A Novel and Efficient Catalyst to One-pot Synthesis of 2-Amino-4H-chromenes by Methanesulfonic Acid

Majid M. Heravi,* Bita Baghernejad and Hossein A. Oskooie
Department of Chemistry, School of Science, Azzahra University, Vanak, Tehran, Iran

Methanesulfonic acid 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.

Keywords: Methanesulfonic acid; 2-Amino-4H-chromenes; One-pot.

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 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. Methanesulfonic acid, CH_3SO_3H (MSA) is an alkanesulfonic acid, which has numerous applications, for example, as an esterification or alkylation catalyst, as a polymer solvent, in the electroplating and electrochemistry industry, etc. MSA also is an effective reagent for the conversion of alcohols into corresponding amides,[5] Fries-rearrangement,[6] Beckmann rearrangement,[7] hydration of nitriles into amides,[8] monoesterification of diols,[9] N-nitrosation of secondary amines,[10] and aromatization of 1,4-dihydropyridines.[11] MSA is a strong acid (pK_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.[12] Furthermore, it has the advantage, as will be shown, 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,[13] herein we report the synthesis of 2-amino-4H-chromenes using MSA in good yields.

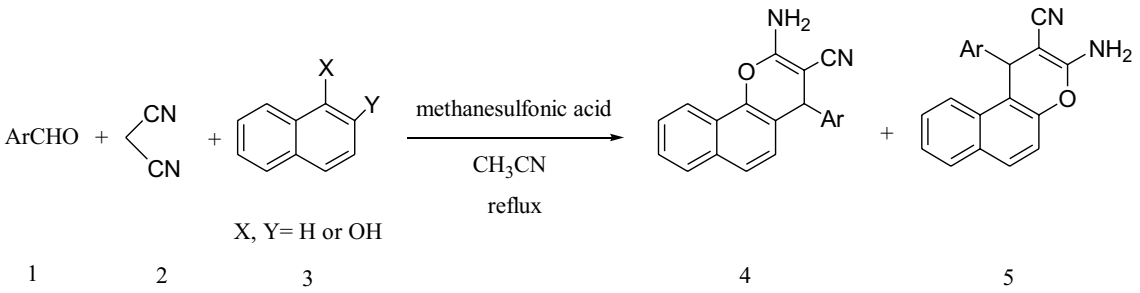
RESULTS AND DISCUSSION

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.[14] A literature survey revealed that several modified procedures using CTACl,[15] TEBA,[16] and γ alumina[17] as catalysts 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,[13] we have studied the three-component synthesis of 2-amino-4H-chromenes via one-pot reaction of aldehydes, malonitrile and α- or β-naphthol using methanesulfonic acid as an available, green and inexpensive catalyst (Scheme I) in good yields (Table 1).

The scope and the generality of the present method

* Corresponding author. Tel: +982188041344; Fax: +982188047861; E-mail: mmh1331@yahoo.com (M. M. Heravi)

Scheme I



1 2 3 4 5

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 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 in Scheme II. 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, methanesulfonic 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}HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}HNMR 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 a 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

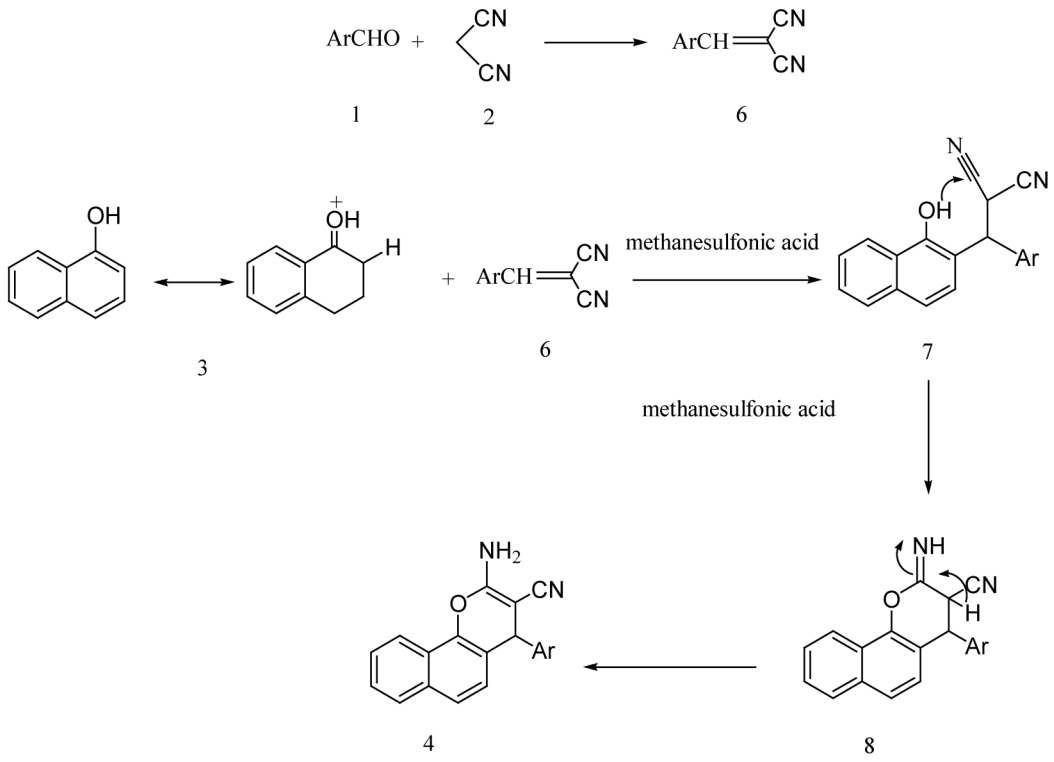
A mixture of an appropriate benzaldehyde (1 mmol), malononitrile (1 mmol), α- or β-naphthol (1 mmol) and

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

Entry	R	Substrate	Product	Time (h)	Yield (%)[a]	m.p. (°C)	
						Observed	Reported
1	C_6H_5	α-naphthol	4a	3	90	209	210-211[18]
2	C_6H_5	β-naphthol	5a	3	91	280	278-280[18]
3	3-$NO_2C_6H_4$	α-naphthol	4b	4	90	212	212-214[18]
4	3-$NO_2C_6H_4$	β-naphthol	5b	4	91	188	188-189[18]
5	4-$MeOC_6H_4$	α-naphthol	4c	3	90	191	190-192[17]
6	4-$MeOC_6H_4$	β-naphthol	5c	3	91	182-183	182[17]
7	4-ClC_6H_4	α-naphthol	4d	4	89	231-232	232[17]
8	4-ClC_6H_4	β-naphthol	5d	4	91	206-208	208[17]
9	4-$NO_2C_6H_4$	α-naphthol	4e	4	90	242	239-241[18]
10	4-$NO_2C_6H_4$	β-naphthol	5e	3	90	186	185-186[18]

[a] Yields refer to isolated products.

Scheme II



methanesulfonic acid (1 mmol), in acetonitrile (5 mL) were refluxed within 3-4 h; after completion of the reaction which was monitored by TLC, the mixture was cooled to room temperature and filtered. The filtrate was washed twice with 5% $NaHCO_3$ (5 mL) 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.

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^+).

ACKNOWLEDGMENT

The authors are thankful for partial financial assistance from Azzahra university research council.

Received November 30, 2007.

REFERENCES

1. Green, G. R.; Evans, J. M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V.; Ed.; Pergamon Press: Oxford, 1995; Vol. 5, p 469.
2. (a) Foye, W. O. *Principi Di Chemico Farmaceutic*; Piccin: Padova, Italy, 1991; p 416. (b) Witte, E. C.; Neubert. P.; Roesch, A. Ger. Offen DE. *Chem. Abstr.* **1986**, *104*, 224915f.
3. Konkoy, C. S.; Fisck, D. B.; Cai, S. X.; Lan, N. C.; Keana, J. F. W. PCT Int. Appl. WO 0075123, 2000; *Chem. Abstr*. **2001**, *134*, 29313a.
4. (a) Hall, N. *Science* **1994**, *266*, 32. (b) Domling, A.; Herdtweck, E.; Ugi. I. *Acta Chem. Scand*. **1998**, *52*, 107.
5. Sharghi, H.; Niknam, K. *Iran. J. Chem. & Chem. Eng*. **1999**, *18*, 36.
6. Sharghi, H.; Kaboudin, B. *J. Chem. Res*. (S) **1998**, 629.
7. Sharghi, H.; Hosseini Sarvari, M. *J. Chem. Res*. (S) **2001**, 446.
8. Sharghi, H.; Hosseini Sarvari, M. *Synth. Commun*. **2003**, *33*, 205.

9. Sharghi, H.; Hosseini Sarvari, M. *Tetrahedron.* **2003**, *59*, 3627.
10. Niknam, K.; Zolfigol, M. A. *Synth. Commun*. **2006**, *36*, 2311.
11. Niknam, K.; Zolfigol, M. A.; Razavian, S. M.; Mohammadpoor-Baltork, I. *J. Heterocycl. Chem*. **2006**, *43*, 199.
12. Gernon, M. D.; Wu, M.; Buszta, T.; Janney, P. *Green Chem*. **1999**, *3*, 127.
13. (a) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Gharib, A.; Jahangir, M. *Applied Cata*. **2006**, *302*, 42. (b) Heravi, M. M.; Hekmatshoar, R.; Pedram, L. *J. Mol. Cata. A: Chem.* **2005**, *89*, 231. (c) Tajbakhsh, M.; Mohajerani, B.; Heravi, M. M.; Ahmadi, A. N. *J. Mol. Cata. A: Chem*. **2005**, *236*, 216-219. (d) Heravi, M. M.; Bakhtiari, K.; Bamoharram, F. F. *Catal. Commun.* **2006**, *7*, 373. (e) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Gharib, A.; Jahangir, M. *J. Mol. Cata. A: Chem.* **2006**, *252*, 90. (f) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Tavakoli, N. *J. Mol. Cata. A: Chem*. **2006**, *252*, 219. (g) Heravi, M. M.; Motamedi, R.; Siefi, N.; Bamoharram, F. F. *J. Mol. Cata*. **2006**, *249*, 1. (h) Bamoharram, F. F.; Heravi, M. M.; Roshani, M. *J. Chin. Chem. Soc*. **2007**, *54*, 1017. (i) Heravi, M. M.; Bakhtiari, K.; Oskooie, H. A. *J. Chin. Chem. Soc*. **2007**, *54*, 579. (j) Heravi, M. M.; Oskooie, H. A.; Baghernejad, B. *J. Chin. Chem. Soc*. **2007**, *54*, 767.
14. Elagamay, A. G. A.; El-Taweel, F. M. A. A. *Indian J. Chem. B*. **1990**, *29*, 885.
15. Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacanni, A.; Righi, P.; Sartori, G. *Tetrahedron* **2001**, *57*, 1395.
16. Shi, D. Q.; Zhang, S.; Zhuang, Q. Y.; Tu, S. J.; Hu, H. W. *Youji Huaxue* **2003**, *23*, 809.
17. Maggi, R.; Ballini, R.; Sartori, G.; Sartorio, R. *Tetrahedron Lett*. **2004**, *45*, 2297.
18. Jin, T.-Sh.; Xiao, J.-Ch.; Wang, S.-J.; Li, T.-Sh. *Ultrason. Sonochem*. **2004**, *11*, 393.