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속보

p-Toluenesulfonic Acid를 이용한 새롭고 효과적인 2-Amino-4H-chromenes의 One-Pot 합성

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A Novel and Efficient Catalyst to One-Pot Synthesis of 2-Amino-4H-chromenes by *p*-Toluenesulfonic Acid

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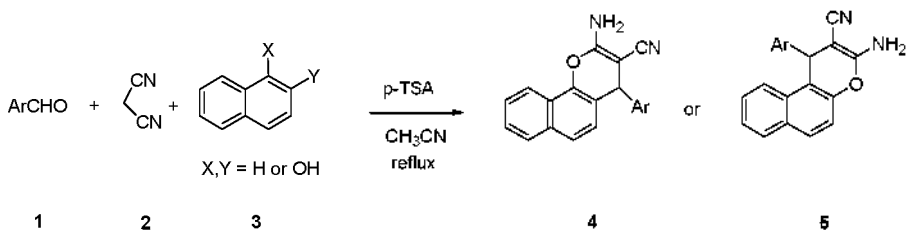
INTRODUCTION

2-amino-4H-chromenes and their derivatives are of considerable interest as they possess a wide range of biological properties,[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 and Down's syndrome as well as for the treatment of schizophrenia and myoclonus.[3]

The increasing attention during the last 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, the process consist of two or more synthetic steps which are carried out without isolation of any intermediate, thus reducing time, saving money, energy and raw materials.[4] As part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of fine chemicals,[5] we performed the synthesis of 2-amino-4H-chromenes through a three-component reaction employing *p*-toluenesulfonic acid as catalyst.

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.[6] A literature survey revealed that several modified procedures using CTACl,[7] TEBA,[8] and γ alumina[9] as catalyst have been recently reported but all these methods require long refluxing hours. Based on previous studies to develop new and heterogeneous catalyst systems for fine chemical preparation,[5] we have studied the three-components synthesis of 2-amino-4H-chromenes using *p*-toluenesulfonic acid as readily available, green and inexpensive catalyst (*Scheme* 1) in



Scheme 1

Table 1. Synthesis of substituted 2-amino-chromenes catalyzed by *p*-toluenesulfonic acid

Entry	R	phenol	Time (h)	Yield (%)[a]	m.p. (°C)	
					Observed	Reported[9,10]
1	C_6H_5	α-naphthol	3	90	209	210-211
2	C_6H_5	β-naphthol	3	91	280	278-280
3	3-$NO_2C_6H_4$	α-naphthol	4	90	212	212-214
4	3-$NO_2C_6H_4$	β-naphthol	4	91	188	188-189
5	4-$MeOC_6H_4$	α-naphthol	3	90	191	190-191.5
6	4-$MeOC_6H_4$	β-naphthol	3	91	182-183	182
7	4-ClC_6H_4	α-naphthol	4	89	231-232	232
8	4-ClC_6H_4	β-naphthol	4	91	206-208	208

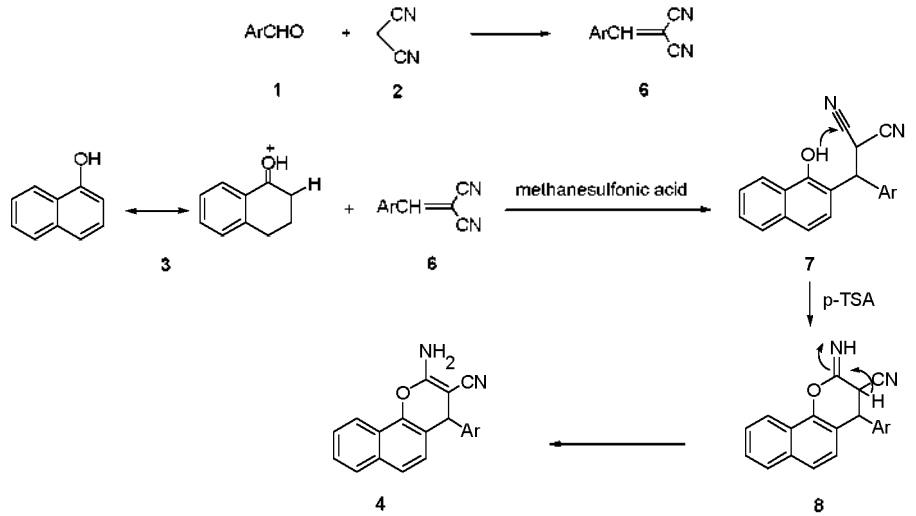
[a]Yields refer to isolated products.

good yield (*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 cases good 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 apparent effect on this conversion (*Table* 1). 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 in *Scheme* 2. The aldehyde 1 first con-



Scheme 2

denses 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, *p*-toluenesulfonic acid 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.

EXPERIMENTAL

All products are known compounds and were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 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.

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

A mixture of an appropriate benzaldehyde (1 mmol), malononitrile (1 mmol), α- or β-naphthol (1 mmol) and *p*-toluenesulfonic acid (0.03 g), in acetonitrile (5 mL) was refluxed for 3 h. After completion of the reaction which was monitored by TLC, the mixture was cooled to room temperature and filterated. The filtrate was washed twice with 5% $NaHCO_3$ (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was obtained. The resulting solid product was recrystallized from methanol to give the pure product. In order to show generality of the procedure, the reaction was repeated with other benzaldehyde derivatives (*Table* 1).

Selected spectal data

Compound 4a:

IR (KBr) (ν_{max}, cm^{-1}): 3465, 3318, 3010, 2910, 2200, 1660, 1600, 1550, 1450, 1370, 1267, 1100, 1022, 811, 744; δ_H (ppm): 4.90 (s, 1H, H-4), 7.10 (s, 2H, NH_2), 7.07-7.12 (m, 6H, H-5, 2′, 3′, 4′, 5), 7.56-7.66 (m, 3H, H-6, 8, 9), 7.94 (d, 1H, J = 8.4, H-7), 8.23 (d, 1H, J = 8.4, H-10); GC/Ms: 298 (M^-).

Compound 4e:

IR (KBr) (ν_{max}, cm^{-1}): 3450, 3320, 2170, 1660, 1600, 1575.1530, 1500, 1352, 1270, 1190, 1100, 800, 770; δ_H (ppm): 5.12 (s, 1H, H-4), 7.29 (s, 2H, NH_2), 7.05 (d, 1H, J = 8.6, H-5), 7.5-7.7 (m, 3H, H-6, 8, 9), 7.52 (d, 2H, H-2′, 6′), 7.90 (d, 1H, J = 8.4, H-7), 8.15 (d, 2H, H-3′, 5′), 8.27 (d, 1H, J = 8.6, H-10); GC/Ms: 343 (M^+).

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