

Poly(vinylpyrrolidonium) perchlorate catalyzed one-pot synthesis of tricyclic dihydropyrimidine derivatives

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Abstract A simple and efficient procedure for the synthesis of benzo[4,5]imidazo[1,2- α]pyrimidine and 2-amino-4-substituted-1,4-dihydrobenzo[4,5]imidazo[1,2- α]pyrimidine-3-carbonitrile derivatives using poly(vinylpyrrolidonium) perchlorate {[PVPH]ClO₄} as a newly reported, modified polymeric catalyst is reported. Some of the advantages of this novel synthetic method are: easy preparation of the catalyst, simple and easy work-up procedure, short reaction times, high to excellent yields of the products and reusability of the catalyst.

Keywords Benzo[4,5]imidazo[1,2- α]pyrimidines · 2-Amino-4-substituted-1,4-dihydrobenzo[4,5]imidazo[1,2- α]pyrimidine-3-carbonitriles · Poly(vinylpyrrolidonium) perchlorate {[PVPH]ClO₄} · Heterogeneous reaction conditions · Polymer-based catalyst

Introduction

Dihydropyrimidine derivatives are among the most important classes of tricyclic compounds which show an interesting wide range of biological and pharmaceutical properties such as antiviral, antibacterial, anti-inflammatory, anti-hypertensive, anti-tubercular, anti-malarial and cytotoxic activities [1–5]. In addition, they can be used as calcium channel blockers and antihypertensive agents [6]. These significant properties have attracted the attention of many organic chemists to the synthesis of these types of compounds, so that their investigations have led to various synthetic methods using

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different types of catalysts. Some of these catalysts are: H_3BO_3 [7], 1,1,3,3-*N,N,N',N'*-tetramethylguanidinium trifluoroacetate [8], tetrabutylammonium hydrogen sulfate [9], thiamine hydrochloride [10], $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ [11], [bmim] BF_4 [12], $\text{H}_2\text{NSO}_3\text{H}$ [13], ionic liquid supported-nanoporous silica (SBA-IL) [14], *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA) [15] and *p*-toluenesulfonic acid [16]. The reaction was also investigated under catalyst-free conditions [17].

Although a number of these methods have their own advantages, some of them suffer from one or more disadvantages, such as use of large amounts of catalysts, long reaction times, unsatisfactory products yields, high temperatures and the use of toxic organic solvents; these disadvantages have limited the use of these methods. Therefore, it is necessary to find more convenient methods for the synthesis of dihydropyrimidines.

Experimental

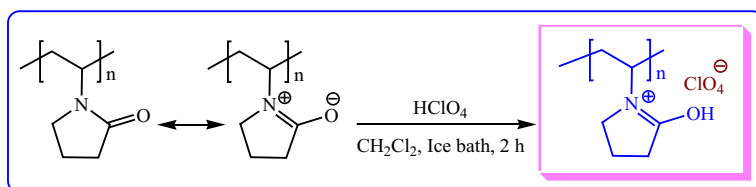
Chemicals were purchased from Fluka, Merck, and Sigma-Aldrich chemical companies. Cross-linked poly(vinylpyrrolidone) was purchased from BASF Corp. (Germany). All products were characterized by comparison of their physical constants, infrared (IR) spectra and nuclear magnetic resonance (NMR) spectroscopy with authentic samples and those reported in the literature.

Preparation of catalyst [PVPH] ClO_4 [18]

HClO_4 (5 mmol, $\cong 0.43$ mL, as a 70 % aqueous solution) was added to a suspension of 0.05 g of powdered poly(vinylpyrrolidone) [crosslinked poly(vinylpyrrolidone) with MW > 1,000,000] in 10 mL of dry CH_2Cl_2 over a period of 10 min in an ice bath. After the addition was completed, the mixture was stirred for 2 h and then filtered. The solid residue was washed with diethyl ether (10 mL) and dried at 80 °C to afford [PVPH] ClO_4 as a white powder (Scheme 1) [18].

General procedure for the synthesis of the benzo[4,5]imidazo[1,2- α]pyrimidine (A) or 2-amino-4-substituted-1,4-dihydrobenzo[4,5]imidazo[1,2- α]pyrimidine-3-carbonitrile (B) derivatives

A mixture of ethyl acetoacetate and/or acetylacetone (1 mmol) or malononitrile (1.1 mmol), 2-aminobenzimidazole (1 mmol), aldehyde (1 mmol) and [PVPH] ClO_4



Scheme 1 Preparation of [PVPH] ClO_4

(30 mg, 6.84 mol %) was heated at 100 °C in an oil bath for the appropriate time. After completion of the reaction [monitored by thin layer chromatography (TLC): *n*-hexane: ethyl acetate (3:1)], the reaction mixture was cooled to room temperature and EtOH (5 mL) was added to it and filtered to separate the catalyst. After evaporation of the solvent from the filtrate, the crude solid product was recrystallized from ethanol to obtain pure A or B products.

The spectral [IR, proton (¹H) NMR and ¹³C NMR] data of new compounds are presented below.

(Compound 4, Table 2): Ethyl 4-(4-methylthiophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate

Yellow solid, m.p. 271–273 °C; IR (KBr): $\nu = 3232, 3103, 3031, 1695, 1611, 1568, 1449, 1251, 1014, 874, 829, 733 \text{ cm}^{-1}$. ¹H NMR [deuterated dimethyl sulfoxide (DMSO-d₆), 400 MHz] σ : 1.17 (t, $J = 7.2 \text{ Hz}$, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.47 (s, 3H, CH₃), 4.0–4.07 (m, 2H, CH₂), 6.40 (s, 1H, CH), 6.96 (t, $J = 7.2 \text{ Hz}$, 1H, ArH), 7.05 (t, $J = 7.6 \text{ Hz}$, 1H, ArH), 7.14 (d, $J = 8.4 \text{ Hz}$, 2H, ArH), 7.25–7.36 (m, 3H, ArH), 7.8 (d, $J = 8 \text{ Hz}$, 1H, ArH), 10.8 (brs, 1H, NH) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): 14.5, 14.8, 19.1, 55.9, 59.8, 98.3, 110.1, 117.26, 120.6, 122.2, 126.0, 128.1, 131.3, 138.2, 139.0, 142.7, 146.0, 146, 9, 165.6 ppm.

(Compound 10, Table 3): 2-Amino-4-(pyridin-3-yl)-1,4-dihydrobenzo[4,5]imidazolo[1,2-a]pyrimidine-3-carbonitrile

m.p. 242–244 °C; IR (KBr): $\nu = 3452, 3315, 3056, 2180, 1663, 1590, 1465, 1399, 712 \text{ cm}^{-1}$. ¹H NMR (DMSO-d₆, 400 MHz) σ : 5.37 (s, 1H), 6.97 (s, 2H, NH₂), 7.03 (t, $J = 7.6 \text{ Hz}$, 1H), 7.14 (t, $J = 7.6 \text{ Hz}$, 1H), 7.26 (d, $J = 7.6 \text{ Hz}$, 1H), 7.40–8.54 (m, 5H), 8.64 (s, 1H, NH) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): 51.6, 61.4, 113, 116.6, 120.5, 123.9, 124.4, 129.7, 134.4, 136, 138.5, 143, 148, 149.5, 150, 152.

Table 1 Effect of temperature, solvent and amount of the catalyst on the synthesis of benzo[4,5]imidazo[1,2- α] pyrimidine derivative of 4-chlorobenzaldehyde

Entry	Catalyst (mg)	Condition	Time (min)	Yield (%) ^a
1	10 (2.28 mol%)	Solvent-free, 100 °C	40	85
2	20	Solvent-free, 100 °C	35	90
3	30	Solvent-free, 100 °C	30	97
4	40	Solvent-free, 100 °C	30	98
5	30	Solvent-free, 50 °C	120	50
6	30	Solvent-free, 120 °C	30	98
7	30	EtOH, Reflux	50	40
8	30	CH ₂ Cl ₂ , Reflux	50	50
9	30	H ₂ O, Reflux	50	30

Reaction conditions: 2-aminobenzimidazole (1 mmol), ethylacetoacetate (1 mmol) and 4-chlorobenzaldehyde (1 mmol)

^a GC yield

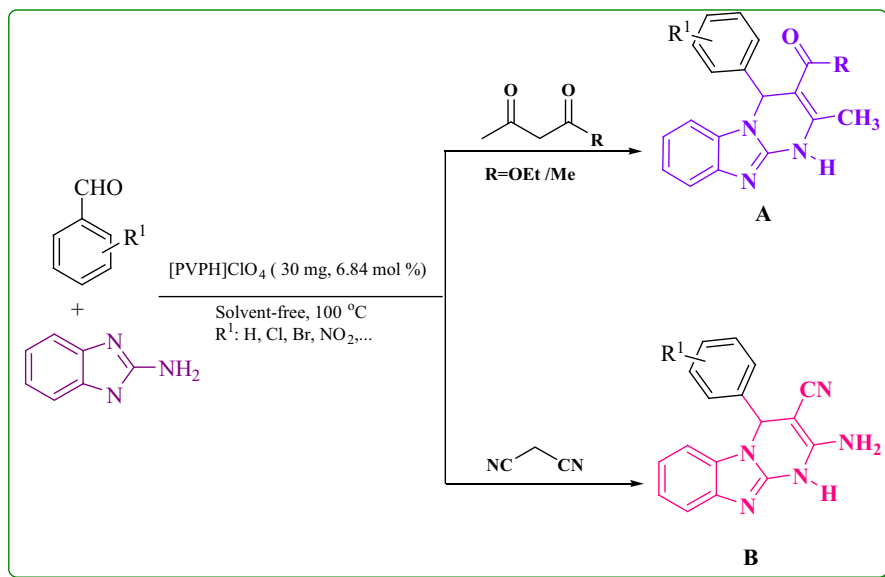
Very recently we reported the preparation of poly(vinylpyrrolidonium) perchlorate {[PVPH]ClO₄} [18] and its applicability in the promotion of the synthesis of polyhydroquinoline derivatives via Hantzsch condensation. Herein and in continuation of this study, we wish to report the applicability of this reagent in the accelerated preparation of tricyclic dihydropyrimidine derivatives.

At the first step, optimization of the reaction conditions was done by studying the reaction of 2-aminobenzimidazole with 4-chlorobenzaldehyde and ethylacetoacetate in the presence of various amounts of [PVPH]ClO₄ in the absence of solvent and also in different solvents such as dichloromethane, ethanol and water under thermal conditions (Table 1). We found that the reaction was rapid and gave excellent yields of the products in the presence of 30 mg of the catalyst at 100 °C in the absence of solvent (Scheme 2).

Results and discussion

Catalytic activity

After optimization of the reaction conditions and in order to show the general applicability of the method, different types of aldehydes were subjected to the same reaction under the determined conditions. The obtained results showed that in all cases the corresponding products were obtained in good to excellent yields in appropriate times (Table 2, entries 1–11). We have also found that the same results were obtained when acetylacetone was used in place of ethylacetoacetate (Table 2,



Scheme 2 Optimized conditions for the preparation of the tricyclic dihydropyrimidine derivatives

entries 12–14). The results showed that in all cases, regardless of the substituent, the reaction gave the products in good to high yields within relatively short reaction times.

After successful synthesis of a series of benzo[4,5]imidazo[1,2- α] pyrimidine derivatives, we decided to study the preparation of 2-amino-4-substituted-1,4-dihydrobenzo[4,5]imidazolo[1,2- α]pyrimidine-3-carbonitriles by the reaction of malononitrile, 2-aminobenzimidazole and aldehydes in the presence of [PVPH]ClO₄ under the above-mentioned reaction conditions (Scheme 2).

The results showed that various aldehydes were reacted with the other starting materials using this method to produce the desired products in excellent yields within very short reaction times (Table 3). It should be noted that only two methods for the preparation of these compounds are reported in the literature [16, 17].

In a plausible mechanism, at first, the aldehyde is activated by the proton of the catalyst. Then, the carbonyl group is attacked by ethylacetoacetate or malononitrile to form the Knoevenagel products (I). In continuation, 2-aminobenzimidazole is reacted with these intermediates via Michael addition reaction to produce the related intermediate (II). Finally, this intermediate is converted to the requested products via intermolecular cyclization and dehydration reactions (Scheme 3).

Table 2 Synthesis of benzo[4,5]imidazo[1,2- α]pyrimidine derivatives catalyzed by [PVPH]ClO₄

Entry	Aldehyde	R	Time (min)	Yield (%)	Melting point (°C)	
					Found.	Reported [references]
1	H	OEt	45	92	281–283	282–285 [14]
2	<i>p</i> -Cl	OEt	30	97	297–300	301–303 [15]
3	<i>p</i> -CN	OEt	60	92	307–309	>275 [10]
4	<i>p</i> -SCH ₃	OEt	15	90	271–273	–
5	<i>p</i> -CH ₃	OEt	35	95	258–260	262.2–262.4 [10]
6	<i>p</i> -CH ₃ O	OEt	40	94	256–258	250–253 [8]
7	<i>p</i> -NO ₂	OEt	30	92	300–302	302–303 [14]
8	<i>m</i> -Br	OEt	40	98	254–257	266–268 [15]
9	<i>m</i> -CH ₃ O	OEt	40	95	210–213	211–214 [15]
10	<i>m</i> -Cl	OEt	20	98	263–266	269.6–269.8 [10]
11	<i>m</i> -NO ₂	OEt	55	96	296–298	294–296 [13]
12	H	Me	30 ^a	90	280–282	>275 [10]
13	<i>p</i> -Cl	Me	30 ^a	97	282–285	>285 [10]
14	<i>p</i> -CH ₃ O	Me	20 ^a	96	268–270	278.6–279.5 [10]

The desired products were characterized by their physical data, comparison with melting points, IR and/or ¹H NMR spectroscopy

Isolated yield

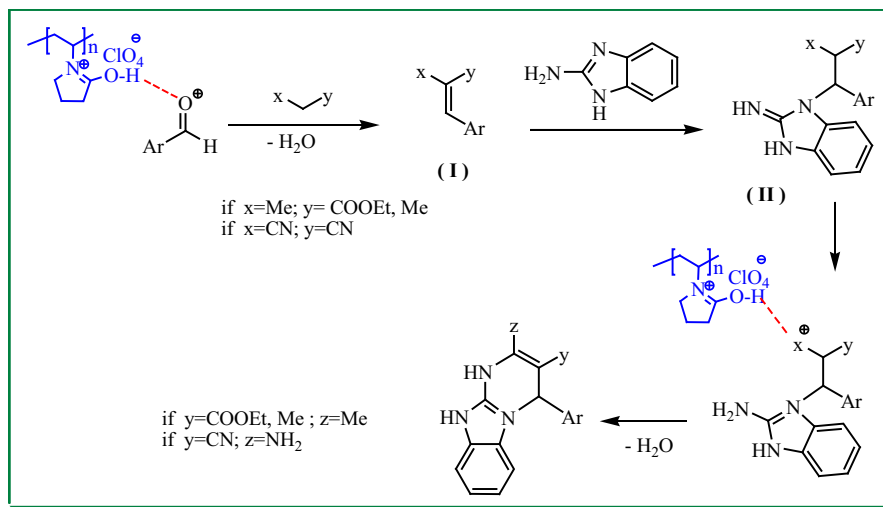
^a 40 mg of catalyst

Table 3 Synthesis of 2-amino-4-substituted-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles derivatives catalyzed by [PVPH]ClO₄

Entry	Aldehyde	Time (min)	Yield (%)	Melting point (°C)	
				Found.	Reported [references]
1	H	2	92	233–236	235–236 [16]
2	<i>p</i> -Cl	15	96	236–238	238 [17]
3	<i>p</i> -Br	20	95	307–309	317–319 [16]
4	<i>p</i> -F	5	90	252–254	266–268 [16]
5	<i>p</i> -(CH ₃) ₂ CH	4	98	232–234	230–232 [16]
6	<i>m</i> -Br	4	98	242–244	240 [17]
7	<i>m</i> -NO ₂	8	90	239–241	236 [17]
8	<i>o</i> -Cl	5	95	234–236	236–238 [16]
9	<i>o</i> -CH ₃	3	97	237–239	236 [17]
10	3-Pyridyl carbaldehyde	10	80	242–244	–

The desired products were characterized by their physical data, comparison with melting points, IR and/or ¹H NMR spectroscopy

Isolated yield



Scheme 3 Plausible mechanism of the reactions

In continuation, we decided to examine the catalytic activity of the recycled catalyst for the synthesis of the title derivatives. After separation of the product, the catalyst was washed with EtOH, dried and reused for the same reaction. This

Fig. 1 Reusability of [PVPH]ClO₄ in the synthesis of ethyl 4-(4-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate

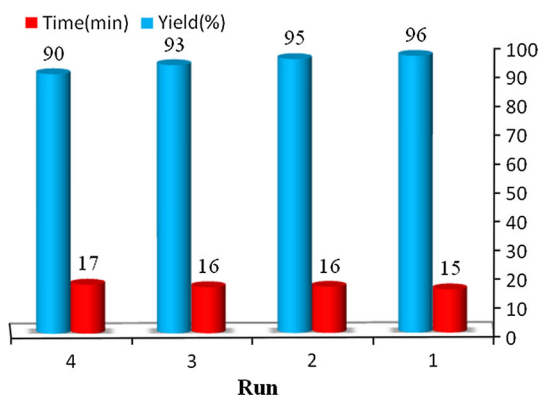
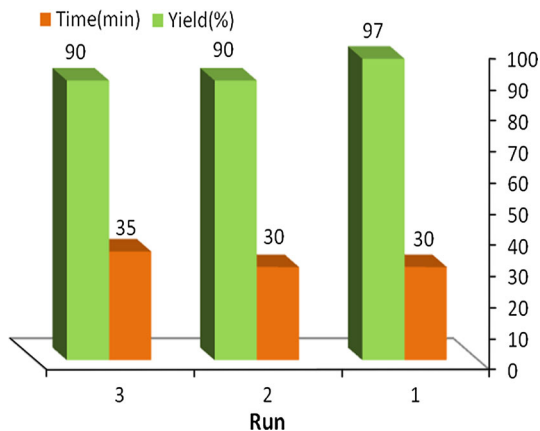
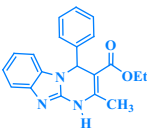
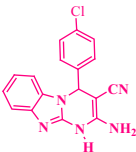


Fig. 2 Reusability of [PVPH]ClO₄ in the synthesis of 2-Amino-4-(4-chlorophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile

process was carried out over three runs and all reactions led to the desired products with high efficiency (Figs. 1, 2). It should be noted that the Fourier transform infrared (FT-IR) and pH analysis of the recovered catalyst showed nearly the same loading of H⁺ as the freshly prepared catalyst. These results suggest that changing of the catalyst and/or leaching of the acid species does not occur during the course of the reaction.

Table 4 compares the efficiency of [PVPH]ClO₄ with the other catalysts in the synthesis of tricyclic dihydropyrimidine derivatives of benzaldehyde. The presented results show that the same reactions are carried out in the presence of the larger amounts of the catalysts (Table 4, entries 1, 4, 8, 10) or the reaction times are longer compared with the present method (Table 4, entries 2, 3, 4, 8).

Table 4 Comparison of various catalysts in the synthesis of benzo[4,5]imidazo[1,2- α]pyrimidine and 2-amino-4-substituted-1,4-dihydrobenzo[4,5]imidazolo[1,2- α]pyrimidine-3-carbonitriles derivatives

Entry	Product	Catalyst (mol%)	Conditions	Time (min)	Yield (%) [references]
1		H ₃ BO ₃ (20)	H ₂ O, r.t.	30	75 [7]
2		TMGT (80 mg)	Solvent-free, 100° C	5 h	73 [8]
3		Thiamine hydrochloride (VB1) (5)	H ₂ O, Reflux	3 h	90 [10]
4		Sulfamic acid (10)	Solvent-free, 85 °C	8 h	88 [13]
5		SBA-IL (20 mg)	Solvent-free, 150 °C	40	87 [14]
6		<i>N,N,N',N'</i> -tetrabromobenzene-1,3-disulfonamide [TBBDA] (5)	Solvent-free, 100° C	80	88 [15]
7		H ₃ PO ₄ -Al ₂ O ₃ (120 mg)	Solvent-free, 100° C	85	90 [19]
8		Silica sulfonic acid (8)	Solvent-free, 110° C	6 h	94 [20]
9		[PVPH]ClO ₄ (6.84, 30 mg)	Solvent-free, 100 °C	45	92 [this work]
10			p-TSA (10)	Solvent-free, 80 °C	30
11	Catalyst-free		H ₂ O, 90 °C	9 h	70 [17]
12	[PVPH]ClO ₄ (6.84, 30 mg)		Solvent-free, 100 °C	15	96 [this work]

Conclusion

In this paper, we have developed an efficient and green procedure for the synthesis of two types of tricyclic compounds including benzo[4,5]imidazo[1,2- α]pyrimidines and 2-amino-4-substituted-1,4-dihydrobenzo[4,5]imidazolo[1,2- α]pyrimidine-3-carbonitriles using [PVPH]ClO₄ as a new polymeric catalyst. These procedures have several advantages, including heterogeneous reaction conditions, easy work-up, simple procedure for the preparation of the catalyst, appropriate times and high to excellent yields of the products. Also, the catalyst could be successfully recovered and reused for at least three runs without significant loss in its activity.

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