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On Water $CuSO_4$. $5H_2O$-catalyzed Synthesis of 2-amino-4H-chromenes

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ABSTRACT. Sustainable development is a balance between environment and development. Sustainable development requires sustainable supplies of clean, affordable, and renewable energy sources that do not cause negative impact to the society. This article introduces a green chemistry method to synthesize 2-amino-4H-chromenes that reduces or eliminates the use and generation of hazardous substances in the design, manufacture, and application of chemical products. This method is described using copper (II) sulfate pentahydrate, as a green and reusable catalyst on water. The products were obtained at very good yields, short reaction time, and at lower cost than other reported procedures.

Key words: Green chemistry, Water, Chromene, $CuSO_4$. $5H_2O$, Synthesis

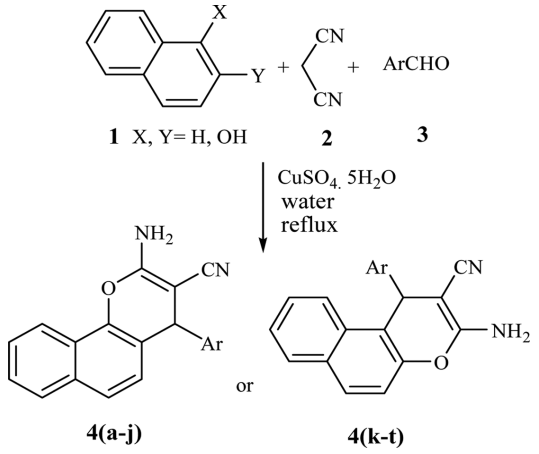
INTRODUCTION

An ultimately practical synthesis is generally regarded as one in which the target molecule is prepared from readily available, inexpensive starting materials in one simple, safe, environmentally, and resource-effective operation that proceeds rapidly in quantitative yield.[1] In recent years, with the increase of environmental consciousness in chemical research and industry, efficient, economic and clean procedures have received increasing attention. Also, water has become an interesting reaction medium, and has particularly captured the interest of organic chemists.[2–6] Reactions previously thought impossible in water are a reality at the present time. In many cases, the catalyst and/or the aqueous medium can be recovered and reused, thereby reducing the environment impact of the reaction process.[7–9] Several Lewis acids work in aqueous medium well,[10,11] such as $AlCl_3$, $SnCl_2$ and $TiCl_4$ which have previously been used under anhydrous conditions, and excellent catalysts are in water now.[4]

Lately, $CuSO_4$. $5H_2O$ has been used as a Lewis acid catalyst for various organic transformations such as tetrahydropyranylation-depyranylation of alcohols and phenols,[12] protection of alcohols and phenols by using hexamethyldisilazane,[13] the one-pot conversion of THP ethers to acetates,[14] the chemo selective synthesis of 1,1-diacetates from aldehydes,[15] the synthesis of quinoxaline derivatives,[16] the synthesis of β-keto esters,[17] the one-pot synthesis of β-hydroxytriazoles from epoxides[18] and the synthesis of 1,2,3-triazoles.[19] $CuSO_4$. $5H_2O$ is an inexpensive, available and extremely safe reagent to be used in chemical reactions.

In recent years functionalized chromenes have played important role in the field of medicinal chemistry.[20] particulary 2-amino-4H-chromenes utility privileged medicinal scaffolds serving for production of small ligands with highly pronounced spasmolitic-, diuretic-, anticoagulant- and antianaphylactic activities,[21–23] and in the treatment of human inflammatory TNFa-mediated diseases.[24]

Recently, several modified catalysts have been used in this reaction such as cetyltrimethylammonium chloride,[25] cetyltrimethylammonium bromide under ultrasound irradiation,[26] KSFclay,[27] KF/Al_2O_3,[28] $TiCl_4$,[29] triethylamine,[30] basic γ–alumina,[31] MgO,[32] heteropoly acids,[33] basic ionic liquids,[34] iodine/K_2CO_3,[35] and DABCO,[36] Na_2CO_3,[37] and other references therein. However, only a few of them (e.g., MgO and basic alumina) are suitable to catalyze the reaction of malononitrile with aromatic aldehydes and



***Scheme* 1.**

active α-naphthol (but not suitable for less active β-naphthols), whereas some others require longer reaction times, hard workup and afford only moderate yields. Due to these reasons and in our continuing interest in the development of green chemistry standpoint protocols for one-pot multi-component reactions,[38–42] herein we report our results for the synthesis of 2-amino-4*H*-chromene using aldehydes, malononitrile and 1-, or 2- naphthols in the presence of $CuSO_4$. $5H_2O$ as an efficient Lewis acid catalyst on water under reflux conditions (*Scheme* 1).

EXPERIMENTAL

Mps were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR which performed a scan between 4000–400 cm^{-1}. ^{1}HNMR spectra were obtained on Bruker DRX-300 MHZ NMR instrument. All products were characterized and compared with those of authentic sample in literature.[26,43,44,46]

Synthesis of 4a. Typical Procedure

To a mixture of benzaldehyde (0.107 g, 1 mmol), malononitrile (0.061, 1 mmol), α-naphtol (0.145 g,1mmol), and water (5 ml), $CuSO_4$. $5H_2O$ (64 mg, 5mol%) was added and the mixture was stirred under reflux condition for1h. After completion of reaction (monitored by TLC), thegenerated solid was filtered off and recrystallized from ethyl acetate and n-hexane (1:7) to obtain 2-amino-4-H-chromenes.

To disclose the worthy and usable of $CuSO_4$ in large scale, we set up reaction with benzaldehyde (100 mmol, 10.7 g), 1-naphthol (100 mmol, 14.5 g), water (500 ml), malononitrile (100 mmol, 6.1 g) and $CuSO_4$ (5.0 mmol, 1.36 g) in a round flask, and then stirred and heated for 1.0 h under reflux condition. The reaction was carried out and the product was obtained in 95% yield. Therefore, $CuSO_4$. $5H_2O$ could be used for the synthesis of 2-amino-4H-chromenes in water under reflux condition even in large scale.

RESULTS AND DISCUSSION

At first, the efforts were focused on the evaluation of varying parameters such as solvent and catalytic amount of the catalyst on rate and the yields of obtained 2-amino-4H-chromenes by reacting 1-, or 2-naphthol, aryl aldehydes, and malononitrile from the principles of green chemistry point of view. The results on these reactions claimed that water is the best solvent in terms of yield, reaction time and green chemistry agreeable (*Table* 1).

***Table* 1.** Effect of the solvent on the yield and reaction time of synthesis of **4a** and **4k**

Entry	Solvent	Time(h)	Yield %[a]
1	free	3	70
2	Water	1	98

[a]Reaction condition: 1-naphtol (1 mmol), or 2-naphtol (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol) and water (5 mml) under reflux conditions.

***Table* 2.** One-pot synthesis of **4a** and **4k**. in the presence of $CuSO_4$. $5H_2O$

Entry	Catalyst (mol%)	Time (h)	Yield (%)[a]
		4a/**4k**	**4a**/**4k**
1	free	15/16	40/20
2	3	2/2:30	90/90
3	5	1/1:15	98/98
4	10	1/1:15	98/98

[a]Reaction condition: 1-naphtol (1 mmol), or 2-naphtol (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol) and ethanol (5 mml) under reflux conditions.

Also, it was clearly found that $CuSO_4$. $5H_2O$ catalyzed 2-amino-4-phenyl-4H-benzo[f]chromene-3-carbonitrile (**4a**) and 2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile (**4k**) (compare *Table* 2). It is noteworthy to observe that corresponding products were obtained in excellent yield, no benzylidene malononitrile was observed.

On the basis of the optimization of the reaction conditions, the scope of this $CuSO_4$-catalyzed multicomponent reaction was explored. Not only electron-rich aryl aldehydes, but also electron-deficient aryl aldehydes in the reactions afforded 2-amino-4H-chromenes in 75 –95% yields (*Table* 3). Comparatively, the rate of the reaction electron-deficient aryl aldehydes is faster than electron-rich aryl aldehydes.

To show the fairly advantages of using copper (II) sulfate as a catalyst in the synthesis of **4a** and **4k**, our protocol was compared with previously reported methods (*Table* 3). From the results given in *Table* 4, the advantages of this work are evident regarding the yields of the reactions which are very important in chemical industry especially when it is combined by easy separation and reusability of the catalyst.

A probable mechanism for the synthesis may be postulated as shown below (*Scheme* 2).

RECYCLING OF THE CATALYST

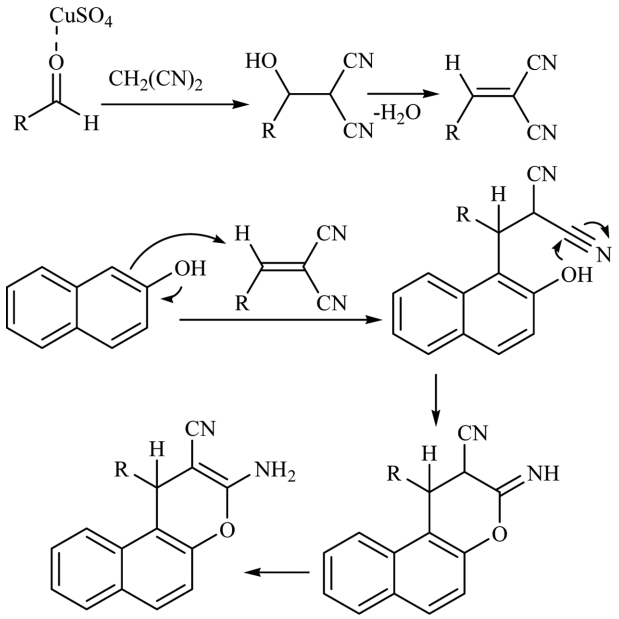
The reusability of the catalyst was also studied. At the end of the reaction, the product wasfiltered off and the liquor moderate was washed with diethyl ether. Then the

***Table* 3.** $CuSO_4$. $5H_2O$-catalyzed synthesis of 2-amino-4H-chromenes

Entry	ArOH	ArCHO	Product	Time (min)	Yield%	m.p.(°C)	
						Found [Ref]	Reported
1	1-naphtol	C_6H_5CHO	4a	60	95	214	210–211[26]
2		2-Cl-C_6H_4CHO	4b	30	80	221–223	236–237[26]
3		3-Cl-C_6H_4CHO	4c	100	92	201–206	229–230[26]
4		4-Cl-C_6H_4CHO	4d	90	95	230	232[26]
5		2,4-$(Cl)_2C_6H_3CHO$	4e	55	86	210–211	214–216[36]
6		3,4-$OMeC_6H_3CHO$	4h	90	91	169–171	209–210[43]
7		3-HO-C_6H_4CHO d	4i	90	90	228–232	250–253[36]
8	2-naphtol	C_6H_5CHO	4k	60	95	273	278–279[44]
9		2-Cl-C_6H_4CHO	4l	50	85	259	265–267[44]
10		4-Cl-C_6H_4CHO	4m	80	85	213	210–211[44]
11		2,4-$(Cl)_2C_6H_3CHO$	4n	100	83	242–243	239–240[44]
12		2-OMe-C_6H_4CHO	4o	185	80	219–222	218–220[46]
13		3-OMe-C_6H_4CHO	4p	50	89	260–260.3	262–263[44]
14		3,4-$OMeC_6H_3CHO$	4q	90	88	148–150	141–143[46]
15		3-HO-C_6H_4CHO	4r	180	90	272–274	280–282[36]
16		hexanal	4t	90	87	207	192[45]

***Table* 4.** The synthesis of **4a**, **4k** using variety of catalysts was compared

Entry	Catalyst	Time (min)	Yield %	Conditions	[Ref]
		4a/4k	**4a/4k**	**4a/4k**	
1	$H_{14}[NaP_5W_{30}O_{110}]$	180/165	91/93	H_2O, reflux / H_2O, reflux	[33]
2	Methanesulfonic acid	180/180	90/90	CH_3CN, Reflux / CH_3CN, Reflux	[47]
3	CTABr/ultrasound irradiation	150/150	92/92	H_2O, r.t / H_2O, r.t	[26]
4	$CuSO_4$. $5H_2O$	60/60	95/95	H_2O, reflux / H_2O, reflux	This work



***Scheme* 2.**

aqueous phase containing catalyst was subjected for three runs. In the case of the model reaction, after three runs the catalytic activity of the catalyst was almost the same as those of the freshly used catalyst (*Table* 5).

***Table* 5.** Reusability of the catalyst was examined by the model reaction.

Entry	Run	Yield (%)
1	Fresh	95
2	1st	95
3	2nd	95
4	3th	94

CONCLUSION

Disclosed work has demonstrated a clean protocol for the catalytic synthesis of 2-amino-4H-chromenes which proceeds efficiently in aqueous medium under reflux conditions. Also the use of green, non toxic, inexpensive and reusable catalyst ($CuSO_4$. $5H_2O$) makes this method eco-friendly, with a very simple isolation procedure that entails the filtration of the precipitated products. Also the aqueous layer containing catalyst that remained after the work-up of the reaction can be reused.

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