Ultrasonic-Promoted One-Pot Synthesis of 4*H*-chromenes, pyrano[2,3-d]pyrimidines, and 4*H*-pyrano[2,3-c]pyrazoles

Davood Azarifar*, Razieh Nejat-Yami, Fatemeh Sameri and Zahra Akrami

Faculty of Chemistry, Bu-Ali Sina University, Zip Code 65178, Hamedan, Islamic Republic of Iran

Received November 05, 2011: Revised March 09 2012: Accepted April 26, 2012

Abstract: A facile and versatile procedure has been explored for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes, pyrano[2,3-d]pyrimidines and 1,4-dihydropyrano[2,3-c]pyrazole-5-yl cyanides. This protocol employs the one-pot three-component condensation of aromatic aldehydes and malononitrile with 5,5-dimethyl-cyclohexane-1,3-dione, 1,3-dimethyl barbituric acid or 3-methyl-1-phenyl-2-pyrazolin-5-ones respectively in ethanol under the catalytic effect of triethylamine and ultrasonic-irradiation conditions. Simple manipulation, high reaction rates, improved yields, use of inexpensive and non-toxic catalyst, and also use of ethanol as a relatively environmentally benign solvent are the main advantages of this protocol.

Keywords: 4H-chromenes, pyrano[2,3-d]pyrimidines, pyrano[2,3-c]pyrazole, ultrasonic-irradiation, triethylamine.

INTRODUCTION

Application of ultrasound in a so called "sonochemistry" has evidently received enormous interests [1, 2], since it offers a versatile and challenging technique in organic synthesis [3]. It is a known fact that, ultrasonic irradiation technique can be used not only to reduce the reaction times but also to improve the yields in a vast variety of organic reactions [1].

In addition, the development of one-pot multicomponent reactions (MCRs) has attracted much attention from the vantage point of combinatorial and medicinal chemistry [4]. Generally, the MCR strategy affords considerable savings both in synthetic time and effort, and has significant preferences over conventional multi-stage reactions in several aspects including variable and high bond forming efficiency.

On the other hand, a wide variety of heterocyclic compounds occur in nature most of which play vital roles in our life. Amongst them, nitrogen-containing heterocycles constitute the largest portion of chemical scaffolds which are part of many natural products, fine chemicals and biologically active pharmaceuticals that are vitally important for enhancing the quality of life [5].

In recent years, synthesis of 4*H*-chromene derivatives has been the focus of much attentions owing to their biological and pharmacological activities. These compounds perform various pharmacological activities as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic agents [6, 7].

Similarly, pyrano[2,3-d]pyrimidines are also well documented over the past years due to their wide range of diverse pharmacological activities and are of significant therapeutic value as antitumors, cardiotonics, hepatoprotectives, antihypertensives and antibronchitics. The general procedures for preparation of pyrano[2,3-*d*]pyrimidines usually include the reaction of benzylidenemalononitriles with barbituric acids in the presence of base catalysts [8, 9], ionic liquids [10], under microwave promotion [11], or electrochemically induced condition [12].

In the domain of heterocyclic compounds, the fused pyrazolones such as pyrano derivatives constitute a very important class of compounds. These fused systems have been widely used as intermediates in medicinal chemistry because of their useful biological and pharmacological properties such as antibacterial, anticoagulant, anticancer, spasmolytic, hypnotic, diuretic, and insecticidal properties. Recently, some new methods have been applied to facilitate these reactions [13, 14].

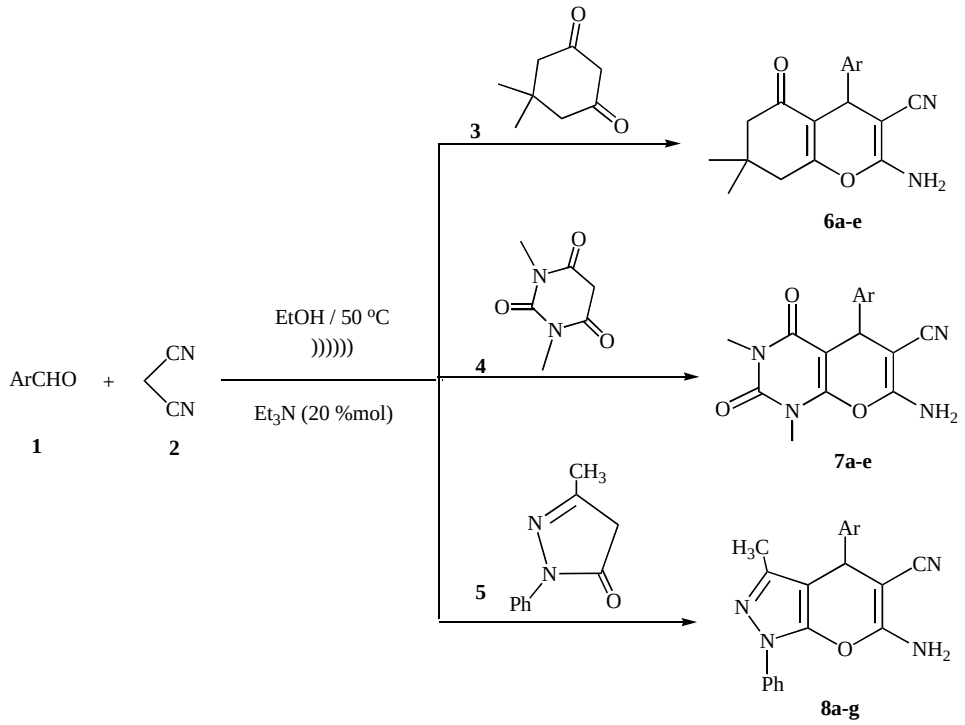
RESULTS AND DISCUSSION

As part of our ongoing interest in the application of ultrasonic irradiation technique as a clean and versatile method in organic synthesis [15], we were encouraged, herein, to report a highly efficient application of ultrasound in one-pot synthesis of a variety of 4*H*-chromenes, 4*H*-pyrano[2,3-d]pyrimidines and 4*H*-pyrano[2,3-c]pyrazole derivatives catalyzed by Et_3N (Scheme **1**). The reactions were completed within a short period of time (10-40 min) to provide the respective products in high yields isolated through a simple workup.

To establish the reaction conditions in order to achieve the best results in terms of reaction times, temperature and the yield, we initially examined the reaction of 4-chlorobenzaldehyde **1**, malononitrile **2**, and 5,5-dimethylcyclohexane-1,3-dione (dimedone) **3** as a model reaction for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes **6**. The effects of solvent and reaction conditions on this reaction were investigated using various solvents such as EtOH, CH_3CN and H_2O under different temperatures and catalyst concentrations (Table **1**). As shown in Table **1**, the reaction works best at 50 °C under ultrasonic irradiation

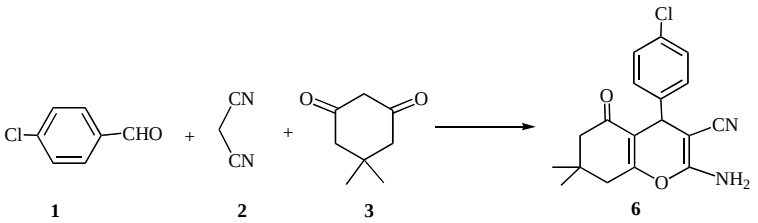
*Address correspondence to this author at the Faculty of Chemistry, Bu-Ali Sina University, Zip Code 65178, Hamedan, Islamic Republic of Iran; Tel: +98(811)8380647; Fax: +98(811)8380709; E-mail: d_azarifar@yahoo.com

1875-6255/12 $58.00+.00



Scheme 1.

Table 1. Screening the Reaction Parameters on the Synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes 6[a]



Entry	Solvent /Temperature °C	Catalyst (mol%)	Method	Time (min)	Yield (%)[b]
1	EtOH / 50	None	sonication	10	Trace
2	EtOH / 50	Et_3N (10)	sonication	10	56
3	EtOH / 50	Et_3N (20)	sonication	10	91
4	EtOH / 50	Et_3N (30)	sonication	10	90
5	EtOH / 60	Et_3N (20)	sonication	10	90
6	EtOH / 40	Et_3N (20)	sonication	10	73
7	EtOH / rt	Et_3N (20)	sonication	10	47
8	H_2O / 50	Et_3N (20)	sonication	10	60
9	CH_3CN / 50	Et_3N (20)	sonication	10	40
10	EtOH / rt	Et_3N (20)	conventional	60	10
11	EtOH / 50	Et_3N (20)	conventional	60	15
12	EtOH / reflux	Et_3N (20)	conventional	60	20

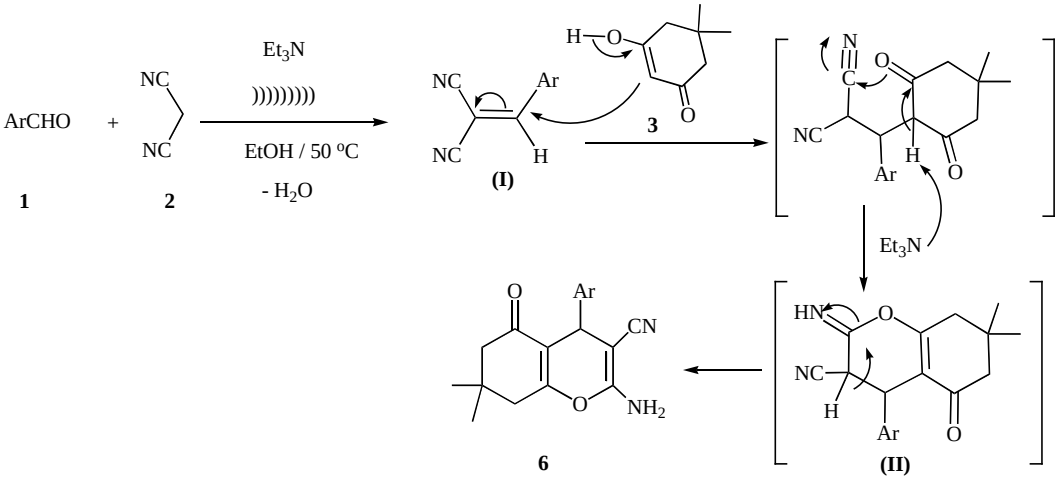
[a] Malononitrile (1 mmol), 4-chlorobenzaldehyde (1 mmol), dimiedone (1 mmol).
[b] Isolated yield.

with a 20 mol% of Et_3N catalyst using ethanol as the solvent of choice (91%). It was noticed that increasing the reaction temperature as well as the catalyst concentration did not exhibit any considerable effect on the reaction time and the yield as well. However, at lower temperatures the yield was found to be significantly reduced. The important role of the

Table 2. Ultrasonic-promoted Synthesis of 4*H*-chromenes 6, pyrano[2,3-d]pyrimidines 7 and 4*H*-pyrano[2,3-c]pyrazol Derivatives 8

Product[a]	R	Product	Time (min)	Yield (%)[a]	Mp (°C)
1	Ph	**6a**	30	86	226-228
2	4-FC_6H_4	**6b**	20	91	211-212
3	4-ClC_6H_4	**6c**	25	90	214-216
4	3-$NO_2C_6H_4$	**6d**	20	91	203-205
5	4-$NO_2C_6H_4$	**6e**	20	88	151-152
6	4-FC_6H_4	**7a**	30	88	230-232
7	3-BrC_6H_4	**7b**	40	86	217-218
8	4-ClC_6H_4	**7c**	25	87	239-241
9	2-ClC_6H_4	**7d**	35	82	238-239
10	4-$NO_2C_6H_4$	**7e**	25	89	213-215
11	Ph	**8a**	40	87	169-170
12	4-FC_6H_4	**8b**	25	90	168-169
13	4-ClC_6H_4	**8c**	30	92	175-188
14	3-ClC_6H_4	**8d**	25	88	158-160
15	4-BrC_6H_4	**8e**	35	87	197-199
16	3-$NO_2C_6H_4$	**8f**	30	90	189-191
17	4-$NO_2C_6H_4$	**8g**	25	91	197-198

[a] Isolated yields.



Scheme 2.

ultrasound irradiation in this reaction was substantiated by conducting the reaction conventionally in EtOH using 20 mol% of Et_3N catalyst at various temperatures without using ultrasound irradiation. Accordingly, as seen in Table **1** (entries 10-12), only very small amounts of the respective product were formed after a longer reaction time (60 min).

This achievement encouraged us to extend the scope of the reaction to a variety of aromatic aldehydes, under the optimized conditions (EtOH / Et_3N (20 mol%) / ultrasound at 50 °C). All of the reactions were proceeded smoothly to furnish the respective 4*H*-chromenes, pyrano[2,3-d]pyrimidines and 4*H*-pyran derivatives in good to excellent yields in relatively short reaction times (10-40 min) (Scheme **1**). The experimental results are summarized in Table **2**. The structures of the products **6a-e**, **7a-e and 8a-g** were established on the basis of their spectral (^{1}H NMR, IR) and physical data which were in accord with those reported in the literature [7,12,14].

Mechanistically, the initial condensation of aromatic aldehyde with malononitrile in the presence of Et_3N leads to dehydrative formation of arylidenemalononitrile intermediate **I**. Subsequent nucleophilic addition of the enolizable dimedone to intermediate **I** was followed by consecutive Et_3N-induced intramolecular cyclization to the intermediate **II** and its rearrangement to afford the 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene derivatives **6** (Scheme **2**). Similar mechanism holds for the synthesis of pyrano[2,3-

d]pyrimidines **7** as well as 1,4-dihydropyrano[2,3-c]pyrazol-5-yl cyanides **8**.

In conclusion, we have explored the application of ultrasonic irradiation technique as a rapid and versatile protocol in the synthesis of 4*H*-chromenes, pyrano[2,3-d]pyrimidines, and 4*H*-pyran derivatives in ethanol under the catalytic effect of triethylamine. Simple manipulation of the products, improved yields, and shorter reaction times, application of Et_3N as an inexpensive and readily available catalyst and also use of ethanol as a relatively environmentally benign solvent are the main advantages of our method.

EXPERIMENTAL

Chemicals used in this work were purchased from Fluka and Merk chemical companies and used without purification. IR spectra were recorded on a Shimadzu 435-U-04 FT spectrophotometer from KBr pellets. ^{1}H NMR spectra were measured for samples in DMSO-d_6 using a BRUKER DRX-300 AVANCE instrument at 300.13 MHz, using Me_4Si as internal standard. Melting points were measured on a SMPI apparatus. Ultrasonication was performed in a TRANSSONI 660/H ultrasound cleaner with a frequency of 35 KHz and an output power of 70 W. The reactions were performed in open vessels.

Typical procedure for the synthesis of 4*H*-chromenes (6), pyrano[2,3-d]pyrimidines (7), and 4*H*-pyran derivatives (8): To a mixture of aromatic aldehyde **1** (1 mmol), malononitrile **2** (0.066 g, 1 mmol), and Et_3N (0.02 g, 20% mol) in EtOH (10 mL) was added 5,5-dimethyl-cyclohexan-1,3-dione (1 mmol) or 1,3-dimethyl barbituric acid (1 mmol) or 3-methyl-1-phenyl-2-pyrazolin-5-ones (1 mmol). The resulting mixture was then sonicated at 50 $^{\circ}$C for an appropriate time (Table **2**). After the completion of the reaction as monitored by TLC analysis, the reaction mixture was cooled to room temperature followed by evaporation under vacuum to give the crude products, which were crystallized from ethyl acetate/n-hexane (1:3) to yield the pure products **6**, **7** or **8**.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile **(6d)**[14a]**:** White powder, m.p 203–205 °C. IR (KBr) (ν_{max}, cm^{-1}): 3395, 3322, 2192, 1651. ^{1}H NMR (DMSO-d_6): δ, ppm; 1.03 (3H, s, Me), 1.07 (3H, s, Me), 2.07-2.29 (2H, AB system, ^{2}JHH = 16.5 Hz, CH_2), 4.41 (1H, s, CH); 7.30-8.08 (6H, m, H–Ar and NH_2).

7-Amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-d]pyrimidine-6-carbonitrile **(7c)**[12]**:** White powder, m.p 239–241 °C. IR (KBr) (ν_{max}, cm^{-1}): 3378, 3312, 2119, 1711. ^{1}H NMR (DMSO-d_6): δ, ppm; 3.07 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 4.57 (s, 1H, CH), 7.30-8.09 (m, 6H, Ar, NH_2).

6-Amino-4-(4-fluorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole **(8b)**[14b]**:** Yellow crystals, m.p 168–169 °C. IR (KBr) (ν_{max}, cm^{-1}): 3455, 3330, 2204, 1655. ^{1}H NMR (DMSO-d_6): δ, ppm; 1.78 (s, 3H, CH_3), 4.96 (s, 1H, 4-H), 7.23-8.14 (11H, m, H–Ar and NH_2).

ACKNOWLEDGEMENT

We wish to thank the research council of the University of Bu-Ali Sina in Hamedan, Iran, for financial support to carry out this research.

CONFLICT OF INTEREST

Declared none.

REFERENCES

[1] (a) Suslick, K.S. Sonochemistry and Sonoluminiscence in Encyclopedia of Physical Science and Technology; Academic Press: San Diego, 2001. (b) Luche, J.L. Synthetic Organic Sonochemistry; Plenum: New York, **1998**, 241.

[2] (a) Mason, T.J. Sonochemistry and the environment-providing a "green" link between chemistry, physics and engineering. *Ultrason. Sonochem*., **2007**, *14*, 476. (b) Kimmel, E. Cavitation bioeffects. *Crit. Rev. Biomed. Eng*. **2006**, *34*, 105. (c) Putterman, S.J.; Weninger, K.R. Sonoluminescence: How Bubbles Turn Sound into Light. *Ann. Rev. Fluid. Mech*., **2000**, *32*, 445.

[3] Lim, H.J.; Keum, G.; Kang, S.B.; Chung, B.Y.; Kim, Y. Indium mediated pinacol coupling reaction of aromatic aldehydes in aqueous media . *Tetrahedron Lett.*, **1998**, *39*, 4367.

[4] Brase, S.; Gil, C.; Knepper, K. The recent impact of solid-phase synthesis on medicinally relevant benzoannelated nitrogen heterocycles. *Bioorg. Med. Chem.*, **2002**, *10*, 2415.

[5] Awadallah, F.M.; Muller, F.; Lehmann, A.H.; Abadi, A.H. Synthesis of novel lactam derivatives and their evaluation as ligands for the dopamine receptors, leading to a D_4-selective ligand. *Bioorg. Med. Chem.*, **2007**, *15*, 5811.

[6] Andreani, L.L.; Lapi, E. On some new esters of coumarin-3-carboxylic acid wit balsamic and bronchodilator action. *Bull. Chim. Farm.*, **1960**, *99*, 583.

[7] (a) Gao, S.; Tsai, C.H.; Tseng, C.; Yao, C.F. Fluoride ion catalyzed multicomponent reactions for efficient synthesis of 4*H*-chromene and *N*-arylquinoline derivatives in aqueous media. *Tetrahedron*, **2008**, *64*, 9143. (b) Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. A facile one-pot green synthesis and antibacterial activity of 2-amino-4*H*-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes. *Eur. J. Med. Chem.*, **2009**, *44*, 3805.

[8] Sharanin, Yu. A.; Klokol, G.V. Nitrile cyclization reactions. XVI. Reaction of arylidene derivatives of malononitrile and ethyl cyanoacetate with barbituric acid. *Zh. Org. Khim*., **1984**, *20*, 2448.

[9] Seeliger, F.; Berger, S.T.A.; Remennikov, G.Y.; Polborn, K.; Mayr, H. Electrophilicity of 5-Benzylidene-1,3-dimethylbarbituric and -thiobarbituric Acids. *J. Org. Chem*., **2007**, *72*, 9170.

[10] Yu, J.; Wang, H. Green synthesis of pyrano[2,3-d]pyrimidine derivatives in ionic liquids. *Synth. Commun*., **2005**, *35*, 3133.

[11] Gao, Y.; Tu, S.; Li, T.; Zhang, X.; Zhu, S.; Fang, F.; Shi, D. Effective synthesis of 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-d]pyrimidine-2,4(1*H*,3*H*)-diones under microwave irradiation. *Synth. Commun*., **2004**, *34*, 1295.

[12] Elinson, M.N.; Ilovaisky, A.I.; Merkulova, V.M.; Zaimovskayab, T.A.; Nikishina, G.I. Electrocatalytic multicomponent assembling of aldehydes, N-alkyl barbiturates and malononitrile: an efficient approach to pyrano[2,3-d]pyrimidines. *Mendeleev Commun*., **2011**, *21*, 122.

[13] (a) Shi, D.; Mou, J.; Zhuang, Q.; Niu, L.; Wu, N.; Wang, X. Three-component One-Pot Synthesis of 1,4-Dihydropyrano[2,3-c]pyrazole Derivatives in Aqueous Media. *Synth. Commun*., **2004**, *34*, 4557. (b) Jin, T.S.; Wang, A.Q.; Cheng, Z.L.; Zhang, J.S.; Li, T. A clean and Simple Synthesis of 6-Amino-4-Aryl-5-Cyano-3-Methyl-1-Phenyl-1,4-Dihydropyrano[2,3-c]Pyrazole in Water. *Synth. Commun*., **2005**, *35*, 137.

[14] (a) Jin, T.S.; Zhao, R.Q.; Li, T.S. Solid state synthesis of 5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives without using solvent and catalyst. *Arkivoc*, **2006**, *11*. 176. (b) Sheibani, H.; Babaie, M.

Three-component reaction to form 1,4-Dihydropyrano[2,3-c]pyrazol-5-yl cyanides. *Synth. Commun*., **2010**, *40*, 257.

[15] (a) Azarifar, D.; Nejat-Yami, R. Ultrasound-assisted one-pot synthesis of pyrano[1.2-a][1.2.4]triazole1.3-diones. *Heterocycles*, **2010**, *81*, 2063. (b) Azarifar, D.; Sheikh, D. A Efficient and Facile Ultrasonic-Accelarated One-Pot Synthesis of *N*-Acetyl-2-aryl-1,2-dihydro-(4*H*)-3.1-benzoxazin-4-ones. *Heteroatom Chem*., **2011**, *22*, 106.