_2$, SiO_2, Al_2O_3, Alum, I_2, *p*-toluene sulfonic acid, AcOH, and VB_1 were employed to improve the yield for the specific synthesis of 3,4-dihydropyridin-2-one derivatives. The results are presented in Table 1. In the preliminary experiment, the above mentioned

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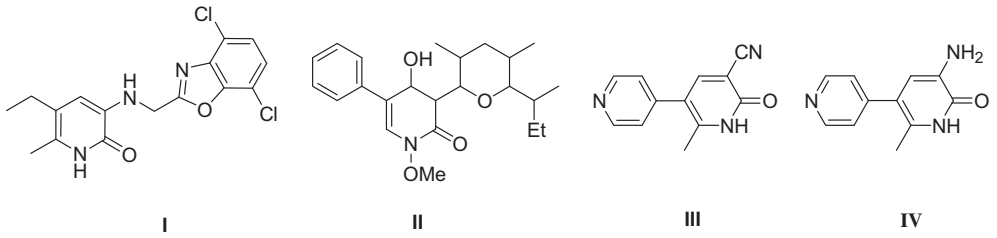
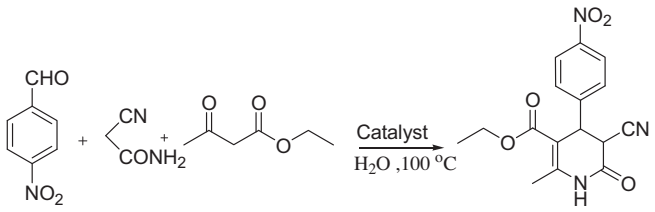
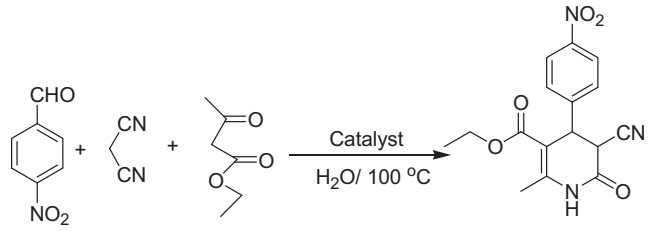


Figure 1. Biologically active pyridin-2-one compounds.



Scheme 1. Synthesis of 3,4-dihydropyridin-2-one using three component coupling reaction of 4-nitrobenzaldehyde, cyanoacetamide, and ethyl acetoacetate.



Scheme 2. Synthesis of 3,4-dihydropyridin-2-one via a three component coupling reaction of 4-nitrobenzaldehyde, malononitrile and ethyl acetoacetate.

reactions were performed in the absence of any catalyst employing water as the solvent. It was evident that the reaction proceeded very slowly in the absence of catalyst and the expected product was isolated in a very small quantity after heating the reaction mixture for about 24 h at 100 °C (Table 1, entry 1). It was also evident that in case of both the synthetic protocols (Schemes 1 and 2), with the use of $ZnCl_2$, $MgCl_2$, SiO_2, Al_2O_3, alum, and I_2 the product was formed in poor yields (Table 1), whereas using strong organic acids like p-toluene sulfonic acid and AcOH (Table 1, entries 8 and 9) the product was obtained in moderate yields by applying the first synthetic protocol. Interestingly, the installation of VB_1 as the catalyst for the first protocol (Scheme 1) not only increased the product yield, but also decreased the reaction time from 8 h to 4 h. In comparison with these Lewis acid catalysts, strong organic acids and VB_1; PEG–SO_3H have proved to be the most efficient catalysts for the synthesis of 3,4-dihydropyridin-2-one derivatives applying the second synthetic method (Scheme 2).

Various solvents were also screened to test the efficiency of these catalysts in different reaction medium and the results are summarized in Table 2. It was evident that the polar solvents afforded better yield than the nonpolar ones and in case of both the synthetic protocols water showed superiority over the other solvents. It is noteworthy to mention that quantity of the catalyst plays a vital role in the formation of the desired product. An

Table 2
Influence of different solvents and catalyst concentration on the synthesis of 3,4-dihydro pyridin-2-one[a]

Entry	Scheme 1	Scheme 2	Solvent	Yield[b] (%)	
	VB_1 (mol %)	PEG–SO_3H (mol %)		Scheme 1	Scheme 2
1	3	6	H_2O	59	39
2	6	10	H_2O	68	47
3	10	15	H_2O	73	68
4	15	20	H_2O	80	81
5	20	25	H_2O	80	81
6	15	20	THF	30	—
7	15	20	Toluene	48	61
8	15	20	MeCN	41	—
9	15	20	MeOH	56	18
10	15	20	EtOH	71	25

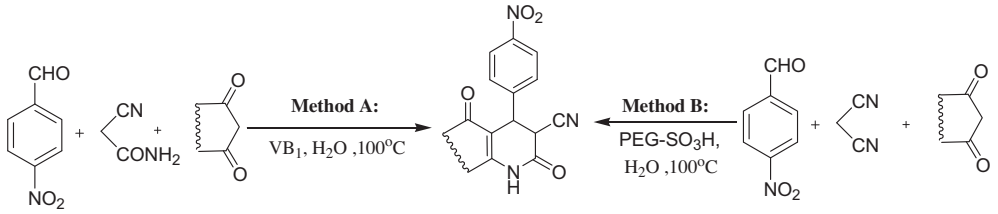
[a] 4-Nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), and ethyl acetoacetate (1 mmol) were stirred in 5 mL solvent in the presence of catalyst under refluxing condition.
[b] Isolated yield of the pure product.

Table 1
Screening of different catalysts for the synthesis of 3,4-dihydro pyridin-2-one

Entry	Catalyst	Time (h)		Yield[c] (%)	
		Scheme 1	Scheme 2	Scheme 1[a]	Scheme 2[b]
1	—	24	48	Trace	—
2	$ZnCl_2$	8	9	—	—
3	$MgCl_2$	8	9	—	—
4	SiO_2	8	9	—	—
5	Al_2O_3	8	9	—	—
6	Alum	8	9	—	—
7	I_2	8	9	—	—
8	*p*-Toluene sulfonic acid	8	7	10	64
9	AcOH	8	7	10	38
10	PEG–SO_3H	8	5.5	5	81
11	VB_1	4	9	80	—

[a] 4-Nitrobenzaldehyde (1 mmol), cyanoacetamide (1 mmol), and ethyl acetoacetate (1 mmol) were stirred in 5 mL H_2O in the presence of catalyst (15 mol %) under refluxing condition.
[b] 4-Nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), and ethyl acetoacetate (1 mmol) were stirred in 5 mL H_2O in the presence of catalyst (20 mol %) under refluxing condition.
[c] Isolated yield of the pure product.

Table 3
VB_1 and PEG–SO_3H catalyzed synthesis of 3,4-dihydropyridin-2-one derivatives in aqueous media



Entry	Ar	1,3-Diketo compound	Product	Time (h)		Yield[c,d] (%)	
				Method A[a]	Method B[b]	Method A	Method B
1	Ph	Ethylacetoacetate	**1a**	4.5	6	78, 72[e]	78, 74[e]
2	4-NO_2-C_6H_4-	Ethylacetoacetate	**1b**	4.0	5.5	80	81
3	3-NO_2-C_6H_4-	Ethylacetoacetate	**1c**	4.5	6	84	80
4	4-F-C_6H_4-	Ethylacetoacetate	**1d**	4.0	6	81	79
5	4-Cl-C_6H_4-	Ethylacetoacetate	**1e**	4.5	6	82	76
6	4-CH_3-C_6H_4-	Ethylacetoacetate	**1f**	4.5	6.5	78	72
7	4-OCH_3-C_6H_4-	Ethylacetoacetate	**1g**[f]	5.0	7	76	70
8	2-Fur	Ethylacetoacetate	**1h**	4.5	6	79	76
9	Ph-	Acetylacetone	**1i**	4.5	6	78	72
10	4-NO_2-C_6H_4-	Acetylacetone	**1j**	4.0	5.5	81	77
11	3-NO_2-C_6H_4-	Acetylacetone	**1l**	4.5	5.5	82	78
12	4-F-C_6H_4-	Acetylacetone	**1l**	4.0	5	85	77
13	4-Cl-C_6H_4-	Acetylacetone	**1m**	4.5	6	83	76
14	4-CH_3-C_6H_4-	Acetylacetone	**1n**	4.5	7	76	73
15	Ph-	Dimedone	**1o**	4.5	9	79	74
16	4-NO_2-C_6H_4-	Dimedone	**1p**	4.0	8.5	81	79
17	3-NO_2-C_6H_4-	Dimedone	**1q**[f]	4.5	8.5	83	77
18	4-F-C_6H_4-	Dimedone	**1r**	4.0	9	83	76
19	4-OCH_3-C_6H_4-	Dimedone	**1s**	5.0	9.5	72	69
20	4-CH_3-C_6H_4-	Dimedone	**1t**	4.5	9	74	72
21	4-N$(CH_3)_2$-C_6H_4	Dimedone	**1u**	5.0	10	71	67
22	2-Fur	Dimedone	**1v**	4.5	9.5	76	71

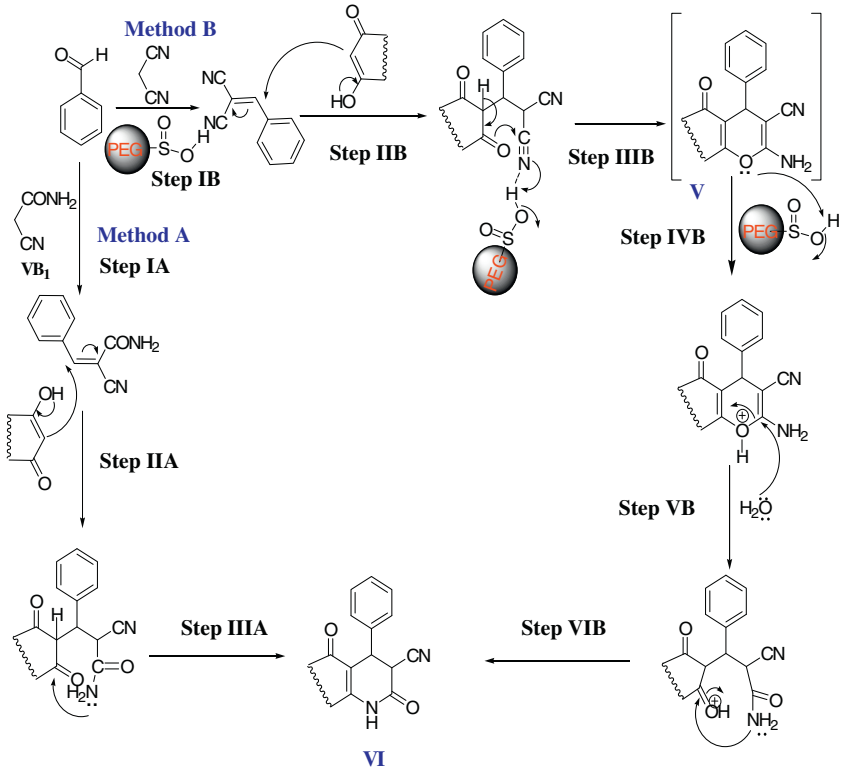
[a] Aldehyde (1 mmol), cyanoacetamide (1 mmol), and 1,3-diketone (1 mmol) were heated in 5 mL H_2O in the presence of 15 mol % VB_1 at 100 °C
[b] Aldehyde(1 mmol), malononitrile (1 mmol), and 1,3-diketone (1 mmol) were stirred in 5 mL H_2O in the presence of PEG–SO_3H (20 mol %) under refluxing condition.
[c] Isolated yield of the pure product.
[d] The products were characterized by ^1H NMR, ^{13}C NMR, IR, HRMS, and elemental analysis.
[e] Yield obtained after five catalytic cycles.
[f] The compounds **1g** and **1q** were crystallized from ethanol/water (7:3). Structure of the compounds were established by single crystal analysis (Supplementary data).[23]

increase in the amount of VB_1 from 3 to 15 mol % increased the yield of the desired product to a great extent (59–80%, Table 2). For the second synthetic method, the best result was obtained by using 20 mol % of PEG–SO_3H as the catalyst at 100 °C temperature in aqueous medium.

Encouraged by the efficiency of the above reaction protocols, we then devised two novel one pot three-component synthetic routes for the synthesis of highly functionalized 3,4-dihydropyridin-2-one derivatives under thermal conditions. To scrutinize the scope, limitations, and generality of these protocols, we have advocated a series of aldehydes and β-dicarbonyl compounds in the presence of 15 mol % VB_1 (Method A) or in the presence of 20 mol % of PEG–SO_3H (Method B) in H_2O under refluxing condition. In case of both the synthetic protocols[22] the reactions occurred smoothly with unsubstituted as well as substituted benzaldehydes. The results are summarized in Table 3. As mentioned in Table 3 heteroaromatic aldehydes also reacted efficiently to give the corresponding 3,4-dihydropyridin-2-one derivatives in good yield.

The formation of 3,4-dihydropyridin-2-one derivatives through VB_1 catalyzed three component coupling reaction involves Knoevenagel condensation, Michael addition, and then intra molecular cyclization as presented in Scheme 3. Only the Knoevenagel condensation product was isolated when PEG–SO_3H was administered as the catalyst but the targeted molecule was formed in poor yield (5%) after long reaction time. VB_1 played a very crucial role in the MCR but the exact role of the catalyst, is not very clear. Whereas in case of PEG–SO_3H catalyzed three component coupling reaction it involves mild polymer supported acid catalyzed Knoevenagel condensation, Michael addition, and then intra molecular cyclization for the formation of 4*H*-pyran intermediate. Subsequently this intermediate undergoes PEG–SO_3H catalyzed sequential ring opening and closing involving hydration and dehydration of the 4*H*-pyran nucleus to form 3,4-dihydropyridin-2-one derivatives in aqueous medium. The mild acid catalyzed Knoevenagel condensation, Michael reaction, ring annulation, and subsequent rearrangement leading to the targeted 3,4-dihydropyridin-2-one derivatives (**VI**) were confirmed by the isolation of the intermediate (**V**). The formation of the 4*H*-pyran intermediate (**V**), was also established by performing the PEG–SO_3H catalyzed rearrangement of the isolated intermediate.[24] These experimental results clearly revealed that in this multi component reaction initially 4*H*-pyran was generated which then undergoes PEG–SO_3H catalyzed rearrangement to 3,4-dihydropyridin-2-one derivative. VB_1 was unable to catalyze the second synthetic protocol. Although in the presence of VB_1, 4*H*-pyran intermediate (**V**) was isolated, the reaction did not proceed further as VB_1 could not catalyze the rearrangement step. Moreover the reaction can be scaled up to 10 mmol scale. In large scale preparation, we have successfully recycled both the catalysts in five new batches of reactions with almost same catalytic activity.[22]

In summary, we have successfully developed simple, convenient, environmentally benign, mild, and safe synthetic methods to afford highly substituted 3,4-dihydropyridin-2-one derivatives



Scheme 3. Plausible mechanistic course of the two methodologies for the synthesis of 3,4-dihydropyridin-2-one.

using the organocatalyst VB_1 and polymer supported acidic catalyst PEG–SO_3H in aqueous media from two different sets of precursors. The significant advantages of these methodologies are high yields, simple work-up procedures, easy preparation of PEG–SO_3H, and handling of both the catalysts. We believe that these one-pot catalytic transformations would be a very attractive choice for the synthesis of 3,4-dihydropyridin-2-one libraries in chemical as well as pharmaceutical industries.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.030.

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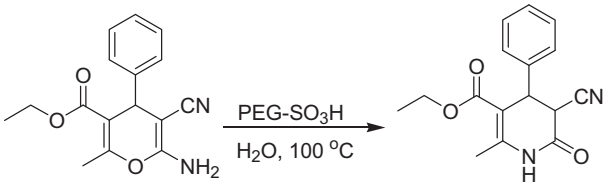
22. *Method A:* A mixture of aldehyde (1.0 mmol), cyanoacetamide (1.0 mmol), 1,3-dicarbonyl compound (1.0 mmol), and VB_1(15 mol %) was stirred in 5 ml of water at 100 °C for the required period of time(TLC). After the completion of the reaction, the mixture was extracted with ethyl acetate (3 × 10 ml) and was purified by column chromatography (silicagel, ethyl acetate, hexane 1:3) to afford the desired product of 3,4-dihydropyridin-2-ones.
The aqueous part was evaporated to dryness under reduced pressure and the resulting solid was washed three times with 5 ml ethyl acetate and was dried under reduced pressure to get back the catalyst which was used for the new set of reaction.
Method B: A mixture of aldehyde (1.0 mmol), malononitrile (1.0 mmol), 1,3-dicarbonyl compound (1.0 mmol), and PEG–SO_3H (20 mol %) was stirred in 5 ml of water at 100 °C for the required period of time(TLC). After the completion of the reaction, the mixture was extracted with ethyl acetate (3 × 10 ml) and was purified by column chromatography (silicagel, ethyl acetate, hexane 1:3) to afford the desired product of 3,4-dihydropyridin-2-ones.
The catalyst was recovered by evaporating the aqueous part under reduced pressure, and the resulting gummy solid was washed with diethyl ether, and dried under reduced pressure.
*5-Cyano-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (**1a**)*
Characteristics: White crystalline solid; Mp: 104 °C; IR (KBr): 3322, 2192, 1676, 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.19(3H, t, J = 6.9 Hz), 2.42 (3H, s), 4.06–4.18 (3H,m), 4.49 (2H,d, J = 6.9 Hz), 7.24–7.35 (5H,m), 8.53(1H,s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.8, 41.2, 41.5, 60.7, 107.7, 114.1, 127.7, 128.4, 128.9, 136.0, 145.9, 163.1, 165.4; Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.57; H, 5.68; N, 9.82. HRMS of [$C_{16}H_{16}N_2O_3$+H^+]: calcd: 285.1240 found: 285.1236
*5-Acetyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyridine-3-carbonitrile (**1i**):*
Characteristics: white crystalline solid; Mp: 156 °C; IR (KBr): 3352, 2188, 1694, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.94 (3H, s), 2.16 (3H, s), 3.80 (2H, d, J = 3.6 Hz), 4.15 (2H, d, J = 3.6 Hz), 6.94–7.18 (5H, m), 8.09 (1H,s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 29.6, 41.5, 47.3, 113.8, 115.7, 116.4, 116.7, 129.8, 129.9, 130.6, 145.1, 161.9, 194.4; Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.82; H, 5.53; N, 11.04; HRMS of [$C_{15}H_{14}N_2O_2$+H^+]: calcd: 255.1134 found: 255.1132.
23. Crystallographic data for the structure **1g** and **1q** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 876417 and CCDC 876418 respectively. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
24. The intermediate 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylicacid ethyl ester was isolated by stirring a mixture of benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), ethyl acetoacetate (1.0 mmol), and PEG–SO_3H (20 mol %) in 5 ml of water at 100 °C for 30 min. After the completion of the reaction, the mixture was filtered to obtain the 4*H*-pyran intermediate (Characterization data presented in Supplementary data).



A mixture of the intermediate 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylic acid ethyl ester (1.0 mmol), and PEG–SO_3H (20 mol %) was stirred in 5 ml of water at 100 °C for 5 h. After completion of the reaction, the mixture was extracted with ethyl acetate (3 × 10 ml) and was purified by column chromatography (silicagel, ethyl acetate, hexane 1:3) to afford the desired product 3,4-dihydropyridin-2-ones.