Efficient and Eco-Friendly Procedure for the Synthesis of 2-Amino-4H-Chromenes Catalyzed by Diammonium Hydrogen Phosphate

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ABSTRACT: *An efficient and eco-friendly protocol for the preparation of 2-amino-4H-chromenes employing a multi-component, one-pot condensation reaction between aromatic aldehydes, malononitrile and 1-naphthol has been developed. The reaction of 1-naphthol with malononitrile and various aromatic aldehydes was carried out in water-ethanol (1:1) at reflux using 20 mol% of diammonium hydrogen phosphate as catalyst. The results show that aromatic aldehydes containing electron-donating groups or electron-withdrawing groups could react smoothly to give the corresponding products in good to excellent yields. It was also found that diammonium hydrogen phosphate can be recycled at least four times without loss of activity. The operational simplicity, easy work-up, short reaction time, together with the use of non-toxic, commercially available, inexpensive and recyclable catalyst are remarkable features of the procedure.*

KEY WORDS: *Diammonium hydrogen phosphate; 2-Amino-4H-chromene; Muit-component reaction; Catalysis.*

INTRODUCTION

The synthesis of 2-amino-4H-chromenes has attracted great interest in recent years because of their wide range of biological and pharmaceutical properties such as antibacterial [1], antiviral [2], mutagenicity [3], sex pheromone [4], antitumor [5] activities. Recently, the synthesis of 2-amino-4H-chromenes has been achieved by the condensation of aromatic aldehydes, malononitrile and 1-naphthol in the presence of a catalyst, such as methanesulfonic acid [6], tetrabutylammonium bromide (TBABr) [7], $TiCl_4$ [8], MCM-41-NH_2 [9], potassium phosphate tribasic trihydrate [10], PEG-400 [11], Mg/Al hydrotalcite [12], nanosized magnesium oxide [13], $NaHCO_3$ [14], hexadecyltrimethylammonium bromide (HTMAB) [15], cetyltrimethylammonium bromide (CTABr) [16], N,N-dimethylaminoethylbenzyl-imethylammonium chloride [17], KF-Al_2O_3 [18] and potassium phthalimide [19]. However, some of these methods suffer from certain disadvantages such as long reaction time, use of toxic catalysts and organic solvents, tedious work-up procedures, the requirement of special apparatus. Thus, the development of clean, efficient, and facile processes to synthesize 2-amino-4H-chromenes is of current interest.

Diammonium hydrogen phosphate is a very cheap, nontoxic and commercially available compound.

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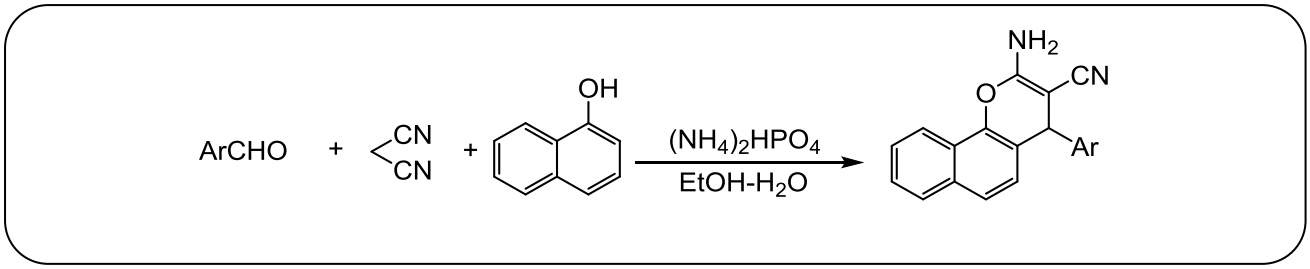

Scheme 1: Synthesis of 2-amino-4H-chromenes catalyzed by diammonium hydrogen phosphate.

The application of diammonium hydrogen phosphate in organic synthetic methodology has been reported [20]. Ethanol-water is considered to be relatively environmentally benign solvent [21]. We now report a clean and efficient method for the synthesis of 2-amino-4H-chromenes by the one-pot three-component condensation of aromatic aldehydes, malononitrile and 1-naphthol in ethanol-water using diammonium hydrogen phosphate as a recyclable catalyst (Scheme 1).

EXPERIMENTAL SECTION

All chemicals were obtained commercially and used without further purification. Melting points were uncorrected. FT-IR spectra were obtained on a Nexus 470 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance III 400 with TMS as internal standard.

Typical procedure for the synthesis of 2-amino-4H-chromenes

A mixture of 1-naphthol (5 mmol), aldehyde (5 mmol), malononitrile (5 mmol) and diammonium hydrogen phosphate (1 mmol) in water-ethanol (v:v=1:1, 10 mL) was stirred at reflux for the appropriate time. The progress of the reaction was monitored by thin layer chromatography (eluent: ethyl acetate/petroleum ether, 1:2). On completion of reaction, the reaction mixture was cooled to room temperature. The solid product obtained was filtered, washed with water-ethanol (v:v=1:1), dried, and recrystallized from ethanol. All of the products are known and the data are found to be identical with those that reported in literature.

RESULTS AND DISCUSSION

In the initial experiments, we examined the reaction of 1-naphthol, malononitrile and benzaldehyde in the presence of 10 mol% of diammonium hydrogen phosphate under different conditions including refluxing in various solvents (H_2O, EtOH, H_2O-EtOH, CH_3OH, THF, CH_3CN, $CHCl_3$, and toluene) and also under solvent-free classical heating conditions. We found that the best results were obtained in H_2O-EtOH (1:1) under reflux. The effect of the amount of catalyst was also examined. It was found that the use of 20 mol% of diammonium hydrogen phosphate was sufficient to progress the reaction. Use of higher amount of catalyst (30 mol%) did not improve the yield. The yield was 33% after 2.5 h in the absence of diammonium hydrogen phosphate (Table 1, Entry 3). This result indicates that the catalyst exhibits a high catalytic activity in this transformation.

Next, we examined the scope of the reaction by condensing 1-naphthol with various aromatic aldehydes in water-ethanol (1:1) at reflux using 20 mol% of diammonium hydrogen phosphate as catalyst, and the results are summarized in Table 2. It can be observed from Table 2 that aromatic aldehydes containing electron-donating groups or electron-withdrawing groups could react smoothly to give the corresponding products in good to excellent yields. No clear electronic effect of the aromatic aldehydes on the reaction was observed.

The recycling performance of the reaction media and/or the catalyst is of great importance from environmental and economic point of view. Recycling of diammonium hydrogen phosphate was then tested by carrying out the reaction with 4-chlorobenzaldehyde (5 mmol), malononitrile (5 mmol) and 1-naphthol (5 mmol) (Table 3). After each run, the solid product was separated by filtration. The filtrate contained diammonium hydrogen phosphate, which was reused directly for the next run. It was found that diammonium hydrogen phosphate can be recycled at least four times without loss of activity (Table 3). The easy recycling performance of the catalyst and reaction media is an attractive feature of this procedure.

Table 1: Effect of different reaction conditions on $(NH_4)_2HPO_4$ catalyzed synthesis of 2-amino-3-cyano-4-phenyl-4H-benzo[h]chromenes. [a]

Entry	Solvent	Catalyst loading (mol%)	Time (h)	Isolated yield (%)
1	H_2O	10	3	62
2	EtOH	10	5	86
3	H_2O-EtOH (1:1)	0	2.5	33
4	H_2O-EtOH (1:1)	5	2.5	83
5	H_2O-EtOH (1:1)	10	2.5	87
6	H_2O-EtOH (1:1)	20	2.5	93
7	H_2O-EtOH (1:1)	30	2.5	87
8	H_2O-EtOH (1:3)	10	2.5	78
9	H_2O-EtOH (3:1)	10	3	79
10	Solvent-free	10	5	46[b]
11	CH_3CN	10	4	60
12	CH_3OH	10	7	64
13	Toluene	10	7	Trace
14	THF	10	7	Trace
15	$CHCl_3$	10	7	Trace

a) Reaction conditions: benzaldehyde (5 mmol), 1-naphthol (5 mmol), malononitrile (5 mmol), solvent (10 mL), H_2O-EtOH (V:V), reflux.
b) The reaction is carried out at 90 °C.

Table 2: $(NH_4)_2HPO_4$ catalyzed synthesis of 2-amino-3-cyano-4-aryl-4H-benzo[h]chromenes.

Entry	Ar	Time (h)	Isolated yield (%)	M.p. (°C)	
				Found	Reported
1	C_6H_5	2.5	93	210-211	210-211[14]
2	4-$CH_3C_6H_4$	1.5	85	197-198	198-200[18]
3	4-$CH_3OC_6H_4$	6.5	84	181-183	182-183[7]
4	4-ClC_6H_4	1.5	92	237-238	238-240[18]
5	4-$NO_2C_6H_4$	1.7	80	227-229	230-231[17]
6	3-$NO_2C_6H_4$	20 min	93	207-209	208-211[13]
7	2-ClC_6H_4	2.8	88	243-244	244-246[15]
8	4-FC_6H_4	2	94	230-232	231-232[10]
9	2,4-$Cl_2C_6H_3$	1.5	89	212-213	212-214[16]
10	4-BrC_6H_4	20 min	88	231-233	234.3[9]

Table 3: Recycling of $(NH_4)_2HPO_4$ for the synthesis of 2-amino-3-cyano-4-(4-chlorophenyl)-4H-benzo[h]chromenes.

Run	Time (h)	Isolated yield (%)
1	1.5	92
2	1.5	95
3	1.5	95
4	1.5	93
5	1.5	90

CONCLUSIONS

In conclusion, we have developed a clean and efficient method for the synthesis of 2-amino-4H-chromenes by the one-pot three-component condensation of 1-naphthol, malononitrile and aromatic aldehydes in ethanol-water using diammonium hydrogen phosphate as catalyst. The operational simplicity, easy work-up, short reaction time, together with the use of non-toxic, commercially available, inexpensive and recyclable catalyst are remarkable features of the procedure.

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