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The One Pot Three Component Synthesis of 2-Amino-4H-Chromenes by using Sulfonic Acid-Functionalized Phthalimide

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Abstract: *Sulfonic acid-functionalized phthalimide efficiently catalyzes the one-pot, three component reaction of an aromatic aldehyde, malonitrile and α or β-naphthol to yield 2-amino-4H-chromenes in very good yields.The catalyst sulfonic acid-functionalized phthalimide (SFP) is reusable and efficient in multicomponent reactions. The reaction is carried out in green approach which is environment friendly with excellent yield.*

Keywords: Sulfonic acid-functionalized phthalimide; 2-Amino-4H-chromenes; One-pot reaction

I. INTRODUCTION

2-Amino-4H-chromenes and their derivatives are of considerable interest as they possess a wide range of biologicalproperties,[1] such as spasmolytic, diuretic, anticoagulant, anticancer and antianaphylactic activity.[2] In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia andDown's syndrome as well as for the treatment of schizophrenia and myoclonus.[3]

The increasing attention during recent decades for environmental protection has led modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost whilst using nontoxic reagents, solvents and catalysts. One of the tools used to combine economic aspects with the environmental ones is the multicomponent reaction (MCR) strategy; this process consists of two or more synthetic steps which are carried out without isolation of any intermediate, thus reducing time and saving money, energy and raw materials.[4]

We performed the synthesis of 2-amino-4H-chromenes through a three-component reaction employing methanesulfonic acid as a catalyst. Sulfonic acid-functionalized phthalimide is heterocyclic sulfonic acid, which has numerous applications, for example, as an esterification or alkylation catalyst, as a polymer solvent, in the electroplating and electrochemistry industry, etc. SFP also is an effective reagent for the conversion of alcohols into correspondingamides,[5]Fries-rearrangement,[6] Beckmann rearrangement,[7] mono-esterification ofdiols,[8] N-nitrosation of secondary amines,[9] and aromatization of 1,4-dihydropyridines.[10]SFPis a strong acid (p*K*a =1.9), which is almost completely ionized at 0.1 M in an aqueous solution and has a low tendency to oxidize organic compounds. It is, however, far less corrosive and toxic than other mineral acids. Under normal conditions, aqueous solutions evolve no dangerous volatiles, making it safe to handle. Finally, it is readily biodegradable within 28 days, only forming CO_2 and sulfate, making them an environmentally benign material.[11] Furthermore, it has the advantage, as will be shown, and that it can be separated readily from the reaction mixture and reused.

As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of fine chemicals, herein we report the synthesis of 2-amino-4H-chromenes using SFP in good yields.

Organic solvents used in most of the synthesis processes in chemical industries evaporate in to atmosphere with nocuous effects on the environment and ozone layer. One of the most effective techniques to solve this problem is solvent-free conditions which make synthesis simpler, save energy, and prevents solvent waste, hazards, and toxicity.

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Experimental

All products are known compounds and were characterized by mp, IR, ^{1}HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}HNMR spectra were recordedon a Bruker AQS AVANCE-300MHz spectrometer using TMS as an internal standard (CDCl3 solution). IR spectra were recorded from a KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an AgilentTechnologies 6890 network GC system and an Agilent 5973 network mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254, was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

II. RESULTS AND DISCUSSION

2-Amino-chromenes are generally prepared by refluxing malononitrile, aldehyde and activated phenol in the presence of hazardous organic bases like piperidine for several hours.[12] A literature survey revealed that several modified procedures using CTACl,[13] TEBA,[14] and γ alumina [15] as catalysts have been recently reported but all these methods require long refluxing hours. Based on previous studies to develop new and homogeneous catalyst systems for fine chemical preparation,[16-19] we have studied the three component synthesis of 2-amino-4H-chromenes via onepotreaction of aldehydes, malononitrile and α or β-naphthol using sulfonic acid-functionalized phthalimide as an available, green and inexpensive catalyst in good yields (Table 1). The scope and the generality of the present method were then further demonstrated by reaction of various aldehydes with malononitrile and α or β-naphtol. In all casesgood yields and selectivity were obtained.

It is noteworthy to mention that the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because they were obtained in high yields in relatively short reaction times. The results are shown in Table 1.

A plausible mechanism for this reaction has been suggested. The aldehyde 1 first condenses with malononitrile 2 to afford a-cyanocinnamonitrile derivative 6. The phenol ortho C-alkylation by reaction with the electrophilic C=C double bond giving the intermediate 7. Then the intermediate 7 was cyclized by the nucleophilic attack of OH group on the cyano (CN) moiety and gave the intermediate 8. Finally the expected products 4 were afforded. In conclusion, sulfonic acid-functionalized phthalimide can serve as an efficient catalyst for the synthesis of 2-amino-4H-chromenes. This procedure offers several advantages including mild reaction conditions, cleaner reaction, high yields of products as well as a simple experimental and work-up procedure which makes it a useful and attractive process for the synthesis of these compounds.

In recent years, sulfonic acid-containing catalysts have attracted much attention by organic chemists. The useof this class of catalysts to promote organictrans formations, is associated with various benefits including: (i) enhanced reactivity as well as selectivity,(ii) uncomplicated work-up, (iii) easy accessibility of the starting materials for the catalyst synthesis, (iv)efficiency, (v) environmentally friendly reaction conditions, and (vi) ability to promote a wide range ofreactions.[20-24]

Table 1. Synthesis of substituted 2-amino-chromenes catalyzed by methanesulfonic acid

Entry	R	Substrate	Product	Time(min)	Yield(%)[a]	M.P.(^{0}C)	
						Observed	Reported
1	C6H5	α-naphthol	4a	60	90	212	210-211[18]
2	C6H5	β-naphthol	5a	60	91	278	278-280[18]
3	3-NO2C6H4	α-naphthol	4b	45	90	212	212-214[18]
4	3-NO2C6H4	β-naphthol	5b	45	91	186	188-189[18]
5	4-MeOC6H4	α-naphthol	4c	60	90	192	190-192[17]
6	4-MeOC6H4	β-naphthol	5c	60	91	182-183	182[17]
7	4-ClC6H4	α-naphthol	4d	45	89	231-232	232[17]
8	4-ClC6H4	β-naphthol	5d	60	91	206-208	208[17]
9	4-NO2C6H4	α-naphthol	4e	45	90	22	29-241[18]
10	4-NO2C6H4	β-naphthol	5e	45	90	184	185-186[18]

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[a] Yields refer to isolated products.

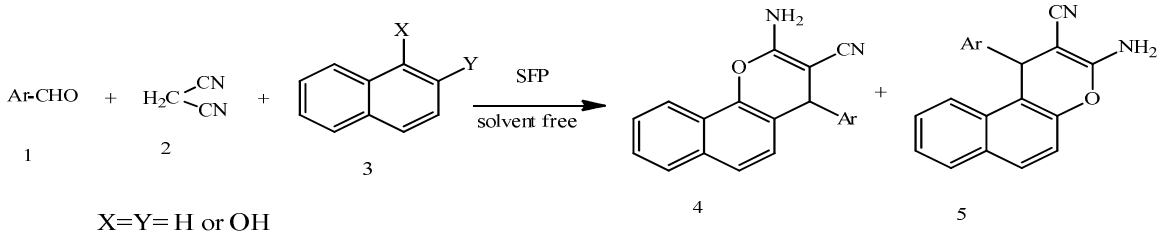
Preparation of 2-amino-2-chromenes: General procedure

A mixture of an appropriate benzaldehyde (1 mmol), malononitrile (1 mmol), α orβnaphthol (1 mmol) and SFP (1 mmol), in acetonitrile (5 mL) were refluxed within 3-4 h; after completion of the reactionwhich was monitored by TLC, the mixture was cooled to room temperature and filtered. The filtrate was washedtwice with 5%$NaHCO_3$ (5mL) and dried over$MgSO_4$. The solvent was evaporated under reduced pressure and a crude product was obtained. The resulting solid product was recrystallized from methanol to give the pure product.

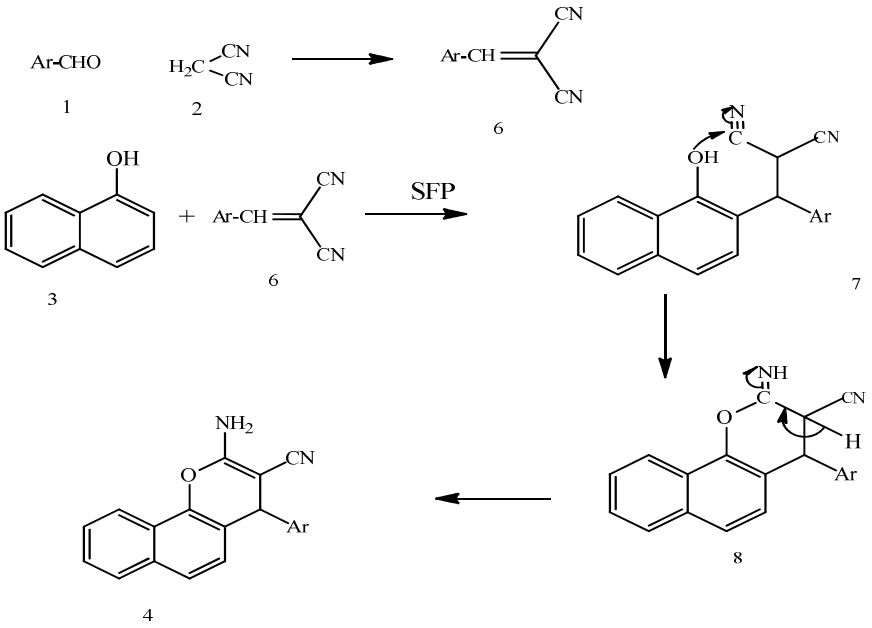
Preparation of SFP

To a round-bottomed flask (50 mL) containing phthalimide (0.736 g, 5 mmol), was addedchlorosulfonic acid (0.594 g, 5.1 mmol) dropwise at10°C. After the addition was completed, the reaction mixture was stirred at room temperature for 5 h, and then at 70 °C for 3 h. At the end of the process, theresidue was washed with CH_2Cl_2 (2×10 mL), and driedto give SFP as a white solid in 98% yield.

Scheme :



Mechanism



II. CONCLUSION

In summary, we have introduced a highly efficient and green SO3H-containing catalyst namely SFP for the reaction of aromatic aldehydes with 2-naphthol. The advantages of this work include generality, efficiency, short reaction times, excellent yields, synthesis of the catalyst using available and inexpensive reactants, performing the reaction in milder

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conditions relative to most of the reported catalysts, and good agreement with the green chemistry protocol, which makes it as a useful method for the preparation of 2-amino-2-chromenes.

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