

AIHMS as an efficient catalyst for the synthesis of chromenes derivatives

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ABSTRACT

Catalytic activity of AIHMS was investigated as a cheap heterogeneous reusable catalyst in some multi-component reactions for the synthesis of various chromenes. Three-component reaction of 2-hydroxy-naphthoquinone with an aromatic aldehyde and dimedone or barbituric acid in H₂O under reflux conditions was performed using AIHMS in relatively good yields. The approach was more extended using pseudo five-component reaction of 2,5-dihydroxy-1,4-benzoquinone, two equivalent of an aromatic aldehyde and two equivalent of dimedone or 1,3-cyclohexadione with efficient catalytic effect of AIHMS. Three-component reaction of an aldehyde, malononitrile and 1-naphthol in the presence of AIHMS gave 2-amino-4-phenyl-4*H*-benzo[*h*]chromene-3-carbonitriles in high yields. The work-up procedures are very simple, and the products do not require further purification. The catalysts can be recycled and reused for several times without observable loss of performance.

Keywords: AIHMS, Chromene, Heterogeneous catalyst, Multi-component, Green chemistry.

1. Introduction

Chromenes are an important class of pharmacologically active compounds which widely present in plants, including edible vegetables and fruits [1]. Some of the natural bioactive compounds with chromene moiety such as pyranokunthone, lambertellin, β -lapachone and α -xiloidone were identified in recent years [2–7]. In this regard, synthesis of chromenes has attracted much attentions [8] which some of them have remarkable effects as pharmaceuticals [9-11].

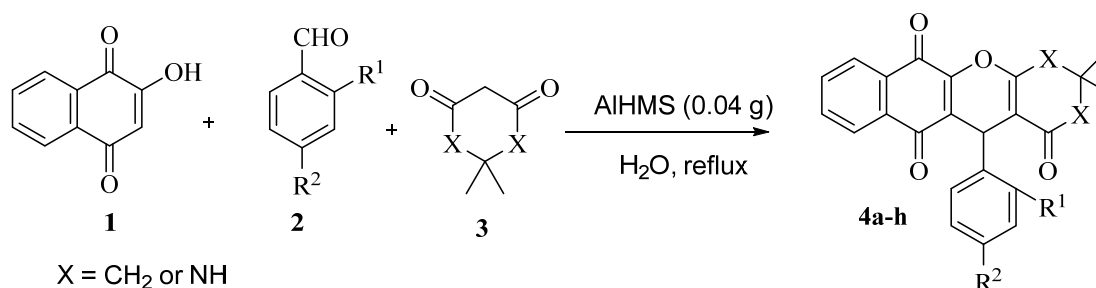
Today, the emphasis of science and technology is shifting more towards environmentally friendly and sustainable processes such as the reactions with the multi-component strategy and heterogeneous catalysts [12]. Heterogeneous catalysis allows production and ready separation of large quantities of fine chemicals with the use of a small amount of catalyst [13]. Majority of the reported supports for catalytic applications are based on inorganic materials due to availability and low costs [14].

Porous inorganic solids have found great utility as a catalyst because of their large internal surface area. The most common types of mesoporous nanoparticles are MCM-41 and SBA-15 which have silicate structure. Mesoporous silicates due to larger pores in compare with acidic zeolites could be good host for bulky organic substrates. So, such substrates have more efficiently contact with acid sites on the interior surfaces of mesoporous silicate [15]. Purely mesoporous silica does not have enough acidity, but acidity can be improved through the insertion of foreign metal ions into its structure during the synthesis [16,17]. Among such materials, Al-incorporated mesoporous molecular sieves which possess the acidic sites and good hydrothermal stability are more favorable. AIHMS is hexagonal mesoporous silica containing Al with a particular wormlike pore structure. It has a simple preparation method using cheap primary alkyl amines which can be extracted without pollution [18].

In continue of our efforts about green chemistry [19-21], here in, a greener approach was developed for the synthesis of dihydropyrano[2,3-*g*]chromene derivatives **4a-h** in the presence of AIHMS as a heterogeneous recyclable catalyst, in H₂O under reflux conditions (Scheme 1).

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Scheme 1. Three-component reaction of 2-hydroxy-naphthoquinone (1), aromatic aldehydes (2), and dimedone (3a) or barbituric acid (3b) in the presence of AIHMS as the catalyst

2. Experimental

2.1. Material and Methods

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded in KBr on a Shimadzu IR-470 spectrometer. ¹HNMR Spectra were recorded on a Bruker DRX-300 Avance spectrometer 250.13 MHz; for all NMR spectra data chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. The chemicals used in this work were purchased from Merck and Fluka Chemical Companies.

2.2. Typical procedure for preparation of 3,3-dimethyl-12-phenyl-3,4-dihydro-1H-benzo[b]xanthene-1,6,11 (2H,12H)-trione (4a)

To a magnetically stirred mixture of 2-hydroxy-naphthoquinone (1, 1 mmol), dimedone (3a, 1 mmol) and AIHMS (0.04 g) in H₂O (5 mL), benzaldehyde (2a, 1.1 mmol) was added at room temperature, and then the reaction mixture was refluxed for 4 hours. After completion of the reaction, solvent was removed under reduced pressure. Then, DMSO was added to the residue and solid catalyst was separated from the reaction mixture by filtration.

2.3. Typical procedure for preparation of 3,3,10,10-tetramethyl-7,14-diphenyl-3,4,10,11-tetrahydrochromeno [2,3-b] xanthene-1,6,8,13 (2H,7H,9H,14H)-tetraone (6a)

To a magnetically stirred mixture of 2,5-dihydroxy-1,4-benzoquinone (5) (1 mmol), dimedone (3a) (2 mmol) and AIHMS (0.04 g) in H₂O (5 mL), benzaldehyde (2a) (2.1 mmol) was added at room temperature, and then the reaction mixture was refluxed for 4 hours. After completion of the reaction, solvent was removed under reduced pressure. Then, DMSO was added to the residue and solid catalyst was separated from the reaction mixture by filtration.

2.4. Typical procedure for preparation of 2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile (8a)

The mixture of benzaldehyde (1 mmol), malononitrile (1 mmol), 1-naphthol (1 mmol) and AIHMS (0.03 g) was taken in a 20 mL flask containing 5 mL H₂O/EtOH (1:1) and stirred for the 15 min. The completion of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure. Then, DMSO was added to the residue and solid catalyst was separated from the reaction mixture by filtration. Then, crystallization in DMSO afforded **8a** in 95% yield.

Selected spectral data

(4a):

Yellow powder (0.28 g, yield 72%). m.p.= 228-230°C. IR (KBr): $\bar{\nu}$ = 3453, 3075, 2955, 2860, 1665, 1620, 1585, 1461, 1366 cm⁻¹. ¹HNMR (250 MHz, DMSO-d₆): δ = 0.95 (3H, s, CH₃), 1.07 (3H, s, CH₃), 2.10-2.53 (4H, m, 2CH₂), 4.89 (1H, s, CH), 7.02-8.11 (9H, m, H-Ar) ppm. Anal. Calcd for C₂₅H₂₀O₄: C 78.11; H 5.24. Found: C 78.09; H 5.19.

(6a):

Orange powder (0.4 g, yield 71%). m.p.= 228-230°C. IR (KBr): $\bar{\nu}$ = 3390, 2970, 2850, 1720, 1645, 1615 cm⁻¹. ¹HNMR (250 MHz, DMSO-d₆): δ = 0.84 (6H, bs, 2CH₃), 0.99 (6H, bs, 2CH₃), 2.11 (4H, bs, 2CH₂), 2.24 (4H, bs, 2CH₂), 5.71 (H, s, CH), 6.04 (H, s, CH), 6.81-7.18 (10H, m, H-Ar) ppm. Anal. Calcd for C₃₆H₃₂O₆: C 77.12; H 5.75. Found: C 77.09; H 5.71.

3. Results and Discussion

AIHMS-20 [21] was synthesized with BET surface area 1289 m²/g, pore volume 2.1 cm³/g and total acidity 0.845 mmol NH₃/g, and evaluated for the synthesis of dihydropyrano[2,3-g]chromenes via three-component reaction of 2-hydroxy-naphthoquinone (1), aromatic aldehydes 2 and dimedone (3a) or barbituric acid (3b).

At first, the reaction conditions was optimized for the reaction of 2-hydroxy-naphthoquinone (**1**) and benzaldehyde (**2a**) with dimedone (**3a**) in the presence of AlHMS. This reaction afforded 3,3-Dimethyl-12-phenyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11-(2*H*,12*H*)-trione (**4a**) as a yellow powder (Scheme 1). As can be seen from Table 1, 0.04 g of catalyst in H₂O as a green solvent was recognized as the optimized reaction conditions.

Treatment of 2-hydroxy-naphthoquinone (**1**) and various aromatic aldehydes **2** with dimedone (**3a**) or barbituric acid (**3b**) in the presence of AlHMS in H₂O at reflux conditions led to the formation of

corresponding dihydropyrano[2,3-*g*]chromenes **4a-h**. (Table 2).

the reaction was examined using 2,5-dihydroxy-1,4-benzoquinone (**5**) instead of 2-hydroxy-naphthoquinone (**1**) with two equivalents of aldehydes **2** and two equivalents of dimedone (**3a**) or 1,3-cyclohexadione (**3b**) in the presence of AlHMS as a catalyst under the same reaction conditions (Scheme 2).

The reaction was proceeded efficiently as a pseudo five-component reaction to afford tetrahydro chromeno [2,3-*b*] xanthenes. Various derivatives of these compounds were obtained using a variety of aromatic aldehydes (Table 3).

Table 1. Effects of catalyst amount and solvent on the reaction yield^a

Entry	Catalyst amount (g)	Solvent	Yield (%) ^b
1	0.02	H ₂ O	51
2	0.03	H ₂ O	59
3	0.04	H ₂ O	72
4	0.05	H ₂ O	72
5	0.04	H ₂ O/EtOH (1:1)	73
6	0.04	EtOH	75
7	0.04	MeOH	68
8	0.04	CH ₃ CN	74
9	0.04	PhCH ₃	21

^aReaction conditions: 2-hydroxy-naphthoquinone (**1**) (1.00 mmol), benzaldehyde (**2a**) (1.00 mmol), dimedone (**3a**) (1 mmol), solvent (5 mL), room temperature, 15 min.

^bIsolated yield.

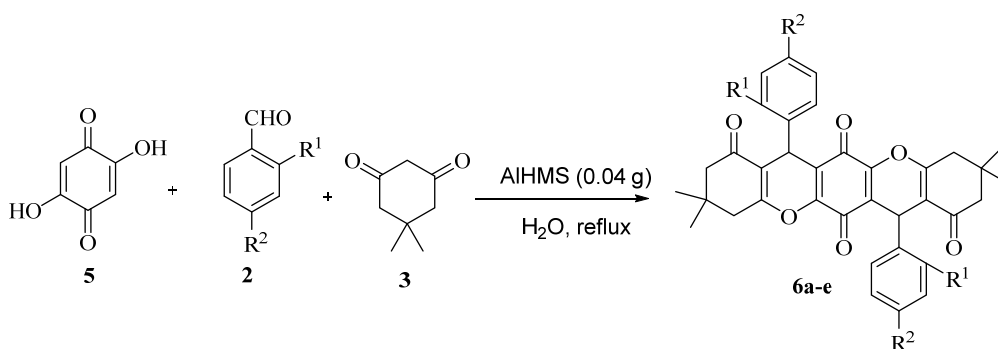
Table 2. Structures, melting points and yields of the products **4a-h**^a.

Entry	Product No.	Yield (%) ^b	m.p. (°C)	
			Found	Reported ^c
1	4a	72	228-230	228-230
2	4b	71	170-172	170-173
3	4c	69	225-227	223-225
4	4d	71	238-240	238-241
5	4e	72	237-239	237-239
6	4f	69	221-223	221-224
7	4g	73	198-200	198-200
8	4h	70	217-219	217-219

^aReaction conditions: 2-hydroxy-naphthoquinone (**1**, 1.00 mmol), aldehyde (**2**, 1.10 mmol), CH-acid (**3**, 1 mmol), H₂O (5 mL), room temperature, 4 h.

^bIsolated yield.

^cAll from ref. [8].



Scheme 2. Pseudo five-component reaction of compounds 6 in the presence of AIHMS as the catalyst.

Table 3. Structures, melting points and yields of the products 6a-e^a.

Entry	Product No.	Yield (%) ^b	m.p. (°C)	
			Found	Reported ^c
1	6a	71	228-230	228-230
2	6b	65	> 260	> 260
3	6c	67	189-191	188-191
4	6d	70	262-264	261-263
5	6e	73	> 290	> 290

^aReaction conditions: 2,5-dihydroxy-1,4-benzoquinone (**5**, 1.00 mmol), aldehyde (**2**, 2.10 mmol), CH-acid (**3**, 1 mmol), H₂O (5 mL), room temperature, 4 h.

^bIsolated yield.

^cAll from ref. [8].

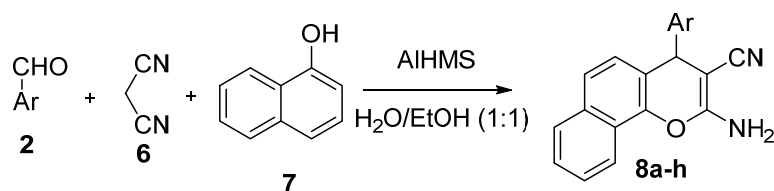
For more evaluation of the catalyst activity of AIHMS, three-component reaction of an aldehyde, a malononitrile and a 1-naphthol was investigated (Scheme 3).

For optimization of the reaction conditions, the reaction of benzaldehyde, malononitrile and 1-naphthol was investigated as a model reaction. After screening a variety of conditions regarding catalyst amount and solvent, 0.03 g of the catalyst and H₂O/EtOH as the solvent was found as the best reaction conditions (Table 4).

In order to investigate the scope and limitations of this reaction, a variety of different substituted benzaldehyde compounds were subjected to this reaction (Table 5). A variety of substituted benzaldehyde possessing a wide range of electron-donating functional group, and electron-withdrawing functional groups afforded the corresponding products in short reaction duration (15 min) with good yields.

Recyclability of the catalysts was examined too. For this reason, catalysts, which were recovered from the reaction of 2-hydroxy-naphthoquinone (**1**) and benzaldehyde (**2a**) with dimedone (**3a**) by filtration, washed with acetone (2 × 5 mL) and dried in the oven (70°C, 6 h), were used again. This procedure was carried out for four times. Results of these successive reactions was 72, 71, 70 and 70 % respectively. It is clear that by successive use of the catalyst, no decrease in the reactivity or performance can be seen for AIHMS.

To assess the standing of the catalyst among other catalysts, comparative experiments were performed with four catalyst. The yield obtained using AIHMS as a catalyst (72%) is very high compared to silica (58%) and TiO₂ (32%), and is comparable with homogeneous catalysts such as *p*-toluenesulfonic acid (73%).



Scheme 3. Three-component reaction of benzaldehyde, malononitrile and 1-naphthole with AIHMS as the catalyst.

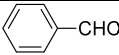
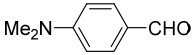
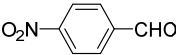

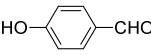
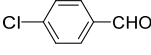
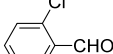
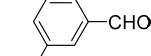
Table 4. Effects of catalyst amount and solvent on the reaction yield^a.

Entry	Catalyst amount (g)	Solvent	Yield (%) ^b
1	0.02	H ₂ O/EtOH (1:1)	83
2	0.03	H ₂ O/EtOH (1:1)	95
3	0.04	H ₂ O/EtOH (1:1)	95
4	0.03	H ₂ O	67
5	0.03	EtOH	95
6	0.03	MeOH	96
7	0.03	CH ₂ Cl ₂	68
8	0.03	CH ₃ CN	74
9	0.03	PhCH ₃	69

^aReaction conditions: benzaldehyde (**1a**) (1.00 mmol), malononitrile (**2**) (1.00 mmol), 1-naphthole (**3a**) (1 mmol), solvent (5 mL), room temperature, 15 min.

^bIsolated yield.

Table 5. Synthesis of 2-amino-chromenes in the presence of AlHMS^a.

Entry	Aldehyde 2	Product No.	Yield (%) ^b	m.p. (°C)	
				Found	Reported ^c
1		8a	95	210-212	210-211
2		8b	95	203-205	203-205
3		8c	96	231-234	231-234
4		8d	89	189-191	191
5		8e	95	243-245	245
6		8f	92	231-232	231-232
7		8g	88	236-238	236-237
8		8h	91	208-210	208-211

^aReaction conditions: aldehyde **2** (1.00 mmol), malononitrile (**6**) (1.00 mmol), 1-naphthol (**7**) (1 mmol), AlHMS (0.03 g), H₂O:EtOH (1:1) (5 mL), room temp., 15 min.

^bIsolated yield.

^cAll from ref. [22].

Here, we tried to solve two problems which imposed cost and pollution: the problems of i) using the homogeneous catalyst such as separation and regeneration, and ii) the application of organic solvent. Successively, we overcome to these problems with

using a heterogeneous catalyst in green solvents. The separation of AlHMS from the reaction medium was easily carried out by filtration. After drying, it was reused for subsequent reactions. Thus, this process could be interested for large-scale synthesis.

4. Conclusions

In conclusion, a rapid and efficient approaches were developed for the synthesis of chromenes in green solvent in the presence of AlHMS. The present method has some advantages of green methods such as use of green solvent, multi-component reaction and heterogeneous catalyst. The catalyst can be recycled and reused for several times without loss of the performance. The work-up procedures are very simple, and the products do not require further purification. The simplicity of the present procedures and environmental friendly of these routes makes them interesting alternatives to other approaches.

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