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$H_3PW_{12}O_{40}$ as an efficient catalyst for one-pot-tricomponent synthesis of chromeno[4,3-b]quinolones under microwave irradiation

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Abstract

Some chromene[4,3-b]quinoline derivatives were synthesized in a three components one-pot reaction of 1,3-cyclohexadione,arylaldehydes and 4-aminocoumarin under microwave irradiation in the solventless system using a heteropolyacid catalyst,$H_3PW_{12}O_{40}$in 80-95% yields and high rates.The shorter reaction times, one-pot, good yields, simple work-up procedure and environmentally friendly conditions are the main advantages of this method compared to the two step method. The product was identified by its ^{1}H NMR, mass and IR spectra, which were compared to those reported previously.

Keywords: Chromeno[4,3-b]quinoline; heteropolyacid; 1,4-dihydropyridines.

Introduction

1,4-Dihydropyridines (DHPs) are commercially used as calcium channel blockers such as nifedipine, nitrendipine and nimodipine for the treatment of cardiovascular diseases[1]. 1,4-DHPs, particularly 4-aryl-substituted-1,4-dihydropridines, possess a wide range of biological activities such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabectic activity [2]. Extensive studies have revealed that these compounds exhibit various medicinal functions such as neuroprotectant, platelet anti aggregatory activity, cerebral antischemic activity in the treatment of Alzheimer's disease, and chemosensitizer in tumor therapy [3].

These examples clearly indicate the interest of the synthetic community in the 1,4-dihydropyridine core[4]. It is well established that slight structural modifications on the DHP ring may result in remarkable changes in the pharmacological effects [5–7]. For this reason, considerable effort has focused on the synthesis of new 1,4-DHPs with wider applicability and higher efficiency.

The use of heteropolyacids as ecofriendly catalysts has been widely studied in recent decades [8]. Due to their strong Brönsted acidity, Keggin-heteropolyacids such as $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$ and $H_4SiW_{12}O_{40}$can be used instead of conventional inorganic

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and organic acids [8-11]. Moreover, they have advantages of easy catalyst separation from reaction medium and lower problems of workup [12].

These findings together with our interest in pharmacological active polycondensed heterocycles[13,14], and reactions catalyzed by heteropolyacids leading to heterocyclic compounds of biological significance [15], prompted us finding a green, fast and more efficient method to synthesize some of DHPs heteroanalogous, chromene[4,3-b]quinoline derivatives.

Experimental

All chemicals and all solvents used in this study were purchased fromthe Merck Company (Darmstadt, Germany) and Sigma-Aldrich Chemical Company (Steinhein, Germany). RPMI 1640, ^{1}H NMR spectra were measured using a Bruker 500 spectrometer (Bruker, Rheinstetten, Germany) and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. The IR spectra were acquired on a Nicollet FT-IR magna 550 spectrographs (KBr disks) (Nicollet, Madison, WI, USA). MS spectra were obtained with a Finnegan MAT TSQ-70 spectrometer (Finnegan Mat,Bremen, Germany). The purity of a compound was confirmed by TLC using different mobile phases. Elemental analysis was taken on a Vario EL III elemental analyzer within ±0.4% of theoretical values for C, H, and N. Microwave experiments were conducted in a Milestone MicroSYNTH apparatus.

General procedure for the synthesis of chromeno[4,3-b]quinoline derivatives 5a-j:

4-Aminocoumarin1(0.16 g,1 mmol), 1,3-cyclohexadione **3** (0.12 g, 1 mmol), arylaldehyde **4** (1 mmol), and heteropoly acid ($H_3PW_{12}O_{40}$)(0.288g, 10%) were mixed in a beaker thoroughly using spatula. The beaker is placed in a microwave oven at 100 °C for specified time (5min), to complete the reaction (monitored by TLC). The crude solid material was washed with acetone (50 mL) and the filtered solution was evaporated and purified by flash column chromatography using ethyl acetate/petroleum ether (20:80) to give **5a-j** (Table 2). All products were identified by their mass and ^{1}H NMR spectra by comparison with authentic samples [13].

7-(3-Bromophenyl)-8,9,10,12-tetrahydro-7H-chromeno[4,3-b]quinoline-6,8-dione(5h).

Yield = 60%, mp = 264-265 °C

IR (KBr) ν: 3436 (N-H), 3078 (C-H aromatic), 2924 (C-H aliphatic), 1671 (C=O) cm^{-1}.

^{1}H NMR (d_6-DMSO) δ: 1.88- 1.99 (m, 2H, H_{10}), 2.24-2.40 (m, 2H, H_{11}), 2.51-2.81 (m, 1H, H_9), 2.83-2.89 (m, 1H, H_9), 4.97 (s, 1H, H_7), 7.18-7.41 (m, 5H, H_4, H_{14}, H_{16}, H_{17}, H_{18}), 7.46 (t, 1H, *J*= 8.0 Hz, H_2), 7.64 (t, 1H, *J* = 8.0 Hz,H_3), 8.33 (d , 1H, *J* = 8.0 Hz, H_1), 9.95 (s, 1H, NH).

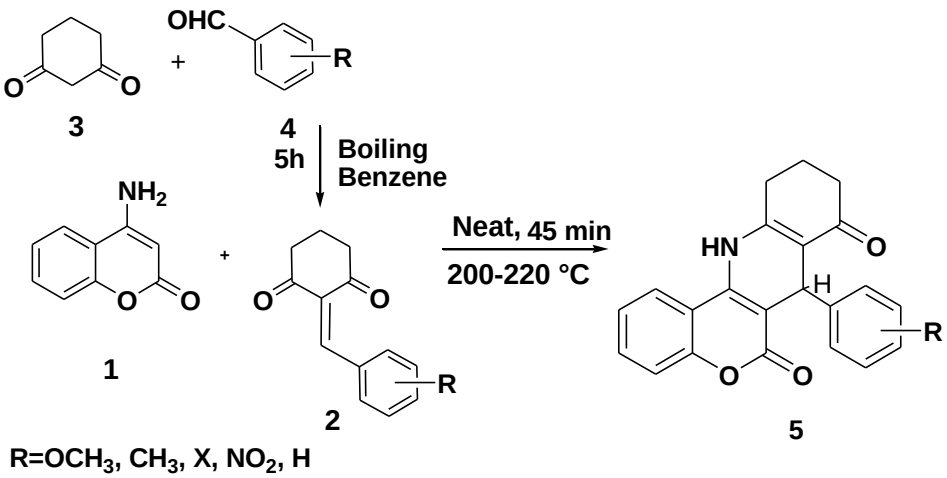
MS : *m/z* (%), 423 (M^++ 2, 24), 421 (M^+, 25), 342 (34), 267 (100), 144 (20), 76 (8), 56(15).

Anal. Calcd for $C_{22}H_{16}BrNO_3$: C, 62.57; H, 3.82.

Results and discussion

Recently, we have introduced synthesis of chromeno[4,3-b]quinoline derivatives as new analogous asymmetrical acridines by a two steps method. First, 2-benzylidene-cyclohexane-1,3-dione derivatives **2** were obtained in 80–90% yields by condensation of 1,3-cyclohexadione **3** and arylaldehydes **4**, in boiling dry benzene for 5 h. Second, the reaction of

4-aminocoumarin with the intermediate **2** at 200-220 ˚C for 45 min affording 7-aryl-8,9,10,12-tetrahydro-7H-chromeno[4,3-b]quinoline-6,8-dione (**5a–j**) in 30–50% yields(Scheme 1)[13].



Scheme 1. Preparation of chromeno[4,3-b]quinoline **5a-j**

We have also tested the cytotoxic and antitumoral activities of chromeno[4,3-b]quinoline derivatives on human cancer cell linesand the results showed moderate cytotoxic and undesirable antitumoral activities [13].

Herein, we wish to report the synthesis of chromeno[4,3-b]quinoline derivatives by one-pot, three component reaction of 4-aminocoumarin **1**, arylaldehydes **4a-j** and 1,3-cyclohexanedione **3** in the presence of $H_3PW_{12}O_{40}$ as a catalystunder solventless conditions using microwave irradiation.

Initially, the condensation reaction of 4-aminocoumarin **1**, 1,3-cyclohexadione **3**, 3-bromobenzaldehyde 4 h, was chosento optimize the reaction conditions such as temperature and quantity of the catalyst (Table 1, Entries 1-4). We found that the best yield was obtained in the presence of $H_3PW_{12}O_{40}$ (molar ratio 10%) at 100 ˚C (Entry 1). The less amount of the catalyst gave low yield even after a prolonged reaction time, and the more amounts could not cause obvious increase for the yield of the product and could not shorten the reaction time.

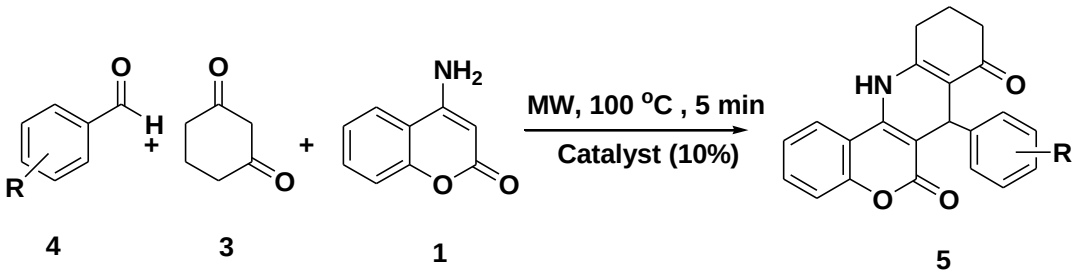
Table 1. One-pot reaction of 4-aminocoumarin **1,** 1,3-cyclohexadione **3**, 3-bromobenzaldehyde 4 h under microwave irradiation

Entry	Catalyst	Yield[a] (%)
1	$H_3PW_{12}O_{40}$ (10%)[b]	90
2	$H_3PW_{12}O_{40}$ (5%)[b]	75
3	$H_3PW_{12}O_{40}$ (20%)[b]	90
4	$H_3PW_{12}O_{40}$ (10%)[c]	-
5	SiO_2 (10%)[b]	50
6	MgO (10%)[b]	70
7	PbO (10%)[b]	10
8	ZrO_2 (10%)[b]	50
9	ZnO (10%)[b]	50
10	MoO_3 (10%)[b]	50
11	$LiClO_4$ (10%)[b]	60
12	Amido Sulfonic Acid (10%)[b]	60
13	$ZrCl_4$ (10%)[b]	60
14	$H_3PMo_{12}O_{40}$ (10%)[b]	80
15	$Mg(OTf)_2$ (10%)[b]	50
16	LiOTf (10%)[b]	50

[a]Isolated yield
[b]Condition: 100 ˚C
[c]Condition: 60 ˚C

In order to show the role of the catalyst, similar reactions were also examined in the presence of different common catalysts (molar ratio 10%) such as SiO_2, MgO, PbO, ZrO_2, ZnO, MoO_3, $LiClO_4$, sulfamic acid, $ZrCl_4$, $H_3PMo_{12}O_{40}$, $Mg(OTf)_2$ and LiOTf under microwave irradiation at 100 ˚C (Scheme 2) (Table 1, Entries 5-16). Under these conditions, the reactions led to the formation of the desiredproduct in low yields.

The reaction of a variety of arylaldehydes **4** with 1,3-cyclohexadione **3** and 4-aminocoumarin **1** was then investigated to confirm the generality of the present method (Scheme 2). The obtained results are summarized in Table 2.



Scheme 2. One-potsynthesis of chromeno[4,3-b]quinoline **5a-j**

Table 2. One-pot synthesis of chromeno[4,3-b]quinoline derivativesunder microwave irradiationusing $H_3PW_{12}O_{40}$

Product	R	mp[a](˚C) (Lit.)	Yield(%)[b]	Yield(%)[c]
5a	2-OMe	246(245-246)	80	75
5b	3-OMe	188(188-189)	80	55
5c	4-OMe	197(196-197)	90	75
5d	3-NO_2	220	80	-
5e	4-NO_2	195(195-197)	80	45
5f	4-Cl	243(244-245)	80	55
5g	4-Me	215(216-215)	95	72
5h	3-Br	264(265-264)	90	60
5i	4-Br	169(170-171)	80	65
5j	H	178	85	-

[a]The numbers in parentheses refer to melting points in the literature [13].
[b]Isolated yields of pure compounds. Conditions: $H_3PW_{12}O_{40}$ (10 mol%), 100 ˚C, 5min
[c]Yields refer to the literature [13]. Conditions: two steps method, 1) Refluxing in benzene, 5 h . 2) Heat 200-220 °C, 1 h

The desired products were obtained in one-pot and very fast method in high yields (Table 2). These results show that the yields of the products are relatively independent of arylaldehydes. All the aforementioned catalyzed reactions delivered excellent product yields, short time and lower temperature compared to our last two steps method [13]. Heteropoly acid is separated by filtration and successfully used in three subsequent runs without any significant loss in catalytic activity. The reactions were monitored by TLC and subsequent work-up afforded a single compound. The products were purified by flash column chromatography and were identified by

its ^{1}H NMR, mass and IR spectra, which were compared to those reported previously [13].

The mechanism for the formation of **5a–j** in the absence of catalyst has been suggested [13]. Generally, reactions catalyzed by HPAs may be represented by the conventional mechanisms of Brönsted acid catalysis [15]. Coordination of the carbonyl groups in the intermediate products by the proton of the catalyst may increase electrophilicity of the carbonyl derivatives in both the Knoevenagel condensation and the Michael addition step.

Conclusion

In this study, we have developed a one-pot and green method using an ecofriendly and reusable heterogeneous inorganic catalyst microwave irradiation forthesynthesis of 7-aryl-8,9,10,12-tetrahydro-7H-chromeno[4,3-*b*]quinoline-6,11-diones derivatives **5a-j**. The short reaction time, one-pot, high yields, simple work-up procedure and environmentally friendly conditions are the main advantages of this method,which can be valuable to use or investigate for similar systems.

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